AF: Milestones Achieved and Future Perspectives

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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

All articles: 1992 - 2012

2012: Type of article

- Clin trials
- Ablation
- Anticoagulation
- AntiADs
- Epidemiology
- Genetics
- Mechanism
1. Compare the effectiveness of treatment strategies for atrial fibrillation including surgery, catheter ablation, and pharmacologic treatment.

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**
  - All-cause death: 27% vs 26% (p=0.058)

- **Years vs. Mortality (% patients)**
  - 0 1 2 3 4 5 6
  - Mortality increases over time with rhythm control.

- **Hazard ratio**
  - SR AFFIRM: p<0.0001
  - Warfarin use: p<0.0001
  - Digoxin use: p=0.0007
  - AAD use: p=0.0005
  - Heart failure: p<0.0001
  - Stroke/TIA: p<0.0001

# Rate Versus Rhythm Control in AF

<table>
<thead>
<tr>
<th>Study</th>
<th>PIAF # pts</th>
<th>STAF F-up, years</th>
<th>HOT CAFÉ F-up, years</th>
<th>RACE F-up, years</th>
<th>AFFIRM F-up, years</th>
<th>AF-CHF F-up, years</th>
<th>J-RHYTHM F-up, years</th>
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<tbody>
<tr>
<td>Primary endpoint</td>
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<tr>
<td>Symptom improvement</td>
<td>252</td>
<td>1.6</td>
<td>1.7</td>
<td>2.3</td>
<td>3.5</td>
<td>3.1</td>
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<td>Hospitalisation</td>
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<td>QoL</td>
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<td>Difference in 1° EP RhyC vs RC</td>
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<td>Improved 6 minute walk P&lt;0.05</td>
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<td>QoL</td>
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</table>

## Results

### Symptom improvement
- **PIAF**: Significant improvement, OR 1.98, 95% CI 0.28-22.3; p >0.71
- **STAF**: Improvement, OR 1.98, 95% CI 0.28-22.3; p >0.71
- **HOT CAFÉ**: Improved 6 minute walk, OR 1.98, 95% CI 0.28-22.3; p >0.71
- **RACE**: Improved 6 minute walk, OR 1.98, 95% CI 0.28-22.3; p >0.71
- **AFFIRM**: Improved 6 minute walk, OR 1.98, 95% CI 0.28-22.3; p >0.71
- **AF-CHF**: Improved 6 minute walk, OR 1.98, 95% CI 0.28-22.3; p >0.71

### Mortality
- **PIAF**: Not assessed
- **STAF**: Not assessed
- **HOT CAFÉ**: Not assessed
- **RACE**: Not assessed
- **AFFIRM**: Not assessed
- **AF-CHF**: Not assessed
- **J-RHYTHM**: Not assessed

### TE
- **PIAF**: Not assessed
- **STAF**: Not assessed
- **HOT CAFÉ**: Not assessed
- **RACE**: Not assessed
- **AFFIRM**: Not assessed
- **AF-CHF**: Not assessed
- **J-RHYTHM**: Not assessed

### CHF
- **PIAF**: Not assessed
- **STAF**: Not assessed
- **HOT CAFÉ**: Not assessed
- **RACE**: Not assessed
- **AFFIRM**: Not assessed
- **AF-CHF**: Not assessed
- **J-RHYTHM**: Not assessed

### Hospitalisation
- **PIAF**: 69% vs 24% (p=0.001)
- **STAF**: 54% vs 26% (p <0.001)
- **HOT CAFÉ**: 74% vs 12% (p <0.001)
- **RACE**: More in RhyC
- **AFFIRM**: 80% vs 73% (p=0.0063)
- **AF-CHF**: 46% vs 39% (p=0.0063)
- **J-RHYTHM**: More in RhyC

