Contemporary Trends in the Management of Atrial Fibrillation

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Disclosures

Consulting Fees – Biosense Webster

Consulting Fees - Medtronic

Learning Objectives

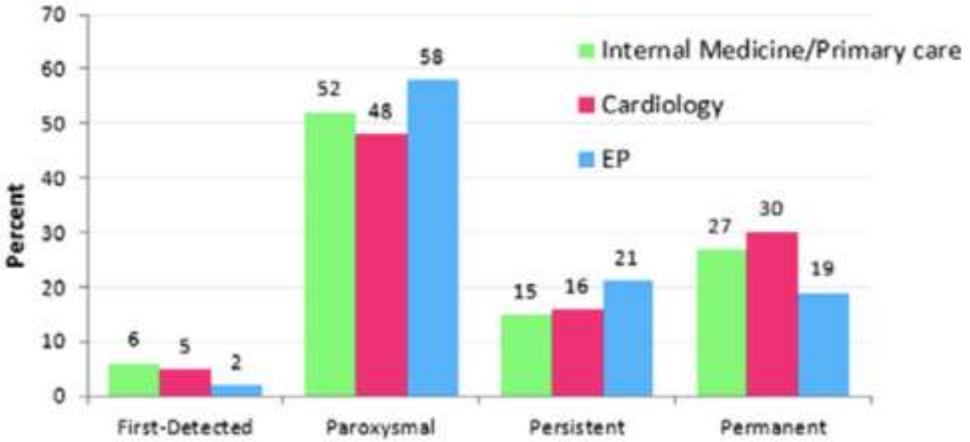
1. Review the data supporting the benefits of early rhythm control in atrial fibrillation.

2. Discuss the benefits of lifestyle modification on outcomes in atrial fibrillation.

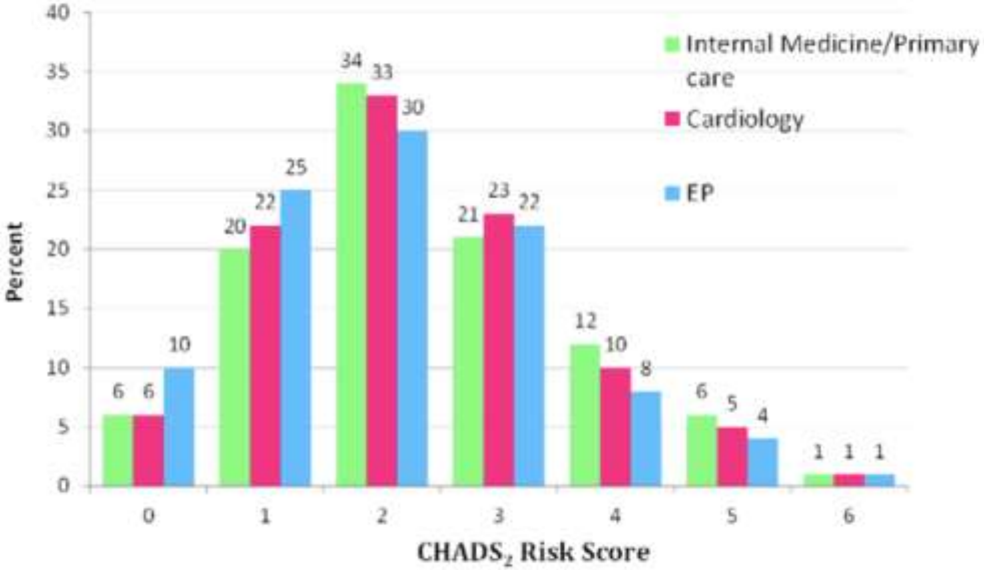
3. Understand the role of Left atrial appendage occlusion.

4. Decide what to do with Atrial Fibrillation detected by wearable devices.

Provider Specialty and Atrial Fibrillation Treatment Strategies in United States Community Practice: Findings From the ORBIT-AF Registry



- A total of 10,097 patients were included;
  - **(15.3%) were cared for by an EP**
  - (65.2%) by a cardiology provider
  - (19.5%) by an internal medicine/primary care provider.



Fosbol, E. L. *et al.* Provider Specialty and Atrial Fibrillation Treatment Strategies in United States Community Practice: Findings From the ORBIT-AF Registry. *J. Am. Hear. Assoc.* **2**, e000110 (2013).

Table 3. Adjusted Relationship Between Specialty of Care Provider and Treatment Strategies

Care Process	Provider Specialty	Adjusted OR	Lower (95% CI for OR)	Upper (95% CI for OR)	*P* Value	Global *P* Value
Rhythm control	EP (vs cardiology)	1.66	1.05	2.61	0.0301	0.0470
	FP/IM (vs cardiology)	0.91	0.65	1.26	0.5512	–
Prior cardioversion	EP (vs cardiology)	1.39	1.03	1.87	0.0292	0.0231
	FP/IM (vs cardiology)	0.88	0.70	1.10	0.2699	–
Oral anticoagulant (warfarin or dabigatran)	EP (vs cardiology)	1.25	0.71	2.19	0.4350	0.1500
	FP/IM (vs cardiology)	0.73	0.49	1.09	0.1233	–
Dabigatran vs warfarin	EP (vs cardiology)	1.11	0.49	2.50	0.8023	0.2395
	FP/IM (vs cardiology)	0.61	0.32	1.13	0.1179	–
Antiplateleta	EP (vs cardiology)	1.34	0.93	1.92	0.1132	<0.0001
	FP/IM (vs cardiology)	0.60	0.47	0.79	0.0002	–
Anticoagulant clinicb	EP (vs cardiology)	3.51	0.90	13.67	0.0705	0.0577
	FP/IM (vs cardiology)	0.60	0.23	1.60	0.3097	–

OR indicates odds ratio; CI, confidence interval; EP, electrophysiology; FP, family practice; IM, internal medicine.

[a]Aspirin, clopidogrel, prasugrel.

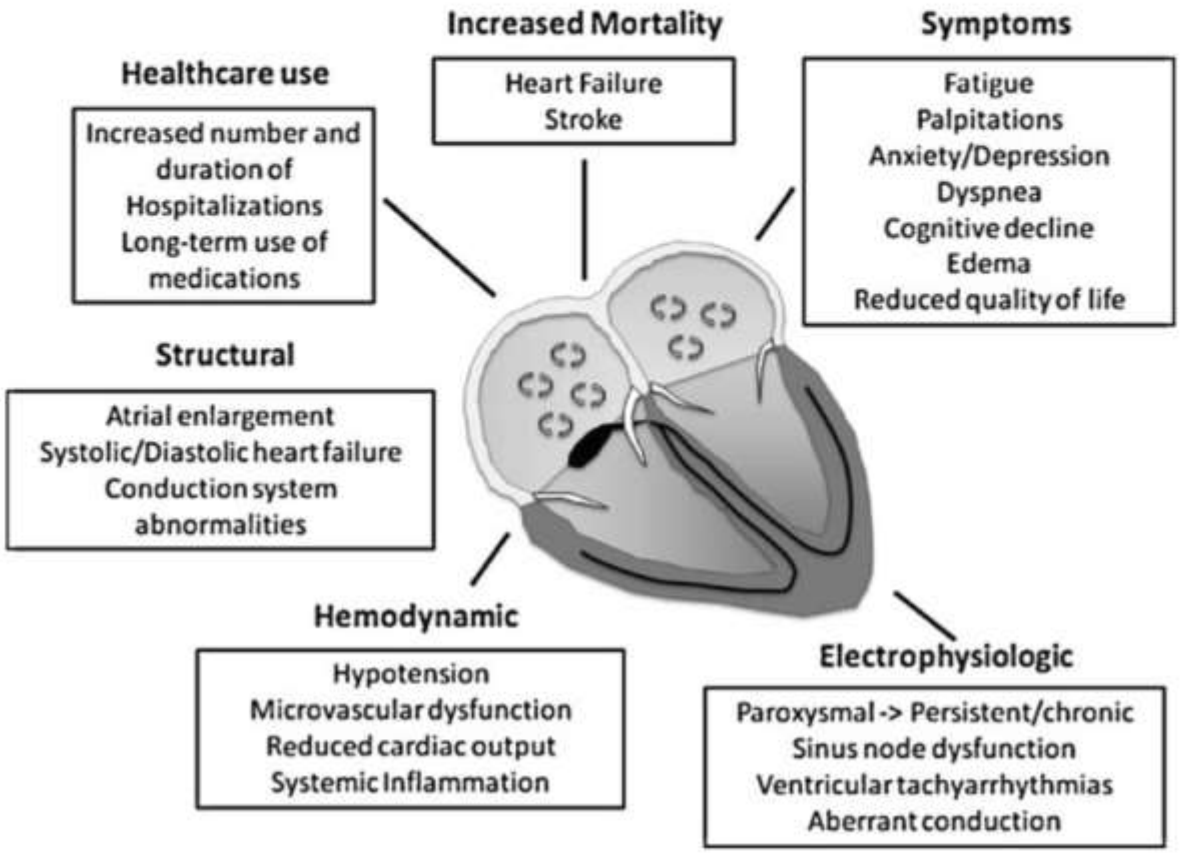
[b]Analyses only among those on warfarin (n=7176).

- After adjusting for case mix, **patients seen by an EP provider were more likely to be on rhythm control** when compared with patients seen by a cardiology provider (adjusted OR, 1.66; 95% CI, 1.05 to 2.61; *P*=0.0301)

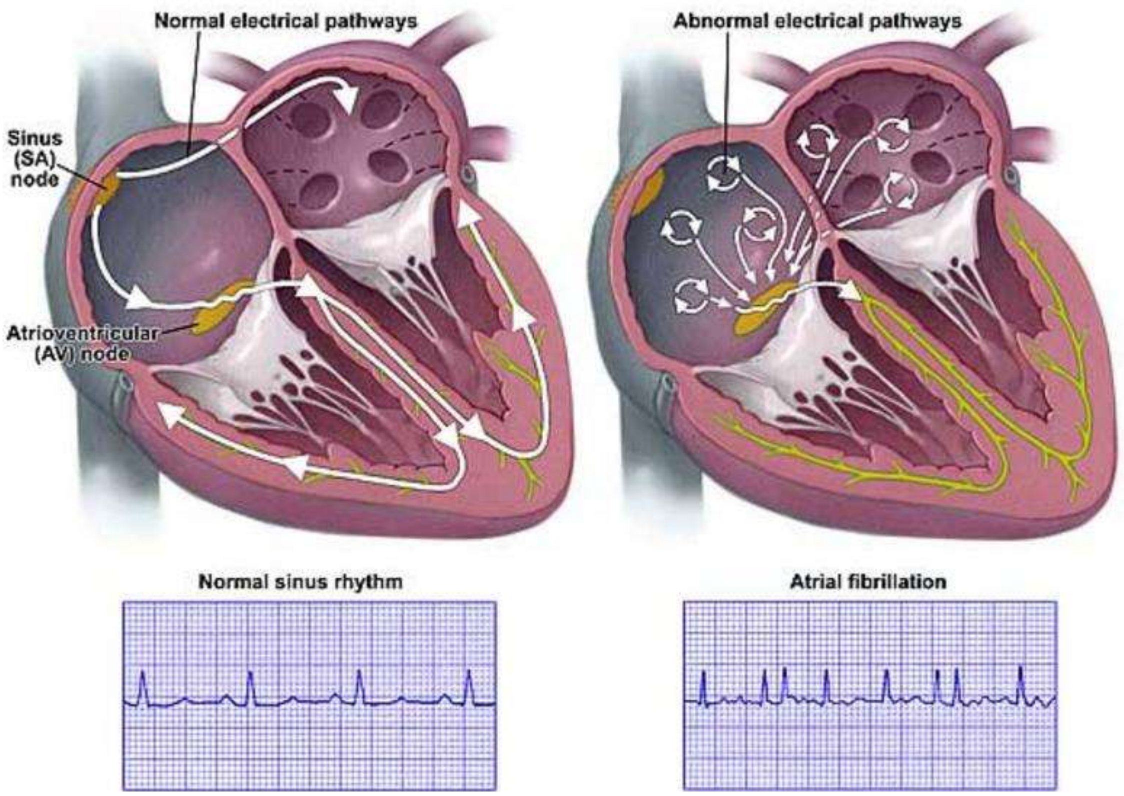
Fosbol, E. L. *et al.* Provider Specialty and Atrial Fibrillation Treatment Strategies in United States Community Practice: Findings From the ORBIT-AF Registry. *J. Am. Hear. Assoc.* **2**, e000110 (2013).

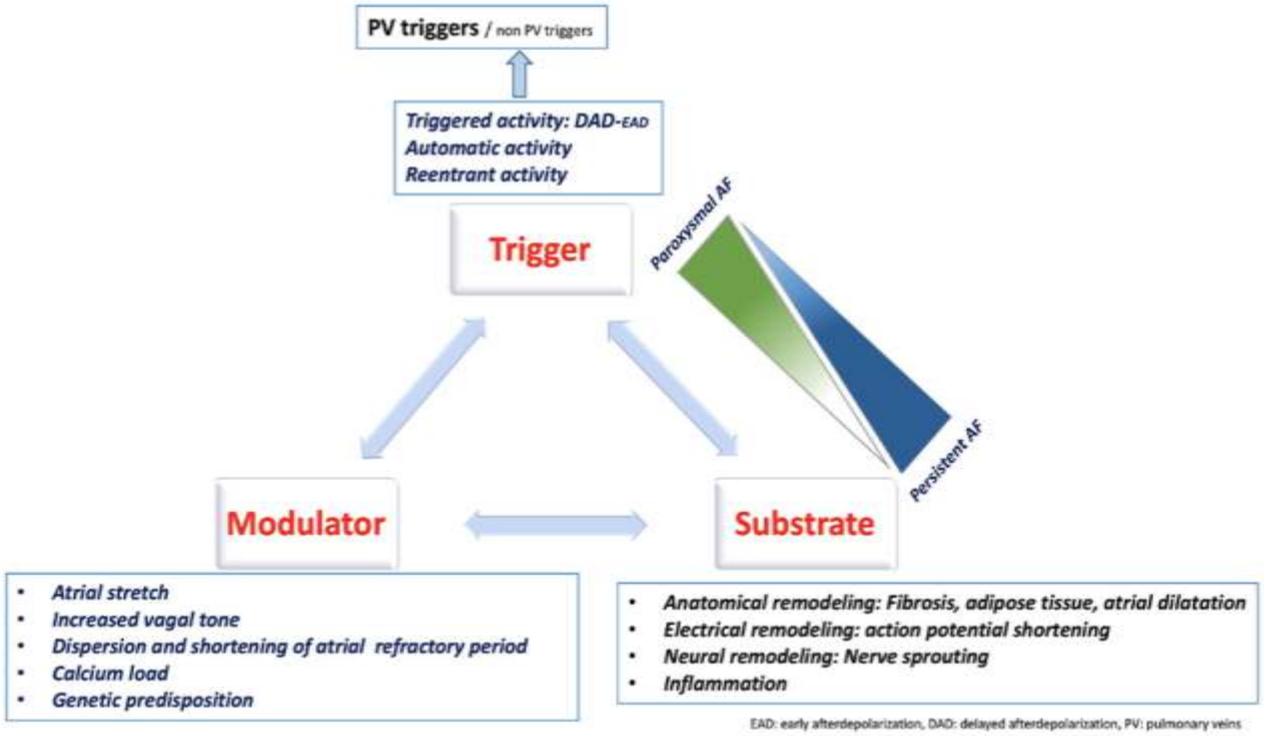
Significance of Atrial Fibrillation

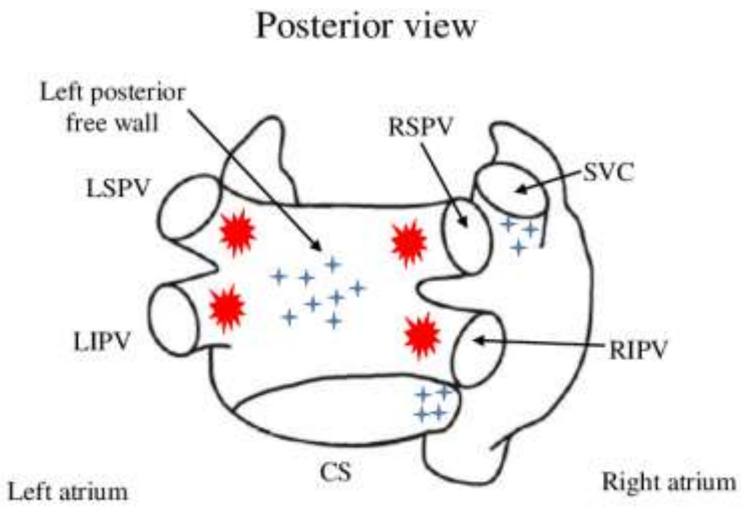
- 33 million cases worldwide.
- In the USA, between 3-5 million people have AF.
- There is a 5-fold increase in the risk of stroke, and strokes are usually more severe.
- AF increased mortality and has been linked to sudden cardiac death.
- AF increases the risk of heart failure
- AF has been linked with the development of Dementia.
- AF affects Quality of life.

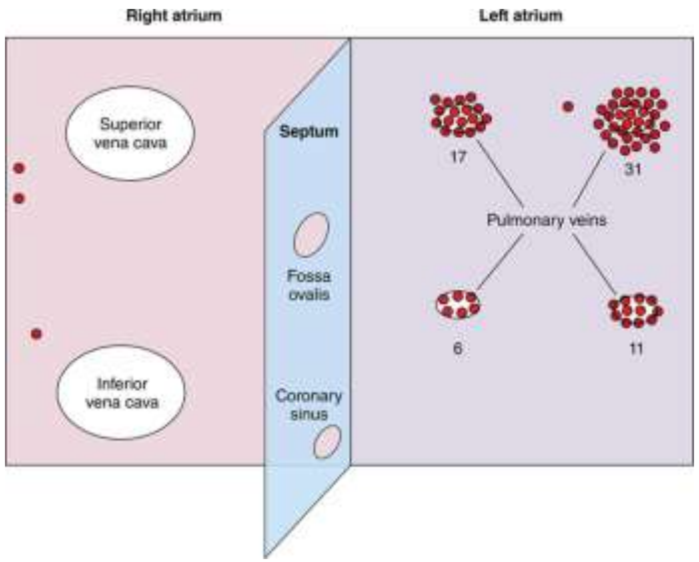


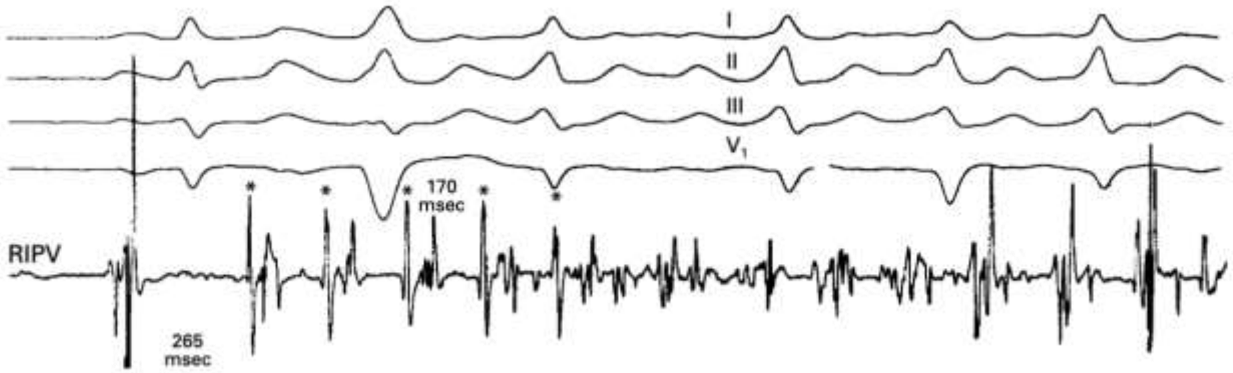
What is Atrial Fibrillation?

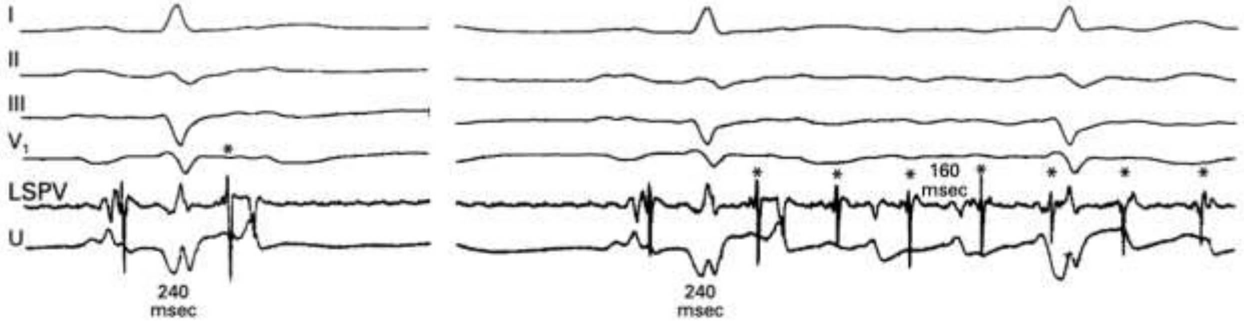




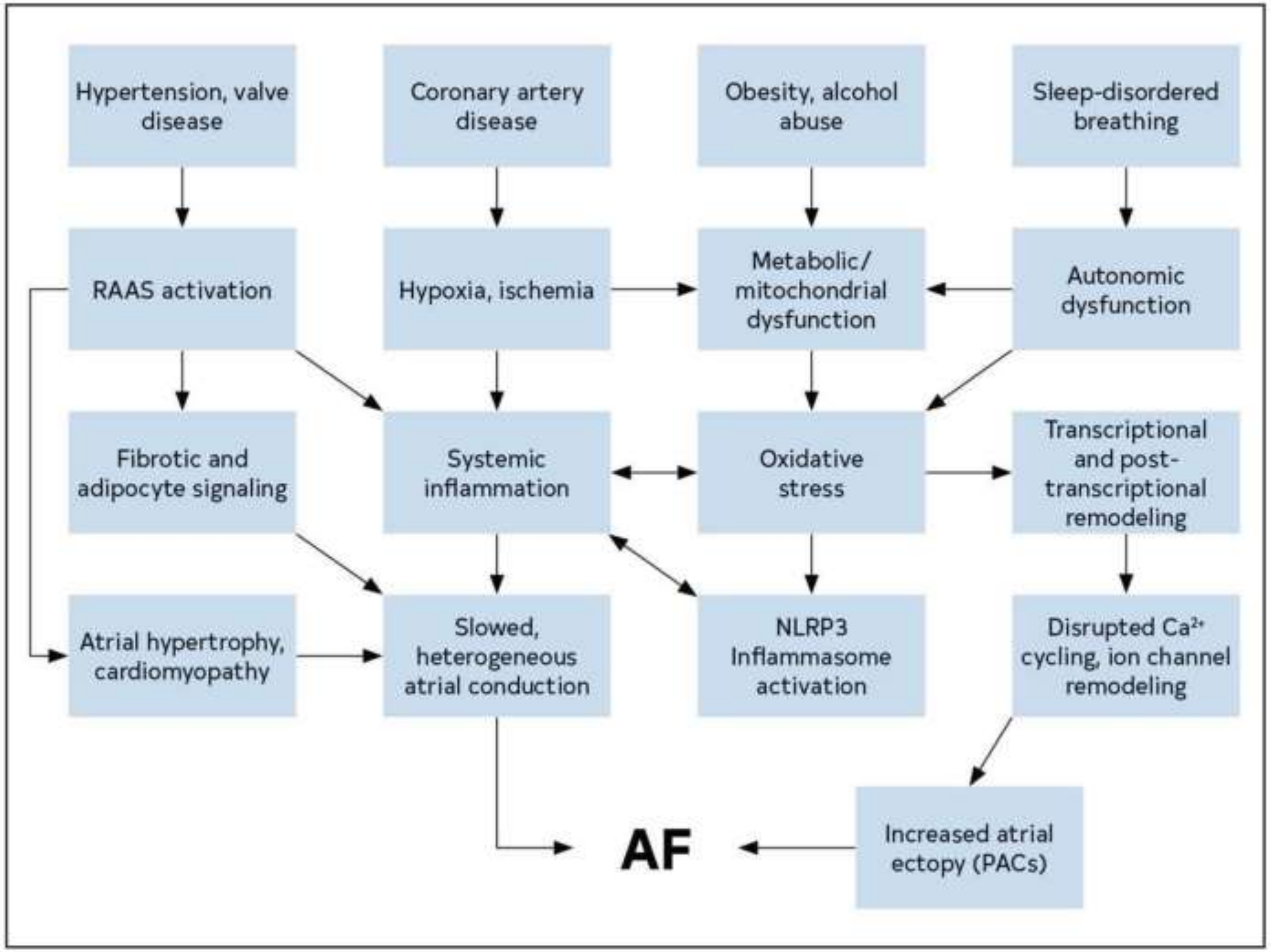






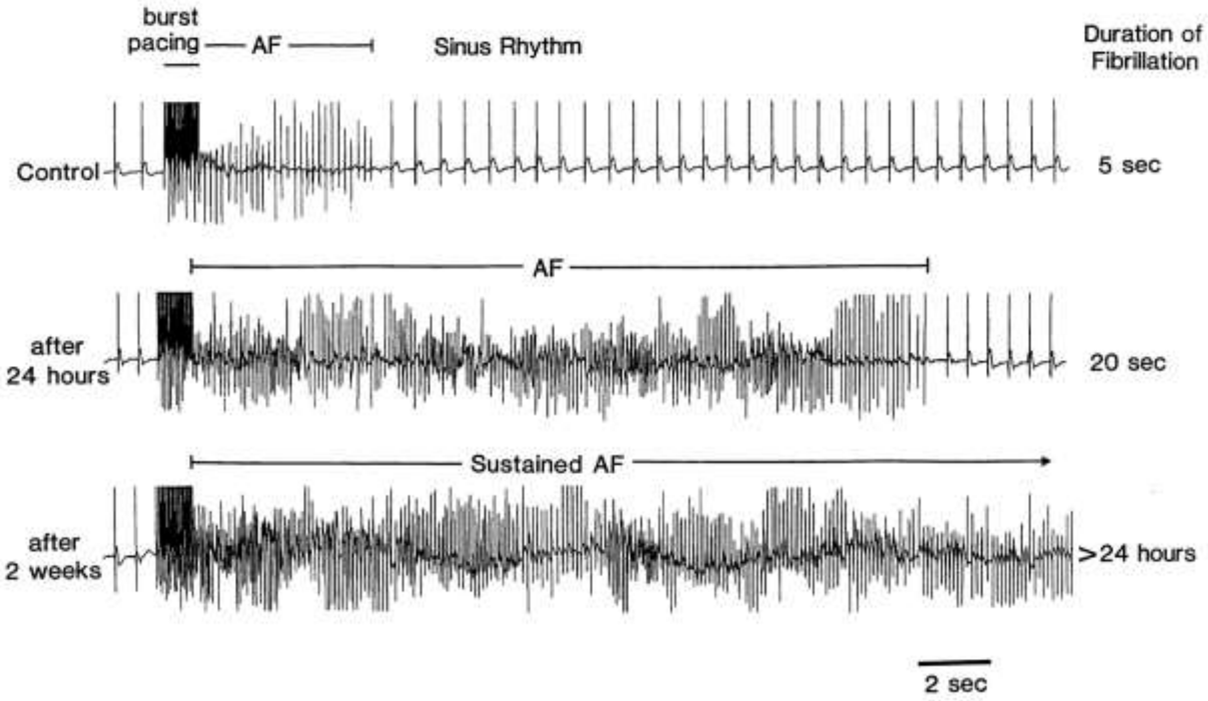


[Haïssaguerre, M. *et al.* Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. *New Engl J Medicine* **339**, 659–666 (1998).]

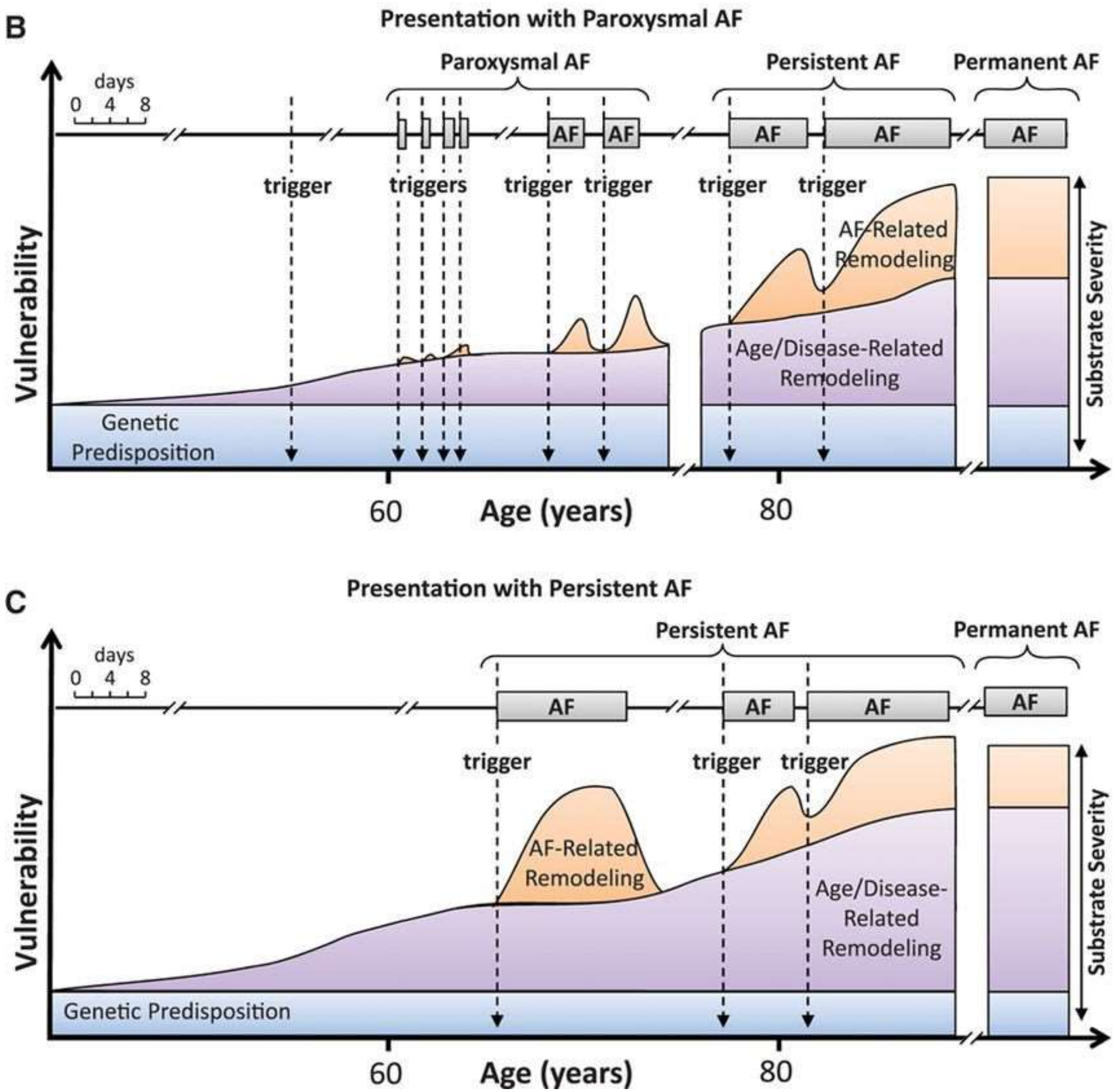


Narayan, S. M., Cain, M. E. & Smith, J. M. Atrial fibrillation. *Lancet* **350**, 943–950 (1997).

