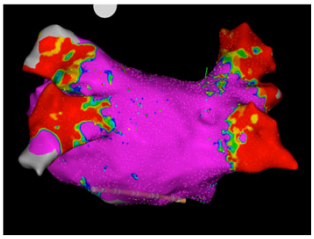
1

Update on Atrial Fibrillation Management: Role of Rhythm Control



Joseph J. Decker, MD
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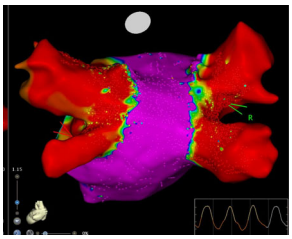

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Disclosures

- None

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Objectives

- Review the epidemiology of atrial fibrillation
- Understand the progressive nature of AF
- Describe lifestyle modifications for reducing AF burden
- Review rate vs rhythm control
- Evaluate the role of catheter ablation
- Explore the most up to date ablative management for AF

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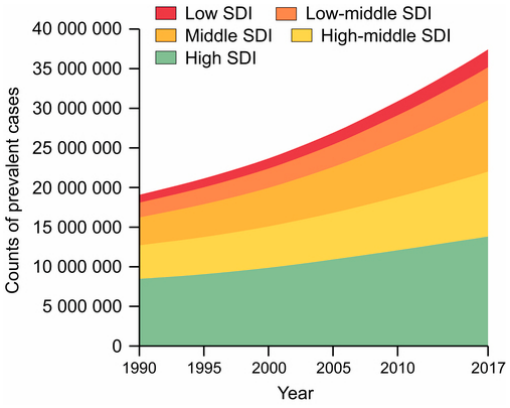
AF Epidemiology

- Prevalence of AF in US
  - ➢ Estimated to be 5.2 million in 2010
  - ➢ Expectation rise to 12.1 million in 2030
- Global prevalence was 50 million in 2020
- AF diagnosis varies by several factors:
  - ➢ Education, income, clinical and genetics
    - Ex. lifetime risk is 30-40% in White individuals
- Median annual direct medical cost per patient $13,333



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José A. Joglar. Circulation. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. DOI: (10.1161/CIR.0000000000001193)

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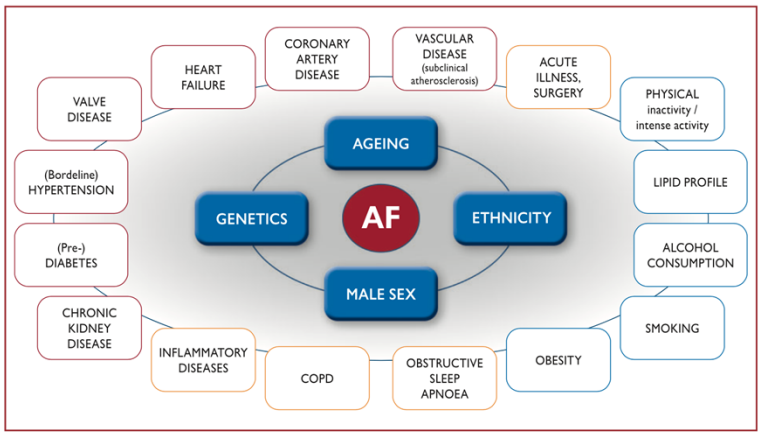
AF Risk Factors


KardiaMobile®


ECG app on Apple Watch

LIFETIME RISK for AF
1 in 3 individuals

of European ancestry
at index age of 55 years
37.0% (34.3% to 39.6%)



Eur Heart J, Volume 42, Issue 5, 1 February 2021, Pages 373–498, https://doi.org/10.1093/eurheartj/ehaa612

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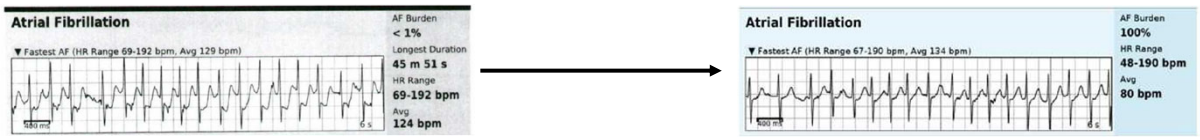
AF Progression

- Structural and electrical remodeling promote AF

- Altered ion channel expression, calcium signaling and contractility
- Interstitial changes and inflammatory infiltrates
  - Increased myofibroblast activity
  - Collagen deposition
  - Fibrofatty deposits



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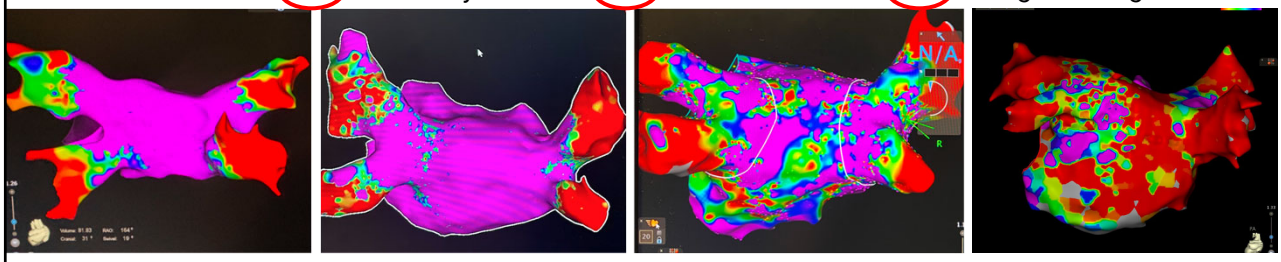
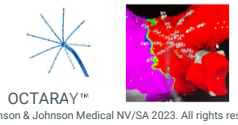
AF Progression: EP Perspective

Pre-AF → Paroxysmal → Persistent → Long Standing Persistent



Example mapping catheter



- AF is associated with a 1.5 to 2-fold increased risk of death
- 2.4-fold risk of stroke
- 1.5-fold risk of cognitive impairment or dementia
- 5-fold risk of heart failure

José A. Joglar. Circulation. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. DOI: (10.1161/CIR.0000000000001193)

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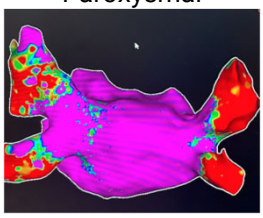
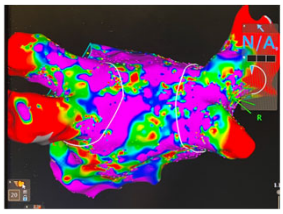
AF Progression

Paroxysmal



Persistent



- N=755, new paroxysmal AF
- Rate of progression to persistent AF
  - 1 year: 9%
  - 5 years: 24%
  - 10 years: 36%
- Factors associated with AF progression
  - Increasing age, MR, aortic stenosis, LA dilation and LVH
- Within 10 years of presenting with paroxysmal AF, >50% progressed to persistent AF or death

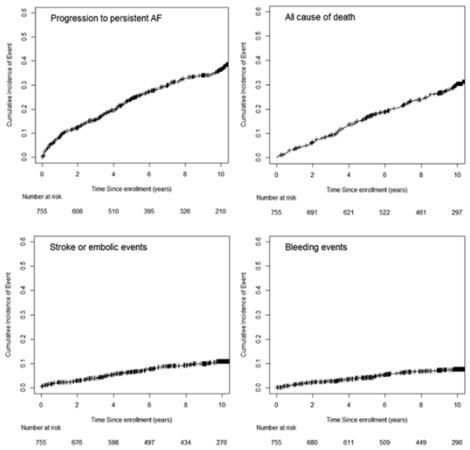


Figure 1 Cumulative incidence of progression to persistent AF, all-cause mortality, stroke or embolic events, and major bleeding events estimated using the Kaplan-Meier method in 755 patients presenting paroxysmal AF unrelated to surgical interventions. AF = atrial fibrillation.

Padfield G.J., Steinberg C., Swampillai J., et al. "Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation". Heart Rhythm. 2017;14:801-807.

