Atrial Fibrillation: Management 2009

John Coyle, M.D.
September 20, 2009
In the last analysis, atrial fibrillation is caused by

Cells that *should* die, but don’t

OR

Cells that *shouldn’t* die, but do
Initiation of ‘Focal’ Atrial Fibrillation

LSPV

RIPV

LIPV

K Shivkumar
Electrophysiology of Ventricular Fibrillation

Risk For Development Of Atrial Fibrillation

1. There are currently ~2.3 million Americans who have atrial fibrillation.

2. Lifetime risk for development of atrial fibrillation at age 40 years is 26% for men and 23% for women. This risk estimate includes both persistent and paroxysmal atrial fibrillation.

3. Lifetime risks do not change substantially with increasing index age despite decreasing remaining years of life because AF incidence rises rapidly with advancing age.

4. At age 80 years, lifetime risks for AF are 22.7% (20.1% to 24.1%) in men and 21.6% (19.3% to 22.7%) in women.

5. Even in the absence of overt heart disease, risk remains high. Counting only those who had development of AF without prior or concurrent congestive heart failure or myocardial infarction, lifetime risks for AF are approximately 16%.

6. It is estimated that 15% of all strokes are attributable to AF, and the proportion increases markedly with age.

7. The odds ratio (OR) of atrial fibrillation for each decade of advancing age was 2.1 for men and 2.2 for women (P < .0001). In addition, after multivariable adjustment, diabetes (OR, 1.4 for men and 1.6 for women), hypertension (OR, 1.5 for men and 1.4 for women), congestive heart failure (OR, 4.5 for men and 5.9 for women), and valve disease (OR, 1.8 for men and 3.4 for women) are significantly associated with risk for atrial fibrillation in both sexes. Myocardial infarction (OR, 1.4) was significantly associated with the development of atrial fibrillation in men. Women were significantly more likely than men to have valvular heart disease as a risk factor for atrial fibrillation. Obesity is also a risk factor, and appears to be mediated by left atrial dilatation.

8. Among those with paroxysmal atrial fibrillation, asymptomatic episodes of AF are ~12 times more common than symptomatic episodes.

Age and Tissue Loss

"The more elderly the patients, the more likely they are once they have developed atrial fibrillation to have a more permanent pattern. Patients replace their atrial tissue very quickly after the age of 50, and so by the time people are in their 80’s and 90’s, as much as 30 or 40 % of their atrial myocardium may be fibrotic, and that obviously provides a substrate. I think the other group of patients are patients who have congestive heart failure, for example, where there are multiple inflammatory and structural changes that predispose them to maintain their arrhythmia. The final thing is the chronicity of the arrhythmia. The longer it has been in place, the more difficult it is to convert."

Peter R. Kowey, M.D., Jefferson Medical School, Philadelphia. September 2009 ACCEL Interview, Antiarrhythmic Agents Targeting the Electrically Remodeled Atrium

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"With aging come a number of changes to the skeletal muscles. Most marked is the loss of mass, which begins as early as 25 years of age. By age 50 the skeletal muscle mass is often reduced by 10 percent, and by age 80 approximately 50 percent of the muscle mass is gone."


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“Atrial fibrillation in older patients is a disease of arterial stiffness, diastolic dysfunction, atrial stretch and changes in atrial histology... Left atrial size was increased and left atrial function was clearly depressed in the heart failure group but were essentially normal in the asymptomatic LVH group. The ability of the atrium to compensate in a sense for the remodeling that occurs over time from hypertension and hypertrophy becomes increasingly important and it may be one of those final straws that breaks the camel's back."

David A. Kass, Johns Hopkins Medical School, Baltimore and Bernard Gersh, M.D. the Mayo Clinic. October 2008 ACCEL Interview. Diastolic Heart Failure: Beyond Recognizing a Preserved Ejection Fraction: New Physiologic Insights
Therapeutic approach to atrial fibrillation

Atrial fibrillation

Ventricular rate control*

Asymptomatic or minimal symptoms

Symptomatic

First arrhythmia episode

Recurrent atrial fibrillation

Rhythm control

Rhythm control

Young or middle-aged patient

Older patient (> approximately 65 years)

Rhythm or rate control on individual basis

Ventricular rate control

*Rate control may include one or more of the following: AV nodal blocking medications (beta-blockers, calcium channel blockers, digoxin), AV nodal ablation/modification, pacemaker algorithms.

