Continuous vs Episodic Prophylactic Treatment With Amiodarone for the Prevention of Atrial Fibrillation
A Randomized Trial

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Atrial fibrillation is not a benign disease. It may cause symptoms, heart failure, and stroke. Recent studies have established that morbidity and mortality are comparable between rate- and rhythm-control therapy. However, long-term maintenance of sinus rhythm provides a variety of benefits, including an improvement in cardiac function and quality of life. Therefore, maintenance of sinus rhythm is still the treatment of choice in symptomatic patients, those with tachycardiomypathy, and when adequate rate control cannot be achieved. However, success of pharmacological rhythm control is rather limited. With a serial antiarrhythmic drug approach, no more than 40% of the patients are in sinus rhythm after a year and only about 30% after 4 years. Of all class I, II, and III antiarrhythmic drugs, amiodarone is the most effective antiarrhythmic drug in preventing atrial fibrillation. Amiodarone maintains sinus rhythm in 45% to 70% of the patients during 12 to 34 months of follow-up. Unfortunately, amiodarone causes many (noncardiac) adverse events, which are mostly

Context Amiodarone effectively suppresses atrial fibrillation but causes many adverse events.

Objective To compare major events in patients randomized to receive episodic amiodarone treatment with those who received continuous amiodarone treatment while still aiming to prevent atrial fibrillation.

Design, Setting, and Participants A randomized trial of 209 ambulatory patients with recurrent symptomatic persistent atrial fibrillation, conducted from December 2002 through March 2007 at 7 Dutch medical centers.

Intervention Patients were randomly assigned to receive either episodic or continuous amiodarone treatment after electrical cardioversion following amiodarone loading. Episodic amiodarone treatment was discontinued after a month of sinus rhythm and reinitiated if atrial fibrillation relapsed (1 month peri–electrical cardioversion). In the continuous treatment group amiodarone was maintained throughout.

Main Outcome Measures The primary end point was a composite of amiodarone and underlying heart disease–related major events. The secondary end points were all-cause mortality and cardiovascular hospitalizations.

Results After a median follow-up of 2.1 years (range, 0.4–2.5 years), 51 (48%) of those receiving episodic treatment vs 64 (62%) receiving continuous treatment had sinus rhythm (P = .05). There were 85 atrial fibrillation recurrences (80%) among the episodic treatment group vs 56 (54%) in the continuous treatment group (P < .001). No significant difference existed in the incidence of the primary composite end point between each group (37 [35%] episodic vs 34 [33%] continuous; incidence rate difference, 0.2; 95% confidence interval [CI], −10.2 to 10.6). However, there were nonstatistically significant differences in the incidence of amiodarone–related major events (20 [19%] episodic vs 25 [24%] continuous; incidence rate difference, −2.0; 95% CI, −8.7 to 4.6) and underlying heart disease–related major events (17 [16%] episodic vs 9 [9%] continuous; incidence rate difference, 3.6; 95% CI, −1.6 to 8.7). All-cause mortality and cardiovascular hospitalizations were higher among those receiving episodic treatment (56 [53%] vs 35 [34%], P = .02).

Conclusions In this study population, there was no difference in the composite of amiodarone and cardiac major adverse events between groups. However, patients receiving episodic treatment had a significantly increased rate of atrial fibrillation recurrence and a significantly higher rate of all-cause mortality and cardiovascular hospitalizations.

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associated with high daily dosages and long-term therapy, but does not increase mortality in patients with heart failure and ischemic heart disease. Efforts to reduce the adverse event rate by using low-dose amiodarone (≤400 mg/d after adequate loading) suggest that they still may occur. Short-term therapy, however, may be more effective in reducing the occurrence of adverse events. The present randomized, prospective study compares the effects of episodic amiodarone treatment vs continuous amiodarone treatment, first, on major events related to amiodarone use and the underlying heart disease and, second, on all-cause mortality and cardiovascular hospitalizations. It is our hypothesis that episodic treatment peri-cardioversion is associated with a lower adverse event rate than continuous treatment while atrial fibrillation is still effectively suppressed.

**METHODS**

**Study Design**

Seven centers in the Netherlands participated in the study. The institutional review boards at each institution approved the study protocol, and all patients gave written informed consent. The study was conducted from December 2002 until March 2007. Mean follow-up was 1.5 years with a maximum of 2.5 years. Enrollment is shown in Figure 1.

