Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation (RAFF2): a partial factorial randomised trial

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Summary

Background Acute atrial fibrillation is the most common arrythmia treated in the emergency department. Our primary aim was to compare conversion to sinus rhythm between pharmacological cardioversion followed by electrical cardioversion (drug–shock), and electrical cardioversion alone (shock-only). Our secondary aim was to compare the effectiveness of two pad positions for electrical cardioversion.

Methods We did a partial factorial trial of two protocols for patients with acute atrial fibrillation at 11 academic hospital emergency departments in Canada. We enrolled adult patients with acute atrial fibrillation. Protocol 1 was a randomised, blinded, placebo-controlled comparison of attempted pharmacological cardioversion with intravenous procainamide (15 mg/kg over 30 min) followed by electrical cardioversion if necessary (up to three shocks, each of ≥200 J), and placebo infusion followed by electrical cardioversion. For patients having electrical cardioversion, we used Protocol 2, a randomised, open-label, nested comparison of anteroposterior versus anterolateral pad positions. Patients were randomly assigned (1:1, stratified by study site) for Protocol 1 by on-site research personnel using an online electronic data capture system. Randomisation for Protocol 2 occurred 30 min after drug infusion for patients who had not converted and was stratified by site and Protocol 1 allocation. Patients and all research and emergency department staff were masked to treatment allocation for Protocol 1. The primary outcome was conversion to normal sinus rhythm for at least 30 min at any time after randomisation and up to a point immediately after three shocks. Protocol 1 was analysed by intention to treat and Protocol 2 excluded patients who did not receive electrical cardioversion. This study is registered at ClinicalTrials.gov, number NCT01891058.

Findings Between July 18, 2013, and Oct 17, 2018, we enrolled 396 patients, and none were lost to follow-up. In the drug–shock group (n=204), conversion to sinus rhythm occurred in 196 (96%) patients and in the shock-only group (n=192), conversion occurred in 176 (92%) patients (absolute difference 4%; 95% CI 0–9; p=0·07). The proportion of patients discharged home was 97% (n=198) versus 95% (n=183; p=0·60). 106 (52%) patients in the drug–shock group converted after drug infusion only. No patients had serious adverse events in follow-up. The different pad positions in Protocol 2 (n=244), had similar conversions to sinus rhythm (119 [94%] of 127 in anterolateral group *vs* 108 [92%] of 117 in anteroposterior group; p=0·68).

Interpretation Both the drug–shock and shock-only strategies were highly effective, rapid, and safe in restoring sinus rhythm for patients in the emergency department with acute atrial fibrillation, avoiding the need for return to hospital. The drug infusion worked for about half of patients and avoided the resource intensive procedural sedation required for electrical cardioversion. We also found no significant difference between the anterolateral and anteroposterior pad positions for electrical cardioversion. Immediate rhythm control for patients in the emergency department with acute atrial fibrillation leads to excellent outcomes.

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Introduction

Acute atrial fibrillation is the most common arrhythmia requiring treatment in the emergency department.[1,2] Atrial fibrillation is characterised by disorganised atrial electrical depolarisation leading to an irregular and rapid heart rate. Acute atrial fibrillation generally refers to symptomatic, recent-onset episodes (first detected, recurrent paroxysmal, or recurrent persistent episodes) where the duration is less than 48 h and cardioversion is a safe option.[3] We estimate that in Canada and the USA, 430 000 visits to the emergency department annually are due to acute atrial fibrillation.[4,5]

The two major approaches to emergency department treatment of this arrythmia are rate control or rhythm control. In rate control, medications are used to reduce the heart rate, but the patient remains in atrial fibrillation

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Research in context

Evidence before this study

Regarding Protocol 1, comparison of electrical versus pharmacological cardioversion for acute atrial fibrillation, we searched PubMed from inception to Oct 1, 2019, using the search terms "atrial fibrillation" and "pharmacological cardioversion". We could find no published studies comparing electrical with pharmacological cardioversion. A trial by Pluymaekers and colleagues compared two approaches to early rhythm control: same-day cardioversion and next-day cardioversion. This study used both chemical and electrical cardioversion strategies, but the two were not compared. Some observational studies have confirmed the effectiveness of early rhythm control but without distinguishing between the value of pharmacological and electrical cardioversion. Other emergency department studies of rhythm control for acute atrial fibrillation have been small or have not compared pharmacological and electrical cardioversion. Previous studies have confirmed the effectiveness and safety of procainamide for acute atrial fibrillation.

Regarding Protocol 2, a comparison of anterolateral and anteroposterior pad positions, we searched PubMed from inception to Oct 1, 2019, using the search terms "atrial fibrillation" and "pad position", and identified five previous randomised trials that used contemporary biphasic devices, although most patients had persistent rather than acute atrial fibrillation. Of these European studies, only one used the right infraclavicular anteroposterior position commonly used in Canada and the USA, and only one started shocks as high as 150 J. Three studies showed no difference in conversion between the two pad positions and two showed a higher proportion of patients converting using the anterolateral position.

Added value of this study

This clinical trial found no significant difference between using either a drug–shock or a shock-only approach as an immediate strategy to treat acute atrial fibrillation in the emergency department; both approaches were highly effective, rapid, and safe in restoring sinus rhythm. The drug–shock strategy was shown to be more effective for patients with first episodes of atrial fibrillation and for patients younger than 70 years than it was for other patients. Both anterolateral and anteroposterior pad positions are highly effective for electrical cardioversion.

