To Ablate or Not to Ablate: Current Management of Atrial Fibrillation

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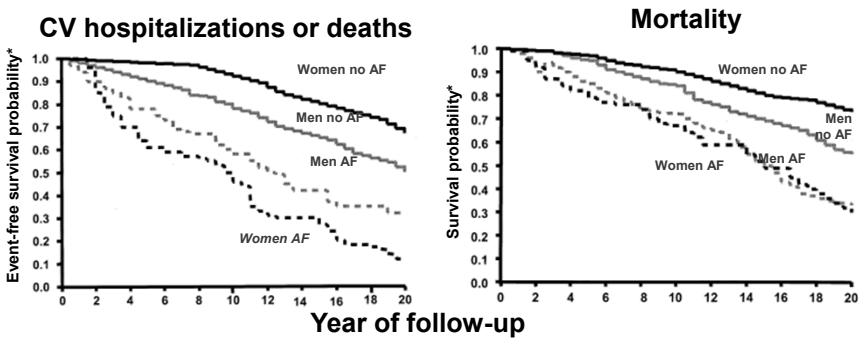
AF: Growing Health Problem

- **Projected that the number of persons with AF in the U.S. will exceed 10 million by the year 2050**
- **Atrial fibrillation is a well established risk factor for:**
  - **Stroke**
  - **Congestive heart failure**
  - **Premature death**

Renfrew / Paisley Study: Long-Term Risks Associated with AF

N = 15,856 aged 45–64 years



*Age-adjusted

https://doi.org/10.1016/S0002-9343(02)01236-6
Stewart S et al. *Am J Med.* 2002;113:359-64.

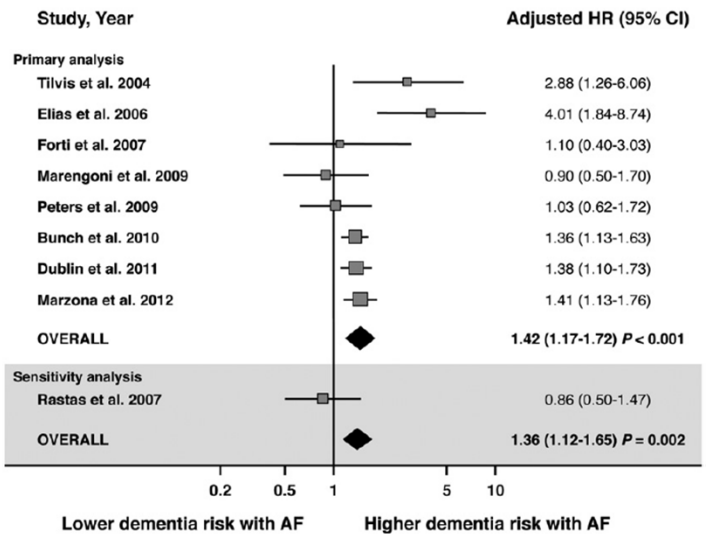
Manitoba Follow-Up Study: Effect of AF on Morbidity and Mortality

N = 3983 male air crew recruits observed continuously for 44 years

Endpoint	Cohort (n)	After AF (n)	Relative risk (95% CI)
Total mortality	1603	136	1.31 (1.08–1.59)
CV mortality	662	92	1.41 (1.11–1.80)
Stroke mortality	83	15	2.48 (1.35–4.57)
Nonstroke CV mortality	579	77	1.37 (1.05–1.78)
Non-CV mortality	941	44	1.10 (0.80–1.53)
Stroke	371	32	2.07 (1.43–3.01)
Congestive heart failure	258	35	2.98 (2.09–4.26)
Myocardial infarction	590	19	1.02 (0.64–1.54)

Krahn AD et al. *Am J Med.* 1995;98:476-84.

Afib and the Risk of Dementia



https://doi.org/10.1016/j.hrthm.2012.07.026

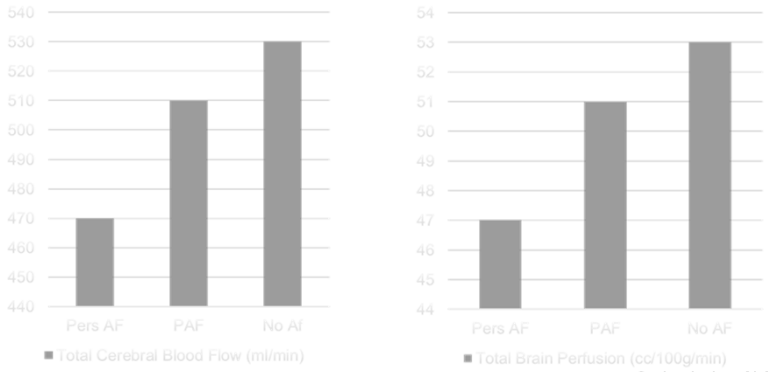
Santangeli, et al, Heart Rhythm 2012

Dementia, AF and Cerebral Blood Flow

4251 pts from Icelandic population:
Association between AF and lower brain volume and gray matter.

2291 Patients in the AGES-Reykjavik Study underwent assessment of blood flow in cervical arteries with phase contrast MRI and brain perfusion estimated.

