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Optimizing Energy Delivery in Cardioversion: A Randomized PROTOCOLENERGYTrial of 2 Different Algorithms in Patients With Atrial Fibrillation

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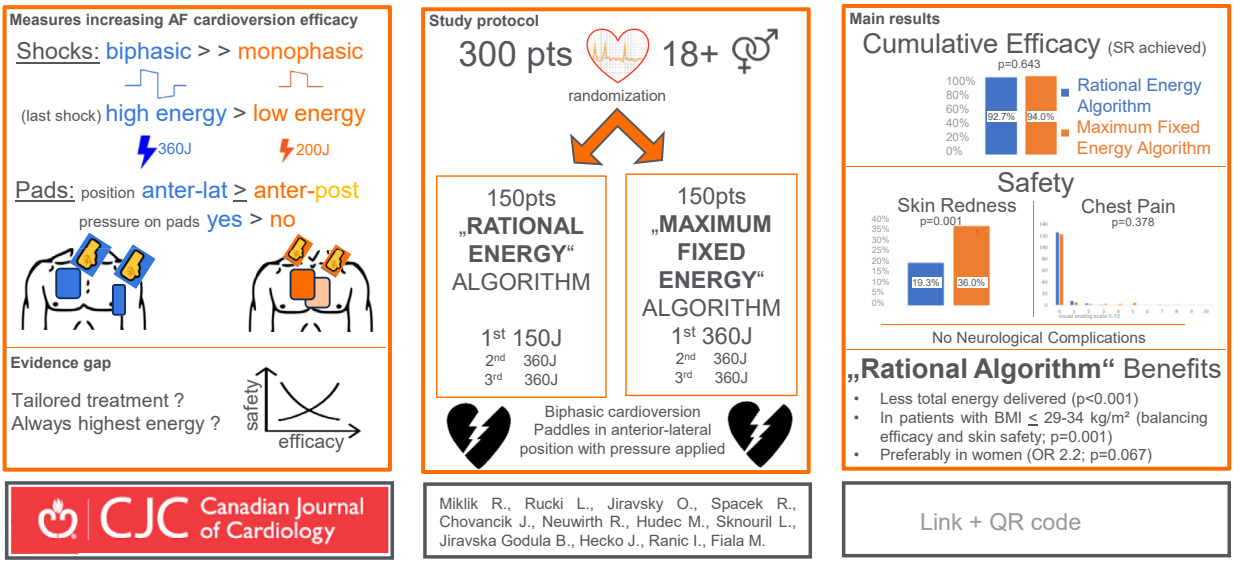
Optimizing Energy Delivery in Cardioversion: A Randomised PROTOCOLENERGY Trial of Two Different Algorithms in Patients with Atrial Fibrillation

In AF cardioversion, both energy protocols (150J, 360J, 360J vs 3x360J) showed similar high cumulative efficacy.
An initial 150J shock proved beneficial in patients with BMI ≤ 29-34 kg/m² and women due to fewer skin complications.



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ABSTRACT

Background: The optimal energy protocol for direct current cardioversion of atrial fibrillation remains uncertain. The Rational vs Maximum Fixed Energy (PROTOCOLENERGY) randomized trial compared a stepwise escalating energy algorithm (RaA, 150 J, 360 J, and 360 J) with a maximum fixed energy algorithm (MfA, 3 x 360 J).

Methods: In a 1:1 randomized trial, 300 patients with atrial fibrillation received biphasic discharges via hand-held paddles in the anterolateral position. Primary endpoints were sinus rhythm at 1 minute and neurologic complications at 2 hours; secondary endpoints included sinus rhythm at 2 hours, skin changes and chest discomfort at 24 hours.

Results: Sinus rhythm at 1 minute was achieved in 92.7% of RaA and 94.0% of MfA patients ($P = 0.643$) and maintained at 2 hours in 91.3% of both groups. There were no neurologic complications. The protocols differed significantly after the first shock (72.7% in RaA vs 83.3% in MfA; $P = 0.026$) but equalized after subsequent maximum energy shocks. Fewer RaA patients experienced skin redness compared with MfA patients (19.3% vs 36.0%, $P = 0.001$), which was attributed to the lower initial 150-J shock and total energy delivered ($r = 0.243$, $P < 0.0001$). Chest discomfort at 24 hours was not different between groups ($P = 0.378$). In multivariate analysis, lower body mass index ($P < 0.001$, cutoff 29 to 34 kg/m^2) was associated with cardioversion success after the initial 150-J shock.

Conclusions: Both protocols showed similar high cumulative efficacy, but RaA with the initial 150-J shock proved to be beneficial in patients with body mass index less than 29 to 34 kg/m^2 because of fewer skin complications.

Clinical Trial Registration No: NCT05148923

RÉSUMÉ

Contexte : Le protocole énergétique optimal pour la cardioversion électrique de la fibrillation auriculaire reste incertain. L'essai randomisé «Rational vs Maximum Fixed Energy» (PROTOCOLENERGY) a comparé un algorithme d'énergie progressif par étape (APE, 150 J, 360 J et 360 J) à un algorithme d'énergie maximale fixe (AEMf, 3 x 360 J).

Méthodes : Dans un essai randomisé 1:1, 300 patients atteints de fibrillation auriculaire ont reçu des décharges biphasiques à l'aide de palettes tenues à la main en position antérolatérale. Les principaux critères d'évaluation étaient le rythme sinusal à 1 minute et les complications neurologiques à 2 heures; les critères d'évaluation secondaires étaient le rythme sinusal à 2 heures, les changements cutanés et l'inconfort thoracique à 24 heures.

Résultats : Le rythme sinusal à 1 minute a été atteint pour 92,7 % des patients avec APE et 94,0 % des patients avec AEMf ($p = 0{,}643$) et maintenu à 2 heures chez 91,3 % pour les deux groupes. Il n'y a pas eu de complications neurologiques. Les protocoles différaient de manière significative après le premier choc (72,7 % dans le groupe avec APE contre 83,3 % dans le groupe avec AEMf; $p = 0{,}026$) mais s'égalisaient après les chocs ultérieurs avec énergie maximale. Les patients APE ont été moins nombreux à présenter des rougeurs cutanées que les patients AEMf (19,3 % contre 36,0 %, $p = 0{,}001$), ce qui a été attribué au choc initial plus faible de 150-J et à l'énergie totale délivrée ($r = 0{,}243$, $p < 0{,}0001$). La gêne thoracique à 24 heures n'était pas différente entre les groupes ($p = 0{,}378$). Dans l'analyse multivariée, un indice de masse corporelle plus faible ($p < 0{,}001$, seuil de 29 à 34 kg/m^2) a été associé au succès de la cardioversion après le choc initial de 150-J.

Conclusions : Les deux protocoles ont montré une efficacité cumulative élevée similaire, mais le protocole APE avec un choc initial de 150-J s'est avéré bénéfique chez les patients dont l'indice de masse corporelle est inférieur à l'intervalle 29 à 34 kg/m^2 en raison d'un nombre moins important de complications cutanées.

