ATRIAL FIBRILLATION: BASIC SCIENCE TO CLINICAL PRACTICE

Focus: May 7, 2013 ACC/AHA guidelines
American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Atrial fibrillation

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Affects 1 in 25 adults 60 years or older and nearly 1 in 10 adults 80 years or older

Single most common SVT
Introduction
Twice as many strokes with atrial fibrillation

- Framingham
- 40 year f/u
- N=5070
  - 398 non afib strokes
  - 103 afib strokes

% Fatal @ 30 days

Stroke. 1996;27:1760-1764
Equal Risk of Stroke from Paroxysmal Afib or Sustained Afib

- SPAF 1-3
- 1987-1997
- 325 mg ASA vs ASA with warfarin
- N=1552 sustained
- N=460 intermittent (paroxysmal)

Hart JACC 2000;35:183
2050 estimated: 15 million atrial fibrillation patients

- **Etiologies**
  - Remodeling
    - Electrical and structural
  - Metabolic
  - Aging
  - Genetics
  - Environmental

- **High risk groups**
  - Hypertension
  - CHF
  - Ischemic heart disease
  - Post cardiac surgery

Atrial fibrillation patient with MS

Circulation 2006;114:119–25
JAMA 2001;285:2370–5
Atrial fibrillation prevalence will increase 2.5 fold in next 50 years

Cross sectional study age 20>Health Maintenance organization California

N=17974

Table 2. Projected Age and Sex Distribution of Adults With Atrial Fibrillation in the United States Between 2000 and 2050*

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2025</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>48.6</td>
<td>46.3</td>
<td>47.4</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>18.0</td>
<td>15.5</td>
<td>11.5</td>
</tr>
<tr>
<td>65-79</td>
<td>45.3</td>
<td>48.7</td>
<td>35.9</td>
</tr>
<tr>
<td>≥80</td>
<td>36.7</td>
<td>35.8</td>
<td>52.6</td>
</tr>
</tbody>
</table>

*Data are presented as percentage.

AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study

JAMA. 2001;285:2370-2375
Genetic associations with atrial fibrillation

- Framingham heart study
  - 1.8 X increase (1 parent with Afib)
    - JAMA 2004;291:2851–5
  - 3.2 X increase (parent <75)
- Iceland study (N=5000—population cohort)
  - 1.77 X increase (1 parent with Afib)
    - Eur Heart J 2006;27:708–12

<table>
<thead>
<tr>
<th>Chromosome 4q25 SNPs</th>
<th>AF by Age 50 Years</th>
<th>No AF by Age 50 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Present</td>
<td>21</td>
<td>8*</td>
</tr>
</tbody>
</table>

*p = 1.21 × 10^{-5} comparing the presence of both common and rare variants in 11 kindreds with familial AF.

AF = atrial fibrillation; SNP = single-nucleotide polymorphism.
Classification of Atrial Fibrillation

- **Paroxysmal (ie, self-terminating)**
  - Terminate spontaneously in **less than seven days**, usually less than 24 hours

- **Persistent AF**
  - Fails to **self-terminate within seven days**

- **Permanent AF**
  - Lasts for **more than one year**

- **Lone AF**
  - Paroxysmal, persistent, or permanent AF in individuals **without** structural heart disease.
  - Lone AF has primarily been **applied to patients <60 years of age** but older patients also may be at low risk

This classification applies to episodes of AF that last more than 30 seconds and that are unrelated to a reversible cause.
Echocardiogram can be very helpful

- **Echo**
  - TTE/TEE-chamber size, function
    - Valvular, LVH, pericardial, **peak RV pressure**
    - Atrial thrombi-low sensitivity
  - 4 weeks of anticoagulation prior to cardioversion
Summary highlights

- History/Physical
  - Symptoms/pattern-onset
    - 90% of episodes not recognized by patient
    - 90% of patients have recurrence
  - 48 hours of Afib frequently unrecognized by patients
  - 40% of patients in NSR think they have afib (prior history)

- History, physical examination, and specific laboratory and cardiologic testing are all part of the evaluation of the patient with AF (Guidelines Heart rhythm 2012;9:632 guidelines)
New guidelines for atrial fibrillation treatment

- Rate control
- Prevention of thromboemboli/ischemic stroke/systemic emboli
- Combination anticoag + anti platelet (NEW)
- Combination anticoag + anti platelet (NEW)
- Oral direct thrombin inhibitor
- Direct cardioversion-others
- Maintaining NSR
- Special conditions

