Direct oral anticoagulants in patients undergoing cardioversion: insights from randomized clinical trials

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Abstract

Anticoagulation, reducing the risk of thromboembolic events in patients undergoing cardioversion, is a cornerstone of peri-cardioversion management in patients with atrial fibrillation. We aimed to analyse published data on the efficacy and safety of direct oral anticoagulants (DOACs) in patients undergoing cardioversion.

We performed a systematic review of randomized prospective clinical trials (RCTs) comparing DOACs with warfarin and reporting data on post-cardioversion outcomes of interest. Outcomes of interest were stroke, systemic thromboembolic events and major bleeding. We reviewed a total of six RCTs including 3900 cardioversions performed using a DOAC for thromboembolic prophylaxis. These studies reported a low incidence overall of adverse outcomes associated with the use of DOACs (around 1% in all studies, except the ROCKET *post-hoc* study which included ablation procedures). The incidence rate of adverse events during DOAC treatment was found to be very similar to that observed with warfarin anticoagulation.

In RCTs DOAC treatment in patients undergoing cardioversion appears to be effective and safe. However, because evidence in this clinical setting is still weak, observational reports could be useful in providing further data about peri-procedural outcomes.

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Introduction

Restoration of sinus rhythm, either obtained with electrical cardioversion or with drugs, carries a periprocedural risk of stroke and systemic embolism which is decreased by prophylactic anticoagulation [1]. A large observational data-set has shown an incidence rate of thromboembolic events of 10.33 per 100 patient-years in the group not receiving anticoagulant therapy after cardioversion, a rate more than two-fold higher when compared to subjects treated with an anticoagulant in the first month after cardioversion [2]. According to international guidelines, patients with atrial fibrillation (AF) lasting more than 48 h, or of uncertain duration, should be treated with adequate anticoagulation for at least 3 weeks before cardioversion and continue it for another 4 weeks after the cardioversion in order to reduce thromboembolic risk [3,4]. Despite never having been validated in large randomized prospective clinical trials (RCTs), the role of vitamin K antagonists (VKAs) during peri-cardioversion, as in all other AF clinical settings, is deep-rooted and they have been routinely used to prevent thromboembolic events for several decades. Meanwhile, based on the results of large RCTs [5-8], which demonstrated the safety and efficacy of the direct oral anticoagulants (DOACs) in patients with non-valvular AF, the availability of these novel oral anticoagulants in the pharmaceutical armamentarium is now changing AF patient management. An important advantage of DOACs in the peri-cardioversion setting is the rapid and predictable onset of action which can shorten the time from the beginning of anticoagulant treatment to cardioversion. Contrarily, the mean time needed to achieve an effective anticoagulation with VKAs is long and variable and it is often necessary to utilize a heparin bridge and delay a scheduled cardioversion.

Materials and Methods

We conducted a systematic review with the purpose of analysing available data about the safety and efficacy of DOACs when used in patients undergoing cardioversion in RCTs.

We searched PubMed database to identify RCTs using this novel oral anticoagulant in non-valvular AF and which reported efficacy and safety outcomes in a peri-cardioversion setting. The search terms included "novel oral anticoagulant" or "dabigatran" or "rivaroxaban" or "apixaban" or "edoxaban" and "cardioversion". The search was restricted to articles in English up to November 2016. References of retrieved articles were also manually searched for additional RCTs not included in

the electronic database search. Studies were included in the review if they: 1) were RCTs; 2) compared DOACs with VKAs in non-valvular AF; 3) reported post-cardioversion outcomes of interest: stroke, systemic thromboembolic events and major bleeding.

Results

We found six articles that reported outcome data in patients using DOACs and undergoing cardioversion during RCTs. The study selection flow diagram is shown in Figure 1. From a total of 177 records identified through database searches, six articles met the inclusion criteria and were retrieved for detailed evaluations of peri-cadioversion outcomes of interest. The selected studies involved a total of 3900 procedures performed with a DOAC (Table 1). The studies reviewed included four *post-hoc* analyses which each evaluated peri-cardioversion data extrapolated by large pivotal RCTs comparing DOACs with warfarin in the general population with non-valvular AF. The remaining two studies reviewed were RCTs that each evaluated an DOAC *vs* warfarin in patients with non-valvular AF and scheduled for cardioversion.

