Vernakalant Hydrochloride for Rapid Conversion of Atrial Fibrillation: A Phase 3, Randomized, Placebo-Controlled Trial

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Background—The present study assessed the efficacy and safety of vernakalant hydrochloride (RSD1235), a novel compound, for the conversion of atrial fibrillation (AF).

Methods and Results—Patients were randomized in a 2:1 ratio to receive vernakalant or placebo and were stratified by AF duration of 3 hours to 7 days (short duration) and 8 to 45 days (long duration). A first infusion of placebo or vernakalant (3 mg/kg) was given for 10 minutes, followed by a second infusion of placebo or vernakalant (2 mg/kg) 15 minutes later if AF was not terminated. The primary end point was conversion of AF to sinus rhythm for at least 1 minute within 90 minutes of the start of drug infusion in the short-duration AF group. A total of 336 patients were randomized and received treatment (short duration, n=220; long duration, n=116). Of the 145 vernakalant patients, 75 (51.7%) in the short-duration AF group converted to sinus rhythm (median time, 11 minutes) compared with 3 of the 75 placebo patients (4.0%; P<0.001). Overall, in the short- and long-duration AF groups, 83 of the 221 vernakalant patients (37.6%) experienced termination of AF compared with 3 of the 115 placebo patients (2.6%; P<0.001). Transient dysgeusia and sneezing were the most common side effects in vernakalant-treated patients. Four vernakalant-related serious adverse events (hypotension [2 events], complete atrioventricular block, and cardiogenic shock) occurred in 3 patients.

Conclusion—Vernakalant demonstrated rapid conversion of short-duration AF and was well tolerated. (Circulation. 2008;117:1518-1525.)

Key Words: antiarrhythmia agents ■ arrhythmia ■ fibrillation ■ vernakalant

Currently available antiarrhythmic agents have modest efficacy in converting atrial fibrillation (AF) to sinus rhythm, and the risk of proarrhythmia or hypotension is of concern.1-3Time to conversion with these drugs often is unpredictable and may be long, especially with oral therapies.4Although electric cardioversion is more effective than drug administration, it is associated with adverse effects such as skin burns, heart block, ventricular proarrhythmia, and pacemaker or internal defibrillator malfunction.2,4,5Electrical cardioversion requires general anesthesia or conscious sedation from which patients must recover and may prolong hospitalization. In addition, the procedure generally is delayed for at least 6 hours after meals.6 A rapidly acting, efficacious, and safe drug that targets the fibrillating atria would be a valuable alternative to current treatments for patients with this common arrhythmia. Prompt pharmacological conversion of AF may prove to be a cost-saving strategy.

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Vernakalant hydrochloride (RSD1235), an investigational compound, is a relatively atrium-selective, early-activating K⁺ and frequency-dependent Na⁺ channel blocker with a half-life of 2 to 3 hours.7,8 In animal models of AF and in a recent clinical study, vernakalant selectively prolonged the
atrial refractory period without affecting ventricular refracto-

ess. Vernakalant effectively converted acute-onset AF
(AF lasting 3 to 72 hours) in a placebo-controlled phase 2 trial
(n=56).10

Methods
Study Design
This prospective, randomized, double-blind, placebo-controlled trial
was conducted in 44 centers in Canada, the United States, and
Scandinavia. Patients were stratified by duration of AF: 3 hours to 7
days (short duration) and 8 to 45 days (long duration). Patients
within the 2 strata were then randomized 2:1 to vernakalant or
placebo using block randomization and a computer-generated cen-
tralized list via an Interactive Voice Response System. This 2:1
randomization scheme was used to gather extra safety data for
vernakalant. The study protocol was developed by the Steering
Committee and the sponsor. Study oversight was provided by the
Steering Committee and an unblinded independent Data Safety
Monitoring Committee. The Data Safety Monitoring Committee held
monthly teleconferences, with 2 planned interim safety evaluations
once 90 and 180 patients, respectively, were enrolled. The protocol
was approved by the institutional or regional review board at each
site, and patients gave written informed consent before starting study
procedures. The Steering Committee approved the text of this
manuscript before publication.

