Mortality in Patients After a Recent Myocardial Infarction
A Randomized, Placebo-Controlled Trial of Azimilide Using Heart Rate Variability for Risk Stratification

A. John Camm, MD; Craig M. Pratt, MD; Peter J. Schwartz, MD; Hussein R. Al-Khalidi, PhD; Maria J. Spyt, MD; Michael J. Holroyde, PhD; Roger Karam, MD; Edmund H. Sonnenblick, MD; Jose M.G. Brum, MD; on Behalf of the AzimiLide post Infarct surVival Evaluation (ALIVE) Investigators

Background—Depressed left ventricular function (LVF) and low heart rate variability (HRV) identify patients at risk of increased mortality after myocardial infarction (MI). Azimilide, a novel class III antiarrhythmic drug, was investigated for its effects on mortality in patients with depressed LVF after recent MI and in a subpopulation of patients with low HRV.

Methods and Results—A total of 3717 post-MI patients with depressed LVF were enrolled in this randomized, placebo-controlled, double-blind study of azimilide 100 mg on all-cause mortality. Placebo patients with low HRV had a significantly higher 1-year mortality than those with high HRV (>20 U; 15% versus 9.5%, $P<0.0005$) despite nearly identical ejection fractions. No significant differences were observed between the 100-mg azimilide and placebo groups for all-cause mortality in either the "at-risk" patients identified by depressed LVF (12% versus 12%) or the subpopulation of "high-risk" patients identified by low HRV (14% versus 15%) or for total cardiac or arrhythmic mortality. Significantly fewer patients receiving azimilide developed atrial fibrillation than did patients receiving placebo (0.5% versus 1.2%, $P<0.04$). The incidences of torsade de pointes and severe neutropenia (absolute neutrophil count $\leq$500 cells/μL) were slightly higher in the azimilide group than in the placebo group (0.3% versus 0.1% for torsade de pointes and 0.9% versus 0.2% for severe neutropenia).

Conclusions—Azimilide did not improve or worsen the mortality of patients after MI. Low HRV independently identified a subpopulation at high risk of mortality. **(*Circulation*. 2004;109:990-996.)**

Key Words: azimilide ■ antiarrhythmia agents ■ trials ■ heart rate

Mortality in the first year after myocardial infarction (MI) has been significantly reduced because of the development of a range of interventions and therapies including thrombolysis, coronary angioplasty, aspirin, β-blockers, ACE inhibitors, and aldosterone antagonists.[1–5] Although the incidence of sudden cardiac death, presumably largely because of ventricular tachyarrhythmia, remains substantial, antiarrhythmic drug therapy has not yet been shown to reduce mortality after MI.[6–8] Failure of antiarrhythmic drugs to reduce sudden cardiac death may be related to limitations of their pharmacological actions or to cardiovascular complications of the therapy. It might also be a result of the inadequate risk stratification, resulting in a study population with a low risk of arrhythmic mortality or a competitive mortality risk from pump failure.[7] To overcome this problem, it has been proposed that trial designs involving large general populations should be powered to detect significant results in subpopulations most likely to be specifically protected by the intervention.[9]

Depressed left ventricular (LV) function is associated with increased all-cause mortality after an MI.[10] This increase in mortality is nonspecific, and the predictive value of LV function is relatively low.[11] Reduced heart rate variability (HRV), which can be assessed by a variety of techniques, is associated with increased sudden cardiac mortality in patients who have suffered an MI.[12,13] The predictive accuracy of HRV is seen in patients irrespective of the underlying LV function.[12,14,15]

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From the Department of Cardiology, St George's Hospital, London, UK (A.J.C.); Baylor College of Medicine, Houston, Tex (C.M.P.); Department of Cardiology, Policlinico S Matteo, IRRCS, and University of Pavia, Italy (P.J.S.); Procter & Gamble Pharmaceuticals Inc, Cincinnati, Ohio (H.R.A., M.J.S., M.J.H., R.K., J.M.G.B.); and Albert Einstein College of Medicine, New York, NY (E.H.S.).

