Late breaking trials
HRS 2022

1/Early rhythm control in patients with atrial fibrillation according to CHA2DS2-VASc score and age-a sub analysis of the EAST-AFNET 4 Trial.

A. RILLING.

2/ A Randomised Trial of High Power versus Standard Power Radiofrequency Ablation for Pulmonary Vein Isolation-The SHORT AF Study.

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HRS 2022 Late breaking clinical trials, San Francisco

Early Rhythm control in patients with atrial fibrillation according to CHA_2DS_2-VASc score and Age

-A subanalysis of the EAST-AFNET4 trial-

A Rillig, K Borof, G Breithardt, AJ Camm, H Crijns, A Goette, KH Kuck, A Metzner, P Vardas, E Vettorazzi, K Wegscheider, A Zapf, P Kirchhof

Aim of this sub analysis

Background

- **Rhythm control therapy can prevent some, but not all recurrences of atrial fibrillation (AF) and is primarily recommended to improve quality of life in symptomatic patients with AF**
- **Rhythm control therapy is primarily offered to young and healthy patients with AF**
- **Concerns over the safety are a main reason to withhold rhythm control therapy in patients with AF, especially in those with cardiovascular (CV) comorbidities**
- **The randomized EAST-AFNET4 (Early Treatment of Atrial Fibrillation for Stroke Prevention) trial demonstrated that early rhythm control (ERC) therapy reduces CV outcomes compared to usual care (UC)**

The efficacy and safety of ERC in patients with multiple CV comorbidities and higher age is not known

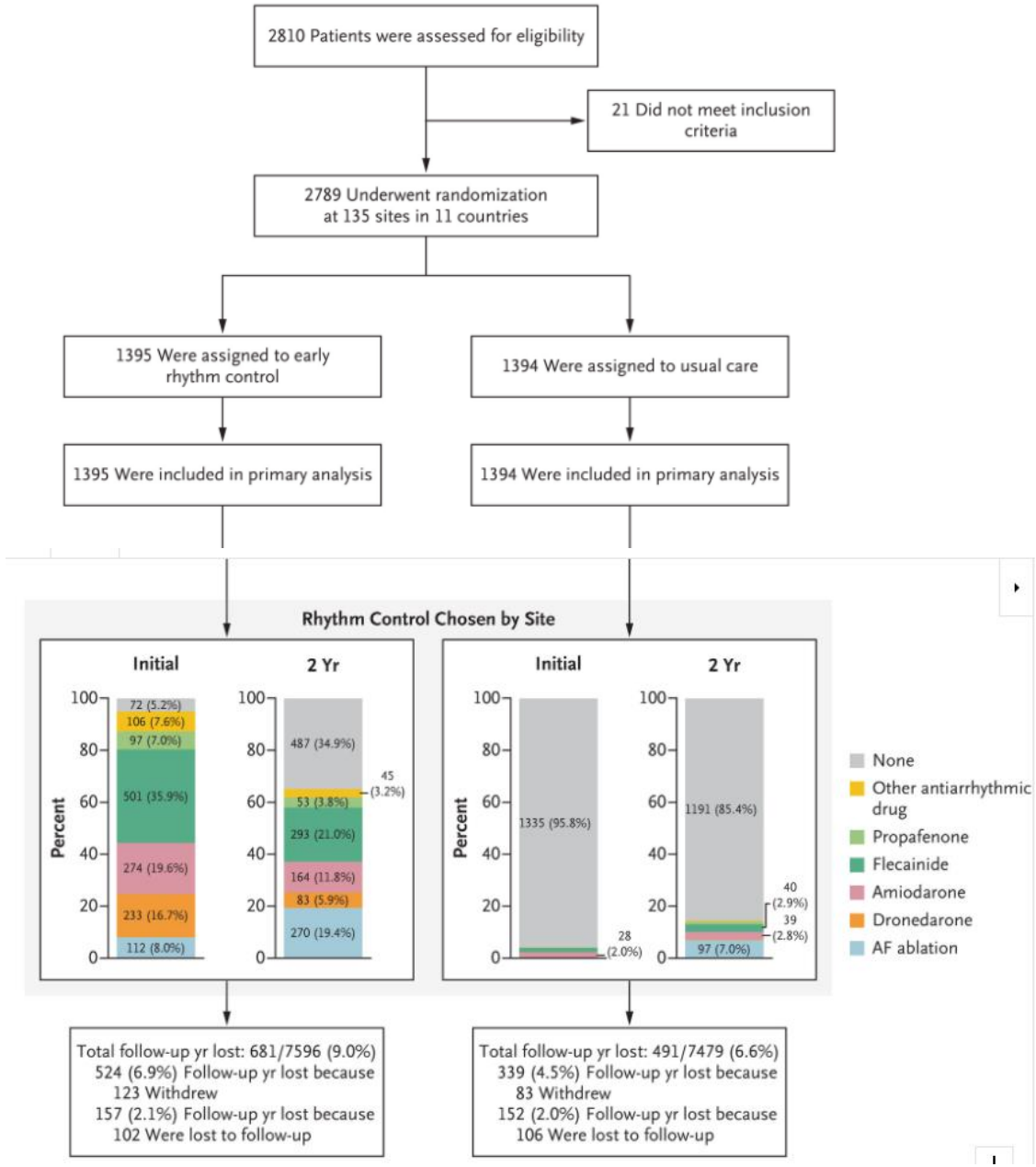
ERC reduces CV events in recently diagnosed AF

2789 patients with AF diagnosed within one year and concomitant conditions approximating CHA_2DS_2-VASc score of 2 or more randomized to systematic ERC therapy or UC including delayed, symptom-restricted rhythm control

Primary Outcome

Composite of:

- CV death
- Stroke
- Hospitalization with worsening of heart failure or acute coronary syndrome



