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?

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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 dabigatrana, 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.[1] 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.[6] 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.[10-14] 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.[15]

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 pathophysiological mechanisms, the use of adequate anticoagulation is recommended three weeks before cardioversion and maintenance, for at least four weeks, regardless of the patient's CHA_2DS_2-VASc.[21] CHA_2DS_2-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 (dabigatran 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 administered to 1504 patients included in the ratio of 2:1. Two CV strategies 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

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(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).[28]

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 [3]1.5 mg/dL) with standard heparin/warfarin therapy in patients who underwent ECV.[29] 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).[29]

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.[28] During the study, 832 ECVs were performed. However, 200 ECVs that occurred after three days of the last dose of anticoagulant 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.[30]

Given the limitations of this retrospective post hoc analysis, the ENSURE-AF trial was conducted,[29] a randomized, multi-center, 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).[31]

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.[32] 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.[32]

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

MANAGEMENT OF CARDIOVERSION WITH DIRECT-ACTING ORAL ANTICOAGULANTS

According to the main guidelines, patients with AF lasting longer than 48 h or indeterminate time who will undergo CV need a minimum of three weeks of adequate anticoagulation before CV or TEE to rule out the presence of thrombus in the left atrium.[2-4]. After cardioversion, anticoagulation must be continued for at least four weeks, regardless of the patient's

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

Study	Design	Intervention	Patients	CVE[1]	Efficacy of DOAC[2] vs. Warfarin	Major bleeding DOAC vs. Warfarin
Nagarakanti et al (2011)[23]	RE-LY, retrospective analysis	Dabigatran vs. Warfarin	1983 CV in 1270 patients	83.6%	SSE[3]:0.3% vs. 0.6 (p=0.40)	0.6% vs. 0.6% (P = 0.99)
Piccini et al (2013)[25]	ROCKET AF, retrospective analysis	Rivaroxaban vs. Warfarin	375 CV in 285 patients + 85 ablations	48.2%	SSE[3]:1.9% vs. 1.9 (p>0.05)	18.8% vs. 13.0% (P = 0.58)
Cappato et al (2014)[26]	X-VeRT, randomized, prospective, open	Rivaroxaban vs. Warfarin	CV in 1504 patients	97.6%	Stroke, TIA, AMI, CV death: 0.51% vs. 1.02% (p>0.05)	0.61% vs. 0.80% (P > 0.05)
Flaker et al (2014)[28]	ARISTOTLE, retrospective analysis	Apixaban vs. Warfarin	743 CV in 540 patients	unknown	SSE[3]:0 vs. 0	0.3% vs. 0.2%
Plitt et al (2016)[30]	ENGAGE-AF, retrospective analysis	Edoxaban vs. Warfarin	632 CV in 365	100%	SSE[3]:0 vs. 0	No bleeding
Goette et al (2016)[31]	ENSURE-AF, randomized, prospective, open	Edoxaban vs. Warfarin	CV 2022 patients	100%	Stroke, TIA, AMI, cardiac death: 0.46% vs. 1.0% (p>0.05)	1% vs. 1% (P > 0.05)
Ezekowitz et al. (2018)[29]	EMANATE, randomized, prospective, open	Apixaban vs. Warfarin	CV in 1504 patients	100%	SSE[3] and death: 0 vs. 0.8% (p = 0.015)	0,4% vs. 0,8% (p>0,05)

1. Electrical cardioversion; 2. Direct Acting Oral Anticoagulant; 3. Stroke and Systemic Embolism. CV: Cardioversion; CVA: TIA: Transient ischemic attack; AMI: Acute Myocardial Infarction.

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CHA$_2$DS$_2$-VASc score.[2-4] Patients with elevated CHA$_2$DS$_2$-VASc ($\geq$2 in men and $\geq$3 in women) should be administered permanent anticoagulation, regardless of the success of CV.[33]

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.[33]

CARDIOVERSION IN PATIENTS WITH PREVIOUS USE OF DOAC ($\geq$ 3 WEEKS)

Several studies previously mentioned in this article[23,25,26,28-31] 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.[33] In the subanalysis of the RE-LY trial, the rate of atrial thrombus in patients undergoing TEE ranged from 1.1% to 1.8%.[23] 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.[34,35]

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

The X-VeRT,[26] ENSURE-AF[31], and EMANATE[29] 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.[29,31]

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).[33]

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

Observational studies suggest lower rates of thromboembolic events in patients with acute AF after CV who were administered anticoagulants.[36,37] The evidence for use of DOAC in this scenario is very scarce. However, given the consistency of the results of the clinical trials proving the efficacy and safety of DOACs in patients with AF lasting longer than 48 h together with pharmacokinetics and pharmacodynamics similar to low-molecular-weight heparins (enoxaparin), the administration of a dose of DOAC 4 h before CV without the need for TEE may be considered. However, in patients with a high thromboembolic risk or with doubts regarding the duration of AF, performing TEE or at least three weeks of anticoagulation before the procedure should be considered.[33]

In summary, the discovery of DOACs and their adoption in clinical practice represent a new era of anticoagulation, facilitating and improving the treatment of patients at risk of ischemic events in different clinical settings. Particularly, studies evaluating the efficacy and safety of DOACs in the context of CV demonstrated similar rates of thromboembolic events and bleeding when compared with warfarin. Therefore, the DOACs present an attractive alternative to warfarin with the potential to reduce the time needed until cardioversion.

CONFLICTS OF INTEREST

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

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study. Stroke. 1991;22(8):983–8.

2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American college of cardiology/American heart association task force on practice guidelines and the heart rhythm society. J Am Coll Cardiol. 2014;64(21):2245–80.

