

Editorial

Facilitated electrical cardioversion: does the selection of the antiarrhythmic drug matter?

ARTICLE INFO

Article history:

Received 17 August 2019

Received in revised form 19 August 2019

Accepted 20 August 2019

Available online 1 September 2019

Atrial fibrillation (AF) is a frequent arrhythmia resulting in increased morbidity and mortality. Contemporary therapy with antiarrhythmic drugs (AADs), along with anticoagulants, is complex and suboptimal [1,2] with recurrence rates of AF after conversion to normal sinus rhythm (SR) remaining high also after ablation and cardiac surgery [3]. AF conversion to SR is an integral part of the rhythm strategy which could be accomplished either electrically (cardioversion – ECV) or pharmacologically (PCV). It may be applied in emergency situations, as with hemodynamic deterioration, when ECV is recommended, or on an elective basis. ECV is superior to PCV in terms of efficacy, with an overall success rate close to 90% [4], correlated inversely with the time of presentation, and in terms of safety. However, in 10–30% of cases either AF patients would not respond to ECV (cardioversion failure) or AF recurs shortly after ECV (immediate AF recurrence – IRAF), depending on different factors including technique (i.e. monophasic vs biphasic shock), duration of the AF episodes, presence of comorbidities and degree of evolution of advanced atrial remodeling. On the other hand, AADs are associated with important side effects including proarrhythmia and a low rate (50–60%) of SR maintenance at one year [1,5]. The AADs' success rate is even lower if one assumes that up to 60% of recent-onset AF episodes convert spontaneously in less than 48 h and approximately 30% of converted patients maintain SR at one year without AADs. Refinement in ECV technique could improve the conversion success rate; one example is the so called Ottawa protocol, consisting of four steps differing in electrode position and energy used [6]. Use of AAD pretreatment is an attractive *hybrid* modality to increase the ECV success rate (facilitated ECV – FECV). In addition to ECV facilitation, AADs use could decrease the risk of IRAF and may also allow testing the tolerability to a specific AAD. Pretreatment with both class III and Ic (Singh-Vaughan-Williams) drugs improved the efficacy of ECV in many AF populations, whereas beta-blockers and digoxin did not demonstrate such virtues [7]. Short-term amiodarone improves restoration and maintenance of SR without significant increase in adverse effects [8]. In small studies verapamil was able to reduce the incidence of IRAF [9], presumably by reducing calcium overload and related atrial remodeling. Small-dose atropine (up to 2 mg) is also able to enhance conversion to SR in previously reported “refractory” AF [10]. In a recent

study including 1313 AF patients [11], use of AADs (amiodarone, flecainide, propafenone and sotalol) given at least 1 month before ECV was accompanied by a higher rate of conversion success with less ECV attempts and lower energy. These patients also demonstrated longer maintenance of SR after ECV without side effects exceeding those in the control group. The guideline [7] recommendations regarding anticoagulation should be strictly followed irrespective if conversion is facilitated or not. This generally means institution of anticoagulation if not already done, 3 weeks of pre-conversion anticoagulation (preferably non-antivitamin K oral anticoagulants) if AF is older than 48 h and at least 4 weeks of post-conversion anticoagulation, especially in patients with CHA2DS2Vasc score ≥ 2 (women) or 1 (men).

The electrophysiological mechanism responsible for FECV is complex and poorly understood. Na-channel blockers could act by suppressing atrial extrasystolic triggers [12]; however, these agents could rise the defibrillation threshold by decreasing sodium channels availability and thus cardiac excitability [13]. Class III AADs prolong refractoriness and decrease the chance of re-entry and the defibrillation threshold. Class I and class III AADs reduce IRAF by stabilizing SR after successful conversion. Vernakalant is a newer AAD with multichannel blocking properties allowing rapid AF termination. It blocks K- and Na-channels thereby reducing peak and late Na-current needed for proper impulse propagation. Vernakalant prolongs atrial refractoriness causing “postrepolarization refractoriness”, slows atrial conduction and increases the excitation threshold, thereby reducing the likelihood of re-entry and arrhythmias [14]. Vernakalant exerts its actions predominantly at rapid cardiac rhythms like AF and possesses rapid binding and dissociation kinetics from the Na-channel, particularly at lower rates. Because of these properties vernakalant causes atrial-selective anti-AF effects without clinically relevant proarrhythmic effects at the ventricular level. A recent systematic review and metaanalysis [15] including 9 comparative studies demonstrated that vernakalant is very effective for rapid restoration of SR in recent-onset AF with good safety profile and could therefore be considered the “first line option” for pharmacologic AF conversion in hemodynamically stable patients.

