CARDIAC ARRHYTHMIAS IN THE EMERGENCY ROOM AND ICU. ANTICOAGULATION OF THE PATIENT WITH ACUTE AF UNDERGOING CARDIOVERSION: CAN WE RELY ON THE NEW ORAL ANTICOAGULANTS?

ARRITMIAS CARDÍACAS NA SALA DE EMERGÊNCIA E UTI. ANTICOAGULAÇÃO DO PACIENTE COM FA AGUDA SUBMETIDO A CARDIOVERSÃO: JÁ PODEMOS CONTAR COM OS NOVOS ANTICOAGULANTES ORAIS?

ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice with a prevalence of 1-2%, and is associated with an almost 5-fold increase in the risk of stroke compared to the general population. Anticoagulation is the best way to prevent thromboembolic events. Warfarin has been used for decades as a safe and effective drug, provided it is strictly controlled. In recent years, new classes of oral anticoagulants have been developed: direct thrombin inhibitors and factor Xa inhibitors, known as direct oral anticoagulants (DOACs). Both electrical and pharmacological cardioversion are associated with an increased risk of thromboembolic events during the first month after the procedure (5-7%). However, with the use of anticoagulants, this rate is less than 1%. In this article, we will review the main scientific evidence related to the use of dabigatran, rivaroxaban, apixaban and edoxaban during cardioversion and a practical approach with antithrombotic management in different clinical scenarios (cardioversion of patients in previous use of DOACs, cardioversion of patients not using oral anticoagulants with episodes of AF longer or shorter than 48 h).

Keywords: Atrial Fibrillation; Stroke; Cardioversion; Warfarin; Anticoagulants.

RESUMO

A fibrilação atrial (FA) é a arritmia cardíaca mais comum na população com uma prevalência de 1-2%, além disso, está associada a um risco, aproximadamente cinco vezes maior de acidente vascular cerebral do que na população em geral. A anticoagulação é a melhor maneira de prevenir os eventos tromboembólicos. A varfarina é utilizada há décadas como uma droga segura e eficaz, desde que rigorosamente controlada. Nos últimos anos, foram desenvolvidas novas classes de anticoagulantes orais: inibidores diretos da trombina e inibidores do fator Xa, conhecidos como anticoagulantes orais de ação direta (DOACs). Tanto a cardioversão elétrica quanto a cardioversão farmacológica estão associadas a um maior risco de eventos tromboembólicos durante o primeiro mês após o procedimento (5-7%). No entanto, com a utilização de anticoagulantes essa taxa é inferior a 1%. No presente artigo, faremos uma revisão das principais evidências científicas relacionadas ao uso da dabigatran, rivaroxabana, apixabana e edoxabana durante a cardioversão e uma abordagem prática com o manejo antitrombótico em diferentes cenários clínicos (cardioversão em pacientes com uso prévio de DOACs, cardioversão em pacientes com FA com duração maior ou menor que 48 horas sem anticoagulação).

Descritores: Fibrilação Atrial; Acidente Vascular Cerebral; Cardioversão; Varfarina; Anticoagulantes.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the population, with a prevalence rate of 1%-2%, and is associated with an approximately 5-fold greater risk of stroke than that in the general population. In addition, because of the increasing aging population, AF has become an important public health problem, with a high consumption...
of health resources (such as increased frequency of hospital admissions and treatment costs).2-4 It has important repercussions on the quality of life, particularly because of its clinical consequences, thromboembolic phenomena, and cognitive alterations.5

Recent epidemiological data suggest a significant increase in the prevalence of AF, as well as its association with stroke.5 In the United States, the percentage of stroke related to AF was 20.4% in 2014 versus 16.4% in 2003, representing an absolute increase of 4%.6 In addition, stroke due to thromboembolic events are more disabling and present higher mortality.5

Anticoagulation is the best way to prevent thromboembolic events.2-4 Warfarin has been used for decades as a safe and effective drug, if strictly controlled. However, maintaining the international normalized ratio (INR) in the therapeutic range is difficult and depends on many factors. Most adverse effects are related to dose adjustment, during which period the patient is exposed to thrombotic and hemorrhagic phenomena.7 These difficulties make INR underused in clinical practice.8 In recent years, new classes of oral anticoagulants have been developed to improve the efficacy and safety profile: direct thrombin and factor Xa inhibitors, known as direct-acting oral anticoagulants (DOACs).9 Dabigatran (direct thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors) are safe and effective medications that are superior to warfarin, with numerous advantages.9,14 Thus, we observed a significant increase in the use of anticoagulants in clinical practice, and DOACs have already outperformed warfarin as the most prescribed antithrombotic therapy worldwide.10