Selection and Description of Participants
To be eligible, patients had to have sustained AF for 3 hours to 45
days, be ≥18 years of age, have a body weight of 45 to 136 kg, be
receiving adequate anticoagulation, and have a systolic blood pres-
sure >90 mm Hg and <160 mm Hg and a diastolic blood pressure
<95 mm Hg. Women could not be pregnant or nursing and, if
premenopausal, had to use an effective form of birth control. Patients
were excluded if they had sick-sinus syndrome or QRS >0.14
seconds without a pacemaker; ventricular rate of <50 bpm; uncor-
rected QT >0.440 seconds; typical atrial flutter; New York Heart
Association class IV heart failure; acute coronary syndrome, myo-
cardial infarction, or cardiac surgery within 30 days before enroll-
ment; an investigational drug within 30 days before enrollment; a
reversible cause of AF; end-stage disease; previously failed electric
conversion; uncorrected electrolyte imbalance; or digoxin toxicity.
Treatment initiation with β-blockers, calcium antagonists, and
digoxin for control of ventricular rate was permitted for up to 2
hours before study drug infusion. Treatment with an intravenous classe I and
III antiarrhythmics was allowed up to 24 hours before study drug
infusion, and background therapy of oral antiarrhythmics was
allowed.

Treatment Plan
Patients received a 10-minute infusion of vernakalant (3.0 mg/kg) or
placebo, followed by a 15-minute observation period. If the patient
did not convert to sinus rhythm, an additional dose of vernakalant
(2.0 mg/kg) or placebo was administered. The infusion was to be
discontinued if the uncorrected QT interval increased to >0.550
seconds or by >25%; heart rate decreased between 40 and 50 bpm
with symptoms or to <40 bpm; systolic blood pressure increased to
>190 mm Hg or decreased to <85 mm Hg; new bundle-branch
block developed or QRS increased ≥50%; or polymorphic ventric-
ular tachycardia, a sinus pause of ≥5 seconds, or intolerable side
effects occurred. The use of other antiarrhythmic medications and
electrical cardioversion was not recommended until at least 2 hours
after study drug infusion.

Patients were observed in the hospital for a minimum of 8 hours
after study drug infusion. ECGs were recorded and vital signs were
measured at screening; at baseline; every 5 minutes from the start
of infusion to 50 minutes after infusion; at 90 minutes and 2, 4, 8, and
24 hours; and at 1 week after dose. Lead II or V5 tracings were used
to measure ECG intervals by a central ECG laboratory. Generally,
the intervals were evaluated from 3 (consecutive if possible) com-

Study End Points
The primary efficacy end point was the proportion of patients in the
short-duration AF (3 hours to 7 days) group who had conversion to
sinus rhythm for at least 1 minute within 90 minutes of drug
initiation. Secondary and exploratory efficacy end points in the
short-duration AF group included the time to conversion from first
exposure to study drug and the proportion of patients who remained
in sinus rhythm at 24 hours, respectively. Other secondary efficacy
end points included the proportion of patients with AF duration of
3 hours to 45 days and 8 to 45 days who had termination of AF
(defined as the absence of AF or atrial flutter, which included
conversion to sinus rhythm and a paced rhythm).

Conversion to sinus rhythm and termination of AF were adjudic-
ated by a Clinical Events Committee blinded to treatment assign-
ment. The Clinical Events Committee also reviewed all episodes of
suspected torsade de pointes. All 12-lead ECGs and 24-hour Holter
recordings were reviewed by a cardiologist at the central ECG
laboratory who was blinded to treatment assignment. Ventricular
tachycardia was defined as ≥3 wide complex beats with a rate of
≥100 bpm.

A serious adverse event was defined as any adverse event
occurring from the start of the infusion through the 30 days after
study treatment that, at any dose of study drug, was fatal or life
threatening, required or prolonged hospitalization, was significantly
incapacitating, or required medical or surgical intervention.

Statistical Considerations
All randomized patients who received any amount of study drug
were included in the efficacy and safety analyses (prespecified

Figure 1. Patient disposition. *Reasons why subjects did not receive study drug were spontaneous conversion to sinus rhythm (n=14), violation of inclusion or exclusion criteria (n=2), myocardial infarction (n=2), study drug unavailability (n=1), and reason not specified (n=1).
Results

Patient Disposition
A total of 356 patients were randomized to either vernakalant or placebo. Twenty patients did not receive study drug and were withdrawn: 14 spontaneously converted to sinus rhythm; 2 violated inclusion or exclusion criteria; 2 were diagnosed with myocardial infarction; 1 could not obtain the study drug; and 1 discontinued for an unspecified reason. Thus, the efficacy and safety evaluable populations included 220 patients in the short-duration AF group and 116 patients in the long-duration AF group (Figure 1).