Patients were included if they experienced recurrence of symptomatic persistent atrial fibrillation or atrial flutter with a duration of less than a year, a heart rate of more than 75/min, and if they were taking oral anticoagulation therapy for at least 2 weeks. This guarantees at least 6 weeks of anticoagulation therapy, as patients are loaded with amiodarone 4 weeks before electrical cardioversion (Figure 1). Patients were deemed to be symptomatic if they reported such events as palpitations, dyspnea, and fatigue due to atrial fibrillation or atrial flutter, which was defined as non-self-terminating atrial fibrillation or atrial flutter requiring electrical cardioversion to obtain sinus rhythm. Excluded were patients with more than 3 relapses of persistent atrial fibrillation during the last 3 years, amiodarone use in preceding 3 months, history of relapse of atrial fibrillation under adequate (desethyl) amiodarone levels, New York Heart Association class III or IV heart failure, contraindications for amiodarone, history of thyroid dysfunction, concomitant treatment with class I or III antiarrhythmic drugs, known sick sinus syndrome, second- or third-degree atrioventricular block, or a pacemaker. Patients were seen at the outpatient department at inclusion, after 2 weeks of amiodarone loading, and at 1, 4, 8, 12, 16, 20, and 24 months after randomization. At screening, hemoglobin, sodium and potassium serum levels, renal function, liver functions, thyroid functions, and glucose levels were measured. Furthermore, a chest x-ray and a transthoracic echocardiogram were done. After 2 weeks of amiodarone loading, an electrocardiogram and a 24-hour Holter monitor were obtained to assess rate control. Rate control medication was halved if deemed necessary. At each visit, complaints were recorded, physical examination was performed, a 12-lead electrocardiogram was recorded, and blood samples were taken for laboratory test results. (Desethyl)amiodarone serum levels were assessed at each follow-up visit. Chest x-rays were repeated every 8 months. All amiodarone or underlying heart disease–related major events were recorded as an end point on a special form. After documentation of a (nonfatal) end point, follow-up was continued to document additional end points.

After taking 600 mg of amiodarone daily for the 4-week loading period, patients underwent an electrical cardioversion if they had not already converted chemically to sinus rhythm (Figure 1). The protocol for electrical cardioversion was described previously. In short, patients underwent an electrical cardioversion under general anesthesia and all shocks were applied to the chest in an anterior-lateral paddle configuration. Immediate outcome of the shock was monitored by...
continuous 12-lead electrocardiogram and rhythm monitoring during 4
hours by telemetry. Thereafter, patients were randomly assigned to re-
ceive either episodic or continuous amiodarone treatment. After cardio-
version, amiodarone was lowered to a maintenance dose of 200 mg daily.
Amiodarone was discontinued in the episodic treatment group 4 weeks af-
ter randomization and was restarted a month before and continued a month
after cardioversion if atrial fibrillation had relapsed. Amiodarone treatment
was maintained for those in the con-
tinuous treatment group. Patients ex-
periencing recurrence in either group
were reloaded with 600 mg of amio-
darone daily for 4 weeks if the sum of their
amiodarone and desethylamiodarone
serum levels was lower than 1 mg/L or
for 2 weeks if the sum was lower than
2 mg/L. Patients in both groups were
subsequently scheduled for an electri-
cal cardioversion. In case the sum of
the levels was more than 2 mg/L, which
are considered to be adequate
(developed)amiodarone serum levels, si-
nus rhythm was no longer pursued and
atrial fibrillation was accepted (ie, per-
manent atrial fibrillation), unless re-
currences under adequate serum lev-
els occurred after 6 months or more of
maintained sinus rhythm. In that case,
electrical recardioversion was deemed
to be reasonable. Otherwise, amio-
darone therapy was discontinued perma-
nently and rate control was instituted
if needed. During reloading with a
higher daily amiodarone dose, rate con-
rol medication was lowered if needed.
Patients were followed up until study
completion.

All patients were taking oral anti-
coagulation (acenocoumarol or fen-
procoumon, target international
normalized ratio [INR], 2.5 to 3.5) con-
tinuously. Careful surveillance was
maintained because amiodarone is
known to reinforce the anticoagulant
effect of acenocoumarol and fenprocou-
mon.1 The thrombosis service was no-
tified when the patient was included in
this study. Furthermore, patients were
instructed to notify the thrombosis
service if there was a change in daily
amiodarone dose so that their dosage of
oral anticoagulation could be adapted ac-
cordingly to ensure adequate anticoagu-
lation.