Implications of all the available evidence

The most important finding from this study is that either approach to immediate rhythm control in the emergency department leads to a very high proportion of patients being discharged in sinus rhythm without serious adverse events. Patients can be rapidly cardioverted in the emergency department, resolving their acute symptoms and enabling discharge home. This avoids unnecessary hospital admission or next-day re-evaluation by cardiologists. This obviates the need for anticoagulation in low-risk patients and the need for medication prescriptions to control heart rate. Patients can quickly return to normal activities and avoid extended stays in crowded emergency departments. We believe that the procainamide infusion leading to rapid conversion in more than 50% of patients is an important advantage of the drug–shock approach. This approach allows physicians to attend to other patients during the procainamide infusion and frequently avoids the need for procedural sedation, which might lead to serious adverse events. Sedation also requires explicit consent and the continuous attendance of additional health-care providers. Nevertheless, the choice between pharmacological and electrical cardioversion should be a shared decision between the patient and the physician. We also found no significant difference between the anterolateral and anteroposterior pad positions for electrical cardioversion. If initial attempts fail, many physicians suggest switching to the other position and applying firm pressure to the pads to reduce transthoracic impedance.

at the time of discharge or admission. With the rhythm control approach, patients are cardioverted back to normal sinus rhythm with drugs or electrical cardioversion (direct-current [DC] cardioversion), and are usually discharged home within a few hours. There is little evidence regarding many important aspects of acute atrial fibrillation management in the emergency department and there is equipoise for most facets of early care.[3,6,7] Few randomised trials have addressed key acute atrial fibrillation questions, such as whether patients should be treated with rate control or rhythm control, whether rhythm control should proceed initially with drugs or with DC cardioversion, and whether DC cardioversion electrode pads should be placed anteroposterior or anterolateral. Much variation in practice exists among Canadian and US physicians.[8,9] Although many physicians believe that rhythm control is better for the patient, to our knowledge, no trials have ever compared rate control with rhythm control for patients with acute atrial fibrillation.[8,10,11]

For acute atrial fibrillation rhythm control in the emergency department, some physicians prefer to start with drugs and then move to DC cardioversion if necessary (drug–shock strategy). Other physicians prefer to start immediately with DC cardioversion (shock-only strategy). We have shown that emergency department physicians are equally divided in their use of these two competing cardioversion strategies.[8,10,11] We have also seen much variation in DC cardioversion pad placement in emergency departments.[11] Our primary aim was to compare conversion to sinus rhythm between two strategies: (1) attempted pharmacological cardioversion with intravenous procainamide followed by DC cardioversion if necessary (drug–shock), and (2) DC cardioversion alone (shock-only). Our secondary aim was

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to compare the anteroposterior versus the anterolateral pad positions in DC cardioversion.

Methods

Study design

We did a partial factorial study of two protocols at 11 academic emergency departments (appendix p 4). The primary protocol (Protocol 1) was a randomised, blinded, placebo-controlled comparison of attempted pharmacological cardioversion with intravenous procainamide (15 mg/kg over 30 min) followed by electrical cardioversion (up to three shocks, each of ≥200 J) if necessary, versus placebo infusion followed by electrical cardioversion. For the subset of patients who required electrical cardioversion, we did a secondary and nested randomised, open-label comparison of the anteroposterior versus anterolateral pad positions (Protocol 2). We also enrolled 71 patients with atrial flutter and these patients will be analysed separately.

Participants

We enrolled stable patients presenting with a primary diagnosis of acute atrial fibrillation of at least 3 h duration, in whom symptoms necessitated early management and for whom pharmacological or electrical cardioversion was an appropriate option. Specifically, the patients had a clear history of onset within 48 h of arrival at the emergency department, or onset within 7 days of arrival and adequately anticoagulated for at least 4 weeks (either with warfarin with international normalised ratio [INR] ≥2·0 or with novel oral anticoagulants), or onset within 7 days of arrival and no left atrial thrombus on transoesophageal echocardiography. Of note, we did not exclude patients with previous episodes of acute atrial fibrillation or with valvular heart disease if they were adequately anticoagulated. We excluded patients who were unable to give consent, had permanent atrial fibrillation, were deemed haemodynamically unstable and required immediate cardioversion (including patients with hypotension [systolic blood pressure <100 mm Hg], rapid ventricular pre-excitation, acute coronary syndrome, or pulmonary oedema), whose primary presentation was for another condition (eg, pneumonia, pulmonary embolism, sepsis), converted spontaneously before randomisation, or were previously enrolled in the study. We also excluded patients for some potential safety issues (appendix p 5). The electrophysiology cardiologist on the adjudication committee reviewed the initial electrocardiogram (ECG) to verify that the rhythm was in atrial fibrillation while masked to group assignment. All participants provided written informed consent and the protocol was approved by the research ethics board at each site (appendix pp 7–21).

Randomisation and masking

On-site research personnel determined allocation for each of the two protocols using an online electronic data capture system. The allocation sequence was computer-generated by an independent statistician using a randomly permuted block design of length 8, stratified by study site. This was a superiority trial with the two groups in Protocol 1 allocated 1:1 and stratified by study site. Allocation for Protocol 2 occurred 30 min after the drug infusion for patients who had not converted and was stratified by site and Protocol 1 allocation. Concealment of treatment allocation was assured using the password-protected electronic data capture system. Patients and research and emergency department staff were masked to group assignment. Masking of drug treatment to all research and emergency department staff was arranged by having local hospital pharmacies prepare premixed intravenous bags of either procainamide or placebo, which were placed in locked containers in the emergency department. These bags were semi-opaque and only identified by a numeric code. In discussions with research personnel, hospital staff were unable to identify the fluid in each bag.

See Online for appendix

Procedures

Treating physicians were encouraged to follow the Acute Atrial Fibrillation Management Guidelines (appendix p 6) to ensure standardised assessment, management, use of anticoagulation, and follow-up.[3,12] Patients allocated to the drug–shock group received a continuous infusion of intravenous procainamide at a dose of 15 mg/kg, in 500 mL of normal saline solution, given over 30 min (maximum dose 1500 mg). The infusion was stopped if the patient converted to sinus rhythm before the maximum dose. The infusion was discontinued if the corrected QT interval increased by more than 35%, the QRS interval exceeded 120 ms, or the patient's heart rate dropped below 60 beats per min. If the patient's systolic blood pressure dropped below 100 mm Hg, the infusion was interrupted for 15 min and an intravenous bolus of 250 mL normal saline was administered. If the patient's blood pressure returned to at least 100 mm Hg, the infusion was resumed; if not, the infusion was discontinued. Patients allocated to the shock-only group received a similar weight-based infusion of normal saline placebo over 30 min.