Dabigatran in patients undergoing cardioversion

The first report evaluating a DOAC in the setting of cardioversion is the *post-hoc* analysis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, the phase 3 trial that demonstrated dabigatran, an oral direct thrombin inhibitor, as being superior [Dabigatran 150 mg bid (D150)] or non-inferior [Dabigatran 110 mg bid (D110)] to warfarin for stroke prevention in AF [5]. In the *post-hoc* analysis, data from a total of 1.983 cardioversions were evaluated [9]. The study found comparably low rates of embolic events and major bleeding in both the dabigatran and warfarin groups [embolic events rates were 0.8% for D110 group, 0.3% for D150, and 0.6% for warfarin (D110 *versus* warfarin, p=0.71; D150 *versus* warfarin, p=0.40) – major bleeding rates were 1.7% for D110 group, 0.6% for D150, and 0.6% for warfarin (D110 *versus* warfarin, p=0.06; D150 *versus* warfarin, p=0.99)]. Pre-cardioversion transoesophageal echocardiography (TEE) was performed in approximately 25% of patients assigned to dabigatran and 13% of patients assigned to warfarin, and stroke and systemic embolism rates were similar in patients undergoing TEE before cardioversion and in patients not performing TEE. This evidence, which shows dabigatran to be as safe and effective as treatment with VKAs in the peri-cardioversion setting, supports the study conclusion that dabigatran is a reasonable alternative to warfarin in patients undergoing cardioversion.

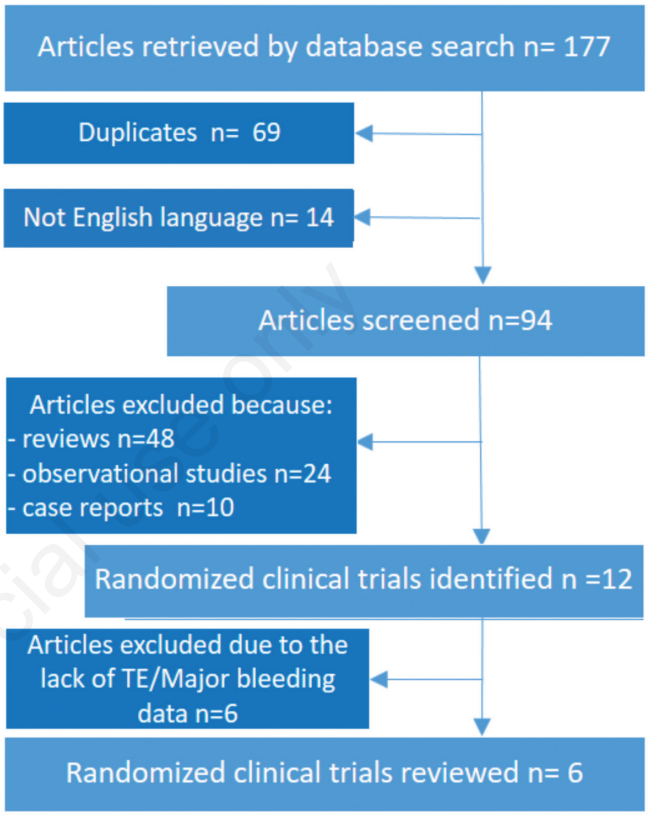

Figure 1. Study selection flow diagram. TE, Thromboembolic events.

Table 1. Studies reviewed and post-cardioversion events.

Author	Study	Anticoagulant	Procedures number	Stroke and systemic embolism (N)	Major bleeding (N)
Nagarakanti, 2011 [9]	RE-LY *post-hoc* analysis	Dabigatran 110 mg bid	647	5	11
		Dabigatran 150 mg bid	672	2	4
		Warfarin	664	4	4
Piccini, 2013 [10]	ROCKET-AF *post-hoc* analysis	Rivaroxaban	160*	3	30
		Warfarin	161*	3	21
Cappato, 2014 [11]	X-VeRT	Rivaroxaban	841	2	6
		Warfarin	326	3	4
Flaker, 2014 [12]	ARISTOTLE *post-hoc* analysis	Apixaban	331	0	1
		Warfarin	412	0	1
Plitt, 2016 [14]	ENGAGE-AF *post-hoc* analysis	Edoxaban higher dose	140°	0	0
		Edoxaban lower dose	111°	2	0
		Warfarin	114°	0	0
Goette, 2016 [15]	ENSURE	Edoxaban	998	3	3
		Enoxeparin/Warfarin	966	4	5

N, total number of events; *including patients performing only catheter ablation procedures; °number of first cardioversions.

