Prevention of Symptomatic Recurrences of Paroxysmal Atrial Fibrillation in Patients Initially Tolerating Antiarrhythmic Therapy

A Multicenter, Double-Blind, Crossover Study of Flecainide and Placebo With Transtelephonic Monitoring

Jeffrey L. Anderson, MD, Edward M. Gilbert, MD, Barry L. Alpert, MD, Richard W. Henthorn, MD, Albert L. Waldo, MD, Anil K. Bhandari, MD, Ronald W. Hawkinson, MS, Edward L.C. Pritchett, MD, and the Flecainide Supraventricular Tachycardia Study Group

Paroxysmal atrial fibrillation (PAF) is a problematic clinical arrhythmia that is usually symptomatic. Unfortunately, few adequate trials and trial methods are available for assessment of the value of therapy, and traditional treatment has often been ineffective or associated with unacceptable side effects. Transtelephonic monitoring is a new method that allows evaluation of paroxysmal arrhythmias and arrhythmia-related symptoms in outpatients. We used a patient-initiated transtelephonic monitor system to evaluate the potential of flecainide, a class 1C antiarrhythmic, in prevention of symptomatic recurrences of PAF. Sixty-four patients qualified for the study (two or more PAF attacks documented within a 4-week baseline period) and entered a dose-finding phase to determine drug tolerance. Dose was incremented at weekly intervals from 200–300 and finally to 400 mg/day. The largest dose that was well tolerated was selected for the 4-month, double-blind, randomized, crossover comparison with placebo. Fifty-five patients entered and 53 received both treatments in the double-blind phase; 48 of these patients without protocol violations were evaluable for efficacy comparisons. Evaluable patients had undergone an average of 3.8 previous drug trials (range, 1–8); 30 were men, 18 had hypertension, and 14 had ischemic heart disease. The study demonstrated a highly significant correlation (\( p<0.0001 \)) between perceived symptoms and documented PAF by transtelephonic monitoring. The rate of symptoms and PAF attacks was also significantly reduced by therapy (median dose, 300 mg/day). The first PAF attack occurred after a median of 3 days on placebo versus 14.5 days on flecainide (\( p<0.001 \)) therapy. Similarly, the time interval between attacks was lengthened, from a median of 6.2 days on placebo to 27.0 days on flecainide (\( p<0.001 \)) therapy. PAF was prevented in 15 patients (31%) during flecainide and four (9%) during placebo therapy (\( p=0.013 \)). However, during the study, 13 patients dropped out, seven because of adverse effects (five cardiac), five for other reasons, and one because of cardiac arrest/death. Adverse cardiac events occurred in a total of seven patients (11%) during flecainide therapy. Thus, transtelephonic monitoring is a useful method for documentation of the occurrence of paroxysmal arrhythmias such as PAF and its related symptoms during daily living and for assessment of new therapies in an outpatient setting. (Circulation 1989;80:1557–1570)

In patients with paroxysmal atrial fibrillation (PAF), symptomatic attacks of fibrillation occur sporadically and are often difficult to suppress with current therapy. In a 1982 editorial, Selzer1 observed, “In the present era of sophisticated electrophysiology, atrial fibrillation has attracted little interest among electrophysiologists; its management still depends largely on the use of the two

From the University of Utah (J.L.A., E.M.G.), Salt Lake City, Utah.
Supported by a grant from Riker Laboratories, St Paul, Minnesota.

Address for correspondence: Jeffrey L. Anderson, MD, c/o LDS Hospital, 8th Ave C Street, Salt Lake City, UT 84143.
Received December 5, 1988; revision accepted August 10, 1989.
oldest cardiac drugs: digitalis and quinidine.” Little has changed in the intervening years. Since 1977, the United States Food and Drug Administration has approved and labeled five class I antiarrhythmic drugs (disopyramide, tocainide, mexiletine, flecainide, and encainide) and one class 3 agent (amiodarone) for treatment of ventricular arrhythmias, but none of these agents has been labeled for treatment of atrial fibrillation or any other supraventricular arrhythmia.

In part, the problem of developing new drugs for the treatment of paroxysmal supraventricular tachycardias such as PAF has related to the nature of these disorders. The sporadic and apparently unpredictable occurrence of symptomatic PAF makes it unsuitable for study with ambulatory electrocardiographic monitoring techniques developed for studying therapy of ventricular arrhythmias. Transtelephonic monitoring is a relatively new technique that allows for documentation and quantification of paroxysmal arrhythmias and their related symptoms in the outpatient setting during daily living. In the current study, transtelephonic monitoring was used to investigate the natural history of symptomatic episodes of PAF during placebo administration and during antiarrhythmic therapy. Flecainide, a class 1C agent effective in suppressing ventricular arrhythmias but not yet approved for use in supraventricular arrhythmia therapy, was selected as the agent to be evaluated. With use of transtelephonic monitoring technology, a novel clinical trial in PAF was conducted with a randomized, placebo-controlled, double-blind, two-period, crossover design.

Methods

Patient Recruitment

Patients with a history of symptomatic PAF of a frequency of two or more attacks per month were candidates for the study. Men or nonpregnant, nonlactating women using effective contraception 18 years or older who gave written informed consent were eligible. PAF was identified by fine oscillation of the electrocardiographic baseline (fibrillatory waves) associated with an irregularly irregular ventricular rhythm. A spontaneous ventricular response averaging 80 or more beats/min during PAF was required, with either normal QRS morphology or rate-related aberration. Paroxysmal atrial flutter, defined by a characteristic regular flutter wave pattern on the electrocardiogram (ECG) with an atrial rate between 240 and 360 beats/min, was an acceptable associated rhythm for inclusion in the study of patients predominantly with PAF. Previously administered antiarrhythmic agents (including the β-adrenergic–blocking agents, verapamil and diltiazem) were discontinued at least four half-lives before the qualifying period of transtelephonic monitoring was begun.

