Atrial Fibrillation Update

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Role of DOACs

ARISTOTLE (21)	Multicenter, randomized, double-blind, active-controlled, noninferiority/superiority	Patients with AF with ≥1 risk factors for stroke (N = 18,201)	Apixaban oral 2.5 or 5 mg bid vs. oral warfarin qd (INR, 2.0–3.0)	Median 1.8 yrs	Stroke or systemic embolism: 1.3% vs. 1.6%/yr (p = 0.01 for superiority)	Major bleeding: 2.1% vs. 3.1%/yr (p < 0.001)	Major or nonmajor clinically relevant bleeding: 4.1% vs. 6.0%/yr (p < 0.001)Major intracranial bleeding: 0.3% vs. 0.8%/yr (p < 0.001)Major GI bleeding: 0.8% vs. 0.9%/yr (p = 0.37)
ROCKET AF (32)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Age ≥18 yrs with AF at moderate to high risk of stroke (N = 14,264)	Rivaroxaban oral 20 mg qd (15 mg qd in patients with CrCl 30–49 ml/min) or warfarin adjusted to maintain an INR of 2.0–3.0	Median 590 days	Stroke or systemic embolism: 1.7% vs. 2.2% (p < 0.001 for noninferiority)	Major and nonmajor clinically relevant bleeding: 14.9% vs. 14.5%/yr (p = 0.44)	Major bleeding: 3.6% vs. 3.4%/yr (p = 0.58)ICH: 0.5% vs. 0.7%/yr (p = 0.02)Fatal bleeding: 0.2% vs. 0.5%/yr (p = 0.003)GI bleeding: 3.2% vs. 2.2% (p < 0.001)
RE-LY (41)	Multicenter, randomized, single-blind, active control, noninferiority	Age ≥18 yrs with AF and ≥1 risk factors for stroke (N = 18,113)	Dabigatran etexilate oral 110 or 150 mg bid vs. oral warfarin qd (INR, 2.0–3.0)	Median 2 yrs	Stroke or systemic embolism: 1.5% and 1.1%/yr vs. 1.7%/yr (p < 0.001 for noninferiority and	Major bleeding: 2.7% and 3.1% vs. 3.4%/yr (p = 0.003 and p = 0.31 vs. warfarin)	Any bleeding: 14.6% and 16.4% vs. 18.2%/yr (p < 0.001 and p = 0.002 vs. warfarin)ICH: 0.23% and 0.30% vs. 0.74%/yr (p < 0.001 vs. warfarin)GI bleeding: 1.1% and 1.5% vs. 1.0%/year (p = 0.43 and p < 0.001 vs. warfarin)Life-

Camm AJ *et al. Eur Heart J* 2012; 33: 2719–47.

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Mixing Anti-coagulation and Anti-Platelets

- Trial with all three DOAC agents
  - AUGUSTUS
    - Apixaban plus Clopidogrel
  - RE-DUAL PCI
    - Dabigatran – higher dose in appropriate patients better
  - PIONEER-AF PCI
    - Rivaroxaban – reduced doses only trialled, stroke data limited

- In patients with combined AF and ACS/PCI mixing NOAC and P2Y12 inhibitors is better than warfarin and aspirin
  - Less bleeding with similar rates of revascularisation
  - Newer DES tend to need less anticoagulation
  - Short term triple therapy (1-3 months) may be required in some patients post stenting, depending on complexity

Anticoagulation Dosing

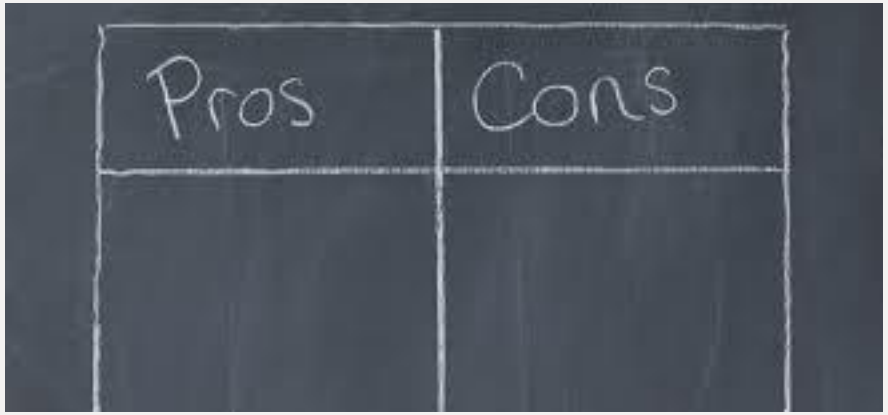
- BMJ 2017
  - Low dose NOAC vs Warfarin
  - Trend to increased stroke risk with Eliquis 2.5mg BD
  - However:
    - 25% were under 80
    - Only 9% were documented to have renal dysfunction
    - Despite the average CHADSVASc being higher in this group (4.3 vs 3-3.6 in other groups)
    - At best 16% were under-treated, at worst a lot more

Atrial fibrillation ablation

- NOT life saving
  - Except for heart failure

- Symptom improvement
  - For whom? Are we ablating the right patients?
  - When?
  - Drug Alternatives?
  - Lifestyle alternatives?

