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ORIGINAL PAPER

# Non-vitamin K antagonist oral anticoagulants in the cardioversion of patients with atrial fibrillation: systematic review and meta-analysis

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**Abstract**
*Background* Non-vitamin K antagonist oral anticoagulants (NOACs) are at least non-inferior to Vitamin K Antagonists (VKAs) for stroke prevention on patients with non-valvular atrial fibrillation (AF). We aimed to evaluate the efficacy and safety of NOACs in patients undergoing cardioversion through a systematic review and meta-analysis.
*Methods* MEDLINE, Cochrane Library, and Web of Science® databases (until September 2014) were searched for studies fulfilling inclusion criteria. Two reviewers independently selected randomized controlled trials (RCTs) evaluating NOACs and VKA in patients with AF undergoing cardioversion. The primary outcome was ischemic stroke or systemic embolism (IS/SE). Secondary outcomes were major bleeding, myocardial infarction, and mortality. Risk ratio (RR) and 95 % confidence intervals were derived through random-effects meta-analysis. Heterogeneity was evaluated through $I^2$ test.
*Results* Four RCTs (3 post-hoc analysis) evaluating apixaban, dabigatran, and rivaroxaban in 3,512 patients with AF were included. The risk of IS/SE with NOACs was similar to VKA (RR 0.60, 95 % CI 0.20–1.80; $I^2 = 17$ %). There was no significant increase in major bleeding (RR 1.27, 95 % CI 0.58–2.81; $I^2 = 0$ %), myocardial infarction (RR 0.71, 95 % CI 0.10–5.04; $I^2 = 0$ %), or mortality (RR 0.87, 95 % CI 0.24–3.08; $I^2 = 0$ %) with NOACs.
*Conclusions* This systematic review and meta-analysis suggests that NOACs may be as safe as VKAs in the setting of AF cardioversion.

**Keywords** Meta-analysis · Electric countershock · Stroke · Anticoagulants · Cardioversion · Transesophageal echocardiography

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## Introduction

Cardioversion is used to restore sinus rhythm in patients with AF, and is done through the administration of antiarrhythmic drugs (pharmacological cardioversion) or electrical cardioversion. In patients with symptomatic AF or with hemodynamic instability, cardioversion can improve hemodynamics, functional status, and quality of life [1]. However, this procedure is associated with an increased risk of stroke, which may result from atrial thrombi dislodgement when sinus rhythm is restored [2]. To prevent these embolic events, patients with AF duration >48 h should have therapeutic anticoagulation with Vitamin K Antagonists (VKAs) for at least 3 weeks, or undergo transesophageal echocardiography to document the absence of intracardiac thrombus pre-cardioversion and fast-acting parenteral anticoagulation (with heparin) administered [3]. Patients with AF duration clearly lasting less than 48 h may be candidates to cardioversion with heparin without requiring TEE. Post-cardioversion anticoagulation is needed for a minimum of 4 weeks, or indefinitely in the presence of stroke risk factors.

Non-vitamin K oral anticoagulants (NOACs) have been evaluated in large clinical trials. In contrast to VKAs, NOACs have a lower risk of major bleeding events such as intracranial hemorrhage [4], a faster onset of action, a predictable dose–response relationship, and does not require frequent anticoagulation intensity evaluation, similar to INR testing in patients treated with VKA [5]. Different from ximelagatran (an oral anti-IIa inhibitor withdrawn due to the high risk of liver injury), recent NOACs did not show increased risk of drug-induced liver injury [6].

The NOACs have been assessed in RCTs and various systematic reviews for their efficacy and safety in patients with atrial fibrillation (AF) [7–10]. We are unaware of any prior systematic review of NOACs when used for cardioversion of AF. In the present analysis, we performed the first systematic review and meta-analysis to assess the efficacy and safety of NOACs in patients with AF undergoing cardioversion.

## Methods

For the purposes of this systematic review, we followed PRISMA guidelines [11].

The protocol was published in PROSPERO website (http://www.crd.york.ac.uk/PROSPERO/) with the following registration number CRD42014013561.

### Study selection and data collection

We intended to identify randomized clinical trials (RCTs) comparing NOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) with Vitamin K Antagonists including or not including heparin (unfractionated or low-molecular weight), published until September 2014. We searched Medline, the Cochrane Collaboration Database and Web of Science. For search strategy details see appendix online. No language restrictions were applied.