3 Groups: PersAF, PAF and no Hx of AF at the time of the MRI
Similar with regard to cardiovascular risk factors.

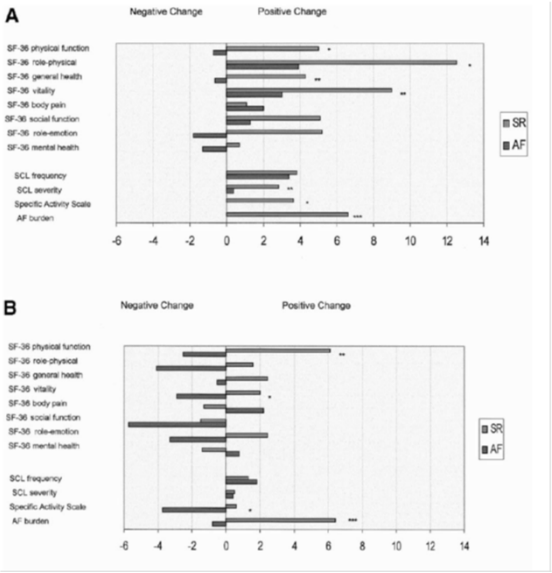


Gardarsdottir et. Al, Europace 2016

QOL Changes AF ⇨ SR

Symptomatic Patients

Asymptomatic Patients



Singh et al, JACC Vol. 48, No. 4, 2006

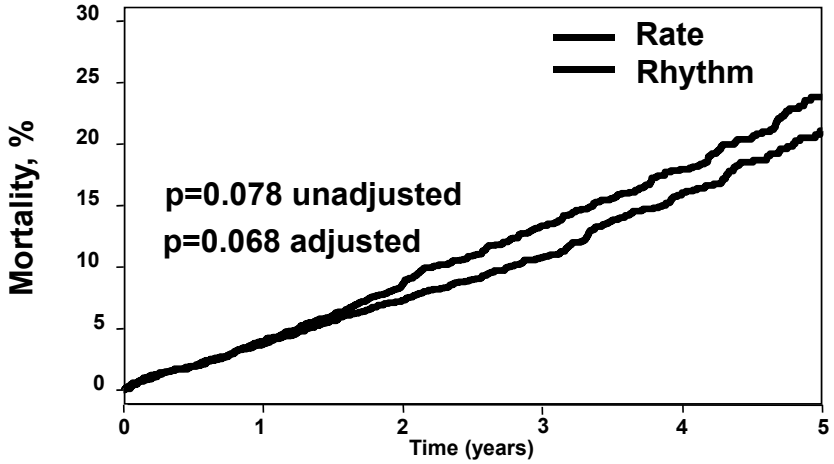
https://doi.org/10.1016/j.jacc.2006.03.051

AFFIRM Trial: Rate vs Rhythm Control Management Strategy Trial

- **Design**
  - **5-year, randomized, rate control vs. AARx**
  - **Primary endpoint: overall mortality**
- **Patient population**
  - **4060 patients with AF and risk factors for stroke**
  - **Minimal symptoms**
  - **Mean Age = 69 yo**
  - **Hx of hypertension: 70.8%**
  - **CAD: 38.2%**
  - **Enlarged LA: 64.7%**
  - **Depressed EF: 26.0%**

The AFFIRM Investigators. *N Engl J Med.* 2002;347:1825-1833.

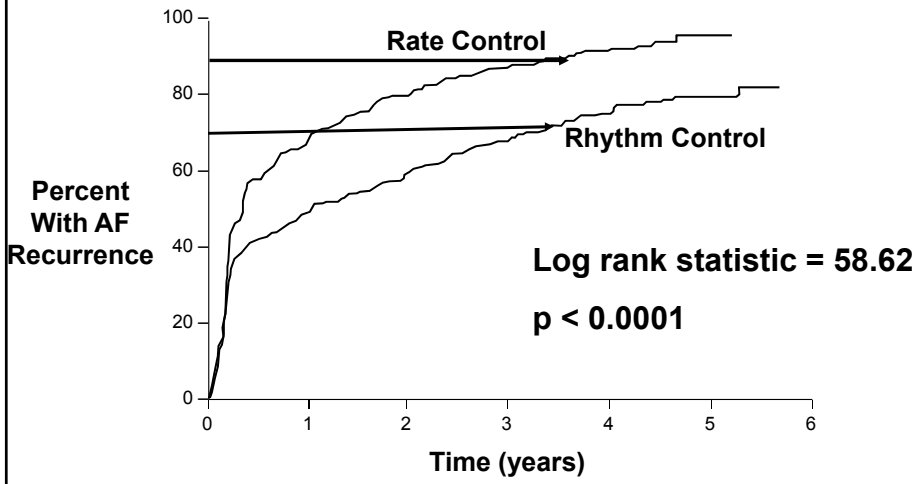
Medical Treatment in AFFIRM:



Do these unabated increases in mortality simply represent *equally poor therapies* allowing CHF, Stroke, and Declines in Cognition to progress?

The AFFIRM Investigators. *N Engl J Med.* 2002;347:1825-1833.

Time to Recurrence of AF in Affirm



% NSR at End of Trial: Affirm 63%, Race 39%, PIAF 56%, STAF 26%

Raitt, et al. *Am H J* 2006

Risk of Death in Affirm: Is Sinus Rhythm the Goal?

AFFIRM: Selected time-dependent covariates associated with survival

Covariate	P	Hazard ratio*	99% CI
Sinus rhythm	<0.0001	0.53	0.39–0.72
Warfarin	<0.0001	0.50	0.37–0.69
Digoxin	0.0007	1.42	1.09–1.86
Antiarrhythmic	0.0005	1.49	1.11–2.01

***HR <1.00: Decreased risk of death, HR >1.00: Increased risk of death**

AFFIRM Investigators. *Circulation*. 2004;109:1509-13.

