International Journal of Cardiology 185 (2015) 72–77

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Efficacy and safety of direct oral anticoagulants in patients undergoing cardioversion for atrial fibrillation: A systematic review and meta-analysis of the literature☆

Francesco Dentali [a,*], Giovanni Luca Botto [b], Monica Gianni [c], Pasquale Ambrosino [d], Matteo Nicola Dario Di Minno [e]

[a] Department of Clinical Medicine, Insubria University, Varese, Italy
[b] EP Unit, Department of Medicine, Sant'Anna Hospital, Como, Italy
[c] Department of Cardiology, Hospital of Tradate, Tradate, Italy
[d] Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy
[e] Unit of cell and molecular biology in cardiovascular diseases, Centro Cardiologico Monzino, IRCCS, Milan, Italy

ARTICLE INFO

Article history:
Received 6 December 2014
Accepted 7 March 2015
Available online 10 March 2015

Keywords:
Direct oral anticoagulants
Cardioversion
Atrial fibrillation

ABSTRACT

Background: DOACs are increasingly used in patients with NVAF. Information on efficacy and safety of these compounds in patients undergoing electrical or pharmacological cardioversion is limited. Thus, we performed a systematic review and a meta-analysis of the literature to address this issue.
Methods: Randomized controlled trials comparing the efficacy and safety of DOACs and VKAs in patients with NVAF were systematically searched in Medline, Web of Science, Scopus, Cochrane, and EMBASE databases (up to September 2014). Pooled relative risk (RR) and the corresponding 95% confidence interval (CI) were calculated for each outcome.
Results: Four randomized controlled trials (3635 patients), for a total of 4517 cardioversions (2869 with DOACs and 1648 with VKAs), were included in the analysis. DOACs and VKAs appeared equally effective in the prevention of stroke/systemic embolism (0.41% vs 0.61%; RR: 0.73, 95% CI: 0.31, 1.72; P = 0.48) and of post-cardiovascular death (0.52% vs 0.81%; RR: 0.73, 95% CI: 0.27, 2.03; P = 0.55), with a similar risk of major bleeding complications (0.81% vs 0.60%; RR: 1.23, 95% CI: 0.55, 2.71). Heterogeneity among studies was generally absent. Furthermore, the Weighted Mean Incidence (WMI) of complications appeared very low in patients randomized to DOACs (WMI: 0.6% and 0.9% for stroke/systemic embolism and major bleeding, respectively).
Conclusion: Our results suggest that DOACs are at least as effective and safe as VKAs in patients with NVAF undergoing to an electrical or pharmacological cardioversion. Thus, DOACs may be considered a valid and practical alternative to VKAs.

1. Introduction

AF is the most frequently encountered sustained cardiac arrhythmia, with a prevalence of about 2% in the general population [1].

AF patients often require cardioversion within a strategy of rhythm control, for symptoms relief [2] or to rapidly restore sinus rhythm [1].

However, cardioversion (both electrical and pharmacological) is associated with a not negligible risk of peri-procedural stroke or SE [3–5]. In the absence of adequate anticoagulation, this risk ranges between 5 and 7% [6–8]. In patients on therapy with VKAs the risk of peri-procedural cardioembolic events is significantly reduced to 0.5%–1.6% [9]. Thus recent guidelines recommend at least 3 weeks of effective anticoagulation before cardioversion, followed by at least 4 weeks of anticoagulation after the procedure [1,10].

In recent years, DOACs have been developed, including factor IIa and FXa inhibitors [11] and a number of trials showed an overall clinical benefit of DOACs compared with VKAs in patients with NVAF [12,13].

Unfortunately, information on the efficacy and safety of DOACs in NVAF patients undergoing electrical or pharmacological cardioversion is still limited and single studies are clearly underpowered to find a

Abbreviations: AF, Atrial Fibrillation; SE, Systemic Embolism; VKAs, Vitamin K Antagonists; DOACs, Direct Oral Anticoagulants; NVAF, Non-Valvular Atrial Fibrillation; ESC, European Society of Cardiology; ISTH, International Society on Thrombosis and Hemostasis; ASH, American Society of Hematology; RCTs, Randomized Controlled Trials; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RR, Risk Ratios; 95% CI, 95% Confidence Interval; TEE, Transesophageal Echocardiography; WMI, Weighted Mean Incidence.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy.
E-mail address: fdentali@libero.it (F. Dentali).

http://dx.doi.org/10.1016/j.ijcard.2015.03.096
0167-5273/

significant difference in the safety and efficacy of these two treatments. Thus, we performed a systematic review and meta-analysis of literature to address this issue.

2. Material and methods

For the study purpose we searched studies that compared the safety and efficacy of DOACs and of standard VKA treatment in patients with AF undergoing electrical and pharmacological cardioversion. Medline, ISI Web of Science, SCOPUS, Cochrane database and EMBASE databases were searched up to September 2014. Research was supplemented by manually reviewing abstract books from congresses of the ESC, the ISTH, and the ASH (2003–2014) and the reference lists of all retrieved articles. Only RCTs or post-hoc analyses of RCTs were considered, whereas low quality observational and nonrandomized studies were excluded. Furthermore, studies evaluating patients undergoing catheter ablation procedures only were not included. The efficacy outcome was defined by the prevention of stroke and SE. A secondary efficacy outcome was the prevention of cardiovascular death. The safety outcome was represented by the occurrence of major bleeding. Bleeding events were defined as major according to the ISTH definition [14]. Search results were reported according to PRISMA guidelines [15]. Data about study (year of publication, study type) and patient characteristics (number of subjects studied, mean age, gender) were extracted from each selected study. Discrepancy between reviewers was resolved by discussion or by the opinion of a third reviewer, if necessary. Statistical analysis was performed using Review Manager [Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] provided by The Cochrane Collaboration. Pooled relative risk (RR) and the corresponding 95% confidence interval (CI) were calculated for each outcome using a random effects model.