Studies were required to include patients with AF or atrial flutter undergoing cardioversion (pharmacological or electrical) treated with NOACs or VKAs. Despite their individual pharmacokinetic and pharmacodynamic differences, NOACs share many similarities, and thus we assumed that these drugs could have a class effect. Studies had to report detailed data about the pretended outcomes in each treatment arm.

Titles and abstracts of records were screened independently by two authors. Doubts and disagreements were solved by a third person. Selected studies were assessed in full text to determine its appropriateness for inclusion. Data about patients' characteristics, antithrombotic strategies, and data of required outcomes were retrieved. In some trials, investigators were able to suspend temporarily the study medication and give open-label VKA for cardioversion. Thus, to evaluate NOACs effect in this context (without any possible interference of open-label VKA), on-treatment analysis data were retrieved whenever possible.

The Cochrane Collaboration Tool was used to assess risk bias and to evaluate reporting quality through the following items: random sequence generation method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, description of withdrawals, and any other risk of bias features [12].

### Outcome measures

The primary outcome was short-term (30–42 days) post-cardioversion ischemic stroke or systemic embolism (IS or SE). The secondary outcomes were major bleeding, myocardial infarction, and mortality, during the same time frame.

### Statistical analysis

Statistical analyses were performed using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Individual studies and meta-analysis estimates were derived, and presented in forest plot graphs.

For the meta-analysis, we used the random-effects model weighted by the inverse-variance method to estimate pooled risk ratios (RRs) and 95 % confidence intervals (95 % CIs) [13]. This method was used by default, independent of the heterogeneity of the pooled analysis. RRs were chosen to report the results because relative measures

tend to be more similar across studies compared to absolute estimates in populations having different baseline characteristics and lengths of follow-up [14]. When zero cells were present in one arm, RevMan automatically added 0.5 to them to perform the calculations.

Heterogeneity was evaluated through the $I^2$ test that measures the percentage of total variation between studies due to heterogeneity [15]. Heterogeneity was considered to be significant if $I^2 \geq 50$ %.

A subgroup analysis was planned according to the strategy considered for cardioversion: transesophageal echocardiogram (TEE)-guided strategy, or cardioversion without TEE.

Publication bias was assessed through visual inspection of funnel plot asymmetry. Egger's and Peters tests were performed to assess objectively this risk [16, 17].

## Results

After removal of duplicates the electronic database search yielded a total of 54 studies. Following our inclusion and exclusion criteria we included four trials for analysis [18–21].

Supplementary Fig. 1 shows the detailed search strategy.

### Description of studies

The four studies reported data of 3,512 patients with AF that underwent cardioversion treated with anticoagulant drugs (2200 NOACs vs. 1312 VKA) [18–21].

There was one cardioversion-based Phase 4 RCT (X-VeRT) [21], and three post-hoc analysis of Phase 3 RCTs [18–20].

Qualitatively, the overall risk of reporting bias was moderate. Supplemental Fig. 2 shows the classification according to The Cochrane Collaboration Tool.

The X-VeRT trial (rivaroxaban vs. VKA) had an open-label design as did the RE-LY study (dabigatran vs. VKA) [18, 21]. The remaining studies had double-dummy double-blinded designs [19, 20]. Because none of the studies were properly powered; we classified all studies as having high risk of bias in 'other bias' field.

Data were heterogeneous regarding the use of transesophageal echocardiography before cardioversion. The use of this technique to exclude intracavitary thrombus ranged from 21 to 64 %. TEE was most commonly used in early elective cardioversions (X-VeRT) [21].

Table 1 details the main characteristics of the various studies.

### Ischemic stroke and systemic embolism

Primary outcome data were available from four studies. Overall 3,512 patients undergoing cardioversion were evaluated. One trial reported zero events in both arms and was excluded for the primary analysis [18]. The risk of IS or SE with NOACs was not different from the standard approach using VKA: RR 0.60, 95 % CI 0.20–1.80; $I^2 = 17$ % (Fig. 1).

