Indian Heart Journal 74 (2022) 212–217

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Efficacy and speed of conversion of recent onset atrial fibrillation using oral propafenone versus parenteral amiodarone: A randomized controlled comparative study

Hesham S. Taha [a, 1], Ghada Youssef [a, *, 1], Ramy M. Omar [b, 1], Ahmed M. Kamal El Din [b, 1], Ahmed A. Shams El Din [c, 1], Marwa S. Meshaal [a, 1]

[a] Cardiology Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[b] National Heart Institute, Cairo, Egypt
[c] Clinical Pathology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 10 February 2022
Received in revised form
11 April 2022
Accepted 17 April 2022
Available online 19 April 2022

Keywords:
Atrial fibrillation
Propafenone
Amiodarone

ABSTRACT

Background: Atrial fibrillation is the most commonly encountered arrhythmia. Several antiarrhythmic agents are effective in restoring and maintaining sinus rhythm.
Aim of the work: To compare the efficacy and rapidity of conversion of recent onset atrial fibrillation using oral propafenone versus intravenous infusion of amiodarone.
Methods: The study included 200 patients with recent onset atrial fibrillation. Patients were equally divided into 2 groups; group A where intravenous infusion amiodarone was given and group B where oral propafenone was administrated. The effectiveness and the time needed for conversion of atrial fibrillation to sinus rhythm were compared in both groups.
Results: The success of conversion of atrial fibrillation to sinus rhythm was 83% in group A and 85% in group B, p-value = 0.699. The time elapsed from drug administration till conversion of atrial fibrillation was 9.07 ± 5.04 hours in group A versus 3.9 ± 1.54 hours in group B, p-value = 0.001. In both groups, patients who showed failed conversion had a significantly larger left atrial diameter and a significantly higher high sensitivity C-reactive protein (hsCRP) level.
Conclusion: Oral propafenone was faster than parenteral amiodarone in the conversion of recent onset atrial fibrillation to sinus rhythm. Patients with failed conversion had a bigger left atrial diameter and a higher hsCRP when compared to patients with successful conversion.

1. Introduction

Atrial fibrillation (AF) is a common worldwide health problem, and Framingham heart study showed that the prevalence of AF had increased 3-folds in the past 50 years.[1] AF shares the pathophysiology of and is commonly associated with many cardiovascular risk factors as old age, diabetes mellitus and hypertension. The role of inflammation in the pathophysiology of AF is complex and incompletely understood. Yet, various inflammatory markers and mediators such as high sensitivity C-reactive protein (hsCRP), and cardiac troponin I (cTnI) have been linked to the presence and the outcome of AF.[2]

The debate of rate versus rhythm control is still going on, as randomized controlled trials showed no outcome benefit of rhythm versus rate control. Yet, it was shown that patients who underwent rhythm control had a slower progression of AF than patients with rate control strategy.[3] Several antiarrhythmic agents are effective in restoring and maintaining sinus rhythm in patients with AF, and selection of a particular drug depends on many factors, including the presence and type of underlying heart disease, concomitant illnesses, and renal or hepatic dysfunction.[4] Class IC and Class III antiarrhythmic drugs have been used successfully to convert recent onset AF.[5] Both amiodarone and propafenone have relatively high efficacy and can be administered by intravenous infusion or orally.[6]

* Corresponding author.
E-mail addresses: heshsalt@yahoo.com (H.S. Taha), ghadayoussef@kasralainy.edu.eg (G. Youssef), ramymomar84@gmail.com (R.M. Omar), amagdy2@gmail.com (A.M. Kamal El Din), ahmed.shamseldin@alma3mal.com (A.A. Shams El Din), marwamashaal2000@yahoo.com (M.S. Meshaal).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ihj.2022.04.006

Propafenone has the advantage of acting rapidly and its efficacy in converting recent onset AF to sinus rhythm has been documented.[7]

This study aimed at comparing the success rate and the time needed for conversion of recent onset AF to sinus rhythm using either oral propafenone tablets or intravenous infusion of amiodarone. It also aimed at studying the impact of specific biomarkers (hsCRP, Troponin & Neutrophil to lymphocyte ratio [NLR]) on the success of conversion of AF to sinus rhythm.

2. Patients and methods

The study included patients with a recent onset paroxysmal AF (defined as a palpitation that proved to be attributable to AF within 48 hours of presentation) who were eligible for pharmacological cardioversion. Patients were recruited from April 2017 to October 2018.

