Persistent Atrial Fibrillation Ablation – Is it Worth It?

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Disclosures: Funded by NIH (R01 HL83359, R01 HL122384, K24 HL103800), British Heart Foundation, Fulbright Foundation, Heart Rhythm Society. SMN is co-inventor of IP owned by the University of California, licensed to Topera. Equity in Topera. Honoraria: ACC, Abbott, Medtronic, St Jude Medical, Uptodate

Is It That Bad? – Perhaps

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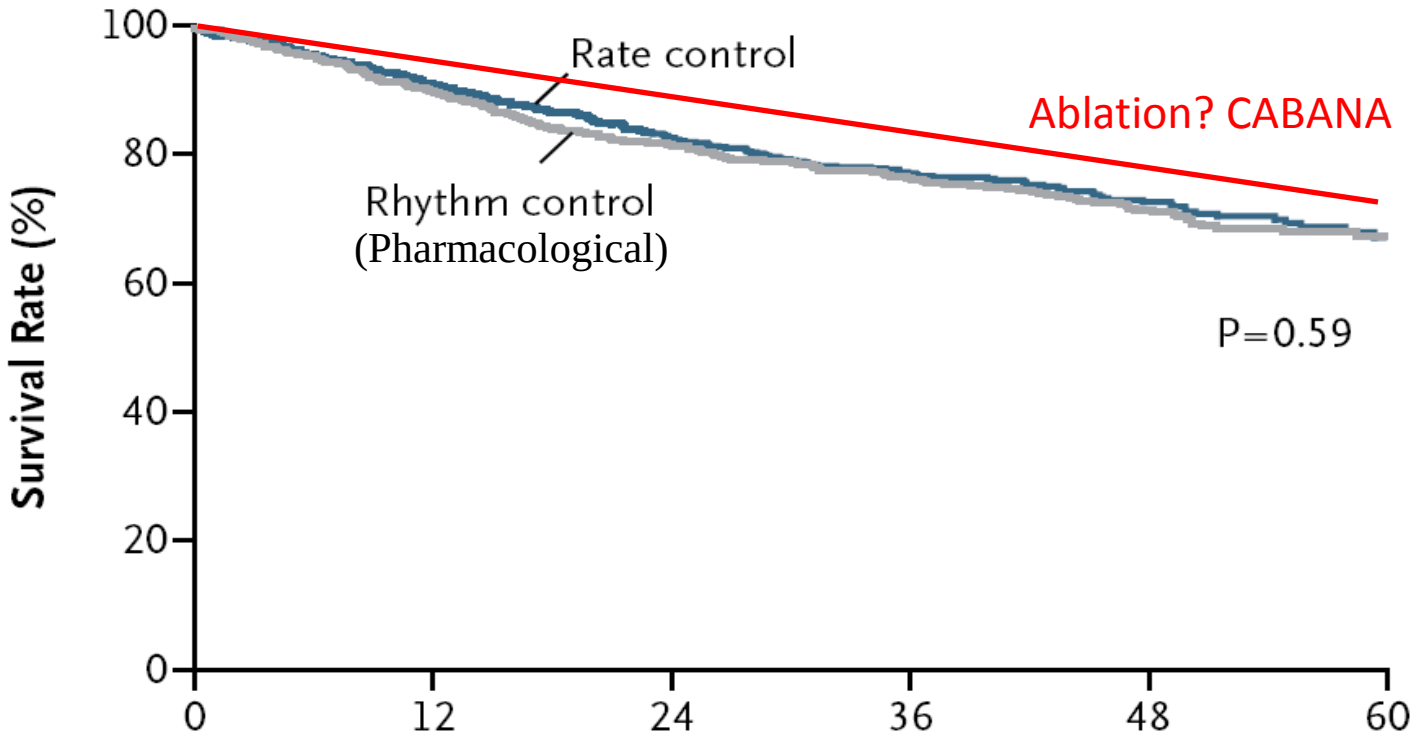
Persistent AF Ablation – Is it worth it?

- [x] Compared to which Alternatives, which Endpoints?
- [ ] Why May Persistent AF Ablation Not Seem Worth it?
- [ ] Addressing Procedural Variability
- [ ] Improved Mechanistic Targeting
- [ ] Conclusions

Wilber et al., JAMA 2010; Packer et al., STOP-AF. JACC 2013; Morillo et al., RAAFT-2, JAMA 2014;
Natale et al. SMART-Touch, JACC 2014; Ganesan, JAHA 2013; 2:e004549; Arbelo, et al, Eur H J 2014; 25: 1466-1478;
Dukkipati, JACC 2015 Laser Balloon

Survival. Is Ablation better than Alternatives? ?



No. at Risk					
Rhythm control	593	514	378	228	82
Rate control	604	521	381	219	69

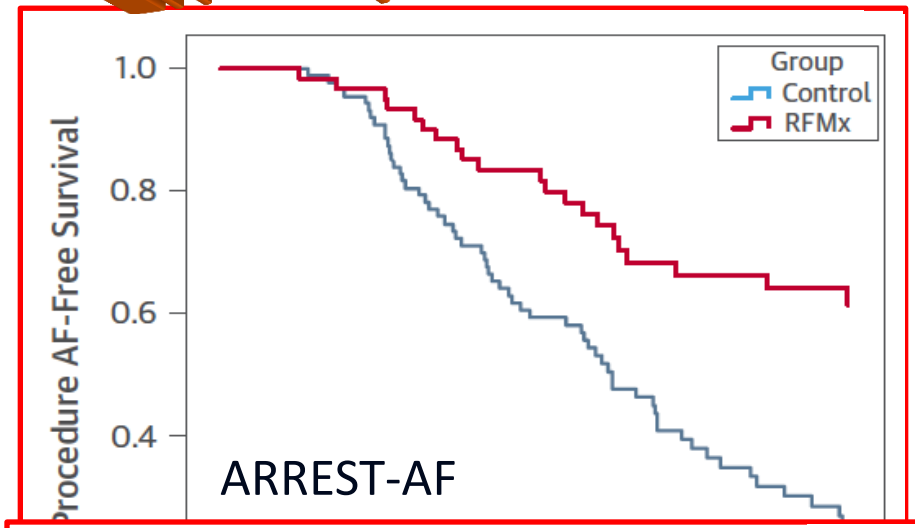
AF in CHF: 1376 patients, LVEF 27±6%, 67% persistent AF

Roy et al., AF-in-CHF, New Engl J Med 2008; 358: 2667-77

AF Freedom. Is Lifestyle Intervention As Good As Ablation?

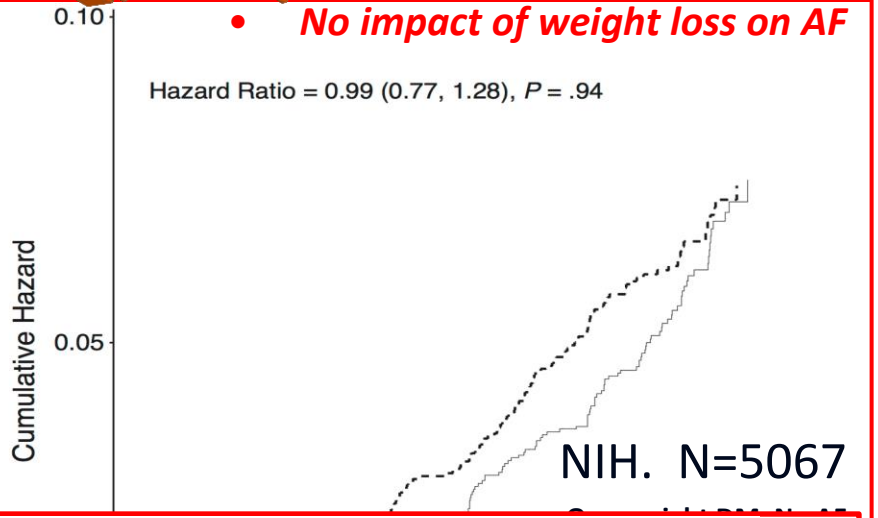
?

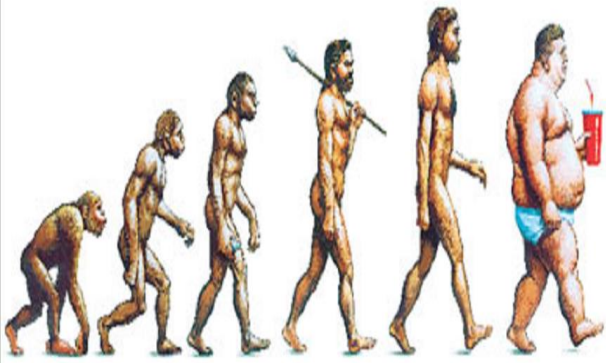
Lifestyle Helps



Lifestyle Less Help

- ***No impact of weight loss on AF***





No AF Drop For Any Quintile of Weight Loss…

	Q1	Q2	Q3	Q4	Q5
Range (% weight loss)	29.2-0.9	0.9 to –2.0	–2.0 to –5.2	–5.2 to –10.2	–10.2 to –43.4
AF events, n	54	53	60	46	51
Person-years	8750	8920	8796	8815	8874
Incidence, per 1000 person-years	6.2	5.9	6.8	5.2	5.8
			HR (95% CI)		
Model 1	1 (ref)	0.95 (0.65-1.38)	1.11 (0.77-1.61)	0.84 (0.57-1.24)	0.91 (0.62-1.33)
Model 2	1 (ref)	0.88 (0.60-1.29)	1.07 (0.74-1.55)	0.80 (0.54-1.19)	0.78 (0.53-1.14)
Model 3	1 (ref)	0.90 (0.59-1.38)	1.09 (0.71-1.67)	0.79 (0.48-1.30)	0.70 (0.41-1.18)