Kirchhof et al., N Engl J Med 2020; 383:1305-1316 DOI: 10.1056

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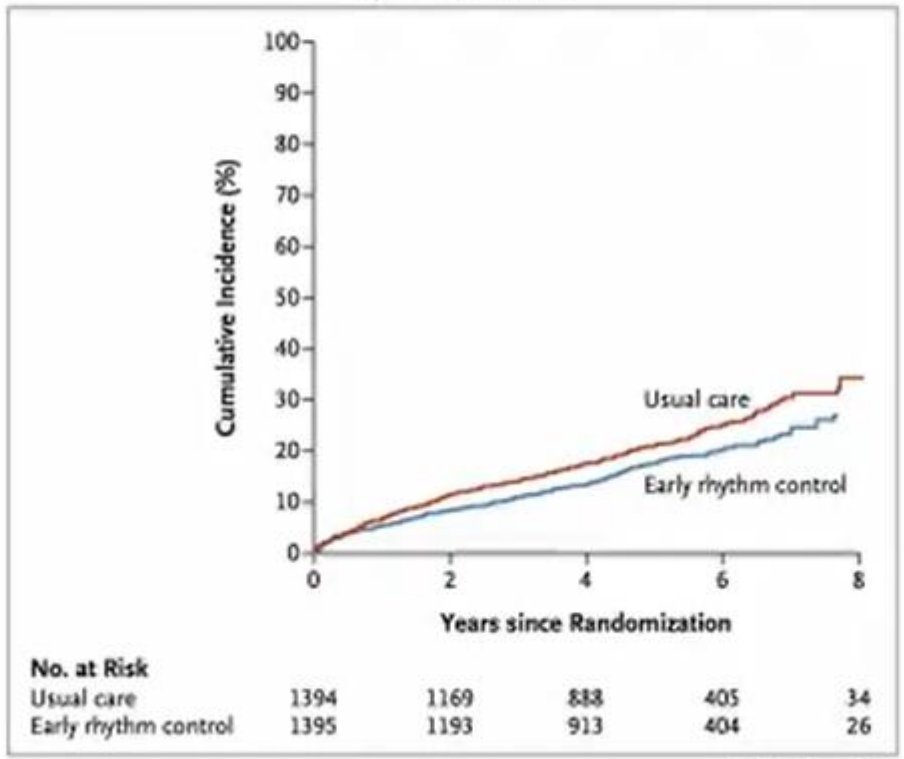
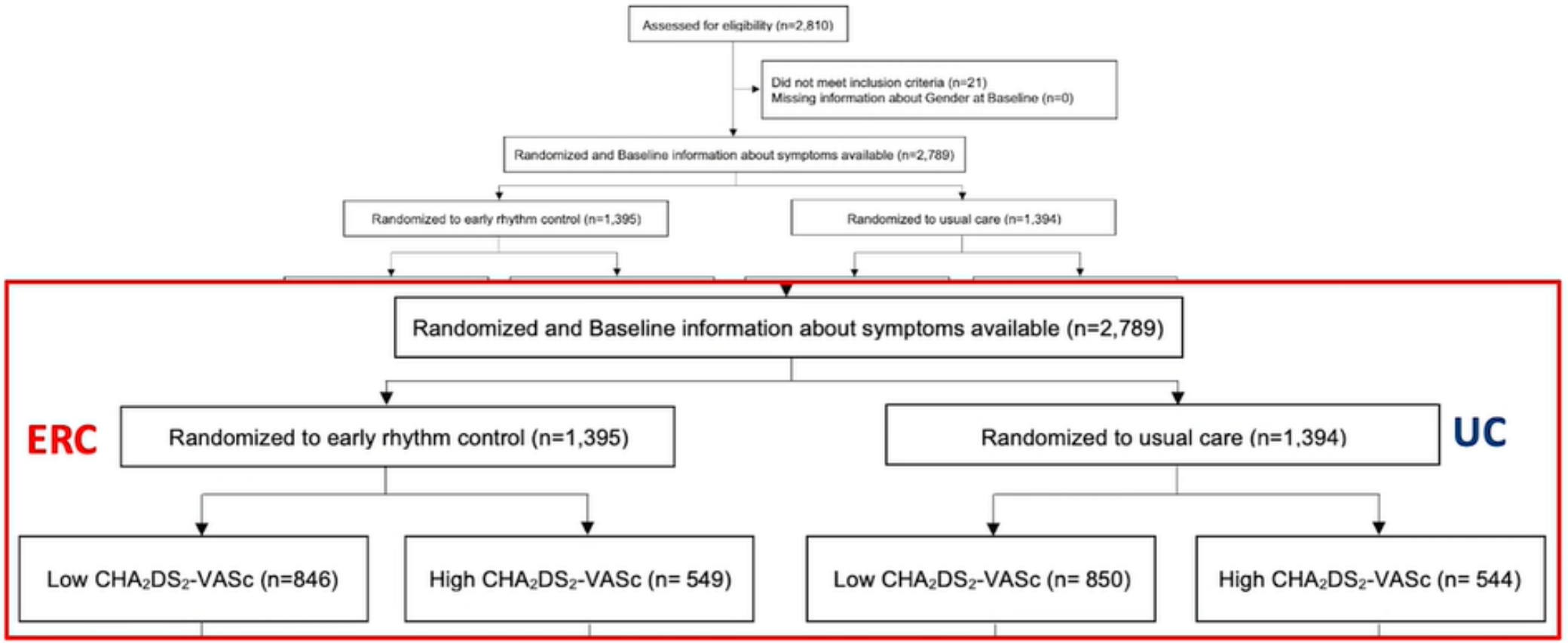


Kirchhof et al., N Engl J Med 2020; 383:1305-1316 DOI: 10.1056

Patients and study design

CONSORT flow chart of this subanalysis

Prespecified analysis of the effect of ERC compared to UC including delayed, symptom-directed rhythm control in all patients in the EAST-AFNET4 trial, with high comorbidity defined as: CHA_2DS_2-VASc score ≥4



Results

Baseline characteristics of EAST-AFNET4 patients with high (n=1093) and lower (n=1696) CHA_2DS_2-VASc score

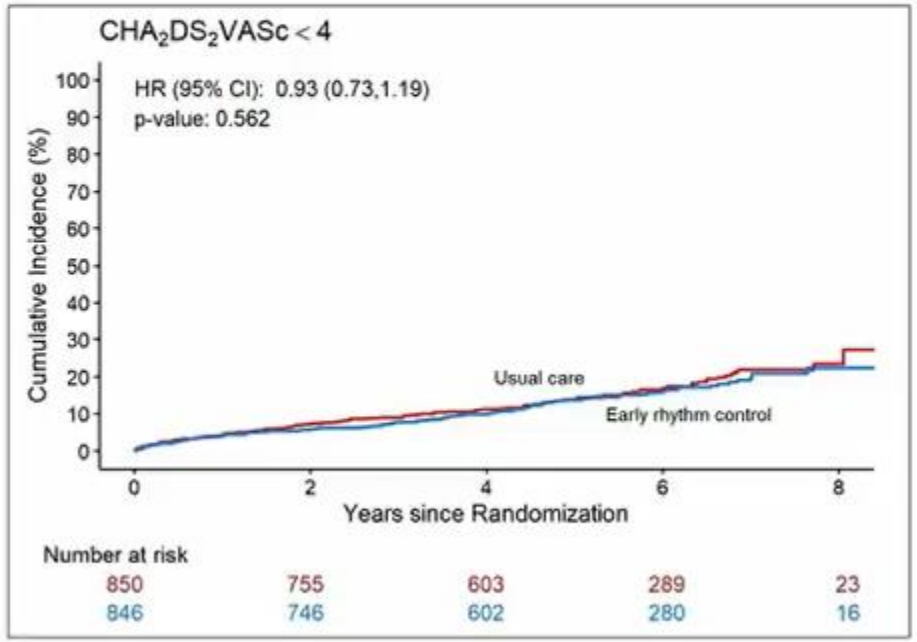
Characteristics	Lower comorbidity burden (CHA_2DS_2-VASc Score (<4)		High comorbidity burden (CHA_2DS_2-VASc Score ≥4)	
	ERC, N = 846[1]	UC, N = 850[1]	ERC, N = 549[1]	UC, N = 544[1]
Age	67 (8.1)	67 (7.8)	75 (6.9)	75 (6.6)
Gender				
Female	308/846 (36%)	320/850 (38%)	337/549 (61%)	328/544 (60%)
Male	538/846 (64%)	530/850 (62%)	212/549 (39%)	216/544 (40%)
Body Mass Index (calculated) [kg/m²]	29.2 (5.5)	29.5 (5.3)	29.2 (5.3)	29.0 (5.4)
AF type				
First episode	320/844 (38%)	321/850 (38%)	208/547 (38%)	199/544 (37%)
Paroxysmal	304/844 (36%)	299/850 (35%)	197/547 (36%)	194/544 (36%)
Persistent or long-standing persistent	220/844 (26%)	230/850 (27%)	142/547 (26%)	151/544 (28%)

