Newer Antiarrhythmic Drugs
What is on the horizon?

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“If antiarrhythmic drugs had adequate clinical efficacy and safety, there probably would never have been any rate versus rhythm control trials”

Albert Waldo, MD
Cleveland Clinic

Emerging AAD for AF
• Rate control
• Rhythm control
• Agents altering atrial substrate
• Anticoagulation
• Ablation may be the future, but…
  – Not indicated if age > 70
  – Only 10% of patients are candidates now

Nontraditional approaches to the management of atrial fibrillation
Potassium Channels and AADs

- Potassium channels in the heart determine heart rate, resting membrane potential, action potential shape and action potential duration (APD).
- Classified into voltage gated and ligand-gated.
- Voltage gated = transient outward current, $I_{to}$, delayed rectifier current $I_{Kr}$, inward rectifier $I_{Ki}$.
- Ligand-gated channels = $I_{KATP}$ or acetylcholine $I_{KACCH}$.

I$_K$ can be divided into ultrarapid ($I_{kur}$), rapid ($I_{kr}$), and slow ($I_{ks}$) components.

Atrium has a greater density of repolarizing K+ currents, including $I_{kur}$ which is functionally considered atrium specific.

$I_{kur}$ is relatively insensitive to class III agents, including amiodarone, dofetilide, sotalol.

Why Not Amiodarone

- In rhythm control group amiodarone most frequently used drug.
- Increased non-cardiovascular death rate in group receiving amiodarone.
- Increased incidence of cancer, also seen in AVID, CAMIAT.
  - Only hypothesis generating.
Dronedarone-SR33589

- Inhibits I_{kr}, I_{kat}, B_{1}, I_{Ca} (L-type), I_{to}
- Lacks iodine moiety
- No thyroid or pulmonary toxicity
- Similar electrophysiology to amiodarone
- Half-life = 24 h, dose BID
- Food increases levels 2-3 x
- Undergoes 1st pass metabolism, ~ 15% Available

Circulation 1999;100:2276

Multichannel blocking effects

<table>
<thead>
<tr>
<th>Guinea Pig (IC50, uM)</th>
<th>Dronedarone</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outward currents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I_{kr} (ventricle)</td>
<td>2-3</td>
<td>10</td>
</tr>
<tr>
<td>I_{ks} (ventricle)</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>I_{kr} (ventricle)</td>
<td>&gt;30</td>
<td>≤30</td>
</tr>
<tr>
<td>I_{kACh} (atrium)</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td><strong>Inward currents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I_{Na} (human; 3uM)</td>
<td>-97%</td>
<td>-41%</td>
</tr>
<tr>
<td>I_{Ca-L} (guinea pig; 50 uM)</td>
<td>0.2</td>
<td>10</td>
</tr>
</tbody>
</table>

J Cardiovasc Electrophysiol 2006;17:S17-S20
**Dronedarone-SR33589**

- Antagonist of $\alpha$ and $\beta$ receptors
- No significant effect on plasma levels of T3, T4, rT3.
- Fewer drug-drug interactions

_J Cardiovasc Electrophysiol 2006;17(Suppl 2):S17-S20_

**Dronedarone-Clinical Trials**

- **DAFNE** - Dronedarone Atrial Fibrillation study aFter Electrical cardioversion
  - Persistent AF, RRR 55% of reversion to AF
- **EURIDIS** - EUropean trial in atrial fibrillation or flutter patients Receiving Dronedarone for the maintenance of Sinus rhythm
- **ADONIS** - American-Australian-African Trial with Dronedarone in Atrial Fibrillation/Flutter Patients for the Maintenance of Sinus Rhythm

**ERUDIS/ADONIS**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause hosp/death</td>
<td>0.73</td>
<td>0.001</td>
</tr>
<tr>
<td>CV Hosp/death</td>
<td>0.80</td>
<td>0.16</td>
</tr>
<tr>
<td>Hosp for AF/Afl</td>
<td>0.71</td>
<td>0.055</td>
</tr>
<tr>
<td>CV hosp excl AF/Afl</td>
<td>1.06</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* Decreased in overall risk of recurrence of AF/Afl and time to recurrence (20-30%), in patients who resumed the VR was significantly lower, incidence of SE = placebo, no TdP, no thyroid or pulmonary toxicities. Overall recurrence rates were 65% for EURIDIS

**EURIDIS/ADONIS Pooled data**

<table>
<thead>
<tr>
<th>Incidence of treatment emergent ADEs(%)</th>
<th>Placebo (n=409) %</th>
<th>Dronedarone* 800 mg(n=828) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>62.8</td>
<td>67.4</td>
</tr>
<tr>
<td>Any serious ADE</td>
<td>15.6</td>
<td>14.3</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Permanent drug DC following ADE</td>
<td>6.1</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*No TdP, thyroid, hepatic or pulmonary side effects
EURIDIS/ADONIS

- A significant and consistent ↓ VR @ 1st AF/AFl recurrence (116.6 v 104.6; 117.5 v 102.3)
- A significant and consistent ↓ 1st recurrence of AF/Afi
- Significant and consistent reduction in symptomatic recurrence

Dronedarone-Clinical Trials

- ERATO-Efficacy and Safety of Dronedarone for the Control of Ventricular Rate during Atrial Fibrillation (↓ VR with rest and exercise)
- ATHENA-A Placebo Controlled Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of CV hospitalizations or Death from any Cause in Patients with AF/Atrial Flutter
- ANDROMEDA-Antiarrhythmic Trial with Dronedarone in Moderate-To-Severe Congestive Heart Failure Evaluating Morbidity Decrease-terminated early due to ↑ mortality