Rate control

- Heart rate at rest (Class I)
  - Beta blocker / nondihydropyridine CCB
    - Esmolol, metoprolol
    - Verapamil, diltiazem (less negative inotrope)
  - Heart failure patient
    - Digoxin/amiodarone
- Ablation AV node / EP (Class II) if not tolerate drugs
- IV procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway

Resting heart rate 110 bpm in patients with persistent AF who have stable ventricular function (LV ejection fraction >0.40)

37 y/o women with occasional lightheadness

After D/C cardioversion
Preventing Thromboembolism

Class I

- Selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient
  - **High risk of stroke** = chronic oral anticoagulant therapy with a vitamin k antagonist (INR 2-3)

  **Highest risk groups**
  - Prior embolization
  - Rheumatic mitral stenosis

  **>1 moderate risk**
  - Age >75 y
  - HT
  - LV systolic dysfunction (EF <35%)
  - Diabetes mellitus

Preventing Thromboembolism
Class I

- Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin k antagonists in low-risk patients or contraindication to Coumadin
- Mechanical heart valves (INR >2.5)
- Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.

It is reasonable to interrupt anticoagulation for up to 1 week without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding.

Percutaneous coronary intervention or revascularization surgery patients with AF

Low-dose aspirin (less than 100 mg per d) and/or clopidogrel (75 mg per d) may be given concurrently with anticoagulation to prevent myocardial ischemic events.

Class IIb
Clopidogrel should be given for a minimum of 1 mo after implantation of a bare metal stent

3 mo for a sirolimus-eluting stent

6 mo for a paclitaxel-eluting stent

12 mo or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event.

When warfarin is given in combination with clopidogrel or low-dose aspirin, the dose intensity must be carefully regulated.

Class IIb

Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients below the age of 60 y without heart disease.
Oral Direct Thrombin Inhibitor Anticoagulant Agents—Class I

- Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism
  - Who do not have a prosthetic heart valve
  - Hemodynamically significant valve disease
  - Severe renal failure (creatinine clearance 15 mL/min)
  - Advanced liver disease (impaired baseline clotting function).

  (Level of Evidence: B)

FDA has approved rivaroxaban / apixaban to prevent stroke in patients with atrial fibrillation

New guidelines for atrial fibrillation treatment

- Rate control
- Prevention of thromboemboli/ischemic stroke/systemic emboli
- Combination anticoag + anti platelet (NEW)
- Combination anticoag + anti platelet (NEW)
- Oral direct thrombin inhibitor

- Direct cardioversion-others
- Maintaining NSR
- Special conditions

Cardioversion of AF

- Class I
  - 1. Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF. (Level of Evidence: A)

  “We prefer direct current (DC) to pharmacologic cardioversion for most patients” ....Uptodate 7 EP physicians
## Pharmacological conversion of (recent-onset) AF (European Society of Cardiology)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amiodarone</strong></td>
<td>5 mg/kg IV over 1 hour</td>
<td>Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm</td>
</tr>
<tr>
<td><strong>Flecainide</strong></td>
<td>2 mg/kg IV over 10 minutes, or 200 to 300 mg orally</td>
<td>Not suitable for patients with marked structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.</td>
</tr>
<tr>
<td><strong>Ibutilide</strong></td>
<td>1 mg IV over 10 minutes</td>
<td>Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate</td>
</tr>
<tr>
<td><strong>Propafenone</strong></td>
<td>2 mg/kg IV over 10 minutes, or 450 to 600 mg orally</td>
<td>Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles</td>
</tr>
</tbody>
</table>

*Eur Heart J 2010; 31:2369*
Before antiarrhythmic medication is initiated, a beta blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs.

Amiodarone reasonable option.

A single oral bolus dose of propafenone or flecainide (pill-in-the-pocket) can be administered to terminate persistent AF outside the hospital once treatment has proved safe in hospital for selected patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the brugada syndrome, or structural heart disease.

Quinidine, procainamide, disopyramide, and dofetilide **should not be started out of hospital** for conversion of AF to sinus rhythm.

Class III
Dronedarone is reasonable to decrease the need for hospitalization for cardiovascular events in patients with paroxysmal AF or after conversion of persistent AF.

Dronedarone can be initiated during outpatient therapy.

Class III: Harm

Dronedarone should not be administered to patients with class IV heart failure or patients who have had an episode of decompensated heart failure in the past 4 weeks, especially if they have depressed left ventricular function (left ventricular ejection fraction <35%).

AF with ongoing myocardial ischemia, symptomatic hypotension, angina, or HF, immediate r-wave synchronized direct-current cardioversion is recommended.

