

Azimilide, A Novel Oral Class III Antiarrhythmic for Both Supraventricular and Ventricular Arrhythmias

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Abstract: Azimilide is an investigational Class III antiarrhythmic that has been developed for treating both supraventricular and ventricular tachyarrhythmias. Similar to other Class III antiarrhythmics, azimilide prolongs myocardial repolarization in a dose-dependent manner by increasing the action potential duration, QT interval, and effective refractory period. The most frequent reported side effect is headache, with rare serious adverse events of early reversible neutropenia and Torsades de Pointes. In long-term follow up, the patient withdrawal rate has been low. Azimilide has very predictable pharmacokinetics, is predominantly hepatically metabolized, and has no significant drug interactions with digoxin or warfarin.

In animal models, azimilide has been shown to be very effective in suppressing both atrial and ventricular tachyarrhythmias, decreasing the defibrillation energy requirement, and preventing post-myocardial infarction ventricular tachycardia and fibrillation. Clinically, in a series of 4 double-blind, randomized, placebo-controlled trials, the Azimilide Supraventricular Arrhythmia Program which included over 1000 patients and approximately 70% with structural heart disease, azimilide showed a significant prolongation in the time to first recurrence of paroxysmal supraventricular tachycardia or atrial fibrillation/flutter.

With respect to ventricular tachyarrhythmias, the AzimiLide post-Infarct surVival Evaluation Trial was a large randomized, multinational, prospective, placebo-controlled study in recent survivors of myocardial infarction at high risk for sudden cardiac death. After 1 year of follow-up, this study showed no statistical difference in all-cause mortality between placebo and azimilide. However, azimilide did statistically reduce the incidence of new atrial fibrillation. Further trials are necessary to evaluate the efficacy of azimilide in patients with symptomatic ventricular arrhythmias.

Key Words: Azimilide, Class III antiarrhythmic agents, atrial fibrillation, paroxysmal supraventricular tachyarrhythmia, ventricular tachyarrhythmia, sudden cardiac death, implantable cardioverting defibrillator, defibrillation energy requirement.

OVERVIEW

Despite the increasing use of non pharmacologic means of treating cardiac rhythm disorders, such as radiofrequency ablation and implantable devices, antiarrhythmic drugs continue to play a very important role in the treatment of these patients. For instance, antiarrhythmic therapy remains the primary mode of treatment for symptomatic atrial fibrillation, and is frequently used as adjunctive therapy in patients with implantable cardioverter defibrillators for suppression of tachyarrhythmias that would otherwise initiate therapy from the device.

The Vaughan-Williams classification of antiarrhythmic medication attempts to broadly organize these drugs into four groups based on their principle mode of action [1]. Although this scheme doesn't take into account all of the drugs' electrophysiologic effects, other attempts at classification have not found favor throughout the medical community [2]. Class I agents block the inward sodium channels; Class II agents block beta adrenergic receptors;

Class III agents block the outward potassium channel; and Class IV agents block the slow inward calcium channels. Class I drugs are further subdivided into three groups because of their unequal effects on the sodium channel (See Table (1)).

With all antiarrhythmic drugs, the potential for proarrhythmic effect exists. This potential may be more significant in patients with structural heart disease. In post-myocardial infarction (MI) patients with reduced left ventricular function, the Cardiac Arrhythmias Suppression Trial (CAST) is perhaps the best example [3]. In this trial although the Class I antiarrhythmics, flecainide and encainide, suppressed ventricular premature beats (VPB's) in this patient population, they caused an increase in total mortality and sudden cardiac death (SCD) compared to placebo.

Because of CAST and other trials [4,5] using class I agents which also showed an increased morbidity and mortality in post-MI patients taking these medicines, the major developments in antiarrhythmic drugs have been mainly in class III agents that prolong repolarization of cardiac tissue. This prolongation has the effect of decreasing the excitable gap, which is necessary for sustaining most clinical tachyarrhythmias that have a re-entrant mechanism.

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Table 1. Vaughan-Williams Antiarrhythmic Drug Classification

Class	Action	Drug
Class I	Sodium channel blockers	
A	<i>Modest Na⁺ channel effect Prolong action potential duration</i>	Quinidine, Procainamide, Disopyramide
B	<i>Lesser Na⁺ channel effect No change in action potential duration</i>	Lidocaine, Mexiletine
C	<i>Potent Na⁺ channel effect Mild prolongation of action potential duration</i>	Flecainide, Propafenone, Moricizine, Tocainide
Class II	Beta-Adrenergic blockers	Propranolol, Metoprolol, etc
Class III	Potassium channel blockers	Amiodarone, Sotalol, Ibutilide, Dofetilide, Azimilide
Class IV	Calcium antagonists	Verapamil, Diltiazem

BASIC ELECTROPHYSIOLOGY OF AZIMILIDE, A NOVEL CLASS III ANTIARRHYTHMIC AGENT

Cardiac depolarization is primarily the result of an inflow of Na⁺ and Ca⁺ ions, and repolarization results from the inactivation of these currents along with the outflow of K⁺ ions (See Fig. (1)). Terminal repolarization, mediated by the delayed rectifier potassium current, I_K, can be separated into 2 components: a rapidly activating component (I_{Kr}), and a slower component (I_{Ks}) [6]. Separate ion channel molecules carry each of these currents; *HERG* channels for I_{Kr}, and *minK* and *KvLQT1* for I_{Ks} (See Fig. (2)). Azimilide is a novel, potassium channel antagonist that uniquely blocks both I_{Kr} and I_{Ks} [7]. This is in contrast to the other conventional Class III agents (i.e. ibutilide, dofetilide, and sotalol) which block only I_{Kr} with little or no effect on I_{Ks} [8].

