Shot Through the Heart and I’m OK:
Procainamide Cardioversion of Recent-Onset Atrial Fibrillation in the Emergency Department

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Learning Objectives
1. Describe the pathophysiology and treatment strategies for pharmacological management of atrial fibrillation
2. Identify electrophysiological effects of procainamide and its effects on cardiac conduction
3. Discuss patient outcomes in emergency department management of recent-onset atrial fibrillation patients with intravenous procainamide
4. Formulate an evidence-based recommendation for role of intravenous procainamide in recent-onset atrial fibrillation patients
I. Atrial Fibrillation (AF)
   A. Introduction
      1. Most common supraventricular tachycardia (SVT)
      2. Characterized by a fast and irregular heart rhythm
   B. Incidence/Prevalence
      1. Between 2.7 and 6.1 million Americans are affected by AF
      2. In US, overall prevalence 0.4 to 1%
         a. Increases with:
            i. Age (8% for patients >80 years old)
            ii. Heart failure (50% for patients in New York Heart Association [NYHA] Stage IV)
      3. Aging population in US; prevalence will increase
      4. Lifetime risk for those ≥40 years old is 1 in 4
   C. Characteristics
      1. Results from multiple reentrant loops in atria
         a. In normal conduction, one impulse is spread throughout heart to create regular rhythm

   Figure 1. Mechanism of AF

   Multiple electrical wavelets appear simultaneously in atria

   Rapid and disorganized atrial activation

   No synchronized contraction of atria

   Variable AV activation

   Irregular ventricle activation

   Irregularly irregular Pulse

   Reprinted from: http://www.yalesurgery.org

   Figure 2. Comparison of Conduction Pathways

   Normal electrical conduction

   Atrial fibrillation

   Reprinted from: http://www.yalesurgery.org

   2. “AF begets AF”
      a. May be harder to terminate long episodes because long-term tachycardia may induce mechanical and/or electrical remodeling

   D. Complications
      1. Thromboembolic events (stroke) due to:
         a. Stasis of blood in atrial appendage
         b. Poorly adherent mural thrombi
         c. Risk higher for AF lasting >48 hours
         d. Validated tool for assessing risk is CHA2DS2-VASc score (Appendix A)
      2. Hemodynamic instability with hypotension, acute coronary syndrome or pulmonary edema → medical emergency
      3. Worsening left ventricular diastolic dysfunction due to:
         a. Loss of atrial kick
      4. Mortality rate with AF is approximately double that for patients in normal sinus rhythm (NSR)

   E. AF Classification
      1. Based on duration of episode
Table 1. Atrial Fibrillation Classifications\textsuperscript{1,2,8}

<table>
<thead>
<tr>
<th>Recent-Onset AF</th>
<th>Paroxysmal AF</th>
<th>Recurrent AF</th>
<th>Persistent AF</th>
<th>Longstanding Persistent AF</th>
<th>Permanent AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;48 hours in duration</td>
<td>Terminates spontaneously or with intervention within 7 days of onset</td>
<td>Two or more episodes of AF</td>
<td>Continuous AF lasting &gt;7 days</td>
<td>Continuous AF &gt;12 months of duration</td>
<td>No more active attempts to restore/maintain sinus rhythm</td>
</tr>
</tbody>
</table>

F. Etiology
1. Often occurs in association with disease states that cause atrial stretch/distension\textsuperscript{1,2,4}
   a. Myocardial ischemia/infarction
   b. Hypertensive heart disease
   c. Valvular disorders
   d. Acute pulmonary embolism
   e. Congenital abnormalities
   f. Lung disease \(\rightarrow\) pulmonary hypertension, chronic obstructive pulmonary disease (COPD)
2. High adrenergic tone is also associated with AF\textsuperscript{1,2,8}
   a. Thyrotoxicosis
   b. Surgery
   c. Alcohol withdrawal
   d. Sepsis
   e. Excessive physical exertion

G. Clinical Presentation
1. May present with a variety of symptoms including:\textsuperscript{2,8,9}
   a. Light-headedness
   b. Fatigue
   c. Breathlessness
   d. Palpitations
   e. Chest-tightness/pain
2. Obtain a thorough history at presentation\textsuperscript{1,2,9–11}
   a. Time of onset
   b. Previous history of AF episodes/treatments
   c. Home medications - focusing on antiarrhythmic agents, anticoagulants
   d. Cardiac history including:
      i. Previous electrocardiogram (ECG)
      ii. Prior myocardial infarction
      iii. Congestive heart failure
      iv. Hypertension
   e. Assess thromboembolic risk factors via CHA\textsubscript{2}DS\textsubscript{2}-VASc score (Appendix A)
3. Clinical findings\textsuperscript{1,2,8,9,12}
   a. Irregularly irregular heart rhythm
   b. Heart rate fluctuates between 110 and 180 beats per minute (BPM)
   c. Typically hemodynamically stable

II. Pharmacological Management of AF
A. Emergency Management\textsuperscript{11,12,14,15}
   1. Assess potential for hemodynamic instability
   2. Identify and treat underlying/precipitating cause of AF
   3. Assess patient history for risk of thromboembolism
   4. Consider emergent cardioversion with expert consultation
B. Chronic Management: Rate v. Rhythm Control\textsuperscript{16-22}

1. Rate control
   a. Target ventricular rate control
      i. Resting heart rate <80 BPM
      ii. Six minute walk test <110 BPM

