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CME

A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to compare the efficacy and safety of intravenous vernakalant and amiodarone for the acute conversion of recent onset atrial fibrillation.

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A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation

Objectives This randomized double-blind study compared the efficacy and safety of intravenous vernakalant and amiodarone for the acute conversion of recent-onset atrial fibrillation (AF).

Background Intravenous vernakalant has effectively converted recent-onset AF and was well tolerated in placebo-controlled studies.

Methods A total of 254 adult patients with AF (3 to 48 h duration) eligible for cardioversion were enrolled in the study. Patients received either a 10-min infusion of vernakalant (3 mg/kg) followed by a 15-min observation period and a second 10-min infusion (2 mg/kg) if still in AF, plus a sham amiodarone infusion, or a 60-min infusion of amiodarone (5 mg/kg) followed by a maintenance infusion (50 mg) over an additional 60 min, plus a sham vernakalant infusion.

Results Conversion from AF to sinus rhythm within the first 90 min (primary end point) was achieved in 60 of 116 (51.7%) vernakalant patients compared with 6 of 116 (5.2%) amiodarone patients ($p < 0.0001$). Vernakalant resulted in rapid conversion (median time of 11 min in responders) and was associated with a higher rate of symptom relief compared with amiodarone (53.4% of vernakalant patients reported no AF symptoms at 90 min compared with 32.8% of amiodarone patients; $p = 0.0012$). Serious adverse events or events leading to discontinuation of study drug were uncommon. There were no cases of torsades de pointes, ventricular fibrillation, or polymorphic or sustained ventricular tachycardia.

Conclusions Vernakalant demonstrated efficacy superior to amiodarone for acute conversion of recent-onset AF. Both vernakalant and amiodarone were safe and well tolerated in this study. (A Phase III Superiority Study of Vernakalant vs Amiodarone in Subjects With Recent Onset Atrial Fibrillation [AVRO]; NCT00668759) (J Am Coll Cardiol 2011;57:313–21) © 2011 by the American College of Cardiology Foundation

Conversion of atrial fibrillation (AF) to sinus rhythm (SR) by pharmacologic or electrical cardioversion is appropriate for many patients with acute symptomatic AF. Early conversion to SR improves symptoms, prevents the detrimental effects of prolonged AF, and avoids hospitalization (1–3). Electrical cardioversion is effective but requires sedation or anesthesia, and patients must be in a fasting state (2,4,5). Currently available antiarrhythmic agents for pharmacologic cardioversion of AF are limited by their delayed onset of action, slow metabolism, and proarrhythmic side effects, all of which may prolong hospitalization (1,4,6,7).

See page 322

A need has been recognized for a rapidly acting, efficacious, and well-tolerated antiarrhythmic drug. Vernakalant is a novel antiarrhythmic agent that shows preferential effects for atrial tissue and has limited actions on ventricular tissue (8,9). Intravenous vernakalant effectively converted recent-onset AF (lasting >3 h to ≤7 days) and was well tolerated in placebo-controlled phase II and III clinical trials (10–12). Conversion with vernakalant was achieved quickly, and the half-life of vernakalant is short (11), allowing for early hospital discharge.

Currently one of the most widely used agents for conversion is the class III antiarrhythmic amiodarone, despite not being approved for that use in most regions (13,14). This study was designed to demonstrate the superiority of vernakalant injection over amiodarone injection in the acute conversion of AF and to assess the safety of vernakalant compared with amiodarone in patients with recent-onset AF.

Methods

Study design. This was a phase III, multicenter, randomized, double-blind, double-dummy, active-controlled study performed in compliance with the guidelines for good

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clinical practice and the Declaration of Helsinki. The protocol and amendments were reviewed and approved by an institutional review board or ethics committee at each site, and written informed consent was obtained from patients prior to enrollment in the study.

Selection of study participants. Eligible patients were men and women between 18 and 85 years with symptomatic recent-onset AF (duration of 3 to 48 h) who were eligible for cardioversion, hemodynamically stable (systolic blood pressure >100 but <160 mm Hg and diastolic blood pressure <95 mm Hg), and taking adequate anticoagulation therapy (if recommended by American College of Cardiology/American Heart Association/European Society of Cardiology guidelines [4]).