**End Points**

**Primary End Point.** Primary end point consisted of amiodarone and under-
lying heart disease–related major adverse events. The major events that were
associated with amiodarone included cardiovascular effects; hyperthyroid-
ism and hypothyroidism; pulmonary and hepatic toxicity; and dermatologi-
cal, ophthalmologic, neurological, and gastrointestinal tract effects. Cardio-
vascular effects were defined as symp-
tomatic sinus bradycardia with a heart
rate lower than 40/min, sinus arrest
longer than 4 seconds, atrioventricu-
lar conduction disturbances necessi-
tating pacemaker implantation, or
ventricular proarhythmia. Thyroid dys-
function could be clinical, biochemi-
cal, or both. Biochemical hyperthyroid-
ism was defined as thyroid-stimulating
hormone (TSH) levels 50% below the
lower limit and free thyroxine (FT4) and
free triiodothyronine (FT3) levels higher
than the normal ranges. Biochemical
hypothyroidism was defined as a re-
peated elevated TSH of 50% higher than
the upper limit and decreasing FT4 and
FT3 or elevated TSH in presence of com-
plaints due to hypothyroidism, which
had to be confirmed by an endocrinolo-
gist. Pulmonary toxicity was defined by
respiratory symptoms and if new chest
x-ray findings were confirmed by a
pneumonologist. Hepatic toxicity was
defined as a 3-fold elevation in he-
aptic transaminases from the normal
value range. Nonphotosensitive rash
and bluish discoloration confirmed by
a dermatologist were defined as der-
matological adverse events. Uncom-
licated photosensitivity was not an end
point event. Blurred or nocturnal halo
vision or other visual complaints con-
firmed by an ophthalmologist were de-
defined as ophthalmologic adverse events.
Tremor, ataxia, or gait disturbance;
numbness or tingling; and severe in-
sonnia confirmed by a neurologist were
defined as neurological adverse events.
Gastrointestinal events included se-
vere nausea, vomiting, diarrhea, or
constipation.

Underlying heart disease–related ma-
ajor events were defined as heart failure,
thromboembolic complications, bleed-
ing, myocardial ischemia or infarction,
and death. Heart failure was defined as
an episode of right or left ventricular fail-
ure necessitating hospitalization. Throm-
boembolic complications included stroke, transient ischemic attack, and pe-
ipheral or pulmonary embolism. Cere-
brovascular events had to be diagnosed
by a neurologist, and the cause was
determined with the use of computed
tomography. Peripheral thrombo-
embolism had to be confirmed by a
surgeon; pulmonary embolism, by a
pneumonologist. Bleeding was re-
corded as an end point if the hemoglo-
bin value decreased by more than 2 g/L,
if blood transfusion or hospitalization
was necessary, if it was a retroperito-
neal or intracranial hemorrhage, or if the
bleeding was fatal. Myocardial ische-
emia was defined as unstable angina pec-
toris, angina necessitating interven-
tion, or a positive exercise test result or
reversible perfusion defect on myocar-
dial scintigraphy.

**Secondary End Point.** Secondary end
points were defined as all-cause mor-
tality and cardiovascular hospitaliza-
tions including hospitalizations for elec-
trical cardioversion, atrial fibrillation,
and underlying heart disease–related
and amiodarone-related major events.

A committee of experts who were un-
aware of the treatment assignments ad-
judicated all possible end points and
classified the end points as amio-
darone or underlying heart disease re-
lated. This was done to prevent bias in
the adjudication.

**Statistical Analysis**

The primary objective was to test our
hypothesis that compared with con-
tinuous amiodarone treatment, epis-
odic treatment is related to lower amio-
darone- and underlying heart disease–
related major events. In the literature
a wide range of the incidence of low-
dose amiodarone-induced adverse events in patients with atrial arrhythmias are reported. In general, an incidence of 5% to 25% is seen.\textsuperscript{18,20} At the end of follow-up in our study, we assumed an incidence rate of amiodarone and underlying heart disease–related major adverse events to be 18% in the episodic treatment group and 38% in the continuous treatment group. To reach statistical significance with a power of 80% and an \textit{α} of .05 (2-sided), 192 evaluable patients were as-essed to be needed. We aimed to in-clude 220 patients to account for withdrawal during the loading phase (before randomization) and unsuccess-ful electrical cardioversions.