Patients who had not converted to sinus rhythm by 30 min after the infusion finished had electrical cardioversion. Patients were allocated to either the anteroposterior or anterolateral pad positions (figure 1) and received up to three consecutive biphasic waveform shocks. The first shock was set at 200 J but could be higher for subsequent shocks. Procedural sedation was provided by a second emergency physician using short-acting drugs as per local protocol. Electrical cardioversion was done with the local site's standard adhesive pads, using the same pad position for all three shocks, without crossover.

Outcomes

The primary outcome was conversion to and maintenance of sinus rhythm for at least 30 min at any time after

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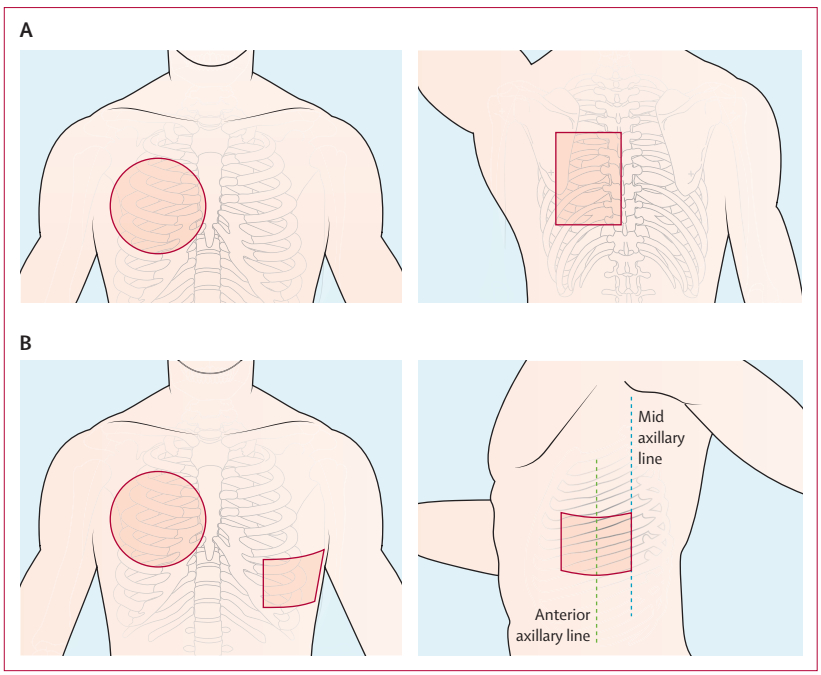

Figure 1: **Pad positions for Protocol 2**
(A) Anterposterior pad position with right infraclavicular and left infrascapular pad placement. (B) Anterolateral pad position with right infraclavicular and left anterior axillary line pad placement.

randomisation and up to a point immediately following three shocks. Patients who had not converted by the time three shocks had been delivered, or who reverted to atrial fibrillation during the 30 min following the shocks, were deemed not to have met the primary outcome criteria. We expected few patients to revert to atrial fibrillation during the 30-min observation period. Spontaneous conversion after random treatment assignment but before study interventions were deemed to have met the primary outcome criteria. The primary outcome was centrally assessed by review of all ECGs by the masked adjudication committee, which was comprised of two emergency physicians and one electrophysiology cardiologist.

Secondary outcomes evaluated during the emergency department visit were cardiac rhythm at disposition, length of stay in the emergency department, and adverse events. Patients were re-assessed in person by research personnel at the hospital at 14 days to determine cardiac rhythm (by ECG), recurrence of atrial fibrillation, return visits to the emergency department, stroke, and survival.

Statistical analysis

The primary analytical approach for Protocol 1 was by intention to treat. We also did a secondary modified intention-to-treat analysis that excluded patients who converted to sinus rhythm before the study infusion was started. The primary outcome, conversion to sinus rhythm, was compared between the drug–shock and shock-only groups using absolute difference between two proportions with 95% Wald confidence intervals, and statistical significance testing using a χ^2 test. Additionally, multiple logistic regression analysis was used to improve precision and control for potential confounding effects of variables possibly related to conversion (chosen a priori): age (continuous), sex, first or repeat episode, time from onset (continuous), history of heart failure. To reduce the risk of bias due to the large number of events, the logistic regression model was estimated using penalised likelihood with the Firth adjustment.[13] To account for the centre effect, site was included as a random effect and standard errors were computed using the Fay and Graubard bias-corrected sandwich covariance estimator.[14]

The secondary outcomes were evaluated according to data type: binary outcomes with χ^2 or Fisher's exact test, and continuous data by Student's *t* test. The independent data safety monitoring board at Western University (London, ON, Canada), reviewed any adverse events and enrolment, protocol adherence, data quality, and data completeness every 6 months. Because we compared two standards of care, we did not do formal interim outcome analyses. The following a-priori subgroup analyses were planned: first episode versus repeat episode; age at least 70 years versus younger than 70 years, duration of episode less than 12 h versus duration at least 12 h. Subgroup analyses were done by calculating absolute differences between two proportions and 95% Wald confidence intervals within subgroups, and by using the Breslow-Day test for homogeneity to determine statistical significance of differences across the subgroups.[15] Subgroup results were presented using forest plots. Fisher's exact test was used to produce p values for subgroups with fewer than five expected events.

The comparison of the anteroposterior and anterolateral pad positions (Protocol 2) was done using a modified intention-to-treat approach, excluding patients who did not receive electrical cardioversion. We used the Cochran-Mantel-Haenszel procedure to test the difference between the pad positions, controlling for the allocation of the patient in Protocol 1. We also tested for a potential interaction with Protocol 1 using the Breslow-Day test for homogeneity.