Patients were excluded if they had an uncorrected QT interval >440 ms; familial long QT syndrome; previous torsades de pointes (TdP), ventricular fibrillation, or sustained ventricular tachycardia (VT); symptomatic bradycardia, known sick sinus syndrome, or ventricular rate <50 beats/min; or QRS interval >140 ms. Patients with a pacemaker; atrial flutter (AFL); atrial thrombus; unstable congestive heart failure, New York Heart Association functional class IV heart failure, or heart failure requiring inotropes; myocardial infarction, acute coronary syndrome, or cardiac surgery within 30 days prior to enrollment; cerebrovascular accident within 3 months prior to enrollment; atrioventricular block; valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis; or end-stage disease states were also excluded from the study. Other exclusion criteria were previously failed electrical cardioversion, secondary causes of AF, uncorrected electrolyte imbalance, digoxin toxicity, contraindications to amiodarone, or previous exposure to vernakalant.

Study interventions. Patients randomized to vernakalant received a 10-min infusion of 3 mg/kg vernakalant in one infusion line, followed by a 15-min observation period and an additional 10-min infusion of 2 mg/kg vernakalant if still in AF. To maintain blinding, a 60-min infusion of placebo (5% dextrose in water) was administered in a second infusion line followed by a maintenance infusion of placebo for an additional 60 min. Patients randomized to amiodarone received a 60-min infusion of 5 mg/kg amiodarone in one infusion line, followed by a maintenance infusion of 50 mg amiodarone over an additional 60 min (equivalent to approximately 15 mg/kg over 24 h). To maintain blinding, these patients received a 10-min infusion of placebo (normal saline) in a second infusion line, followed by a 15-min observation period and a second 10-min infusion of placebo if still in AF.

Both infusion lines were permanently stopped if any of the following was observed: QTc >550 ms or QRS >180 ms; symptomatic bradycardia or heart rate <40 beats/min; symptomatic hypotension or systolic blood pressure <85 mm Hg; new bundle branch block; asymptomatic VT lasting ≥10 consecutive beats, symptomatic VT, or any TdP or ventricular fibrillation; one or more sinus pauses of ≥5 s or complete heart block; or intolerable side effects.

Patients were not permitted to receive class I or III antiarrhythmic drugs from 24 h pre-dose to 24 h after the start of infusion and intravenous or oral amiodarone within 30 or 90 days pre-dose, respectively. Electrical cardioversion or rate control medications were permitted 2 h after the start of study drug infusion if the patient was still in AF. Patients remained in the clinic facility for at least 6 h post-dose and attended a follow-up visit 7 (± 2) days after treatment and received a follow-up telephone call at 30 (± 3) days.

Abbreviations and Acronyms

- **AE** = adverse event
- **AF** = atrial fibrillation
- **AFL** = atrial flutter
- **ECG** = electrocardiogram
- **SAE** = serious adverse event
- **SR** = sinus rhythm
- **TdP** = torsades de pointes
- **VAS** = visual analog scale
- **VT** = ventricular tachycardia

Efficacy and safety analyses. The primary efficacy end point in this study was the proportion of patients with conversion of AF to SR within 90 min of first exposure to study drug and for a minimum duration of 1 min. All 12-lead electrocardiograms (ECGs) were adjudicated by a clinical events committee, blinded to treatment allocation.

Secondary efficacy end points included the time to conversion of AF to SR within the first 90 min after the start of infusion, proportion of patients exhibiting no AF symptoms at 90 min, and the change in EQ-5D quality of life assessment visual analog scale (VAS) (15) from screening to hour 2.

Exploratory efficacy end points included the time to conversion within the first 240 min after the start of infusion, proportion of patients who met the primary end point and maintained SR with no AF relapse at hour 4, and proportion of patients ready for discharge at 2 h.

Safety was assessed at regular intervals during the study through the monitoring of adverse events (AEs), vital signs, 12-lead ECG intervals, and clinical laboratory parameters. In addition, continuous telemetry monitoring was performed from baseline to discharge, and continuous 12-lead Holter monitoring was performed from 1 h pre-dose until a minimum of 4 h post-dose. All ventricular arrhythmias were adjudicated by a ventricular events committee, blinded to treatment allocation.

Statistical analyses. A sample size of 230 treated patients (n = 115 per group) was calculated to provide 90% power to detect a treatment effect of 20% (assuming an amiodarone conversion rate of 25%).

