

Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: The PRECEDENT study

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Background Dobutamine is commonly used as a means of treating decompensated congestive heart failure (CHF). Although typically effective at improving short-term hemodynamics and symptomatology, the frequent occurrence of arrhythmias and tachycardia is undesirable. In this randomized, multicenter trial, we compared the safety and clinical effectiveness of the cardiac hormone nesiritide (human B-type natriuretic peptide) with dobutamine in hospitalized patients with decompensated CHF.

Methods The study population consisted of 255 patients who were randomized to 1 of 2 doses of intravenous nesiritide (0.015 or 0.03 $\mu\text{g}/\text{kg}/\text{min}$) or dobutamine (≥ 5 $\mu\text{g}/\text{kg}/\text{min}$) and stratified by means of an earlier history of ventricular tachycardia. Patients were also assessed with 24 hour Holter recordings immediately before and during study drug therapy and by means of signs and symptoms of CHF.

Results Dobutamine significantly increased the mean (1) number of ventricular tachycardia events per 24 hours by 48 ± 205 ($P = .001$), (2) repetitive ventricular beats per hour by 15 ± 53 ($P = .001$), (3) premature ventricular beats per hour by 69 ± 214 ($P = .006$), and (4) heart rate by 5.1 ± 7.7 beats per minute ($P < .001$). These end points were significantly decreased or unchanged in the nesiritide groups. Nesiritide did not increase heart rate, despite a greater reduction of blood pressure. Both drugs were similarly effective means of improving signs and symptoms of CHF.

Conclusions Dobutamine is associated with substantial proarrhythmic and chronotropic effects in patients with decompensated CHF, whereas nesiritide actually reduces ventricular ectopy or has a neutral effect. Compared with dobutamine, nesiritide may be a safer, short-term treatment for patients with decompensated CHF. (*Am Heart J* 2002;144:1102-8.)

Congestive heart failure (CHF) involves complex autonomic and neurohormonal responses characterized by sympathetic overactivity, parasympathetic withdrawal, and the activation of renin-angiotensin-aldosterone and vasopressin systems. Although current inotro-

pic therapies for CHF, including dobutamine¹⁻⁵ and milrinone,⁶ are associated with favorable hemodynamic and symptomatic effects, they also cause arrhythmias and tachycardia and may increase myocardial oxygen demand, the risk of ischemia, and mortality.

Human B-type natriuretic peptide (BNP), a cardiac hormone, is secreted predominantly by the ventricular myocardium in response to ventricular wall stress and fluid overload in CHF,⁷ and it unloads the heart through vasodilatation and natriuresis.⁸ As a member of a new pharmacologic class of drugs for acute decompensated CHF (natriuretic peptides), nesiritide has been shown to reduce preload and afterload, increase cardiac output without increasing heart rate, and improve symptoms in patients with acutely decompensated CHF.^{9,10} Nesiritide may also increase glomerular filtration rate and filtration fraction, suppress the renin-angiotensin-aldosterone system, promote natriure-

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Supported by a grant from Scios Inc, Sunnyvale, Calif.

Submitted October 26, 2001; accepted April 4, 2002.

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0002-8703/2002/\$35.00 + 0 4/1/125620

doi:10.1067/mhj.2002.125620

sis, and have sympathoinhibitory cardiac and renal effects.^{8,10-14}

In an earlier trial that evaluated the safety of nesiritide versus other intravenous agents used for treatment of acute decompensated CHF, the subgroup of patients who were treated with dobutamine experienced significantly more adverse events of ventricular tachycardia (VT) and tachycardia than the subgroup of patients treated with nesiritide.¹⁵ Therefore, this study was conducted as a means of determining prospectively the differential effects of nesiritide and dobutamine on heart rate and the genesis or aggravation of ventricular arrhythmias in patients with decompensated CHF.

Methods

Study design

The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) study was a multicenter, randomized, open-label, active-control trial designed as a means of comparing the relative safety of a low dose of dobutamine (≥ 5 $\mu\text{g}/\text{kg}/\text{min}$) and 2 fixed doses of nesiritide (0.015 or 0.030 $\mu\text{g}/\text{kg}/\text{min}$, with no preceding bolus) for their effects on Holter-measured heart rate and ventricular arrhythmias in patients with decompensated CHF.