![FIGURE 1. Schematic representation of study design.](Time intervals are in weeks.)

Patients were excluded from consideration for the trial for the following reasons: potentially dangerous symptoms associated with PAF, such as syncope, angina, or transient ischemic attacks, precluding the ethical administration of placebo; history of cerebral vascular accident associated with occurrence of PAF; functional class III or IV heart failure; PR interval 0.28 or more second; significant or symptomatic sinus node disease, unless protected by a permanent pacemaker; second or third degree atioventricular block; a pacemaker-dependent rhythm (all ventricular beats, pacemaker dependent); PAF caused by reversible, noncardiac disease; recent (1 month or less) myocardial infarction; recent (2 months or less) cardiac surgery; requirement for ongoing therapy with excluded antiarrhythmic medications (stabilized regimen of digitalis permitted); use of investigational agents or drugs with known organ toxicity within 1 month; and significant noncardiac disease that might interfere with disposition of flecainide.

Study Plan

The study was designed in three parts as an outpatient evaluation of the natural history of PAF and treatment response to flecainide (Figure 1). The general approach was developed by one of us (E.P.), based on well-known principles of clinical trial design, and adapted specifically for application in supraventricular tachyarrhythmias, as detailed elsewhere. Treatment periods and patient numbers were designed so that the study would have a power of 0.80 to detect improvement by a factor of only two in median time to first attack, using the maximum tolerated flecainide dose as compared with placebo.

**Baseline screening phase.** Patients who met the inclusion criteria and signed an informed consent were given a transtelephonic monitor with memory capability (Cardiobeeper, Memory Monitor, Heart System, Survival Technology, Inc., Rockville, Maryland) for a period of 4 weeks and were instructed to
transmit every episode of symptoms possibly relating to an arrhythmia episode. Two attacks of PAF lasting at least 1 minute as documented by transmitted ECG recordings, occurring on two different calendar days, and separated by an asymptomatic period during which normal rhythm was documented by transtelephonic transmission, were required as a baseline criterion before the patient qualified for entry into the therapeutic trial. Patients not transmitting two attacks of PAF during the baseline period were excluded from further participation in the study. Patients could be advanced to drug therapy (dose ranging) before the end of the 4-week period on documentation of two or more attacks of PAF.

Open-label, dose-ranging phase. Qualifying patients entered a 3-week upward titration phase to determine the maximally tolerated individual drug dose. During week 1, 100 mg (one tablet) of flecainide was administered twice a day (every 12 hours). In the absence of limiting side effects, the dose was increased during week 2 to 150 mg twice a day, and similarly, to 200 mg twice a day during week 3. No evaluation as to efficacy was to be made by the investigator during this phase, although a marked worsening in arrhythmia, in the subjective judgment of the physician and patient, was allowed to form the basis for discontinuation from further participation. Other reasons to lower or discontinue drug included a PR interval greater than 0.30 second, QRS interval duration greater than 0.18 second, second degree or greater atrioventricular block, development of symptomatic bradycardia (sinus node dysfunction), and other unacceptable cardiac or noncardiac adverse effects. On the last day of dose ranging, interval history, vital signs, 12-lead ECG, blood sample for plasma flecainide, and adverse experience summary were obtained, and the optimal dose (maximal dose not causing limiting side effects) was selected for the double-blind phase.

Double-blind, efficacy phase. After completion of dose ranging, patients advanced to a randomized, double-blind, two-period crossover phase to determine chronic efficacy. During weeks 1–8 of the efficacy phase (treatment period A), the “optimal” dose of flecainide or placebo (in random order) was administered. During weeks 9–16 (treatment period B), patients were crossed over to the alternate therapy. Early termination of treatment A or B was permitted if four separate attacks of PAF were documented to occur for that treatment in less than 8 weeks or if limiting side effects prevented a full 8-week study. To allow for adequate drug loading, the observation period for attacks was begun after three calendar days on each treatment. On the last day of each treatment period, patients were given an appointment so that history could be reviewed (including diary results), adverse events recorded, physical examination, 12-lead ECG, and routine laboratory tests performed, and blood sample for plasma flecainide determination drawn.

During the study, attacks of PAF that did not terminate spontaneously or with nonpharmacologic maneuvers (e.g., Valsalva, carotid sinus massage) were treated under medical direction with additional acute pharmacologic or nonpharmacologic therapy.

Statistics. Quantitative data presented for the demographic parameters are given as mean±1 SD. Quantitative data presented for the efficacy parameters are given as mean±1 SEM. The primary comparisons of the study included the effects of flecainide and placebo therapy on symptomatic PAF attacks during blinded therapy for the following interdependent measures: 1) number of patients having no attacks, 2) time to first attack, and 3) average time interval between attacks. A secondary comparative measure of interest was ventricular rate during attacks in patients in whom PAF was not prevented. Data from all centers and all doses were combined in the analyses. McNemar’s test for significant change12 was used to compare the number of patients who had no attacks while receiving placebo and flecainide therapy.

In determining the time to first attack and the interval between attacks, the first 3 days of each treatment period were excluded to allow for achievement of steady-state plasma drug concentrations. Day 4 of each period was defined as the first treatment day. Time to first attack was defined as the number of treatment days until the first attack. If a patient did not have any attacks during the treatment, the time to first attack was defined as the number of days of observation plus one and was considered a censored observation. To determine the interval between attacks, the number of days on treatment was divided by the number of attacks. If a patient did not have any attacks, the interval between attacks was defined to be the number of treatment days plus one and was treated as a censored observation in the data analysis.

According to the protocol, a treatment period was to end after four attacks or 8 weeks, whichever came first. However, some patients had more than four attacks or went longer than 8 weeks before crossing over to the next treatment. For those patients who went beyond 60 days during a treatment period, the length of the period was truncated to 60 days, and the time to first attack and interval between attacks were determined as previously stated. If a patient had more than four attacks, the interval between attacks was defined as the number of treatment days up to the fifth attack or 60 days, whichever came first, divided by four.

