Short Report

Impact of new oral anticoagulants on gastrointestinal bleeding in atrial fibrillation: A meta-analysis of interventional trials

Lorenzo Loffredo*, Ludovica Perri, Francesco Violi

Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy

1. Introduction

Atrial fibrillation (AF) is the most common cause of cardiac arrhythmia and is known to be associated with both thromboembolic and cardiovascular events [1,2]. Until recently vitamin K antagonists (VKA), such as warfarin and acenocoumarol, represented the cornerstone of anticoagulant therapy in AF [3]. The anticoagulant effect of VKA consists in inhibiting the gamma-carboxylation of coagulation factors II, VII, IX and X [3]. The need for frequent monitoring, the variability in dosing, the influence of genetic polymorphisms, and the interaction with other drugs and diet have complicated VKA use [3,4]. In the last decade, a new class of anticoagulants has been developed in order to solve these limitations. These drugs, also called “new oral anticoagulants” (NOACs), are: ximelagatran, dabigatran etexilate, rivaroxaban, edoxaban and apixaban; their mechanism of action consists in directly inhibiting the coagulation factors Xa (rivaroxaban, apixaban, edoxaban) and IIa (dabigatran, ximelagatran) [3]. Compared to standard therapy with VKA, NOACs have some advantages, such as rapid onset of action, minimal interactions with food and drugs and a predictable anticoagulant effect [3]; this latter effect eliminates the need of monitoring blood coagulation.

Although NOACs are recommended by several guidelines (American Chest Physicians [5], Canadian Cardiovascular Society [6]) there are heterogeneous and inconclusive data about their safety. Particular concern has been expressed regarding the relationship between NOACs and the occurrence of gastrointestinal bleeding (bleeding) in AF, but data in this regard are still unclear. Thus, while some meta-analyses [7,8] found no negative impact of NOACs on bleeding, another recent meta-analysis showed an enhanced risk of bleeding in patients treated with NOACs [9]. Even if such effect seemed to be attributable to the high dose regimens in this latter meta-analysis [9], pooled analysis did not permit to establish differences among NOACs inhibiting thrombin or factor Xa. Thus, NOACs have different bioavailability, absorption and elimination based on the molecule and this could have a different impact of NOACs on bleeding. To address this still open issue, we analyzed whether NOACs are associated with an enhanced risk of bleeding in AF patients and the differences among NOAC molecules.
2. Methods

We evaluated trials comparing the harmful effect of bleeding in AF patients treated with NOACs vs VKA. We conducted all analyses according to the intention-to-treat principle evaluating the effect of different NOACs on bleeding. A detailed description of methods is reported in Appendix A (Supplementary methods). There was no predefined protocol for this meta-analysis.

Briefly, the studies were identified by searching electronic databases. This search was applied to Medline, ISI Web of Science, SCOPUS and Cochrane database. The last search was run on December 24th 2014. Reference lists of all studies included in the present systematic review were screened for potential additional eligible studies.

We used the following key words to search all trial registers and databases:


Studies were included if they met the following selection criteria: patients with AF randomized to NOACs vs warfarin. Only prospective randomized controlled trials were included in this meta-analysis. Reviews, case-reports, letters, abstracts, phase II trials and non-human studies were excluded.

This review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement issued in 2009 [10]. Flow of information through the different phases of this meta-analysis is reported in Supplementary Figure S1.

To evaluate the effect of NOACs in patients with AF on bleeding we allocated the results of each randomized controlled trial as dichotomous frequency data. We considered a p value < 0.05 as significant. Risk Ratios (RR) and 95% confidence intervals (CIs) were calculated. Data were pooled and compared with a random-effects model [11].

Statistical heterogeneity was calculated by the P [12].

The presence of publication bias was evaluated by using the Begg’s [13] and Egger’s [14] tests (reporting the 1-tailed p-value).

3. Results

Clinical characteristics of the included studies are reported in Supplementary Table S1.

