ORIGINAL ARTICLE

Vernakalant in hospital emergency practice: safety and effectiveness

José Carbajosa Dalmau[1,2], Juan Cosín-Sales[3], María José Pérez-Durá[4], José Noceda[5], Amós Urtubia-Palacios[6], Néstor Hernández-Sori[1,2], Ana Peiró-Gómez[7], Javier Jacob[8], Pere Llorens[9], Luis Ruescas-Gómez[7], Alfonso Martín-Martínez[2,10]

Objectives. To study the effectiveness and safety of vernakalant for restoration of sinus rhythm in patients with atrial fibrillation (AF) in routine hospital emergency department care, and to evaluate factors associated with a more effective response.

Methods. Prospective multicenter cohort study enrolling consecutive patients who were administered vernakalant for medical cardioversion of AF between September 2014 through March 2016 in 5 hospitals in the Spanish autonomous community of Valencia.

Results. We studied 165 cases. The median (interquartile range) was 68 years (56–77) years. Cardioversion with vernakalant was effective in 77.6% (95% CI, 71.1%–84%). The median time to conversion was 8 (6–12) minutes after a first dose and 34 (22–62) minutes after a second dose. A prior history of cardiac insufficiency was nonsignificantly less common in patients who converted with vernakalant (6.3%) than in those who did not (18.9%) (adjusted odds ratio [OR], 0.45 [95% CI, 0.13–1.56]; *P*=.208). Having no prior history of AF was nonsignificantly related to greater effectiveness (in 54.7% *vs* in 35.1% with prior AF). Duration less than 12 hours was significantly associated with greater effectiveness (83.6% *vs* 59.5%; adjusted OR, 2.76 [95% CI, 1.12–6.80]; *P*=.028). Adverse events were reported for 30 patients. None of the events had clinically important consequences, and in only 2 cases (1.2%) was it necessary to suspend treatment.

Conclusion. Vernakalant is effective and safe for restoring sinus rhythm in the hospital emergency department.

Keywords: Atrial fibrillation. Cardioversion. Vernakalant. Emergency health services.

Seguridad y eficacia de vernakalant en la práctica clínica de los servicios de urgencias

Objetivo. Describir la eficacia y seguridad de vernakalant para la reversión de la fibrilación auricular (FA) a ritmo sinusal en la práctica clínica habitual de los servicios de urgencias hospitalarios (SUH), así como evaluar las características asociadas a mayor respuesta eficaz.

Método. Estudio de cohortes multicéntrico, analítico, prospectivo, con inclusión consecutiva de pacientes en los que se administra vernakalant para realizar cardioversión farmacológica de una FA, llevado a cabo desde Septiembre 2014 hasta Marzo 2016 en 5 hospitales de la Comunidad Valenciana.

Resultados. Se analizaron 165 casos con una mediana de edad de 68 años [rango intercuartil (RIC): 56-77]. La reversión eficaz fue de 77,6% (IC 95%: 71,1%-84,0%). La mediana del tiempo de reversión fue de 8 minutos (RIC: 6-12) con la primera dosis y de 34 minutos (RIC: 22-62) con la segunda. La presencia de insuficiencia cardiaca previa fue menos frecuente en el grupo que revirtió con vernakalant, 6,3% frente a 18,9%, con una OR ajustada de 0,45 (IC 95%: 0,13-1,56), p = 0,208. Ser un primer episodio de FA y tener una duración de menos de 12 horas se relacionó con mayores tasas de reversión, 54,7% frente a 35,1% y de 83,6% frente a 59,5%, respectivamente, pero solo la segunda fue significativa con una OR ajustada de 2,76 (IC 95%: 1,12-6,80), p = 0,028. Se notificaron eventos adversos en 30 pacientes. Ninguno de ellos tuvo consecuencias relevantes y sólo dos (1,2%) motivaron la suspensión del fármaco.