### Secondary outcomes

The incidence of major bleeding with NOACs was reported in three studies (3,208 patients), and NOACs were not statistically different from VKA, with a RR 1.27 and 95 % CI 0.58–2.81 (Fig. 2a). Myocardial infarction (RR 0.71, 95 % CI 0.10–5.04; Fig. 2b) and mortality (RR 0.87, 95 % CI 0.24–3.08; Fig. 2c) incidences were not different among interventions. No heterogeneity was noticed in any evaluation of secondary outcomes ($I^2 = 0$ %).

### Subgroup analysis according to the use of transesophageal echocardiogram

Three RCTs provided data for the primary outcome in the subgroup of patients undergoing a transesophageal echocardiogram-guided cardioversion. For RE-LY trial we considered in the denominator the number of cardioversions because we were unable to retrieve the number of patients treated in each arm with this strategy (some patients had more than one cardioversion). Meta-analysis showed that patients treated with NOACs undergoing TEE-guided cardioversion had a non-significant RR 0.18 (95 % CI 0.02–1.35; $I^2 = 0$ %). This estimate was not different ($p$ value for interaction = 0.28) from pooled analysis of NOACs vs. VKA in patients that did not perform TEE before cardioversion (RR 0.75, 95 % CI 0.15–3.76; $I^2 = 19$ %). Figure 3 shows the forest plot of subgroup analyses.

### Analyses using Peto's odds ratio and risk difference measures

We further explored the impact of using different effect measurements on pooled estimates, because the events' rates were low or null in some studies [22–24].

Peto's odds ratio (OR) in circumstances of rare events has been reported to be an adequate and more reliable effect measurement for dichotomous outcomes [22]. Risk difference (RD) is a measure that has the advantage to consider studies with zero events in both arms for meta-analysis estimate [22, 23].

**Table 1** Main characteristics of RCTs included in the review

| Study | Type of study | Population | Mean age/ female (%) | Number CV/ TEE (%) | Electrical/ pharmacological CV | Urgent or emergent cardioversions | Post-cardioversion outcomes | Primary outcome |
|---|---|---|---|---|---|---|---|---|
| ARISTOTLE | Post-hoc analysis of a double-blinded RCT | 540 patients (OTA 451 patients) | 67; 27 % | 609/33.3 % | N/R | N/R | 30-day SSE; MI, MB and Mortality | SSE |
| | | 228 Apixaban vs. 223 VKA | | | | In the ITT analysis there were 4 lethal events. The CV was urgent/emergent in 3 of these patients | | |
| RE-LY | Post-hoc analysis of a open-label RCT | 1,270 patients | N/R | 1,983/ 21.0 % | 83.7/16.3 % | N/R | 30-day SSE and MB | SSE |
| | | 834 Dabigatran Etexilate vs. 436 VKA | | | | CV was urgent/emergent in 3 of the 7 deaths registered | | |
| ROCKET-AF | Post-hoc analysis of a double-blinded RCT | 285 patients (OTA 245 patients) | N/R | 375/N/R | 48.3 %/51.7 % | N/R | 30-day SSE | SSE |
| | | 124 Rivaroxaban vs. 121 VKA | | | | | | |
| X-VeRT | Open-label RCT designed to assess outcomes after elective CV | 1,504 patients | 65/27 % | Early CV 872/64.7 % | >90 % electrical CV | None | 42-day SSE; MI, MB, and mortality | 42-day SSE, MI, and cardiovascular death |
| | | 978 Rivaroxaban vs. 492 VKA | | Delayed CV 632/10.1 % | | | | |

*CV* cardioversion INR, *ITT* intention-to-treat, *MB* major bleeding, *MI* myocardial infarction, *N/R* not reported, *OTA* on-treatment analysis, *RCT* randomized controlled trial, *SSE* stroke or systemic embolism, *TEE* transesophageal echocardiogram

