Vernakalant and electrical cardioversion for AF – Safe and effective

Alexander Simon *, Jan Niederdoeckl, Karin Janata, Alexander Oskar Spiel, Nikola Schuetz, Sebastian Schnaubelt, Harald Herkner, Filippo Cacioppo, Anton Norbert Laggner, Hans Domanovits

Department of Emergency Medicine, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria

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ABSTRACT

Aims: Rapid restoration of sinus rhythm is an integral part of the management of recent-onset atrial fibrillation. We aimed to assess safety and efficacy of vernakalant, a multi-channel blocking agent, in combination with external electrical cardioversion.

Methods: This prospective cohort study comprised 230 patients (female 35%; median age 50 IQR 42–55) with recent-onset AF presenting to a university tertiary care center during a 6-year period. Management included intravenous vernakalant followed by electrical cardioversion in case of pharmacological failure.

Results: Within 11 min (IQR 8–29), sinus rhythm could be restored by sole pharmacological management in 167 patients (73%). A left ventricular function lower than 55% (OR 3.51 (1.45–8.52)) and prior atrial fibrillation episodes being classified as persistent (OR 2.33 (1.13–4.80)) were significant predictors for non-response to vernakalant. Electrical cardioversion was successful in all patients but one within 196 min (IQR 149–300) of administration of first dosage of vernakalant. No serious adverse events could be observed. 3 patients needed further in-patient care.

Conclusion: Management of recent-onset atrial fibrillation consisting of intravenous vernakalant followed by electrical cardioversion in case of failure appears safe and efficacious. Achieving a rapid conversion, this approach could potentially save resources and costs.

1. Introduction

Rapid restoration of sinus rhythm is an integral part of the management of recent-onset atrial fibrillation (AF). External electrical cardioversion is regarded as the treatment of choice, but requirements may not always be met in the respective hospital setting. Efficacy of intravenous pharmacological agents is still unconvincing. On the other hand pharmacological cardioversion does not require preprocedural fasting [1].

Vernakalant, a novel atrial selective antiarrhythmic drug blocking potassium channels and frequency- and voltage- dependent sodium ion channels, has been introduced for rapid conversion of recent-onset AF. Conversion rates of up to 70% and a median time to SR between 8 and 14 min have been reported recently [2,3]. Compared to i. v. amiodarone and class I antiarrhythmics like flecainide and propafenone, i.v. vernakalant is as effective but faster in converting AF to SR. [4,5]

We aimed to assess safety and efficacy of a sequential approach, starting with intravenous vernakalant followed by external electrical cardioversion in case of failure in an outpatient setting.

2. Methods

2.1. Design/setting

Consecutive adult patients presenting with recent-onset (<7 days) AF to the emergency department of the Medical University of Vienna from December 2010 to November 2016 were eligible for study inclusion. Following written informed consent, demographic data, comorbidities, medication and onset of AF were recorded in a local AF registry. Intervention comprised intravenous vernakalant (up to 2 short infusions with 3 mg/kg and 2 mg/kg over 10 min, 15 min in between according to manufacturer's recommendation) followed by DC biphasic electrical cardioversion in anterior-lateral electrode position in case of failure of the primary intervention. Patients without sufficient anticoagulation received 1 mg/kg of enoxaparin subcutaneously prior to treatment. Local Ethics Committee approved all study related procedures (registered at http://www.clinicaltrials.gov;uniqueidentifier: NCT03272620).

2.2. Statistics

Discrete data are reported as counts and percentages, continuous data as median and respective interquartile ranges. Non-parametric test statistics were applied for basic comparisons. To identify risk predictors for

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* Corresponding author.
E-mail address: alexander.simon@meduniwien.ac.at (A. Simon).

initial treatment response, a multivariate logistic regression model was then applied: inclusion of covariates was clinical-driven as by univariate analysis. Precision and calibration of the final model were confirmed by Hosmer-Lemeshow test as c-statistics. Calculations were performed using SPSS 22.0 for MacOsX (IBM Inc., Somers, NY, USA) and a two-sided p-value of 0.05 was considered statistically significant.