Conclusiones. Vernakalant es un fármaco eficaz y seguro para la restauración del ritmo sinusal en los SUH.

Palabras clave: Fibrilación auricular. Cardioversión. Vernakalant. Urgencias.

Authors affiliation:
[1]Servicio Urgencias,Hospital General de Alicante; Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL-Fundación FISABIO), Alicante, Spain.
[2]Grupo de Arritmias Cardiacas, SEMES.
[3]Servicio Cardiología, Hospital Arnau de Villanova, Valencia, Spain.
[4]Servicio Urgencias, Hospital Universitario y Politécnico La Fe, Valencia, Spain.
[5]Servicio Urgencias, Hospital de Sagunto, Valencia, Spain.
[6]Servicio Urgencias, Hospital de Elda, Alicante, Spain.
[7]Servicio Urgencias, Hospital Arnau de Villanova, Valencia, Spain.
[8]Servicio de Urgencias, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain.
[9]Servicio de Urgencias, Unidad de Corta Estancia y Hospitalización a Domicilio, Hospital General de Alicante; Departamento de Medicina Clínica, Universidad Miguel Hernández; Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL-Fundación FISABIO), Alicante, Spain.
[10]Servicio Urgencias, Hospital Universitario Severo Ochoa, Madrid, Spain.

Contribution of authors:
All authors have confirmed their authorship in the author's responsibilities documents publication agreement and assignment of rights to EMERGENCIAS.

Corresponding author:
José Carbajosa Dalmau
C/ Manuel Azaña, 2, pta. 30
03540 Alicante, Spain

E-mail:
jcarbajosad@hotmail.com

Article information:
Received: 10-3-2017
Accepted: 20-07-2017
Online: 9-10-2017

Editor in charge:
Agustín Julián-Jiménez, MD, PhD.

Introduction

Atrial fibrillation (AF) is the cardiac arrhythmia maintained most frequently treated in the hospital emergency services (HES), with a prevalence of 3-4% of general emergencies and greater than 2% in the general population, which is calculated that will double in the next few years due to population aging[1-3]. It is estimated that it affects 5-6% of those over 65 and increases above 10% in those over 80[4], representing an impor-

tant health problem, since it is associated with a higher death rate, heart failure (HF), cerebrovascular accident (CVA) and other thromboembolic episodes[5].

Current guidelines for the management of AF[1,6,7] recommend cardioversion and maintenance of the patient in sinus rhythm (SR), whenever possible. For this, we have two strategies: electrical and pharmacological cardioversion. Regardless of the chosen strategy, it is important to carry it out as soon as possible, with the intention of minimizing the electrical and structural remodelling that begins already in the first hours, and that favours the perpetuation of the arrhythmia[8-10]. Until now, for the pharmacological strategy, IC antiarrhythmics are recommended, with success rates between 65-80%, but contraindicated in patients with structural heart disease due to their pro-arrhythmic risk[11]. Another option recommended in the guidelines is amiodarone[7], although it has the disadvantage of its lower efficacy and delayed cardioversion, which causes an increase in the length of hospital stay[12]. Vernakalant is a drug recommended in the European guidelines of the AF since 2012[7] that offers greater safety than flecainide and propafenone in patients with structural heart disease and greater efficacy and speed than amiodarone; with an excellent safety profile in patients with structural heart disease[13]. It acts mainly in the atrium, with little impact on the ventricle due to its lower expression of the receptors where it acts, thus reducing the risk of pro-arrhythmia. Clinical trials have shown efficacy around 50% achieving rapid reversion, in about 11 minutes on average[13-16]. We have little information on efficacy and safety outcomes in routine clinical practice (real life data), outside of the criteria for the selection of clinical trials. In this regard, the study carried out at the University of Malmö (Sweden)[17] performed in the emergency hospital setting, as well as other studies done in our environment, suggest that success rates could be higher in routine clinical practice[18,19].