Study population

Patients (age ≥ 18 years) were eligible for the study if they had a history of New York Heart Association (NYHA) class III or IV CHF and had symptomatic, decompensated CHF for which inpatient, single-agent, intravenous therapy with either nesiritide or dobutamine (with or without diuretics) was deemed appropriate. Patients were taking no antiarrhythmic medications or were taking a stable dose of such drugs for at least 48 hours before starting study treatment. Oxygen, intravenous and oral diuretics, and all nonintravenous cardiac medications were permitted. The investigational review boards on human research of all participating study sites approved the study protocol, and all patients gave informed consent.

Exclusion criteria included recent myocardial infarction (≤ 48 hours before study entry); unstable angina or ongoing myocardial ischemia; cardiogenic shock; baseline systolic blood pressure consistently < 85 mm Hg or significant hemodynamic instability requiring immediate inotropic support, pressor support, or both; stroke within the past month; severe aortic stenosis; obstructive cardiomyopathy; and constrictive pericarditis. Patients were excluded when they had been treated for > 4 hours with an intravenous vasoactive agent for this episode of CHF. Patients were also excluded from the study when they could not tolerate a 24-hour baseline Holter period without intravenous vasoactive medications, could not tolerate the specified washout period for intravenous vasoactive medications received before the baseline Holter period (6 hours for milrinone and 30 minutes for dobutamine, nitroprusside, nitroglycerin, and dopamine), or both.

Holter monitoring

All patients had a Holter monitor recording for the 24-hour period immediately before the start of the study drug (baseline Holter tape). After at least 20 hours of the baseline Holter was collected, patients were stratified by the presence or absence of a known history of sustained or nonsustained VT and randomized to treatment with 0.015 or 0.03 $\mu\text{g}/\text{kg}/\text{min}$ of nesiritide (with no preceding bolus) or dobutamine. At the initiation of the study drug therapy, another Holter recording was obtained for the first 24 hours of drug treatment (treatment Holter tape). All Holter tapes were interpreted at a core laboratory that was blinded to treatment groups. The 3-channel (leads V_1 , V_5 , and aVF) Holter recordings were analyzed on a commercially available scanner (model 2010, Zymed Medical Instruments, Camarillo, Calif). After a normal QRS was chosen, computer-assisted rate and arrhythmia analyses were performed with a technician overreading and editing. Excessive noise and artifact were deleted, and cardiac ectopy was quantified. After technician analysis, a physician review of all studies was performed.

Study drug administration

The assignment to nesiritide or dobutamine was open-label; assignment to the 2 nesiritide doses was double-blinded. Study drugs were administered as a single-agent therapy for at least 24 hours. Dobutamine was administered at a dose of ≥ 5 $\mu\text{g}/\text{kg}/\text{min}$. No additional intravenous vasoactive medications were permitted for the first 24 hours of therapy. After completion of the treatment Holter tape, the investigator could continue or discontinue giving the study drug, add other intravenous vasoactive medications to the study drug, or substitute another medication for the study drug. There were no restrictions on the use of any other cardiac medications. All patients were observed for 14 days.

End points

The primary end points of the study were changes from baseline in (1) mean heart rate, (2) mean hourly premature ventricular beats (PVBs), and (3) mean hourly repetitive beats (total number of beats involved in ventricular couplets or runs of VT). Secondary end points included the frequency of VT, triplets, and couplets per 24 hours.

Two previously described proarrhythmia criteria were applied as a means of determining for each patient whether increases in ventricular ectopy or VT from the baseline to the treatment tape were proarrhythmic. The Velebit criteria include a ≥ 4 -fold increase in PVBs, a ≥ 10 -fold increase in couplets or repetitive forms (couplet or runs of nonsustained VT), and occurrence of a new, sustained VT.¹⁶ The Cardiac Arrhythmia Pilot Study (CAPS) criteria include a ≥ 10 -fold increase in PVBs when ectopy at baseline was 10 to 50 PVBs/hour, a 5-fold increase in PVBs when ectopy at baseline was 51 to 100 PVBs/hour, a 4-fold increase in PVBs when ectopy at baseline was 100 to 300 PVBs/hour, and a 3-fold increase in PVBs when ectopy at baseline was > 300 PVBs/hour.¹⁷ A 10-fold increase in runs of nonsustained VT also define a proarrhythmic effect, regardless of the baseline frequency of episodes.