The following authors were consultants and members of the ALIVE Steering Committee: Drs Camm, Pratt, Schwartz, and Sonnenblick. In addition, the following authors are Procter & Gamble employees: Drs Al-Khalidi, Spyt, Holroyde, Karam, and Brum.

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Correspondence to Prof A. John Camm, MD, Department of Cardiology, St George's Hospital Medical School, Cranmer Terrace, London, SW17 ORE, UK. E-mail jcamm@sghms.ac.uk

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TABLE 1. Baseline Demographics

Characteristics	At Risk (All Randomized)		High Risk (HRV≤20 Units)	
	Placebo (n=1690)	Azimilide (n=1691)	Placebo (n=642)	Azimilide (n=622)
No. days from MI to randomization	13±5	12±5	12±5	12±5
Demography				
Male	1318 (78)	1318 (78)	475 (74)	443 (71)
Age, y	61±11	60±10	62±10	61±10
LVEF, %	29.3±0.12	29.4±0.12	28.8±0.20	28.9±0.19
15%–25%	407 (24)	379 (22)	176 (27)	152 (24)
26%–35%	1283 (76)	1312 (78)	466 (73)	470 (76)
NYHA class				
0–I	809 (48)	796 (47)	290 (45)	271 (44)
II	693 (41)	717 (42)	255 (40)	265 (43)
III	188 (11)	178 (11)	97 (15)	86 (14)
Risk factors				
History of diabetes	416 (25)	439 (26)	214 (33)	211 (34)
History of hypertension	952 (56)	936 (55)	368 (57)	348 (56)
Current smoker	257 (15)	256 (15)	84 (13)	88 (14)
Thrombolysis/CABG/angioplasty	975 (58)	1005 (59)	380 (59)	370 (60)
Previous MI	504 (30)	507 (30)	179 (28)	175 (28)
Treatment at baseline				
Diuretic	770 (46)	792 (47)	349 (54)	351 (56)
β-Blocker	1252 (74)	1232 (73)	459 (72)	430 (69)
ACE inhibitor	1463 (87)	1468 (87)	561 (87)	540 (87)
Digoxin	221 (13)	276 (16)	99 (15)	130 (21)
Statin	490 (29)	478 (28)	193 (30)	185 (30)
Aspirin	1490 (88)	1487 (88)	564 (88)	543 (87)
Warfarin	156 (9)	178 (11)	62 (10)	82 (13)

Values are given as mean±SD or n (%). n indicates number of patients.

Azimilide is an investigational antiarrhythmic drug with a novel molecular structure and mode of action, blocking both the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier potassium current, leading to prolongation of the myocyte action potential, which is not dependent on heart rate.[16–18] Oral azimilide doses of 75 and 125 mg have been shown to reduce the frequency of ventricular arrhythmias in a clinical study of patients with an implantable cardioverter-defibrillator.[19]

