Predictors of Successful Cardioversion with Vernakalant in Patients with Recent-Onset Atrial Fibrillation

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Background: Vernakalant is a novel atrial-selective antiarrhythmic drug able to convert recent-onset atrial fibrillation (AF) with reportedly low proarrhythmic risk. Successful cardioversion predictors are largely unknown. We sought to evaluate clinical and electrocardiographic predictors of cardioversion of recent-onset AF with vernakalant.

Methods: Consecutive patients with AF ≤ 48 hours admitted for cardioversion with vernakalant ($n = 113$, median age 62 years, 69 male) were included. Sinus rhythm (SR) within 90 minutes after infusion start was considered to be successful cardioversion. Predictive values of demographics, concomitant therapy, comorbidities, and electrocardiographic parameters were assessed. Atrial fibrillatory rate (AFR), exponential decay, and mean fibrillatory wave amplitude were measured from surface ECG using QRST cancellation and time-frequency analysis.

Results: Cardioversion was achieved in 66% of patients. Conversion rate was higher in women than in men (80% vs 58%, $P = 0.02$) while none of other clinical characteristics, including index AF episode duration, could predict SR restoration. Female gender was predictive of vernakalant's effect in logistic regression analysis (OR = 2.82 95%CI 1.18–6.76, $P = 0.020$). There was no difference in AFR (350 ± 60 vs 348 ± 62 fibrillations per minute [fpm], $P = 0.893$), mean fibrillatory wave amplitude (86 ± 33 vs $88 \pm 67 \mu V$, $P = 0.852$), or exponential decay (1.30 ± 0.42 vs 1.35 ± 0.42 , $P = 0.376$) between responders and nonresponders.

Conclusions: Female gender is associated with a higher rate of SR restoration using intravenous (i.v.) vernakalant for recent-onset AF. ECG-derived indices of AF organization, which previous studies associated with effect of rhythm control interventions, did not predict vernakalant's effect.

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atrial fibrillation; atrial fibrillatory rate; vernakalant; recent-onset atrial fibrillation; predictors of conversion; time frequency analysis

Atrial fibrillation (AF) is the most common sustained arrhythmia, accounting for approximately one-third of all hospital admissions for cardiac rhythm disturbances.¹ Lifetime risk for developing AF is one in four, in both men and women older than 40 years of age, according to the Framingham

Heart study.² The incidence is increasing due to rising prevalence of predisposing conditions in the aging population.³

Vernakalant is a novel atrial-selective antiarrhythmic drug (AAD) able to convert recent-onset AF with reportedly low proarrhythmic risk.^{4–8} It

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acts as sodium- and potassium-channel blocking agent, increasing atrial effective refractory period, reducing reentry and causing AF termination without prolonging ventricular refractoriness.^{9,10} The reported conversion rate for new-onset AF with vernakalant is 52%, and median time to conversion is 11 minutes.⁴ However, clinical predictors of successful cardioversion are largely unknown. Atrial activity analysis using various signal-processing techniques on surface electrocardiography (ECG) in order to guide AF treatment strategy has received considerable attention in recent years.^{11–14} Atrial fibrillatory rate (AFR) measured in fibrillations per minute (fpm) accessed from surface electrocardiography (ECG) is considered a noninvasive index of atrial remodeling,^{15–19} and thus may predict the atria's ability to restore and maintain sinus rhythm (SR).^{20,21} A baseline fibrillatory rate <360 fpm has predicted successful cardioversion of AF with intravenous (i.v.) ibutilide¹⁶ or oral flecainide.²² In addition to AFR, alternative ECG-derived indices of atrial signal organization, such as exponential or harmonic decay in the frequency-power spectrum, have been described and an association between greater degree of organization and higher likelihood of SR maintenance following AF cardioversion has been shown.²³ High fibrillatory wave (F-wave) amplitude has also been shown to predict AF termination during catheter ablation of persistent AF,²⁴ SR maintenance following catheter ablation,²⁵ and electrical cardioversion.²⁶ However, no studies have been done on the clinical value of these electrocardiographical markers in acute settings of vernakalant use in patients with recent-onset AF.