The sample size for Protocol 1 was determined to achieve 90% power to detect an absolute difference of 10% between the groups, assuming a control conversion rate of 85% for the shock-only group. This difference was determined by a poll of investigators as the minimum clinically important difference. A total sample size of 396 evaluable patients with atrial fibrillation (198 per group) was required using the unpooled Z test with continuity correction at a significance level of 5%. We estimated 70% power to show equivalence between the two pad positions in Protocol 2. Statistical analysis was done using SAS version 9.4. This study is registered at ClinicalTrials.gov, NCT01891058.

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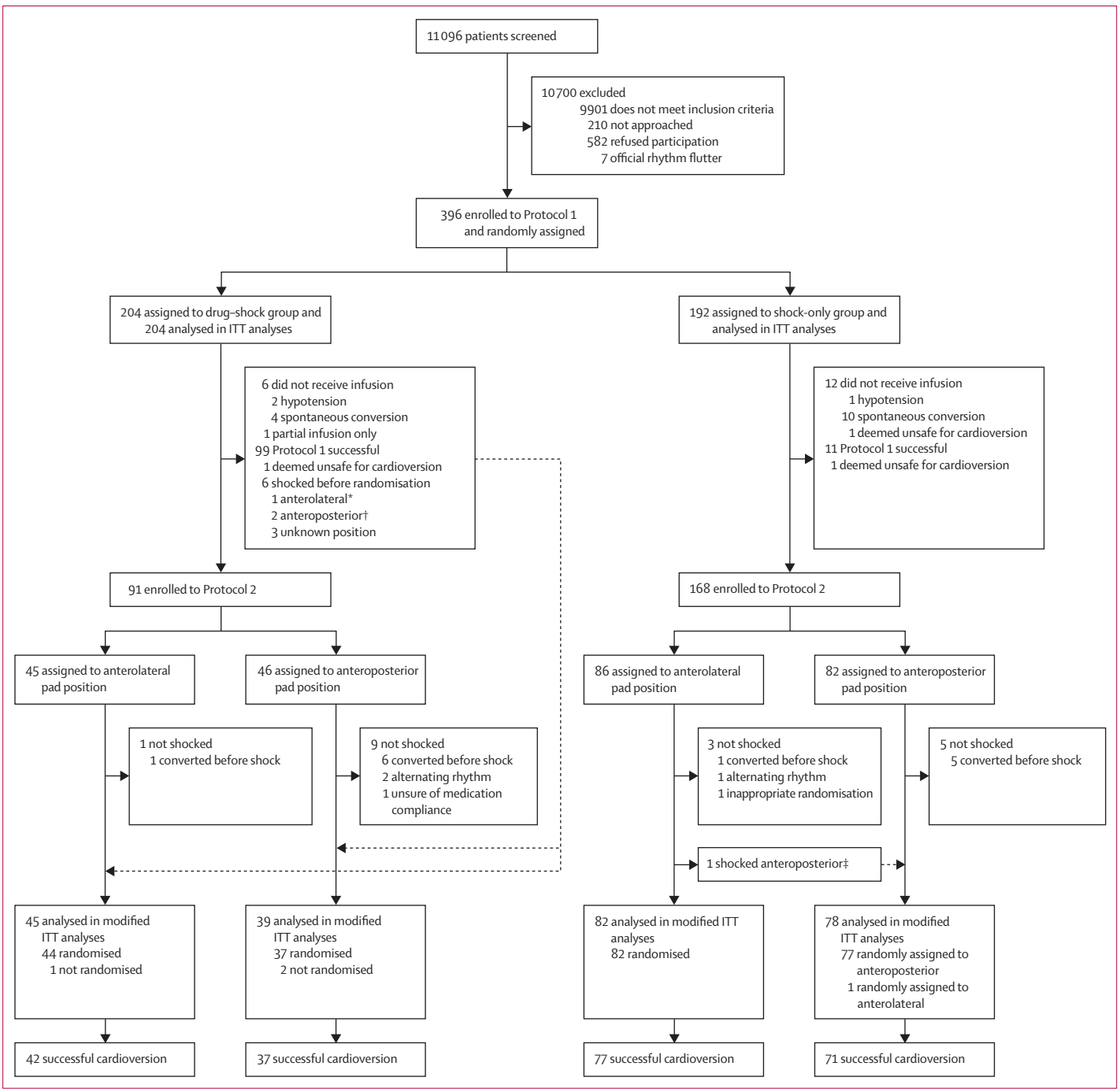

***Figure 2*: Trial profile**
ITT=intention to treat. *Patient included in anterolateral modified ITT analysis. †Patients included in anteroposterior modified ITT analysis. ‡Patient crossed over and included in anteroposterior modified ITT analysis.

Role of the funding source
The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Patients were enrolled at 11 different emergency departments from July 18, 2013, to Oct 17, 2018. Of 1188 eligible patients, 582 did not want to participate, 210 were not approached, and 396 were enrolled (figure 2). None were lost to follow-up for the primary outcome.

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	Drug–shock (n=204)	Shock-only (n=192)
Age and sex		
Age (mean, years)	60 (15·1)	60·1 (14·8)
Age range (years)	22–92	19–90
Sex (male)	134 (66%)	126 (66%)
Duration of arrhythmia		
Duration (mean h)	14·3 (20·6)	16·8 (25·8)
Range (h)	2–144	2–168
<12	130 (64%)	122 (64%)
12–48	63 (31%)	58 (30%)
>48	11 (5%)	12 (6%)
Main presenting symptom		
Palpitations	185 (91%)	162 (84%)
Chest pain	9 (4%)	21 (11%)
Shortness of breath	5 (3%)	6 (3%)
Other	5 (3%)	3 (2%)
Initial vital signs		
Heart rate (mean, beats per min)	114·4 (28·8)	115·8 (30·1)
Systolic blood pressure (mean, mm Hg)	130·8 (20·5)	133·8 (21·7)
Median Canadian triage and acuity scale level	2 (2–3)	2 (2–3)
Previous atrial fibrillation	139 (68%)	131 (68%)
Electrical cardioversion	85 (42%)	80 (42%)
Pharmacological cardioversion	34 (17%)	40 (21%)
Ablation	25 (12%)	20 (10%)
$CHADS_2$ criteria		
Hypertension	75 (37%)	67 (35%)
Age ≥75 years	29 (14%)	34 (18%)
Type 1 diabetes	18 (9%)	11 (6%)
Stroke or transient ischaemic attack	15 (7%)	13 (7%)
Congestive heart failure	6 (3%)	5 (3%)
$CHADS_2$ score		
0	65 (32%)	57 (30%)
1	45 (22%)	54 (28%)
≥2	94 (46%)	81 (42%)
Other medical history		
Coronary artery disease	16 (8%)	21 (11%)
Valvular heart disease	17 (8%)	14 (7%)
Pacemaker or implantable cardioverter-defibrillator	3 (2%)	7 (4%)
Chronic obstructive pulmonary disease or asthma	19 (9%)	14 (7%)