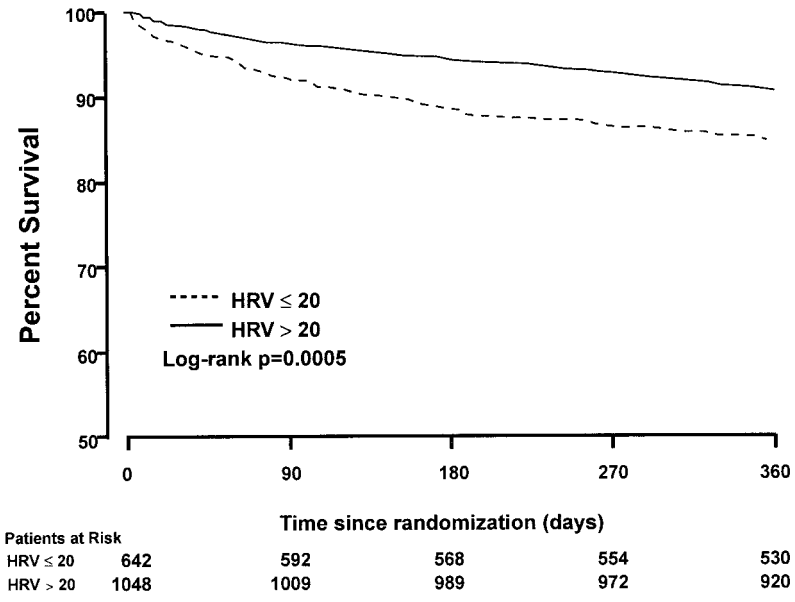

Figure 1. Kaplan-Meier curve of all-cause mortality in placebo patients in high-risk group (HRV ≤20 U) and low-risk group (HRV >20 U).

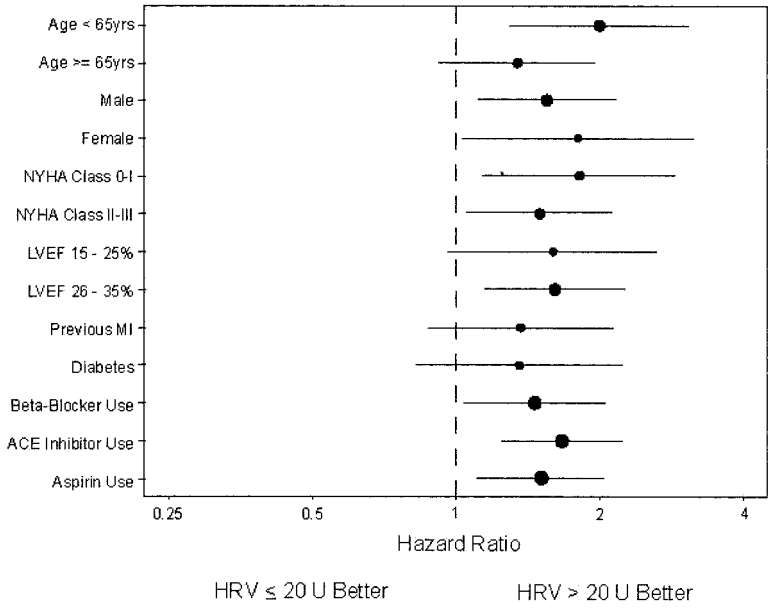

Figure 2. Relative risk of all-cause mortality in subgroups of high-risk and low-risk placebo patients.

The purpose of the present study was to evaluate the effect of azimilide on all-cause and cause-specific mortality in patients with depressed LV function after a recent MI and in a subpopulation of these patients at higher risk, identified by low HRV.

Methods

The AzimiLide Post-Infarct SurVival Evaluation (ALIVE) trial was conducted at 483 sites in 26 countries. Institutional Review Board/Ethics Committee approval and written informed consent were obtained before study start.

Patients were included in this study if they were 18 to 80 years old, had had a documented MI within the previous 5 to 21 days, and had an LV ejection fraction (LVEF) of 15% to 35%, determined at least 1 day after the MI.

Patients were excluded if they had a history of torsade de pointes (TdP), unstable angina pectoris or a high-degree heart block, a QTc interval of ≥450 ms, a resting heart rate <50 bpm, New York Heart Association (NYHA) class IV congestive heart failure, implantable cardioverter-defibrillator, serum potassium concentrations of <4 mEq/L, amiodarone use within 1 month before enrollment, or current use of class I or III antiarrhythmic drugs.

All randomized patients were referred to as the "at-risk" population. A unique feature of this study design was the acquisition of a 24-hour ambulatory ECG recording at baseline from which HRV was analyzed by a central laboratory by the triangular index method previously described by Malik et al.[20] The HRV triangular index is a geometric method of quantifying HRV that was used in the ALIVE trial to identify patients at increased mortality risk and was based on data from a previous post-MI trial (the European Myocardial Infarction Amiodarone Trial [EMIAT]). These data provided the dichotomy value used to differentiate between preserved and reduced HRV (20 baseline width units) and the basis for the power calculation for the ALIVE trial.