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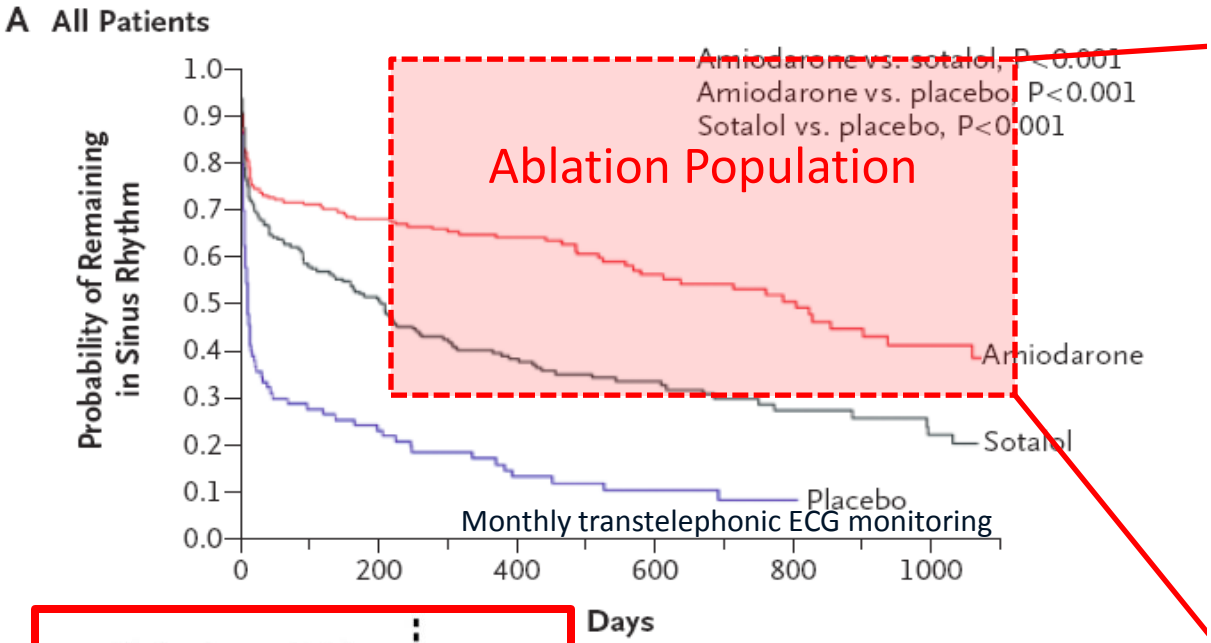
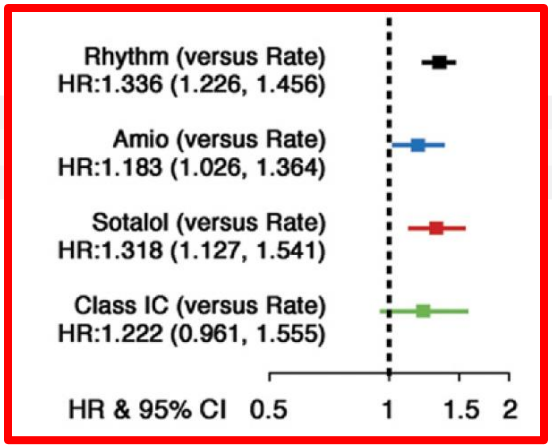
Abed et al., JAMA 2013; Pathak, Sanders et al. JACC 2014; 64(21): 2222-2231

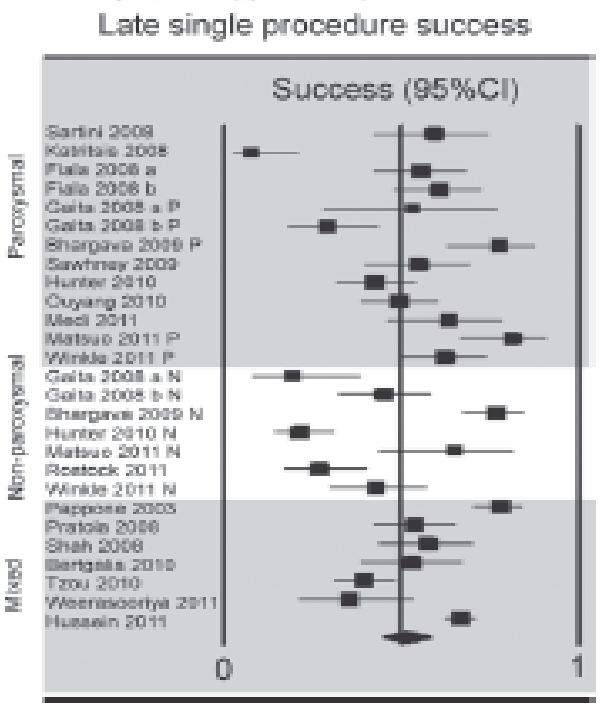
Alonso A et al. Look AHEAD. Am Heart J. 2015;170:770-777 e5

Persistent AF Freedom. Is Ablation Better than Anti-Arrhythmic Medications?





Anti-arrhythmic medications raise cardiovascular death and hospitalization

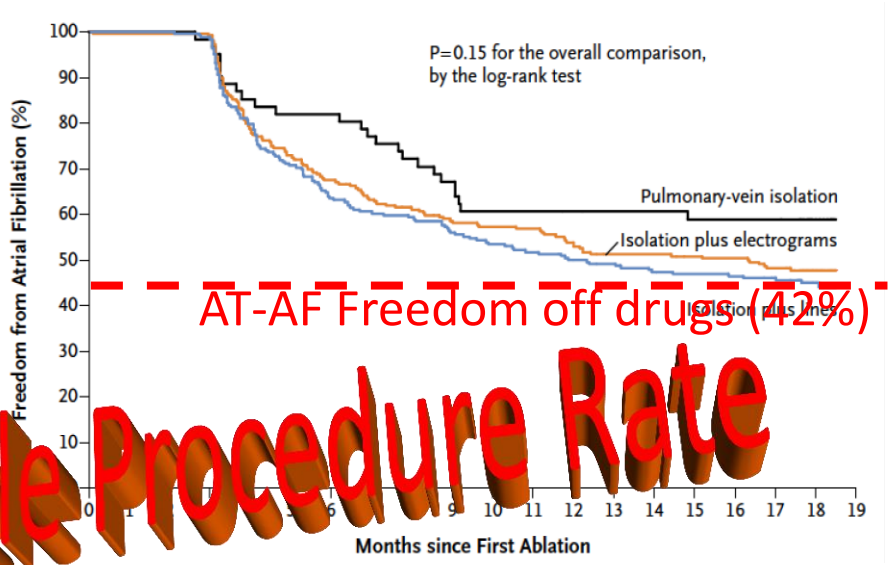


Singh et al., SAFE-T. NEJM 2005; 352(18): 1861-1872; Ganesan, JAHA 2013; 2:e004549
Saksena, JACC 2010 (AFFIRM subanalysis)

Is Ablation for Persistent AF Worth It – Compared to Ablation for Paroxysmal AF?

Paroxysmal AF (single procedure)

Persistent AF (single procedure)



AT-AF Freedom off drugs (42%)

40-60% Success Single Procedure Rate

- **Needs to Improve, but within reach?**
- **Very Long Term Outcomes (3-5Y) for each – suboptimal**

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Dukkipati et al., Heartlight trial. J Am Coll. Cardiol. 2015;66:1350-60;
Verma et al. STAR-AF 2 Trial. N Engl J Med. 2015;372:1812-22

Persistent AF Ablation – Is it worth it?

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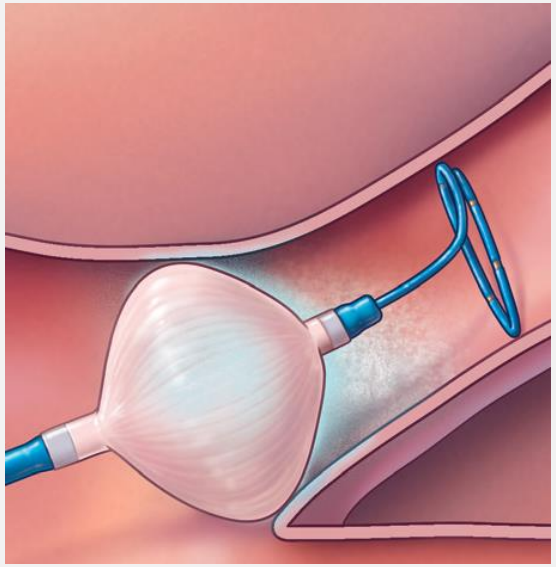
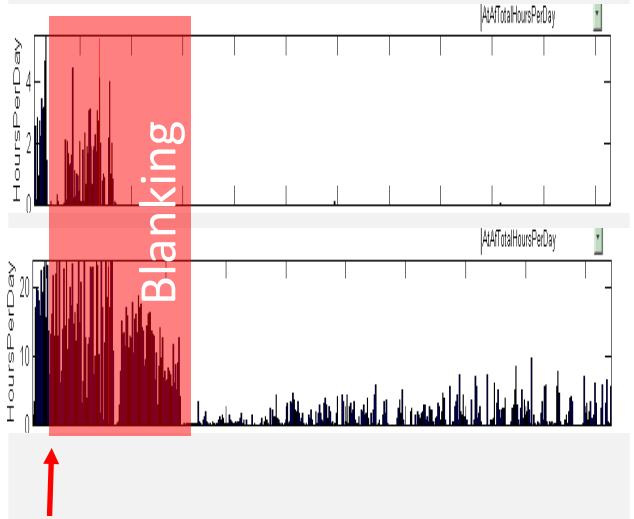
Con: Why may Persistent AF Ablation *not seem worth it?*

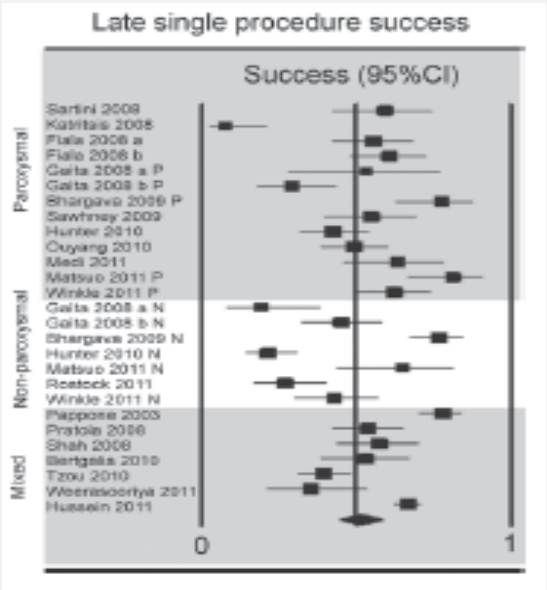
Procedures Not Rapid, Easy



Early Recurrences, difficult to manage (cardiovert etc)