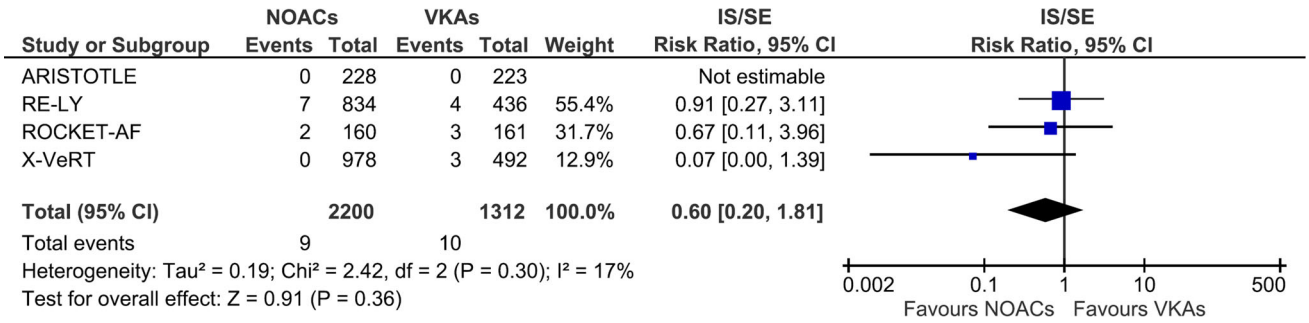


**Fig. 1** Forest plot of NOACs vs. VKAs for ischemic stroke or systemic embolism (primary outcome)

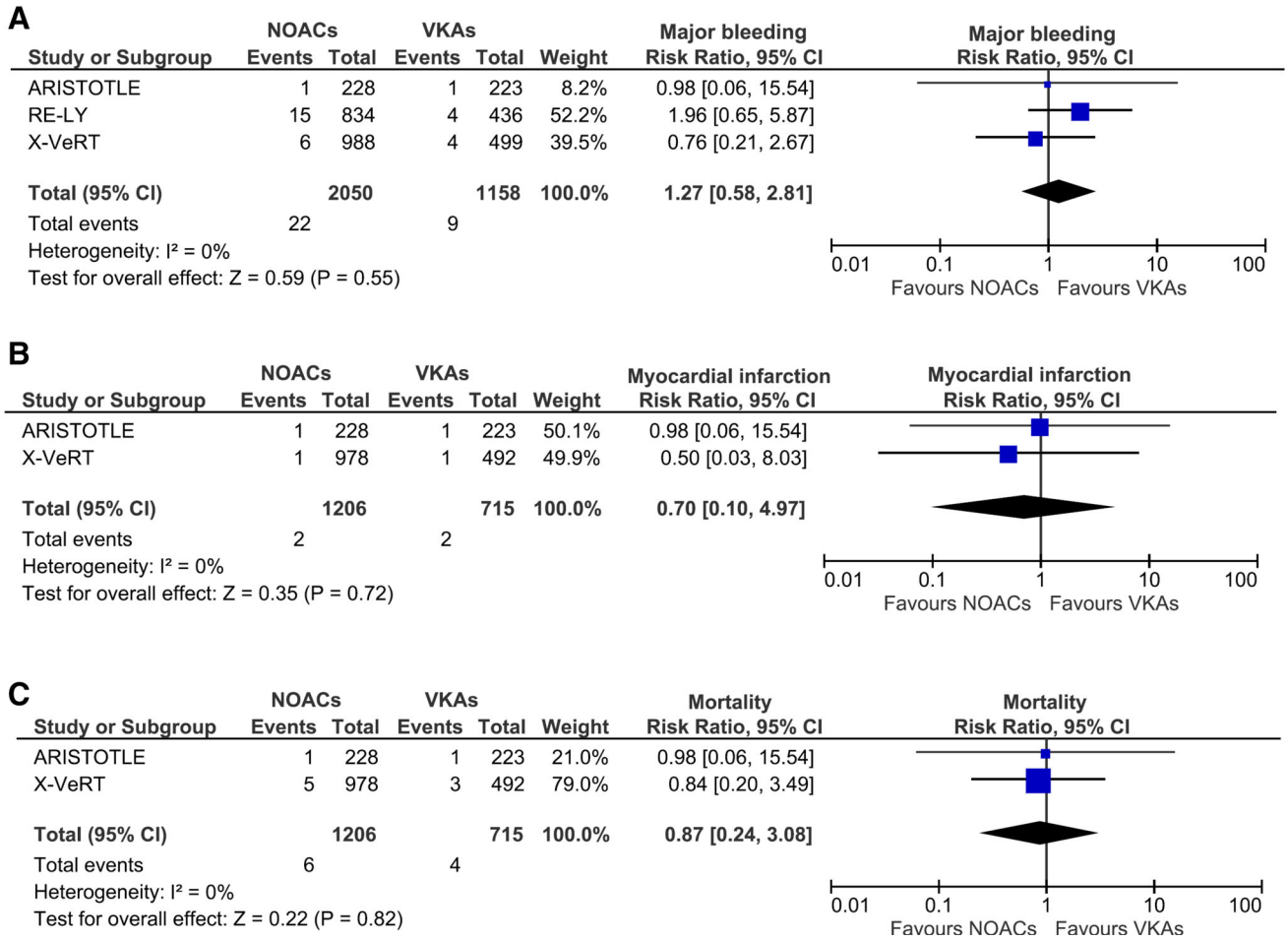


**Fig. 2** Forest plots of NOACs vs. VKAs for: **a** major bleeding; **b** myocardial infarction; **c** mortality

For the primary outcome, IS or SE, NOACs and VKA were not statistically different using Peto's OR as a summary measure: Peto's OR 0.54 (95 % CI 0.21–1.37) with a significant heterogeneity ($I^2 = 56$ %). Using RD for the primary outcome allowed us to include ARISTOTLE data in the quantitative evaluation. Pooled analysis