Enregistrement de l'essai clinique : NCT05148923

Direct current cardioversion (DCCV) is an established procedure that is commonly used in the acute and elective management of patients with atrial fibrillation (AF). For years, many investigators have searched for the optimal strategy/protocol in studies using predominantly monophasic discharges, in terms of which type of waveform to use,[1,2] how and under what pressure to place the pads/handheld paddles,[3,4] which energy to choose for the first and subsequent discharges,[5-7] or whether to use periprocedural antiarrhythmic drug support.[8] In addition, many positive and negative clinical (eg, body mass index [BMI], age, sex, comorbidities) or structural (echocardiographic parameters) predictors of the short-term success of DCCV have been identified.[9-15] This suggests that the correct indication for DCCV and its optimal performance are essential for the restoration of sinus rhythm (SR).

The current standard for DCCV is the use of biphasic shock waves, which have been shown to be more effective and safer than monophasic shock waves.[2] A recent study by Schmidt et al.[16] showed—in a randomized fashion—that anterior-lateral electrode positioning was more effective than anterior-posterior electrode positioning for biphasic cardioversion. The study was published in 2021 and therefore could not have been included in the 2020 European Society of Cardiology guidelines, which still recommend anterior-posterior electrode positioning.[17]

With regard to the choice of self-adhesive electrodes vs hand-held electrodes with manual pressure and energy of the first and subsequent discharges, neither the aforementioned guidelines nor other international guidelines provide clear recommendations.[18-20] A study by Ramirez et al. demonstrated higher discharge efficiency using hand paddles with an applied external force of 80N. This approach was able to reduce the transthoracic impedance significantly compared with discharges performed with adhesive electrodes without pressure.[21] This conclusion suggests that the use of hand

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See page 2140 for disclosure information.

paddles with manual pressure may be more advantageous than the use of adhesive electrodes.

It has been repeatedly confirmed that even high-energy discharges above 200 to 300 J do not lead to an increase in cardiac troponins as a marker of myocardial damage.[22,23] This may indicate the routine use of high-energy discharges from the first discharge. On the other hand, elective cardioversions are—in most cases—outpatient procedures, and it is certainly desirable that the procedure is performed without complications: that is, without skin redness or burns after the discharges, without residual pain on the sternum, and especially without the need for hospitalization because of postdischarge arrhythmias. Previous experience at our cardiac centre suggests that physicians performing cardioversion often unnecessarily choose high-energy discharges, especially in patients with obesity and those on long-term amiodarone. The rationality of this approach was not confirmed in a multivariate analysis.[24]

Based on these facts and our experience, we designed and conducted a study to compare the efficacy and safety of 2 different cardioversion protocols using biphasic discharges delivered by manually controlled paddles in the anterior-lateral position. The aim of the study was to determine whether the use of a lower initial discharge energy is clinically justified in terms of patient safety and comfort, without compromising the overall clinical efficacy of subsequent energy escalation, compared with a protocol with a fixed maximum discharge energy.

Material and Methods

Study design

The Rational vs Maximum Fixed Energy (PROTOCOLENERGY) trial was an interventional, randomized, investigator-initiated, monocentric, parallel-assignment study conducted at the Agel Trinec-Podlesi Cardiocentre, Czech Republic. The study was registered on ClinicalTrials.gov (NCT05148923) and started on January 1, 2022, with the last patient randomized on December 22, 2022. Inclusion criteria were as follows: subjects older than 18 years with a diagnosis of AF, clinically indicated for elective outpatient DCCV; established therapeutic anticoagulation for at least 3 weeks before DCCV or performed esophageal echocardiography excluding the presence of intracardiac thrombus; and provided verbal and written informed consent to participate in the study. Exclusion criteria were identical to the known contraindications to elective cardioversion. Patients with implanted pacemakers or defibrillators were not excluded. When designing the study, we followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines[25] (the CONSORT checklist is available in Supplemental Table S1).The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee.

Defibrillation waveform characteristics

In the PROTOCOLENERGY trial, we used biphasic truncated exponential shocks with impedance compensation delivered with the Mindray BeneHeart D3 defibrillator (Shenzhen Mindray Bio-Medical Electronics Co, Ltd, Shenzhen, China). This technology adjusts the peak current in response to the patient's chest impedance, thus customizing the shock to achieve an optimal current distribution across the myocardium without the need for manual adjustment by the operator. In short, the defibrillator charges to a high voltage level, which is then truncated at a predetermined time. The leading-edge voltage varies depending on the impedance of the chest cavity it encounters. For example, for a 360 J shock, the leading-edge voltage ranges from approximately 1500 V to 2000 V across the different impedances from 25 Ω to 175 Ω. The duration of each phase of the biphasic waveform is impedance dependent, with the first phase being longer than the second (5.1-12.5 ms and 3.2-8.6 ms, respectively, Supplemental Fig. S1). Finally, the defibrillator automatically adjusts the energy delivered based on real-time impedance measurements to maximize defibrillation success while minimizing potential tissue damage. As the transthoracic impedance increases, the actual energy delivered decreases slightly (ie, for a 360-J shock: 50 Ω-360 J, 75 Ω-349 J, 100 Ω-332 J).[26]

Randomization and treatment

Patients were admitted to a 1-day cardiology outpatient clinic. Study criteria were reviewed, and informed consent was obtained. Relevant demographic and clinical data were collected from patients and available medical records. Because of the large variability in echo data available at the time of cardioversion from referring physicians, only left atrial diameter and left ventricular ejection fraction (LVEF) were recorded. Randomization was performed in blocks of 20 using computer-generated sequences. Allocation concealment was ensured using sequentially numbered opaque sealed envelopes. Participants were assigned to 1 of 2 study protocols: rational energy algorithm (RaA), 150-J initial shock followed by maximum 360 J and 360 J or maximum fixed energy algorithm (MfA): maximum 360-J initial shock followed by 360 J and 360 J.

We used hand-held paddles with manual pressure placed in the anterior-lateral configuration. The setting was as follows: With the patient in the supine position on the bed, the attending physician leaned over the patient's chest and placed the lefthand paddle in the right inferoclavicular region and the righthand paddle in the left axial line near the suggested cardiac apex, avoiding the left breast nipple. When the device was charged, the physician applied a force equivalent to a "push-up" to the paddles[27] covered with echocardiographic gel, waited for maximum expiration, and fired the shock.

Subsequent second and possibly third shocks were applied in a smooth sequence after the previous one if AF was still present on the monitor, or AF recurred within 1 minute after the first or second shock if SR had been temporarily restored. The physician administering the shocks was not blinded to the allocated study arm, but the patients and a physician assessing skin changes were blinded. All subjects were sedated with 1 mg midazolam (2 mg for patients weighing more than 90 kg) and 0.15 mg/kg etomidate. After the procedure, patients were monitored for 2 hours and then discharged home if no complications occurred. All patients were contacted by telephone the following day for safety reasons and to collect secondary endpoints.

Endpoints and analyses

The primary efficacy endpoint was the presence of SR 1 minute after DCCV, and the primary safety endpoint was the incidence of neurologic adverse events 2 hours after DCCV.