Table I. Baseline clinical characteristics

	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)			<i>P</i>
	0.015 (<i>n</i> = 85*)	0.03 (<i>n</i> = 84*)	Dobutamine (<i>n</i> = 86*)	
Age (y)	60 \pm 14	61 \pm 14	62 \pm 14	.87
Males (%)	58 (68)	58 (69)	54 (63)	.65
Ethnicity (%)				.87
White	47 (55)	41 (49)	48 (56)	
Black	23 (27)	23 (27)	25 (29)	
Hispanic	13 (15)	16 (19)	11 (13)	
Other	2 (3)	4 (5)	2 (2)	
NYHA classification (%)				.04
III	68 (80)	65 (77)	55 (64)	
IV	17 (20)	19 (23)	31 (36)	
CHF etiology (%)				.27
Ischemic	44 (52)	44 (52)	42 (49)	
Idiopathic dilated cardiomyopathy	13 (15)	24 (29)	22 (26)	
Hypertensive	14 (16)	6 (7)	10 (12)	
Comorbid conditions (%)				
Hypertension	56 (67)	51 (65)	54 (65)	.96
Diabetes mellitus	36 (42)	40 (48)	44 (51)	.52
Previous myocardial infarction	43 (51)	46 (58)	37 (45)	.23
Atrial fibrillation	18 (21)	21 (27)	29 (35)	.15
Nonsustained VT	22 (26)	19 (24)	25 (30)	.68
Sustained VT	7 (8)	5 (6)	7 (8)	.87

*Sample size is for all randomized patients (intent-to-treat).

Statistical analysis

As prespecified, the analysis was stratified according to known history of VT at baseline. Continuous data were analyzed with the omnibus F test followed by pairwise contrast; ordinal data were analyzed with the Kruskal-Wallis test followed by pairwise 2-sample Wilcoxon procedures; and categorical data were analyzed with the generalized Fisher exact test followed by pairwise Fisher exact tests. Within-group changes from baseline were tested with either a paired *t* test, 1-sample Wilcoxon test, or binomial test, as appropriate for the end point. Assuming 80 subjects in each of the 3 treatment groups and a 2-sided significance level of $\alpha = 0.05$, the Omnibus F test had a 74% to 86% power in detecting a treatment difference of 100 PVBs/hour, depending on the value of the intermediate population mean difference, assuming a common standard deviation of 200 PVBs/hour, and if the greatest pairwise population mean difference is 100 PVBs/hour. All reported values are presented as mean \pm SD. All reported *P* values are 2-sided, and a *P* value $<.05$ was considered to be significant. Analyses were performed by use of SAS software, version 6.12, running on a Digital Equipment Corporation Alpha server 4100 5/300 (SAS Institute, Cary, NC).

Results

A total of 255 patients were randomized at 46 US clinical sites from January 1998 to July 1999. Nine patients who were randomized were not treated because they did not meet all of the inclusion/exclusion crite-

ria at the time of treatment initiation. Of the 246 patients who were randomized and treated, 84 received 0.015 $\mu\text{g}/\text{kg}/\text{min}$ of nesiritide, 79 received 0.03 $\mu\text{g}/\text{kg}/\text{min}$ of nesiritide, and 83 received dobutamine. Twenty-one patients were terminated from the study early (ie, received ≤ 22 hours of study drug infusion) because of adverse events (6 [7%] dobutamine patients and 4 [5%] and 11 [11%] nesiritide 0.015 and 0.03 $\mu\text{g}/\text{kg}/\text{min}$ patients, respectively).

