







AF: Milestones Achieved and Future Perspectives John Camm St. George's University of London **United Kingdom**

Advisor / Speaker : Astra Zeneca, Gilead, Merck, Menarini, Sanofi Aventis, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionics, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda

Atrial Fibrillation - Publication Volume





Institute of Medicine





100 Initial Priority Topics for Comparative Effectiveness Research

- 1. <u>Compare the effectiveness of treatment strategies for atrial fibrillation including</u> <u>surgery, catheter ablation, and pharmacologic treatment.</u>
- 2. Compare the effectiveness of the different treatments (e.g., assistive listening devices, cochlear implants, electric-acoustic devices, habilitation and rehabilitation methods

Rate vs. Rhythm Dilemma in AFFIRM

AFFIRM **Hazard ratio** All-cause death 27% vs 26% (p=0.058) 30 p<0.0001 **SR AFFIRM** Mortality (% patients) 25 Warfarin use p<0.0001 20 **Rhythm control Digoxin use** p=0.0007 15 AAD use p=0.0005 10 Heart failure p<0.0001 **Rate control** 5 Stroke/TIA p<0.0001 0 0 0.5 1.5 2 5 2 3 4 6 0 Years

2.5

Corley SD et al. Circulation 2004; 109: 1509–1513.

Rate Versus Rhythm Control in AF

Study	PIAF	STAF	HOT CAFÉ	RACE	AFFIRM	AF-CHF	J-RHYTHM
# pts	252	200	205	522	4060	1376	823
F-up, years	1	1.6	1.7	2.3	3.5	3.1	1.6
Primary endpoint	Symptom improve- ment	ACM, CV events, CPR, TE	ACM, TE, bleeding	CVD, CHF, TE, bleeding, PM, AAD adverse effects	ACM	СVМ	ACM, TE, bleeding, CHF hosp., adverse effects
Difference in 1º EP RhyC vs RC	Improved 6 minute walk P<0.05	5.54%/yr vs 6.09%/yr (p=0.99)	OR, 1.98, 95% Cl, 0.28-22.3; p >0.71	22.6% vs 17.2% (HR, 0.73; p=0.11)	23.8% vs 21.3% (HR, 1.15; p=0.08)	27% vs 25% (HR, 1.06; p=0.59)	<u>15.3% vs 22%</u> _ <u>(p=0.0128)</u>
Mortality	Not assessed	2.5%/yr vs 4.9%/yr	3 (2.9%) vs 1 (1%)	6.8% vs 7%	As above	32% vs 33% (p=0.68)	4 (1%) vs 3 (0.7%)
те	Not assessed	3.1%/yr vs 0.6%/yr	3 (2.9%) vs 1 (1%)	7.9% vs 5.5% RhyC vs RC	Stroke: 7.1% vs 5.5% (p=0.79)	3% vs 4% (p=0.32)	2.39% vs 2.97%
CHF	Not assessed	Better with RC	No difference	4.5% vs 3.5%	2.7% vs 2.1% (p=0.58)	28% vs 31% (p=0.17)	0.5% vs 1.5%
Hospitali- sation	69% vs 24% (p=0.001)	54% vs 26% (p <0.001)	74% vs 12% (p <0.001)	More in RhyC	80% vs 73% (p <0.001)	46% vs 39% (p=0.0063)	Not reported
QoL	No difference	No difference	Not reported	No difference	No difference	No difference	Better with RhyC

Savelieva I, et al. Evidence Based Cardiology, Chapter 35, 2009



Temporal Changes in AAD Use Prior to First Ablation for AF

Danish nationwide registry 2000-09
 3302 patients with first AF ablation

• $CHA_2DS_2VASc \ge 2: 23.9\% \rightarrow 41.5\%$

• Median age: 55 (48-61) \rightarrow 61 (55-66) yrs

No AADs within 2 yrs prior to ablation



Use of specific AADs prior to ablation



Karasoy D, et al. Europace 2012;10.1093/europace/eus418

ATHENA and PALLAS



Permanent versus Non-Permanent AF ATHENA PALLAS

12



Cumulative Hazard HR = 1.95P = 0.0018 4 **Months** 0 2 3 5 6 0 Stroke, MI, SEE or CV Death % 4 Cumulative Hazard HR = 2.29P = 0.0023 2 1 **Months** 0 5 6 0 4

CV hospitalization or death %

Hohnloser SH et al. N Engl J Med. 2009;360:668-78

Connolly S et al. N Engl J Med. 2011;365:2268-76

AF Ablation or Antiarrhythmic Drugs?