Azimilide uniquely appears to be 'rate-independent' and thereby prolongs the action potential duration, QT and QT corrected (QTc) interval (see Fig. (1)), and myocardial refractoriness over a wide range of heart rates [9,10]. This is in contrast to other Class III antiarrhythmic agents which have reverse-use dependency [11-13] which means that these other drugs have their maximal effect at slower rates with progressively diminished effects at higher rates. This unique rate independent effect of azimilide is likely because it also blocks I_{Ks}, which has been implicated in the repolarization process at higher heart rates and under states of sympathetic stimulation [7]. Thus, azimilide when compared with other Class III agents that only block I_{Kr}, may be expected to provide greater antiarrhythmic efficacy at higher rates that are typical during tachyarrhythmias. More importantly, azimilide's 'rate-independence' may reduce proarrhythmias, such as Torsades de Pointes (Tdp), at slower heart rates.

As noted previously, it is the concern about proarrhythmic potential that has continued to limit the use of antiarrhythmic drugs. In fact, Class III agents which work to increase the QT interval can cause excessive prolongation of repolarization, increase early afterdepolarizations, and promote triggered arrhythmias like Tdp [14,15]. Carlsson has documented the sensitivity of the adrenergically stimulated rabbit to study the proarrhythmic potential of Class III agents [16]. Using this model of proarrhythmia,

azimilide has been compared to other Class III agents to identify if it has less malignant arrhythmic potential. Using pharmacologically equivalent doses that prolonged the QTc interval by 20% with each drug, significantly less cumulative times in sustained ventricular tachycardia (VT) or combined nonsustained and sustained VT were observed in rabbits after an intravenous (IV) infusion of azimilide when compared with other Class III agents (including dofetilide and sotalol) [15]. Specifically, in this model, dofetilide-treated rabbits was ten times more likely to be in VT than those treated with azimilide [15]. As discussed above, it is azimilide's unique blockade of both I_{Kr} and I_{Ks}, relative to other typical Class III antiarrhythmics such as dofetilide and sotalol, which likely explains this lower proarrhythmic potential.

MECHANISM AND CLINICAL PHARMACOLOGY

Azimilide has been developed for use on an outpatient basis and is continuing to be studied in treating both supraventricular and ventricular tachyarrhythmias. The drug has very predictable pharmacokinetics and pharmacodynamics which are not affected by age or gender [17]. It is completely absorbed after oral administration via the gut and is not affected by food. Azimilide is 94% bound to plasma proteins, and it undergoes extensive hepatic metabolism while renal clearance accounts for <10% of total clearance [18]. Only one active metabolite with Class III antiarrhythmic activity is found at concentrations in plasma of <5% of the parent drug. A pharmacokinetics study involving patients with normal and severely impaired renal dysfunction found that azimilide blood concentrations were essentially unaffected by renal function suggesting that dose adjustment based on renal function is not required [19]. In fact in the large clinical studies to date with azimilide, dosing based on renal function has not been done, however, it should be noted that patients with significant chronic liver or renal dysfunction have typically been excluded (e.g. blood urea nitrogen >50 mg/dL or creatinine >2.0 mg/dL) [20-23]. No significant interactions with digoxin or warfarin have been observed such that coadministration requires no dosing adjustments [18]. Additionally, no significant effects on azimilide clearance are seen when coadministered with

