

# Predictors of Conversion of Recent-Onset Atrial Fibrillation Treated with Vernakalant

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**Background:** Vernakalant is an available drug for the treatment of recent-onset atrial fibrillation, producing conversion between 55% and 87% of the patients treated. In this sense, little is known about the predictors of conversion with this agent. The aim of our study was to analyze the predictors of conversion in our 2-year experience using vernakalant for the treatment of recent-onset atrial fibrillation.

**Methods:** One hundred twenty-one patients with recent-onset atrial fibrillation without hemodynamic impairment received pharmacological treatment with vernakalant. Clinical variables, history of cardiovascular diseases, and echocardiographic data were recorded.

**Results:** Mean age was  $58.1 \pm 13.9$  years and 13.4% of patients had structural heart disease. Conversion to sinus rhythm was achieved in 84.5% of patients, and 46% required the second dose of vernakalant. After analyzing the predictors of conversion, the presence of structural heart disease was significantly larger in the group without conversion (35.3 vs 9.7%;  $P = 0.02$ ). The mean ejection fraction in the group with conversion was  $61.05 \pm 5.7\%$  versus  $54.9 \pm 8.4\%$  in the group without conversion ( $P = 0.016$ ). After dichotomizing the variable ejection fraction, patients with ejection fraction  $<55\%$  had a lower conversion rate ( $P = 0.001$ ).

**Conclusion:** In our study, the absence of any kind of structural heart disease and preserved systolic function were associated with greater conversion rate with vernakalant. (*PACE* 2015; 38:196–200)

**predictors, recent-onset atrial fibrillation, vernakalant**

## Introduction

Pharmacologic cardioversion of recent-onset atrial fibrillation can be accomplished with several antiarrhythmic agents. Vernakalant is a safe and effective drug used intravenously that has been recently introduced in the Argentine market. Vernakalant has been widely studied and validated in Europe in patients with and without structural heart disease.<sup>1–4</sup>

Time to conversion to sinus rhythm has proved to be significantly shorter with vernakalant than with propafenone, flecainide, or amiodarone.<sup>1,4,5</sup> Conversion rate ranges between 55% and 87% in the published literature, meaning that between 13% and 45% of patients remain with atrial fibrillation after the infusion.<sup>2–5</sup> In this sense, little is known about the predictors of conversion with vernakalant.

The aim of our study was to analyze the predictors of conversion in our 2-year experience using vernakalant for the treatment of recent-onset atrial fibrillation.

## Methods

We conducted a single-center, retrospective study in the Emergency Department of the Instituto Cardiovascular de Buenos Aires (ICBA). The emergency department receives patients  $>18$  years who seek medical care by themselves or are referred from other centers. The information is recorded electronically and includes the clinical characteristics of the patients, cardiovascular risk factors, cardiovascular history, cause of consultation, medication administered, length of stay, and discharge diagnoses.

From March 1, 2012 to January 30, 2014, 121 patients consulted with recent-onset atrial fibrillation without hemodynamic impairment and received vernakalant for atrial fibrillation conversion. As recommended by the clinical guidelines, an initial dose of 3.0 mg/kg was administered over 10 minutes, followed by a 15-minute observation period and, if conversion to sinus rhythm did not occur, a second dose of 2 mg/kg was administered.

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**Inclusion Criteria**

Patients >18 years, weighing between 45 kg and 136 kg, with clear symptoms in the last 48 hours, systolic blood pressure >90 mm Hg and <160 mm Hg, and diastolic blood pressure <95 mm Hg were included. Pregnancy, atrial flutter, sinus node disease, QRS duration >140 ms in nonpaced beats, uncorrected QT interval >440 ms, heart failure, or recent coronary syndrome within 30 days prior to enrollment were considered exclusion criteria. Patients with severe valvular heart disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, and those with known ejection fraction (EF) <35% were excluded.

Clinical, laboratory, and electrocardiographic variables were recorded. All the patients underwent strict, continuous electrocardiographic monitoring. All the patients underwent color Doppler echocardiography with measurement of structural and functional parameters within 30 days after the clinical event.

**Conversion Criterion**

Time to conversion was considered at the moment of conversion to sinus rhythm that persisted until hospital discharge. Persistent atrial fibrillation after 2 hours of the second dose was considered as failure of pharmacological conversion with vernakalant according to the recommendations of the international protocols. After this time interval, the attending physician decided how to manage the arrhythmia.

Significant heart disease was defined as the presence of at least one of the following: (1) valvular heart disease, (2) myocardial infarction, (3) hypertensive heart disease (hypertension [HT] and left ventricular posterior wall or septal thickness >13 mm) or systolic dysfunction (EF < 55%).