In the management of patients with AF, in addition to the prevention of thromboembolic phenomena, it is important to discuss the strategies for rhythm versus rate control.16,17 Usually, the rhythm control strategy is reserved for those patients who remain symptomatic despite adequate heart rate control. Both electrical cardioversion (ECV) and pharmacological cardioversion (PCV) are associated with an increased risk of thromboembolic events during the first month after the procedure, especially in the first 10 days.18 Observational studies demonstrate that without the use of anticoagulation, the rate of stroke and systemic embolism is approximately 5%-7%, but it may reach 9.8% in high-risk patients (elderly, heart failure, and diabetes).19 However, the rate is <1% with the use of anticoagulants.20

On the basis of observational data and pathophysiolog-ical mechanisms, the use of adequate anticoagulation is recommended three weeks before cardioversion and maintenance, for at least four weeks, regardless of the patient’s CHA2DS2-VASc.21 CHA2DS2-VASc is the most used clinical score for predicting thromboembolic phenomena in patients with AF and serves as a guide to evaluate the indication of anticoagulation in these patients.2-4 The time of cardioversion can be shortened in cases of AF lasting <48 h or when transesophageal echocardiography (TEE) is performed.2-4

In this scenario, warfarin has been the standard therapy for decades. However, with the ease of use and increasing scientific evidence of the efficacy and safety of DOACs during cardioversion, real-world data has demonstrated a significant increase in its use in clinical practice.22

In this article, the main scientific evidence related to the use of DOACs during CV and a practical approach toward antithrombotic management in different clinical scenarios will be reviewed.

A post hoc analysis of the RE-LY trial was conducted to assess the efficacy and safety of dabigatran against warfarin in the CV scenario.23 Of 18,113 patients in the study, 1983 cardioversions were performed in 1270 patients (86% ECV and 14% PCV). Dabigatran doses of 110 and 150 mg twice daily were compared to warfarin. The performance of TEE before the procedure was left to the investigator’s discretion, and TEE occurred in 25.5%, 24.1%, and 13.3% of the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively. No difference was observed in the incidence of intracavitary thrombi between groups. The rates of stroke and systemic embolism in the first 30 days after CV were low and similar between groups (0.8% for dabigatran 110 mg, 0.3% for dabigatran 150 mg, and 0.8% for warfarin). The rates of major bleeding were also similar between groups (0.6%).23

A Danish real-world study evaluated 1230 patients (dabi- gatran n = 456, warfarin n = 774) with first episode of AF and no previous anticoagulant therapy from 2011 to 2012.22 The median time for cardioversion was four and seven weeks in the dabigatran and warfarin groups, respectively. The outcome of stroke, bleeding, or death at 30 weeks occurred in 1.0% and 2.0% in the dabigatran and warfarin groups, respectively (hazard ratio [HR], 1.33; 95% confidence interval [CI], 0.33–5.42).24

The efficacy and safety of rivaroxaban was compared to those of warfarin in a post hoc analysis of the ROCKET AF trial.25 The dose of rivaroxaban used in the study was 20 mg once daily (or 15 mg once daily if creatinine clearance between 30 and 49 mL/min). Of 14,264 patients included in the study with a mean follow-up of 2.1 years, 375 cardioversions were performed in 285 patients (48.2% ECV and 51.8% PCV) and 85 ablations in 79 patients. The rates of stroke or systemic embolism were similar between groups, at 1.88% and 1.86% in the rivaroxaban and warfarin groups, respectively.25

In view of the limitations of the observational study, the X-VeRT trial was performed, which was a randomized, multicenter, open-label trial that compared the efficacy and safety of rivaroxaban against those of warfarin in the CV scenario.26 Rivaroxaban 20 mg once daily (or 15 mg once daily if creatinine clearance 30–49 mL/min) or warfarin (INR, 2–3) was adminis- tered to 1504 patients included in the ratio of 2:1. Two CV stra- tegies were possible: early (1–5 days after randomization) with mandatory use of TEE or late (3–8 weeks after randomization). The primary outcome of stroke, systemic embolism, infarction, or cardiovascular death occurred in 0.51% and 1.02% in the rivaroxaban and warfarin groups, respectively (RR, 0.5; 95% CI, 0.15–1.73). The incidence rate of major bleeding was 0.6% and 0.8% in the rivaroxaban and warfarin groups, respectively (RR, 0.76; 95% CI, 0.21–2.67). Among the patients who performed late CV, those who received rivaroxaban were able to perform CV earlier (mean, 25 days) compared with those who were administered warfarin (mean, 34 days) (p < 0.001).26