### QoL
- **PIAF**: No difference
- **STAF**: No difference
- **HOT CAFÉ**: Not reported
- **RACE**: No difference
- **AFFIRM**: No difference
- **AF-CHF**: No difference
- **J-RHYTHM**: Better with RhyC

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*Savelieva I, et al. Evidence Based Cardiology, Chapter 35, 2009*
Atrial Fibrillation/History of Atrial Fibrillation

Antithrombotic therapy according to guidelines

Clinical evaluation, ECG, Echocardiogram, Thyroid Function Tests, etc

Manage any underlying cardiovascular/pulmonary or other cause of AF

Rate Control

Paroxysmal AF

Persistent AF

Permanent AF

Rhythm Control

If remains symptomatic
Temporal Changes in AAD Use Prior to First Ablation for AF

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

No AADs within 2 yrs prior to ablation

8.7% → 22.7%

Use of specific AADs prior to ablation

- Sotalol 63% → 6.3%
- Amiodarone
- Class IC 40% → 24%

- $\text{CHA}_2\text{DS}_2\text{VASc} \geq 2$: 23.9% → 41.5%
- Median age: 55 (48-61) → 61 (55-66) yrs

ATHENA and PALLAS

ATHENA

Screen

Recurrent AF
AF episode < 6m
+ CV risk
No unstable or class IV NYHA CHF

PALLAS

Screen

Permanent AF
≥ 6m, but 70% > 2y
+ CV risk
No unstable or class IV NYHA CHF

DRONEDARONE

2 years, recruitment; 12 m min FU; average 21 m

4,628 patients;
1651 primary outcome events

PLACEBO

DRONEDARONE

2 years, recruitment; 12 m min FU; terminated: 3.6 m (median)

3236 of 10,800 patients recruited;
64 / 844 1st co-primary outcome events

PLACEBO
Permanent versus Non-Permanent AF

ATHENA

CV hospitalization or death %

Cumulative Hazard

HR = 0.76

P < 0.001

Placebo

Dronedarone

Months

0

6

12

18

24

30

0

10

20

30

40

50

CV hospitalization or death %

HR = 0.74

“permanent”

P = 0.096

Mean follow-up

21 ± 5 months

Months

0

6

12

18

24

30

0

10

20

30

40

50

PALLAS

CV hospitalization or death %

Cumulative Hazard

HR = 1.95

P = 0.001

Stroke, MI, SEE or CV Death %

HR = 2.29

P = 0.002

0

1

2

3

4

5

6

0

1

2

3

4

5

6

Months

Months


### AF Ablation or Antiarrhythmic Drugs?

**Thermocool**

- N = 167
- Freedom from AF recurrence [%]: PVI AAD
  - PVI: 66, p<0.001
  - AAD: 16

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts</th>
<th>Type of AF</th>
<th>Pre AAD</th>
<th>AF free at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krittayaphong, et al. 2003</td>
<td>30</td>
<td>Paroxysmal, persistent</td>
<td>≥1</td>
<td>79%</td>
</tr>
<tr>
<td>Wazni, et al. 2005, (RAAFT)</td>
<td>70</td>
<td>Mainly paroxysmal</td>
<td>No</td>
<td>87%</td>
</tr>
<tr>
<td>Stabile, et al. 2005</td>
<td>137</td>
<td>Paroxysmal, persistent</td>
<td>≥2</td>
<td>56%</td>
</tr>
<tr>
<td>Oral, et al. 2006</td>
<td>146</td>
<td>Persistent</td>
<td>≥1</td>
<td>74%</td>
</tr>
<tr>
<td>Pappone, et al. 2006</td>
<td>198</td>
<td>Paroxysmal</td>
<td>≥2</td>
<td>86%</td>
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<tr>
<td>Jais, et al. 2008, (A4 study)</td>
<td>112</td>
<td>Paroxysmal</td>
<td>≥1</td>
<td>89%</td>
</tr>
<tr>
<td>Forleo, et al. 2008</td>
<td>70†</td>
<td>Paroxysmal, persistent</td>
<td>≥1</td>
<td>80%</td>
</tr>
<tr>
<td>Wilber, et al. 2009</td>
<td>167</td>
<td>Paroxysmal</td>
<td>≥1</td>
<td>66%</td>
</tr>
<tr>
<td>Packer, et al. 2010</td>
<td>245</td>
<td>Paroxysmal</td>
<td>≥1</td>
<td>69.9%</td>
</tr>
</tbody>
</table>