The aim of this study is to describe the efficacy and safety of treatment with vernakalant in patients with AF in the real conditions of the hospital emergency services (HES) and to evaluate the characteristics associated with a higher rate of successful response to vernakalant.

Method

This is a multicentre, analytical, prospective cohort study with consecutive inclusion of patients in whom vernakalant is administered to perform pharmacological cardioversion of an AF. It was carried out from September 2014 to March 2016 in 5 hospitals of the Valencian Community: Hospital Arnau de Villanova, Hospital General Universitario de Alicante, La Fe University and Polytechnic Hospital of Valencia, Sagunto Hospital and Elda Hospital.

The inclusion criteria were to present an AF candidate for pharmacological cardioversion with vernakalant according to the current guidelines[7] and obtain informed consent. Patients with contraindications specific to the use of vernakalant according to the data sheet were excluded from the study: hypersensitivity to the active principle or to any of the components, severe aortic stenosis, systolic blood pressure < 100 mmHg and patients with HF in class NYHA III and IV. Also, patients with uncorrected electrolyte abnormalities, prolonged QT interval in the initial situation (> 440 ms uncorrected), severe bradycardia, sinus node dysfunction or second and third degree atrioventricular block in the absence of pacemaker, acute coronary syndrome within the last 30 days, and refusal of the patient to participate in the registry. The inclusion of patients treated with administered antiarrhythmics (class I and III) was allowed at least 4 hours before.

A first dose adjusted to weight (3 mg/kg) administered in 10 minutes was prescribed by an intravenous infusion pump. After a period of 15 minutes of their end, they received a second dose (2 mg/kg in 10 min.) If the first one did not achieve reversion to SR. The treated subjects remained monitored (blood pressure, heart rate, heart rate and pulse oximetry) during the infusion and until at least 2 hours after the end of the last dose of drug and, in the event of no cardioversion, electrical cardioversion was considered. The study was approved by the Clinical Research Ethics Committee of the General University Hospital of Alicante. The registration was made following the guidelines of the Declaration of Helsinki on the ethical principles for medical research.

All patients underwent an electrocardiogram, which was assessed by an emergency doctor and transcribed in the patient's clinical history, according to the usual clinical practice. Efficacy and safety data were collected until discharge from the emergency department, at least 2 hours after drug administration.

We collected demographic data (age and sex), baseline characteristics (cardiovascular personal history: arterial hypertension, diabetes mellitus, peripheral arterial disease, stroke, HF, and we calculated the CHA_2DS_2-VAS^c and $CHADS_2$ scores for each of them), antiarrhythmic treatment (amiodarone, beta-blocker, calcium antagonist, flecainide, propafenone, digoxin or dronedarone) and whether or not taking anticoagulant prior to the administration of vernakalant, as well as the characteristics of AF (first episode or paroxysmal/persistent and duration). The duration of the arrhythmia was calculated by measuring the time in minutes from the onset of symptoms until the time of drug infusion, and was classified according to current guidelines[1,6,7]. The times were recorded (time between admission to the emergency department and the first dose of vernakalant, time between the 1st dose of vernakalant and the reversal to SR, time between the 2nd dose of vernakalant and the reversal to SR, length of stay in the emergency room); and adverse events until discharge from the HES.

For the description of the qualitative variables we used absolute and relative frequencies and for the

quantitative ones, the median and the interquartile range (IQR). For the comparisons, the chi-square test was used for the first ones (or in the 2 × 2 tables the Fisher exact test when the expected strengths were less than 5) and for the second the Student's t test for independent measurements or the Mann-Whitney U test if the variables did not follow a normal distribution, which was checked with the Kolmogorov-Smirnov test. The main outcome dependent variable was "successful cardioversion with vernakalant". A logistic regression model with "introduction method" was performed for the main variable of cardioversion success, adjusted to the variables that in the bivariate study were associated with $p < 0.2$. The differences were considered to be statistically significant when the p-value was less than 0.05 or when the confidence interval (CI) at 95% of the odds ratio (OR) excluded the value 1. The statistical program used was SPSS 19.0.