†Rhythm control may include one or more of the following: electrical or pharmacologic cardioversion, antiarrhythmic drugs, percutaneous catheter ablation, pacemaker algorithms, surgical approaches. Long-term anticoagulation should be strongly considered irrespective of the treatment strategy used.
Atrial Fibrillation: Rate Control + LVEF: Response to i.v. Diltiazem

N = 14 patients
Diltiazem dosing: 0.25 mg/kg over 2 minutes. 15 minutes later additional 0.35 mg/kg over 2 minutes if HR > 100 BPM. Then 10-15 mg/hr to keep HR < 100 BPM.

Pinter A. Cardiovasc Pharmacol Therapeut 8:7, 2003. (Univ. of Toronto)
Critically Ill Patients With Atrial Fibrillation/Flutter: Amiodarone vs Diltiazem For Rate Control

20 patients per treatment group. 46/60 pts receiving mechanical ventilation. 57/60 patients with atrial fibrillation. Avg. APACHE III score = 70. 44/60 on catecholamine therapy. HR<120 achieved in 100% of diltiazem pts and 95% of amiodarone drip pts. 30% of diltiazem pts and 5% of amiodarone drip pts required discontinuation of therapy due to development of hypotension (= mean arterial BP <60mmHg for 10 minutes). Karth GD. Crit Care Med 29:1149, 2001. University of Vienna.

Group 1: Diltiazem 25 mg iv over 15 min followed by 20mg/hr for 24 hours.

Group 2: Amiodarone 300mg iv over 15 minutes. No subsequent amiodarone drip.

Group 3: Amiodarone 300 mg iv over 15 minutes then 45mg/hr for 24 hours.
Emergency Room Treatment of Atrial Fibrillation: Diltiazem vs Metoprolol

20 pts in each group. All pts had systolic BP >= 95mmHg. Randomized double-blind iv administration of diltiazem or metoprolol. None of the pts had hypotension. Diltiazem Rx: 0.25mg/kg (maximum 25 mg). After 20 min., if HR > 100, give 0.35mg/kg. Metoprolol Rx: 0.15mg/kg (maximum 10 mg). After 20 min., if HR > 100, give 0.25mg/kg.

Amiodarone vs. Placebo For Conversion Of Recent-Onset AFib

In a randomized, placebo-controlled trial of 100 patients with paroxysmal atrial fibrillation of recent onset (<48 h) the investigators compared the effects of treatment with continuous intravenous amiodarone 125 mg per hour (total 3 g) and intravenous placebo. Patients in the placebo group who did not convert to normal sinus rhythm within 24 h were started on amiodarone therapy. (Galve et al. have demonstrated that amiodarone administered intravenously at a rate of 1.2 g in 24 h after a bolus of 5mg/kg over 30 min. is only marginally better than placebo in converting paroxysmal atrial fibrillation to normal sinus rhythm.)

Figure 4  Conversion from paroxysmal atrial fibrillation within 48 h (amiodarone (●) vs placebo (■) groups), including the cross-over to amiodarone in the placebo group at 24 h.

Diltiazem for Atrial Fibrillation/Flutter: IV-to-Oral Transition

1. Diltiazem 20mg iv over 2 min
2. If HR not decreased by >=20%, or if HR not <100 BPM, give additional 25 mg iv over 2 min.
3. As soon as above criteria met, start diltiazem at 10mg/hr iv.
4. If control lost during iv drip, give 10mg iv over 2 min and increase drip to 15mg/hr.
5. If excessive HR slowing occurs, decrease drip to 5mg/hr.

Blackshear JL. Am J Cardiol 78:1246, 1996.
Conversion To Normal Sinus Rhythm From Atrial Fibrillation/Flutter After Treatment With Amiodarone Or Ibutilide