					Pre	AF free at 1 year			
Thermocool N = 167			loooo	Study #P	# Pts	Type of AF	AAD	Ablation	AAD
			67	Krittayaphong, et al. 2003	30	Paroxysmal, persistent	≥1	79%	40%
e [%]	ן 100			Wazni, et al. 2005, (RAAFT)	70	Mainly paroxysmal	No	87%	37%
rrenc	80	66	p<0.001	Stabile, et al. 2005 (CACAF)	137	Paroxysmal, persistent	≥2	56%	9%
recui	60 ⁻		16	Oral, et al. 2006	146	Persistent	≥1	74%	4%
n AF	40			Pappone, et al. 2006 (APAF)	198	Paroxysmal	≥2	86%	22%
n fror				Jais, et al. 2008, (A4 study)	112	Paroxysmal	≥1	89%	23%
edor				Forleo, et al. 2008	70†	Paroxysmal, persistent	≥1	80%	43%
Fre-	0	ΡΛΙ ΔΔ		Wilber, et al. 2009 (Thermocool)	167	Paroxysmal	≥1	66%	16%
				Packer, et al. 2010, (STOP-AF)	245	Paroxysmal	≥1	69.9%	7.3%

Modified from Camm J, et al. Nat Rev Cardiol 2009;6:332-4

MANTRA-PAF First Treatment for PAF - Results after 24 Months

294 pts randomized; 1.6 RFAs/pt 194 pts followed for 24 months; 7D Holter



SAEs	RFA	AAD
Death	3	4
Stroke	1	0
ΤΙΑ	1	1
PV stenosis	1	0
Tamponade	3	0
Pericardial effusion	0	1
?perforation	1	0
Atrial flutter, 1:1	0	2
AFI/AT	3	3
CHF	0	2
Total	25	22

Any AF

No AF

Nielsen JC et al. NEJM in press 2012 AAD



FIRM Focal Impulse and Rotor Modulation

92 pts (107 consecutive procedures)

Paroxysmal or persistent (72%) AF.

Prospective 2-arm 1:2 design FIRM-guided followed by conventional ablation (n 36) FIRM-blinded - conventional ablation (n 71;)

Localized rotors or focal impulses: 98 (97%) of 101 sustained AF, 2.1±1.0 sources.

Acute endpoint 86% of FIRM-guided, versus 20% of FIRM-blinded (p <0.001)

Total ablation time did not differ between groups (57.8 ± 22.8 min vs. 52.1 ± 17.8 min, p= 0.16).

Naryan S, et al. J Am Coll Cardiol 2012;60:628–36





Off antiarrhythmic drugs

Renal Artery Denervation for AF

Symptomatic PAF /PeAF Refractory to 2 AADs Drug-resistant hypertension (BPs > 160 mm Hg despite 3 drugs)

Randomized: PVI only (14) PVI+RAD (13) Follow-up: 1 year

Systolic: 181±7 to 156±5, p<0.001 Diastolic 97±6 to 87±4, p<0.001

PVI + RAD: 9 / 13 patients (69%) AF free **PVI alone:** p <0.033 4 /13 4 (29%)

Pokushalov E, et al. J Am Coll Cardiol 2012;60:1163–70



Stroke Outcome After Ablation vs AAD Therapy: Propensity-Matched Analysis

- Market Scan Research Database
- 2005-2009

0.50

0

- Ablation: n = 3194
- AAD: n = 6028
- Used in propensity-matched analysis: 801 pairs
- Follow-up: 27 months



Ablation AAD Characteristic n = 801 n = 801 Age group, % 35-49 8.49 8.61 50-64 42.57 46.69 65-80 44.19 40.57 3.37 > 80 4.0 Men, % 60.92 62.55 **Hypertension**, % 42.7 40.7 **Diabetes**, % 18.73 15.23 8.3% **CHF. %** 17.35 15.73 14.1% **CAD**, % 35.33 33.46 Stroke/TIA, % 2.87 4.12 CHADS₂, % 36.2 34.83 37.95 40.32 2 19.73 17.23 > 3 6.12 7.61 Warfarin 69.91 69.54

Reynolds MR, et al. <u>Circ Cardiovasc Qual Outcome</u>s 2012;5 [epub ahead of press]

2

2.5

3

1.5

Years

Warfarin use decline to 50% in both groups

0.5

1

AF: Rhythm vs. Rate (drug scripts) Risk of Stroke/TIA

Population-based observational study of Quebec pts \geq 65 ys with a diagnosis of AF during the period 1999 – 2007. 16,325 rhythm control, 41,193 rate control. 16,325 matched pairs of pts.

