Yakima Medical Conference 2022

Contemporary Management of Atrial Fibrillation

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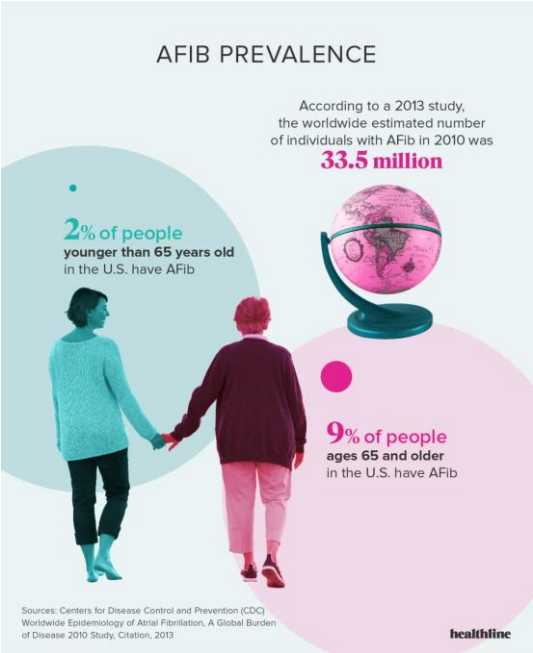
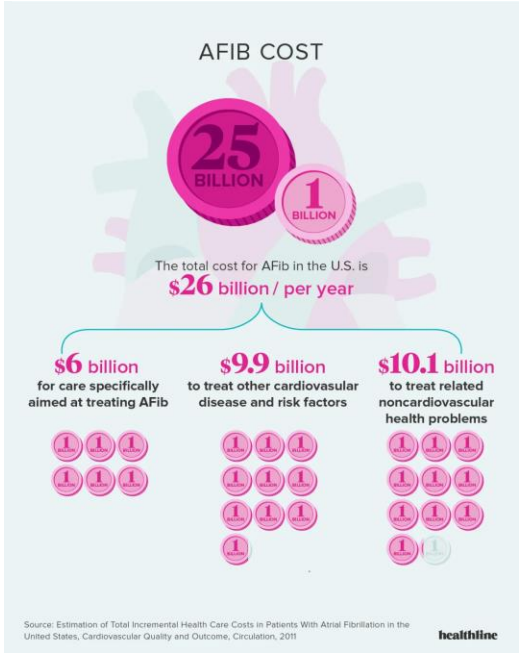
Disclosures

- Medtronic- consultant, advisory board & steering committee member
- Abbott- consultant, advisory board

Sobering facts about AF





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Sobering facts about AF

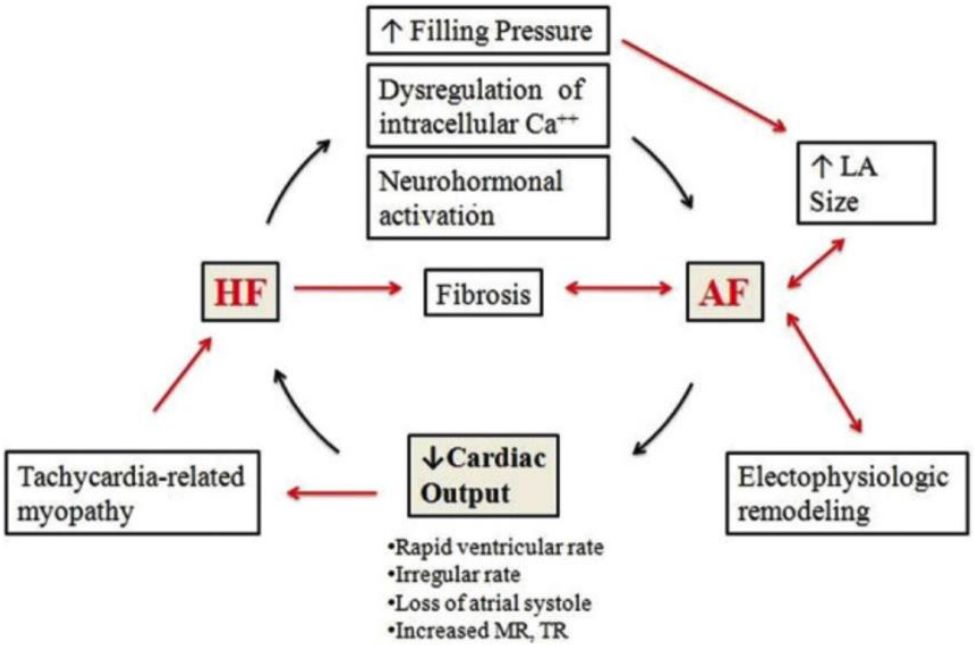
- Often associated with structural heart disease & other co-occurring chronic conditions
- 5-fold increased risk of stroke that increases with age
- AF-related stroke more severe than non-AF related stroke
- 3-fold risk of HF & 2-fold increased risk of both dementia and mortality
- Hospitalizations with AF as the primary diagnosis: >467,000 annually in the US
- Contributes to >99,000 deaths per year
- Hospitalized twice as often as patients without AF
  - 3x likely to have multiple admissions
  - 2.1% with AF die in the hospital compared to 0.1% without it

Similarities with HF

- Increasing prevalence with age
- Complex disease processes associated with similar risk factors
  - Age, HTN, DM, CAD, valvular heart disease
- Lifetime illnesses requiring multiple treatment modalities
- Often coexist & have worse prognosis
  - Framingham Heart Study
  - 37% new onset AF pts had HF
  - 57% with new onset HF had AF

Santhanakrishnan R et al., Circulation 2016

Similarities with HF

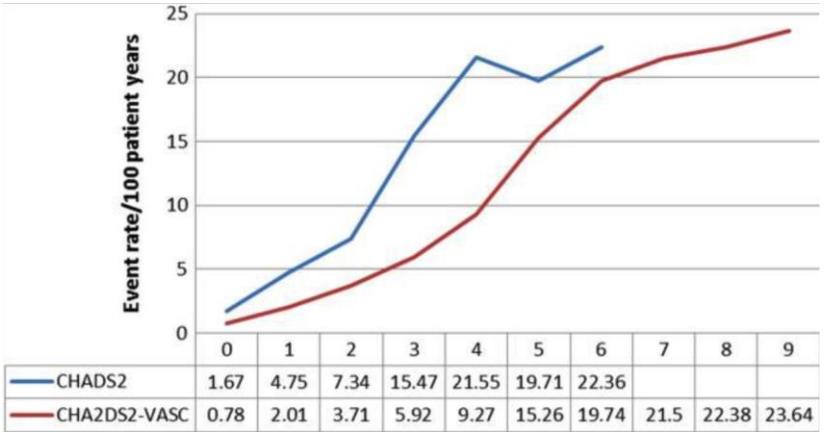


Pulignano et al., Heart Int. 2016

Treatment Strategies

- **Anticoagulation**
  - OAC
  - Left atrial appendage occlusion
- **Rate control strategies**
  - Pharmacotherapy
  - AV junction ablation
- **Rhythm control strategies**
  - Antiarrhythmics vs. Ablation
- **Modifiable risk factors**

Thromboembolic Risk Assessment



	0	1	2	3	4	5	6	7	8	9
CHADS2	1.67	4.75	7.34	15.47	21.55	19.71	22.36			
CHA2DS2-VASC	0.78	2.01	3.71	5.92	9.27	15.26	19.74	21.5	22.38	23.64

- **Oral anticoagulation superior to antiplatelet therapy**
  - As age increases, efficacy of antiplatelet therapy decreases
  - Efficacy with OAC remains unchanged
  - Smaller benefit with Clopidogrel + ASA but not similar to OAC

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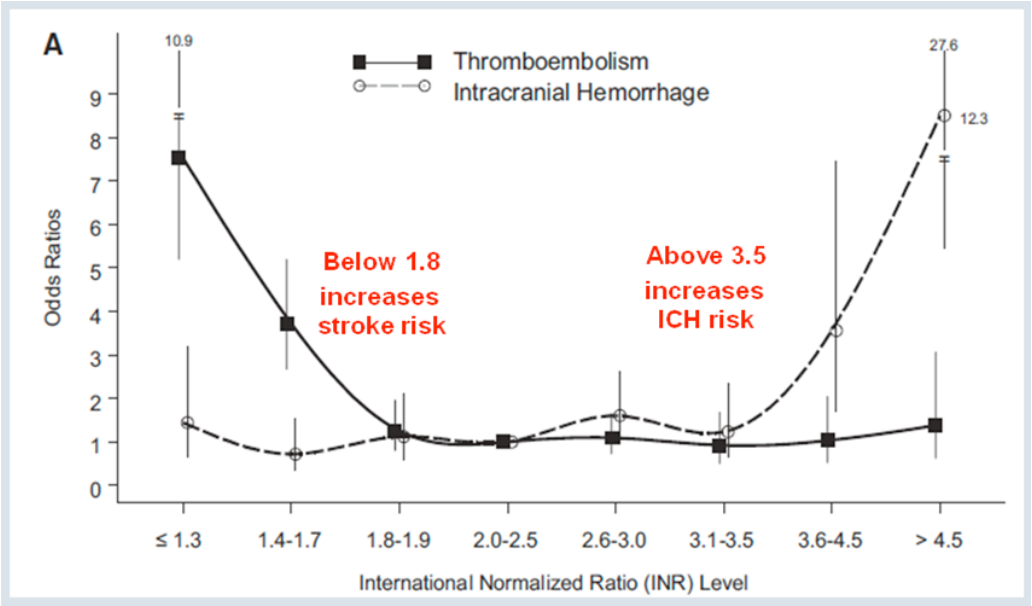
Warfarin: A Narrow Therapeutic Index