3. 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. Eur Heart J. 2016;37(38):2893–962.

4. Magalhães LP, Figueiredo MJO, Cintra FD, Saad EB, Kuniyoshi RR, Teixeira RA, et al. II Diretrizes Brasileiras de Fibrilação Atrial. Arq Bras Cardiol. 2016;106(4 Supl. 2):1–22.

5. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, et al. Association of Preceding Antithrombotic Treatment With Acute Ischemic Stroke Severity and In-Hospital Outcomes Among Patients With Atrial Fibrillation. Jama. 2017;317(10):1057–67.

6. Alkhouli M, Alqahtani F, Aljohani S, Alvi M, Holmes DR. Burden of Atrial Fibrillation-Associated Ischemic Stroke in the United States. JACC Clin Electrophysiol. 2018;4(5);618-25.

7. Lip GYH, Haguenoer K, Saint-Etienne C, Fauchier L. Relationship of the SAMe-TT2R2score to poor-quality anticoagulation, stroke,

clinically relevant bleeding, and mortality in patients with atrial fibrillation. Chest. 2014;146(3):719–26.

8. Biria M, Batrash A, Piallarisetti J, Vacek J, Berenbom L, Lakkireddy D. Underutilization of Warfarin Therapy in Elderly Patients with Atrial Fibrillation - Fear or False Sense of Security! J Atr Fibrillation. 2008;1(3):119.

9. Nunes Filho ACB, Vianna FF, Braga VCSP. Novos anticoagulantes orais – parte I – Fibrilação atrial. einstein: Educ Contin Saude. 2011;9(4 Pt 2):209–11.

10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2009;361(12):1139–51.

11. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 2011;365(10):883–91.

12. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2011;365(11):981–92.

13. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2013;369(22):2093–104.

14. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.

15. Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand JP, Berge E, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart. 2017;103(4):307–14.

16. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation. N Engl J Med. 2002;347(23):1825–33.

17. van Gelder IC, Hagens VE, Bosker HA, Kingman JH, Kamp O, Kingma T, et al. A Comparison Of Rate Control And Rhythm Control In Patients With Recurrent Persistent Atrial Fibrillation. N Engl J Med. 2002;347(23):1834–40.

18. Berger M, Schweitzer P. Timing of thromboembolic events after electrical cardioversion of atrial fibrillation or flutter: a retrospective analysis. Am J Cardiol. 1998;82(12):1545–7, A8.

19. Airaksinen KE, Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: The FinCV (Finnish CardioVersion) study. J Am Coll Cardiol. 2013;62(13):1187–92.

20. Itäinen S, Lehto M, Vasankari T, Mustonen P, Kotamäki M, Numminen A, et al. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients undergoing elective cardioversion. Europace. 2018;20(4):565–8.

21. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: A comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke. 2010;41(12):2731–8.

22. Femia G, Fetahovic T, Shetty P, Lee A. Novel Oral Anticoagulants in Direct Current Cardioversion for Atrial Fibrillation. Hear Lung Circ. 2018;27(7):798-803.

23. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion. Circulation. 2011;123(2):131–6.

24. Pallisgaard JL, Lindhardt TB, Hansen ML, Schjerning AM, Olesen JB, Staerk L, et al. Cardioversion and Risk of Adverse Events with Dabigatran versus Warfarin—A Nationwide Cohort Study. PLoS One. 2015;10(10):e0141377.

25. Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, et al. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF Trial. J Am Coll Cardiol. 2013;61(19):1998–2006.

26. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J. 2014;35(47):3346–55.

27. Lip GY, Hammerstingl C, Marin F, Cappato R, Meng IL, Kirsch B, et al. Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). Am Heart J. 2016;178:126–34.

28. Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: Insights from the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). J Am Coll Cardiol. 2014;63(11):1082–7.

29. Ezekowitz MD, Pollack CV Jr, Halperin JL, England RD, VanPelt Nguyen S, Spahr J, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. Eur Heart J. 2018;39(32):2959-71.

30. Plitt A, Ezekowitz MD, De Caterina R, Nordio F, Peterson N, Giugliano RP, et al. Cardioversion of Atrial Fibrillation in ENGAGE AF-TIMI 48. Clin Cardiol. 2016;39(6):345–6.

31. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet. 2016;388(10055):1995–2003.

32. Renda G, Ricci F, De Caterina R. Non-Vitamin K Antagonist Oral Anticoagulants for Cardioversion in Atrial Fibrillation: An Updated Meta-analysis. Am J Med. 2017;130(4):457–61.

33. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330-93.

34. Schaeffer B, Rüden L, Salzbrunn T, Pinnschmidt HO, Akbulak RÖ, Moser JM, et al. Incidence of intracardiac thrombus formation prior to electrical cardioversion in respect to the mode of oral anticoagulation. J Cardiovasc Electrophysiol. 2018;29(4):537–47.

35. Bertaglia E, Anselmino M, Zorzi A, Russo V, Toso E, Peruzza F, et al. NOACs and atrial fibrillation: Incidence and predictors of left atrial thrombus in the real world. Int J Cardiol. 2017;249:179–83.

36. Hansen ML, Jepsen RM, Olesen JB, Ruwald MH, Karasoy D, Gislason GH, et al. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. Europace. 2015;17(1):18–23.

37. Grönberg T, Hartikainen JEK, Nuotio I, Biancari F, Ylitalo A, Airaksinen KE. Anticoagulation, CHA2DS2VASc Score, and Thromboembolic Risk of Cardioversion of Acute Atrial Fibrillation (from the FinCV Study). Am J Cardiol. 2016;117(8):1294–8.