‘Atrial Fibrillation Begets Atrial Fibrillation’



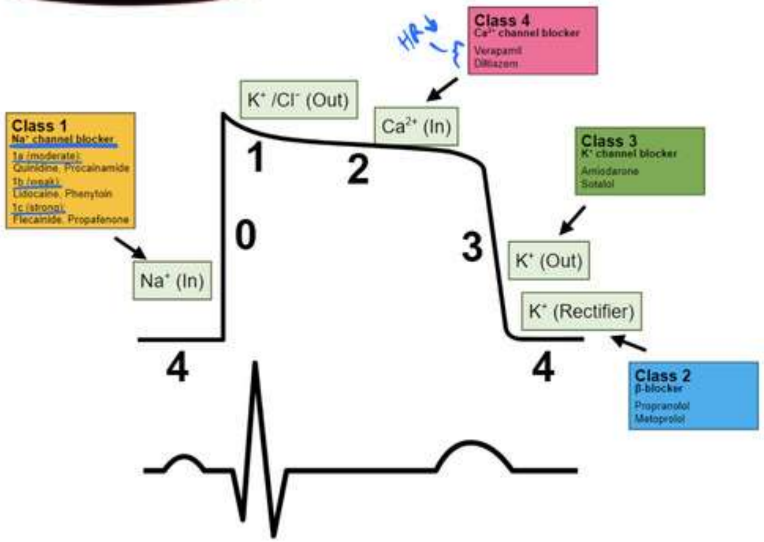
Wijffels, M. C. E. F., Kirchhof, C. J. H. J., Dorland, R. & Allessie, M. A. Atrial Fibrillation Begets Atrial Fibrillation: A Study in Awake Chronically Instrumented Goats. *Circulation* **92**, 1954–1968 (1995).



Heijman, J., Voigt, N., Nattel, S. & Dobrev, D. Cellular and Molecular Electrophysiology of Atrial Fibrillation Initiation, Maintenance, and Progression. *Circ. Res.* **114**, 1483–1499 (2014).

Rhythm Control

Goal is to significantly reduce the frequency and duration of AF episodes but not eliminate all future episodes of AF



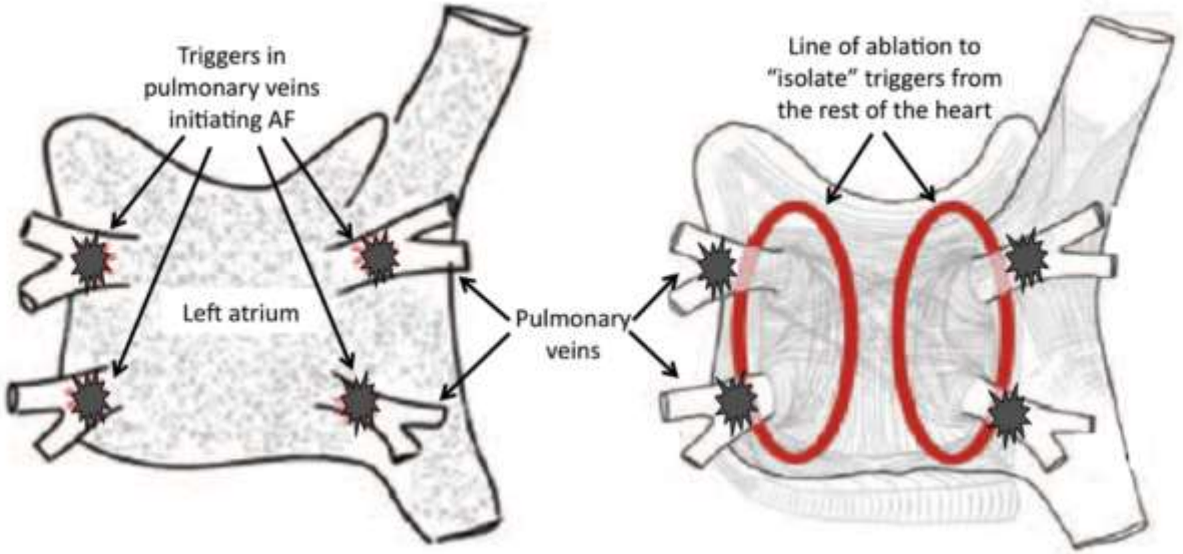


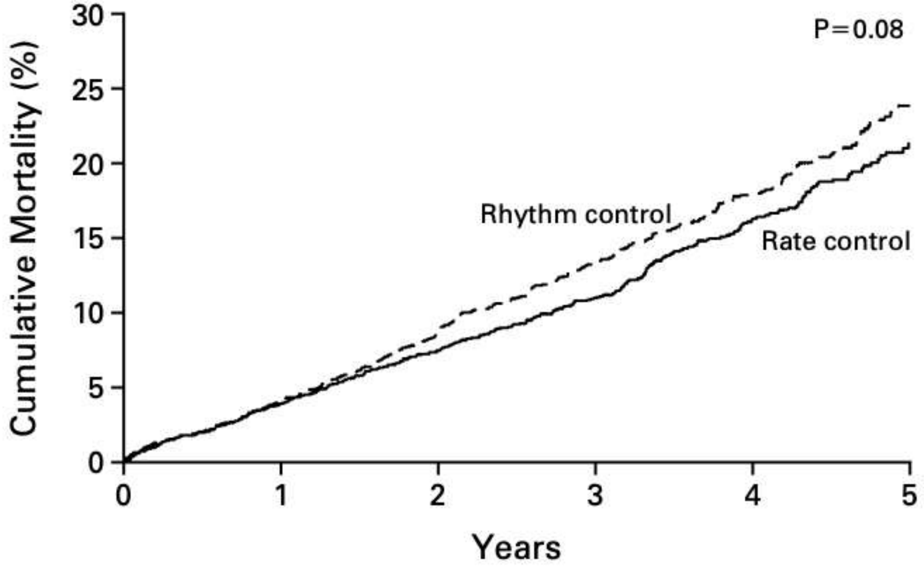
TABLE 2 Key Outcomes of Trials Using Rhythm- and Rate-Control Strategies in Treatment of AF

Trial	Primary Endpoint	Primary Endpoint Result	Patients in SR
PIAF[17]	Improvement in AF-related symptoms (palpitations, dyspnea, and dizziness)	No significant difference between treatment arms	Rhythm control: 56% at study end Rate control: 10% at study end
AFFIRM[18]	Overall mortality	Rhythm control: 24% at 5-y follow-up Rate control: 21% at 5-y follow-up (NS across follow-up period)	Rhythm control: 62.6% at 5-y follow-up Rate control: 34.6% at 5-y follow-up
RACE[19]	Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for a pacemaker, or severe AEs	Rhythm control: 22.6% at study end Rate control: 17.2% at study end (noninferior, approaching superior)	Rhythm control: 39% at study end Rate control: 10% at study end
STAF[147]	Composite of death, stroke or transient ischemic attack, systemic embolism or cardiopulmonary resuscitation	Rhythm control: 5.54%/y Rate control: 6.09%/year (NS)	Rhythm control: 38% at last follow-up Rate control: 9% at last follow-up
AF-CHF[20]	Death from cardiovascular causes	Rhythm control: 27% at study end Rate control: 25% at study end (NS)	Rhythm control: 73% at 4-y follow-up Rate control: 30% to 41% during follow-up[b]
J-RHYTHM[22]	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure[a] and physical/psychological disability requiring strategy alteration	Rhythm control: 15.3% at study end Rate control: 22.0% at study end (HR: 0.664; $P = 0.0128$)	Rhythm control: 72.7% at 3 y Rate control: 43.9% at 3 y

[a]Requiring intravenous administration of diuretics. [b]Data reported are patients with AF (59% to 10%).

AE = adverse event; HR = hazard ratio; NS = nonsignificant; SR = sinus rhythm; other abbreviation as in Table 1.

AFFIRM Trial



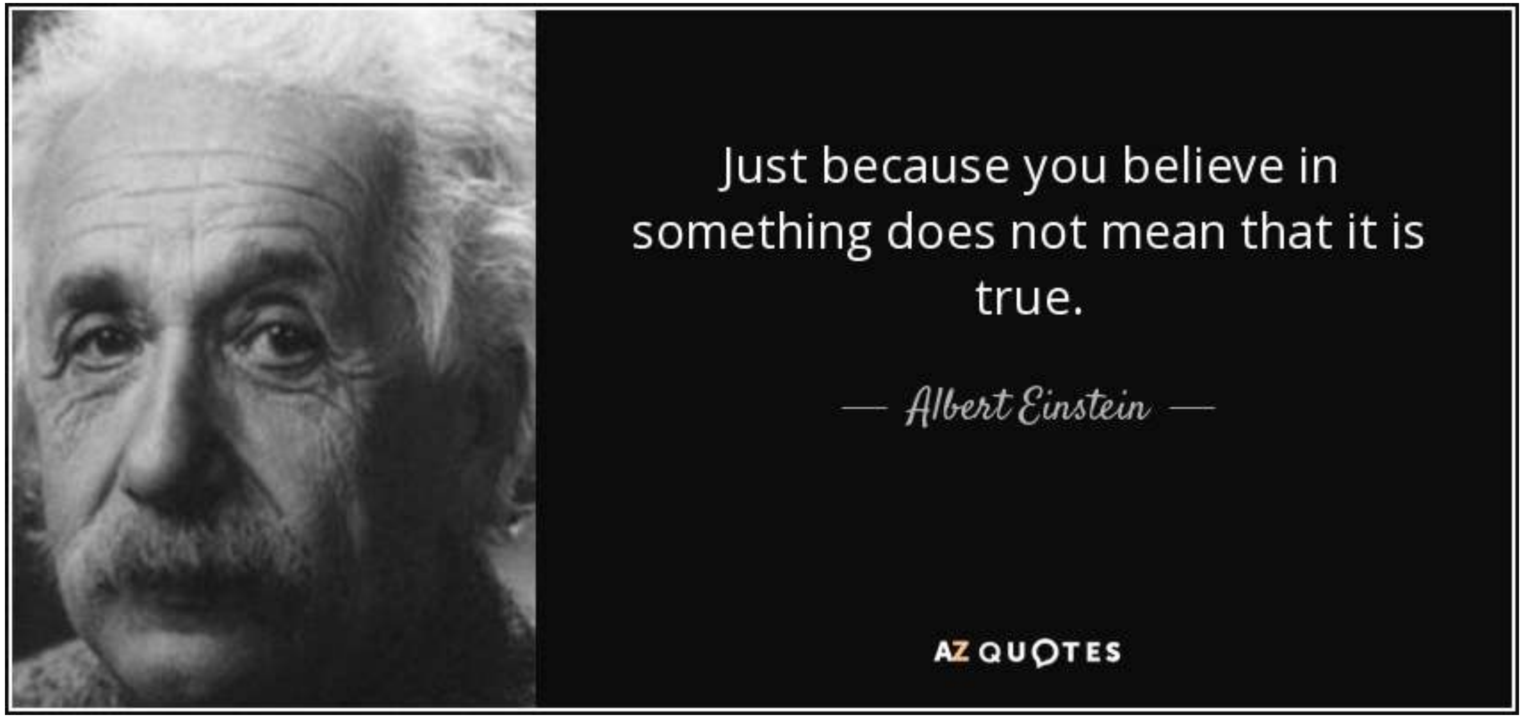
No. of Deaths	number (percent)					
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.

Time zero is the day of randomization. Data have been truncated at five years.

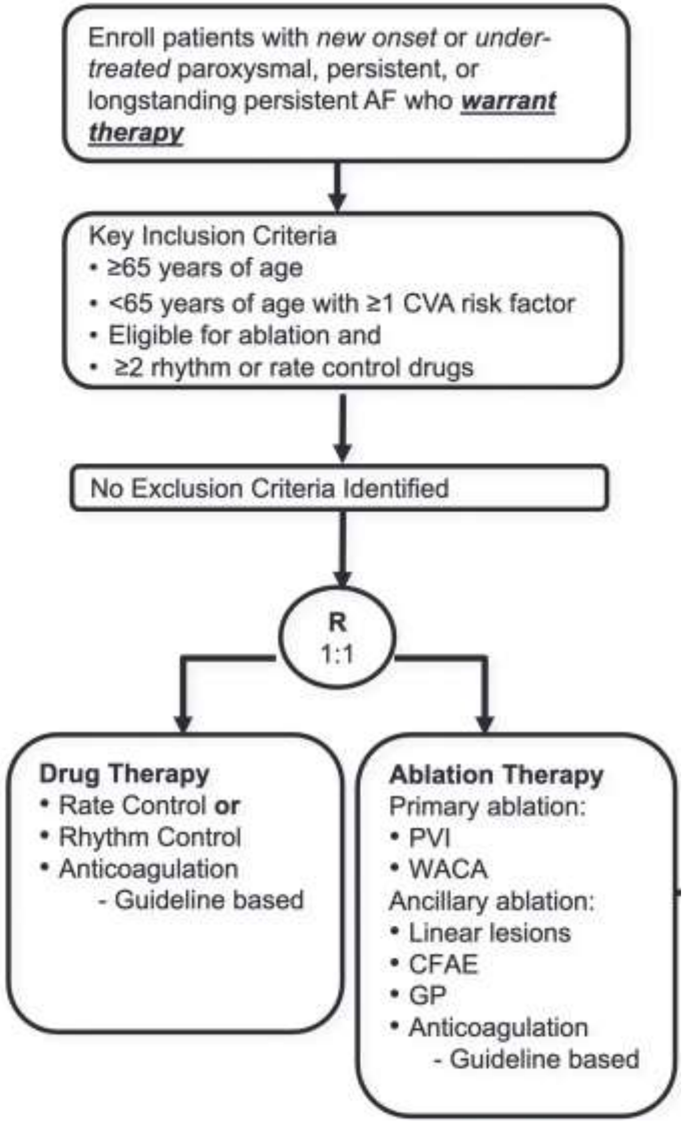
Wyse, D. *et al.* A comparison of rate control and rhythm control in patients with atrial fibrillation. *The New England journal of medicine* **347**, 1825–33 (2002).

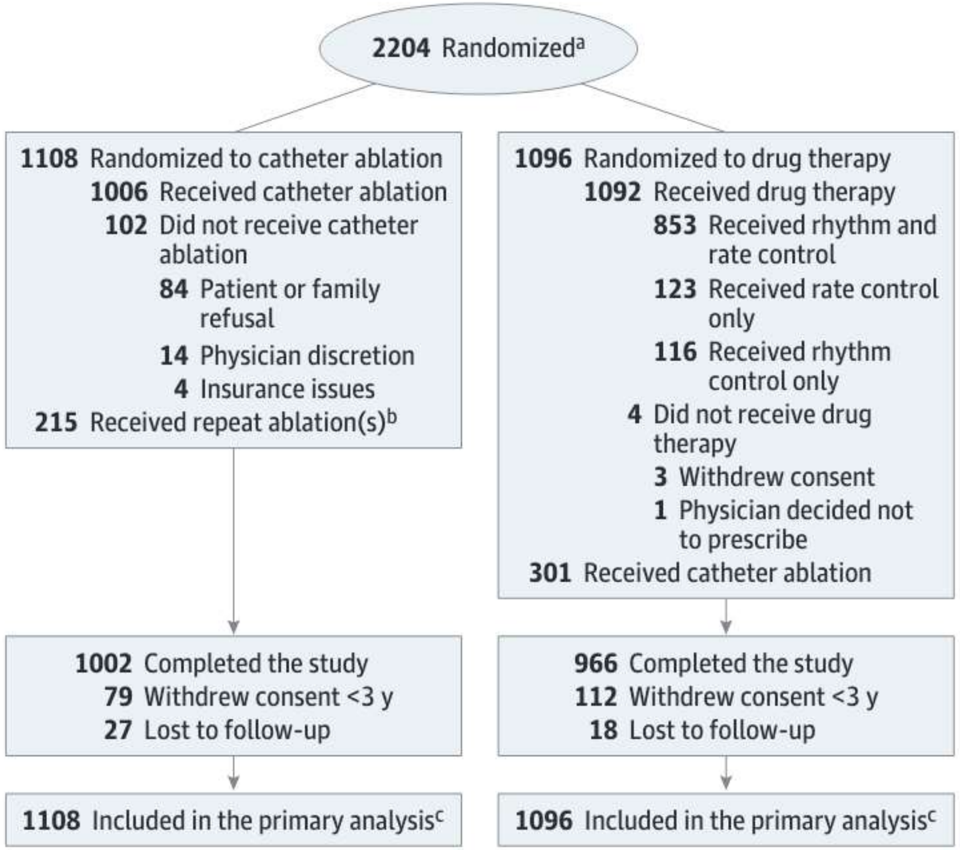
Rhythm Control Preferred by Electrophysiologist



Electrophysiologists have always asserted the superiority of rhythm control over rate control.

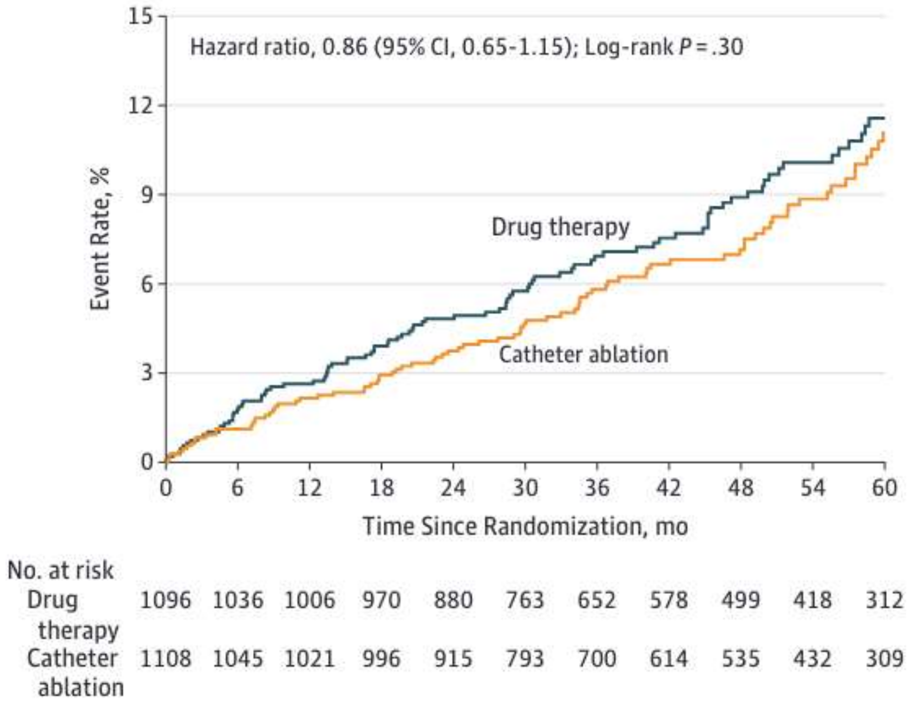
CABANA Trial

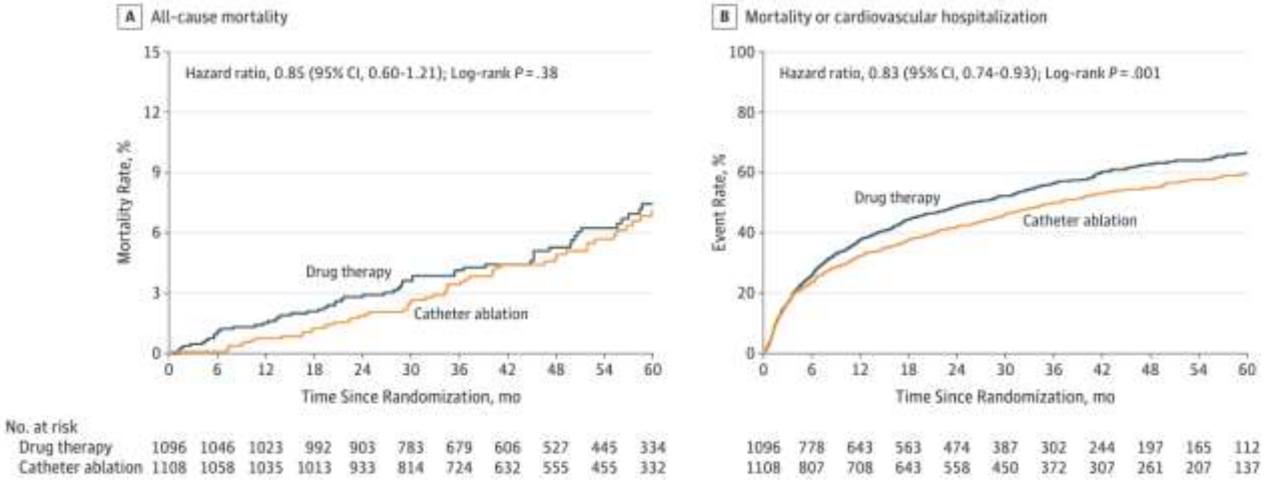




Packer, D. L. *et al.* Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation. *Jama* **321**, 1261–1274 (2019).

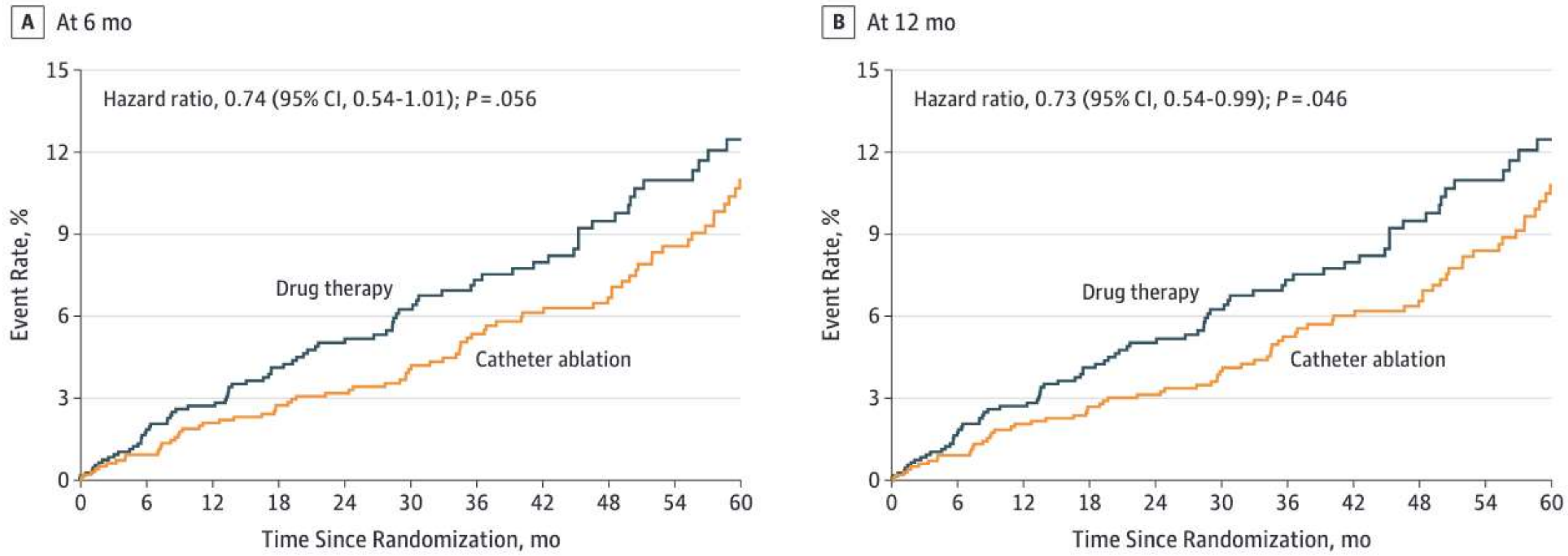
CABANA Trial





A, The median (25th, 75th percentiles) length of patient follow-up was 4.1 years (2.5, 5.1) in the catheter ablation group and 4.0 years (2.5, 5.2) in the drug therapy group. B, The median (25th, 75th percentiles) length of patient follow-up was 4.1 years (2.5, 5.1) in the catheter ablation group and 4.0 years (2.5, 5.2) in the drug therapy group.

Packer, D. L. *et al.* Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation. *Jama* **321**, 1261–1274 (2019).



No. at risk

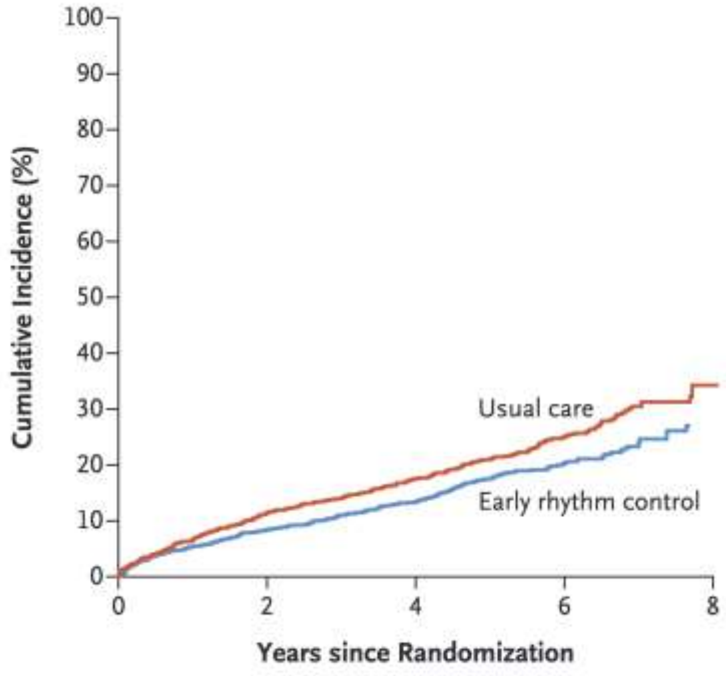
Drug therapy	1096	954	860	778	680	566	464	396	330	275	204
Catheter ablation	970	941	920	901	835	721	636	555	483	397	287

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

Packer, D. L. *et al.* Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation. *Jama* **321**, 1261–1274 (2019).

EAST-AFNET 4

- 2,789 patients with early AF (<1 yr)
- A first-primary-outcome event occurred in 249 of the patients assigned to early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to usual care (5.0 per 100 person-years)
- Primary Outcomes: Composite of death, Stroke, Hospitalization from HF of ACS
- Trail stopped in 3rd interim analysis (median 5.1y)
- HR, 0.79; 96% (confidence interval, 0.66 to 0.94; P = 0.005).



No. at Risk					
Usual care	1394	1169	888	405	34
Early rhythm control	1395	1193	913	404	26

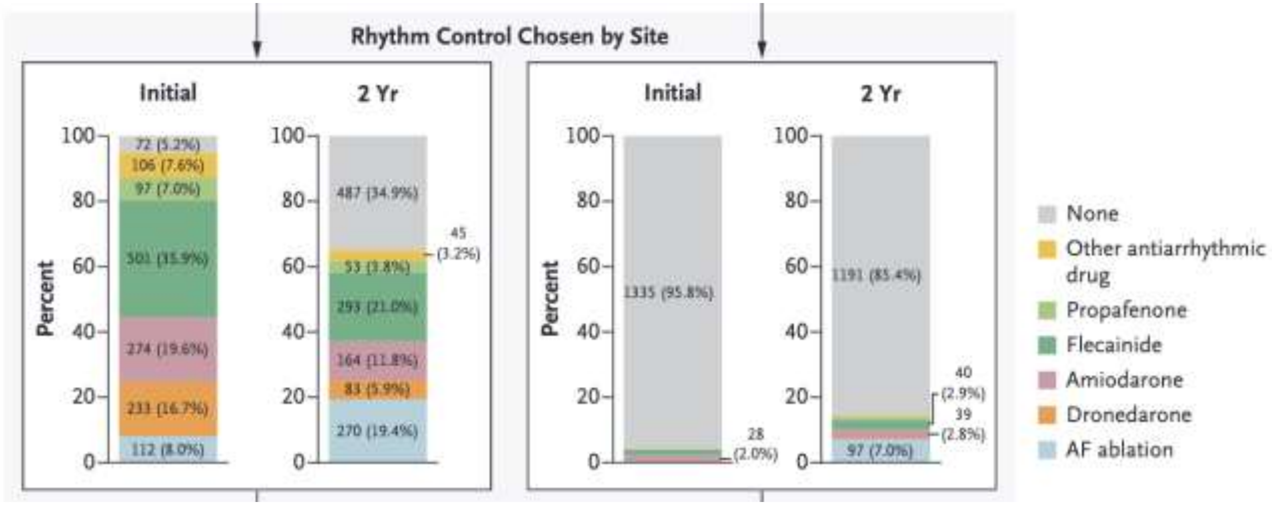
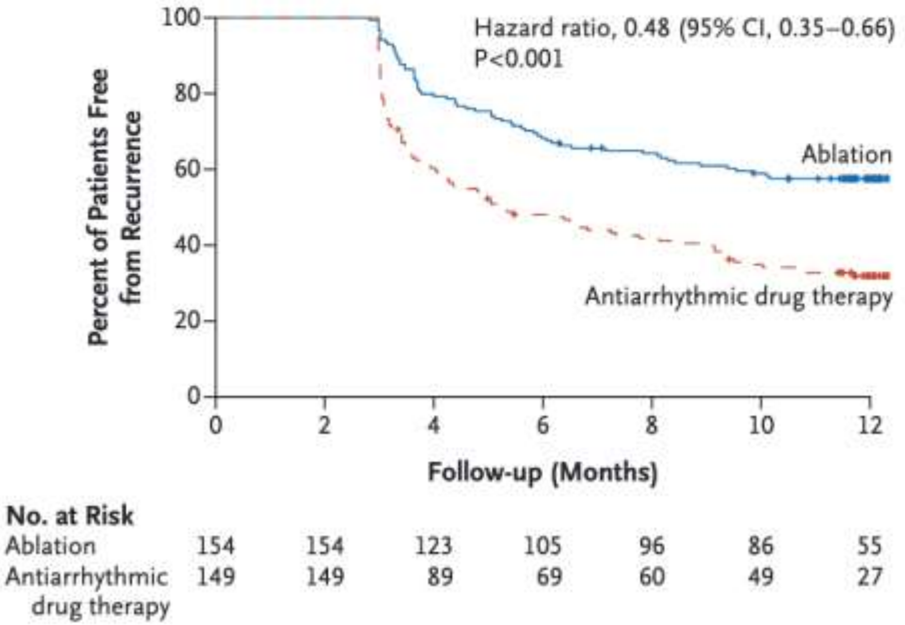


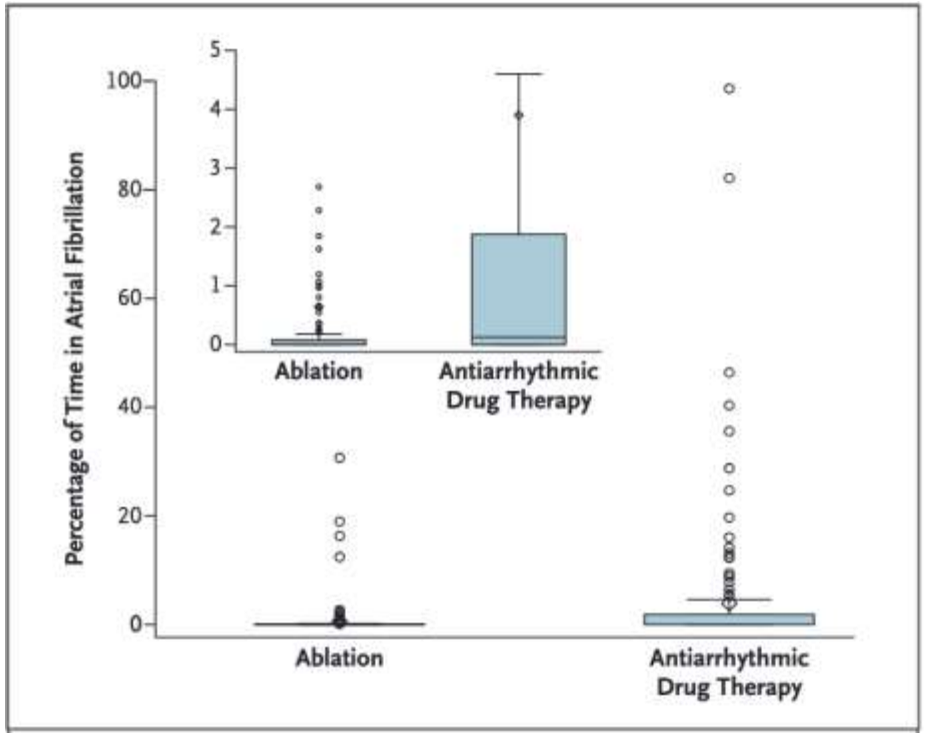
Table 3. Safety Outcomes.*

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)

Kirchhof, P. *et al.* Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *New England Journal of Medicine* **383**, (2020).