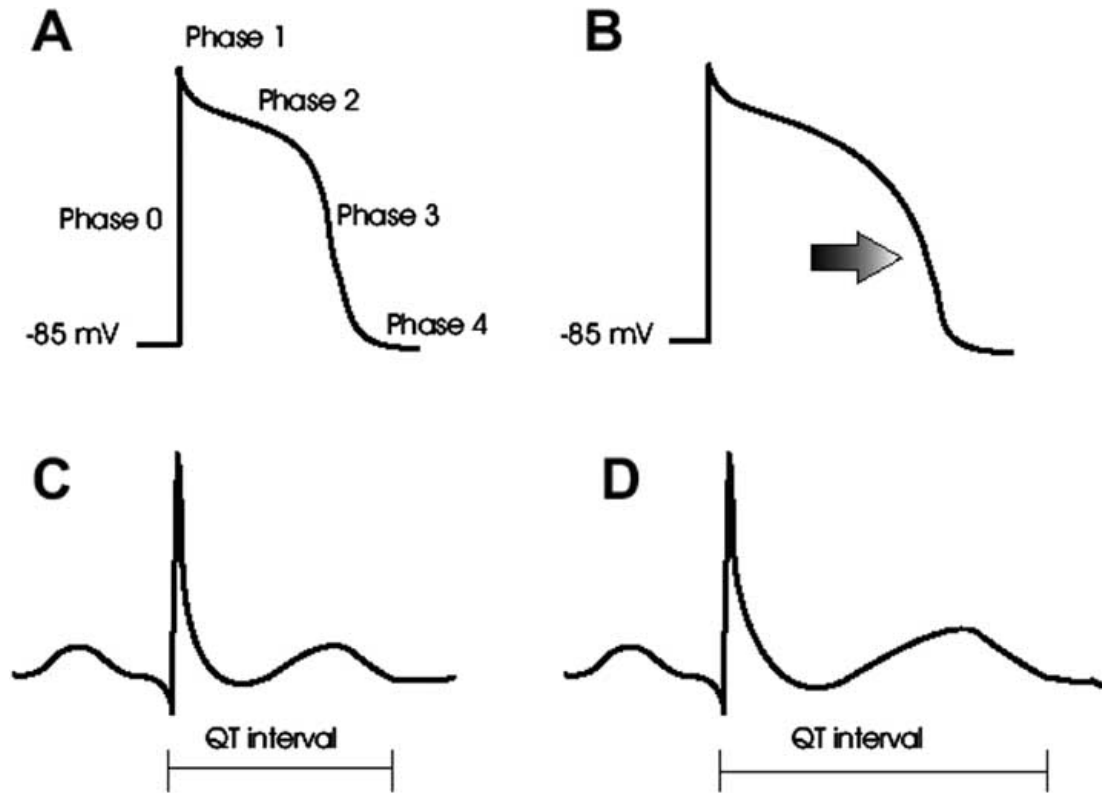


Fig. (1). Class III Antiarrhythmic Effect on the Action Potential and Electrocardiogram.

Class III antiarrhythmic effect is due to the blockage of the potassium channel during phase 3 of the action potential. This results in prolongation of the action potential duration and a delay in cellular repolarization. The prolongation of the repolarization is reflected in an increase in the QT interval on a surface ECG.

A. Ventricular action potential. Phase 0 is characterized by a rapid influx of Na^+ . An initial rapid influx of K^+ (transient outward current) accounts for Phase 1. Then there is a plateau phase, phase 2, which is due to entry of Ca^+ . Phase 3 is characterized by the outward flow of K^+ by both the rapid and slow currents (I_{Kr} and I_{Ks}). Phase 4 represents the resting membrane potential.

B. Ventricular action potential demonstrating the effect of class III antiarrhythmic agents, such as azimilide. The arrow shows prolongation in action potential duration due to delay in repolarization.

C. Normal surface ECG with normal QTc interval 0.440 seconds for males and 0.460 seconds for females (QTc = the measured QT interval divided by the square root of the R-R interval (in seconds)).

D. Surface ECG showing prolongation of QT interval due to Azimilide and other class III antiarrhythmic agents.

Cytochrome P450 inhibitors and inducers, including Cytochrome 3A4 which is at least partially involved in its metabolism. The time to peak plasma concentration is 5.2-5.6 hrs and the elimination half-life is 4-5 days. Because of its relatively long elimination half-life, azimilide is typically loaded for 3 days with twice daily dosing of 100-125 mg to more rapidly obtain therapeutic blood concentrations.

On the cardiac delayed-rectifier channels, azimilide's clinical efficacy occurs at plasma concentration of 0.1-3 μM , with much less potency at other receptors, such as α - and β -adrenergic, muscarinic receptors, or the L-type Ca^{2+} channel at this dose range [24,25]. In preclinical and clinical studies, it has been shown that azimilide prolongs repolarization in a dose-dependent manner by increasing the action potential duration, QTc interval, and effective refractory period. In human population studies, azimilide in daily doses up to 125 mg over a period of 6-9 months caused an average maximum increase in the QTc of 14-16% compared to baseline [18]. In pharmacokinetic studies with healthy male and female

volunteers, azimilide in doses up to 200 mg/day prolonged the mean maximum QTc in a range from 24-28% from baseline [17]. Patients with lower serum potassium levels (<3.5 mEq/L) are more sensitive to azimilide-induced QTc prolongation [18]. Azimilide has no effect on the PR or QRS intervals and little effect on the hemodynamic parameters of heart rate and blood pressure [18].