2. Rhythm control
   a. Variety of antiarrhythmic agents available to maintain NSR

3. Evidence\textsuperscript{16-22}
   a. Does not address management of recent-onset AF
   b. Five randomized controlled trials examine rate v. rhythm for patients with chronic AF (Appendix B)
      i. Largest trial focused on patients ≥65 years old
      ii. No significant difference in mortality between rate v. rhythm management in any individual trial
      iii. Meta-analysis of results found a trend towards better outcomes with rate control driven by large patient population in atrial fibrillation follow-up investigation of rhythm management (AFFIRM) trial

   \textbf{Figure 4. Odds Ratios for the End Point of All-cause Mortality in Major Rate v. Rhythm Control Trials}\textsuperscript{16}

\begin{tabular}{|c|c|c|}
\hline
Trial & Rate & Rhythm & 0.1 & 1 & 10 \\
\hline
HOT CAFE & 1/101 & 3/104 &  &  &  \\
PIAF & 2/125 & 2/127 &  &  &  \\
RACE & 18/256 & 18/266 &  &  &  \\
STAF & 8/100 & 4/100 &  &  &  \\
AFFIRM & 310/2027 & 356/2033 &  &  &  \\
Combined & 339/2609 & 383/2630 &  &  &  \\
\hline
Percentage & 13.0 & 14.6 &  &  &  \\
\hline
\end{tabular}

\( \text{OR, 0.87 (95\% CI; 0.74 - 1.02), P = .09} \)

iv. Increased rates of hospitalization in rhythm control
   1) Attributed to side effects of antiarrhythmic drugs

v. Limitations of trials
   1) Did not include patients with
      a) Paroxysmal AF at low risk of recurrence
      b) Recent-onset AF
      c) Low risk of thromboembolism
      d) Heart failure
   2) All open-label trials
   3) Compared treatment strategies, not treatment agents

C. Anticoagulation

1. Initiate if AF lasts >48 hours and patient has risk factors for stroke with CHA\textsubscript{2}DS\textsubscript{2}-VASc score\textsuperscript{1}

III. Clinical Practice - Guidelines

A. 2014 AHA/ACC/HRS AF Guideline\textsuperscript{1}

1. Initial rate control strategy is reasonable for many patients, but there are several considerations for selecting rhythm control
   a. Persistent symptoms
   b. Younger patients
   c. Difficulty achieving rate control
   d. First episode of AF
   e. AF precipitated by acute illness
   f. Patient preference

2. Recommendations for pharmacological cardioversion
   a. Flecainide, dofetilide, propafenone, or intravenous ibutilide are recommended for pharmacological cardioversion of AF provided contraindications to the selected drug are absent (Level of Evidence: A; Class Ia recommendation)
   b. Amiodarone is a reasonable option for pharmacological cardioversion of AF (Level of Evidence: A; Class IIa recommendation)

3. Changes from 2006 recommendations\textsuperscript{8}
   a. Procainamide/quinidine were removed
   b. Previously stated that both agents may be used for pharmacological cardioversion of AF, but that their usefulness was not established
c. Included the need to assess patient for contraindications to agents
d. Removed definitive timeline for cardioversion effectiveness
   i. Previously within 7 days of AF episode onset

B. 2010 AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

1. Management of AF should focus on ventricular rate control, conversion of hemodynamically unstable AF to sinus rhythm or both
   a. Stable patients require ventricular rate control with IV beta-blockers or nondihydropyridine calcium channel blockers (such as diltiazem)
2. Electric or pharmacological cardioversion should not be attempted unless patient is unstable
3. Alternatively, may elect cardioversion after anti-coagulation with heparin and performance of transesophageal echo-cardiography to ensure absence of a left atrial thrombus
4. No specific agent recommendations for cardioversion
   i. Variety of agents are effective
   ii. Recommend consulting an expert

C. Canadian Cardiovascular Society AF Guidelines 2010: Management of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Department (ED)

1. ED should assess instability, identify and treat an underlying or precipitating cause, and assess a patient’s risk of a thromboembolic event
2. May consider rate or rhythm control
   a. If choosing rhythm control, there are several drug options that may be considered

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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Risks</th>
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<tr>
<td>Procainamide</td>
<td>15–17 mg/kg IV over 60 min</td>
<td>++</td>
<td>5% hypotension</td>
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<tr>
<td>Propafenone</td>
<td>450–600 mg PO</td>
<td>+++</td>
<td>Hypotension, 1:1 flutter, bradycardia</td>
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<tr>
<td>Flecainide</td>
<td>300–400 mg PO</td>
<td>+++</td>
<td>Hypotension, 1:1 flutter, bradycardia</td>
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<tr>
<td>Ibutilide</td>
<td>1–2 mg IV over 10–20 min; pretreat with 1–2 g IV magnesium sulfate</td>
<td>++</td>
<td>2–3% torsades de pointes</td>
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</table>

3. Amiodarone and sotalol are not recommended for recent-onset AF
   a. No more effective than placebo in initial 6–8 hours
   b. Associated with adverse reactions

IV. Recent-onset AF Management in the ED

A. Strategies for ED management of AF

1. Aggressive treatment = rhythm control
   a. Methods utilized in the ED include
      i. Direct current cardioversion (DCC)
         1) Preferred method for unstable patients
         2) Requires use of procedural sedation and fasting
      ii. Pharmacological cardioversion
         1) Typically lower conversion rates to sinus rhythm than DCC
         2) Use limited by adverse effects of medications
         3) Preferred agent varies by country
            a) IV procainamide preferred in Canada
            b) IV amiodarone preferred in US, UK, Australia
         4) If successful, patient may be discharged home
         5) Less commonly pursued in US than Canada (26% v. 65.9%)