EARLY - AF





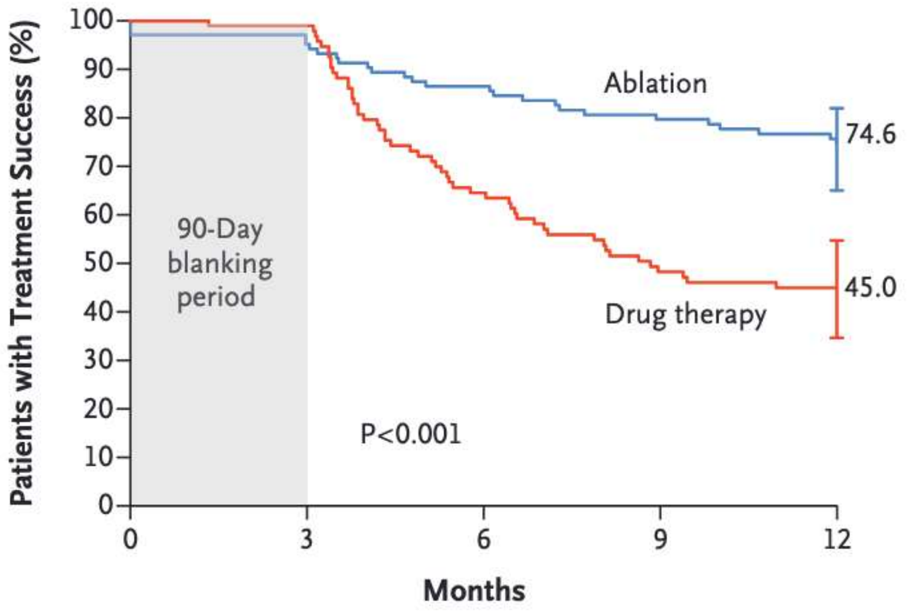
Serious adverse events occurred in 5 patients (3.2%) who underwent ablation and in 6 patients (4.0%) who received antiarrhythmic drug

Andrade, J. G. *et al.* Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *New Engl J Med* **384**, (2020).

STOP – AF First

- 203 participants underwent randomization and received treatment, 104 underwent ablation, and 99 initially received drug therapy

- The percentage of patients with treatment success at 12 months was 74.6% in the ablation group and 45.0% in the drug-therapy group
- (P<0.001 by log-rank test)

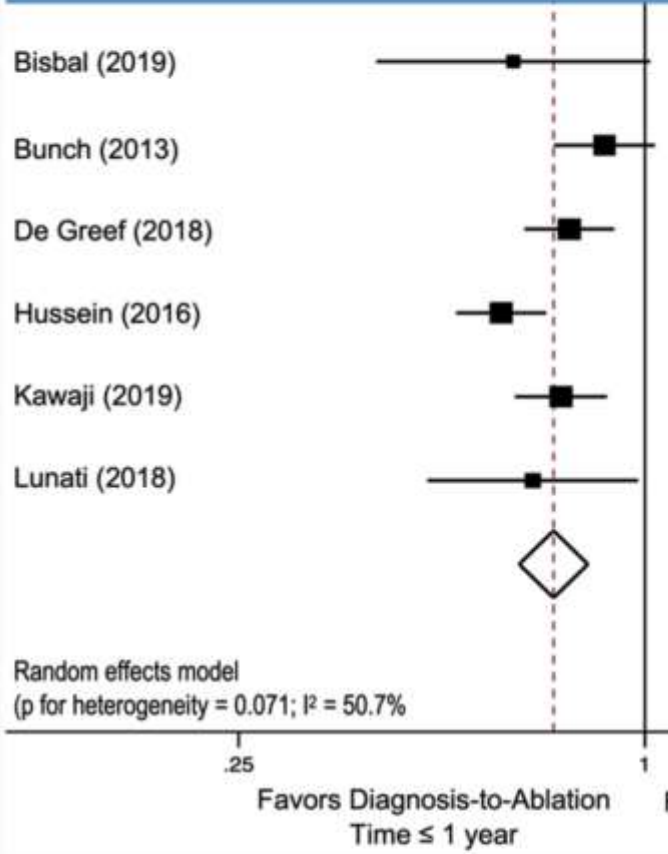


No. at Risk					
Ablation	104	99	88	81	70
Drug therapy	99	93	60	44	39

Serious Adverse Event	Ablation (N=104)		Drug Therapy (N=99)	
	no. of events	*no. of patients (%)*	*no. of events*	*no. of patients (%)*
Any serious adverse event	22	15 (14)	16	14 (14)

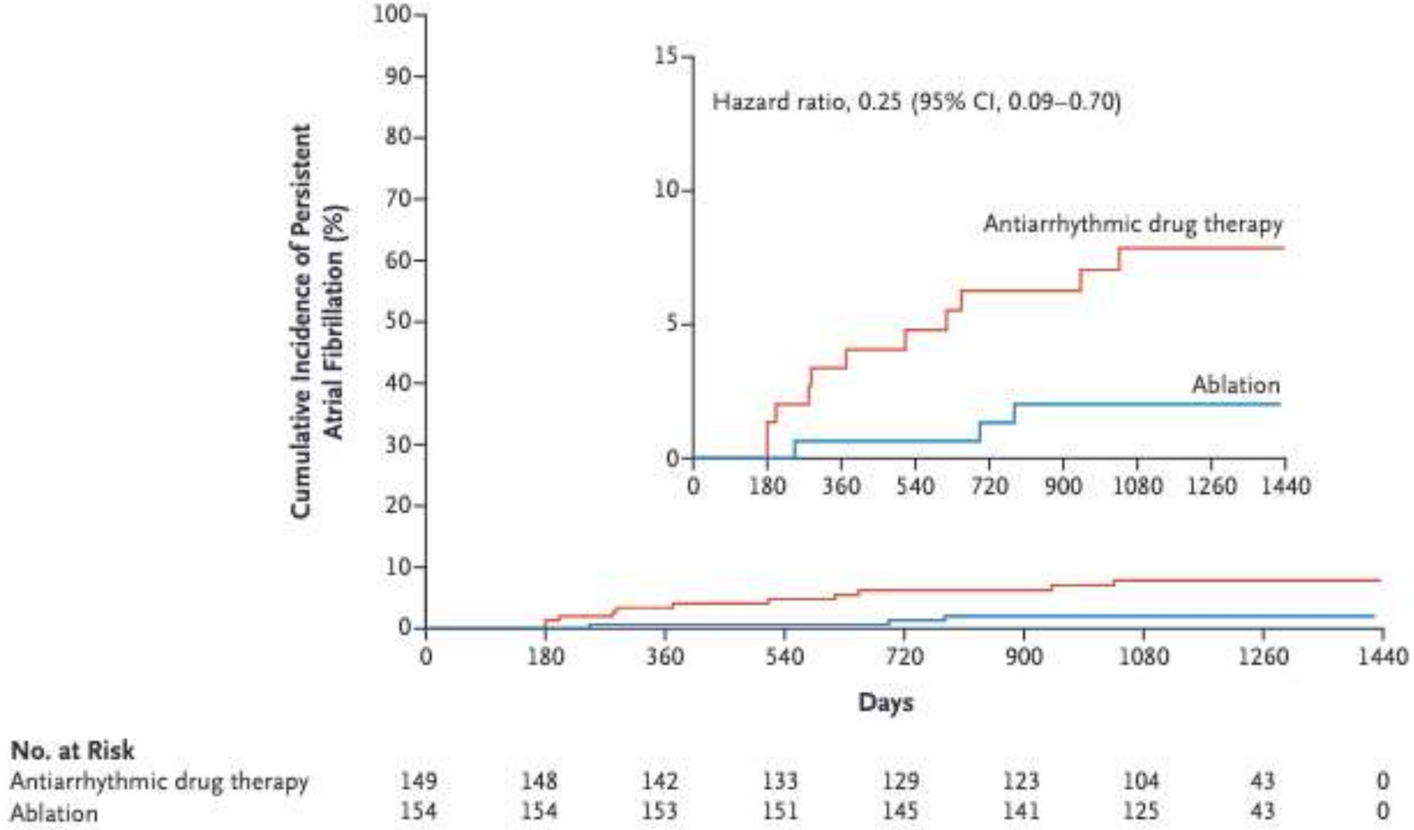
Wazni, O. M. *et al.* Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *New Engl J Med* **384**, 316–324 (2020).

Does time between first diagnosis of atrial fibrillation and catheter ablation affect procedural success?



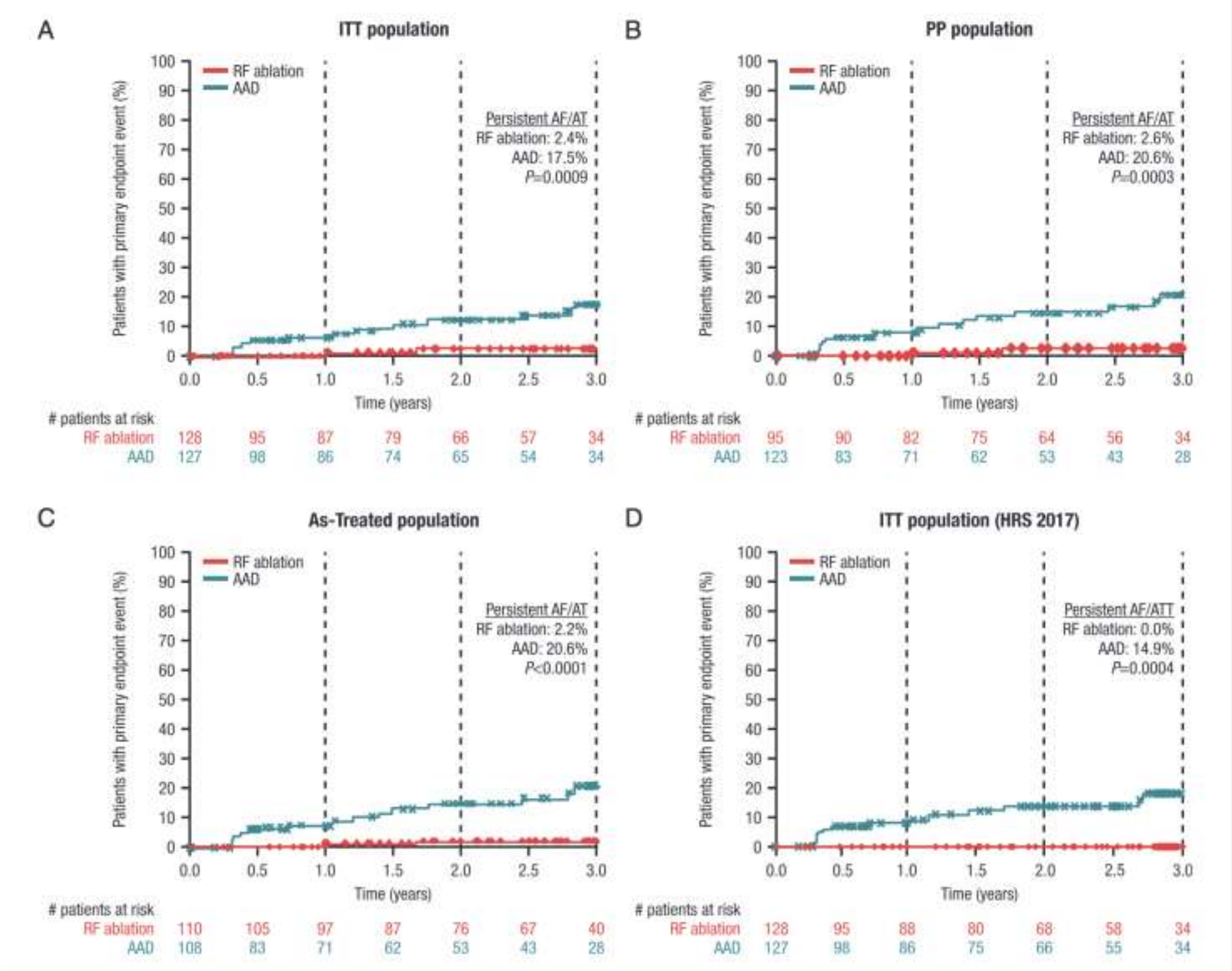
	Relative Risk (95% CI)	Diagnosis to Ablation Time ≤ 1 year Events	N	> 1 year Events	N	Weight (%)
Bisbal (2019)	0.64 (0.40, 1.02)	14	51	111	258	5.4
Bunch (2013)	0.87 (0.73, 1.03)	124	303	179	381	20.2
De Greef (2018)	0.77 (0.66, 0.90)	108	244	433	756	22.2
Hussein (2016)	0.61 (0.53, 0.71)	128	382	470	859	22.2
Kawaji (2019)	0.75 (0.64, 0.88)	133	389	372	817	21.8
Lunati (2018)	0.68 (0.48, 0.98)	28	130	120	380	8.2
	0.73 (0.65, 0.82) p for overall effect < 0.001	535	1499	1685	3451	100.0

1.Chew, D. S. *et al.* Diagnosis-to-Ablation Time and Recurrence of Atrial Fibrillation Following Catheter Ablation: A Systematic Review and Meta-analysis of Observational Studies. *Circulation Arrhythmia Electrophysiol* (2020) doi:10.1161/circep.119.008128.



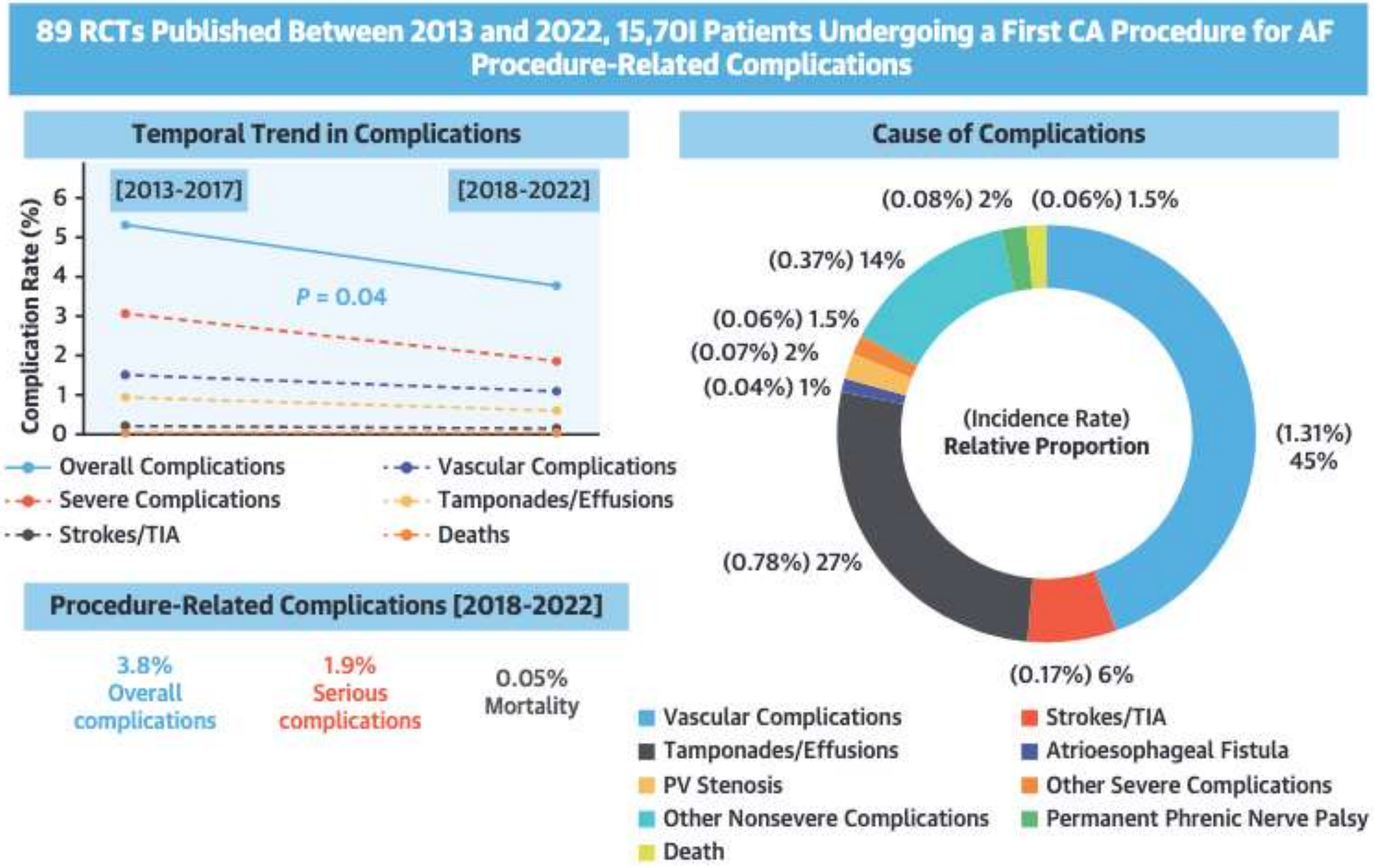
End Point	Ablation Group (N=154)	Antiarrhythmic Drug Group (N=149)	Hazard Ratio (95% CI)
	number (percent)		
Progression to persistent atrial fibrillation from 91 days after treatment initiation to final follow-up	3 (1.9)	11 (7.4)	0.25 (0.09–0.70)
Recurrence of any atrial tachyarrhythmia			
From 91 days to 12 mo after treatment initiation†	66 (42.9)	101 (67.8)	0.48 (0.35–0.66)
From 91 days to 36 mo after treatment initiation	87 (56.5)	115 (77.2)	0.51 (0.38–0.67)

Andrade, J. G. *et al.* Progression of Atrial Fibrillation after Cryoablation or Drug Therapy. *N. Engl. J. Med.* **388**, 105–116 (2022).



- Ablation seemed to delay the progression of AF disease
- Fewer patients receiving Ablation progressed to persistent AF
- 2.4% vs 17.5%

Kuck, K.-H. *et al.* Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST). *EP Eur.* **23**, 362–369 (2020).



Benali, K. *et al.* Procedure-Related Complications of Catheter Ablation for Atrial Fibrillation. *J. Am. Coll. Cardiol.* **81**, 2089–2099 (2023).

Early Rhythm control for Atrial Fibrillation

- In a contemporary study comparing rate and rhythm control, rhythm control was associated with reduced composite end point including; death, stroke, and hospitalization for HF or ACS.
  - EAST AFNET4 utilized ablation (20%) and more Class I AAD therapy than in the AFFIRM trial

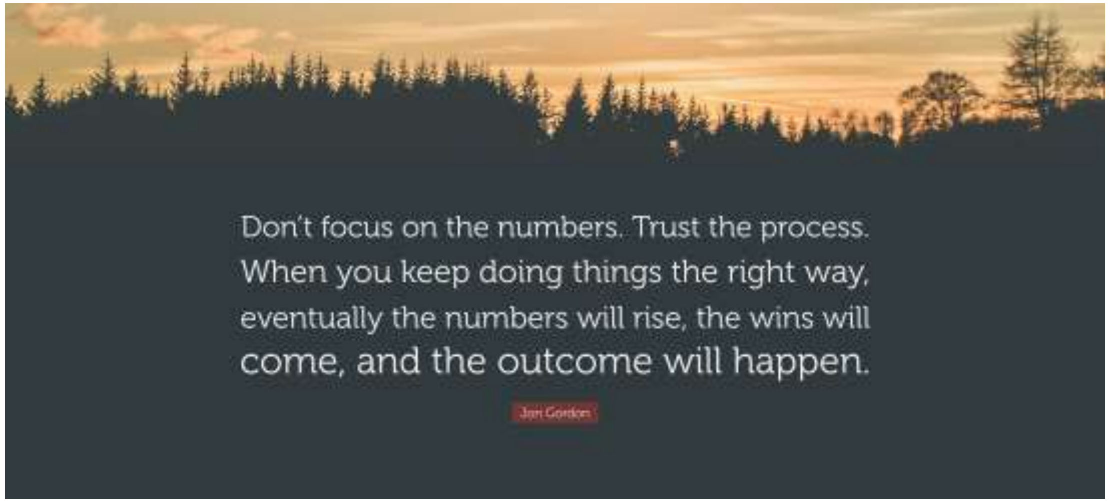
- Subsequent studies comparing contemporary ablation to AAD therapy for rhythm control show the superiority of catheter ablation in maintaining rhythm control.

- In all these studies, patients were randomized early (within one year of diagnosis)
  - In about 30% after the first episode (EAST AFNET4)

Early Rhythm control for Atrial Fibrillation

- Reduced Burden and Symptoms with ablation compared to usual therapy or AAD
- Mortality Benefits to rhythm control
- Slower progression – Disease Modification
- Reduced Heart Failure
- Likely reduced risk of stroke
- Less subsequent Healthcare utilization

- Increased upfront Cost & Risk
- Less risk over the long term



H·CUP HEALTHCARE COST AND UTILIZATION PROJECT

AHRQ Agency for Healthcare Research and Quality

Most Frequent Principal Diagnoses for Inpatient Stays in U.S. Hospitals, 2018

Figure 1. Aggregate cost of nonmaternal, nonneonatal hospital inpatient stays, by mean cost and number of stays, 10 most frequent principal diagnoses, 2018

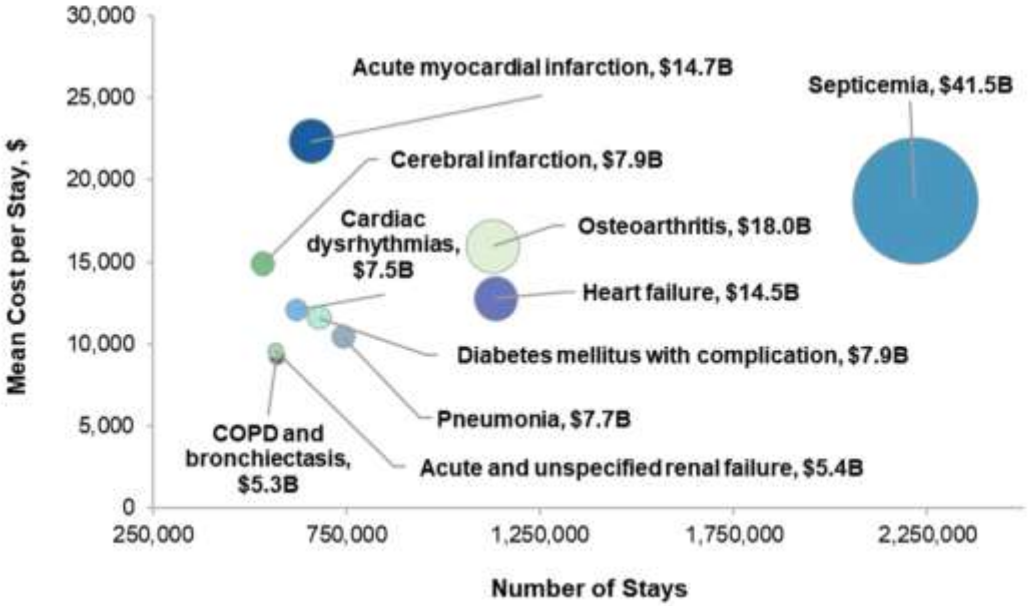


Table 1. Top 20 principal diagnoses among nonmaternal, nonneonatal inpatient stays, 2018

Rank	Principal diagnosis	Number of stays	Percent of stays	Aggregate cost, $ billions	Percent of aggregate cost	Mean cost per stay, $
All nonmaternal/nonneonatal stays		**27,833,500**	**100.0**	**403.6**	**100.0**	**14,500**
Top 20 diagnoses		**13,236,300**	**47.6**	**188.3**	**46.7**	**14,200**
1	Septicemia	2,218,800	8.0	41.5	10.3	18,700
2	Heart failure	1,135,900	4.1	14.5	3.6	12,800
3	Osteoarthritis	1,128,100	4.1	18.0	4.5	16,000
4	Pneumonia (except that caused by tuberculosis)	740,700	2.7	7.7	1.9	10,500
5	Diabetes mellitus with complication	678,600	2.4	7.9	1.9	11,600
6	Acute myocardial infarction	658,600	2.4	14.7	3.6	22,300
7	Cardiac dysrhythmias	620,000	2.2	7.5	1.9	12,100
8	COPD and bronchiectasis	569,600	2.0	5.3	1.3	9,200
9	Acute and unspecified renal failure	565,800	2.0	5.4	1.3	9,600
10	Cerebral infarction	533,400	1.9	7.9	2.0	14,900
11	Skin and subcutaneous tissue infections	529,600	1.9	4.0	1.0	7,600
12	Depressive disorders	525,000	1.9	2.8	0.7	5,400
13	Spondylopathies/ Spondyloarthropathy	519,600	1.9	12.5	3.1	24,000
14	Urinary tract infections	508,700	1.8	3.8	0.9	7,500
15	Respiratory failure; insufficiency; arrest	506,800	1.8	9.1	2.2	17,900
16	Schizophrenia spectrum and other psychotic disorders	399,900	1.4	3.7	0.9	9,300
17	Coronary atherosclerosis and other heart disease	358,900	1.3	8.7	2.2	24,400
18	Biliary tract disease	349,900	1.3	4.5	1.1	13,000
19	Fluid and electrolyte disorders	349,800	1.3	2.7	0.7	7,600
20	Complication of select surgical or medical care, injury, initial encounter*	338,800	1.2	6.0	1.5	17,700

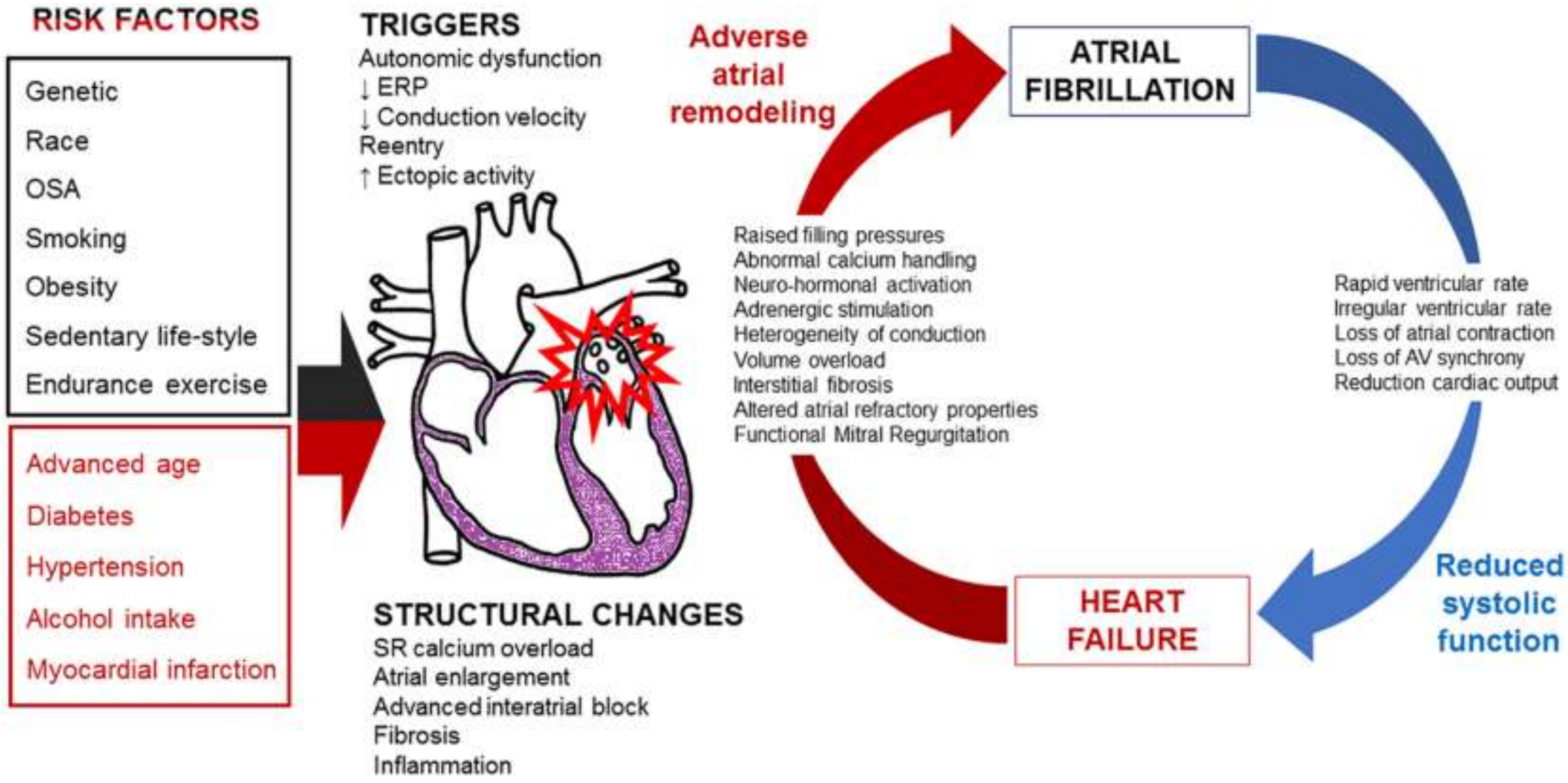
Interaction between Atrial Fibrillation and Heart Failure

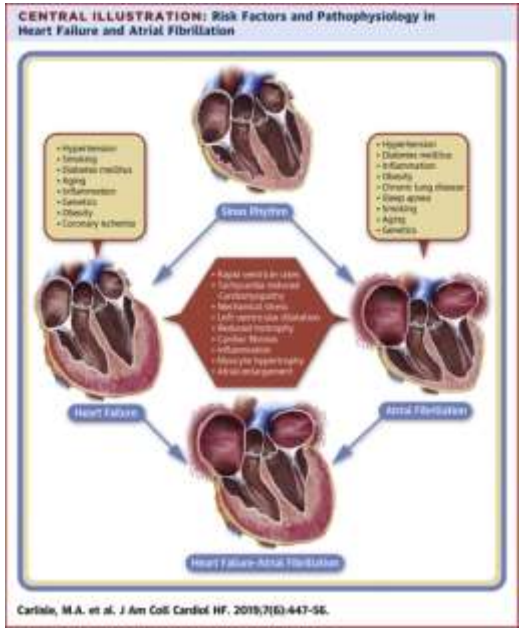
- AF and HF frequently coexist, and either can predispose to the development of the other.
  - In patients with newly diagnosed AF, 37% concurrently will have HF.
  - Conversely, 57% of newly diagnosed HF patients will have AF.

