Atrial repolarizing delaying agents
(Vernakalant, Xention)

DISCLOSURES

- Consulting fees: Sanofi-Aventis, Menarini

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Universidad Complutense, UCM/CSIC. Madrid
Treatment of atrial fibrillation

1. AADs represent the mainstay therapy in AF, but:
   • Present poor efficacy (< 50% remain in SR 1 year after CV)
   • Serious AEs: proarrhythmia (Class I and III) and organ toxicity (amiodarone)
   • Most are contraindicated in pts with structural heart diseases
   • We need safer and more effective AADs

2. An attractive prospect - Atrial repolarization delaying agents (ARDAs)
   • Targeting cardiac K+ channels selectively expressed in the atria
   • Atrial-selective Na+ channel blockade via state-selective blocking properties that produce more block for atrial than for ventricular action potentials, or that are highly selective for rapid rhythms like AF
Almost 25 years without new AADs!

1914 - Quinidine
1946 - Digitalis
1962 - Verapamil
1964 - Propranolol
1965 - Bretilium
1969 - Diltiazem
1948 - Lidocaine
1951 - Procainamide
1956 - Ajmalina
1962 - Disopyramide
1967 - Amiodarone
1972 - Mexiletine
1973 - Aprindine, Tocainide
1975 - Flecainide
1976 - Propafenone

CAST, 1989
2000 - Dofetilide
2009 – Dronedarone
2010 - Vernakalant

Vernakalant is used to rapidly restore normal SR in adult patients with recent-onset AF
Vernakalant blocks the $I_{Na}$

- Frequency- and voltage-dependent $I_{Na}$ blocker
  - $I_{Na}$ block increases at fast rates and depolarized $E_m$
  - Atrial RMP is $\approx 10$ mV more positive than that of the ventricle
    - This difference increases during AF: selectivity
- Rapid onset/offset kinetics: less risk of conduction disturbances or proarrhythmia once the heart rate slows ($I_{Na}$ block is no longer required)

![Graph showing the relationship between Concentration of Vernakalant (µM) and Sodium current (µA/cm²)](image)

- **$IC_{50}$** = 43 µM at -80 mV, 1 Hz
- **$IC_{50}$** = 9 µM at -80 mV, 20 Hz

<table>
<thead>
<tr>
<th>$E_m$ (mV)</th>
<th>$IC_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-120</td>
<td>107 ±11</td>
</tr>
<tr>
<td>-100</td>
<td>60 ± 4</td>
</tr>
<tr>
<td>- 80</td>
<td>43 ± 8</td>
</tr>
<tr>
<td>- 60</td>
<td>31 ± 1</td>
</tr>
</tbody>
</table>
Atrial repolarization delaying agents (ARDAs)
Ionic currents involved in the genesis of the atrial and ventricular action potentials

ATRIAL

VENTRICULAR

I_{to1}, I_Kur

I_{CaL}, I_{NaL}

I_Kr

I_Ks, I_K1, I_{KACH}, I_{KATP}

I_{Na}

I_{K1}, I_{KACH}, I_{KATP}

I_{CaL}, I_{NaL}

I_Kr

I_Ks

I_K1, I_{KATP}
Vernakalant blocks K⁺ channels important in atrial repolarization

- Vernakalant blocks K⁺ channels that are present in human atria rather than ventricles ($I_{Kur}$, $I_{KACh}$ and $I_{to}$)
  - Some modest $I_{Kr}$ block
  - Atrial-selective APD and ERP prolongation during AF
  - Little effect on ventricular repolarization

<table>
<thead>
<tr>
<th>Current</th>
<th>Potency ($IC_{50}$, µM)</th>
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<tbody>
<tr>
<td>$I_{to}$</td>
<td>5-30</td>
</tr>
<tr>
<td>$I_{Kur}$</td>
<td>3-13</td>
</tr>
<tr>
<td>$I_{KACh}$</td>
<td>10</td>
</tr>
<tr>
<td>$I_{Kr}$</td>
<td>7-21</td>
</tr>
<tr>
<td>$I_{NaL}$</td>
<td>&lt;30</td>
</tr>
<tr>
<td>$I_{Ks}$</td>
<td>&gt;100</td>
</tr>
<tr>
<td>$I_{K1}$</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Vernakalant predominantly increase atrial ERP

