Vernakalant versus procainamide for rapid cardioversion of patients with acute atrial fibrillation (RAFF4): randomised clinical trial

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ABSTRACT

OBJECTIVE

To conduct a randomised, open label comparison of the effectiveness and safety of intravenous vernakalant and intravenous procainamide for the management of acute atrial fibrillation in the emergency department.

DESIGN

Randomised clinical trial (RAFF4 trial).

SETTING

12 tertiary care emergency departments in Canada.

PARTICIPANTS

Patients with acute atrial fibrillation for whom acute rhythm control was a safe option.

INTERVENTIONS

Patients were randomised (1:1) to an intravenous infusion of vernakalant or procainamide; when rapid conversion did not occur, patients were offered electrical cardioversion.

MAIN OUTCOMES AND MEASURES

The primary outcome was conversion to sinus rhythm within 30 minutes of drug infusion completion. Secondary outcomes included time to conversion to sinus rhythm and whether the patient required electrical cardioversion.

RESULTS

Of the 350 enrolled eligible patients, baseline characteristics were similar in the procainamide (n=172) and vernakalant (n=178) groups. For the primary outcome of conversion success, vernakalant was more effective (62.4% *v* 48.3%; adjusted absolute difference 15.0%, 95% confidence interval 4.6% to 25.0%, P=0.005; adjusted odds ratio 1.87, 95% confidence interval 1.2 to 2.9, P=0.006). With vernakalant, time to conversion was faster (21.8 *v* 44.7 minutes; mean difference −22.9, 95% confidence interval −29.9 to −16.0, P<0.001), and fewer patients underwent attempted electrical cardioversion (33.7% *v* 44.2%; odds ratio 0.62, 95% confidence interval 0.39 to 0.96, P=0.033). Adverse events were similar in both groups, were generally mild and brief, and most patients were discharged home. Subgroup analysis strongly favoured vernakalant for conversion in patients younger than 70 years (73.3% *v* 47.2%; adjusted odds ratio 3.1, 95% confidence interval 1.7 to 5.5, P=0.001, interaction P=0.005).

CONCLUSIONS

In this head-to-head comparison, vernakalant was superior to procainamide for patients with higher conversion rates and faster times to conversion. Therefore, vernakalant is a safe and highly effective intravenous alternative for the rapid cardioversion and discharge home of patients with acute atrial fibrillation.

TRIAL REGISTRATION

ClinicalTrials.gov NCT04485195.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Patients with acute (onset <48 hours) atrial fibrillation usually present to the emergency department because of intolerable symptoms

Most Canadian emergency department physicians try immediate cardioversion, with drugs or electrically, often using the older and modestly effective drug procainamide

The newer drug vernakalant has theoretical advantages and randomised comparisons to procainamide are needed

WHAT THIS STUDY ADDS

In this head-to-head, randomised comparison, intravenous vernakalant was superior to intravenous procainamide, with higher conversion rates and faster times to conversion in patients with acute atrial fibrillation

Vernakalant is a safe and highly effective intravenous alternative for the rapid cardioversion and discharge of patients with acute atrial fibrillation

Patients could be discharged home more quickly and frequently avoid electrical cardioversion with vernakalant infusion

Introduction

Acute (recent onset) atrial fibrillation is the most common arrhythmia requiring management in the emergency department.[1-4] Our focus is on acute episodes of atrial fibrillation, which are usually less than 48 hours since onset and are symptomatic, requiring rapid treatment in the emergency department.[5 6] We estimate that there are 500 000 acute atrial fibrillation visits annually to the emergency department in Canada and the United States combined.[7-10] For acute atrial fibrillation, it is routine in Canadian emergency departments for physicians to attempt cardioversion to sinus rhythm, either with drugs or electrically. Compared with a rate control

strategy, early rhythm control allows patients to be discharged home sooner, frees up valuable monitors, frees up nursing staff, and is associated with lower one year mortality rates.[6 11-13] In the recent RAFF2 trial, we showed good outcomes for acute atrial fibrillation managed with rhythm control in the emergency department.[14] An alternative strategy of patients returning the next day for electrical cardioversion by cardiology is not feasible in most hospitals and would see many patients miss the 12-24 hour window for safe cardioversion.[15 16]

If rhythm control with drugs fails, then patients often undergo urgent electrical cardioversion, which is effective but may be associated with major delays in assembling the team and has been shown to have adverse events requiring treatment in 13.9% of patients.[17] Cardioversion with drugs avoids some of the issues associated with electrical cardioversion; that is, the need for several skilled staff at the bedside, procedural sedation risks, and patient anxiety. Intravenous procainamide is a type IA antiarrhythmic agent and is recommended by the Canadian Cardiovascular Society and the Canadian Association of Emergency Physicians.[5 18] Procainamide is the most commonly used antiarrhythmic for acute atrial fibrillation in Canadian emergency departments.[6 19] Intravenous vernakalant acts preferentially in the atria by blocking several ion channels and was approved in Europe in 2010. This drug has recently been approved in Canada, but is not yet widely used and is not available in the US.[20 21] Intravenous ibutilide has a 2-3% risk of torsade de pointes, a potentially lethal arrhythmia,[22 23] and is not currently recommended by the Canadian Cardiovascular Society and the Canadian Association of Emergency Physicians. Intravenous amiodarone and oral sotalol are not recommended in the emergency department as they are no more effective than placebo in the first six to eight hours.[16 24-29] Oral propafenone or flecainide, both class IC antiarrhythmic agents, have much slower onset of action than intravenous drugs and their intravenous formulations are not available in North America.[30 31]