The comparison of conversion rates between groups used a 2-sided Cochran Mantel-Haenszel test stratified by country. The log-rank test was used to compare the time to conversion. The change in EQ-5D quality of life assessment VAS was modeled using a fixed-effects general linear model with change as the dependent variable, baseline score and age as covariates, treatment as a fixed effect, and a treatment by baseline interaction. Estimates of the change from baseline in QTcF were obtained from a repeated-measures mixed-effect model with change as the dependent variable; treatment, time, and rhythm status as fixed effects; baseline

JACC Vol. 57, No. 3, 2011
January 18, 2011:313–21

and term to account for the time that had elapsed between conversion to SR and the time of the ECG recording as covariates; and patient as a random effect. For all analyses, a significance level of 0.05 was used.

Results

Study population. From April 2008 to November 2009, a total of 254 patients were enrolled at 66 sites in Australia, Canada, and Europe. The 2 treatment groups were well balanced in regards to demographic and baseline characteristics (Table 1). Of all randomized patients, 232 (116 in each group) received at least 1 dose of study drug and were included in the efficacy and safety analyses (Fig. 1).

Efficacy. Sixty of 116 (51.7%) vernakalant patients met the primary end point, compared with 6 of 116 (5.2%) amiodarone patients ($p < 0.0001$); relative risk 10.0 (95% confidence interval: 4.5 to 22.2).

Conversion from AF to SR within the first 90 min post-dose was significantly faster in vernakalant patients compared with amiodarone patients ($p < 0.0001$) (Fig. 2A). In the group of patients who responded to vernakalant (n = 60), the median time to conversion was 11.0 min.

All patients enrolled in this study reported at least 1 AF symptom at screening. The most common presenting symptoms were palpitations, irregular pulse, rapid heart beat, fatigue, shortness of breath, dizziness, and chest tightness/pain. There were 62 of 116 (53.4%) vernakalant patients with no AF symptoms at 90 min, compared with 38 of 116 (32.8%) amiodarone patients ($p = 0.0012$); relative risk 1.63 (95% confidence interval: 1.20 to 2.23). Treatment with vernakalant resulted in a significantly greater improvement in patient perception of state of health (as measured by the EQ-5D quality-of-life assessment VAS) at hour 2 compared with amiodarone. In the vernakalant group, a mean adjusted increase (from baseline) of 10.9 points was seen compared with a mean adjusted increase of 5.6 points in the amiodarone group ($p = 0.0006$).

As shown in Figure 2B, a significantly greater proportion of vernakalant patients (54.4%) converted to SR within the first 4 h post-dose compared with amiodarone patients (22.6%) ($p < 0.0001$). In patients who converted to SR

Table 1 Demographic and Baseline Characteristics

	Treatment Group		
	Vernakalant (n = 116)	Amiodarone (n = 116)	Total (n = 232)
Baseline characteristics			
Male, n (%)	75 (64.7)	71 (61.2)	146 (62.9)
White, n (%)	111 (95.7)	111 (95.7)	222 (95.7)
Age (yrs), mean (SD)	63.1 (10.81)	62.2 (11.63)	62.7 (11.21)
No previous episode of AF	34 (29.3)	33 (28.4)	67 (28.9)
1–3 previous episodes of AF	44 (37.9)	40 (34.5)	84 (36.2)
>3 previous episodes of AF*	38 (32.8)	42 (36.2)	80 (34.5)
Median duration of current AF, h (25%, 75% quartiles)	17.7 (9.1, 28.7)	17.9 (9.7, 31.4)	17.7 (9.3, 30.4)
AF duration ≤24 h, n (%)	73 (62.9)	65 (56.0)	138 (59.5)
Medical history, n (%)			
Hypertension	86 (74.1)	80 (69.0)	166 (71.6)
Structural heart disease†	36 (31.0)	45 (38.8)	81 (34.9)
Ischemic heart disease	22 (19.0)	30 (25.9)	52 (22.4)
Myocardial infarction	11 (9.5)	8 (6.9)	19 (8.2)
Valvular heart disease	4 (3.4)	12 (10.3)	16 (6.9)
Heart failure	20 (17.2)	26 (22.4)	46 (19.8)
NYHA functional class I‡	9 (45.0)	12 (46.2)	21 (45.7)
NYHA functional class II‡	11 (55.0)	14 (53.8)	25 (54.3)
LADD (mm), mean (SD)	40.6 (6.77)	41.0 (6.04)	40.8 (6.40)
LADD >50 mm	5 (4.3)	7 (6.0)	12 (5.2)
LVEF (%), mean (SD)	57.6 (7.34)	59.5 (6.97)	58.5 (7.21)
LVEF <50%	15 (12.9)	4 (3.4)	19 (8.2)
Medications used within 7 days, n (%)			
Any rate control§	71 (61.2)	78 (67.2)	149 (64.2)
Beta-blockers	63 (54.3)	76 (65.5)	139 (59.9)
Calcium-channel blockers	10 (8.6)	4 (3.4)	14 (6.0)
Digitalis glycosides	6 (5.2)	10 (8.6)	16 (6.9)