The most frequently reported adverse effect of azimilide is headache, with rare serious adverse events of an early, reversible neutropenia and QTc prolongation leading to Tdp [26]. Azimilide-associated severe neutropenia (i.e. an absolute neutrophil count <500 cells/ μl) has a predictable time of onset after drug initiation (typically between 19-48 days), and reverses after drug withdrawal and without leading to life-threatening infections [27]. Other more common adverse events reported by patients include fatigue, dyspnea, nausea, diarrhea, and dizziness, with none of these individually seen significantly more than placebo [20,26]. Furthermore, in long-term studies, the patient withdrawal

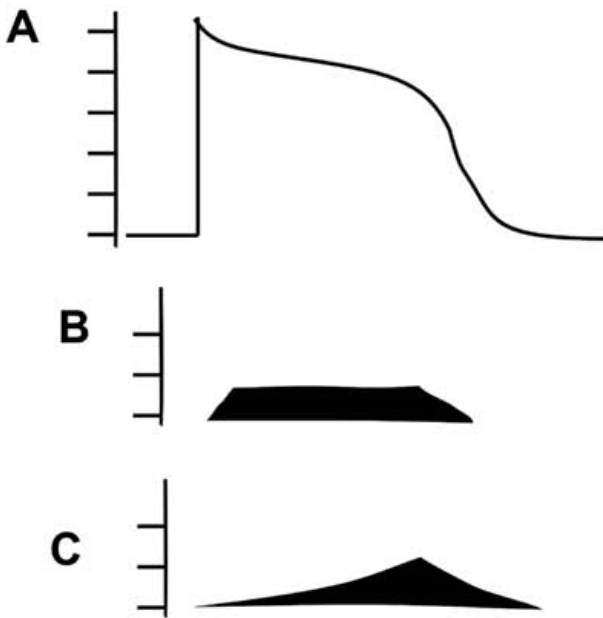


Fig. (2). Cardiac Delayed Rectifier Current (I_K).

The delayed rectifier current I_K is important in the repolarization of the cardiac action potential. It becomes activated as the membrane potential becomes more positive than -40mV . This produces an outward current that repolarizes the cell. At least two channel subtypes with different properties mediate I_K : I_{Kr} (rapidly activating current) and I_{Ks} (slowly activating current).

A. Ventricular action potential.

B. The ion channel protein responsible for I_{Kr} is encoded by the *HERG* gene. I_{Kr} is activated rapidly (compared to I_{Ks}) and results in a small outward current during the initial plateau phase of the action potential and a progressive increase in magnitude during terminal repolarization [2].

C. The ion channel proteins responsible for I_{Ks} are encoded by the *minK* and *KvLQT1* genes. I_{Ks} is activated slowly and increases gradually during the plateau phase of the cardiac action potential [2].

rate due to adverse events has been noticeably low and does not seem to increase with higher doses used [20,26]. Table (2) outlines clinically relevant comparisons of Azimilide with respect to other existing Class III antiarrhythmics.

USE FOR SUPRAVENTRICULAR TACHYARRHYTHMIAS

In animal models, azimilide has been shown to be very effective in the acute treatment of atrial tachyarrhythmias. In a canine model of sustained vagally-induced atrial fibrillation (AF), azimilide terminated AF in 93% while dofetilide was only 50% effective in terminating AF ($p < 0.05$) [13]. In canine functional models of atrial flutter, IV azimilide was 100% effective in terminating and preventing the reinduction of this arrhythmia [28,29]. No human studies to date have been published focusing on the efficacy of azimilide in the acute conversion rates of any supraventricular arrhythmias to sinus rhythm, thus this is a clinical niche that would be useful for further study. In an analysis of a small subgroup of patients ($n=93$) from the

AzimiLide post-Infarct surVival Evaluation (ALIVE) Trial, there was a trend toward more azimilide-treated patients converting from AF to sinus rhythm [27]. However, this analysis was over the period of one year, in a more difficult to treat patient population that was post-MI with moderate to severely reduced ejection fraction.

With respect to the chronic maintenance therapy, azimilide's efficacy in prolonging the time to first recurrence of AF/atrial flutter or paroxysmal supraventricular tachycardia (PSVT) was studied in a series of 4 double-blind, randomized, placebo-controlled trials of the Azimilide Supraventricular Arrhythmia Program (ASAP) in 1380 total patients [26]. These 4 trials (referred to as Supraventricular Arrhythmia (SVA) studies 1-4) had similar protocols and differed only in maximum duration of the study (270 days for SVA 1 and 2, 180 days for SVA 3 and 4) and in doses of azimilide tested (100 mg/day in SVA 1; 35 and 75 mg/day in SVA 2; 50, 100, and 125/mg day in SVA 3; and 125 mg/day in SVA 4).

In these trials, patients received oral azimilide or matching placebo twice daily for a 3 day loading period then followed by once/daily dosing. Eligible patients were men or women >18 years old, had documented AF, atrial flutter, or PSVT within the previous 24 months and were in sinus rhythm at the time of randomization. Patients were excluded if they had angina at rest, heart failure symptoms at rest, a resting heart rate <50 beats/minute, Wolff-Parkinson-White Syndrome, a history of Tdp, or a QTc interval >440 ms. In enrolled patients, structural heart disease was present in 73%, known ischemic heart disease in 28%, and a history of congestive heart failure (CHF) in 13%. For initiation of therapy, ninety-one percent of the patients had study medication loaded as an outpatient. Thirty-two percent of study patients were on concomitant beta-blockers, 50% on digoxin, and 25% on non-dihydropyridine calcium channel blockers. Transtelephonic Electrocardiogram (ECG) monitoring provided objective documentation of the rhythm routinely every 2 weeks and also after the onset of any symptoms. ECG's obtained during any clinical visits were also used. Blinded event committee review standardized the interpretation of these ECG's.

