Flecainide is effective in CPVT patients with incessant exercise-induced ventricular arrhythmias despite optimal conventional drug therapy

Christian van der Werf
Heart Failure Research Center, Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands

No disclosures
Introduction

- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
  - Malignant inherited arrhythmia syndrome
  - Physical/emotional stress-induced polymorphic ventricular tachycardia (VT)
  - Structurally normal heart
  - Mutations in RyR2 (~60%) or CASQ2 (~2%)
Conventional therapy in CPVT

- **First-line therapy: β-blockers**
  - 8-year (near-)fatal event rate: 11%*
- **Ca$^{2+}$-channel blockers**
- **Left cardiac sympathetic denervation**
- **Implantable cardioverter-defibrillator**

*Hayashi et al. Circulation 2009*
Flecainide in CPVT

- Flecainide directly targets molecular defect CPVT
  - Blocks RyR2 channel
  - Prevents RyR2-mediated premature Ca^{2+} release
  - Suppresses triggered beats (I_{na} block)
- Flecainide was effective in 2 highly symptomatic CPVT patients

Watanabe et al. Nat Med 2009
Participants and study design

• All genotype-positive CPVT patients started on flecainide before December 2009
• Eight centers worldwide
• Decisions on flecainide dose made by treating cardiologist
• Retrospective chart review
Primary outcome measures

- Primary outcome
  - Ventricular arrhythmias during exercise testing
  - Stable β-blocker dose
  - Baseline vs. first test on stable flecainide dose
Primary outcome measures

- Primary outcome
  - Ventricular arrhythmias during exercise testing

- Ventricular arrhythmia score
  I. None / isolated ventricular premature beats (VPB)
  II. Bigeminal VPBs and/or frequent VPBs (>10/min)
  III. Couplet
  IV. Non-sustained VT
Outcome measures

• Primary outcome
  – Ventricular arrhythmias during exercise testing

• Secondary outcomes
  – Incidence of cardiac events
  – Side effects
  – Proarrhythmic effects
**Patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPVT patients (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years</td>
<td>18 [3-57]</td>
</tr>
<tr>
<td>Female</td>
<td>23 (70%)</td>
</tr>
<tr>
<td>RyR2 mutation</td>
<td>32 (97%)</td>
</tr>
<tr>
<td>Probands</td>
<td>15 (45%)</td>
</tr>
<tr>
<td>Symptomatic before diagnosis</td>
<td>21 (64%)</td>
</tr>
<tr>
<td>Previous cardiac arrest</td>
<td>4 (12%)</td>
</tr>
</tbody>
</table>
Conventional and flecainide therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPVT patients (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker at baseline</td>
<td>31 (94%)</td>
</tr>
<tr>
<td>Ca(^{2+})-channel blocker at baseline</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>12 (36%)</td>
</tr>
<tr>
<td>Age at start of flecainide, years</td>
<td>25 [7-68]</td>
</tr>
<tr>
<td>Severe ventricular arrhythmias at baseline</td>
<td>26 (79%)</td>
</tr>
<tr>
<td>(≥2 consecutive VPBs)</td>
<td></td>
</tr>
<tr>
<td>Flecainide discontinuation</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>β-blocker dose increased</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
Significant improvement in ventricular arrhythmia score

P < 0.001

Ventricular arrhythmia score

NSVT, n
Couplet, n
Bigeminy/frequent VPB, n
No/isolated VPB, n

Standard therapy baseline
Flecainide therapy test 1 (21 days)
Significant improvement primary outcome measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard therapy baseline (n=31)</th>
<th>Flecainide therapy test 1 (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after start flecainide, days</td>
<td>-</td>
<td>21 [5-363]</td>
<td>-</td>
</tr>
<tr>
<td>SR at baseline, bpm</td>
<td>58 ± 13</td>
<td>60 ± 10</td>
<td>0.108</td>
</tr>
<tr>
<td>SR at maximal exercise, bpm</td>
<td>146 ± 23</td>
<td>136 ± 21</td>
<td>0.005</td>
</tr>
<tr>
<td>Maximum workload attained, METS</td>
<td>11 ± 3</td>
<td>12 ± 4</td>
<td>0.02</td>
</tr>
<tr>
<td>SR at onset of ventricular arrhythmias, bpm</td>
<td>115 ± 19</td>
<td>120 ± 19</td>
<td>0.04</td>
</tr>
<tr>
<td>Max number of VPBs during 10s</td>
<td>13 ± 5</td>
<td>6 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Couplet</td>
<td>22 (71%)</td>
<td>3 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>13 (42%)</td>
<td>1 (3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Dose-dependence of flecainide