AF Wreaks Havoc in CHF

- **AF in HF patients increases the 3-year risk of:**
  - **mortality (hazard ratio 1.13)**
  - **all-cause readmission (HR, 1.15)**
  - **HF (HR, 1.22)**
  - **stroke (HR, 1.57).**
- ***New-onset* AF in CHF pts convey a greater increased risk**
- **The adverse impact of AF on mortality in HF greatest in mild-to-moderate HF.**

AF Status	Overall (N=24 175)
Death from any cause, adjusted* hazard ratio (95% CI)	
No AF	Reference
Preexisting AF	1.13 (1.07 to 1.20)
Incident AF	1.67 (1.52 to 1.84)
Hospitalization for heart failure, adjusted* hazard ratio (95% CI)	
No AF	Reference
Preexisting AF	1.22 (1.15 to 1.29)
Incident AF	2.00 (1.83 to 2.18)
Hospitalization for any cause, adjusted* hazard ratio (95% CI)	
No AF	Reference
Preexisting AF	1.15 (1.11 to 1.19)
Incident AF	1.45 (1.37 to 1.54)
Ischemic stroke, adjusted† hazard ratio (95% CI)	
No AF	Reference
Preexisting AF	1.57 (1.34 to 1.83)
Incident AF	2.47 (1.97 to 3.09)

If NSR is Beneficial for Most People, it Should be Easy to See In the CHF Population

McManus et. Al, JAHA 2013

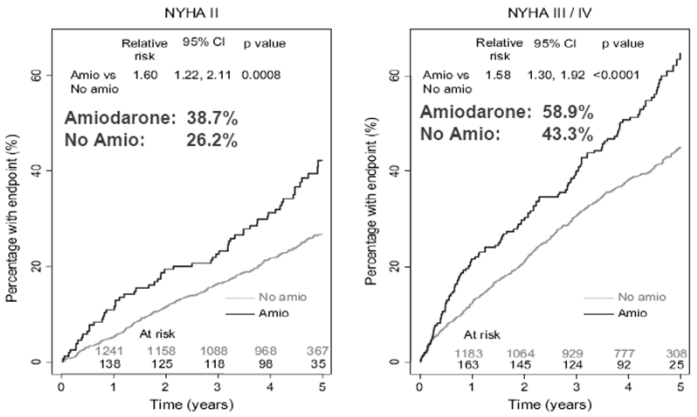
AFCHF

- 1376 pts. with LVEF ≤ 35%, symptomatic CHF, and Hx/o AF
- 682 in the rhythm-control group, 694 in the rate-control group
- Primary Outcome: Death from CV causes
- Amiodarone 82% of rhythm control medication
- ~ 70% of patients in NSR at 2 years
- No Difference In:
  - Death from any cause
  - Stroke
  - Heart Failure Hospitalization
  - Composite outcome

Roy et. Al, NEJM 2008

COMET: Effect of Amiodarone on All-cause Mortality

N = 3029 with chronic HF randomized to carvedilol or metoprolol Median follow-up 58 months



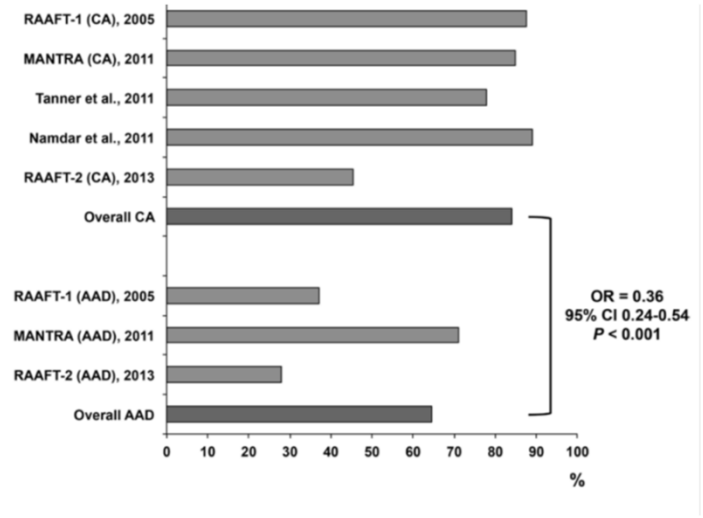
COMET = Carvedilol or Metoprolol European Trial

https://doi.org/10.1016/j.cardfail.2007.02.009

Torp-Pedersen C et al. *J Card Failure.* 2007;13:340-5.

Catheter Ablation as the Initial Rhythm Control Strategy

SUCCESS RATES



American Heart Association. Ablation Versus Drugs: What Is the Best First-Line Therapy for Paroxysmal Atrial Fibrillation? Pasquale Santangeli, MD, Luigi Di Biase, MD, PhD, and Andrea Natale, MD

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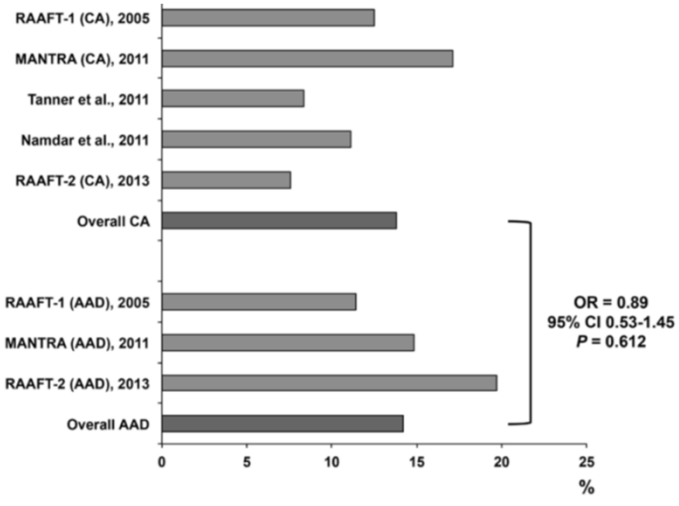
Catheter Ablation as the Initial Rhythm Control Strategy