The following factors were considered involved in the conversion to sinus rhythm and were included in the analysis: weight, height, body surface area, age, sex, HT, chronic obstructive pulmonary disease, diabetes mellitus, left atrial dimension, body surface area, left atrial dimension adjusted for body surface area, EF, the presence of structural heart disease, previous antiarrhythmic treatment, number of episodes of atrial fibrillation (AF), and AF duration.

**Statistical Analysis**

Discrete variables are expressed in percentages and continuous variables in mean or median according to their distribution. The  $\chi^2$  test was used to compare discrete variables, and continuous variables were analyzed using Student's *t*-test or the Mann-Whitney, as applicable. A P value < 0.05 was considered statistically significant. All the statistical calculations were

**Table I.**

General Characteristics of the Population

Variables	Value
Age (years)	58.1 ± 13.9
Male gender (%)	67.9
Weight (kg)	79.5 ± 14.9
Height (cm)	173.5 ± 12.5
Body surface area (m <sup>2</sup> )	1.93 ± 0.23
HT (%)	46.4
DBT (%)	1.8
Chronic obstructive pulmonary disease (%)	1.8
Ejection fraction (%)	60.2 ± 6.4
Ejection fraction < 55% (%)	5.3
Structural heart disease (%)	13.4
Left atrial area (cm <sup>2</sup> )	20.6 ± 4.4
LV mass (g)	173 ± 59
Left atrial area/body surface area (cm <sup>2</sup> /m <sup>2</sup> )	10.8 ± 2.7
Heart rate (bpm)	118.9 ± 27
Time from symptom onset (hours)	4 (2–10)
First AF episode (%)	29.5
Requirement of second dose (%)	46
Conversion to sinus rhythm (%)	84.5

AF = atrial fibrillation; DBT = diabetes; HT = hypertension; LV = left ventricle.

performed using Statistix 8.0 software package (Analytical Software, Tallahassee, FL, USA).

This investigation was in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by an institutional review board or ethics committee at ICBA, and written informed consent was obtained from patients prior to include in the study.

**Results**

Data from 121 consecutive patients treated with vernakalant were included. Mean age was 58.1 ± 13.9 years and 67.9% of patients were men. HT was present in 46.4% of the patients and only 1.8% of patients were diabetics (Table I).

Structural heart disease was present in 13.4% of patients, with an average ejection fraction of 60.2 ± 6.4 and left atrial area of 20.6 ± 4.4.

The episode of AF motivating the first consultation was the first event in 29.5% of patients, with average heart rate of 118.9 ± 27 beats per minute (bpm) and median time from symptoms onset of 4 hours.<sup>2–10</sup>

**Table II.**  
Variables Analyzed for Conversion

Variables	With Conversion (n = 102)	Without Conversion (n = 19)	P Value
Age (years)	58.8 ± 14	53.8 ± 13.7	0.51
Male gender (%)	68.8	70.6	0.11
Weight (kg)	80.4 ± 14.7	76.4 ± 16.7	0.36
Height (cm)	173.6 ± 10.4	174 ± 20.7	0.36
Body surface area (m <sup>2</sup> )	1.94 ± 0.21	1.9 ± 0.33	0.69
HT (mm Hg)	47.3	47.1	0.4
DBT (%)	1.1	5.9	0.3
Chronic obstructive pulmonary disease (%)	2.2	1.1	0.5
EF (%)	61.05 ± 5.7	54.9 ± 8.4	0.016
EF < 55%	2.1	23	0.001
Structural heart disease (%)	9.7	35.3	0.02
Left atrial area (cm <sup>2</sup> )	20.7 ± 4.1	20.4 ± 6.2	0.4
LV mass (g)	171.5 ± 39.6	170.2 ± 20.5	0.5
Left atrial area/body surface area (cm <sup>2</sup> /m <sup>2</sup> )	10.7 ± 2.27	11.6 ± 4.9	0.57
Heart rate (bpm)	122.3 ± 25.8	99.3 ± 27	0.093
Time from symptom onset (hours)	7.46 ± 10	11 ± 9.4	0.57
First AF episode (%)	30.1	23.5	0.69

bpm = beats per minute; EF = ejection fraction. Other abbreviations as in Table I.

Conversion to sinus rhythm was achieved in 84.5% of patients, and 46% required the second dose of vernakalant. Time to conversion was 10 minutes.