Results

In the HES of the 5 hospitals of the Valencian Community, 165 cases of AF treated with vernakalant were recruited. The median age of the patients was 68 years (IQR: 56-77) and 46.1% were women. Vernakalant reversed 77.6% (95% CI: 71.1%-84%) of the treated episodes, 60.6% (95% CI: 53.1%-68.1%) with the first dose. This implies that 78.1% (95% CI: 70.9% -85.4%) of the total AF that vernakalant reversed did with the first dose.

Table 1 shows the demographic characteristics and cardiovascular risk factors of the patients treated, as well as the differences depending on whether or not they reversed SR with vernakalant. 45% of the cases had received antiarrhythmics, either as usual treatment or had been administered before the first dose of vernakalant. None of the antiarrhythmics studied (amiodarone, beta blockers, flecainide and propafenone) showed significant differences in terms of success in cardioversion with vernakalant. Previous HF was less frequent in patients who responded to the drug, 6.3% versus 18.9%, but with a non-significant adjusted OR of 0.45 (95% CI: 0.13-1.56), p = 0.208 (Table 2).

50.3% were patients who had a first episode of AF diagnosed against a paroxysmal or persistent episode. This fact was related to a greater tendency to cardioversion, 54.7% versus 35.1%, but with a non-significant adjusted OR of 1.77 (95% CI: 0.68-4.58), p = 0.242 (Table 2).

78.2% of the patients had less than 12 hours of evolution with symptoms. This variable was more frequent in the group of patients who responded to treatment with vernakalant (83.6% vs. 59.5%); Adjusted OR of 3.64 (95% CI: 1.62-8.19, p = 0.002), as shown in Table 2.

Table 3 shows the results related to the times since the arrival of the patient to the HES. The median time to revert to SR of the patients who responded to the first dose of vernakalant was 8 (IQR: 6-12) minutes and 34 (IQR: 22-62) minutes those who did it with the second. The median delay in administering the drug since the arrival of the patient in the emergency department was 87 (IQR: 50-160) minutes in total. Overall, the emergency room was 271 (IQR: 214-471) minutes,

Table 1. General characteristics of the cases collected and comparative study depending on whether there is reversion or not to sinus rhythm with vernakalant

	Total N = 165 n (%)	Reverse with vernakalant N = 128 n (%)	No reverse with vernakalant N = 37 n (%)	p
Demographics				
Age [median (IQR)]	68 (56-77)	68 (56-77.8)	65 (53-75)	0.555
Age > 75 years	49 (29.7)	41 (32.0)	8 (21.6)	0.222
Female	76 (46.1)	63 (49.2)	13 (35.1)	0.130
Personal history				
Arterial hypertension	99 (60.0)	77 (60.2)	22 (59.5)	0.939
Mellitus diabetes	16 (9.7)	14 (10.9)	2 (5.4)	0.317
Arteriopathy peripheral	3 (2.8)	3 (3.9)	0 (0)	0.296
Vascular accident cerebral	12 (7.5)	9 (7.4)	3 (8.1)	0.883
Heart failure	15 (9.1)	8 (6.3)	7 (18.9)	0.018
CHA_2DS_2-VASc, [median (IQR)]	2 (1-4)	2 (1-4)	2 (1-3)	1.000
$CHADS_2$ [mean (IQR)]	1 (0-2)	1 (0-2)	1 (0-2)	1.000
Previous treatment				
Previous anticoagulation	34 (29.6)	24 (27.9)	10 (34.5)	0.502
Beta-blockers	31 (20.4)	23 (19.0)	8 (25.8)	0.402
Amiodarone	11 (7.2)	8 (6.6)	3 (9.7)	0.557
Antiarrhythmic IC group	5 (3.3)	3 (6.5)	2 (2.5)	0.270
No antiarrhythmic base	99 (65.1)	83 (68.6)	16 (51.6)	0.077
Characteristics of atrial fibrillation				
First episode	83 (50.3)	70 (54.7)	13 (35.1)	0.036
Less than 12 hours	129 (78.2)	107 (83.6)	22 (59.5)	0.002

IQR: Interquartile range.