A recent observational study evaluated the rate of resolution of atrial or left atrial appendage thrombus in patients with AF or atrial flutter after six weeks of rivaroxaban. The resolution of thrombus, confirmed by TEE, was observed in 41.5% of the patients, similar to that observed in the retrospective registry CLOT-AF (62.5%) with the use of warfarin.27

To evaluate the efficacy and safety of apixaban in the CV scenario, a post hoc analysis of the ARISTOTLE trial, which included 201 patients, was performed.12 In 540 patients
(apixaban, n = 265; warfarin, n = 275). 743 CVs were performed. After 30 days of follow-up, no stroke or systemic embolism was observed in both groups. The incidence of major bleeding was also similar between the groups (0.3% with apixaban and 0.2% with warfarin).20

In 2018, the EMANATE study, a randomized, multicenter, open-label trial study, compared the efficacy and safety of apixaban at a dose of 5 mg twice daily (reduced to 2.5 mg twice daily in the presence of 2 of 3 criteria: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL) with standard heparin/warfarin therapy in patients who underwent ECV.20 At the investigator’s discretion, the administration of the loading dose of 10 mg of apixaban was allowed, followed by 5 mg twice daily (n = 342) or performing TEE (n = 855) before ECV. The study included 1500 patients. Among these patients, 1038 ECVs were performed: 300 spontaneous CVs, and 168 patients were not cardioverted. Six episodes of stroke or systemic embolism occurred in the heparin/warfarin group (6/747) and none in the apixaban group (0/753) (RR, 0; 95% CI, 0–0.64; p = 0.015). No difference was found between the groups regarding the incidence of major or clinically relevant bleeding (14 events in the apixaban group and 18 events with warfarin).

The prevalence of atrial or left atrial appendage thrombus in the 855 patients who underwent TEE was 7.1%. The rate of resolution of the thrombus after 37 days of anticoagulation was similar between the groups (52% with apixaban and 55% with warfarin).20 

A post hoc analysis of the ENGAGE-AF trial was performed to evaluate the efficacy and safety of edoxaban against warfarin in the CV scenario.20 During the study, 832 ECVs were performed. However, 200 ECVs that occurred after three days of anticoagulation were excluded. Edoxaban doses of 60 and 30 mg once daily were compared to those of warfarin. After 30 days of follow-up, no stroke or systemic embolism was observed in the edoxaban 60 mg and warfarin groups; however, two events occurred in the edoxaban 30 mg group. No major bleeding episodes were observed in all three groups.20

Given the limitations of this retrospective post hoc analysis, the ENSURE-AF trial was conducted,20 a randomized, multicenter, open-label clinical trial with blind adjudication of clinical events, comparing the efficacy and safety of edoxaban 60 mg once daily (reduced to 30 mg/day in the presence of one of the factors, namely: creatinine clearance 15–50 mL/min, weight ≤60 kg or concomitant use of P-glycoprotein inhibitor) against enoxaparin/warfarin in the ECV scenario. Between March 2014 and October 2015, 2199 patients were included (edoxaban n = 1095, enoxaparin/warfarin n = 1104). The primary outcome of stroke, systemic embolism, infarction, or cardiovascular death occurred in five patients (<1%) in the edoxaban group compared with 11 patients (1%) in the enoxaparin/warfarin group (OR, 0.46; 95% CI, 0.12–1.43). The incidence of major or clinically relevant bleeding was similar between the groups (1.5% edoxaban and 1% enoxaparin/warfarin) (OR, 1.48; 95% CI, 0.64–3.55).21

In 2017, a meta-analysis, including 6148 patients who underwent 6864 CVs, of the post hoc analyses of the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF trials and the randomized X-VeRT and ENSURE-AF trials was conducted.22 No difference was found between the DOACs and warfarin in the incidence of stroke or systemic embolism (RR, 0.82; 95% CI, 0.38–1.75) and major bleeding (RR, 0.98; 95% CI, 0.51–1.87). A secondary analysis did not demonstrate significant heterogeneity among the six trials.22

Table 1 shows a summary of the main comparative studies between DOACs and warfarin in CV.