<table>
<thead>
<tr>
<th>Variable</th>
<th>No suppression (n=13)</th>
<th>Partial suppression (n=6)</th>
<th>Complete suppression (n=12)</th>
<th>$P$ no vs. partial/complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide dose, mg</td>
<td>113 ± 39</td>
<td>142 ± 38</td>
<td>150 ± 60</td>
<td>0.038</td>
</tr>
</tbody>
</table>
Dose-dependence of flecainide

![Graph showing dose-dependence of flecainide with data points for NSVT, Couplets, Bigeminy/frequent VPB, and No/isolated VPB at different stages: Standard therapy baseline, Flecainide therapy starting dose (39 days), and Flecainide therapy stable dose (70 days). The graph illustrates a decrease in arrhythmia with increasing dose of flecainide, with statistical significance indicated by P-values.]
Secondary outcome measures

- 3 patients discontinued flecainide within 6 months due to side effects
- One cardiac event during median follow-up of 17 [9-37] months (n=29)
  - Several appropriate ICD shocks (low flecainide levels) → no further events during 14-month follow-up
- No worsening in ventricular arrhythmias
- PR and QRS duration normal
Long-term follow-up case

• 1977: 14 years old boy with multiple syncopes with seizures during exercise since the age of 4 (epilepsy?)

• 1981: diagnosed with CPVT
  - Multiple antiarrhythmic drugs ineffective in controlling ventricular arrhythmias → flecainide 200 mg/day + sotalol 160 mg/day successful

• 1981-2008: asymptomatic
Long-term follow-up case

- **July 2008:** *RYR2* mutation detected
  - Exercise test after drug discontinuation: non-sustained VTs
  - Exercise test after restarting combined therapy: only isolated VPBs

- **Free of arrhythmic events for 29 years**
Limitations

- Relatively small number of patients
- Short follow-up duration (17 [9-37] months)
- Exercise-induced ventricular arrhythmias as surrogate outcome

- Prospective randomized crossover trial in CPVT patients with ICD in US

Prince Kannankeril  prince.kannankeril@vanderbilt.edu
Bjorn Knollmann  bjorn.knollmann@vanderbilt.edu
Conclusions

• In CPVT patients refractory to standard therapy flecainide was safe and effective in suppressing exercise-induced ventricular arrhythmias.
Thank you
Reproducibility of exercise testing

![Graph showing the reproducibility of exercise testing with NSVT, Couplet, Bigeminy/frequent VPB, and No/isolated VPB scores. The graph displays the frequency of these arrhythmias during standard therapy baseline -1 (26 months) and standard therapy baseline (n=14) with a p-value of 0.831.](image)
Reproducibility of exercise testing

![Graph showing reproducibility of exercise testing]
Recommendations ICD implantation

- **Class I (level of evidence: C)**
  - Survivors of cardiac arrest

- **Class IIa (level of evidence: C)**
  - Syncope and/or documented sustained VT while receiving β-blockers
Primary outcome measures

- Primary outcome
  - Ventricular arrhythmias during exercise testing

- Sinus rate at onset of ventricular ectopy
  Sinus rate = 80 bpm
Primary outcome measures

- Primary outcome
  - Ventricular arrhythmias during exercise testing

- Maximum number of VPBs during 10s

  Number of VPBs = 23
Arrhythmogenic resection in CPVT


Watanabe et al. Nat Med 2009

Flecainide's action in CPVT

Diagram showing the mechanism of arrhythmia in CPVT, highlighting the role of FKBP12.6 and its interaction with RyL2, TRD, JCN, CASQ2, and other calcium regulatory proteins. The diagram also illustrates changes in cytosolic calcium concentration and membrane potential.