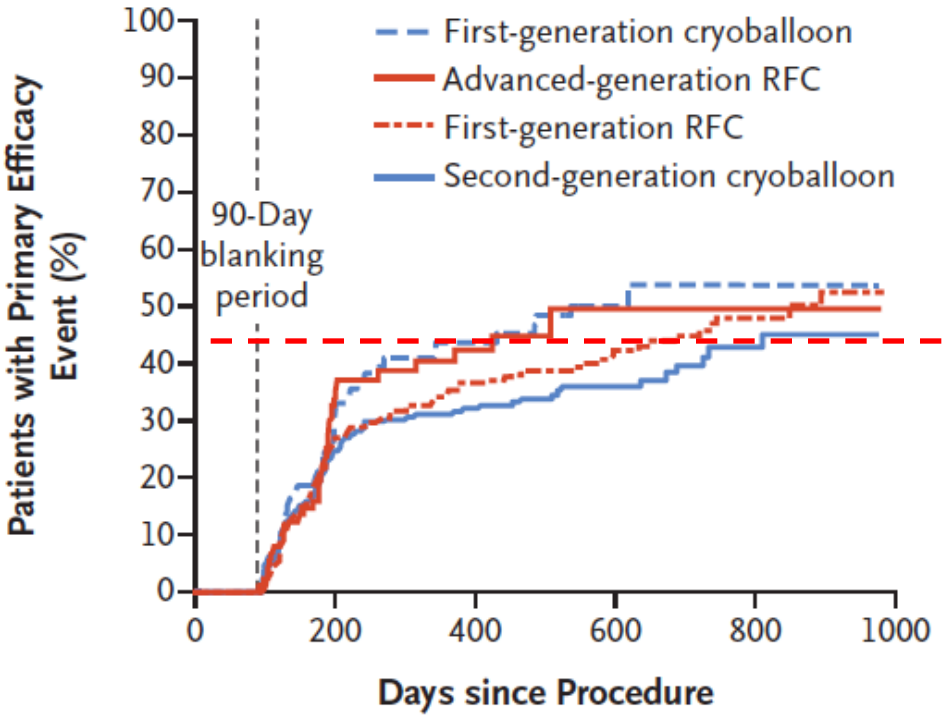
Too Much Variation in Outcome



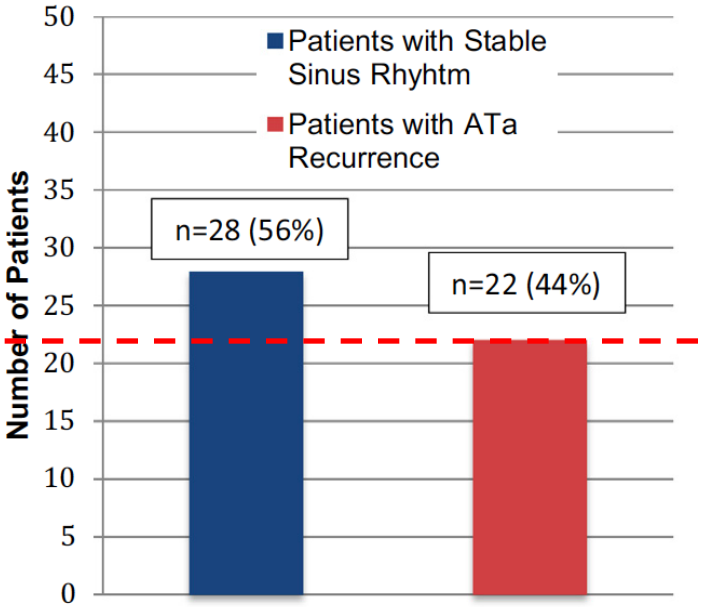
Long-term Success Rates Need to Improve

Can Persistent AF Ablation Be Quick/"Easy"? Yes – Potentially (PVI 40-60%)

Paroxysmal AF



Persistent AF - Cryoballoon



N=50 patients

Kuck et al., Fire and Ice. NEJM 2016; **Tscholl** et al. Two years outcome persistent AF after PVI using the second-generation cryoballoon. Heart Rhythm 2016; 13(9): 1817-1822.

Can Troublesome Early Recurrences after Persistent AF Ablation Be Reduced?

BOCA – To Reduce AT, Don't Ablate CFAE?

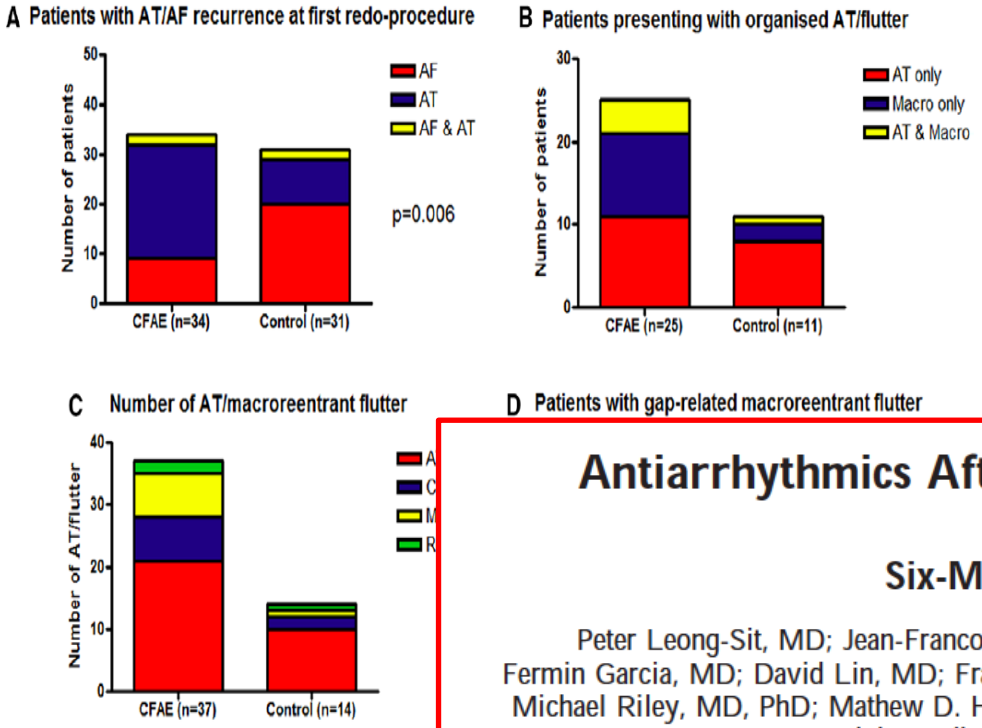


Figure 4. A, Graph showing atrial tachycardia (AT)/atrial fibrilla
senting with AT/flutter. C, Graph showing the number of AT/flu
complex fractionated atrial electrogram.

Routine use of Anti-arrhythmics in blanking period reduces ERAF

Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study)

Six-Month Follow-Up Study

Peter Leong-Sit, MD; Jean-Francois Roux, MD; Erica Zado, PA-C; David J. Callans, MD; Fermin Garcia, MD; David Lin, MD; Francis E. Marchlinski, MD; Rupa Bala, MD; Sanjay Dixit, MD; Michael Riley, MD, PhD; Mathew D. Hutchinson, MD; Joshua Cooper, MD; Andrea M. Russo, MD; Ralph Verdino, MD; Edward P. Gerstenfeld, MD

Conclusions—Although short-term use of AADs after AF ablation decreases early recurrence of atrial arrhythmias, early use of AADs does not prevent arrhythmia recurrence at 6 months. Early AF recurrence on or off AADs during the initial 6-week blanking period is a strong independent predictor of long-term AF recurrence.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00408200.

(*Circ Arrhythm Electrophysiol*. 2011;4:11-14.)

Wong, Rajappan, Betts et al. BOCA, Circ A/E 2015

Leong-Sit, Gerstenfeld, 5A Study. Circ Arrhythm Electrophysiol 2011 ;4(1): 11-14.

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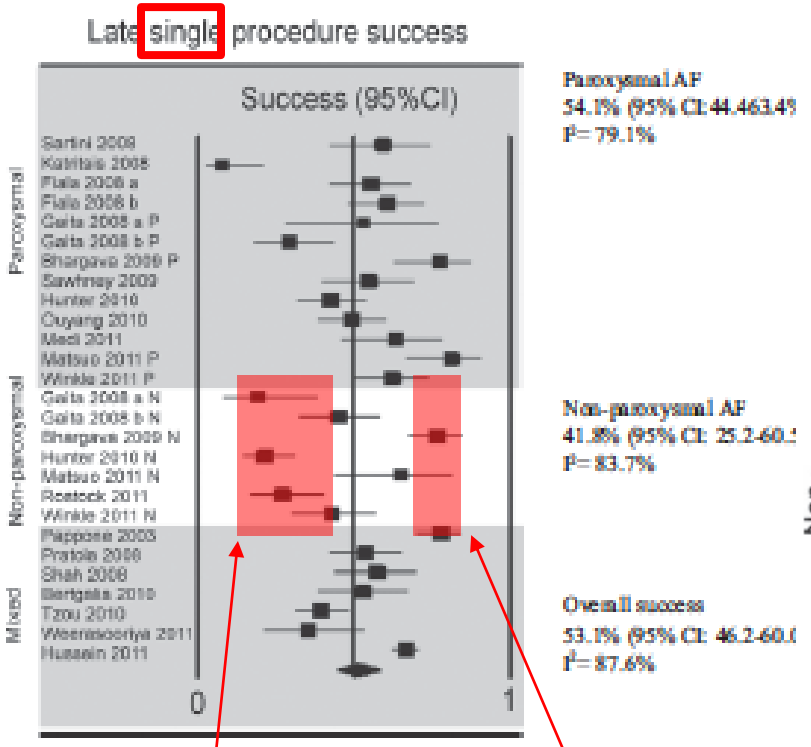
Dukkipati, JACC 2015 Laser Balloon

Is there Consistency with Persistent AF Ablation?

1st Procedure Modest at most centers

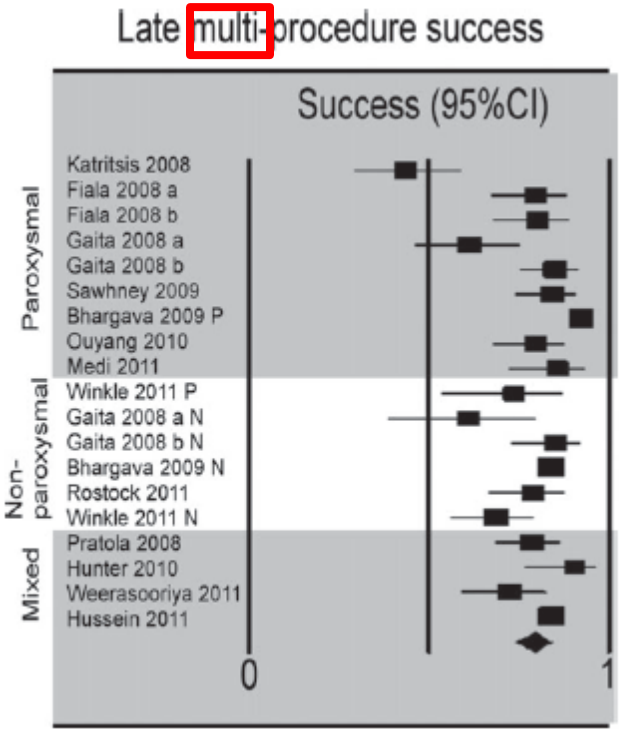
Multi Procedure better



Paroxysmal AF
54.1% (95% CI: 44.4-63.4%)
I²= 79.1%

Non-paroxysmal AF
41.8% (95% CI: 25.2-60.
I²= 83.7%

Overall success
53.1% (95% CI: 46.2-60.
I²= 87.6%



Paroxysmal AF
79.0% (95% CI: 67.6%-87.1%)
I²= 89.8%

Non-paroxysmal AF
77.8% (95% CI: 68.7-84.9%)
I²= 71.9%

Overall success
79.8% (95% CI: 75.0-83.8%)
I²= 83.9%

Gaita
Hunter
Rostock
WInkle

Natale
Pappone

➢i.e. Most Groups are actually consistent, with a few outliers (2016 update pending)