Furthermore, the maximum risk of cardioembolic and major bleeding complications in patients on DOACs was estimated calculating the weighted mean incidence of these complications in the included studies using the random effect model and considering the upper limit of their CI. Statistical heterogeneity was evaluated through the use of Cochran's Q and of I^2 statistics. The presence of publication bias was explored using funnel plots of effect size against standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect [16].

Impact on the use of DOACs on the time of anticoagulation before cardioversion was reported in a descriptive manner.

3. Results

After excluding duplicates, the search provided 215 results, of which 200 were excluded because they were nonrandomized studies or judged off the topic after scanning the title and/or the abstract. Other 11 studies were excluded after full-length paper evaluation (Fig. 1).

Thus, 4 RCTs [17–20] with 3635 patients undergoing cardioversion for AF were included in the analysis. Of these, 1 study [17] evaluated dabigatran as the experimental drug, 2 rivaroxaban [18,20] and 1 apixaban [19]. While the two studies on rivaroxaban [18,20] considered the first cardioversion only for each patient, the 2 other studies [17,19] reported all cardioversions performed during the study period. Thus, the outcome data are available for a total of 4517 procedures (2869 performed under DOACs and 1648 under VKAs).

3.1. Study characteristics

Principal characteristics of included studies are shown in Table 1. The number of patients varied from 321 to 1504, the mean age from 64 to 71 years, and the prevalence of male gender from 36.6% to 73.1%.

Three studies were subgroup analyses of RCTs comparing the efficacy and safety of DOACs and VKAs in patients with AF and one was a study that specifically compared these two compounds in the setting of electrical or pharmacological cardioversion. In this study a group of patients was selected for early cardioversion strategy (872 patients) or for delayed cardioversion strategy (632 patients).

Information on the use of pre-cardioversion TEE was available for 3 studies [17,19,20]. TEE was slightly but not significantly more frequently used in patients on DOACs than in patients on VKAs (31.4% vs 26.1%; P = 0.30).

3.2. Outcomes

Four studies [17–20] for a total of 4517 cardioversions evaluated the incidence of stroke and SE in patients on treatment with DOACs or VKAs (2869 with DOACs and 1648 with VKAs). These two compounds appeared to have a similar efficacy in the stroke and SE prevention without heterogeneity among the studies (0.41% vs 0.61%; RR: 0.73, 95% CI: 0.31, 1.72, P = 0.48, I^2: 0%, P = 0.61) (Fig. 2). Analysis that considered only first cardioversion (3601 patients) gave similar results (data not shown). WMI of stroke/SE in the DOACs group was 0.6% (95% CI: 0.3, 1.0%). Three studies [18–20] (2534 cardioversions) evaluated the efficacy of these compounds in preventing cardiovascular death. DOACs and VKAs appeared equally effective in the prevention of this outcome without heterogeneity among the studies (0.52% vs 0.81%; RR: 0.73, 95% CI: 0.27,2.03, P = 0.55, I^2: 0%, P = 0.85). Exclusion from the analysis of one study [18] that included also subjects undergoing catheter ablation gave similar results for the two efficacy endpoints (stroke/SE RR: 0.65, 95% CI: 0.24, 1.78; cardiovascular death RR: 0.91, 95% CI: 0.25, 3.29).

Three studies [17,19,20] (4213 cardioversions) provided separate data on the risk of major bleeding complications (Fig. 3). The post hoc analysis of the rocket trial provided only data on the composite end point of major and clinically relevant nonmajor bleeding complications and was excluded from this analysis. Treatment with DOACs and VKAs appeared associated with a similar risk of major bleeding complications with no heterogeneity among the studies (0.81% vs 0.60%; RR: 1.23, 95% CI: 0.55, 2.71). WMI of major bleeding complication in the DOACs group was 0.9% (95% CI 0.6%, 1.4%).

Given the low number of included studies, the presence of publication bias could not be evaluated with the use of funnel plots.

3.3. Time of anticoagulation before cardioversion

Information on the time of anticoagulation before cardioversion was provided only in the XVeRT trial [19]. In this study, in the group in which cardioversion was delayed, significantly more patients on rivaroxaban were cardioverted within the target time range in comparison to patients on VKAs (77.0% vs 36.0%; P < 0.001). Furthermore, the time between randomization and cardioversion was shorter in patients assigned to rivaroxaban [median: 22 (interquartile range 21–26) days vs 30 (23–42) days, P < 0.001].

3.4. Use of Transesophageal Echocardiography (TEE)

One study [18] did not report data about the use of TEE in the study population. The other 3 studies [17,19,20] showed that TEE was performed in 31.4% of DOACs patients and in 26.1% of those treated with VKAs (OR: 1.25, 95% CI: 0.82, 1.92, P = 0.30). Interestingly, the rate of stroke and SE was similar among DOAC and VKA patients, regardless the execution of TEE (Fig. 4).

4. Discussion

Results of our systematic review of the literature that included about 3600 patients for more than 4500 cardioversions suggested that DOACs are at least as effective and safe as VKAs in this setting.

Furthermore, in our study the incidence of complications appeared very low in this group of patients (Stroke/SE WMI: 0.6%; MB WMI: 0.9% respectively), and even the 95% upper confidence limits of incidences for cardioembolic (1.0%) and major bleeding events (1.4%) in the DOACs group were similar or lower to the range of those reported in previous series of VKA-treated patients [8,21] and much lower than those reported in the absence of anticoagulant therapy [22].

Although our results were based on a number of cardioversions that were about three times larger than the number performed in the largest single study published in this setting, our meta-analysis is still