Baseline Characteristics
There were no statistical differences in patient demographics between the 2 treatment arms in the short-duration AF, long-duration AF, or overall groups (Table 1). The median AF duration at baseline in the placebo and vernakalant groups was 28.4 and 28.2 hours, respectively, in the short-duration AF group, and 465.2 and 613.0 hours, respectively, in the long-duration AF group.

Efficacy End Points
In the primary efficacy analysis, 75 of the 145 vernakalant patients (51.7%) in the short-duration AF (3 hours to 7 days) group converted to sinus rhythm within 90 minutes compared with 3 of the 75 placebo patients (4.0%; P<0.001; Figure 2). Figure 3 shows the cumulative success of conversion relative to time after the start of the infusion. Patients with AF lasting 3 to 48 hours given vernakalant demonstrated the highest conversion rate (62.1% versus 4.9% with placebo; P<0.001; Figure 2).

Table 1. Baseline Clinical Characteristics

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<th>Short Duration</th>
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<th>Overall Study Population</th>
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<td>Placebo (n=75)</td>
<td>Vernakalant (n=145)</td>
<td>Placebo (n=40)</td>
<td>Vernakalant (n=76)</td>
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<td></td>
<td></td>
<td>Placebo (n=115)</td>
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<td></td>
<td>Vernakalant (n=221)</td>
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<tr>
<td>Male sex, n (%)</td>
<td>48 (64.0)</td>
<td>102 (70.3)</td>
<td>27 (67.5)</td>
<td>57 (75.0)</td>
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<td>White, n (%)</td>
<td>73 (97.3)</td>
<td>138 (95.2)</td>
<td>40 (100)</td>
<td>74 (97.4)</td>
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<td>Age (mean±SD), y</td>
<td>59.9±11.8</td>
<td>60.4±14.0</td>
<td>64.6±9.7</td>
<td>65.9±12.5</td>
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<td>Atrial fibrillation duration (median range), h</td>
<td>28.4 (1.2–165)</td>
<td>28.2 (1.2–372)</td>
<td>465.2 (18.2–1081.6)</td>
<td>613.0 (130.4–1040.8)</td>
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<td>History of significant medical conditions, n (%)</td>
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<td>Hypertension*</td>
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<td>57 (39)</td>
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<td>Ischemic heart disease*</td>
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<td>22 (15)</td>
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<td>Myocardial infarction*</td>
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<td>14 (10)</td>
<td>13 (32)</td>
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<td>Current smoker, n (%)</td>
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<td>20 (13.8)</td>
<td>5 (12.5)</td>
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<td>Concomitant therapy, n (%)</td>
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<td>β-Blockers</td>
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<td>80 (55.2)</td>
<td>29 (72.5)</td>
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<td>Calcium channel blockers</td>
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<td>Digoxin</td>
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<td>21 (52.5)</td>
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<td>Class I antiarrhythmic drugs†</td>
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<td>9 (6.2)</td>
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<td>5 (6.6)</td>
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<td>Class III antiarrhythmic drugs†</td>
<td>2 (2.7)</td>
<td>10 (6.9)</td>
<td>3 (7.5)</td>
<td>2 (2.6)</td>
</tr>
</tbody>
</table>

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*Derived from verbatim terms in medical history after the study database was locked and unblinded.
†Class I antiarrhythmics included procainamide, quinidine, propafenone, and flecainide. Class III antiarrhythmics included dofetilide and amiodarone.