- AF can either be the only reason for cardiomyopathy (AF-induced) or can exacerbate LV dysfunction and HF in a patient with concomitant structural heart disease.

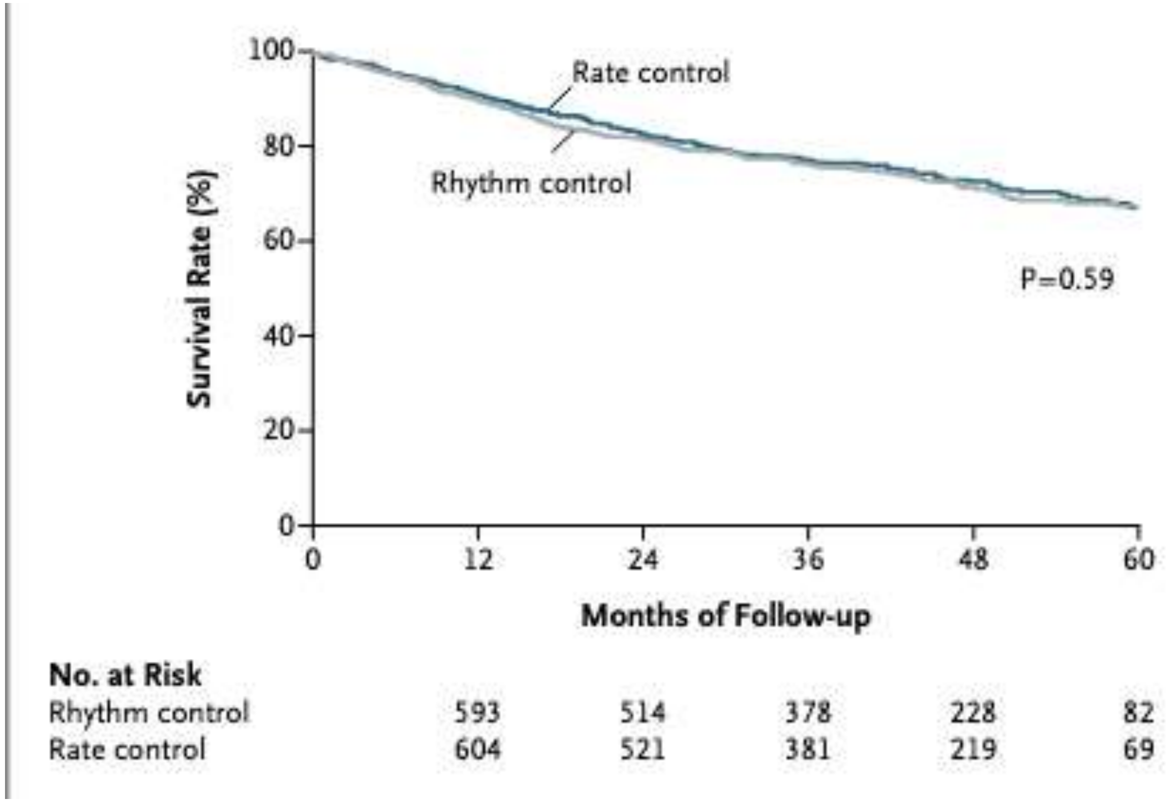
- Mortality is higher among patients with HF and AF than HF alone.

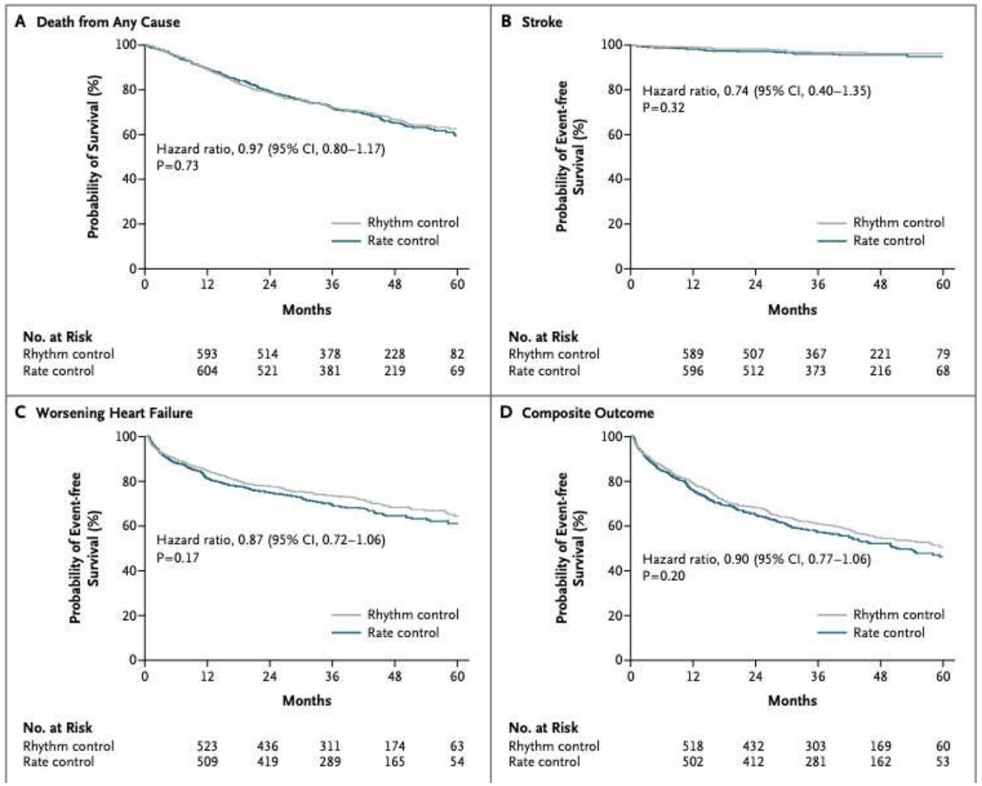
- AF was associated with increased total mortality, irrespective of LV systolic dysfunction, with an OR of 1.40 (95% CI, 1.321.48) in randomized trials and an OR of 1.14 (95% CI, 1.03-1.26) in observational studies.





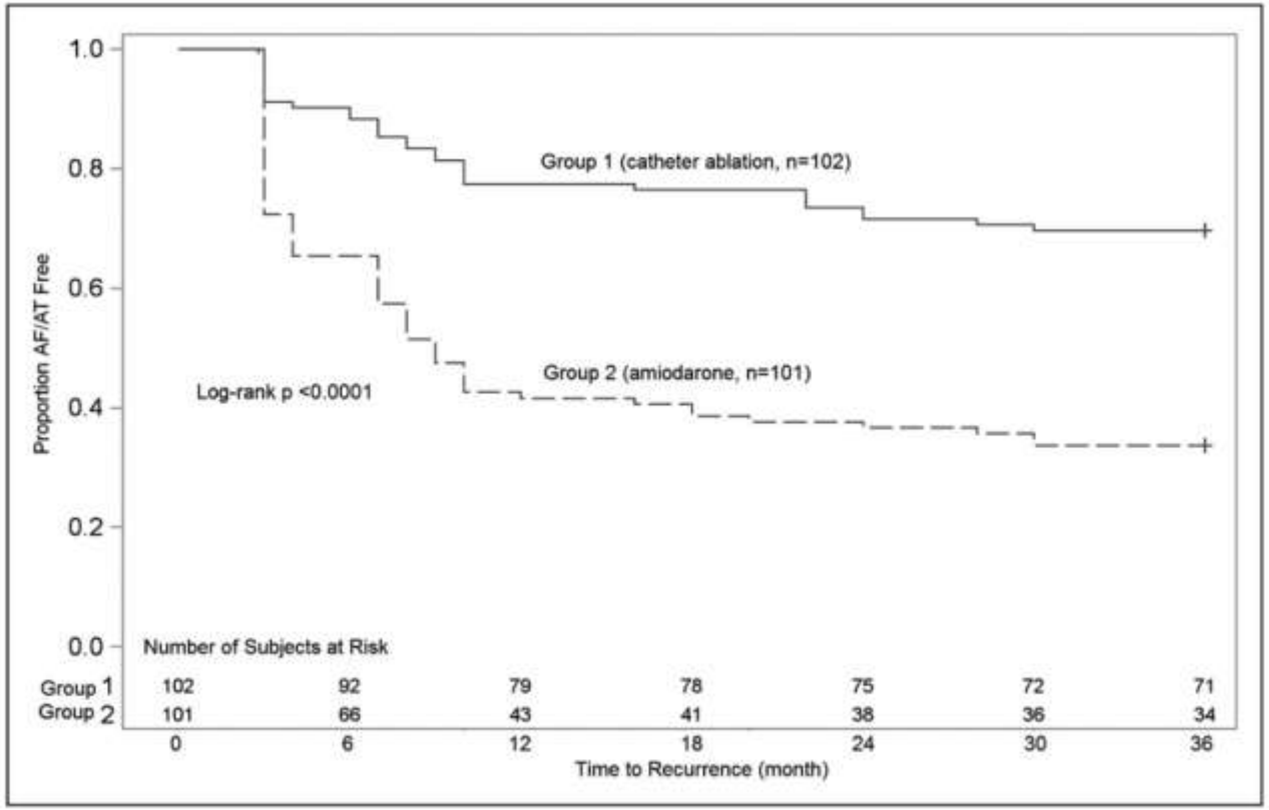
Carlisle, M. A., Fudim, M., DeVore, A. D. & Piccini, J. P. Heart Failure and Atrial Fibrillation, Like Fire and Fury. *JACC: Hear. Fail.* **7**, 447–456 (2019).





Roy, D. *et al.* Rhythm control versus rate control for atrial fibrillation and heart failure. *The New England journal of medicine* **358**, 2667–77 (2008).

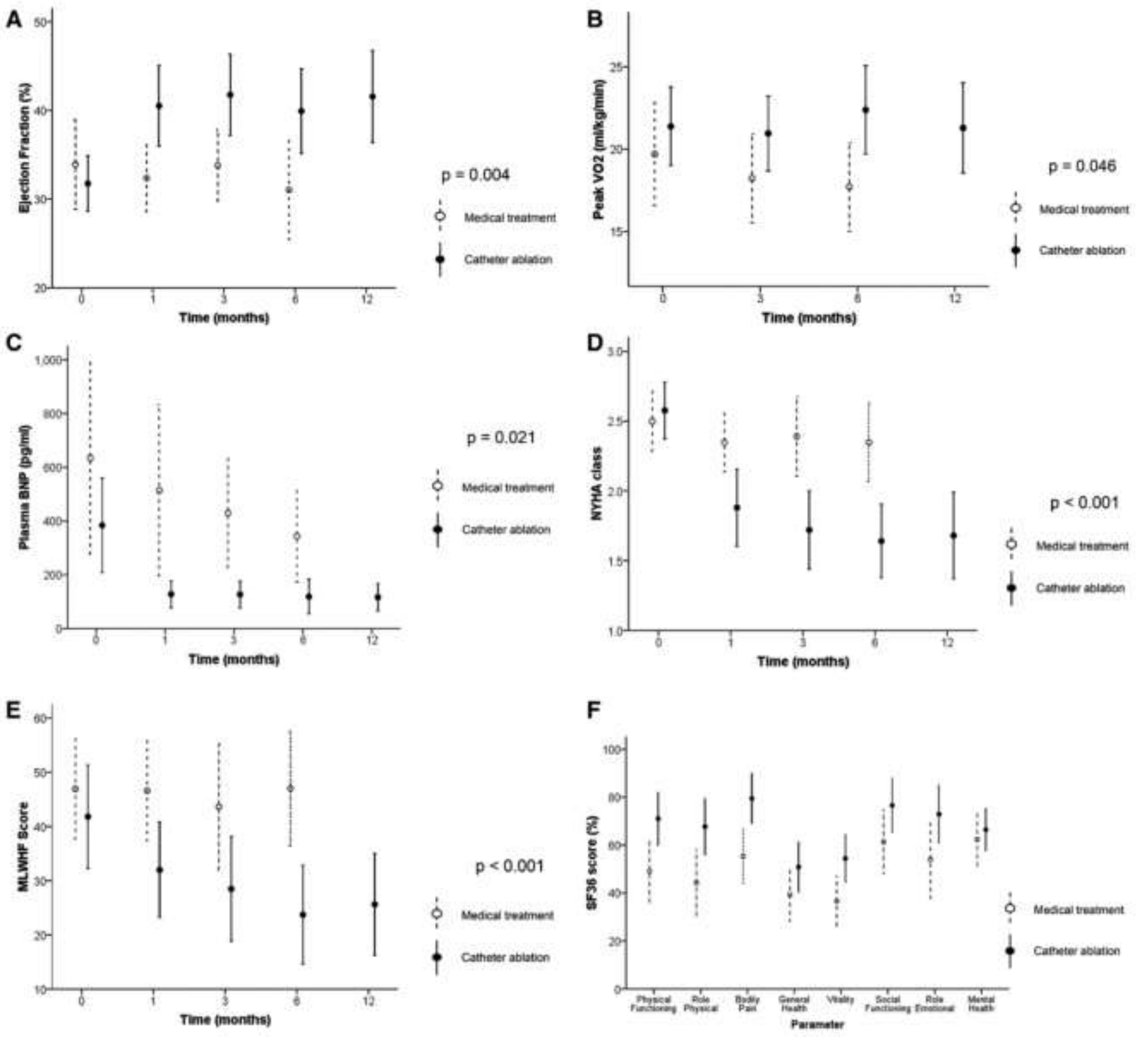
AATAC



	No Recurrence (n=91)		Recurrence (n=86)		*P* (Comparing Change Between Groups)
	Baseline	Change (Median)	Baseline	Change (Median)	
LVEF, %	28.8±10	9.6±7.4 (9.4)	30.2±9	4.2±6.2 (4.0)	<0.001
6MWD, meters	347±113	27±38 (24)	352±128	8±42 (2)	<0.001
MLHFQ	53±24	−14±18 (−12)	49±26	−2.9±15 (−2.2)	<0.001

Biase, L. *et al.* Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device Results From the AATAC Multicenter Randomized Trial. *Circulation* **133**, 1637–1644 (2016).

CAMTAF Trial



Hunter, R. J. *et al.* A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure (The CAMTAF Trial). *Circ.: Arrhythmia Electrophysiol.* **7**, 31–38 (2018).

CASTLE - AF

- Patients with left ventricular dysfunction and atrial fibrillation were randomized to catheter ablation (n = 179) vs. conventional treatment (n = 184)
- Death or hospitalization for heart failure: 28.5% of the catheter ablation group vs. 44.6% of the control group (p = 0.007)
- Among patients with left ventricular dysfunction and atrial fibrillation, catheter ablation was associated with a reduction in deaths or hospitalizations for heart failure

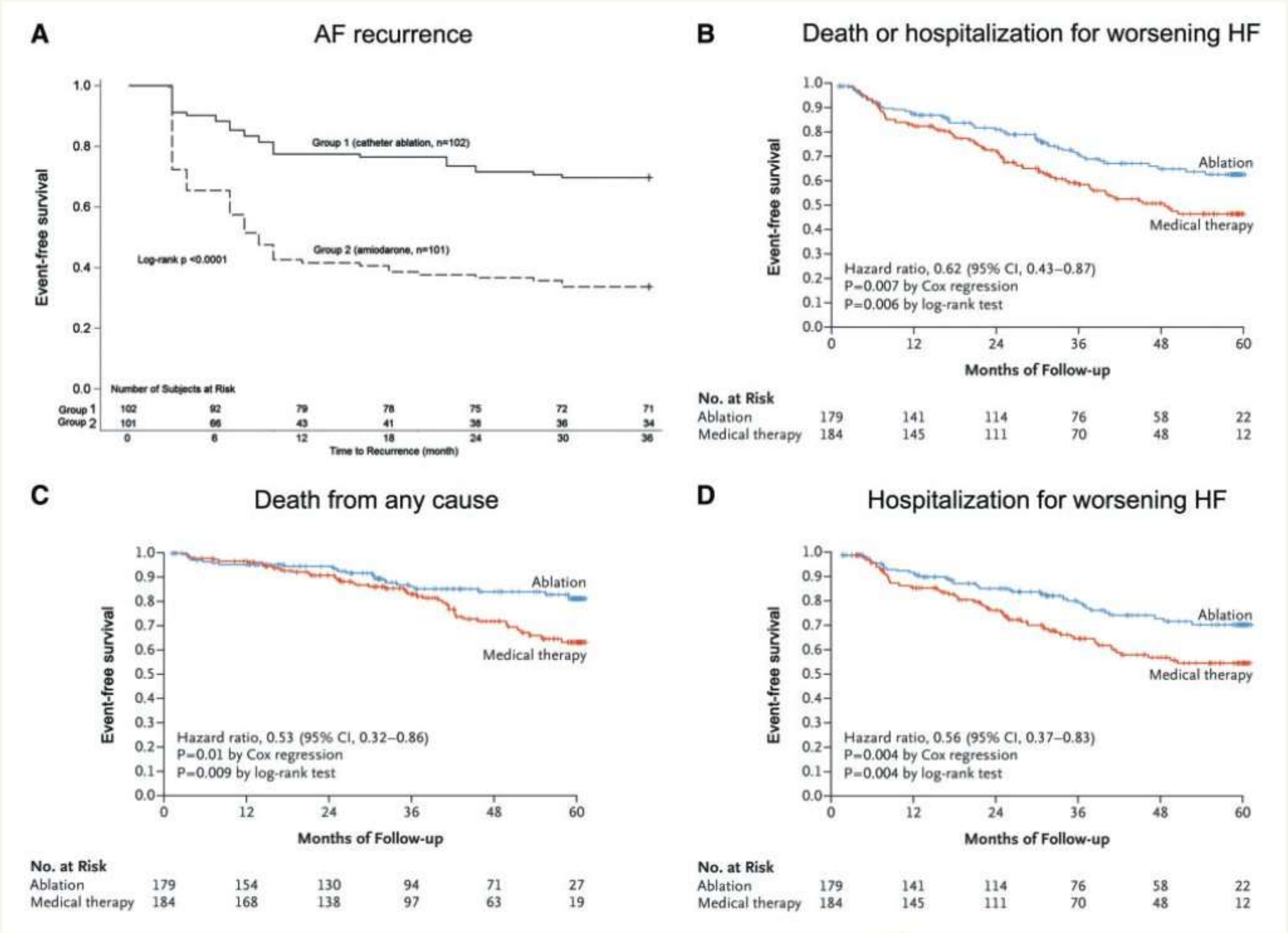


Figure 2 The Kaplan–Meier estimates of event-free survival of the primary endpoint in AATAC-AF[60] (*A*) and primary (*B*) and secondary (*C* + *D*) endpoints in CASTLE-AF.[61] See text for detailed information. AF, atrial fibrillation; HF, heart failure. Modified with permission from Refs.[60,61]

Marrouche, N. F. *et al.* Catheter Ablation for Atrial Fibrillation with Heart Failure. *The New England Journal of Medicine* **378**, 417–427 (2018).

CASTLE - HTx

•The trial aimed to determine the potential therapeutic effect of catheter ablation for symptomatic atrial fibrillation (AF) in patients with end-stage heart failure with reduced ejection fraction (HFrEF).

•Patients with symptomatic AF and end-stage HFrEF undergoing evaluation for left ventricular assist device (LVAD) implantation or heart transplantation (HT) were randomized to undergo catheter ablation of AF and guideline-directed medical therapy (n = 97) or medical therapy alone (n = 97).

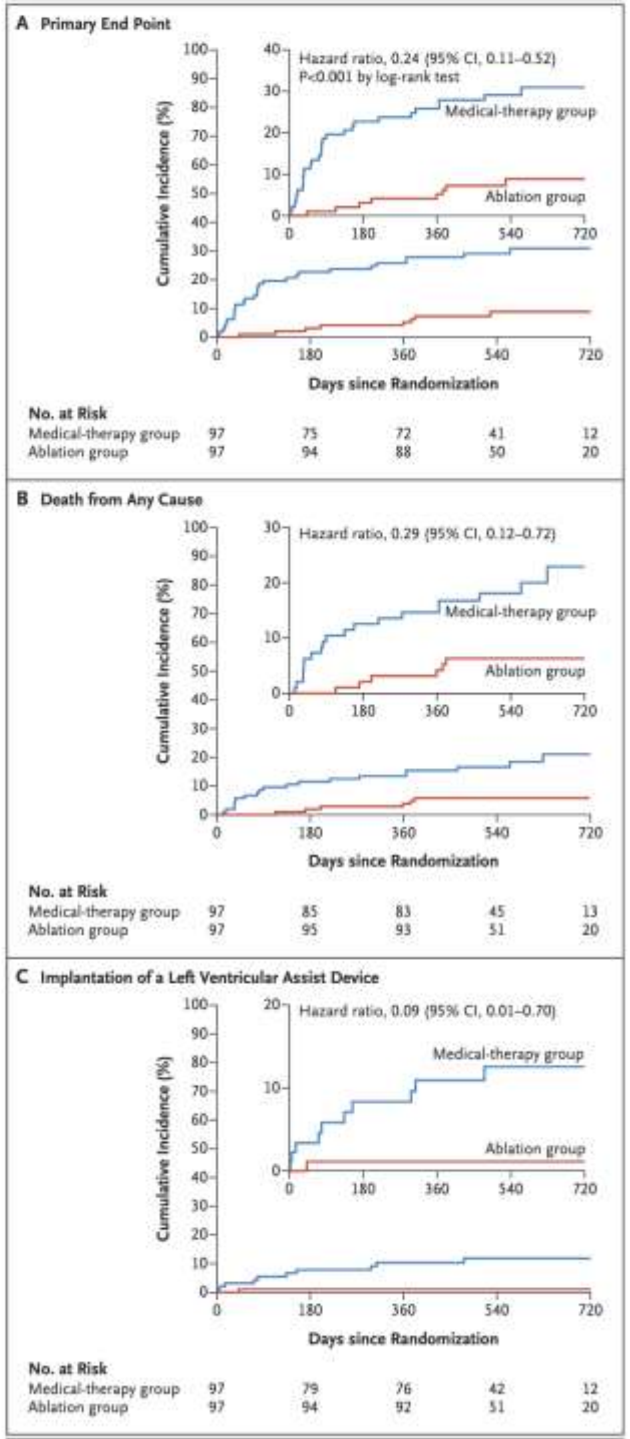
•Antiarrhythmic drugs were discontinued after catheter ablation but could be resumed for AF recurrence. As appropriate, patients in the medical therapy arm could undergo rhythm or rate control.

•Total number of enrollees: 194

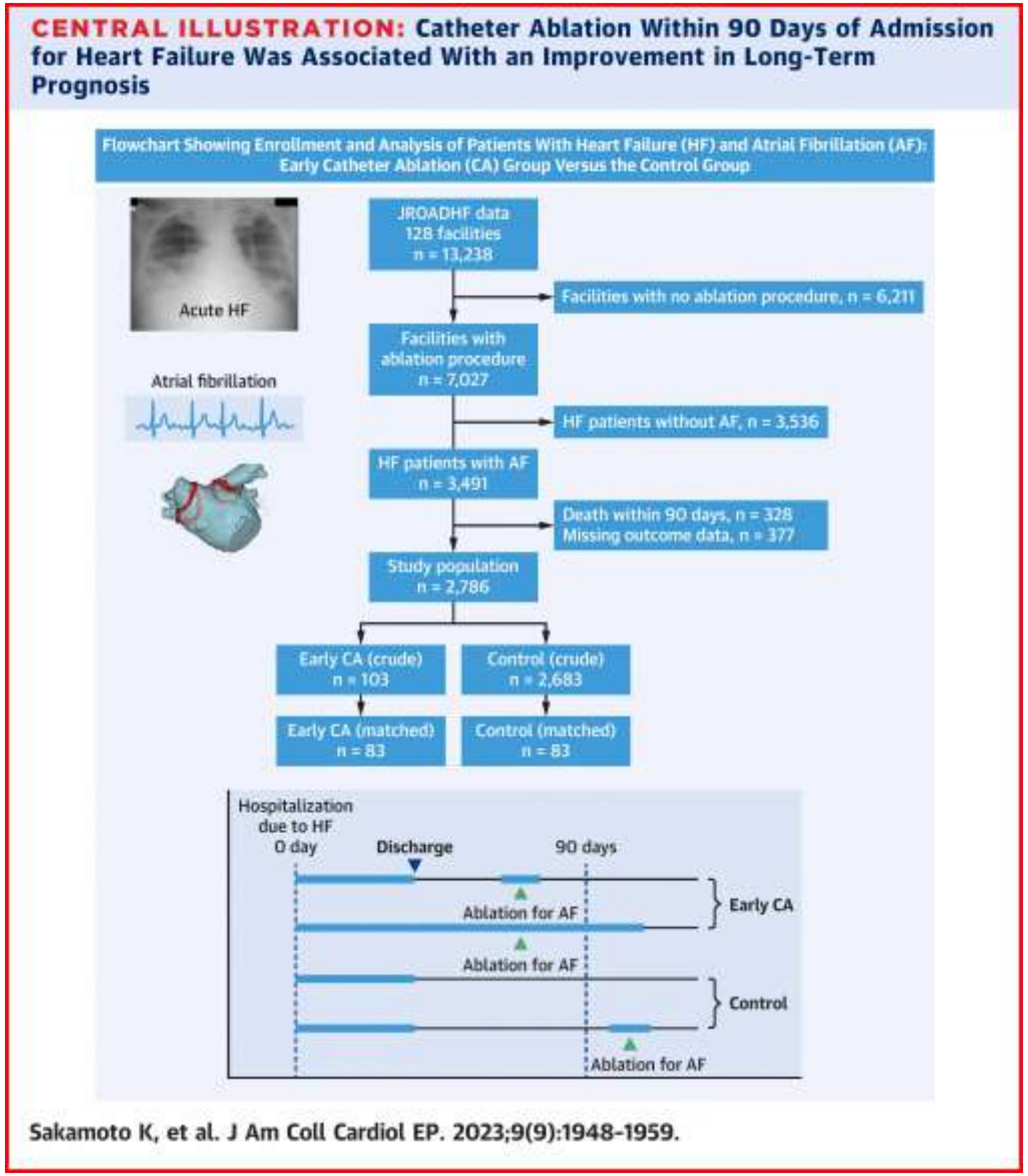
•Median duration of follow-up: 18 months

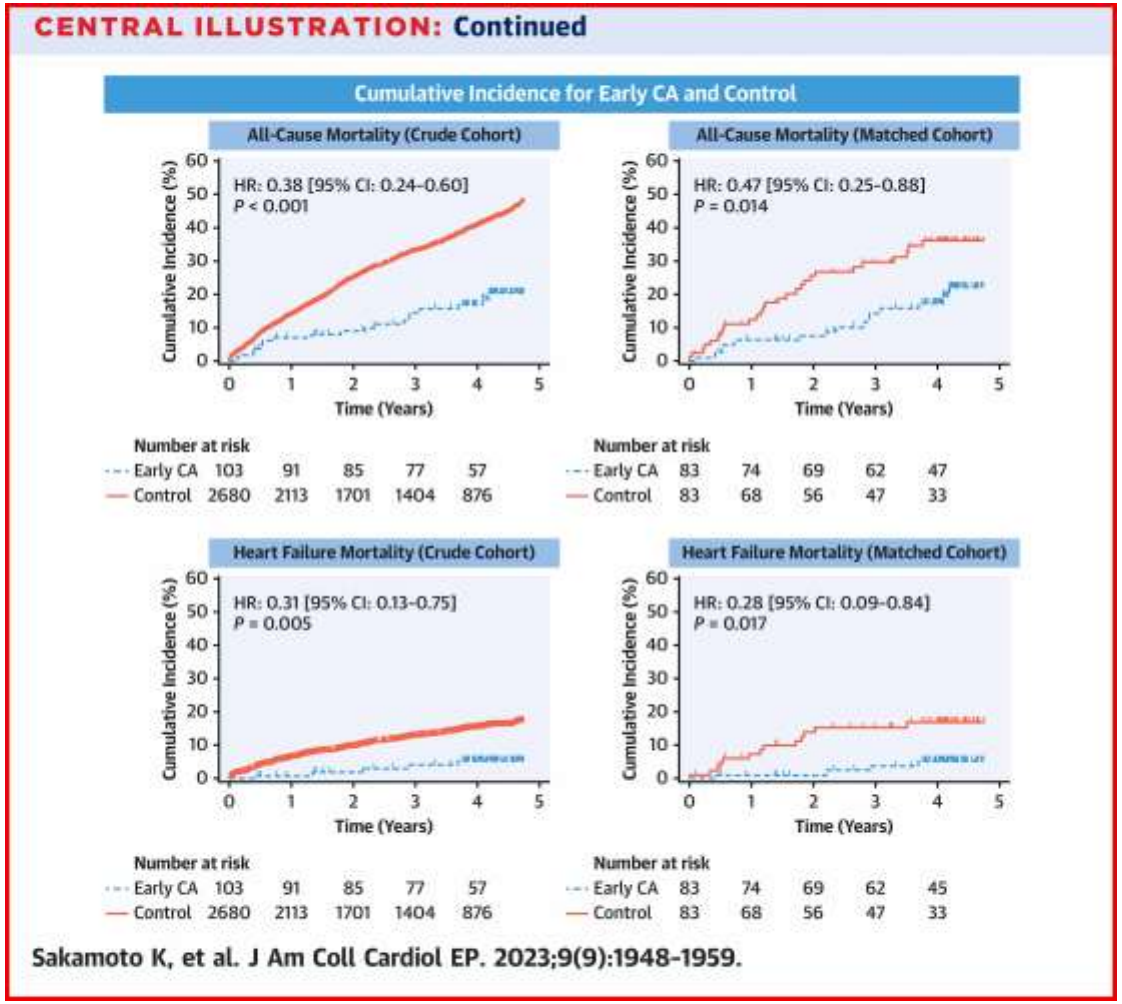
•Principal Findings:

- The trial was terminated early due to evidence of overwhelming efficacy in the catheter ablation arm.
- The primary outcome, a composite of all-cause mortality, LVAD implantation, or urgent HT, at a median of 18 months for catheter ablation vs. medical therapy, was: 8% vs. 30% (p < 0.001).