Our secondary objective investigated differences in the occurrence of accepted atrial fibrillation (ie, perma-nent atrial fibrillation) between both groups. In addition, we compared all-cause mortality and cardiovascular hos-pitalizations including amiodarone- and cardioversion-related hospitalizations. In total 5 patients were lost to follow-up immediately after randomization. These 5 patients were therefore excluded from the analysis (Figure 1). Baseline descrip-tive statistics are presented as the mean (SD) or median (range) for continuous variables, and numbers with percent-ages for categorical variables. The pa-tient characteristics at baseline and dur-ing follow-up were compared with \textit{χ}^2 and \textit{t} tests. For all time-to-event analy-ses, Kaplan-Meier estimates were used and were compared by the log-rank test. Hazard ratios were calculated in order to assess whether the predefined study-related morbidity reduction of about 50% was accomplished. The number of and incidence rates per 100 person-years of the primary end point (first-occurring end point in a patient) were calculated. Furthermore, the number of first-occurring secondary end points was calculated. All analyses were based on the intention-to-treat principle. A \textit{P} value <.05 was considered statistically sig-nificant. The statistical analyses were car-ried out using the statistical program SPSS, version 14.0 (SPSS Inc, Chicago, Illinois).

**RESULTS**

**Patient Characteristics**

A total of 209 patients were eligible for analysis: 103 in the continuous amio-darone treatment group and 106 in the episodic treatment group (Table 1). The characteristics of the patients were typical of a population of patients with persistent atrial fibrillation.\textsuperscript{3,9,21}

**Treatment**

The median follow-up was 2.1 years (range, 0.4–2.5 years). The median cumu-lative dose of amiodarone in the episodic group was 48 g (range, 16–178 g) vs 123 g (range, 19–203 g) in the con-tinuous treatment group (\textit{P} < .001). During follow-up, the sum serum lev-els of amiodarone and desethylamio-darone were significantly higher in the continuous group. In the episodic group, more first atrial fibrillation recurrences occurred (85 [80%] vs 56 [54%], \textit{P} < .001). In total, 132 relapses occurred in the episodic group vs 77 in the continuous treatment group. At the time of first atrial fibrillation recur-rence, 56 of 85 patients (66%) in the episodic group did not use amiodarone, whereas 18 of 56 patients (32%) did not use amiodarone in the continu-ous group. More patients in the epi-sodic group underwent chemical (36 [34%] vs 14 [14%]) and electrical con-versions (38 [36%] vs 22 [21%]; \textit{P} < .001) after the first recurrence. At the end of follow-up, 51 (48%) in the episodic vs 64 (62%) in the continu-ous treatment group had sinus rhythm (\textit{P} = .05, Table 2).

**Outcome**

The incidence of the primary end point—any amiodarone- or underlying heart disease–related major event—was 37 (35%) in the episodic vs 34 (33%) in the continuous treatment group (incidence rate per 100 person-years, 22.5 vs 22.3; incidence rate difference, 0.2; 95% confidence interval [CI], −10.2 to 10.6; \textit{P} = .97; Table 3 and Figure 2). The median cumulative dose at the time of the primary end point was significantly lower in the episodic than in the continuous treatment group (44 g; range, 16–178 g vs 70 g; range, 22–203 g; \textit{P} = .009). There were differences in the incidence of amiodarone major events (20 [19%] vs 25 [24%], incidence rate per 100 person-years, 10.0 vs 12.0; incidence rate difference, −2.0; 95% CI, −8.7 to 4.6; \textit{P} = .55) and underlying heart disease–related major events (incidence, 17; [16%] vs 9 [9%]; incidence rate per 100 person-years; 8.5 vs 4.9; incidence rate difference, 3.6; 95% CI, −1.6 to 8.7; \textit{P} = .19), although they did not reach statistical significance, possibly due to lack of power (Table 3 and Figure 2).