Although the HRV measurement results were not part of the eligibility requirements, they were used to prospectively stratify the at-risk trial population. Patients with baseline HRV of ≤20 U were assigned to the "high-risk" cohort. Patients with baseline HRV >20 U are referred to as the "low-risk" group.

Patients were randomly assigned to receive azimilide 75 mg, azimilide 100 mg, or identical placebo. Treatment could be initiated in hospital or out of hospital within 5 to 21 days after MI, at the investigators' discretion. Because of enrollment difficulties, the azimilide 75 mg arm was discontinued before study completion after enrollment of 336 patients. All patients were followed up to study

TABLE 2. Causes of Death in At-Risk, Low-Risk, and High-Risk Groups (Numbers of Patients)

	At Risk (All Randomized)		Low Risk (HRV >20 Units)		High Risk (HRV ≤20 Units)	
Cause of Death*	Placebo (n=1690)	Azimilide (n=1691)	Placebo (n=1048)	Azimilide (n=1069)	Placebo (n=642)	Azimilide (n=622)
All cause	196 (12)	197 (12)	100 (9.5)	109 (10.2)	96 (15)	88 (14)
Noncardiac	38 (2)	23 (1)	13 (1.2)	9 (0.8)	25 (4)	14 (2)
Cardiac	158 (9)	174 (10)	87 (8.3)	100 (9.4)	71 (11)	74 (12)
Nonarrhythmic	66 (4)	60 (4)	36 (3.4)	36 (3.4)	30 (5)	24 (4)
Total arrhythmic	92 (5.4)	114 (6.7)	51 (4.9)	64 (6.0)	41 (6.4)	50 (8.0)
Documented†	9 (1)	13 (1)	3 (0.3)	7 (0.7)	6 (1)	6 (1)
Undocumented	83 (5)	101 (6)	48 (4.6)	57 (5.3)	35 (6)	44 (7)

Values are given as n (%).

*Classifications were done by an independent Event Committee.

†Arrhythmic events that were documented by ECG at the time of death.

completion, but only the azimilide 100 mg and placebo arms are presented in this article.

Patients were evaluated at baseline, at 2 weeks, and at months 1, 2, 4, 8, and 12. Standard laboratory tests and 12-lead ECGs were performed. Study drug was discontinued if ECGs revealed a QTc of ≥525 ms or absolute neutrophil count was <1000/μL.

Statistical Methods

The primary efficacy analysis compared all-cause mortality in patients treated with azimilide 100 mg and placebo at high risk of death. An additional prespecified primary efficacy analysis was all-cause mortality in all randomized patients (at risk). Both analyses were based on longitudinal intention-to-treat observations for 365 days after each patient's randomization date. Patients who were alive at 365 days were censored at that point; patients with unknown survival status were considered dead the day after the last day they were known to be alive. All statistical testing had a 2-sided, alternative hypothesis, with type I error (α=0.0366) allocated to the primary efficacy analysis (all-cause mortality in the high-risk group). An additional proportion of the total type I error (0.0034) was used on 3 planned interim analyses using Lan-DeMets α spending function.[21] The remaining type I error (0.01) supported the alternative primary analysis of all-cause mortality in the at-risk patients. Kaplan-Meier life table estimates of survival and hazard ratios using the Cox proportional hazards model were computed.[22]

Statistical assumptions were based on 15% 1-year mortality in the placebo high-risk group and 45% reduction in high-risk azimilide 100 mg patients. High-risk patients were expected to compose 37% of those recruited. On the basis of these statistical assumptions using previous HRV databases, it was determined that to ensure 90% power for the primary efficacy analysis, 1250 high-risk patients (azimilide 100 mg or placebo) should be randomized and followed up for 365 days.