**Table 1. Studies comparing DOACs vs. warfarin in cardioversion.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Patients</th>
<th>CVE</th>
<th>Efficacy of DOAC2 vs. Warfarin</th>
<th>Major bleeding DOAC vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagarakanti et al (2011)</td>
<td>RE-LY, retrospective analysis</td>
<td>Dabigatran vs. Warfarin</td>
<td>1983 CV in 1270 patients</td>
<td>83.6%</td>
<td>SSE3:0.3% vs. 0.6 (p=0.40)</td>
<td>0.6% vs. 0.6% (P = 0.99)</td>
</tr>
<tr>
<td>Piccini et al (2013)</td>
<td>ROCKET AF, retrospective analysis</td>
<td>Rivaroxaban vs. Warfarin</td>
<td>375 CV in 285 patients + 85 ablations</td>
<td>48.2%</td>
<td>SSE3:1.9% vs. 1.9 (p&gt;0.05)</td>
<td>18.8% vs. 13.0% (P = 0.58)</td>
</tr>
<tr>
<td>Cappato et al (2014)</td>
<td>X-VeRT, randomized, prospective, open</td>
<td>Rivaroxaban vs. Warfarin</td>
<td>CV in 1504 patients</td>
<td>97.6%</td>
<td>Stroke, TIA, AMI, CV death: 0.51% vs. 1.02% (p&gt;0.05)</td>
<td>0.61% vs. 0.80% (P &gt; 0.05)</td>
</tr>
<tr>
<td>Flaker et al (2014)</td>
<td>ARISTOTLE, retrospective analysis</td>
<td>Apixaban vs. Warfarin</td>
<td>743 CV in 540 patients</td>
<td>unknown</td>
<td>SSE3:0 vs. 0</td>
<td>0.3% vs. 0.2%</td>
</tr>
<tr>
<td>Pilt et al (2016)</td>
<td>ENGAGE-AF, retrospective analysis</td>
<td>Edoxaban vs. Warfarin</td>
<td>632 CV in 365 patients</td>
<td>100%</td>
<td>SSE3:0 vs. 0</td>
<td>No bleeding</td>
</tr>
<tr>
<td>Goette et al (2016)</td>
<td>ENSURE AF, randomized, prospective, open</td>
<td>Edoxaban vs. Warfarin</td>
<td>CV 2022 patients</td>
<td>100%</td>
<td>Stroke, TIA, AMI, cardiac death: 0.46% vs. 1.0% (p&gt;0.05)</td>
<td>1% vs. 1% (P &gt; 0.05)</td>
</tr>
<tr>
<td>Ezekowitz et al (2018)</td>
<td>EMANATE, randomized, prospective, open</td>
<td>Apixaban vs. Warfarin</td>
<td>CV in 1504 patients</td>
<td>100%</td>
<td>SSE3 and death: 0 vs. 0.8% (p = 0.015)</td>
<td>0.4% vs. 0.8% (p&gt;0.05)</td>
</tr>
</tbody>
</table>

Patients with elevated CHA₂DS₂-VASc (‘2 in men and ‘3 in women) should be administered permanent anticoagulation, regardless of the success of CV.  

During cardioversion, we may have different clinical situations. For example, it is necessary to differentiate patients who are already taking a DOAC and need CV from those with a recent diagnosis of AF and with no previous anticoagulant treatment.  

CARDIOVERSION IN PATIENTS WITH PREVIOUS USE OF DOAC (≥ 3 WEEKS)  

Several studies previously mentioned in this article suggest the safety of performing CV in patients using at least three weeks of anticoagulation with a DOAC without the need for TEE before the procedure. However, because no routine laboratory test is performed to evaluate the effectiveness of anticoagulation, it is essential to evaluate the patient’s adherence to the DOAC in the last weeks and include it in the medical record. If the patient is not adherent or there is doubt about adherence, TEE is recommended before CV, particularly in patients with a high thromboembolic risk. In the subanalysis of the RE-LY trial, the rate of atrial thrombus in patients undergoing TEE ranged from 1.1% to 1.8%. Recent studies have shown that the rate of thrombus in the atrium or the left atrial appendage may reach 3.6% even in the case of adequate anticoagulation.  

CARDIOVERSION IN PATIENTS WITH AF LASTING LONGER THAN 48 HOURS WITHOUT ANTICOAGULATION  

The X-VeRT, ENSURE-AF, and EMANATE clinical trials, which evaluated rivaroxaban, edoxaban and apixaban, respectively, provided robust clinical data on the efficacy and safety of DOACs in the ECV scenario in patients with no previous anticoagulant treatment. In this situation, two strategies are possible: early cardioversion with the use of TEE or late cardioversion after three to eight weeks of adequate anticoagulation. Overall, the efficacy and safety of DOACs were not statistically significantly different compared with warfarin in any of the strategies (early or late cardioversion). However, none of the studies had statistical power to carefully evaluate the non-inferiority of DOACs compared with warfarin for both efficacy and safety outcomes.  

In the strategy of early cardioversion, the dose of DOAC can be administered at least 4 h before the procedure associated with TEE to rule out the presence of left atrial thrombus. The other possibility is to administer at least three weeks of DOAC and perform CV in adherent patients without the need for TEE (late cardioversion).  

CONFICTS OF INTEREST  

The author declares that he has no conflicts of interest in this work.  

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