The search of Medline, and Cochrane database provided a total of 295 citations. A total of four studies (RE-LY [15], ROCKET AF [16], ARISTOTLE [17] and ENGAGE AF–TIMI 48 [18], met the inclusion criteria and were included in this systematic review.

The four selected studies [15–18] ranged from 14,264 to 21,105 patients.

Female patients were 37.6%, and the prevalence of persistent/permanent and paroxysmal AF was 75.7% and 24.3%, respectively. Incidence of prior myocardial infarction was 14.9%. Median follow-up was 2.1 years. The average time in therapeutic INR range (TTR) was 64.8% (range 58–68%).

![Fig. 1. Forest plots for outcomes of gastrointestinal bleeding. NOACs, new oral anticoagulants; VKA, vitamin K antagonists.](image-url)
The incidence rate for bleeding was 2.2% (2.4% vs 2.1% in patients treated with NOACs and warfarin, respectively). The pooled analysis showed that, compared to warfarin, NOACs significantly increased bleeding (RR: 1.23; 95% CI 1.03–1.46; p = 0.01, Fig. 1, Panel A), with an absolute risk increase of 0.3%; no evidence of publication bias (Begg’s test, p = 0.452; Egger’s test, p = 0.464) was observed. The heterogeneity among trials was: $I^2 = 80$ (p = 0.001) for total overall effect. Compared with warfarin, no significant reduction of bleeding was observed with Xa factor inhibitors (RR: 1.07; 95% CI 0.78–1.46; p = 0.653) (Fig. 1, Panel A). Conversely, a significant increase of bleeding was observed with Ila factor inhibitors (RR: 1.30; 95% CI 1.06–1.61; p = 0.012). Furthermore, we evaluated whether the interplay between NOACs and bleeding was influenced by dosage regimens and drugs. Thus, compared with warfarin, no significant reduction of bleeding was observed with apixaban and with low dosages of dabigatran (110 mg) and edoxaban (30 mg, Fig. 1, Panel B). Low dosage of edoxaban (30 mg) significantly reduced bleeding (RR: 0.68; 95% CI 0.54–0.84; p = 0.001, Fig. 1, Panel B). Conversely, rivaroxaban (RR: 1.46; 95% CI 1.2–1.8; p < 0.001), 60 mg of edoxaban (RR: 1.22; 95% CI 1.01–1.47; p = 0.038) and 150 mg of dabigatran (RR: 1.50; 95% CI 1.20–1.88; p < 0.001) significantly increased bleeding (Fig. 1, Panel B).

4. Discussion

While the results of this meta-analysis are consistent with an increase of bleeding with NOACs, we show that this effect is detectable with both inhibitors of thrombin and Xa factor, and is observed essentially with high dosages of NOACs. Consistent with this suggestion is the null effect of apixaban, whose dosage is lower compared to the other NOACs, vs warfarin.

A possible interpretation of these findings could rely on the bioavailability of these drugs and their persistence in the gastrointestinal lumen [19]. Thus, compared to warfarin bioavailability that is 97%, NOACs have a lower bioavailability (dabigatran 7%, rivaroxaban 66%, apixaban 50%, edoxaban 68%) with a potentially higher persistence in the gastrointestinal lumen and ensuing increased risk of bleeding particularly in case of high dosage [19]. This meta-analysis may have an important implication in the management of AF patients as it suggests that in patients at risk of gastrointestinal bleeding, such as those with a history of bleeding or on concomitant treatment with aspirin [20], the use of rivaroxaban and high dosage of edoxaban and dabigatran should be avoided. A recent retrospective cohort study, confirmed that dabigatran is associated with an increased risk of gastrointestinal haemorrhage in patients with AF [21].

This study has limitations due to different study populations, to lack of direct comparison among different NOACs, to the limited number of trials selected and to the absence of predefined protocol.

In conclusion, this meta-analysis shows that NOACs are associated with enhanced bleeding risk independently from the principal mechanism of action. Such side effect is detected essentially with high dosages of dabigatran and edoxaban and with rivaroxaban.

Conflict of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.01.159.

References