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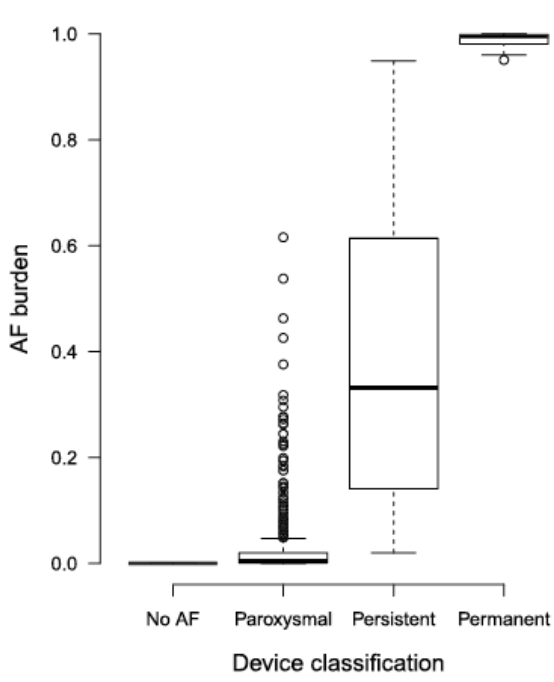
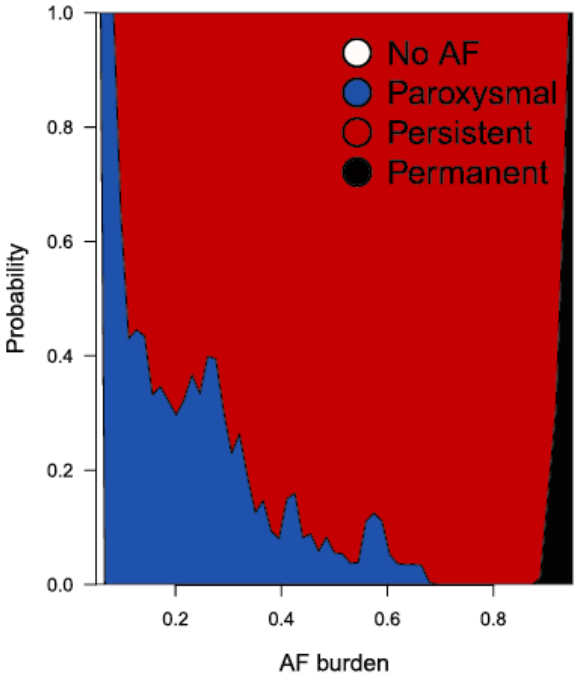
Ganesan, J. Am Heart Association 2013; 2:e004549

Persistent AF Ablation – Reasons for Variability

1 Mixing Patient Types

Early/Paroxysmal — POORLY SEPARATED — Persistent



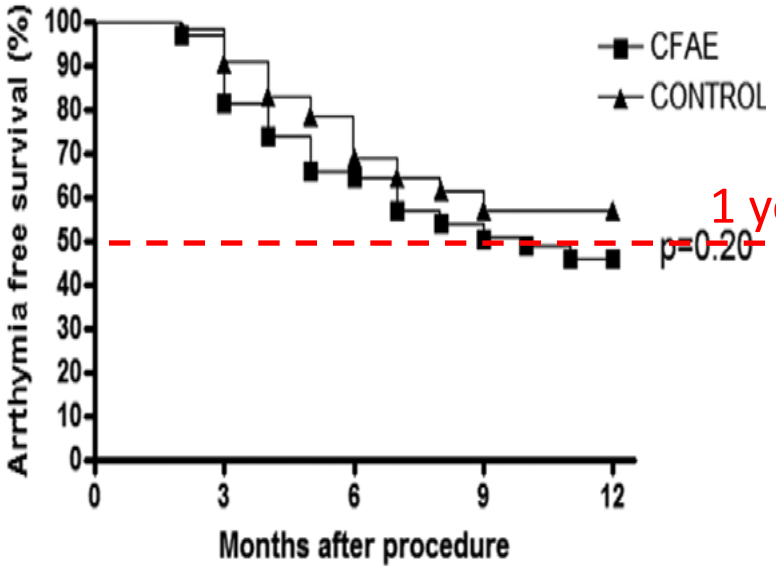


2 Comorbidities

Charitos et al. Clinical classifications of AF poorly reflect its temporal persistence. J Am Coll Cardiol 2014; 63(25 Pt A): 2840-2848.

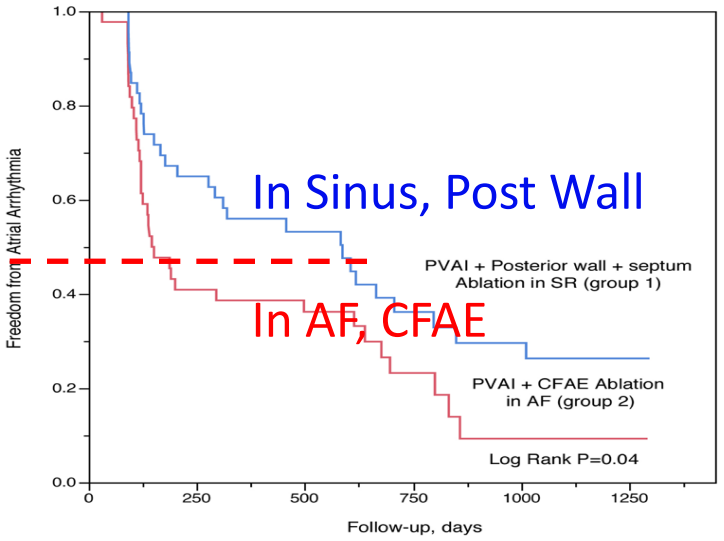
3. More (Empirical) ablation not better?

BOCA Trial



No. at risk					
CFAE	65	53	42	33	30
CONTROL	65	59	45	37	37

Cleveland Clinic



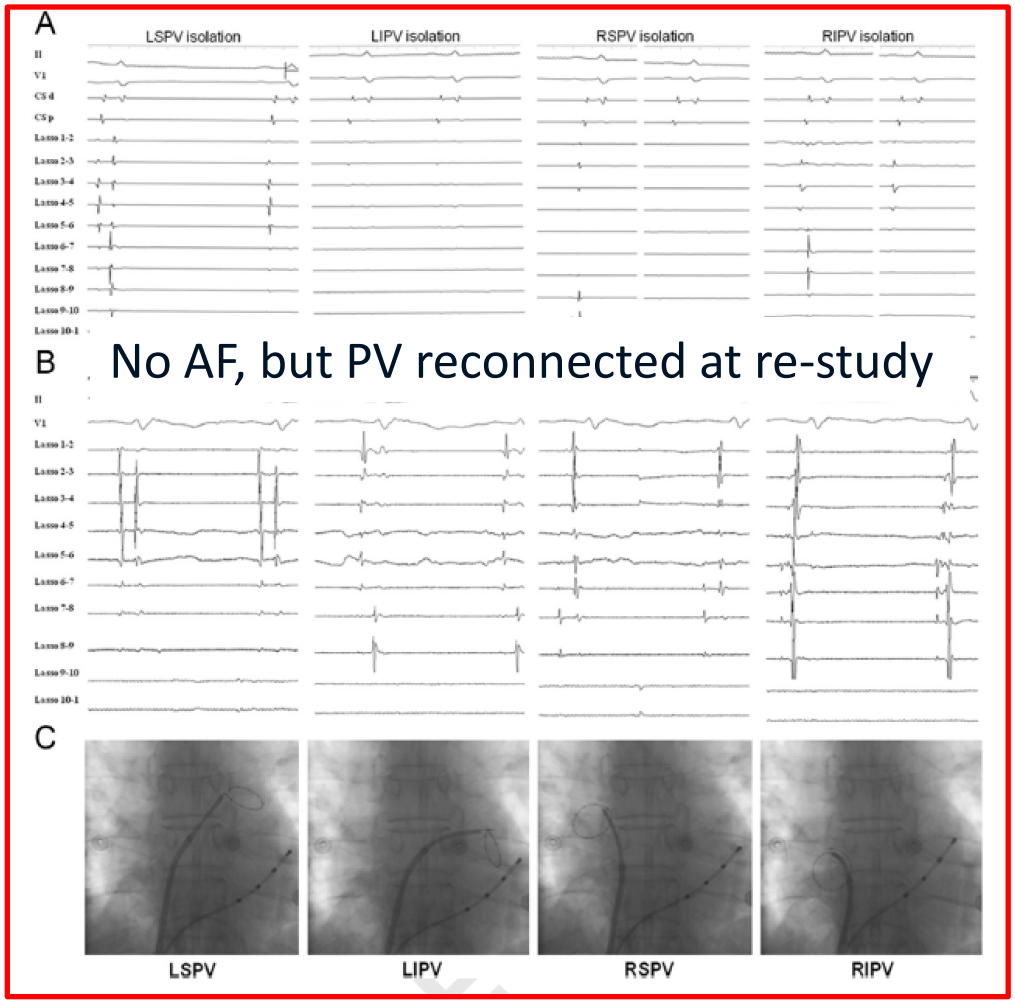
Number of patients at risk						
Group 1:	46	30	20	13	10	7
Group 2:	44	19	16	7	2	1

And, STAR-AF2; Verma et al. New Engl J Med 2015
CHASE-AF, JACC 2015

Wong, Rajappan, Betts et al. BOCA, Circ A/E 2015

Bassiouny , Lindsay, Wazni et al. Randomized Study of Persistent AF Ablation. *Circ Arrhythm Electrophysiol*. 2016;9:e003596.

When PV Ablation Works: It May Be Due to Adjacent Mechanisms (not "PV Isolation")



PV reconnections with, without AF

Pratola, Circulation 2008
Kuck, GAP-AF. Circ A/E 2016
Birnie Systematic Analysis. JACC: Clin EP; 2016

Hypothesis: After ablating a critical mass of PV tissue, other patient specific mechanisms should be targeted

Jiang RH, Po SS, Tung R, et al. Incidence of PV conduction recovery in patients without clinical recurrence after ablation of paroxysmal AF. Heart Rhythm. 2014;11:969-976

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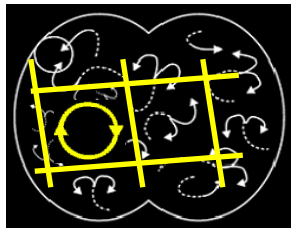
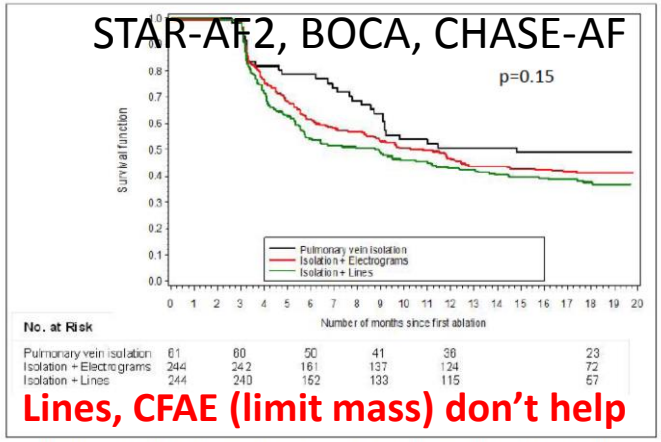
Natale et al. SMART-Touch, JACC 2014; Ganesan, JAHA 2013; 2:e004549; Arbelo, et al, Eur H J 2014; 25: 1466-1478;
Dukkipati, JACC 2015 Laser Balloon

Is AF 'Random' Waves..?