of 4 trials with 3,512 patients showed a non-significant RD decrease of −0.3 % (95 % CI −0.8 to 0.2 %) without heterogeneity ($I^2 = 0$ %) (Fig. 4). The results for secondary outcomes are exposed in Table 2.

## Publication bias

The small number of included studies does not allow an adequate visual evaluation of publication bias risk (supplementary Fig. 3) [25]. Egger's ($p = 0.27$) and Peters

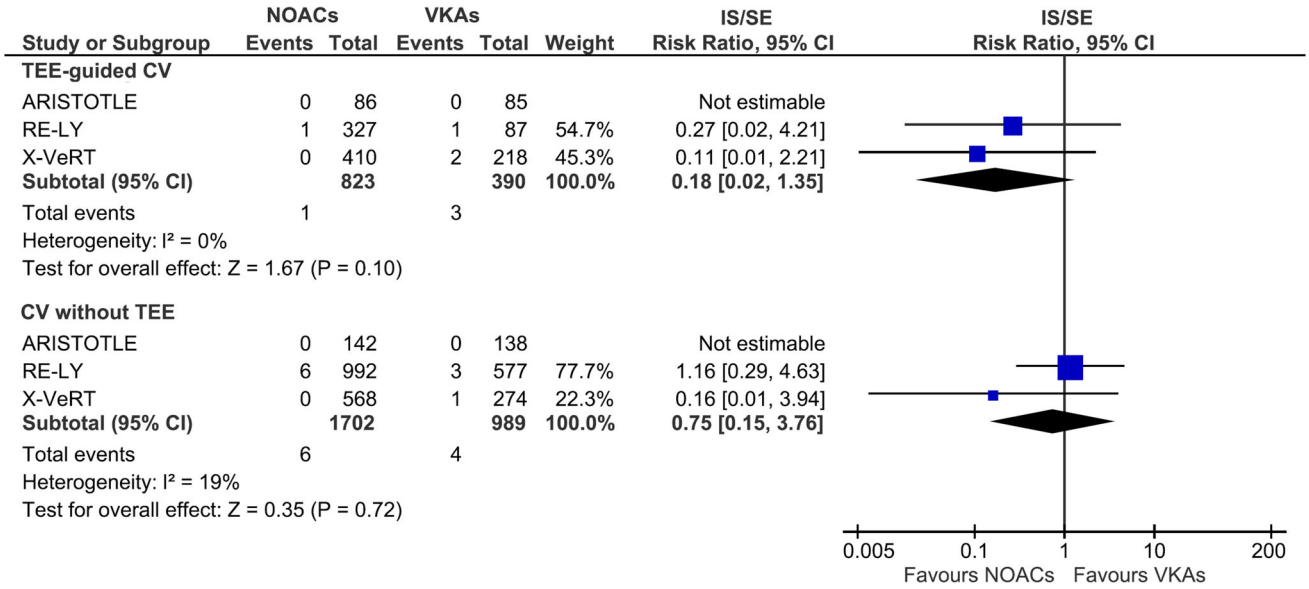


**Fig. 3** Forest plot of NOACs vs. VKAs for ischemic stroke or systemic embolism (IS/SE) according to the use of transesophageal echocardiogram (TEE) before the cardioversion (CV)