Cardioversion with procainamide is relatively safe, but has only a moderate efficacy (50%), requires slow infusion typically over one hour, and has a moderate rate of adverse events including hypotension.[14] We hypothesise that vernakalant has the advantages of a higher conversion rate, more rapid administration and onset, and fewer adverse events,[13 20 32-35] and could therefore give clinicians an important alternative for pharmacological cardioversion of acute atrial fibrillation. Therefore, our objective was to conduct a randomised comparison of the effectiveness and safety of intravenous vernakalant and intravenous procainamide for the management of acute atrial fibrillation in the emergency department (RAFF4 trial).

Methods

Design and setting

We conducted a comparative effectiveness, patient randomised (1:1) trial with an open label comparison of cardioversion with intravenous vernakalant and intravenous procainamide in patients with acute atrial fibrillation attending the emergency department (detailed methods in supplementary appendix 1 and 2). We chose an open label approach because both drugs are available for routine use in Canada and other countries, and we wanted to mirror actual clinical use. The study included an investigator who is a patient engagement expert and a patient advisor, following existing recommendations.[36] The study was conducted in the emergency departments of 12 tertiary care hospitals in Canada.

Study population

We included patients presenting with an episode of acute atrial fibrillation of at least three hours' duration but no longer than seven days, whose condition was stable but symptoms required urgent management, and where immediate cardioversion was a reasonable option according to current guidelines.[16 18 37] Specifically, cardioversion was considered safe if the patient had adequate anticoagulation for more than three weeks (warfarin and international normalised ratio >2.0 or direct oral anticoagulant compliant), or did not have adequate anticoagulation for more than three weeks with no history of stroke, transient ischaemic attack, or valvular heart disease, and onset was <12 hours ago, onset was 12-48 hours ago and fewer than two CHADS-65 (Canadian Society of Cardiology guideline) criteria applied (age≥65, diabetes, hypertension, heart failure—which are the CHADS criteria, but with age ≥65), or patient was negative for thrombus on transesophageal echocardiography or computed tomography during emergency department visit.[16 18 37] We did not exclude patients with previous episodes of acute atrial fibrillation. We excluded patients for appropriateness (eg, unstable vital signs) or safety (eg, prolonged QT interval) reasons (see detailed exclusion criteria in supplementary appendix).

Randomisation and masking

The 1:1 allocation sequence was computer generated by a statistician at the Methods Center of the Ottawa Hospital Research Institute. Allocation was stratified by site, age (<70 *v* ≥70 years), and first ever versus repeat episode. We used a randomly permuted block design with randomly varying lengths. There was no blinding of drug treatment, according to the open label approach.

Eligible patients were approached to provide verbal or written informed consent according to local research ethics board requirements. The research assistants obtained the randomised allocation by using an online electronic data capture system, which ensured concealment.

Procedures

To standardise management of study patients, the site investigators agreed to encourage local use of the 2021 Canadian Association of Emergency Physicians acute atrial fibrillation best practices checklist.[18]

Patients randomised to the vernakalant group received an initial infusion of 3 mg/kg over 10 minutes by a preprogrammed intravenous pump.[38] If conversion did not occur within 15 minutes after the end of the first infusion, and the patient remained stable, a second 10 minute infusion of 2 mg/kg was administered. If conversion occurred during the first or second infusion, that infusion was continued to completion. If conversion had not occurred within 30 minutes after infusion completion, patients were offered electrical cardioversion.

Patients randomised to the procainamide arm received a continuous infusion of intravenous procainamide with a dose of 15 mg/kg in 500 mL of normal saline given over 60 minutes (maximum dose 1500 mg) by a preprogrammed pump. Based on our previous RAFF2 trial, we believed that a 60 minute period would avoid some episodes of hypotension.[14] The infusion was stopped if there was conversion to sinus rhythm before the maximum dose. If conversion was not achieved within 30 minutes after the infusion ended, patients were offered electrical cardioversion.

The primary outcome was conversion to and maintenance of sinus rhythm for at least 30 minutes at any time after randomisation until 30 minutes after completion of the drug infusion. This was a clinical and patient centred outcome because patients experience immediate relief from their symptoms once sinus rhythm is achieved. If conversion was not achieved by this time, it was considered a treatment failure. Reversion back to atrial fibrillation is highly unlikely in the emergency department when patients have been in sinus rhythm for 30 minutes.[14] When reversion back to atrial fibrillation occurred after conversion, during the 30 minute observation period, this was considered a treatment failure. Spontaneous conversion after randomisation but before study intervention was considered a treatment success. These patients were analysed in the group to which they were allocated according to the analysis plan (details given below). When the electrocardiogram interpretation was uncertain, rhythm eligibility was determined by an electrophysiology cardiologist who was also masked to the allocation group and any other clinical factors. Patients who were determined post hoc not to be in atrial fibrillation on presentation were excluded from all analyses.