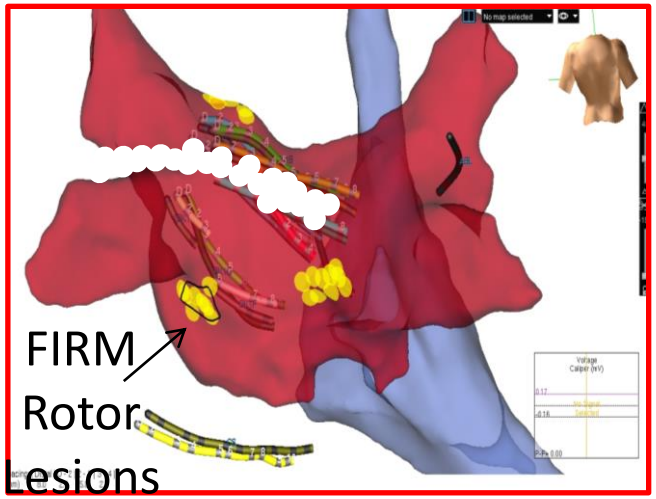
1. Lines Should limit 'random' – but don't..



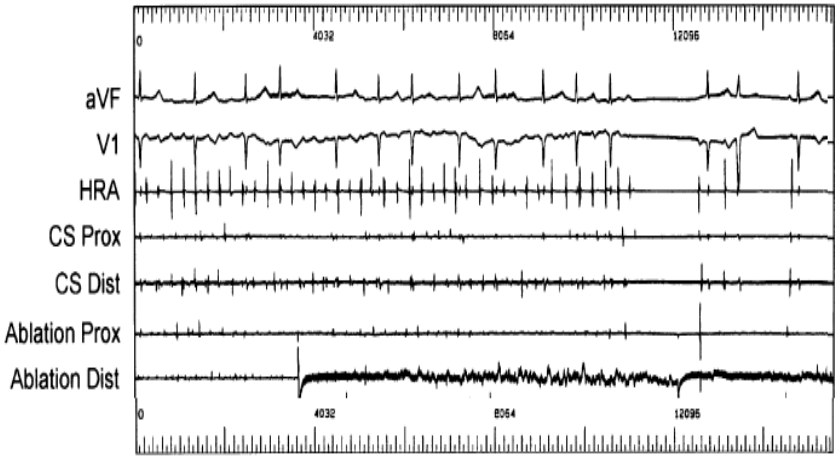
Documented AF > 30 seconds after one procedure with or without AAD

☐ Yes

☒ No

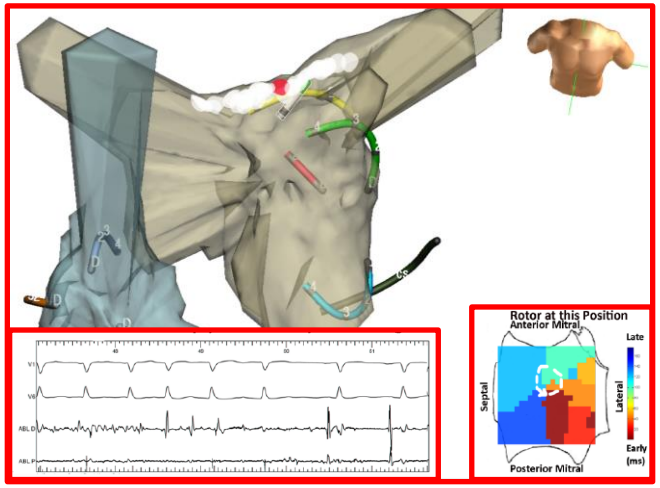


2. Localized Efficacy Argues against "random"



☐ Yes

☒ No



Cannot cardiovert, 1st lesion terminates AF; Herweg 2003

Also Narayan JACC 2012; Shivkumar JCE2012; Miller JCE 2014; …..

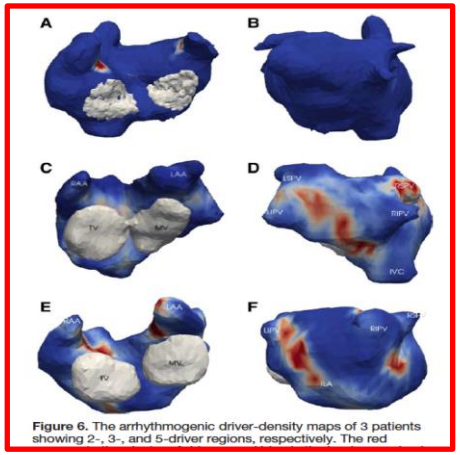
Verma, NEJM 2015; Wong, Circ A/E 2015; Herweg, PACE 2003; Shivkumar, JCE 2012; Miller JCE 2014
Narayan, JACC 2014

Numerous Approaches Show Human AF Drivers

Whose Ablation May Improve Outcomes

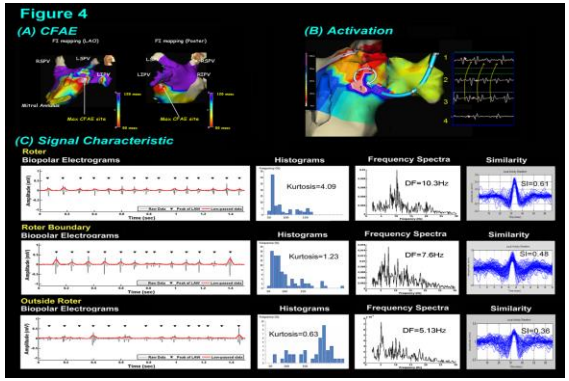
Non-Invasive AF Mapping

Haissaguerre, Circulation 2014

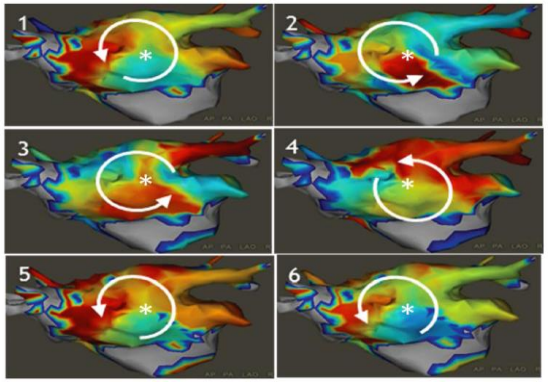


Contact AF Mapping

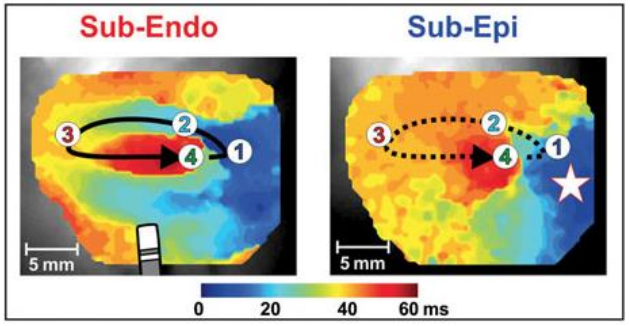
Wave Similarity. Lin, Chen SA Circ AE 2013. Stable, multipolar maps



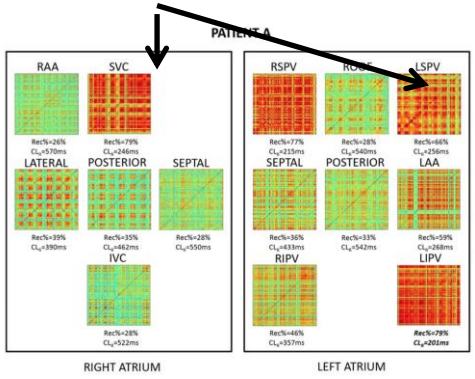
Cartofinder/Basket, Daoud et al., JACC: EP 2016



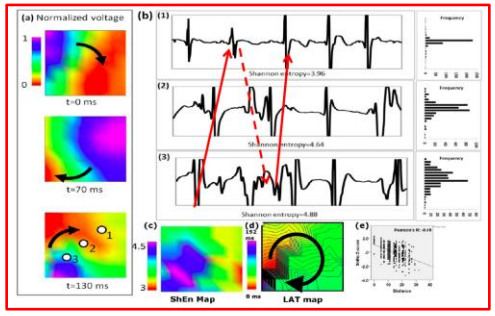
➢Human Optical: Stable AF Drivers (endocardium). Hansen/Fedorov, EHJ 2015



Stable Shape; Goldberger Ng, Heart rhythm 2014



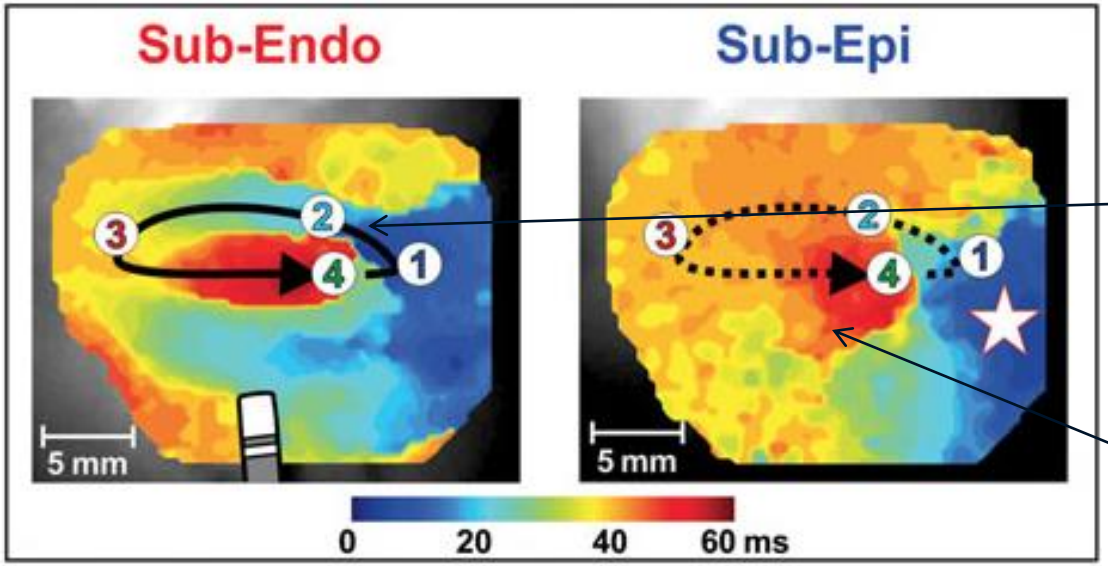
Stable Entropy Ganesan Circ AE 2013. Bipolar EGM