We sought to evaluate clinical and electrocardiographic cardioversion predictors in patients with recent-onset AF (lasting for <48 hours) treated with i.v. vernakalant.

METHODS

Inclusion and Exclusion Criteria

We identified and reviewed medical records of all adult patients with recent-onset AF treated with i.v. vernakalant between December 2010 and December 2012 at Skåne University Hospital (a large tertiary care teaching hospital in Sweden).

The study complies with the Declaration of Helsinki, and was approved by the local ethics committee.

Included in the study were patients over 18 years of age, with recent-onset AF with symptom duration <48 hours, who were assessed for pharmacological AF conversion with weight-adjusted i.v. vernakalant by attending cardiologist, and received at least part of the recommended drug dose. Excluded from the study were patients with severe aortic stenosis, systolic blood pressure <100 mmHg, New York Heart Association (NYHA) class III or IV heart failure, QT prolongation at baseline (uncorrected QT interval >440 ms), severe bradycardia, sinus node dysfunction, second- or third-degree atrioventricular block without pacemaker, acute coronary syndrome in the past 30 days, or treatment with class I or III AADs within 4 hours prior to enrolment, as these patients were considered to have contraindications for vernakalant therapy. Patients received a 10-minute infusion of vernakalant (3 mg/kg), followed by a 15-minute observation period, and then a second 10-minute infusion (2 mg/kg) if AF was not terminated by the first infusion as documented in the patients' medical records.

The primary endpoint was the proportion of patients achieving conversion to SR within 90 minutes after the start of the first infusion.

Data Acquisition and Processing

Baseline characteristics, demographics, and electrocardiographic parameters were collected and analyzed for all patients in the study.

When available, left atrial end-diastolic diameter (LADD) and left ventricular ejection fraction (LVEF) from transthoracic echocardiography were assessed. LADD >50 mm and LVEF <50% were used as cutoff values for dichotomization.

AF duration was defined as time elapsed from symptom onset to infusion start.

A standard 12-lead ECG recorded at admission was retrieved from the hospital digital ECG database and processed offline. AFR, exponential decay, and F-wave amplitude were estimated using a 10-second recording of lead V₁ using AFRtracker software (CardioLund Research AB, Lund, Sweden). The method is described in detail elsewhere.^{15,17,19,27} In short, ECG signals were preprocessed, including baseline filtering, beat detection, and cross-correlation-based beat classification. Subsequently, spatiotemporal QRST cancellation was used, in which an amplitude- and morphology-adjusted average beat is subtracted

from each beat in the signal. Individual beat averages were used for beats from different beat classes. The resulting residual ECG showing mainly atrial activity was analyzed using sequential atrial signal characterization, which performs time frequency analysis using overlapping windows in order to provide second-by-second AFR trends. Using this method, signal structure of each window is continuously analyzed through its harmonic frequency pattern in order to ensure that the corresponding signal contains an oscillatory atrial signal. Exponential decay was evaluated by estimating the relationship between main peak magnitude and harmonics magnitude. Exponential decay reflects the slope of the line connecting dominant frequency and its first harmonic. More organized rhythms with distinct waveforms have stronger harmonics, resulting in a shallower curve and lower exponential decay.

Statistical Analysis

Descriptive analysis was used to compare demographics and baseline characteristics between responders and nonresponders, including patients who did not receive full treatment due to adverse events (AEs). For patients who received several administrations of vernakalant, only the first treatment outcome was included in the statistical analysis.

Normally distributed data were expressed as mean + standard deviation; otherwise, median and range were used. Statistical significance was assessed using the Student's *t*-test on parametric data, and the Mann-Whitney test on nonparametric data.

Categorical variables are expressed as numbers and percentages, and analyzed using the chi-square test.

All statistical analysis was performed using SPSS (version 21.0, IBM Corp., Armonk, NY, USA).

RESULTS

Study Population and Data Availability

Baseline characteristics and demographics of our study population ($n = 113$, 69 male, median age 62 years) are outlined in Table 1. Twenty-two patients received vernakalant on several treatment occasions, but only the first treatment outcome was included in our statistical analysis.