The following secondary outcomes were assessed during the first emergency department visit: time to conversion to sinus rhythm (in minutes) from time of start of infusion; whether the patient required electrical cardioversion; emergency department disposition—admission or discharge; length of stay in emergency department (in hours) from time of arrival to time of disposition; and adverse events, which were classified as during or after the infusion, or during or after electrical cardioversion.

The following secondary outcomes were assessed at 30 days: return visit to the emergency department and whether cardioversion or hospital admission was required; stroke; death; return to normal activities and number of days; and patient's heart rate—determined manually or by a smartphone application (Heartify, Heartify Health, Boston, MA, USA). A cost effectiveness analysis will be conducted from the Canadian public payer's perspective and published separately.

Follow-up

Patients underwent a structured telephone interview at 30 days. Return hospital visits were verified by review of hospital records and electrocardiograms. We evaluated outcomes of patients lost to follow-up by reviewing local hospital records and provincial registries when available.

Sample size

The sample size for this superiority trial was determined using the primary outcome: conversion to sinus rhythm using two independent groups with a 1:1 allocation. Based on a poll of investigators, an absolute difference of 15% was considered the minimum clinically important difference. According to clinical studies of patients with acute atrial fibrillation performed in the emergency department, we expected a conversion rate of 65% for the vernakalant group.[13 32 33] A total of 340 patients (170 per group) achieves 80% power to detect an absolute difference in conversion rates of 15%.

Data analysis

Descriptive statistics were used to describe the baseline characteristics of patients randomised to each treatment group: frequency and percentage for categorical variables and mean and standard deviation (or median and interquartile range if skewed) for continuous variables. The primary analysis of the primary outcome, conversion to sinus rhythm, was conducted on an intention-to-treat basis, in which all randomised patients were analysed in the group to which they were allocated. We did not analyse patients who were mistakenly included because the treating physician's interpretation of the electrocardiogram was incorrect; that is, the patients did not have atrial fibrillation.[39] To obtain correct inferences, increase power and precision, and protect against chance imbalances,[40 41] the primary analysis used multiple logistic regression analysis controlling for the stratification variables (age, first or repeat episode as fixed effects, and site as a random effect) and the following prespecified prognostic variables: sex, time from onset, and history of heart failure, all specified as fixed effects. The treatment effect was expressed as absolute difference and odds ratio, together with 95% confidence intervals. All tests were carried out at the two sided 5% significance level. We also used a secondary per protocol analysis to exclude patients who were randomised but never received the study drug.

The secondary outcomes were evaluated according to data type: binary outcomes (ie, attempted electrical cardioversion, disposition) were analysed using multiple logistic regression with covariates as specified for the primary outcome; continuous outcomes (length

of stay, time to conversion among those who had successful conversion with the drugs) were analysed using multiple linear regression with covariates as specified for the primary outcome analysis. Time to conversion was also analysed using Cox proportional hazards regression; patients in whom conversion did not occur, spontaneous conversion occurred after the observation period, or conversion occurred with electrical shock were retained in the analysis by censoring their event times at 55 minutes (25 minute infusion+30 minute observation) and 90 minutes (60 minute infusion+30 minute observation) in the vernakalant and procainamide groups, respectively. The treatments were compared using adjusted hazard ratio and difference in restricted mean survival time (area under the survival curve). Additional sensitivity analyses of continuous outcomes used log transformations to account for skewness.

Because we compared two standards of care, we did not conduct formal interim analyses for efficacy. Every six months, an independent data safety monitoring board reviewed any adverse events, enrolment figures, protocol adherence, data quality, and data completeness.

The following subgroup analyses were planned a priori: episode first ever or repeat, age ≥70 or <70 years, onset <12 or ≥12 hours. We had planned to evaluate history of heart failure, but found the incidence was too low. We added the post hoc subgroup of sex (male or female) that was not in the protocol. Subgroup analyses were conducted by including the subgroup variable and its interaction with the treatment variable in the multiple logistic or linear regression analysis. We conducted all analyses using Statistical Analysis Software (SAS) version 9.4.

Patient and public involvement

We included a patient partner (CC, mentioned in acknowledgments) in the study planning and a coauthor (SGN) who is the facilitator for our institution's Office for Patient Engagement in Research Activities (OPERA) and who advised on patient engagement.

Results

We enrolled patients from June 2021 to August 2024. Among the 960 patients approached for the study, 606 refused to participate and 354 gave consent and were randomly allocated (fig 1). Four patients were