The secondary efficacy endpoint was the presence of SR 2 hours after DCCV, and the secondary safety endpoints were the incidence of skin changes (no change, redness, burn) 2 hours after DCCV and the severity of skin discomfort or chest pain assessed using a visual analogue scale (VAS) 1 day after DCCV. The incidence of clinically relevant tachy/brady-arrhythmias was also assessed, as was the patient's self-reported rhythm status 1 day after DCCV.

With regard to the primary objective of the study, we performed a series of analyses to compare the efficacy and safety of the initial shocks of the 2 protocols: that is, 150 J vs 360 J, and to explore possible variables that, if present, would favour the use of one protocol over the other.

Statistical analysis

As we intended to compare 2 DCCV protocols that differed only in the energy of the initial shock, and then used maximum discharge energies in both protocols, we did not expect a significant difference in overall efficacy. To demonstrate a 3% significant difference in efficacy between the 2 protocols, approximately 3000 patients would need to be randomized. Therefore, we decided to perform an exploratory analysis with fewer patients, based on the expected differences in efficacy and safety of the first discharge: that is, 150 J vs 360 J. As a rationale for the sample calculation, we used the results of our recently published DCCV registry.[24] The success rate of the first low-energy shock to restore SR was 77.1%, and the cumulative success rate after the last high-energy shock was 89.6%. Therefore, we assumed a 12% difference in the success rate in favour of MfA (78% vs 90%). Based on 80% power and a significance level of 0.05, we estimated that approximately 145 patients would be needed in each arm. All randomized patients were included in the intention-to-treat (ITT) analysis.

Data were analyzed using IBM SPSS Statistics for Windows, version 29 (IBM Corp, Armonk, New York, USA). Nonparametric tests were used because of the non-normal distribution of the data, as confirmed by the Shapiro-Wilk test. Continuous variables are presented as median (interquartile range [IQR]) and categorical variables as number (percentage). Comparisons were made using the Mann-Whitney U test for continuous variables, the Pearson χ^2 test for categorical variables, and the Jonckheere-Terpstra test for ordinal variables.

Univariate analysis was performed to identify parameters associated with the effectiveness of the initial 150-J shock in achieving SR. Multivariate logistic regression was then performed, including parameters with a significance level of $P < 0.1$ in the univariate analysis, to further elucidate the independent predictors of 150 J DCCV efficacy. When appropriate, Spearman's correlation coefficient (r, 95% confidence interval [CI]) was determined to express the degree of association among parameters, receiver operating characteristic (ROC) curve analysis, and area under the curve (AUC) calculations were used to establish cutoff values and provide an overall measure of the discriminatory power of significant variables. In addition, Youden's J statistic was used to identify optimal cutoffs by maximizing the sum of sensitivity and specificity, providing a comprehensive visualization of ROC curve performance.

Results

Patients

During the study recruitment period, 579 patients were considered for DCCV procedures. Of these, 300 patients met the study criteria and were randomized 1:1, resulting in 150 subjects in the RaA and MfA protocols. Patients in both arms were well balanced (Table 1). During cardioversion, a total of 3 patients in the RaA arm and 4 patients in the MfA arm did not undergo a third discharge after 2 previous unsuccessful discharges. The reasons were problems with analgosedation in 5 patients, intermittent SR and AF in 1 patient (physician decided to discontinue DCCV), and junctional bradycardia in 1 patient. All these patients were considered DCCV failures and were included in the ITT analysis (Fig. 1).

Efficacy

The primary endpoint—that is, SR 1 minute after DCCV—was achieved in 139 (92.7%) patients in the RaA group and in 141 (94.0%) patients in the MfA group, $P = 0.643$. Similarly, no difference was found between the measured SR rates at 2 hours post-DCCV (both groups equal 137 [91.3%] patients, $P = 1.0$). In addition, the patient self-reported rhythm status on the following day did not differ between the groups (palpated or a device-detected regular rhythm considered as SR in 125 [90.6%] vs 127 [91.4%] cases, respectively, $P = 0.819$).

Safety

No cardioversion-related neurologic abnormalities or complications were observed. There were significant differences between the study arms in terms of skin changes 2 hours after DCCV ($P = 0.001$, Table 2), with the RaA group having fewer patients with skin redness. This difference was mainly because of the low vs high energy of the initial shock (Fig. 2). There were no cases of skin burns in either group.

The mean cumulative energy delivered per subject was 361.6 $\pm$ 232.2 J. There was a significant difference between the groups (RaA median 150 J, range 150 J to 870 J; MfA median 360 J, range 360 J to 1080 J; $P < 0.001$). A positive correlation was found between the total energy dose and the incidence of skin redness ($r = 0.243$, 95% CI, 0.130-0.350; $P < 0.0001$).

There were no significant differences in the severity of chest pain 1 day after DCCV between the 2 study arms ($P = 0.378$, Table 2). With regard to other safety measures, as mentioned earlier, 5 subjects experienced problems with analgesia leading to protocol deviations, but these did not have clinically relevant consequences. Three subjects in the RaA group experienced clinically relevant junctional bradycardia, 2 of whom required overnight monitoring without the need for pacemaker implantation.

Table 1. Baseline characteristics of the study participants

	Total	Study arm		*P*-value
		Rational energy algorithm (150, 360, 360 J)	Maximum fixed energy algorithm (360, 360, 360 J)	
Total	300	150	150	
Sex				
Male	199 (66%)	97 (65%)	102 (68%)	0.541
Female	101 (34%)	53 (35%)	48 (32%)	
Age (years)	68 [13]	68 [13]	69 [12]	0.425
BMI (kg/m^2)	31.8 [8.0]	31.8 [8.5]	31.9 [7.7]	0.986
CHA_2DS_2-VASC				
0	10 (3.3%)	5 (3.3%)	5 (3.3%)	0.429
1	39 (13.0%)	21 (14.0%)	18 (12.0%)	
2	85 (28.3%)	44 (29.3%)	41 (27.3%)	
3	90 (30.0%)	45 (30.0%)	45 (30.0%)	
4	38 (12.7%)	17 (11.3%)	21 (14.0%)	
5	24 (8.0%)	10 (6.7%)	14 (9.3%)	
6	7 (2.3%)	7 (4.7%)	0	
7	6 (2.0%)	0	6 (4.0%)	
8	1 (0.3%)	1 (0.7%)	0	
Anticoagulation type				
Warfarin	13 (4.3%)	7 (4.7 %)	6 (4.0%)	0.961
NOAC	285 (95.0%)	142 (94.7%)	143 (95.3%)	
LMVH	2 (0.7%)	1 (0.7%)	1 (0.7%)	
Antiarhythmic drugs				
No antiarrhythmics	83 (27.7%)	39 (26.0%)	44 (29.3%)	0.69
Propafenone	67 (22.3%)	36 (24.0%)	31 (20.7%)	
Sotalol	32 (10.7%)	18 (12.0%)	14 (9.3%)	
Amiodarone	117 (39.0%)	57 (38.0%)	60 (40.0%)	
Dronedarone	1 (0.3%)	0	1 (0.7%)	
Beta blockers				
On beta blockers	222 (74.0%)	114 (76.0%)	108 (72.0%)	0.43
RAAS				
No RAAS	88 (29.3%)	47 (31.3%)	41 (27.3%)	0.484
ACEI	139 (46.3%)	72 (48.0%)	67 (44.7%)	
Sacubitril/valsartan	8 (2.7%)	4 (2.7%)	4 (2.7%)	
Sartan	65 (21.7%)	27 (18.0%)	38 (25.3%)	
BP systole (mm Hg)	143 [28]	142 [27]	144 [28]	0.617
BP diastole (mm Hg)	83 [15]	83 [15]	83 [15]	0.847
Heart rate (per minute)	88 [25]	89 [26]	88 [23]	0.88
Left atrial diameter (mm)	47 [7]	47 [7]	48 [7]	0.701
LVEF (%)	54 [8]	54 [8]	55[8]	0.9

ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; BP, blood pressure; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K antagonist oral anticoagulants; RAAS, renin-angiotensin-aldosterone system.