All means, standard errors, and medians presented in the summary tables are Kaplan-Meier product limit estimates13 for censored data. Comparisons between placebo and flecainide therapy were performed with the paired Prentice-Wilcoxon test14 for censored data.

To compare ventricular rates during PAF attacks for placebo and flecainide therapy, only patients
with attacks during both periods were included. The average ventricular rate during attacks was calculated separately for each patient for each treatment. The analysis of variance model, with sequence, patient within sequence, period, and treatment effects, was used to test for differences between placebo and flecainide therapy. A \( p \) value of \( \leq 0.05 \) (two-tailed hypothesis) was considered statistically significant.

**Results**

**Characteristics and Course of Study Patients**

A total of 64 patients met screening criteria, qualified for the study by experiencing two or more baseline attacks of PAF during the 4-week baseline period, signed consent, and entered the open-label, dose-ranging treatment phase. Characteristics of the 64 entering patients are summarized in Table 1. Of these (Figure 2), 55 completed dose ranging and entered treatment A of the double-blind phase, and nine were excluded (four because of cardiac adverse effects, one because of inadequate response, one because of intercurrent illness, one because of death [see below], and two for personal reasons). Of the 55 patients who entered the double-blind phase of the trial, four patients discontinued while on flecainide therapy, two during the first treatment period (one noncardiac adverse effect, one inadequate response), and two during the second treatment period (one cardiac, one noncardiac adverse effect). The two patients discontinuing flecainide therapy during double-blind treatment period B had sufficient data during both treatment periods to allow their inclusion in the efficacy analysis. Of the 53 patients who had data on both treatments in the double-blind phase, five were not evaluable because of protocol violations (i.e., use of concomitant antiarrhythmic therapy).

Characteristics of all entered patients (\( n=64 \)), patients evaluable for efficacy (\( n=48 \)), and excluded patients (\( n=16 \)) are presented and compared in Table 1. Evaluable patients were on average 56 years old (range, 23–83), and 30 (63%) were men. An excess of smokers was the only significant difference between patients excluded compared with those included in the efficacy analysis. Digitalis (digoxin) was continued for rate control of PAF during the study period in 55% of patients overall (35 of 64) and 56% of patients included in the efficacy analysis (27 of 48). Detailed reasons for premature discontinuation from the study are provided in Table 2.

In evaluable patients, PAF was associated with hypertension in 18, ischemic heart disease in 14, no demonstrable disease in 12, and a variety of other diseases or diagnoses in several patients as shown in Table 3. Paroxysmal atrial flutter was observed as an associated rhythm in nine patients with PAF.

**Flow Chart of Patient Progression in the Study**

![Flow chart showing patient progression in the study. See text for details.](http://circ.ahajournals.org/)

---

**Table 1. Demographics of Study Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Efficacy-evaluable patients</th>
<th>Efficacy-excluded patients</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>48</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56±13 (23–83)</td>
<td>60±12 (24–74)</td>
<td>57±13 (23–83)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>45</td>
<td>16</td>
<td>61</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Smokers</td>
<td>5</td>
<td>8*</td>
<td>13</td>
</tr>
<tr>
<td>Alcohol users†</td>
<td>22</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81±17 (49–122)</td>
<td>79±15 (43–101)</td>
<td>81±16 (43–122)</td>
</tr>
<tr>
<td>Digitalis therapy</td>
<td>27</td>
<td>8</td>
<td>35</td>
</tr>
</tbody>
</table>

*Intergroup comparison significant (\( p<0.05 \)).
†Almost all patients indicated their use of alcohol was social.
Among the 48 analyzed patients, previous therapeutic trials for PAF control had included a mean of 3.8 other drugs (range, 1–8). These included 71 trials of class I antiarrhythmics, 39 trials of β-blockers, 44 trials of digitalis glycosides, 25 trials of calcium entry blockers, and two trials of amiodarone. Previous drugs were described as partially effective in 54 trials, ineffective or adversely effective in 124 trials, and of unknown effect in six trials.

### TABLE 3. Associated Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Cardiovascular diagnoses</th>
<th>Efficacy-evaluable patients (n=48)</th>
<th>Efficacy-excluded patients (n=16)</th>
<th>All patients (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n) (%)</td>
<td>(n) (%)</td>
<td>(n) (%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (38)</td>
<td>6 (38)</td>
<td>24 (38)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>14 (29)</td>
<td>4 (25)</td>
<td>18 (28)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>5 (10)</td>
<td>1 (6)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Heart failure (classes I and II)</td>
<td>4 (8)</td>
<td>2 (13)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>4 (8)</td>
<td>1 (6)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>2 (4)</td>
<td>2 (13)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Sinus node disease</td>
<td>1 (2)</td>
<td>1 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Miscellaneous rhythm disorder</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Miscellaneous cardiac disease</td>
<td>7 (15)</td>
<td>1 (6)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>None</td>
<td>12 (25)</td>
<td>7 (44)</td>
<td>19 (30)</td>
</tr>
</tbody>
</table>

Patients could have more than one associated disorder. Values given are number of patients; values in parentheses are percent.

### TABLE 4. Electrocardiographic Effects of Flecainide Therapy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Screening phase</th>
<th>Change (Δ) from baseline during therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Dose-ranging phase</td>
</tr>
<tr>
<td>Ventricular rate (beats/min)</td>
<td>69±12 (57)</td>
<td>0±9 (48)</td>
</tr>
<tr>
<td>Atrial rate (beats/min)</td>
<td>67±11 (52)</td>
<td>1±7 (43)</td>
</tr>
<tr>
<td>PR interval (sec)</td>
<td>0.18±0.03 (52)</td>
<td>0.03±0.04† (44)</td>
</tr>
<tr>
<td>QRS interval (sec)</td>
<td>0.08±0.02 (57)</td>
<td>0.02±0.02† (47)</td>
</tr>
<tr>
<td>QTc interval (sec)</td>
<td>0.41±0.04 (55)</td>
<td>0.02±0.05† (46)</td>
</tr>
</tbody>
</table>

Values are mean±SD (n).
*Significantly different from placebo (p<0.05, analysis of variance for a two-period crossover design).
†Statistically significant change from baseline (p<0.05, two-tailed t test).
was explained by the increment in QRS. Similar differences during flecainide therapy were also observed in the double-blind phase.