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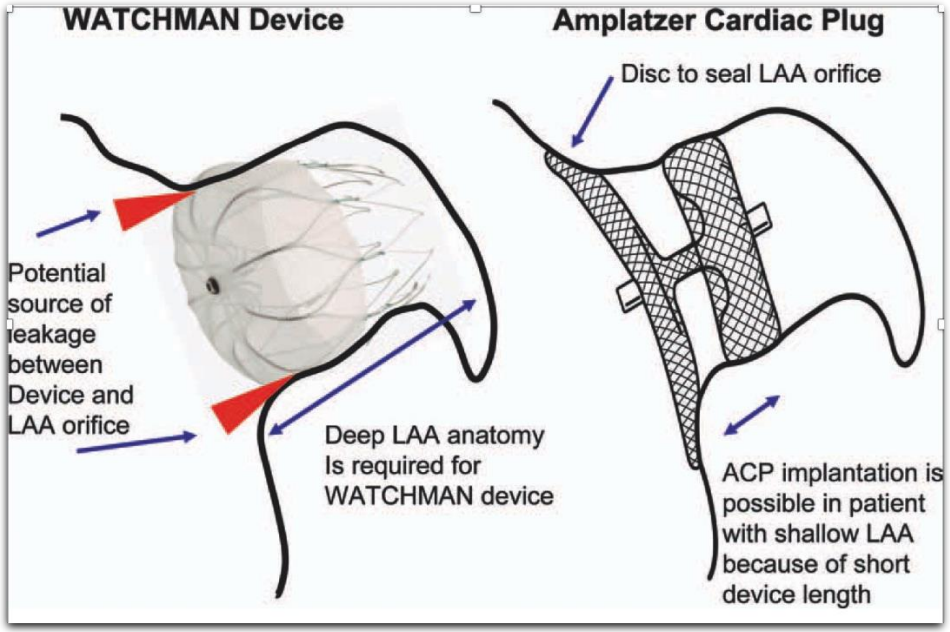
DOAC Therapy in the Elderly

Comparison of novel oral anticoagulants in patients ≥75 years

Novel agent	Trial	Intervention versus warfarin unless specified	Number of participants ≥75 years	Hazard Ratio for Stroke Risk	Hazard Ratio for major Hemorrhage
Dabigatran	RE-LY [10]	Dabigatran 110 mg bid	7,258	0.88 (0.66–1.17)	1.01 (0.83–1.23)
		Dabigatran 150 mg bid		0.67 (0.49–0.90)	1.18 (0.98–1.42)
Rivaroxaban	ROCKET-AF [11]	Rivaroxaban 20 mg bid (15 mg od if eCrCl 30–49 ml/min)	6,229	0.88 (0.75–1.03)[a]	1.04 (0.90–1.20)[a]
Apixaban	ARISTOTLE [12]	Apixaban 5 mg bid	5,678	0.79 (0.65–0.95)[b]	0.69 (0.60–0.80)[b]
	AVERROES [47]	Apixaban 5 mg bid (2.5 mg bid if 2 out of 3 of the following criteria; serum creatinine ≥133 ml/min, age ≥80 years or weight ≤60 kg) vs. Aspirin	1,897	0.46 (0.33–0.65)[b]	1.13 (0.74–1.75)[b]

Left Atrial Appendage Occlusion (LAAO)

- Several in the market
  - Percutaneous vs. Epicardial approaches (catheter based vs. minimally invasive)
- Rapidly growing in market share but limitations will be cost



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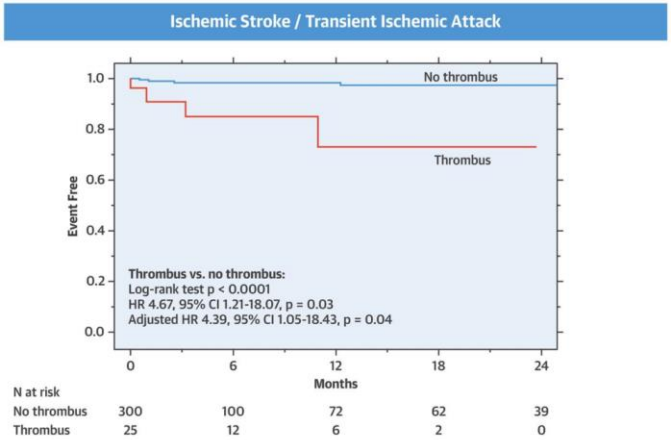
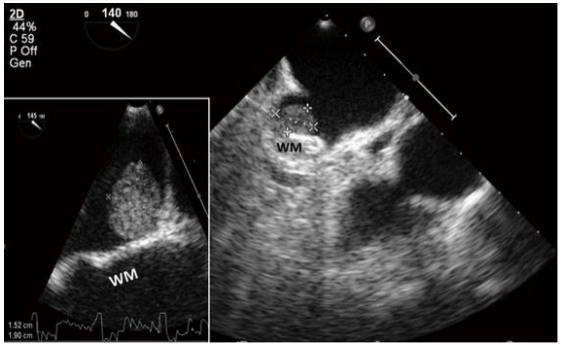
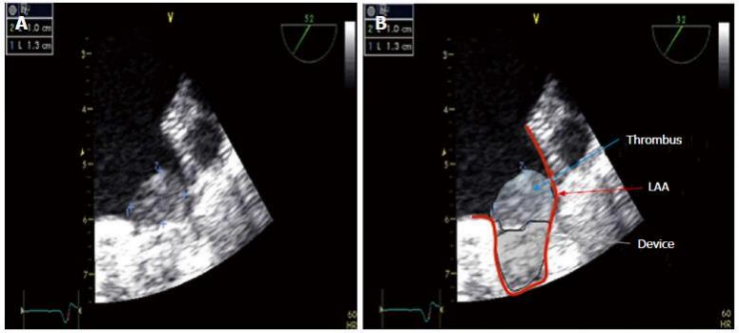
Device Related Thrombus (7.2% per year)



Fauchier, L. et al. J Am Coll Cardiol. 2018;71(14):1528-36.





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Rate Control Strategies

- Predominant initial strategy
- AFFIRM[1] (age >65, HF 23%, normal EF in 74%, resting HR <80; <110 bpm with 6-minute walk test)
  - No survival advantage between rate & rhythm control
  - Ischemic stroke rates similar in both groups
  - Adverse events similar in HF pts
- RACE II[2] (age <80, LVEF <40%-15%, target HR <110 bpm at rest)
  - No difference in cardiovascular events

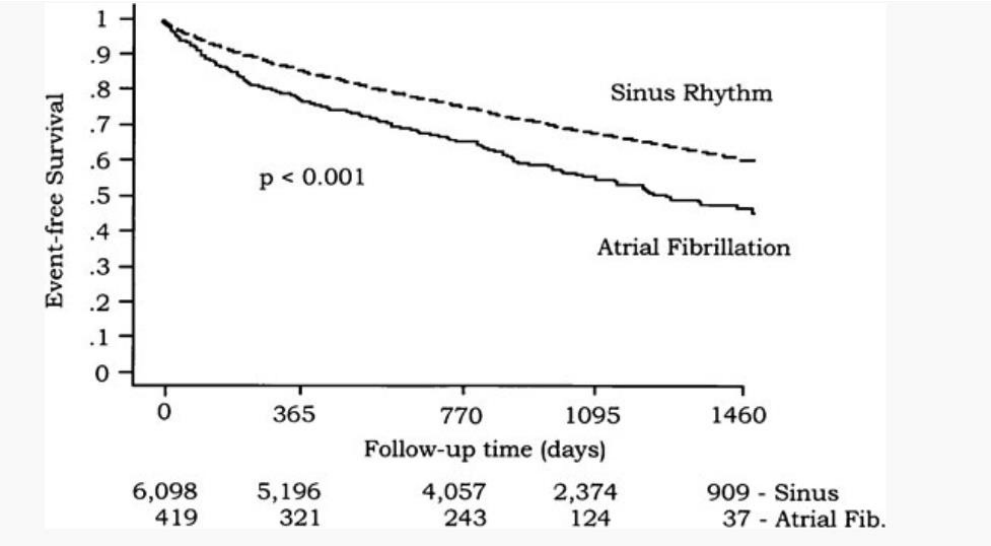
1. Wise DG et al., NEJM 2002
2. Van Gelder IC et al., NEJM 2010

Rate Control Strategies

- **Beta blockers**
  - First line therapy; may need to be used in HF situations as well
  - Better outcomes in patients treated in sinus rhythm than in AF[1]
  - Do not improve mortality or reduce HF admissions[2]
- **Digoxin**
  - DIG trial showed no mortality benefit in HF pts & sinus rhythm (did result in less hospitalizations)[3]
  - Controversial if it increases mortality
- **Calcium channel blockers**
  - Non-dihydropyridines not routinely recommended in HF pts with AF
  - Can use for acute rate control (start without IV bolus)
- **Amiodarone**
  - Can be used for rate control (has beta blocker and calcium channel blocker properties) for both acute and chronic control

1. *Rienstra M et al., JACC-HF 2013*
2. *Kotecha D et al., Lancet 2014*
3. *The Digitalis Investigation Group, NEJM 1997*

Rhythm Control (SOLVD trial)