After analyzing the predictors of conversion, the presence of structural heart disease was significantly greater in the group without conversion (35.3 vs 9.7%;  $P = 0.02$ ; Table II). The mean EF in the group with conversion was  $61.05 \pm 5.7\%$  versus  $54.9 \pm 8.4\%$  in the group without conversion ( $P = 0.016$ ). After dichotomizing the variable EF, patients with EF < 55% had a lower conversion rate. Figure 1 shows the conversion rates for normal EF and presence of structural heart disease.

There was a trend toward higher heart rate at presentation in the conversion group ( $122.3 \pm 25.8$  bpm vs  $99.3 \pm 27$  bpm,  $P = 0.093$ ). The rest of the parameters did not present differences between the groups.

When we performed a multivariate analysis, both variables were associated with conversion (structural heart disease,  $P = 0.03$ ; EF < 55%,  $P = 0.04$ ).

### Discussion

In our study, the absence of structural heart disease and the EF were the only predictors of conversion in the patients treated with venakalant.

Vernakalant is an atrial-selective antiarrhythmic agent that prolongs the refractory period, with little effect on ventricular repolarization. Vernakalant has a rapid distribution and onset of action; plasma concentrations decline approximately 50% in 10 minutes with a mean elimination half-life of 3 hours.<sup>6,7</sup>

The ACT and ACT 3 trials demonstrated the safety of vernakalant with low risk of proarrhythmia or hypotension and a conversion rate of 61% and 62% within 90 minutes compared with placebo, respectively.<sup>2,3</sup> The AVRO study showed that vernakalant is safe in patients with moderate structural heart disease, excluding patients with obstructive cardiomyopathy, severe valvular heart disease, or recent infarction, among others.<sup>1</sup> In order to get these results, in 2012, the European guideline recommended the use of vernakalant for conversion of recent-onset atrial fibrillation, excluding patients with EF < 35% due to lack of experience, severe valvular heart disease, ongoing heart failure, or coronary events.<sup>6,8</sup>

In our study, we found an inverse correlation between the presence of structural heart disease and conversion. This might be due to increased filling pressures that have an impact on the atrium as a common denominator of entities as hypertensive heart disease, valvular heart disease, or ischemic cardiomyopathy. This pressure overload or volume overload would facilitate neurohumoral

## PREDICTORS OF ACUTE ATRIAL FIBRILLATION

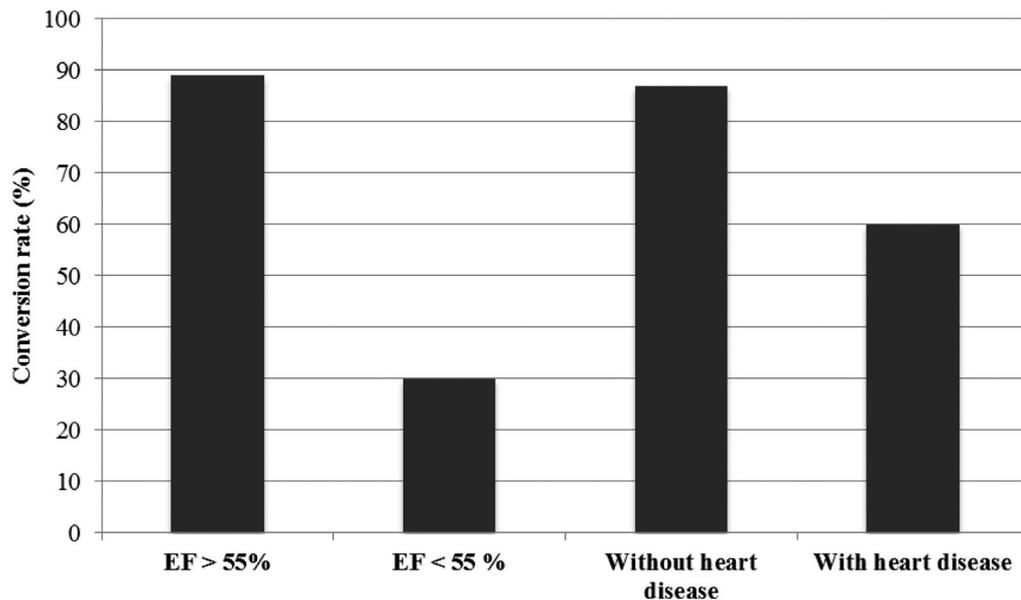


Figure 1. Conversion rate by variable.

activation, development of fibrosis, and atrial remodeling, and these factors tend to perpetuate the arrhythmia.<sup>9,10</sup> The number of patients in our sample may have influenced the lack of statistical power of atrial size by itself to become a predictor, as opposed to heart disease (which includes atrial enlargement).