The majority of major amiodarone-related events were thyroid dysfunc-tion (55% of all events in the episodic treatment group and 40% in the continu-ous treatment group), occurring at comparable rates in both groups. All pa-tients with cardiovascular complications had bradyarrhythmias, necessi-tating pacemaker implantation in the majority of patients (8 out of 10). No torses de pointes were docu-mented. Pulmonary toxicity was only seen twice in the continuous treat-ment group, after a relatively high accumulative amiodarone dose and with a fatal outcome in one patient.

In 2 out of 4 patients in the episodic treatment group who were hospital-ized for heart failure, atrial fibrillation was present at the time of event, and 3 out of 4 had discontinued amiodarone prior to this event. All patients experi-encing bleeding were taking anti-coagulant therapy. In 3, the INR near-est to the moment of the event was more than 3.5. Thromboembolic com-plications were only seen in the episodic treatment group, while receiving inadequate anticoagulation therapy (INR < 2) and in persistent sinus rhythm. In both treatment strat-egies, 3 patients died, 1 due to sudden unwitnessed cardiac death in each treatment strategy. Both had dis-continued amiodarone treatment for more than 3 months. The other patients died from noncardiac causes (pneumonia, pancreatic cancer, bladder cancer, and ruptured aortic aneurysm).
Currently, because many patients with atrial flutter are treated with ablation, we also performed the primary end point analysis after excluding the 9 patients with atrial flutter. This did not change the outcome of the primary end point (data not shown).

### All-Cause Mortality and Cardiovascular Hospitalizations

A total of 91 patients—56 (53%) in the episodic vs 35 (34%) in the continuous treatment group—encountered a secondary end point, including 2 mortalities (Table 4, Figure 2). There was a trend for more electrical cardioversions in the episodic group than in the continuous treatment group (34 [32%] vs 22 [21%]; 95% CI, 3.3 to 24.7, respectively). When we compare hospitalizations without hospitalizations for rhythm control, ie, electrical cardioversions, the difference between both treatment strategies is 22 (21%) vs 13 (12%) (P = .08).

### Discontinuation of Amiodarone Therapy

Amiodarone was discontinued in 96 patients (91%) in the episodic vs 43 (42%) in the continuous treatment group, predominantly according to the protocol (69 [65%] vs 7 [7%] patients). In addition, amiodarone was discontinued because of major events (9 [8%] vs 22 [21%] patients), or accepted atrial fibrillation, due to relapses within 6 months while having adequate (desethyl)amiodarone serum levels (18 [17%] vs 14 [14%] patients).

### COMMENT

This study shows that episodic amiodarone treatment— in contrast to our expectations—has no clinical advantage over continuous treatment because it did not lower morbidity in patients with persistent atrial fibrillation over 2 years of follow-up. In addition, episodic treatment is associated with more frequent recurrences of atrial fibrillation and cardioversion procedures, more patients with multiple recurrences, and a lower rate of chronic sinus rhythm at 2 years.