- SO risk management for a symptomatic procedure is important



Castle-AF

- AF and CHF
  - Current medical practice (184)
  - Ablation (179)

  - Mean age 64, NYHA II, low EF 32%, prior ICD,
    - 60% non-ischaemic
    - 5 years follow up 38% reduction in death or worsening HF
    - 8% increase in EF

  - BUT 2-3 procedures may be required
    - Success rates are approximately 67%
    - (AATAC AF)/Camera MRI

  - Some outcome differences may be driven by coming off antiarrhythmics
    - HOWEVER only a 30% reduction in burden is required for benefit

CABANA

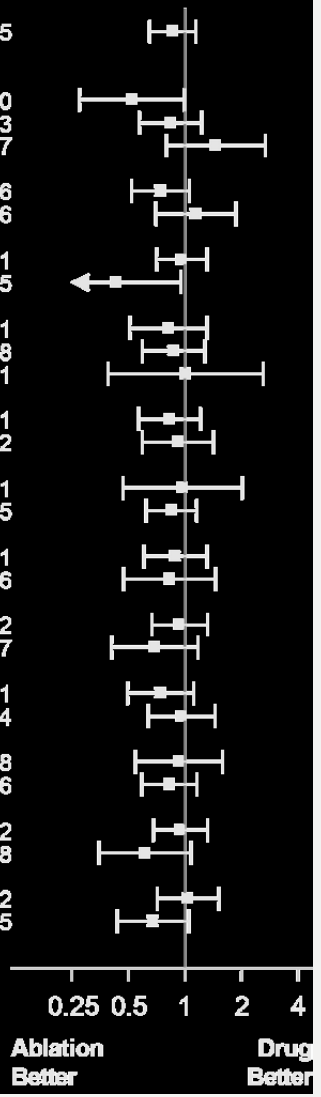
- Patients randomised to Ablation or Drugs
  - On intention to treat analysis no different!
  - Is AF ablation just a complicated placebo??

  - In the on-treatment analysis significant benefit from ablation over drugs

- Issues:
  - 27% of patients in the medical arm got ablation
  - 9% in the ablation arm didn't get ablation!
  - 14% of patients were >75

Outcomes by subgroup analysis -ITT

Group	Interaction P-Value	N	Hazard Ratio	95% CI
All Subjects		2204	0.86	0.65, 1.15
Age	0.074			
< 65 years old		766	0.52	0.27, 1.00
≥ 65 and < 75 years old		1130	0.84	0.57, 1.23
≥ 75 years old		308	1.46	0.80, 2.67
Sex	0.161			
Male		1385	0.74	0.52, 1.06
Female		819	1.14	0.70, 1.86
Minority status	0.065			
White		1979	0.96	0.71, 1.31
Minority*		225	0.43	0.20, 0.95
AF type	0.925			
Paroxysmal		946	0.82	0.51, 1.31
Persistent		1042	0.87	0.59, 1.28
Long-standing persistent		215	1.01	0.39, 2.61
Years since onset of AF	0.718			
≤ 1 year		1063	0.83	0.57, 1.21
> 1 year		1122	0.92	0.59, 1.42
Hypertension	0.734			
Absent		427	0.97	0.47, 2.01
Present		1776	0.85	0.62, 1.15
Hypertension with LVH	0.843			
Absent		1176	0.89	0.61, 1.31
Present		587	0.83	0.47, 1.46
Sleep apnea	0.339			
Absent		1695	0.94	0.67, 1.32
Present		508	0.69	0.41, 1.17
BMI	0.378			
< 30		1064	0.74	0.49, 1.11
≥ 30		1106	0.96	0.64, 1.44
CHADS-VASc score	0.716			
≤ 2		959	0.93	0.54, 1.58
> 2		1245	0.83	0.59, 1.16
History of congestive heart failure	0.196			
No		1865	0.95	0.68, 1.32
Yes		337	0.61	0.35, 1.08
Baseline NYHA class	0.147			
No heart failure or Class I		1408	1.04	0.71, 1.52
≥ Class II		778	0.68	0.44, 1.05