The EF is directly related to structural heart disease; however, in our study EF by itself had statistical significance in the conversion rate. Akkaya et al. have shown the relation between reduced systolic function and atrial fibrosis evaluated by magnetic resonance imaging, and they even suggest that persistent atrial fibrillation could generate ventricular fibrosis, leading to depressed contractility.<sup>11</sup> This feedback between systolic dysfunction and atrial fibrillation makes atrial fibrillation conversion more difficult, and is associated with increased recurrence rate as has been demonstrated in studies evaluating radiofrequency catheter ablations.<sup>12–14</sup>

Viñolas et al. found that the absence of structural heart disease, lack of obesity, and atrial fibrillation duration <1 year were predictors of conversion with amiodarone.<sup>15</sup> Although this study was performed in patients with chronic

atrial fibrillation, in our study body mass index did not have any relation with conversion. We believe that this is related with vernakalant pharmacology, as the drug is poorly affected by fat mass.<sup>7</sup>

To our understanding, this is the first study evaluating the factors associated with conversion to sinus rhythm with vernakalant, and may help at the moment of deciding the antiarrhythmic agent in the treatment of patients with atrial fibrillation.

### Study Limitations

As with any retrospective study, a bias may exist with the recollection of data. The sample size reduces the power of showing the differences in other variables.

### Conclusion

In our study, the absence of any kind of structural heart disease and preserved systolic function was associated with greater conversion rate with vernakalant.

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### References

1. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G, et al. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011; 57:313–321.
2. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Nielsen T, et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: A phase 3, randomized, placebo-controlled trial. *Circulation* 2008; 117:1518–1525.

3. Roy D, Rowe BH, Stiell IG, Coutu B, Ip JH, Phaneuf D, Lee J, et al. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004; 44:2355–2361.
4. Conde D, Costabel JP, Aragon M, Lambardi F, Klein A, Corrales Barbosa A, Trivi M, et al. Propafenone versus vernakalant for conversion of recent-onset atrial fibrillation. *Cardiovasc Ther* 2013; 31:377–380.
5. Conde D, Costabel JP, Caro M, Ferro A, Lambardi F, Corrales Barboza A, Cobo AL, et al. Flecainide versus vernakalant for conversion of recent-onset atrial fibrillation. *Int J Cardiol* 2013; 168:2423–2425.
6. Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: Evidence in support of the ESC Guidelines. *Europace* 2014; 16:162–173.
7. Brown RA, Lau YC, Lip GYH. Vernakalant hydrochloride to treat atrial fibrillation. *Expert Opin Pharmacother* 2014; 15:865–872.
8. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; 33:2719–2747.
9. Mayyas F, Niebauer M, Zurick A, Barnard J, Gillinov AM, Chung MK, Van Wagener DR. Association of left atrial endothelin-1 with atrial rhythm, size, and fibrosis in patients with structural heart disease. *Circ Arrhythm Electrophysiol* 2010; 3:369–379.
10. Knackstedt C, Gramley F, Schimpf T, Mischke K, Zarse M, Plisiene J, Schmid M, et al. Association of echocardiographic atrial size and atrial fibrosis in a sequential model of congestive heart failure and atrial fibrillation. *Cardiovasc Pathol* 2008; 17:318–324.
11. Akkaya M, Higuchi K, Koopmann M, Damal K, Burgon NS, Kholmovski E, McGann C, et al. Higher degree of left atrial structural remodeling in patients with atrial fibrillation and left ventricular systolic dysfunction. *J Cardiovasc Electrophysiol* 2013; 24:485–491.
12. Cha Y-M, Wokhlu A, Asirvatham SJ, Shen WK, Friedman PA, Munger TM, Oh JK, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: A comparison to systolic dysfunction and normal ventricular function. *Circ Arrhythm Electrophysiol* 2011; 4:724–732.
13. Wilton SB, Fundytus A, Ghali WA, Veenhuyzen GD, Quinn FR, Mitchell LB, Hill MD, et al. Meta-analysis of the effectiveness and safety of catheter ablation of atrial fibrillation in patients with versus without left ventricular systolic dysfunction. *Am J Cardiol* 2010; 106:1284–1291.
14. Anselmino M, Grossi S, Scaglione M, Castagno D, Bianchi F, Senatore G, Matta M, et al. Long-term results of transcatheter atrial fibrillation ablation in patients with impaired left ventricular systolic function. *J Cardiovasc Electrophysiol* 2013; 24: 24–32.
15. Viñolas X, Freire F, Romero-Menor C, Alegret JM. Predictors of reversion to sinus rhythm previous to electrical cardioversion in patients with persistent atrial fibrillation treated with reanti-arrhythmic drugs. *Med Clin* 2013; 140:351–355.