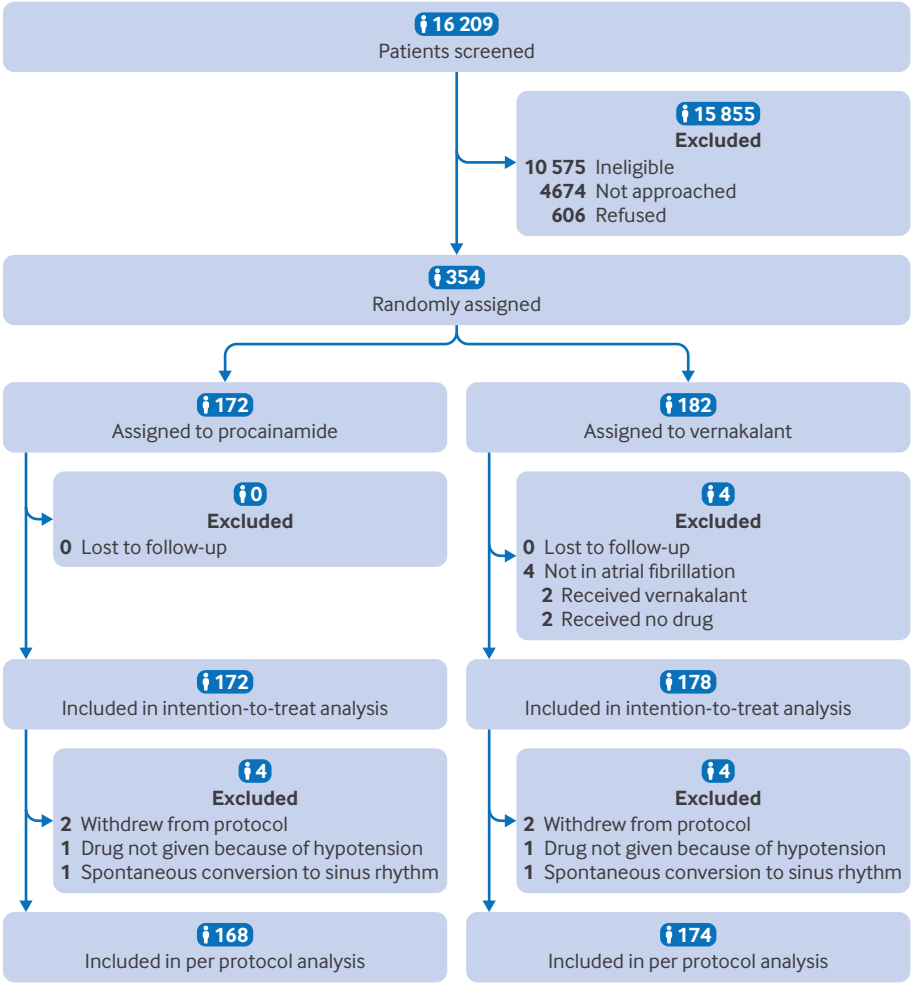

Fig 1 | Flow of patients in RAFF4 trial (rapid cardioversion of patients with acute atrial fibrillation)

Table 1 | Characteristics and emergency department management for 350 patients enrolled in RAFF4 trial

Characteristics	Procainamide (n=172)	Vernakalant (n=178)
Age (years), mean (SD)	62.4 (15.2)	63.5 (15.0)
Range	25-92	24-91
Male	114 (66.3)	108 (60.7)
Duration of arrhythmia (h), mean (SD)	18.2 (29.9)	20.6 (28.8)
Range	3-168	3-168
<12 h	112 (65.1)	102 (57.3)
12-48 h	45 (26.1)	49 (27.5)
>48 h	15 (8.9)	25 (14.1)
Main presenting symptom		
Palpitations	149 (86.6)	152 (85.4)
Chest pain	10 (5.8)	18 (10.1)
Shortness of breath	8 (4.7)	3 (1.7)
Dizziness	1 (0.6)	1 (0.6)
Weakness	2 (1.2)	2 (1.1)
Syncope	0 (0)	1 (0.6)
Other	2 (1.2)	1 (0.6)
Initial vital signs, mean (SD)		
Heart rate (beats/min)	109.3 (27.6)	114.2 (29.4)
Systolic blood pressure (mm Hg)	130.1 (20.5)	131.2 (20.9)
Oxygen saturation (%)	97.1 (1.9)	97.2 (1.8)
Temperature (°C)	36.4 (0.6)	36.4 (0.5)
Canadian triage and acuity scale level, median (IQR)	3 (2-3)	3 (2-3)
Previous atrial fibrillation and treatments	130 (75.6)	127 (71.8)
Electrical cardioversion	79 (60.3)	85 (66.9)
Cardioversion with drugs	25 (19.1)	21 (16.5)
Ablation	30 (22.9)	23 (18.1)
$CHADS_2$ criteria		
Hypertension	81 (47.1)	75 (42.4)
Age ≥75 years	42 (24.4)	47 (26.6)
Diabetes mellitus	21 (12.2)	17 (9.6)
Stroke or transient ischaemic attack	10 (5.8)	8 (4.5)
Congestive heart failure	6 (3.5)	7 (4.0)
$CHADS_2$* score		
0	72 (41.9)	78 (43.8)
1	53 (30.8)	56 (31.5)
≥2	47 (27.3)	44 (24.7)
Other medical history		
Coronary artery disease	26 (15.1)	14 (7.9)
Valvular heart disease	3 (1.7)	3 (1.7)
Pacemaker or implantable cardioverter defibrillator	1 (0.6)	5 (2.8)
Chronic obstructive pulmonary disease or asthma	11 (6.4)	11 (6.2)
Current drugs taken at home		
Anticoagulants	92 (53.5)	102 (57.3)
Direct anticoagulants	88 (51.2)	97 (54.8)
Warfarin	2 (1.2)	3 (1.7)
Low molecular weight heparin	2 (1.2)	2 (1.1)
Antiarrhythmics	7 (4.1)	11 (6.2)
Amiodarone	7 (4.1)	8 (4.5)
Propafenone	0 (0)	1 (0.6)
Sotalol	0 (0)	2 (1.1)
Antiplatelet agents	18 (10.5)	17 (9.6)
Acetylsalicylic acid	18 (10.5)	14 (7.9)
Clopidogrel	0 (0)	4 (2.2)
Cardiac medications		
Beta blocker	72 (41.9)	79 (44.6)
Calcium channel blocker	28 (16.3)	26 (14.7)
Investigations		
Initial ECG calculated heart rate, mean (SD)	118.3 (25.2)	118.9 (26.7)
Range	62-182	66-178
International normalised ratio, mean (SD) (n=65 and 71)	1.2 (0.6)	1.2 (0.4)
Transoesophageal echocardiography	9 (5.2)	9 (5.1)
Left atrial clot	0 (0)	1 (0.6)
Cardiac computed tomography scan	1 (0.6)	3 (1.7)
Other treatments in emergency department		
Rate control agents	20 (11.6)	20 (11.3)
Antithrombotic treatment	29 (16.9)	25 (14.1)