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<tr>
<th>Benefits</th>
<th>Risks</th>
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<tr>
<td>Improved quality of life</td>
<td>Thromboembolic event</td>
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<td>No hospitalization</td>
<td>Ventricular arrhythmias</td>
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<td>No tachycardiomyopathy</td>
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2. Conservative treatment = rate control or observation approach
   a. Pursue rate control with anticoagulation in patients at risk for thromboembolic event
   b. May alternatively consider allowing patient to convert spontaneously
   c. Many centers admit patients to inpatient cardiology service
Table 4. Benefits and Risks of Conservative Treatment Approach in the ED

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<tr>
<td>• Lesser chance of thromboembolic event</td>
<td>• Hospitalization</td>
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<tr>
<td>• Lesser chance of ventricular arrhythmia</td>
<td>• Symptoms of AF may continue</td>
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<tr>
<td>• Hospitalization</td>
<td>• Tachycardiomypathy</td>
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B. Economic Perspective on ED Rhythm Control of AF

1. If successful, patients can be discharged home from the ED
   a. Benefits: minimal disruption of patient’s quality of life, reduced healthcare costs

2. Median costs for patients
   a. Cardioverted and discharged from the ED: $5,460
   b. Admitted with no attempt at cardioversion: $23,202

C. ED Management Protocols

1. Canadian Cardiovascular Society AF Guidelines 2010: Management of Recent-onset Atrial Fibrillation and Flutter in the ED based on Ottawa Hospital protocol for AF management in the ED

Figure 5. Details of Ottawa Protocol for ED Patients with Recent-onset AF
2. Retrospective cohort study evaluated the efficacy and safety of the Ottawa Aggressive Protocol
   a. Results cited in 2010 guidelines management recommendations

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<td><strong>Outcomes</strong></td>
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<td><strong>Interventions</strong></td>
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<th>Results</th>
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<tr>
<td><strong>Baseline characteristics</strong></td>
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<tr>
<td>• AF patients, N = 628</td>
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<td>• Mean age (range): 64.6 years (19–92)</td>
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<td>• Primary presenting symptom, n (%): palpitations 491 (78.2)</td>
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<td>• Past medical history, n (%): previous AF, 526 (83.8); coronary heart disease, 267 (42.5)</td>
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<td>• Previous successful conversion with procainamide, n (%): 305 (48.6%)</td>
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<tr>
<td>• Number of ED visits during study period:</td>
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<td>◦ One, n = 341; two, n = 108; three, n = 54; four or more, n = 153</td>
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<tr>
<td><strong>Primary outcomes</strong></td>
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<tr>
<td>Efficacy of Ottawa Aggressive Protocol</td>
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<tr>
<td>Table 5. Rates of Successful Cardioversion</td>
</tr>
<tr>
<td>n (%)</td>
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<tr>
<td>Procainamide only</td>
</tr>
<tr>
<td>Procainamide and electrical cardioversion</td>
</tr>
<tr>
<td>• Median (interquartile range, IQR) arrival to discharge, all AF patients, hr: 4.8 (3.3)</td>
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<tr>
<td>• Median (IQR) arrival to discharge, AF patients successfully cardioverted with procainamide, hr: 3.9 (2.2)</td>
</tr>
<tr>
<td>Table 6. Patient Disposition from ED</td>
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<tr>
<td>Disposition</td>
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<tr>
<td>Home in NSR</td>
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<tr>
<td>Home</td>
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<tr>
<td>Admitted to hospital</td>
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</table>

| Safety of Ottawa Aggressive Protocol |
| • Hypotension (SBP <100 mmHg) in AF patients, n (%): 46 (7.3) |
| • Arrhythmias, n (%) |
| ◦ AV Block: 2 (0.3) |
| ◦ Ventricular tachyarrhythmia: 1 (0.2) |
| ◦ Atrial tachyarrhythmia: 2 (0.3) |
| • No torsades de pointes observed |
Secondary outcomes

- No deaths or strokes were observed
- AF relapse within 7 days, n (%): 55 (8.8)

Conclusions

Author’s conclusions

- Recent-onset AF can be treated with medications or electrical cardioversion in the ED
- Procainamide has an excellent safety profile
- Rhythm control resulted in few adverse effects

Strengths

- Largest reported study of an aggressive ED treatment strategy for patients with recent-onset AF or atrial flutter
- Reported outcomes separately for AF v. flutter patients
- Majority of primary outcomes were objective variables that minimize potential bias
- Reviewed relapse rates at 7 days
- Evaluated adverse effects – thromboembolic event rate

Limitations

- Observational, retrospective study
- Only reported results in descriptive statistics - proportions, means, medians, IQR
  - No 95% confidence intervals or significance tests
- Cardiology literature generally reports 30 day outcomes
- Did not report cardioversion rates for patients with repeat visits
- Limited information about excluded patients (n = 400) who did not receive aggressive management

Take-home points

- Ottawa Aggressive Protocol is highly effective for initial conversion of recent-onset AF patients
- No thromboembolic events were reported with 660 ED cardioversions
- Few new, dangerous arrhythmias observed
- Majority of patients (97%) discharged home

i. Provided evidence for IV procainamide as part of an aggressive management protocol
ii. Many pharmacoeconomic implications for patients
  1) ↓ healthcare cost
  2) ↑ quality of life

V. Focus on Antiarrhythmic Agents and Procainamide

A. Cardiac Electrophysiology

  1. Definitions\textsuperscript{2,29}

a. Conduction velocity: speed with which an electrical impulse can be transmitted through the heart
b. Refractory period: period of depolarization and repolarization of the cell membrane after excitation
   i. Cell is unable to respond to a second stimulus during this period
   c. Automaticity: capacity of cell to initiate an impulse without an external stimulus