Rivaroxaban in patients undergoing cardioversion

The second study reviewed is the *post-hoc* analysis of the ROCKET AF (Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients with Non-valvular Atrial Fibrillation) trial, the phase 3 clinical trial that showed rivaroxaban as being non-inferior to warfarin for the prevention of embolic events [6]. The ROCKET AF post-hoc analysis investigated outcomes associated with both cardioversion and catheter ablation procedures [10]. The analysis included 143 patients that underwent electrical cardioversion, 142 that underwent pharmacological cardioversion and 79 that underwent catheter ablation. Rate of embolic events was similar in patients randomized to rivaroxaban and in patients randomized to warfarin (1.88% and 1.86% respectively). Major bleeding rates were 18.75% in rivaroxaban group and 13.04% in warfarin group. The non-negligible events rate observed in this study has to be evaluated considering that 87% of the ROCKET AF patient population had a CHADS2 score ≥3, indicating a high presence of comorbidities. Furthermore, the events reported included outcomes following either cardioversion or catheter ablation. Another important limitation of this study is the lack of data regarding the use of pre-cardioversion TEE. Given the numerous limitations of peri-cardioversion data with rivaroxaban drawn from the ROCKET AF trial, a prospective randomized trial has been designed in the setting of elective cardioversion. The third study reviewed, X-VeRT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion), is the first RCT comparing a DOAC to warfarin in patients scheduled for cardioversion [11]. It randomized a total of 1504 patients with non-valvular AF lasting ≥48h. The trial sample size was established with the aim of having findings comparable with the data obtained from the post hoc analysis of cardioversions in the RE-LY trial. Indeed, researchers recognized that the trial sample size necessary to have statistically significant results to demonstrate the non-inferiority of rivaroxaban in peri-cardioversion setting would be too large (around 25,000-30,000 patients) and not feasible. According to the timing of scheduled cardioversion, two strategies have been investigated. The first strategy was an early cardioversion, in which the anticoagulant was given 1-5 days before cardioversion (in the rivaroxaban arm a cardioversion was performed at least 4 hours after the first dose of rivaroxaban). The second strategy was a delayed cardioversion approach that intended to adequately anticoagulate patients for a minimum of 3 weeks and a maximum of 8 weeks before the procedure. Prophylaxis with rivaroxaban was considered adequate if the pill count was ≥80% in the three weeks preceding the cardioversion. A total of 585 patients assigned to rivaroxaban were scheduled for early cardioversion. The procedure was TEE guided in 65% of patients treated with an early strategy, whereas a TEE guided cardioversion was performed in 10% of patients using a delayed strategy, with no significant difference in the rate of TEE employment between the two treatment groups. In terms of outcomes, the primary efficacy endpoint (the composite of stroke, transient ischaemic attack, peripheral embolism, myocardial infarction, and cardiovascular death) occurred in 0.51% of patients in the rivaroxaban arm and 1.02% of patients in the VKAs arm, with an estimated risk ratio of 0.50 [95% confidence interval (CI) 0.15-1.73]. Major bleeding occurred in 0.6% of patients in the rivaroxaban group and in 0.8% of patients in the VKAs group (risk ratio 0.76; 95% CI 0.21-2.67). Overall, rivaroxaban was associated with low rates of adverse outcomes similar to those of VKAs even when data from the early and delayed strategies were analysed separately. However, the estimated risk ratio reported in this study showed a tendency of less adverse outcomes such as thromboembolic events and major bleeding in patients treated with rivaroxaban compared to VKAs. On the basis of the X-VeRT findings, rivaroxaban seems to be an effective and safe alternative to VKAs.

Apixaban in patients undergoing cardioversion

The fourth study examined is the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial *post-hoc* analysis [12]. The ARISTOTLE is the phase 3 trial that showed apixaban, another factor Xa inhibitor, to be superior to warfarin in preventing stroke and systemic embolism and in causing less bleeding. The post-hoc analysis evaluated the rate of major clinical events, including stroke, systemic embolism, myocardial infarction, major bleeding, and death, in 540 patients who underwent cardioversion during trial follow-up. Among patients included in this study a total of 265 patients were treated with apixaban. During the 30 days after cardioversion, a very low and comparable rate of clinical events was found in patients treated with either apixaban or warfarin (no stoke or systemic embolism was reported in either treatment, 1 case of myocardial infarction was reported for each treatment group, major bleeding occurred in 1 patient in each treatment group, and death occurred in 2 patients in each treatment group). In the majority of cases, cardioversion occurred after months of treatment, with a mean time from enrolment to cardioversion of 243±231days for patients assigned to warfarin and of 251±248 days for patients assigned to apixaban. Given the long-term anticoagulation before cardioversion reported by this study (far longer than the 3 weeks recommended by international guidelines), some uncertainties remain about the apixaban anticoagulation time necessary before performing a cardioversion in order to avoid exposing the patient to an embolic risk. Among patients undergoing cardioversion in the ARISTOTLE trial, a pre-procedural TEE was performed in about 27% of cases, a rate similar to that reported in patients assigned to the dabigatran group and undergoing cardioversion in the RE-LY trial. Similar to previous studies, this *post-hoc* analysis does not have sufficient statistical power to find small differences in outcomes, however available data reporting very few peri-cardioversion adverse events with either apixaban or warfarin treatment are reassuring. Currently, a prospective RCT comparing apixaban with the standard care of warfarin in anticoagulation-naïve patients undergoing cardioversion is ongoing [13] and will provide further useful information.