Patient demographics

The study population was predominantly white, elderly, and male, with ischemic or idiopathic dilated cardiomyopathy (Table I). Frequent comorbid conditions included hypertension, diabetes mellitus, previous myocardial infarction, and significant cardiac arrhythmias. Baseline characteristics were generally well balanced among the 3 treatment groups, except that more patients given dobutamine had a chronic history of NYHA class IV CHF before this hospitalization (*P* = .04). At baseline, 90% of patients had dyspnea and fatigue, 63% had peripheral edema, 38% had decreased peripheral circulation, and 28% had lightheadedness.

Dobutamine dosing

The mean and median minimum doses of dobutamine during the first 24 hours of therapy were 5 $\mu\text{g}/$

Table II. Baseline Holter end points

	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)			<i>P</i> *
	0.015 (n = 84)	0.03 (n = 79)	Dobutamine (n = 83)	
VT (events/24 hours)	13 \pm 39	27 \pm 89	30 \pm 144	.224
Triplets (events/24 hours)	10 \pm 33	20 \pm 61	27 \pm 129	.279
Couplets (events/24 hours)	139 \pm 372	228 \pm 561	310 \pm 1008	.258
Mean repetitive beats/hour	14 \pm 36	23 \pm 58	30 \pm 102	.327
Mean PVBs/hour	110 \pm 170	165 \pm 265	192 \pm 338	.330
Mean heart rate (beats/min)	82 \pm 15	85 \pm 14	83 \pm 17	.586

*Wilcoxon procedure stratified by history of VT (van Elteren test).

kg/min (25th/75th percentile 2.5/5.0, range 0-8.3); the mean and median peak doses of dobutamine were 5.3 and 5 $\mu\text{g}/\text{kg}/\text{min}$, respectively (25th/75th percentile 5/5, range 5-10).

Holter analysis

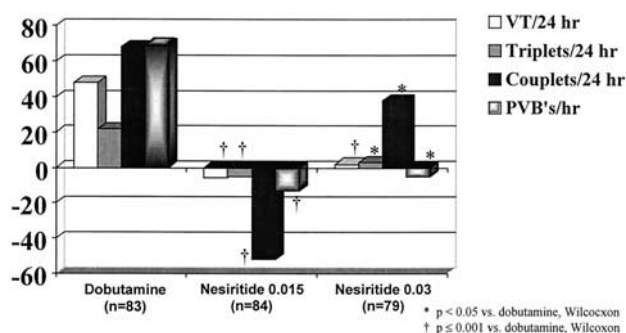
Similar rates of ventricular ectopy and heart rate were revealed in all 3 treatment groups by means of baseline Holter monitoring (Table II). With within-group comparisons to the baseline Holter tape, dobutamine significantly increased all measures of ventricular ectopy ($P < .05$ for each end point), whereas 0.015 $\mu\text{g}/\text{kg}/\text{min}$ of nesiritide reduced the frequency of VT per 24 hours ($P = .001$), hourly repetitive beats ($P = .006$), hourly ventricular couplets ($P = .006$), and hourly PVBs ($P = .054$) relative to baseline.

During the treatment Holter tape, changes from baseline in VT per 24 hours ($P < .001$ for dobutamine vs each nesiritide dose [0.015 and 0.030 $\mu\text{g}/\text{kg}/\text{min}$]), triplets per 24 hours ($P < .001$ and $P = .008$, respectively), couplets per 24 hours ($P < .001$ and $P = .017$, respectively), and PVBs per hour ($P = .001$ and $P = .002$, respectively) were increased more in the dobutamine group than in each nesiritide dose group (Figure 1 and Table III).

With 2 proarrhythmia criteria used as a means of quantifying the most clinically significant ventricular arrhythmias, dobutamine (but neither dose of nesiritide) was proarrhythmic. The Velebit criteria were met in 23% of patients treated with dobutamine, compared to only 2% of patients treated with nesiritide ($P < .001$). Similarly, the CAPS criteria were met in 10% of patients treated with dobutamine and in 0% of patients treated with nesiritide ($P = .001$).

There were no significant differences among the 3 treatment groups (Table IV) during the baseline period in the average heart rate or amount of time that patients were tachycardic (heart rate >100 beats/min). During the 24-hour treatment tape, dobutamine significantly increased the average heart rate ($P < .001$) and

Figure 1



Mean changes from baseline in ventricular ectopy in patients treated with dobutamine or nesiritide.

the amount of time in tachycardia ($P = .01$) from the baseline Holter tape. These increases were statistically significant compared with each nesiritide dose.