Correlation of Symptoms and Arrhythmias

The study plan instructed patients to call the monitor nurse or technician (Heart Systems, Inc.) routinely at specified intervals as well as for every significant symptomatic event that might be related to a cardiac arrhythmia. A total of 2,375 transtelephonic rhythm strips and accompanying symptom reports was logged. Of these, 1,314 (55.3%) represented symptomatic calls and 1,061 (44.7%), asymptomatic (routine) calls.

A strong correlation was found between symptoms reported at the time of the monitoring calls and cardiac arrhythmias documented transtelephonically during the same call. Of symptomatic calls, 69.2% \((n=909)\) were accompanied by documented attacks of PAF as compared with 10.6% of asymptomatic calls \((n=112)\) \((p<0.0001)\). Sensitivity for PAF of a symptomatic call is 89%, specificity 70%, positive predictive value 69%, and negative predictive value 89%. An additional 18.3% \((240 \text{ calls})\) were associated with other rhythm disorders thought likely to cause symptoms (e.g., sinus tachycardia, frequent premature atrial, and frequent premature ventricular complexes). Thus, symptomatic calls were predictive of an accompanying rhythm change 87.5% of the time.

The predictive value of five specific symptoms for PAF attacks in our population was especially good (associated with PAF on 70% or more of calls). These symptoms included palpitations (78% predictive), dizziness (77%), dyspnea (76%), tachycardia (73%), and diaphoresis (79%). (Patients often reported more than one symptom during calls.)

Efficacy Results

Time to first attack. A Kaplan-Meier estimate of the time to first attack is presented in Figure 3 and demonstrates a highly significant difference \((p<0.001)\) between flecainide and placebo treatments. The median time to first attack was extended fivefold, from 3 days on placebo to 14.5 days on flecainide therapy (corresponding mean times to first attack, censored at 60 days, were more than 7.6±1.2 days and more than 17.9±2.2 days, respectively). Individually, 20 patients had substantial increases in time to first attack, three had decreases, and 25 had minor or no change (Figure 4).

Because three patients dropped out during dose ranging due to an “inadequate” or “adverse” response of PAF to therapy and were not formally evaluated for efficacy, a separate “intention-to-treat” analysis was made assuming a worst-case scenario. For this analysis, it was arbitrarily assumed that these three patients would have experienced an attack on the first day of active therapy but would have completed 60 days of placebo without PAF recurrence (however unlikely). The results of this
placebo to 27.0 days during flecainide therapy. (Corresponding mean time between attacks, censored at 60 days, was 14.8±2.7 days and more than 31.7±3.3 days, respectively.) Individually, 21 patients had substantial increases in the time between attacks, three had decreases, and 24 had minor or no changes (Figure 6).

**Patients free of paroxysmal atrial fibrillation.** During the 8-week observation periods, only four patients (8%) experienced no attacks of PAF while on placebo, whereas 15 patients (31%) were attack-free on flecainide therapy. This more than threefold increase was statistically significant (p=0.013).

**Ventricular rate during paroxysmal atrial fibrillation.** The average ventricular rate was compared for the 30 patients experiencing PAF attacks during both treatment periods. (Rates were determined by 1-minute rhythm strip counts for each episode and averaged for all episodes on each therapy.) Overall, ventricular rate averaged 123±4 beats/min (range, 83–175) on placebo and 118±4 beats/min (range, 81–150) on flecainide. The mean reduction in rate on flecainide, although small (5 beats/min), was significant (p=0.017). Individual results are shown in Figure 7. Although reductions in ventricular rate with therapy appeared to be greater in those with initially faster rates, interpretation and clinical extrapolation of this finding should be made with caution because of the statistical phenomenon of regression toward the mean.

Rates were also compared during attacks for those who were and were not receiving concomitant digoxin therapy. For those taking digoxin (n=15), ventricular rates during PAF averaged 120±6 beats/min on placebo and 112±4 beats/min on flecainide therapy. For those not taking digoxin (n=15), rates were 128±6 beats/min on placebo and 124±5 beats/min on flecainide therapy. No significant interaction effect for the use of digoxin on the overall result was seen. Rates tended to be lower with the concomitant use of digoxin, but the difference did not reach significance.

**Effects of therapy on symptoms.** Because therapy for PAF is given primarily for reduction of symptoms, treatment effects on symptoms per se are of independent interest. Comparisons were thus made between active and placebo therapies of the frequency of symptoms severe enough to warrant a call in during the double-blind phase. As shown in

---

**FIGURE 5.** Line graph showing time intervals (days) between attacks of paroxysmal atrial fibrillation in 48 patients, given as cumulative proportion of intervals between attacks at each time, censored at 60 days (end of double-blind phase). Solid line, flecainide therapy; dashed line, placebo therapy. Graph shows a product-limit estimate. Interval for patients who went the entire treatment period without having an attack was estimated as days on treatment+1, and the observation was classified as censored.

**FIGURE 6.** Graph showing days between attacks on each treatment plotted for each patient (n=48). p=0.001 by paired Prentice-Wilcoxon test for censored data.