Edoxaban in patients undergoing cardioversion

The fifth study we examined is the *post-hoc* analysis of ENGAGE (Effective Anticoagulation With Factor Xa Next Generation) AF-TIMI48 trial [14], a large pivotal trial that showed edoxaban, another direct factor Xa inhibitor, as being non-inferior for stroke prevention and safer in non-valvular AF as compared to warfarin. The post-hoc study evaluated outcomes of 365 patients undergoing cardioversion on average 348 days post-randomization. No data has been collected about the number of TEE guided cardioversions performed during the trial. In the 30 days after cardioversion, the events observed were: 2 embolic events in the low-dose edoxaban regimen (30mg/15mg), 1 death in the high-dose edoxaban regimen (60mg/30mg) and no major bleeding. Overall, post-cardioversion adverse events were infrequent with both treatments. However, the few events reported in this study are insufficient to support any inference for clinical practice. Further data about anticoagulation with edoxaban in patients undergoing cardioversion

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are provided by the ENSURE-AF trial (Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation) [15], the sixth study reviewed. To date, it is the largest randomized trial with an NOAC in the setting of electrical cardioversion with available results. In this trial 2,199 patients scheduled for cardioversion were randomized (1:1) to edoxaban 60 mg or enoxaparin/warfarin. The rate of the primary efficacy endpoint (composite of stroke, systemic embolic events, myocardial infarction and cardiovascular mortality) was around 1% in both the edoxaban group and the enoxaparin/warfarin group [odds ratio (OR) 0.46, 95% CI 0.12-1.43]. Patients treated with edoxaban and enoxaparin/warfarin also had similar rate of major bleeding (<1%; OR 1.48, 95% CI 0.64-3.55). No differences in outcome rates have been found regardless of the approach to cardioversion, whether TEE-guided or non-TEE-guided, prior anticoagulant use and the edoxaban dose adjustment. Of note, because of low event rates, the sample study size in this trial is also not large enough to show statistically significant differences in adverse outcomes.

Discussion

This systematic review reports outcome data observed in a total of 3900 cardioversion procedures performed during DOAC treatment in RCTs. The rate of post-cardioversion stroke and bleeding events in patients treated with a DOAC was found to be around 1% in each trial (except in the ROCKET AF *post-hoc* analysis which included catheter ablation procedures) and the events rate was very similar to that found in patients randomized to warfarin. A recent meta-analysis, involving data collected from the same six trials we reviewed, calculated an overall incidence of thromboembolic events in patients treated with DOACs of 0.4% [16]. Notably, the post-cardioversion events rate reported in DOAC RCTs is far lower than the thromboembolic rate observed with VKAs in the real world (4.00 per 100 patient years) [2]. The relevant difference may be accounted for by the RCTs' design which demanded carefully controlled adherence to treatment.

In the studies with available data regarding the outcomes associated with the use of pre-procedural TEE, DOACs efficacy in the prevention of thromboembolic events seems to be irrespective of TEE-guided strategy [9,15]. However, because there are no laboratory analyses available to routinely test the effective anticoagulation with DOACs in the weeks preceding the cardioversion, it is recommended to clearly and carefully interview the patient about drug intake during the 3 weeks preceding the procedure and to explicitly report the data in the medical record. If there are uncertainties about patient adherence a pre-procedural TEE is recommended in order to rule-out intra-atrial thrombi [17].

Despite the simple size not being large enough in any study to demonstrate statistically significant differences in terms of peri-cardioversion adverse events between DOAC and standard treatment with warfarin, DOACs seem to be effective and safe in the cardioversion setting considering the low events rate observed.

In conclusion, reported findings provide insights in favour of DOACs as an alternative strategy to warfarin for peri-cardioverison thromboembolic prophylaxis. Currently it seems difficult to perform RCTs large enough to obtain rigorous and significant statistical analysis showing DOAC non-inferiority or superiority, and therefore additional useful findings could be drawn from observational studies. Indeed, the use of DOACs in cardioversion is growing and in over one third of procedures they are currently used in place of warfarin for thromboembolic prophylaxis [18].

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