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Episodic Amiodarone Treatment (n = 106)</th>
<th>Continuous Amiodarone Treatment (n = 103)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>67 (9)</td>
<td>66 (9)</td>
<td>.28</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>70 (66)</td>
<td>66 (64)</td>
<td>.94</td>
</tr>
<tr>
<td>Atrial flutter, No. (%)</td>
<td>4 (4)</td>
<td>5 (4)</td>
<td></td>
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<tr>
<td>Atrial fibrillation, No. (%)</td>
<td>102 (96)</td>
<td>98 (95)</td>
<td>.78</td>
</tr>
<tr>
<td>Total duration, median (IQR), d</td>
<td>514 (48-11750)</td>
<td>407 (48-9857)</td>
<td>.99</td>
</tr>
<tr>
<td>Duration of present episode, median (IQR), d</td>
<td>37 (0-255)</td>
<td>36 (0-917)</td>
<td>.54</td>
</tr>
<tr>
<td>Complaints of atrial fibrillation, No. (%)</td>
<td>101 (95)</td>
<td>93 (90)</td>
<td>.79</td>
</tr>
<tr>
<td>Palpitations</td>
<td>42 (40)</td>
<td>38 (37)</td>
<td>.99</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>67 (63)</td>
<td>64 (62)</td>
<td>.76</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (48)</td>
<td>51 (50)</td>
<td>.57</td>
</tr>
<tr>
<td>CHADS2 score, median (IQR)</td>
<td>1 (0-5)</td>
<td>1 (0-4)</td>
<td>.75</td>
</tr>
<tr>
<td>Underlying diseases, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>18 (17)</td>
<td>15 (15)</td>
<td>.85</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>14 (13)</td>
<td>7 (7)</td>
<td>.17</td>
</tr>
<tr>
<td>Mitral</td>
<td>8 (8)</td>
<td>5 (5)</td>
<td>.57</td>
</tr>
<tr>
<td>Aortic</td>
<td>0</td>
<td>1 (1)</td>
<td>.49</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>.93</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (39)</td>
<td>43 (42)</td>
<td>.89</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>18 (17)</td>
<td>9 (9)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (10)</td>
<td>10 (9)</td>
<td>.96</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>6 (6)</td>
<td>11 (11)</td>
<td>.30</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (4)</td>
<td>9 (9)</td>
<td>.55</td>
</tr>
<tr>
<td>NYHA heart failure class, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>35 (33)</td>
<td>33 (32)</td>
<td>.34</td>
</tr>
<tr>
<td>II</td>
<td>71 (67)</td>
<td>70 (68)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>135 (17)</td>
<td>136 (17)</td>
<td>.45</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84 (11)</td>
<td>86 (10)</td>
<td>.09</td>
</tr>
<tr>
<td>Atrial size, mean (SD), mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long axis</td>
<td>48 (7)</td>
<td>45 (6)</td>
<td>.01</td>
</tr>
<tr>
<td>Apical view</td>
<td>66 (8)</td>
<td>66 (8)</td>
<td>.06</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical view</td>
<td>63 (8)</td>
<td>61 (7)</td>
<td>.11</td>
</tr>
<tr>
<td>Left ventricular end diastolic diameter, mean (SD), mm</td>
<td>51 (7)</td>
<td>51 (6)</td>
<td>.97</td>
</tr>
<tr>
<td>Left ventricular end systolic diameter, mean (SD), mm</td>
<td>36 (9)</td>
<td>35 (7)</td>
<td>.76</td>
</tr>
<tr>
<td>Septal thickness, mean (SD), mm</td>
<td>11 (2)</td>
<td>10 (2)</td>
<td>.45</td>
</tr>
<tr>
<td>Posterior wall thickness, mean (SD), mm</td>
<td>10 (1)</td>
<td>10 (1)</td>
<td>.92</td>
</tr>
<tr>
<td>Fractional shortening, mean (SD), %</td>
<td>30 (12)</td>
<td>31 (10)</td>
<td>.42</td>
</tr>
<tr>
<td>Medication at screening, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>104 (98)</td>
<td>97 (94)</td>
<td>.97</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>70 (66)</td>
<td>69 (67)</td>
<td>.54</td>
</tr>
<tr>
<td>Diuretics</td>
<td>34 (32)</td>
<td>34 (33)</td>
<td>.78</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>50 (47)</td>
<td>35 (34)</td>
<td>.08</td>
</tr>
<tr>
<td>ARB</td>
<td>13 (12)</td>
<td>11 (11)</td>
<td>.83</td>
</tr>
<tr>
<td>Digoxin</td>
<td>28 (26)</td>
<td>25 (24)</td>
<td>.98</td>
</tr>
<tr>
<td>Verapamil or diltiazem</td>
<td>15 (14)</td>
<td>17 (17)</td>
<td>.62</td>
</tr>
<tr>
<td>Statin</td>
<td>22 (21)</td>
<td>19 (18)</td>
<td>.86</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CHADS2, congestive heart failure, hypertension, age more than 75 years, diabetes mellitus, and stroke; NYHA, New York Heart Association.

*Patients may have had more than 1 underlying disease or had been receiving more than 1 heart disease medication at screening.
was a decreased incidence of amiodarone-related events and an increased incidence of underlying heart disease-related events; while these differences were not statistically significant, this study was underpowered to make this determination. In addition, patients in the episodic group had a significantly higher rate of all-cause mortality and cardiovascular hospitalizations than those in the continuous treatment group. Considering the above, episodic amiodarone treatment cannot be advocated for most patients with persistent atrial fibrillation.