**Table 2** Results of pooled analysis according to summary measures

| | RR (95 % CI); $I^2$ (%) | RCTs; patients | Peto's OR (95 % CI); $I^2$ (%) | RCTs; patients | RD (95 % CI); $I^2$ (%) | RCTs; patients |
|---|---|---|---|---|---|---|
| IS or SE | 0.60 (0.20, 1.81); 17 % | 3; 3,061 | 0.54 (0.21, 1.37); 56 % | 3; 3,061 | −0.3 % (−0.8, 0.2); 0 % | 4; 3,512 |
| Major bleeding | 1.27 (0.58, 2.81); 0 % | 3; 3,208 | 1.31 (0.62, 2.75); 0 % | 3; 3,208 | 0.1 % (−0.5, 0.8); 0 % | 3; 3,208 |
| Myocardial infarction | 0.71 (0.10, 5.04); 0 % | 2; 1,921 | 0.70 (0.09, 5.24); 0 % | 2; 1,921 | −0.09 % (−0.5, 0.3); 0 % | 2; 1,921 |
| Mortality | 0.87 (0.24, 3.08); 0 % | 2; 1,921 | 0.86 (0.24, 3.17); 0 % | 2; 1,921 | −0.01 % (−0.8, 0.6); 0 % | 2; 1,921 |

*IS* ischemic stroke, *OR* odds ratio, *RCTs* randomized controlled trials, *RD* risk difference, *RR* risk ratio, *SE* systemic embolism

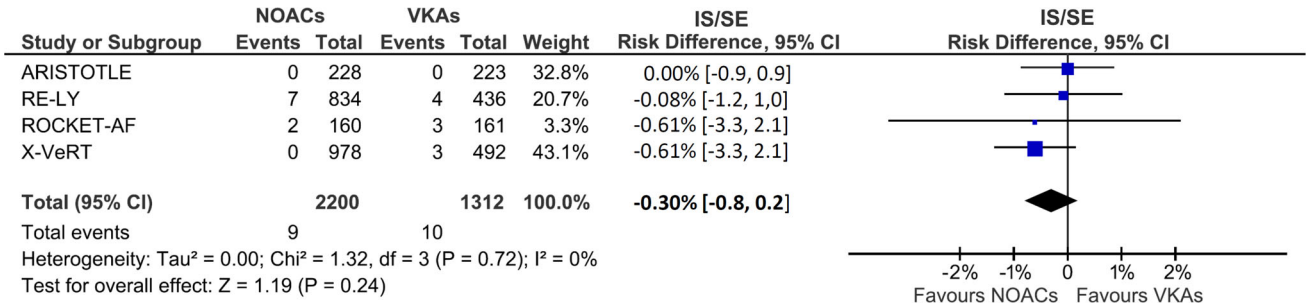


**Fig. 4** Forest plot of NOACs vs VKAs for ischemic stroke or systemic embolism, using risk difference measure

($p = 0.91$) tests were not suggestive of publication bias risk

## Discussion

Taken together, this systematic review and meta-analysis summarizes the best available evidence on NOACs for cardioversion of AF. The principal findings of our study are the following: (1) NOACs were as safe as VKA in the prevention of stroke or systemic embolism in patients undergoing cardioversion; (2) The rate of primary events was very low in the four studies and in both therapeutic arms (19 events in 3,500 patients). The confidence intervals of estimates were still wide and pooled data were not powered enough to establish non-inferiority of NOACs

compared to VKA [21], nonetheless, the data provided information about the safety of NOACs in this context. (3) The rates of other clinically significant outcomes such as major bleeding, myocardial infarction, and mortality did not differ significantly among interventions.

Anticoagulation is known to reduce the risk of stroke or systemic embolism in the cardioversion setting [2, 26]. It is recommended that effective anticoagulation for a minimum of 3 weeks before cardioversion when AF duration is >48 h (delayed cardioversion method) is needed, while post-cardioversion anticoagulation is required for at least 4 weeks to prevent embolic events related to atrial stunning/incomplete atrial contraction recovery or early AF recurrences [27, 28].