CHA_2DS_2-VASc: Congestive heart failure (1 point); Hypertension (1 point); Age ≥75 years (2 points); Diabetes mellitus (1 point); previous Stroke or transient ischemic attack (TIA) or thromboembolism (2 points); Vascular disease (1 point); Age 65 to 74 years (1 point); Sex category (female) (1 point).

Initial 150-J shock analysis

Regarding the initial success rates of the RaA and MfA protocols to restore SR, we found that the protocols differed significantly: that is, after 150 J vs 360 J (109 [72.7%] vs 125 [83.3%] patients, $P = 0.026$). After subsequent maximum energy shocks in both protocols, the success rates were similar (Fig. 3). In univariate analysis, we assessed differences in all recorded parameters between patients who achieved SR after the initial 150-J discharge and those who did not. Both weight (mean 104 [IQR: 20] kg in AF vs 91 [IQR: 29] kg in SR, $P < 0.001$) and BMI (mean 34.1 [IQR: 7.4] kg/m^2 in AF vs 30.5 [7.8] kg/m^2 in SR, $P < 0.001$) were statistically significant. In addition, female sex showed a notable trend toward restoration of SR ($P = 0.086$, Supplemental Table S2). Given the collinearity between weight and BMI, and the widespread use of BMI in clinical practice, we chose to include only BMI in the multivariate regression analysis. The results were consistent with the univariate analysis. In particular, for each unit increase in BMI, the odds of achieving SR decreased by 10.8% (odds ratio (OR), 0.892; 95% CI, 0.832-0.956; $P < 0.001$). In addition, being female was associated with 2.2-fold increased odds of achieving SR, although this was borderline significant ($P = 0.067$, Supplemental Table S3).

Association of BMI and initial 150-J shock success

While the cumulative DCCV success rate including all 300 patients did not show a pronounced variance based on low or high BMI ($P = 0.984$, Supplemental Fig. S2), in the RaA group BMI values seemed to play an important role ($P = 0.076$, Fig. 4A). To find an optimal cutoff value for BMI to justify the use of 150 J as the initial DCCV shock to reduce the risk of skin redness while maintaining a high rate of SR recovery, we performed an ROC analysis with BMI as the pivotal variable. This revealed an AUC of 0.675 (95% CI, 0.582-0.769) with a standard error of 0.048 ($P = 0.001$, Fig. 4B). Subsequent Youden's J statistics identified 2 zeniths, with the BMI range of 29 to 34 kg/m^2 as the most appropriate cutoff that harmonized both sensitivity and specificity (Fig. 4C).

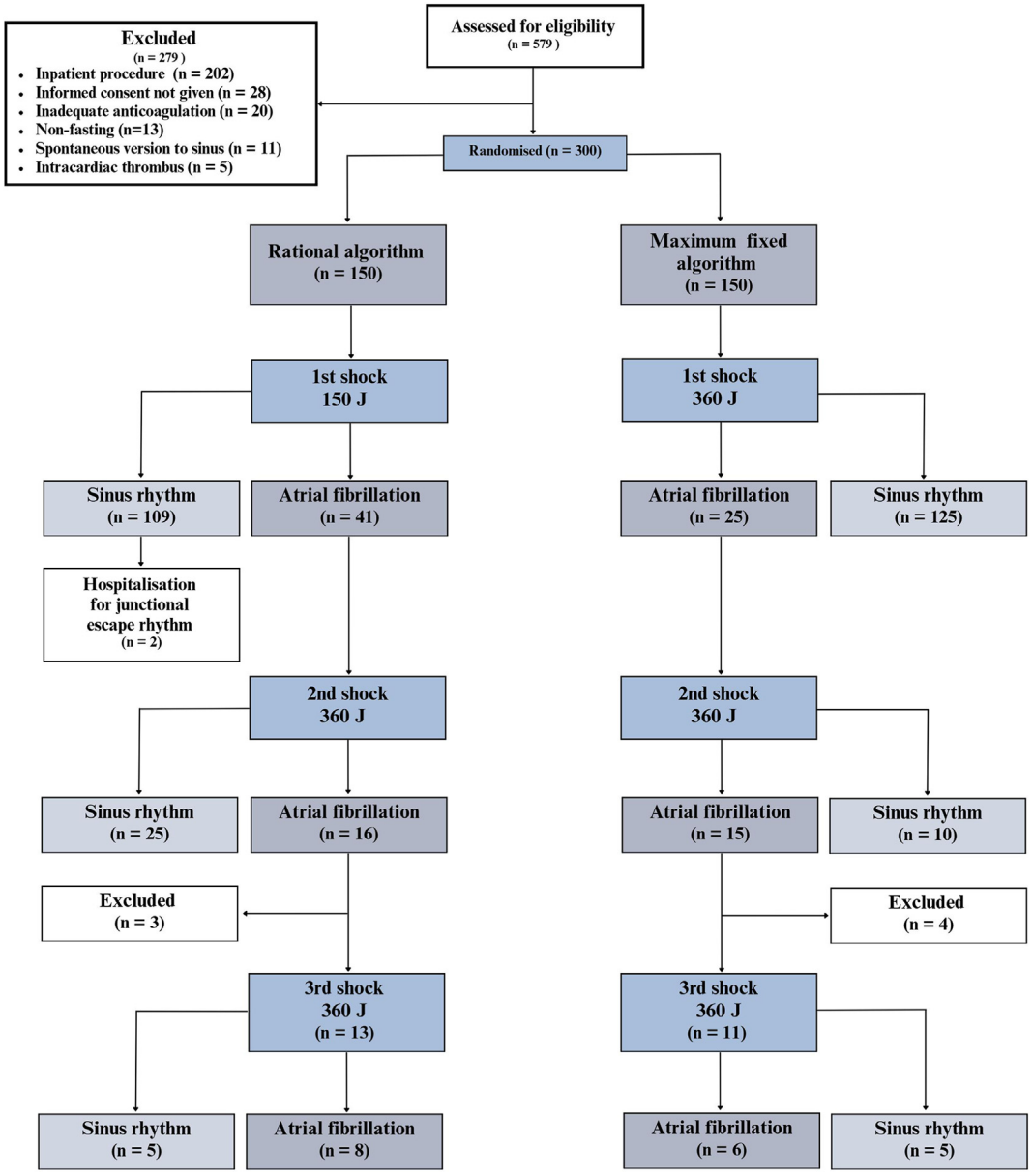

Figure 1. CONSORT flow diagram of the PROTOCOLENERGY study.