\textbf{Figure 6. Ion Channels and the Effect of Class Ia Antiarrhythmic Agents on Cardiac Repolarization} \textsuperscript{2,30,31}

![Figure 6. Ion Channels and the Effect of Class Ia Antiarrhythmic Agents on Cardiac Depolarization](http://www.cvpharmacology.com)
Table 7. Role of Ion Channels in Cardiac Depolarization

<table>
<thead>
<tr>
<th></th>
<th>Open</th>
<th>Closed</th>
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<tbody>
<tr>
<td>Phase 0: Depolarization</td>
<td>• Fast Na⁺ channels: allow Na⁺ ions into cell</td>
<td>• Fast Na⁺ channels</td>
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<tr>
<td>Phase 1: Peak</td>
<td>• L-type Ca²⁺ channels: allow Ca²⁺ ions to enter cell</td>
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<td></td>
<td>• Slow delayed rectifier K⁺ channels: allow K⁺ to exit cell</td>
<td></td>
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<tr>
<td>Phase 2: Plateau</td>
<td>• Slow delayed rectifier K⁺ channels: allow K⁺ to exit cell</td>
<td>• L-type Ca²⁺ channels</td>
</tr>
<tr>
<td>Phase 3: Repolarization</td>
<td>• Slow delayed rectifier K⁺ channels: allow K⁺ to exit cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rapid delayed rectifier K⁺ channels: allow K⁺ to reenter cell</td>
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<tr>
<td>Phase 4: Automaticity</td>
<td>• Sodium-potassium pump (K⁺ pump): pumps one Na⁺ ion out for one K⁺ ion in to maintain electrical gradient</td>
<td>• Slow delayed rectifier K⁺ channels</td>
</tr>
<tr>
<td></td>
<td>• Sodium-calcium exchanger (Ca²⁺ exchanger): exchanges three Na⁺ ion in for one Ca⁺ ion out to maintain electrical gradient</td>
<td>• Rapid delayed rectifier K⁺ channels</td>
</tr>
</tbody>
</table>

B. Vaughan Williams Classification System

1. Most commonly used classification system for antiarrhythmic drugs
2. Categories are based on dominant electro-physiologic effect
3. Weaknesses:
   a. Many antiarrhythmic drugs may fit into multiple categories
   b. Does not differentiate drugs based on efficacy for different types of arrhythmias
   c. Additional antiarrhythmic agents are not included in classification
      i. Digoxin, adenosine, magnesium sulfate

Table 8. Vaughan Williams Classification of Antiarrhythmic Agents Studied in Recent-onset AF

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Conduction Velocity</th>
<th>Refractory Period</th>
<th>Automaticity</th>
<th>Ion Block</th>
</tr>
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<tbody>
<tr>
<td>Ia</td>
<td>Procainamide</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Na⁺ (Intermediate) K⁺</td>
</tr>
<tr>
<td>Ic</td>
<td>Propafenone</td>
<td>↓↓</td>
<td>0</td>
<td>↓</td>
<td>Na⁺ (slow on-off)</td>
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<tr>
<td>III</td>
<td>Amiodarone</td>
<td>0</td>
<td>↑↑</td>
<td>0</td>
<td>K⁺</td>
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<tr>
<td></td>
<td>Ibutilide</td>
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Adapted from: Pharmacotherapy: A Pathophysiologic Approach, 9th Ed.

C. Antiarrhythmic drugs utilized in acute management of AF

Table 9. Properties of Key Agents Used in Recent-onset AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties</th>
</tr>
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</table>
| Procainamide  | **Mechanism of action**: Blocks fast sodium channels to prolong atrial conductive tissue recovery after repolarization → decreasing impulse conduction velocity in atria, His-Purkinje system and ventricular muscle; also has variable effects on A-V node  
**Pharmacokinetics**: Only available as intravenous medication in US; metabolized by acetyltransferase; forms N-acetyl procainamide (NAPA): active metabolite cleared renally; half-life: 2–5 hours; renal elimination  
**Black box warning**: Fatal blood dyscrasias; cardiac arrhythmias; systemic lupus erythematosus  
**Major side effects**: Hypotension, QT prolongation |
| Ibutilide     | **Mechanism of action**: Promotes influx of sodium through slow inward sodium channels → prolonging action potential duration → slowing sinus rate/AV conduction  
**Pharmacokinetics**: Intravenous agent; metabolized via oxidation in the liver; has 8 metabolites → only one metabolite has antiarrhythmic properties; half-life: 6 hours; renal and fecal elimination  
**Black box warning**: Fatal arrhythmias  
**Major side effects**: Ventricular tachycardias (e.g. torsades), hypotension, QT prolongation |
Amiodarone

**Mechanism of action:** Inhibits potassium channels during plateau and repolarization phases → delaying repolarization of the cell → prolonging refractory period; mild inhibition of sodium fast channels → slows cell depolarization and impulse conduction; direct depression of sinoatrial (SA) and atrioventricular (AV) node automaticity → slowing conduction in His-Purkinje system

**Pharmacokinetics:** Administered intravenously and orally; metabolized in liver via CYP450 enzymes: 3A4, 2C8; half-life: 53 days; hepatic elimination

**Black box warning:** Cardiac arrhythmias; liver disease; pulmonary fibrosis/pneumonitis

**Major side effects:** Hypotension, cardiac arrhythmias, hypersensitivity pneumonitis with long term use - corneal microdeposits, optic neuritis, skin discoloration, hepatic toxicity, thyroid disorders (hypo- and hyper-), peripheral neuropathy, ataxia, tremor