3. Results

Between December 2010 and November 2016, a total of 3011 patients with AF were recorded in the AF-registry, of which 230 patients (median age 61, IQR 49-69; 77 females, 34%) were enrolled in this prospective study design (Fig. 1).
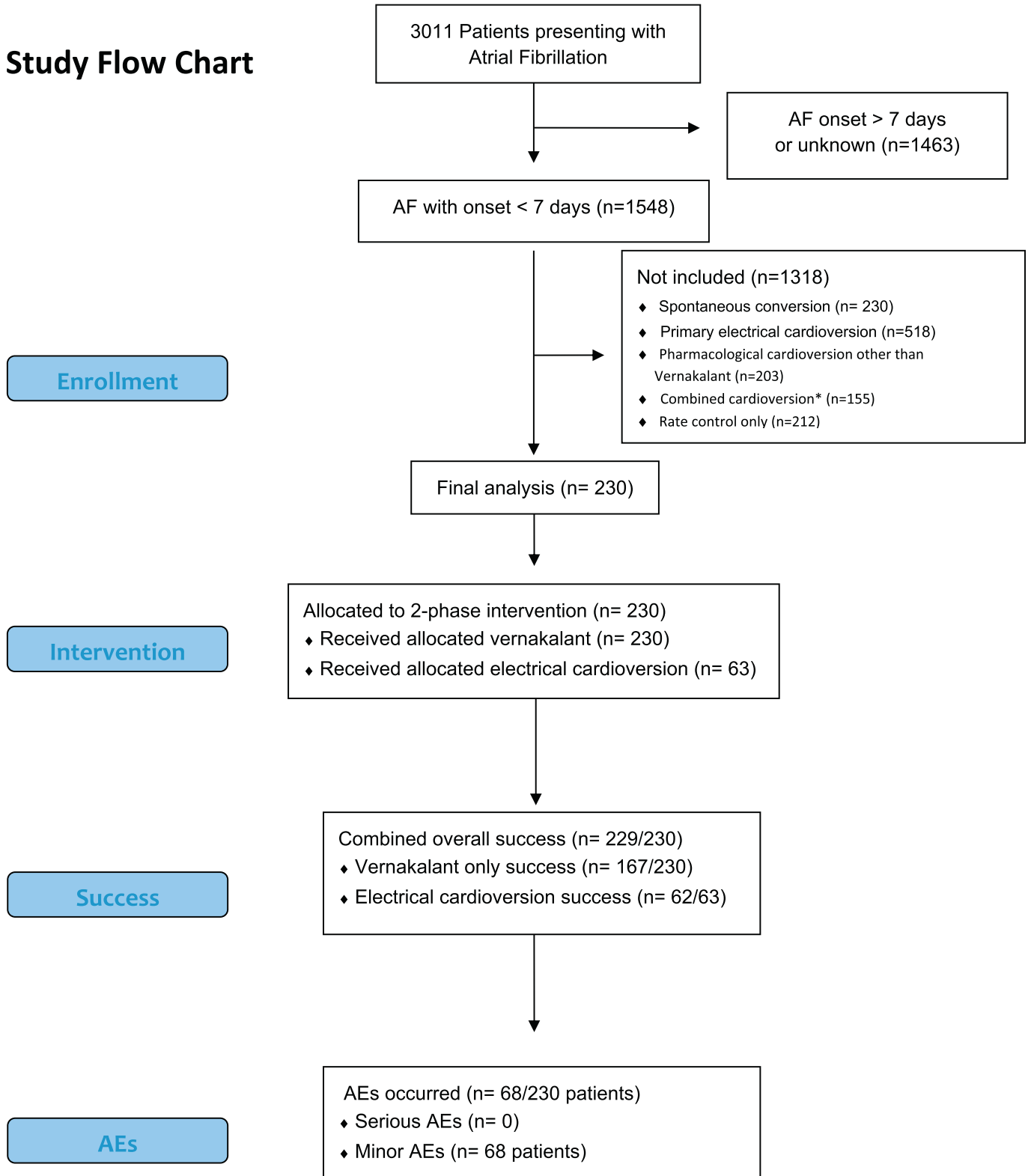
Study Flow Chart

Fig. 1. Study flow chart.

Table 1
Descriptive characteristics of the cohort.

