

Received: February 09, 2016
Accepted: February 20, 2017
Published: March 03, 2017

Effectiveness and Safety of Direct Oral Anticoagulants Compared With Vitamin K Antagonists in Non-Valvular Atrial Fibrillation Patients Undergoing Electrical Cardioversion

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1 Abstract

Introduction: Direct Oral Anticoagulants (DOACs) have positioned themselves as an effective therapy in Non-Valvular Atrial Fibrillation (NVAf). Recently, they have been approved for use in Electrical Cardioversion (ECV). Our aim was to assess the effectiveness and safety of DOACs in this context, compared to Vitamin K Antagonists (VKAs).

Methods: Observational, retrospective study of consecutive patients with NVAf undergoing a scheduled ECV under oral anticoagulants (DOACs or VKAs). Thromboembolic events, bleeding and death were registered on the first month after ECV and at one-year follow-up.

Results: Between June 2012 and June 2014, 342 patients underwent ECV. In 138 patients (40.4%) ECV was performed with DOACs, and in the remaining 204 (59.6%), under VKAs. No thromboembolic events associated with ECV (at 30 days) were documented in none of the groups. At one year follow-up, no patient with DOACs suffered thromboembolic events, compared to 3 (1.3%) with VKAs ($p=0.828$). Seven (5.8%) patients with DOACs and 27 (14.5%) with VKAs ($p=0.017$) presented bleeding events. None of the patients experienced intracranial bleeding. Two patients (1.4%) under DOACs and 4 (2.0%) under VKAs died during follow-up.

Conclusions: In real-world NVAf patients undergoing ECV, DOACs are effective and safe, both short and mid-term after the procedure.

2 Keywords:

Atrial fibrillation; Cardioversion; Anticoagulants; Embolism; Hemorrhage;

3 Abbreviations

DOAC: Direct Oral Anticoagulants

VKA: Vitamin K Antagonists

ECV: Electrical Cardioversion

NVAf: Non-Valvular Atrial Fibrillation

4 Introduction

Direct oral anticoagulants (DOACs) have been shown to have at least the same efficacy and a better safety profile than vitamin K antagonists (VKAs) in patients with non-valvular atrial fibrillation (NVAf). The subanalysis of patients undergoing electrical cardioversion (ECV) in the large pivotal studies of DOACs in NVAf suggests that these drugs are also effective and safe in this field [1, 2]. Recently, the X-VerT study demonstrated an efficacy and safety of rivaroxaban similar to warfarin in individuals undergoing ECV [3]. In addition, these data are supported by some real-world observational studies [4].

The main objective of our study was to analyze the efficacy (incidence of thrombotic complications and mortality) and safety (hemorrhagic events) of DOACs compared to VKAs in a real-life population of NVAf patients undergoing ECV.

5 Patients and Methods

We performed an observational, retrospective study on the evolution of a cohort of patients with NVAf undergoing ECV in a tertiary hospital in Spain. All patients received anticoagulant treatment before ECV for at least 3 weeks, as indicated by clinical practice guidelines [5]. The choice of the type of anticoagulant treatment was decided by the responsible physician before the patient was referred to the Arrhythmia Unit for ECV. In order to perform the ECV, in patients with VKAs, international normalized ratio (INR) values in therapeutic range (between 2 and 3) were required during the previous 3 weeks, and in those who received DOACs, therapeutic compliance was required (at least 80% of dose).

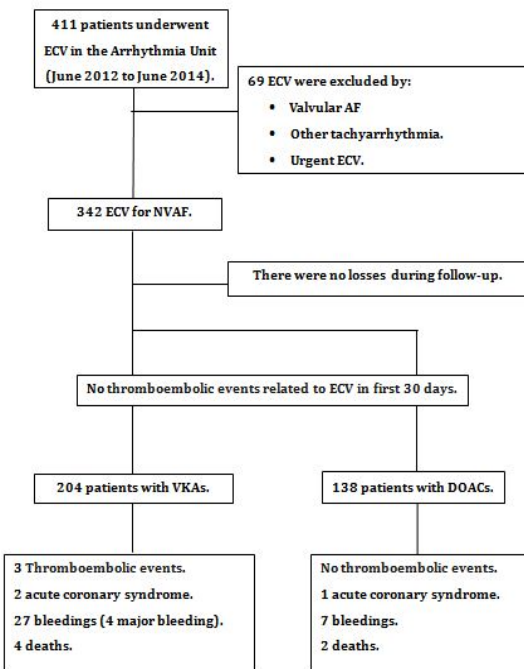


Figure 1: Flow chart of patients

After the ECV, the occurrence of thromboembolic events, acute coronary syndrome, mortality and hemorrhages, both on the first 30 days after the procedure and at one year follow-up was evaluated. This study was approved by the Ethical Committee of Alicante University Hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients gave their informed consent prior to their inclusion in the study.