- N = 19 with a clinical indication for diagnostic EP
- 53% male; age, 48±11 years
- 4 mg/kg i.v. over 10 min followed by 1 mg/kg/hr for 35 min

<table>
<thead>
<tr>
<th>CL (ms)</th>
<th>300</th>
<th>400</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERP</td>
<td>172 ± 24</td>
<td>182 ± 30</td>
<td>203 ± 31</td>
</tr>
<tr>
<td></td>
<td>193 ± 21*</td>
<td>207 ± 27*</td>
<td>228 ± 24*</td>
</tr>
</tbody>
</table>

| Heart rate | No change |
| VERP, QT and HV | No significant changes |
| QRS         | Prolongation (+15 ms at CL 400 ms) |

Median C_p = 2-3 μg/mL
100 bpm pacing

CRAFT (Conversion of Rapid Atrial Fibrillation) phase II trial

- 56 pts with AF (3-72 h duration) randomized to vernakalant or placebo
- VPBs in 2 pts and sinus bradycardia in 1 patient
- Vernakalant did not prolong the QTcB intervals vs placebo

Roy et al. J Am Coll Cardiol 2004;44:2355-2361
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Phase</th>
<th>Patient characteristics</th>
<th>Dose (mg/kg)</th>
<th>Primary endpoint</th>
<th>Outcome vs placebo</th>
<th>MTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT 1</td>
<td>336 AF</td>
<td>III, PC</td>
<td>AF 3 h-45 d AF 3 h – 7 days</td>
<td>3 for 10’ and 2 after 15’</td>
<td>Conversion to SR within 90 min</td>
<td>52 vs 4% (P &lt; 0.01)</td>
<td>11 min</td>
</tr>
<tr>
<td>ACT 2</td>
<td>161 AF</td>
<td>III, PC</td>
<td>AF 3 -72 h after cardiac surgery</td>
<td></td>
<td></td>
<td>47 vs 14%</td>
<td>12 min</td>
</tr>
<tr>
<td>ACT 3</td>
<td>265 AF</td>
<td>III, PC</td>
<td>AF 3 h-45 d 3 h – 7 d, n=170 8– 45 d, n=116</td>
<td></td>
<td></td>
<td>51.2 vs 3.6% (P &lt; 0.01)</td>
<td>8 min</td>
</tr>
<tr>
<td>ACT 4</td>
<td>236 AF</td>
<td>IV, Open</td>
<td>AF 3 h-45 d 3 h – 7 d, n=170 8– 45 days, n=69</td>
<td></td>
<td></td>
<td>51% 58% ≤48 h</td>
<td>14 min</td>
</tr>
<tr>
<td>AVRO</td>
<td>232 AF</td>
<td>IV vs AMIOD</td>
<td>AF 3 h-48 h</td>
<td>3 + 2 AMIOD: 5 + 50 mg for 2h</td>
<td></td>
<td>51.7 vs 5.2% (P&lt;0.001)</td>
<td>11 min</td>
</tr>
</tbody>
</table>

MTC: mean time to conversion. PC: placebo-controlled

Vernakalant for conversion of AF to normal sinus rhythm

- Effective and rapid (10-13 min) CV of recent onset AF
- Resulted in approx 50% conversion rates
  - Maintenance of sinus rhythm at 24 hours - > 95%
  - Background rate (72%) or rhythm control (20%) drugs

* = p = 0.0014
** = p < 0.0001
*** = p = 0.0001

** (% conversion of AF to SR)**

- CRAFT: 52.9% Vernakalant, 5.3% Placebo
- ACT-I: 51.9% Vernakalant, 4.0% Placebo
- ACT-II: 47.9% Vernakalant, 14.0% Placebo
- ACT-III: 51.2% Vernakalant, 3.6% Placebo
- ACT-IV: 50.9% Vernakalant, 5.2% Placebo
- AVRO: 51.7% Vernakalant, 5.2% Amiodarone