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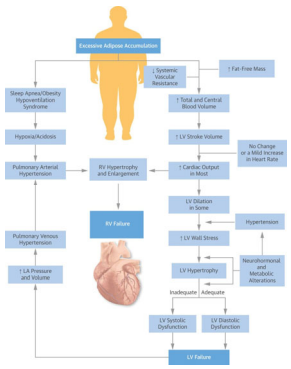
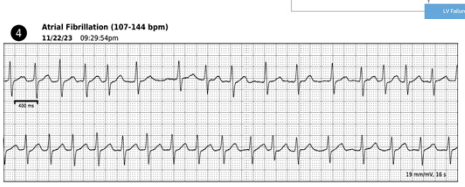
Lifestyle/Risk Factor Modification for AF

- Targets
  - Obesity
  - Physical inactivity
  - Unhealthy alcohol consumption
  - Smoking
  - Diabetes
  - Hypertension





Lavie CJ, et al. Obesity and Atrial Fibrillation. J Am Coll Cardiol. 2017

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10

Pre AF: Adiposity and Atrial Myopathy

- ARIC: Community-based prospective cohort study with participants from 4 US communities
  - Suburbs of Minneapolis, MN
  - Washington County, MD
  - Forsyth County, NC
  - Jackson, MS

Visit 1	Visit 2	Visit 3	**Visit 4**	**Visit 5**	Visit 6
1987-1989	1990-1992	1993-1995	**1996-1998**	**2011-2013**	2016-2017

- N=4008
- Measurements taken at V4 and V5
  - BMI
  - Waist circumference
  - Waist to hip ratio

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Reyes, J., Decker, J. Chen, LY et al. Greater Central Adiposity is Associated with Poorer Left Atrial Function: the Atherosclerosis Risk in Communities (ARIC) Study. Revisions under review with Mayo Clinic Proceedings.

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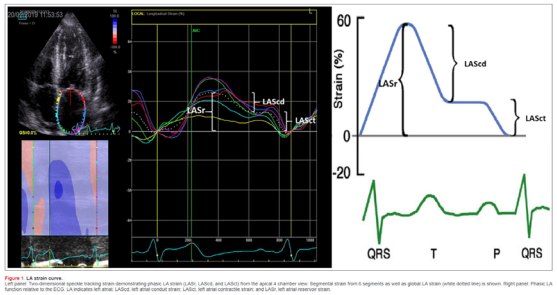
Pre AF: Adiposity and Atrial Myopathy

Visit 1	Visit 2	Visit 3	Visit 4	**Visit 5**	Visit 6
1987-1989	1990-1992	1993-1995	1996-1998	**2011-2013**	2016-2017

- 2D speckle tracking echocardiographic LA strain data at Visit 5
  - LA reservoir function
    - LA fills/stretches
    - Peak strain during systole
  - LA conduit function
    - Passive LA emptying
    - Early peak strain during diastole
  - LA contractile functions
    - Late peak strain during diastole



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Reyes, J., Decker, J. Chen, LY et al. Greater Central Adiposity is Associated with Poorer Left Atrial Function: the Atherosclerosis Risk in Communities (ARIC) Study. Revisions under review with Mayo Clinic Proceedings.

Gan GCH, et al. Left Atrial Reservoir Strain by Speckle Tracking Echocardiography: Association With Exercise Capacity in Chronic Kidney Disease. J Am Heart Assoc. 2021 Jan 5;10(1):e017840.

12

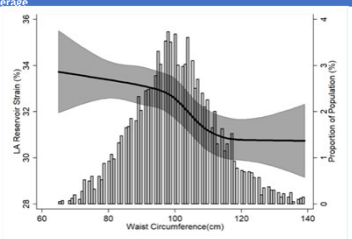
Pre AF: Adiposity and Atrial Myopathy

- Adiposity changes
  - Consistently low (reference group)
  - Consistently elevated, increasing, and decreasing
  - Multivariable linear regression used to evaluate the association of change in adiposity with LA function
- Compared to consistently low waist circumference (WC), increasing WC and consistently elevated WC significantly associated with worse LA reservoir and conduit function
- Change in WC not associated with LA contractile function
- Worsening adiposity indicated by longitudinal changes in WC, BMI and WHR were associated with worse LA function
- Maintaining low adiposity may play a key role in preventing atrial myopathy

Table 2: Associations of Measures of Central Adiposity with Left Atrial Function, Atherosclerosis Risk in Communities Study

	Waist Circumference			
	Consistently low (n=962)	Decreasing (n=349)	Increasing (n=476)	Consistently elevated (n=2221)
	β Estimate (95% CI)			
LA Reservoir Function, %				
Model 1	Ref	-0.51 (-1.42, 0.40)	-1.40 (-2.21, -0.60)	-2.05 (-2.64, -1.47)
Model 2	Ref	-0.28 (-1.18, 0.63)	-1.16 (-1.96, -0.35)	-1.57 (-2.18, -0.96)
Model 3	Ref	-0.27 (-1.18, 0.63)	-1.15 (-1.96, -0.34)	-1.56 (-2.18, -0.94)
Model 4	Ref	-0.04 (-0.84, 0.76)	-0.90 (-1.61, -0.18)	-1.00 (-1.56, -0.44)

Model 1: adjusted for age, sex, race/field center, education
Model 2: adjusted for Model 1 plus systolic blood pressure, antihypertensive medication use, diabetes, CAD, stroke, smoking, alcohol intake, total cholesterol, triglycerides and HDL
Model 3: adjusted for Model 2 plus physical activity trajectory
Model 4: adjusted for Model 3 plus + LAVi, LV peak longitudinal strain, LV mass index, LV RWT, LVEDV, E/e' average



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Reyes, J., Decker, J. Chen, LY et al. Greater Central Adiposity is Associated with Poorer Left Atrial Function: the Atherosclerosis Risk in Communities (ARIC) Study. Revisions under review with Mayo Clinic Proceedings.

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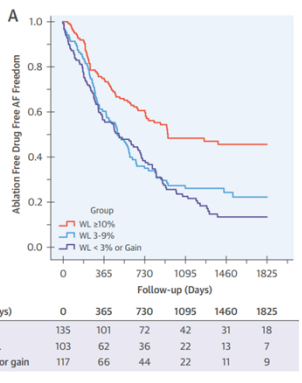
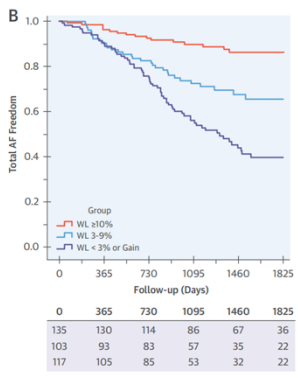
AF Management with Long Term Weight Loss

- N=355
  - Paroxysmal and non-paroxysmal AF
  - BMI ≥27 kg/m^2
- Structured motivational and goal directed weight loss program
  - Face-to-face counseling
  - Meal plans
  - Behavior modification
- Long term weight loss maintenance associated with a 6-fold greater freedom from AF

FIGURE 2 Atrial Fibrillation Freedom Outcome According to Group





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

(A) Kaplan-Meier curve for AF-free survival without the use of rhythm control strategies. **(B)** Kaplan-Meier curve for AF-free survival for total AF-free survival (multiple ablation procedures with and without drugs). Abbreviations as in Figure 1.

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Pathak, R, Middeldorp, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). JACC. 2015 May, 65 (20) 2159–2169.https://doi.org/10.1016/j.jacc.2015.03.002

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Rate vs Rhythm Control

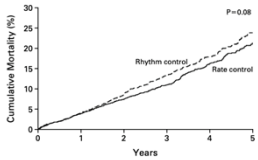

The New England Journal of Medicine

VOLUME 347 DECEMBER 5, 2002 NUMBER 23

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

- Randomized, multicenter comparison rate vs rhythm control
- N=4060
- Mortality at five years
  - Rhythm control 24%
  - Rate control and 21%



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.

TABLE 3. ADVERSE EVENTS.*

	EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
		no. of patients (%)			
	Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
	Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
*	Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
	Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
	Cardiac arrest followed by resuscitation				
	Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
	Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
	Central nervous system event				
	Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
	Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
	After discontinuation of warfarin	69	25	44	
	During warfarin but with INR <2.0	44	27	17	
	Concurrent atrial fibrillation	67	42	25	
	Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
	Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68
	Disabling anoxic encephalopathy	9 (0.3)	4 (0.2)	5 (0.4)	0.74
	Myocardial infarction	140 (5.5)	67 (4.9)	73 (6.1)	0.60
	Hemorrhage not involving the central nervous system	203 (7.3)	107 (7.7)	96 (6.9)	0.44
	Systemic embolism	16 (0.5)	9 (0.5)	7 (0.4)	0.62
	Pulmonary embolism	8 (0.3)	2 (0.1)	6 (0.5)	0.16
*	Hospitalization after base line	2594 (76.6)	1220 (73.0)	1374 (80.1)	<0.001

*Percentag

†The P val … terim mon-
itoring analys

‡One patie … torsade de
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§Informati … he rhythm-
control group … rate-control
group and 13

None of the presumed benefits of rhythm control noted above were confirmed in this study. The implication is that rate control should be considered a primary approach to therapy and that rhythm control, if used, may be abandoned early if it is not fully satisfactory. Our data also suggest that continuous anticoagulation is warranted in all patients with atrial fibrillation and risk factors for stroke, even when sinus rhythm appears to be restored and maintained.

Minneapolis Heart Institute Foundation | GRAND ROUNDS

Wyse DG, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 Dec 5;347(23):1825-33. doi: 10.1056/NEJMoa021328.