Study group: 40 consecutive patients who developed atrial fibrillation within 3 hours after hospital admission. 
(1) Ibutiilde pts received ibutilide 0.008 mg/kg over 10 min; treatment was repeated 10 min after end of initial infusion if atrial fib or flutter persisted. 4 hours later, if afib persisted, amiodarone 15 mg/kg was given over 24 hours.
(2) Amiodarone pts received amiodarone 5 mg/kg over 30 min. 4 hours later, if afib persisted, amiodarone 15 mg/kg was given over 24 hours.
(3) At 29 hrs after initiation of treatment, 95% of ibutilide and 85% of amiodarone pts had converted to NSR (P = NS). The other 4 patients underwent successful DC cardioversion to NSR.
(4) At 7 days after initiation of treatment, afib/flutter recurred in 55% of ibutilide pts and 35% of amiodarone pts (P = NS).
(5) 2 amiodarone pts were eliminated from the study due to development of severe hypotension.
(6) There was no significant ventricular arrhythmia, but pts with LVEF<30%, VT, prior antiarrhythmic Rx, and a variety of other serious problems were excluded from entry into the study.
Amiodarone Given Prophylactically With Heart Surgery (PAPABEAR Study) - Efficacy

Dosage schedule: Amiodarone 10 mg/kg per day orally, given 6 days before the day of surgery, on the day of surgery, and for six days after the day of surgery.

Atrial tachyarrhythmia overall and by subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of patients</th>
<th>Amiodarone</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>601</td>
<td>16.1</td>
<td>29.5</td>
<td>0.52 (0.34–0.69)</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>341</td>
<td>11.2</td>
<td>21.1</td>
<td>0.51 (0.28–0.94)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>260</td>
<td>21.7</td>
<td>41.2</td>
<td>0.45 (0.27–0.75)</td>
</tr>
<tr>
<td>CABG only</td>
<td>389</td>
<td>11.3</td>
<td>23.6</td>
<td>0.45 (0.26–0.79)</td>
</tr>
<tr>
<td>Valve replacement/repair with or without CABG</td>
<td>212</td>
<td>23.8</td>
<td>44.1</td>
<td>0.51 (0.31–0.84)</td>
</tr>
<tr>
<td>Perioperative beta-blocker use</td>
<td>344</td>
<td>15.3</td>
<td>25.0</td>
<td>0.58 (0.34–0.99)</td>
</tr>
<tr>
<td>No perioperative beta-blocker use</td>
<td>257</td>
<td>16.3</td>
<td>35.8</td>
<td>0.40 (0.22–0.71)</td>
</tr>
</tbody>
</table>

12. Amiodarone Given Prophylactically With Heart Surgery (PAPABEAR Study) - Hazards

Dosage schedule: Amiodarone 10 mg/kg per day orally, given 6 days before the day of surgery, on the day of surgery, and for six days after the day of surgery.


<table>
<thead>
<tr>
<th>Presumed adverse event</th>
<th>Amiodarone (n=299)</th>
<th>Placebo (n=302)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>11.4</td>
<td>5.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiac</td>
<td>7.0</td>
<td>2.0</td>
<td>0.002</td>
</tr>
<tr>
<td>- Bradycardia requiring temporary pacing</td>
<td>5.7</td>
<td>2.0</td>
<td>0.02</td>
</tr>
<tr>
<td>- QT prolongation &gt;650 ms</td>
<td>1.3</td>
<td>0</td>
<td>0.06</td>
</tr>
</tbody>
</table>
## Amiodarone vs placebo: AF incidence and related hospitalization and cost after CABG

<table>
<thead>
<tr>
<th>End point</th>
<th>Amiodarone, n=53</th>
<th>Placebo, n=53</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative AF* (%)</td>
<td>34</td>
<td>85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU length of stay (d)</td>
<td>1.8</td>
<td>2.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total hospitalization (d)</td>
<td>11.3</td>
<td>13.0</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Per-patient total cost (€)</td>
<td>18 400</td>
<td>19 300</td>
<td>&lt;0.007</td>
</tr>
</tbody>
</table>

*Developing within one week of surgery
AF=atrial fibrillation
ICU=intensive care unit

All pts were high-risk for post-op AF according to SAECG.

Clinical Pathway for Management of Postoperative Atrial Fibrillation After Cardiac Surgery

Patient should be hemodynamically stable with a ventricular rate <120bpm and SBP>90mmHg when these orders are initiated. Notify surgeon, cardiologist or internist, as appropriate. Fax a STAT EKG to the physician to allow for confirmation of the rhythm.

1. Beta-blocker: If no beta blocker ordered, start metoprolol 25 mg BID. Hold for SBP < 90; HR < 60; CI < 2.2 or if on inotropic agents.