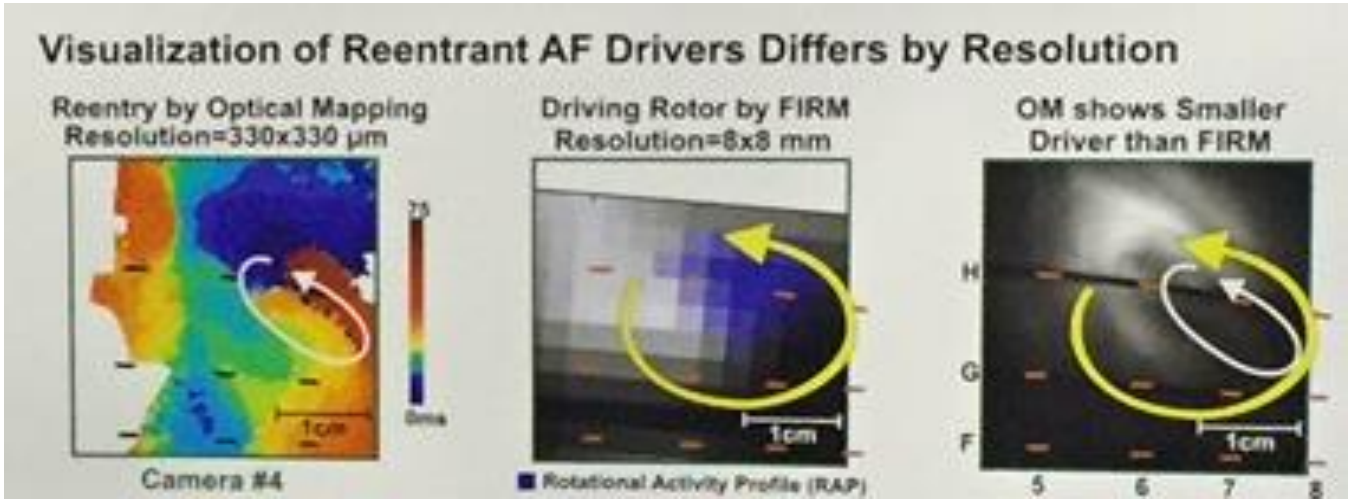
✔ Human atria

Optical Mapping of Human AF

Disorder present, DRIVEN by Stable Endocardial Sources



- Diseased human RA (1) and LA (2)
- Stable Endocardial (≈1-2 cm2) related to fibers, micro-fibrosis)
- Transient foci ,variable on epicardium



- 1st validation of clinical AF maps by human optical maps – FIRM

1. Hansen, Fedorov et al. *Eur Heart J. 2015. epub*

2. Zhao, Fedorov et al. Two Localized AF Rotors in Human Left Atrium. *Circulation A/E 2015; epub*

3. Hansen, Fedorov, Circulation 2015 (AHA Abstract)

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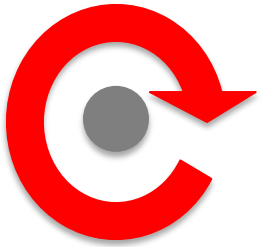
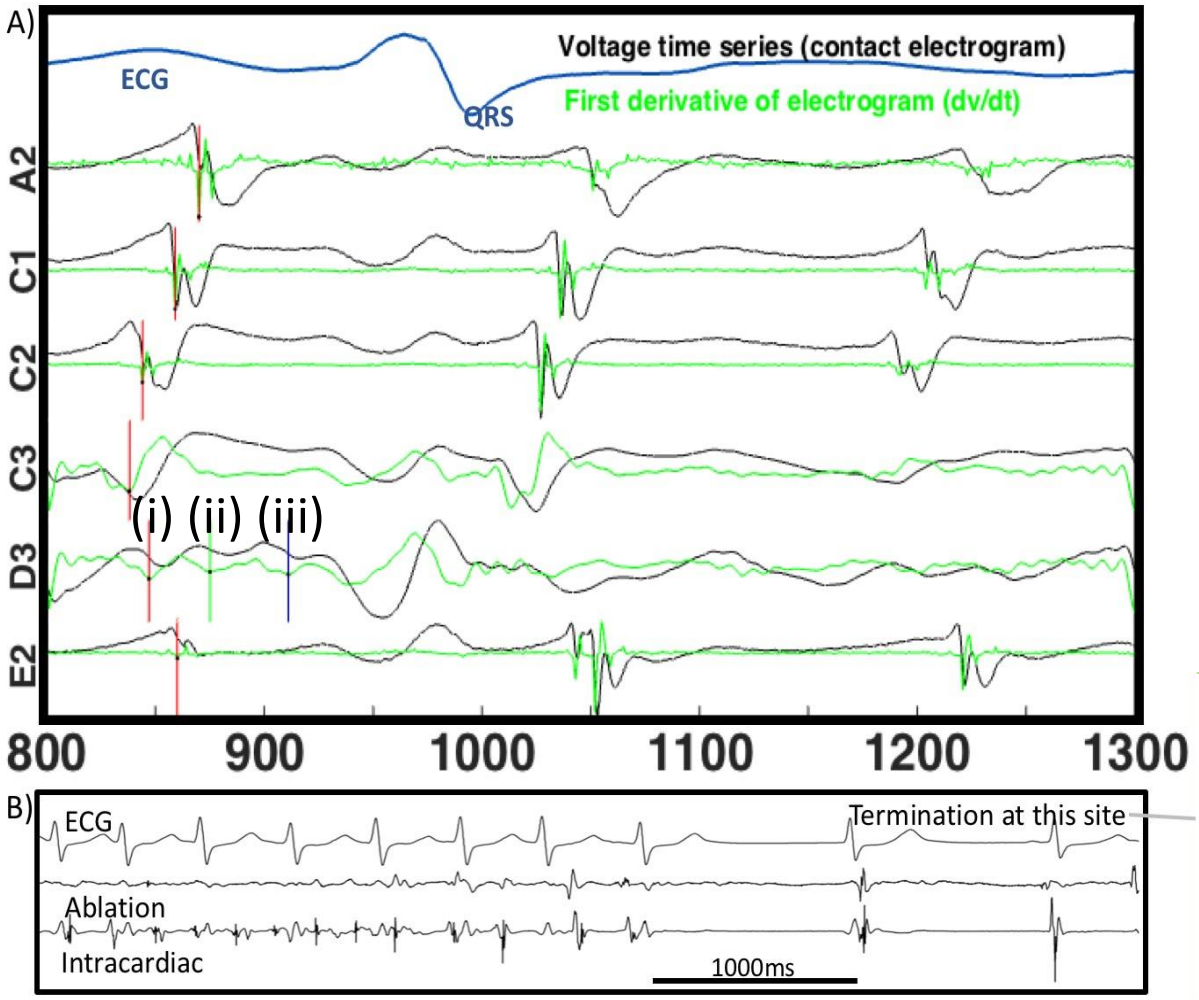


Classical Marking of AF Electrogram Times Often Ambiguous
Q: Can it explain clinical AF Observations?



N=60 patients persistent AF; N=5 Centers; Ablation at AF Source only terminates AF

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Zaman et al., submitted 2016

Persistent AF Ablation – Is it worth it?

- [x] Compared to which Alternatives, which Endpoints?
- [x] Why May Persistent AF Ablation Not Seem Worth it?
- [x] Addressing Procedural Variability
- [x] Improved Mechanistic Targeting – FIRM
- [ ] Conclusions

Wilber et al., JAMA 2010; Packer et al., STOP-AF. JACC 2013; Morillo et al., RAAFT-2, JAMA 2014;
Natale et al. SMART-Touch, JACC 2014; Ganesan, JAHA 2013; 2:e004549; Arbelo, et al, Eur H J 2014; 25: 1466-1478;
Dukkipati, JACC 2015 Laser Balloon

Summary, FIRM-Guided Ablation

Year	Authors	N	Persistent AF (N)	Auto Rotor Detect?	Endpoint	Estimated Cases/ Operator	1-Proc AF/AT Free Persist AF (%)	1-Proc AF Free All Cohort (%)	1-Proc AF/AT Free All (%)
2015	Sommer, Hindricks, JCE 2015	20	18	Yes	Elimination on remap	20	**80**	**85**	**80**
2015	Tomassoni, JICRM 2015	80	60	Yes	Elimination on remap	80	**70**	**95**	**75**
2015	Rashid, JICRM 2015	56	43	Yes	Elimination on remap	56	**77**	**82**	**79**
2015	Hoummse, Hummel, HRS '15	22	15	Yes	Elimination on remap	11	**60**	**73**	**n/a**
2015	Tilz, ESC 2015	25	15	Yes	Elimination on remap	15	**n/a**	**88**	**76**
2015	Prystowsky, Foreman HRS'15	125	72	Yes	Elimination on remap	30	**63**	**69**	**64**
2016	Shivkumar, Buch HR 2015	43	19	**No (<20%; pre 2013)**	**Termination, AF slowing**	**6**	**25**	**37**	**21**
2016	Steinberg, HR '16	47	35	**No (pre 2013)**	**Termination, AF slowing**	**6**	**n/a**	**12**	**n/a**
2016	Miller, Das, HR '16	170	106	Yes (>80% of cases)	Elimination on remap	55	**62**	**74**	**60**
2016	Schade, JCE 2016 Gianni, HRS abs 2015 Gianni, HR 2016 Mohanty, OASIS, HR '16	42	42	Yes	**AT (residual rotors) Not ablated**	**7**	**52**	**n/a**	**52**
2016	Spitzer, BAF '16	53	53	Yes	Elimination on remap	26	**79**	**n/a**	**79**
TOTAL	**11 (15) Studies**	**681**	**478**				**65%**	**70%**	**65%**

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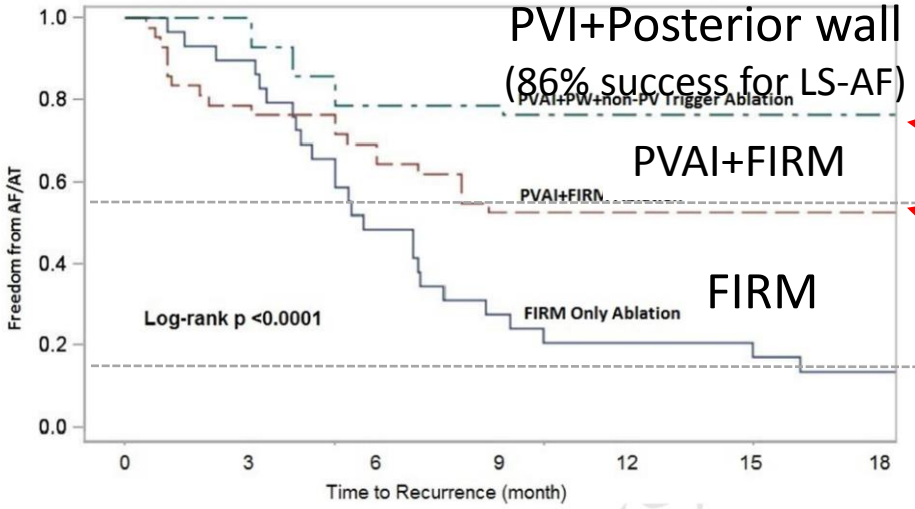
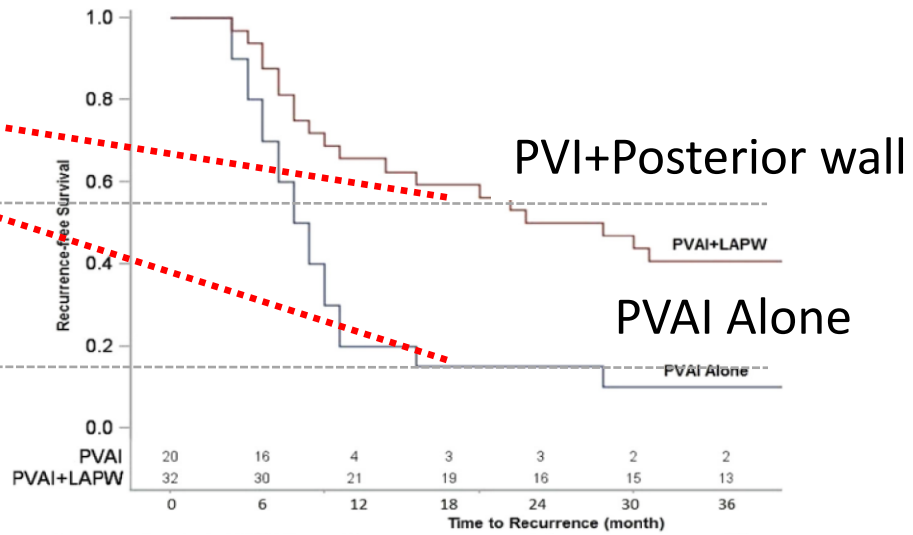
Baykaner, Narayan, Wang et al., in review