15

Risk of AF Progression

- 1-year observational study of the treatment of community-based patients with recent onset AF
- AF rhythm at entry was the strongest predictor of AF progression (AF vs sinus rhythm at entry)
- Rate control was the second strongest predictor of AF progression

Table 2
Atrial fibrillation (AF) status at 12 months stratified by baseline treatment strategy and atrial fibrillation (AF) status

AF Status	Treatment Strategy at Baseline				p Value
	Rate-Control (n = 546)		Rhythm-Control (n = 370)		
	Paroxysmal at Baseline	Persistent at Baseline	Paroxysmal at Baseline	Persistent at Baseline	
Patients at baseline (n)	334 (61.2%)	212 (38.8%)	298 (80.5%)	72 (19.5%)	<0.001*
Patients at 12 mo (n)	265	159	238	57	
Paroxysmal	227 (85.7%)	38 (23.9%)	231 (97.1%)	27 (47.4%)	
Persistent	15 (5.7%)	42 (26.4%)	1 (0.4%)	20 (35.1%)	
Permanent	23 (8.7%)	79 (49.7%)	6 (2.5%)	10 (17.5%)	<0.001†
AF progression	38 (14.3%)	79 (49.7%)	7 (2.9%)	10 (17.5%)	<0.001‡; <0.001§
Total progression	117 (27.6%)		17 (5.8%)		<0.001‖

Data from subjects whose AF status was assessed at both baseline and 12 months.
p Values from Fisher's exact tests for comparison of percentage of patients between rate-control and rhythm-control groups.
* For comparison of percentages of patients with paroxysmal AF at baseline.
† For comparison of percentages of patients with permanent AF at 12 months, disregarding their AF status at baseline.
‡ For comparison of percentage of AF progression among patients with paroxysmal AF at baseline.
§ For comparison of percentage of AF progression among patients with persistent AF at baseline.
‖ For comparison of percentage of AF progression, disregarding patient AF status at baseline.

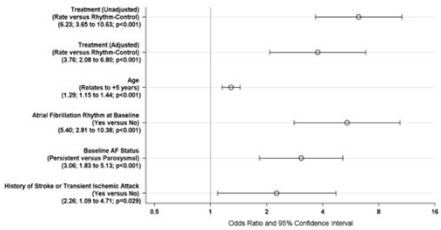


Figure 1. Forest plot (plotted on a binary logarithmic scale) of ORs and corresponding 95% CIs of baseline AF treatment strategy and other baseline characteristics predictive of AF progression at 12 months.

Minneapolis Heart Institute Foundation | GRAND ROUNDS

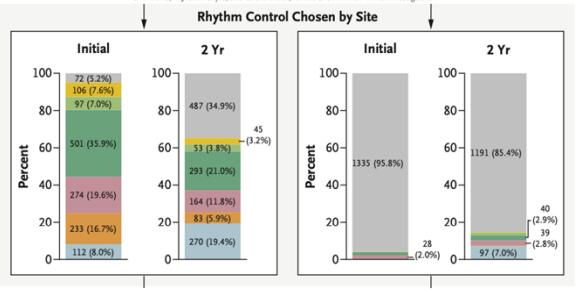
Zhang Y.Y., et al. "Predictors of progression of recently diagnosed atrial fibrillation in REgistry on Cardiac Rhythm DisORDers Assessing the Control of Atrial Fibrillation (RecordAF)-United States cohort". Am J Cardiol . 2013;112:79-84.

16

Early Rhythm Control

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

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



- 2789 patients with AF diagnosed ≤12 months before enrollment
- 30% asymptomatic

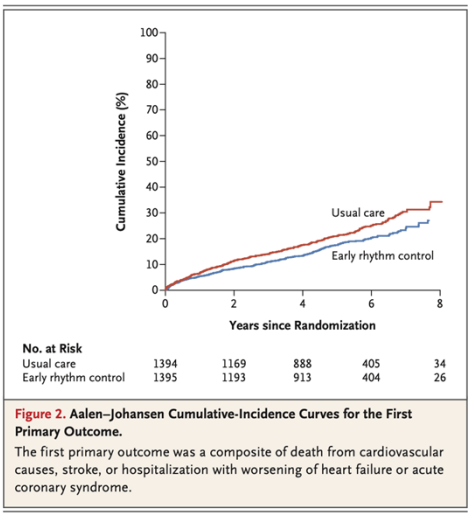


Figure 2. Aalen–Johansen Cumulative-Incidence Curves for the First Primary Outcome.

The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.

- Included atrial fibrillation ablation
- Continued to receive anticoagulation

Kirchhof P et al. N Engl J Med2020;383:1305-1316

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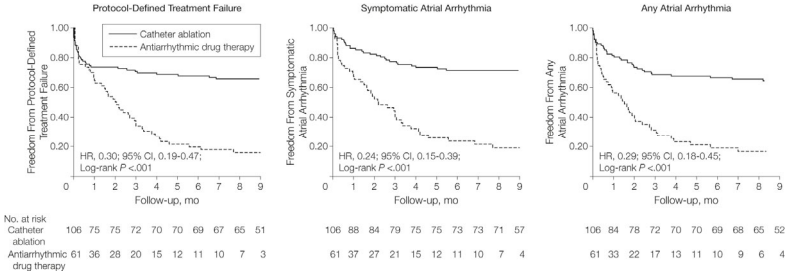
Class 1 Recommendations AF Ablation

- Consistent with 2014 AF guidelines

Recommendations for AF Catheter Ablation
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

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]

- Antiarrhythmic Drug Therapy vs Radiofrequency Catheter Ablation
  - Multicenter and randomized (2:1)
  - Paroxysmal AF, failed one AAD
  - Catheter ablation (n = 106) or ADT (n = 61)
  - 70% of patients treated by catheter ablation remained free of symptomatic recurrent atrial arrhythmia vs 19% treated with ADT



José A. Joglar. Circulation. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. DOI: (10.1161/CIR.0000000000001193)

Wilber DJ, Pappone C, Neuzil P, et al. Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation: A Randomized Controlled Trial. *JAMA*.2010;303(4):333–340. doi:10.1001/jama.2009.2029

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18

2023 Updated Class 1 Recommendations AF Ablation

- Consistent with 2014 AF guidelines
- **New:** Catheter ablation of AF receives Class 1 indication as first-line therapy in selected patients

Recommendations for AF Catheter Ablation
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

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]

Minneapolis Heart Institute Foundation | GRAND ROUNDS

José A. Joglar. Circulation. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. DOI: (10.1161/CIR.0000000000001193)

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First Line: Ablation vs AAT

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Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation

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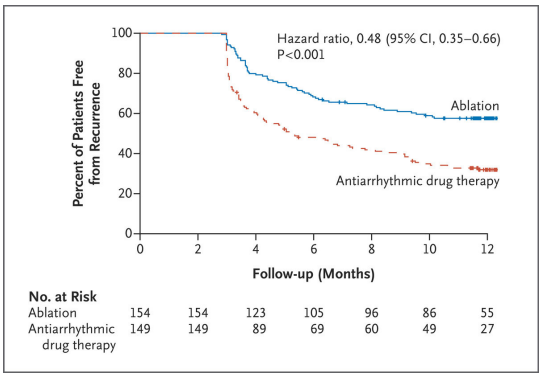

- Symptomatic, paroxysmal, untreated AF
- 154 patients underwent ablation vs 101 antiarrhythmic drugs
- All the patients received implantable cardiac monitoring device
- Followed for 12 months

Reveal LINQ, Medtronic™

- Atrial tachyarrhythmia at 1 year
  - 43% in ablation group vs 68% on antiarrhythmic drugs
  - Symptomatic atrial tachyarrhythmia recurred in 11% who underwent ablation vs 26% on AAT

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JG Andrade et al. N Engl J Med 2021;384:305-315.