COMPLICATIONS



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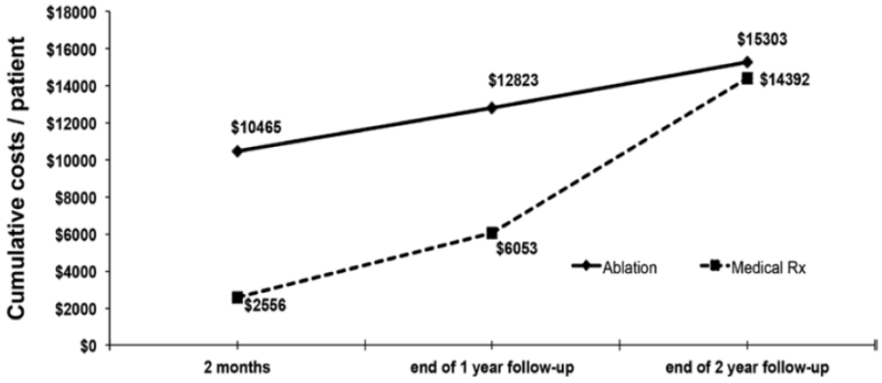
Catheter Ablation as the Initial Rhythm Control Strategy

Costs



American Heart Association. Ablation Versus Drugs: What Is the Best First-Line Therapy for Paroxysmal Atrial Fibrillation? Pasquale Santangeli, MD, Luigi Di Biase, MD, PhD, and Andrea Natale, MD

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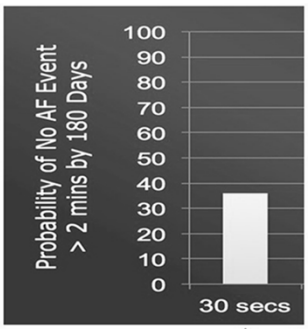
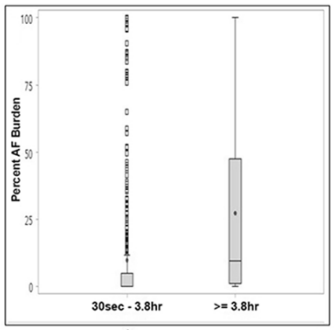
The 30-Second Gold Standard for the Definition of AF: Is It Clinically Meaningful?





36% never experience another AF > 2min over 180d

Median AF burden only 0.3% over 3.7 years

Conclusion
In a population of 615 pacemaker registry patients, a single detected 30sec AF episode was not predictive of subsequent AF events or meaningful AF burden.

An initial AF episode of 30 seconds does not predict clinically meaningful AF patterns, > 3.8 hours did.

American Heart Association. Thirty-Second Gold Standard Definition of Atrial Fibrillation and Its Relationship With Subsequent Arrhythmia Patterns. Jonathan S. Steinberg, MD, Heather O'Connell, MS, Shelby Li, MD, MS and Paul D. Ziegler, MS

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AF and CHF Ablation Trials

Study	Publication Year	Sample Size	Catheter Ablation Arm (*n*)	Comparator Arm (*n*)	Follow-up (months)	Primary Endpoint	Results
PABA-CHF[26]	2008	81	PVI (41)	AV node ablation with biventricular pacing (40)	6	Composite of ejection fraction, 6-minute walk distance and MLWHF score	Catheter ablation was superior to AV nodal ablation and biventricular pacing
MacDonald et al., 2001[27]	2011	41	PVI ± linear ablations ± CFAE ablation (22)	Rate control (19)	6	Cardiac MRI ejection fraction	No significant difference between groups
ARC-HF[36]	2013	52	PVI ± linear ablations ± CFAE ablation (26)	Rate control (26)	12	Peak VO_2	Improvement in peak VO_2 in the catheter ablation group compared with rate control
CAMTAF[37]	2014	50	PVI ± linear ablations ± CFAE ablation (26)	Rate control (24)	12	Left ventricular ejection fraction at 6 months	Improvement in left ventricular ejection fraction at 6 months in catheter ablation group
AATAC[28]	2016	203	PVI ± posterior wall isolation ± CFAE ablation (102)	Amiodarone (101)	36	Freedom from AF	Significant improvement in freedom from AF in the catheter ablation group
CAMERA-MRI[29]	2017	68	PVI + posterior wall isolation (34)	Rate control (34)	6	Left ventricular ejection fraction	Significant improvement in ejection fraction in catheter ablation group
CASTLE-AF[30]	2018	363	PVI ± linear ablations ± CFAE ablation (179)	Medical rate or rhythm control (184)	60	Death or heart failure hospitalisation	Significant improvement in composite endpoint of death and heart failure hospitalisation in catheter ablation group

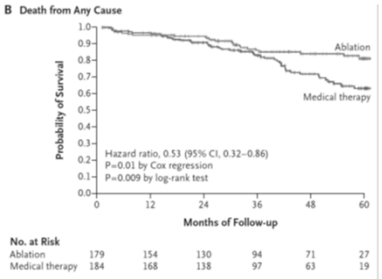
AV = atrioventricular; CFAE = complex fractionated atrial electrograms; MLWHF = Minnesota Living with Heart Failure; PVI = pulmonary vein isolation; VO_2 = maximum rate of oxygen consumption.