The lack of usefulness of episodic compared with continuous amiodarone treatment may be explained, in part, by the fact that the majority of events were thyroid dysfunction occurring at comparable rates in both groups. Other studies have shown a similar incidence of thyroid dysfunction.20,22 Another factor that may have contributed to the observed results is the higher, unforeseen, amiodarone-related cardiovascular complication rate in the episodic treatment group. These patients underwent more electrical cardioversions, facilitating recognition of significant bradycardia and, hence, pacemaker implantations. Most pacemakers in the study were indeed implanted after sinus arrests had been seen after cardioversion. The association between amiodarone dose and the rate of pacemaker implantation in patients with atrial fibrillation was previously investigated by Essebag et al.23 The incidence rate of pacemaker implantation was 2.2% per person-year and occurred more often early after start of therapy, at the moment of high daily dosages during the loading phase: 5.2% per person-year during the first 90 days of amiodarone treatment. In our study, patients in the episodic treatment group had more recurrences of atrial fibrillation and were often reloaded with high daily dosages of amiodarone before an electrical cardioversion because of inadequate (desethyl)amiodarone serum levels.

Apart from the higher than expected amiodarone-related morbidity, cardiovascular morbidity (other than

<table>
<thead>
<tr>
<th>Table 2. Rhythm at End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%) of Patients Receiving Amiodarone Treatment</strong></td>
</tr>
<tr>
<td>Sinus rhythm</td>
</tr>
</tbody>
</table>
| Accepted atrial fibrillation
d | 44 (42) | 30 (29) | .05 |
| Waiting for re-ECV | 11 (10) | 9 (9) | .82 |

Abbreviation: ECV, electrical cardioversion. A atrial fibrillation.

<table>
<thead>
<tr>
<th>Table 3. Incidence of Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary End Point</strong></td>
</tr>
<tr>
<td>Composite primary end point</td>
</tr>
<tr>
<td>Amiodarone-related major events</td>
</tr>
<tr>
<td>Dermatological complications</td>
</tr>
<tr>
<td>Gastrointestinal tract complications</td>
</tr>
<tr>
<td>Hepatic effects</td>
</tr>
<tr>
<td>Pulmonary complications</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Neurological complications</td>
</tr>
<tr>
<td>Ophthalmological complications</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
</tr>
<tr>
<td>Underlying heart disease-related major events</td>
</tr>
<tr>
<td>Ischemia</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Thromboembolic complications</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval. Only first occurring end point events are reported herein.
bradycardias) was more frequent than anticipated with episodic vs the continuous treatment group. These major events consisted mainly of heart failure, major bleeding, ischemia, and thromboembolic complications. Heart failure hospitalization occurred in 50% of the patients in the presence of atrial fibrillation. A higher heart rate during a relapse of atrial fibrillation after discontinuation of amiodarone therapy may have contributed to this difference. Amiodarone is known to lower heart rate during atrial fibrillation. Alternatively, heart failure may have been ischemia induced, even though only 1 patient out of 4 with a hospital admission for heart failure was known to have a history of coronary artery disease. It is well known that amiodarone has anti-ischemic properties. Also more bleeding was seen in the episodic treatment group. Almost all occurred while receiving adequate anticoagulation therapy. Nevertheless, amiodarone is known to increase serum levels of anticoagulants. Although patients were carefully surveyed through the thrombosis service, especially when discontinuing or restarting amiodarone, this episodic treatment strategy may have induced significant INR instability compared with continuous amiodarone treatment.

Continuous treatment tended to be more effective in preventing accepted atrial fibrillation after 2 years of follow-up. This difference can possibly be attributed to more electrical cardioversions in the episodic treatment group and the unwillingness of patients to undergo any more electrical cardioversions. In the continuous treatment group, most patients were taking amiodarone at the time of a recurrence of atrial fibrillation.