Propafenone

**Mechanism of action:** Inhibits fast sodium channels → increase recovery period after repolarization → decreasing conduction velocity and automaticity

**Pharmacokinetics:** Oral agent; metabolized in liver via CYP450 enzymes: 2D6; half-life: ~10 hours; fecal and urine elimination

**Black box warning:** Cardiac arrhythmias

**Major side effects:** Cardiac arrhythmias, bronchospasm, congestive heart failure (CHF)

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VI. Literature review: Procainamide for Pharmacological Cardioversion of Recent-onset AF in the ED

**Stiell IG et al. Emergency department use of intravenous procainamide for patients with acute atrial fibrillation or flutter. Acad Emerg Med 2007; 14:1158-64.**

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**Interventions**

All patients were managed by ED physicians using the Ottawa Aggressive Protocol (see Figure 5)

- Rhythm control is routine care at Ottawa Hospital
- Pharmacological cardioversion with procainamide infusion: 1g IV over 60 minutes
  ◦ Discontinued if hypotension persists or bradyarrhythmia occurred
- Electrical cardioversion pursued if pharmacological cardioversion failed

**Results**

**Baseline characteristics**

- AF patients, N = 316
- Mean age (range): 68 years (19–92)
- Primary presenting symptom, n (%): palpitations, 236 (74.7)
- Past medical history, n (%): previous AF, 214 (67.7); coronary heart disease, 104 (32.9)
- Previous successful conversion with procainamide, n (%): 45 (14.2)
Primary outcomes

**Efficacy of IV procainamide**
- Successful cardioversion of AF patients with procainamide only, \( n(\%) \): 165 (52.2)
- Successful cardioversion of AF patients with procainamide and electrical cardioversion, \( n(\%) \): 116 (36.7)
  - Median (range) total number of shocks given: 1 (1–5)
- AF patients discharge home in normal sinus rhythm, \( n(\%) \): 281 (88.9)
- AF patients discharged to home, \( n(\%) \): 299 (94.6)

**Safety of IV procainamide**
- Hypotension (SBP <100 mmHg) in AF patients, \( n(\%) \): 27 (8.5)
- Arrhythmias, \( n(\%) \)
  - Bradycardia (HR <65 BPM): 2 (0.6)
  - AV block: 2 (0.6)
  - Ventricular tachyarrhythmia: 1 (0.3)
  - Atrial tachyarrhythmia: 2 (0.6)
- No syncope, cerebrovascular accidents, torsades de pointes, myocardial infarction, or death observed

Secondary outcomes

- Median (range) time to conversion, min: 55 (2–390)
- Mean (range) procainamide dose, mg: 863.9 (250–1,500)
- QTc interval mean, ms
  - Pre-conversion: 405.9
  - Post-conversion: 428
- Admission to hospital, \( n(\%) \): 17 (15.4)
- AF relapse within 7 days, \( n(\%) \): 9 (2.9)

Conclusions

**Author’s conclusions**
- IV procainamide is a safe and effective option for treating acute AF in the ED
- Procainamide use resulted in median time to conversion <1 hour and brief ED visits
- Few significant adverse effects occurred

**Strengths**
- Largest review of IV procainamide for AF conversion in the ED
- Reported outcomes separately for AF versus flutter patients
- Majority of primary outcomes were objective variables that minimize potential bias

**Limitations**
- Observational, retrospective study
- Only reported results in descriptive statistics: proportions, means, medians
  - No 95% confidence intervals or significance tests
- Cardiology literature generally reports 30 day outcomes
- May have missed adverse events that occurred after hospital discharge
- No comparator antiarrhythmic agents studied

**Take-home points**
- Use of IV procainamide in the ED was effective with >50% conversion rate
- Procainamide use does not preclude electric cardioversion
- Few clinically significant adverse events were reported

Outcomes

Primary efficacy outcome
- Conversion rates of AF and flutter

Primary safety outcomes
- Mean change from baseline for systolic and diastolic blood pressure
- Significant 12-lead ECG changes from baseline
- Adverse events requiring termination of study infusions/occurring up to 72 hours after infusion

Methods

- 10-minute baseline period before 1st infusion
- Treatment initiated for patients still in AF/flutter at end of baseline period
- During 30-minute infusion period
  - Blood pressure and HR recorded every 5 min
  - Continuous ECG monitoring
- Post-infusion period lasted for 1st 24 hours from end of infusion

Interventions

Ibutilide group
- Up to two 10-minute IV infusions of 1 mg ibutilide, separated by 10-minute infusion of dextrose 5% in water (D5W)

Procainamide group
- Up to three 10-minute IV infusions of 400 mg procainamide

Other Considerations
- Treatment infusions were discontinued at time of arrhythmia termination or adverse event
  - Threatening arrhythmias or changes in AV conduction, hypotension (decrease in SBP >20 mmHg or SBP <80 mmHg)
- AV node blockers (Ca-channel blockers, beta-blockers, digoxin) were permitted for rate control
- Class I or Class III antiarrhythmic medications were discontinued at least 5 half-lives before infusion of study medicine
- Administration of additional antiarrhythmic medications delayed for 6 hours after end of infusion

Results

Baseline characteristics
- No significant differences between patient populations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ibutilide group (n = 60)</th>
<th>Procainamide group (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.3</td>
<td>67.7</td>
</tr>
<tr>
<td>Mean duration of arrhythmias (days)</td>
<td>22.3 ± 24.7</td>
<td>17 ± 23</td>
</tr>
<tr>
<td>Median</td>
<td>9.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>22 (38.3)</td>
<td>32 (53.3)</td>
</tr>
</tbody>
</table>