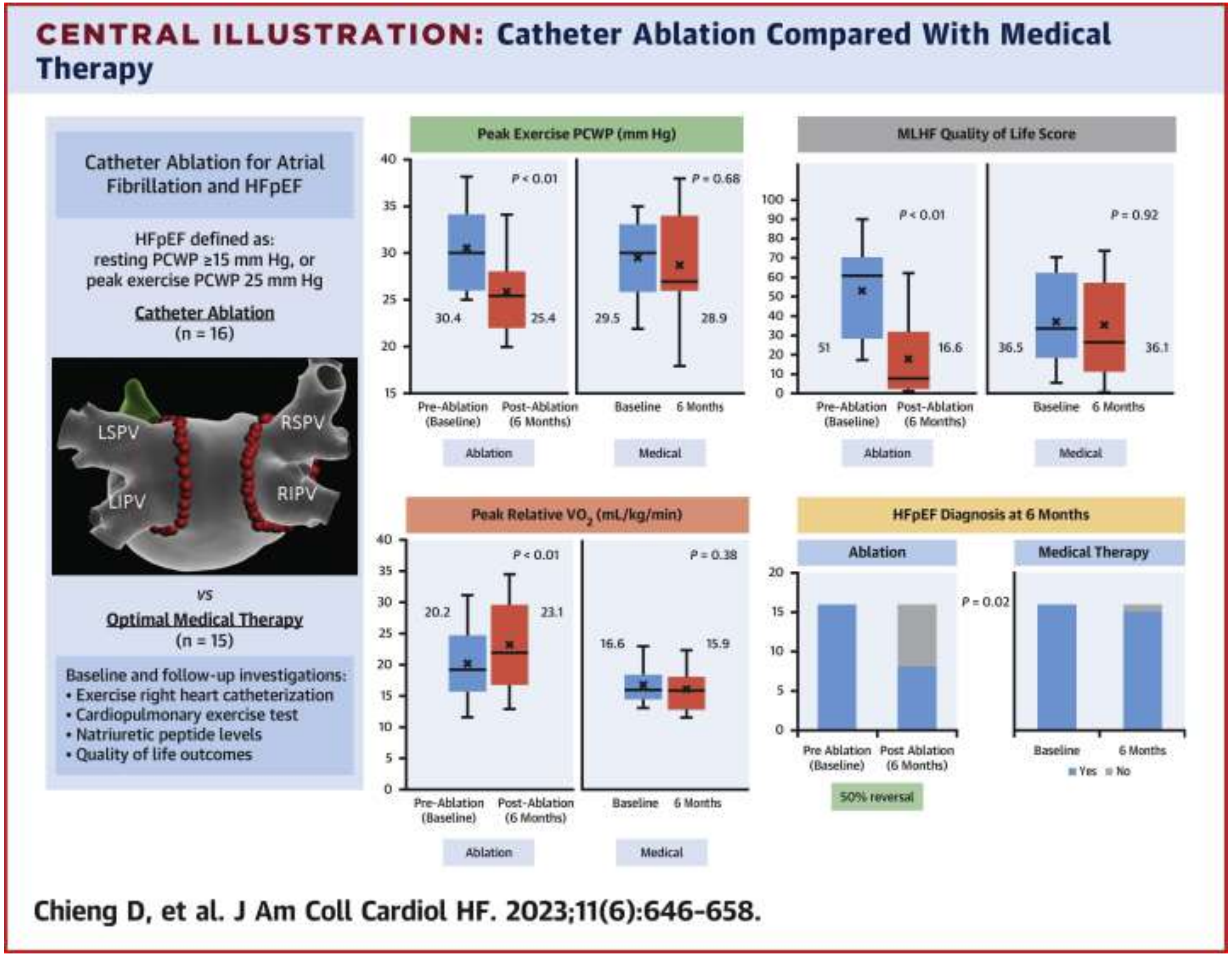


Sohns, C. *et al.* Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation. *N. Engl. J. Med.* **389**, 1380–1389 (2023).





Sakamoto, K. *et al.* Efficacy of Early Catheter Ablation for Atrial Fibrillation After Admission for Heart Failure. *JACC: Clin. Electrophysiol.* **9**, 1948–1959 (2023).



Chieng, D. *et al.* Atrial Fibrillation Ablation for Heart Failure With Preserved Ejection Fraction A Randomized Controlled Trial. *JACC: Hear. Fail.* **11**, 646–658 (2023).

COR	LOE	Recommendations
1	A	1. In patients with symptomatic AF in whom antiarrhythmic drugs have been ineffective, contraindicated, not tolerated or not preferred, and continued rhythm control is desired, catheter ablation is useful to improve symptoms.[1–10]
1	A	2. In selected patients (generally younger with few comorbidities) with symptomatic paroxysmal AF in whom rhythm control is desired, catheter ablation is useful as first-line therapy to improve symptoms and reduce progression to persistent AF.[11–16]
1	A	3. In patients with symptomatic or clinically significant AFL, catheter ablation is useful for improving symptoms.[17–19]
2a	B-NR	4. In patients who are undergoing ablation for AF, ablation of additional clinically significant supraventricular arrhythmias can be useful to reduce the likelihood of future arrhythmia.[17,18,20–27]
2a	B-R	5. In patients (other than younger with few comorbidities) with symptomatic paroxysmal or persistent AF who are being managed with a rhythm-control strategy, catheter ablation as first-line therapy can be useful to improve symptoms.[11–13,28]

Nebraska Medicine

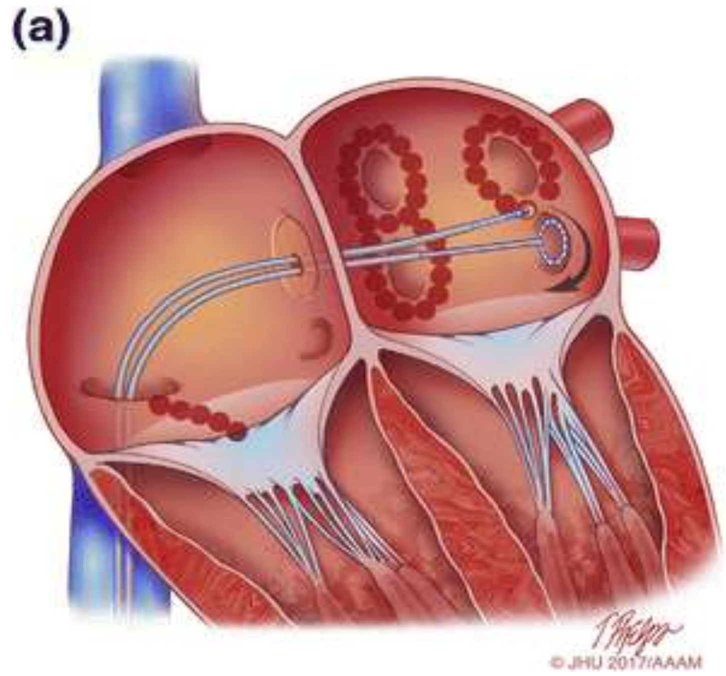
COR	LOE	Recommendations
1	B-NR	1. In patients who present with a new diagnosis of HFrEF and AF, arrhythmia-induced cardiomyopathy should be suspected, and an early and aggressive approach to AF rhythm control is recommended.[1,2]
1	A	2. In appropriate patients with AF and HFrEF who are on GDMT, and with reasonable expectation of procedural benefit (Figure 24), catheter ablation is beneficial to improve symptoms, QOL, ventricular function, and cardiovascular outcomes.[3–13]

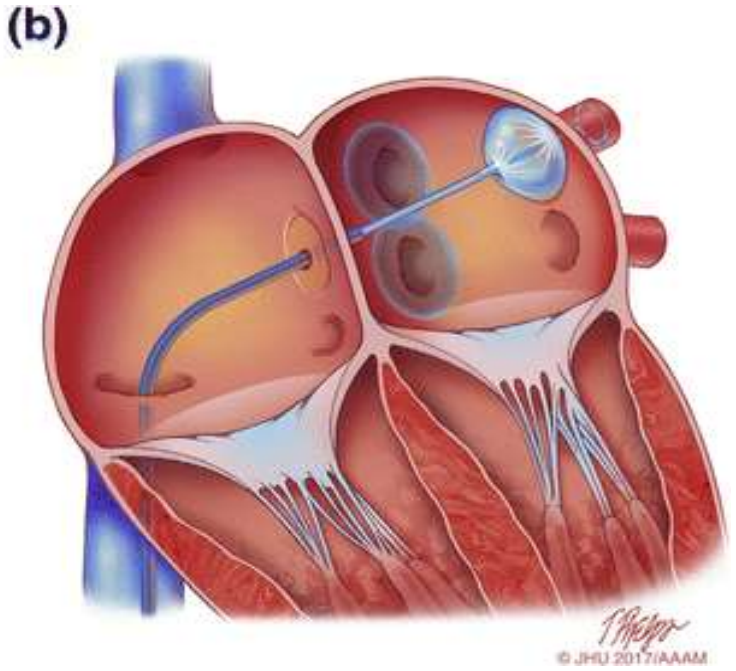
Joglar, J. A. et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 149, e1–e1

Atrial Fibrillation Ablation

- 360,000 ablations in US per year
  - 2/3 are for Afib; 240,000 ablations per year
- In our lab Afib ablation is the most commonly performed procedure.
- The indications for afib are increasing
  - 1st line for rhythm control (Early)
  - 1st line for patients with heart failure
- We are recognizing it earlier due to better monitoring and smartwatches
- There will be continued growth in afib ablation over the next ten years.

Currently ablation is performed using <u>thermal</u> ablation: Either hot (Radiofrequency) or Cold (Cryoablation)





- Radiofrequency (heat/cautery)is effective but requires point-by-point ablation and connecting the dots to ablate around the pulmonary veins.
- This requires a lot of time.
- The patient must be still and so general anesthesia is a must.
- Even so, stability becomes an issue and limits success.
- **Highly variable results.**
- **High risk of collateral damage.**

- Cryoballoon improved on radiofrequency ablation by offering a **'single shot' technique** to ablate the pulmonary veins; which are the source of most AF.
- Cryo lesions take minutes to apply.
- Despite this, the result was a maintenance of effectiveness while reducing procedure time.
- Can also be done without general anesthesia as stability is much improved due to cryo adhesion.
- **Results are very consistent.**
- **Risk for collateral Damage.**

Biophysics of RF Ablation

- Alternating Current at a Frequency of 300-750 Hz (grid 50Hz)
- Alternating current is delivered via the catheter electrode and passes through the tissue (and patient) before returning to the generator by the indifferent electrode.
- The patient represents an important part of the ablation circuit
- Resistance to AC produces heat
- Highest resistance (and current density) at the catheter tip

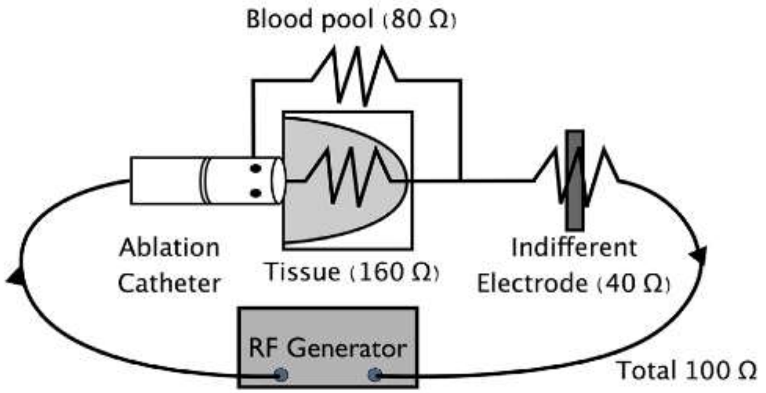
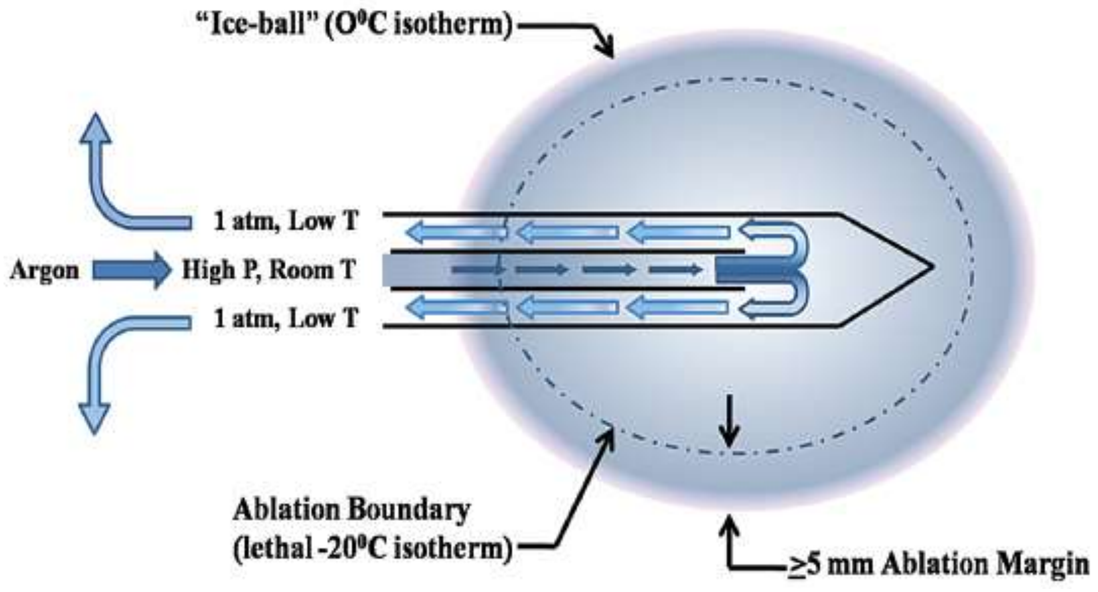


Fig. 1 The RF ablation circuit consists of an RF generator, the ablation catheter, and the indifferent electrode. Current is delivered via the catheter electrode, passes through the tissue (and patient) before returning to the generator by the indifferent electrode. The myocardial tissue and blood pool represent resistance circuits in parallel, with the indifferent electrode and patients body representing resistance circuits in series. In this theoretical example the total resistance is 100 Ω.

Biophysics of Cryo Ablation

- Cooling is created using the Joule–Thomson effect
  - Rapidly expanding gas boils and absorbs energy from surrounding particles
  - Cryorefrigerant absorbs heat from the surrounding tissue before returning to the console
- Convective cooling then occurs to the tissue

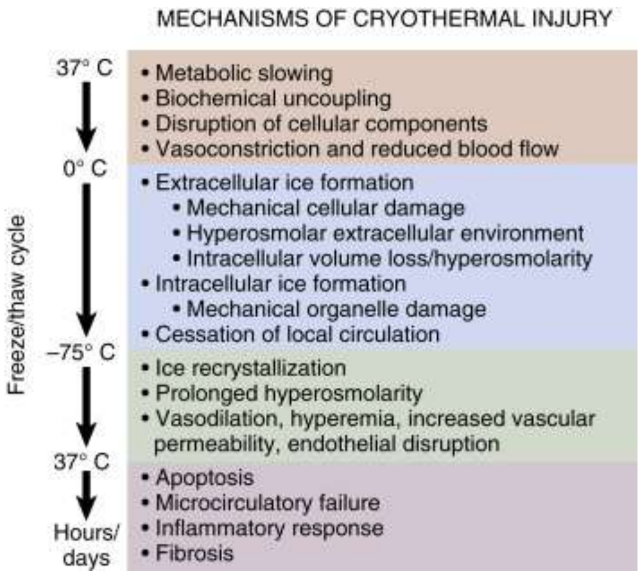


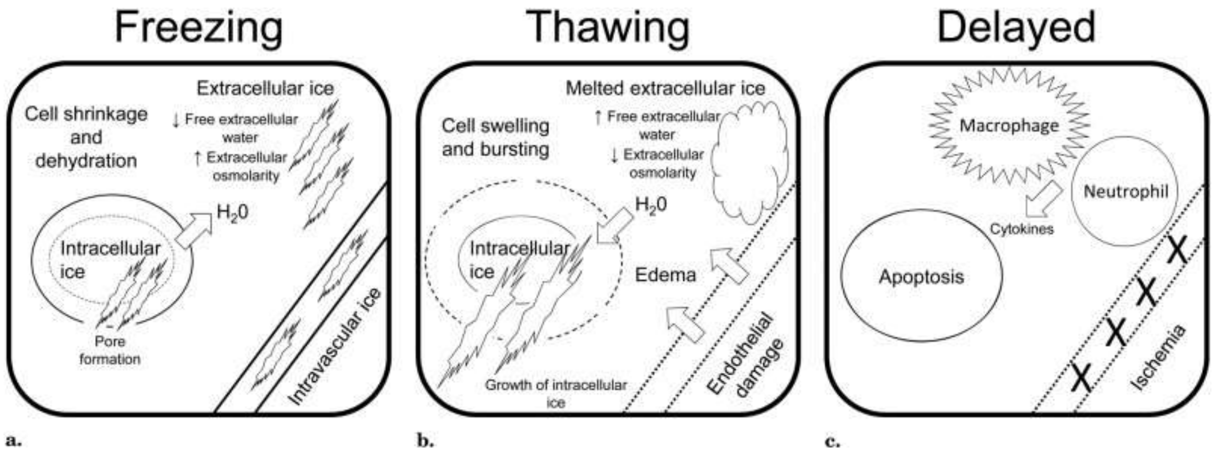
Biophysics of Cryo Ablation

This results in cold-induced cellular and tissue injury is due to a combination of:

1. direct cellular damage due to the deleterious effects of ice crystal formation during hypothermia and
2. ischemic cell death due to microcirculatory failure and subsequent vascular stasis during thawing

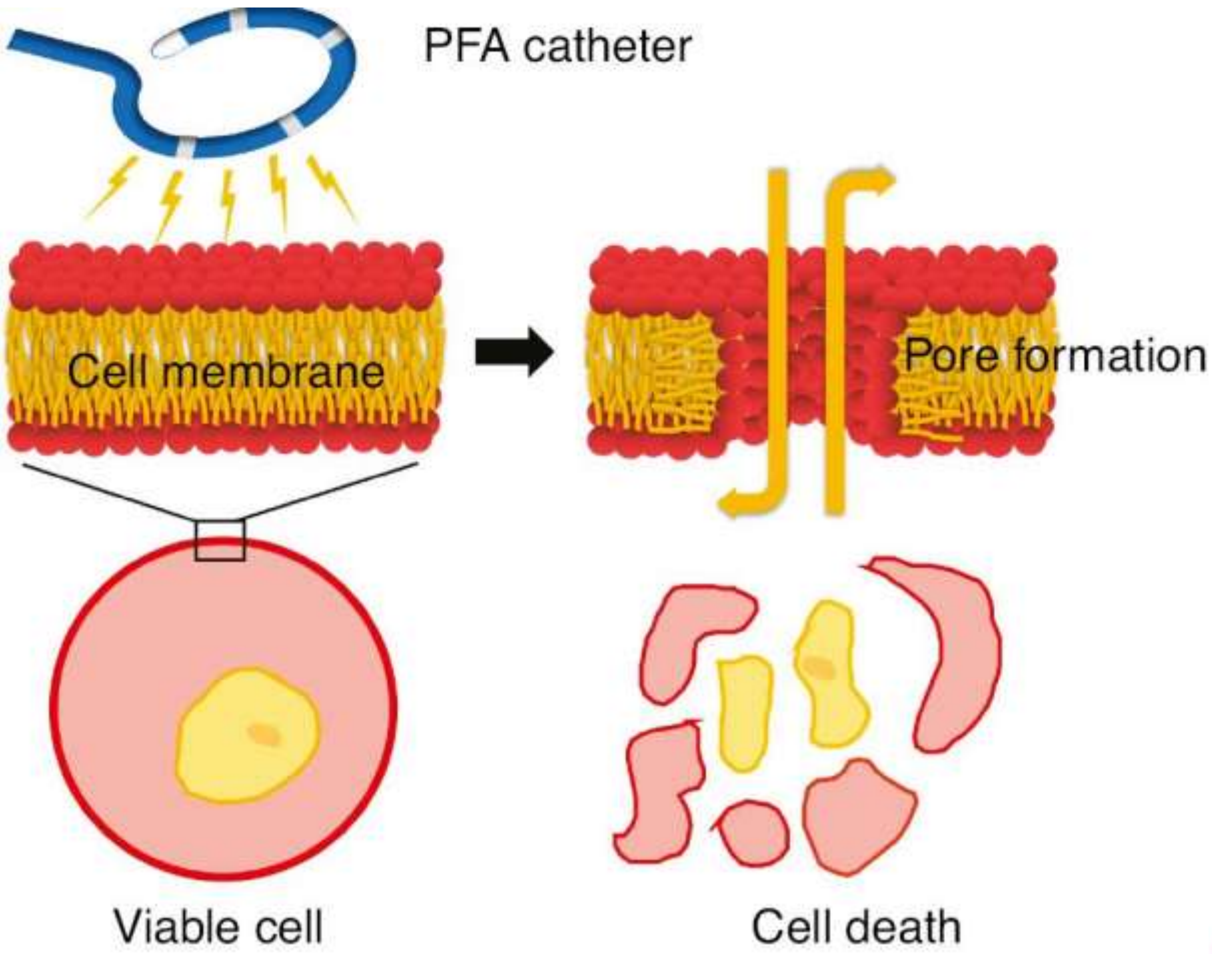
These complex mechanisms occur in the sequence of: (1) freezing, (2) thawing, (3) hemorrhage and inflammation, and (4) replacement fibrosis



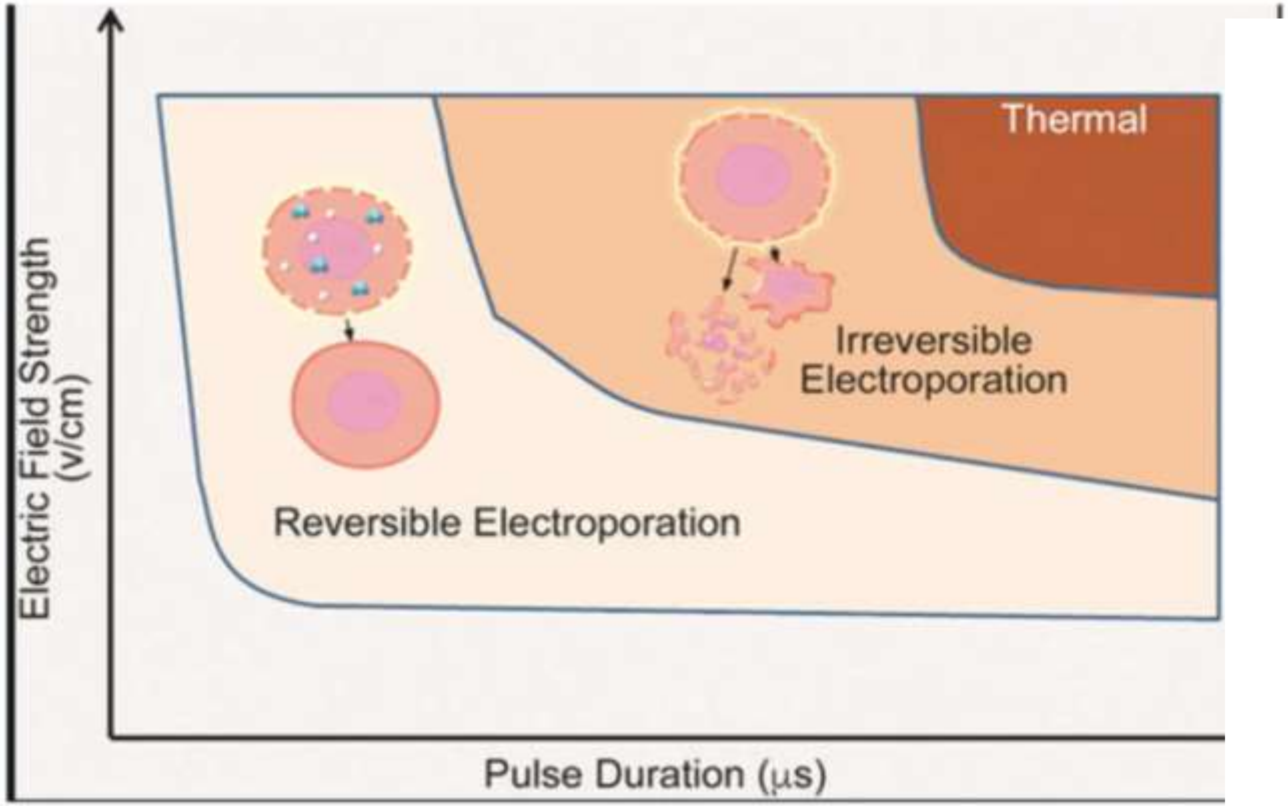


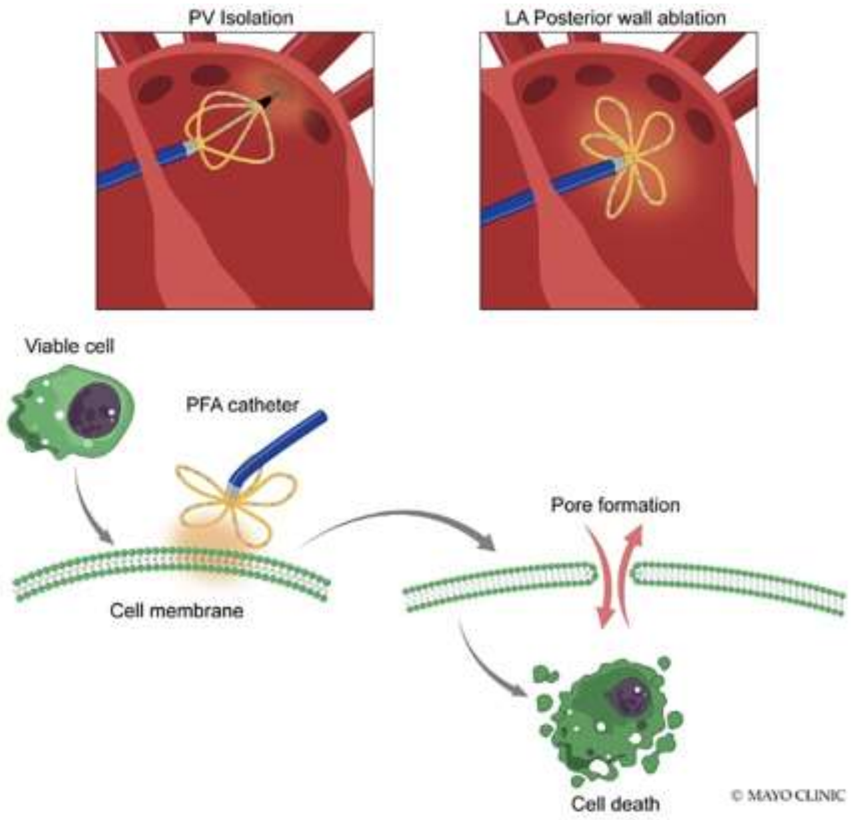
Non-Thermal method of tissue ablation that uses High-Amplitude electrical fields to cause irreversible electroporation (IRE) in tissues