Characteristics	Lower comorbidity burden (CHA_2DS_2-VASc Score (<4)		High comorbidity burden (CHA_2DS_2-VASc Score ≥4)	
	ERC, N = 846[1]	UC, N = 850[1]	ERC, N = 549[1]	UC, N = 544[1]
Concomitant cardiovascular conditions				
Prior AF ablation	0/846 (0%)	0/850 (0%)	0/549 (0%)	3/544 (0.6%)
Previous stroke or transient ischemic attack	24/846 (2.8%)	21/850 (2.5%)	151/549 (28%)	132/544 (24%)
At least mild cognitive impairment	319/797 (40%)	305/819 (37%)	263/529 (50%)	279/522 (53%)
Arterial hypertension	709/843 (84%)	703/850 (83%)	518/547 (95%)	517/544 (95%)
Systolic blood pressure [mmHg]	137 (19.1)	136 (19.3)	136 (19.9)	139 (19.2)
Diastolic blood pressure [mmHg]	82 (11.8)	82 (12.1)	79 (12.4)	81 (11.8)
Stable heart failure	161/846 (19%)	161/850 (19%)	235/549 (43%)	241/544 (44%)
Chronic kidney disease of MDRF stage 3 or 4	68/846 (8.0%)	62/850 (7.3%)	104/549 (19%)	117/544 (22%)
Diabetes mellitus	131/843 (16%)	128/850 (15%)	220/547 (40%)	215/544 (40%)
Severe coronary artery diseases (prev. MI, CABG or PCI)	76/846 (9.0%)	69/850 (8.1%)	167/549 (30%)	167/544 (31%)

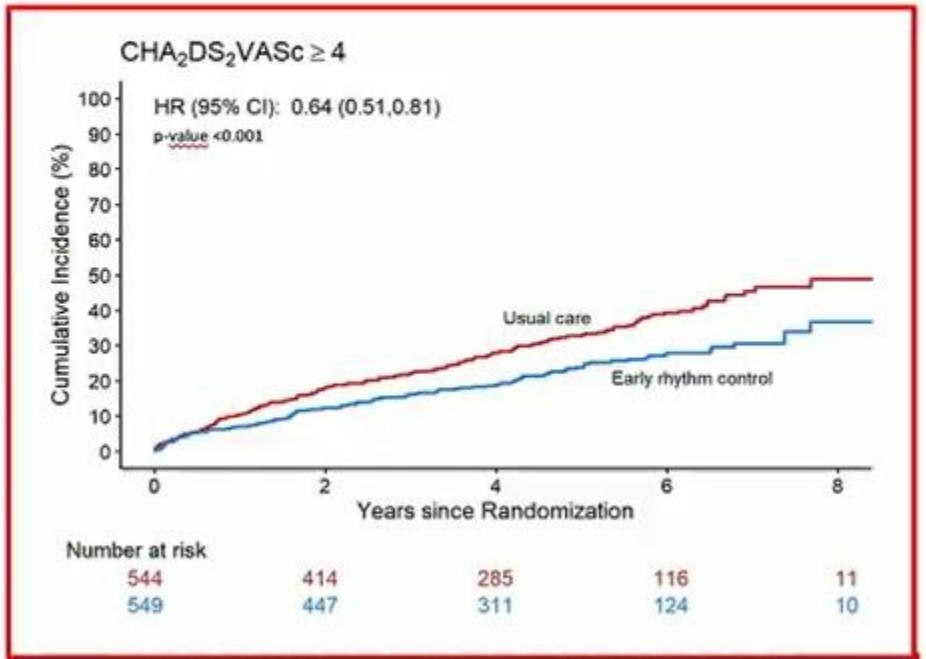
Primary outcome by comorbidity strata

Primary Outcome of EAST – AFNET4

Composite of: CV Death, Stroke, Hospitalization with worsening of heart failure or acute coronary syndrome