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Delaying AF Progression: ATTEST

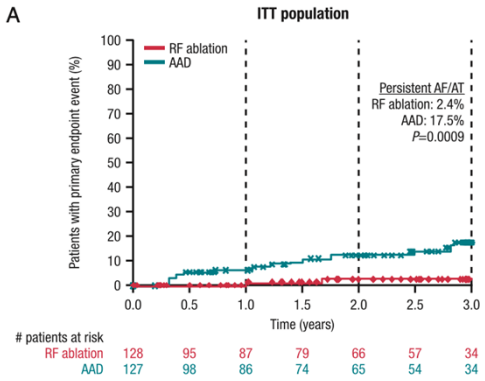
ESC European Society of Cardiology Europace (2021) 23, 362–369s doi:10.1093/europace/euaa298

CLINICAL RESEARCH
Ablation for atrial fibrillation

Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST)

Karl-Heinz Kuck[1*], Dmitry S. Lebedev[2], Evgeny N. Mikhaylov[2], Alexander Romanov[3], László Gellér[4], Oskars Kalējs[5], Thomas Neumann[6], Karapet Davtyan[7], Young Keun On[8], Sergey Popov[9], Maria Grazia Bongiorni[10], Michael Schlüter[11], Stephan Willems[12], and Feifan Ouyang[1*]

- Randomized 1 : 1 to RF ablation or AAD treatment in drug refractory symptomatic paroxysmal AF
  - RF: N=128
  - AAD: N=127
- Primary end-point was the rate of persistent AF/AT at 3 years
- Patients treated with RF ablation were almost 10 times less likely to develop persistent AF/AT vs AAD



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Karl-Heinz Kuck, et al. Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST), *EP Europace*, Volume 23, Issue 3, March 2021, Pages 362–369a, https://doi.org/10.1093/europace/euaa298

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2023 Class 1 Recommendations AF Ablation

- Consistent with prior guidelines →
- **New:** Catheter ablation of AF receives Class 1 indication as first-line therapy in selected patients →
- Early and aggressive approach in heart failure →

Recommendations for AF Catheter Ablation
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

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]

Recommendations for Management of AF in Patients With HF*
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

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.[9–13]

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José A. Joglar. Circulation. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. DOI: (10.1161/CIR.0000000000001193)

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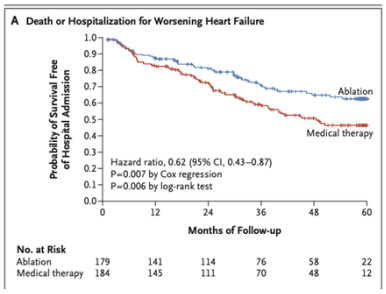
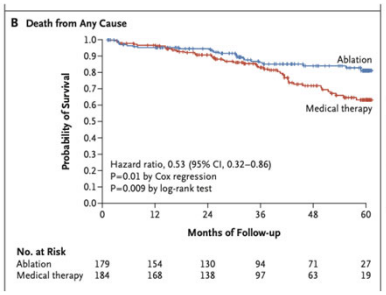
AF and CHF: CASTLE-AF

- 179 patients catheter ablation vs 184 rate or rhythm control
- LVEF 35% or less and ICD
- A rhythm-control strategy was used in approximately 30% of the patients in the medical-therapy group
- Median follow-up of 38 months





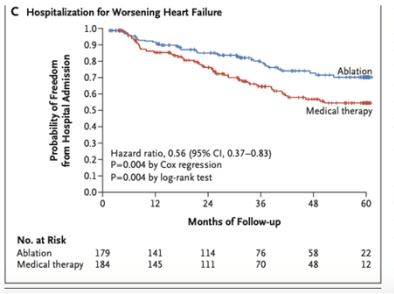


Table S9. AF Burden Derived from the Memory of Implanted Devices*

	AF Burden per Patient (in % of Time) at Different Follow-Ups							
	Baseline	3 M	6 M	12 M	24 M	36 M	48 M	60 M
Mean ± SD								
Ablation	51 ± 47	27 ± 39	23 ± 37	20 ± 38	23 ± 39	25 ± 40	27 ± 41	27 ± 42
Pharmacological	51 ± 46	51 ± 47	51 ± 46	52 ± 46	48 ± 47	50 ± 47	54 ± 47	64 ± 45

Marrouche NF et al. N Engl J Med2018;378:417-427

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Rate vs Rhythm

- Patient and Clinical Considerations
  - ➢ Patient preference
  - ➢ Younger
  - ➢ Short duration
  - ➢ Symptoms
  - ➢ LV dysfunction
  - ➢ LA size

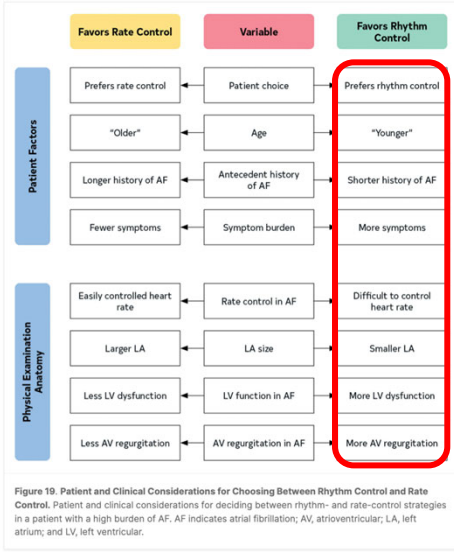
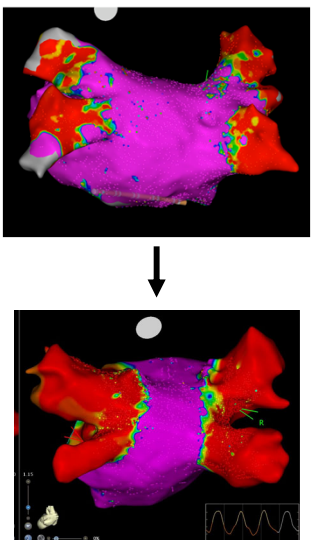


Figure 19. Patient and Clinical Considerations for Choosing Between Rhythm Control and Rate Control. Patient and clinical considerations for deciding between rhythm- and rate-control strategies in a patient with a high burden of AF. AF indicates atrial fibrillation; AV, atrioventricular; LA, left atrium; and LV, left ventricular.



José A. Joglar. Circulation. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. DOI: (10.1161/CIR.0000000000001193)

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AF Triggers

- 45 patients with frequent AF
- Earliest activation was found to have occurred 2-4 cm inside the PVs in 94% of patients

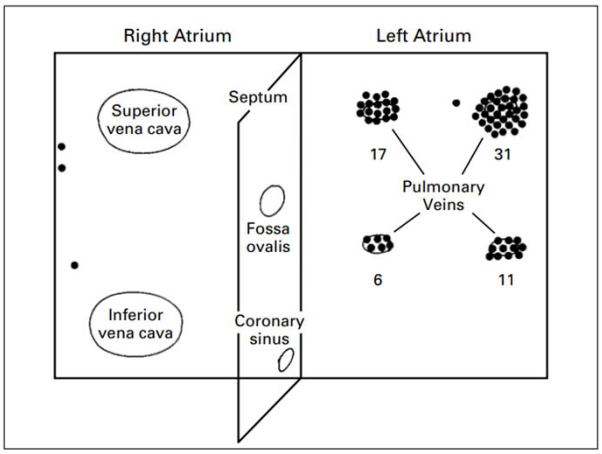

Figure 1. Diagram of the Sites of 69 Foci Triggering Atrial Fibrillation in 45 Patients.
Note the clustering in the pulmonary veins, particularly in both superior pulmonary veins. Numbers indicate the distribution of foci in the pulmonary veins.

Haïssaguerre, M et al. "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins." *The New England journal of medicine* vol. 339,10 (1998)

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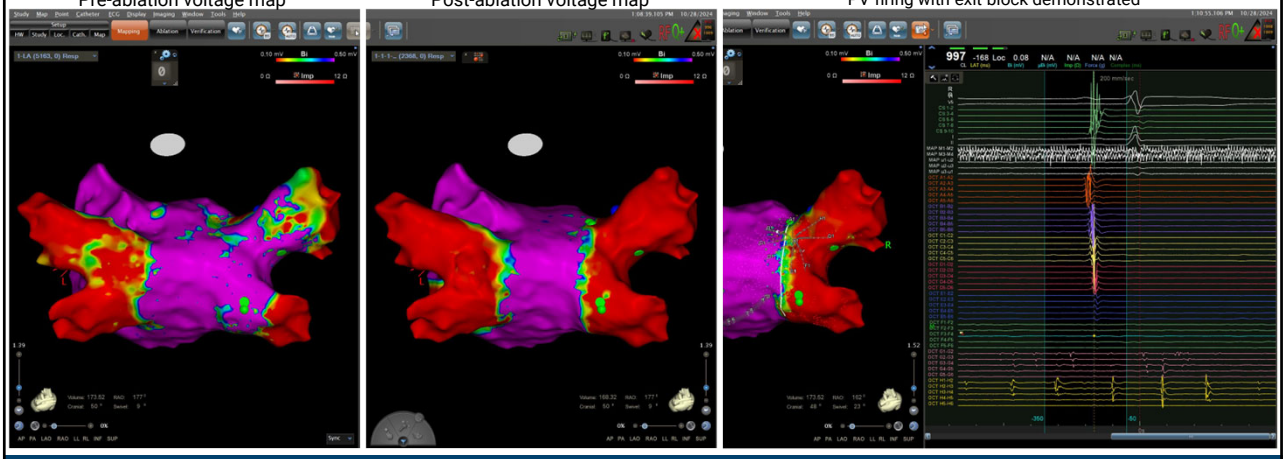
Pulmonary Vein Triggers