(Continued)

Table 1 | (Continued)

Characteristics	Procainamide (n=172)	Vernakalant (n=178)
Direct oral anticoagulant	28 (16.3)	22 (12.4)
Acetylsalicylic acid	1 (0.6)	2 (1.1)
Clopidogrel	1 (0.6)	2 (1.1)
Heparin	2 (1.2)	2 (1.1)
Other conditions identified while in emergency department		
Congestive heart failure	1 (0.6)	1 (0.6)
Acute coronary syndrome	1 (0.6)	0 (0)

Data are numbers (%) unless indicated otherwise.
ECG=electrocardiogram; IQR=interquartile range; SD=standard deviation.
*$CHADS_2$ is a clinical scoring system used to estimate risk of stroke in patients with atrial fibrillation. It is composed of the variables listed in the table.

later determined not to have atrial fibrillation and were excluded from the primary analysis (two had atrial flutter, two had supraventricular tachycardia). Four patients in each group were included in the analysis but did not receive the study drug because spontaneous conversion to sinus rhythm occurred, they developed hypotension, or they withdrew from the study intervention. No patients were lost to follow-up for the primary outcome. We were unable to reach 8% of patients by telephone, but had complete 30 day follow-up for all patients through their hospital records.

Table 1 compares the characteristics in the procainamide (n=172) and vernakalant (n=178) groups. Both groups were similar in terms of age (62.4 *v* 63.5), male sex (66.3% *v* 60.7%), duration of symptoms in hours (18.2 *v* 20.6), mean electrocardiogram heart rate (118.3 *v* 118.9), previous atrial fibrillation (75.6% *v* 71.8%), CHADS-65 positivity (58.1% *v* 56.2%), and oral anticoagulant drugs taken at home (52.3% *v* 56.2%).

For the primary outcome of conversion to sinus rhythm within 30 minutes of infusion completion, vernakalant was more effective than procainamide (62.4% *v* 48.3%; adjusted absolute difference 15.0%, 95% confidence interval 4.6% to 25.0%, P=0.005; adjusted odds ratio 1.87, 95% confidence interval 1.20 to 2.91, P=0.006; table 2). Fewer patients underwent attempted electrical cardioversion (33.7% *v* 44.2%; odds ratio 0.62, 95% confidence interval 0.39 to 0.96, P=0.033). Among patients who had successful conversion on the drugs, time from start of infusion to conversion was faster for the vernakalant group (21.8 *v* 44.7 minutes; mean difference −22.9, 95% confidence interval −29.9 to −16.0, P<0.001). Results were similar when including patients with censored event times (adjusted hazard ratio 2.5, 95% confidence interval 1.8 to 3.4; difference in restricted mean survival time −32.9 minutes, 95% confidence interval −42.8 to −23.0, P<0.001). Most patients were discharged home from the emergency department (vernakalant 96.1% *v* procainamide 97.7%, P=0.52) and total length of stay in the emergency department was similar (8.9 *v* 9.2 hours, P=0.54). Conversion did not occur in the 11 patients who were admitted and their heart rates could not be controlled.

Results were similar in the per protocol analysis, which excluded eight patients who did not receive the

Table 2 | Intention-to-treat analysis: outcomes and disposition for 350 patients enrolled in RAFF4 trial

Outcome measure	Procainamide (n=172)	Vernakalant (n=178)	Treatment effect (95% CI)*	P value
Primary outcome				
Conversion to and maintenance of sinus rhythm within 30 minutes of study drug infusion, n (%)	83 (48.3)	111 (62.4)	Odds ratio 1.87 (1.20 to 2.91)	0.006
			Absolute risk difference 15.0 (4.6 to 25.0)†	0.005
Final conversion status, n (%)				
Infusion	83 (48.3)	111 (62.4)	—	—
Electrical cardioversion	76 (44.2)	54 (30.3)	—	—
Spontaneous	7 (4.1)	5 (2.8)	—	—
Not converted	6 (3.5)	8 (4.5)	—	—
Secondary outcomes				
Conversion time (min) among patients with successful conversion (n=194; start of infusion to conversion), mean (SD)	44.7 (28.4)	21.8 (20.4)	Mean difference −22.9 (−29.9 to −16.0)	<0.001
Median (IQR)	40 (21-58)	14 (9-26)		
Conversion time (min) among randomised patients (n=342; start of infusion to conversion or censoring), restricted mean survival time (standard error)	75.7 (3.0)	42.8 (4.1)	Hazard ratio 2.5 (1.8 to 3.4)	<0.001
			Mean difference −32.9 (−42.8 to −23.0)	<0.001
Attempted electrical cardioversion, n (%)	76 (44.2)	60 (33.7)	Odds ratio 0.62 (0.39 to 0.96)	0.033
Disposition: discharged home, n (%)	168 (97.7)	171 (96.1)	Odds ratio 0.65 (0.18 to 2.38)	0.52
Total emergency department length of stay (h), mean (SD)	9.2 (6.9)	8.9 (7.9)	Mean difference −0.58 (−2.1 to 0.92)	0.11
Median (IQR)	7.4 (5.8-9.7)	7.0 (5.3-8.8)	—	—