Forty-three percent of the study population had lone AF. Seven patients were treated with concomitant class I and III AAD. However, none of the patients in our study received AAD within 4 hours of vernakalant treatment. LADD and LVEF measurements were available for 83 and 84 patients, respectively. Left atrial dilatation was present in 45.3% of converters versus 60% of nonconverters ($P = 0.255$). Reduced LVEF was observed in seven patients (5.7% converters vs 12.9% nonconverters, $P = 0.415$).

Median episode duration (time from symptom onset to infusion start) was 8.2 hours, with median time to ECG of 3.1 hours. Twenty-eight percent of patients presented with new-onset AF.

Discontinuation of Vernakalant due to AEs

Vernakalant was administered to 113 patients on 148 treatment occasions. A total of 15 AEs occurred in 14 (1.4%) study patients on 14 vernakalant administration occasions (Table 2). AEs caused discontinuation of the drug administration for seven patients (6.2%). The most common AE that lead to drug discontinuation was hypotension ($n = 3$) that responded promptly to saline infusion, while other AEs resolved spontaneously shortly after the infusion was discontinued.

Proarrhythmic events were observed in seven (6.2%) patients, with the most common being atrial flutter ($n = 4$). In three patients, conversion to SR occurred via 2:1 conducted typical counter-clockwise atrial flutter. One patient developed regular small-QRS tachycardia with a ventricular rate of 210 bpm shortly after infusion start, and his arrhythmia was judged as 1:1 conducted atrial flutter by consultant cardiologist. The vernakalant infusion was discontinued and the patient was treated with emergency DC-cardioversion.

Two patients had 5- respective 10-second long asystoles during vernakalant infusion. None of the patients using concomitant class I or III AADs experienced any AEs. There were no cases of ventricular arrhythmia or death following vernakalant administration.

Clinical Predictors of Vernakalant Effect

Cardioversion was successful in 75 patients (66%). Median time to conversion in responders was 10 minutes [range 4–90 minutes, IQR 8–15

Table 1. Demographics, Baseline Characteristics, and Electrocardiographic Parameters

	Study Population (n = 113)	Responders (n = 75)	Nonresponders (n = 38)	P Value
Female/male	44 /69	35/40	9/29	0.024
Age (median years) (range)	63 (23–87)	64 (23–87)	62.5 (37–85)	0.932
Height (cm)	176 ± 9	174 ± 10	180 ± 7	0.014
Weight (kg)	82 ± 13	81 ± 14	83 ± 12	0.344
BMI	26 ± 3	27 ± 4	26 ± 3	0.323
AF characteristics				
Time to ECG (hours) [IQR]	3.1 [1.4–9.9]	2.8 [1.4–9.5]	5.5 [2.0–12.8]	0.223
Median duration of current AF (hours) [IQR]	8.2 [4.7–16.3]	8 [4.4–16.2]	9.1 [5.7–16.7]	0.400
New-onset AF, n (%)	32 (28.3)	25 (33.3)	7 (18.4)	0.123
AF ablation earlier, n (%)	7 (6.2)	4 (5.3)	3 (7.9)	0.686
Lone AF, n (%)	49 (43.4)	35 (46.7)	14 (36.8)	0.422
Medical history				
Hyperlipidemia	30 (26.5)	17 (22.7)	13 (34.2)	0.259
Hypertension	57 (50.4)	37 (49.3)	20 (52.6)	0.843
Ischemic heart disease	18 (15.9)	9 (12.0)	9 (23.7)	0.172
Diabetes mellitus	8 (7.1)	5 (6.7)	3 (7.9)	1.000
Congestive heart failure	3 (2.7)	1 (1.3)	2 (5.3)	0.261
Concomitant medications				
Beta-blockers, n (%)	88 (77.9)	59 (78.7)	29 (76.3)	0.813
Calcium channel blockers, n (%)	12 (10.6)	7 (9.3)	5 (13.2)	0.534
RAAS-inhibitors, n (%)	35 (31.0)	21 (28.0)	14 (36.8)	0.391
Class I or III AAD, n (%)	7 (6.2)	4 (5.3)	3 (7.9)	0.686
ECG parameters				
AFR (fpm)	350 ± 60	350 ± 60	348 ± 62	0.893
Exponential decay	1.32 ± 0.42	1.30 ± 0.42	1.35 ± 0.42	0.376
F-wave amplitude (μV)	87 ± 47	86 ± 33	88 ± 67	0.852

Bold face values indicate statistical significance ($p < 0.05$), IQR = Interquartile range.