Exclusion criteria included; uncontrolled congestive heart failure, acute myocardial infarction within 7 Days, previous atrial flutter (for fear of 1:1 AV conduction with propafenone), previous thrombo-embolic episodes or stroke, presence of left atrial thrombi, a known hepatic or renal impairment, advanced bronchopulmonary disease, rheumatic valvular heart disease or significant valve stenosis or regurgitation, significant structural heart disease, ejection fraction (EF) < 50%, long QT or pre-excitation syndrome, pregnancy, haemodynamic instability (baseline systolic Bp $\leq$ 90 mmHg), previous electrocardiographic documentation of atrioventricular block or sick sinus syndrome, use of antiarrhythmic drugs at the time of admission (e.g., Beta Blockers (BBs) or Calcium Channel Blockers (CCBs)) and history of hypersensitivity to any of the study medications.

The local institutional ethical committee approved the current study (registration number is I-140314) and a written informed consent was obtained from all included patients.

2.1. Sample size calculation

A total of 192 patients (96 patients per group) was needed to produce the desired effect based on the results of Boriani et al.[8] who showed a 57% success of conversion with IV amiodarone and a 76% success with oral propafenone. The sample size was calculated using an online sample size calculator (https://clincalc.com/stats/SampleSize.aspx), with a study power of 80% and a significance level of <0.05.

2.2. Clinical assessment

Patients included in this study were subjected to history taking focusing mainly on history of any previous attacks of AF and duration of the current AF attack and thorough clinical examination with special attention to baseline heart rate and blood pressure measurements and complete cardiac examination. A baseline 12-lead electrocardiograms (ECG) was performed and the diagnosis of AF was established based on the following criteria: 1) Absence of p waves, 2) Presence of irregular atrial electrical activity and 3) Irregular RR intervals.

2.3. Laboratory work up

Baseline laboratory work up included: complete blood picture (NLR was calculated as the ratio of neutrophils to lymphocytes), liver function tests (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Bilirubin: total, direct and indirect), renal function tests (Urea and creatinine), thyroid function tests, serum potassium level and random blood sugar.

Blood samples were also collected for specific biomarkers evaluation. About 5 mL of venous blood was collected from an arm vein into one or more tubes. Within an hour the samples were centrifuged at 3.200 g for 10 min at a temperature of about 41 C°. The serum was separated into aliquots and was stored at −70 to −80 C° until the assay analysis was performed. The following markers were measured:

- *Plasma troponin-I (cTnI)*: was measured by using an electrochemical (amperometric) sensor and a high-sensitivity enzyme-linked immunosorbent assay (ELISA) technique (via Stratus CS®, Siemens, Germany ELISA kit, the results were calculated by (ng/ml) following the manufacturer's instructions. The 99th percentile of the URL was calculated to be 0.65 ng/mL based on a sample of 100 healthy patients from the hospital adherence region. Therefore, a troponin I of 0.65 ng/mL or higher was defined as a positive troponin I, between 0.15 and 0.65 ng/mL as a minor elevation, and a level of $\leq$0.15 was defined as non-detectable.
- *High sensitivity C reactive protein (hsCRP)*: The test was based on the photometric measurement of the agglutination between anti-hsCRP coated latex particles and CRP present in the sample. The hsCRP detection was done by using automated immunometric assay analyzer. The analysis was performed on the BNA nephelometer by micro-particle-enhanced immunonephelometric assay (Cardiophase hsCRP, Dade Behring, Siemens Healthcare Diagnostics, Eschborn, Germany) on a Behring BN ProSpec clinical chemistry analyzer, for which the measuring range was 0.06–10.2 mg/L.

2.4. Conventional echocardiography

A complete M-mode, two-dimensional and pulsed colour Doppler echocardiography were performed using a 2.5 MHz phased array of PHILIPS IE-33 machine. Patients were examined in the supine and left lateral positions to obtain adequate images in the parasternal long and short axis views, the four, five and two chamber apical views, the apical long axis as well as the subcostal views. The M-mode measurements of the left ventricular as well as the left atrial dimensions were taken.