Discussion

Efficacy

This study compared 2 protocols for cardioverting AF, both using the maximum available 360-J energy shocks but differing in the energy of the initial shock. The main finding was that the cumulative success rates were similar, but patients who received the lower 150-J initial shock had less frequent skin irritation related to the cumulative energy dose delivered. The low escalating (rational) energy protocol was shown to be feasible for patients with lower BMI and for women in whom the initial 150-J shock was sufficient to restore SR.

The optimal DCCV algorithm is a daily dilemma in clinical practice. Despite a large number of previously published observational studies and reports,[28] there is a paucity of randomized data addressing the issue of energy selection or escalation. The first randomized trial using impedance-compensated biphasic shocks with pads in anterior-lateral position (self-adhesive, no manual pressure applied), the **B**iphasic **E**nergy **S**election for **T**ransthoracic Cardioversion of **A**trial **F**ibrillation (BEST-AF) trial,[29] compared a low escalation protocol (100-150-200-200 J) with a fixed energy protocol (200-200-200 J). The authors found no difference in the overall success rate, defined as the restoration of SR for at least 30 seconds (90% vs 88%, $P = 0.56$) and also demonstrated that a higher initial shock energy resulted in a higher initial success rate (48% vs 71%, $P < 0.01$), particularly in patients with obesity and BMI > 25 kg/m^2 (44% vs 75%, $P = 0.001$). The second study, the **C**omparison of **H**igh vs **E**scalating **S**hock**s** (CHESS) trial,[23] used biphasic shocks with self-adhesive pads (no manual pressure, no impedance compensation) in the anterior-posterior position, and compared an

Table 2. Secondary safety endpoints

	Total	Study arm		*P* value
		Rational energy algorithm (150, 360, 360 J)	Maximum fixed energy algorithm (360, 360, 360 J)	
Skin changes 2 hours post- DCCV				
No skin changes	217 (72.3%)	121 (80.7%)	96 (64.0%)	**0.001**
Skin redness	83 (27.7%)	29 (19.3%)	54 (36.0%)	
Skin burns	0	0	0	
Chest pain (VAS 1-10) 24 hours post DCCV				
0	249 (89.9%)	126 (91.3%)	123 (88.5%)	0.378
1	12 (4.3%)	7 (5.1%)	5 (3.6%)	
2	5 (1.8%)	3 (2.2%)	2 (1.4%)	
3	3 (1.1%)	1 (0.7%)	2 (1.4%)	
4	2 (0.7%)	0	2 (1.4%)	
5	4 (1.4%)	0	4 (2.9%)	
7	1 (0.4%)	1 (0.7%)	0	
8	1 (0.4%)	0	1 (0.7%)	

Bold values indicate statistical significance ($P < 0.05$).
DCCV, direct current cardioversion; VAS, visual analogue scale.

energy-escalating protocol with a maximum energy of 200 J of the last shock with a fixed-energy protocol using novel maximum energy shocks of 3 x 360 J. The authors found a profound difference between the protocols in terms of initial and cumulative efficacy in favour of the fixed maximum-energy protocol.

Compared with our study, subjects in both protocol groups of the PROTOCOLENERGY study had higher rates of successful cardioversion after both the first and last protocol-guided shock (comparison of studies in Table 3). In addition, high rates (> 90%) of restoration of SR at 2 hours were observed. This may be because the PROTOCOLENERGY trial incorporated the best of previous studies: in particular, the use of maximum high energy in cardioversion protocols, the use of impedance-compensated waveforms that automatically adjust the peak current to match patients with different chest impedances, and the use of manual pressure to increase shock effectiveness. Under these conditions, the cumulative efficacy of DCCV can be as high as 94%, regardless of the initial shock energy.

It is important to note that there are different definitions of DCCV success. In the aforementioned studies, 30 seconds to

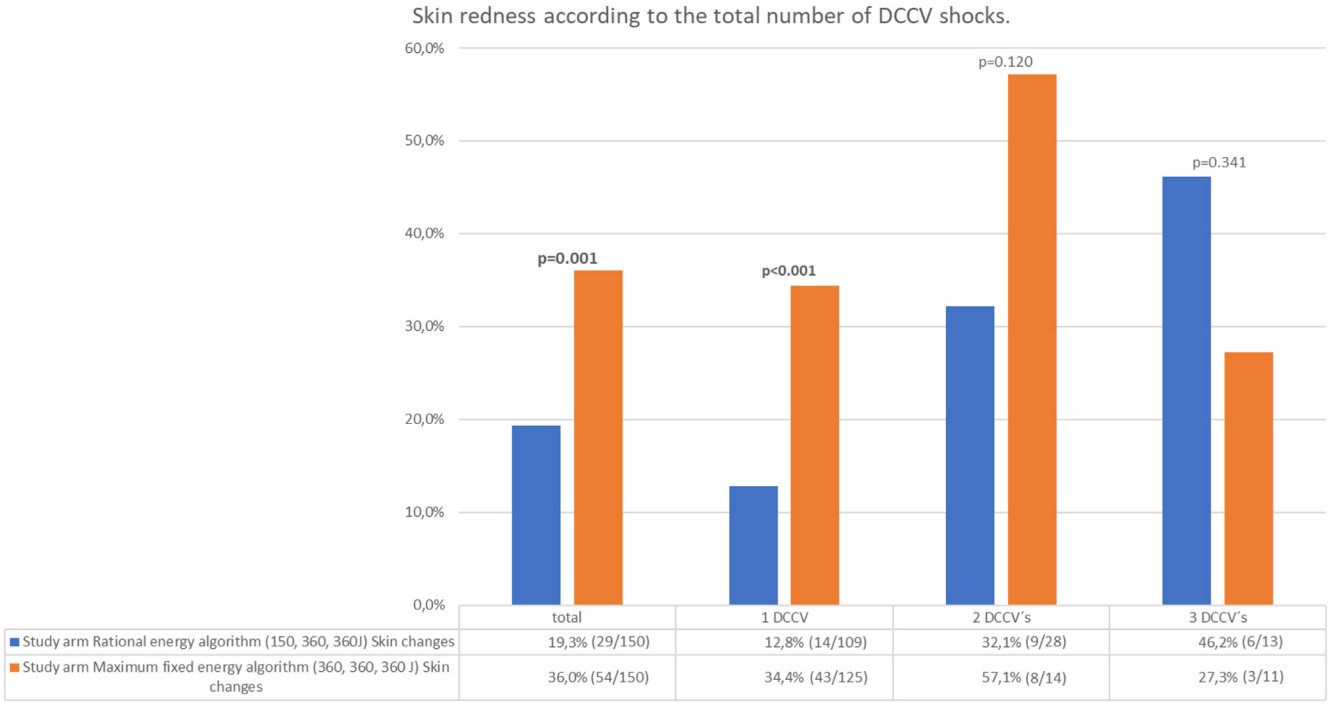

Figure 2. Incidence of skin redness postcardioversion by DCCV shock number and algorithm. Significant differences in the incidence of skin erythema were observed between the 2 algorithms overall (**left, total bars**) and between patients receiving only 1 (initial) DCCV shock, favouring RaA with 150-J shock. The differences in skin redness were not statistically significant in patients receiving 2 or 3 DCCV shocks, likely because of the uniform energy level (360 J) used in subsequent shocks in both protocols, underscoring the skin-protective effect of the low energy of the initial shock. DCCV, direct current cardioversion; RaA, rational energy algorithm.