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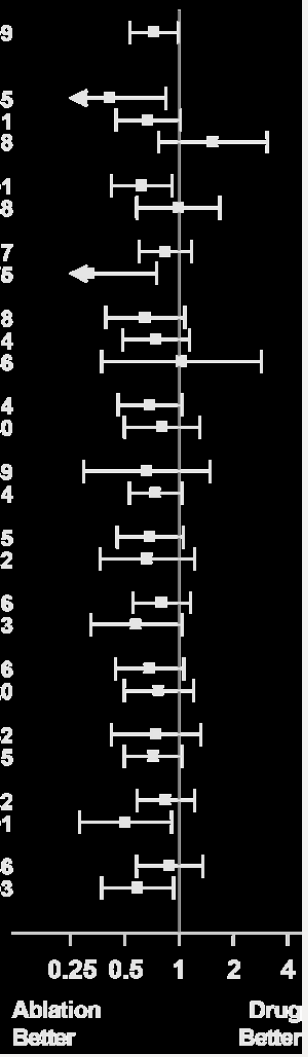
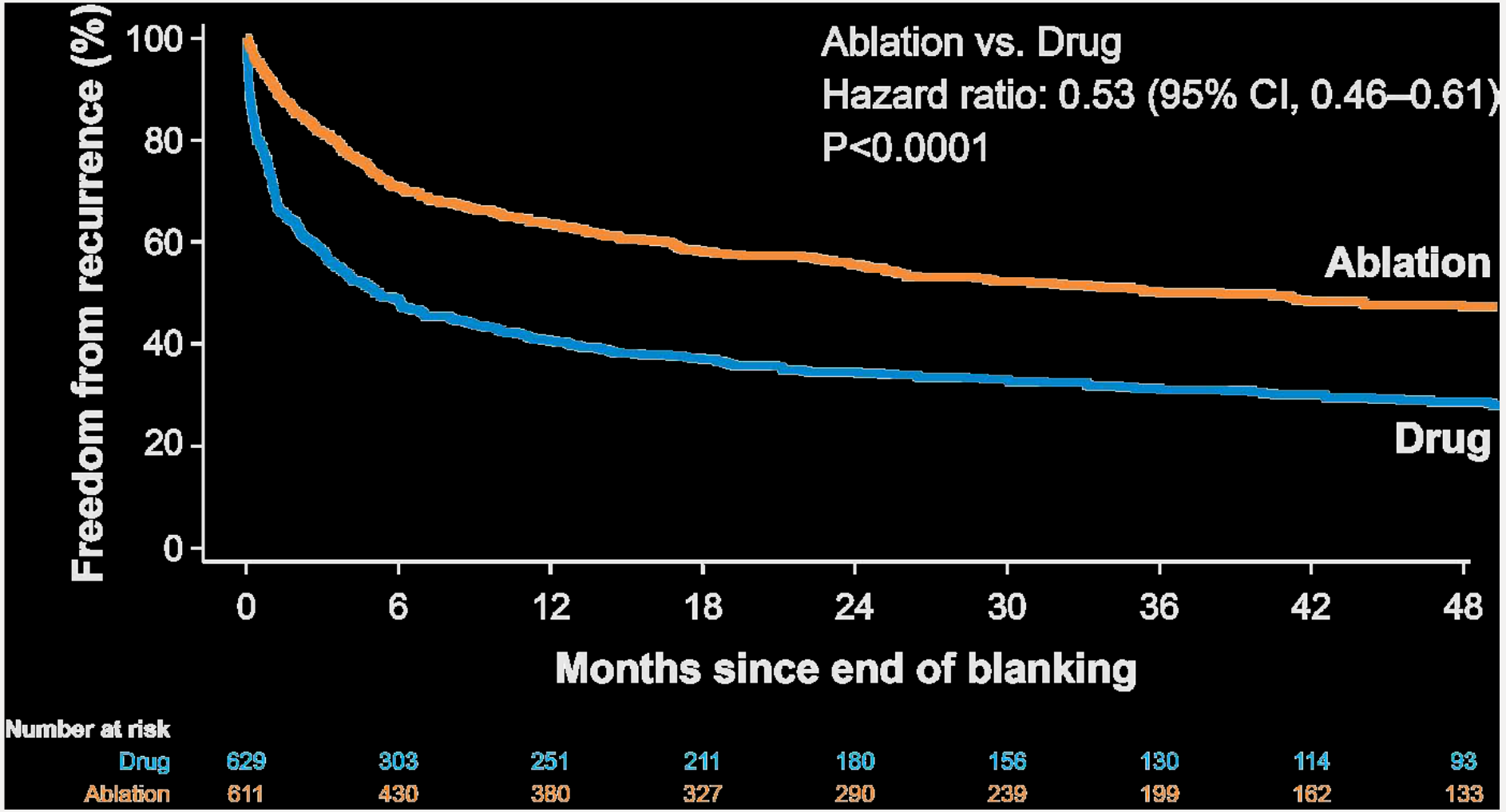
Per Protocol analysis