Patients were then randomly assigned into 2 groups, using a closed envelope randomization method. Group (A) consisted of 100 patients who received intravenous amiodarone over a 24-hour period as follows:

1 Loading (rapid) infusions: 3 mL of amiodarone intravenous (I.V.) ampoules (150 mg) were added to 100 mL Dextrose 5% in water (D5W) (concentration = 1.5 mg/mL) and the rate of the infusion was set to (15 mg/min) so that 150 mg amiodarone was infused over the first 10 min.
2 Maintenance (slow) infusion: following the rapid infusion, 360 mg amiodarone were infused over the next 6 hours (the rate of the infusion was 1 mg/min). Then 18 mL of amiodarone I.V. (900 mg) were added to 500 mL D5W (concentration = 1.8 mg/mL) and 540 mg amiodarone was infused over the remaining 18 hours (the rate of infusion was 0.5 mg/min).

The second group (group B) consisted of 100 patients who received a single oral dose of propafenone (600 mg oral dose once).

Conversion to sinus rhythm was verified by continuous 24-hour ECG monitoring after drug intake. Blood pressure was measured hourly to ensure hemodynamic stability. No other rate control drugs were given to the patients. Patients who did not convert to

sinus rhythm within 24 hours, were considered drug failure and were offered the usual care of AF patients.

CHA2DS2-VASc score was calculated upon admission, and all patients were given parenteral anticoagulants (Heparin/Low molecular weight heparin) provided absence of any contraindication to anticoagulation.

2.5. Statistics

Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 17 (SPSS Inc., Chicago, Illinois). For quantitative data, the mean and the standard deviation were calculated. Comparison between the studied groups was performed with independent samples student *t*-test/ANOVA tests for continuous variables and Chi-Square/Fischer Exact test for categorical variables, and a p value < 0.05 was considered statistically significant.

3. Results

The study included 200 patients, equally randomized to 2 groups, group (A) patients who received parenteral amiodarone and group (B) patients who received oral propafenone. The baseline characteristics are shown in Table 1. Both groups were comparable as regards risk factors, echocardiographic dimensions and left ventricular systolic function, as well as laboratory findings. The mean admission serum potassium level was low, and this could be explained by the high sympathetic tone caused by the anxiety of palpitations and hospital admission. The high sympathetic tone can increase the K influx to the cells causing hypokalemia. Another explanation was that the low potassium level might be the predisposing factor for induction of AF. These low potassium levels were corrected once we received the laboratory results.

Most patients had no previous episodes of AF (68% in group A and 66% in group B) and the difference between both groups was insignificant ($p = 0.92$).

The success rate of conversion to sinus rhythm was comparable in both groups, Fig. 1. Group B patients showed numerically higher percentages of success of conversion as compared to group A and the pattern was similar in hypertensive and in diabetic patients in each group. The duration from drug administration to conversion to sinus rhythm was significantly shorter in group B (3.9 ± 1.5 hours in group B vs 9.1 ± 5.0 hours in group A, p-value = 0.001). The success of conversion occurred in the majority of group A patients in the interval between >6 and ≤12 hours while in group B, the conversion mostly occurred in less than 3 hours (p-value = 0.001), Fig. 2. None of the patients experienced drug-induced degeneration of atrial fibrillation to atrial flutter with increasingly rapid rates.

There was a higher failure rate of conversion in hypertensive patients of both groups when compared to normotensive patients (failure rate was 15% vs 2% in group A, p-value = 0.001, and it was 14% vs 1% in group B, p-value<0.001).

Similarly, the failure rate was higher in diabetic patients of both groups as compared to non-diabetic patients (failure rate was 15% vs 2% in group A, p-value = 0.001, and it was 13% vs 2% in group B, p-value <0.001).

After conversion to sinus rhythm, the mean heart rate was 73.1 ± 3.5 bpm in group A and 72.1 ± 7.0 bpm in group B, p-value = 0.539).

When comparing patients who had a successful conversion versus those who had a failed conversion, the successfully

Table 1
Baseline clinical, echocardiographic and laboratory data.