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

Nielsen JC et al. NEJM in press 2012

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

<table>
<thead>
<tr>
<th>SAEs</th>
<th>RFA</th>
<th>AAD</th>
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<tbody>
<tr>
<td>Death</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TIA</td>
<td>1</td>
<td>1</td>
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<tr>
<td>PV stenosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tamponade</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0</td>
<td>1</td>
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<tr>
<td>?perforation</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Atrial flutter, 1:1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>AFl/AT</td>
<td>3</td>
<td>3</td>
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<tr>
<td>CHF</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Total</td>
<td>25</td>
<td>22</td>
</tr>
</tbody>
</table>
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).

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:
4 /13 4 (29%)  p <0.033

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

### Market Scan Research Database
- **2005-2009**
- **Ablation:** n = 3194
- **AAD:** n = 6028
- Used in propensity-matched analysis: 801 pairs
- Follow-up: 27 months

### Market Scan Research Database

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ablation n = 801</th>
<th>AAD n = 801</th>
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<tbody>
<tr>
<td><strong>Age group, %</strong></td>
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<tr>
<td>35-49</td>
<td>8.49</td>
<td>8.61</td>
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<tr>
<td>50-64</td>
<td>42.57</td>
<td>46.69</td>
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<td>65-80</td>
<td>44.19</td>
<td>40.57</td>
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<td>&gt; 80</td>
<td>4.0</td>
<td>3.37</td>
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<td><strong>Men, %</strong></td>
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<td></td>
<td>60.92</td>
<td>62.55</td>
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<td><strong>Hypertension, %</strong></td>
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<td></td>
<td>42.7</td>
<td>40.7</td>
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<td><strong>Diabetes, %</strong></td>
<td>18.73</td>
<td>15.23</td>
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<td><strong>CHF, %</strong></td>
<td>17.35</td>
<td>15.73</td>
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<tr>
<td><strong>CAD, %</strong></td>
<td>35.33</td>
<td>33.46</td>
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<tr>
<td><strong>Stroke/TIA, %</strong></td>
<td>2.87</td>
<td>4.12</td>
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<td><strong>CHADS$_2$, %</strong></td>
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<tr>
<td>0</td>
<td>36.2</td>
<td>34.83</td>
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<tr>
<td>1</td>
<td>37.95</td>
<td>40.32</td>
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<tr>
<td>2</td>
<td>19.73</td>
<td>17.23</td>
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<td>≥ 3</td>
<td>6.12</td>
<td>7.61</td>
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<tr>
<td><strong>Warfarin</strong></td>
<td>69.91</td>
<td>69.54</td>
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*Reynolds MR, et al.*
*Circ Cardiovasc Qual Outcomes 2012;5 [epub ahead of press]*

**Stroke/TIA free survival**

![Stroke/TIA free survival graph]

- AF, ablation
- AF, no ablation

**HR = 0.60 (0.43 – 0.84)**

![Log-rank p = 0.005 graph]

Log-rank p = 0.005

Warfarin use decline to 50% in both groups
### AF: Rhythm vs. Rate (drug scripts)

**Risk of Stroke/TIA**

Population-based observational study of Quebec pts ≥ 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.