	Patients receiving vernakalant solely (n = 167)	Patients receiving vernakalant and ecv (n = 63)	P-value
Demographics			
Age, median (IQR)	61 (48–68)	59 (52–70)	0,698
Female, n (%)	58 (34,7)	19 (30,2)	0,512
Body mass index, median (IQR)	27 (24–30)	27 (24–30)	0,236
Chronic health conditions			
Hypertension, n (%)	105 (62,9)	42 (66,7)	0,593
Diabetes, n (%)	10 (6,0)	10 (15,9)	0,065
COPD, n (%)	8 (4,8)	1 (1,6)	0,264
Serum creatinine >200 mmol/l, n (%)	10 (6,0)	3 (4,8)	0,720
Coronary artery disease, n (%)	11 (6,6)	6 (9,5)	0,448
Preexisting risk factors			
Valvular heart disease, n (%)	18 (10,8)	11 (17,5)	0,173
Previous atrial fibrillation ablation therapy, n (%)	26 (15,6)	18 (28,6)	0,384
Concomitant anti-arrhythmic treatment			
Beta-blocker, n (%)	86 (51,5)	22 (34,9)	0,078
Calcium channel blocker, n (%)	14 (8,4)	6 (9,5)	0,784
Amiodarone, n (%)	11 (6,6)	7 (11,1)	0,255
Dronedarone, n (%)	8 (4,8)	3 (4,8)	0,993

Unless otherwise indicated, data are numbers (percentages); ecv = electrical cardioversion; IQR = interquartile range; n = number; COPD = chronic obstructive pulmonary disease.

We compared comprehensive baseline characteristics of patients who received vernakalant solely with those who underwent additional electrical cardioversion in the further course. No significant differences between the two groups could be observed. (Table 1 and Table 2) Within the total population median duration of episode was 6 h (IQR 3-12) and previous episodes of AF have been classified as "persistent" in 145 (63%) and "paroxysmal" in 25 (11%) cases.

3.1. Efficacy of vernakalant and electrical cardioversion (Table 3)

In 55% of episodes, conversion to SR could be achieved after the first dosage of vernakalant. Overall, sinus rhythm could be restored by pharmacological management only in 167 patients (73%) within a median of 11 min (IQR 8-29). In 152 (91%) cases, restoration of SR was achieved within 90 min. In one patient immediate recurrence of atrial fibrillation (IRAF) occurred. He initially converted to SR 6 min after the first dosage of vernakalant, relapsed to AF within a minute, and finally converted successfully to SR another 2 min later without any further intervention. No significant gender differences could be observed (p = 0.51). A comprehensive baseline comparison between responders and non-responders is provided in Table 5.

Electrical cardioversion was performed successfully in 62 of the remaining 63 pharmacological non-responders, resulting in an overall success rate of >99% of this proposed treatment strategy within

196 min (IQR = 149–300) of the first dosage of vernakalant. No IRAF was observed in any patients undergoing electrical cardioversion.

3.2. Safety of Vernakalant and electrical cardioversion

No serious rhythm disorders such as torsade de pointes tachycardia, ventricular fibrillation, polymorphic or sustained/non-sustained VT as well as no premature ventricular contractions (PVC) could be observed during and after vernakalant treatment. However, recent-onset of atrial flutter was recorded in 31 (14%) patients as minor adverse event. Nineteen of those converted to SR without intervention, whereas 12 required further electrical cardioversion. 1:1 atrio-ventricular conduction was absent in all cases. Other transient and minor complications are given in detail in Table 4. Overall, no serious adverse events could be observed. 3 patients needed further in-patient care for other reasons.

3.3. Predictors for non-response of intravenous vernakalant

Univariate analysis revealed that a left ventricular function lower than 55% (OR 3.36 (1.44–7.83)) and prior atrial fibrillation episodes being classified as persistent (OR 2.55 (1.31–4.98)) were significant predictors for primary treatment failure. Following adjustment for previous

Table 2
Baseline characteristics prior treatment.

	Patients receiving vernakalant solely (n = 167)	Patients receiving vernakalant and ecv (n = 63)	P-value
Vital signs			
Systolic blood pressure in mmHg, median (IQR)	128 (119–137)	130 (120–140)	0,927
Heart rate, median (IQR)	124 (110–140)	120 (102–140)	0,481
NYHA stage >1, n (%)	17 (10,2)	13 (20,6)	0,728
NT-proBNP, median (IQR)	445 (117–1194,25)	527 (176,5–1173)	0,491
Echocardiographic assessment			
Normal left ventricular function (>55%), n (%)	153 (91,6)	52 (82,5)	0,654
Impaired left ventricular function (<55%), n (%)	12 (7,2)	13 (20,6)	0,651
Normal atrial size, n (%)	91 (54,5)	36 (57,1)	0,232
Atrial enlargement, n (%)	76 (45,5)	27 (42,9)	0,200
Classification of prior AF episodes and duration of current AF episode			
No prior episode of atrial fibrillation, n (%)	49 (29,3)	11 (17,5)	0,753
Paroxysmal atrial fibrillation, n (%)	21 (12,6)	4 (6,3)	0,648
Persistent atrial fibrillation, n (%)	96 (57,5)	49 (77,8)	0,723
Duration of current episode in hours, median (IQR)	5,5 (3−11)	6 (3–14)	0,500