In patients with AF or atrial flutter ($n=384$), a combined efficacy analysis of the 100-125 mg groups showed a significant lengthening to the first symptomatic arrhythmia recurrence when compared to placebo, 60 versus 17 days respectively ($p = 0.005$ and Hazard Ratio was 1.58 (95% Confidence Interval (CI) = 1.15-2.16)) [20]. Noteworthy, all types of AF were included, such as paroxysmal or chronic. In an analysis of patients with PSVT ($n=193$), azimilide at doses of 100-125 mg showed a significant prolongation of the time to first recurrence ($p = 0.02$) [21]. Collectively in the ASAP trials, although no significant treatment effect was seen at doses lower than 100 mg/day, log-rank trend tests showed that there was a significant dose-dependent relationship across incremental azimilide doses [20,21]. Azimilide was well-tolerated with few adverse events independent of dose. Patient withdrawal rates were infrequent and did not appear to increase with higher doses of azimilide used. In subgroup analyses, patients with a

Table 2. Comparison of Class III Antiarrhythmic Drugs

Drug	Clinical Indication: Based on Type of Tachyarrhythmia		Typical Dose Range (all doses oral unless otherwise specified)	Method of Drug Initiation	Mechanism of Anti- arrhythmic Effect	Drug Elimin- ation	Potential Harmful Effects
	Atrial	Ventricular					
Amiodarone	X	X	200-400 mg daily (may load 400 mg twice/three times daily to 10 grams) (also may load IV: 150 mg over 10 min, then 1mg/min x 6 hrs., then 0.5 mg/min x 18 hrs)	As outpatient (monitoring recommended if patient at risk for bradycardia)	Multiple channel blocking effects (K ⁺ /Na ⁺ / Ca ⁺⁺ channels, Alpha/Beta- adrenergic and muscarinic receptors)	Tissue uptake predomin-antly (accumulates in adipose and other tissues)	Brady-arrhythmias, lung toxicity, hepatitis, hyper/hypo- thyroidism, skin/eye toxicity, tremor, ataxia, neuropathy
Sotalol	X	X	80 mg daily to 160 mg twice daily (dosing based on Creatinine Clearance)	48-72 hr. hospitalization recommended for loading (if structurally normal heart, may consider outpatient initiation)	Blocks Ikr and has Beta- blocking effects	>90% renal	Brady-arrhythmias, QTc, Tdp, CHF exacerbation, broncho- spasm
Ibutilide	X (only indicated for acute conversion of atrial fibrillation or flutter)		1 mg IV over 10 min. (may repeat x 1)	Inpatient monitoring required for at least 4 hrs after infusion completed	Appears to increase slow inward Na ⁺ currents during 2 nd plateau phase of action potential; also blocks Ikr	Hepatic predomin-antly	QTc and Tdp (increased risk in presence of hypokalemia or hypo- magnesemia)
Dofetilide	X		125 µg to 500 µg twice daily (starting dose based on Creatinine Clearance and QTc)	Hospitalization for atleast 3 days required for ECG monitoring and restricted access in U.S.	Blocks Ikr	20-30% hepatic, 70-80% renal	QTc and Tdp
Azimilide	X	?X (possibly as adjunctive therapy in ICD patients)	100 to 125 mg daily (load 100-125 mg twice daily x 3 days)	As outpatient	Blocks Ikr and Iks	90% hepatic, 10% renal	QTc and Tdp, rare reversible neutropenia

history of ischemic heart disease and/or CHF had a significantly greater treatment effect than those without it.

At the therapeutic dose range for azimilide in the ASAP trials, the incidence of Tdp was 0.9% and no cases of Tdp

led to death [26]. This compares to collective data from 22 clinical trials with sotalol to a risk of Tdp of 1.9% in men and 4.1% in women (over a median follow up of 164 days) [30]; while clinical trials with dofetilide have found a

varying risk of Tdp between 0.9-3.3% [31]. There also was an incidence of an early, reversible severe neutropenia (absolute neutropenia <500 cells/ μ L) of 0.2% in the ASAP trials with azimilide [26]. There was no significant difference in overall mortality or in arrhythmic mortality between azimilide and placebo, yet it should be noted that these studies were underpowered to reliably detect a difference. Collectively, the risk of serious adverse events was not significantly increased compared to placebo (8.5% azimilide vs. 6.4% placebo, p =Not statistically Significant (NS)).