To evaluate whether differences observed in arrhythmogenesis between dobutamine and nesiritide were attributable to imbalance in NYHA class between the treatment arms at randomization, we analyzed various Holter parameters in the NYHA class III and IV populations separately. Even with the reduced statistical power resulting from dividing the patients into subsets, the differences among the 3 treatment groups retained statistical significance for all parameters (NYHA class III, $P < .0001$; NYHA class IV, $P = .05-.01$).

Adverse events

Table V summarizes the cardiovascular adverse events that were reported in $\geq 5\%$ of patients in any treatment group during the first 24 hours of study drug treatment. The most common cardiovascular adverse event associated with nesiritide was dose-related hypotension ($P < .001$). The most common cardiovas-

Table III. Effects of study drugs on ventricular ectopy

	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)		Dobutamine (n = 83)
	0.015 (n = 84)	0.030 (n = 79)	
Change in VT/24 hours	$-5.6 \pm 17^\dagger$	$1.5 \pm 60^\dagger$	48 ± 205
Change in triplets/24 hours	$-5 \pm 15^\dagger$	$3 \pm 38^*$	22 ± 86
Change in couplets/24 hours	$-51.6 \pm 200^\dagger$	$38 \pm 317^*$	68 ± 427
Change in repetitive beats/hour	$-5.1 \pm 19^\dagger$	$3.3 \pm 34^\dagger$	15 ± 53
Change in PVBs/hour	$-13 \pm 83^\dagger$	$-5.2 \pm 96^*$	69 ± 214

* $P < .05$ versus dobutamine, Wilcoxon.† $P \leq .001$ versus dobutamine, Wilcoxon.**Table IV.** Effects on average heart rate and duration of tachycardia

	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)		Dobutamine (n = 83)	P^*
	0.015 (n = 84)	0.03 (n = 79)		
Average heart rate (beats/min)				
Baseline	82.4 ± 15	84.7 ± 14	83.4 ± 17	.586
Change from baseline	-0.7 ± 6	1.2 ± 7	5.1 ± 8	<.001
P value vs. dobutamine	<.001	.002	–	
Mean time (hours) in tachycardia				
Baseline	3.7 ± 6.8	3.2 ± 5.6	4.0 ± 6.3	.755
Change from baseline	-0.1 ± 4.2	0.8 ± 3.5	1.7 ± 5.3	.044
P value vs. dobutamine	.019	.413	–	

*Wilcoxon procedure stratified by history of VT (van Elteren test).

Table V. Cardiovascular adverse events occurring in $\geq 5\%$ of patients during the first 24 hours of treatment

	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)		Dobutamine (n = 83)	P^*
	0.015 (n = 84)	0.030 (n = 79)		
Symptomatic hypotension (%)	14 (17)	19 (24)	2 (2)	<.001
Nonsustained VT (%)	5 (6)	4 (5)	11 (13)	.127
Ventricular extrasystoles (%)	3 (4)	5 (6)	9 (11)	.177
Tachycardia (%)	1 (1)	2 (3)	11 (13)	.001
Bradycardia events (%)	2 (2)	4 (5)	1 (1)	.310

*Fisher's exact test.

cular adverse events in the dobutamine group were nonsustained VT ($P = .127$), tachycardia ($P = .001$), and ventricular extrasystoles ($P = .177$). Six deaths occurred through day 14 (2 per treatment group), none of which were believed by the investigator to be attributed to the study drug.

Discussion

In this randomized investigation of patients hospitalized for acutely decompensated heart failure, we com-

pared the relative safety and efficacy of dobutamine (a commonly used agent for the management of CHF) with nesiritide (a cardiac hormone with hemodynamic, renal, and neurohormonal effects). Although the arrhythmogenic effects of dobutamine are well known, we have for the first time objectively quantified the substantial proarrhythmic and tachycardic effects of dobutamine by use of Holter monitoring in patients with decompensated CHF. We used the Velebit and CAPS criteria as secondary end points to benchmark

proarrhythmic effects during therapy with data from earlier trials. Unlike dobutamine, nesiritide significantly reduced or had no effect on any of the measured parameters of ectopy and proarrhythmia. Despite its greater effect on blood pressure, nesiritide did not cause changes in heart rate.