Variable	Amiodarone group ($n = 100$)	Propafenone group ($n = 100$)	*p*-value
Age, years	54.7 ± 5.3	53.9 ± 7.4	0.380
Male sex	61 (61%)	63 (63%)	0.884
Hypertension	34 (34%)	36 (36%)	0.441
Diabetes mellitus	49 (49%)	47 (47%)	0.443
Palpitations	73 (73%)	76 (76%)	0.372
SOB	24 (26%)	22 (22%)	0.433
Systolic BP, mmHg	129.8 ± 23.2	126.2 ± 18.8	0.229
Diastolic BP, mmHg	64.7 ± 30.8	66.2 ± 31.1	0.732
Heart rate, bpm	129.37 ± 5.34	128.41 ± 9.08	0.363
Echocardiography	**mean ± SD**	**mean ± SD**	
LVEF, %	56.41 ± 11.4	57.26 ± 9.3	0.564
LVEDD (mm)	54.1 ± 2.1	53.6 ± 2.7	0.145
Septal wall thickness (mm)	10.3 ± 1.31	9.8 ± 2.82	0.109
Posterior wall thickness (mm)	9.2 ± 3.1	8.8 ± 3.4	0.385
Left atrial diameter (LAD) (mm)	41.2 ± 2.4	39.7 ± 8.4	0.087
Laboratory work up	**mean ± SD**	**mean ± SD**	
Serum potassium (mmol/l)	3.8 ± 2.53	3.9 ± 1.81	0.748
Hemoglobin level (gm/dl)	12.8 ± 3.6	13.2 ± 2.9	0.387
White blood cells count (WBCs) ($x10^3$/HPF)	7.8 ± 2.3	7.71 ± 2.8	0.804
Serum creatinine (gm/dl)	0.82 ± 0.6	0.79 ± 0.8	0.764
ALT (U/L)	35 ± 7	36 ± 6	0.279
AST (U/L)	33 ± 6	31 ± 7	0.385
TSH (U/ml)	1.3 ± 0.4	1.4 ± 0.7	0.216
Troponin I (ng/mL)	0.44 ± 0.34	0.45 ± 0.46	0.861
NLR	2.9 ± 1.46	2.8 ± 1.63	0.648
hs CRP (mg/dL)	2.8 ± 1.61	2.9 ± 1.37	0.636
CHA2DS2-VASc score	2.31 ± 1.38	2.26 ± 1.28	0.79

ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, BP; Blood pressure, hsCRP; High sensitivity C-reactive protein, LAD; Left atrial diameter, LVEDD; Left ventricular end-diastolic dimension, LVEF; Left ventricular ejection fraction, NLR; Neutrophil to lymphocyte ratio, SD; Standard deviation, SOB; Shortness of breath, TSH; Thyroid stimulating hormone, WBC; White blood cells.
Data are presented either as frequency and (%) or as mean ± SD.
p value was considered significant at a level <0.05.

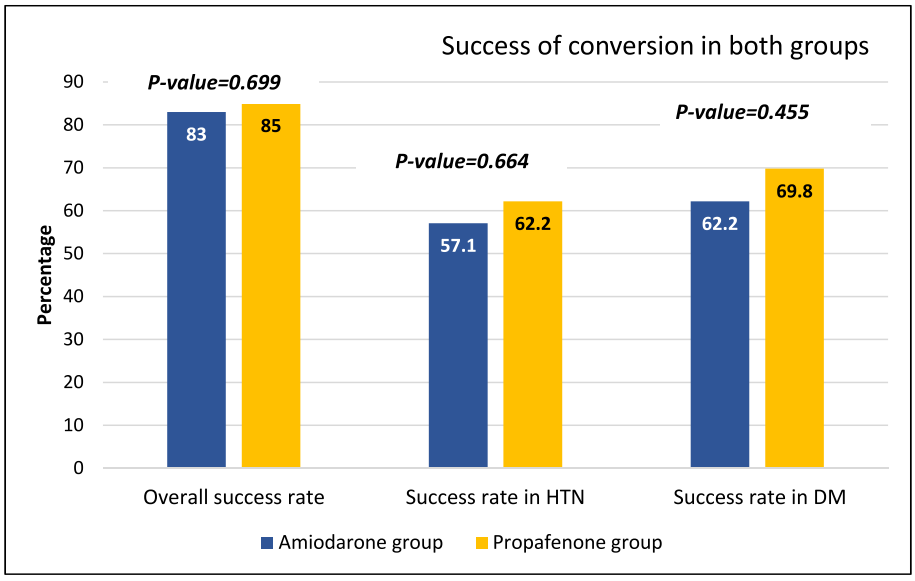

Fig. 1. The percentage of success of conversion to sinus rhythm in both groups, the overall success in all patients and the success in patients with HTN and patients with DM. *p* value was considered significant at a level <0.05.