	Unadjusted				Adjusted				
	HR	95% CI			HR	95% CI			
All patients	0.72	0.67, 0.78			0.80	0.74, 0.87	-		
CHADS2 = 0 n = 4,876	0.86	0.65, 1.13		-	0.93	0.70, 1.24			
CHADS2 = 1 N = 15,551	0.71	0.61, 0.83	-		0.80	0.68, 0.93	-		
CHADS2 ≥ 2 N= 37,091	0.77	0.70, 0.84	-		0.84	0.77, 0.93	-		
Propensity matched	0.75	0.67, 0.85	-		0.77	0.68, 0.87	+		
rhythm 0.5 1.0 1.5 rate 0.5 1.0 1.5									

Adjusted for sex, co-morbidities, type of AF, treating physician, age, antithrombotic treatments *Tsadok MA et al Circulation 2012 epub*

Efficacy and Safety of Budiodarone

PASCAL: Paroxysmal Atrial fibrillation Study with Continuous Atrial fibrillation Logging

- Phase IIb
- N = 72 with PAF and DDD PM
- AF burden at baseline: 3-70%
- Dose: Budiodarone
 200, 400, 600 mg bd
- Duration: 4 weeks baseline, 12 weeks therapy

Reduction in AF burden from baseline at 1-3 months, %



Ezekowitz MD, et al JICE 2012;34:1-9

Ranolazine versus Amiodarone AF Prophylaxis After CABG

- Retrospective cohort study
- 393 pts undergoing CABG
- Amiodarone (400 mg preoperative followed by 200 mg twice daily for 10-14 days)
 N=211 (53.7%)
- Ranolazine (1500 mg preoperative followed by 1000 mg twice daily for 10-14 days)
 N=182 (46.3%)
- Mean age 65 ± 10 years,
 72% male





Synergistic Effect on AF of Combination of Ranolazine and Dronedarone

- Canine isolated coronary-perfused RA, LA, PV, and LV preparations
- Ranolazine 5 μmol/L
- Dronedarone 10 μmol/L

- Open-chest Yorshire pigs
- Proximal LCX occlusion (75%)
- Ranolazine i.v. 0.6 mg/kg+0.035 mg/kg/min
- Dronedarone i.v. 0.5 mg/kg



Antzelevitch C, et al. JACC 2010;56:1216-24



Verrier RL, et al. Heart Rhythm 2012 [In press]

Pharmacological Cardioversion of AF With Combination of Amiodarone and Ranolazine

Pilot RCT

- N = 51 with AF < 48 h</p>
- Age 63 ± 8 years, 65% men
- HTN 68-77%, CAD 20-27%
- I.V. amio 5 mg/kg for 1 h followed by infusion of 50 mg/h for 24 h
- I.V. amio + ranolazine 1500 mg p.o.
- 1° EP: conversion within 24 h



Median time to conversion: 18 h (Amio) vs 10 h (Amio+Rano)

Fragakis N, et al. Am J Cardiol 2012;110:673-7

Dronedarone in PAF: HESTIA



A placebo-controlled, double-blind, randomized, multi-center study to assess the effects of Dronedarone 400 mg BID for 12 weeks on atrial fibrillation (AF) burden in subjects with permanent pacemakers

1° EP: changes in AF burden from baseline at 12 weeks, %



- Patients with PAF and DDD PM
- Planned n = 290,
 Enrolled n = 112
- AF burden at baseline Placebo vs Dronedarone: 16% vs 21%
- Duration: 4 weeks baseline, 12 weeks therapy

HARMONY

A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation

- PAF with pacemakers
- N = 150, 45 centres
- Follow-up: 12 weeks
- Ranolazine vs Dronedarone vs Ranolazine + Dronedarone
- Primary endpoint: reduction in AF burden
- 2⁰ endpoints: AF burden at each visit (4, 8, 12 weeks) and # episodes



Rhythm Control and Mortality in AF Long term Benefit

- Population-based administrative databases, Quebec
- 26,130 patients
- 1999 to 2007
- > 65 years
- AF hospitalization
- No AF-related drug prescriptions < 1year
 < admission (first documented AF)
- AAD < 7 days
 > discharge



Ionescu-Ittu R, et al. Arch Intern Med. 2012;172:997-1004.



If early onset, little atrial remodelling or remains symptomatic

EAST: Early treatment of Atrial fibrillation for Stroke prevention Trial

Pre-study screening

Study procedures



Antiarrhythmic drug therapy; pulmonary vein isolation (PVI) In case of AF recurrence: Re-PVI, adaptation of antiarrhythmic

drug therapy

ECG monitoring of therapy

Usual care

Rate control, supplemented by rhythm control only in symptomatic patients despite optimal rate control therapy, as mandated by the 2010 ESC auidelines for AF

Composite primary endpoint: CV death, stroke / TIA, CHF or ACS hospitalization

Outpatient follow-up at months 12, 24, 36 (both study groups)

Antithrombotic therapy Therapy of underlying heart disease (both study groups)

Where Are We Going?

2002 2007 2012



PubMed data interrogated, January 2013

A Last Thought

Rem[ember] how the early Greeks had mystic anticipations of nearly all great modern scientific truths: the problem really is what place has imagination and the emotions in science: and primarily rem[ember] that man must use all his faculties in the search for truth: in this age we are so inductive that our facts are outstripping our knowledge – there is so much observation, experiment, analysis – so few wide conceptions . . . we want more ideas and [fewer] facts: the magnificent generlizations of Newton and Harvey c[oul]d never have been completed in this mod[ern] age

Oscar Wilde, Oxford Notebooks