Legend:
- Thick blue bars: Vernakalant
- Light blue bars: Placebo
- Green bars: Amiodarone
Conversion rates (%) to SR within 90 min after the start of infusion of vernakalant in the ACT Trials I to IV

- More effective between 3 and 72 hours
- It is not effective for cardioversion of AF

ACT Trials:
- ACT I
- ACT II
- ACT III
- ACT IV

AF 3-72 h
AF < 7 d
AF 8-45 d
Flutter
Placebo

Conversion rates in different trials:
- ACT I: 78%
- ACT II: 47%
- ACT III: 71%
- ACT IV: 51%
Patient characteristics and design details of phase III trials evaluating the therapeutic efficacy of I.V. Vernakalant

<table>
<thead>
<tr>
<th>Medical history (%)</th>
<th>Nonsurgically related AF</th>
<th>POAF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACT I¹</td>
<td>ACT III²</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Congestive HF</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Ischaemic HD</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Valvular HD</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

**Inclusion criteria**
≥ 18 y of age (mean age 61-68y); had non-surgically related AF for ≥3 hrs and ≤45 d¹-³; non-surgically related AF for 3-48 h⁴; or AF or AFL of 3-72 hrs duration occurring 24 hrs to 7 d after cardiac surgery⁵; hemodynamically stable

**Exclusion criteria**
- NYHA class IV CHF, or HF requiring I.V. inotropic therapy
- QT interval >440¹-³ or >500 msec⁵ (12-lead ECG), or QRS >140 msec unless the patient had a pacemaker
- MI, acute coronary syndrome or cardiac surgery (except ACT II⁵) in the previous 30 d
- I.V. class I or class III AADs within 24 h prior to Vernakalant
Vernakalant IV: Pharmacokinetic properties

- $C_{\text{max}}$ and AUC were dose proportional between 0.5 and 5 mg/kg
  - Mean $C_{\text{max}}$ at the end of a 10-min infusion 3.8-8.69 μg/mL
- Poor protein bound (53-63%): minimal interactions

- Metabolism: extensive and rapid via CYP2D6
- Renal excretion (11% unchanged)
- Mean elimination half-life ~3 hrs

- No dose adjustments by age, gender, history of CHF, CAD or renal impairment
  - Patients with hepatic impairment - not sufficiently represented

- No interaction with CYP2D6 inhibitors (beta blockers), warfarin, metoprolol, furosemide, digoxin or calcium channel blockers
Safety profile of I.V. vernakalant

- Drug discontinuation due to AEs: 3.6% vs 0.3%
- Low ventricular proarrhythmic risk
- Before its use: patients should be adequately hydrated

### Occurrence of Torsades de Pointes, hypotension and rapid conduction AFL with AADs in cardioversion of recent onset atrial fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Torsade de Pointes (%)</th>
<th>Hypotension (%)</th>
<th>1:1 atrial flutter (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>0.7</td>
<td>1.6–3.0</td>
<td>-</td>
</tr>
<tr>
<td>Flecaïnide/propafenone</td>
<td>0.5</td>
<td>2.0</td>
<td>3.5–5</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>3.6–5.6</td>
<td>2.0</td>
<td>-</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>0.1</td>
<td>2.8–5.6</td>
<td>-</td>
</tr>
</tbody>
</table>

European Medicines Agency. Assessment report for brinavess [online, 2011]


Duggan & Scott. Drugs 2011;71:237-52
Mean changes in heart rate, QRS, QT and QTcB over time in phase 2/3 trials (FDA Advisory Committee Meeting 2007)

- Heart Rate (bpm)
- QRS Duration (ms)
- QT (ms) Uncorrected
- QT Fridericia Correction (ms)

Values:
- 22.1
- 18.8
- 8.1 ms
1. Mixed ion channel blocker with preferential effects on the atria

2. EU – rapid conversion of recent-onset AF:
   • ≤7 days or ≤3 days postoperatively
   • “Inject, convert and discharge”, can it be an innovative approach?