Table 2. Crude and adjusted odds ratios of the independent predictor variables of response to vernakalant in the bivariate study

	Raw OR (95% CI)	p	Adjusted OR* (95% CI)	p
Personal history				
Previous heart failure	0.29 (0.10-90.85)	0.018	0.45 (0.13-1.56)	0.208
Characteristics of AF				
First episode of AF	2.23 (1.04-4.76)	0.036	1.77 (0.68-4.58)	0.242
Duration of the episode of AF				
Less than 12 hours	3.47 (1.55-7.78)	0.002	2.76 (1.12-6.80)	0.028

AF: Atrial fibrillation.
* OR adjusted for female gender, previous heart failure, no antiarrhythmic based, first episode of AF and episode duration less than 12 hours.

Table 3. Times from the arrival of the patient to the hospital emergency department until the administration of the drug and for the passage to sinus rhythm

Timing (minutes) [mean (IQR)]	Total N = 165	Reverse with vernakalant N = 128	No revierten con vernakalant N = 37	p
Time 1	87 (50-160)	83 (45-154)	91.5 (56-217)	0.231
Time 2	8 (6-12)	8 (6-12)	–	–
Time 3	37 (22-60)	34 (22-62)	–	–
Total stay in emergency department	271 (214-471)	243 (201-375)	493 (374-664)	< 0.001

IQR: Interquartile range
Time 1: door time - Vernakalant; Time 2: time vernakalant 1st dose - reversion to sinus rhythm; Time 3: Vernakalant time 2nd dose - reversion to sinus rhythm.

and was significantly shorter in the patients who responded to the vernakalant: median of 243 (IQR: 201-375) versus 493 (IQR: 374-664) minutes, p < 0.001. Twenty patients (12.1%) received electrical cardioversion in the emergency room, carried out at least 2 hours after the end of the administration of the drug. There were no complications except one of them who presented a hypertensive crisis with acute pulmonary oedema after the electric shock, resolved with conventional treatment, and who was discharged home 8 hours later.

32 adverse events were reported in 30 patients (Table 4), mostly mild (dysgeusia, cough, nausea, sneezing, etc.). Although there were 4 episodes of non-sustained ventricular tachycardia (two reversed SR with the first dose), 2 hypotension and 2 bradycardia, no death or torsade de pointes episodes were reported during treatment with vernakalant. Of these last 8 patients, only one had a history of HF and none of these episodes had relevant consequences. In 2 cases the appearance of an adverse effect led to the suspension of the treatment by the responsible physician.

Discussion

We submit the data obtained from a study on the use of vernakalant in 5 HES. This is to date one of the studies with the largest number of patients collected internationally on the use of vernakalant in usual medical practice. As in most of the few published works of real-life data with vernakalant[17-21], the efficacy of the drug in our study has been clearly superior, 77.6% (95% CI 71.1% -84%), to the published in the ACT I-IV and AVRO[13-16] studies, which was around 50%; and even better to 70% published in the study carried out in 351 patients at the Skäne University Hospital in Malmö (Sweden)[17]. Congruently with this last study, which describes a 76% success in patients with less than 10 hours of evolution in, versus 66% in those with more than 10 hours of evolution, the key to the greater efficacy of vernakalant in our work is probably the time of evolution of the arrhythmia, since the duration of the episode less than 12 hours was one of

Table 4. Description of adverse events related to the administration of vernakalant

Adverse effects	Total N = 165 n (%)
Sneezing	9 (5.5)
Dysgeusia	7 (4.2)
Ventricular tachycardia	4 (2.4)
Cough	4 (2.4)
Nausea	4 (2.4)
Hypotension (SBP < 90 mmHg))	2 (1.2)
Bradycardia	2 (1.2)

SBP: systolic blood pressure.

the variables independent predictors of response to vernakalant.