In this issue of the Journal Simon et al. [16] proposed vernakalant for FECV in 230 patients with recent-onset AF, the majority of which had

DOI of original article: <https://doi.org/10.1016/j.ijcha.2019.100398>.

<https://doi.org/10.1016/j.ijcha.2019.100416>

2352-9067/© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

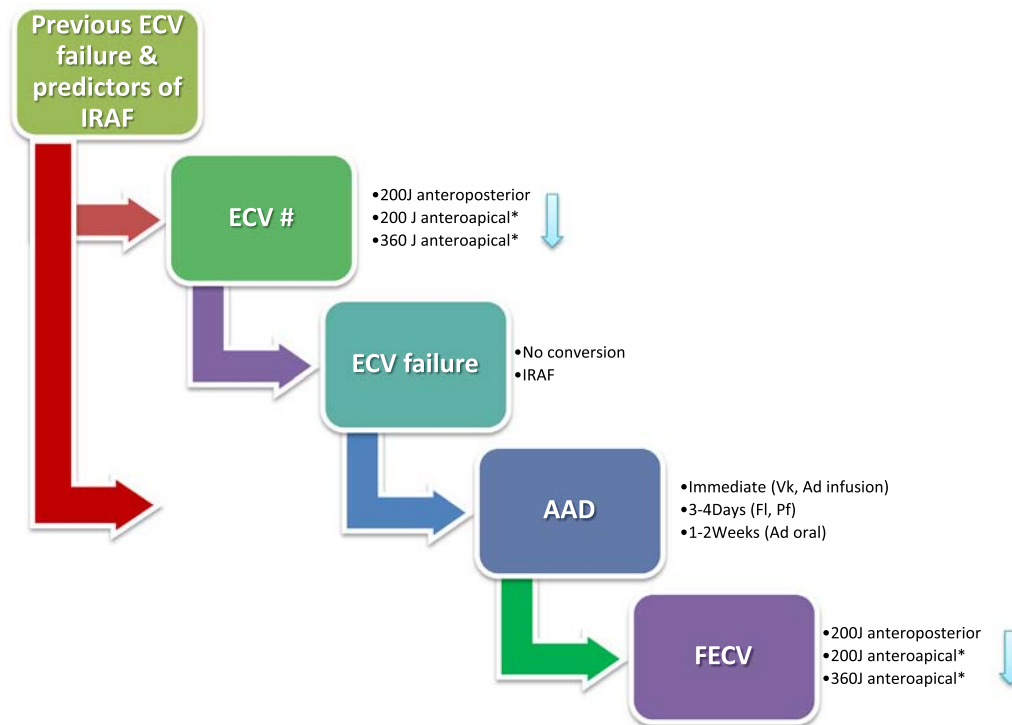


Fig. 1. proposed algorithm for facilitated cardioversion. ECV: electrical cardioversion; IRAF: immediate AF recurrence; AAD: antiarrhythmic drugs; Vk: vernakalant; Ad: amiodarone; Fl: flecainide; Pf: propafenone; FECV: facilitated cardioversion. #ECV stepped protocol could be applied before tempting FECV. *During this protocol pressure should be applied on the patient by means of defibrillator paddles [6].

hypertension but normal ejection fraction. They have administered two infusions (3 mg/kg and 2 mg/kg in 10 min, respectively) of vernakalant 15 min apart (as per drug protocol) followed by bi-phasic ECV in patients not converted to SR by the pharmacologic protocol. Vernakalant converted 73% of patients to SR, with 91% being converted within 90 min. ECV increased the conversion rate to SR to 99%, with a global time of 196 min from the first infusion. Despite the good safety profile of the method, 14% of patients developed atrial flutter after vernakalant infusion (none with 1:1 conduction), with the majority of them converting spontaneously to SR (and the rest after ECV). In multivariate analysis, low ejection fraction and previous episodes of persistent AF were independent predictors of cardioversion failure.