AF involving preexcitation when very rapid tachycardia or hemodynamic instability

Frequent repetition of direct-current cardioversion is not recommended for patients who have relatively short periods of sinus rhythm between relapses of AF.....Class III
Pharmacological Enhancement of Direct-Current Cardioversion.

Class IIa

- Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol
AF of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation (INR 2.0 to 3.0) is recommended for **at least 3 wk** prior to and **4 wk after cardioversion**, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. (Level of Evidence: B)
As an **alternative to anticoagulation prior to cardioversion of AF**, it is reasonable to perform transesophageal echocardiogram in search of thrombus in the left atrium or left atrium appendage. (Level of Evidence: B)

No identifiable thrombus, cardioversion is reasonable immediately after anticoagulation with unfractionated heparin (eg, initiate by intravenous bolus injection and an infusion continued at a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value **until oral anticoagulation has been established with a vitamin K antagonist** (eg, warfarin), as evidenced by an INR equal to or greater than 2.0.) (Level of Evidence: B).

Transesophageal echocardiography can detect thrombi in both the left atrium and left atrial appendage--specificity varying from 93% to 100%.
Table 3. Summary of Studies of Transesophageal Echocardiography (TEE)-Guided Approach to Cardioversion of Atrial Fibrillation, Including the Incidence of Thrombus by TEE and Recorded Embolic Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference Number</th>
<th>n</th>
<th>Atrial Thrombi</th>
<th>Embolic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orsinelli (1993)</td>
<td>103</td>
<td>39</td>
<td>9 (23%)</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>Stoddard (1995)</td>
<td>113</td>
<td>206</td>
<td>37 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>Klein (1997)</td>
<td>4</td>
<td>126</td>
<td>7 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Weignier (1998)</td>
<td>114</td>
<td>466</td>
<td>64 (13.9%)</td>
<td>1 (0.21%)</td>
</tr>
<tr>
<td>Grimm (1998)</td>
<td>115</td>
<td>417</td>
<td>28 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Corrado (1999)</td>
<td>116</td>
<td>123</td>
<td>11 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>ACUTE (2000)</td>
<td>16</td>
<td>619</td>
<td>79 (13.6%)</td>
<td>5 (0.81%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,996</td>
<td>235 (11.8%)</td>
<td>7 (0.35%)</td>
</tr>
</tbody>
</table>

ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography.
Thrombus resolution in 40-90% by 17 weeks

### Table 5. Previous Studies Documenting Resolution of Atrial Thrombus by Serial Transesophageal Echocardiography

<table>
<thead>
<tr>
<th>Study (Reference no.)</th>
<th>n</th>
<th>Frequency of Thrombus</th>
<th>Anticoagulation Duration</th>
<th>Atrial Thrombus Resolved on Second TEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoddard 1995 (106)</td>
<td>21</td>
<td>NA</td>
<td>5 to 17 weeks</td>
<td>9/21 (43%)</td>
</tr>
<tr>
<td>Collins 1995 (120)</td>
<td>18</td>
<td>NA</td>
<td>4 weeks (median)</td>
<td>16/18 (89%)</td>
</tr>
<tr>
<td>Tsai 1997 (121)</td>
<td>8</td>
<td>10%</td>
<td>NA</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td>Klein 1997 (4)</td>
<td>7</td>
<td>13%</td>
<td>6 weeks</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Jaber 2000 (122)</td>
<td>164</td>
<td>NA</td>
<td>6.7 weeks (mean)</td>
<td>131/164 (80%)</td>
</tr>
<tr>
<td>Corrado 1999 (116)</td>
<td>11</td>
<td>11%</td>
<td>4 weeks (median)</td>
<td>9/11 (82%)</td>
</tr>
</tbody>
</table>