(Table 1 continues in next column)

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	Drug–shock (n=204)	Shock-only (n=192)
Current home medications		
Anticoagulants	66 (32%)	66 (34%)
Novel anticoagulants	51 (25%)	52 (27%)
Warfarin	15 (7%)	14 (7%)
Antiarrhythmics	13 (6%)	13 (7%)
Amiodarone	9 (4%)	9 (5%)
Propafenone	3 (2%)	0 (0%)
Flecainide	1 (1%)	1 (1%)
Sotalol	0 (0%)	1 (1%)
Antiplatelet agents	59 (29%)	48 (25%)
Aspirin	55 (27%)	46 (24%)
Clopidogrel	4 (2%)	2 (1%)
Cardiac medications	101 (50%)	83 (43%)
β blocker	75 (37%)	61 (32%)
Calcium channel blocker	26 (13%)	22 (12%)
Investigations		
Initial ECG-calculated heart rate (mean, beats per min)	119·4 (27·9)	118·5 (26·9)
Heart rate range (beats per min)	52–199	60–185
Chest radiograph shows congestive heart failure	2 (1%)	1 (1%)
International normalised ratio (mean)*	1·2 (0·5)	1·3 (0·6)
Troponin above 99th percentile†	23 (11%)	37 (19%)
Thyroid stimulating hormone below reference value‡	4 (2%)	1 (1%)
Transoesophageal echocardiography	12 (6%)	8 (4%)
Left atrial clot	0 (0%)	0 (0%)
Other treatments in the emergency department		
Heart rate control agents	33 (16%)	27 (14%)
Antithrombotic therapy	19 (9%)	15 (8%)
Aspirin	8 (4%)	9 (5%)
Heparin	9 (4%)	3 (2%)
Warfarin	2 (1%)	5 (3%)
Adenosine	2 (1%)	0 (0%)
Other conditions identified while in the emergency department		
Congestive heart failure	0 (0%)	2 (1%)
Acute coronary syndrome	1 (1%)	1 (1%)

Data are mean SD, range, n (%), or median (IQR). ECG=electrocardiogram. *Patients with available data (n=138:127). †Patients with available data (n=175:166). ‡Patients with available data (n=86:73).

Table 1: **Characteristics and emergency department management for 396 patients in the RAFF-2 trial**

Patients in the drug–shock (n=204) and shock-only (n=192) groups were well balanced for demographics, clinical characteristics, and investigation results (table 1; appendix p 1). The mean age of the patients was 60 years, 260 (66%) patients were men, and the patients presented within a mean of 10 h from onset. 270 (68%) patients had previous episodes of atrial fibrillation, and the initial mean ECG heart rate was 119 beats per min.

Table 2 shows the outcomes for the primary intention-to-treat analyses. Conversion to sinus rhythm occurred in 196 (96%) patients in the drug–shock group, compared with 176 (92%) in the shock-only group (absolute difference 4%; 95% CI 0–9; p=0·07). Median time to conversion from the start of the infusion in the drug–shock group was 23 min (IQR 14–35). The multivariable adjusted odds ratio for conversion in the drug–shock group was 2·16 (95% CI 0·88–5·28). 18 patients did not receive the study intervention, primarily because of spontaneous conversion, and were removed from the secondary modified intention-to-treat

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	Drug–shock (n=204)	Shock-only (n=192)	Absolute difference or odds ratio (95% CI)	p value*
Intention-to-treat unadjusted analysis				
Converted to normal sinus rhythm	196 (96%)	176 (92%)	4% (0 to 9)	0·066
Converted by infusion	106 (52%)	18 (9%)	..	..
Converted by electrical cardioversion	82 (40%)	148 (77%)	..	..
Converted spontaneously	8 (3·9%)	10 (5%)	..	..
Discharged home	198 (97%)	183 (95%)	2% (–2 to 6)	0·36
Total emergency department length of stay (mean, h [SD])	7·1 (5·5)	7·6 (5·4)	0·4 (–0·6 to 1·5)	0·42†
Total patients on anticoagulants at discharge	91 (45%)	87 (45%)	1% (–9 to 11)	0·89
Intention-to-treat adjusted analysis				
Odds of conversion by drug–shock group (primary outcome)	..	..	2·16 (0·88 to 5·28)	0·091‡
Modified intention-to-treat analysis§¶				
Converted to normal sinus rhythm	192 (97·0%)	166 (92%)	5% (0 to 9)	0·040
Discharged home from the emergency department	198 (97%)	183 (95%)	2% (–5 to 8)	0·60
Total emergency department length of stay (mean, h [SD])	7·1 (5·5)	7·6 (5·4)	0·4 (–0·6 to 1·5)	0·42
Total patients on anticoagulants at discharge	91 (45%)	87 (45%)	1% (–9 to 11)	0·89
Details of Protocol 1				
Conversion after infusion	106 (52%)	18 (9%)	..	..
Time from arrival to first random treatment assignment (median, min [IQR])	143·5 (107·5–204·0)	133·5 (94·0–210·0)	..	..
Time from random treatment assignment to infusion started (median, min [IQR])	16·5 (10·0–25·0)	15·0 (9·0–23·5)	..	..
Time from start of infusion to conversion (median, min [IQR])	23·0 (14·0–35·0)	57·5 (20·0–81·0)	..	..
Details of Protocol 2‖				
Shock attempted	84 (89%)	160 (95%)	..	..
Successful conversion**	82 (98%)	148 (92%)	..	..
Time between stopping infusion and second random treatment assignment (median, min [IQR])	39 (33–49)	37 (32–46)	..	..
Time between second random treatment assignment and first shock	22·0 (16·0–33·0)	22·0 (14·5–41·0)	..	..