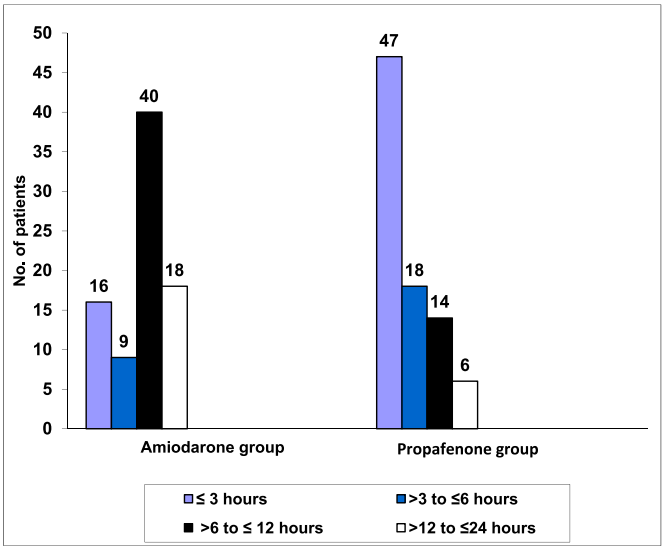

Fig. 2. The duration from drug administration till conversion to sinus rhythm in both groups.

converted patients had a significantly lower left atrial dimension (LAD) and a lower hsCRP in both groups, Table 2.

As regards complications, 4 (4%) patients had bradycardia, 5 (5%) patients had hypotension and 4 (4%) patients had phlebitis in group A, while in group B, 8 (8%) patients had bradycardia.

Table 2
Characteristics of patients who were successfully converted to sinus rhythm per group.

Variable	*Successful conversion*	*Failed conversion*	*p-value*
LAD, mm			
- Amiodarone group	37.5 ± 7.4	42.7 ± 7.1	0.001*
- Propafenone group	38.1 ± 7.3	42.6 ± 6.2	0.005*
LVEF, %			
- Amiodarone group	54 ± 4	53 ± 9	0.311
- Propafenone group	53 ± 8	54 ± 6	0.318
LVEDD, mm			
- Amiodarone group	54.2 ± 3.0	55.1 ± 5.0	0.124
- Propafenone group	53.8 ± 2.7	54 ± 3.2	0.633
Troponin I, ng/mL			
- Amiodarone group	0.44 ± 0.28	0.46 ± 0.37	0.667
- Propafenone group	0.45 ± 0.21	0.46 ± 0.35	0.806
NLR			
- Amiodarone group	2.7 ± 1.5	2.6 ± 1.7	0.659
- Propafenone group	2.6 ± 1.32	2.8 ± 1.48	0.314
hsCRP level, mg/dL			
- Amiodarone group	2.9 ± 1.5	3.8 ± 1.4	0.019*
- Propafenone group	2.6 ± 1.4	3.4 ± 1.5	0.013*

hsCRP; High sensitivity C-reactive protein, LAD; Left atrial diameter, LVEDD; Left ventricular end-diastolic dimension, LVEF; Left ventricular ejection fraction, NLR; Neutrophil to lymphocyte ratio.
Data are presented as mean ± SD.
**p* value was considered significant at a level <0.05.

4. Discussion

Atrial fibrillation (AF) is an irregular cardiac rhythm that leads to loss of the left atrial contractile function.[9] The disorganized heart rhythm invites left atrial (LA) thrombosis and may lead to serious thromboembolic events (e.g., stroke). Atrial fibrillation is considered the commonest cardiac arrhythmia, and its incidence increases with age.[2]

Lone atrial fibrillation is defined as AF without a structural heart disease, and it is usually seen in young individuals who are at a lower risk of thromboembolism. There are 2 options when treating AF, either to restore and maintain sinus rhythm, or to control the ventricular rate. Restoration of sinus rhythm leads to return of the beneficial atrial kick and this improves the cardiac hemodynamics and exercise tolerance.[10,11]

Many antiarrhythmic drugs have shown efficacy in conversion of AF to sinus rhythm. Of these, amiodarone and propafenone were particularly useful and widely used in clinical practice.

The conversion rate of amiodarone ranged from 41% to 100% within the first 24 h after administration[12] while propafenone has the advantage of rapid action and its efficacy in converting AF to sinus rhythm has been documented.[13]

This study investigated the efficacy of these two commonly used antiarrhythmic drugs, oral propafenone versus intravenous

infusion of amiodarone. This study is a continuation of a pilot study that tested only 50 patients and was published in 2017.[14] In the current study, we investigated 200 patients who suffered from a recent onset AF within the last 48 hours. The success rate of conversion in group A was 83%, while in group B, the success rate was 85%. Similar success rates were demonstrated in other studies; Balla et al[15] (success rate 86.2% with amiodarone), Cotter et al[16] (82% success with amiodarone) and Kosior et al[17] (83% success with propafenone).