Unless otherwise indicated, data are numbers (percentages); ecv = electrical cardioverison; IQR = interquartile range; n = number; NYHA = New York Heart Association; NT-proBNP = N-terminal pro b-type natriuretic peptide.

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Table 3
Treatment outcome.

	N overall = 230	
Vital signs		
Systolic blood pressure in mmHg, median (IQR)	125	(120–140)
Heart rate, median (IQR)	80	(70–100)
Restoration of sinus rhythm		
Overall success, n (%)	229	(99%)
Vernakalant - only success, n (%)	167	(73%)
Time to conversion in minutes, median (IQR)	19	(10–139)
Electrical CV, n (%)	63	(27%)
Electrical CV attempts, median (range)	1	[1–4]

Unless otherwise indicated, data are numbers (percentages); IQR = interquartile range; n = number; CV = cardioversion.

ablation therapy, these results sustained in multivariate regression analysis (Table 6).

4. Discussion

Rapid restoration of sinus rhythm is an integral part of the management of recent-onset atrial fibrillation (AF) [1]. In our prospective single center study, comprising 230 consecutive outpatients, we could demonstrate that a sequential management of recent-onset atrial fibrillation consisting of intravenous vernakalant followed by electrical cardioversion in case of failure of primary therapy appears safe and effective. With a success rate of >70% following intravenous vernakalant, rapid response rates of 11 min (median, IQR 8-29), no serious adverse events occurring and an overall success rate of 99,5%, this treatment approach could potentially save resources and costs.

Concerning the management of patients with recent-onset AF, current guidelines recommend, that therapeutic decisions should be based on hemodynamic status, severity of symptoms, available treatment options and on patients and physicians preferences [1]. Large clinical trials like AFFIRM and RACE showed similar outcomes following rhythm and rate control strategies [6,7]. In contrast to the respective trials, our study cohort consisted of younger patients without relevant comorbidities but with profound symptoms, thus, requiring a rhythm control strategy. Further, any delay in restoration of sinus rhythm might contribute to electrical, autonomic and structural remodeling, that may promote the risk of AF-recurrences [8].

There are previous and recent data, showing that a wait-and-watch strategy is not inferior to an early cardioversion approach, especially because of high spontaneous conversion rates in patients with short episodes [9,10]. Nevertheless, we opted for an immediate

Table 4
Safety profile.

	N overall = 230	
Serious adverse events		
Prolonged systolic hypotension <90 mmHg, n (%)	0	(0%)
Acute heart failure, n (%)	0	(0%)
TdP – tachycardia, n (%)	0	(0%)
VT (s, ns), n (%)	0	(0%)
Minor adverse events		
Any* minor AE, n (%)	68	(30%)
Atrial flutter, n (%)	31	(14%)
Paraesthesia, n (%)	15	(7%)
Sneezing, n (%)	14	(6%)
Dysgeusia, n (%)	6	(3%)
Nausea, n (%)	1	(1%)
Others, n (%)	2	(1%)

Unless otherwise indicated, data are numbers (percentages); n = number; * cumulative patients experiencing one or more minor AEs; TdP = torsade de pointes; VT = ventricular tachycardia; s = sustained; ns = non-sustained; AE = adverse events;

Table 5
Distribution of patients by different acute and chronic health and risk conditions stratified to pharmacologic cardioversion success.