- Other variables evaluated included: weight, cardiovascular history, gender

Primary outcomes

Efficacy outcome

![Figure 7. Rate of Successful Conversion of AF and Flutter in the Ibutilide and Proca

(*p < 0.0001  **p = 0.0001  ***p = 0.005)
Primary outcomes

Safety outcomes

- Three patients discontinued ibutilide secondary to adverse ECG changes - extra systole, non-sustained ventricular tachycardia, QT prolongation
- Three serious medical events occurred in ibutilide group, but all were excluded from analysis
  - Sustained polymorphic ventricular tachycardia
  - Pre-syncpe
  - Acute delirium

Conclusions

Author’s conclusions
- Ibutilide is significantly more effective than procainamide in the acute conversion of AF/flutter
- Hypotension is a major adverse effect seen with IV procainamide
- Incidence of serious arrhythmias with ibutilide is low

Strengths
- Prospective study comparing IV procainamide to IV ibutilide with strict inclusion/exclusion criteria
- Multicenter study involving 16 hospitals across the US
- 72 hour post-infusion adverse effect follow-up

Limitations
- Included patients with AF up to 90 days in duration
- Hypotensive changes from baseline may have been due to aggressive procainamide administration
- Post-hoc analysis excluded patients suffering major adverse events from ibutilide group
- Hypotension based on change from baseline blood pressure not actual blood pressure readings

Take-home points
- May have over reported hypotensive effect
- Lacks external validity to readily apply results to patients presenting in first 48 hours due to inclusion of patients with longer duration atrial fibrillation
- Ibutilide was associated with more serious pro-arrhythmias relative to procainamide


Overview

Objective
To compare the safety and efficacy of IV procainamide, propafenone, and amiodarone v. placebo in the restoration of recent-onset AF to NSR

Trial Design
Randomized, placebo-controlled study

Patients

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF &lt;48-hour duration</td>
<td>Cardiac history including recent MI, heart surgery in last 6 months, unstable angina, acute myocarditis/pericarditis, hypertrophic obstructive cardiomyopathy, severe uncontrolled HF, cardiogenic shock</td>
</tr>
<tr>
<td></td>
<td>Baseline SBP &lt;100 mmHg</td>
</tr>
<tr>
<td></td>
<td>Other comorbidities: COPD, pulmonary embolism, pneumonia, liver or kidney failure, thyroid disease, electrolyte disturbances, digoxin intoxication</td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmic therapy (other than digoxin) within &lt;5 half-lives of study drug</td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Primary efficacy outcome</th>
<th>Primary safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression rate to sinus rhythm</td>
<td>Adverse events/drop outs during study period</td>
</tr>
</tbody>
</table>
Methods
• Patients randomized to receive procainamide, propafenone, amiodarone, or placebo

Interventions

<table>
<thead>
<tr>
<th>Patients randomized to receive</th>
<th>Procainamide group</th>
<th>Propafenone group</th>
<th>Amiodarone group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procainamide group</td>
<td>1 g IV over 30 minutes, followed by 2 mg/min IV over 24 hours</td>
<td>2 mg/kg IV over 15 minutes, followed by a total of 10 mg/kg IV over 24 hours</td>
<td>300 mg IV over 1 hour, followed by a total of 20 mg/kg IV over 24 hours</td>
<td>Received an identical amount of IV saline solution over 24 hours</td>
</tr>
</tbody>
</table>

Other considerations
• All patients received digoxin
  ◦ Initial 0.5 mg IV dose, followed by 0.25 mg after 2 hours and 0.25 mg every 6 hours until completion of anti-arrhythmic infusion
• Treatment infusions were discontinued at time of arrhythmia termination or adverse event
  ◦ Threatening arrhythmias or changes in AV conduction, hypotension (decrease in SBP >0 mmHg or SBP <80 mmHg)
• If NSR not achieved after study drug use, other antiarrhythmic drugs or electric cardioversion attempted after 21 days of anticoagulation therapy
• All patients underwent continuous ECG and blood pressure monitoring
• Kept under observation ≥2 days before discharge from hospital

Results

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Table 11. Characteristics of Patients Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Procainamide (n = 89)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Underlying heart disease, n (%)</td>
<td>37 (41.6)</td>
</tr>
<tr>
<td>No. of episodes</td>
<td>5 ± 5</td>
</tr>
</tbody>
</table>

Primary outcomes

<table>
<thead>
<tr>
<th>Efficacy outcome</th>
<th>Table 12. Conversion to NSR by group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion to NSR, n (%)</td>
<td>Procainamide (n = 89)</td>
</tr>
<tr>
<td>Procainamide (n = 89)</td>
<td>61 (68.53)</td>
</tr>
<tr>
<td>Propafenone (n = 91)</td>
<td>68 (75.27)</td>
</tr>
<tr>
<td>Amiodarone (n = 92)</td>
<td>73 (80.21)</td>
</tr>
<tr>
<td>Placebo (n = 90)</td>
<td>59 (65.56)</td>
</tr>
</tbody>
</table>

• All 3 drugs superior to placebo in conversion and rate to progression (p < 0.001)
Primary outcomes (continued)

<table>
<thead>
<tr>
<th>Safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Study treatment discontinued in:</td>
</tr>
<tr>
<td>◦ One amiodarone patient (allergy)</td>
</tr>
<tr>
<td>◦ Four propafenone patients (excessive QRS widening)</td>
</tr>
<tr>
<td>• Significant decreases in blood pressure (SBP &lt;90 mmHg) occurred in 15 amiodarone patients and six procainamide patients</td>
</tr>
<tr>
<td>◦ All responded to fluids</td>
</tr>
<tr>
<td>• Phlebitis in 17 amiodarone patients → continued treatment at more central site</td>
</tr>
<tr>
<td>• No proarrhythmic events in any treatment group</td>
</tr>
</tbody>
</table>