*Data for 1 patient in the amiodarone group are missing. †Patients may have had >1 condition listed under the structural heart disease category. ‡Denominators are based on those who had a history of heart failure. §Beta-blockers included intravenous or oral nonselective and selective beta-blockers (excluding sotalol) and alpha- and beta-blocking agents (e.g., carvedilol); calcium-channel blockers included diltiazem and verapamil; and digitalis glycosides included digoxin, digitoxin, and digitalis.

AF = atrial fibrillation; LADD = left atrial diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

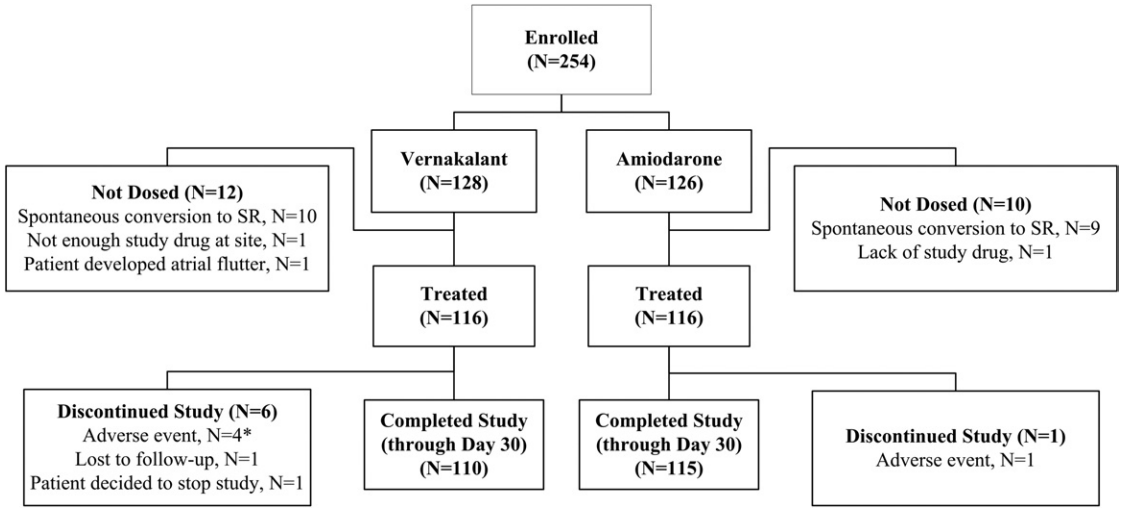

Figure 1 **Disposition of Patients**

*One vernakalant patient did not complete the study because of death owing to chronic obstructive pulmonary disease and pulmonary embolism on day 24. SR = sinus rhythm.

within 90 min, SR was maintained through 4 h for 59 of 60 (98.3%) vernakalant patients and 6 of 6 (100%) amiodarone patients. According to the investigator, 37.1% (43 of 116) of vernakalant patients and 9.5% (11 of 116) of amiodarone patients were ready for discharge at 2 h ($p < 0.0001$).

Safety. Table 2 outlines the incidence of treatment-emergent AEs, serious adverse events (SAEs), and discontinuations because of AEs within 24 h post-dose. There was 1 death in this study, due to chronic obstructive pulmonary disease exacerbation and pulmonary embolism, which occurred 24 days after vernakalant administration. There was an SAE of monomorphic unsustained VT in the vernakalant group, not associated with QT prolongation, which began 10 min after the start of infusion and resolved spontaneously. An SAE of cardiac arrest, consisting of asystole with a loss of consciousness, occurred in the amiodarone group 37 min after the start of infusion and resolved after cardiac massage and atropine were administered. Within 2 to 24 h post-dose, there were SAEs of atrial thrombosis and syncope (related to pulmonary embolism) in the vernakalant group and sinus bradycardia in the amiodarone group, all of which were considered to be serious owing to prolongation of hospitalization and were not related to study drug. There were no cases of TdP, ventricular fibrillation, or polymorphic or sustained VT in either group.