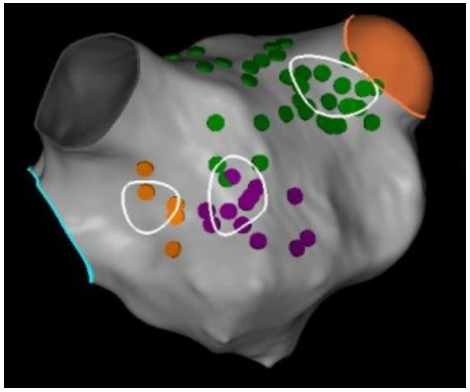
Excluding: CONFIRM (Narayan), Multicenter Registry (Miller)

FIRM+PVAI (Mohanty) vs PVAI in Same Lab

- Mohanty/Natale, JACC 2016
  - OASIS: NO PVI Only Limb
- Bai/Natale, Heart Rhythm 2016; 13(1): 132-140.

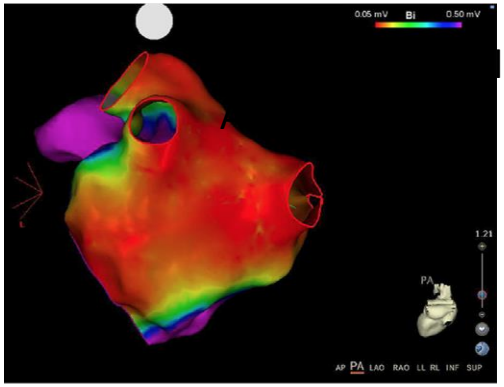






FIRM Only

- ✓ FIRM adds 20-30% success to PVI
- ✓ FIRM only ≈ PVAI only
- ✓ Learning curve for FIRM, n=6/user (222±49 min FIRM only) vs experienced for PV+Post wall (131± 51 mins)
- ✓ AT not ablated in FIRM group



PVAI+Post Wall

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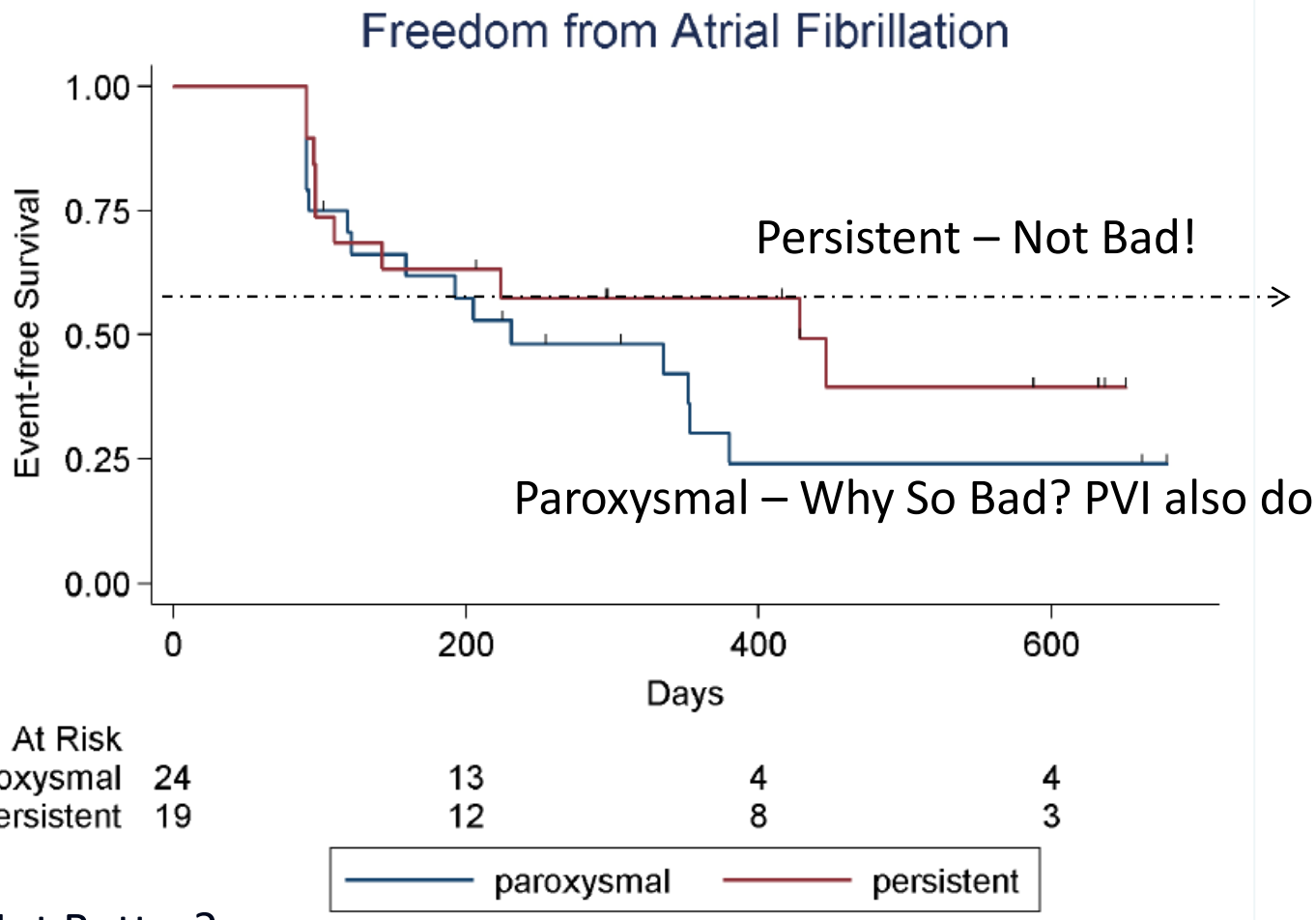
- Mohanty et al. JACC 2016; OASIS Persistent/Longstanding Persistent AF
- Bai et al. Heart Rhythm 2016; 13: 132-140

FIRM+PVI – Buch, Shivkumar et al



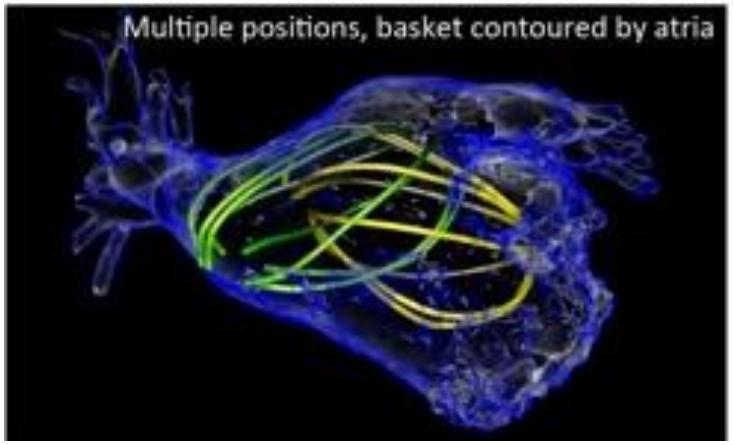
Why Not Better?

- Several had Multiple Prior Failed – PVs now isolated
- Cases in 2010-13, Prototype system, Learning curve?

Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J. et al, Heart Rhythm 2016

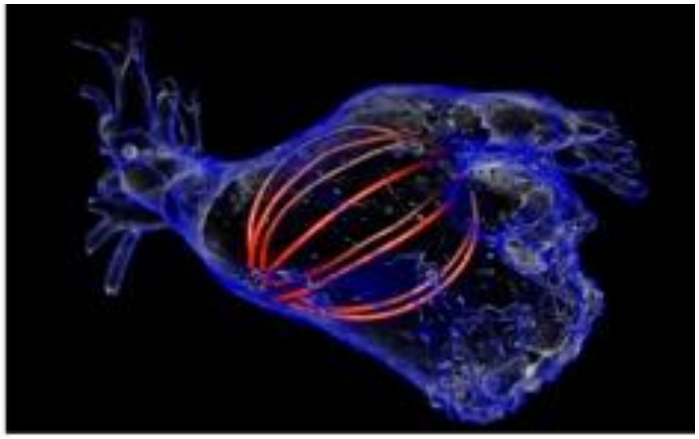
Rotor Ablation – Pearls and Pitfalls

Good Basket Position

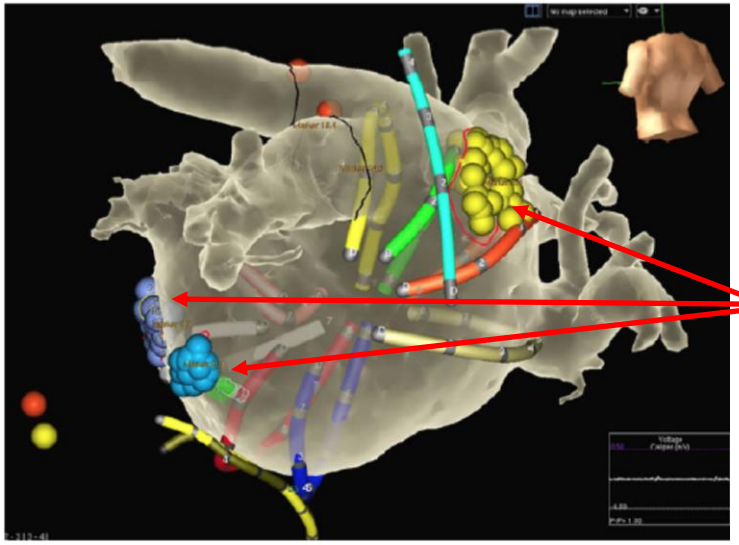


Good Ablation: Sommer et al., JCE 2015; 27(3): 274-280.