2. If atrial fibrillation persists > 4 hours, begin procainamide 1 gram over 1 hour followed by 2 mg/min; stop the infusion after 4 hours, regardless of patient's rhythm.

3. Begin amiodarone, 400mg po TID for 3 days, then 200 mg po QD x 10 days.

4. If patient receiving digoxin, hold unless specifically restarted.


6. Schedule patient for cardioversion the next day and make patient NPO after Midnight.


8. Thyroid function tests.

9. If > POD #1 and no hemorrhagic complications, then begin IV heparin without a bolus, then continue in accordance with the weight-adjusted protocol.

10. If patient becomes hemodynamically unstable, notify surgeon immediately.

11. Benefits: This clinical pathway has been in use for about 5 years. It has shortened hospital stay by 1.8 days and duration of atrial fibrillation by 2.4 days, improved follow-up and enhanced efficiency. There have been 4 proarrhythmic events since its inception. (Source: Personal communication.)

Daoud EG. Cardiol Clin. 2004 Feb;22(1):159-66
Amiodarone Lung Disease In The AFFIRM Trial

• Of the 4060 pts in the AFFIRM Trial, 1468 received amiodarone (36%). Amiodarone was given at the attending physician’s discretion and amiodarone use was NOT randomly assigned. The possibility of selection bias must be recognized in applying the following observations.

• 591 of the 4060 pts in the AFFIRM Trial had chronic lung disease (15%). Among those with chronic lung, 238 (40%) received amiodarone, versus 1230 (35%) of the patients who did not have chronic lung disease.

• By year 4, approximately 58% of those prescribed amiodarone had discontinued taking the drug. Amiodarone use was discontinued at the same rate whether or not pulmonary disease was diagnosed.

• Amiodarone-induced pulmonary toxicity was identified in 52 of 1,468 patients taking amiodarone (3.5% at 4 years). It was diagnosed more often in patients with preexisting pulmonary disease (14 of 238 patients, 5.9%) than in those without preexisting pulmonary disease (38 of 1,230 patients, 3.1%) at 4 years (p 0.0152).

• Pulmonary death due to amiodarone was diagnosed in 3 of 1,468 exposed to the drug (0.2%). Two were among the 238 patients with pulmonary disease (0.84%), and 1 was among 1,230 patients without pulmonary disease (0.08%, p 0.071).

Cardioversion: Versed (midazolam) Anesthesia – Method
(Study Group = 368 Consecutive Patients)

1. Give O2 by facemask.
2. Give Versed 2.5 mg IV.
3. 2 minutes after first dose of Versed, give 1 mg of Versed.
4. Continue to give Versed in 1 mg increments every 1-2 minutes, maximum 12 to 16 mg.
5. The patient is considered adequately sedated when: (1) He or she appears sleepy with the eyelids closed or half closed and (2) No longer continues a conversation and (3) There is no response to soft verbal commands and mild tactile stimuli.
6. Using bi-phasic, synchronized DC shock, a 75-joule shock is applied for atrial fibrillation, 50-joule shock for atrial flutter. If initial shock is not effective, 120-joule and 200-joule shocks are applied.
7. After cardioversion all patients receive 200 micrograms of Romazicon (flumazenil) to reverse the Versed (midazolam).
Cardioversion: Versed (midazolam) Anesthesia: Results

1. Cardioversion was successful in 94.6% of 368 patients.
2. The mean energy of shock needed for cardioversion was 118 ± 57 joules.
3. The mean dose of Versed (midazolam) needed was 7 ± 5 mg.
4. 2/368 patients required general anesthesia, as they had not become sedated despite 16 mg and 12 mg of Versed (midazolam).
5. 0/368 patients had episodes of apnea or other respiratory complications.
6. Patients had either no cutaneous reaction or only mild erythema of the chest wall. No hydrocortisone cream or silver sulfadiazine cream was needed.
7. The shocks were remembered by 10.3% of patients and 3.5% considered them unpleasant.
8. 12 of 380 visits (3.2%) were cancelled on the day of the procedure, as four patients were back in sinus rhythm; eight patients had a low INR and had been added to the list at short notice without being seen at the precardioversion clinic.
9. Of 295 patients having a postcardioversion ECG, 65 patients (22%) at one week and a further 52 patients at four weeks (for a total of 117 (39.6%) were found to be back in AF. 24% of all patients were receiving antiarrhythmic drugs.