No impact on Primary outcome in patients with LOWER CHA_2DS_2-VASc score <4

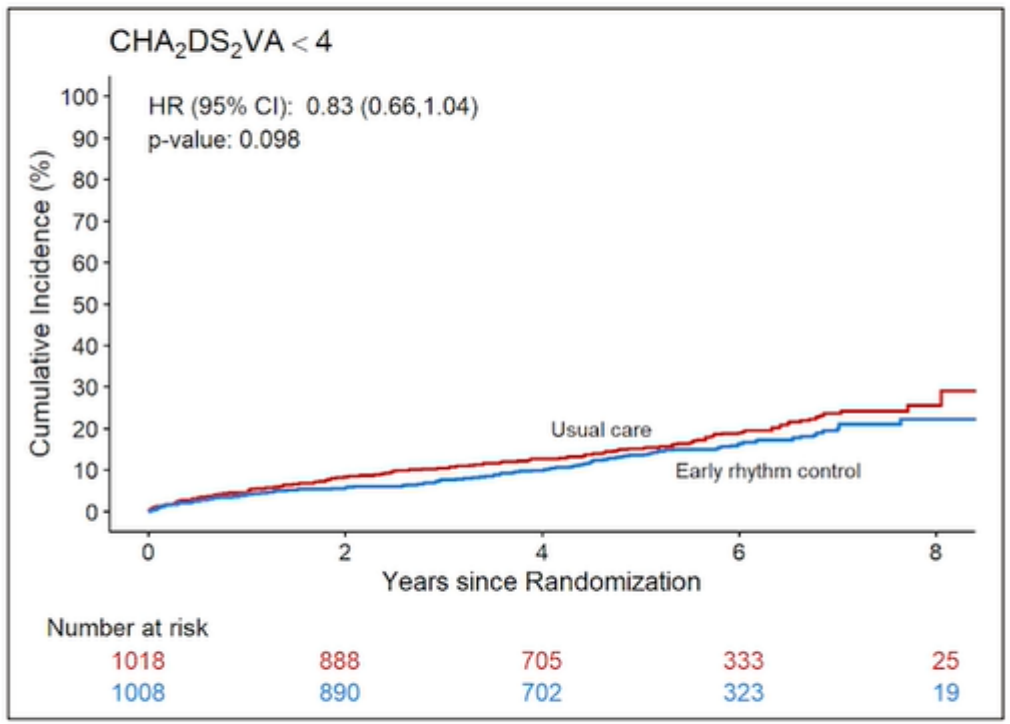


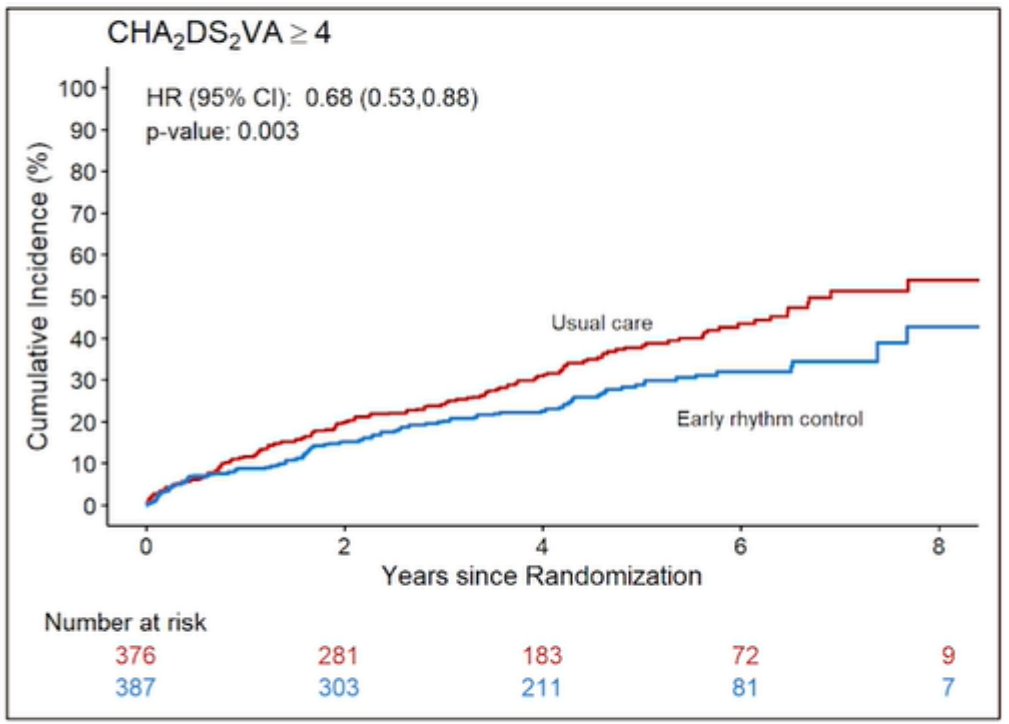
Reduced primary outcome of patients with HIGH CHA_2DS_2-VASc score ≥4

Outcome according to CHA_2DS_2-VA score

Primary Outcome of EAST – AFNET4

Composite of: CV Death, Stroke, Hospitalization with worsening of heart failure or acute coronary syndrome





Interaction p=0.250

Primary safety outcome

Primary safety outcome

Composite of: Death, Stroke and Serious adverse events related to rhythm-control therapy

⇨ ***Not significantly different*** **between study groups in patients with HIGH CHA_2DS_2-VASc scores ≥4**
(ERC 112/549 patients with events; UC 132/544 patients with events, HR 0.84 [0.65, 1.08], p=0.175)

⇨ ***Occurred more often*** **in patients with LOWER CHA_2DS_2-VASc scores *randomized to ERC***
(ERC 119/846 patients with events; UC 91/850 patients with events, HR 1.39 [1.05-1.82], p=0.019)
interaction p=0.008

Primary safety outcome

Primary safety outcome

Composite of: Death, Stroke, Serious adverse events related to rhythm-control therapy

	Lower comorbidity burden (CHA_2DS_2-VASc Score (<4)				High comorbidity burden (CHA_2DS_2-VASc Score ≥4)				
Outcome	ERC	UC	HR (95CI)	p-value	ERC	UC	HR (95CI)	p-value	p-value interaction
Death	66 (7.8)	70 (8.2)	0.97 (0.69, 1.36)	0.860	72 (13.1)	94 (17.3)	0.74 (0.54, 1.01)	0.0563	0.255
Stroke	21 (2.5)	19 (2.2)	1.14 (0.61, 2.12)	0.683	19 (3.5)	43 (7.9)	0.43 (0.25, 0.74)	0.0023	0.021
Serious adverse events related to rhythm control therapy, including	41 (4.8)	14 (1.6)	3.11 (1.7, 5.72)	<0.001	27 (4.9)	5 (0.9)	5.51 (2.12, 14.3)	<0.001	0.337
Torsades de pointes	0 (0)	0 (0)	na	na	1 (0.2)	0 (0)	na (0, Inf)	0.9997	0.998
Non-fatal cardiac arrest	0 (0)	0 (0)	na	na	1 (0.2)	1 (0.2)	1.03 (0.06, 16.4)	0.9856	>0.99
Drug toxicity related to atrial fibrillation treatment	7 (0.8)	2 (0.2)	3.57 (0.74, 17.19)	0.112	3 (0.5)	1 (0.2)	2.97 (0.31, 28.6)	0.3451	0.3451
Drug-induced bradycardia	9 (1.1)	4 (0.5)	2.34 (0.72, 7.61)	0.156	5 (0.9)	1 (0.2)	4.97 (0.58, 42.58)	0.1430	0.1430
Drug-induced AV block	2 (0.2)	*0 (0)*	na (0, Inf)	>0.99	0 (0)	0 (0)	na	na	>0.99
Pericardial tamponade	1 (0.1)	0 (0.0)	na (0, Inf)	>0.99	2 (0.4)	0 (0.0)	na (0, Inf)	0.9996	>0.99
Major bleeding due to AF ablation	1 (0.1)	0 (0.0)	na (0, Inf)	>0.99	5 (0.9)	0 (0.0)	na (0, Inf)	0.9993	>0.99
Nonmajor bleeding due to AF ablation	1 (0.1)	2 (0.2)	0.55 (0.05, 6.06)	0.624	0 (0.0)	0 (0.0)	na	na	>0.99
Hospitalizations due to atrial fibrillation	8 (0.9)	1 (0.1)	8.33 (1.04, 66.68)	0.046	3 (0.5)	2 (0.4)	1.52 (0.25, 9.11)	0.6461	0.6461
Other cardiovascular event	3 (0.4)	1 (0.1)	3.16 (0.33, 30.44)	0.320	2 (0.4)	0 (0.0)	na (0, Inf)	0.9994	0.997

Conclusion

- This prespecified subanalysis of the EAST – AFNET 4 trial found that ERC therapy markedly reduces a composite of CV death, stroke, or hospitalization for heart failure or acute coronary syndrome in patients with recently diagnosed AF and a high comorbidity burden (CHA_2DS_2-VASc ≥4)
- In patients with fewer comorbidities, ERC was not effective, but therapy-related bradycardia, hospitalizations, and drug toxicity were increased
- When sex was ignored to estimate high comorbidity burden (CHA_2DS_2-VA ≥4), the results showed a similar direction, but the interaction between the effectiveness of ERC and comorbidity burden was no longer significant
- The results of this subanalysis suggest that elderly patients with recently diagnosed AF and multiple comorbidities should be preferentially treated with ERC
- Dedicated trials are needed to validate these hypothesis-generating findings. Until such trials report, the main findings of the EAST – AFNET 4 trial should be considered in context with the results of this subanalysis

