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Non-vitamin K antagonists oral anticoagulants are as safe and effective as warfarin for cardioversion of atrial fibrillation: A systematic review and meta-analysis

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ABSTRACT

Background: Current guidelines recommend anticoagulation using warfarin with bridging parenteral anticoagulation or one of the non-vitamin K antagonist oral anticoagulants (NOACs) to prevent thromboembolic events in patients undergoing cardioversion for atrial fibrillation (AF). We aimed to compare by meta-analytical techniques, the safety and efficacy of NOACs versus warfarin in patients undergoing cardioversion.

Methods: PUBMED, EMBASE, Cochrane CENTRAL and CINAHL were searched electronically in addition to manual search for randomized controlled trials (RCTs) comparing NOACs and warfarin in patients undergoing cardioversion for AF. Mortality, major bleeding and ischemic and hemorrhagic stroke were compared between the two agents.

Results: A total of 7 trials with 7588 total patients were included in the meta-analysis. NOACs, as compared to warfarin, resulted in similar risk of ischemic stroke [odds ratio (OR): 0.49 (95% confidence interval (CI): 0.20–1.19; $P = 0.12$], major bleeding [0.71 (0.37–1.38), $P = 0.32$], mortality [0.73 (0.32–1.67); $P = 0.45$], and hemorrhagic stroke [0.96 (0.11–8.70); $P = 0.97$]. The results were consistent across subgroup analyses.

Conclusions: Based on the current meta-analysis, NOACs and warfarin have comparable efficacy and safety in patients with atrial fibrillation undergoing cardioversion.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice with lifetime risk of 1 in 4 in both men and women of 40 years of age [1,2]. Cardioversion by direct current (DCCV) or pharmacologic agents is performed to restore sinus rhythm in symptomatic or hemodynamically unstable patients with AF. Cardioversion is associated with an increased risk of periprocedural thromboembolic events with a stroke rate as high as 7% in patients without adequate anticoagulation [3]. Current guidelines recommend appropriate therapeutic anticoagulation prior to and after cardioversion to reduce the risk of thromboembolic events [4,5].

Warfarin, a vitamin K antagonist (VKA) has been traditionally used as oral anticoagulation for the peri-procedural period in patients undergoing cardioversion and is the only Food and Drug Administration approved anticoagulant for this purpose [6]. The pivotal trials of non-vitamin K antagonist oral anticoagulants (NOACs) showed these agents to be safe and effective alternatives to warfarin for stroke prevention in patients with non-valvular AF [7–10]. The post-hoc analyses of these pivotal trials and a limited number of prospective randomized trials have compared the use of NOACs and warfarin in periprocedural setting of cardioversions [11–13]. To evaluate the role of NOACs versus warfarin in AF patients undergoing cardioversion, we designed this systematic review and meta-analysis of randomized trials.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DCCV, direct current cardioversion; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; TEE, transesophageal echocardiography; TIA, transient ischemic attack; RCT, randomized controlled trial; VKA, vitamin K antagonist.

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2. Methods

2.1. Data sources and search strategy

We conducted the meta-analysis according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14]. We searched electronic databases of PubMed, EMBASE, Cochrane Central Register of Clinical Trials and CINAHL without

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language restriction from inception through August 2017 using the search terms: "NOAC" OR "Non-Vitamin K oral anticoagulants" OR "edoxaban" OR "dabigatran" OR "rivaroxaban" OR "apixaban" AND "warfarin" AND "atrial fibrillation" AND "cardioversion". In addition, we performed manual search of relevant bibliography including previously published meta-analysis and systematic reviews in the month of August 2017. Updated PubMed search was performed by including search terms "DOAC" OR "direct-acting oral anticoagulants" on 1/9/2017, which did not result in additional studies for inclusion in the current meta-analysis. The search was limited to randomized trials. In addition, we performed search for major cardiology conference proceedings from inception through August 2017. Two investigators (N. T. and K.D.) independently performed the database search including manual search and agreed on final study selection.

2.2. Study inclusion and exclusion

Randomized trials comparing the outcomes of NOACs and warfarin in adult patients (≥18 years) who underwent cardioversion for atrial fibrillation were selected for meta-analysis. Primary studies and the post-hoc analyses of primary studies reporting on at least one outcome of interest were included. The studies that did not compare NOACs versus warfarin were excluded.

2.3. Data extraction

Two investigators (N.T. and C.K.) extracted data from the selected studies in duplicate using standardized data-extraction form and a third investigator (K.D.) confirmed the data for their accuracy. We obtained data on study characteristics (study design, inclusion and exclusion criteria, follow-up duration, number of patients, type and dosing of NOACs and outcomes), patient characteristics, and crude events on the major outcomes at follow-up. For dabigatran, we only extracted data for 150 mg dose as 110 mg dose is not approved for stroke prevention in AF patients in the United States. Similarly, for edoxaban we only analyzed data for standard dose (60/30 mg) since the lower dose (30/15 mg) is not currently approved. In ROCKET-AF trial, there was not separate report of major bleeding outcome and it was reported as major bleeding or clinically relevant non-major bleeding. Therefore, for uniformity we excluded this trial from analysis of major bleeding outcome.

2.4. Outcomes

Mortality, ischemic stroke, major bleeding and hemorrhagic stroke were the major outcomes. All major outcomes were considered primary outcomes. Major bleeding was defined by the International Society of Thrombosis and Hemostasis Guidelines in all trials [15]. When available, we performed separate analyses for early versus late cardioversion.