57 year old man with PMHx of paroxysmal AF s/p ablation (PVI and CTI) in 2020 undergoing repeat AF ablation

Pre-ablation voltage map | Post-ablation voltage map | PV firing with exit block demonstrated



Images courtesy of Dr. Zakaib

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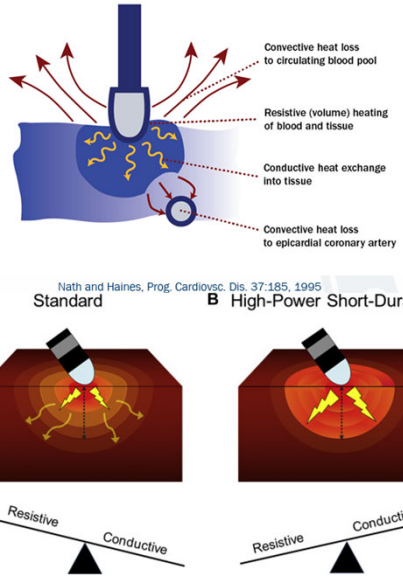
RF Ablation

2 consecutive phases of thermal heating

- 1. Resistive
  - Electrical current at the catheter-tissue interface leads to immediate heating of the superficial tissue layer
- 2. Conductive
  - Heat source that then extends passively to deeper tissue layers
  - Time dependent and the result of the current applied and heat produced in the resistive phase
  - Tissue permanently inactive at 50℃



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Leshem E, et al. High-power and short-duration ablation for pulmonary vein isolation: biophysical characterization. J Am Coll Cardiol EP 2018;4: 467–79.

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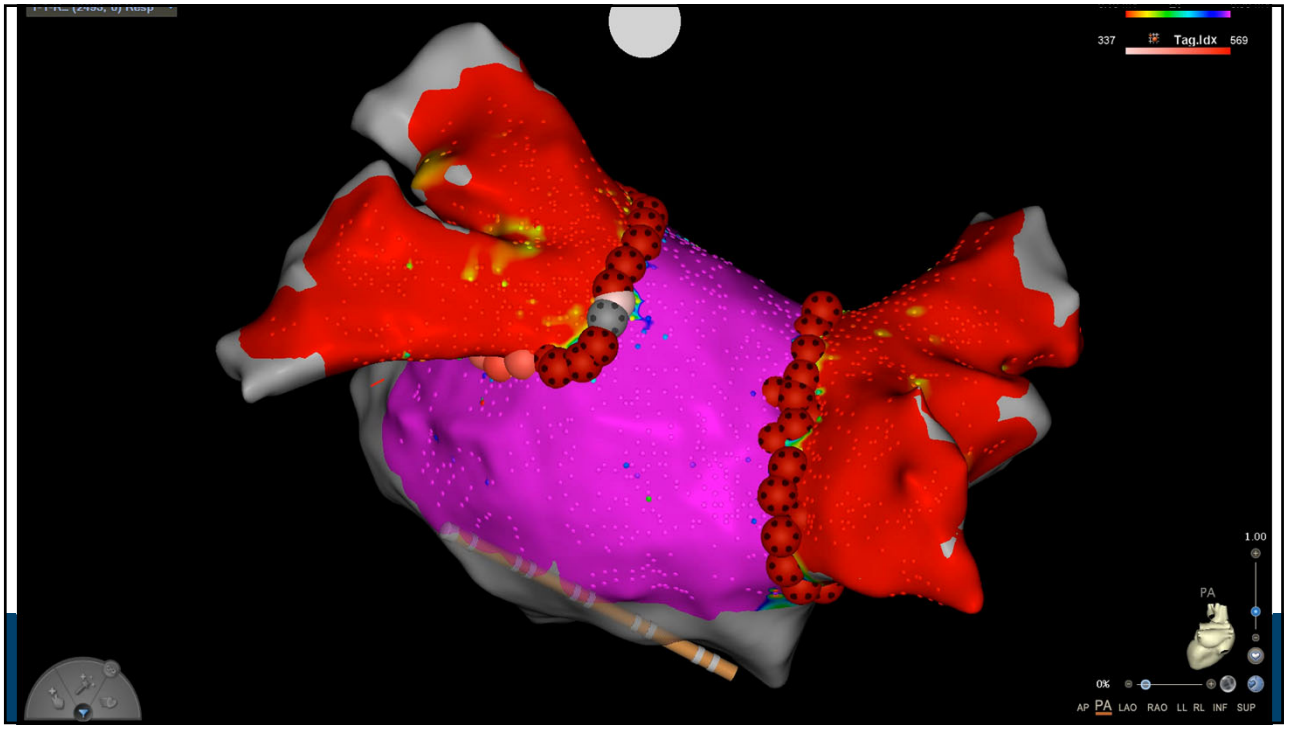

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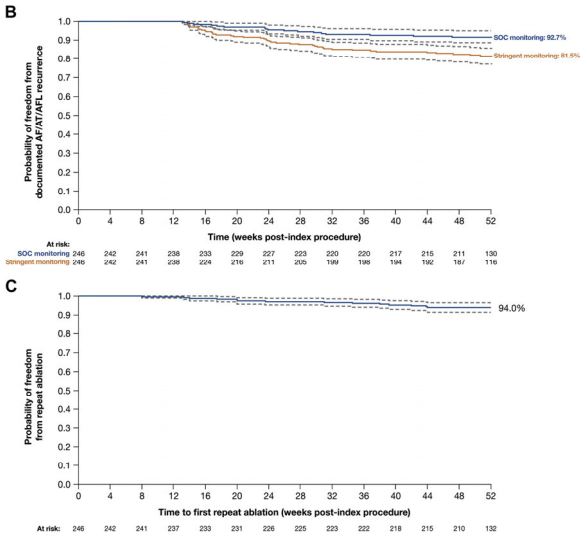
Evolution of RF

- 246 patients
- Drug-refractory symptomatic paroxysmal AF

THERMOCOOL SMARTTOUCH® SF Catheter
© Johnson & Johnson

- Ablation index
  - Incorporates contact force, power, and time as an objective surrogate marker of ablation lesion quality
- At 12 months, freedom from documented AF/AFL/AT
  - 82% per stringent monitoring
  - 93% per standard-of-care monitoring (no TTM)



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Di Biase L, Monir G, **Melby D**, Tabereaux P, Natale A, Manyam H, Athill C, Delaughter C, Patel A, Gentlesk P, Liu C, Arkles J, McElderry HT Jr, Osorio J; SURPOINT Postapproval Trial Investigators. Composite Index Tagging for PVI in Paroxysmal AF: A Prospective, Multicenter Postapproval Study. JACC Clin Electrophysiol. 2022 Sep;8(9):1077-1089

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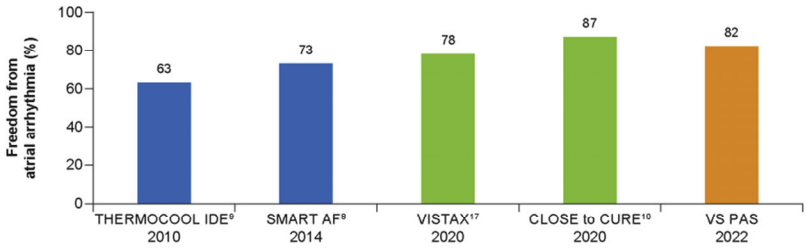
Evolution of RF

Ablation Technology		Non-CF RF	CF, Non-VS	CF, VS		
Arrhythmia monitoring methods	12-Lead ECG	Yes	Yes	Yes	Yes	Yes
	Holter monitor	24 hours at baseline and 12 months	None	24 hours	None	24 hours at 12 months
	Other stringent monitoring	Scheduled and symptom-driven TTM	Symptomatic, weekly (for first 8 weeks), and monthly thereafter TTM	Weekly and symptom-driven TTM	ICM data review performed at enrollment, symptomatic, and each follow-up visit	Symptomatic, weekly (months 2–5), and monthly (months 6–12) TTM
Follow-up visit		1, 3, 6, 9, 12 months	1, 3, 6, 9, 12 months	3, 6, 12 months	1, 3, 6, 12, 18, 24 months	1, 3, 6, 12 months



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Di Biase L, Monir G, **Melby D**, Tabereaux P, Natale A, Manyam H, Athill C, Delaughter C, Patel A, Gentlesk P, Liu C, Arkles J, McElderry HT Jr, Osorio J; SURPOINT Postapproval Trial Investigators. Composite Index Tagging for PVI in Paroxysmal AF: A Prospective, Multicenter Postapproval Study. JACC Clin Electrophysiol. 2022 Sep;8(9):1077-1089

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Pulsed Field Ablation: The Next Frontier