Group	Interaction P-Value	N	Hazard Ratio	95% CI
All Subjects		2083	0.73	0.54, 0.99
Age	0.029			
< 65 years old		725	0.41	0.20, 0.85
≥ 65 and < 75 years old		1069	0.67	0.45, 1.01
≥ 75 years old		289	1.54	0.77, 3.08
Sex	0.159			
Male		1311	0.62	0.42, 0.91
Female		772	0.99	0.58, 1.68
Minority status	0.040			
White		1883	0.84	0.60, 1.17
Minority*		200	0.32	0.13, 0.75
AF type	0.719			
Paroxysmal		897	0.65	0.39, 1.08
Persistent		983	0.74	0.49, 1.14
Long-standing persistent		202	1.03	0.37, 2.86
Years since onset of AF	0.643			
≤ 1 year		1000	0.69	0.46, 1.04
> 1 year		1066	0.80	0.50, 1.30
Hypertension	0.805			
Absent		403	0.66	0.30, 1.49
Present		1679	0.74	0.53, 1.04
Hypertension with LVH	0.919			
Absent		1108	0.69	0.45, 1.05
Present		561	0.67	0.36, 1.22
Sleep apnea	0.350			
Absent		1598	0.80	0.55, 1.16
Present		484	0.58	0.32, 1.03
BMI	0.710			
< 30		1003	0.69	0.44, 1.06
≥ 30		1051	0.77	0.50, 1.20
CHADS-VASc score	0.928			
≤ 2		907	0.75	0.42, 1.32
> 2		1176	0.72	0.50, 1.05
History of congestive heart failure	0.147			
No		1772	0.84	0.59, 1.22
Yes		309	0.51	0.28, 0.91
Baseline NYHA class	0.198			
No heart failure or Class I		1327	0.89	0.58, 1.36
≥ Class II		740	0.59	0.37, 0.93



Per protocol symptom control



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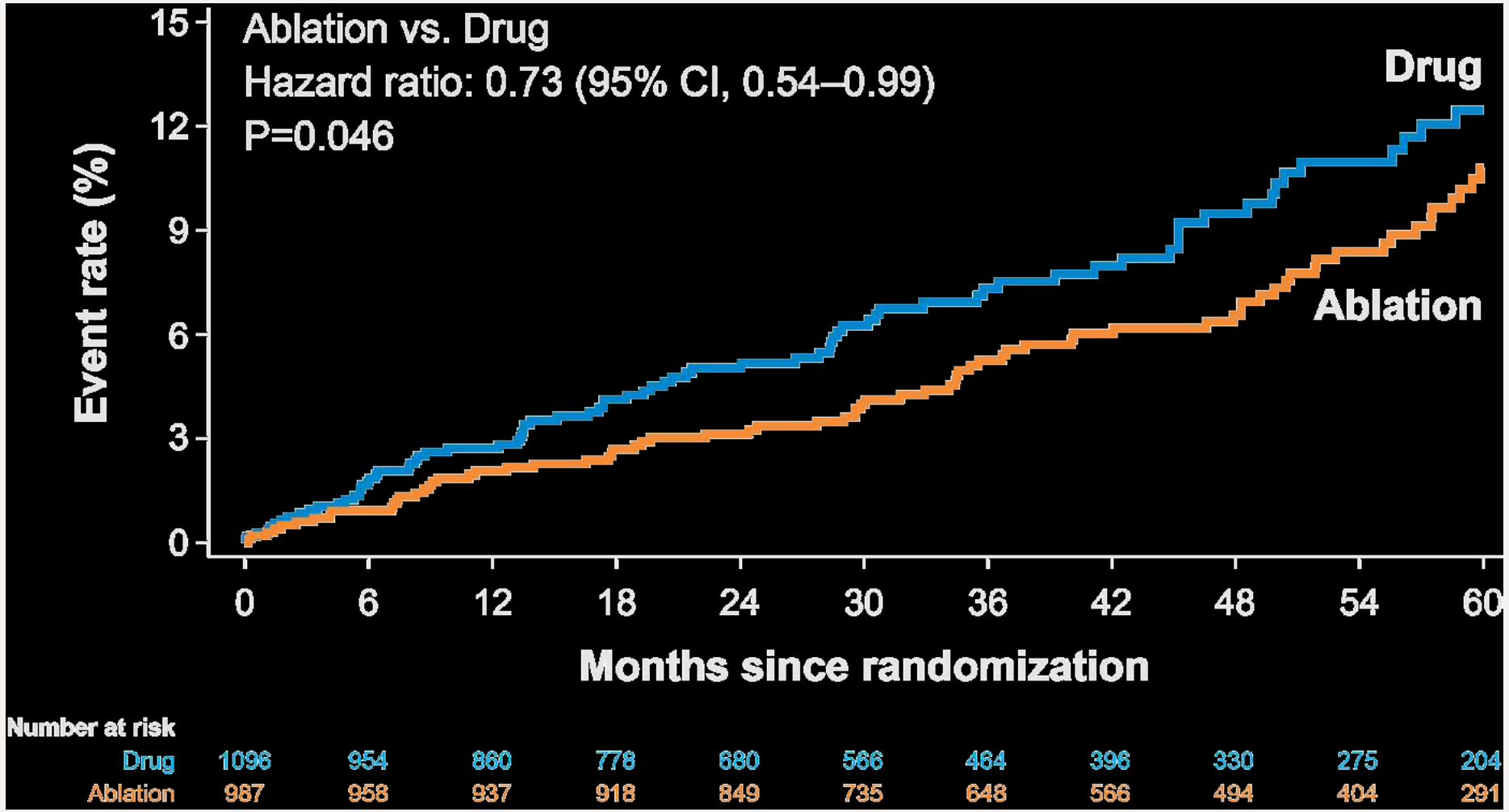
Per Protocol analysis – combined endpoint