Out of 7 trials and 650 patients only one trial found no benefit

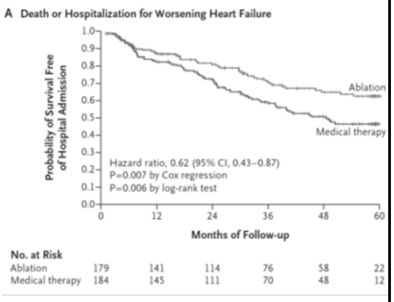
https://doi.org/10.15420/aer.2018.17.2 **Baher et. Al,** AER-Volume 7, Issue 2, 2018

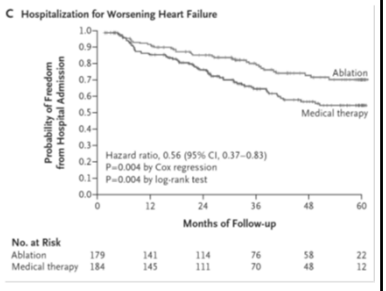
Afib Ablation In CHF: Castle CHF

- 397 pts with AF and LVEF ≤35%
- Randomized to RFA or AArx. Mean FU 38 months
- Primary endpoint: composite of all-cause mortality and hospitalization for worsening CHF.
- **Results**:
- Composite endpoint was significantly lower in the ablation (28.5 percent) vs. control (44.6 percent) over period of 37.8 months.
- Secondary endpoints:
  - all-cause mortality in ablation 13% vs. 25%
  - heart failure hospitalization significantly lower in ablation group 21% vs. 36%



https://doi.org/10.1056/NEJMoa1707855





Marrouche et al, NEJM 2018

Relative Risk of Ablation vs. Medication

AF Ablation

- Stroke
- Phrenic Nerve Paralysis
- Vascular Complication
- Esophageal Injury
- Valve Injury
- Chest Pain

Medication

- Life threatening arrhythmia
- CHF
- Liver toxicity
- Thyroid toxicity
- Headache
- Fatigue

Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation - CABANA

- Description:
- Goal: Compare the safety and efficacy of catheter ablation with drug therapy for treatment of new-onset or untreated atrial fibrillation (AF).
- Study Design
- Pts randomized in a 1:1 fashion to catheter ablation (n = 1,108) or drug therapy (n = 1,096).
- Duration of follow-up: 5 years
- Mean patient age: 67.5 years
- Percentage female: 37%
- Inclusion criteria:

Presented by Dr. D.Packer at HRS 2018

Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation - CABANA

- Study Design
- Paroxysmal, persistent, or longstanding persistent AF patients who warrant therapy
- ≥65 years of age
- <65 years of age with ≥1 cerebrovascular accident (CVA)/cardiovascular (CV) risk factor
- Eligible for ablation
- On ≥2 rhythm or rate control drugs

Other Salient Features/Characteristics:

- Cardiomyopathy: 9%
- Chronic heart failure: 15%
- Prior CVA/transient ischemic attack (TIA): 10%
- Type of AF: paroxysmal: 43%, persistent 47%
- Prior hospitalization for AF: 39%
- Crossover:
  - ablation to drug: 9.2%
  - drug to ablation: 27.5%

ITT Outcomes

- **The primary outcome [death, disabling stroke, serious bleeding, or cardiac arrest] at 5 years:**
  - **ablation = 8%**
  - **drug therapy = 9.2%, p = 0.3**
- **Death: 5% vs. 6% for ablation vs. drug therapy, p = 0.38**
- **Serious stroke: 0.3% vs. 0.6% for ablation vs. drug therapy, p = 0.19**
- **Death or CV hospitalization:**
  - ✓ **51.7% vs. 58.1% for ablation vs. drug therapy, HR 0.83, 95% CI 0.74-0.93, p = 0.002**

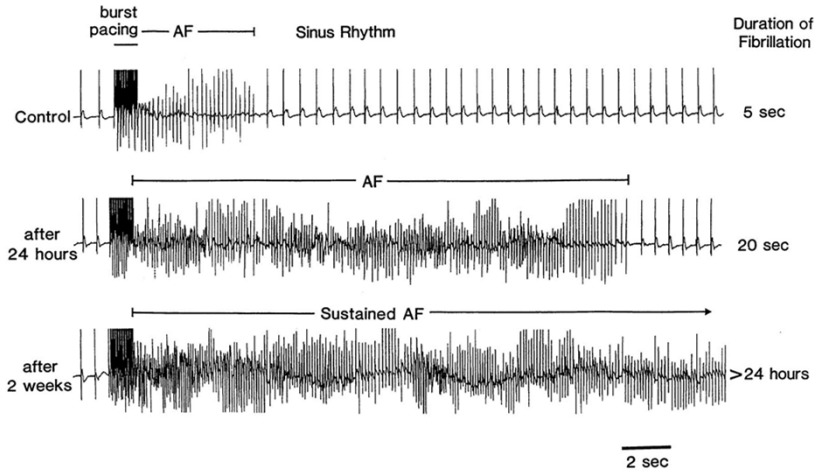
Outcomes Based on Treatment Received

- **Primary endpoint**
  - **Ablation=7%**
  - **Drug Therapy=10.9% p=0.006**
- ***Death: 4.4% vs. 7.5% for ablation vs. drug therapy: p = 0.005***
- ***Death or CV hospitalization: 41.2% vs. 74.9% for ablation vs. drug therapy: p = 0.002***

Cabana Conclusions

- **Catheter ablation did not result in reduction in primary endpoint over drug therapy**
- **Ablation significantly reduced combined mortality or hospitalization by 17% over drug therapy**
- **There was a 47% reduction in AF with ablation compared to drug therapy**
- **There was a 40% reduction in mortality and a 33% reduction in the primary endpoint with ablation in on-treatment analysis.**

Prolongation of the duration electrically induced episodes of atrial fibrillation (AF) after maintaining AF for 24 hours vs. 2 weeks.