Transesophageal echocardiogram allows physicians to accurately diagnose or exclude thrombus in the left atrial appendage or in other cardiac chambers. The exclusion of intracavitary thrombi enables immediate cardioversion using a fast-acting anticoagulant (immediate cardioversion method), with post-cardioversion events similar to the delayed method [3]. In this review we performed a meta-analysis of subgroups of patients undergoing a transesophageal echocardiogram-guided strategy and the results showed a trend favoring NOACs regarding IS or SE, thus ensuring the safety of these drugs using this strategy. In stable AF patients with a TEE without intracardiac thrombus, cardioversion should only be performed under adequate antithrombotic environment. If no drugs were given before, physicians should be aware that NOACs only have their effective onset of action about 4 h after oral intake [21].

In our review we evaluated whether TEE guidance improves the safety of cardioversion under NOACs; there was a trend toward higher safety with undergoing TEE which could be due to underpowered comparisons despite the meta-analysis.

Due to the linear relationship of dose–effect, NOACs provide effective anticoagulation as long as the medication adherence is warranted. This is particularly important in the delayed cardioversion because the classical anticoagulation with VKA is susceptible to INR fluctuations, leading to sub-therapeutic levels and increased thrombotic burden [29]. Furthermore sub-therapeutic INR levels are an important source of costs related to postponement of the cardioversion procedure [30]. In patients undergoing immediate cardioversion, NOACs have a fast onset of action, without the need of further bridging or switching anticoagulants after performing the cardioversion [31].

Altogether the results of this review are of interest to all stakeholders:

Patients now have a safe and convenient alternative to VKA, without the need of serial analysis of hemostatic parameters, and cardioversions are postponed due to ineffective anticoagulation.

Indeed, physicians can reliably consider patients for effective anticoagulation with NOACs before, during, and after cardioversions, without the need for switching or bridging. Nevertheless it is of capital importance to assess the medication adherence in the 3 weeks before a cardioversion, and in case of doubt about compliance a TEE-guided strategy should be considered [32, 33]. Once-daily dosing regimens are classically associated with improved medication adherence [34], but in this context, particularly with NOACs, data are scarce. Nevertheless, only twice-daily regimens (apixaban and dabigatran 150 mg) have shown to decrease significantly the risk of stroke compared to VKA [35].

For policymakers, NOACs can also decrease costs associated with elective cardioversion cancelations or postponements, as occurs frequently with patients treated with VKA.

"Real-world" observational data are scarce but are consistent with our findings, highlighting the safety of NOACs in cardioversion [36]. The ongoing phase 4 RCTs ENSURE-AF trial using edoxaban (aiming for a sample size of 2,200 patients) [37], and EMANATE trial using apixaban (planned to enroll 1,500 patients) [38], will provide more robust data of cardioversions with NOACs. These trials will be also underpowered and, albeit unknown, it is not probable that a meta-analysis after data dissemination will be able to answer any of the relevant questions. According to sample size calculation of X-VeRT, a sample size of 25,000–30,000 patients would be required to properly answer clinically relevant questions in this context.

## Limitations

This analysis is limited by methodological issues associated with meta-analysis and individual studies. The results of our meta-analysis are based on study-level data and not on individual patients' data.

The overall quality of included studies moderate: we considered that most of the trials were at high risk of selective reporting bias due to the unplanned nature of the analysis of patients undergoing cardioversion; two of the trials were performed with an open-label design; and none of the studies were properly powered to answer the question raised.

Data for some outcomes were not available and restrains our review for robust conclusions.

Pooling data of studies with different designs (confounding bias in observational studies) that evaluated patients in different settings (elective cardioversions and acute hospitalization cardioversions; referral bias) should also be accounted as limitations to our conclusions.

Nevertheless, it increases the power and external validity of the data obtained.

We also pooled the different NOACs under the assumption of a class effect of these drugs in cardioversion. Despite the pharmacodynamic and pharmacokinetic differences among NOACs [32, 34], there were no significant differences of estimates in the meta-analysis.

## Conclusions

The best available evidence is underpowered to establish non-inferiority of NOACs compared to VKA. However, our meta-analysis suggests that NOACs (apixaban, dabigatran, and rivaroxaban) may be as safe as VKA for stroke and systemic embolism prevention in AF patients undergoing cardioversion. Other outcomes of interest such as major bleeding, myocardial infarction, and mortality were not different between NOACs and VKA.

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**Conflict of interest** DC, and JC do not have any competing interests to disclose. JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme. GYHL had consultant fees from Bayer, Astellas, Merck, Astra Zeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim; and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. FJP had consultant and speaker fees with Astra Zeneca, Bayer, and Boehringer Ingelheim.

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