Data are n (%) unless otherwise specified. *χ^2 test unless otherwise noted. †t test. ‡p value from random effects multiple logistic regression analysis; adjusted for age, sex, first or repeat episode, time from onset, history of heart failure, and centre. §18 patients were excluded: cardiology stopped the study treatment (one patient), drug not given because of hypotension after random assignment (three), and spontaneous conversion before infusion (14). ¶Patients with available data (n=198:180). ‖ Patients with available data (n=94:168). **Patients with available data (n=87:160).

Table 2: **Patient outcomes, study interventions, and disposition for 396 patients in the RAFF-2 trial**

analysis. In this secondary analysis, the proportion of patients with conversion to sinus rhythm in the drug–shock group was 192 (97%) versus 166 (92%) in the shock-only group (absolute difference 5% [95% CI 0–9]; p=0·04). Almost all patients were discharged home (198 (97%) in the drug–shock group *vs* 183 (95%) in the shock-only group; p=0·60).

Comparing the anterolateral and anteroposterior pad positions in Protocol 2 (n=244), we found similar proportions of patients converting to sinus rhythm in both groups (119 (94%) of 127 in the anterolateral group *vs* 108 (92%) of 117 in the anteroposterior group; relative difference 1·01; 95% CI 0·95–1·09; p=0·68) with no evidence of statistical interaction with Protocol 1 (table 3; appendix p 3). The median number of shocks required in each group was 1 (IQR 1 to 1).

Adverse events during the infusion were more common in the drug–shock group but most were transient hypotension during the infusion (table 4). Electrical cardioversion was associated with adverse events in 23 (9%) of 244 patients. One patient in the shock-only-group had a cardiac arrest when the electrical cardioversion was done without appropriate synchronisation; the patient survived. Overall, no patients in either group died in the emergency department or had a subsequent stroke.

Patients were followed up for 14 days with similar outcomes in both groups (table 5). No strokes occurred and the one death (due to cancer) was not related to atrial fibrillation. Of the 306 (77%) of 396 patients who returned for an ECG at day 14, 290 (95%) were in sinus rhythm. Within 14 days after treatment, 42 (11%) patients returned to the emergency department because of recurrence of atrial fibrillation, 13 (3%) had cardioversion, and 8 (2%) required hospital admission.

We did a-priori subgroup analyses (figure 3) and found that in the drug–shock group, a significantly higher proportion of patients presenting with a first episode of atrial fibrillation converted to sinus rhythm than did patients who had had a previous episode of atrial

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	Anterolateral (n=127)	Anteroposterior (n=117)	Relative risk (95% CI)	p value	p value for interaction
Conversion to sinus rhythm					
Drug–shock	42 of 45 (93%)	37 of 39 (95%)	0·98 (0·88–1·09)	1·00*	·
Shock-only	77 of 82 (94%)	71 of 78 (91%)	1·03 (0·94–1·13)	0·49†	··
Pooled across both groups	119 of 127 (94%)	108 of 117 (92%)	1·01 (0·95–1·09)	0·68‡	0·53§
Number of shocks¶					
Median (IQR)	1 (1–1)	1 (1–1)	··	0·14‖	··
1 shock	112 (88%)	95 (81%)	··	0·56**	··
2–3 shocks††	15 (12%)	22 (19%)	··	··	··
Adverse events					
Drug–shock	5 of 45 (11%)	1 of 39 (3%)	4·33 (0·53–35·52)	0·21*	··
Shock only	7 of 82 (9%)	10 of 78 (13%)	0·66 (0·27–1·66)	0·38†	··
Pooled across both groups	12 of 127 (10%)	11 of 117 (10%)	1·01 (0·46–2·22)	0·97‡	0·08§

*Fisher's exact test. †χ^2 test. ‡Cochran-Mantel-Haenszel test. §Breslow-Day test for homogeneity. ¶Patients with available data (n=127:117). ‖Wilcoxon test. **No difference in number of shocks between pad position groups. ††No patients had more than three shocks.

Table 3: **Results of the pad position protocol**

	Drug–shock (n=204)	Shock-only (n=192)
Infusion		
Any adverse event during or after infusion*	53 (26%)	5 (3%)
Infusion interrupted (any cause)	10 (5%)	2 (1%)
Infusion discontinued (any cause)	20 (10%)	2 (1%)
Urgent electrical cardioversion	5 (3%)	0 (0%)
Hypotension (systolic blood pressure <90 mm Hg)	38 (19%)	4 (2%)
Infusion interrupted because of hypotension	8 (4%)	2 (1%)
Infusion discontinued because of hypotension	17 (8%)	2 (1%)
Infusion interrupted for other reasons	2 (1%)	0 (0%)
Infusion discontinued for other reasons	3 (2%)	0 (0%)
Electrical cardioversion before random treatment assignment	5 (3%)	0 (0%)
Bradycardia (heart rate <50 beats per min)	2 (1%)	0 (0%)
Ventricular tachyarrhythmia	0 (0%)	1 (1%)
Tachyarrhythmia	1 (1%)	0 (0%)
QRS widening (≥120)	6 (3%)	0 (0%)
QT lengthening (>35%)	3 (2%)	1 (1%)
Sinus pause	1 (1%)	1 (1%)
Accelerated heart rate >200 beats per min	1 (1%)	0 (0%)
Transient paraesthesia	1 (1%)	0 (0%)
Multifocal premature ventricular contractions	1 (1%)	0 (0%)
Nausea	2 (1%)	0 (0%)
Dizziness	3 (2%)	0 (0%)
Cardioversion		
Any adverse events during or after electrical cardioversion†‡	6 (7%)	17 (11%)
Cardiac arrest during or after electrical cardioversion	0 (0%)	1 (1%)
Hypoxia during or after electrical cardioversion	1 (1%)	3 (2%)
Airway manoeuvres applied during or after electrocardioversion	6 (7%)	17 (11%)

Data are n (%) unless otherwise specified. Patients might have had more than one event. *p<0·0001 †Patients who had electrical cardioversion (n=266 [99:167]). ‡p=0·34.