American Heart Association. Atrial Fibrillation Begets Atrial Fibrillation
Maurits C.E.F. Wijffels , MD , Charles J.H.J. Kirchhof , MD, PhD , Rick Dorland , BS , and Maurits A. Allessie , MD, PhD

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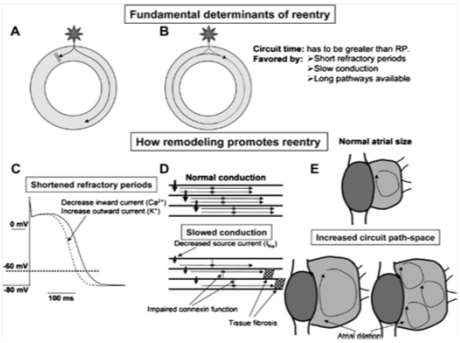
AF begets AF

AF itself causes arrhythmogenic milieu that further promotes and maintains AF:

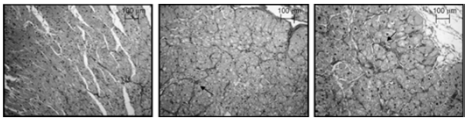
- **Atrial electrical remodeling**
  - **↓Atrial ERP, ↑spatial heterogeneity of ERP, ↓normal ERP rate adaptation**
  - **Slow conduction**
    - **Modulation of Na channels, gap junctions (connexins), altered tissue structure**
- **Structural remodeling**
  - **Macro-atrial dilation**
  - **Micro-atrial fibrosis**



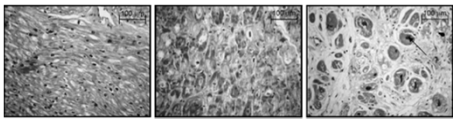
https://doi.org/10.1016/j.pbiomolbio.2012.07.011

Spectrum of Disease
At Different Stages of AF, Different Sustaining Mechanisms May Dominate

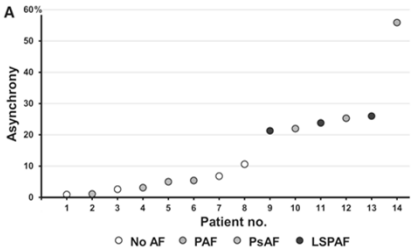
Degrees of Fibrosis (Sirius Red stained paraffin sections)



Degrees of Cell Degeneration (hematoxyline– eosin)



https://doi.org/10.1016/j.cardiores.2005.04.016



Endo-Epi Asynchrony

More advanced remodeling may not reverse after resumption of NSR

American Heart Association. Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans. Natasja de Groot, MD, et al © Copyright 2016 American Heart Association, Inc.

Kottkamp et al; JCE 2016

W. Anne´ et al. / Cardiovascular Research 67 (2005)

de-Groot et al, Circ Arrhythmia 2016

Does the Form of AF Management Affect LA Remodeling?

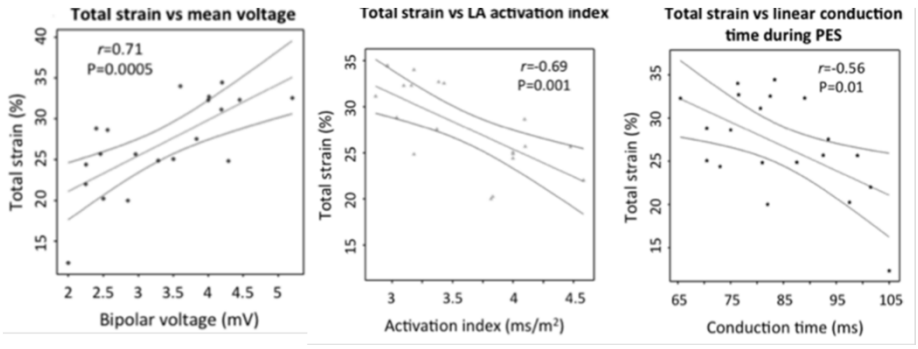
- **With PAF:**
  - **risk of Persistent AF 15% at one year**
  - **risk of Persistent AF 25% at 5 years**
- **Conflicting data as to whether AF-associated remodeling reverses after effective ablation vs. medical management**
- **The progression or regression of atrial remodeling over a 12-month period with medical management or catheter ablation was assessed in 83 patients**
- **Prospective, nonrandomized cohort analysis**

Walters et al, Heart Rhythm, Vol 13, No 2, February 2016

Remodeling of LA With Different Forms of Management

- 83 pts recruited into 3 groups:
  - PAF undergoing medical management (group 1,n = 38)
  - PAF undergoing ablation (group 2,n = 20)
  - Control pts without Hx of AF(group 3,n = 25).
- Two blinded, baseline assessments of:
  - BP,anthropometric measurements,
  - Digital ECG (with P wave duration and dispersion)
  - TTE assessment of myocardial strain (total and peak positive strain taken to be indirect markers of LA structural remodeling and of atrial myocardial fibrosis)
  - Sleep evaluation
- Ablation patients evaluated for LA voltage, LA activation times
- Repeat ECG and echocardiography at 4, 8, and 12 months.
- AF groups underwent ILR implant