The baseline characteristics of the patients in our study are similar to those of other records of AF performed in Spain[22], so our sample is representative of the population with AF of recent start attended in Spanish HES and the results applicable to that population. The median age was higher than that of the clinical trials performed with vernakalant[13-16] which, as seen in other registers, reflects the reality of the Spanish HES[23-25].

Although in our study the patients who reverted to SR were older than those who did not, the difference was not statistically significant. The oldest group (> 75 years) was specifically studied without showing any differences either. For that reason, in agreement with other works[17], we consider that the age is not an influential factor in the likelihood of successful reversal to SR with vernakalant. This fact is of undoubted clinical relevance, since, although cardioversion is performed to a lesser extent in elderly patients, our data suggest that it should be the patient's profile (type of AF, time of evolution, history of HF, etc.) and not your age which is decisive to when proposing the restoration of SR in the recently started AF[1]. Our sample contains a high percentage of women and, unlike what was published in the Juul-Möller study[17], women's sex (although more prevalent in the group that did respond to the drug) decreasing has not been related to a higher probability of cardioversion. This data is also consistent with other studies[18].

Of all the variables collected as cardiovascular history, only HF was associated with a lower tendency to revert to SR. This is probably due to the greater alteration of the atrial cellular structure of these patients, which favours the perpetuation of the arrhythmia and makes its reversion more difficult[26]. As we have mentioned previously, it is important to highlight the efficacy in patients with an AF of less than 12 hours of evolution. This is explained by the fact that early cardioversion is associated with higher rates of success in restoration to SR and a reduction in the risk of recurrences due to reduced electrical remodelling (changes in the effective refractory period), structural and contractile remodelling, which already appear in the first hours of the beginning of AF[27,28].

Compared with other antiarrhythmics, vernakalant is a drug that achieves a rapid cardioversion to SR (8 mi-

nutes median those that respond to the first dose and 34 minutes with the second in our study). Therefore, we think that it is a drug with an excellent profile for its use in HES, in many cases with structural and human resources difficulties for performing electrical cardioversion, and it is a good alternative if the pharmacological option is chosen, since it could reduce the workload and personnel to carry out a necessary cardioversion. In addition, we know that hospital expenditure is the main determinant of the total cost of AF in Europe[29]. As shown in this study, vernakalant reduces the hospital stay of patients who responded to treatment (77.6% of the treated) and therefore could reduce the number of admissions and therefore the overall costs derived from the hospital care of this disease.

Regarding safety, as in clinical trials, vernakalant has behaved as a safe drug, with few adverse effects, mostly mild and transient (dysgeusia, sneezing, nausea) and already described in clinical trials. The drug was suspended in 2 cases at the discretion of the responsible physician. One for increased heart rate, in a patient with no relevant history and without prior antiarrhythmic treatment, which resolved within a few minutes of stopping the drug. The second was due to a symptomatic sinus pause immediately after the reversal to SR, in a woman with a history of interventional aortic stenosis, resolved without further incidents.

In other studies[20] HF has been related to a higher probability of serious adverse effects (ventricular tachycardia and hypotension, fundamentally). In our study, 4 episodes of non-sustained ventricular tachycardia (2 of them reverted to SR), 2 episodes of hypotension and 2 episodes of bradycardia are cited as the most relevant events, all of them without consequences and that were resolved with conservative treatment. Only one of these patients had a history of HF. On the other hand, it is known that the majority of patients with AF treated in our HES are polymedicated1 and this can be a problem, since the administration of several antiarrhythmics together is not recommended because they enhance the proarrhythmic effect[30]. In our work, almost 35% of the patients had taken a previous antiarrhythmic (at least 4 hours before) to the administration of vernakalant, there were no reported problems in terms of safety or having found significant differences in effectiveness. Calcium antagonists, dronedarone and digoxin were not studied due to lack of sample size.