CI=confidence interval; IQR=interquartile range; SD=standard deviation.
*Comparison of vernakalant versus procainamide from multivariable regression analysis adjusted for stratification factors and prespecified prognostic variables: site, age, sex, first or repeat episode, time from onset, and history of heart failure. Site modelled as random effect except where convergence failure when it was modelled as fixed effect.
†Site modelled as fixed effect.

Table 3 | Per protocol analysis: outcomes and disposition for 342 patients enrolled in RAFF4 trial

Outcome measure	Procainamide (n=168)	Vernakalant (n=174)	Treatment effect (95% CI)*	P value
Primary outcome				
Conversion to and maintenance of sinus rhythm within 30 min of study drug infusion, n (%)	82 (48.8)	109 (62.6)	Odds ratio 1.81 (1.16 to 2.82)	0.009
			Absolute risk difference 14.1 (3.7 to 24.6)†	0.008
Final conversion status, n (%)				
Infusion	82 (48.8)	109 (62.6)	—	—
Electrical cardioversion	73 (43.5)	52 (29.9)	—	—
Spontaneous	7 (4.2)	5 (2.9)	—	—
Not converted	6 (3.6)	8 (4.6)	—	—
Secondary outcomes				
Conversion time (min) among patients with successful conversion (n=191; start of infusion to conversion), mean (SD)	44.7 (28.4)	21.8 (20.4)	Mean difference −22.9 (−29.9 to −16.0)	<0.001
Median (IQR)	40 (21-58)	14 (9-26)		
Conversion time (min) among randomised patients (n=342; start of infusion to conversion or censoring), restricted mean survival time (standard error)	75.7 (3.0)	42.8 (4.1)	Hazard ratio 2.5 (1.8 to 3.4)	<0.001
			Mean difference −32.9 (−42.8 to −23.0)	<0.001
Attempted electrical cardioversion	73 (43.5)	58 (33.3)	Odds ratio 0.64 (0.41 to 1.01)	0.053
Disposition: discharged home, n (%)	164 (97.6)	168 (96.6)	Odds ratio 0.70 (0.17 to 2.79)†	0.61
Total emergency department length of stay (h), mean (SD)	9.3 (6.9)	8.9 (7.9)	Mean difference −0.63 (−2.2 to 0.90)	0.076
Median (IQR)	7.4 (5.8-10.0)	6.8 (5.3-8.7)	—	—

CI=confidence interval; IQR=interquartile range; SD=standard deviation.
*Comparison of vernakalant versus procainamide from multivariable regression analysis adjusted for stratification factors and prespecified prognostic variables: site, age, sex, first or repeat episode, time from onset, and history of heart failure. Site was modelled as random effect except where convergence failure when it was modelled as fixed effect.
†Site modelled as fixed effect.

study drug (table 3). For conversion to sinus rhythm, vernakalant was more effective than procainamide (62.6% *v* 48.8%; absolute difference 14.1%, 95% confidence interval 3.7% to 24.6%, P=0.008; adjusted odds ratio 1.81, 95% confidence interval 1.2 to 2.8, P=0.009).

Adverse events during or after the drug infusion were similar in both groups (17.4% *v* 25.0%; absolute difference −7.6%, 95% confidence interval −16.1% to 0.95%, P=0.11; table 4). These events were generally mild and brief, with hypotension requiring the infusion to be stopped in 8.7% of patients in the procainamide group. Adverse events during or after electrical cardioversion were uncommon and not serious in both groups (5.1% *v* 6.6%, P=0.71).

During the 30 days after the first emergency department visit, 14.0% of the vernakalant group and 16.9% of the procainamide group returned to the emergency department and a small proportion required electrical cardioversion (5.6% *v* 7.0%; table 5). No patients died from atrial fibrillation, none had a stroke, and only one required hospital admission for atrial fibrillation (procainamide group). Most patients returned to normal daily activities (94.0% *v* 91.0%). Of the patients reached by day 30, heart rate was determined by the smartphone application for 111 and manually by 81. Comparing vernakalant with procainamide, the mean heart rates were 71 versus 69 beats/min.