Table 4: **Adverse events while in the emergency department**

fibrillation (Fisher's exact p value=0·02). We also found that in the drug–shock group, a significantly higher proportion of patients younger than 70 years converted to sinus rhythm than did patients aged 70 years or older (χ^2 p value=0·01).

Discussion

This large, randomised, blinded clinical trial found no significant difference between the strategy of attempting chemical cardioversion first and a strategy of proceeding directly to electrical cardioversion for patients with acute atrial fibrillation in the emergency department. Both the drug–shock and shock-only strategies were highly effective in safely and quickly returning patients to normal sinus rhythm. Almost all patients were discharged home from the emergency department, usually within a few hours of cardioversion and, thus, avoided the need to return to the hospital for follow-up. We administered procainamide more quickly (over 30 min) than in previous studies and used a weight-based dosing (15 mg/kg). Procainamide converted half the patients in a median time of 23 min, thereby preventing the need for sedation and electrical cardioversion. The drug–shock strategy was found to be more effective for patients with a first episode of atrial fibrillation and for patients younger than 70 years than it was for other patients. Although the drug–shock group had more adverse events, most were transient hypotension, and none were serious. After 14 days, no patients had had a stroke, one had died because of an unrelated condition, and 95% were still in sinus rhythm. Repeat presentations to the emergency department or hospital admissions were uncommon. Although both drug–shock and shock-only approaches were highly effective and safe, we believe that initial rhythm control with procainamide has the advantage of avoiding resource intensive procedural sedation required for electrical cardioversion.

A trial by Pluymaekers and colleagues[16] compared two approaches to early rhythm control: same day cardioversion and next day cardioversion. Both chemical and electrical cardioversion strategies were used, but the two were not compared. Unfortunately, most hospitals do not have the capability to have patients seen by a cardiologist for cardioversion within 24 h, 7 days a week. We believe that same-day cardioversion is more efficient for both the patient and the hospital. Some observational studies have confirmed the effectiveness of early rhythm control but without distinguishing between the value of pharmacological and electrical cardioversion.[2,17–19] Other emergency department studies of rhythm control for acute atrial fibrillation have been small and have not compared pharmacological with electrical cardioversion.[20–24]

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	Drug–shock (n=204)	Shock-only (n=192)
Death*	1 (1%)	0 (0%)
14-day follow-up visit made (total)	185 (91%)	182 (95%)
14-day follow-up visit made in person	148 (73%)	158 (82%)
14-day follow-up visit made by telephone	37 (18%)	24 (13%)
Electrocardiogram done at day 14	148 (73%)	158 (82%)
Heart rate (mean beats per minute)†	64·5 (13·7)	65·4 (14·0)
Normal sinus rhythm‡	141 (95%)	149 (95%)
Atrial fibrillation‡	6 (4%)	5 (3%)
Atrial flutter‡	1 (1%)	3 (2%)
Return emergency department visit (total)	24 (12%)	31 (16%)
Return emergency department visit related to atrial fibrillation or atrial flutter	21 (10%)	21 (11%)
Outpatient visits (total)	66 (32%)	68 (35%)
Cardiology outpatient visits	26 (13%)	30 (16%)
Internal medicine outpatient visits	2 (1%)	4 (2%)
Family physician outpatient visits	42 (21%)	43 (22%)
Hospital admission (total)	4 (2%)	4 (2%)
Hospital admission related to atrial fibrillation or atrial flutter	3 (2%)	3 (2%)
Electrical cardioversion (total)	8 (4%)	5 (3%)
Time until electrical cardioversion after leaving the emergency department (mean days)	4·3 (3·5)	6·6 (6·3)
Electrical cardioversion in emergency department	8 (4%)	4 (2%)
Electrical cardioversion in clinic	0 (0%)	1 (1%)
Transthoracic echocardiography	15 (7%)	21 (11%)

Data are n (%) or mean (SD). *No deaths were related to stroke or atrial fibrillation. †Patients with available data (n=141:154). ‡Patients with available data (n=148:157).

Table 5: **14-day follow-up for 396 patients with recent-onset atrial fibrillation**

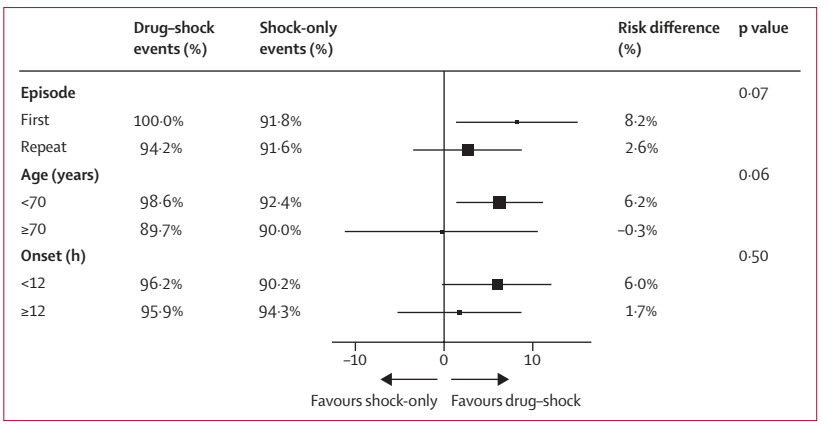

Figure 3: **Forest plot**
Events refers to conversions to normal sinus rhythm. p values are for the Breslow-Day test for homogeneity of the odds ratios.