This study presents a series of limitations. The conclusions of this work must be handled with caution. In the case of an observational study, there may be an uncontrolled selection bias. The proportion of patients with AF of few hours of evolution has been surprisingly high, as well as the percentage of patients with their first episode of AF. The data recorded that were used for the analysis were limited until discharge from the HES and no subsequent efficacy and safety data were investigated. Taking into account that patients who had previously participated in the registry were not excluded, it is likely that the treatment was applied more than once to the same patient, although in different episodes. It would also have been interesting to know the number of patients with AF that went to the HES in the study period, to obtain the percentage of all patients treated with vernakalant, as well as the number of patients treated with vernakalant during the study period. not included or excluded by any of the defined criteria. Unfortunately, we do not have these data, since they were not considered in the design of the study.

As conclusions of this work, we can point out that the need for information in the real healthcare setting is an increasingly relevant fact, which influences health care decision making and resource management. Our study shows a greater efficacy of vernakalant than that described in clinical trials, with a rapid reversal to SR and with an adequate safety profile. For all these reasons, and based on our experience, we believe that vernakalant is a drug with excellent characteristics for use in hospital emergency services.

Conflict of interests

José Carbajosa Dalmau has received fees from Cardiome for giving presentations. Juan Cosin-Sales has received fees from Cardiome for giving a presentation. José Noceda has received fees from Cardiome for giving presentations. The remaining authors declare no conflicts of interest in relation to this article.

Financing

The authors declare the non-existence of external financing of this article.

Ethical Responsibilities

The study was approved by the Clinical Research Ethics Committee of the General University Hospital of Alicante.

Informed consent was obtained from participants.

All authors have confirmed the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS.

Article not commissioned by the Editorial Committee and with external peer review

References

1 Martín A, Fernández-Lozano I, Coll-Vinent B, Tercedor-Sánchez L, Del Arco C, Arribas F, et al. Manejo de los pacientes con fibrilación auricular en los servicios de urgencias hospitalarios (actualización 2012). Emergencias. 2012;24:300-24.

2 Gómez-Doblas JJ, Muñiz J, Alonso Martín JJ, Rodríguez-Roca G, Lobos JM, Awamleh P, et al. Prevalencia de fibrilación auricular en España. Resultados del estudio OFRECE. Rev Esp Cardiol. 2014;67:259-69.

3 Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart. 2001;86:516-21.

4 Greenlee RT, Vidaillet H. Recent progress in the epidemiology of atrial fibrillation. Curr Opin Cardiol. 2005;20:7-14.

5 Laguna P, Martín A, del AC, Gargantilla P. Risk factors for stroke and thromboprophylaxis in atrial fibrillation: what happens in daily clinical practice? The GEFAUR-1 study. Ann Emerg Med. 2004;44:3-11.