Cardioversion: Midazolam and Morphine Anesthesia

(1) After written informed consent was obtained, patients were sedated in the postabsorptive state and underwent cardioversion to sinus rhythm. Cardioversion was performed according to the following protocol:

(2) The patient was attached to a monitor, blood pressure cuff, and defibrillator by external pads.

(3) With the attending physician present, a nurse certified in the administration of conscious sedation infused 1 mg of midazolam intravenously after obtaining baseline vital signs. The patient was observed over the next 3 to 5 minutes for level of consciousness, assessed by response to mild tactile and verbal stimulation. If the patient required more sedation, 1 to 2 mg of morphine sulfate and midazolam were administered every 3 to 5 minutes to achieve adequate sedation.

(4) The patient was deemed adequately sedated when there was no response to soft verbal and mild tactile stimuli yet respiratory drive was still intact. In this state, the patients were able to be aroused by vigorous stimuli but quickly fell back to sleep without recollection of the stimuli.

(5) An anesthetist was always available for emergencies and known to be less than 5 minutes from where the cardioversion took place. The electrophysiologist and nurse were both certified in advanced cardiac life support, such that they could provide ventilatory support with a bag-mask valve while waiting for sedatives to clear, an anesthetist to arrive, or for flumazenil or naloxone to take effect.

(6) When adequate sedation was achieved, cardioversion was performed with 50 to 360 J of synchronized energy.

(7) Once the cardioversion procedure was completed, the patient recovered for 3 hours, with vital signs assessed every 10 to 15 minutes for the first hour and every 30 minutes for the second and third hours. Outpatients were then asked to ambulate for 1 hour before discharge. Inpatients were returned to a monitored unit after the first hour of recovery and were permitted to ambulate after the third hour.

(8) Using this method, only 1/26 patients recalled being shocked. Time to sedation was 9.4 minutes. Time to return to consciousness was 14.8 minutes. Patients required 5.2 mg of midazolam plus 4.2 mg of morphine sulfate.
Atrial Fibrillation Often Goes Undetected, Even Among The Vigilant

72 pts with paroxysmal (37) or persistent (35) drug-refractory AF underwent circumferential RFA of the pulmonary vein ostia.

Mean age 62 ± 9.1 years (range: 36 to 78 years), with mean duration of arrhythmia of 4 years.

69% of patients had structural heart disease. LVEF 59±8%.

Of the 20 patients having at least one episode of recurrent atrial fibrillation, 10 had at least one asymptomatic episode, and in 8 patients ALL episodes were asymptomatic.

Among patients having an episode of palpitations, rhythm strip ALWAYS showed atrial fibrillation (27/27).

Recurrence of atrial fibrillation at one year among patients with conversion at baseline

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Amiodarone group (n=267)</th>
<th>Sotalol group (n=261)</th>
<th>Placebo (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (%)</td>
<td>48</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>Atrial fibrillation &lt;1 y (%)</td>
<td>31</td>
<td>56</td>
<td>79</td>
</tr>
<tr>
<td>Atrial fibrillation &gt;1 y (%)</td>
<td>45</td>
<td>74</td>
<td>92</td>
</tr>
<tr>
<td>Ischemic heart disease patients (%)</td>
<td>40</td>
<td>50</td>
<td>83</td>
</tr>
<tr>
<td>Nonischemic heart disease patients (%)</td>
<td>34</td>
<td>63</td>
<td>83</td>
</tr>
<tr>
<td>Symptomatic atrial fibrillation (%)</td>
<td>38</td>
<td>59</td>
<td>83</td>
</tr>
<tr>
<td>Asymptomatic atrial fibrillation (%)</td>
<td>31</td>
<td>62</td>
<td>80</td>
</tr>
</tbody>
</table>

Estimating Stroke Risk In Atrial Fibrillation

### CHADS2 scores, stroke risk, and risk levels

<table>
<thead>
<tr>
<th>CHADS2 score*</th>
<th>Stroke risk per 100 pt-yr</th>
<th>CHADS2 risk level</th>
<th>Warfarin recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>High</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
<td>High</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
<td>High</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*The CHADS2 stroke risk index assigns 1 point for each of four risk factors (congestive heart failure, hypertension, age > 75 years, diabetes mellitus) and 2 points for a previous stroke.