Results

The baseline demographic comparison of azimilide 100 mg and placebo patients is presented in Table 1 for both high-risk and at-risk groups. The patient population was primarily male (78%), with a mean LVEF of 29%. More than half of the patients had NYHA II or III congestive heart failure. Several cardiovascular risk factors were more frequent in the high-risk group than in the at-risk group, notably NYHA class III status and diabetes. Concomitant medications at baseline were similar in both treatment groups, with a very high percentage of patients appropriately taking β-blockers, ACE inhibitors, and aspirin. Therapy was initiated out of hospital in 27% of the patients.

Placebo patients in the high-risk group had a significantly higher mortality rate (96/642, 15%) than placebo patients in the low-risk group (100/1048, 9.5%; hazard ratio, 1.64; 95% CI, 1.24 to 2.17; log-rank P=0.0005) (Figure 1).

Low HRV remained an independent predictor of mortality among placebo patients after control for the following risk factors: age (<65 or ≥65 years), LVEF (15% to 25% or 26% to 35%), NYHA class (0–I or II–III), sex, diabetes, and β-blocker use at baseline (hazard ratio, 1.46; 95% CI, 1.10 to 1.94; P=0.009) (Figure 2). However, low HRV did not predict arrhythmic mortality (Table 2).

Kaplan-Meier survival curves comparing azimilide 100 mg and placebo treatment in the high-risk and at-risk groups are presented in Figure 3. Neither analysis showed a significant difference between azimilide and placebo. The hazard ratio in the high-risk group was 0.95 (95% CI, 0.71 to 1.27; log-rank P=0.74), whereas the hazard ratio in the at-risk group was 1.0 (95% CI, 0.82 to 1.22; log rank P=0.98).

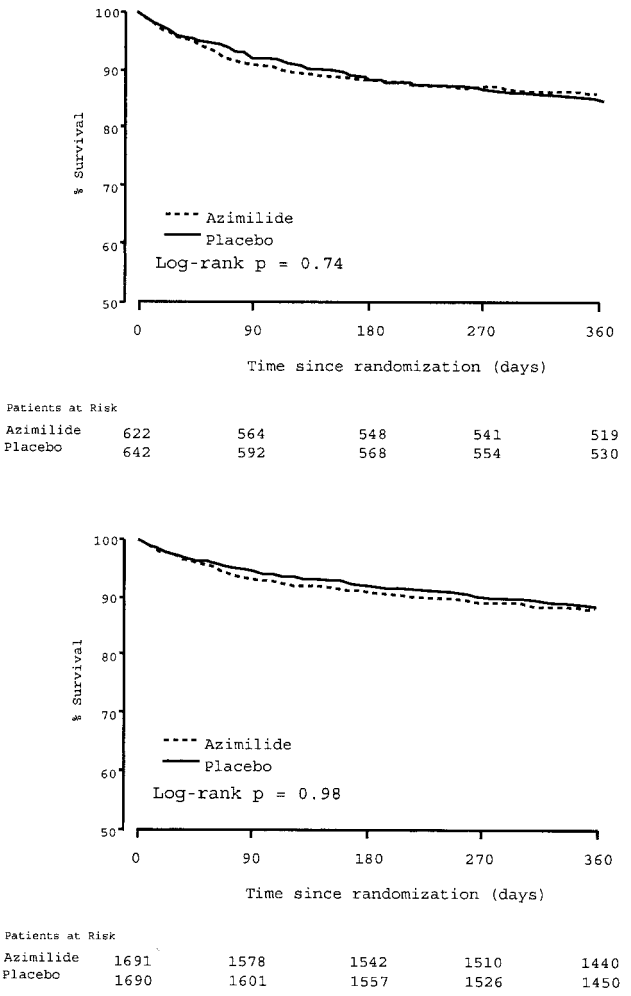

Figure 3. Kaplan-Meier curves of all-cause mortality in high-risk group and at-risk group.

The majority of deaths were classified as cardiac deaths, and more than half of these were arrhythmic, with no statistical difference between the treatment groups (Table 2). The vast majority of cardiac deaths classified as arrhythmic had no ECG available, occurred in the outpatient setting, and were unwitnessed. Because more than half of the events, 51% (201/393), occurred in the first 90 days, a 2-piece proportional hazards model was fitted over the periods day 1–90 and day 91–365, and there was no statistical significance between the treatment groups over either period.