Table 2. Adverse Events

Adverse Event	n (%)	Treatment Discontinuation due to AE (n)
Hypotension	3	3
Bradycardia	1	1
Atrial flutter with 1:1 conduction	1	1
Atrial flutter with 2:1 conduction	3	0
QRS-widening	1	1
Sinus arrest	2	0
Transient paresthesia	2	1
Dysgeusia	1	1
Sneezing	1	0

minutes). Conversion rate was higher in women than in men (80% vs 58%, $P = 0.024$) (Fig. 1), and in patients with shorter rather than taller stature (mean height 174 ± 10 cm in responders vs 180 ± 7 cm in nonresponders, $P = 0.014$). Body height was strongly linked to gender, being significantly

less in women than in men (167 ± 8 vs 181 ± 6 cm, $P < 0.00001$). No other patient characteristics showed any relationship to treatment outcome.

Female gender was a significant predictor of cardioversion in logistic regression analysis (OR 2.82, 95% CI 1.18–6.76, $P = 0.020$).

Figure 1. Gender and conversion to SR. Kaplan-Meier curve analysis of time from infusion start to conversion depending on gender.

ECG-Derived Indices of AF Organization

AFR and exponential decay could not be accessed in five patients due to absence of, or poor quality of, ECG records.

Mean AFR value for the entire group was 350 ± 60 fpm. No statistically significant difference in AFR was found between responders and nonresponders (350 ± 60 vs 348 ± 62 fpm, $P = 0.47$). As expected, AFR was negatively correlated to patients' age (Fig. 2) and showed weak but significant correlation to AF episode duration ($r = 0.221$, $P = 0.021$).

Women had lower mean AFR, exponential decay, and F-wave amplitude compared to men (321 ± 42 vs 367 ± 63 , $P < 0.001$; 1.25 ± 0.35 vs 1.36 ± 0.46 , $P = 0.184$; and 85 ± 30 vs 88 ± 56 , $P = 0.768$). However, there was a large overlap between genders.

Figure 2. Correlation between AFR and patient age.

None of these electrocardiographic parameters had any value in predicting treatment outcome (Tables 1 and 3).

DISCUSSION

We report an experience of real-life use of vernakalant for converting short-lasting (<48 hours) AF in a tertiary-care hospital. Population size in our observational study ($n = 113$) is comparable to the number of patients exposed to vernakalant in the ACT I-III and AVRO trials ($n = 84$ –150).^{4–8}

The observed conversion rate appears to be higher than previously reported—although those previous studies had included patients with prolonged AF duration,^{10–13} which may be the cause of the observed difference in effect.

While ECG-derived atrial remodeling markers failed to predict responders to vernakalant, female gender was identified as an important clinical predictor of conversion.

Table 3. Logistic Regression Analysis of ECG-Derived Indices of AF Organization

	Odds Ratio	95% CI	P Value
AFR	1.00	0.994–1.009	0.652
F-wave amplitude	1.00	0.991–1.008	0.916
Exponential decay	0.72	0.266–1.931	0.510

Gender differences in the age of onset, comorbidities, treatment patterns, and drug-induced events in patients with AF have been long acknowledged.^{28–31} A recent study by our group reported that women are more prone to spontaneous AF termination.²¹ Women in our study had lower mean AFR than men. On the other hand, AF incidence has been found to be consistently higher in males of all age categories, both in the Framingham study² and in a recent study in the city of Malmö (Sweden), where our study was also conducted.³² It is unlikely that the difference in treatment outcome between genders can be explained by estrogen effect, since only three women in our study were under the age of 50. Nor can treatment response in women be attributed to extensive drug metabolism, since no gender differences in pharmacokinetics of vernakalant have been found.³³ One possible explanation may be the observed gender-related difference in body height. In previous studies, greater height has been associated with development of AF.^{34,35} Taller stature may correspond to larger atrial size, thus providing more anatomical substrate for the development and maintenance of AF. However, only height and gender, but not LA dilatation, were associated with treatment effect in our study. Genetic studies have shown that some genetic variants associated with AF in genome-wide association studies such as PITX2³⁶ and ZFHX3³⁷ are also involved in growth pathways.