There was a higher incidence of AFL in vernakalant patients (8.6%) compared with amiodarone patients (0.9%) within 4 h post-dose. Of the 10 vernakalant patients who developed AFL, 5 spontaneously converted and 4 were electrically cardioverted to SR within 4 h, and 1 patient spontaneously converted to SR within 24 h. No AFL events were considered to be serious, and none of the patients who developed AFL had 1:1 atrioventricular conduction during the AFL episodes.

Heart rate decreased over time in both groups; however, in vernakalant patients, the decrease was primarily due to conversion, and the decrease appeared to be independent of conversion in amiodarone patients (Fig. 3). In the vernakalant group, QTcF transiently increased with infusion, whereas in the amiodarone group, QTcF progressively increased throughout the 4-h observation period (Fig. 4).

Discussion

This study shows that vernakalant provides a safe and effective alternative to amiodarone for the acute conversion of recent-onset AF. Conversion with vernakalant was rapid and significantly more effective than amiodarone (52% vs. 5% within 90 min). Patients treated with vernakalant had significantly greater symptom relief at 90 min and a greater perceived feeling of well-being at 2 h.

The low conversion rate in the amiodarone group may be attributed to the characteristics of the AF population enrolled in this trial. A previous study (3) in AF of ≤48 h with a similar dosing regimen suggested that a conversion rate of approximately 20% to 25% would be expected in the amiodarone group within 90 min post-infusion. However, the AVRO study population was older, with greater comorbidities (i.e., structural heart disease and hypertension), and had a longer duration of AF. In other studies, successful cardioversion with amiodarone took several hours and required infusions up to 24 h (16,17).

The rapid time to conversion in vernakalant-treated patients is consistent with previous phase III studies of intravenous vernakalant in patients with AF (10,11). The benefits of early cardioversion include a reduction in the risk of recurrent AF, less need for long-term anticoagu-