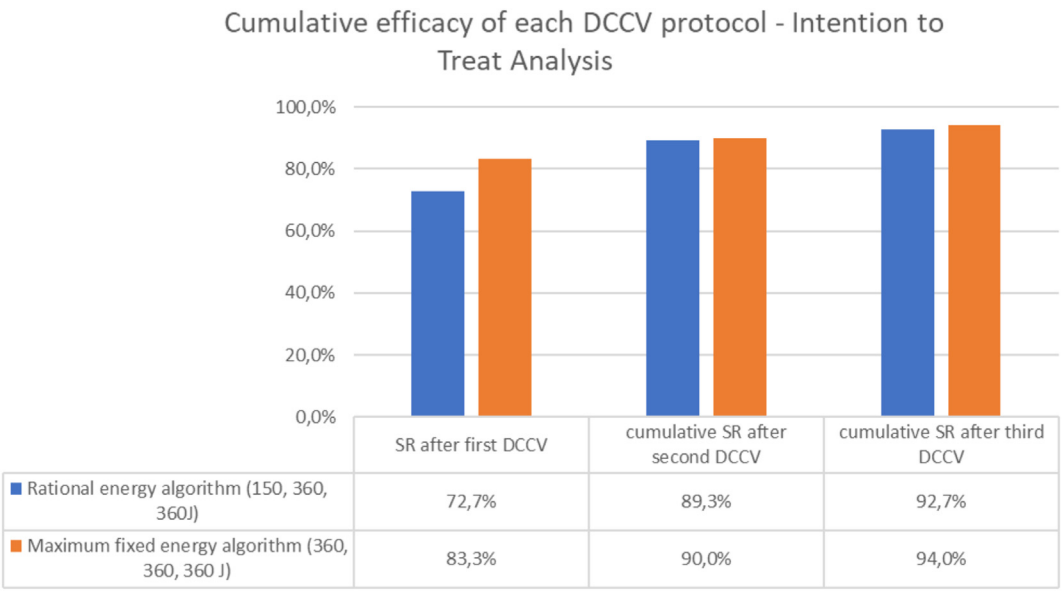

Figure 3. Efficacy of each DCCV protocol after first, second and third shock. The DCCV success rate after the first shock was significantly higher in the MfA protocol group using a maximum energy of 360 J. The cumulative success rates after subsequent shocks, delivered uniformly at 360 J for both algorithms, were not significantly different, highlighting similar efficacy in SR restoration beyond the first shock. DCCV, direct current cardioversion; MfA, maximum fixed-energy algorithm; SR, sinus rhythm.

1 minute of postshock SR preservation was considered successful DCCV. In the Ottawa AF Cardioversion Protocol published by Ramirez et al.,[27] implementing similar measures as in our study, the DCCV success reached 99.2%, but was defined as $\geq$ 2 consecutive sinus beats or atrial-paced beats in patients with implantable devices. As the CHESS trial used 3 x 360 J energy in the fixed-energy group but differed in the energy-escalating group, we chose to use the same endpoint definition as the CHESS trial to allow for better comparison among trials and protocols.

Safety

There was no evidence of an increased risk of clinically relevant arrhythmias or neurologic complications with either protocol or when comparing the incidence of adverse events

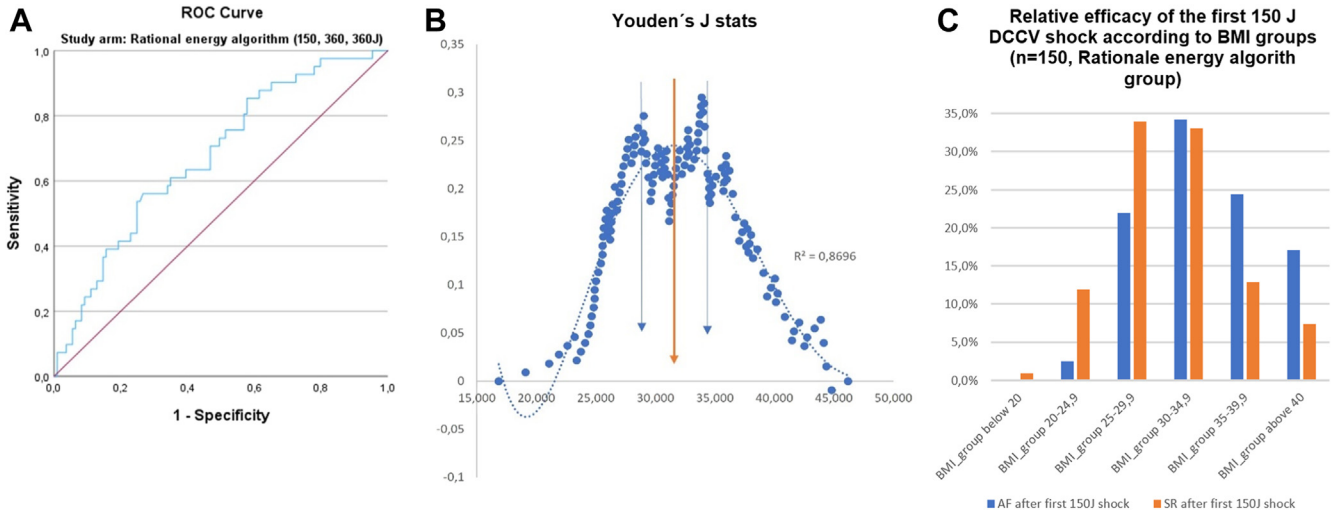

Figure 4. Analysis of association of BMI with success of initial 150J shock. (**A**) Relative efficacy of the initial 150-J DCCV shock across different BMI categories. The graph clearly shows that—despite the statistical insignificance—the percentage of successful cardioversions was much higher in the lower BMIs than in the higher BMIs. (**B**) The ROC curve analysis for BMI and DCCV success after the initial 150-J shock. The AUC value of 0.675 indicates a moderate predictive value of BMI for cardioversion success in patients with AF. (**C**)Visualization of 2 BMI peaks using Youden's J statistic. The peaks identify a BMI of 29 to 34 kg/m^2 as the most appropriate cutoff for predicting 150J shock success, combining both sensitivity and specificity. AF, atrial fibrillation; AUC, area under the curve; BMI, body mass index; DCCV, direct current cardioversion; ROC, receiver operating characteristic.