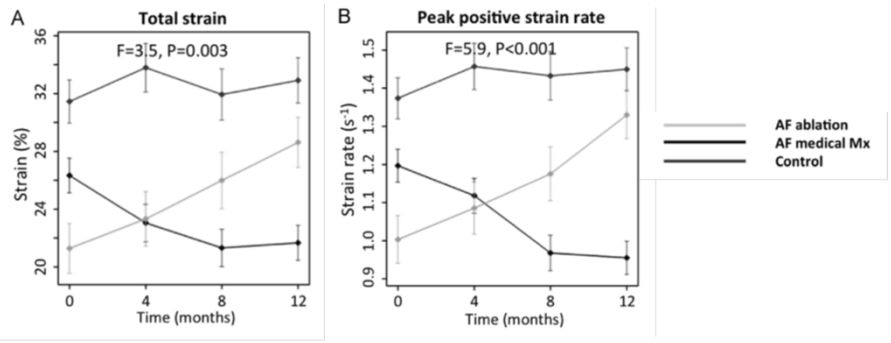
Correlation of Echo with EA Mapping Markers of La Disease



- AF burden in Medication Group: 8% (3-53%)
- AF burden in Ablation Group: 0% (0-1%)
- The echo is a good measure of LA reserve and extent of remodeling

https://doi.org/10.1016/j.hrthm.2015.10.028

Effect of Ablation vs. Med Management of LA Remodeling



- **AF Burden ≥ 10% predicted significant drop in strain (remodeling)**
- **P wave duration and dispersion significantly increased in medical management group , not ablation group**
- **Inclusion of co-morbidities in regression models did not attenuate between group differences based on presence of AF**

https://doi.org/10.1016/j.hrthm.2015.10.028

How long are we waiting? STAR AF II

- **589 Persistent AF assigned to PVI, PVI+complex EGM, PVI+lines (roof, mitral valve isthmus) in a 1:4:4 ratio**
  - **48 centers in 12 countries**
  - **Failed >=1 AAD**
  - **Continued AAD use allowed**
  - **Enrolled between 2010-2012**

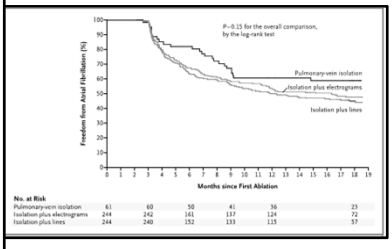


Table 1. **Characteristics of the Patients at Baseline.***

Characteristic	Isolation Alone (N=67)	Isolation plus Electrograms (N=263)	Isolation plus Lines (N=259)
Age — yr	58±10	60±9	61±9
Male sex — no. (%)	52 (78)	213 (81)	196 (76)
Ejection fraction — %	55±11	57±10	57±10
Left atrial diameter — mm	44±6	44±6	46±6
Time from first diagnosis of atrial fibrillation — yr	4.3±6.3	4.2±5.0	3.6±4.2
Burden of atrial fibrillation at baseline — hr/mo†	83±36	85±33	80±37
Constant atrial fibrillation for >6 mo — no. (%)	52 (78)	207 (79)	186 (72)
Medical history — no. (%)			
Hypertension	32 (48)	143 (54)	158 (61)
Diabetes	6 (9)	31 (12)	26 (10)
Coronary disease	2 (3)	21 (8)	29 (11)
Stroke or transient ischemic attack	6 (9)	14 (5)	19 (7)
Heart failure	3 (4)	10 (4)	15 (6)
$CHADS_2$ score — no. (%)			
0	31 (46)	93 (35)	81 (31)
1	25 (37)	126 (48)	127 (49)
2	6 (9)	31 (12)	29 (11)
>2	5 (7)	10 (4)	19 (7)
Baseline CCS SAF score — no./total no. (%)			
0	2/63 (3)	12/248 (5)	14/243 (6)
1	14/63 (22)	55/248 (22)	53/243 (22)
2	19/63 (30)	79/248 (32)	70/243 (29)
3	24/63 (38)	86/248 (35)	89/243 (37)
4	4/63 (6)	16/248 (6)	17/243 (7)

Verma A et al. NEJM 2015; 372:1812-22

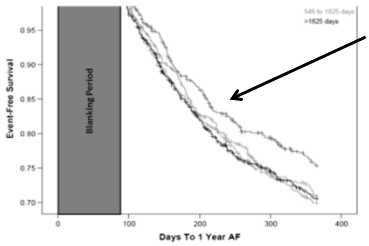
Longer Waiting Time After AF Dx Decreases AF Ablation Success?

Intermountain Healthcare database N=4535

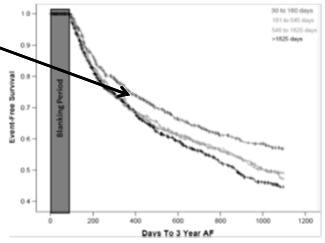
Table 1 Baseline patient demographics separated by the time interval from first known diagnosis of AF and first AF ablation procedure

Characteristic	30–180 days (n = 187)	181–545 days (n = 116)	546–1825 days (n = 186)	>1825 days (n = 195)	*P* value
Age (years)	63.7 ± 11.1	62.6 ± 11.8	66.4 ± 10.2	67.6 ± 9.7	<.0001
Sex (male)	62.6%	62.1%	56.5%	64.1%	.45
Hypertension	64.7%	82.8%	74.7%	80.0%	.001
Hyperlipidemia	28.9%	25.9%	36.0%	32.3%	.25
Diabetes	21.4%	25.0%	21.5%	24.6%	.79
Heart failure	19.8%	24.1%	41.4%	31.3%	<.0001
Prior myocardial infarction	4.3%	6.9%	7.5%	8.7%	.37
Prior cerebrovascular accident	2.7%	7.8%	5.9%	7.2%	.18
Prior cardioversion	44.9%	38.8%	35.5%	48.2%	.06
Paroxysmal	56.1%	58.6%	57.0%	59.5%	.92
Persistent	28.3%	25.0%	30.6%	27.2%	.74
Permanent	16.0%	17.2%	12.4%	13.3%	.58
Ejection fraction (%)	51.8 ± 13.1	51.0 ± 13.8	52.3 ± 13.8	54.8 ± 14.0	.001
Coronary artery disease (>50%)	5.3%	12.9%	17.7%	15.4%	.002