Dries DL et al. JACC 1998

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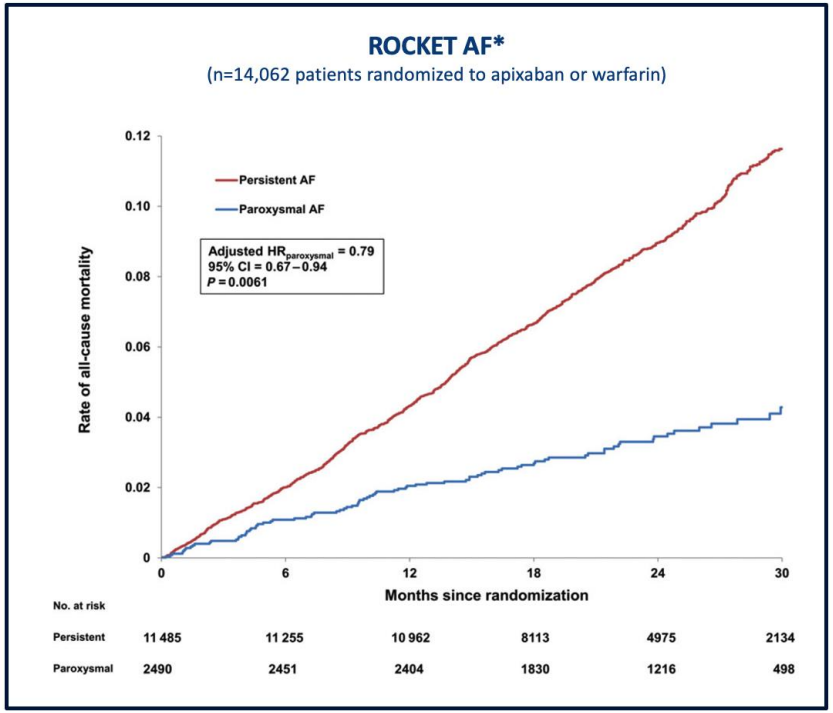
Mortality Differences (PAF vs. PeAF)



Steinberg BA et al. Eur Heart J 2015

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EAST-AFNET 4 Trial

EAST – AFNET 4 trial population
2789 patients with atrial fibrillation diagnosed within a year prior to randomization and cardiovascular conditions approximating a CHA_2DS_2VASc score of ≥ 2
2633 with known AF-related symptoms (EHRA score) at baseline
randomized to Early Rhythm Control or Usual Care

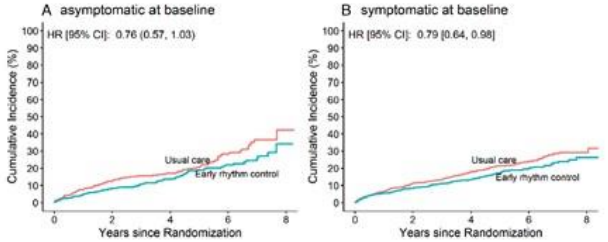
Early Rhythm Control in all patients (n=1305/2633)		**Usual Care, including symptom-directed rhythm control therapy** (n=1328/2633)	
Asymptomatic at baseline (n=395)	**Symptomatic** at baseline (n=910)	**Asymptomatic** at baseline (n=406)	**Symptomatic** at baseline (n=922)

No difference in treatment pattern between asymptomatic and symptomatic patients.
Excellent symptom control in both randomized groups at two years.

Ca. 1/4 treated with AF ablation and 3/4 treated with antiarrhythmic drugs at 2 years

Ca. 8% treated with AF ablation and 9% treated with antiarrhythmic drugs at 2 years

Similar reduction of cardiovascular death, stroke, or hospitalisation for heart failure or acute coronary syndrome in symptomatic and asymptomatic patients



Our findings support the systematic, early initiation of rhythm control therapy in asymptomatic patients with atrial fibrillation and concomitant cardiovascular conditions.

Willems S et al., EHJ 2021

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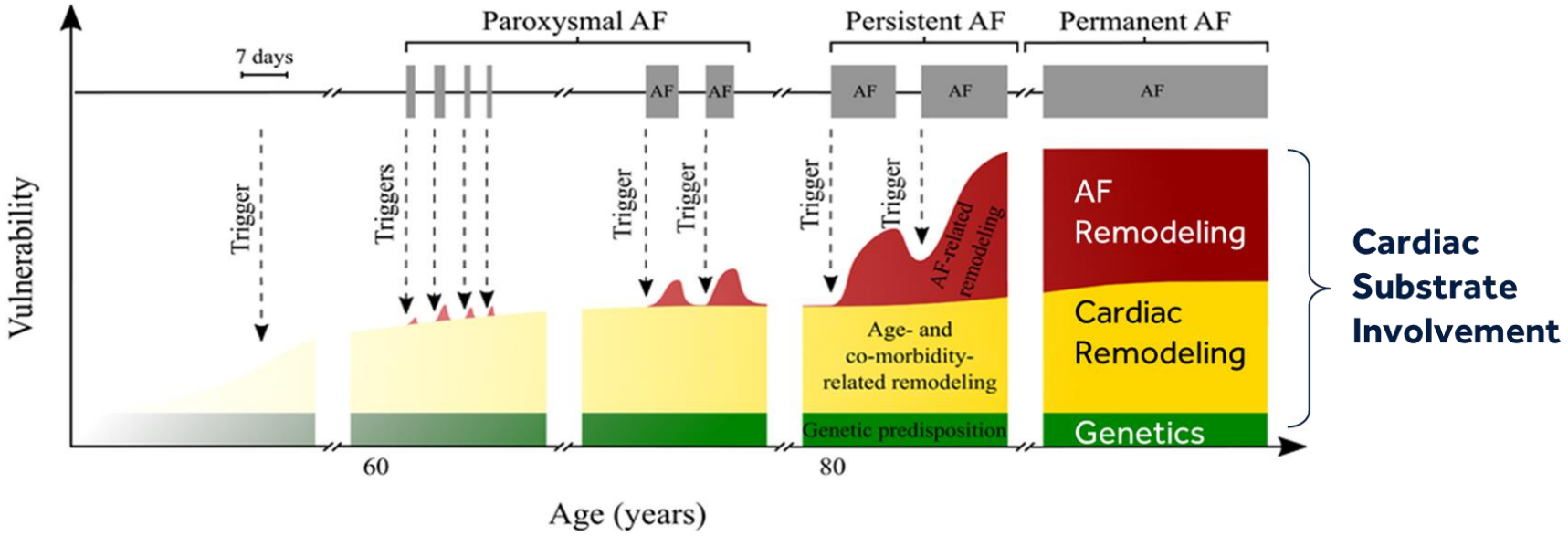
Adverse Atrial Remodeling



Heijman et al. Circ Res. 2014

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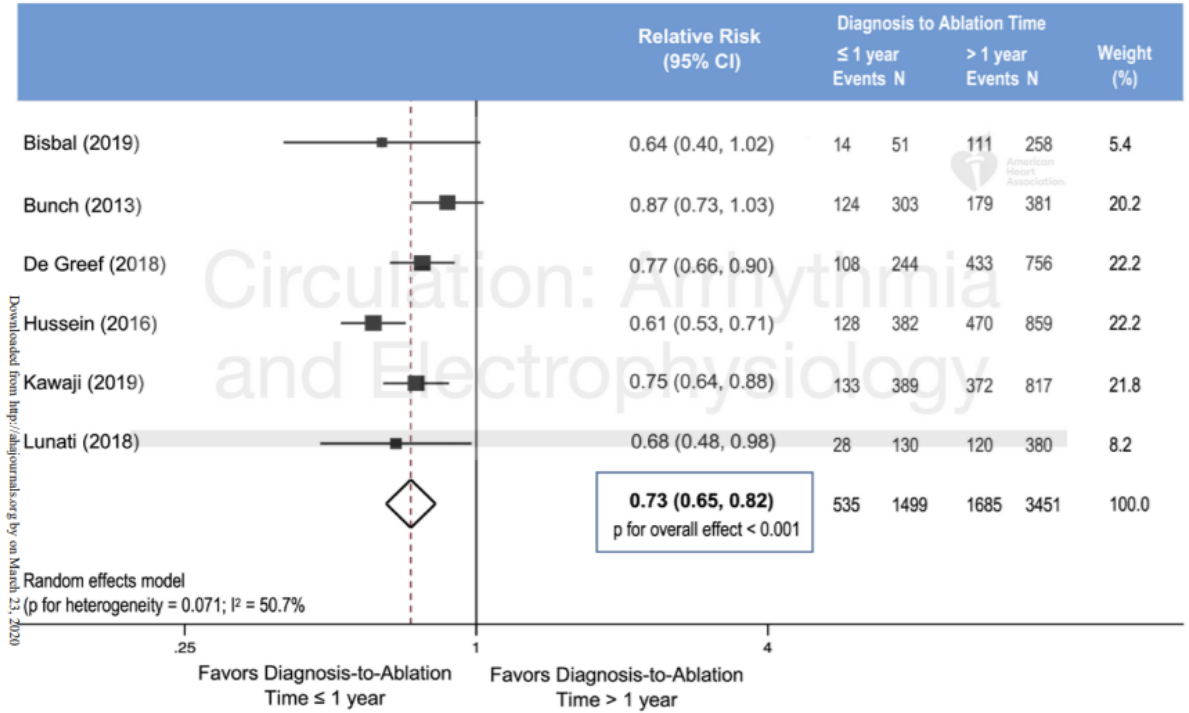
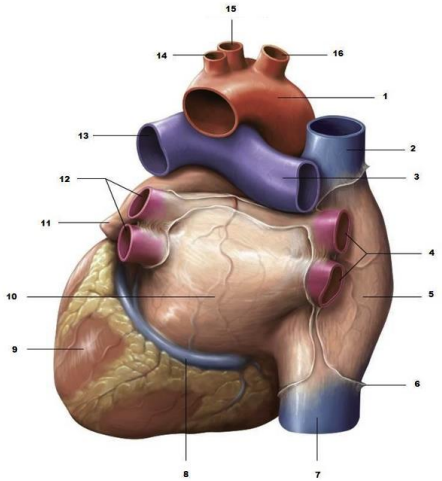
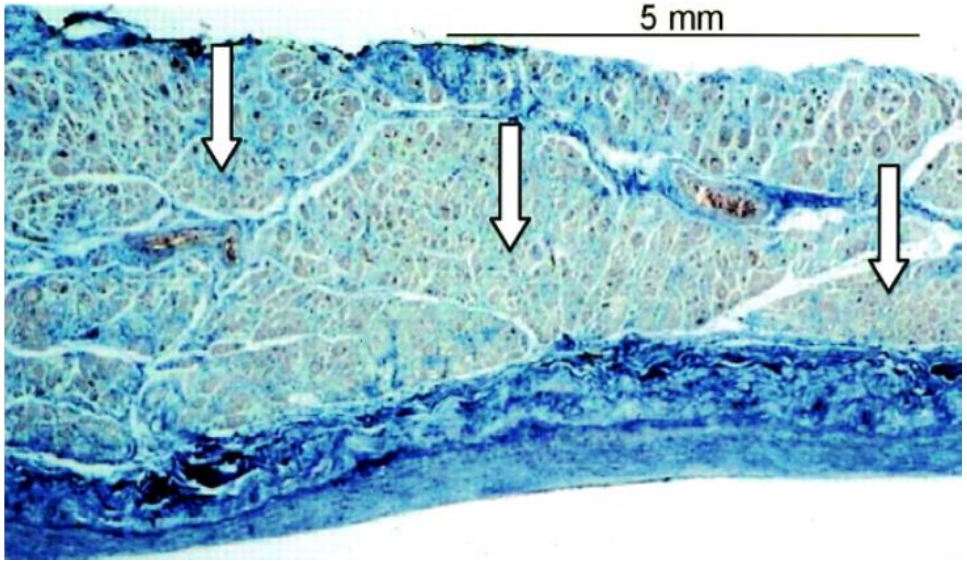
Does Timing of AF ablation Matter?