The azimilide group showed a median maximal change in QTc (50 ms) that was higher than that of the placebo group (23 ms). Because the therapeutic effects of azimilide (I_{Kr} and I_{Ks} blockade) result in QTc prolongation, an exploratory analysis was performed to determine whether the QTc changes in both azimilide and placebo patients who died differed from those in both treatment groups who survived for 1 year. The median maximal increases in QTc for azimilide patients who died (47 ms) or survived (51 ms) were similar, whether all-cause (Figure 4A) or arrhythmic (Figure 4B) mortality was considered. The same was true of placebo

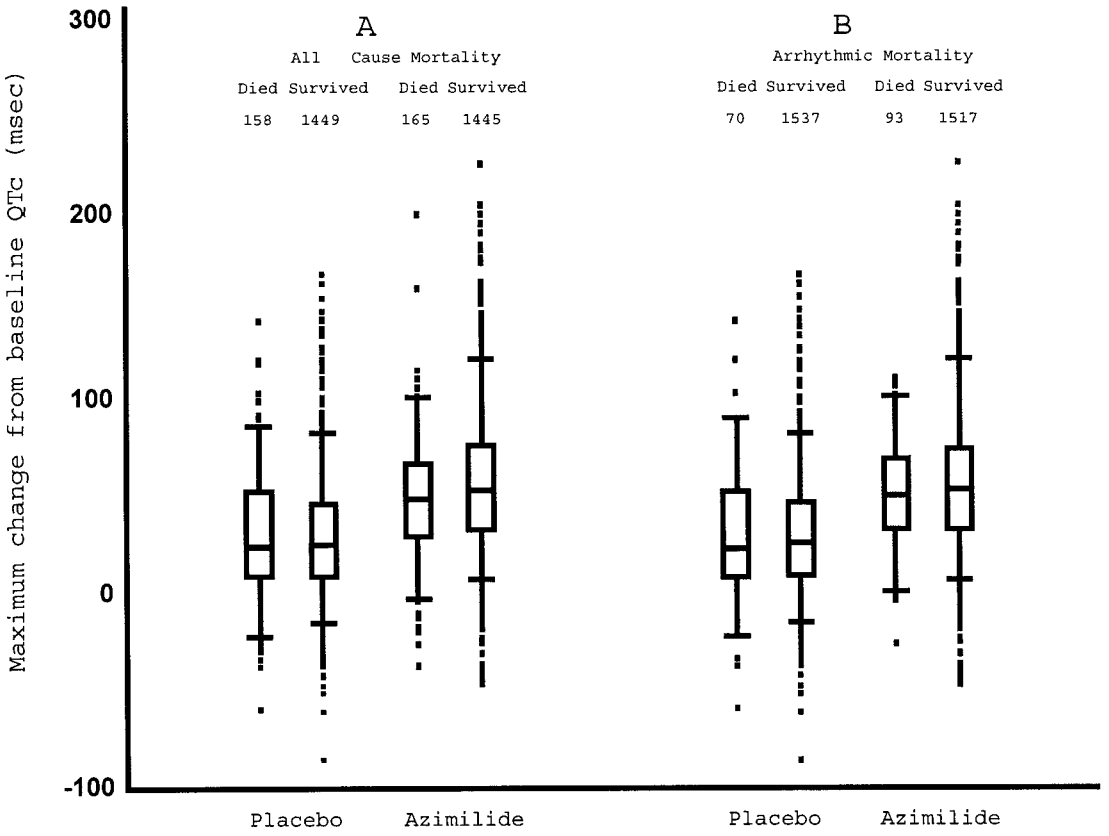

Figure 4. Comparison of maximal change from baseline QTc in patients who died and patients who survived. Horizontal row inside box represents median maximal change.

patients (23 ms for both patients who died and patients who survived).