StarTribune

Creator: Leila Navidi | Credit: Star Tribune

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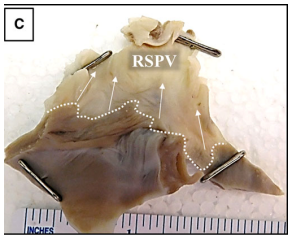
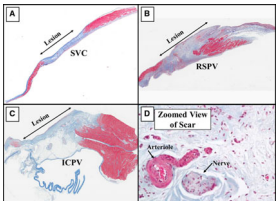
Pulsed Field Ablation

- Cardiac cells are exposed to high electric field gradients
- **Irreversible electroporation:** Cell membranes undergo increased permeability
  - Leading to cell death without substantial protein denaturation or tissue scaffolding damage
  - Some preferentiality to myocardial tissue ablation





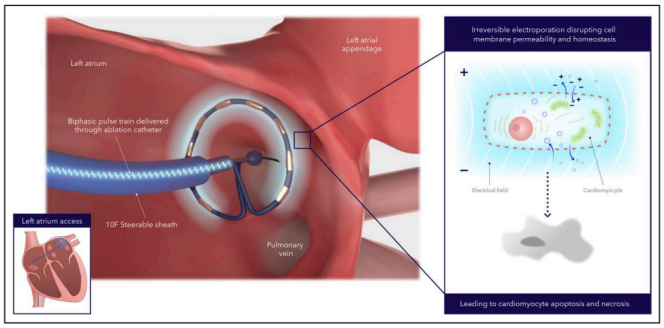


Figure 1. Catheter ablation method with pulsed field ablation system.
Alternating positive and negative electrodes sustains a bipolar electrical field around the catheter that extends into the tissue. The electrical field increases cell membrane permeabilization, which then leads to cell function disruption and eventually to cell death (ie, apoptosis and necrosis).

Zhai Z, Ling Y, Wang Y, Shi L, Liu X. Preclinical evaluation of reversible pulsed electrical field: electrophysiological and histological assessment of myocardium. Front Cardiovasc Med. 2024 Aug 1;11:1426920.

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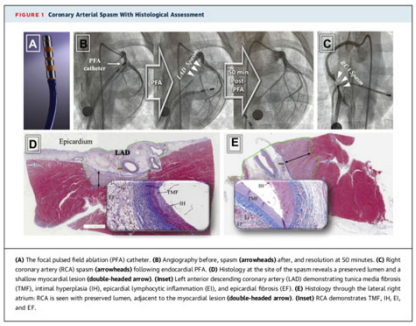
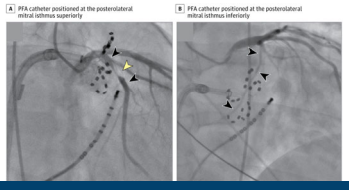
Coronary Artery Spasm During Pulsed Field Ablation

- Histopathological assessment of the LAD and RCA in a porcine model
  - The PF lesion penetrated through the epicardial fat pad surrounding the LAD to reach a depth of 5.2 mm into the myocardium
  - Histology: minimal intimal hyperplasia and mild tunica medial fibrosis (25% of circumference)
- Evidence that PFA can cause subtotal coronary arterial spasm during CTI ablation
- During mitral isthmus ablation, LCx vasospasm can during PFA at the posterolateral mitral isthmus
- Mechanism of spasm remains unknown
  - Possible activation of smooth muscle cells from the excitatory nature of PF
  - Can be potentially be attenuated by prophylactic administration of nitroglycerin





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Zhang C, et al. Coronary Artery Spasm During PF vs RF Catheter Ablation of the Mitral Isthmus. JAMA Cardiol. 2024 Jan 1;9(1):72-77.

Koruth, J, Kawamura, I, Buck, E. et al. Coronary Arterial Spasm and Pulsed Field Ablation: Preclinical Insights. *J Am Coll Cardiol EP.* 2022 Dec, 8 (12) 1579–1580.

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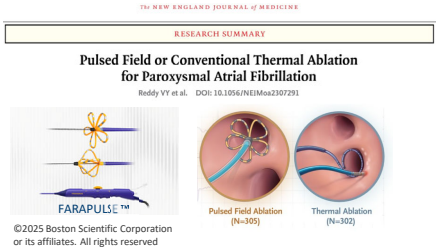
Conventional Thermal Ablation vs PFA



- RF ablation or cryoballoon ablation vs PFA
- Freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, AAT use, cardioversion, or repeat ablation
- At 1 year, the primary efficacy end point was met (i.e., no events occurred)
  - PFA: 204 patients (est probability 73%)
  - RFA/Cryo: 194 patients (est probability 71%)

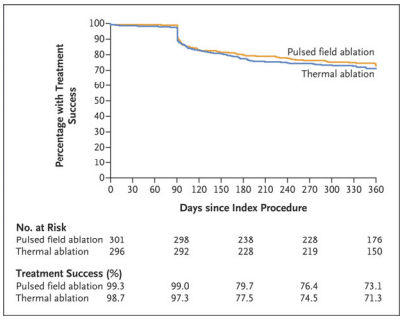


Table 3. Serious and Nonserious Adverse Events.*

Event	Serious Adverse Events†		Serious or Nonserious Adverse Events‡	
	Pulsed Field Ablation (N=305)	Thermal Ablation (N=302)	Pulsed Field Ablation (N=305)	Thermal Ablation (N=302)
	number of patients (percent)			
Any event	6 (2.0)§	4 (1.3)	7 (2.3)§	6 (2.0)
Death	1 (0.3)	0	1 (0.3)	0
Myocardial infarction	0	0	0	0
Persistent phrenic-nerve palsy	0	0	0	2 (0.7)
Stroke	0	1 (0.3)	0	1 (0.3)
TIA	1 (0.3)	0	1 (0.3)	0
Systemic thromboembolism	0	0	0	0
Cardiac tamponade or perforation	2 (0.7)	0	2 (0.7)	0
Pericarditis	1 (0.3)	0	2 (0.7)	0
Pulmonary edema	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Vascular-access complication	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)
Heart block	0	0	0	0
Gastric motility or pyloric spasm	0	0	0	0
Pulmonary vein stenosis	0	0	0	0
Atrioesophageal fistula	0	0	0	0

* All data are derived from the modified intention-to-treat population. Details regarding these adverse events are provided in Table S15.
† The primary safety end point was a composite of prespecified device- and procedure-related serious adverse events within 7 days after the procedure. Atrioesophageal fistula and pulmonary vein stenosis were included as serious adverse events regardless of the timing of occurrence.
‡ These events include all device- or procedure-related adverse events that were prespecified in the primary safety end point but without regard to the seriousness categorization of the event.
§ One patient who had a cardiac tamponade subsequently died; accordingly, the individual components add to more than the total number of patients with any event.

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Reddy VY, et al.Pulsed Field or Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation. N Engl J Med. 2023 Nov 2;389(18):1660-1671

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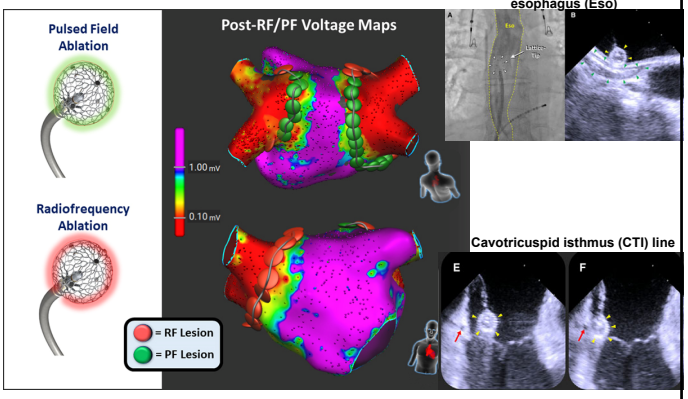
Allina Health Minneapolis Heart Institute first in Minn., Upper Midwest to use new, FDA-approved device to treat persistent atrial fibrillation

Affera™ Mapping and Ablation System



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Reddy VY, Anter E, et al. Lattice-Tip Focal Ablation Catheter That Toggles Between Radiofrequency and Pulsed Field Energy to Treat Atrial Fibrillation: A First-in-Human Trial. Circ Arrhythm Electrophysiol. 2020 Jun;13(6):e008718

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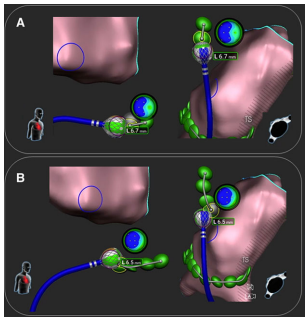
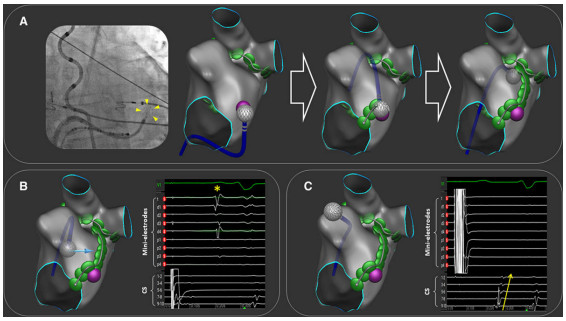
First-in-human RFA + PFA Experience