A Randomized Trial of High Power vs Standard Power Radiofrequency Ablation for Pulmonary Vein Isolation

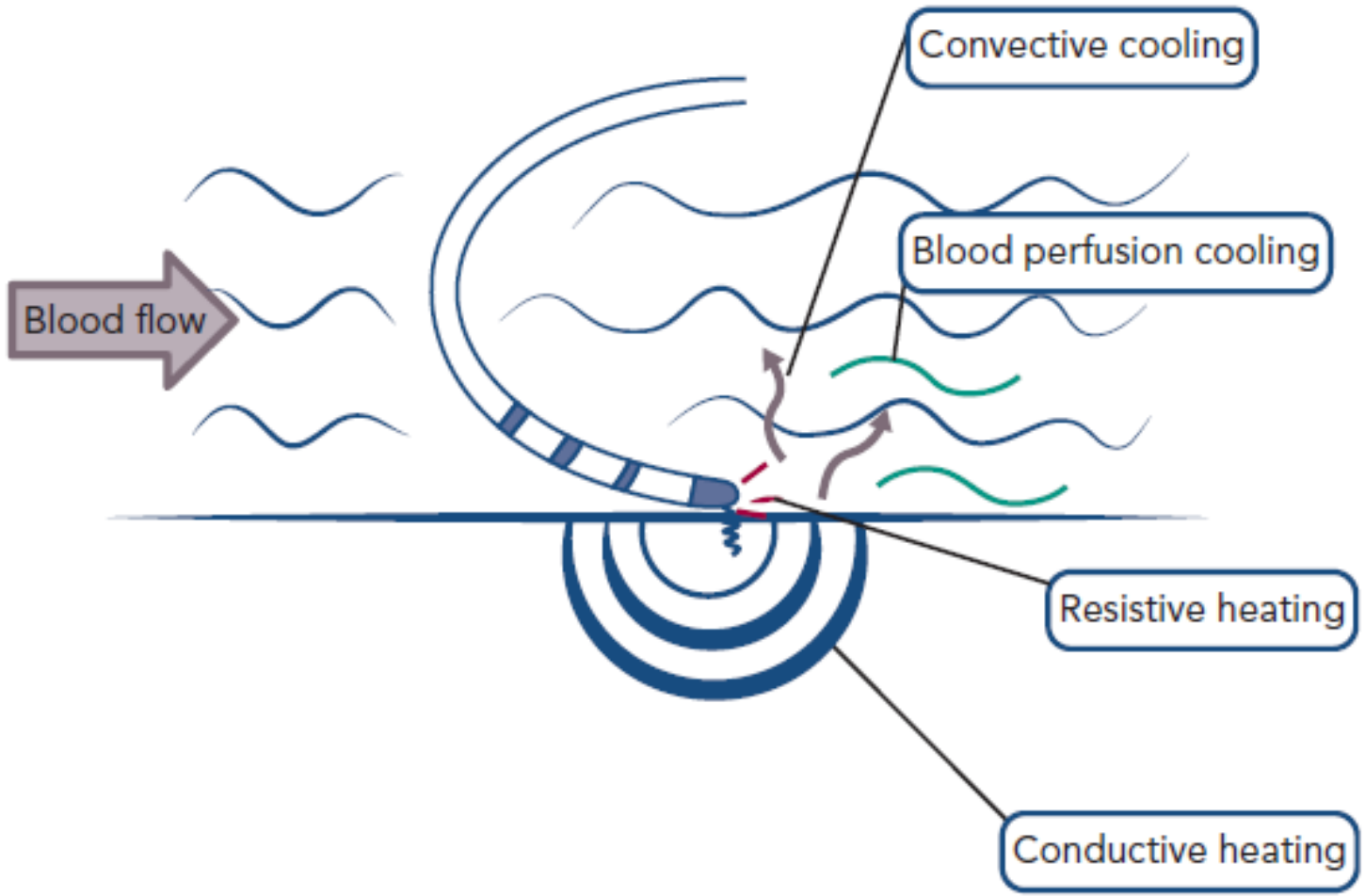
The SHORT-AF Study

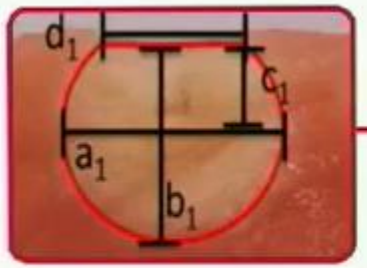
Lee AC[1*], Voskoboinik A[1,2*], Cheung CC[1], Yogi S[1], Tseng ZH[1], Moss JD[1], Dewland TA[1], Lee BK[1], Lee RJ[1], Hsia HH[1], Marcus GM[1], Vedantham V[1], Chieng D[2], Kistler PM[2], Dillon W[1], Vittinghoff E[1], Gerstenfeld EP[1]

*Contributed equally to this study

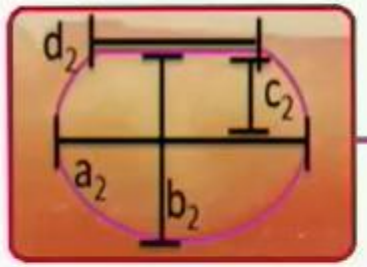
[1]The University of California San Francisco, San Francisco CA USA

[2]The Alfred, Melbourne, VIC, Australia

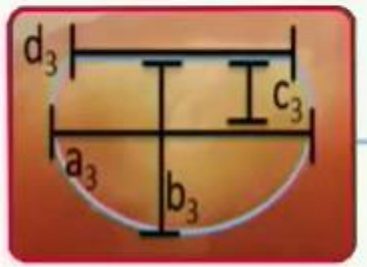

Convective cooling
Blood perfusion cooling
Blood flow
Resistive heating
Conductive heating