Thus far, published clinical studies with azimilide have only compared it relative to placebo in the chronic maintenance of sinus rhythm. It will be important to compare azimilide's efficacy in maintaining sinus rhythm to other commonly used antiarrhythmic agents, such as amiodarone, dofetilide, or sotalol. One comparator trial involving a sotalol study arm has been undertaken [32], and more active head to head trials in the future will be useful. Currently with respect to azimilide's clinical efficacy relative to other agents, the only objective comparison that can be made is the percent of patients maintaining sinus rhythm over a given time period. It should be noted that this is likely an imperfect comparison when analyzing efficacy rates derived in separate trial populations. Based on the ASAP-SVA 3 study, the percentage of patients with AF or atrial flutter maintained in sinus rhythm at 180 days was approximately 50% with 100-125 mg/day of azimilide, and likely >60% in patients with a history of PSVT, compared with approximately 30% on placebo [20]. From the Canadian Trial of Atrial Fibrillation [33], amiodarone maintained sinus rhythm up to 1 year in 69%, and either sotalol or propafenone maintained sinus rhythm in 39%. From clinical studies with dofetilide, approximately 50-70% will maintain sinus rhythm over 6-12 months [31,34]. Comparing across placebo-controlled studies in the population of post-MI patients with reduced left ventricular ejection fraction (LVEF), placebo-subtracted efficacy rates in maintaining sinus rhythm are similar: 28% for azimilide, 25% for dofetilide, and 23% for amiodarone [27,35-38]. A more subjective but appropriate comparison to make between any arrhythmic drugs is their relative risk-benefit ratios based on a variety of clinical parameters. Relative to other antiarrhythmic agents most often used for AF, atrial flutter, or PSVT, azimilide appears to have a favorable risk-benefit ratio in terms of safety of use in patients with structural heart disease (relative to Ic agents, flecainide or propafenone), ease of initiation and dosing (relative to sotalol or dofetilide), and degree of tolerability/lack of systemic side-effects (relative to amiodarone and likely sotalol).

One potential criticism of analyzing the treatment effect of antiarrhythmic agents on the occurrence of symptomatic AF is that these drugs may only make AF less symptomatic by slowing the heart rate during the tachyarrhythmia or by shortening the duration of the arrhythmia. Thus, antiarrhythmic drug therapy may have a clinical effect of reducing symptoms by converting symptomatic arrhythmia episodes into asymptomatic ones. This concept was analyzed systematically with respect to azimilide in the ASAP studies [39]. Along with demonstrating the efficacy of azimilide for symptomatic AF, flutter, and PSVT, these trials also showed

that azimilide may reduce the occurrence of asymptomatic AF. In routine transtelephonic ECG monitoring done every 2 weeks throughout the clinical follow-up of the study period, asymptomatic AF was seen in 49 of 382 (13%) patients taking azimilide compared with 43 of 233 (18%) of the patients taking placebo. The estimated hazard ratio was 0.70 (95% CI=(0.46-1.06), p =0.09) which represented a non-statistically significant trend toward reducing asymptomatic AF. When repeated episodes among given patients were considered, there was a significant treatment effect seen (p =0.03) and an estimated 40% reduction in the occurrence of asymptomatic AF for azimilide treated patients compared with placebo.

While in the ASAP studies azimilide did not appear to lead to more asymptomatic AF episodes, it did seem to reduce the number of symptoms reported by patients at the time of their first documented AF recurrence [40]. This data collected in the ASAP studies found that 125 mg/day of azimilide compared to placebo significantly reduced a symptom score (i.e. a novel, previously unvalidated score based on patients reporting during their first AF recurrence whether they experienced any of the following 6 symptoms: palpitations, fatigue, chest pain, shortness of breath, dizziness, or sweating). Of note, although doses of 100 and 125 mg/day of azimilide were both significantly effective in prolonging the time to arrhythmia recurrence in the ASAP studies, only the 125 mg/day dose of azimilide provided a significant reduction in patients experiencing the symptoms of fatigue, shortness of breath, chest pain, and dizziness. The investigators also identified that this beneficial effect of azimilide on reducing these symptoms was predominantly independent of any heart rate reduction at the time of arrhythmia recurrence relative to placebo. The actual mechanism of this benefit and the reason why the azimilide dose of 125 mg/day only had this effect are unclear. Nevertheless, the investigators noted that along with azimilide prolonging the time to first episode of AF, atrial flutter, or PSVT, it may provide another tangible benefit to patients in reducing the symptom burden at the time of arrhythmia recurrence.

Three more on-going studies will further test the role of azimilide in the treatment of symptomatic supraventricular tachyarrhythmias [32]. The Azimilide Supraventricular Tachy-Arrhythmia Reduction (A-STAR) Trial will test the efficacy of 125 mg of azimilide/day versus placebo in patients with symptomatic AF. For the data analysis, the trial will have 2 separate groups of patients with and without ischemic heart disease or CHF. The Azimilide CardiQversion Maintenance Trial (A-COMET) I will compare 125 mg azimilide/day with placebo in prolonging the time to first recurrence of supraventricular tachyarrhythmias in patients who have undergone electrical cardioversion of AF. Finally, the A-COMET II Trial, conducted in Europe, will be similar to the A-COMET I Trial except it will have a third comparator arm with patients on a sotalol regimen. Hopefully, these trials will further clarify the role of azimilide in treating symptomatic supraventricular tachyarrhythmias within more specific target populations of patients and identify azimilide's efficacy relative to another antiarrhythmic agent.