	No success (N = 63) vs. Success (N = 167)		P
Demographics			
Age, median (IQR)	65 (49–70)	60 (49–68)	0.10
Female sex, n (%)	20 (32%)	57 (34%)	0.76
Body mass index, median (IQR)	26 (23–29)	27 (25–30)	0.35
Chronic health conditions and risk factors			
Coronary artery disease, n (%)	6 (10%)	11 (7%)	0.57
Impaired left ventricular function, n (%)	13 (21%)	12 (7%)	0.007
Left atrial enlargement, n (%)	32 (51%)	71 (43%)	0.53
NT-proBNP, median (IQR)	518 (160–1125)	428 (112–1086)	0.55
Persistent atrial fibrillation, n (%)	49 (78%)	96 (58%)	0.006
Previous ablation therapy, n (%)	17 (27%)	27 (16%)	0.09
Vital signs and duration of arrhythmia			
Systolic blood pressure, median (IQR)	130 (120–140)	130 (120–140)	0.89
Heart rate, median (IQR)	120 (102–140)	124 (110–140)	0.92
Duration of episode in hours, median (IQR)	6 (3–13)	6 (3–12)	0.71
Concomitant antiarrhythmic therapy			
Class III antiarrhythmic agent, n (%)	12 (19%)	30 (18%)	0.85

Unless otherwise indicated, data are numbers (percentages); IQR = interquartile range; n = number, NT-proBNP = N-terminal pro b-type natriuretic peptide.

restoration of SR: hereby symptom relief by restoring SR can be achieved earlier and patients can be discharged without the need for a follow up visit. Also, pharmacological cardioversion success is higher if AF duration is shorter, particularly when using i.v. vernakalant [3,9].

External electrical cardioversion is the treatment of choice in hemodynamic unstable patients with atrial fibrillation [1]. Success rates of at least 90% have been reported [11]. However, waiting time for a recommended fasting state before non-emergency electrical cardioversion may not be met in the respective situation [12].

According to a recent review of Wodchis et al. [13] the largest resource, time and cost component in the treatment of atrial fibrillation is acute, inpatient care. An effective outpatient treatment approach could therefore be cost- and resource-saving.

Efficacy of pharmacological cardioversion with vernakalant has been reported to be up to >70% [2,3]. In our cohort, the primary conversion rate of 73% is in-line with previous publications [2,3]. Vernakalant has been introduced for rapid conversion of recent-onset atrial fibrillation. In contrast to other pharmacologic agents available, no serious adverse events as acute, life-threatening rhythm disorders or acute heart failure have been observed so far, ensuring the optimal safety profile for Vernakalant in an outpatient setting [3].

A left ventricular function lower than 55% and prior atrial fibrillation episodes being classified as persistent were significant predictors for non-response to vernakalant. These particular subgroups have been reported to have lower success rates for electrical and pharmacologic cardioversion strategies in general [14]. Importantly we have to note, that baseline proBNP values were rather low (average 447, IQR 119-1086)

Table 6
Predictors of primary treatment failure – binary logistic regression model.

	Multivariate	Univariate	P
OR (95% CI)			
Impaired left ventricular function	3.36 (1.44–7.83)	3.51 (1.45–8.52)	0.02
Persistent atrial fibrillation	2.55 (1.31–4.98)	2.33 (1.13–4.80)	0.005
Previous ablation therapy	1.92 (0.96–3.83)	1.27 (0.59–2.70)	0.54

Hosmer-Lemeshow test p = 0.756; OR = odds ratio; CI = confidence interval.

which correlates with the low proportion of patients with an EF < 55% in our cohort.

Further, the results of our trial could support the speculation, that vernakalant pretreatment may enhance the success rate of consequential electrical cardioversion, as previously suggested by other authors [15]. As to our observation, sinus rhythm could be restored in all but one of vernakalant non-responders (63 out of 64). A 98.4% success rate of electrical cardioversion is higher than reported earlier in similar outpatient settings [16].

To summarize, outpatient management of recent-onset of atrial fibrillation, consisting of intravenous vernakalant followed by electrical cardioversion in case of non-response appears safe and efficacious; achieving a conversion to SR as early as possible, might not only benefit patients by symptom relief, but also the system, by potentially saving resources and costs.

5. Limitations and strengths

An important limitation is the single-center and non-randomized design of our trial. However, this study covers a large cohort of consecutive patients within a period of 6 years, which decreases the potential negative impact on our conclusions. Second, since the final decision whether vernakalant was administered was at the discretion of the physician in charge, a selection bias has to be taken into account. This might be reflected by the high overall success rate. In order to test the generalizability of our conclusions, the hypothesis has to be tested in different settings and study designs.

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