**FIGURE 7.** Graph showing effect of therapy on rate of ventricular response during paroxysmal atrial fibrillation (PAF) for individual patients, together with group mean (±SEM). Only patients with attacks of PAF during both treatment periods are included (n=29). p≤0.017 for comparison between treatment groups.
Table 5, significant reductions were observed in the number of patients reporting one or more occurrences of palpitations or dyspnea, and increases were noted in the intervals between symptoms of palpitations, tachycardia, dyspnea, and chest pain. Thus, parallel reductions in PAF and associated symptoms were observed.

Adverse Effects

Subjective adverse reactions. During the drugtitration period, when the entire range of doses was explored (200–400 mg), the majority of patients (80%) noted at least one subjective complaint (Table 6): 47% experienced visual abnormality (e.g., blurred vision, difficulty accommodating); 42%, dizziness or lightheadedness; 14%, nausea; 13%, headache; 11%, fatigue; 8%, tremor; and 8%, dyspnea. A variety of other miscellaneous complaints were experienced by a small minority (less than 8%). Because these observations were unblinded and uncontrolled, the true proportion of these complaints attributable to drug, especially those occurring infrequently, was difficult to assess.

The incidence of common subjective complaints occurring during the double-blind phase on flecainide and placebo therapy is presented in Table 7. A significant excess of visual symptoms was observed during flecainide therapy (27% vs. 8%) and a trend toward more dizziness or lightheadedness (20% vs. 11%). Other adverse effects occurred approximately equally on the two therapies and in a small minority of patients (10% or less). Noncardiac adverse effects attributable to flecainide during the double-blind phase were generally mild and tolerable; these noncardiac adverse effects required discontinuation of drug in only two patients.

Cardiac adverse experiences. Therapy with flecainide was discontinued in four patients during the dose-ranging phase and in one additional patient early during treatment period B because of cardiac adverse experiences. Adverse rhythm effects (“proarrhythmia”), identified clinically by the investigator, were observed in three patients (5%) and consisted of prolonged duration/severity (n=3) or increased frequency of PAF (n=2). These effects led to discontinuation of drug during the dose-ranging phase in two and during double-blind ther-

Table 6. Possible Side Effects Reported During Dose Ranging Among 64 Patients

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Patients* (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual abnormality</td>
<td>30 (47)</td>
</tr>
<tr>
<td>Dizziness/lightheadedness</td>
<td>27 (42)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Tremor</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Misc (≤3 per complaint)</td>
<td>36 (63)</td>
</tr>
<tr>
<td>None</td>
<td>13 (20)</td>
</tr>
</tbody>
</table>

*Patients could report more than one adverse reaction.
TABLE 7. Adverse Reactions During Double-Blind Therapy

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo (n=53)</th>
<th>Flecainide (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual abnormality</td>
<td>4 (8)</td>
<td>15 (27)*</td>
</tr>
<tr>
<td>Dizziness or lightheadedness</td>
<td>6 (11)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (6)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (11)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (6)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (9)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (9)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Tremor</td>
<td>0 (0)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>3 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Misc (37 entries) (≤2 complaints per treatment)</td>
<td>25 (. . .)</td>
<td>31 (. . .)</td>
</tr>
<tr>
<td>None</td>
<td>33 (62)</td>
<td>23 (42)*</td>
</tr>
</tbody>
</table>

Values given are number of reactions and percent. *Significant intergroup difference, p<0.05.

Study Summary and Implications

This trial applied a novel technology (transtelephonic ECG monitoring) and a novel design to the study of paroxysmal supraventricular tachyarrhythmias 1) to investigate the natural history of PAF (during placebo therapy), 2) to correlate perceived symptoms with documented paroxysmal arrhythmias during daily living, and 3) to evaluate the effects of therapy on occurrence of arrhythmia and related symptoms. In our patients, symptoms were good predictors of a rhythm disorder, which was demonstrated on simultaneous transtelephonic monitoring in 88% of calls (PAF was present in 69%). About 75% of calls with one or more of five associated symptoms—palpitations, tachycardia, dyspnea, diaphoresis, and dizziness—were found to be accompanied by PAF.

Efficacy. Flecainide, a class 1C drug not yet approved for a supraventricular arrhythmia indication, was selected for investigation in this study, and four interrelated outcome variables were measured to assess its therapeutic effects: 1) time to first symptomatic attack of PAF, 2) average time between symptomatic attacks, 3) number of patients free of symptomatic attacks during a 60-day follow-up period, and 4) heart rate during PAF. All four variables were improved by treatment (median dose, 300 mg/day): The median time to a first attack of PAF was increased about fivefold, from 3 days on placebo to 14.5 days on flecainide therapy, and the median interval between attacks increased four- to fivefold, from 6.2 days to 27.0 days. During the 8-week blinded periods, 15 patients (31%) were free of symptomatic PAF on flecainide compared with four (8%) on placebo therapy. When PAF occurred, the average ventricular rate was reduced from 123±4 on placebo therapy to 118±4 beats/min by treatment with flecainide. Finally, the frequency of arrhythmia-associated symptoms was reduced, including palpitations, tachycardia, dyspnea, and chest pain. The study did not evaluate treatment effects on duration of PAF, because the event monitor/recorder does not usually capture the exact onset and offset of attacks. Patients did not generally complain of an increased symptom duration, however, except for three, in whom therapy was discontinued as described below.

Adverse effects. Flecainide was usually well tolerated subjectively at a median dose of 300 mg/day. Visual symptoms and lightheadedness were observed more frequently during flecainide than placebo, but only two patients required discontinuation of therapy because of these noncardiac adverse effects.

Flecainide,15,16 like other antiarrhythmics,17,18 is known to have proarrhythmic potential. Thus, cardiac adverse effects deserve careful scrutiny. In our PAF patients, seven cardiac adverse effects on rhythm, conduction, or automaticity were observed. No new heart failure occurred, although functional class III and IV patients were excluded. Proarrhythmia was reported in three patients (in two during initial dose titration) and was manifested as supraventricular tachycardia (paroxysmal atrial fibrillation or flutter) of longer duration or greater frequency.

