Azimilide vs. placebo and sotalol for persistent atrial fibrillation: the A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial

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Aims Treatment of atrial fibrillation remains a major clinical challenge owing to the limited efficacy and safety of anti-arrhythmic drugs, particularly in patients with structural heart disease.

Methods and results To evaluate the efficacy of azimilide, a new class III anti-arrhythmic drug, we studied 658 patients with symptomatic persistent atrial fibrillation, adequate anticoagulant therapy, and planned electrical cardioversion. Patients were randomized to placebo, azimilide (125 mg o.d.), or sotalol (160 mg b.i.d.). Primary efficacy analysis was based on event recurrence, which was defined as atrial fibrillation lasting > 24 h, or requiring DC cardioversion. Median time to recurrence was 14 days for azimilide, 12 days for placebo, and 28 days for sotalol (P = 0.0320 when comparing azimilide with placebo; P = 0.0002 when comparing azimilide with sotalol). The placebo-to-azimilide hazard ratio was 1.291 (95% CI: 1.022–1.629) and the sotalol-to-azimilide hazard ratio was 0.652 (95% CI: 0.523–0.814). Adverse events causing patient withdrawal were more frequent (P < 0.01) in patients on azimilide (12.3%) and on sotalol (13.9%) than on placebo (5.4%). Eight patients in the sotalol (3.5%) and 16 in the azimilide (7.6%) group interrupted the study because of QTc prolongation. Torsade de pointes was reported in five patients of the azimilide group. The percentage of patients who completed the 26 week study period without events were 19% for azimilide, 15% for placebo, and 33% for sotalol (P < 0.01). Unsuccessful day 4 cardioversion, arrhythmia recurrence, and adverse events were the main causes of withdrawal from the study.

Conclusion This study demonstrates that the anti-arrhythmic efficacy of azimilide is slightly superior to placebo but significantly inferior to sotalol in patients with persistent AF. The modest anti-arrhythmic efficacy and high rate of torsade de pointes and marked QTc prolongation limit azimilide utilization for the treatment of AF.

Introduction

Treatment of atrial fibrillation remains a major clinical challenge.1–3 Sound clinical judgement and experimental data indicate that conversion to and maintenance of sinus rhythm represent the principal therapeutic objective, although strategy selection remains controversial due to the limited efficacy and safety of anti-arrhythmic therapy over long periods of time, especially in patients with congestive heart failure. The issue has become even more controversial after the publication of recent studies4–7 that have proved that in selected subgroups of patients, rhythm control did not offer any significant advantage over rate control in terms of survival once appropriate anticoagulant therapy is prescribed.

Recently, the Sotalol Amiodarone atrial Fibrillation Efficacy Trial (SAFE-T) investigators8 have demonstrated that amiodarone is superior to sotalol for maintaining sinus rhythm, but both drugs have similar efficacy in patients with ischaemic heart disease. Thus, potassium channel blocker activity seems one of the principle mechanisms to exert an effective anti-fibrillatory action, particularly in patients with structural heart disease.8–12 In the last 10 years, new class III anti-arrhythmic drugs have been developed and tested in patients with atrial fibrillation: dofetilide and azimilide have been object of several investigations.13–18 Dofetilide has been approved by regulatory agencies to convert atrial fibrillation and maintain sinus rhythm.13,14 Azimilide has been proved effective in increasing time to first atrial fibrillation recurrence at doses of 100–125 mg per day.15–18
The A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial was designed and performed to compare prospectively the efficacy of azimilide in comparison with placebo and sotalol in maintaining sinus rhythm after electrical cardioversion in patients with persistent atrial fibrillation.

Methods

Study population

Patients aged between 18 and 80 years were eligible if they had documented (12 lead ECG) history of symptomatic atrial fibrillation lasting more than 48 h and less than 6 months, adequate anticoagulant therapy, and planned electrical cardioversion. Epidemiological data and clinical characteristics of patients are in Table 1.

The following patients were excluded: (i) patients with qualifying arrhythmias due to transient causes such as electrolyte disturbances, hyperthyroidism, or pericarditis; (ii) patients with a history of syncope or angina pectoris precipitated by attacks of arrhythmia; (iii) patients with a history of torsade de pointes or other forms of polymorphic ventricular tachycardia as well as two degree or three degree atrio-ventricular block without a permanent pacemaker; (iv) patients with a recent myocardial infarction, unstable angina, or heart failure NYHA class IV; (v) patients with a family history of prolonged QT syndrome or with a baseline QTc > 440 ms.