Conclusions

<table>
<thead>
<tr>
<th>Author’s conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All three agents are effective and safe for restoration of NSR in recent-onset AF</td>
</tr>
<tr>
<td>• Amiodarone and propafenone are more efficacious than procainamide or placebo</td>
</tr>
<tr>
<td>• Procainamide and propafenone act more quickly than other agents studied</td>
</tr>
<tr>
<td>• Lack of serious arrhythmias may be due to stringent exclusion criteria</td>
</tr>
</tbody>
</table>

Strengths

| Prospective study comparing three commonly used antiarrhythmic agents including amiodarone |
| Post-hoc Bonferroni analysis conducted to minimize error associated with multiple measurements |

Limitations

| Results possibly confounded by digoxin use |
| No post-study follow-up regarding adverse event rates |
| All patients were admitted to hospital for ≥36 hours to complete study |

Take-home points

| Less serious adverse effects with procainamide |
| Safety of agents may be due to stringent exclusion of cardiac patients |
| Similar efficacy rate of IV procainamide to studies in AF <48 hours |
| Administration of fluids may help counteract hypotensive effect of procainamide |

VII. Summary of Literature

A. Efficacy

1. IV procainamide may used for pharmacological cardioversion of recent-onset AF in the ED
   a. Conversion to NSR occurs ~50 to 60% of patients if used within 48 hours of onset
   b. Literature supports slow 1 g infusion over 30 to 60 minutes rather than many, smaller, rapid infusions over 10 minutes
      i. No standardized dosing available
      ii. Generally administered at rates of <20 mg/min and rate should not exceed 50 mg/min due to risk of hypotension/decreased cardiac output
2. Use of IV procainamide does not prevent immediate use of direct current cardioversion for patients who fail to cardiovert with medication alone
3. If successful, allows for discharge home from the ED within a median time of 3.9 hours

B. Safety

1. IV procainamide associated with hypotension
   a. Literature reports using IV fluids to maintain adequate blood pressure if significant decrease
   b. Decreases in blood pressure may not always be clinically significant
   c. Should have close cardiac monitoring during infusion period
2. Few serious arrhythmias noted with procainamide administration compared to other IV antiarrhythmic agents
3. Lower event rates in studies that excluded patients with active cardiovascular disease

C. Other Considerations

1. Literature largely driven by Ottawa Hospital and one author, I.G. Stiell
2. No long-term follow-up studies available for patients who undergo pharmacological cardioversion in the ED

VIII. Future Directions

A. Chemical v. Electrical Cardioversion for Emergency Department Patient with Acute AF

1. Randomized, double-blind clinical trial to compare IV procainamide v. electrical cardioversion in order to determine ED length of stay, conversion rates to sinus rhythm, adverse events up to 30 days after treatment (clinicaltrials.gov: NCT01994070)

B. Trial of Electrical Versus Pharmacological Cardioversion for Recent-onset Atrial Fibrillation and Flutter (RAFF) in the ED (RAFF-2)

1. Randomized, single blind trial of 468 RAFF patients to determine if a drug (procainamide) then shock if necessary strategy will lead to more patients being converted to NSR than shock only and additionally, study heart rhythm at discharge, need for hospital admission, ED length of stay, adverse events, patient satisfaction and 14-day follow-up (Clinicaltrials.gov: NCT01891058)
IX. Conclusions
A. No universally accepted approach for the management of acute AF in the ED
B. Limited evidence for rhythm control in recent-onset AF patients
C. Outcomes in limited trials suggest potential benefit of IV procainamide may outweigh risks (hypotension, arrhythmia in select patients)
D. Fully consider the risks and benefits of an aggressive approach to management of patients with recent-onset AF in the ED
   1. Benefits of rhythm control
      a. Effects of prolonged AF on quality of life
      b. No hospitalization
      c. Reduced healthcare costs
      d. Tachycardiomyopathy due to long standing AF
      e. Younger patients
      f. Patient preference
   2. Risks of rhythm control
      a. Thromboembolic event
         i. Consider duration of AF
            1) If unknown or >48 hours, must rule out atrial thrombi before pursuing aggressive therapy
            ii. Proarrhythmic episodes due to use of antiarrhythmic agents
E. Recommendations
   1. Consider IV procainamide in select patients presenting to ED with recent-onset AF
   2. Must inform patient of benefits and risks associated with each approach
      a. Patient preference should be taken into account

Figure 10. Proposed Algorithm for Use of IV Procainamide in the ED

Hemodynamically stable with symptomatic AF

YES

Duration > 48 hours or unknown?

YES

Proceed with anticoagulation and rate control

NO

Collect thorough patient history

Significant cardiac history?

YES

Proceed with anticoagulation and rate control

NO

Identify/address precipitating factors

Normal sinus rhythm?