Regarding statistical analysis, quantitative variables are expressed as mean \pm standard deviation or median (IQR: interquartile range). Qualitative variables, as absolute and relative frequencies. Continuous variables were analyzed to verify a normal distribution using the Kolmogorov-Smirnov test. Comparison between variables was performed using Pearson's χ^2 test, Student's T test and Log rank test. Hazard ratio (HR) and the 95% confidence intervals (CI) were calculated from the estimated parameters by the regression model. A value of $p < 0.05$ was considered statistically significant. Data were analyzed using the statistical

Table 1 Baseline Characteristics of Patients

Baseline characteristics	VKAs	DOACs	P
	(n=204)	(n=138)	
Age, years	66.8 \pm 11.1	62.5 \pm 12.3	0.001
Men	143 (70.1)	105 (76.1)	0.13
CHA2DS2VASc	3 (1-4)	2 (1-3)	0.001
HASBLED	2 (1-3)	1 (1-3)	0.001
Arterial hypertension	145 (71.1)	78 (56.5)	0.006
Diabetes Mellitus	46 (22.5)	21 (15.2)	0.094
Heart failure	69 (33.8)	23 (16.7)	0.001
Concomitant heart disease	69 (33.8)	36 (26.1)	0.128
Active smoking	37 (20.6)	22 (17.6)	0.52
Previous stroke	26 (12.7)	9 (6.5)	0.062
Antiplatelet treatment	37 (18.1)	24 (17.4)	0.86
Estimated glomerular filtration rate, ml/min;	74.6 \pm 20.9	83.4 \pm 20.2	0.615
Hb, g/dL	14.1 \pm 1.7	14.5 \pm 1.4	0.033

Qualitative variables are expressed as absolute number (percentage) and continuous variables as mean \pm standard deviation or median (interquartile range). Hb: hemoglobin.

Table 2 Events during follow-up

Events	VKAs	DOACs	P
	(n=204)	(n=138)	
Thromboembolism	3 (1.5%)	0 (0%)	0.828
Bleedings	27 (13.2 %)	7 (5.1%)	0.017
Acute coronary syndrome	2 (1.0%)	1 (0.7%)	1
Death	4 (2.0%)	2 (1.4%)	0.763
At least 1 event	36 (17.2%)	10 (7.2%)	0.012

software SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois).

6 Results

During the inclusion period (june 2012 to june 2014), 342 patients with NVAf underwent ECV in the Arrhythmia Unit of Alicante General University Hospital. 138 patients (40.4%) received DOACs and the rest, VKAs. The patient flow chart can be seen in Figure 1.

Baseline characteristics of the two groups of patients differed in several of the analyzed variables (Table 1). Patients who received VKA were older and had more comorbidities. The thromboembolic risk score CHA2DS2-VASc was lower in the DOACs group, with a median of 2 (IQR 1-3) compared to 3 (IQR 1-4) in the VKAs ($p < 0.001$), as well as the HASBLED score, with a median of 1 (IQR 1-3) and 2 (IQR 1-3) respectively ($p < 0.001$).

There were no thromboembolic events related to ECV (in the first 30 days after the procedure) in any of the groups.

At 1 year follow-up, all the events were more frequent in the VKA group (Table 2), but only the presentation of any type of bleeding showed significant differences among groups

($p=0.017$). The most frequent origin of bleeding was gastrointestinal (29.6%). Four patients with VKA suffered major bleeding, compared to none in the DOACs group (14.8 vs 0%, $p=0.559$), all cases were extracranial hemorrhages.

The presence of at least one event was present in 45 patients (13.2%), being more frequent in the VKAs group (17.2%) compared to 7.2% in the DOACs group ($p=0.012$), with an absolute risk increase of 10.0% (95% CI = 2.7 to 16.5%). Survival graph until the first event can be seen in figure 2.