Eligible patients were considered to have structural heart disease if their history included one of the following: left bundle branch block, coronary artery disease, remote myocardial infarction, unstable angina, or heart failure NYHA class IV; (v) patients with a family history of torsade de pointes or other forms of syncope or angina pectoris precipitated by attacks of arrhythmia; (iv) patients with a recent myocardial infarction, unstable angina, or heart failure NYHA class IV; (v) patients with a family history of prolonged QT syndrome or with a baseline QTc > 440 ms.

Eligible patients were considered to have structural heart disease if their history included one of the following: left bundle branch block, coronary artery disease, remote myocardial infarction, congestive heart failure, valvular heart disease, hypertension with cardiomyopathy, or hypertension with left ventricular hypertrophy.

In addition, patients using class I or III anti-arrhythmic agents or beta-blockers had to discontinue treatment for at least five half-lives before receiving the first dose of study. Amiodarone must have been discontinued for at least 1 month. Beta-blockers were not allowed during the study.

All patients provided written informed consent, and the Ethical Committee at each site approved the protocol.

Study design

This was a randomized, 6 month double-blind, placebo controlled, parallel group-design study to compare the efficacy of azimilide 125 mg per day with placebo or sotalol 160 mg b.i.d. in patients with persistent atrial fibrillation. Procter & Gamble funded the trial and provided study manager to supervise its conduct.

Maintenance study doses were azimilide 125 mg daily plus one placebo, placebo twice-daily, or sotalol 160 b.i.d. Owing to possible side effects thought to be related to beta-adrenergic blockade, patients in all three treatment groups were allowed to undergo a blinded dose reduction at the investigator’s discretion according to predefined criteria.

The efficacy period started on day 4 when a successful electrical or spontaneous cardioversion was documented. Outpatient visits at each study site were scheduled at weeks 2, 4, 6, 8, 10, 12, and 26. Patients could also return for unscheduled visits at anytime during the course of the study.

The primary objective of the study was to assess the efficacy of azimilide vs. placebo in prolonging the time from the start of the efficacy period to the first symptomatic or asymptomatic atrial fibrillation episode, flutter, or PSVT event. An event was defined as symptomatic or asymptomatic atrial fibrillation, flutter, or PSVT lasting > 24 h (the arrhythmic episode had to be confirmed during a second electrocardiogram performed after 24 h from its onset); atrial fibrillation, flutter, or PSVT < 24 h for which the patient had to be admitted to hospital or DC cardioverted, cardioversion failure on day 4 and withdrawal prior to cardioversion. Patients who entered the efficacy period but withdrew from the study were censored on the date of study discontinuation.

The secondary objective of the study was an effectiveness analysis, comparing azimilide with sotalol, as defined by the composite time to first event or all-cause withdrawal.

Tertiary objectives of the study were to assess the effects of azimilide vs. placebo on facilitating successful DC cardioversion and on symptom frequency load during the first recurrence. Drug conversion to sinus rhythm during the loading phase was also considered.
Symptomatic load during recurrences was calculated in relation to six pre-specified symptoms (chest pain/palpitation, light-headedness/dizziness, fatigue, palpitations, sweating, and shortness of breath) and ranked accordingly.

Among several variables used to define additional subgroup analyses, only structural heart disease is considered in this article.

Electrocardiographic criteria for withdrawal were the following: ventricular fibrillation, sustained monomorphic ventricular tachycardia, incessant ventricular tachycardia, polymorphic VT, QTc exceeding 525 ms, or a documented and persistent heart rate below 50 b.p.m. during the waking hours. Additionally, a neutrophil count < 1000/μL or a derived [(140 – age) x weight (kg)/72 serum creatinine (mg/dL)] creatinine clearance < 60 mL/min on two consecutive measurements were causes of withdrawal.

**Statistical analysis**

The distribution of time to first documented event was assumed to follow an exponential distribution. Sample size was calculated using the method of Schoenfeld20 assuming a two-sided hypothesis test of the primary endpoint (azimilide vs. placebo) at a significance level of 5% (α = 0.05). An equal number of patients in each of the three groups was planned. In patients who required cardioversion, the median time to event was estimated to be no more than 90 days for placebo. A sample size of 190 patients in each treatment group was calculated to achieve a hazard ratio of 0.67 to be detected with a 0.90 probability (90% power). After assuming 15% for dropouts, the total number of patients to be enrolled was calculated to be 657 (219 patients per treatment group). A "gatekeeper" method20 was employed for the secondary analysis. This method allows the secondary hypothesis to be tested at a significance level of 5% only if the analysis of primary endpoint is significant (P < 0.05). All hypothesis tests are two-sided. Gatekeeper approach was taken with alpha allocated to the primary and secondary endpoints. None of the additional analyses were adjusted.