3. Good safety profile and low ventricular proarrhythmic risk

4. Contraindicated in:
   • SBP <100 mm Hg
   • Severe aortic stenosis
   • Heart failure (class III and IV)
   • ACS within the previous 30 days
   • QTc interval prolongation

4. Comparative trials with ibutilide or flecainide are awaited with interest
   • Little experience in class III-IV HF, patients with AMI or ACS
Atrioselective $I_{Kur}$ blockers – possible advantages

- **Atrio-selective current**
  - Atrial Cell vs. Ventricular Cell
  - Control vs. 4AP 50µM
  - 4AP-Sensitive

- **Prolong LA > RA ERP**
  - Graph showing increase in atrial ERP
  - LA vs. RA
  - Significance levels indicated

- **PAF increases Kv1.5 mRNA levels**
  - Gene expression graphs for Kv1.5, Kv4.2, and Kv4.3
  - Duration of Rapid Pacing (hrs)

- **SR – Shortens APD**
  - Graph showing 4-AP effect on action potential duration
  - C vs. 4-AP

- **SR – Prolongs APD**
  - Graph showing 4-AP effect on action potential duration
  - C vs. 4-AP

- **Increase atrial contractility**
  - Graph showing Ca²⁺ concentration over time
  - Atria vs. Ventricle

References:
**I**\textsubscript{ sus } in right and left atria from patients with CAF

1. CAF-induced remodeling reduced the RA-to-LA resemblance:
   - Increased \( I_{\text{sus}} \)-predominant cells in the RA
2. In SR, \( I_{\text{sus}} \) amplitude and density was significantly greater in RA than in LA myocytes
3. In CAF, \( I_{\text{sus}} \) amplitude decreased only in the RAA, but remained unchanged in the LAA (the RA-to-LA gradient was annulated)
<table>
<thead>
<tr>
<th>Drug</th>
<th>$I_{\text{Kur}}$</th>
<th>Kv1.5</th>
<th>$I_{K1}$</th>
<th>$I_{\text{lo}}$</th>
<th>$I_{Kr}$</th>
<th>$I_{Ks}$</th>
<th>$I_{\text{K Ach}}$</th>
<th>$I_{Na}$</th>
<th>$I_{\text{Ca,L}}$</th>
<th>Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acacetin</td>
<td>3.2</td>
<td>0*</td>
<td>9.3</td>
<td>32</td>
<td>81</td>
<td>20%</td>
<td>0* at 3 µM</td>
<td>0*</td>
<td>0*</td>
<td>HA, GP, HEK293</td>
</tr>
<tr>
<td>AVE0118</td>
<td>1.1</td>
<td>1.5</td>
<td>10</td>
<td>1.8</td>
<td>10</td>
<td>3.4</td>
<td>4.5 - 5</td>
<td>NS*</td>
<td>30</td>
<td>CHO, XO, GP, PA</td>
</tr>
<tr>
<td>AVE01231</td>
<td>1</td>
<td>3.6</td>
<td>&gt; 10</td>
<td>3.4</td>
<td>30</td>
<td>5.9</td>
<td>8.5</td>
<td>NS*</td>
<td>&lt;20*</td>
<td>CHO, XO, GPM, PA, CA</td>
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<tr>
<td>AZD1305</td>
<td></td>
<td></td>
<td>24</td>
<td>16</td>
<td>0.4</td>
<td>&gt;30</td>
<td>11</td>
<td>1.5</td>
<td>1.2</td>
<td>CHO</td>
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<tr>
<td>AZD7009</td>
<td></td>
<td></td>
<td>27</td>
<td>24</td>
<td>0.6</td>
<td>193</td>
<td>10</td>
<td>4.3</td>
<td>90</td>
<td>CHO</td>
</tr>
<tr>
<td>C9356</td>
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<td></td>
<td>4.4</td>
<td>60</td>
<td>34</td>
<td>97</td>
<td>34</td>
<td>168</td>
<td>335</td>
<td>HEK293</td>
</tr>
<tr>
<td>ISQ-1</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>&lt;20*</td>
</tr>
<tr>
<td>DPO-1</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
<td>1</td>
<td>5.3</td>
<td>-</td>
<td>-</td>
<td>&lt;20*</td>
<td>&lt;20*</td>
<td>CHO, HA</td>
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<tr>
<td>NIP-142</td>
<td>5.3</td>
<td>4.75</td>
<td>16.3</td>
<td>44</td>
<td>12</td>
<td>0.64</td>
<td>0</td>
<td></td>
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<td>HA, HEK293, XO</td>
</tr>
<tr>
<td>NIP-151</td>
<td></td>
<td></td>
<td></td>
<td>58</td>
<td>-</td>
<td>0.0016</td>
<td></td>
<td>GP</td>
<td></td>
<td></td>
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<tr>
<td>S9947</td>
<td>0.5</td>
<td>0.5</td>
<td>15*</td>
<td>&lt;30%*</td>
<td>NS*</td>
<td>24%*</td>
<td></td>
<td>CHO, HA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XEN-D0101</td>
<td>0.15</td>
<td>0.24</td>
<td>&gt;200</td>
<td>4.3</td>
<td>13</td>
<td>72</td>
<td>30</td>
<td>&gt;200</td>
<td>HA</td>
<td></td>
</tr>
</tbody>
</table>