Chew DS et al. Circ Arrhythm Electrophysiol. 2020

Pulmonary Vein Sleeve





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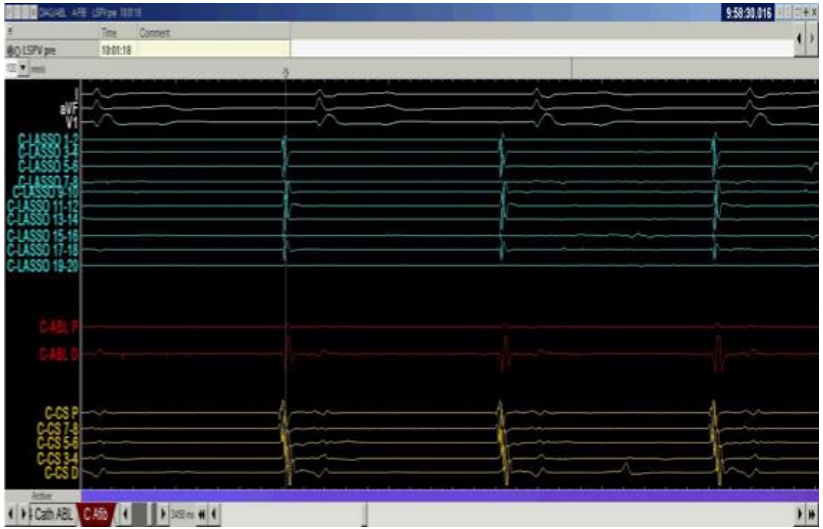
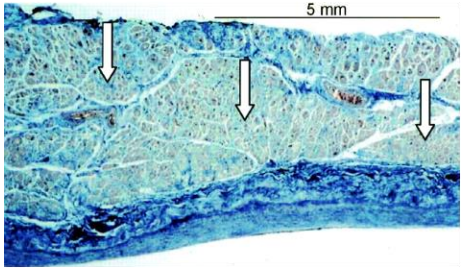
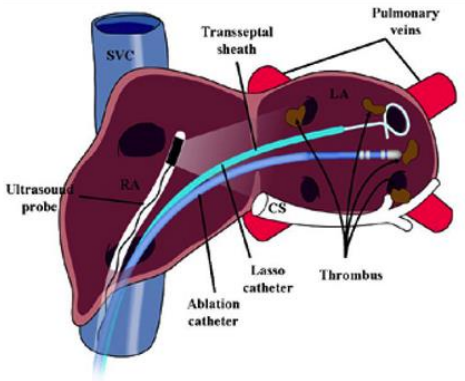
Pulmonary Vein Isolation







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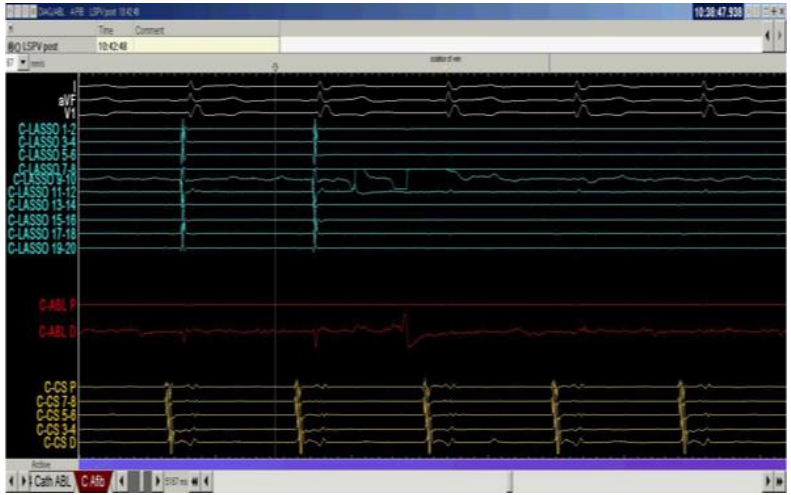

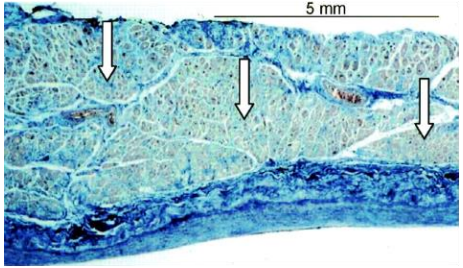

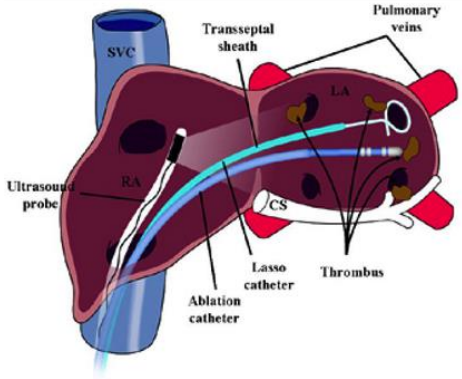

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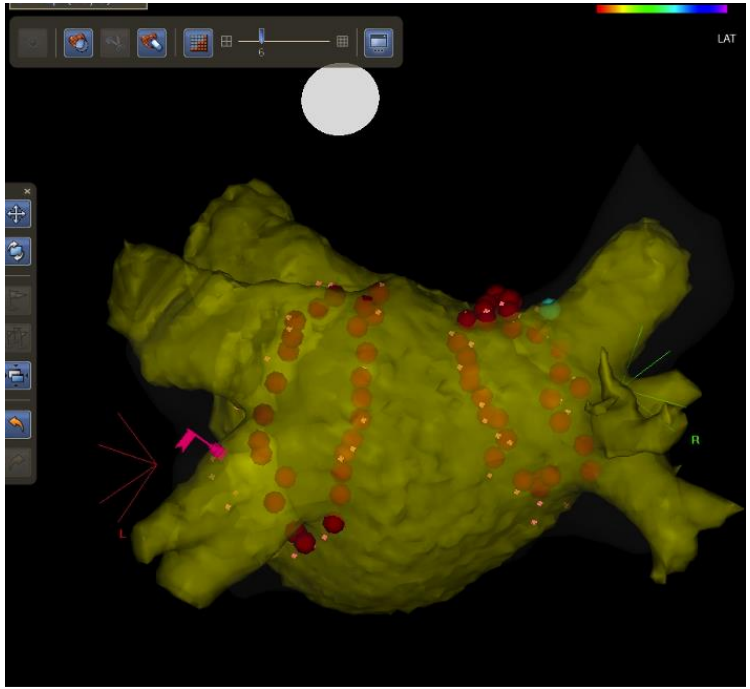

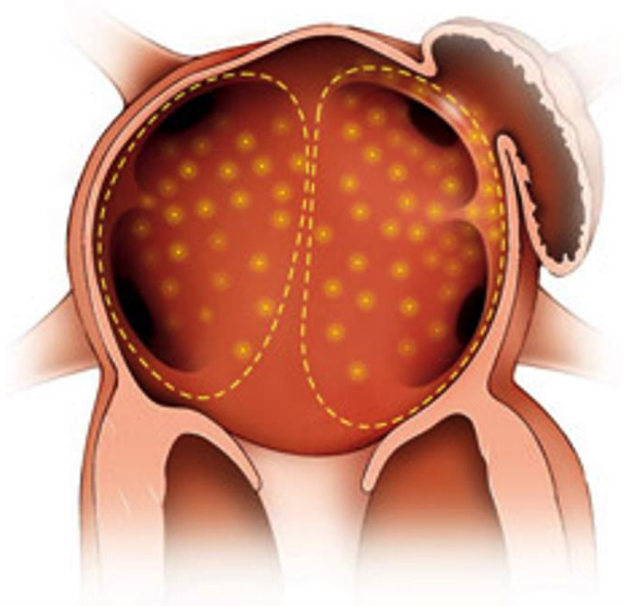

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CABANA Trial

Purpose of CABANA

Compare Ablation to state-of-the-art drug therapy for patients with new onset / undertreated AF

Primary Endpoint

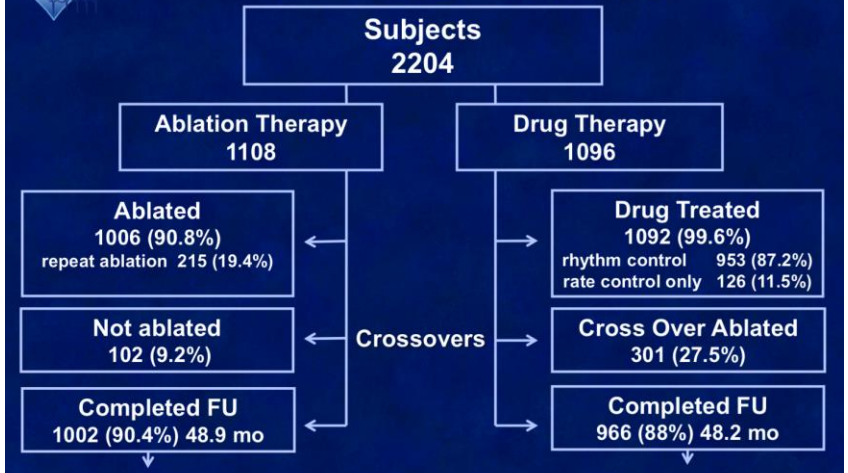
- All-cause mortality, disabling stroke, serious bleeding, or cardiac arrest