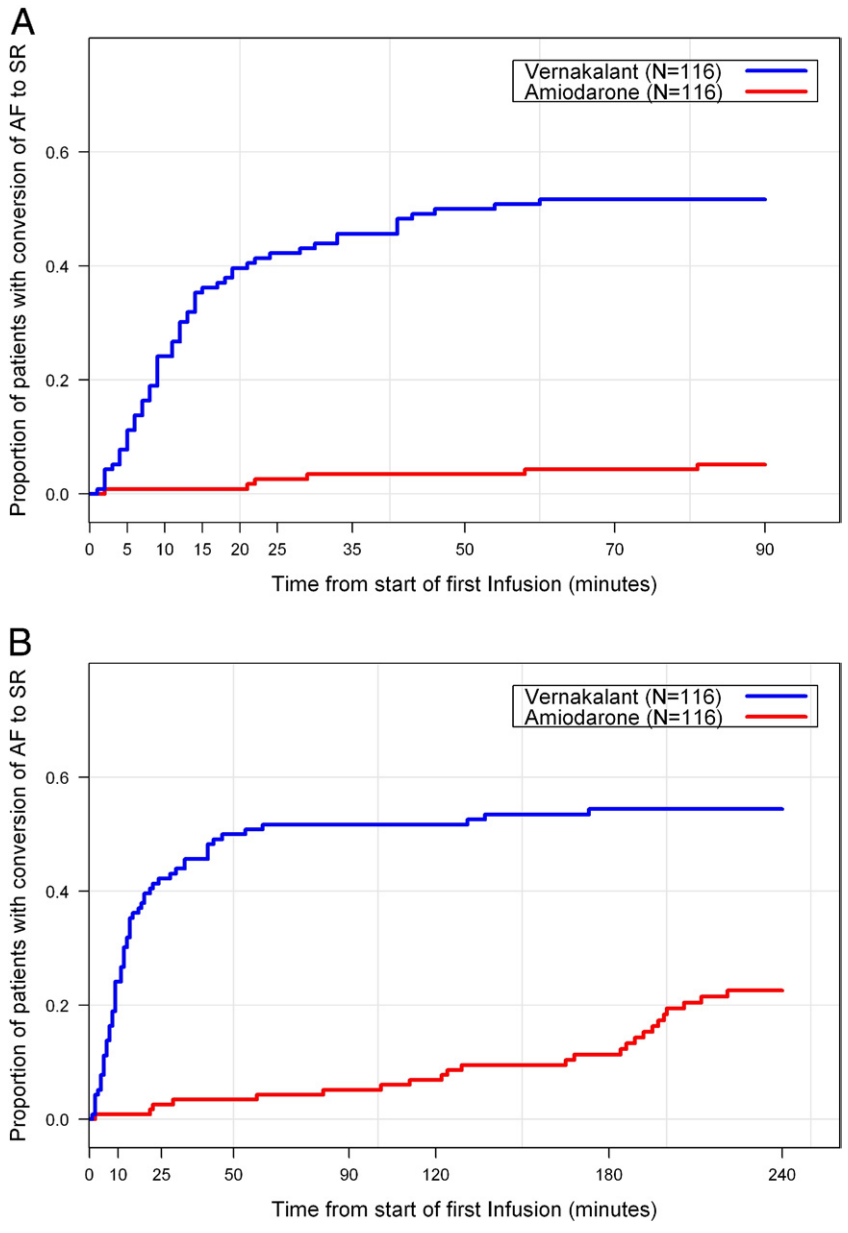

Figure 2 **Time to Treatment-Induced Conversion**

Time to treatment-induced conversion from atrial fibrillation (AF) to sinus rhythm (SR) within **(A)** 90 and **(B)** 240 min post-dose. Patients who had electrical cardioversion attempted were censored at the time of electrical cardioversion.

lation or electrical cardioversion, and avoidance of lengthy and costly hospital admissions (2,5,18). According to their physicians, a greater proportion of vernakalant patients could be safely discharged home at 2 h to resume normal activities.

Vernakalant had a significantly greater proportion of patients with no symptoms at 90 min compared with amiodarone. Amiodarone did, however, slow heart rate within the first 90 min, which may have provided symptom relief in some of the amiodarone patients, including those who did not convert to SR.

The use of available antiarrhythmic agents is limited because of their delayed onset of action and increased proarrhythmic risk. In recent-onset AF, intravenous propafenone converted 23% to 28% of patients within 60 min, with a mean time to conversion of >2 h (19,20), and intravenous flecainide converted 56% of patients within 90 min (21). However, because of their proarrhythmic potential, these class IC antiarrhythmics are contraindicated in patients with AF with structural heart disease (4,16). Ibutilide, a class III antiarrhythmic with a rapid onset of action, has shown conversion rates within 90 min of 28% to

Table 2 Summary of AEs Occurring Within 24 h Post-Dose

	0–2 h Post-Dose		2–24 h Post-Dose	
	Vernakalant (n = 116)	Amiodarone (n = 116)	Vernakalant (n = 116)	Amiodarone (n = 116)
Any treatment-emergent AE*	32 (27.6)	10 (8.6)	21 (18.1)	15 (12.9)
Any related treatment-emergent AE	22 (19.0)	1 (0.9)	4 (3.4)‡	1 (0.9)‡
Common related treatment-emergent AEs†				
Dysgeusia	8 (6.9)	0	0	0
Sneezing	4 (3.4)	0	0	0
Cough	3 (2.6)	0	0	0
Any treatment-emergent SAE	3 (2.6)	1 (0.9)	2 (1.7)	1 (0.9)
Any related treatment-emergent SAE	3 (2.6)	1 (0.9)	0	0
Discontinuations due to AEs	3 (2.6)	1 (0.9)	0	0

Values are patients, n (%). *Treatment-emergent AEs were defined as any AE that began or worsened following the start of study drug infusion. †Common related treatment-emergent AEs were those that occurred in >2 patients in the study. ‡Related treatment-emergent AEs occurring within 2 to 24 h post-dose included bradycardia, supraventricular tachycardia, prolonged electrocardiogram QT, and decreased heart rate in the vernakalant group, and increased blood bilirubin in the amiodarone group.

AE = adverse event; SAE = serious adverse event.