Previous studies have confirmed the effectiveness and safety of procainamide for acute atrial fibrillation. Case series of procainamide for this condition, with between 11 and 180 patients, found the proportion of patients converting to be between 50% and 91%.[2,25–28] Several randomised trials involving intravenous procainamide for recent-onset atrial fibrillation found the proportion of patients converting to be between 63% and 83%.[29–33] We previously described our use of procainamide in a series of 628 patients with acute atrial fibrillation in the emergency department (aged 19–92 years), with 60% of patients converting overall.[17,34]

We identified five randomised trials of pad position using contemporary biphasic devices, although most patients in these trials had persistent atrial fibrillation, not acute atrial fibrillation.[35–39] Of these European studies, only one used the right infraclavicular anteroposterior position commonly used in Canada and the USA, and only one started shocks as high as 150 J. Three studies showed no difference in conversion between the two pad positions, and two showed higher proportions of patients converting for the anterolateral position.[40]

We did not directly compare lengths of stay in the emergency department because the need for masking required the shock-only group to have a 30-min placebo infusion followed by a 30-min observation period. Furthermore, assembling the personnel and monitoring space necessary for procedural sedation can lead to variable and increasing delays in most emergency departments because of crowding and competing clinical priorities. Nevertheless, rhythm control, once started, was quite rapid, with a median time of 23 min for patients responding to procainamide, and immediate response for patients receiving electrical cardioversion. Although only 367 (93%) of 396 patients were reached on day 14, all patients were available for the primary outcome assessment. We acknowledge that we missed eligible patients because research staff could not always be present during off hours. We chose to study intravenous procainamide because that is the most commonly used drug for acute atrial fibrillation in Canada and because some European preparations were not available in Canada (eg, intravenous flecainide and propafenone). Although the 14-day follow-up could have missed subsequent thromboembolic events, our ongoing 6-month and 12-month follow-ups have not shown this to be the case. Finally, many patients refused participation, most often because they had a strong preference for either pharmacological or electrical cardioversion.

The most important finding from this study is that either approach to immediate rhythm control in the emergency department leads to a very high proportion of patients being discharged in sinus rhythm without serious adverse events. Patients can be rapidly cardioverted in the emergency department, resolving their acute symptoms and enabling discharge home. This avoids unnecessary hospital admission or next-day re-evaluation by cardiologists. This obviates the need for anticoagulation in

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low-risk patients or the need for medication prescriptions for heart rate control. Patients can quickly return to normal activities and avoid protracted stays in crowded emergency departments.

We believe that the drug–shock approach has an important advantage over the shock-only approach: a procainamide infusion leads to rapid conversion in more than 50% of patients. This approach allows physicians to attend to other patients during the procainamide infusion, and frequently avoids the need for procedural sedation, which might lead to serious adverse events. Sedation also requires explicit consent and the continuous attendance of additional health-care providers. Nevertheless, the choice between pharmacological and electrical cardioversion should be a shared decision between the patient and the physician. Physicians in other countries might consider using alternative drugs, such as intravenous flecainide or propafenone.

Stroke prevention is an essential element in the management of acute atrial fibrillation in the emergency department. We did not administer antithrombotic therapy to patients who presented less than 48 h from onset or who were already fully anticoagulated. The 48-h rule has been recently questioned because of Finnish registry studies by Airaksinen and colleagues,[41] who noted an overall 0·7% occurrence of thromboembolic events in non-anticoagulated patients.[42] The strokes were found in patients with CHA_2DS_2-VASc score risk criteria (heart failure, hypertension, age ≥75 years, diabetes, stroke) and who presented more than 12 h after onset. Consequently, Canadian guidelines now suggest avoiding immediate cardioversion in non-anticoagulated patients who have had a recent stroke or transient ischaemic attack, or who present after 12 h and have a $CHADS_2$ score of 2 or more.[7] We strongly advocate that emergency department physicians should prescribe oral anticoagulants to all high risk patients (ie, men with a CHA_2DS_2-VASc score of ≥1, women with a CHA_2DS_2-VASc score ≥2, or anyone who is CHADS-65 positive) on discharge.[7,43–45] Future studies are needed to better define who can be safely cardioverted without need for anticoagulation but will require very large samples to identify rare thromboembolic events.

Regarding pad placement for electrical cardioversion, both anterolateral and anteroposterior positions are highly effective. If initial attempts fail, many suggest switching to the other position and applying firm pressure to the pads to reduce transthoracic impedance.

This clinical trial found no significant difference between a drug–shock and a shock-only approach to treat acute atrial fibrillation in the emergency department; both approaches were highly effective, rapid, and safe in restoring sinus rhythm. The drug–shock strategy was shown to be more effective for patients with first episodes of atrial fibrillation and for patients younger than 70 years than for other patients. The drug infusion worked for about half of patients and avoided the resource intensive procedural sedation required for electrical cardioversion. We also found no significant difference between the anterolateral and anteroposterior pad positions for electrical cardioversion. Immediate rhythm control for patients in the emergency department with acute atrial fibrillation leads to excellent outcomes.

Contributors

IGS and JJP conceived the idea, prepared the manuscript, and secured research funding. CMC managed the budget, contracts, and personnel. JB coordinated the study and supervised data collection. JB, CS, and EB supervised the recruitment of patients and management of data. MT and M-JN did the statistical analyses. All authors supervised the trial and data collection or drafted the manuscript and contributed to its revision, and all approved the final version. IGS is guarantor.

Declaration of interests

We declare no competing interests.

Data sharing

We do not have consent from patients or hospital research ethics boards to share individual case data. We will, however, make summary data available to corresponding investigators.

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