Major Secondary Endpoints

- All-cause mortality
- Death (all-cause) or cardiovascular hospitalization

MAYO CLINIC | Duke Clinical Research Institute | NIH National Heart, Lung, and Blood Institute

Patient Randomization



MAYO CLINIC | Duke Clinical Research Institute | NIH National Heart, Lung, and Blood Institute

* Withdrew <3 years

Packer DL et al., Circulation 2021

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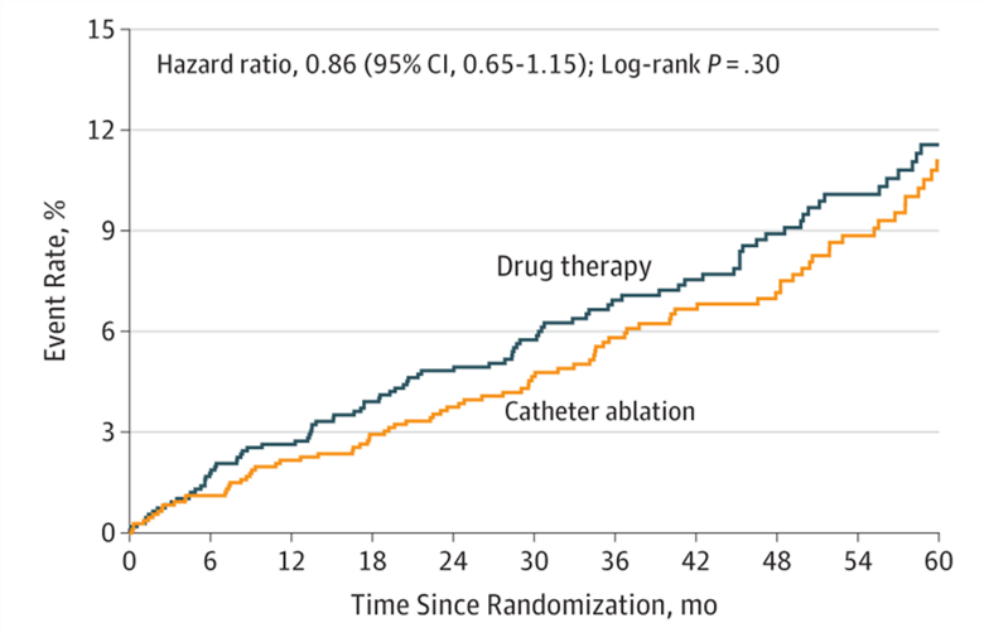
CABANA Trial
Primary Endpoint



Packer DL et al.,JAMA 2019

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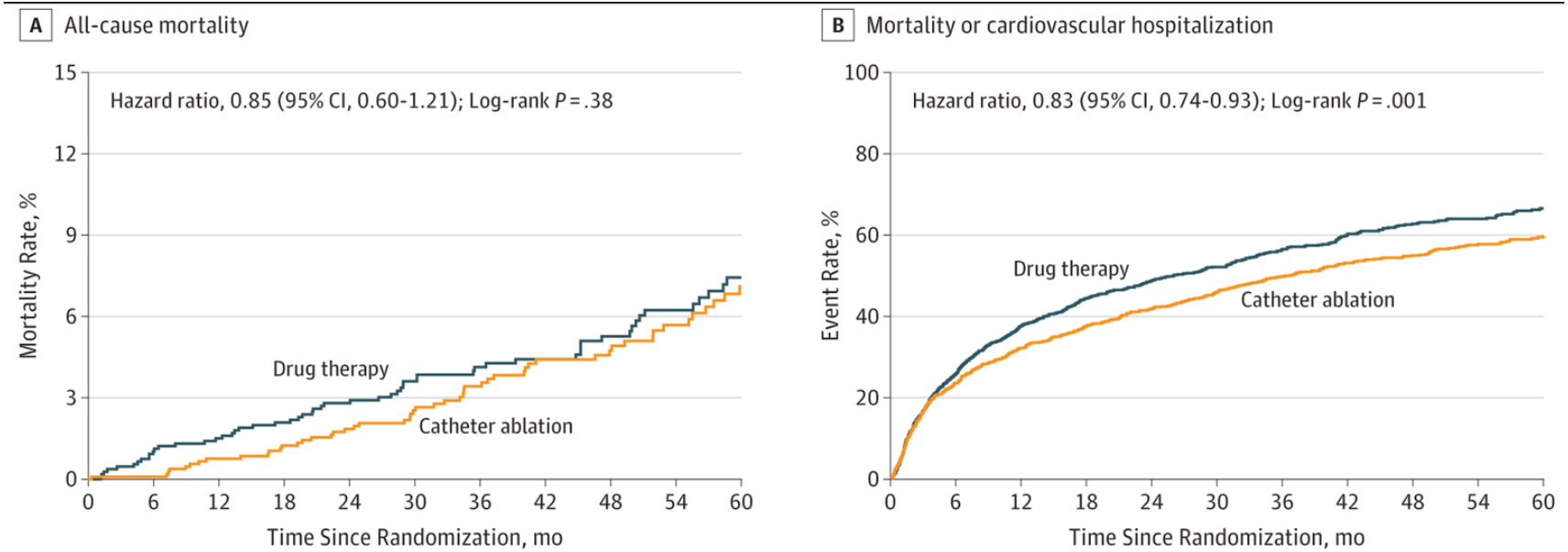
CABANA Trial
Intention-to-Treat Analysis



Packer DL et al., JAMA 2019

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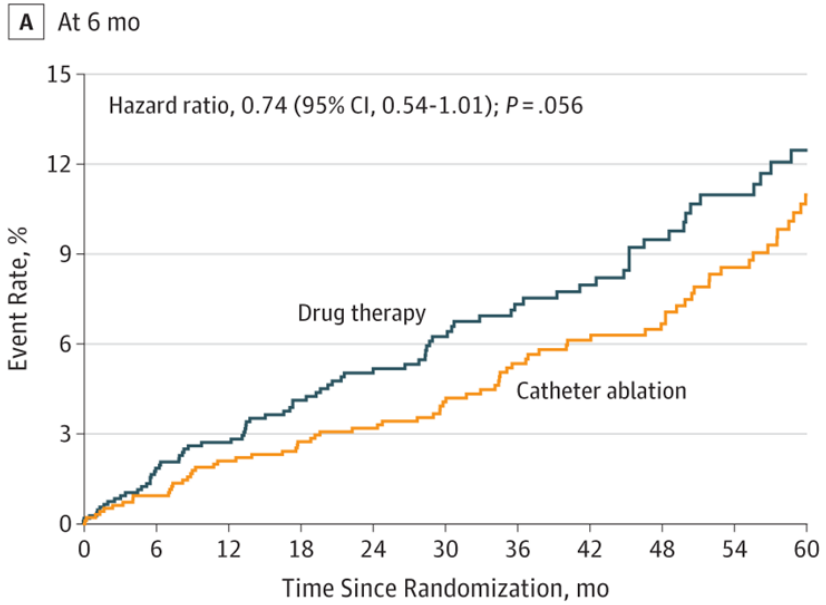
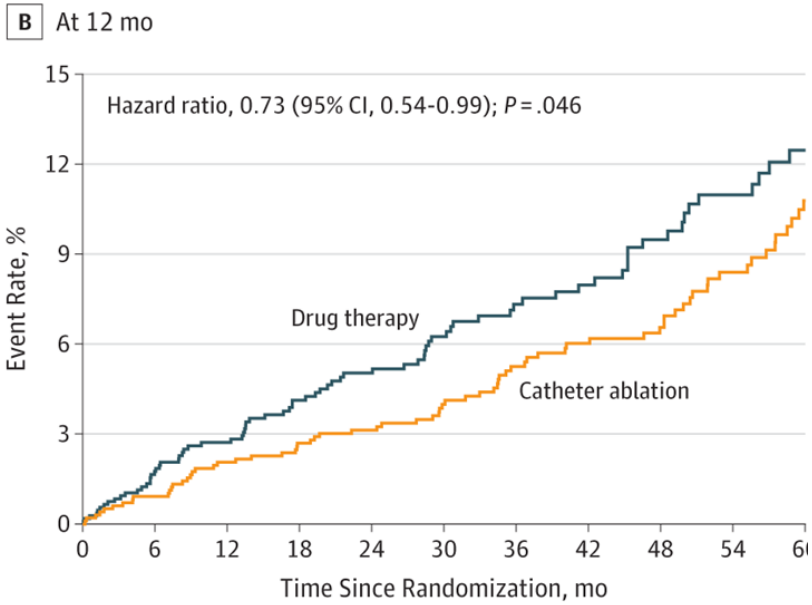
CABANA Trial
Per-Protocol Analysis