31% compared with placebo (22,23) and 44% to 51% compared with other antiarrhythmic agents (24,25), with higher efficacy in patients with AFL. Although ibutilide is approved in the U.S., the risk of TdP (3.6% to 8.3%) is a concern with its use (5), and this drug is not available in many European countries.

Amiodarone was selected as a comparator in this study because it is one of the most commonly used antiarrhythmic agents for the conversion of AF, can be used in a broad AF population, and was available in all participating countries in this study. Although class IC agents, such as flecainide, are sometimes the first choice for conversion of AF in many European countries, they were not chosen as comparators in this study because the intravenous formulations are not available in all countries and they are contraindicated in patients with AF with structural heart disease.

Safety considerations. Both vernakalant and amiodarone were well tolerated in this study population, which included older patients (>75 years) and those with structural heart disease. Although there was a higher incidence of AEs in vernakalant patients, dysgeusia (altered taste) was the most common event, as observed in previous trials (10,11). The rate of SAEs and discontinuations owing to AEs was low in both groups, and there were no drug-related deaths.

Vernakalant and amiodarone have both been shown previously to cause hypotension. Accordingly, patients in this study were adequately hydrated and hemodynamically optimized before receiving treatment. The incidence of

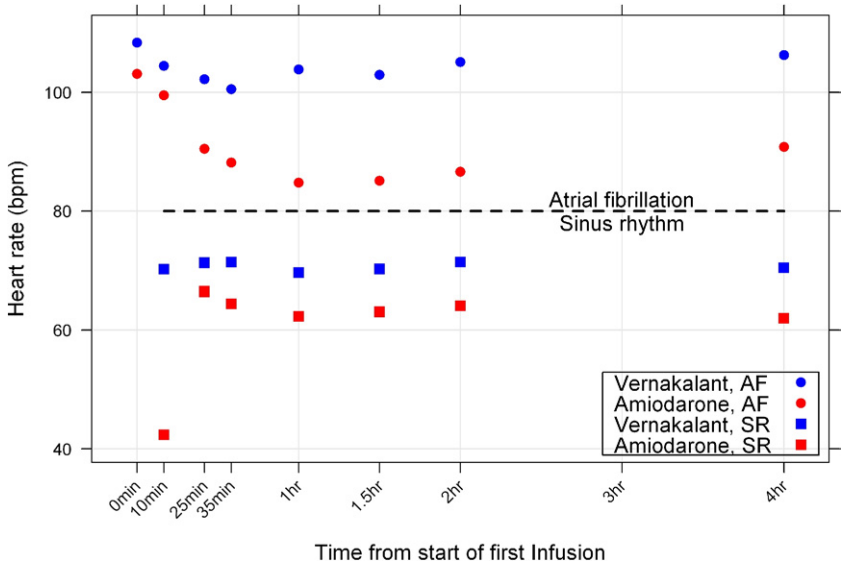

Figure 3 Mean Heart Rate for Patients in AF and for Patients in SR Over 4 h Post-Dose

There was 1 patient in SR in the amiodarone group who had a heart rate of 42 beats/min (bpm) at 10 min post-dose. Abbreviations as in Figure 2.