Framingham Heart Study-Based Free PDA Program
From StatCoder

Many Low-Risk Atrial Fibrillation Patients Do Not Benefit Substantially From Warfarin Therapy

“The impressive relative risk reduction in stroke with adjusted-dose warfarin does not imply clinically important benefits for all patients who have atrial fibrillation. The intrinsic risk for stroke among such patients varies 20-fold. Many low-risk patients do not benefit substantially from warfarin, and low-risk patients who have atrial fibrillation can be reliably identified (56, 58–60). High-risk patients (particularly those with previous stroke or TIA) have large absolute reductions in stroke rate with anticoagulation therapy. The choice of antithrombotic prophylaxis is best individualized and should consider the patient’s inherent stroke risk and the best estimate of the absolute benefits, as well as bleeding risk, access to high quality anticoagulation monitoring, and patient preferences.”


## Vascular events and major bleeding: ACTIVE-W final results

<table>
<thead>
<tr>
<th>End point</th>
<th>Clopidogrel + ASA</th>
<th>Warfarin</th>
<th>Relative risk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular events (%/year)</td>
<td>5.64</td>
<td>3.63</td>
<td>1.45</td>
<td>0.0002</td>
</tr>
<tr>
<td>Major bleeding (%/year)</td>
<td>2.4*</td>
<td>2.2</td>
<td>1.06</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* Please note: This unexpectedly high rate of major bleeding with ASA+Clopidogrel may have been influenced by prior use of warfarin. (This possibility was only recognized post hoc.)

N = 6600 pts
Main results of meta-analysis of antithrombotic therapy in AF patients

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials (n)</th>
<th>Patients (n)</th>
<th>Reduction in stroke (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin vs control</td>
<td>6</td>
<td>2900</td>
<td>64</td>
<td>49–74</td>
</tr>
<tr>
<td>Antiplatelet agents vs control</td>
<td>8</td>
<td>4876</td>
<td>22</td>
<td>6–35</td>
</tr>
<tr>
<td>Warfarin vs antiplatelet agents</td>
<td>12</td>
<td>12,963</td>
<td>39</td>
<td>22–52</td>
</tr>
</tbody>
</table>

ACTIVE W: Accuracy Of Anticoagulation vs. Efficacy In Preventing Vascular Events

Cumulative risk of stroke, MI, systemic embolism or vascular death for patients treated at centers with a time in therapeutic range (TTR) below or above the study median (65%). RR indicates relative risk: C+A, clopidogrel plus aspirin; OAC, the Vitamin K antagonist used locally at each study center.

(Please see detailed discussion of this study and the study abstract in Notes at the bottom of this PowerPoint slide.)

COUMADIN (WARFARIN) INITIATION IN THE ELDERLY

Patients over 70 years of age will be started on Coumadin 4mg each evening x three days.

The patient will have a protime drawn on the fourth day.

The following is the maintenance (daily) dose to be started the evening of day four.

- INR 1.0 to <1.3 : 5mg
- INR 1.3 to <1.5 : 4mg
- INR 1.5 to <1.7 : 3mg
- INR 1.7 to <1.9 : 2mg
- INR 1.9 to <2.5 : 1 mg
- INR 2.5 or higher : Measure INR daily and hold Coumadin until INR drops to <2.5, then resume at 1 mg.

The protime will be rechecked seven to ten days (to avoid weekend draws) after the first dose.

Efficacy: 96 pts, average age = 84.6 yrs. The dose predicted by the algorithm on day 4 was equal to the actual maintenance dose in 73% of the patients (95% confidence interval 64%–81%). The average time needed to achieve a therapeutic INR (2.0 – 3.0) was 6.7 days. No patient had an INR greater than 4.0 during the study.

Siguret V. Am. J. Med 118:137, 2005
### Self-monitoring vs routine anticoagulation: Odds ratio (OR) of major events

<table>
<thead>
<tr>
<th>Event</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic events</td>
<td>0.45</td>
<td>0.30–0.68</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.61</td>
<td>0.38–0.98</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.65</td>
<td>0.42–0.99</td>
</tr>
</tbody>
</table>

### Self-monitoring and self-dosing vs routine anticoagulation: Odds ratio of major events

<table>
<thead>
<tr>
<th>Event</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic events</td>
<td>0.27</td>
<td>0.12–0.59</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.37</td>
<td>0.16–0.85</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.93</td>
<td>0.42–2.05</td>
</tr>
</tbody>
</table>

N = 3049 patients in 14 randomized studies.