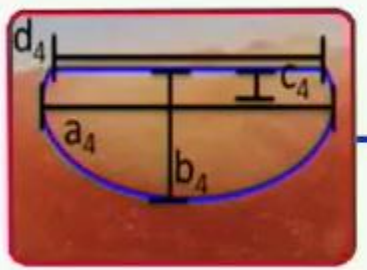
30W, 30S



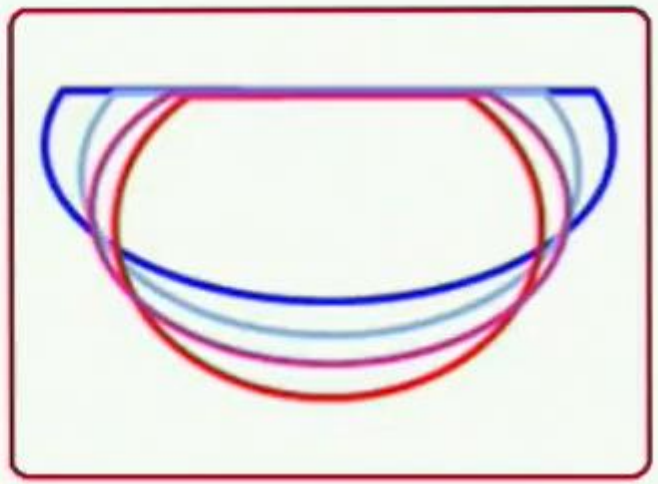
50W, 13S



60W, 10S



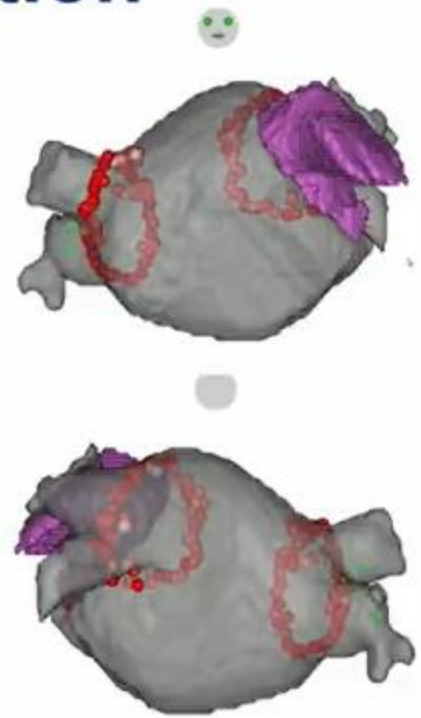
70W, 7S



Bourier, JCE 2019

High Power Short Duration RF Ablation

- A strategy increasingly utilized for pulmonary vein isolation (PVI)
- Theoretical benefits:
  - Better lesion contiguity[1]
  - Faster procedure[2]
- Prospective studies confirming efficacy and safety are limited



[1]Leshem E. JACC EP. 2018;4:467-579
[2]Winkle R. PACE 2011;34:531-539

theAlfred

UCSF Health

The SHORT-AF Study

- A multi-center, prospective, single-blind randomized controlled trial
  - University of California San Francisco (USA)
  - The Alfred (Melbourne, Australia)
- Investigator initiated and funded
- Comparing two strategies of RF ablation in patients undergoing PVI with paroxysmal or persistent AF
  - High Power, Short Duration (HP)
  - Standard Power, Standard Duration (SP)

UCSF Health

theAlfred

Objectives

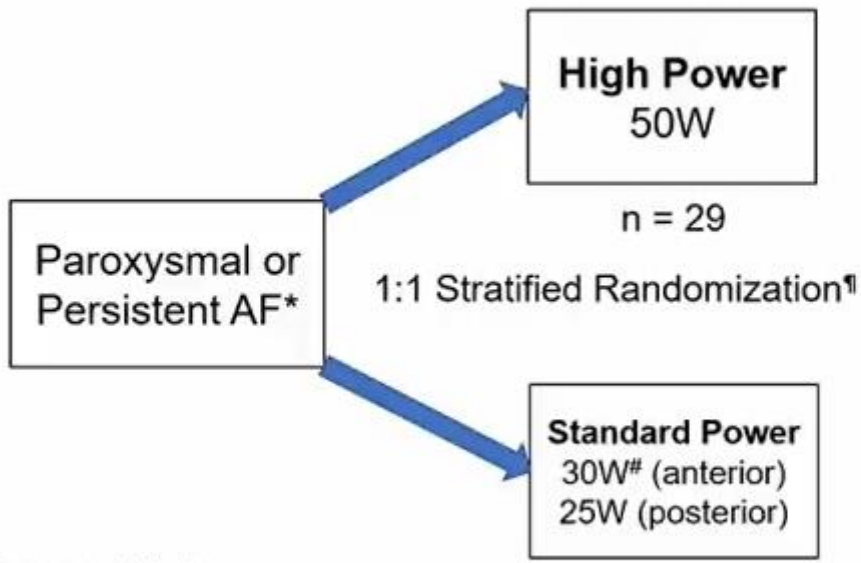
- To assess key efficacy and safety outcomes of HP vs SP strategies:
  - **PVI time** (primary outcome)
    - Sample size: Hypothesize reduction 55 ± 19 mins SP to 38 ± 14 mins HP[1].
    - For 2-sided $\alpha = 0.05$ and 80% power, sample size of 60 AF patients
  - Key secondary outcomes:
    - Procedural: Left atrial dwell time, total procedure time, first pass PV isolation, adenosine PV reconnection rates
    - Efficacy: Freedom from recurrent atrial arrhythmias (AF/AFL/AT)
    - Safety: Esophageal temperature rise, acute cerebral lesions on MRI imaging

[1]Baher A. JACC EP 2018;4:1583-94

Key Inclusion/Exclusion Criteria

- Inclusion
  - Age > 18 with paroxysmal or persistent AF
  - No prior AF or LA ablation
- Exclusion
  - Persistent AF > 1 year
  - Stroke/TIA within prior 6 months
  - Intent to perform adjunctive LA ablation
  - LV ejection fraction <35%
  - Implanted pacemaker, ICD or other MRI contraindication

