“New” in Atrial Fibrillation
September 2011

Stroke prevention – more options

Rhythm Control
- drugs
- alternatives to drugs; ablation

Rate Control
- pace + ablate
Dell

A-FIB

Stroke

Risk

AFib
Two Principles

1. Nerve cells survive only 4 minutes without oxygen

2. Nerve cells do not regenerate. Hence, acute treatment will never be the answer; the emphasis must be on stroke prevention.
Stroke

- 15-20 % due to emboli
- Majority of emboli with atrial fibrillation
Atrial Fibrillation

3-8% chance of stroke/year
Stroke Risk in Atrial Fibrillation

- Data from the Control / Non-Rx groups in clinical trials
- Weighting of variables associated with increased stroke risk resulted in creation of CHADS$_2$ risk score (Gage et al)
CHADS2 score

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (any history)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension (prior history)</td>
<td>1</td>
</tr>
<tr>
<td>Age 75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Secondary prevention in patients with a prior ischemic stroke or a transient ischemic attack; most experts also include patients with a systemic embolic event</td>
<td>2</td>
</tr>
<tr>
<td>CHADS$_2$ Score</td>
<td>Warfarin</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
</tr>
<tr>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>2</td>
<td>1.27</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>4</td>
<td>2.35</td>
</tr>
<tr>
<td>5 or 6</td>
<td>4.6</td>
</tr>
</tbody>
</table>
“1/2” “CHADS” Points

Conjecture
- Women (vs men)
- Estrogen use
- Malignancy
- Previous venous thrombosis
- Vascular disease

In future - ? Factor V Leiden
- ? Prothrombin gene mutation
- ? Other
# Risk of first stroke on aspirin

<table>
<thead>
<tr>
<th># of risk factors</th>
<th>Stroke/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>&lt; 2%</td>
</tr>
<tr>
<td>1</td>
<td>2-4%</td>
</tr>
<tr>
<td>2 or more</td>
<td>&gt; 4%</td>
</tr>
</tbody>
</table>
Stroke Prevention in Atrial Fibrillation

Treatment Options 2011 – defined by clinical trials

1. Warfarin
2. Aspirin
3. Clopidogrel
4. Dabigatran
Five Randomized Trials

Stroke Reduction on Warfarin (INR 2-4)

- SPAF I: 67%
- Copenhagen (AFASAK): 58%
- Canadian (CAFA): 45%
- VA (SPINAF): 74%
- Boston (BAATAF): 86%

\[ \pm 70\% \]

Serious bleeds on warfarin 1-4%
<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin(INR 2-3)</td>
<td>70%</td>
</tr>
<tr>
<td>ASA (325 mg)</td>
<td>41%</td>
</tr>
<tr>
<td>ASA (75 mg QD or 325 mg QOD)</td>
<td>no effect</td>
</tr>
</tbody>
</table>
Important Caveat

Stroke risk the same in those with constant vs intermittent atrial fibrillation

- In controls
- In treatment group
Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

TheACTIVE Writing Group on behalf of the ACTIVE Investigators*

2006; 367: 1903-12
Balance –

Warfarin (INR 2-3) vs ASA (325mg)

- CVA – 65% vs 41%
- major bleed - ~ 3.4% vs 1.0%
- CNS bleed - ~ 0.5% vs 0.2%
## Antithrombotic Rx for Atrial Fibrillation (2010)

<table>
<thead>
<tr>
<th>Anticoagulation Candidate</th>
<th>Risk Factors for Thromboemboli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>CHADS 0</strong></td>
</tr>
<tr>
<td>Good</td>
<td>A/W</td>
</tr>
<tr>
<td>Poor</td>
<td>A</td>
</tr>
</tbody>
</table>

_A = aspirin 325 mg QD  
W = warfarin INR 2-3_
Dabigatran versus Warfarin inPatients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RELY Steering Committee and Investigators*
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.
Thrombin Inhibitor

ASA

Warf

Thrombin Inhibitor
Rx Discussions in 2011

# of CHADS₂ Points

<table>
<thead>
<tr>
<th>Points</th>
<th>Good</th>
<th>A</th>
<th>A/W/D</th>
<th>W or D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>A/W/D</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>W or D</td>
<td>A</td>
<td></td>
<td>A/D</td>
</tr>
</tbody>
</table>

Anticoagulation Candidate

- Good
  - A
  - A/W/D
  - W or D
- Poor
  - A
  - A
  - A/D
Dabigatran Issues

• Transition from warfarin
  – Start 48-72 hours after stopping warfarin

• Interruption for surgery
  – Stop 24-36 hours before surgery

• Avoid/caution antiplatelet agents
  – 1/3 of total study pts were on concomitant ASA
  – NSAID use minimal in study

• Reversal
  – No definitive agents
  – a Factor VII, plasma
“New” Anticoagulants – compared to warfarin