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<tr>
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<th>Unadjusted</th>
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<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>All patients</td>
<td>0.72</td>
<td>0.67, 0.78</td>
<td>0.80</td>
<td>0.74, 0.87</td>
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<tr>
<td>CHADS2 = 0</td>
<td>0.86</td>
<td>0.65, 1.13</td>
<td>0.93</td>
<td>0.70, 1.24</td>
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<tr>
<td>n = 4,876</td>
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<tr>
<td>CHADS2 = 1</td>
<td>0.71</td>
<td>0.61, 0.83</td>
<td>0.80</td>
<td>0.68, 0.93</td>
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<td>N = 15,551</td>
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<td>CHADS2 ≥ 2</td>
<td>0.77</td>
<td>0.70, 0.84</td>
<td>0.84</td>
<td>0.77, 0.93</td>
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<td>N= 37,091</td>
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<tr>
<td>Propensity</td>
<td>0.75</td>
<td>0.67, 0.85</td>
<td>0.77</td>
<td>0.68, 0.87</td>
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<td>matched</td>
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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, %

Not approved

<table>
<thead>
<tr>
<th>Budiodarone dose, mg bid</th>
<th>Placebo</th>
<th>200</th>
<th>400</th>
<th>600</th>
<th>600*</th>
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<tbody>
<tr>
<td>Overall p=0.0001</td>
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<td>n.s. p=0.16</td>
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<td>-10 p=0.015</td>
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<td>-54 p=0.015</td>
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<td>-75 p=0.005</td>
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<td>-83 p=0.009</td>
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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

Murdock D. et al, ACC Abstracts 2011
Synergistic Effect on AF of Combination of Ranolazine and Dronedarone

- Canine isolated coronary-perfused RA, LA, PV, and LV preparations
- Ranolazine 5 \( \mu \text{mol/L} \)
- Dronedarone 10 \( \mu \text{mol/L} \)

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

Induction or termination of persistent AF, %

- ACh
- ACh+Dronedarone
- ACh+Ranolazine
- ACh+R+D

AF induction
AF termination

AF threshold, mA

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

Pharmacological Cardioversion of AF With Combination of Amiodarone and Ranolazine

- Pilot RCT
- N = 51 with AF < 48 h
- 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<sup>o</sup> EP: conversion within 24 h

Proportion of patients converted to SR, %

<table>
<thead>
<tr>
<th></th>
<th>Amio + Rano</th>
<th>Amio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to conversion:</td>
<td>18 h (Amio) vs 10 h (Amio+Rano)</td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.81 (0.74 - 0.88)

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.

**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**

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

- **Placebo:** 12.8%
- **Dronedarone:** -54.4%
- **Placebo-extracted change:** -59.1%

At 12 weeks: 23 vs 18%

\[ \text{p} = 0.0015 \]
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
- $2^0$ endpoints: AF burden at each visit (4, 8, 12 weeks) and # episodes

Diagram:

- Placebo + Placebo
- Dronedarone + Placebo
- Ranolazine + Placebo
- Ranolazine + Dronedarone dose 1
- Ranolazine + Dronedarone dose 2
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 < 1 year < admission (first documented AF)
- AAD < 7 days > discharge

Antithrombotic therapy according to guidelines

Clinical evaluation, ECG, Echocardiogram, Thyroid Function Tests, etc

Manage and underlying cardiovascular/pulmonary or other cause of AF

Rate Control

Paroxysmal AF ➔ Persistent AF ➔ Permanent AF

Rhythm Control

If early onset, little atrial remodelling or remains symptomatic
EAST: Early treatment of Atrial fibrillation for Stroke prevention Trial

Pre-study screening

Patients at risk for cardiovascular events
e.g., recruited in cardiology offices, medicine offices, neurology departments, hypertension clinics, pacemaker clinics, and others

Patients with recent-onset AF (≤ 1 year)

Patients without known AF: ECG screening
Enrolment in case of documentation of recent-onset AF

Study procedures

Early rhythm control
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 guidelines 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?

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 generalizations of Newton and Harvey could never have been completed in this modern age

Oscar Wilde, Oxford Notebooks
Thank you for your attention