Subgroup analyses revealed only one significant finding favouring vernakalant for conversion in

Table 4 | Adverse outcomes for 350 patients enrolled in RAFF4 trial

Outcome measure (%)	Procainamide (n=172)	Vernakalant (n=178)	P value
Adverse event during or after infusion	43 (25.0)	31 (17.4)	0.11
Urgent electrical cardioversion	1 (0.6)	0 (0)	—
Hypotension (systolic blood pressure <90)	15 (8.7)	3 (1.7)	—
Bradycardia (heart rate <50)	4 (2.3)	5 (2.8)	—
Ventricular tachycardia (≥30 s)	5 (2.9)	1 (0.6)	—
Atrial tachyarrhythmia (heart rate >100)	3 (1.7)	7 (3.9)	—
QRS widening (≥120)	3 (1.7)	0 (0)	—
QT lengthening (>35%)	2 (1.2)	1 (0.6)	—
Sinus pause	2 (1.2)	0 (0)	—
Transient paresthesia	0 (0)	3 (1.7)	—
Nausea	4 (2.3)	7 (3.9)	—
Dizziness	4 (2.3)	4 (2.3)	—
Other events			
Infusion interrupted	24 (14.0)	0 (0)	—
Infusion discontinued	15 (8.7)	4 (2.3)	—
Hypotension treated with intravenous normal saline	11 (7.0)	0 (0)	—
Adverse event during or after electrical cardioversion (n=76 and 59)	5 (6.6)	3 (5.1)	0.71
Hypoxia	1 (0.6)	0 (0)	—
Jaw thrust	5 (2.9)	3 (1.7)	—
Given oxygen	1 (0.6)	0 (0)	—

Data are numbers (%). Patients may have had more than one event.

Table 5 | 30 Day follow-up for 350 patients enrolled in RAFF4 trial

Characteristics	Procainamide (n=172)	Vernakalant (n=178)
Return emergency department visit	29 (16.9)	25 (14.0)
Related to atrial fibrillation	24 (14.0)	23 (12.9)
Rate control given in emergency department	4 (2.3)	1 (0.6)
Antiarrhythmic given in emergency department	7 (4.1)	8 (4.5)
Electrical cardioversion	12 (7.0)	10 (5.6)
Spontaneous conversion	9 (5.2)	8 (4.5)
Admitted for atrial fibrillation	1 (0.6)	0 (0)
Converted to normal sinus rhythm while in emergency department	21 (12.2)	23 (12.9)
Days returned after first visit, mean (SD)	13.6 (9.6)	12.7 (7.8)
Stroke	0 (0)	0 (0)
Outpatient visits	27 (15.7)	22 (12.4)
Cardiology	27 (15.7)	20 (11.2)
Internal medicine	1 (0.6)	2 (1.1)
Death*	0 (0)	2 (1.1)
Related to atrial fibrillation	0 (0)	0 (0)
30 day follow-up call	156 (90.7)	166 (93.3)
Patient returned to normal daily activities since emergency department	142 (91.0)	156 (94.0)
Mean days (SD)	2.3 (3.6)	2.4 (3.8)
Average heart rate, mean (SD) (n=96 and 96)	69.3 (12.1)	70.7 (14.9)

Data are numbers (%) unless indicated otherwise.
SD=standard deviation.
*Deaths caused by cancer and sepsis.

patients younger than 70 years (73.3% *v* 47.2%; adjusted odds ratio 3.07, 95% confidence interval 1.71 to 5.50, P<0.001, interaction P=0.005; table 6). Sensitivity analyses of continuous outcomes using log transformations found no substantive differences in the results.

Discussion

Interpretation

This clinical trial compared intravenous procainamide with intravenous vernakalant in patients with acute atrial fibrillation. In the primary analysis group of 350 patients, vernakalant was superior to procainamide with a 15% absolute improvement in conversion rate, as well as time to conversion that was 50% faster. Fewer patients in the vernakalant group underwent attempted electrical cardioversion. Results were similar in the per protocol analysis. The conversion advantage was particularly marked in patients younger than 70 years. Adverse events were similar in both groups and were generally mild and brief, although hypotension requiring the infusion to be stopped was seen in 8.7% of patients in the procainamide group. Patient outcomes were good, with almost all patients being discharged home in sinus rhythm. There were no meaningful differences between groups at 30 days and no recurrence of atrial fibrillation was recorded.

Previous studies

We are aware of no previous studies directly comparing intravenous procainamide with intravenous vernakalant. In the RAFF2 trial, we showed that a strategy of rhythm control for acute atrial fibrillation with intravenous procainamide avoided the need for electrical cardioversion in about half of patients.[14] The results of our current study suggest that use of vernakalant could prevent the need for resource intensive procedural sedation required for electrical cardioversion in two thirds of patients with acute atrial fibrillation. Our reported conversion rates and

Table 6 | Primary outcome subgroup analyses for 350 patients enrolled in RAFF4 trial

Characteristics	Procainamide (n=172)	Vernakalant (n=178)	Odds ratio (95% CI)*	Treatment effect P value	Interaction P value
Sex					
Male (n=222)	49 (43.0)	64 (59.3)	1.90 (1.11 to 3.26)	0.02	0.51
Female (n=128)	34 (58.6)	47 (67.1)	1.41 (0.68 to 2.92)	0.36	—
First or repeat episode					
First (n=92)	21 (50.0)	34 (68.0)	2.10 (0.89 to 4.96)	0.09	0.60
Repeat (n=258)	62 (47.7)	77 (60.2)	1.60 (0.97 to 2.64)	0.06	—
Age ≥70 years					
Yes (n=137)	32 (50.0)	34 (46.6)	0.85 (0.43 to 1.68)	0.63	0.005
No (n=213)	51 (47.2)	77 (73.3)	3.07 (1.71 to 5.50)	0.0002	—
Onset length ≥12 h					
Yes (n=135)	28 (46.7)	39 (52.0)	1.22 (0.61 to 2.44)	0.57	0.12
No (n=214)	55 (49.1)	72 (70.6)	2.49 (1.41 to 4.41)	0.002	—