Table 3. Comparison of BEST-AF, CHESS and PROTOCOLENERGY randomized trials in patients undergoing biphasic elective cardioversion

	BEST-AF[29]		CHESS[23]		PROTOCOLENERGY	
Pads position	Anterior-lateral		Anterior-posterior		Anterior-lateral	
Manual pressure applied	No		No		Yes	
Waveform type	Truncated exponential, impedance compensated		Truncated exponential		Truncated exponential, impedance compensated	
Cardioversion success definition	Sinus rhythm 30 seconds after cardioversion		Sinus rhythm 1 minute after cardioversion		Sinus rhythm 1 minute after cardioversion	
Patients total	380		276		300	
	Energy escalating: 100,150,200,200 J	Fixed energy: 200,200,200 J	Energy escalating: 125,150,200 J	Fixed energy: 360,360,360 J	Energy escalating: 150,360,360 J	Fixed energy: 360,360,360J
Success rate: (1) Initial shock	48%	71%†	34%	75%‡	73%	83%*
(2) Cumulative	90%	88%	66%	88%‡	93%	94%*
Number of shocks (Average [± SD], median [IQR])	1.88 (± 1.04)	1.46 (± 0.76)†	2 [1-3]	1 [1-1]§	1.36 (± 0.64)	1.24 (± 0.58)*
Energy applied (Average [± SD], median [IQR])	202 J (± 135)	251 J (± 110)†	275 J (125-475)	360 J (360-360)§	150 J (150-870)	360J (360-1080) ***
Initial shock success predictors	BMI < 25 kg/m^2		N/A		BMI < 29-34 kg/m^2, female	
Cumulative success predictors	Short duration of AF		N/A		N/A	
Safety: (1) Arrhythmias	No difference		Low rates, no difference		Low rates, no difference	
(2) Skin changes	N/A		Redness/burns no difference		No burns, more redness in Fixed	

AF, atrial fibrillation; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

* $P < 0.05$ between the protocols within the study.

† $P < 0.01$ between the protocols within the study.

‡ $P < 0.001$ between the protocols within the study.

§ P value unknown between the protocols within the study.

with previous studies. Although there was no difference in skin redness between the low-escalation (up to 200 J) and maximum-fixed (360 J) protocol groups in the CHESS trial using self-adhesive anterior-posterior pads, in our study using hand-held paddles in the anterior-lateral position and manual pressure, the incidence of skin redness was significantly higher in the maximum-fixed energy group, especially after the first shock. This may be because of the use of impedance-compensated shocks with different peak currents, independent of the total energy delivered, depending on chest impedance, which is generally higher in patients with obesity and women and lower in patients with heart failure and those with reduced hemoglobin levels.[30] Chest impedance is significantly influenced by pad size, pad position, and skin-to-pad contact and generally decreases with the number of shocks delivered. However, increased impedance has not been associated with cardioversion success.[12]

Relationship among BMI, sex, and initial 150-J shock success rate

In the post-hoc analysis, a BMI of 29-34 kg/m^2 was identified as a potential cutoff for initiating DCCV with a 150-J shock. In the BEST-AF trial, overweight patients (BMI $>$ 25 kg/m^2) were also significantly less likely to regain SR with the initial 150-J vs 200-J shock (44% vs 75%, $P <$ 0.001).[29] This may be explained by higher defibrillation thresholds in patients with obesity.[31] The current study confirms previous findings and recommends a BMI cutoff to be considered when choosing between low or high energy of the initial shock.

Although not statistically significant, women were more likely than men to restore SR after the initial 150 J. Our daily practice supports the clinical relevance of such an observation and is consistent with the results of previous studies.[32] With a concept of less skin irritation and maintained efficacy, initiating cardioversion with lower energy—especially in women rather than in men—seems to be a feasible approach.

Future directions

Recently, a meta-analysis comparing different approaches to DCCV was published after the trial was completed.[28] The results of this analysis demonstrated the superiority of biphasic waveforms, high energy shocks, and manual pressure. The PROTOCOLENERGY study has already used these approaches and added further data to support the use of a maximum energy of 360 J, which is feasible to start with but essential to end with during the course of DCCV.

There is growing evidence that the simultaneous use of 2 defibrillators, known as dual DCCV, further increases the overall success rate of electrical cardioversion, with no safety issues when 200-J shocks are used. Darrat et al.[33] incorporated dual DCCV into a step-up institutional protocol and achieved 99.3% success in restoring SR, and in a randomized trial in patients with obesity and AF (BMI $>$ 35 kg/m^2) the success rate of single vs dual DCCV was 86% vs 98%, with a higher likelihood of failure with single DCCV (adjusted OR, 12.6; 95% CI, 1.3-118.9).[34] Despite higher success rates compared with single DCCV studies including PROTOCOLENERGY, further studies are needed to elucidate the optimal output energy for dual DCCV and to justify its use in daily clinical practice. Potential indications for dual DCCV may include failure of single DCCV[34] or patients with known extensive cardiac fibrosis, which has recently been associated with endocardial damage, thrombus formation, conduction abnormalities, and atrial re-entry.[35]

Limitations

The study has several limitations. First, it is a single-centre study. However, the approach to patients with AF and DCCV is similar between complex cardiology centres in the Czech Republic. Second, not all patients indicated for DCCV were enrolled. For logistic reasons, we chose to randomize patients with stable AF who were indicated for an elective outpatient procedure, and excluded hospitalized patients, those with decompensated heart failure, and those indicated for acute DCCV. Therefore, it is questionable whether the results can be generalized to all patients with AF. Third, we did not record detailed information on biochemical variables (potassium, magnesium, renal function, N-terminal pro-B-type natriuretic peptide [NT-proBNP]), echocardiographic parameters other than LVEF and left atrial diameter (left/right atrial volume, valvular disease, ischemic heart disease, diastolic filling pressure calculations, left atrial and ventricular strain), or duration/type of AF, which are known to potentially influence the onset and course of AF and were therefore not included in our analyses. The aim was to keep the study as simple and real-world as possible, and this information was not available for patients referred for elective DCCV from different centres. Fourth, the cumulative energy delivered during DCCV may be slightly less than the output energy set on the defibrillator, depending on the individual patient's thoracic impedance values, pulse duration, and leading-edge voltage. These values were not recorded. Fifth, a total of 7 patients did not receive a third shock as per protocol and were included as failures in the ITT analysis. These protocol deviations did not change the overall results of the study, as an on-treatment analysis (not shown) excluding these patients produced the same results. Finally, the physician administering the shock was not blinded, but the patients and the physician assessing the skin changes and all outcome assessments were blinded.

Conclusions

Energy escalation (150 J-360 J-360 J) and maximum fixed energy (3 x 360 J) DCCV protocols showed similar high cumulative efficacy. Starting with 150 J, the initial shock appeared to be adequate for most patients with BMI less than 29 to 34 kg/m^2 and for women who benefited from less skin erythema compared with the initial 360-J shock. With its high efficacy but better tolerability, the energy escalation protocol should be preferred to the maximum fixed energy protocol in elective cardioversion patients.

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Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of Agel Hospital Trinec-Podlesi (approval number EK1/21). All participants provided written informed consent prior to their inclusion in the study. The researchers ensured that patient confidentiality and data protection measures were strictly adhered to throughout the research process. The study protocol and procedures were designed to minimize risks to participants while maximizing potential benefits to scientific knowledge and patient care in the field of cardiology.