Discussion

Study Summary and Implications

This trial applied a novel technology (transtelephonic ECG monitoring) and a novel design to the
Attributing increases in arrhythmia frequency to a proarrhythmic effect of drug rather than to chance alone in individual cases assessed over brief time periods is difficult if not impossible to do with statistical certainty. Ventricular arrhythmias are subject to substantial variability in spontaneous frequency over time. Proarrhythmia was thus defined subjectively as an increase in arrhythmia and its associated symptoms of a degree, judged by the clinical investigator, to be unacceptable for continuation of drug.

Although the numbers are small, the 5% incidence of supraventricular proarrhythmia in PAF patients may be compared with the 3–7% average incidence of ventricular proarrhythmia reported during flecainide therapy of ventricular arrhythmia and to the range of ventricular proarrhythmia rates of about 3–15% for other antiarrhythmics given to patients with malignant or potentially malignant ventricular arrhythmias.

Significant automaticity disturbance, manifested as bradyarrhythmia, was also observed in three (5%) of our patients. Antiarrhythmic agents in general, and flecainide specifically, have known potential to exacerbate conduction problems, particularly in predisposed patients with preexistent disease. Thus, excluding those with PAF associated with sinus or atrioventricular node disease (bradycardia/tachycardia variant of sick sinus syndrome) was important to the selection of patients for the present study and will be important for the safe clinical application of flecainide therapy for PAF. Even so, in retrospect one patient in whom bradycardia developed had a latent form of sick sinus syndrome and has subsequently received a pacemaker.

One primary episode of ventricular tachycardia was documented after therapy with catecholamines for extreme bradyarrhythmia; it resolved spontaneously with observation. The cardiac arrest leading to death in one patient with ventricular ectopy is also of concern; although the circumstances suggest the possibility of subendocardial injury as a precipitant mechanism, a proarrhythmic event (i.e., drug-related ventricular tachycardia) must also be considered. Thus, although our study suggests that the risk of ventricular proarrhythmia in the PAF population is probably lower than in patients with ventricular arrhythmias, observations in larger groups of patients, including those with mixed atrial and ventricular arrhythmias, and with organic (especially ischemic) versus idiopathic disease, will be required to adequately define this risk.

Safety Concerns Raised by Cardiac Arrhythmia Suppression Trial and Other Studies

Concern about the proarrhythmic potential of flecainide in patients with non–life-threatening arrhythmias is further raised by the recent Cardiac Arrhythmia Suppression Trial (CAST). In CAST, patients with generally asymptomatic ventricular arrhythmias and a recent history of myocardial infarction were randomized to treatment with one of three antiarrhythmic drugs or matching placebos to assess mortality effects. The encainide and flecainide limbs (both class 1C drugs) were recently stopped prematurely because of an excess in total and sudden death mortality. In a preliminary report, among 1,455 patients treated with encainide, flecainide, or matching placebos for a mean of 10 months, rates of death or cardiac arrest were 7.7% in active versus 3.0% in placebo-treated patients. The findings of CAST suggest that further careful considerations of safety will be required before approval by the Food and Drug Administration of flecainide’s use in PAF can be expected.

Concern has also been recently raised by reports of ventricular tachycardia or fibrillation induced by extreme exercise in patients treated with flecainide for rate control in chronic atrial fibrillation. One mechanism of this effect may be amplification of flecainide-induced ventricular conduction slowing by exercise and tachycardia, shown recently by Ranger et al. It has been suggested that exercise testing be used to screen for possible proarrhythmic effects of therapy, especially in physically active patients, before embarking on long-term therapy.

Flecainide remains experimental in its application for paroxysmal supraventricular tachycardia or PAF. In making a decision to initiate drug therapy for PAF, the efficacy of flecainide demonstrated in this study must be considered in light of the uncertain risk of serious proarrhythmic events raised by CAST, other studies, and the one death in our study. Patients with chronic atrial fibrillation should not be treated. Patients may be at particular risk if they have a history of myocardial infarction and possibly other manifestations of ischemic disease (e.g., angina) and ventricular arrhythmias in addition to PAF. In these patient groups, it appears prudent to avoid flecainide except for life-threatening ventricular tachyarrhythmias shown to be drug responsive.

Rationale for the Study Design

The design for this study was based on previous observations regarding the behavior of paroxysmal supraventricular tachycardia and the assumption that PAF would behave similarly as well as general principles of clinical trial design requiring prolonged observations of each patient. These previous studies established that the successive occurrences of paroxysmal supraventricular tachycardia were uncorrelated (or clinically independent) and that the time periods between attacks fit an exponential probability distribution. Systems in which the intervals between events fit this particular probability distribution are often called “Poisson processes.” In a Poisson process, the probability of an event (such as an attack of PAF) occurring during a specified time interval is independent of when the preceding event occurred. In the current clinical trial, we capitalized on this principle in
being able to use a crossover design. Using a crossover design was important for two reasons. First, it reduced the number of patients required; PAF is a relatively uncommon problem compared with other cardiac disorders (e.g., hypertension or heart failure) in which treatment may be easily studied with parallel designs. Second, the crossover design was useful in reducing variability in the outcome measure; intersubject variability in the occurrence of paroxysmal arrhythmias is high.

Previous studies of paroxysmal supraventricular tachycardia were used to develop the qualifying criterion of two attacks of PAF in 30 days for entry into the study. These earlier studies predicted that patients meeting this criterion would have a high probability of having at least one attack of tachycardia during the placebo treatment period, which was an important requirement for assessment of efficacy outcome. In the current study, 41 of 44 patients had at least one attack during the placebo treatment period. Previous experience also predicted that approximately 45% of patients who were screened would qualify for study using an entry requirement of two attacks in 30 days. This fraction of qualifiers was judged reasonable for allowing recruitment of a sample of adequate size for efficacy assessments. Recruitment results and natural history observations in this study during untreated periods confirm and extend these and other initial assessments of PAF behavior.