<table>
<thead>
<tr>
<th></th>
<th>Available</th>
<th>Likely Available Soon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran†</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Embolic Events</td>
<td>better (HR .66)</td>
<td>equivalent (HR .88)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>better (HR .40)</td>
<td>better (HR .67)</td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>equivalent (HR .91)</td>
<td>equivalent (HR 1.03)</td>
</tr>
<tr>
<td>Mortality</td>
<td>equivalent (HR .88)</td>
<td>equivalent (HR .85)</td>
</tr>
<tr>
<td>MI</td>
<td>worse (HR 1.29)</td>
<td>equivalent</td>
</tr>
<tr>
<td>Cost (charges)</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

† Direct Thrombin Inhibitor

* Factor Xa inhibitors, a 3rd, (edoxaban) being studied
## Outcome (%/yr)

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaraxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic Events</td>
<td>~2.0</td>
<td>1.1</td>
<td>2.1</td>
<td>1.27</td>
</tr>
<tr>
<td>Hemorrhagic Strokes</td>
<td>~0.5</td>
<td>0.1</td>
<td>0.5</td>
<td>0.47</td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>~3.4</td>
<td>2.7</td>
<td>3.4</td>
<td>2.13</td>
</tr>
<tr>
<td>Mortality</td>
<td>~4.5</td>
<td>3.64</td>
<td>4.5</td>
<td>3.52</td>
</tr>
<tr>
<td>Stroke, death, bleed</td>
<td>~9</td>
<td>~7.5</td>
<td>9.5</td>
<td>6.13</td>
</tr>
</tbody>
</table>

- Discontinuation rates ~15-20% for all agents
- No clinical research direct comparison of D, R, or A to each other
Reasons to continue warfarin vs. New agent

1. Trials limited duration
2. Reversal options not well defined for new agent
3. Relative value of new agents less when INR control is good
4. Compliance possibly enhanced by required INR visits
Reasons to use Thrombin Inhibitor (eventually Xa inhibitor)

1. Better protection against embolic stroke
2. Fewer CNS bleeds
3. No serial blood test monitoring
## Conclusions

<table>
<thead>
<tr>
<th>Presumed benefits of maintaining sinus rhythm</th>
<th>Outcome of patients in the rhythm control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewer symptoms / better exercise tolerance</td>
<td>Functional status no different</td>
</tr>
<tr>
<td>Lower risk of stroke</td>
<td>Similar rates of combined secondary endpoints, including stroke</td>
</tr>
<tr>
<td>Long-term anticoagulation not needed</td>
<td>Most strokes (65/84) occurred off warfarin or with INR &lt; 2.0</td>
</tr>
<tr>
<td>Better quality of life</td>
<td>Quality of life no different, but more hospitalizations</td>
</tr>
<tr>
<td>Better survival</td>
<td>No survival benefit; a trend toward increased late risk</td>
</tr>
</tbody>
</table>
Rate Control

AFFIRM trial suggests this approach acceptable for survival, stroke risk, group quality of life

But

What about patient with good rate control

• Who still dislikes “fibrillation feeling”?  
  - Answer: Consider rhythm control attempt

• Who is tired, fatigued, depressed?  
  - Answer: Consider rate control drugs as potential explanation  
  - Option – Rhythm control  
    - AV node ablation + pacemaker
Rhythm Control – When is it worth it?

- ? In the young
- ? If symptoms despite rate control

If worth it - Drugs:
- flecainide
- dofetilide
- sotalol
- amiodarone
- Atrial fib ablation
Antiarrhythmia Drugs

- **Class IA** – quinidine, procainamide, disopyramide
- **Class IC** – flecainide, propafenone
- **Class III** – amiodarone, sotalol, dofetilide, dronedarone

Underlined: Those I generally use
Ablation Approaches

- Endocardial – “catheter”
- Epicardial
  - Thorascopic
  - “Mini” thoracotomy
Mechanisms of Atrial Fibrillation

ACC/AHA/ESC Guidelines - J Am Coll Cardiolol 2001;38:1266i-lxx
Ablation lines created during left atrial ablation.
Catheter Ablation for Atrial Fibrillation

- Discussion points
  - 75% “Success” Rate (Improvement)
  - 1.5% Risk
    - CVA, cardiac damage, rare death
  - Repeat procedure in 25%
- Argument can be made for using after drug treatment has failed
- Currently used as primary therapy at some centers
Catheter Ablation

CABANA Study

- randomized trial: drug Rx vs catheter ablation
- 1º endpoint overall mortality
- 2º endpoints: rhythm termination, strokes, Q of L
- so far (less than 100 pts out of planned 3000)
  - At 1 yr – recurrent atrial rhythms
    - 72% with drug Rx
    - 66% with ablation
- ongoing ($48 million: 30% NIH, 70% industry)
Preliminary Results of a Limited Thoracotomy: New Approach to Treat Atrial Fibrillation

JAMES H. MCCLELLAND, M.D., DAVID DUKE, M.D., and RAMAKOTA REDDY, M.D.

From the Oregon Heart and Vascular Institute and Oregon Cardiology, Eugene, Oregon, USA

“New” in Atrial Fibrillation

Stroke prevention – more options
  - individualize

Rhythm Control
  - drugs
  - alternatives to drugs
  - in general, meds first, then consider ablate

Rate Control
  - pace + ablate
  - consider, particularly in elderly