Primary efficacy analysis was based on intention to treat and measured the time to the first symptomatic or asymptomatic event during a 6 month period. All patients who withdrew for unsuccessful cardioversion or for any reason prior to day 4 were considered to have had an event on the first day of the efficacy period. Kaplan–Meier estimates of the survival curves were generated and treatment comparisons made using the log-rank test. Differences between the times to event distribution were also quantified by the hazard ratio from a population of hazard regression, Kaplan–Meier estimates of the median time to event, and Kaplan–Meier estimates of the proportion event-free through 6 months.

The incidence of adverse event, as categorized by the COSTART coding dictionary, was summarized by counting patients who experienced an adverse event.

**Results**

A total of 658 patients were enrolled into the study (Table 1). Of note, previous cardioversion was performed in ~25% of cases, duration of atrial fibrillation > 27 days was present in more than 70% of subjects, and symptoms related to NYHA class I–II were present in almost 50% of patients. Russia, Poland, Hungary, and Western Europe enrolled, respectively, 25, 26, 17, and 32% of the patients.

Five patients on placebo, nine on azimilide, and seven on sotalol were withdrawn from the study prior to start of the efficacy period for different reasons including bradycardia, QTc prolongation, and refuse of continuing the study. Spontaneous cardioversion on day 4 occurred in 6.9, 4.1, and 6.3% of patients in, respectively, azimilide, placebo, and sotalol groups. These figures were not significantly different. The percentage of withdrawal from the study due to unsuccessful cardioversion on day 4 was 15% for azimilide, 19% for placebo, and 12% for sotalol (P = 0.116).

The percentages of patients who completed the 26 week study period were 19% for azimilide, 15% for placebo, and 33% for sotalol (P < 0.01). Arrhythmia recurrence, cardioversion failure on day 4, and adverse event were the most important causes of withdrawal from the study.

**Azimilide vs. placebo**

As illustrated in Figure 1, there was a slight but statistically significant difference in time to event between azimilide and placebo groups. Median time to recurrence was 12 days for placebo and 14 days for azimilide (P = 0.032; hazard ratio 1.29; 95% CI = 1.02–1.62). Symptomatic event episodes lasting > 24 h and asymptomatic events occurred in 23.2 and 12.3% of patients in the azimilide group and in 29 and 15.6% of patients in the placebo group, respectively. Arrhythmia recurrence necessitating hospitalization or DC cardioversion was more frequent (P = 0.033) in the placebo (9.8%) than in the azimilide (3.8%) group. About 50% of recurrences were subacute occurring during the first weeks of the efficacy period. In patients with structural heart disease (Figure 2), the difference in time to event was
more evident and reflected by a placebo–azimilide hazard ratio of 1.41 (95% CI: 1.05–1.91). When the analysis was restricted to patients in sinus rhythm on day 4, the difference between median time to event was greater (26 vs. 15 days), with a placebo–azimilide hazard ratio of 1.37 (95% CI: 1.04–1.82; \( P = 0.0261 \)) in the whole study population and 1.61 (95% CI: 1.16–2.23; \( P = 0.0041 \)) in patients with structural heart disease.

Symptom frequency burden (Figure 3) and mean ventricular response (Figure 4) during arrhythmia recurrence were not significantly different between azimilide and placebo groups.

**Azimilide vs. sotalol**

As illustrated in Figure 5, in the secondary efficacy analysis of the intention to treat study population, there was a statistically significant difference in time to event or withdrawal (\( P = 0.0002 \)) between the azimilide and sotalol groups in favour of sotalol. The median time to recurrence was 14 days for azimilide and 28 days for sotalol. The sotalol-to-azimilide hazard ratio was 0.65 (95% CI: 0.52–0.81). Symptomatic event episodes lasting > 24 h and asymptomatic events occurred in 16.1 and 10.3% of patients in sotalol group.

Arrhythmia recurrence necessitating hospitalization or DC cardioversion occurred in 3.1% of sotalol patients. By comparing azimilide and sotalol curves outlined in Figure 5, it appears that the number of subacute recurrences was smaller in sotalol-treated patients.

When considering patients with and without a diagnosis of structural heart disease, the difference in time to event, in favour of sotalol, was confirmed with a hazard ratio of 0.71 (95% CI: 0.55–0.92) and 0.50 (95% CI: 0.33–0.77), respectively.