The relative risk of mortality for prespecified subgroups in the at-risk group is summarized in Figure 5. Although there was no significant difference in mortality between azimilide 100 mg and placebo for any subgroup, there was a trend toward improved survival in patients receiving azimilide without β-adrenergic blocking drugs ($P=0.06$). These results were similar in the high-risk group (not shown). In addition, no difference was seen in all-cause mortality between the at-risk patients who received azimilide 75 mg (n=336) and the placebo patients who were randomized at the same time

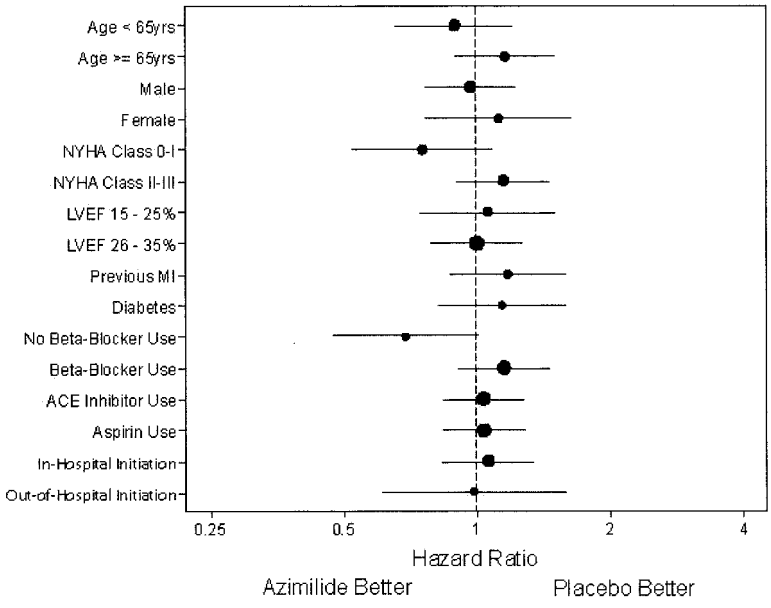

Figure 5. Relative risk of all-cause mortality in prespecified subgroups of patients.

TABLE 3. Serious Adverse Events Occurring in 2% or More of the Study Population

Serious Adverse Event	Placebo (n=1690)	Azimilide (n=1691)
Heart failure*	136 (8.0)	102 (6.0)
Angina pectoris	128 (7.6)	118 (7.0)
Myocardial infarction	94 (5.6)	108 (6.4)
Sudden death	75 (4.4)	76 (4.5)
Chest pain	42 (2.5)	50 (3.0)
Edema lung	44 (2.6)	49 (2.9)

Values are given as n (%). *P=0.026.

(n=336) (hazard ratio, 0.76; 95% CI, 0.48 to 1.20; log-rank P=0.24).

Patient compliance in the placebo and azimilide 100 mg groups was similar (94%). Withdrawal because of excessive QTc prolongation (>525 ms) occurred more frequently in azimilide 100 mg patients (3.7%) than in placebo patients (0.2%) and accounted for a higher rate of study drug discontinuation among azimilide 100 mg patients (19%) compared with placebo patients (15%). Withdrawals because of adverse events were similar in both groups (7.1% in the azimilide group versus 6.6% in the placebo group). Frequent reasons for discontinuation included ventricular tachycardia, which was similar in both groups, and rash, which tended to be more common in azimilide patients (0.5%, versus 0.2% in placebo patients; P=NS). Overall, the number of serious adverse events was similar among azimilide and placebo patients (38% for both groups) (Table 3).

With the exception of new or worsening heart failure, serious cardiovascular events occurred at a similar rate in both treatment groups (28% for azimilide and 31% for placebo). Fewer azimilide patients reported new or worsening heart failure than placebo patients (6% versus 8%, respectively; P=0.026). Significantly fewer patients who took azimilide developed atrial fibrillation documented by ECG than did patients who took placebo (0.5% versus 1.2%, P<0.04). TdP occurred more frequently in patients taking azimilide (0.3%) than in patients taking placebo (0.1%). Severe neutropenia occurred in 15 azimilide patients (0.9%) and 4 placebo patients (0.2%).