Outcomes	30–180 days	181–545 days	546–1825 days	>1825 days	*P* trend
Dead	11.7%	15.8%	20.4%	17.1%	<.0001
Recurrent AF	38.1%	45.7%	47.8%	46.0%	.001
Antiarrhythmic drug use	23.8%	33.3%	35.9%	34.5%	.11
Stroke/transient ischemic attack	3.4%	6.4%	6.5%	8.3%	<.0001
Heart failure admission	8.5%	11.1%	16.1%	17.7%	<.0001



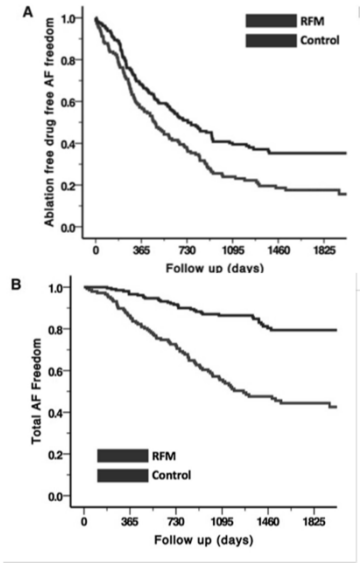
30-180 days



Bunch TJ et al. Heart Rhythm 2013;10:1257-1262

https://doi.org/10.1016/j.hrthm.2013.05.013

Elephant in The Room: Modifiable AF Risk Factors

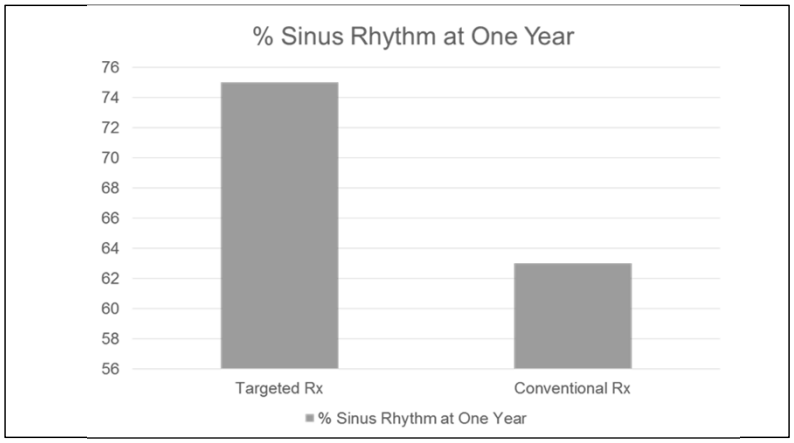


Prathak et al, JACCEP 2017

https://doi.org/10.1016/j.jacep.2016.12.015.

Race-3

Patients with CHF and Afib randomized to rhythm control with and without (i) MRA, (ii) statins, (iii) ACE-I and/or ARB, and (iv) cardiac rehabilitation



Rienstra et al, EHJ 2018

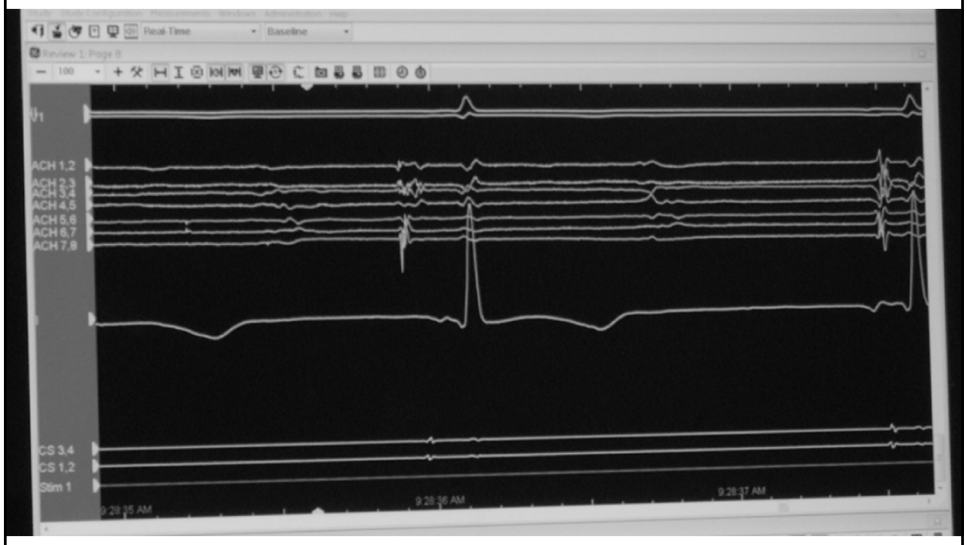
Conclusions

- **Atrial fibrillation carries risk of significant morbidity and mortality**
- **Risk Factor Modification is Critical**
- **Successful suppression (burden less than 10%) is likely safe and effective**
- **Progression of AF should be countered with early ablation as:**
  - **Progressive disease make the outcomes worse for PAF**
  - **Persistent AF has worse outcome**
  - **Early ablation confers better response**

The ablation procedure

Video of Ablation Procedure

Pre image



Post image