*: at 10 µM. NS: no significant.
XEN-D0101: AP Studies – Human Atrial Tissue

- XEN-D0101 selectively inhibits Kv1.5 channels
- Prolongs atrial, but not ventricular APD

XEN-D0101: Atrial-selective and antiarrhythmic effects in dogs with atrial tachycardiac (for 7 days) remodeling

Shiroshita-Takeshita et al. Heart Rhythm 2006

- For Model 1 (cf. paroxysmal AF):
  - Con, 0.1, 1, and 10 mg/kg XEN-D0101 (mg/kg)
  - AF Duration in seconds

- For Model 2 (cf. persistent AF):
  - Con, 0.1, 1, and 10 mg/kg XEN-D0101 (mg/kg)
  - AF Duration in seconds

Graphs showing:
- % Increase Right AERP vs. Basic Cycle Length (ms)
- % Sites AF Induced
- % Increase Right VERP vs. Basic Cycle Length (ms)

Key:
- ● 0.3, □ 1 and ♦ 3 mg/kg
- P<0.05; § P<0.01; # P<0.005
XEN-D0103 – Potency and selectivity

- **Atrial-selectivity**
- **Canine model of persistent AF:**
  - Reduced AF duration
  - Prolonged AERP
- **XEN-D0103 is currently in Phase 1**
- Phase 2 efficacy:
  - 240 patients with persistent AF
  - Three dose levels plus placebo
  - 28 days of treatment
  - Start 4Q 2011

<table>
<thead>
<tr>
<th>Kv1.5 (IC₅₀)</th>
<th>XEN-D0101</th>
<th>XEN-D0103</th>
</tr>
</thead>
<tbody>
<tr>
<td>hERG selectivity</td>
<td>241 nM</td>
<td>100 nM</td>
</tr>
<tr>
<td>Nav1.5 selectivity</td>
<td>54x</td>
<td>100x</td>
</tr>
<tr>
<td>AF efficacy</td>
<td>1 mg/kg</td>
<td>0.3 mg/kg</td>
</tr>
</tbody>
</table>

![Graph showing AERP and AF duration for different doses](image)
Conclusions

1. A new therapeutic approach is the development of new ADDs with atrial selectivity: atrial repolarization delaying agents (ARDAs) represent a new therapeutic approach

2. Vernakalant is a new AAD with atrial-selective blocking properties, safe and effective for PCV of recent-onset AF

3. XEN-D103 represents a new, potent and atrio-selective hKv1.5 channel blocker

   • However, clinical proof of concept with regard to AF efficacy and safety has not yet been established with selective $I_{Kur}$ inhibitors

4. Agents with activity against novel targets require extensive testing to fully disclose their true efficacy and safety
Pharmacological cardioversion of AF

1. Early restoration of SR using electrical shocks (ECV) or AADs (PVC) is part of a rhythm-control strategy
   - Rapid conversion of recent AF (< 48 hrs): improves symptoms, reduces atrial remodeling and may prolong SR maintenance

2. ECV is more effective than PCV, but requires sedation or anesthesia, and patients must be in a fasting state
   - Risks: hypotension, sinus arrest, AVB, bradycardia, VT, pacemaker malfunction, skin burns, aspiration and early recurrence of AF