There are several limitations of the present study. First, there is no control or comparison group. Second, the protocol was initiated after a mean of 6 h, a very short interval that could obscure the percentage of spontaneous conversion to SR. A similar experience was communicated from Leipzig Heart Center [17]. In that study 63 patients were included who suffered ECV failure (lack of conversion) or IRAF (defined as AF recurrence in less than 5 min after ECV) without AAD premedication. In 90% of those patients the duration of AF was >48 h. A double facilitation protocol was employed: 52% of patients received one infusion of vernakalant (3 mg/kg over 10 min) and 48% received amiodarone infusion (5 mg/kg over 10 min). After 2 ECV attempts (360 J in anteroapical then anteroposterior patch position), the pharmacologic therapy was initiated, and after 10 min the ECV was re-attempted with the same protocol as before. All patients were continuously monitored for 15 min after conversion. In that rigorous study the success conversion rate was similar for vernakalant and amiodarone (66.7% vs 46.7%; $p = \text{NS}$). In the multivariate analysis vernakalant, but not amiodarone, was an independent predictor for FECV success. One interesting finding of the subgroup analysis was that vernakalant was more efficient than amiodarone in patients with previous AF ablation. The differences of the FECV success rates between the 2 mentioned studies could be explained by differences in the population studied (more patients proven as being “refractory” in the Leipzig study), timing of intervention and follow-up

intervals, and the pharmacologic protocol (higher vernakalant doses in the first study). Both studies have the limits of being observational and non-randomized. However, both studies reinforce the concept of FECV and emphasize the utility of vernakalant in this setting because of its unique electrophysiological actions, rapid-onset of antiarrhythmic effects, satisfactory safety profile and ease of administration. A possible algorithm for FECV integrating improved ECV techniques and pharmacological facilitation is shown in Fig. 1. Future prospective randomized studies assessing the superiority of vernakalant for FECV in comparison to other AADs will be needed to validate the therapeutic value of individual AADs for facilitated ECV.

Declaration of competing interest

None (both authors).

Acknowledgments

The authors' work is supported by the National Institutes of Health (R01-HL131517, R01-HL136389, and R01-HL089598 to D.D.) and the German Research Foundation (DFG, Do 769/4-1 to D.D.).

References

- [1] G.-A. Dan, D. Dobrev, Antiarrhythmic drugs for atrial fibrillation: imminent impulses are emerging, *Int. J. Cardiol. Heart Vasc.* 21 (2018) 11–15.
- [2] T.-Y. Chang, J.-N. Liao, T.-F. Chao, J.J. Vicera, C.-Y. Lin, T.-C. Tuan, Y.-J. Lin, S.-L. Chang, L.-W. Lo, Y.-F. Hu, F.-P. Chung, S.-A. Chen, Oral anticoagulant use for stroke prevention in atrial fibrillation patients with difficult scenarios, *Int. J. Cardiol. Heart Vasc.* 20 (2018) 56–62.
- [3] C.S. Engelsgaard, K.B. Pedersen, L.P. Riber, P.A. Pallesen, A. Brandes, The long-term efficacy of concomitant maze IV surgery in patients with atrial fibrillation, *Int. J. Cardiol. Heart Vasc.* 19 (2018) 20–26.
- [4] O.T. Gurevitz, N.M. Ammash, J.F. Malouf, K. Chandrasekaran, A.G. Rosales, K.V. Ballman, S.C. Hammill, R.D. White, B.J. Gersh, P.A. Friedman, Comparative efficacy of monophasic and biphasic waveforms for transthoracic cardioversion of atrial fibrillation and atrial flutter, *Am. Heart J.* 149 (2005) 316–321.