Packer DL et al., JAMA 2019

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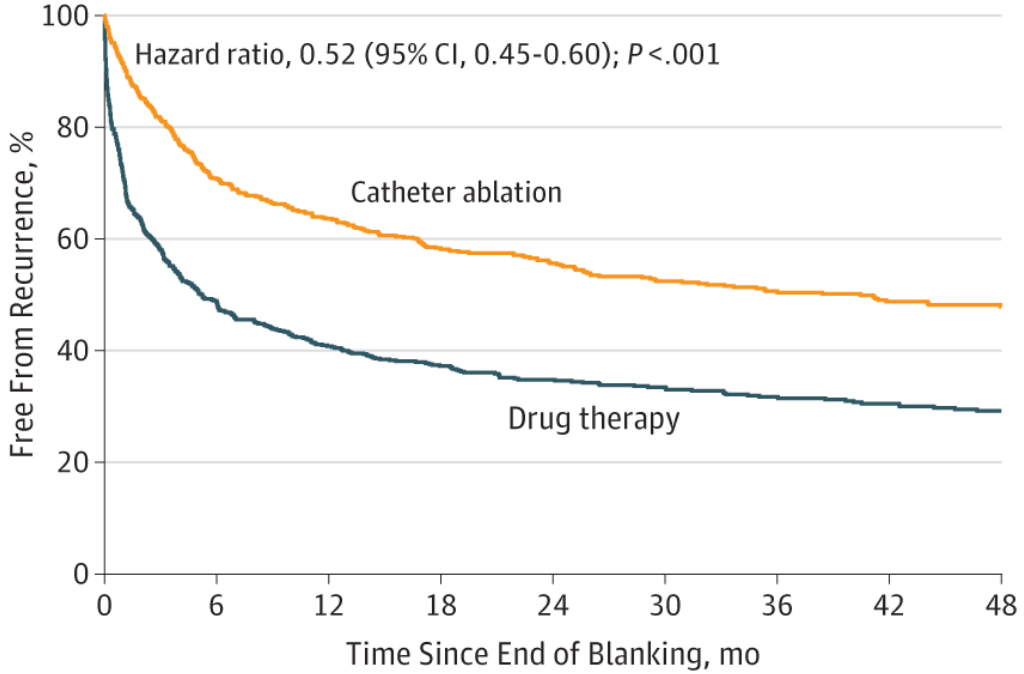
Intention-to-Treat Analysis



Packer DL et al., JAMA 2019

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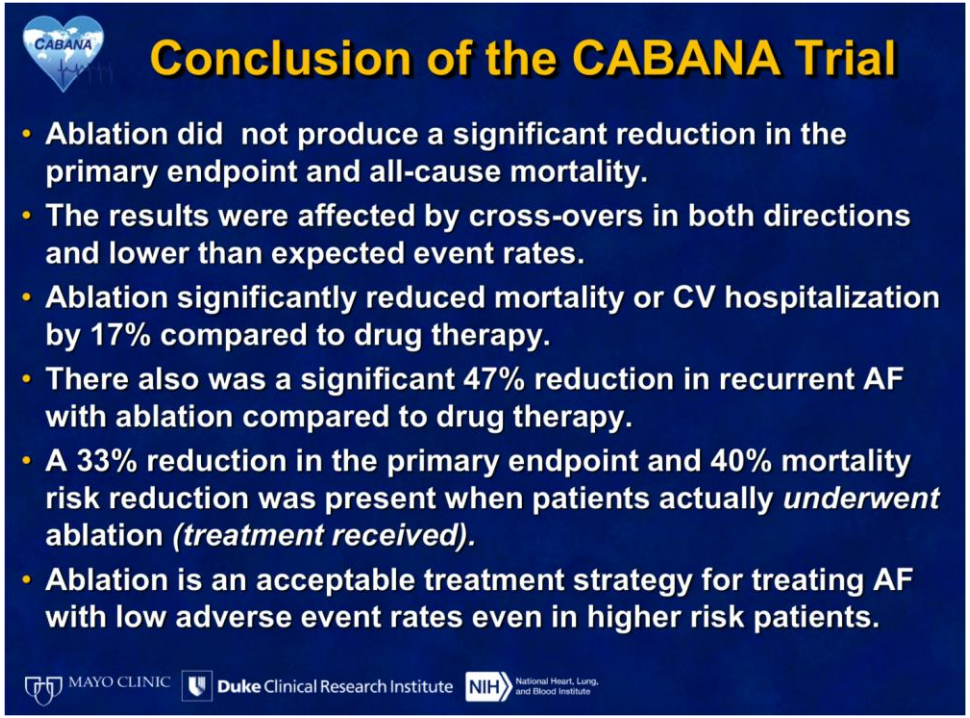
CABANA Trial



Packer DL et al., Circulation 2021

CASTLE-AF
Rationale and Objective

CASTLE-AF

- Study the effectiveness of *catheter ablation* of Atrial Fibrillation in patients with heart failure in *improving hard primary endpoints of mortality and heart failure progression* when compared to conventional standard treatment

Marrouche NF et al., NEJM 2018

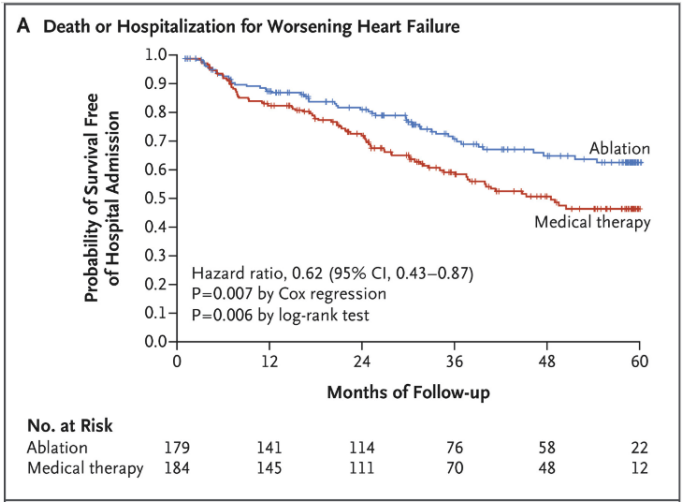
CASTLE-AF
Inclusion Criteria

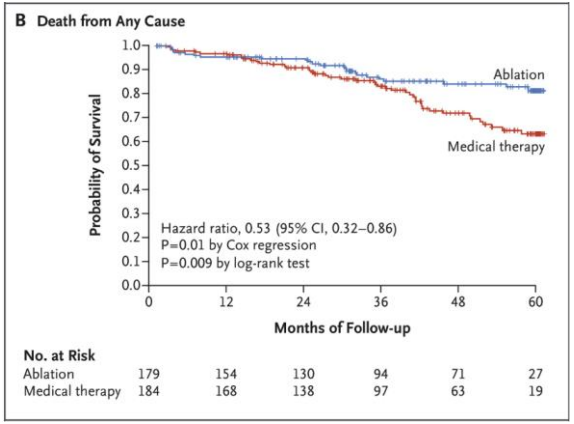
CASTLE-AF

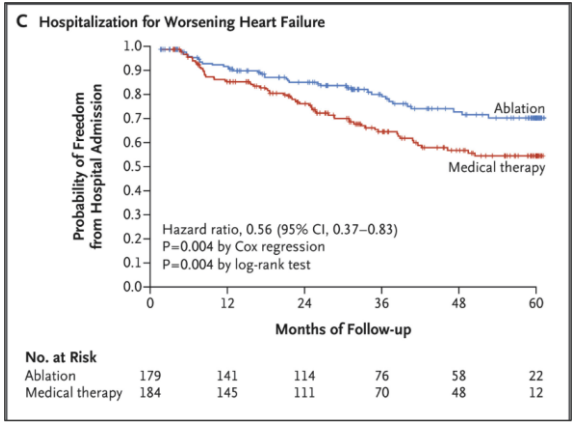
- Symptomatic paroxysmal or persistent AF
- Failure or intolerance to ≥ 1 or unwillingness to take AAD
- LVEF ≤ 35%
- NYHA class ≥ II
- ICD/CRTD with Home Monitoring™ capabilities already implanted due to primary or secondary prevention

Marrouche NF et al., NEJM 2018

CASTLE-AF







Marrouche NF et al., NEJM 2018

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Evidence for Cryoablation as First Line Rx

Is cryoablation superior to antiarrhythmics as initial therapy for the prevention of atrial arrhythmia recurrence in symptomatic patients?

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Study Designs

STUDY	Cryo-FIRST[1]	STOP AF First[2]	EARLY-AF[3]
SPONSOR	Medtronic	Medtronic	Investigator initiated
# SITES (COUNTRIES)	20 Sites (Belgium, Croatia, France, Germany, Italy, Netherlands, Norway, Argentina and Australia)	24 Sites (United States)	18 Sites (Canada)
# ENROLLED	220	225	303
MONITORING USED	12-lead ECG and 7-day Holter at 1, 3, 6, 9 and 12 months	Patient-activated TTMs (weekly and when symptomatic post-blanking); 24 Hour Holter at 6 and 12 mo, 12-lead ECG at 1, 3, 6 and 12 months	Continuous monitoring with the LINQ insertable cardiac monitor (ICM) from therapy initiation through end of follow-up; 24 hr. Holter and 12-lead ECG at 3, 6, and 12 months
ABLATION STRATEGY	PVI completion / focal trigger allowed w/Freezor MAX; re-ablation allowed during blanking	Only PVI in LA, no re-ablation procedures allowed	PVI only, no re-ablation procedures allowed
ABLATION DOSING	At discretion of investigator	2 applications, each 3 minutes in duration	2 applications, each 3 minutes in duration
ABLATION CATHETER USED	AFA and Freezor MAX	AFA and Freezor MAX	AFA and Freezor MAX

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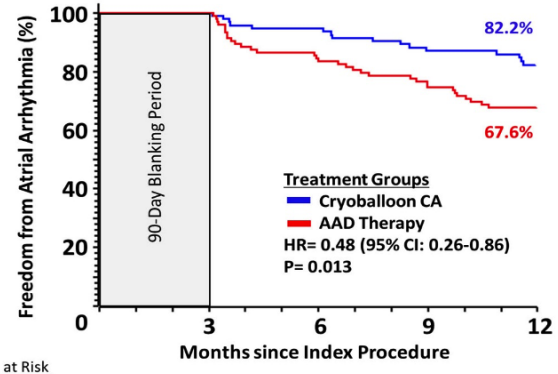
1. *Kuniss M et al. EP Europace 2021*
2. *Wazni OM et al. N Engl J Med 2021*
3. *Andrade JG et al. N Engl J Med 2021*