modified intention-to-treat population). Baseline characteristics were compared between groups by use of a 1-way ANOVA with a fixed effect for treatment for continuous variables and a χ² test or Fisher’s exact test for categorical variables. The primary end point was analyzed with the Cochran-Mantel-Haenszel test stratified by center; this test also was used in the analysis of the secondary end point in the group of patients with AF duration of 3 hours to 45 days. Fisher’s exact test was used in the analysis of the secondary end point in the group with AF duration of 8 to 45 days. The Kaplan-Meier method was used to summarize time to conversion, with the log-rank test used to compare the distributions. The sample sizes were based on assumed conversion rates of 25% and 50% for the placebo and active groups, respectively, in the short-duration AF group and 5% and 30% in the long-duration AF group. Based on a 2-sided χ² test (significance level, P=0.05), 240 patients in the short-duration AF group and 120 patients in the long-duration AF group, each allocated in a 2:1 ratio of vernakalant to placebo, provided >90% power to detect a 25% difference between treatments. Except for AF duration, data are given as mean±SD.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
conversion to sinus rhythm, 1 had paced rhythm) compared with 0 of the 40 placebo patients ($P=0.09$; Figure 2). In the overall population, 83 of the 221 vernakalant patients (37.6%) experienced termination of AF compared with 3 of the 115 placebo patients (2.6%; $P<0.001$). An additional 2 of 4 vernakalant patients with pacemakers in the short-duration AF group converted to a paced rhythm but were considered treatment failures in the prespecified primary analysis of conversion to sinus rhythm.

Nineteen vernakalant patients (8.6%) displayed atrial flutter in the first 90 minutes, 5 of whom subsequently converted to sinus rhythm. Each of the 19 patients had AF confirmed at baseline. None of these episodes of atrial flutter were associated with 1:1 atrioventricular conduction.

### Safety Results

Deaths were assessed up to 30 days after study drug infusion. Three patients died; all 3 had received vernakalant. None of these deaths were considered to be related to study drug. A 68-year-old woman received vernakalant and died 28 hours later during a gastroscopy procedure; an autopsy revealed rupture of a dissecting aneurysm of the ascending aorta. A 90-year-old woman died of pulmonary edema and congestive heart failure 26 days after receiving vernakalant. A 67-year-old man with lung cancer died of pneumonia and respiratory arrest 8 days after successful conversion with vernakalant.

### Serious Adverse Events

In the overall study population, investigator-reported serious adverse events were recorded from the time of study drug infusion through the 30-day follow-up assessment. There were 21 placebo patients (18.3%) and 29 vernakalant patients (13.1%) with serious adverse events. Most events were of cardiac origin, with the most common being recurrent AF requiring hospitalization (placebo, 12.2%; vernakalant, 5.9%). Four serious adverse events occurring in 3 patients were considered to be possibly or probably related to vernakalant. One patient developed hypotension 14 minutes after receiving a partial second infusion (mean baseline blood pressure, 120/81 mm Hg; lowest recorded blood pressure, 88/53 mm Hg), which responded to a saline intravenous bolus infusion. A second patient had hypotension (mean baseline blood pressure, 113/83 mm Hg; lowest recorded blood pressure, 82/68 mm Hg) after the first infusion, which responded to a saline intravenous bolus infusion, and he did not receive the second infusion; he underwent electrical cardioversion a few hours later and then developed cardiogenic shock. He was successfully treated and later diagnosed as having a tachyarrhythmia-induced cardiomyopathy. The previously mentioned 90-year-old woman had complete heart block after electrical cardioversion, which was performed =2.5 hours after the second vernakalant infusion.

### Ventricular Arrhythmia During the First 24 Hours

A full characterization of possible ventricular arrhythmia events during the 24-hour period after the administration of vernakalant included investigator-reported adverse events (such as syncope), 12-lead ECGs, and Holter recordings. The incidence of ventricular arrhythmia from all sources was 17.4% for placebo and 9.0% for vernakalant. Confirmed nonsustained ventricular tachycardia was reported in 14.8% of the placebo patients and 6.3% of the vernakalant patients.
There were no reports of sustained ventricular tachycardia during this 24-hour interval.

**Torsade de Pointes**

There were no reports of torsade de pointes or ventricular fibrillation during the first 24 hours after infusion. The 90-year-old woman referenced above experienced an episode of torsade de pointes 32 hours after vernakalant administration. Another patient had 3 episodes of torsade de pointes, 2 of which occurred 16 days after treatment with vernakalant (2 days after cardiac surgery). The third episode occurred 17 days after treatment and resulted in cardiac arrest, for which the patient received an internal defibrillator.