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On Treatment Analysis

	Ablation (N = 1307)	Drug (N = 897)	HR (95% CI)	P-Value
Primary Outcome	92 (7.0%)	98 (10.9%)	0.67 (0.50, 0.89)	0.006
Secondary Outcomes				
All-cause mortality	58 (4.4%)	67 (7.5%)	0.60 (0.42, 0.86)	0.005
Death/CV hospitalization	538 (41.2%)	672 (74.9%)	0.83 (0.74, 0.94)	0.002

Registry Data

- Mortality benefit and fewer strokes post ablation
- BUT stroke timing is not correlated to atrial fibrillation episodes
- So is this an effect on the "atrial cardiomyopathy"
- OR are ablation patients more likely to take their anticoagulants
- Appropriate anticoagulation is the only drug strategy to reduce mortality in AF without heart failure

Fire and Ice...

- Cryotherapy vs. RF ablation NEJM 2016
  - 378 vs 384
- Procedure times shorter
  - 124 vs 141 minutes
- Success rates similar
  - CI 0.71-1.17
- Mean fluoroscopy times
  - Cryo-balloon 22 mins
  - Radio Frequency 17 minutes
  - Low rad with ICE – mean 3.59 minutes
    - Mean procedure time 129 minutes

Rate Control

- Digoxin
  - Primarily acts by neurohormonal modulation
  - Good rate control at rest, poor with exercise
    - Diltiazem more effective in head-to-head
  - Effective as additive to beta-blocker or calcium blocker (AFFIRM)
  - No evidence for rhythm control, and conceptually may worsen paroxysmal AF by altering myocardial refractory period
  - Variable data on increasing mortality
    - Post MI
    - In HF

Rhythm Control

- Class Ic agents
  - Flecainide
    - Gets a bad name from CAST – but misused data
      - Applies to patients with IHD/STRUCTURAL heart disease
    - I always use with an AV nodal blocker
      - (not digoxin)
      - 13 percent conversion to atrial flutter, may get 1:1 conduction
    - Side Effects:
      - Torsades
      - Bradycardia
      - Parasthesia, dizziness, blurred vision, other less common

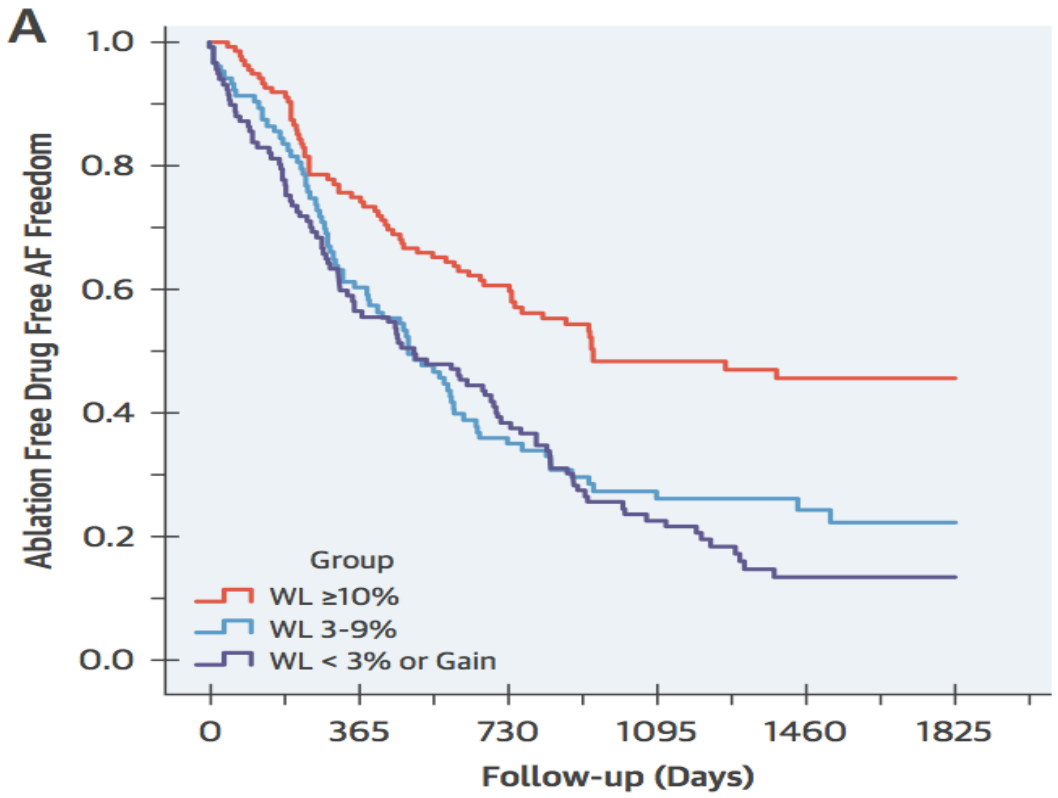
- Class III Agents
  - Sotalol
    - 1 year SR rates 37%
    - Side effects: TdP, Beta-blocking, Heart Failure
    - 11% annual discontinuation
  - Amiodarone
    - 1 year SR rates 45-60%
    - Side effects: Skin, Liver, Pulm Fibrosis, Thyroid, etc.
    - 18% annual discontinuation
  - (Ibutilide/Dofetilide)
    - Not Available, complicated
  - (Dronedarone)
    - Didn't live up to hopes, ok for paroxysmal with no CHF
    - Increased mortality with CHF