Suboptimal Basket Position

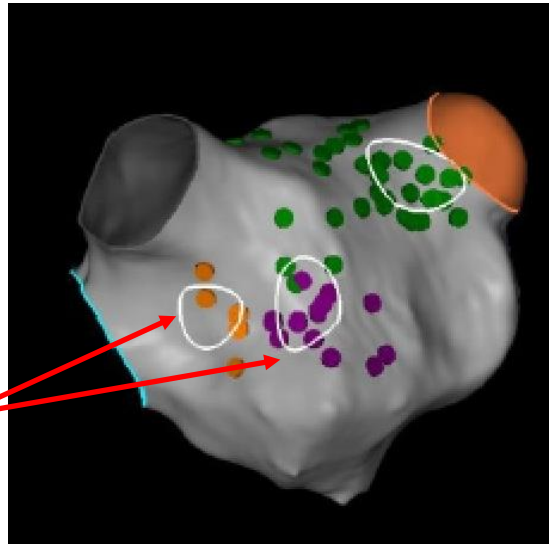


Disappointing Ablation: Gianni et al. Heart Rhythm, 2016; 13:830-5; fig.2



Dense

Incomplete

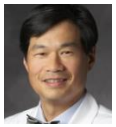


Conclusion – Ablation of Persistent AF is Definitely worth it …

- **Overall success is not so different from ablation of paroxysmal AF** which is 50-60% for a single procedure in randomized trials;
- **Optimize patient selection** if "simple" procedures are preferred, and manage expectations in blanking period and beyond;
- **Identify causes of variability** – patient selection, operator experience/learning curves, technical issues;
- **Need to improve success beyond current 40-50%.** This is likely not by extensive unguided/empirical ablation. This may be at localized AF mechanisms, possibly related to low voltage/MRI abnormalities.

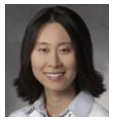
Stanford Complex Arrhythmia Program/Funding

NIH 2001-2020, AHA, ACC, HRS, Fulbright

EP Clinical/ Physiology



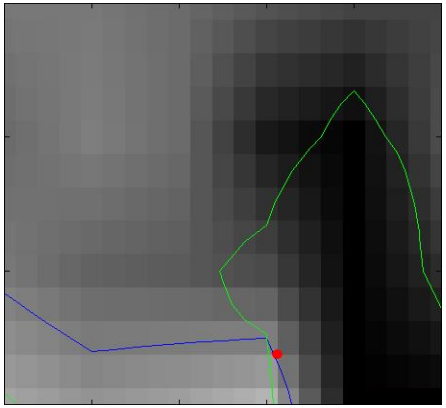



Narayan
NIH HL83359 (2014-2019)
NIH HL103800 (2015-2020)

Tina Baykaner
HRS Fellowship (2015-6)


Imaging

Philip Yang, Mike McConnell
NIH HL103800 (2015-2020)
Several other grants



AJ Rogers
Resident

George Leef
Resident

Computer Modeling


Wouter Rappel/Narayan
NIH HL122384 (2014-2019)

Junaid Zaman
Fulbright Scholar 2015-6
British Heart Found 2014-5
AHA Young Invest. 2015

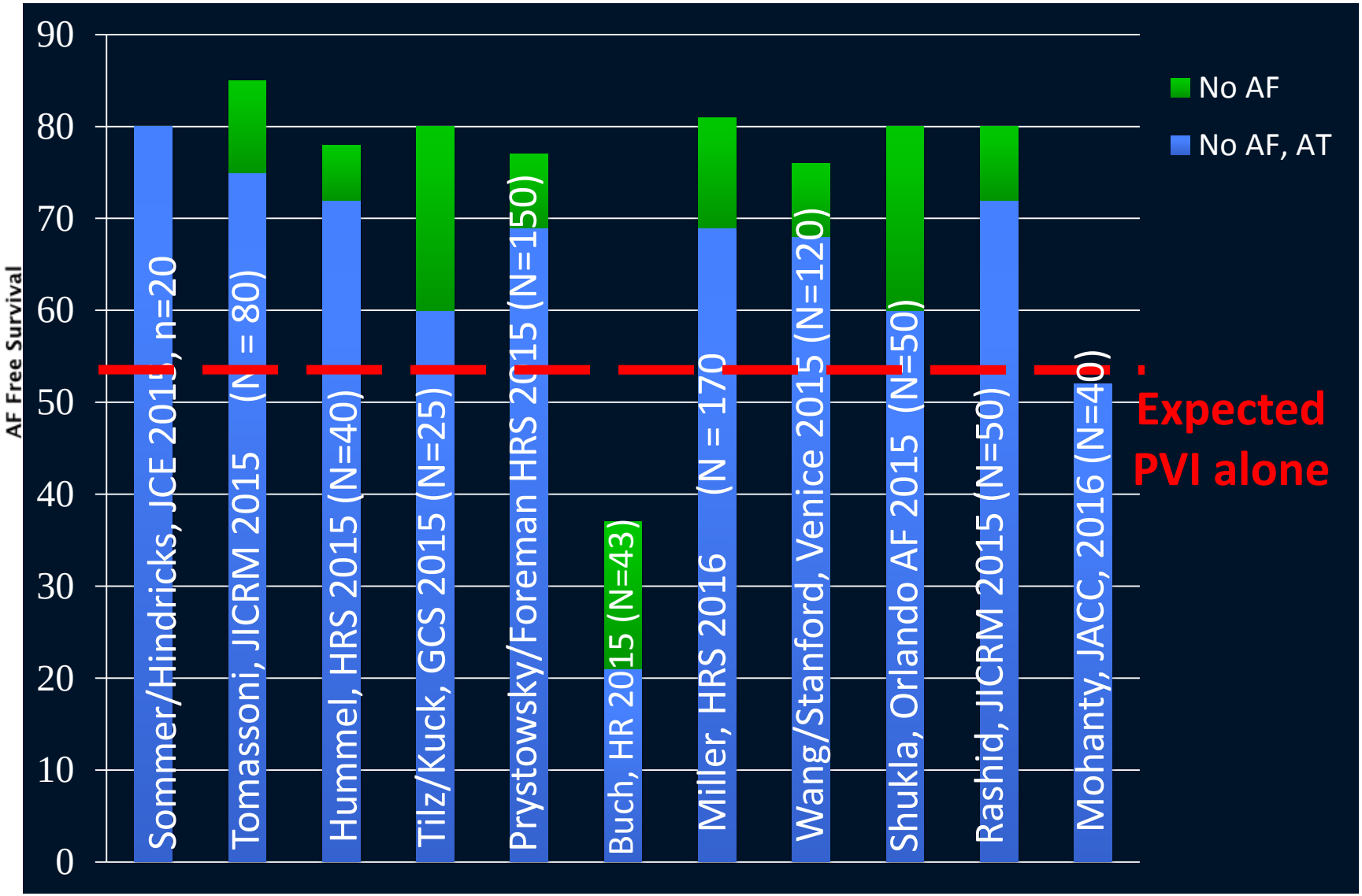
Trials/Out comes


Mintu Turakhia, Kenneth Mahaffey (Bob Harrington)
Narayan: NIH HL103800 (2015-2020)

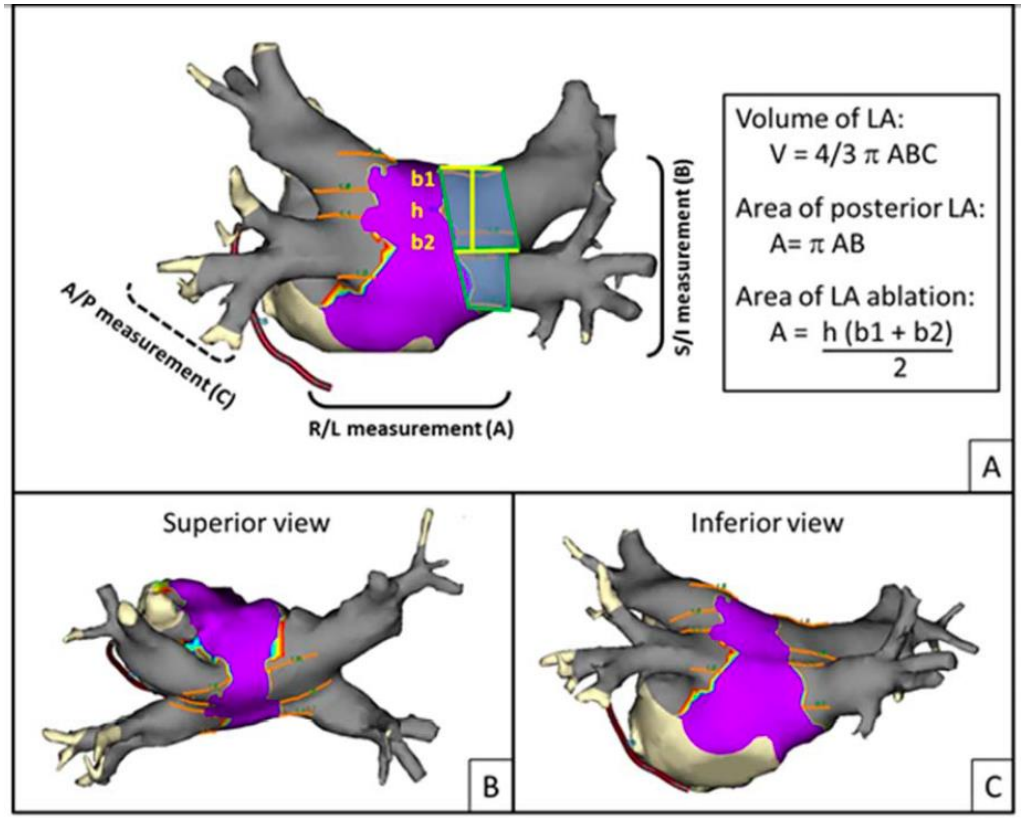
Ongoing Clinical Trials

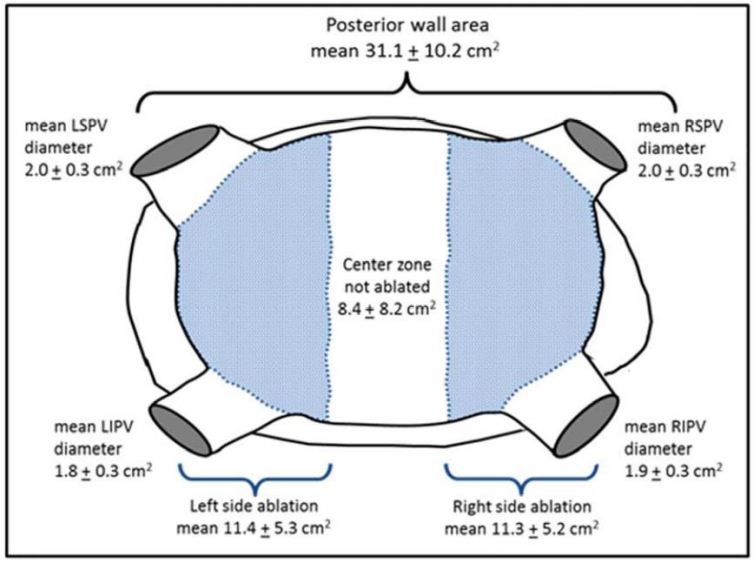
Europe
US

FIRM+PVI, 1-Procedure Outcome. Why Heterogeneous? (N>600) 2/3rd Persistent/LS AF



Cryoballoon Ablates Many Adjacent Mechanisms (82% of posterior wall), but not rest of LA, RA





And Success 65% at 1 Y, 50% at 1.5 year <u>in paroxysmal AF</u>

1. **Need to target rest of LA?**
2. **Need to target in RA?**

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Kenigsberg, Ellenbogen et al., Heart Rhythm 2014
Karl Heinz Kuck et al., NEJM 2016; Fire and Ice