Warfarin: Self-Monitoring Technology

Product Demo
360° View
Product Features
- Easy To Use
- Small Sample Size
- Two-Minute Results
- Easy Calibration
- Quality Controls

INR = 2.6
PT = 19.5 sec

The CoaguChek™ System provides immediate PT results for patients who self-test.
### Warfarin: Managing High INR or Bleeding

<table>
<thead>
<tr>
<th>BLEEDING</th>
<th>INR</th>
<th>VITAMIN K</th>
<th>FFP</th>
<th>WARFARIN</th>
<th>NEXT INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bleeding</td>
<td>&lt;5</td>
<td>None</td>
<td>None</td>
<td>Hold 1-2 days. -- Adjust dose?</td>
<td>1-2 days</td>
</tr>
<tr>
<td>No bleeding</td>
<td>5-9</td>
<td>None (No bleeding risk) *</td>
<td>None</td>
<td>Hold 1-2 days. -- Adjust dose</td>
<td>1 day</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>&lt;10</td>
<td>2.5 mg po</td>
<td>None</td>
<td>Hold ----- Adjust dose</td>
<td>1 day</td>
</tr>
<tr>
<td>No bleeding or minor bleeding</td>
<td>10-20</td>
<td>2.5-5.0 mg po</td>
<td>None</td>
<td>Hold ----- Adjust dose</td>
<td>12-24 hours</td>
</tr>
<tr>
<td>Bleeding tendency or bleeding</td>
<td>&gt;20</td>
<td>5-10 mg IV (&lt;1 mg/min)</td>
<td>FFP?</td>
<td>Hold</td>
<td>6-12 hours</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>Target or high INR</td>
<td>10 mg IV (&lt;1 mg/min)</td>
<td>FFP</td>
<td>Hold</td>
<td>Following FFP</td>
</tr>
</tbody>
</table>

* * or Vitamin K 2.5 mg p.o.
FPF - Fresh Frozen Plasma

Source: Anticoagulant Clinic Guidelines. To view the entire guidelines set, return to the Zunis Library and click on the Anticoagulant Clinic Guidelines link.
Clot drug 'safer than warfarin'

A drug which thins the blood and can be taken as a pill is being hailed as a major breakthrough in the prevention of stroke.

It could have fewer side effects and be easier to take than warfarin, which is used by thousands of patients in the UK.

The drug is the first in a new class of anticoagulants. Unlike many other similar drugs it can be swallowed instead of injected.

Called ximelagatran, research shows it is at least as safe and effective as warfarin, a drug more commonly known for its use as rat poison.

Doctors have relied on warfarin for the past 50 years to reduce the risk of stroke in patients with a condition called atrial fibrillation, abnormal heart rhythms.

"These are remarkable results and this is a major breakthrough"

Dr Jean-Pierre Bassand, cardiologist
We found that ximelagatran could improve the quality adjusted survival of patients who had a low utility for warfarin or a high bleeding risk at an acceptable cost, but this assumes that it is prescribed only in patients with low risk of hepatotoxicity and is carefully monitored. Not only would patients with alcoholism or liver disease need to avoid ximelagatran, but so would patients with impaired renal function because the active metabolites of ximelagatran are renally cleared.

O'Brien CL. JAMA. 2005;293:699-706 (Washington University School of Medicine)

2-14-06 Press Release:
AstraZeneca will no longer market or develop the oral anticoagulant ximelagatran (Exanta) because of "serious liver injury" observed in a study of venous-thromboembolism prophylaxis after orthopedic surgery.

Above the horizontal line, ximelagatran costs less than $50000 per quality-adjusted life-year (QALY); below the line, warfarin costs less than $50000 per QALY. To the left of the nearly vertical line, both of these anticoagulants cost more than $50000 per QALY but aspirin is cost-effective.

"We found that ximelagatran could improve the quality adjusted survival of patients who had a low utility for warfarin or a high bleeding risk at an acceptable cost, but this assumes that it is prescribed only in patients with low risk of hepatotoxicity and is carefully monitored. Not only would patients with alcoholism or liver disease need to avoid ximelagatran, but so would patients with impaired renal function because the active metabolites of ximelagatran are renally cleared."

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