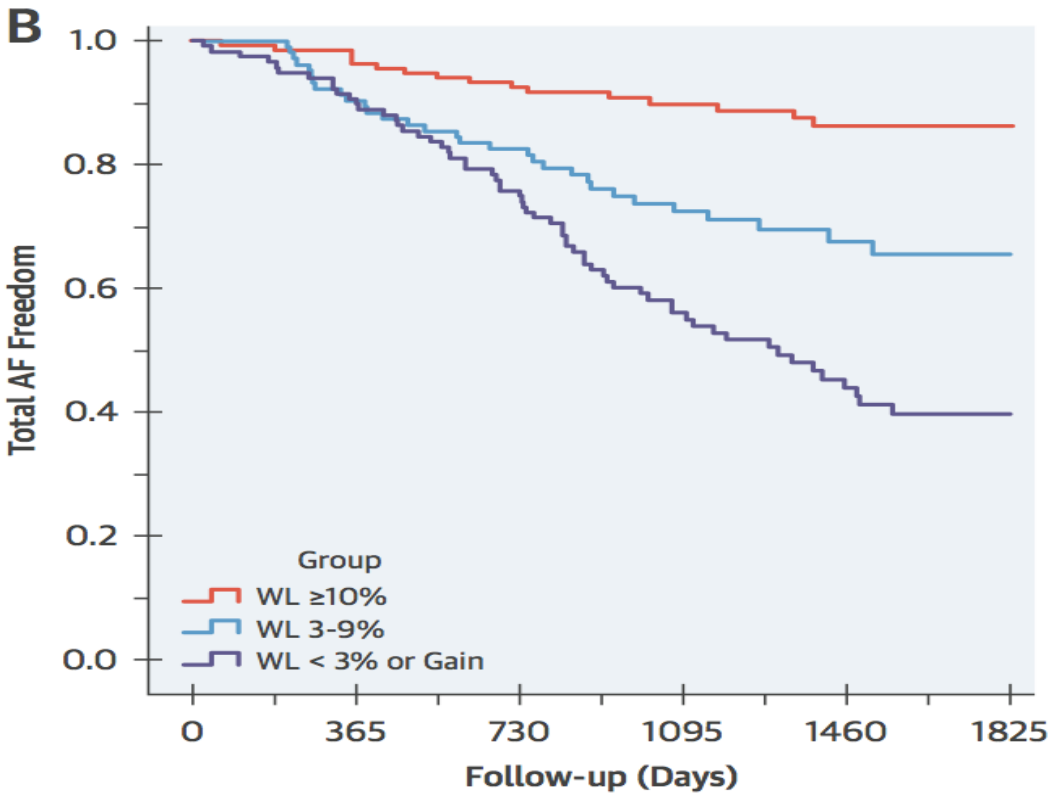
Rate Control isn't always rate control

- Symptoms and rate can vary between exercise and rest
  - Aim resting <85
  - Aim moderate exercise <110
  - If not sure look at exercise test
- Pace-Ablate
  - AIRCRAFT study (Perth) – better symptom control
  - If EF<45% should use CRT (PAVE/BLOCK-HF)
    - Even in normal EF, RVP can increase hospitalisaiton
    - His-Bundle Pacing is an evolving alternative
  - BLOCK-HF
    - Pacing if reduced EF to begin with can worsen it 45 vs 55.6% for RV pacing
  - PAVE
    - Effective if LVEF<45% and NYHA II or III
  - In observational studies, AVNA is required for benefit

Low risk, lots of benefit – Lifestyle modification

FIGURE 2 **Atrial Fibrillation Freedom Outcome According to Group**





Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9

0	365	730	1095	1460	1825
135	130	114	86	67	36
103	93	83	57	35	22
117	105	85	53	32	22

(A) Kaplan-Meier curve for AF-free survival without the use of rhythm control strategies. **(B)** Kaplan-Meier curve for AF-free survival for total AF-free survival (multiple ablation procedures with and without drugs). Abbreviations as in **Figure 1**.