Vernakalant is used to rapidly restore normal SR in adult patients with recent-onset AF
Electrical and pharmacological CV of recent-onset AF

I, A

Pill-in-the-pocket

IIa, B

i.v. flecainide or i.v. propafenone

I, A

i.v. amiodarone

IIb, A

i.v. ibutilide

i.v. vernakalant

BBs, digoxin, diltiazem, verapamil and ajmaline are ineffective (III, A/B/C)

Camm et al. ESC AF guidelines. Eur Heart J 2010
Conversion from AF to sinus rhythm within 90 min
Time to conversion 11 min in responders

The AVRO trial. Camm et al. JACC 2011; 57: 313-21

- Vernakalant group: 1 monomorphic unsustained VT, not associated with QT prolongation, resolved spontaneously
- Amiodarone group: 1 cardiac arrest. Resolved after cardiac massage and atropine
- No cases of TdP, VF or polymorphic or sustained VT
- 10 patients in the V group developed AFL (6 spontaneously converted). No 1:1 AV conduction
Mean heart rate for patients in AF and for patients in sr over 4 h post-dose in the AVRO trial

- Heart rate decreased over time in both groups.
  - In vernakalant patients, the decrease was primarily due to CV
  - It appeared to be independent of conversion in amiodarone patients

- In vernakalant patients, QTcF transiently increased with infusion, whereas in the amiodarone group, QTcF progressively increased throughout the 4-h observation period

Vernakalant - Adverse effects

- **Bradycardia** (7.6%) - drug discontinuation and/or atropine
- **Hypotension** – transient, responded to IV fluids (AVRO trial)
- Asymptomatic, monomorphc, nonsustained VT
- **CHF** - higher incidence of hypotension (16.1% vs 4.7%) and ventricular arrhythmia (7.3% vs 1.6%) within 2 hrs
- **4 Torsades de pointes** (3 vernakalant, 1 placebo):
  - after 2.5 hrs in a patient who later received i.v. ibutilide
  - The other 2 occurred occurred 32 and 16 hrs (?)
- **2 VF**: in an ill patient with severe aortic stenosis and an ACS; 1 related to asynchronous discharge during electrical CV performed 1 h following vernakalant infusion
- **6 deaths**: 1 was considered related to vernakalant
  - A 64-y old patient with severe aortic stenosis, ACS with ST elevation (protocol violation)
  - 5 cases of ventricular arrhythmias occurring within the first 2 hrs after drug administration, 3 cases in patients with a history of HF
1. **Heart Failure.** Higher incidence of hypotension (16.1% vs 4.7%) and asymptomatic monomorphic, nonsustained VT (7.3% vs 1.6% for placebo) during the first 2 hrs
   - Limited experience in patients with LVEF ≤35%

2. **Valvular Heart Disease:** higher incidence of ventricular arrhythmia

3. **Atrial flutter (AFL):** Vernakalant is not effective in converting AFL to SR

4. **Use of AADs (antiarrhythmic drugs) prior to or after vernakalant**
   - NO in patients who received IV AADs (class I and III) within 4 hrs prior as well as in the first 4 hours after vernakalant administration
   - Not recommended in patients treated 4-24 hrs prior to vernakalant
   - Oral AAD therapy can start 2 hrs after administration of vernakalant
   - Conversion to AFI within the first 2 hrs postdose (patients on class I AADs)

ACT V trial

1. ACT V is currently evaluating the safety and efficacy of vernakalant in patients (n » 470) with recent-onset AF (but excluding patients with evidence or history of CHF)

2. Primary Outcome Measures:
   • Composite of occurrences of hypotension, ventricular arrhythmias and death within the first two hours after start of study treatment
   • Successful conversion to SR for at least 1 minute within 90 minutes of first exposure to study treatment
   • Enrolment was suspended in October 2010 pending investigation of a safety issue (a single serious case of cardiogenic shock that occurred after drug infusion)
**Oral Vernakalant – oral administration**  
*Phase IIb, placebo-controlled trials*

