Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix 1. Inclusion and Exclusion Criteria

Inclusion Criteria
1. Age > 18 and ≤ 75 years old.
2. Symptomatic, recurrent paroxysmal AF lasting > 30 seconds (at least 4 episodes within the prior 6 months). At least one episode must be documented by Holter, 12-lead ECG, event monitor or rhythm strip.

Exclusion Criteria
1. Documented LVEF <40%.
2. Documented left atrial diameter >5.5cm.
3. Moderate to severe LVH (LV wall thickness >1.5cm).
4. Documented valvular disease, coronary heart disease (defined as the presence of >70% stenosis of coronary arteries or documentation of active myocardial ischemia), post-CABG, postoperative cardiac surgery or peripheral artery disease.
5. Untreated hypothyroidism or hyperthyroidism. Patients who are euthyroid on thyroid hormone replacement therapy are acceptable.
6. Contraindication for the use of sotalol, dofetilide and 1C antiarrhythmic drugs (liver enzymes and serum creatinine that are outside the upper normal lab values, e.g. > 3 times ULN with 2 abnormal lab values).
7. Previous left heart ablation procedure, either by surgery or by percutaneous catheter, for atrial fibrillation.
8. Current enrollment in another investigational drug or device study.
9. Presence of any other condition that the investigator feels would be problematic or would restrict or limit the participation of the Patient for the entire study period.
10. Absolute contra-indication to the use of heparin and or warfarin.
11. Increase risk of bleeding, current peptic ulceration, proliferative diabetic retinopathy, history of severe systemic bleeding, or other history of bleeding diathesis or coagulopathy.
12. Severe pulmonary disease e.g. restrictive pulmonary disease, chronic obstructive disease (COPD).
13. Documented intra-atrial thrombus, tumor, or another abnormality which precludes catheter introduction.
14. Previous use of full therapeutic dose of an antiarrhythmic drug, including amiodarone, propafenone, flecainide, sotalol, quinidine.
15. Pacemaker or Implantable Cardioverter Defibrillator.
16. Women with a positive pregnancy test.
17. Evidence of active cardiac or systemic infection.
18. Medical condition limiting expected survival to less than one year.
eAppendix 2. RAAFT Trial Antiarrhythmic Selection Guidelines

The following guidelines and recommendations for the treatment of atrial fibrillation of patients randomized to the drug therapy arm of the RAAFT trial are suggested from: ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation:

Class IC:
Propafenone:
- 300 mg every 12 hours or 150 mg every 6 hours in patients 70 years or younger that weigh at least 70 kg (155 pounds).
- 150 mg every 8 hours in patients older that 70 years or with a weight less than 70 kg (155 pounds).

Flecainide:
- 50 mg every 12 hours, maximum dose 300 mg in patients weighing over 70 kg (155 pounds).
- Patients weighing less that 70 Kg (155 pounds) maximum dose should be 200 mg.

Class III:
Sotalol:
- 160 mg every 12 hours to men 70 years of age or younger with a creatinine concentration of 1.5 mg per deciliter (130µmol per liter) or less and who weighed at least 70 kg (155 pounds).
- 80 mg every 8 hours to men who were older than 70, men with a creatinine concentration greater than 1.5 mg per deciliter (130µmol per liter), men who weigh less than 70 kg (155 pounds).
- Women 70 or younger who have a creatinine concentration of 1.2 mg per deciliter (110µmol per liter) or less.
- 80 mg every 12 hours to women who were older than 70, or with a creatinine concentration greater than 1.2 mg per deciliter (110µmol per liter).

Dofetilide:
- Dofetilide should not be used in patients with a baseline QTc > 440msec
- If Creatinine Clearance is > than 60 ml/min give 500 µg every 12 hours
- Check QTc 2-3 hours after the first dose, if increase in QTc is less than 15% continue current dose if QTc increase is greater than 15% or more than 500msec the next dose should be 250µg.
- If QTc increases > 500msec at any time after the second dose dofetilide should be discontinued. (see algorithm below)

Patients randomized to the anti-arrhythmic treatment group should fail at least one Class I or III of the listed medications at the maximum tolerated dose prior to being started on Amiodarone.

Amiodarone:
- Amiodarone will be given at a dose of 10 mg per kg of body weight each day for 14 days followed by 300 mg per day for 4 weeks, after which a maintenance dose of 200 mg per day will be given.