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Ambler JJS, Deakin CD. A randomized controlled trial of efficacy and ST change following use of the Welch-Allyn MRL PIC biphasic waveform versus damped sine monophasic waveform for external DC cardioversion. Resuscitation 2006;71:146-51.
2. Page RL, Kerber RE, Russell JK, et al. Biphasic versus monophasic shock waveform for conversion of atrial fibrillation: the results of an international randomized, double-blind multicenter trial. J Am Coll Cardiol 2002;39:1956-63.
3. Zhang B, Li X, Shen D, Zhen Y, Tao A, Zhang G. Anterior-posterior versus anterior-lateral electrode position for external electrical cardioversion of atrial fibrillation: a meta-analysis of randomized controlled trials. Arch Cardiovasc Dis 2014;107:280-90.
4. Kirchhof P, Mönnig G, Wasmer K, et al. A trial of self-adhesive patch electrodes and hand-held paddle electrodes for external cardioversion of atrial fibrillation (MOBIPAPA). Eur Heart J 2005;26:1292-7.
5. Boodhoo L, Mitchell ARJ, Bordoli G, Lloyd G, Patel N, Sulke N. DC cardioversion of persistent atrial fibrillation: a comparison of two protocols. Int J Cardiol 2007;114:16-21.
6. Gallagher MM, Guo XH, Poloniecki JD, Guan Yap Y, Ward D, Camm AJ. Initial energy setting, outcome and efficiency in direct current cardioversion of atrial fibrillation and flutter. J Am Coll Cardiol 2001;38:1498-504.
7. Joglar JA, Hamdan MH, Ramaswamy K, et al. Initial energy for elective external cardioversion of persistent atrial fibrillation. Am J Cardiol 2000;86:348-50.
8. Singh SN, Tang XC, Reda D, Singh BN. Systematic electrocardioversion for atrial fibrillation and role of antiarrhythmic drugs: a substudy of the SAFE-T trial. Heart Rhythm 2009;6:152-5.
9. Döring C, Richter U, Ulbrich S, et al. The impact of right atrial size to predict success of direct current cardioversion in patients with persistent atrial fibrillation. Korean Circ J 2023;53:331-43.
10. Jaakkola S, Lip GYH, Biancari F, et al. Predicting unsuccessful electrical cardioversion for acute atrial fibrillation (from the AF-CVS score). Am J Cardiol 2017;119:749-52.
11. Hellman T, Kiviniemi T, Vasankari T, et al. Prediction of ineffective elective cardioversion of atrial fibrillation: a retrospective multi-center patient cohort study. BMC Cardiovasc Disord 2017;17:33.
12. Roh S-Y, Ahn J, Lee K-N, et al. The impact of personal thoracic impedance on electrical cardioversion in patients with atrial arrhythmias. Medicina (Kaunas) 2021;57:618.
13. Rochlani YM, Shah NN, Pothineni NV, Paydak H. Utilization and predictors of electrical cardioversion in patients hospitalized for atrial fibrillation. Cardiol Res Pract 2016;2016:8956020.
14. Wałek P, Gorczyca I, Sielski J, Wożakowska-Kapłon B. Left atrial emptying fraction determined during atrial fibrillation predicts maintenance of sinus rhythm after direct current cardioversion in patients with persistent atrial fibrillation. PLoS One 2020;15:e0238002.
15. Wałek P, Roskal-Wałek J, Dłubis P, Tracz J, Wożakowska-Kapłon B. Left atrial wall motion velocity assessed during atrial fibrillation predicts sinus rhythm maintenance after electrical cardioversion in patients with persistent atrial fibrillation. Int J Environ Res Public Health 2022;19:15508.
16. Schmidt AS, Lauridsen KG, Møller DS, et al. Anterior-lateral versus anterior—posterior electrode position for cardioverting atrial fibrillation. Circulation 2021;144:1995-2003.
17. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J 2020;42(5):373-498.
18. Stiell IG, de Wit K, Scheuermeyer FX, et al. 2021 CAEP acute atrial fibrillation/flutter best practices checklist. CJEM 2021;23:604-10.
19. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council Guidelines 2021: adult advanced life support. Resuscitation 2021;161:115-51.
20. Cheung CC, Nattel S, Macle L, Andrade JG. Management of atrial fibrillation in 2021: an updated comparison of the current CCS/CHRS, ESC, and AHA/ACC/HRS guidelines. Can J Cardiol 2021;37:1607-18.
21. Ramirez FD, Fiset SL, Cleland MJ, et al. Effect of applying force to self-adhesive electrodes on transthoracic impedance: implications for electrical cardioversion. Pacing Clin Electrophysiol 2016;39:1141-7.
22. Lobo R, White RD, Donato LJ, et al. Absence of significant myocardial injury following elective direct current cardioversion for atrial fibrillation. Heart Rhythm O2 2023;4:180-6.
23. Schmidt AS, Lauridsen KG, Torp P, Bach LF, Rickers H, Løfgren B. Maximum-fixed energy shocks for cardioverting atrial fibrillation. Eur Heart J 2020;41:626-31.
24. Jiravsky O, Rucki L, Hudec M, et al. Identifying parameters associated with the use of higher discharge energy in electrical cardio version for persistent atrial fibrillation. J Atrial Fibrillation Electrophysiol 2023;16:6-11.
25. Schulz KF, Altman DG, Moher D; the CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med 2010;8:18.

26. BeneHeart D3/BeneHeart D2 Defibrillator/Monitor Operator's Manual. Available from, www.mindray.com.

27. Ramirez FD, Sadek MM, Boileau I, et al. Evaluation of a novel cardioversion intervention for atrial fibrillation: the Ottawa AF cardioversion protocol. Europace 2019;21:708-15.

28. Nguyen ST, Belley-Côté EP, Ibrahim O, et al. Techniques improving electrical cardioversion success for patients with atrial fibrillation: a systematic review and meta-analysis. Europace 2023;25:318-30.

29. Glover BM, Walsh SJ, McCann CJ, et al. Biphasic energy selection for transthoracic cardioversion of atrial fibrillation: the BEST AF trial. Heart 2008;94:884-7.

30. Fumagalli S, Boni N, Padeletti M, et al. Determinants of thoracic electrical impedance in external electrical cardioversion of atrial fibrillation. Am J Cardiol 2006;98:82-7.

31. Kistler PM, Sanders P, Morton JB, Vohra JK, Kalman JM, Sparks PB. Effect of body mass index on defibrillation thresholds for internal cardioversion in patients with atrial fibrillation. Am J Cardiol 2004;94:370-2.

32. Lip GYH, Merino JL, Banach M, et al. Clinical factors related to successful or unsuccessful cardioversion in the EdoxabaN versus warfarin in subjectS UndeRgoing cardiovErsion of Atrial Fibrillation (ENSURE-AF) randomized trial. J Arrhythm 2020;36:430-8.

33. Darrat Y, Leung S, Elayi L, et al. A stepwise external cardioversion protocol for atrial fibrillation to maximize acute success rate. Europace 2023;25:828-34.

34. Aymond JD, Gullatt T, Bernard ML, et al. EFficacy and safety of dual direct current cardioversion versus single direct current cardioversion as an initial treatment strategy in obese patients with atrial fibrillation. Heart Rhythm 2023;20:S69-70.

35. Nattel S. Atrial fibrosis, endocardial damage, and thrombosis in atrial fibrillation: association with underlying conditions or causal? JACC: Clin Electrophysiol 2023;9:1169-71.

Supplementary Material

To access the supplementary materiál accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2024.06.003.