USE FOR VENTRICULAR TACHYARRHYTHMIAS

Effective and safe pharmacological prophylaxis against ventricular arrhythmias and SCD especially in post-myocardial infarction (MI) has been an elusive goal for years. Early experience with other antiarrhythmic agents, notably Class I antiarrhythmics in high-risk post-MI patients was disappointing yielding an increased mortality with drug therapy compared to placebo [3-5]. Subsequently, Class III antiarrhythmics have been sequentially tested for their effect on all-cause mortality [37,41-43] and have thus far not been found to improve survival. Shortcomings of these trials have been noted in that they enrolled a relatively broad spectrum of patients, including those at more low risk for ventricular arrhythmias and SCD and were then subjecting them to potentially adverse effects of these various antiarrhythmic agents [41,44].

With respect to azimilide, previously in a canine model of post-MI SCD, it had been shown to be effective in suppressing programmed electrically stimulated VT and in preventing ischemia-induced ventricular fibrillation (VF) [45]. This led to a subsequent clinical study initially presented at the American Heart Association Meeting in November, 2001 and then recently published, the AzimiLide post-Infarct survival Evaluation (ALIVE) Trial [46]. It was a large multinational, prospective, placebo-controlled, randomized trial in recent survivors of MI at high risk for arrhythmia-induced SCD testing the effects of azimilide on all-cause mortality. In comparison to prior clinical trials in post-MI patients with other antiarrhythmic agents [3,41,42], the ALIVE Trial Investigators aimed to target those at highest risk for arrhythmic death, including only those patients with low LVEF and recent MI, and then further stratified the study population based on heart rate variability [22]. Reduced heart rate variability has been shown to be associated with increased risk of SCD in post-MI patients irrespective of underlying LVEF [47]. Thus, the ALIVE Trial included patients with low LVEF (defined as 15-35% determined at least 1 day post-MI), recent survivors of MI (within 5-21 days post-MI), and further risk-stratified patients as "high-risk" by low heart rate variability (HRV) (defined as 20 baseline width units).

A total of 3717 post-MI patients were enrolled, 1690 randomized to placebo and 1691 were randomized to 100 mg of azimilide daily, at 483 centers worldwide. Baseline clinical characteristics were similar between treatment groups [46]. Of note, most patients were male (78%) with an average age of 60 years and 73% were on beta-blockers and 87% were on angiotension converting enzyme-inhibitors, because use of these drugs was encouraged by investigators. Mean LVEF was 29% and more than half of patients had New York Heart Association Class II or III CHF, while Class IV patients were excluded. Overall results with 1 year of follow-up showed no statistical increase or decrease in all-cause mortality between the placebo and azimilide groups (12% versus 12% respectively in the whole population, and 15% versus 14% respectively in the "high-risk" subgroup based on a low HRV, $p=NS$). Accordingly, in prespecified subgroup analysis, there was no significant difference in mortality between azimilide and placebo, except there was a trend toward improved survival in patients receiving

azimilide without α -adrenergic blocking drugs ($p=0.06$). Interestingly, this study did confirm prospectively that low HRV independently predicting a higher mortality among patients with depressed LVEF.

In the ALIVE Trial, azimilide did reduce the incidence of new AF from 19/1648 (1.2%) in the placebo group to 8/1630 (0.5%) in the active therapy group ($p<0.04$) [27]. Also, azimilide-treated patients were less likely than placebo patients to develop new or worsening heart failure (6% versus 8% respectively, $p=0.05$) [27]. Finally, consistent with observations from the supraventricular tachycardia studies in which azimilide did not cause excess harm, the overall incidence of Tdp in this study was less than 0.3% and the incidence of neutropenia was less than 0.9%. Patient compliance and withdrawals because of adverse events were similar in the placebo and azimilide groups.

Despite these above results regarding the role of azimilide in the primary prevention of ventricular arrhythmias in high-risk patients, further trials are necessary to evaluate if azimilide is effective for secondary prevention in patients with symptomatic ventricular arrhythmias. Currently, azimilide is being studied in a large randomized, placebo-controlled trial whether it can reduce the frequency of shocks and anti-tachycardia pacing (ATP) in patients with an implantable cardioverting defibrillator (ICD) in the SHock Inhibition Evaluation with AzimiLiDe (SHIELD) Trial. A significant reduction in ICD therapies had been seen in an early Phase 2 trial with azimilide versus placebo [48]. Then in a recently published multicenter pilot study of 172 patients with prior VT, azimilide at three doses (35, 75, and 125 mg) demonstrated a significant reduction in appropriate ICD shocks and ATP for VT or VF compared with placebo [23]. The majority of these patients had a LVEF $<35\%$ and most had a history of a previous MI. In this adjunctive therapeutic role, azimilide was efficacious at all administered doses, had no significant impact on hemodynamic status or LVEF, and was well tolerated with no significant differences in adverse event rates compared to placebo. The larger ongoing SHIELD Trial will look to confirm these results.