ANDROMEDA

- Assess benefit of donedarone in ↓ mortality from HF hosp (class III, IV)
- Confirm absence of ADE
- ↑ RR 1.38
- Not superior to placebo
- Mortality d/t non sudden death
- Inc death due to DC ACEI/ARB with ↑ Scr
- ATHENA is new morbidity/mortality study

Dronedarone-Conclusions

- Better tolerated
- Fewer drug drug interactions
- Increase in serum creatinine due to secretion/reabsorption, not due to ↓ GFR
Atrial specific AADs

- Little to no role in ventricular physiology
- Act on more than atrial channel
- Some species have different channel expression in R v L atria
- Atrial properties may change with remodeling, may be different when in NSR
- Clinical focus may be pharmacologic cardioversion, prevention, ideal if IV/po

Atrial Specific AADs

- RSD1235
- AVE0118
- AVE1231
- AZD 7009
- C9356
- NIP142
- MPS
- JTV519
- S1185
- Azimilide
- AT12042
- Piboserod-5HT4 receptor antagonist
- Tediasamii
- ZP123 (GAP486)-rotigaptide, a gap junction modifier
- GSMb4 (SAC blocker)

Emerging $I_{kur}$ Blockers or Atrial-Specific Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Block</th>
<th>Industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSD1235</td>
<td>$I_{kur} + I_{na}$</td>
<td>Cardiome</td>
</tr>
<tr>
<td>C9356</td>
<td>$I_{kur}$</td>
<td>Cardiome</td>
</tr>
<tr>
<td>NIP142</td>
<td>$I_{kur} + I_{KACH}$</td>
<td>Nissan Chem</td>
</tr>
<tr>
<td>AZD7009</td>
<td>$I_{kur} + I_{Na} + I_{Kr}$</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>AVE0118</td>
<td>$I_{kur} + I_{to} + I_{KACH}$</td>
<td>Aventis</td>
</tr>
<tr>
<td>S9947-S20951</td>
<td>$I_{kur}$</td>
<td>Aventis</td>
</tr>
<tr>
<td>S0100176</td>
<td>$I_{kur}$</td>
<td>Aventis</td>
</tr>
</tbody>
</table>


RSD1235

- Mixed frequency-dependent Na+ channel and atrial preferential K+ channel blocker
- Blocks $I_{kur}$, $I_{to}$, $I_{KACH}$
- Prolongs atrial refractoriness, no significant effects on ventricles or QT
- Mean T ½ = 3.1 hours
- Available IV and orally
RSD1235

- No drug related proarrhythmias
- No adverse hemodynamic effects
- 56% conversion rate within 2 h
- Small sample size, requires confirmation

Cumulative percentage of patients terminating atrial fibrillation (AF) after infusions of placebo, 0.5 and 1.0 mg/kg RSD1235, or 2.0 and 3.0 mg/kg RSD1235 in patients with recent onset AF. Efficacy was significantly higher after 2 + 3 mg/kg RSD1235 than after placebo (p = 0.0003) and was significantly different between the two RSD1235 (p = 0.002) dosing regimens. The median time for termination of AF was 11 min from the start of the first infusion in the RSD1235 treatment groups. (JACC Volume 44, 2004, Pages 2355-2361)

RSD1235

- Studies versus placebo ACT1
  - Conversion of recent AF, 52% v 4%
  - Conversion of all AF (3 h-45d), 38% v 3%
  - Ineffective for AFI
  - Potentially serious ADEs 1.4% v 0%

AVE0118

- Blocks $I_{Kur}$, $I_{to}$
- Prolongs atrial ERP L > R
- No effect on VERP
- Increases atrial APD with + inotropic effects on the atria

Circulation 2006;114:1234-42
ZP123-Rotigaptide
Guerra JM, Everett TH, Lee KW and Olgin JE, Circulation 2006;114:110-8

• Gap junction enhancer
• Selective for atrial electrophysiology
• Derivative of naturally occurring antiarrhythmic peptide that improves cell coupling
• ↓ AF vulnerability in MR but not HF

Tedisamil

• Class III antiarrhythmic
• Blocks multiple K channels and slows SR
• Blocks $I_{to}$, $I_{KATP}$, $I_{Kr}$, $I_{Ks}$, $I_{kur}$
• Prolongs APD atria > ventricles
• Excreted by the kidney
• T ½ 8-13 hours
• Has significant anti-anginal, anti-ischemic properties
Azimilide (A-COMET-1)
Azimilide-Cardioversion Maintenance Trial-1

- Class III antiarrhythmic drug
- Blocks $I_{Kr}$ and $I_{Ks}$
- Patients with structural heart disease who converted to sinus
- NS difference in rate of recurrence compared with placebo

*Am Heart J 2006;151:1043-9*

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What's New-Antithrombotics

- Ximelagatran is OUT!
- Fondarinux - parenteral anti-Xa inhibitor
- Razaxaban - orally active FXa inhibitor
- Dabigatran - direct thrombin inhibitor
- Odiparcil - ß-D-xyloside, prime glycosaminoglycan (GAG) activity

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New AADs-Summary

- Current AADs are limited by suboptimal efficacy, tolerance and safety
- These offset the benefits of NSR
- Traditional most effective class III drugs need to be started in hospital
- Other agents safer to start out of hospital if NSR
New AADs-Summary

- Need to consider the contribution of other drugs, e.g. ACEIs, ARBs, Statins, fish oils which have all been reported to influence incidence of AF
- Competition from AF ablation and AFFIRM rate control data decrease enthusiasm for new drug development

New AADs-Conclusion

- Atrial specific AADs are effective during atrial remodeling
- May be effective in immediate recurrence, early recurrence and in pharmacologic conversion of longer-standing AF
- Differential effects on L versus R atrium