The results of this trial are consistent with earlier studies in patients with decompensated CHF in which nesiritide therapy was not associated with either tachycardia or ventricular ectopy.^{8-15,18} A recent randomized controlled trial of 305 hospitalized patients with decompensated CHF demonstrated a significantly higher incidence of sustained and nonsustained VT and cardiac arrest in patients treated with dobutamine compared with patients treated with nesiritide.¹⁵ Nesiritide has previously been shown to suppress catecholamines, and its use has not caused sympathetic activation.^{14,18} The aforementioned sympathoinhibitory effects likely explain the observations in this trial that nesiritide did not affect heart rate or cause reflex tachycardia and, in some cases, appeared to suppress baseline ectopy (including VT).

End points for this trial were selected because of their physiologic and clinical relevance. Heart rate is a crucial determinant of myocardial oxygen demand, which, when increased in patients with advanced CHF, can aggravate their condition. Hourly premature ventricular beats and repetitive beats as well as VT and couplets (secondary end points) are clinically relevant because the genesis or aggravation of ventricular ectopy may significantly reduce stroke volume (resulting in worsening of CHF) and increase the likelihood of ventricular fibrillation and sudden death. Also, the new onset of VT in patients with CHF who do not have a known history of VT identifies a patient with a new or preexisting substrate for significant ventricular arrhythmias. It may be important to prevent the new onset of such arrhythmias in the acute setting because conventional antiarrhythmic agents in patients with severe CHF do not reduce the incidence of sudden death or prolong survival in these patients.¹⁹

We also note that the reporting of VT and ectopy as adverse events is inconsistent with what was documented with Holter monitoring. Possible explanations include the under-reporting of adverse events with a commonly used agent (dobutamine) and the over-reporting of events with use of an investigational agent (nesiritide) in an open-label trial. It is also plausible that the surveillance of telemetry findings is not done consistently in a busy hospital unit.

Limitations of the study

Whereas analysis of ventricular arrhythmias in the setting of decompensated CHF may be complicated by a heterogeneous patient population, sporadic variability in ventricular ectopy, and confounding arrhythmo-

genic variables (such as serum electrolyte disturbances, hypoxia, or acid/base abnormalities), the randomization of a relatively large number of patients should have helped to minimize major differences between groups. Furthermore, comparing each patient's on-drug Holter parameters with pre-drug parameters helps to eliminate intrapatient variability. Although more patients with NYHA class IV CHF were randomized to the dobutamine arm, subset analyses of Holter parameters by NYHA class demonstrate that the observed differences in arrhythmogenicity between dobutamine and nesiritide cannot be attributed to this randomization imbalance.

We cannot exclude the possibility that antiarrhythmic therapy may have prevented or attenuated the effect of parenteral vasoactive therapy on the occurrence of ventricular arrhythmias. However, the use of antiarrhythmic drugs and β -blockers at baseline was not significantly different between the treatment groups.

Conclusion

In this randomized, controlled study of hospitalized patients with acute decompensated CHF, we demonstrated significantly fewer serious ventricular arrhythmias and no increased heart rate in patients treated with nesiritide compared with patients treated with a low dose of dobutamine. Although nesiritide was associated with a higher incidence of hypotension than dobutamine, this effect of the drug was easily treated with dose reduction or discontinuation. Notably, the doses of nesiritide studied in this trial were higher than the currently recommended dose of a 2 $\mu\text{g}/\text{kg}$ bolus followed by an infusion of 0.01 $\mu\text{g}/\text{kg}/\text{min}$.^{20,21} Thus, it appears that nesiritide may be a safer drug than dobutamine for the short-term management of decompensated CHF, especially in patients with tachycardia, a history of serious atrial or ventricular arrhythmias, or evidence of ventricular irritability. Our findings suggest that, although the use of dobutamine may require continuous electrocardiographic monitoring with telemetry, such monitoring is not required when using nesiritide because of its lack of proarrhythmic effects.

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Appendix

Participating investigators and study centers:

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