Theoretically supported by observations that drugs that cause potassium channel blockade and prolong repolarization can decrease the defibrillation energy requirement [49], it has then been studied and shown in canine models that azimilide significantly reduces the defibrillation energy requirement (DER) [50,51]. In one study [51], while azimilide significantly reduced the DER ($p<0.05$), acidemia (defined by an arterial pH of 7.15) raised the DER, and then the combination of acidemia with azimilide treatment still resulted in an increase in the DER. The authors hypothesized that azimilide may be efficacious in lowering the DER, but a clinical effect may not occur *in vivo* when systemic acidosis or widespread myocardial ischemia/infarction occurs [51]. In fact, in the multicenter pilot study of 172 patients with prior VT and an ICD discussed above, minimal energy requirements for pacing and defibrillation was determined at baseline and at 1 month, and did not change with azimilide therapy [23]. Finally, other Class III agents such as dofetilide and sotalol have been shown to have some lowering effect on the ventricular refractoriness and DER's [52,53], however in contrast to azimilide and these other two agents, neither

acute or chronic treatment with amiodarone has been shown to change the DER [54].

Thus at this point, the clinical role for azimilide in treating ventricular arrhythmias has not been firmly established. The final results of the ALIVE Trial indicate that azimilide is not harmful, but also not helpful for the primary prevention of SCD in high-risk patients. Early studies suggest that azimilide has an adjunctive therapeutic role in patients with ICD's in decreasing appropriate ICD therapies. These ICD therapies can be painful and psychologically traumatic for patients, therefore reducing them would be a worthwhile clinical benefit. We must await the results of the SHIELD Trial, and other potential future trials to further understand the clinical efficacy of azimilide if any in the primary prevention of SCD, in patients with prior symptomatic ventricular arrhythmias, and in patients already with ICD's to prevent device therapies and in decreasing the DER.

SUMMARY

Azimilide, is a novel Class III antiarrhythmic that uniquely block I_{ks} and I_{kr} and appears to be rate independent. The drug is in late phase clinical trials to further refine its efficacy in the treatment of AF, atrial flutter, PSVT, and on-going Phase III trials in ventricular tachyarrhythmias. Clinically in patients with and without structural heart disease, azimilide has been shown to be effective in maintaining sinus rhythm in patients with prior symptomatic supraventricular arrhythmias, to decrease episodes of asymptomatic AF, and to limit the amount of symptoms patients experience with AF recurrences. Azimilide's efficacy relative to other antiarrhythmic agents in the chronic maintenance therapy of AF is not yet clearly known. Animal studies suggest it may have a role in the acute conversion of supraventricular arrhythmias, but no data is available yet in humans. Early studies also suggest a role for azimilide in the secondary prevention of ventricular arrhythmias, but the ALIVE Trial confirms azimilide has little if any role in the primary prevention of ventricular arrhythmias. Thus, at present, the best established target populations for azimilide seem to be in patients with AF, atrial flutter, or PSVT to maintain sinus rhythm and in patients with ICD's to prevent device therapies. Finally and importantly relative to many other antiarrhythmic drugs, azimilide appears to be easy to use, safe in the patient populations tested thus far, and well-tolerated in patients with and without structural heart disease and in patients at high-risk of SCD.

ABBREVIATIONS

MI	=	Myocardial Infarction
CAST	=	Cardiac Arrhythmias Suppression Trial
VPB's	=	Ventricular Premature Beats
SCD	=	Sudden Cardiac Death
I_{kr}	=	Rapidly-activating component of the delayed-rectifying potassium channel

I_{ks}	=	Slowly-activating component of the delayed-rectifying potassium channel
QTc	=	QT corrected (for heart rate) interval
Tdp	=	Torsades de Pointes
VT	=	Ventricular Tachycardia
IV	=	Intravenous
ALIVE Trial	=	<u>A</u> zimi <u>L</u> ide post- <u>I</u> nfarct sur <u>V</u> ival <u>E</u> valuation Trial
PSVT	=	Paroxysmal Supraventricular Tachycardia
AF	=	Atrial Fibrillation
ASAP	=	Azimilide Supraventricular Arrhythmia Program
SVA Study	=	Supraventricular Arrhythmia Study
CHF	=	Congestive Heart Failure
ECG	=	Electrocardiogram
CI	=	Confidence Interval
NS	=	Not statistically Significant
LVEF	=	Left Ventricular Ejection Fraction
A-STAR Trial	=	<u>A</u> zimilide <u>S</u> upraventricular <u>T</u> achy- <u>A</u> rrhythmia <u>R</u> eduction Trial
A-COMET Trial	=	<u>A</u> zimilide <u>C</u> ardi <u>O</u> version <u>M</u> aint <u>E</u> nance <u>T</u> rial
VF	=	Ventricular Fibrillation
HRV	=	Heart Rate Variability
ATP	=	Anti-Tachycardia Pacing
ICD	=	Implantable Cardioverting Defibrillator
SHIELD Trial	=	<u>S</u> hock <u>I</u> nhibition <u>E</u> valuation with <u>A</u> zimi <u>L</u> i <u>D</u> e Trial
DER	=	Defibrillation Energy Requirement

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