We used amiodarone and desethylamiodarone serum levels to differentiate between effective and ineffective amiodarone dosages at the moment of a relapse. Indeed, the relationship between serum concentrations of amio-
Amiodarone and desethylamiodarone and clinical efficacy is not well established. It has been suggested that effective levels for treatment of atrial arrhythmias with amiodarone are a sum of the amiodarone and desethylamiodarone levels between 1 and 2 mg/L.24 Several investigators, however, have demonstrated only a weak or even an absent concentration effect relation,25,26 whereas others found a clear concentration-related effect of amiodarone on QT-interval prolongation, slowing of heart rate, and suppression of ventricular arrhythmias.27,28 We previously showed that for conversion of atrial fibrillation, serum concentrations of desethylamiodarone were more important than those of the parent compound. In contrast, reduction of the ventricular rate during atrial fibrillation was correlated with serum levels of amiodarone itself.28 The rate of main- tained sinus rhythm in the continuous treat- ment group is consistent with figures from previous studies of con- tinuous amiodarone treatment.10,11 Is there still a role for amiodarone prophylaxis in atrial fibrillation and should it always be administered con- tinuously? To start with, patient prefer- ence together with the evidence- based physician’s opinion should play a role in choosing any treatment strategy. Rhythm control is the most fre- quent strategy in patients with symp- tomatic atrial fibrillation. Pharmacological rhythm control is the first choice, but atrial catheter ablation may be per- formed after failure of only 1 antiar- rhythmic drug.29 Clearly, this does not apply to all patients. Atrial catheter ab- lation is most effective for paroxysmal atrial fibrillation and less effective for persistent atrial fibrillation, especially in the setting of underlying diseases. Furthermore, atrial ablation may cause adverse events in as many as 6% of pa- tients,30 which may cause patients to re- frain from selecting this therapy. Al- ternatively, amiodarone may be instituted after failure of other antiar- rhythmic drugs. On the basis of the pri- mary outcome of this study, physi- cians should not advise episodic amiodarone treatment as a first option because not only more frequent elec- trical cardioversions are a problem but also underlying heart disease–related events occur more frequently while the risk for amiodarone-related adverse events may not be less. In clinical prac- tice, however, patients may choose epi- sodic treatment because it potentially produces fewer amiodarone-related ad- verse events, while expecting fewer under- lying disease–related events and ac- cepting that more frequent admissions for electrical cardioversion are needed. This may hold for younger patients with less severe underlying disease. Thus, for clinical decision making, balancing the positive and negative aspects of each strategy should be done on an indi- vidual basis and should include pa- tient preference.

There are several limitations to this study. The study was relatively small and follow-up was fairly short. There- fore, the present data should be re- garded as a preliminary contribution. Clearly, more study on this issue is needed. A longer follow-up period might have exposed a higher rate of amiodarone-related events as well as a further decrease in maintenance of sinus rhythm. More amiodarone-related events could hold especially true for those in the continuous treatment group, which may be counterbal- anced by a greater rate of heart disease- related events in the episodic treatment group. The study was unblinded. The primary end point consists of outcomes with widely varying clinical impor- tance. Weighting of the end points was done by the secondary end point that investigated cardiovascular end points necessitating hospitalization, even though our study was not specifically designed for this purpose. Clearly, this secondary end point analysis might have favored continuous treatment.

In conclusion, in this study population, there was no difference in the com- posite of amiodarone and major card- ial adverse events between groups assigned to either episodic or continu- ous amiodarone treatment. However, patients in the episodic treatment group had a significantly increased rate of atrial fibrillation recurrence and a sig- nificantly higher rate of all-cause mor- tality and cardiovascular hospitaliza- tions.

Table 4. Secondary End Point: All-Cause Mortality and Cardiovascular Hospitalizationa

<table>
<thead>
<tr>
<th>End Points</th>
<th>No. (%) of Patients Receiving Amiodarone Treatment</th>
<th>Absolute Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of end points</td>
<td>56 (53)</td>
<td>35 (34)</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8 (8)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Thromboembolic complications</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Electrical cardioversion</td>
<td>34 (32)</td>
<td>22 (21)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

aOnly first occurring end point events are reported herein.
Acquisition of data: Ahmed, Rienstra, Bosker, Lok, Van Gelder.


Drafting of the manuscript: Ahmed, Links, Lok, Van Veldhuisen, Van Gelder.

Critical revision of the manuscript for important intellectual content: Ahmed, Rienstra, Crijns, Links, Wiesfeld, Hillege, Bosker, Lok, Van Veldhuisen, Van Gelder.

Statistical analysis: Ahmed, Hillege, Van Gelder.

Obtained funding: Crijns, Van Gelder. Administrative, technical, or material support: Rienstra, Van Veldhuisen, Van Gelder.

Study supervision: Crijns, Links, Wiesfeld, Hillege, Lok, Van Veldhuisen, Van Gelder.

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REFERENCES