- 3-center, single-arm trial
- 7.5F lattice catheter used to treat paroxysmal or persistent AF
- Mean PVI therapy duration time (transpiring from first to last lesion) was 22.6±8.3 min/patient

Cavotricuspid isthmus (CTI) line



Mitral isthmus line



Safety Observations

	Study Cohort (n=76 Patients)
Major complications	
Stroke	0
Pericardial tamponade	0
Phrenic nerve paralysis	0
Pulmonary vein stenosis	0
Atrioesophageal fistula	0
Death	0
Vascular—major complications	1/76 (1.3%)
Minor complications	
Transient ischemic attack	0
Vascular—minor complications	4/76 (5.3%)
Pericardial effusion without tamponade	0
Esophageal observations	
Any esophageal abnormality	2/60 (3.3%)
Minor erythema	2/60 (3.3%)
Moderate erosion	0/60 (0%)
Ulceration	0 (0%)
Esophageal abnormality as function of ablation strategy	
RF/PF	2/36 (5.6%)
PF/PF	0/24 (0%)

*Required surgical repair.
†These patients had hematomas that were managed conservatively without intervention.

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Reddy VY, Anter E, et al. Lattice-Tip Focal Ablation Catheter That Toggles Between Radiofrequency and Pulsed Field Energy to Treat Atrial Fibrillation: A First-in-Human Trial. Circ Arrhythm Electrophysiol. 2020 Jun;13(6):e008718

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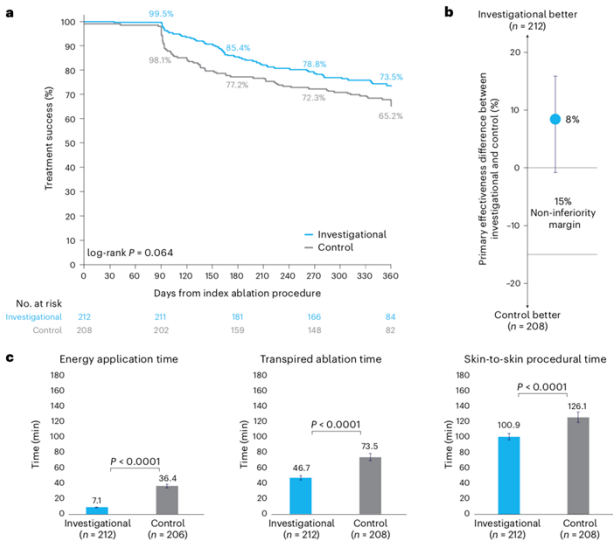
SPHERE Per-AF

- Randomized, single-blind, non-inferiority trial
- Persistent AF
  - N=210 Sphere-9 Mapping/Affera Mapping and Ablation System
  - N=202 THERMOCOOL SMARTTOUCH® SF radiofrequenc ablation catheter
  - LA posterior wall isolation including roof lines performed in 93% and 67% in the investigational and control groups, respectively
- Primary composite effectiveness endpoint was evaluated through 1 year
  - Freedom from acute procedural failure
  - Repeat ablation at any time
  - Arrhythmia recurrence
  - Drug initiation or escalation
  - DCCV after a 3-month blanking period
- Conclusion: RFA/PFA with Sphere-9 non-inferior to the conventional RF in both safety and effectiveness



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Anter, E., Mansour, M., Nair, D.G. et al. Dual-energy lattice-tip ablation system for persistent atrial fibrillation: a randomized trial. Nat Med **30**, 2303–2310 (2024).

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PFA vs RFA Safety

- **Neurological substudy analysis**
  - Brain MRI that examined the presence of silent ischemic lesions after ablation
    - 3 out of 37 patients in the investigational group
    - 2 out of 35 patients in the control group were found to have fluid-attenuated inversion recovery (FLAIR)-hyperintense acute lesions
  - Follow-up MRI scans at 90 days
  - 2/3 in the investigational group
  - 1/2 patients in the control group demonstrated full resolution

Table 3 | Primary safety endpoint summary

Primary safety event	Investigational (n=212)	Control (n=208)
Patients with any primary safety event, n (%)	3 (1.4%)	2 (1.0%)
Within 7 d		
Death	0	0
Myocardial infarction	0	0
Phrenic nerve paralysis	0	0
Transient ischemic attack	0	0
Stroke/cerebrovascular accident	0	0
Thromboembolism	0	0
Major vascular access complications/ bleeding	0	0
Heart block	0	0
Gastroparesis	0	0
Severe pericarditis	0	0
Hospitalization (initial and prolonged) due to cardiovascular or pulmonary adverse event[a]	3	2
Within 30 d		
Cardiac tamponade/perforation	0	0
Within 90 d		
Atrio-esophageal fistula	0	0
Within 180 d		
PV stenosis	0	0
Myocardial infarction	0	0
Summarized results		
90% CI of event rate	(0.4%, 3.6%)	(0.2%, 3.0%)
Difference (90% CI) Farrington–Manning one-sided non-inferiority test P value[b]	0.4% (−2.8%, 3.7%) P<0.0001	

[a] Excludes hospitalization due to atrial arrhythmia recurrence. [b] Based on a pre-defined non-inferiority margin of 8%.

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Anter, E., Mansour, M., Nair, D.G. et al. Dual-energy lattice-tip ablation system for persistent atrial fibrillation: a randomized trial. Nat Med **30**, 2303–2310 (2024).

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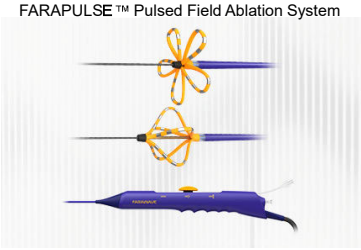
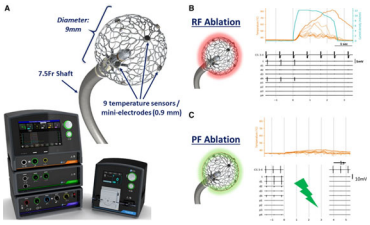
An Evolving Landscape

FARAPULSE™ Pulsed Field Ablation System



Affera™ Mapping and Ablation System



The VARIPULSE™ Platform

Dual Energy
THERMOCOOL
SMARTTOUCH™ SF
Catheter

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Summary

- Global prevalence of AF has increased substantially
- AF is a progressive condition marked by structural and electrical changes (atrial myopathy)
- Incident AF and its clinical consequences are related in part risk factors that can be modified by lifestyle changes
- Rhythm control > rate control
  - Patient preference
  - Younger
  - Short duration
  - Symptoms
  - LV dysfunction
- Catheter ablation is now first line management specific subgroups
  - Paroxysmal AF in younger/few comorbidities
  - Cardiomyopathy
- PFA represents a promising modality on its own (”single shot”) and as adjunctive treatment to RFA

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Thank You

Questions

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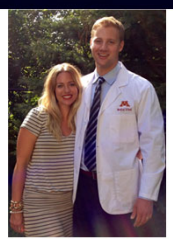

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Supplemental Slides

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Alcohol and AF

The NEW ENGLAND JOURNAL of MEDICINE

Alcohol Abstinence for Atrial Fibrillation

OPEN-LABEL, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL

	Abstinence (no alcohol for 6 mo)	Control
140 Adults with atrial fibrillation and regular alcohol consumption ≥10 standard drinks per week	(N=70)	(N=70)
Atrial fibrillation recurrence	53%	73%
	HR, 0.55; 95% CI, 0.36–0.84; P=0.005	
Median percentage of time in atrial fibrillation during 6 mo follow-up	0.5%	1.2%

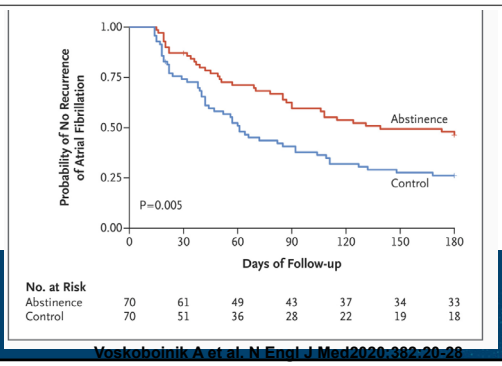
A. Voskoboinik et al. 10.1056/NEJMoa1817591

Atrial fibrillation–related hospital admissions occurred in 6 patients (9%) in the abstinence group and in 14 patients (20%) in the control group

Table 2. Alcohol Intake at Baseline.