Reasons for changing therapy will include:
- Intolerable Side effects
- Recurrence of symptomatic atrial fibrillation documented by ECG lasting more than 30 seconds.
Desing Algorithm Used in the Tikosyn® (dofetilide) Clinical Program

1. Place Patient on Telemetry
2. Check Baseline QTc
   - if QTc > 440 msec, Do Not Use dofetilide
   - if QTc ≤ 440 msec, Proceed
3. Calculate Creatinine Clearance (Clcr)
   - Male Clcr = \(\frac{(140 - \text{age}) \times \text{actual body weight in kg}}{72 \times \text{serum creatinine (mg/dL)}}\)
   - Female Clcr = 0.85 x male
4. If Clcr is < 20 mL/min, dofetilide is CONTRAINDICATED
5. If Clcr is > 60 mL/min, give 500 mcg dofetilide BID
6. If Clcr is 40 - 60 mL/min, give 250 mcg dofetilide BID
7. If Clcr is 20 - < 40 mL/min, give 125 mcg dofetilide BID
8. Post dose adjustment: 2 - 3 hours after dose check QTc
   - (First dose only) If increase in QTc is ≤ 15%, continue current dose
   - (First dose only) If increase in QTc is > 15% or > 500 msec, decrease current dose (see text)
   - If at any time after the second dose QTc increases > 500 msec, dofetilide should be discontinued

Appendix 3. EQ-5D

Appendix 1

By placing a tick (thus ☑) in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about  ☐
- I have some problems in walking about  ☐
- I am confined to bed  ☐

Self-Care
- I have no problems with self-care  ☐
- I have some problems washing or dressing myself  ☐
- I am unable to wash or dress myself  ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities  ☐
- I have some problems with performing my usual activities  ☐
- I am unable to perform my usual activities  ☐

Pain/Discomfort
- I have no pain or discomfort  ☐
- I have moderate pain or discomfort  ☐
- I have extreme pain or discomfort  ☐

Anxiety/Depression
- I am not anxious or depressed  ☐
- I am moderately anxious or depressed  ☐
- I am extremely anxious or depressed  ☐

Compared with my general level of health over the past 12 months, my health state today is:
- Better  ☐
- Much the same  ☐
- Worse  ☐
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.
eAppendix 4. Adverse Events

AF Ablation Adverse events: Adverse events for this arm of the trial are determined by the proportion of patients with of any of the following serious complications:

1. Death
2. Cardiac tamponade
3. Severe pulmonary vein stenosis ≥ 70%
4. Atrio-esophageal fistula
5. Thromboembolism
6. Vascular complications, including arterial pseudoaneurysm, arteriovenous fistula and hematoma leading to transfusion
7. Phrenic nerve injury
8. Complete AV block requiring permanent pacemaker implantation

Antiarrhythmic Drug Adverse events: Adverse events for this arm of the trial are determined by the proportion of patients with any of the following serious complications:

1. Death
2. Torsade de pointes
3. Bradycardia leading to pacemaker insertion
4. Syncope
5. QRS duration prolongation ≥ 50% of baseline QRS duration.
6. 1:1 Atrial flutter
7. Any other significant adverse events that lead to drug discontinuation.

Bleeding complications associated with oral anticoagulant therapy were also be recorded.
eTable 1. AAD during treatment and follow-up periods

<table>
<thead>
<tr>
<th>Antiarrhythmic Drug</th>
<th>Mean Dose mg (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>68.9% 176 (51)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>24.6% 487 (122)</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>3.3% 600 (283)</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>45.9% 128 (119)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>26.2% 461 (233)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3.3% 327 (102)</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>3.3% 0.5 (0.4)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>1.6% 160 (0.0)</td>
</tr>
</tbody>
</table>
### eTable 2. Serious Adverse events

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>NO. OF EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>RFA</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Tamponade</td>
<td>4</td>
</tr>
<tr>
<td>Severe pulmonary vein stenosis &gt; 70%</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia leading to pacemaker insertion</td>
<td>1</td>
</tr>
<tr>
<td>Atrio-esophageal fistula</td>
<td>0</td>
</tr>
<tr>
<td>Atrial flutter with 1:1 atrioventricular conduction</td>
<td>0</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
</tr>
</tbody>
</table>
eFigure 1. Kaplan-Meier Curve for time to first recurrence of symptomatic AF, obtained by 12 lead ECG, Holter, TTM recordings or rhythm strip recordings
eFigure 2. Kaplan-Meier Curve for time to first recurrence of symptomatic/asymptomatic AF, atrial flutter and atrial tachyarrhythmias, obtained by 12 lead ECG, Holter, TTM recordings or rhythm strip recordings.