Pulsed Field Ablation

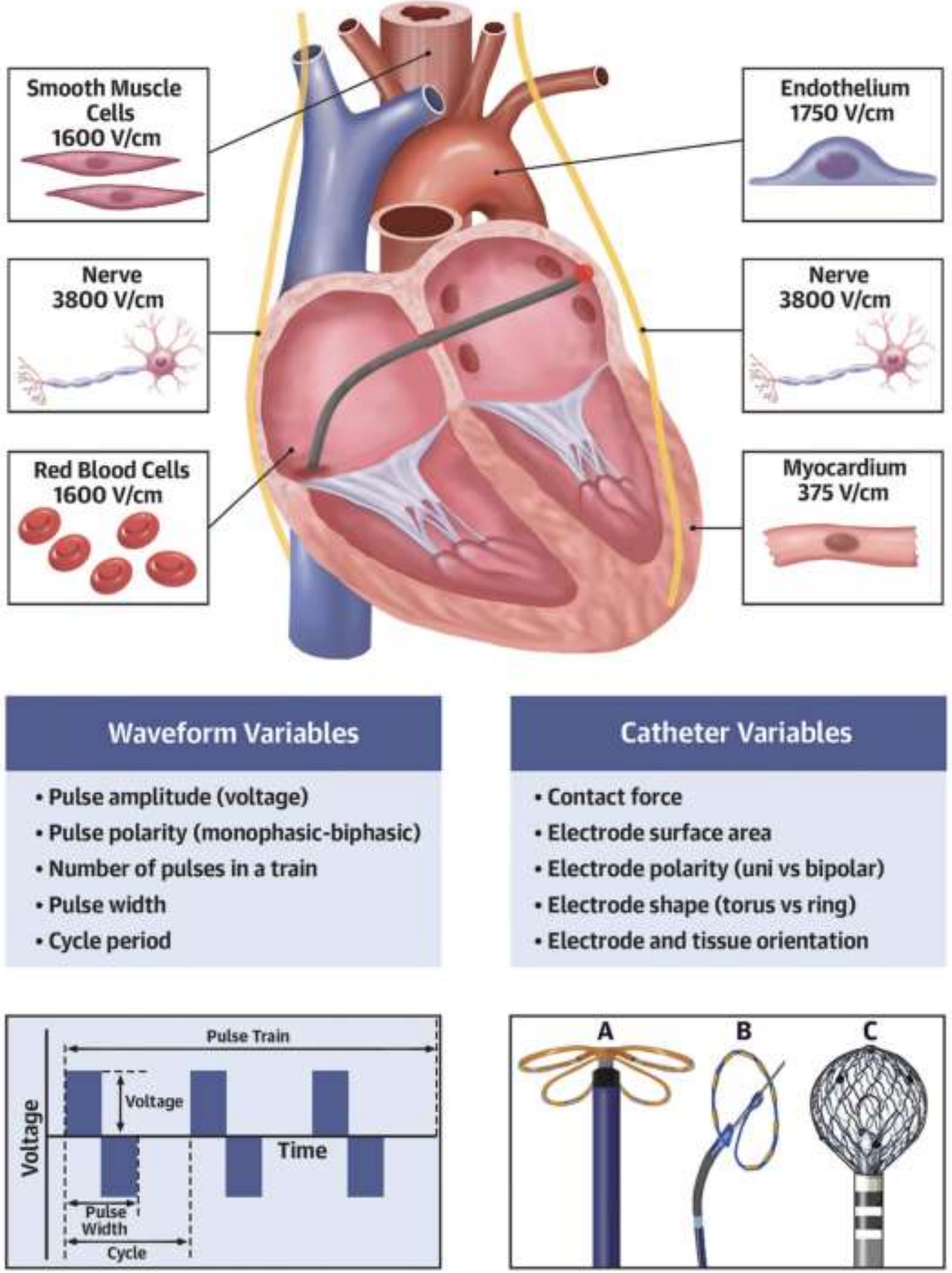


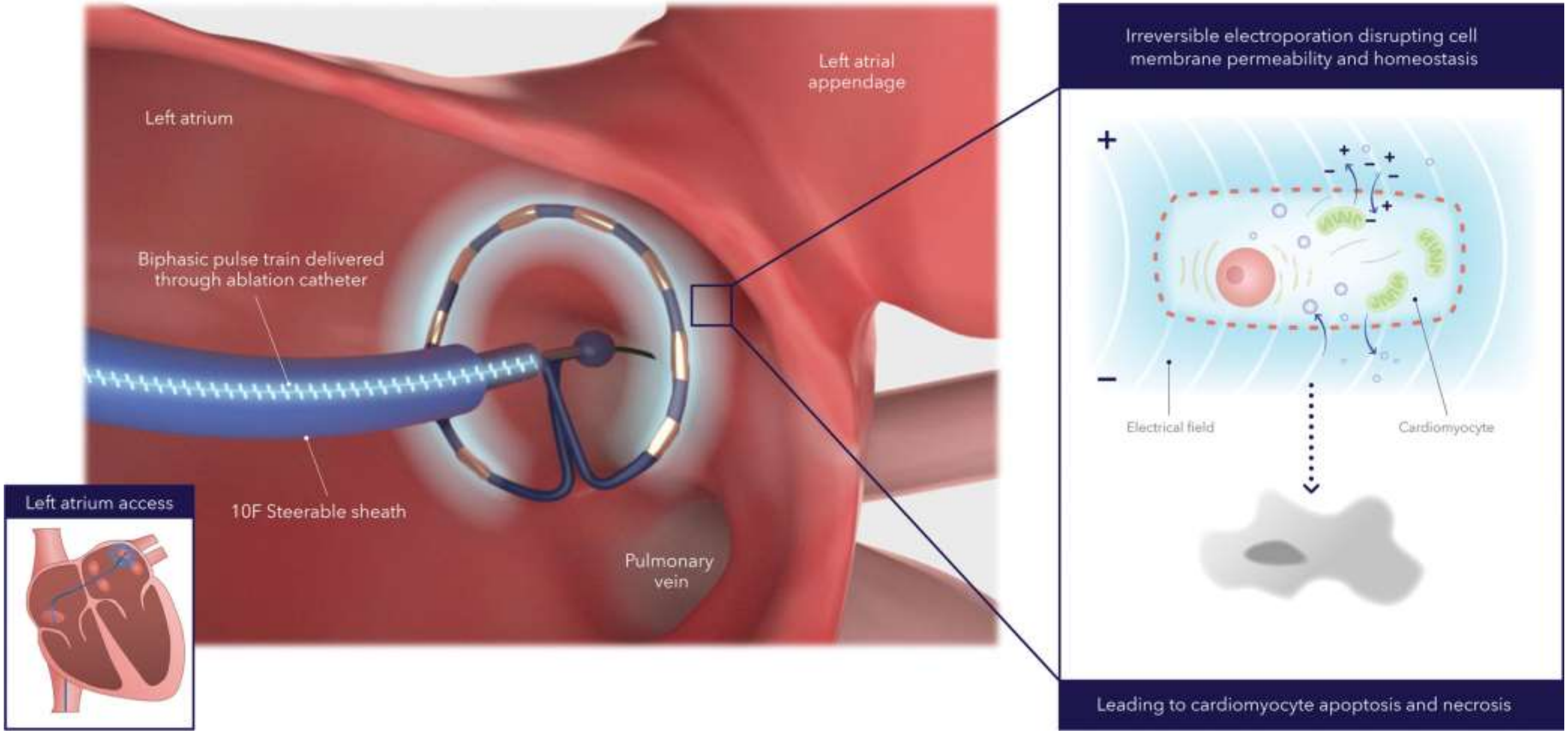
Electroporation





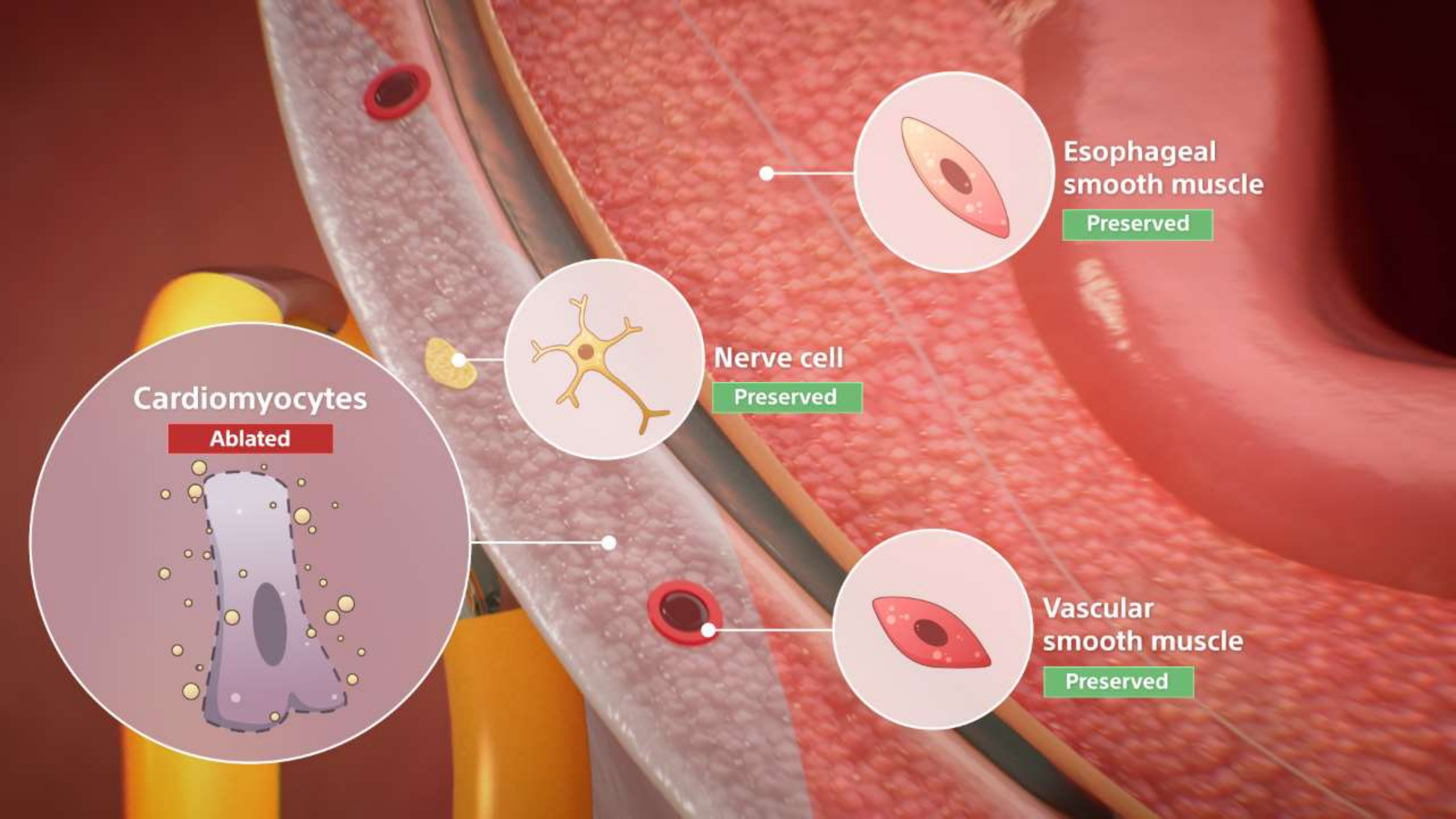
Differential Tissue Effect

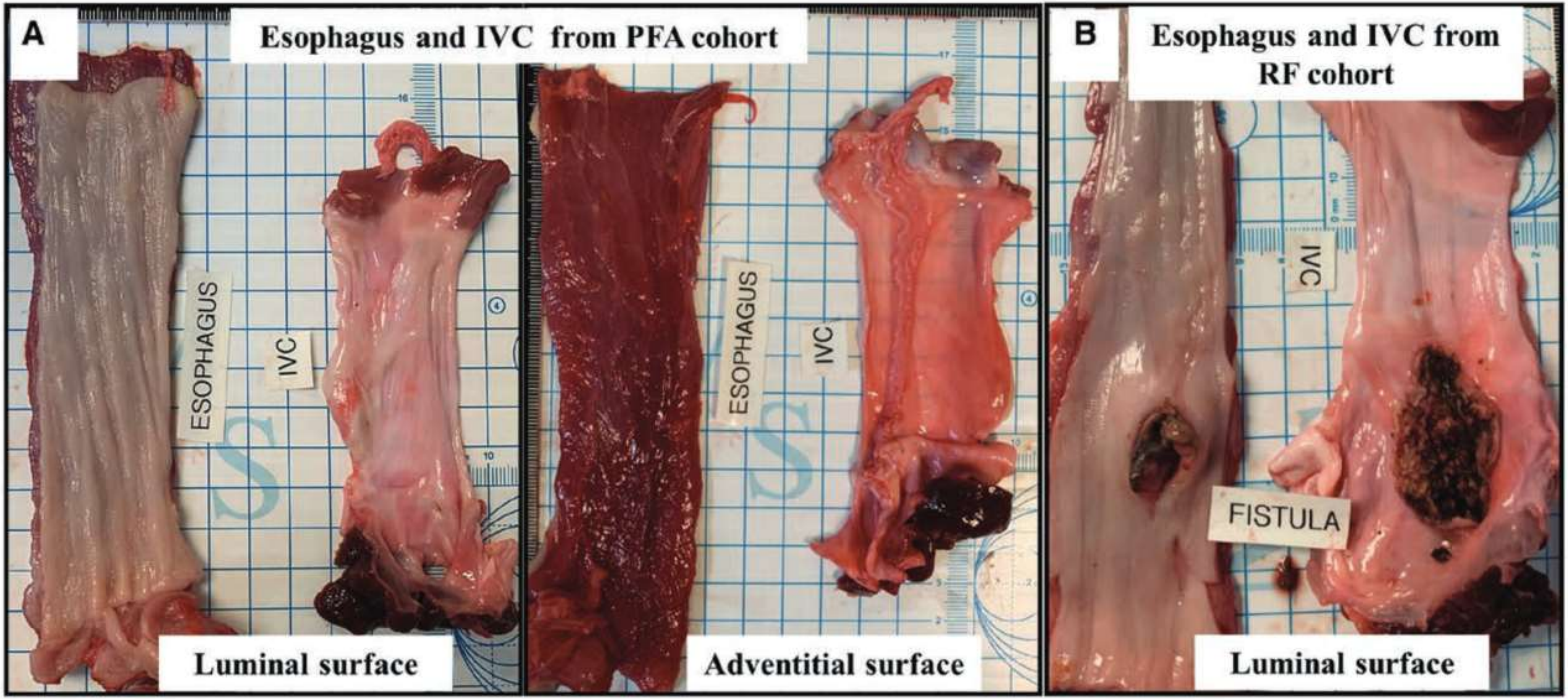


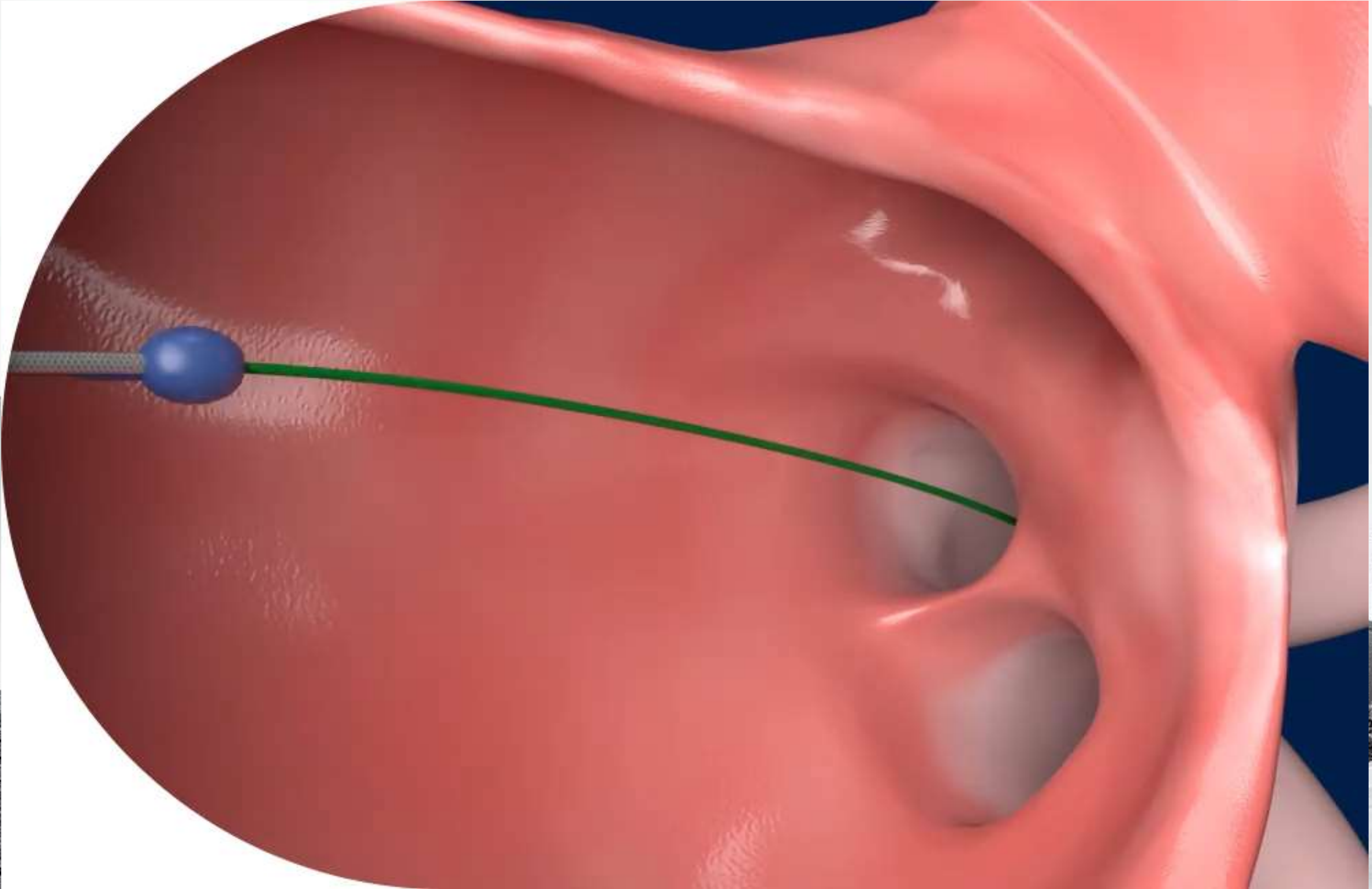


PulseSelect takes the success seen with ‘single shot’ cryo balloon ablation and further improves on it.

- Effective energy is delivered in milliseconds rather than minutes
- It only affects cardiac tissue, preserving the structures around the heart (less complications)
- Does not require contact with tissue so stability is not even a consideration


Esophageal smooth muscle
Preserved
Nerve cell
Preserved
Cardiomyocytes
Ablated
Vascular smooth muscle
Preserved


A
Esophagus and IVC from PFA cohort
ESOPHAGUS
IVC
ESOPHAGUS
IVC
Luminal surface
Adventitial surface
B
Esophagus and IVC from RF cohort
IVC
FISTULA
Luminal surface




Benefits of PFA

In a recent metanalysis, the **mean procedure time for PFA afib ablation was 94.7 minutes**

We are currently at 234 minutes with this procedure

In the Medtronic Pulse AF trial, the Skin-to-skin time was 160 minutes

- Pilot study

This time will continue to improve with physician experience

For us this is a game changer.

The time improvement is <u>meaningful</u> and will give us at conservatively a 50% increase in Afib ablation output.

Clinical success

Freedom from recurrence of any symptomatic atrial arrhythmias (post-hoc analysis).

PAF patient population **80%**

PsAF patient population **81%**

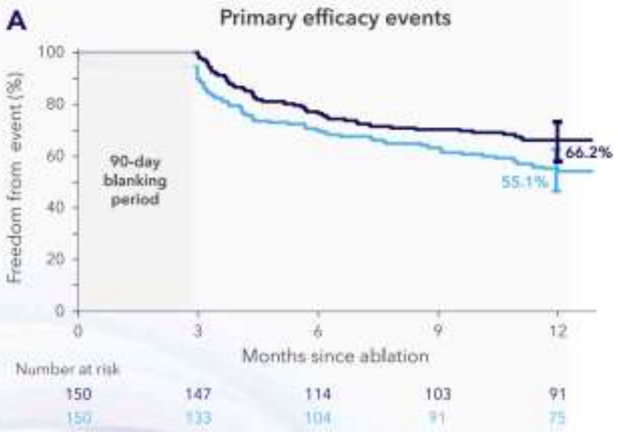
Primary effectiveness

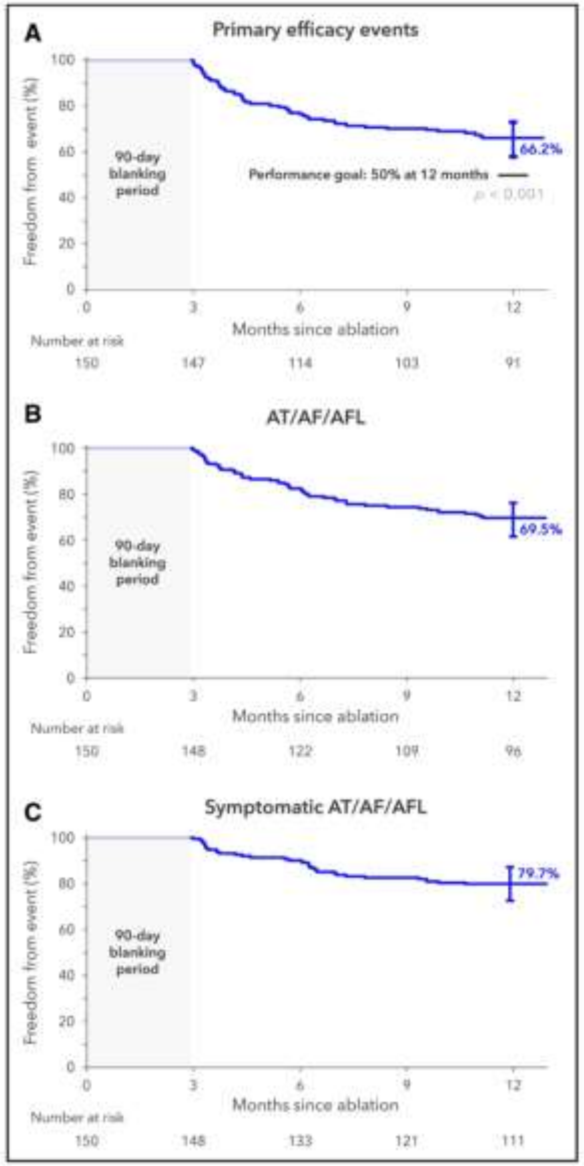
(composite endpoint definition)

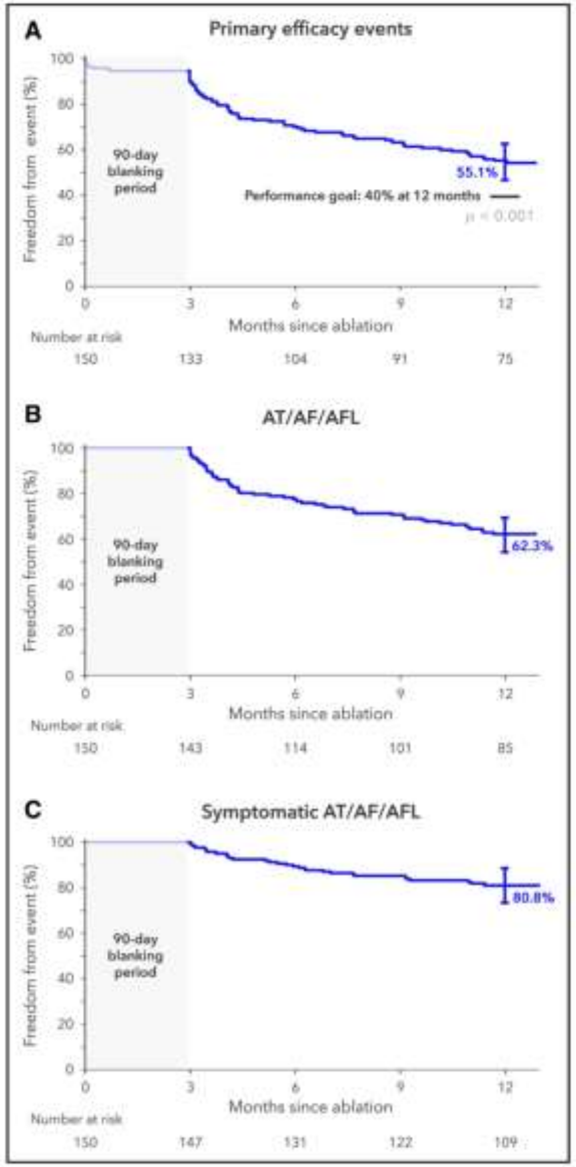
Acute procedure failure, AF/AFL/AT recurrence, cardioversion, repeat ablation, new/re-initiated/increased AADs, any subsequent AF surgery.

66% PAF

55% PsAF





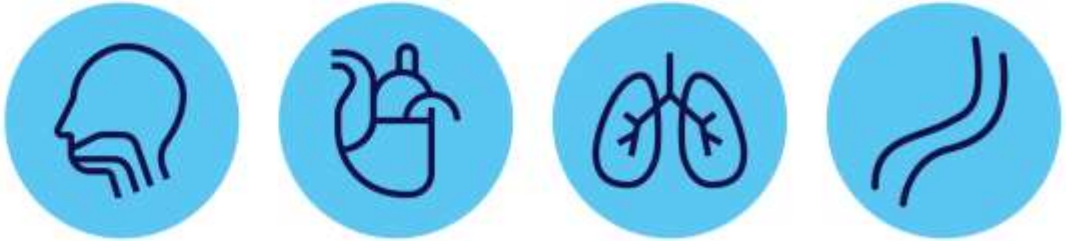


Unmatched safety[1,2]

- One of the lowest safety event rates of any IDE trial for AF ablation to date
- No esophageal events, phrenic nerve injury, PV stenosis, or coronary spasm observed
- Performance goal of < 13%

0.7%
safety event rate

0 esophageal events	0 PV stenosis	0 phrenic nerve injury	0 coronary artery spasm



1/300 cerebrovascular accident
1/300 tamponade
0/300 transient ischemic attack
0/300 major bleeding

0/300 myocardial infarction
0/300 pericarditis
0/300 vagal nerve injury
0/300 systemic pulmonary embolism

0/300 pulmonary edema
0/300 vascular access complications
0/300 cardiovascular hospitalization
0/300 death

Table 4. Primary Safety End Point Summary

Primary safety event	Number with a primary safety event	
	Paroxysmal atrial fibrillation cohort (n=150)	Persistent atrial fibrillation cohort (n=150)
Within 6 months		
Pulmonary vein stenosis (>70% diameter reduction)	0	0
Phrenic nerve injury/diaphragmatic paralysis ongoing at 6 months postablation	0	0
Atrio-esophageal fistula	0	0
Within 30 days		
Cardiac tamponade/perforation	0	1
Cerebrovascular accident	1	0
Transient ischemic attack	0	0
Major bleeding requiring transfusion	0	0
Myocardial infarction	0	0
Pericarditis requiring intervention	0	0
Vagal nerve injury resulting in esophageal dysmotility or gastroparesis	0	0
Vascular access complications requiring intervention	0	0
Death	0	0
Any pulsed field ablation system-related or pulsed field ablation procedure-related cardiovascular and pulmonary adverse event that prolongs or requires hospitalization for >48 hours (excluding recurrent atrial fibrillation/atrial flutter/atrial tachycardia)	0	0
Summarized results		
Patients with any primary safety event (%)	1 (0.7)	1 (0.7)
95% log–log confidence interval	0.1–4.6	0.1–4.6
P value vs performance goal of 13%	0.002	0.002

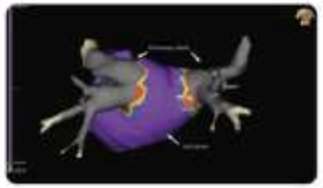
Procedure times

PULSED AF procedure time

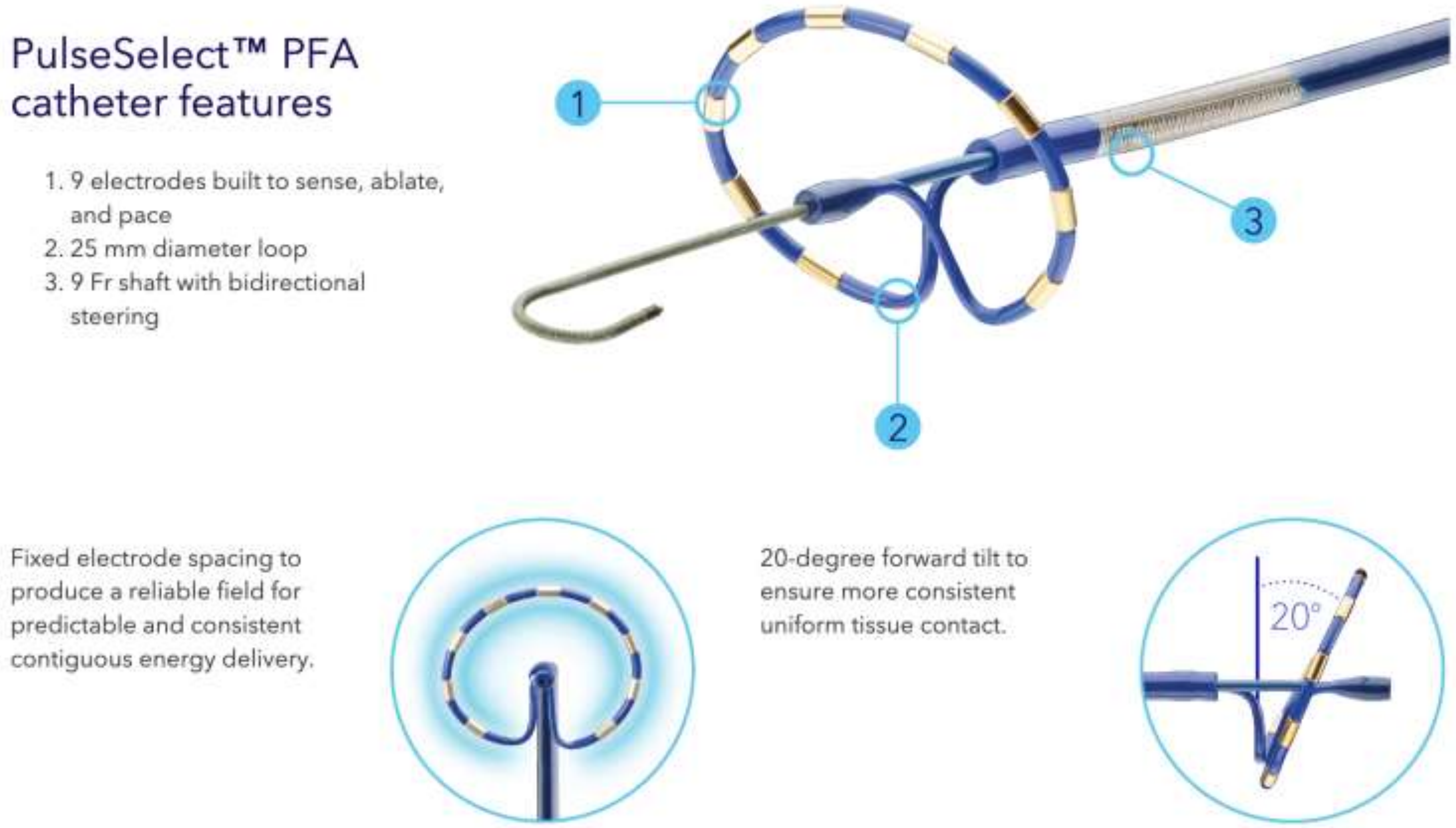
Parameter	Paroxysmal (n = 150)	Persistent (n = 150)
Skin-to-skin procedural time (min)*	134 ± 50	145 ± 60
Device left atrial dwell time (min)†	65 ± 29	70 ± 31
Fluoroscopy time during procedure (min)	26 ± 17‡	29 ± 21
Number of applications per procedure	48 ± 15	57 ± 20

PULSED AF patients were sedated with general anesthesia, deep sedation, or conscious sedation, and paralytics were not required.