Variable	Abstinence Group (N=70)	Control Group (N=70)
Alcohol intake — no. of standard drinks/wk	16.8±7.7	16.4±6.9
Beverages consumed — no. (%)		
Wine	48 (69)	47 (67)
Beer	34 (49)	34 (49)
Spirits	13 (19)	9 (13)
Binge drinking — no. (%)*	20 (29)	16 (23)

* Binge drinking was defined as consumption of 5 or more drinks on a single occasion at least once a month.



Voskoboinik A et al. N Engl J Med 2020;382:20-28

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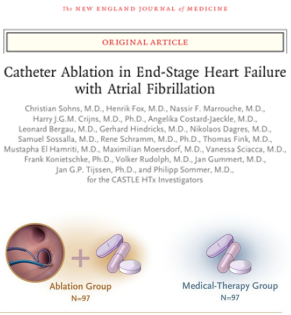
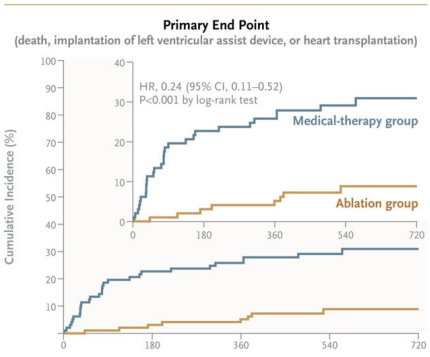
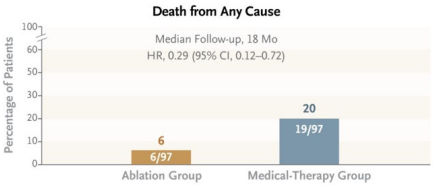
CASTLE-HTx



- Symptomatic AF and end-stage HF referred for transplantation evaluation
- Mean LVEF less than 30%
- Assigned to receive catheter ablation + GDMT vs medical therapy alone
- Median follow-up of 18.0 months





Sohns C et al. N Engl J Med2023;389:1380-1389

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AF Ablation and Quality of Life

Figure 3. Mayo Atrial Fibrillation–Specific Symptom Inventory (MAFSI) Frequency Scores

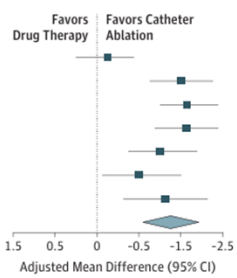
Mayo AF Symptom Inventory (MAFSI) Worksheet

Think back over the past month. Please tell us how often you have had each symptom listed below:

	How Often? (mark one)				
	Never	Rarely	Sometimes	Often	Always
Palpitations heart fluttering/racing	☐	☐	☐	☐	☐
Slow heart beat	☐	☐	☐	☐	☐
Lightheadedness/dizziness	☐	☐	☐	☐	☐
Fainting/blackout/loss of consciousness	☐	☐	☐	☐	☐
Chest pain, pressure or fullness WITHOUT palpitations	☐	☐	☐	☐	☐
Shortness of breath	☐	☐	☐	☐	☐
Unable to exercise	☐	☐	☐	☐	☐
Tired/lack of energy	☐	☐	☐	☐	☐
Weakness	☐	☐	☐	☐	☐
Feeling warm/flushed	☐	☐	☐	☐	☐

B Between-group 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)



- CABANA Randomized trial of 2204 patients with symptomatic AF
- Catheter ablation (vs med therapy) significantly improved quality of life at 1 year

Mark DB, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019.

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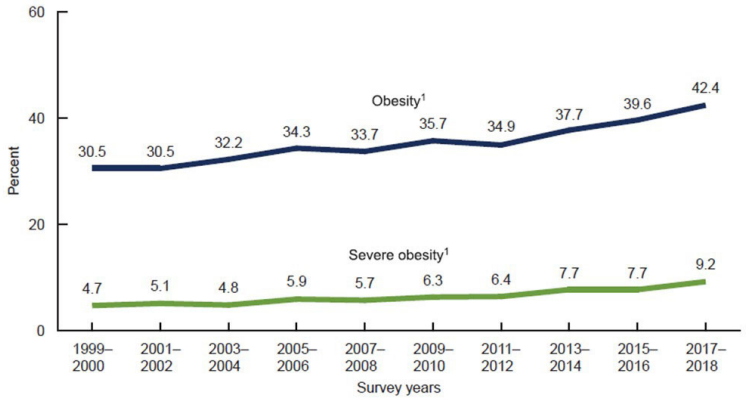
Obesity in the US



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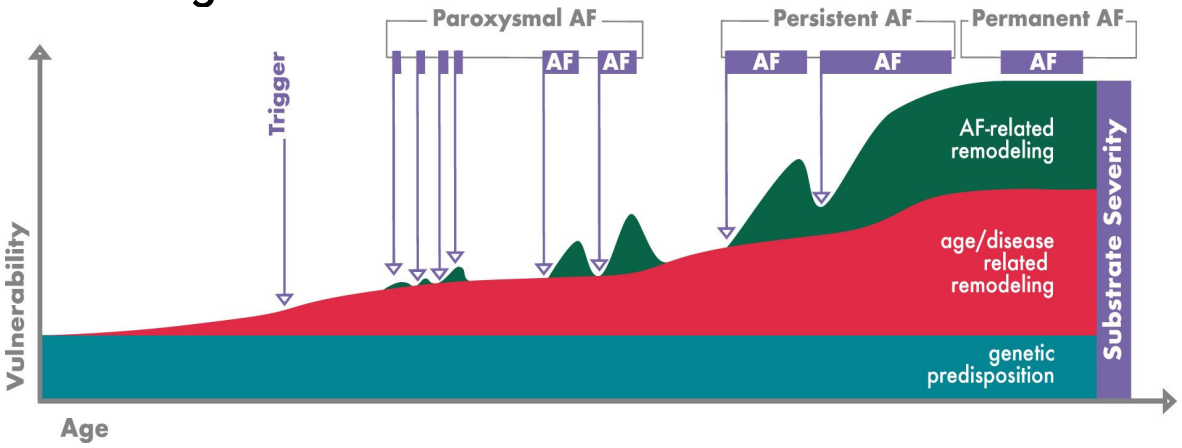
AF Progression



- Structural and electrical remodeling promote AF
  - Interstitial changes, increased myofibroblast activity, collagen deposition, fibrofatty deposits, altered ion channel expression, calcium signaling and contractility, and inflammatory infiltrates

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Melanie A Gunawardene, et al. Atrial fibrillation progression and the importance of early treatment for improving clinical outcomes, *EP Europace* 2022.

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Before → After

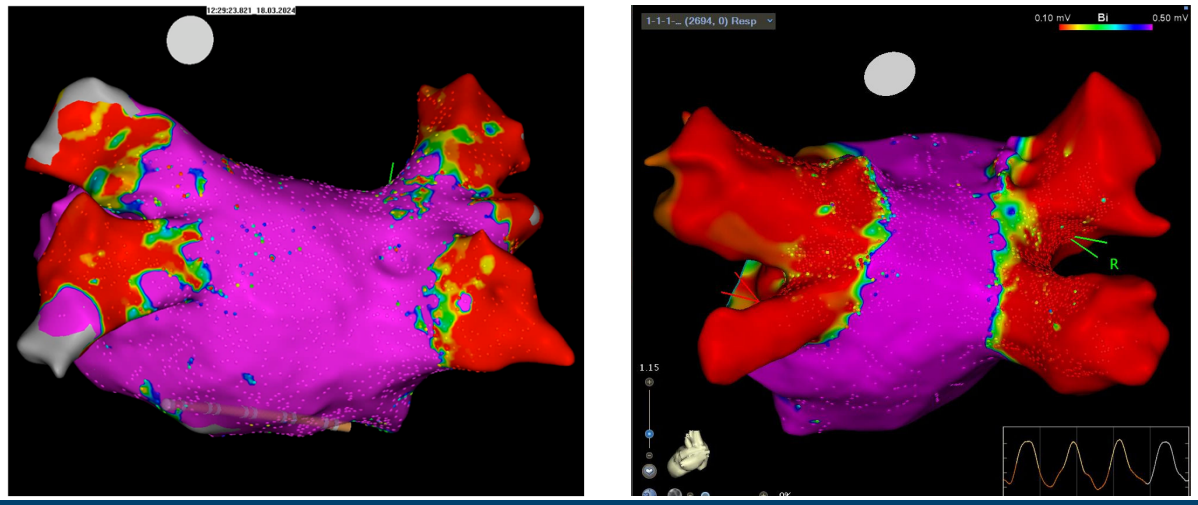

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Table 3. Safety Outcomes.*

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

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