Discussion

In this study, long-term treatment with azimilide 100 mg did not reduce or increase chances of survival and had a 1-year all-cause mortality rate similar to that of placebo in both high-risk and at-risk populations. In addition to azimilide, several other potassium channel blockers (class III antiarrhythmic drugs), including sotalol, amiodarone, and dofetilide, have been shown to have no effect on all-cause mortality in patients after MI.[23–25]

The ALIVE results, together with those of previous trials, suggest that antiarrhythmic drug trials in this patient population may no longer be appropriate until new antiarrhythmic strategies are developed. However, such mortality trials have been used to establish the overall safety of antiarrhythmic drugs for the purposes of registration. At present, the best target populations for antiarrhythmic drug therapy and drug development may be patients with atrial fibrillation or patients with an implantable cardioverter-defibrillator. These 2 populations are the current focus of azimilide development, and the results seen in the ALIVE trial support the safety of azimilide in these patients. As shown in pervious studies, the occurrence of atrial fibrillation was significantly reduced in those patients assigned to treatment with azimilide.[19,26]

TdP, a recognized complication of antiarrhythmic therapy, occurred more frequently among patients taking azimilide 100 mg (0.3%) than among placebo patients (0.1%) but was generally lower than in other recent studies with class III antiarrhythmic agents. A TdP rate of 3.1% in patients with a history of MI has been reported among patients taking sotalol.[27] In the DIAMOND-MI trial, in which continuous 3-day in-hospital ECG monitoring was used, a TdP rate of 0.94% was reported among patients taking dofetilide.[28] Severe neutropenia was also more frequent in azimilide 100 mg patients than placebo patients.

The ALIVE trial differs from previous antiarrhythmic drug mortality trials in patients surviving MI. For the first time, low HRV was studied prospectively to assess its predictive power and was used, in addition to depressed LV function, to identify the target high-risk population. The combination of low HRV and depressed LVEF was selected to identify the high-risk group in ALIVE. The additive value of using HRV along with LVEF is exemplified by the observation that the mean LVEF in placebo patients with low and high HRV were similar (28.8% versus 29.7%, respectively), yet the placebo patients characterized by low HRV had a 64% higher mortality rate than placebo patients with a similar EF and high HRV. This HRV effect among placebo patients was significant even after all relevant covariates were considered.

The 15% 1-year placebo mortality rate in the ALIVE high-risk patient population compares favorably with the EMIAT trial evaluating amiodarone (13.7% mortality at 21 months) and the DIAMOND trial evaluating dofetilide (23% mortality at 12 months).[24,28] The EMIAT trial included patients with a higher LVEF than the ALIVE trial (≤40% in the EMIAT trial and 35% in the ALIVE trial), resulting in the lower mortality rate seen in EMIAT.[24] Patients in the DIAMOND trial had an LVEF similar to those in ALIVE, but DIAMOND enrollment was restricted to hospitalized patients, many of whom were very sick.

Conclusions

In summary, low HRV independently predicts significantly higher mortality in post-MI patients with depressed LV function. Azimilide, a potent class III antiarrhythmic drug that is currently under active investigation for the treatment of atrial fibrillation and for patients with an implantable cardioverter-defibrillator, did not improve or worsen the mortality of post-MI patients. The results of ALIVE provide important safety data relating to azimilide in patients with congestive heart failure and/or ischemic heart disease.

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Mortality in Patients After a Recent Myocardial Infarction: A Randomized, Placebo-Controlled Trial of Azimilide Using Heart Rate Variability for Risk Stratification

A. John Camm, Craig M. Pratt, Peter J. Schwartz, Hussein R. Al-Khalidi, Maria J. Spyt, Michael J. Holroyde, Roger Karam, Edmund H. Sonnenblick and Jose M.G. Brum
on Behalf of the AzimiLide post Infarct surVival Evaluation (ALIVE) Investigators

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