Study Design

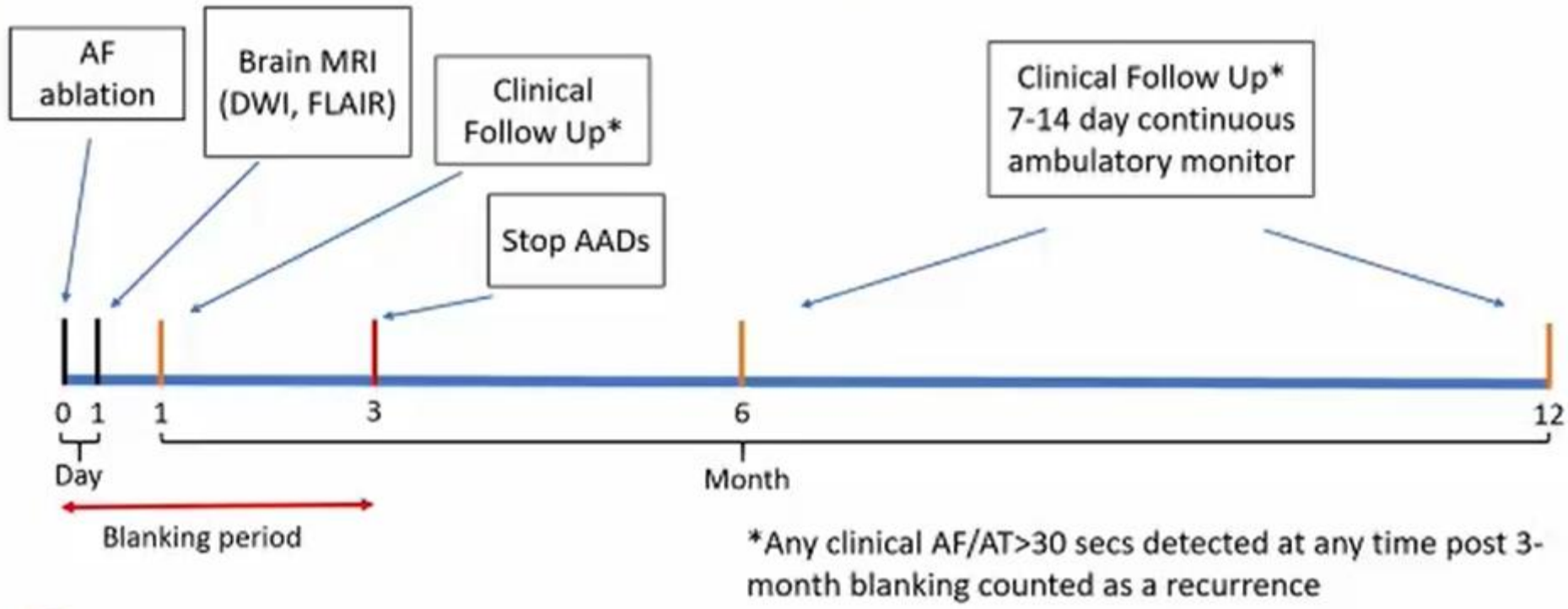


*< 1 year persistent
¶Randomized stratified by attending
#Uptitrating to 35W was permitted at operator discretion

Ablation Parameters

- CARTO
  - ThermoCool STSF
  - 2 mm lesion tags (radius)
  - Ablation index targets:
    - Anterior: 450 – 550
    - Posterior: 350 – 400
- Ensite
  - TactiCath SE
  - 3 mm lesion tags (diameter)
  - Lesion size index targets:
    - Anterior: 5.5 – 6.0
    - Posterior: 4.5 – 5.0

Enrolment Flow Chart



Demographics

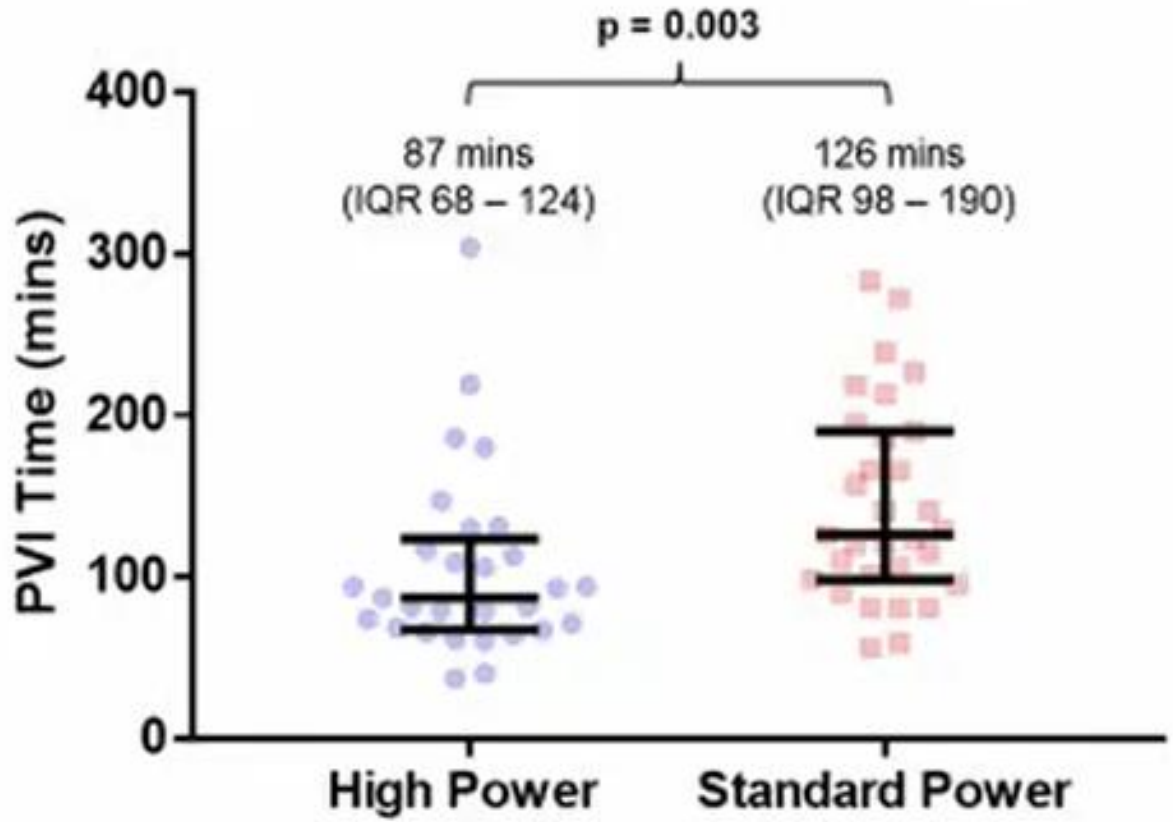
	High Power (n = 29)	Standard Power (n = 31)
Age (years)	67 (IQR 62 – 73)	63 (IQR 59 – 68)
Sex		
Male	20 (69%)	25 (81%)
Female	9 (31%)	6 (19%)
BMI (kg/m^2)	29.5 (IQR 25.6 – 34.3)	28.0 (IQR 26.1 – 31.7)
AF Type		
Paroxysmal	17 (59%)	17 (55%)
Persistent	12 (41%)	14 (45%)
LVEF (%)	60 (IQR 50 – 65)	60 (IQR 55 – 60)

Comorbidities

	High Power (n = 29)	Standard Power (n = 31)
Hypertension	12 (41%)	19 (61%)
Diabetes mellitus	2 (7%)	4 (13%)
Coronary artery disease	5 (17%)	7 (23%)
Obstructive sleep apnea	5 (17%)	9 (29%)
Prior stroke	2 (7%)	3 (10%)
Cardiomyopathy (LVEF < 50%)	6 (21%)	5 (16%)
CHA_2DS_2VASc score	2 (IQR 1 – 3)	2 (IQR 1 – 3)