Data are numbers (%).
CI=confidence interval.
*Odds ratios obtained from random effects logistic regression analysis with site specified as random effect.

times for procainamide and vernakalant were similar to those found in previous studies. An observational study of 316 patients receiving procainamide found a conversion rate of 52.2% and a median time to conversion of 55 minutes, and the RAFF2 trial reported a conversion rate of 52.0%.[14 42] For vernakalant, SPECTRUM is a postmarketing surveillance registry in Europe that reported on 1289 patients with acute atrial fibrillation treated in emergency departments.[13 32 33 43] Overall, successful conversion occurred in 70.2%, with a median conversion time of 12 minutes.

Intravenous drugs available elsewhere (flecainide, propafenone) are not available in Canada, leaving three possible choices: ibutilide, procainamide, and vernakalant.[1] Intravenous ibutilide has a 2-3% risk of torsade de pointes, a potentially lethal arrhythmia,[22 23] and is not currently recommended by the Canadian Cardiovascular Society and the Canadian Association of Emergency Physicians. Intravenous flecainide and propafenone are available in Europe and are listed as alternatives to vernakalant by the European Society of Cardiology.[44]

Strengths and limitations

Randomised clinical trials of interventions in the emergency department for acute atrial fibrillation are uncommon owing to the inherent difficulties of performing these procedures in an acute setting. This trial was conducted with rigorous methodology and data analysis. Our open label trial design allowed the true effectiveness of the two drugs to be evaluated in a typical clinical setting. We obtained the primary outcome for all enrolled patients.

Although compliance with the protocol was good overall, we had to exclude four patients enrolled in the study by attending physicians because post hoc review revealed they did not have atrial fibrillation. Because these patients did not have the condition of interest, their exclusion was consistent with the goal of the intention-to-treat analysis. While delays in care in these busy emergency departments led to four patients withdrawing from the protocol, they were included in the intention-to-treat analysis. However, the per protocol analysis mirrored the intention-to-treat analysis. We were unable to reach 8% of patients by telephone, but had satisfactory follow-up for all patients through their hospital records. Many patients refused to participate, mostly because they had a strong preference for procainamide or electrical cardioversion. Nevertheless, we believe our findings are generalisable because the included patients had a wide range of characteristics. There were no differences in the overall length of stay, which was much longer than normally expected because of study protocol requirements. In the usual non-study situation, one could expect patients treated with vernakalant to be discharged much more quickly. Although procainamide is not commonly used for atrial fibrillation in several countries, it is widely available because it is recommended for some advanced cardiac life support indications.[45]

Clinical implications

The study findings provide compelling evidence of the superiority of intravenous vernakalant over procainamide for rapid cardioversion in patients with acute atrial fibrillation. Vernakalant was more effective and faster acting, without an increase in adverse events. Additionally, vernakalant did not result in discontinued infusions because of hypotension that were observed with procainamide. Although procainamide is not often used for atrial fibrillation, our positive findings for vernakalant should lead to consideration of a change in practice worldwide. The rapid effectiveness observed for vernakalant should encourage more clinicians and patients to try cardioversion with drugs, rather than the electrical cardioversion or rate control approaches. Our results indicate that vernakalant could prevent the need for resource intensive procedural sedation required for electrical cardioversion in two thirds of cases. Vernakalant is particularly effective in the 60% of patients younger than 70 years. Regardless of the country, there are benefits for the patient and the hospital. Our patient partners told us that they would prefer to be discharged more quickly and to avoid electrical cardioversion. Many emergency departments worldwide are crowded and access to cardiac monitors is limited. Therefore, more rapid treatment and discharge home, which we observed with vernakalant, could improve patient flow, reduce waiting times, and improve access to care for other patients.

Research implications

We plan to conduct a cost effectiveness analysis to compare vernakalant with procainamide. This economic evidence will provide policy makers and healthcare providers with the information needed to make informed choices about resource allocation, ensuring that treatment options deliver the greatest value for patients and the healthcare system.

Conclusions

In this randomised comparison, our clinical trial showed that intravenous vernakalant was superior to procainamide for patients with acute atrial fibrillation. Vernakalant showed a 15% absolute improvement in conversion rate, and time to conversion that was 50% faster and was well tolerated. Therefore, vernakalant is a safe and highly effective alternative for the rapid cardioversion and discharge home of patients with acute atrial fibrillation, particularly in those younger than 70 years.

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Data sharing: The protocol for this project is publicly available. Requests for secondary use of the data should be addressed to the corresponding author. RAFF4 trial data underlying the results will be available and will encompass all anonymised data on individual patients on which the analyses, results, and conclusions reported in the paper are based. The authors will make the data available in a publicly accessible repository, the Canadian Federated Research Data Repository (FRDR: https://www.frdr-dfdr.ca/repo/dataset/9547ab29-882b-4c2a-a0e1-68ebb596d9f4).

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Web appendix 1 and 2: RAFF4 detailed methods; Protocol