2.5. Statistical analysis

We calculated pooled odds ratio (OR) with 95% confidence interval (CI) using Mantel Haenszel Method from the individual studies using the total number of events and patients and followed random-effects model. The quality of randomized studies were assessed with Cochrane Collaboration's Bias Assessment Tools [16]. Study heterogeneity was evaluated with Cochran's Q and I^2 index. Significant heterogeneity ($I^2 > 60\%$ and $P < 0.10$) was explored further with sensitivity analyses. In addition, we performed Jackknife sensitivity analysis by removing one study at a time. We planned pre-specified subgroup analyses based on dedicated randomized studies vs. post-hoc analyses, factor Xa inhibitors vs. antithrombin inhibitors and individual NOAC agents. Statistical analyses were performed with Review Manager (RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark).

3. Results

3.1. Description of included studies

The flow diagram of study selection is shown in e-Fig. 1. Electronic search of four databases (PUBMED, EMBASE, CENTRAL and CINAHL) and manual search retrieved a total 179 citations. After removal of 19 duplicates, 160 were assessed for eligibility in the study. Full-text review was performed in a total of 22 studies, of which 15 studies did not meet the inclusion criteria leaving a total of 7 studies in the final quantitative and qualitative analysis.

The individual study and patient characteristics are shown, respectively, in Tables 1 and 2. A total of 7588 patients (RELY trial reported the number of cardioversion but not the actual number of patients) were included in the meta-analysis. Follow-up duration was 30 days in all except ENSURE-AF, for which it was 28 days on study drug and 30 days to assess safety. Three randomized trials (X-VeRT, ENSURE, EMANATE) were primary prospective randomized studies designed to compare NOACs vs. warfarin in patients undergoing AF cardioversion [12,13,17], whereas four studies were post-hoc analyses of pivotal trials of NOACs for atrial fibrillation in stroke prevention that reported the outcomes for cardioversion [11,18–20]. In each of the four studies one of the following agents namely, apixaban, edoxaban, rivaroxaban or dabigatran was used.

3.2. Major outcomes

NOACs, as compared to warfarin, resulted in similar risks of ischemic stroke [0.19% vs. 0.53%; odds ratio (OR): 0.49 (95% confidence interval (CI): 0.20–1.19; $P = 0.12$; $I^2 = 0\%$; $Q = 3.40$; $p = 0.49$], hemorrhagic stroke [0.11% vs. 0.08%; 0.96 (0.11–8.70); $P = 0.97$; $I^2 = 0\%$; $Q = 0.81$; $p = 0.37$], mortality [0.34% vs. 0.49%; 0.73 (0.32–1.67); $P = 0.45$; $I^2 = 0\%$; $Q = 3.89$; $p = 0.45$] and major bleeding [0.44% vs. 0.58%; 0.71 (0.37–1.38), $P = 0.32$; $I^2 = 0\%$; $Q = 0.71$; $p = 0.95$] (Figs. 1 and 2).

3.3. Outcomes after early cardioversion

Early cardioversion was defined differently in the three dedicated trials: <48 h of apixaban or heparin/VKA in the EMANATE trial, within three days of randomization with edoxaban or warfarin in the ENSURE-AF and 1–5 days of rivaroxaban or VKA prior to cardioversion in the X-VeRT. In the analyses restricted to early cardioversion, NOACs, compared to warfarin, resulted in similar risks of ischemic stroke [0.31 (0.06–1.52), $P = 0.15$, $I^2 = 0\%$; $Q = 1.75$], major bleeding [0.65 (0.26–1.62), $P = 0.36$, $I^2 = 0\%$; $Q = 1.13$] and mortality [0.92 (0.27–3.17), $P = 0.90$, $I^2 = 0\%$; $Q = 1.54$] (e-Fig. 2). Although we planned analysis for late cardioversion outcomes, due to limited number of studies we did not perform such analysis.

3.4. Sensitivity and subgroup analyses

We performed several subgroup analyses as mentioned below. Analysis restricted to the studies designed primarily to compare NOACs vs. warfarin for AF cardioversion showed that the NOACs compared to warfarin had similar risks of ischemic stroke [0.39 (0.03–6.02), $P = 0.50$, $I^2 = 75\%$; $Q = 7.91$], major bleeding [0.62 (0.28–1.35), $P = 0.23$, $I^2 = 0\%$; $Q = 0.2$] and mortality [0.69 (0.23–2.1), $P = 0.52$, $I^2 = 5\%$; $Q = 2.11$] and unchanged risk of hemorrhagic stroke. Analyses restricted to factor Xa inhibitors showed similar risks of ischemic stroke [0.60 (0.14–2.68), $P = 0.51$, $I^2 = 57\%$; $Q = 9.22$] and major bleeding [1.04 (0.63–1.71), $P = 0.88$, $I^2 = 0\%$; $Q = 3.1$] and unchanged risk of mortality and hemorrhagic stroke.

Similarly, analysis restricted to individual NOAC compared to warfarin was not performed due to limited number of studies.

The Jackknife sensitivity analysis was performed by removing one study at a time, which did not change the magnitude and direction of all the results.

3.5. Study quality and publication bias

The quality of the prospective randomized studies was moderate to high per Cochrane collaboration's tools and presented as e-Fig. 3. Publication bias was not tested due to small number of studies (<10) for any meaningful assessment of publication bias per Cochrane Group's recommendations [16]. In addition, as EMANATE trial has not been published as full-text manuscript at the time of completion of this meta-analysis, the assessment of study quality was limited due to unclear detection, attrition and reporting biases.

4. Discussion

Our meta-analysis showed similar risks of ischemic stroke, major bleeding, mortality and hemorrhagic stroke with NOACs and warfarin in atrial fibrillation patients undergoing cardioversion with consistent