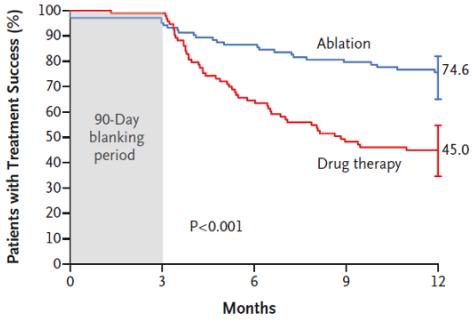
Primary Efficacy

Cryo-FIRST



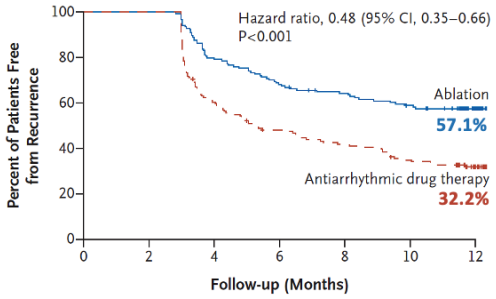
No. at Risk					
Cryoballoon CA	107	94	88	80	53
AAD Therapy	111	104	86	75	38

STOP AF First



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

EARLY-AF



No. at Risk							
Ablation	154	154	123	105	96	86	55
Antiarrhythmic drug therapy	149	149	89	69	60	49	27

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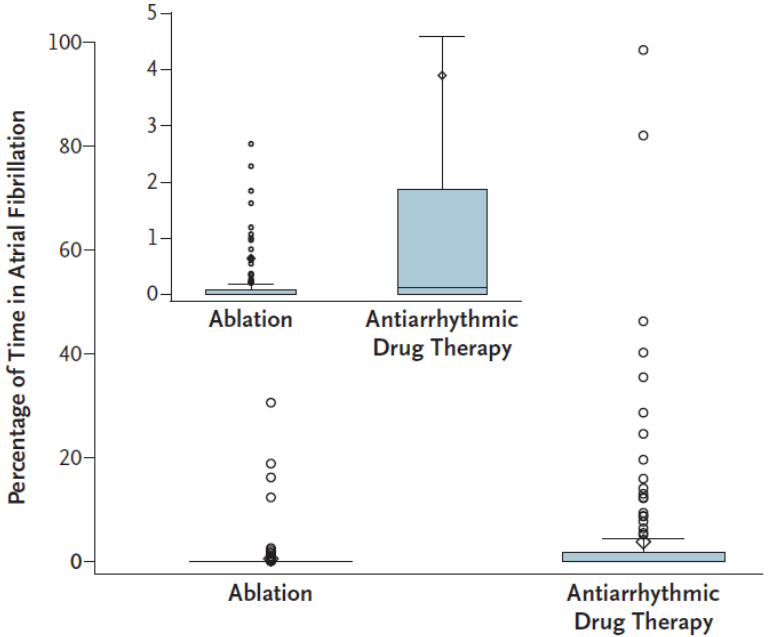
1. *Kuniss M et al. EP Europace 2021*
2. *Wazni OM et al. N Engl J Med 2021*
3. *Andrade JG et al. N Engl J Med 2021*

Arrythmia Burden Reduction in EARLY-AF



Andrade JG et al. N Engl J Med 2021

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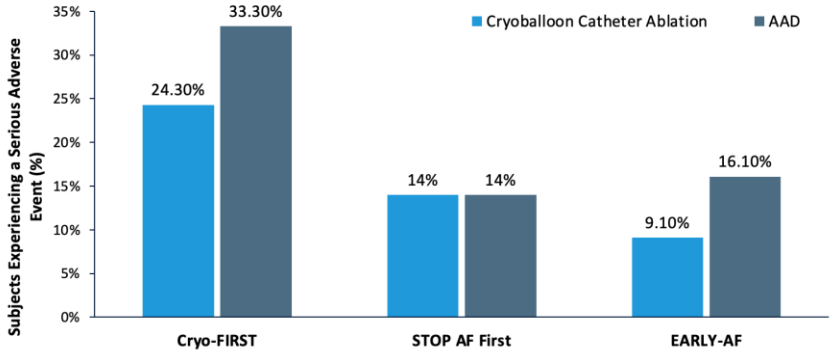
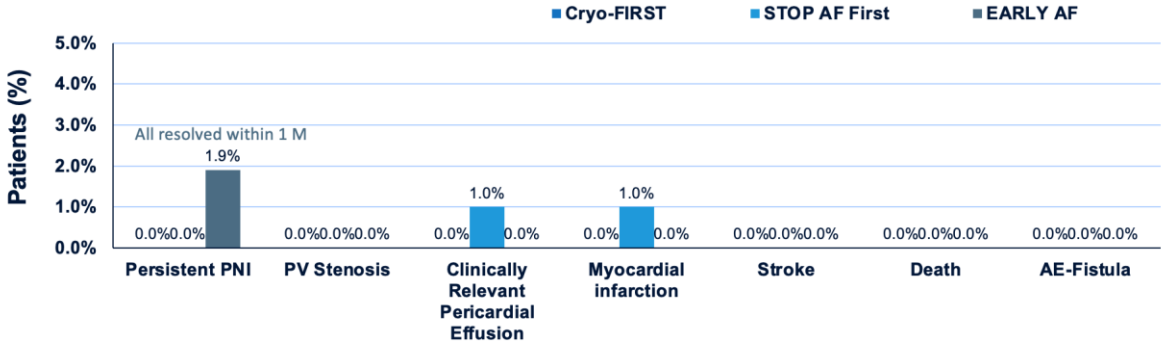
Safety Signals





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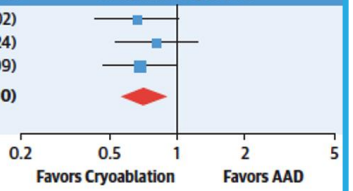
Healthcare Burden

HEALTHCARE UTILIZATION

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	25	107	39	111	30.2%	0.66 (0.43-1.02)
EARLY-AF	30	154	36	149	29.8%	0.81 (0.53-1.24)
STOP-AF First	31	104	43	99	39.9%	0.69 (0.47-0.99)
Total (95% CI)		**365**		**359**	**100.0%**	**0.71 (0.56-0.90)**
Total events	86		118			

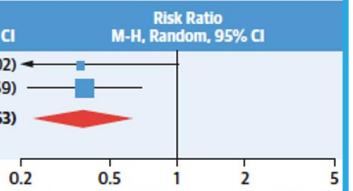
Heterogeneity: $Tau^2 = 0.00$; chi-square = 0.46, df = 2 ($P = 0.79$); $I^2 = 0\%$
Test for overall effect: Z = 2.83 ($P = 0.005$)



HOSPITALIZATION

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
EARLY-AF	5	154	13	149	25.1%	0.37 (0.14-1.02)
STOP-AF First	13	104	32	99	74.9%	0.39 (0.22-0.69)
Total (95% CI)		**258**		**248**	**100.0%**	**0.38 (0.23-0.63)**
Total events	18		45			

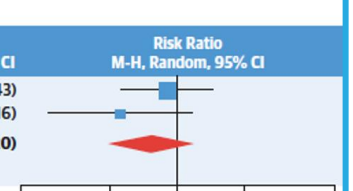
Heterogeneity: $Tau^2 = 0.00$; chi-square = 0.00, df = 1 ($P = 0.95$); $I^2 = 0\%$
Test for overall effect: Z = 3.73 ($P = 0.0002$)



EMERGENCY DEPARTMENT VISIT

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
EARLY-AF	28	154	30	149	68.2%	0.90 (0.57-1.43)
STOP-AF First	10	104	17	99	31.8%	0.56 (0.27-1.16)
Total (95% CI)		**258**		**248**	**100.0%**	**0.78 (0.50-1.20)**
Total events	38		47			

Heterogeneity: $Tau^2 = 0.02$; chi-square = 1.17, df = 1 ($P = 0.28$); $I^2 = 15\%$
Test for overall effect: Z = 1.14 ($P = 0.25$)



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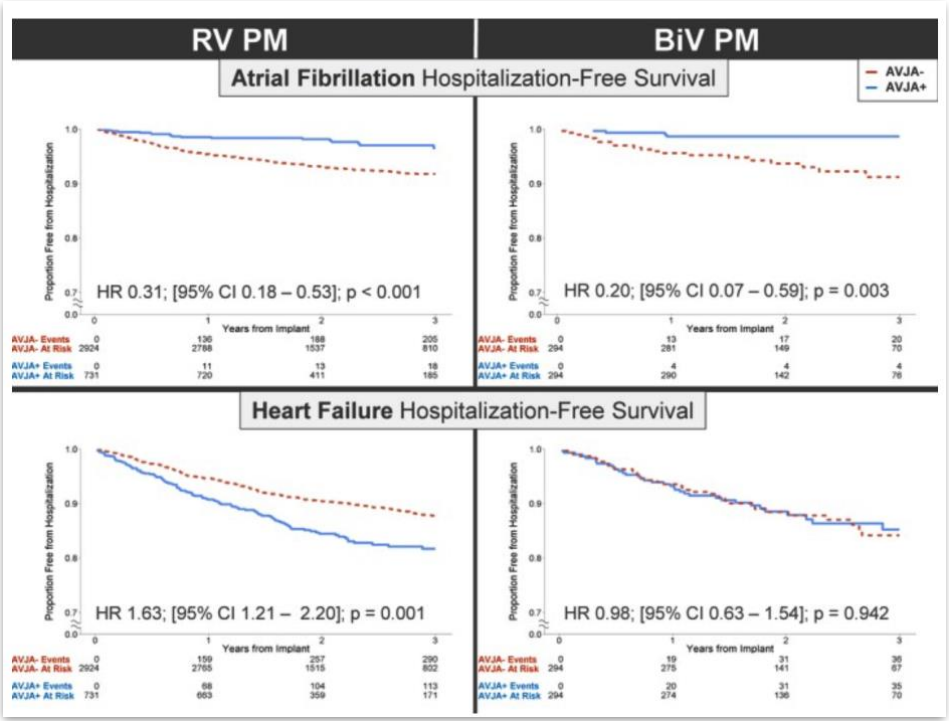
Andrade JG et al. J Am Coll Cardiol. 2021