**Other Adverse Events**

The most common treatment-emergent adverse events reported during the first 24 hours in patients given vernakalant were dysgeusia (29.9% vernakalant, 0.9% placebo), sneezing (16.3% vernakalant, 0% placebo), paresthesia (10.9% vernakalant, 0% placebo), nausea (9.0% vernakalant, 0.9% placebo), and hypotension (6.3% vernakalant, 3.5% placebo). The median duration of related adverse events in vernakalant patients was 12 minutes for dysgeusia, 3 minutes for sneezing, 7 minutes for paresthesia, 12.5 minutes for nausea, and 15 minutes for hypotension.

A total of 5 patients, 4 vernakalant and 1 placebo, had study drug discontinued because of adverse events. Adverse events that led to study drug discontinuation in 3 of the 4 vernakalant patients were bradycardia (n=1), hypotension (n=1), and prolonged uncorrected QT (>25%, as per protocol; n=1); 1 of the 4 patients discontinued as a result of ventricular bigeminy and multiple other minor complaints. The placebo patient discontinued study drug prematurely because of prolonged QT.

**Effects of Vernakalant on ECG**

ECG effects of vernakalant were compared with those of placebo in patients who remained in AF. Except for a transient 4.5-bpm increase at 10 minutes, the effect of vernakalant on heart rate was unremarkable (Figure 4A).

Patients given vernakalant who demonstrated termination of AF had higher mean heart rates at baseline (110 ± 26 versus 91 ± 22 bpm in those who remained in AF). There was a correlation between AF duration and baseline heart rate (log

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**Figure 4.** Change in heart rate, QRS, QTcB, and QTcF intervals over time for vernakalant-treated patients vs placebo-treated patients. Data are shown for patients who remained in AF. Vernakalant-treated patients who demonstrated termination of AF (wide error bars) are included in A.
event in 14 vernakalant patients (6.3%) and 4 placebo patients.

There were no significant changes from baseline in mean systolic or diastolic blood pressure in vernakalant patients compared with those given placebo. In the 24 hours from the start of drug infusion, hypotension was reported as an adverse event in 14 vernakalant patients (6.3%) and 4 placebo patients (3.5%). Hypotensive episodes occurred within 15 minutes of the end of either infusion of vernakalant, were transient, and resolved without pharmacological intervention. Two previously described hypotensive events were reported as serious; both cases responded to saline, and 1 led to discontinuation of treatment.

**Discussion**

The identification of an intravenous antiarrhythmic drug that can provide reliable, safe, and prompt pharmacological cardioversion is highly desirable. Vernakalant was effective in converting AF to sinus rhythm. Vernakalant was especially effective in treating short-duration AF. Fifty-two percent of vernakalant patients in the short-duration AF group converted to sinus rhythm compared with only 4% of placebo patients, and patients with the shortest duration of AF demonstrated the highest rate of conversion. The majority (76%) converted after receiving only the first infusion. Additionally, conversion to sinus rhythm was rapid; the median time to conversion was 11 minutes. These findings are consistent with results from the phase 2 study, which provided the first clinical evidence of effective intravenous cardioversion with vernakalant.10 Vernakalant was associated with a minimal risk of early recurrence of AF.

Efficacy comparisons with other drugs used for acute cardioversion of AF must be made with caution because the drugs are used in different patient populations. The most relevant comparison to vernakalant is ibutilide, a class III agent and the only intravenous drug approved by the Food and Drug Administration for the conversion of AF.5 Results from 3 large, randomized, placebo-controlled ibutilide trials indicate placebo-subtracted conversion rates of 28% to 31% for AF.11–13 Studies comparing ibutilide with other agents have reported AF conversion rates of 32% to 51%.14–16 In this study, vernakalant displayed an AF conversion rate that exceeded that reported for ibutilide.