The PulseSelect PFA system was used in conjunction with multiple commercially available mapping systems.



Pulse Select Catheter



	Medtronic (9)	Boston scientific (21)	Johnson & johnson (22)	Kardium (23)
Year of Study	2021	2019	2020	2019
Device	PulseSelect	Farawave (Farapulse)	Varipulse	Globe
Energy Type	Biphasic, Bipolar waveform	Monophasic (15) and Biphasic (66) PFA	Biphasic, 1,800 Volts	Bipolar and biphasic pulse train
Size of Catheter	Over-the-wire, circular array with 9 gold electrodes. 9F shaft	12F (Over the wire)	7.5F. 10 electrodes. Circular PFA lasso catheter with adjustable diameter between 25 and 35 mm.	Globe Catheter with 122 electrodes. Size of the electrodes ranges from 9.0 to 13.6 mm^2. Electrodes fanned to form a spherical array with a diameter of 30 mm inside the left atrium.
LA Dwell Time	Average = 82 ± 35 min	23 ± 9 min	82.4 ± 20 min	16 min
Acute Isolation	100%	100%	100%	99.1%
Major Complication (s)	1 patient developed pericardial effusion	Tamponade in 1 patient	No complications.	Pericardial tamponade in 2 patients.
Image				

Patient Selection

Since PulseSelect is designed for PVI

- 1st time ablation
- Redo if high likelihood of PV reconnection (Phrenic or esophagus limitations)

Cannot be used in patient with metal in left atrium

- Prior Watchman
- Mechanical Valves

Patient with devices

- Program Asynchronous, Deactivate Tachydetection

Peri-operative Considerations

Pre Operative

Similar to RF ablation and Cryoablation

CT heart

- Early cases – abnormal PV anatomy

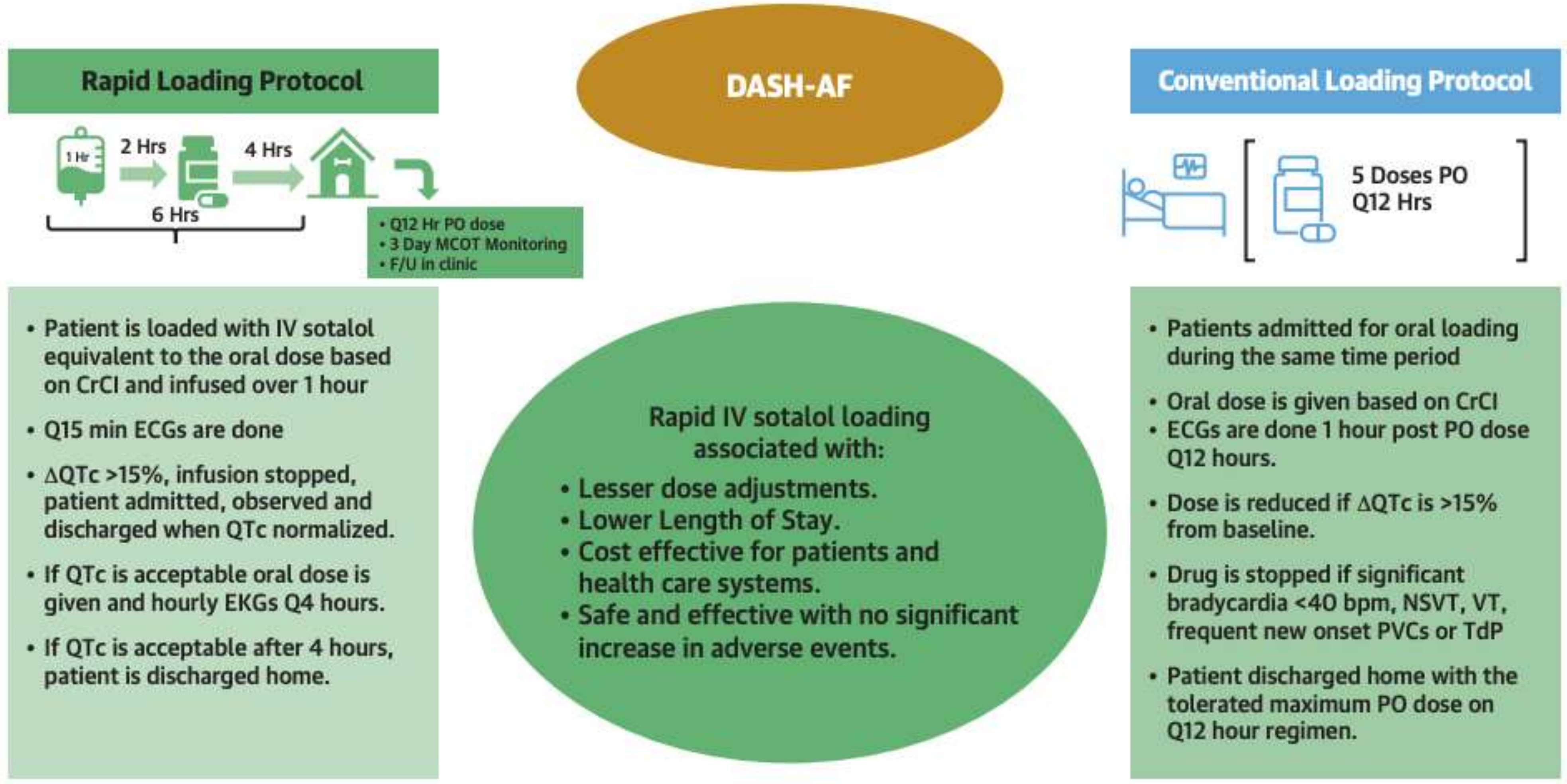
Mapping System? Ensite

Post op

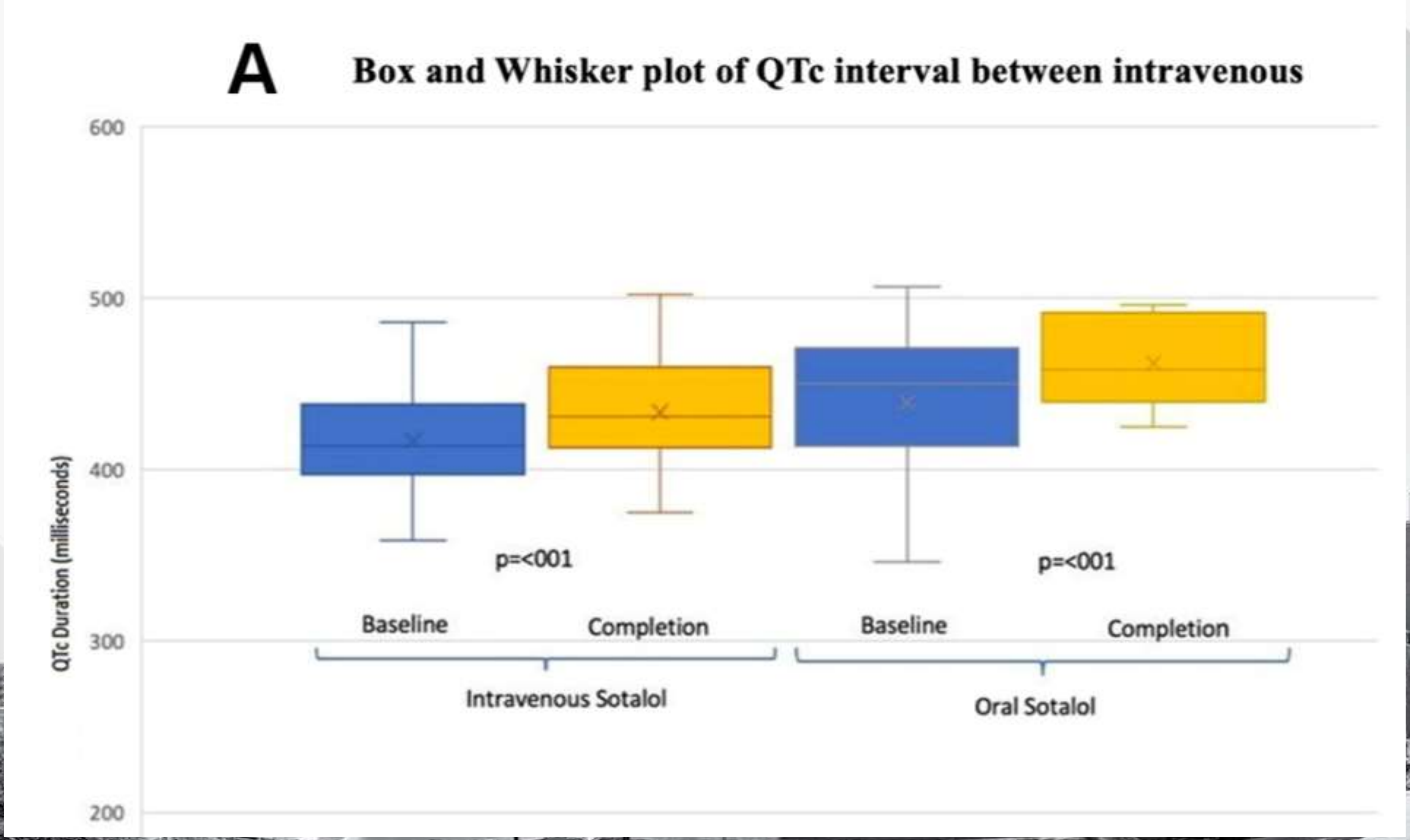
Same day Discharge

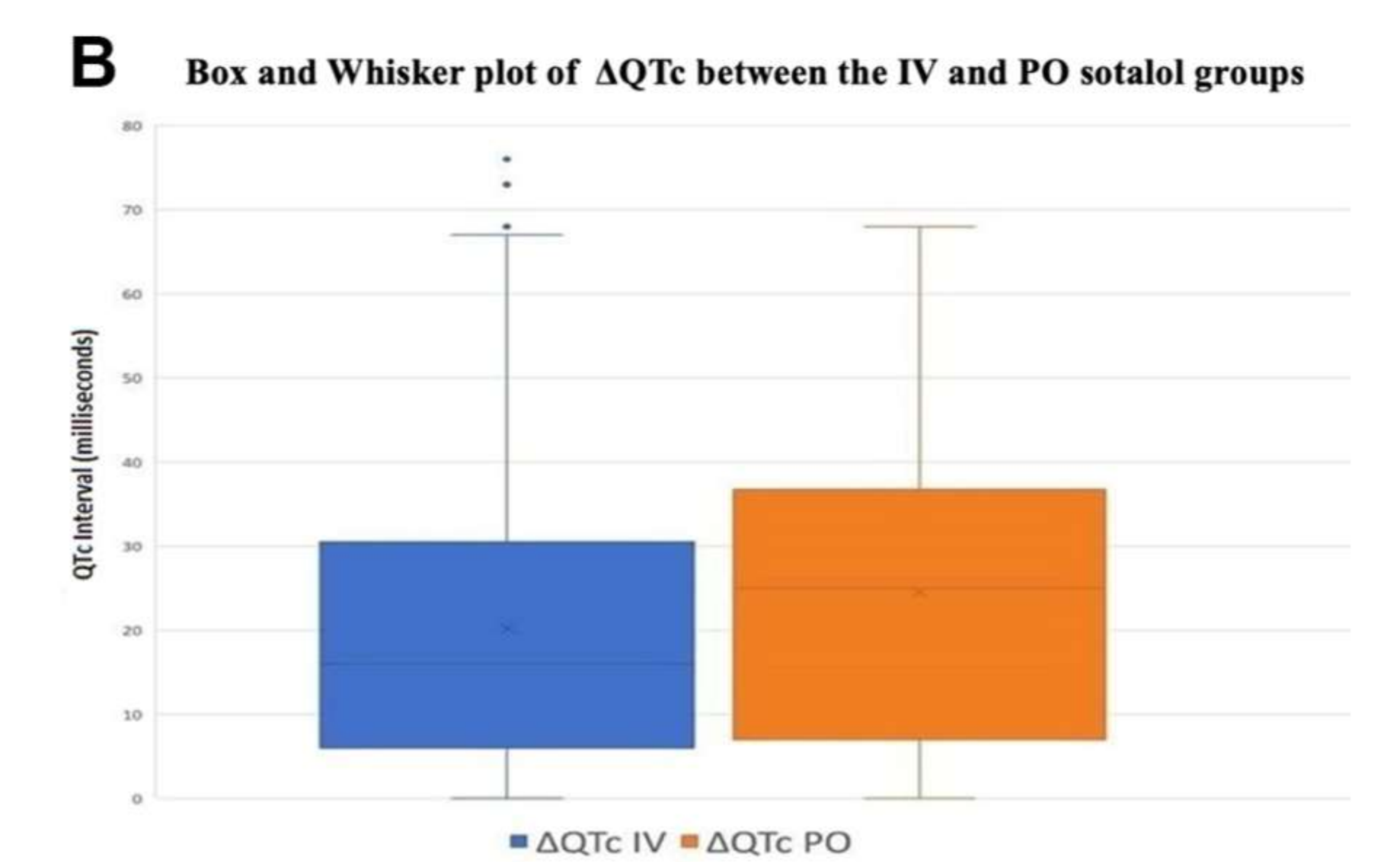
Loop Recorder implant

- Initial Experience

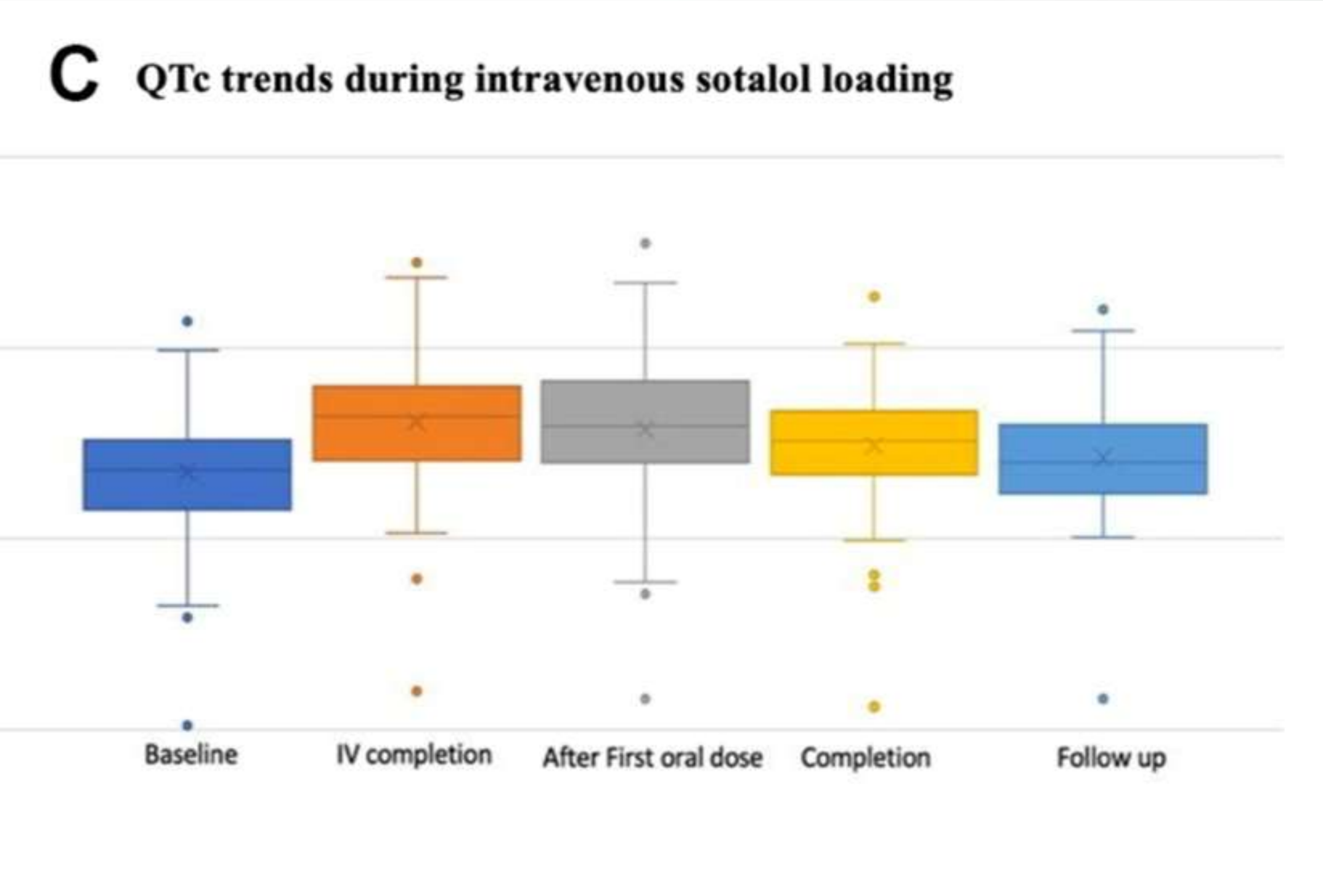


Lakkireddy D, et al. J Am Coll Cardiol EP. 2022;■(■):■-■.


A
Box and Whisker plot of QTc interval between intravenous
600
500
400
300
200
QTc Duration (milliseconds)
p=<001
p=<001
Baseline
Completion
Baseline
Completion
Intravenous Sotalol
Oral Sotalol



B
Box and Whisker plot of ΔQTc between the IV and PO sotalol groups
QTc Interval (milliseconds)
80
70
60
50
40
30
20
10
0
ΔQTc IV
ΔQTc PO


C
QTc trends during intravenous sotalol loading
Baseline
IV completion
After First oral dose
Completion
Follow up

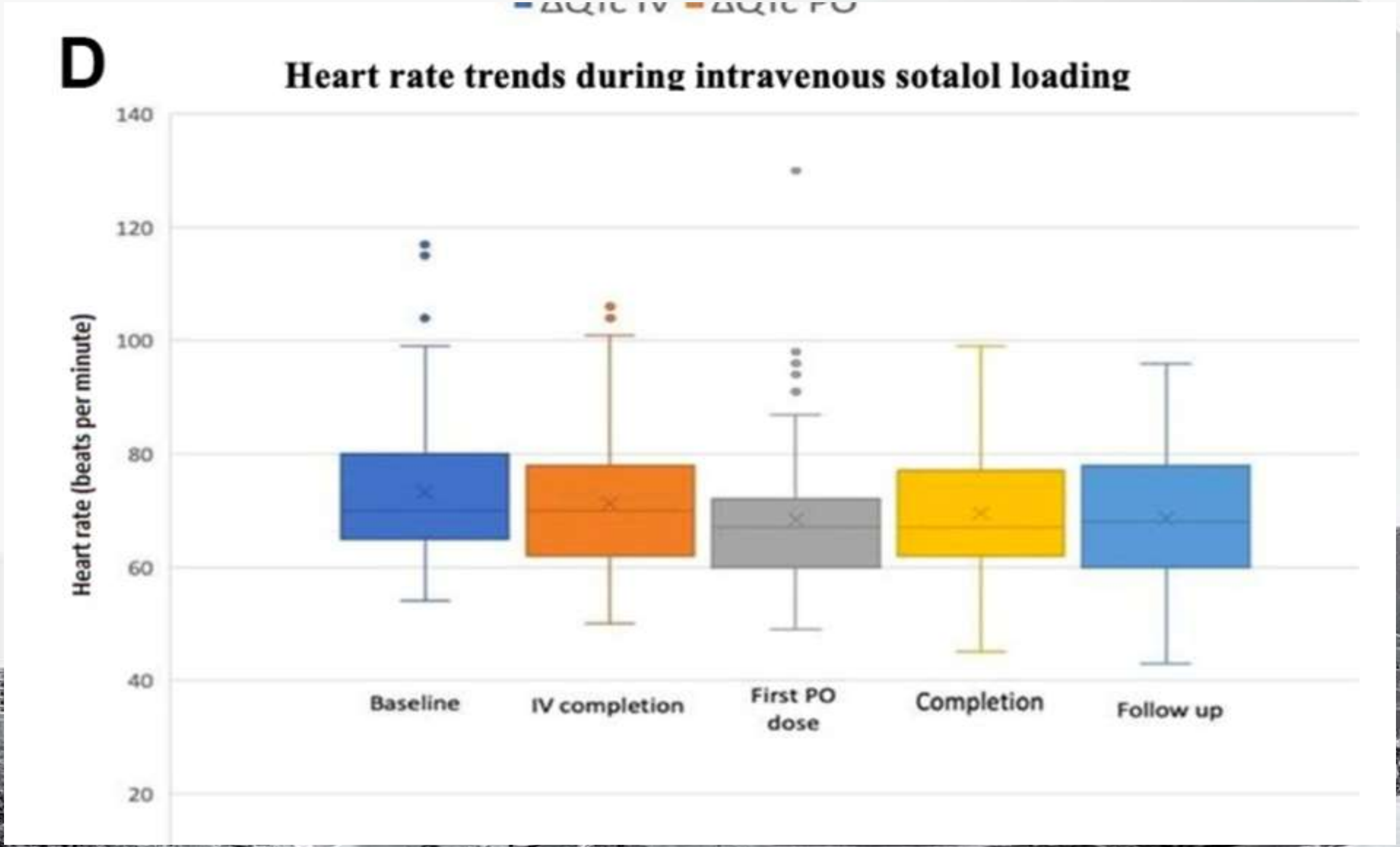

ΔQTc IV ΔQTc PO
D
Heart rate trends during intravenous sotalol loading
Heart rate (beats per minute)
140
120
100
80
60
40
20
Baseline
IV completion
First PO dose
Completion
Follow up

TABLE 3 Safety Outcomes

	IV Sotalol	PO Sotalol	*P* Value
Torsades de pointes	0	1 (0.8)	-
Sustained VT	0	0	-
Nonsustained VT	1 (0.8)	2 (1.6)	0.57
New onset PVCs	0	0	-
Sinus arrest	0	1 (0.8)	-
High-grade AV block	0	1 (0.8)	-
Permanent pacemaker	0	1 (0.8)	-
Sotalol stopped owing to QTc and severe bradycardia	4 (3.3)	7 (5.8)	0.36
Mortality	0	0	-

Values are n (%).

AV = atrioventricular; PO = oral; IV = intravenous; PVCs = premature ventricular contractions; VT = ventricular tachycardia.

- One case of QTc prolongation in PO group (after 3rd dose) leading to TdP, requring discontinuation of Sotalol
- One patient in IV arm had NSVT leading to dose reduction (120mg -> 80mg)
- Two patients in PO group had NSVT resulting in dose reduction in 1, and drug discontinuation in the other
- One patient in PO group developed sinus arrest & severe high-grade AV block necessitation pacemaker
- None in IV group required PPM or experienced sinus bradycardia

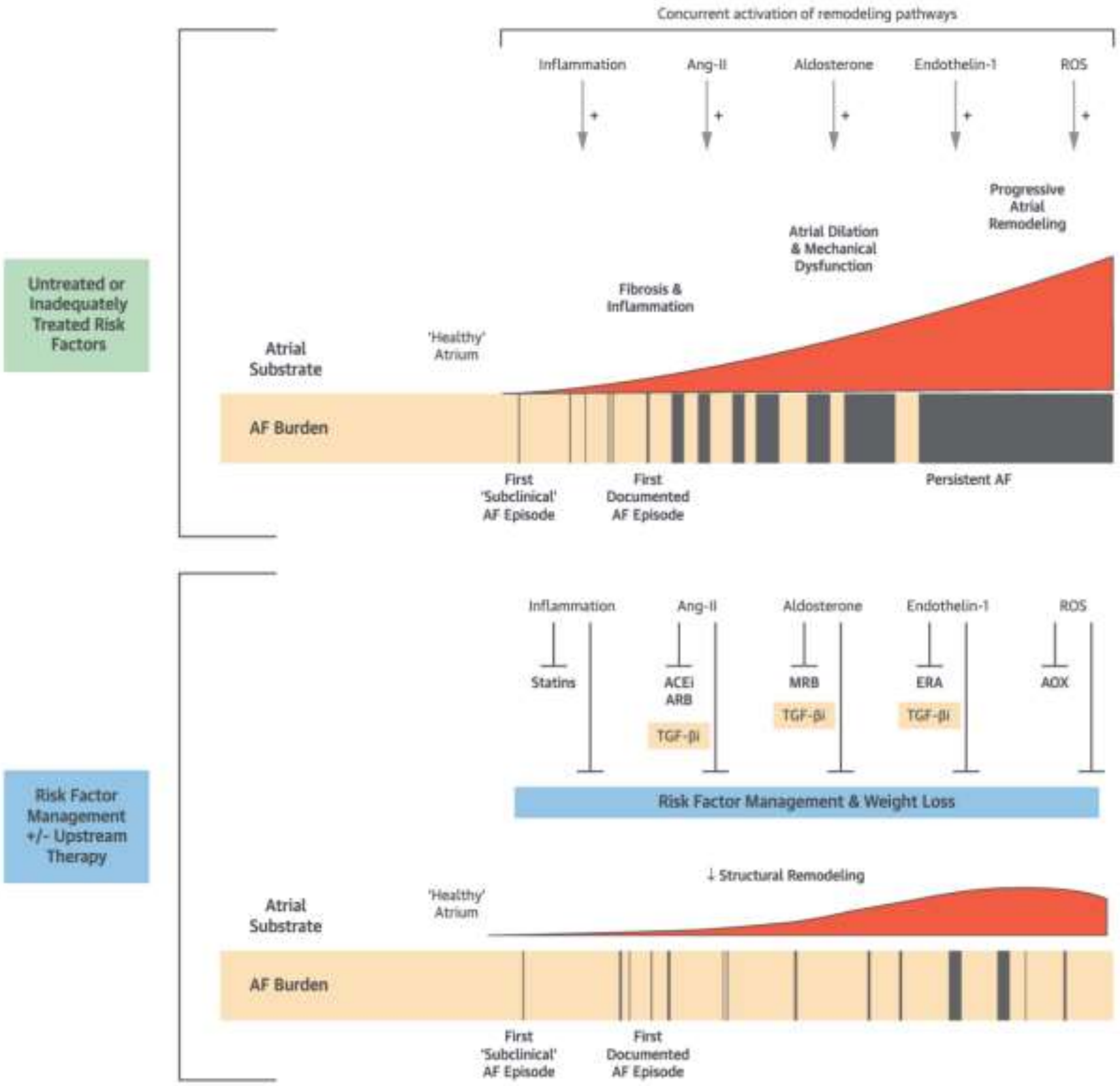
TABLE 4 Cost Analysis

	Cost for IV Sotalol	Cost of 3-Day Oral Loading From Historical Data[a]
Drug cost	$2,734	$27
Labs	$37.32	$111.96
ECGs[b]	$762	$762
MCOT for 3 days[c]	$650	-
Hospital bundle cost[d]	$1,535	$7,347.37
Average cost per admission	$5,068.32	$8,569
Median projected cost for 100 patients	$506,832.00	$856,900

[a]Cost model reproduced from Varela et al.[17] [b]Cost calculated per total of 6 ECGs required during the initiation. [c]MCOT was used in this study to demonstrate safety of IV sotalol, which demonstrated excellent safety profile; therefore, MCOT may not be needed in routine care and the cost of MCOT not included the average cost analysis. [d]Hospital bundle cost includes physician and nurse labor and charges for telemetry, room, and miscellaneous equipment.

ECG = electrocardiogram; MCOT = mobile cardiac outpatient telemetry; IV = intravenous.