NA = not available; TEE = transesophageal echocardiography.
Table 1. Reported Incidences of Embolic Events After Electrical and Chemical Cardioversion From Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference Number</th>
<th>n</th>
<th>AC Rx</th>
<th>Percent Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lown (1963)</td>
<td>44</td>
<td>50</td>
<td>Some</td>
<td>1.7</td>
</tr>
<tr>
<td>Killip (1963)</td>
<td>45</td>
<td>62</td>
<td>In 45%</td>
<td>0.0</td>
</tr>
<tr>
<td>Morris (1964)</td>
<td>48</td>
<td>70</td>
<td>In 6%</td>
<td>3.4</td>
</tr>
<tr>
<td>Oram (1964)</td>
<td>49</td>
<td>100</td>
<td>Some</td>
<td>1.9</td>
</tr>
<tr>
<td>Hurst (1964)</td>
<td>50</td>
<td>121</td>
<td>No</td>
<td>1.3</td>
</tr>
<tr>
<td>Morris (1966)</td>
<td>51</td>
<td>108</td>
<td>Some</td>
<td>2.5</td>
</tr>
<tr>
<td>Korsgren (1965)</td>
<td>52</td>
<td>138</td>
<td>Yes</td>
<td>0.0</td>
</tr>
<tr>
<td>Halmos (1966)</td>
<td>53</td>
<td>175</td>
<td>No</td>
<td>0.4</td>
</tr>
<tr>
<td>Selzer (1966)</td>
<td>54</td>
<td>189</td>
<td>No</td>
<td>2.1</td>
</tr>
<tr>
<td>Lown (1967)</td>
<td>55</td>
<td>350</td>
<td>In 29%</td>
<td>0.9</td>
</tr>
<tr>
<td>Resnekov (1967)</td>
<td>56</td>
<td>204</td>
<td>Some</td>
<td>0.6</td>
</tr>
<tr>
<td>Hall (1968)</td>
<td>57</td>
<td>142</td>
<td>In 39%</td>
<td>0.8</td>
</tr>
<tr>
<td>Radford (1968)</td>
<td>58</td>
<td>156</td>
<td>In 17%</td>
<td>0.0</td>
</tr>
<tr>
<td>Aberg (1968)</td>
<td>59</td>
<td>207</td>
<td>Most</td>
<td>0.7</td>
</tr>
<tr>
<td>Bjerkelund (1969)</td>
<td>60</td>
<td>437</td>
<td>Yes</td>
<td>1.1</td>
</tr>
<tr>
<td>McCarthy (1969)</td>
<td>61</td>
<td>149</td>
<td>Some</td>
<td>1.6</td>
</tr>
<tr>
<td>Henry (1976)</td>
<td>62</td>
<td>37</td>
<td>Some</td>
<td>5.6</td>
</tr>
<tr>
<td>Roy (1986)</td>
<td>63</td>
<td>152</td>
<td>In 72%</td>
<td>1.3</td>
</tr>
<tr>
<td>Arnold (1992)</td>
<td>64</td>
<td>454</td>
<td>Most</td>
<td>1.3</td>
</tr>
</tbody>
</table>

1.4 ± 1.3*
5.6% risk of stroke in the week after cardioversion in non-anticoagulated patients

Cardioversion increases or concentrates the embolic risk of AF by perhaps 50-fold during the week after the procedure.

Table 1. Reported Incidences of Embolic Events After Electrical and Chemical Cardioversion From Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference Number</th>
<th>n</th>
<th>AC Rx</th>
<th>Percent Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical cardioversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sokolow (1956)</td>
<td>42</td>
<td>177</td>
<td>Some</td>
<td>1.3</td>
</tr>
<tr>
<td>Goldman (1960)</td>
<td>43</td>
<td>400</td>
<td>No</td>
<td>1.5</td>
</tr>
<tr>
<td>Freeman (1963)</td>
<td>46</td>
<td>100</td>
<td>Yes</td>
<td>0.0</td>
</tr>
<tr>
<td>Rokseth (1963)</td>
<td>47</td>
<td>274</td>
<td>Yes</td>
<td>1.6</td>
</tr>
<tr>
<td>Carlsson (1996)</td>
<td>65</td>
<td>1,152</td>
<td>Some</td>
<td>0.26</td>
</tr>
<tr>
<td>Mitchell (1997)</td>
<td>66</td>
<td>110</td>
<td>Some</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2 ± 1.0*</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2001;37:691–704
Maintenance of Sinus Rhythm

Class I

- Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended.

- 2011 Updated Recommendation: Catheter ablation performed in experienced centers§ is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease

New developments in molecular biology
- Protonomics/microRNA technology

- **Gene activation**

- miRNA-29

- Collagen and fibrillin in fibroblasts

- ↓ Extracellular matrix proteins

- Atrial fibrillation ↓↓↓ miRNA-29

MicroRNAs (miRs) non-coding RNAs that block mRNA-translation and/or promote mRNA-breakdown of target-genes.

DOI: 10.1161/CIRCULATIONAHA.112.001207
Atrial fibrillation – reduces miRNA 29b with associated increased atrial fibrosis

DOI: 10.1161/CIRCULATIONAHA.112.001207

VTP-ventricular tachy pacing
5 take home points

- Afib increases risk for embolization
- Anticoagulation 1 month before and 1 month after cardioversion
- Warfarin INR 2-3
  - Can add ASA/antiplatelet agents carefully
- Anti-arrhythmics – aminodarone
- Afib ablation – Class I in good centers, appropriate cases
- Future of research - impressive

Thank you