Other antiarrhythmic drugs are used for pharmacological cardioversion of AF. Patterns of usage vary in different countries.17–19 Amiodarone generally is considered of limited value for the acute cardioversion of AF because prolonged infusions generally are required for efficacy.17,18,20,21 Intravenous flecainide and propafenone reportedly successfully terminate recent-onset AF in >50% to 60% of patients.22–28 These formulations are not available in North America,4,19 however, and they have significant proarrhythmic and negative inotropic potential.22,23,25,26 Procainamide is used despite a risk-to-benefit profile that is inferior to ibutilide or flecainide.15,28 Studies of intravenous dofetilide have shown modest results.29–31 Tedisamil, an investigational class III drug, successfully converted 57% of patients with recent-onset AF to sinus rhythm in a preliminary trial; however, an increased risk of proarrhythmia was seen.32

**Safety Considerations of Vernakalant**

Vernakalant was well tolerated in most patients. A transient alteration in taste, sneezing, paresthesia, and nausea were the most common adverse reactions with vernakalant. Hypotension may occur; however, most episodes of hypotension in this study were transient. The exception was the patient with
tachyarrhythmic cardiomyopathy previously described. Atrial flutter may occur with vernakalant, and atrioventricular nodal-blocking drugs for rate control may be needed.

Vernakalant-treated patients who remained in AF showed statistically significant increases in QRS duration, QT, QTcB, and QTcF. In those who remained in AF, vernakalant had little effect on heart rate. Patients given vernakalant who were successfully treated had a higher baseline heart rate, which was likely related to a shorter duration of AF. Two patients had torsade de points: 1 patient 32 hours after treatment with vernakalant and the second patient 16 to 17 days after treatment. These episodes were not considered to be due to vernakalant because the half-life of vernakalant is 2 to 3 hours. There were 3 deaths during the study, none of which were considered to be related to vernakalant because they occurred 28 hours and 8 and 26 days after study drug infusion.

Conclusion
Vernakalant demonstrated rapid conversion of short-duration AF and was well tolerated.

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Disclosures
Dr Roy has received consultant fees from and is an advisory board member for Cardiome Pharma Corp, Astellas Pharma US, Inc, Sanofi-aventis, and CyroCath Technologies Inc. Dr Roy also held stock in Cardiome Pharma Corp and is fully divested. Dr Pratt has received consultant fees and honoraria from Astellas Pharma US, Inc and Cardiome Pharma Corp. Dr Torp-Pedersen has received grant support and honoraria from Astellas Pharma US, Inc and Cardiome Pharma Corp. Dr Wyse has received consultant fees from Astellas Pharma US, Inc, Boehringer Ingelheim, Cardiome Pharma Corp, CV Therapeutics, Medtronic, Novartis, Sanofi-aventis, and Transoma Medical; grant support from Astellas Pharma US, Inc, Cardiome Pharma Corp, and Medtronic; and speaker’s fees from Astellas Pharma US, Inc, Cardiome Pharma Corp, and Eisai Inc. Dr Stell has received research support from the Canadian Institutes of Health Research and the National Institutes of Health. Dr Ip has received grant support from Aryx Therapeutics, Astellas Pharma US, Inc, Biotronik, Cardiome Pharma Corp, Guidant, Reliant Pharmaceuticals, Inc, SCTR/NIH, St Jude, and Vitatron. Dr Pritchett has received consultant fees from Astellas Pharma US, Inc, Cardiome Pharma Corp, NovaCardia Inc, Procter & Gamble, Reliant Pharmaceuticals, Inc, Sanofi-aventis, and Solvay Pharma BV. Dr Camm has received consultant fees, honoraria, and speaker’s fees from Astellas Pharma US, Inc and Cardiome Pharma Corp. The remaining authors report no conflicts.

References
CLINICAL PERSPECTIVE

Pharmacological cardioversion often is used to restore sinus rhythm in patients with hemodynamically stable and recent-onset atrial fibrillation. However, currently available antiarrhythmic agents have modest efficacy, and the risk of proarrhythmia is of concern. Vernakalant is a new and relatively atrium-selective antiarrhythmic agent undergoing investigation for the conversion of atrial fibrillation to sinus rhythm. The results of this placebo-controlled trial demonstrate the efficacy of intravenous vernakalant in terminating recent-onset atrial fibrillation. Moreover, conversion was rapid and not associated with ventricular proarrhythmia. The clinical implication is that intravenous vernakalant may represent a valuable new antiarrhythmic drug for the acute conversion of atrial fibrillation to sinus rhythm, and it may be particularly useful in patients with recent-onset atrial fibrillation in the emergency room setting.
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for the Atrial Arrhythmia Conversion Trial Investigators

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