The symptom frequency burden reported by patients on sotalol was not significantly different from that of patients on azimilide or placebo (Figure 3) in spite of the fact that mean ventricular response was significantly lower (Figure 4).

**Adverse events**

The overall percentage of patients who reported adverse event was similar among azimilide, sotalol, and placebo (51.7, 61.9, and 50.9%). The most common adverse events in the azimilide and sotalol groups were hypertension, prolonged QTc, and bradycardia. Four patients in the azimilide group and four patients in the sotalol group died during the study. There were no deaths in the placebo group. Two deaths in the azimilide group were classified as arrhythmic deaths, one as a cardiac non-arrhythmic death, and one as unknown. Three deaths in the sotalol group were classified as arrhythmic deaths and one as cardiac non-arrhythmic death. The mortality rates for 100 patient-years were significantly greater (\( P < 0.01 \)) in azimilide (9.22) and sotalol (6.35) in comparison with placebo (0). Major arrhythmic cardiac events were defined as death, torsade de pointes, ventricular tachycardia, or fibrillation leading to withdrawal from the study. Data related to the loading period and the entire study are presented in Table 2. All five patients reporting torsade de pointes had been treated with the azimilide group. They were older than 65 years (range 66–76 years) and female gender was prevalent (\( n = 3 \)). In all but one case, the arrhythmia occurred in the first few days after the loading period.

A greater number of patients on azimilide (12.3%) and on sotalol (13.9%) than on placebo (5.4%, \( P < 0.01 \)) were
withdrawn from the study due to adverse events. Neutropenia requiring withdrawal was observed in one patient on azimilide. Two patients on placebo (0.9%), eight in the sotalol (3.5%), and 16 in the azimilide (7.6%) groups interrupted the study because of QTc prolongation (P < 0.01 when comparing azimilide vs. placebo). But one case in sotalol and two cases in azimilide group occurred in the maintenance period. Values >525 ms were confirmed in nine patients on azimilide (4.2%), eight patients on sotalol (3.6%), and one patient on placebo. Sinus bradycardia caused withdrawal from the study in 15 (6.7%) patients on sotalol and three patients on azimilide (1.4%).

Discussion

This study demonstrates that azimilide is slightly superior to placebo but inferior to sotalol in prolonging time to first documented recurrence after successful electrical cardioversion in patients with persistent atrial fibrillation with and without structural heart disease. Marked QTc prolongation or torsade de pointes occurred in ~10% of patients on azimilide. No episodes of torsade de pointes were observed in placebo and sotalol groups.

Class III drugs in persistent atrial fibrillation

Previous studies have documented the efficacy of class III drugs in preventing arrhythmia recurrences in patients with persistent atrial fibrillation.2,8–18 In the Canadian Trial of Atrial Fibrillation study,9 amiodarone was found to be more effective than sotalol or propafenone in prolonging time to the first recurrence after DC cardioversion in patients with a history of symptomatic paroxysmal or persistent atrial fibrillation. More recently, the SAFE-T investigators8 reported the results of a double-blind, placebo controlled study designed to compare the anti-arrhythmic efficacy of amiodarone, sotalol, and placebo in patients with persistent atrial fibrillation undergoing cardioversion. The median time to first recurrence was 487 days in the amiodarone, 74 days in the sotalol, and six days in the placebo group according to intention to treat analysis. Times to first arrhythmic event were therefore markedly different from those observed in the present study, in which the median time to recurrence for azimilide was 14 or 26 days according to, respectively, primary or secondary efficacy analysis. These figures, in addition, were also markedly different from those observed in the previously reported SVA studies16–18 where a mean value ranging from 38 to 130 days was observed. By comparing these studies, it appears that also the time to recurrence in the placebo groups of SVA studies were longer, ranging from 17 to 50 days. Differences in the qualifying episode of atrial fibrillation, percentage of patients who underwent electrical cardioversion, number of patients exposed to azimilide 125 mg, and duration of arrhythmia may partially explain these different results.16–18 Moreover, symptomatic atrial fibrillation was reported in 62% of SAFE-T patients, whereas in the Canadian Trial of Atrial Fibrillation study and in A-COMET-II studies, this was an inclusion criterion. Timing of scheduled control visits, indications for transtelephonic transmission of electrocardiogram, and duration of episodes classified as recurrence were also different among the three studies. For example, only episodes lasting longer than 10 min were considered to be clinically significant in the Canadian Trial of Atrial Fibrillation study, whereas two electrocardiographic documentations <24 h apart were required for the SAFE-T study.9,9

Our study provides information on drug-induced cardioversion and electrical cardioversion rate. The incidence of spontaneous cardioversion during the loading phase was small and not substantially different from placebo, thus confirming the limited efficacy of azimilide in restoring sinus rhythm. In addition, these data unfortunately indicate that azimilide and sotalol did not enhance electrical cardioversion rate because success of the procedure was similar in all three groups.