- [5] G.-A. Dan, A. Martinez-Rubio, S. Agewall, G. Boriani, M. Borggrefe, F. Gaita, Gelder I. van, B. Gorenek, J.C. Kaski, K. Kjeldsen, G.Y.H. Lip, B. Merkely, K. Okumura, J.P. Piccini, T. Potpara, B.K. Poulsen, M. Saba, I. Savelieva, J.L. Tamargo, C. Wolpert, C. Sticherling, J.R. Ehrlich, R. Schilling, N. Pavlovic, Potter T. De, A. Lubinski, J.H. Svendsen, K. Ching, J.L. Sapp, C. Chen-Scarabelli, et al., Antiarrhythmic drugs—clinical use and clinical decision making: a consensus document from the European heart rhythm association (EHRA) and European Society of Cardiology (ESC) working group on cardiovascular pharmacology, endorsed by the heart rhythm Soci, *Europace* 20 (2018) 731–732an.
- [6] F.D. Ramirez, M.M. Sadek, I. Boileau, M. Cleland, P.B. Nery, G.M. Nair, C.J. Redpath, M.S. Green, D.R. Davis, K. Charron, J. Henne, T. Zakutney, R.S.B. Beanlands, B. Hibbert, G.A. Wells, D.H. Birnie, Evaluation of a novel cardioversion intervention for atrial fibrillation: the Ottawa AF cardioversion protocol, *Europace* 21 (2019) 708–715.
- [7] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, M. Castella, H.C. Diener, H. Heidbuchel, J. Hendriks, G. Hindricks, A.S. Manolis, J. Oldgren, B.A. Popescu, U. Schotten, Putte B. Van, P. Vardas, S. Agewall, J. Camm, G. Baron Esquivias, W. Budts, S. Carerj, F. Casselman, A. Coca, Caterina R. De, S. Deftereos, D. Dobrev, J.M. Ferro, G. Filippatos, D. Fitzsimons, et al., 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS, *Europace* 18 (2016) 1609–1678.
- [8] K.J. Um, W.F. McIntyre, J.S. Healey, P.A. Mendoza, A. Koziarz, G. Amit, V.A. Chu, R.P. Whitlock, E.P. Belley-Côté, Pre- and post-treatment with amiodarone for elective electrical cardioversion of atrial fibrillation: a systematic review and meta-analysis, *Europace* 21 (2019) 856–863.
- [9] E.G. Daoud, J.D. Hummel, R. Augostini, S. Williams, S.J. Kalbfleisch, Effect of verapamil on immediate recurrence of atrial fibrillation, *J. Cardiovasc. Electrophysiol.* 11 (2000) 1231–1237.
- [10] E. Kaluski, A. Blatt, M. Leitman, R. Krakover, Z. Vered, G. Cotter, Atropine-facilitated electrical cardioversion of persistent atrial fibrillation, *Am. J. Cardiol.* 92 (2003) 1119–1122.
- [11] E. Toso, M. Iannaccone, D. Caponi, F. Rotondi, A. Santoro, C. Gallo, M. Scaglione, F. Gaita, Does antiarrhythmic drugs premedication improve electrical cardioversion success in persistent atrial fibrillation? *J. Electrocardiol.* 50 (2017) 294–300 Elsevier Inc.
- [12] Im S. Il, D.H. Park, B.J. Kim, K.I. Cho, H.S. Kim, J.H. Heo, Clinical and electrocardiographic characteristics for prediction of new-onset atrial fibrillation in asymptomatic patients with atrial premature complexes, *Int. J. Cardiol. Heart Vasc.* 19 (2018) 70–74.
- [13] R. Sung, Facilitating electrical cardioversion of persistent atrial fibrillation by antiarrhythmic drugs: update on clinical trial results, *Card. Electrophysiol. Rev.* 7 (2003) 300–303.
- [14] C.M. Hanley, V.M. Robinson, P.R. Kowey, Status of antiarrhythmic drug development for atrial fibrillation: new drugs and new molecular mechanisms, *Circ. Arrhythm. Electrophysiol.* 9 (2016) 1–9.
- [15] W.F. McIntyre, J.S. Healey, A.K. Bhatnagar, P. Wang, J.A. Gordon, A. Baranchuk, B. Deif, R.P. Whitlock, É.P. Belley-Côté, Vernakalant for cardioversion of recent-onset atrial fibrillation: a systematic review and meta-analysis, *Europace* 21 (2019) 1159–1166.
- [16] A. Simon, J. Niederdoeckl, K. Janata, A.O. Spiel, N. Schuetz, S. Schnaubelt HH, F. Cacioppo, A.N. Laggner HD, Vernakalant and electrical cardioversion for AF – safe and effective, *Int. J. Cardiol. Hear. Vasc.* 24 (2019) 100398.
- [17] A. Müssigbrodt, S. John, J. Kosiuk, S. Richter, G. Hindricks, A. Bollmann, Vernakalant-facilitated electrical cardioversion: comparison of intravenous vernakalant and amiodarone for drug-enhanced electrical cardioversion of atrial fibrillation after failed electrical cardioversion, *Europace* 18 (2016) 51–56.

Gheorghe-Andrei Dan

“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

“Colentina” University Hospital, Cardiology Department, Bucharest,

Romania

Corresponding author.

E-mail address: andrei.dan@gadan.ro

Dobromir Dobrev

Institute of Pharmacology, West German Heart and Vascular Center,

University Duisburg-Essen, Essen, Germany

17 August 2019

Available online 1 September 2019