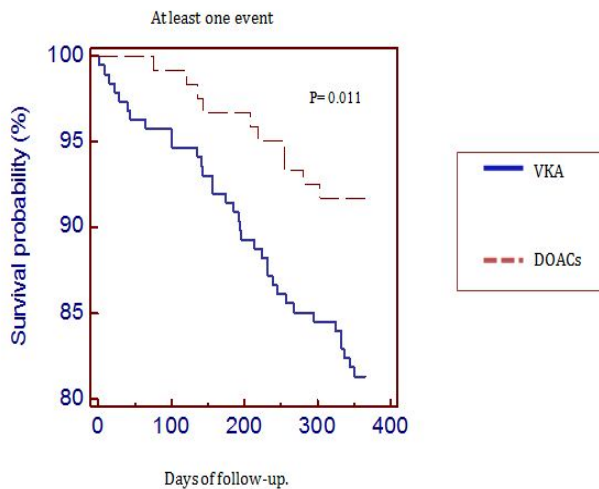


Figure 2: Survival graph until the first event (Kaplan meier curve)

Using multivariate analysis, the independent predictors of bleeding were hemoglobin (HR 0.77 [95% CI 0.63-0.96]) and VKA use (HR 2.41 [95% CI 1.5, 81]).

7 Discussion

DOACs are an increasingly used alternative in the management of patients with NVAF and are becoming a first-line tool in the context of ECV. In our series, DOACs were effective and safe for ECV in NVAF patients, without registering any early event. During mid-term follow-up, patients treated with DOACs had a significantly lower bleeding risk. Being a real-life population, our results are of great interest, because DOACs represent a simpler treatment to administer, with more stable anticoagulant activity, less interactions and less risk of intracranial bleeding than the classic treatment. In addition, DOACs have shown to decrease the required time interval to ECV [3], as the significant variability in anticoagulation levels in patients treated with VKAs makes it difficult to maintain the therapeutic range before the ECV, and this often forces to delay the procedure.

As we know, in many patients with persistent AF, ECV is a fast and efficient mechanism to restore sinus rhythm, but it requires oral anticoagulation for at least 3 weeks in patients with AF lasting more than 48 hours. In non-anticoagulated patients the periprocedure risk of ischemic event associated with ECV is between 5 and 7%, but warfarin treatment reduces the incidence of thromboembolic events between 0.5 and 1.6% [6]. International guide-

lines recommend at least 3 consecutive weeks of effective anticoagulation prior to cardioversion, followed by at least another 4 weeks of anticoagulation thereafter [5, 7].

The X-Vert study randomized individuals with NVAF to rivaroxaban or warfarin prior to ECV [3]. In this study, along with analysis of the RE-LY and ARISTOTLE studies [1, 2], and similarly to our study, the incidence of systemic stroke or embolism at 30 days of ECV was less than 1%, with no difference from the type of anticoagulant therapy received.

At mid-term follow-up, the rate of thromboembolic events of our series was similar of pivotal studies, being in these a 1.3% in VKA group and 0% in DOAC group; on the other hand, the rate of bleeding of any type was greater in VKA group (14.5%) than in DOAC group (5.8%), with only four major bleedings, all of them extracranial, in the group with VKA; in contrast, in pivotal trials with DOACs, these had a higher bleeding rate than warfarin at expense of digestive bleeding, but less incidence of severe and intracranial bleeding.

Our main limitation is inherent to the design of the study, since it is an observational study, the treatment groups were not randomized, but the allocation of treatment with VKAs or DOACs was performed by the cardiologist who attended the patient previously. Therefore, the study groups were not similar with respect to some of their baseline characteristics. The greater comorbidity of the patients under treatment with VKA could explain, at least in part, the increase of hemorrhagic and thromboembolic events in the follow-up in this subgroup. It should be noted that this is a study of real-life patients and we have found that, during the inclusion period, DOACs were used in people with less comorbidities, probably due to physicians initial distrust on these new treatments. However, a multivariate analysis was performed to control the heterogeneity of the groups under study. Despite these limitations, we believe that the conclusions of the study are of interest for daily clinical practice.

8 Conclusion

In a real population of individuals with NVAF undergoing ECV, DOACs were effective in prevention of short and mid-term thromboembolic events, showing also an adequate safety profile.

9 References

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