Safety and efficacy of azimilide

Azimilide is an orally active class III drug that blocks rapid (I\text{Na}) and slow (I\text{Kr}) components of the delayed rectifier cardiac potassium channels.15,21,22 In animals and humans, this blockade results in dose-dependent increase of the QT interval, as well as prolongation of atrial and ventricular refractory periods.15 In previous clinical studies, azimilide, at a dosage of 100–125 mg/day, has been shown to be safe and effective in increasing the time to first recurrence of symptomatic atrial fibrillation or flutter.16–18 Incidence of torsade de pointes or other ventricular arrhythmia was low (<1%) and consistent with other class III anti-arrhythmic agent. Severe neutropenia was reported in 0.20% of patients. Recently, two studies carried out in post-myocardial infarction patients with depressed left ventricular function and in patients with implantable cardioverter

| Table 2 | Number of patients with death, torsades de pointes, VT/VF, and MACE during the loading and whole study period |
| Loading period | | Whole study period |
| Azimilide (n = 211) | Sotalol (n = 223) | Placebo (n = 224) | Azimilide (n = 211) | Sotalol (n = 223) | Placebo (n = 224) |
| Deaths | 0 | 1 | 0 | 4 (1.9) | 4 | 0 |
| Torsade de pointes | 1 | 0 | 0 | 5 (2.4) | 0 | 0 |
| Ventricular fibrillation | 0 | 0 | 0 | 1 (0.5) | 0 | 0 |
| Patients with MACE (%) | 1 (0.5) | 1 (0.4) | 0 | 9 (4.3) | 4 (1.8) | 0 |

VT/VF, ventricular tachycardia/ventricular fibrillation; MACE, major arrhythmic cardiac events. Note that individual patients may have more than one MACE.
defibrillator have demonstrated, respectively, the safety and efficacy of azimilide also in these subgroups of patients.21,24

The incidence of torsade de pointes was unexpectedly high (2.4%) in the azimilide group, whereas no cases were reported in placebo and sotalol groups. In all but one case, the arrhythmia occurred in the first 72 h after completion of the loading period. Patients were older, female gender was prevalent, and hypokalaemia was documented in two cases. No specific study population characteristics or modality of electrocardiographic monitoring could explain this pro-arrhythmic rate in comparison with previous SVA studies. Moreover, the occurrence of torsade de pointes just after the in-hospital loading period opens additional questions in relation to the duration of electrocardiographic monitoring during the loading period of class III drugs and, in particular, azimilide.

Sotalol vs. azimilide

Sotalol was administered at a dose of 160 b.i.d. and was well tolerated and effective. In spite of the fact that the dosage was greater than that commonly used in clinical practice, the percentage of patients withdrawing due to marked bradycardia was <7%. Of relevant clinical interest, was the finding that no cases of torsade de pointes were observed during either the loading phase or the follow-up period, thus confirming the efficacy and safety of sotalol in patients with symptomatic atrial fibrillation.8,9,25-27

When considering time-to-event curves, subacute (within 2 weeks) recurrences were similar in azimilide and placebo groups, whereas a smaller number of events occurred in patients treated with sotalol. These findings are of clinical interest28 because they provide additional support to the concept that adrenergic mechanism may play a major pro-arrhythmic role in the first weeks after electrical cardioversion29,30 and that drugs that combine anti-adrenergic properties in addition to the prolongation of action potential may exert a greater anti-arrhythmic effect. The possibility of increasing azimilide efficacy by concomitant beta-blockers therapy is a hypothesis that, in our opinion, deserves to be tested.

Finally, at variance with previous reports,8,9 we were unable to observe a significant reduction in symptom load during atrial fibrillation recurrences in patients on sotalol in comparison with azimilide and placebo groups in spite of a significant reduction of mean ventricular response.

Conclusions

In the first placebo and active control study, we were able to demonstrate that azimilide is slightly superior to placebo but inferior to sotalol in prolonging time to the first arrhythmia recurrence in patients with persistent atrial fibrillation. The modest increase in the median time to recurrence in comparison with placebo and the incidence of torsade de pointes and marked QTc prolongation limits the utilization of this drug in patients with persistent atrial fibrillation.

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Conflict of interest: All authors have received honoraria from Procter & Gamble as members of European Scientific Advisory Board.

Appendix

A-COMET-II trial

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