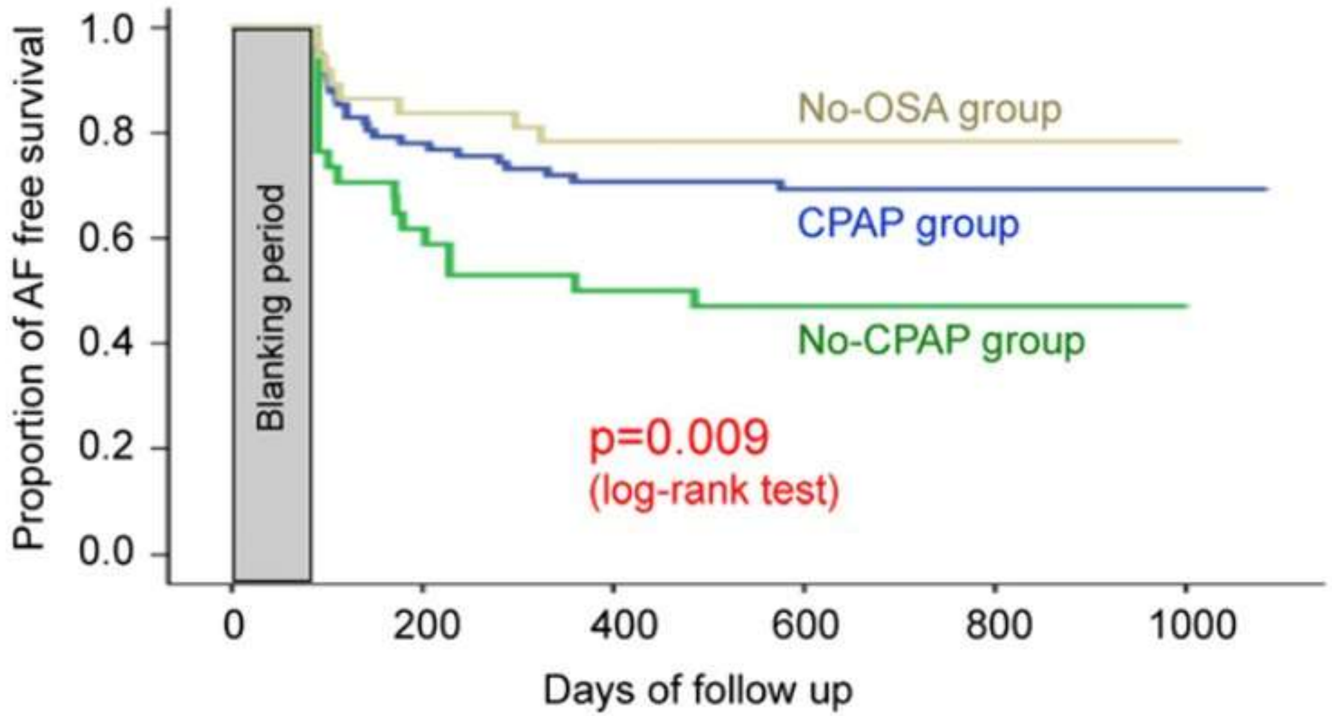
- Average cost per IV Sotalol load: $5068
- CMS reimbursement for 3-day load: $9263
- Potential for cost savings per admission: $3500
- Potential for cost savings per 100,000 pts: $350,000
- NOTE: additional cost savings of improved patient satisfaction, wages, and bed availability not included in analysis



Concurrent activation of remodeling pathways
Inflammation
Ang-II
Aldosterone
Endothelin-1
ROS
Progressive Atrial Remodeling
Atrial Dilation & Mechanical Dysfunction
Fibrosis & Inflammation
Untreated or Inadequately Treated Risk Factors
Atrial Substrate
'Healthy' Atrium
AF Burden
First 'Subclinical' AF Episode
First Documented AF Episode
Persistent AF
Inflammation
Ang-II
Aldosterone
Endothelin-1
ROS
Statins
ACEi ARB
TGF-βi
MRB
TGF-βi
ERA
TGF-βi
AOX
Risk Factor Management & Weight Loss
Risk Factor Management +/- Upstream Therapy
↓ Structural Remodeling
Atrial Substrate
'Healthy' Atrium
AF Burden
First 'Subclinical' AF Episode
First Documented AF Episode

Obstructive Sleep Apnea

Study	Study Type	Number of Patients	Intervention or Risk Factor Studied *	Population	Change in Risk Factor(s)	Average Follow-Up Duration (Months)	Number of Procedures	Outcomes
Fein et al., 2013 [79]	Retrospective cohort	62	Treatment of obstructive sleep apnoea vs. non-treatment	AF patients, BMI 30, 53% persistent AF 32 with OSA on CPAP 30 with OSA no CPAP	Not specified	12	Not specified	Higher atrial tachyarrhythmia-free survival rate with CPAP than without (72% vs. 37%) ($p = 0.01$)
Patel et al., 2010 [84]	Retrospective cohort	3000	Treatment of obstructive sleep apnoea vs. non-treatment	AF patients, BMI 27, 53% paroxysmal 315 with OSA on CPAP 325 with OSA no CPAP	CPAP vs. no CPAP	32	1	Higher AF-free survival rate with CPAP than without (79% vs. 68%) ($p = 0.001$)
Naruse et al., 2013 [83]	Prospective case–control	153	Treatment of obstructive sleep apnoea vs. non-treatment	AF patients, BMI 25, 54% paroxysmal 82 with OSA on CPAP 34 with OSA no CPAP	CPAP vs. no CPAP	19	1	Lower AF recurrence with OSA + CPAP vs. OSA no CPAP (30% vs. 53%) (HR 0.41, CI 0.22–0.76, $p < 0.01$)
Jongnarangsin et al., 2008 [76]	Retrospective cohort	324	Treatment of obstructive sleep apnoea vs. non-treatment	AF patients, BMI 30, 72% paroxysmal 18 with OSA on CPAP 14 with OSA no CPAP	CPAP vs. no CPAP	7	1	Lower AF recurrence with OSA + CPAP vs. OSA no CPAP (50% vs. 71%) (underpowered for this outcome, $p = 0.289$)



Patients at risk

No-OSA	37	34	31	30	29	29	26	16	10	6	0
No-CPAP	34	26	21	18	17	16	14	11	10	4	1
CPAP	82	75	64	60	58	57	48	41	23	9	1

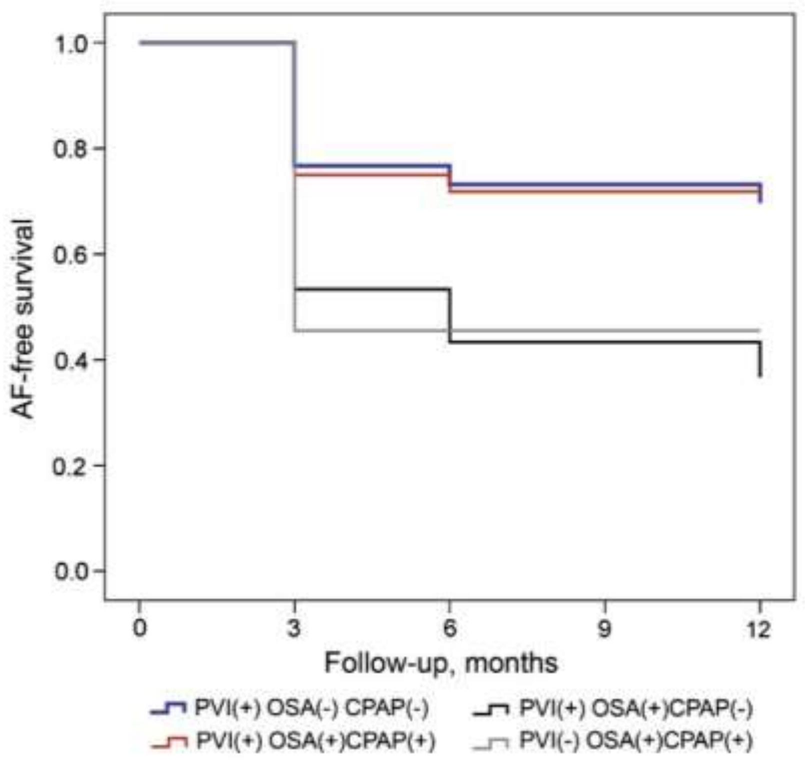


Figure 2 **Kaplan-Meier Survival Curves According to Treatment Group**

Log-rank p = 0.02. AF = atrial fibrillation; other abbreviations as in Figure 1.

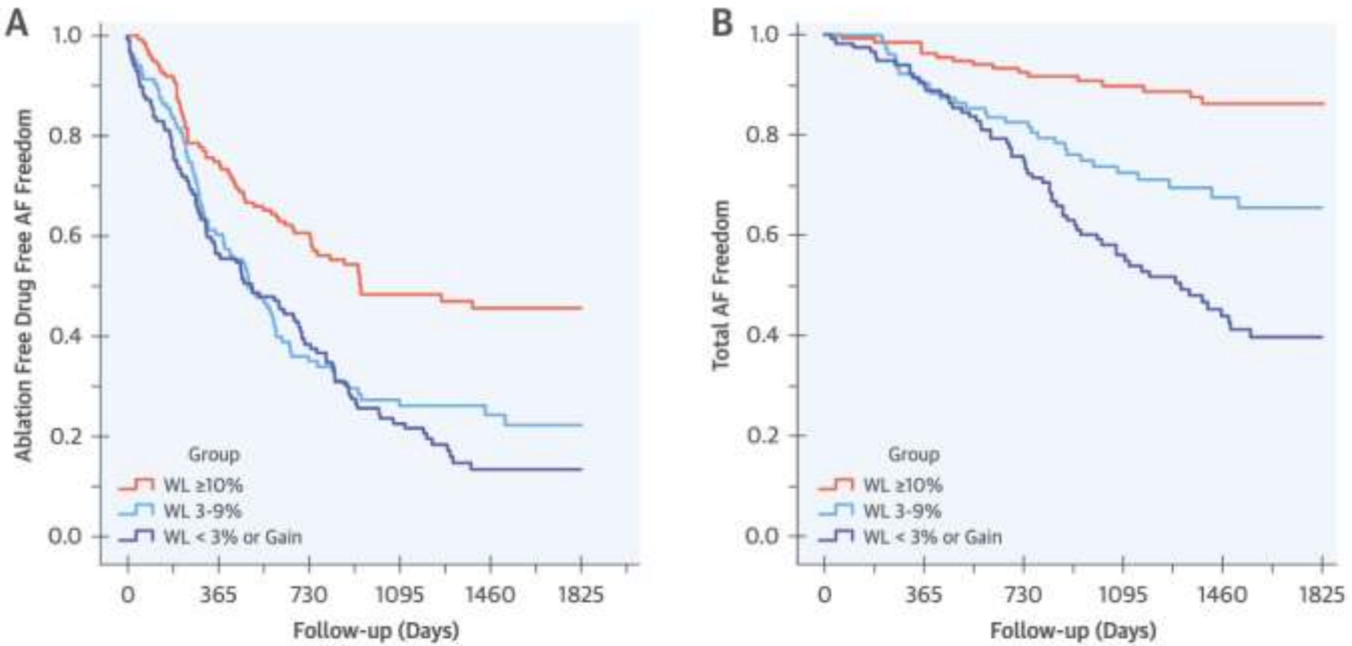
Fein, A. S. *et al.* Treatment of Obstructive Sleep Apnea Reduces the Risk of Atrial Fibrillation Recurrence After Catheter Ablation. *J Am Coll Cardiol* **62**, 300–305 (2013).

Naruse, Y. et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: Clinical impact of continuous positive airway pressure therapy. Heart Rhythm 10, 331

HTN Management

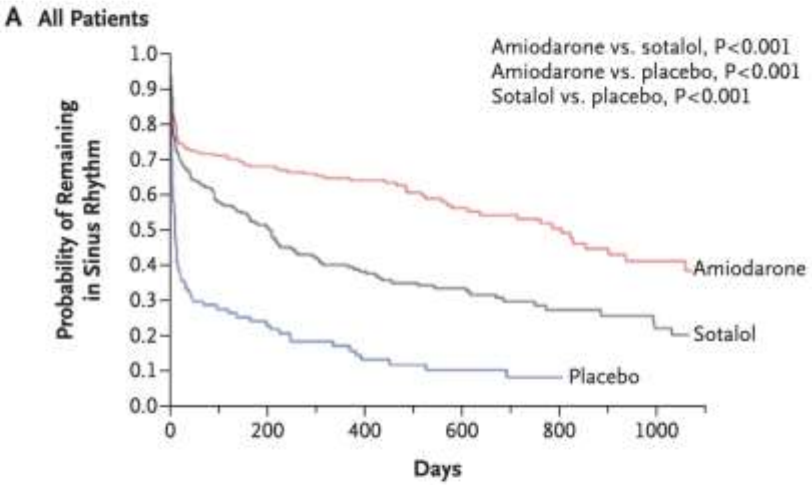
Pokushalov et al., 2012 [67]	Randomised controlled trial	27	Renal denervation in addition to pulmonary vein isolation versus pulmonary vein isolation alone	AF patients refractory to 2 AADs with drug-resistant hypertension, BMI 28 14 PVI only 13 PVI + renal denervation	Intervention group: BP improved from 181/97 to 156/87	12	1	Intervention group: 69% arrhythmia-free Control group: 29% arrhythmia-free ($p = 0.033$)
Pokushalov et al., 2014 [91]	Meta-analysis of combined data from 2 randomised controlled trials	80	Renal denervation in addition to pulmonary vein isolation versus pulmonary vein isolation alone	AF patients BMI not stated 39 PVI only 41 PVI + renal denervation	Intervention group: BP	12	1	Intervention group: 63% AF-free Control group: 41% AF-free ($p = 0.014$)
Steinberg et al., 2020 (ERADICATE-AF) [68]	Randomised controlled trial	302	Renal denervation in addition to pulmonary vein isolation versus pulmonary vein isolation alone	Paroxysmal AF patients, BMI not stated, 16.8% obese 154 PVI + renal denervation 148 PVI alone	Intervention group: mean BP reduced 150–135 mmHg vs. control group 151–147 mmHg ($p < 0.001$)	12	1	Greater freedom from AF recurrence (72%) in treatment vs. (57%) control group ($p = 0.006$)
Parkash et al., 2017 (SMAC-AF) [70]	Randomised controlled trial	184	Aggressive BP treatment (target <120 mmHg) vs. standard BP treatment (target <140 mmHg)	AF patients, BMI 32, (57% paroxysmal) 92 aggressive BP treatment 92 standard BP treatment	Aggressive BP treatment group mean BP reduced 143–123 mmHg vs. control group 142–135 mmHg ($p < 0.001$)	14	1	Intervention group recurrence of AF/atrial tachycardia/atrial flutter not different to control group (both 61%) ($p = 0.763$)

LEGACY



Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9

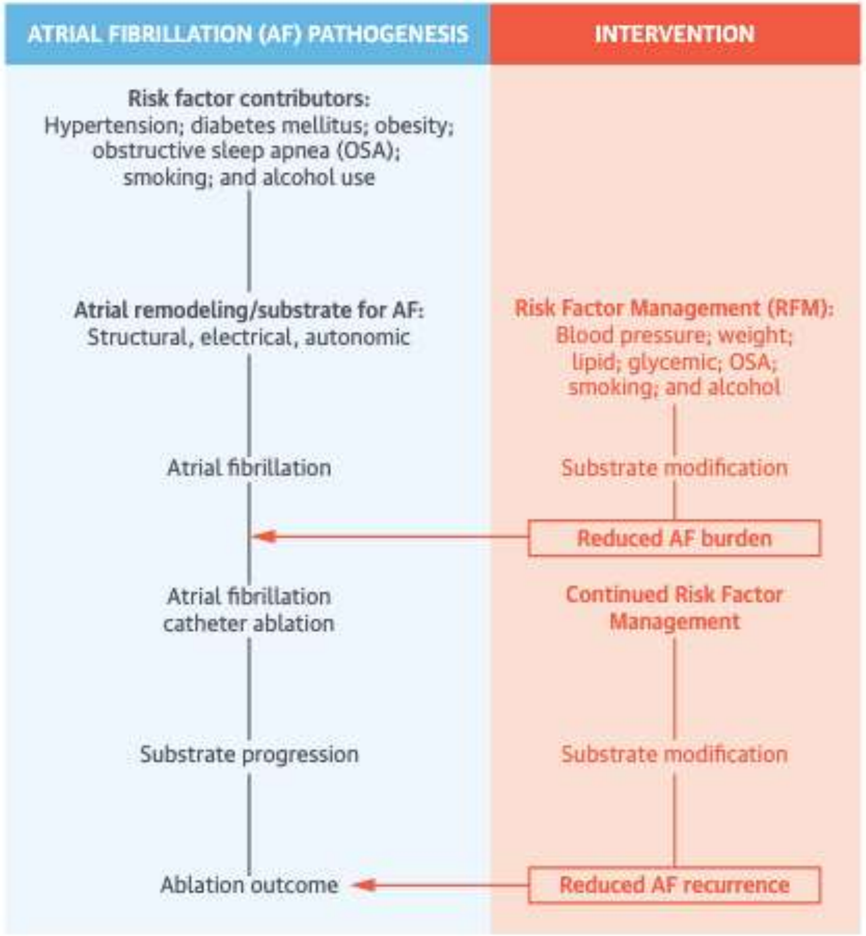
	0	365	730	1095	1460	1825
	135	130	114	86	67	36
	103	93	83	57	35	22
	117	105	85	53	32	22

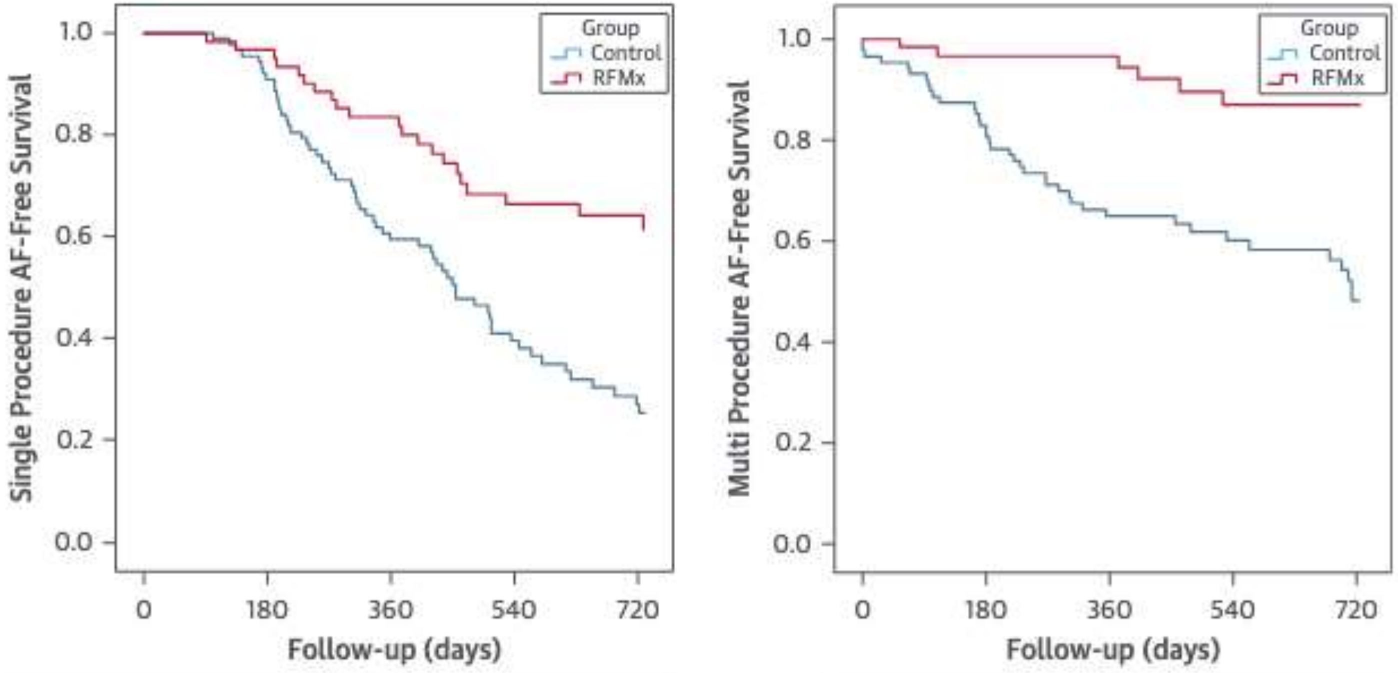


No. at Risk						
Amiodarone	206	131	98	60	38	18
Sotalol	195	97	61	38	21	13
Placebo	90	21	11	8	5	2

Pathak, R. K. *et al.* Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort A Long-Term Follow-Up Study (LEGACY). *J. Am. Coll. Cardiol.* **65**, 2159–2169 (2015).
Singh, B. N. *et al.* Amiodarone versus Sotalol for Atrial Fibrillation. *N. Engl. J. Med.* **352**, 1861–1872 (2005).

ARREST - AF

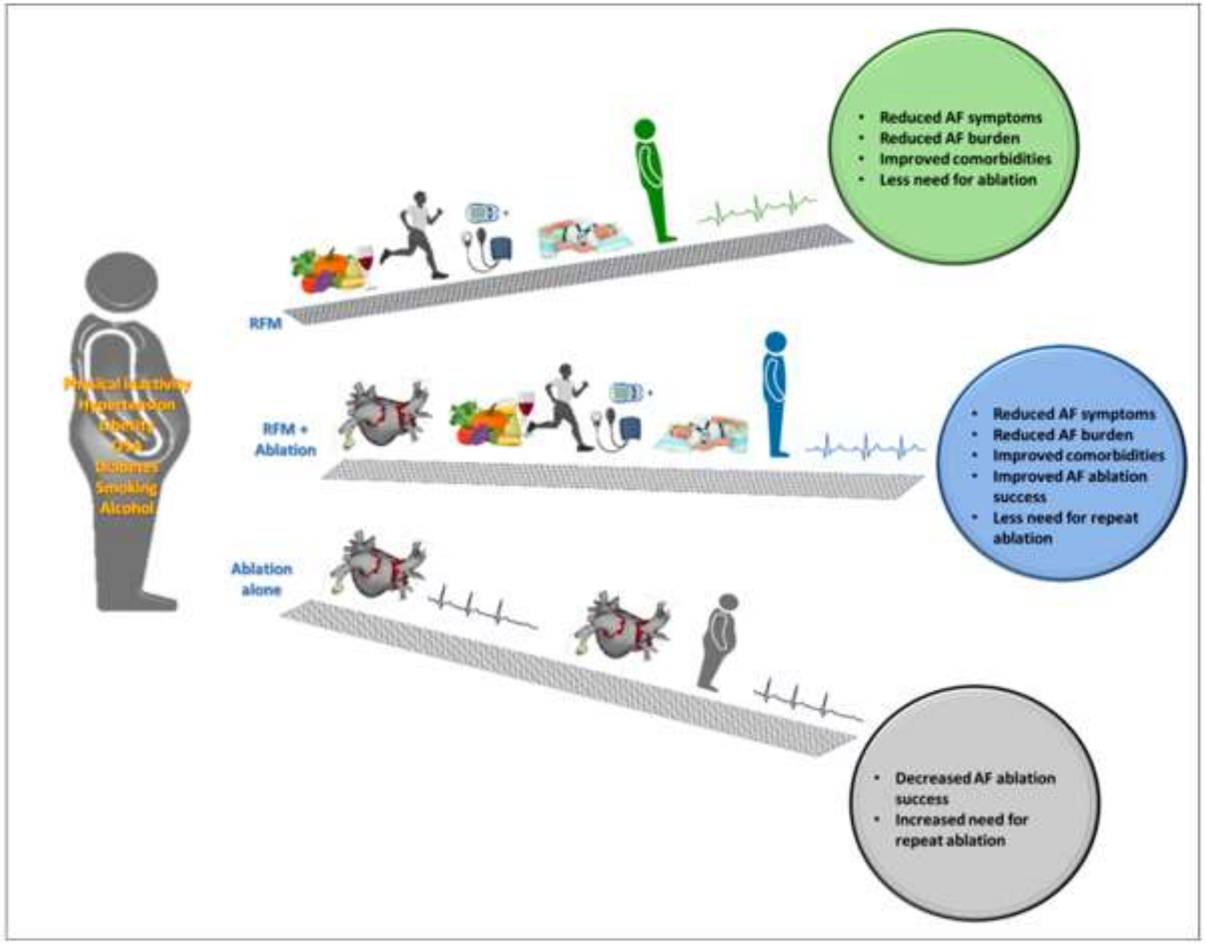


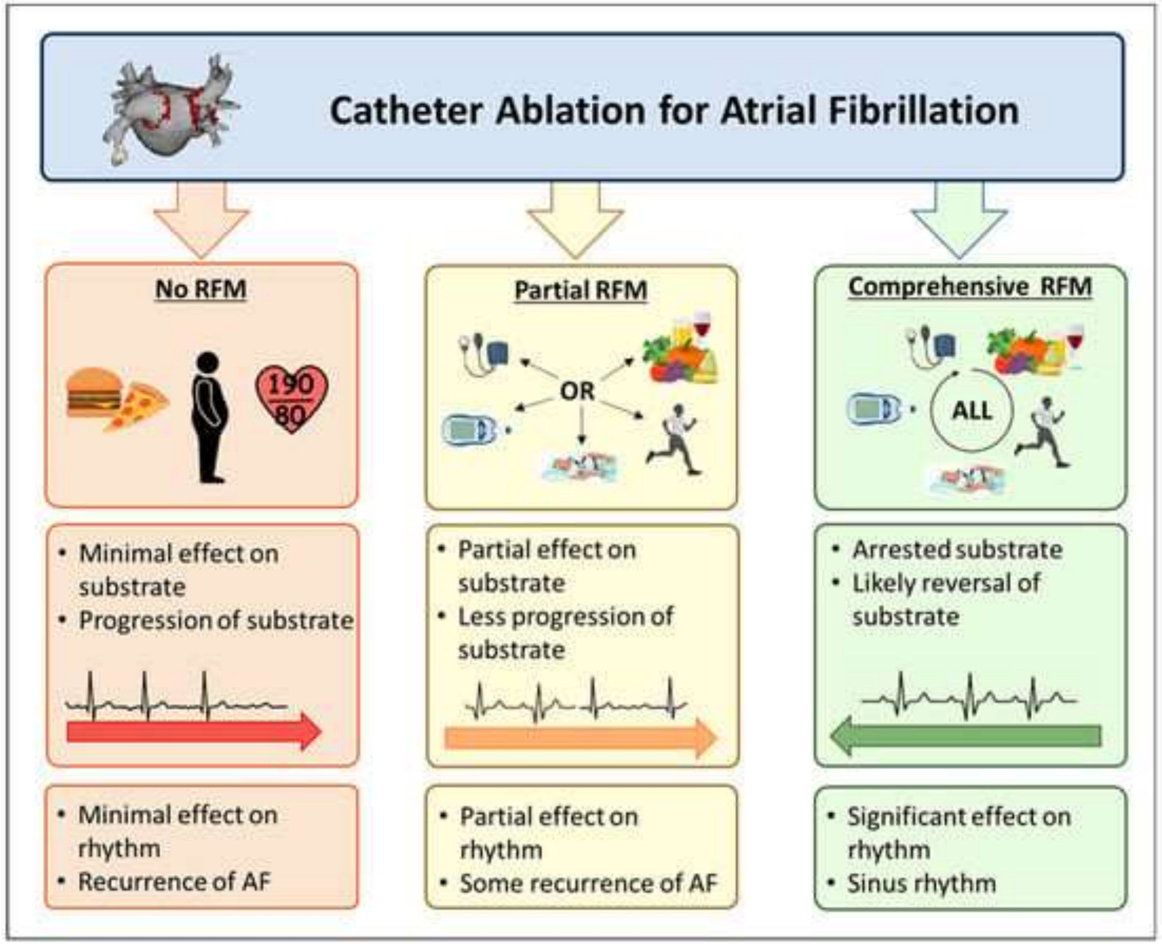


Time (days)	0	180	360	540	730	0	180	360	540	730
RFM	61	59	48	33	27	61	55	46	32	25
Control	88	79	51	28	16	88	72	51	36	23

Pathak, R.K. et al. J Am Coll Cardiol. 2014; 64(21):2222-31.

Pathak, R. K. *et al.* Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation The ARREST-AF Cohort Study. *J Am Coll Cardiol* **64**, 2222–2231 (2014).





1.Fitzgerald, J. L., Middeldorp, M. E., Gallagher, C. & Sanders, P. Lifestyle Modification and Atrial Fibrillation: Critical Care for Successful Ablation. *J. Clin. Med.* **11**, 2660 (2022).

Risk Factor Modification

- Risk Factor Modification necessary to slow age/disease-related atrial remodeling
  - Can be Primary or Secondary
- There is a robust treatment effect to treating OSA and HTN
  - Conversely, failure to treat HTN and OSA reduces the efficacy of ablation
- Mixed Data for Weight Loss
  - Weight loss was hard to achieve and must be substantial (> 10%)
  - Studies with Bariatric Surgery were also positive
  - Studies of GLP-1 agonists on genetically modified mice with known susceptibility show feasibility
- Must be prescriptive with Risk factor Modification Recommendations

RFM prescription

- Optimal BP control
- Optimal glycemic control
- Tobacco Cessation
- Screen for OSA
- Weight loss is recommended, with an ideal target of at least 10% weight loss
- Moderate-to-vigorous exercise training to a target of 210 minutes per week
  - caution should be considered in pursuing years of regular, high-volume (≥3 h/day) high-intensity endurance training
- ≤3 standard alcoholic drink/week
- Tobacco cessation
- NO Benefit to Caffeine Cessation

Monitoring Atrial Fibrillation with a Wearable Mobile Device

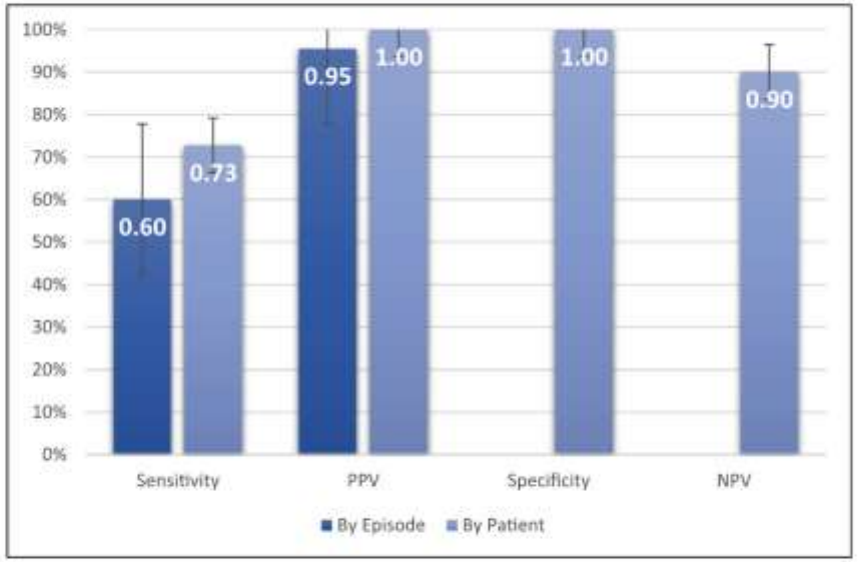


FIGURE 2 Accuracy of the IRN by episode and by patient. IRN, irregular rhythm notification; NPV, negative predictive value; PPV, positive predictive value.

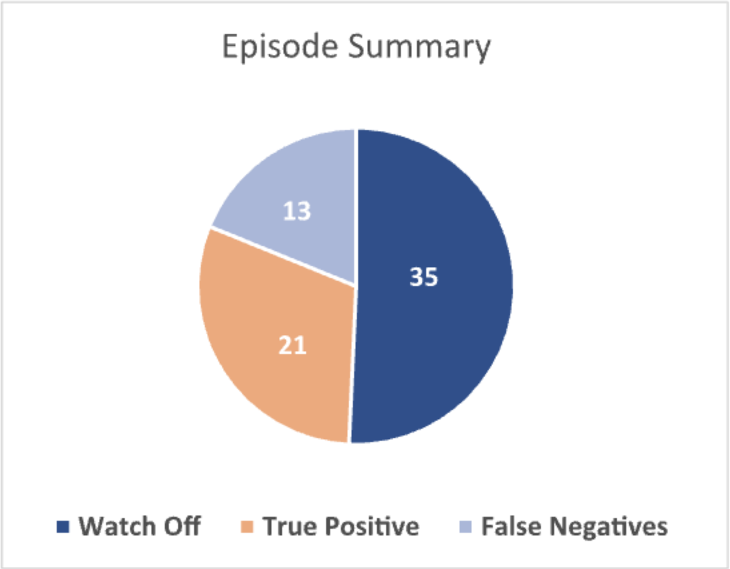


FIGURE 3 Summary of AF episodes by detection. AF, atrial fibrillation.

"by subject" 72% sensitivity, 100% specificity, 100% PPV, and 90% NPV

- There were a total of 70 AF episodes on ICM/CIED, 35 of which occurred while the AW was being worn
- Five subjects had AF only when the AW was not worn

Wasserlauf, J. *et al.* Accuracy of the Apple watch for detection of AF: A multicenter experience. *J. Cardiovasc. Electrophysiol.* **34**, 1103–1107 (2023).

- Smartphone and smartwatch technologies can differentiate SR from AF but provide only a brief rhythm assessment without information on AF duration or burden.
- Are sensitivity to detect and accurately characterize Afib as a screening tool but not sensitive as a long-term continuous monitoring strategy.
- **“The current IRN algorithm appears accurate for AF screening as currently indicated, but increased sensitivity and wear times may be necessary for disease management.”**

Questions?

Nebraska Medicine