Other Studies of Flecainide for Paroxysmal Atrial Fibrillation

Earlier studies with intravenous and oral flecainide therapy in supraventricular arrhythmias have indicated therapeutic promise in supraventricular tachyarrhythmias. Flecainide has been successful in terminating atrial fibrillation of recent onset in about two thirds of reported cases and has been efficacious for prophylactic long-term therapy in a similar percentage; therapy for atrial flutter has given less successful results. Goy and colleagues administered intravenous followed by oral flecainide to 69 patients with atrial fibrillation and observed restoration of sinus rhythm in 49 (71%). Higher conversion rates were observed with atrial fibrillation of shorter duration (less than 10 days) and in patients with smaller atria. In a smaller series, Hellestrand observed a similar high conversion rate of recent onset atrial fibrillation (7 of 9, 78%) but found atrial flutter to be less responsive (2 of 9, 22%). Chouty and Coumel found flecainide to be active for therapy of atrial fibrillation ascribed to a vagally mediated mechanism.

Comparisons of Flecainide With Other Therapies of Paroxysmal Atrial Fibrillation

Digitalis glycosides, β-blockers, and verapamil have been frequently used acutely and chronically to control the rate of ventricular response during atrial fibrillation but are regarded as poorly effective for conversion and prophylaxis. Traditional prophylactic antiarrhythmic therapy thus has included quinidine or related class 1A agents. However, these drugs are often ineffective or cause intolerable noncardiac (e.g., diarrhea, rash) and cardiac (e.g., torsades de pointes proarrhythmia) adverse effects. As a result, symptomatic patients with PAF often go untreated or are inadequately treated. Assuming that adverse effects (especially noncardiac side effects) are similar for those with supraventricular and ventricular arrhythmias, class IC agents (e.g., flecainide, encainide) may be better tolerated long-term than other available agents used for atrial fibrillation, including the traditional agents in class 1A (i.e., quinidine, procainamide, disopyramide) and amiodarone.

Limited actual trial information is currently available comparing flecainide with other drugs in treating atrial fibrillation, but these studies suggest generally favorable relative efficacy and tolerance for flecainide. In a parallel-design German study, 45 patients with PAF were randomly given therapy with oral digoxin alone (0.25–0.5 mg/day), or combined with quinidine sulfate (750–1,000 mg/day) or flecainide (200–300 mg/day). During a mean follow-up of 11 months, digoxin was less effective than the combined therapies (p<0.05), and flecainide with digoxin was more effective than the other two regimens (p<0.05). Adverse effects occurred significantly more often with quinidine (n=8) than digoxin (n=2) or flecainide (n=2).

The usefulness of propafenone, another class 1C antiarrhythmic, for prevention of recurrent PAF was recently reported in a small series by Connolly and Hoffert. Of 18 eligible patients, seven withdrew during dose ranging, four because of inadequate efficacy or poor compliance, two because of intolerable side effects, and one because of sudden death (on placebo). During a 2-month, double-blind crossover phase in 11 patients, PAF occurred during 27% of propafenone treatment days versus 51% of placebo days (p<0.01). Three patients (27%) had no attacks during propafenone therapy. Side effects, generally tolerable, were reported more commonly with propafenone (29 versus 11 complaints). Flecainide proved useful in replacing or supplementing amiodarone in 40 refractory patients with “vagally induced” PAF in one French study. PAF was controlled with flecainide in 32 patients, given alone in 11, and in combination with reduced doses of amiodarone in 21.

Additional comparative experience is available from acute intervention studies. Suttrop et al compared intravenous flecainide (2 mg/kg/10 min) to verapamil (10 mg/1 min) for acute conversion of sustained episodes of PAF to sinus rhythm. Conversion occurred within 1 hour in 82% (14 of 17) of patients after flecainide versus 6% (1 of 17) after verapamil (p<0.0001). Borgeat et al compared flecainide and quinidine for pharmacologic conversion of atrial fibrillation of variable duration to sinus
rhythm. In a consecutive series of 60 patients, conversion occurred in 20 (67%) in the flecainide group and 18 (60%) in the quinidine group. If atrial fibrillation was present for less than 10 days, the conversion rates were 86% (18 of 21) and 80% (12 of 15), respectively. Adverse effects attributed to drug occurred in two flecainide and eight quinidine patients.

Limitations of the Study

The study design, by employing an initial open-label drug titration and tolerance phase, limits conclusions of the efficacy comparison between flecainide and placebo therapy to patients initially able to tolerate antiarrhythmic therapy without limiting noncardiac or cardiac adverse effects and whose response could be evaluated in both double-blind treatment periods. However, an inadequate or adverse response of PAF was a reason for exclusion from double-blind evaluation in only three (4.7%), and none were excluded from entering the blind-evaluation phase because of initial noncardiac adverse effects. Based on both indirect (summary information) and direct comparisons of side effect potential for flecainide and other agents, it appears that traditional antiarrhythmic drugs are not as well tolerated initially. Further, inclusion of these three dropout patients in a "worst case" intention-to-treat analysis still gave a statistically significant comparison versus placebo for times to PAF attacks.

The study design we used is efficient and mimics the usual clinical approach to patient management; patients are first challenged with drug and only those who are initially tolerant are continued into long-term therapeutic testing. The ongoing CAST is testing the potential of therapy for ventricular antiarrhythmias to reduce sudden death. This National Institutes of Health–sponsored trial has also employed an open-label drug titration phase preceding a double-blind, placebo-controlled efficacy phase. The reasons for this design, as in our study, include the greater statistical power afforded the efficacy comparison (by prospectively eliminating treatment-intolerant patients who contaminate an intention-to-treat analysis) and the closer correspondence to a clinical practice approach.