We have analyzed the electrophysiological parameters, which, in previous studies, were shown to predict therapy response in rhythm control interventions. Notably, the population mean for AFR is in striking agreement with other cohorts analyzed using this methodology.^{20,21} Our study has confirmed previous findings, suggesting an inverse association between AFR and age,³⁸ which can be attributed to slower conduction and longer refractory periods in aging atria.³⁹ The positive correlation between AFR and AF episode duration is in agreement with previous reports,^{11,38} and reflects atrial refractoriness shortening during persistent AF.⁴⁰ A recent study using implantable loop recorders has shown that AFR increases during the first 3 hours of spontaneous AF episode, and then becomes stable.¹¹ Mean time to ECG in our study was 3.1 hours, which allows AFR to reach plateau and be reliably used for analysis.

Lower AFR has been associated with spontaneous conversion,²¹ favorable outcome

of cardioversion,^{16,20,22,41} and intraprocedural termination of AF during catheter ablation.^{42,43} Contrary to our expectations and findings from earlier studies, we found no association between lower AFR and better response to vernakalant. The reasons for this are unclear at this time. The size of the population eligible for AFR assessment in our study is comparable with populations' sizes in previous reports, where this marker was studied in different clinical contexts. This suggests that the lack of association with the conversion to SR is probably not due to small population size. Vernakalant pharmacokinetics is influenced by cytochrome p450 2D6 (CYP2D6).³³ Drug effects may be drug-specific and related to individual sensitivity, including the CYP2D6 genotype ("poor vs extensive metabolizers"), and possibly genetically determined ion-channel protein function and its response to pharmacological blockade. Another explanation of the absence of association between lower AFR and positive treatment outcome is that vernakalant's sodium channel inhibitory effect becomes more pronounced at higher rates,⁹ thus perhaps making the drug effect more pronounced in patients who are otherwise less likely to restore SR.

The AEs observed in this study were similar to AEs reported by ACT and AVRO trials.^{6–8} The incidence of AEs in our retrospective study was generally much lower than in previous prospective trials. One reason may be that minor and transient AEs were not recorded in patient charts, which is a common occurrence in real-life nontrial settings. Percentage of AE leading to vernakalant treatment discontinuation in our study (5.4%) was slightly higher (although in the same range) than that reported in AVRO and ACT studies (3.5–4.5%).^{4–8}

Previous reports show that serious AEs related to vernakalant are uncommon. In pooled safety data from vernakalant trials (773 vernakalant patients and 335 patients on placebo), there was one death of a patient with severe aortic stenosis, one case of torsades de pointes related to vernakalant, two cases of complete AV block, and two cases of sinus arrest.⁴⁴ In our study, we observed two cases of transient sinus arrest, and one case of 1:1 conducted atrial flutter that was not observed in ACT or AVRO trials, but has been previously reported elsewhere.^{45,46} We have not observed any ventricular proarrhythmias associated with vernakalant use.

CONCLUSION

Our results indicate that gender could be a prognostic factor for response to vernakalant, with possible implications for AF conversion therapy choice. On the other hand, ECG-derived markers of atrial signal organization during AF (which, in earlier studies, were associated with effect of rhythm control interventions) failed to predict vernakalant effect.

Study Limitations

The retrospective nature of our study, as well as our reliance on electronic medical charts is a potential limitation of all retrospective analyses. Minor AEs that did not result in treatment discontinuation may not have been recorded, leading to underestimating the true AE rate. However, it is unlikely that severe AEs were not documented.

Despite the limitations inherent to the retrospective nature of our study, we believe that our study provides valuable information on real-life use of vernakalant in nontrial clinical settings.

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