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patient characteristics</th>
<th>Dose (mg/kg)</th>
<th>Primary endpoint</th>
<th>Outcome vs placebo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td>159</td>
<td>Persistent AF postcardioversion</td>
<td>Oral 300 or 600 b.i.d.</td>
<td>SR at 1 month</td>
<td>61 vs 43% (p &lt; 0.05)</td>
<td>Difference at 300 mg b.i.d.</td>
</tr>
<tr>
<td>Prevention</td>
<td>446</td>
<td></td>
<td>Oral 150, 300 or 500 b.i.d.</td>
<td>SR at 90 days</td>
<td>52 vs 32% (P &lt; 0.05)</td>
<td>MTR on 500 mg 90 vs 39 days (p &lt; 0.05)</td>
</tr>
</tbody>
</table>

- The oral bioavailability: 58% to 71% with a $C_{max}$ of 1.8 – 1.9 µg/ml.
- The drug did not prolong the QTc or QRS intervals or produce TdP
- 4 deaths: placebo, 150 mg and 300 mg

http://www.cardiome.com/ -cardiome
## AADs for pharmacological conversion of recent-onset AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>First choice with structural heart disease (HF, CAD, LVH, or HTN)</td>
<td>- I.V.: phebitis, hypotension, bradycardia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Delayed AF conversion to SR (several hrs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Will slow ventricular rate</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>- Patients with HF</td>
<td>- QT prolongation, TdP. Adjust dose for renal function, body size and age. 72 h in-hospital</td>
</tr>
<tr>
<td>Flecainide</td>
<td>- Fast onset (2-4 hrs vs 8 hrs)</td>
<td>- Contraindicated in marked structural heart disease; may prolong QRS duration; may increase ventricular rate due to conversion to AFL and 1:1 conduction to the ventricles</td>
</tr>
<tr>
<td>Propafenone</td>
<td>- Pill-in-the pocket approach</td>
<td>- P: severe obstructive lung disease</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>- Rapid onset (~30 min)</td>
<td>- Can cause QT prolongation and TdP (~4%); normal K⁺; close ECG monitoring for 4 hrs.</td>
</tr>
<tr>
<td></td>
<td>- More effective for CV of AFL</td>
<td>- Will slow ventricular rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No in patients with low LVEF or HF</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>- Very rapid onset (10-15 min)</td>
<td>- Hypotension, bradycardia. No in HF (NYHA class III-IV)</td>
</tr>
</tbody>
</table>

Modified from Camm et al. ESC AF guidelines. Eur Heart J 2010
Drug discovery efforts have focused on

1. **Atrial repolarization delaying agents (ARDAs):**
   - Target ion channel(s) expressed exclusively or predominantly within the atria
     - $I_{kur}$ blockers: XEN-0D101/103
     - $I_{K_Ach}$ blockers: KB130015
     - Vernakalant
     - $I_{Na}$ blockers: ranolazine, pilsicainide
     - Small conductance $Ca^{2+}$-activated $K^+$ channels
     - Stretch-activated nonselective cation channels (TPRC1/6/7): amiloride, PUFAs
     - $I_{CNX}$ inhibitors: KB-R7943

2. **Exploit the differences in $I_{Na}$ between atria and ventricles:** ranolazine

3. **Multichannel blockers:**
   - Amiodarone analogues: Budiodarone (ATI-2042), Celivarone

4. **Gap-junction enhancers:** AAP10, Rotigaptide (ZP123), GAP-134, HP5, ZP-1210,

5. **Upstream therapy:** ACEIs, ARBs, aldosterone antagonists, statins, omega-3 fatty acids, steroids
Atrioselective $I_{Kur}$ blockers – possible advantages


Atrioselective $I_{Kur}$ blockers – possible advantages

1. Prolong AERP
   - LA < RA
2. No changes in QT
3. Prolong AERP in AF
4. Increase atrial contractility
\( I_{\text{sus}} \) in right and left atria from patients with CAF

- In SR, \( I_{\text{sus}} \) amplitude and density significantly greater in RA than in LA myocytes.
- In CAF, \( I_{\text{sus}} \) amplitude and density decreased only in the RAA, but remained unchanged in the LAA.
- \( I_{\text{sus}} \) density became similar in both atria and the RA-to-LA gradient was annulated.

Caballero et al., JACC 2010;55:2346-54