The study design does not allow determination of a minimum effective drug dose, which would have complicated study analysis. Rather, patients were titrated, by protocol, to a maximally tolerated dose or to 400 mg/day. Thus, the efficacy and side effect comparisons we observed represent those in a nearly maximally dosed population. (The question of minimum dose is being addressed in a separate study.)

Because not all patients experienced episodes of PAF during the 8-week blinded observation period, mean values represent a product-limit estimate rather than exact averages of times of first PAF attack and intervals between attacks. However, life-table analysis provides an accurate comparison of responses and shows a clear difference between the two groups for the 2-month observation period. Also, the median times are exact values and allow estimates by treatment of relative PAF recurrence times.

Other limitations of the study should be borne in mind. The study endpoint was symptomatic events rather than Holter-monitored arrhythmia frequency. Effects of therapy on frequency of asymptomatic arrhythmias and isolated atrial ectopy were not assessed. However, symptomatic endpoints are more relevant to the clinical goals of therapy (i.e., patient comfort and sense of well-being) than is asymptomatic ectopy. Quantification and confirmation of symptomatic events transtelephonically is also an easier and more efficient method for long-term evaluation of response than is ambulatory (Holter) monitoring repeated at frequent intervals. Symptoms were shown to be good predictors of arrhythmia occurrence in our study.

Patients with many disease processes causing atrial fibrillation secondarily were excluded, including those with advanced or untreated valvular disease, conduction system disease (e.g., sick sinus syndrome, higher grades of atrioventricular block), recent myocardial infarction or cardiac surgery, and heart failure. It is not known whether flecainide can be given safely and effectively to selected patients with any of these disease exclusions. (The CAST study suggests continued exclusion of the myocardial infarction group.) On the other hand, our patients were a medically resistant group that had tried multiple other medications (average, 3.8) without adequate success; efficacy in a therapeutically more virgin population may have been greater. Although PAF attacks were substantially reduced, they were not eliminated in the majority (69%) of patients. Finally, the risk of adverse cardiac events (11% in our population) requires further evaluation, particularly because one of the adverse events was an arrhythmic arrest.

In summary, a new study design and method have been applied to the evaluation of the natural history of a common, problematic arrhythmia, symptomatic PAF, and its therapy with a new agent, flecainide. By using the endpoint of symptomatic clinical events as documented by a transtelephonic monitoring system, the course of PAF and the therapeutic benefit and net adverse potential of flecainide have been quantified within a double-blind, randomized, crossover design. Flecainide provides active therapy for PAF, increasing time between attacks by over fourfold and eliminating attacks in one third of patients tolerating initial drug dosing. Tolerance is good but cardiac adverse events occurred in 11%, including one death. This, plus the findings of CAST and other studies, suggests the importance of a careful risk/benefit ratio assessment before considering the use of flecainide in PAF.
Appendix

The U.S. Flecainide Supraventricular Tachycardia Study Group included the following centers and individuals: Western Pennsylvania Hospital, Pittsburgh, PA: Barry L. Alpert, MD, Connie M. Feck, BSN, RN; University of Utah, LDS Hospital, Salt Lake City, UT: Jeffrey L. Anderson, MD, E. Michael Gilbert, MD, Linda Johnson, RN, Marian Bartholomew, BS; University of Alabama, Birmingham, AL: Albert L. Waldo, MD, Richard W. Henthorn, MD, Donna Kerns, RN; Los Angeles County-University of Southern California Medical Center, Los Angeles, CA: Anil K. Bhandari, MD, Shahbudin H. Rahimtoola, MD, Judith Clarke, RN, Cheryl Leon, RN; Henry Ford Heart & Vascular Institute, Detroit, MI: Charles R. Webb, MD, Karen Bielinski, RN; Winchester, VA: James C. Laidlaw, MD, Linda Stollings, RN; The Graduate Hospital, Philadelphia, PA: Leonard N. Horowitz, MD, Joel Morganroth, MD, Shiela Senior, RN, Louise Hertzog, RN; Vanderbilt University School of Medicine, Nashville, TN: Raymond L. Woosley, MD, Mark D. Lineberry, MD, Christian Funck-Brentano, MD, Leslie Jared, RN, MSN; University of California, Los Angeles Medical Center, Ventura, CA: William L. Hart, MD, Newton J. Friedman, MD, Suzanne Neumann, RN; Jewish Hospital at Washington University, St. Louis, MO: Rodolphe Ruffy, MD, Roop Lal, MD, Eugenia Newport, RN, Jill Newgent, RN; Duke University Medical Center, Durham, NC: Edward L.C. Pritchett, MD, Elizabeth A. McCarthy, RN; University of Western Ontario, London, Ontario, Canada: George J. Klein, MD, Arjun D. Sharma, MD, Raymond Yee, MD, Caro Norris, RN; University of Virginia Medical Center, Charlottesville, VA: John DiMarco, MD, Ginny Berry, RN; Montreal General Hospital, Montreal, Quebec, Canada: Michael Rosengarten, MD, University of Texas Health Science Center, Dallas, TX: Michael D. Winniford, MD, L. David Hillis, MD, Suzie Murray, RN; Massachusetts General Hospital, Boston, MA: Jeremy Ruskin, MD; University Hospital, Ontario, Canada: George Klein, MD; Riker Laboratories, Inc., St. Paul, MN: Michael Cullen, MD, Patricia A. Fredell, Ronald W. Hawkinson, Andrina J. Hougham, Dan M. Jolivette, MD, Mary Jane Maser, Sally E. McCarrville, Inara Porietis, Judith A. Sellers, RN, Richard R. Wilson, MD.

References


**KEY WORDS** • atrial fibrillation • clinical trials • flecainide • arrhythmias

J L Anderson, E M Gilbert, B L Alpert, R W Henthorn, A L Waldo, A K Bhandari, R W Hawkinson and E L Pritchett

_Circulation_. 1989;80:1557-1570
doi: 10.1161/01.CIR.80.6.1557

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/80/6/1557