AV Junction Ablation



Mittal S et al., JAHA 2017

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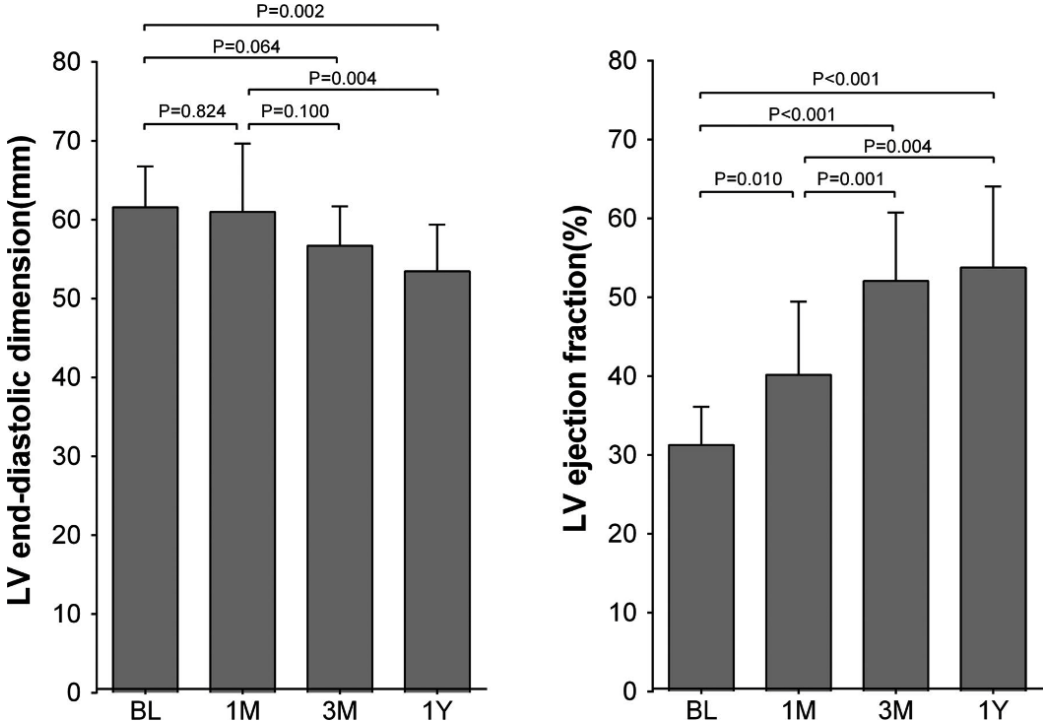
AV Junction Ablation & His Bundle Pacing



Huang W et al., JAHA 2017

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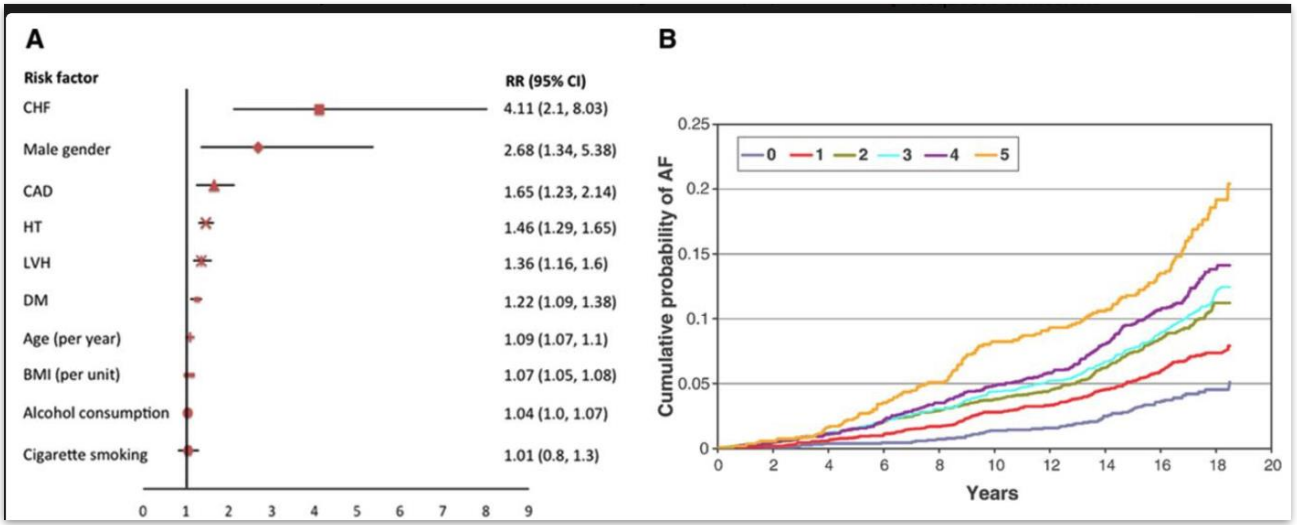
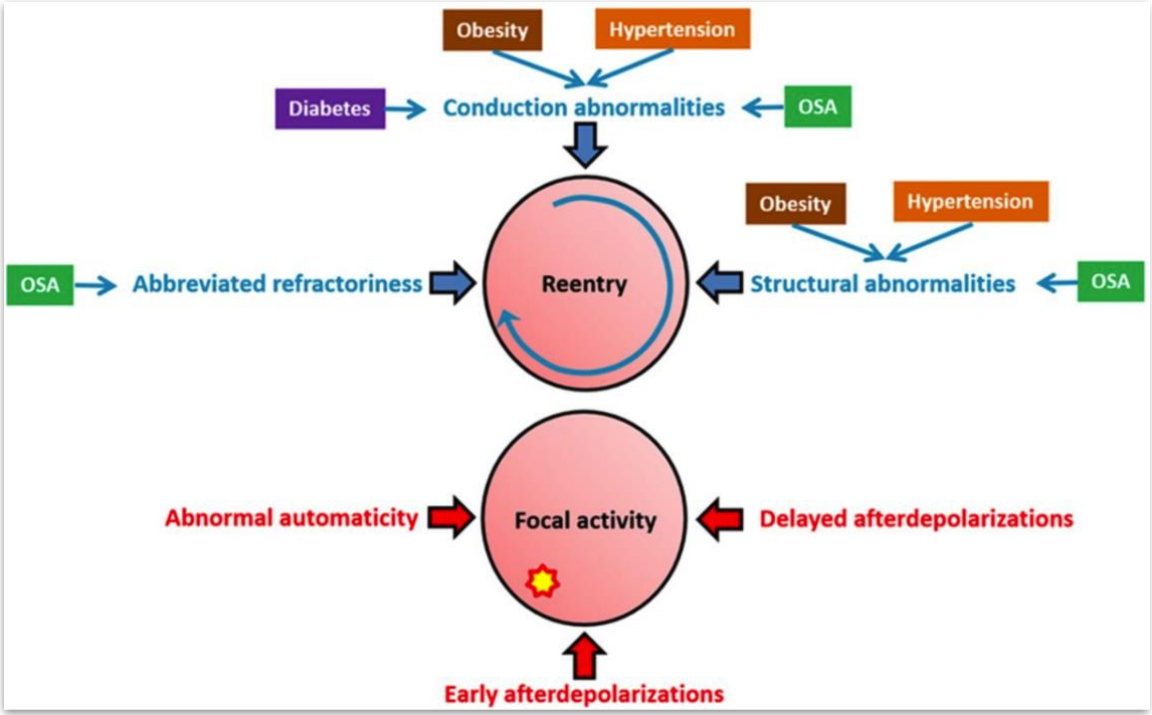
“Other” Non-pharmacological Strategies



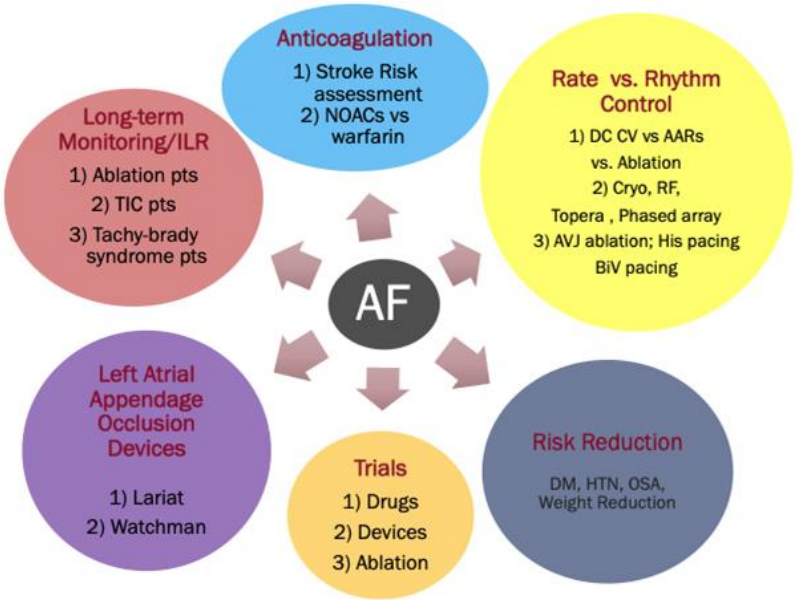
Lau et al., Circulation 2017

Role of Risk Factors



Lau et al., Circulation 2017

VMFH AF Center



Summary

- AF is a chronic myopathic disease rather than an arrhythmia
- HF and AF are chronic disease processes that require an integrated & coordinated multidisciplinary care to achieve the best long-term outcomes
- AF patients are at higher risk for HF admissions and cardiovascular events
- When feasible, long-term restoration of sinus rhythm in HF patients & symptomatic patients with AF should be sought after to reduce morbidity & mortality
- Ablation for AF has become a mainstay therapy with demonstration of improved outcomes and overall cost benefit to society

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