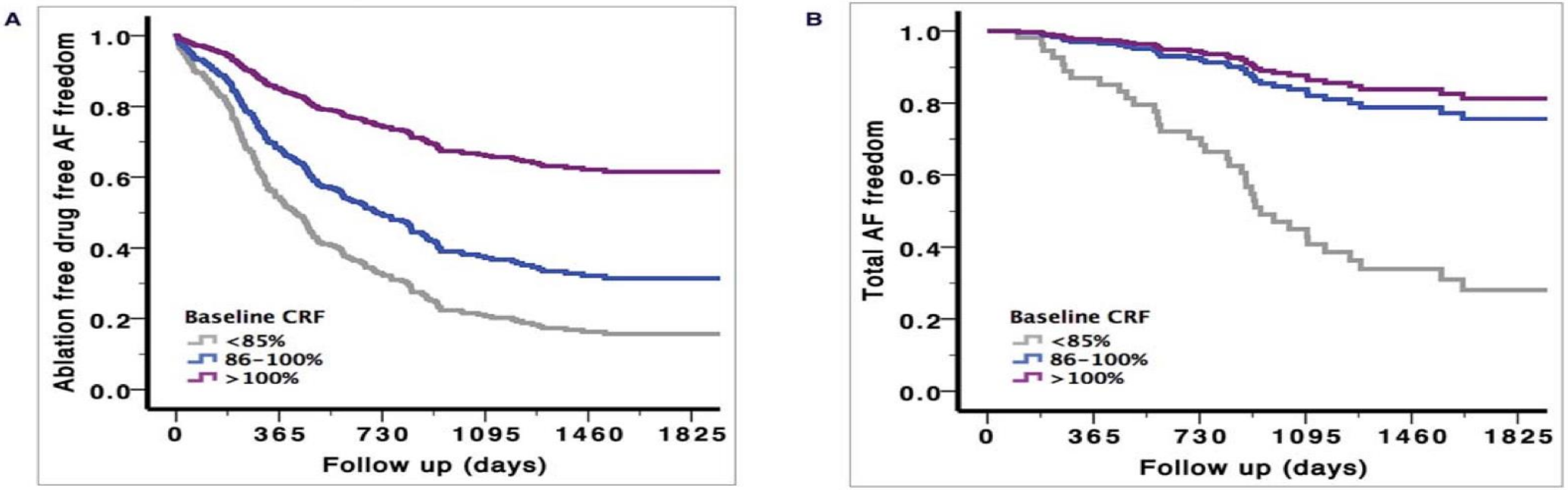
CARDIO-FIT

- 308 Patients
- Baseline Cardiorespiratory fitness (CRF) effect
- > 2 MET gain effect
  - 9% long term AF free effect per MET
  - LA Volume and Inflammatory effect
- Exclusion: Persistent AF, Previous MI, Recent Cardiac Surgery (12 months), malignancy, severe hepatic or renal disease
- >2 Mets and 10% WL 76 % Af free vs 13.6 % in those who did neither

Components

- Structured Exercise Program
  - Initial 20mins light 3/wk increasing to >200mins/wk of moderate intensity
- Meal Plan, behavioural modification
  - High protein, Low GI, calorie control
- Smoking Cessation
- BP control (RAAS drugs first line)
- OSA management if AHI >30 or if >20 and HT
- Alcohol to <30g/week
- For many patient a Chronic Disease Management Plan and allied health referrals are a major component of long term success