JACC Vol. 57, No. 3, 2011
January 18, 2011:313–21

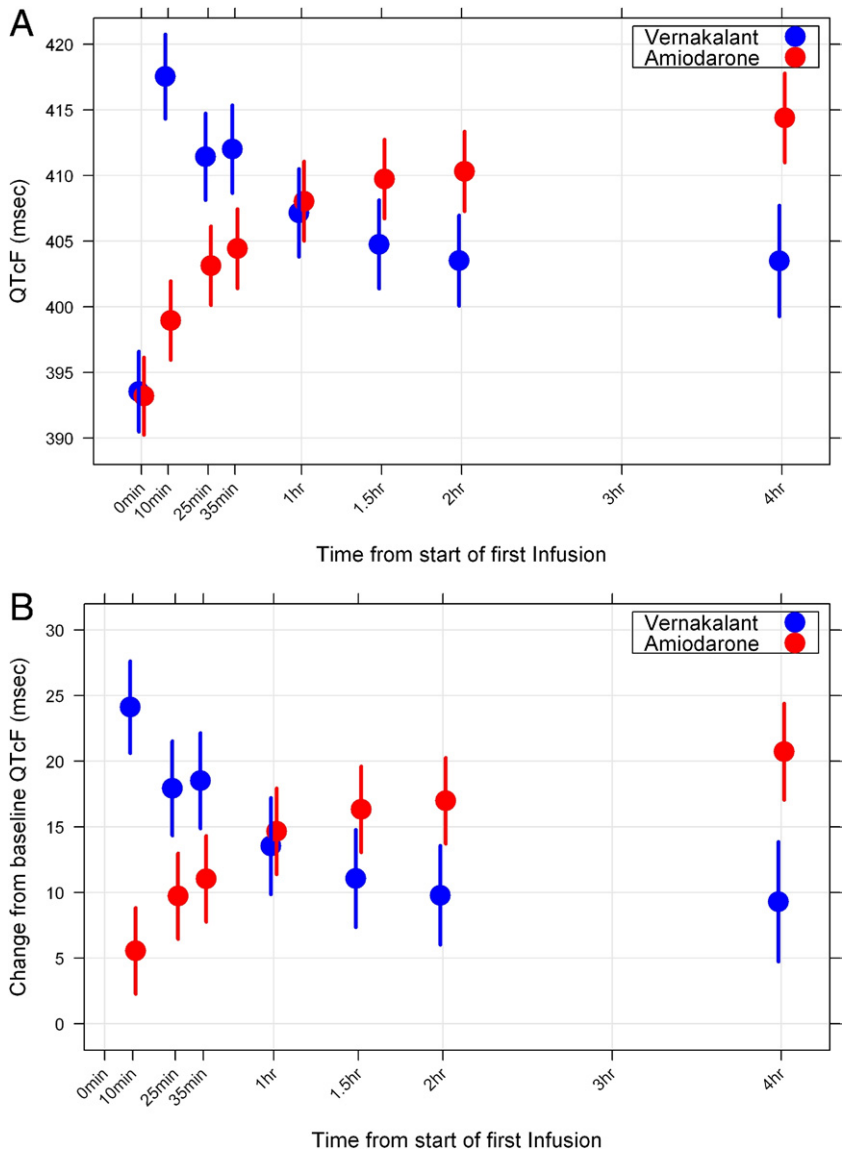

Figure 4 **Mean QTcF Interval and Mean Change From Baseline Over 4 h Post-Dose**

(A) Mean QT interval corrected for heart rate using Fridericia's formula. **(B)** Mean change from baseline. Estimates are based on a mixed-effects model with time, treatment group, time by treatment group interaction, and rhythm (SR vs. not SR) as fixed effects; baseline and elapsed time post-conversion to SR as covariates; and patient as a random effect. Values shown are the estimated adjusted mean and 95% confidence interval for patients not in SR. Abbreviations as in Figure 1.

hypotension in this study was lower compared with previous experience with vernakalant (11) and amiodarone (17).

In vernakalant patients, transient increases in QTcF occurred during infusion, whereas in amiodarone patients, QTcF progressively increased throughout the 4-h observation period. Decreases in heart rate in the vernakalant group were associated with conversion to SR, whereas amiodarone showed decreases in heart rate that appeared to be independent of conversion, reflecting its rate control properties (4,13).

Study limitations. A limitation of this study was the short follow-up period for efficacy (90 min) and the short infusion period (i.e., <24 h) for amiodarone. The 90-min efficacy evaluation period was chosen because it is consistent with preceding phase III studies of vernakalant injection (10,11). A short observation period before patients could proceed to electrical cardioversion was used because the aim of this study was to examine the advantages of vernakalant compared with current therapy. The choice of the dosing regimen for amiodarone was based on the United Kingdom Summary of Product Characteristics (26). Although amiodarone was not administered over 24 h, the dosing regimen used in this study produced the expected pharmacologic effects and was similar to that used in previous studies of amiodarone injection (3).

Conclusions

This study demonstrated that vernakalant infusion was superior to amiodarone infusion for the conversion of recent-onset AF, and the efficacy results were consistent with previous studies of intravenous vernakalant. Both vernakalant and amiodarone were safe and well tolerated. Vernakalant has low proarrhythmic potential and provides a rapidly acting therapeutic alternative for the conversion of AF.

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Key Words: atrial fibrillation ■ amiodarone ■ antiarrhythmics ■ cardioversion ■ vernakalant.

APPENDIX

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