6 Craig TL. Samuel Wann. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. Circulation. 2014;130:e199-e267.

7 Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, endorsed by the European Stroke Organisation (ESO). Eur Heart J. 2016;37:2893-962.
8 Wakai A, O'Neill JO. Emergency management of atrial fibrillation. Postgrad Med J. 2003;79:313-9.
9 Laszlo R, Laszio S, Grade H, Schreieck J. Electrical cardioversion for atrial fibrillacion. Dtsch Med Wochenschr. 2010;135:750-4.
10 Martínez-Marcos FJ, García-Garmendia JL, Ortega-Carpio A, Fernández-Gómez JM, Santos JM, Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversión of acute atrial fibrillation to sinus rhythm. Am J Cardiol. 2000;86:950-53.
11 Burashnikov A, Antzelevitch C. New pharmacological strategies for the treatment of atrial fibrillation. Ann Noninvasive Electrocardiol. 2009;14:290-300.
12 Herrera D, Mamarbachi A, Simoes M, Parent L, Sauv R, Wang Z, et al. A Single Residue in the S6 Transmembrane Domain Governs the Differential Flecainide Sensitivity of Voltage-Gated Potassium Channels. Mol Pharmacol. 2005;68:305-16.
13 Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, 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;57:313-21.
14 Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ, et al., for the Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. Circ Arrhythm Electrophysiol. 2009;2:652-9.
15 Roy D, Pratt C. M, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, et al, for the Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for rapid conversion of atrial fibrillation. A phase 3, randomized, placebo controlled trial. Circulation. 2008;117:1518-25.
16 Roy D, Rowe BH, Stiell IG, Coutu B, Ip JH, Phaneuf D, et al, for the CRAFT Investigators. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. J Am Coll Cardiol. 2004;44:2355-61.
17 Juul-Möller S. Vernakalant in recently developed Atrial Fibrillation: How to translate pharmacological trials into clinical practice. European Journal of Cardiovascular Medicine. 2013;2:226-33.
18 Cosin-Sales J, Loscos A, Peiró A, Sorando MR, Buendía F, Ruescas L. Eficacia en nuestro entorno del vernakalant para la cardioversión farmacológica del paciente con fibrilación auricular de reciente comienzo. Rev Esp Cardiol. 2016;69:619-20.
19 Urtubia Palacios A, Carbonell Torregrosa MA. Vernakalant en fibrilación auricular: experiencia en un servicio de urgencias. Emergencias. 2016;28:69-70.
20 Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: evidence in support of the ESC Guidelines. Europace. 2014;16:162-3.
21 Mochalina N, Juhlin T, Öhlin B, Carlson J, Holmqvist F, Platonov PG. Predictors of successful cardioversion with vernakalant in patients with recent-onset atrial fibrillation. Ann Noninvasive Electrocardiol. 2015;20:140-7.
22 Del Arco C, Martín A, Laguna P, Gargantilla P. Analysis of current management of atrial fibrillation in the acute setting: GEFAUR-1 study. Ann Emerg Med. 2005;46:424-30.
23 Carbajosa Dalmau J, Llorens Soriano P, Diéguez Zaragoza S, Carratalá Perales JM, Díaz Dámaso J, Martínez Beloqui E, et al. Influencia del sexo del paciente en el manejo del síndrome coronario agudo con elevación del ST en los servicios de urgencias. Emergencias. 2011;23:87-92.
24 Llorens P, Escoda R, Miró O, Herrero-Puente P, Martín-Sánchez FJ, Jacob J, et al. Características clínicas, terapéuticas y evolutivas de los pacientes con insuficiencia cardiaca aguda atendidos en servicios de urgencias españoles: Registro EAHFE. Emergencias. 2015;27:11-22.
25 Sánchez M, Bauset JL, Cuervo R, Carbajosa J, Oria MC, Povar J, et al. Atención médica al síndrome coronario agudo sin elevación del ST en los servicios de urgencias según el tamaño del hospital receptor. Contribuciones del registro MUSICA. Emergencias. 2011;23:447-54.
26 Van Gelder IC, Hemels ME. The progressive nature of atrial fibrillation: a rationale for early restoration and maintenance of sinus rhythm. Europace. 2006;8:943-9.
27 Fedida D, Orth PM, Hesketh JC, Ezrin AM. The role of late INa and antiarrhythmic drugs in EAD formation and termination of Purkinje fibers. J Cardiovasc Electrophysiol. 2006;17:S71-8.
28 Krogh-Madsen T, Abbott GW, Christini DJ. Effects of Electrical and Structural Remodeling on Atrial Fibrillation Maintenance: A Simulation Study. PLoS Comput Biol. 2012;8:e1002390.
29 Ringborg A, Nieuwlaat R, Lindgren P, Jönsson B, Fidan D, Maggioni A, et al. Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. Europace. 2008;10:403-11.
30 Lafuente-Lafuente C, Mouly S, Longás-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation. Arch Intern Med. 2006;166:719-28.