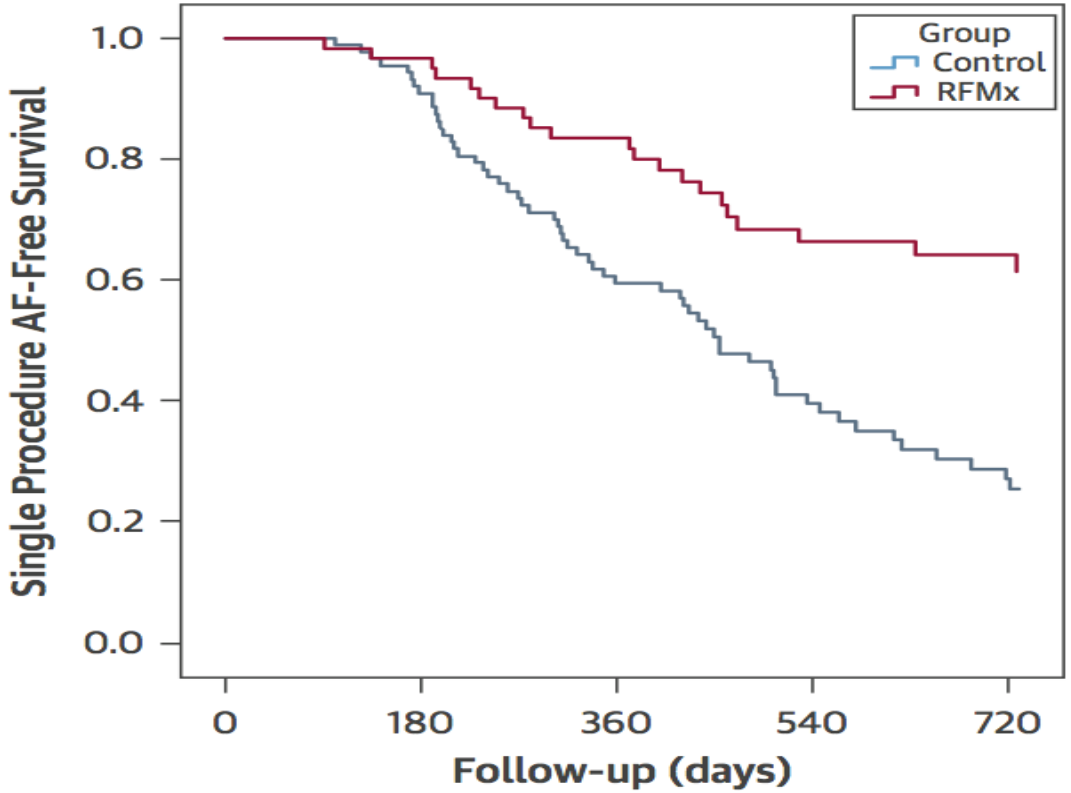
Figure 1



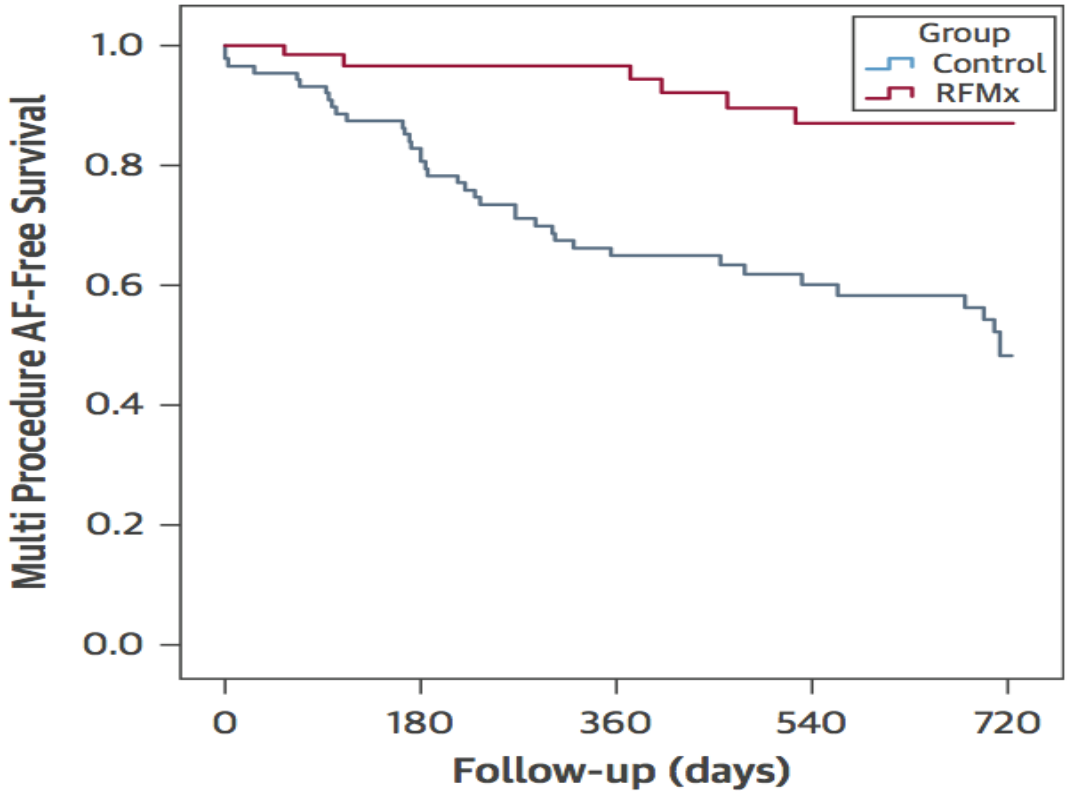
Time (Days)	0	365	730	1095	1460	1825	0	365	730	1095	1460	1825
<85% Predicted	95	54	36	16	12	6	95	78	58	33	20	11
86-100% Predicted	134	93	56	34	19	11	134	133	119	86	56	33
>100% Predicted	79	63	50	36	26	18	79	78	63	51	36	21

ARREST-AF, JACC 2014

- Lifestyle management in AF ablation population
- Average 1.5 procedures per patient
- Most patients underwent more than just PVI



Time (days)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16



0	180	360	540	730
61	55	46	32	25
88	72	51	36	23

FIGURE 3 Outcomes of AF Ablation

Kaplan-Meier curves for single-procedure, drug-free, AF-free survival **(left)** and for total AF-free survival (multiple procedures ± drugs) **(right)**. Curves for 2 years are provided, after which <20% of patients completed follow-up. Note that data are provided after the last procedure using a 3-month blanking period. RFM = risk factor management; other abbreviation as in Figure 1.

Summary

- Appropriate anticoagulation is the basis of all therapies
  - Other drugs vary in success but discontinuation rates are high
- Ablation outperforms drugs when used in the right patients, sometimes both are required
  - Management of potential risks and complications is key
- If ablation is unsuccessful or not feasible then a pacemaker and AV node ablation can work
  - If EF is reduced then CRT should be used
- **Lifestyle measures are a powerful tool in AF management and can outperform ablation as well as having multiple benefits!**
  - **Stop drugs, improve outcomes from ablation**