The mean time needed for conversion of AF to sinus rhythm was significantly shorter in the propafenone group (3 hours and 9 min) as compared to the amiodarone group (9 hours and 1 min). This was similarly demonstrated by Kochiadakis, et al[18] who found that the mean conversion time was 9 hours with amiodarone and 1 hour with intravenous propafenone. Balla, et al[15] stated that the highest conversion rates with amiodarone were between 6 and 12 hours and that for propafenone was between 3 and 6 hours after administration. In addition, Conde et al[19] who studied the effect of oral loading dose of propafenone 600 mg for conversion of recent-onset AF in patients without structural heart disease had found that the mean time to conversion to sinus rhythm was 166 min (120–300 min) which is quite similar to our results. findings are important because being able to convert AF to sinus rhythm in a shorter time (using propafenone) permits a shorter hospital stay and a subsequent reduction of the overall economic burden of treatment. Besides, it alleviates much of the patient's stress and anxiety related to prolonged hospitalization.

Patients who were successfully converted to sinus rhythm had a significantly smaller LAD and a lower hsCRP as compared to patient who failed to convert, and this association was demonstrated in both study groups. Similar results were found by Kochiadakis et al.[18] and Abhayaratna, et al.[20] and Xinyuan Han, et al.[21] It is well known that an increase in the LAD leads to a structural remodelling of the LA wall. The pathophysiologic mechanism most consistent with this is that a chronic hemodynamic burden initially produces left atrial enlargement which in turn predisposes to atrial fibrillation.[22] Darniellis, et al. had assessed the level of hsCRP in paroxysmal recent onset AF and its relation to successful cardioversion. He concluded that hsCRP level is increased in AF and the higher the level of hsCRP the lower the success rate of cardioversion.[23] Left ventricular ejection fraction, left ventricular end-diastolic dimension, cTnI level and NLR showed no difference between patients with successful versus patients with failed conversion to sinus rhythm.

Vernakalant is a promising investigational drug that was shown to be more effective than parenteral amiodarone in conversion of recent onset AF to sinus rhythm.[24] Despite that the drug is approved in Europe and some other countries, it is not yet FDA approved.

To our knowledge, this is the first study to demonstrate the comparable efficacy and the faster mode of action of oral propafenone as compared to parenteral amiodarone. These findings are important because oral propafenone is readily available, easy to administrate and does not need admission to the hospital. Using oral propafenone instead of parenteral amiodarone can reduce the cost and the burden over the healthcare system because simply, the patient can be treated at home.

5. Limitation

A considerable number of AF patients, especially those with recent onset AF, could spontaneously revert to sinus rhythm without the need for pharmacologic and/or electric treatment, as proved by Dell O'Frano et al.[25] One limitation in our study is that we did not include a placebo group to test for the rate of spontaneous cardioversion. It is possible that some patients could have been spontaneously reverted without or despite the type of antiarrhythmic drug used.

6. Conclusion

Oral Propafenone and intravenous infusion of Amiodarone are effective antiarrhythmic drugs for conversion of recent onset AF to sinus rhythm. Oral propafenone has the advantage of a faster onset of action than amiodarone. The bigger the left atrial diameter and the higher the hsCRP, the lower the conversion success rate.

Declaration of competing interest

Authors have nothing to declare.