YES

Evaluate need for anticoagulation

NO

Consider cardioversion with IV procainamide
X. References


### Appendix A. CHA$_2$DS$_2$-VASc Score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong> Congestive heart failure (CHF) (or left ventricular dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td><strong>H</strong> Hypertension: blood pressure consistently &gt;140/90 mmHg (or on antihypertensive medication for hypertension treatment)</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong>$_2$ Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td><strong>D</strong> Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong>$_2$ Prior stroke or transient ischemic attack or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td><strong>V</strong> Vascular disease (e.g. peripheral artery disease, MI, aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong> Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sc</strong> Sex category (i.e. female sex)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk</th>
<th>Anticoagulation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>No antithrombotic therapy (or aspirin [ASA])</td>
</tr>
<tr>
<td>1</td>
<td>Moderate</td>
<td>Oral anticoagulant (or ASA)</td>
</tr>
<tr>
<td>2+</td>
<td>High</td>
<td>Oral anticoagulant</td>
</tr>
</tbody>
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M. Curran | 18
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Major Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological Intervention in Atrial Fibrillation (PIAF) n = 252</td>
<td>2000</td>
<td>18 to 75 years old with symptomatic persistent AF between 7 and 360 days</td>
<td>Rate control using diltiazem 90 mg two or three times a day with additional therapy at discretion of treating MD</td>
<td>Improvement in AF symptoms (palpitations, dyspnea, dizziness)</td>
<td>No significant differences in symptomatic improvement between 2 groups</td>
<td>Small sample size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rhythm control using pharmacological and electrical cardioversion, if necessary followed, by anti-arrhythmic therapy with amiodarone 600 mg daily for 3 weeks</td>
<td>Assessment of 6-min walking tests</td>
<td>Significantly more hospital admissions in rhythm</td>
<td>Variable rhythm control strategy dependent on amiodarone therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change in mean heart rate during AF</td>
<td>No validated scoring system for assessing AF symptoms</td>
<td>No validated scoring system for assessing AF symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of hospital admissions</td>
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<td></td>
<td>Quality of life</td>
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<tr>
<td>Strategies of Treatment of Atrial Fibrillation (STAF) n = 200</td>
<td>2003</td>
<td>18 years or older with either: AF for &gt;4 weeks, left atrial size &gt;45 mm, CHF, NYHA class II or greater, LVEF &lt;45%, 1+ prior cardioversion</td>
<td>Rate control used beta-blockers, digitals, calcium channel blockers or AV-node ablation/modification with or without pacemaker implantation</td>
<td>Rhythm control cardioverted by external or internal methods and then, with the use of anti-arrhythmic therapy including sotalol, class I antiarrhythmic or amiodarone if impaired LV function</td>
<td>No difference in composite endpoint between rate and rhythm control groups (p = 0.99)</td>
<td>Compared treatment strategies not specific therapies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Composite of death, stroke/transient ischemic attack, systemic embolism, cardiopulmonary resuscitation</td>
<td>Significantly more hospitalizations in rhythm control group than rate control group</td>
<td>Few patients maintained normal sinus rhythm at the end of the study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Syncope</td>
<td>Higher rate of cerebrovascular events in rhythm control group (5 v. 1)</td>
<td>Can not be applied to asymptomatic AF or recent-onset AF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bleeding</td>
<td></td>
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<td></td>
<td></td>
<td>Echocardiograph parameters</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Resting HR</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Maintenance of sinus rhythm</td>
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<td></td>
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<tr>
<td>Rate Control versus Electrical Conversion (RACE) n = 522</td>
<td>2002</td>
<td>Persistent AF and atrial flutter with an index episode shorter than one year with prior cardioversion</td>
<td>Rate control using digitals and/or a calcium channel blocker and/or a beta blocker to target resting heart rate &lt;100 beats per minute</td>
<td>Morbidity (death, heart failure, serious side effects of drugs, thromboembolic complications, bleeding, pacemaker placement)</td>
<td>Morbidity did not differ at a mean follow-up of 2.3 years</td>
<td>Can not generalize to patients who have not undergone electrical cardioversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serial electrical cardioversion with antiarrhythmic therapy using sotalol, flecainide or propafenone; or amiodarone with relapses</td>
<td>Differences in quality of life</td>
<td>No significant difference in quality of life between groups</td>
<td></td>
</tr>
</tbody>
</table>
### Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) \( n = 4,060 \)

- **2002**
  - **Age ≥65 or other risk factors for stroke or death with a diagnosis of AF requiring long-term treatment**
  - **Rhythm control** using choice of amiodarone, disopyramide, flecaïnine, moricizine, procainamide, propafenone, quinidine, sotalol, and combinations of these drugs
  - **Rate control** using beta-blockers, diltiazem, and verapamil to target heart rate (<80 BPM at rest and <110 BPM during 6-min walking test)
- **Overall mortality combining death, disabled stroke, disabling anoxic encephalopathy, major bleeding, cardiac arrest**
- **Secondary analyses conducted to adjust primary end point for baseline characteristics**
- **More deaths occurred in rhythm control group than rate control group** \( (p = 0.08; \text{hazard ratio } 1.15 [95\% \text{ CI } 0.99 \text{ to } 1.34]) \)
- **Significantly more hospitalization and adverse drug events in rhythm control group**

### How to Treat Chronic Atrial Fibrillation (HOT-CAFE) \( n = 205 \)

- **2004**
  - **Age 50 to 75 years and AF had to be known for 7 days, but not >2 years**
  - **Rate control group with target HR between 70–90 beats/min during rest**
  - **Rhythm control underwent electrical cardioversion with antiarrhythmic drug therapy including propafenone, disopyramide, or sotalol**
- **Composite of death from any cause, thromboembolic complications, intracranial or other major hemorrhage**
- **Rate control**
- **Rhythm maintenance**
- **Hospitalization**
- **Composite end point is not significantly different between rate and rhythm control group** \( (p > 0.71) \)
- **Significantly more hospitalizations in rhythm control group** \( (p = 0.001) \)

- **Results can not be generalized to younger patients without risk factors for stroke or paroxysmal atrial fibrillation**

- **Small sample size**
- **Use of anticoagulation was low**