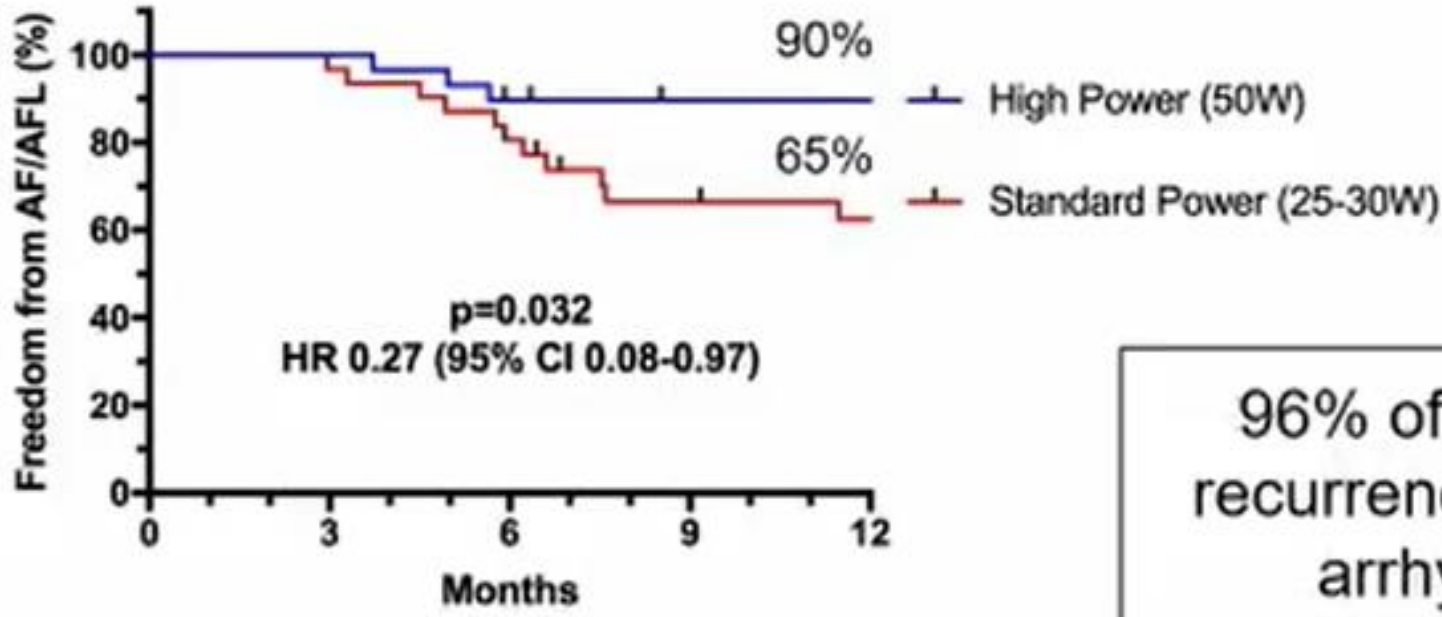
RESULTS

Shorter PVI Times with High Power



Greater Freedom from Recurrent Atrial Arrhythmias with High Power

Kaplan-Meier Survival Curve for Freedom from Recurrent Atrial Fibrillation/Flutter



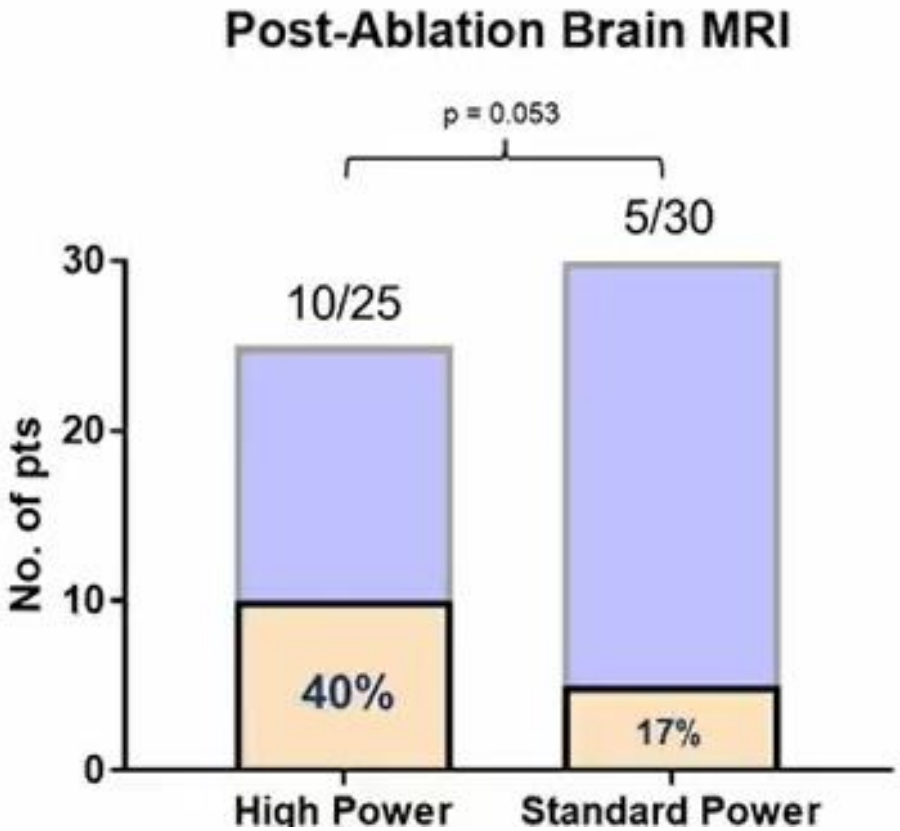
Number at Risk					
High Power	29	29	22	20	20
Standard Power	31	30	24	18	16

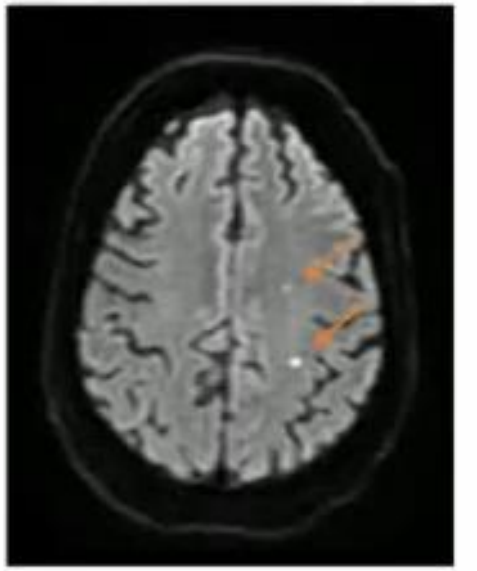
96% of patients without recurrence were OFF anti-arrhythmic agents

Key Secondary Procedural Outcomes

	High Power (n = 29)	Standard Power (n = 31)	p-value
LA Dwell Time (mins)	157 (IQR 125 – 196)	180 (154 – 244)	**0.04**
Total Procedure Time (mins)	236 (193 – 304)	286 (219 – 350)	0.11
First Pass Isolation	80%	76%	0.65
Adenosine Reconnection	12%	20%	0.26
Max Esophageal Temp Rise (°C)	1.4 (IQR 0.5 – 1.8)	1.3 (IQR 0.6 – 1.9)	0.78

More Acute Cerebral Lesions with High Power?





No Acute Lesions

Acute Lesion(s)

No clinical strokes/TIA occurred

Missing patients:

High Power (4 pts)

- Body habitus
- Pt refusal
- Claustrophobia
- Metallic shrapnel

Standard Power (1 pt)

- Body habitus

Complications

High Power (1x pt)	Standard Power (1x pt)
Urinary tract infection	Deep vein thrombosis and liver abscess

No pericardial effusions, phrenic nerve injury or atrio-esophageal fistulae in either group

Limitations

- No continuous post-ablation AF monitoring
- No neurocognitive assessment performed
- Esophageal endoscopy was not performed
- Study may have been underpowered for secondary outcomes

Conclusions

- High power (50W) as compared to standard power (30W/25W) radiofrequency ablation results in:
  - Reduced time to achieve pulmonary vein isolation
  - Greater freedom from atrial arrhythmias at 12 months
  - A trend towards a higher incidence of post-procedure cerebral emboli