References

1. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386(9989):154–162.
2. Balta S, Aparci M, Yildirim AO, Demir M, Ozturk C, Celik T. The relation between flow mediated dilation and atrial fibrillation. *Int J Cardiol*. 2016;203:1157.
3. Zhang Y-Y, Qiu C, Davis PJ, et al. Predictors of progression of recently diagnosed atrial fibrillation in REgistry on cardiac rhythm DisORDers assessing the control of atrial fibrillation (RecordAF)-United States cohort. *Am J Cardiol*. 2013;112(1):79–84.
4. Lüker J, Sultan A, Sehner S, et al. Use of antiarrhythmic drugs during ablation of persistent atrial fibrillation: observations from a large single-centre cohort. *Heart Ves*. 2016;31(10):1669–1675.
5. Giménez-García E, Clua-Espuny JL, Bosch-Príncep R, et al. [The management of atrial fibrillation and characteristics of its current care in outpatients. AFABE observational study]. *Atención Primaria*. 2014;46(2):58–67.
6. Epstein AE, Olshansky B, Naccarelli GV, Kennedy Jr JI, Murphy EJ, Goldschlager N. Practical management guide for clinicians who treat patients with amiodarone. *Am J Med*. 2016;129(5):468–475.
7. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol*. 2001;37(2):542–547.
8. Boriani G, Biffi M, Capucci A, et al. Conversion of recent-onset atrial fibrillation to sinus rhythm: effects of different drug protocols. *Pacing Clin Electrophysiol : PACE*. 1998;21(11 Pt 2):2470–2474.
9. Battaglia A, Anselmino M, Ferraris F, Gaita F. Left persistent superior vena cava as a source of focal atrial arrhythmias: a late arrhythmia recurrence due to a latent proximal focus. *Int J Cardiol*. 2016;203:523–524.
10. Kerr CR, Boone J, Connolly SJ, et al. The Canadian Registry of Atrial Fibrillation: a noninterventional follow-up of patients after the first diagnosis of atrial fibrillation. *Am J Cardiol*. 1998;82(8a):82n, 5n.
11. Shinagawa K, Shiroshita-Takeshita A, Schram G, Nattel S. Effects of antiarrhythmic drugs on fibrillation in the remodeled atrium: insights into the mechanism of the superior efficacy of amiodarone. *Circulation*. 2003;107(10):1440–1446.
12. Bhave PD, Lu X, Girotra S, Kamel H, Vaughan Sarrazin MS. Race- and sex-related differences in care for patients newly diagnosed with atrial fibrillation. *Heart Rhythm*. 2015;12(7):1406–1412.
13. Cicogna R, Mascioli G, Bonomi FG, et al. Carotid sinus hypersensitivity and syndrome in patients with chronic atrial fibrillation. *Pacing Clin Electrophysiol : PACE*. 1994;17(10):1635–1640.
14. Omar Ramy M, Taha Hesham S, Kamal El-Din Ahmed M, et al. Pharmacological conversion of recent onset atrial fibrillation: a randomized study of propafenone and amiodarone. *Med J Cairo Univ*. 2017;85(7):2669–2674.
15. Balla I, Petrela E, Kondili A. Pharmacological conversion of recent atrial fibrillation: a randomized, placebo-controlled study of three antiarrhythmic drugs. *Anadolu Kardiyol Derg*. 2011;11(7):600–606.
16. Cotter G, Blatt A, Kaluski E, et al. Conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm: the effect of no treatment and high-dose amiodarone. A randomized, placebo-controlled study. *Eur Heart J*. 1999;20(24):1833–1842.
17. Kosior DA, Kochanowski J, Scislo P, et al. Efficacy and tolerability of oral propafenone versus quinidine in the treatment of recent onset atrial fibrillation: a randomized, prospective study. *Cardiol J*. 2009;16(6):521–527.
18. Kochiadakis GE, Igoumenidis NE, Hamilos ME, Marketou ME, Chlouverakis GI, Vardas PE. A comparative study of the efficacy and safety of procainamide versus propafenone versus amiodarone for the conversion of recent-onset atrial fibrillation. *Am J Cardiol*. 2007;99(12):1721–1725.
19. Conde D, Costabel JP, Aragon M, et al. Propafenone versus vernakalant for conversion of recent-onset atrial fibrillation. *Cardiovasc Therap*. 2013;31(6):377–380.

20. Abhayaratna WP, Seward JB, Appleton CP, et al. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol*. 2006;47(12):2357–2363.
21. Han X, Chen C, Cheng G, et al. Serum fibroblast growth factor 21 levels are increased in atrial fibrillation patients. *Cytokine*. 2015;73(1):176–180.
22. D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol*. 2013;167(5):1984–1989.
23. Dernellis J, Panaretou M. C-reactive protein and paroxysmal atrial fibrillation: evidence of the implication of an inflammatory process in paroxysmal atrial fibrillation. *Acta Cardiol*. 2001;56(6):375–380.
24. Camm AJ, Capucci A, Hohnloser SH, et al. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol*. 2011;57(3):313–321.
25. Dell'Orfano JT, Patel H, Wolbrette DL, Luck JC, Naccarelli GV. Acute treatment of atrial fibrillation: spontaneous conversion rates and cost of care. *Am J Cardiol*. 1999;83(5):788–790.