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REVIEW

Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis

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Abstract The new oral anticoagulants/non-vitamin K antagonists oral anticoagulants (NOACs) have recently reached the market and less is known about their safety in comparison to their efficacy. Therefore, we aimed to evaluate intracranial hemorrhage (ICH) risk with NOACs, the most feared adverse event of anticoagulation treatment. This is a systematic review and meta-analysis of phase III randomized controlled trials (RCTs) comparing NOACs versus any control and reporting ICH events. Studies were searched through Medline and Cochrane Library (April 2014). Reviews and reference lists were also screened. Random effects' meta-analysis was performed to derive pooled estimates expressed as relative risk (RR) and 95 % CI. Number needed to treat/harm (NNT/NNH) taking into account the baseline risk was also calculated. Heterogeneity was evaluated with I^2 test. 18 RCTs evaluating 148,149 patients were included. NOAC significantly reduced ICH risk compared to vitamin K antagonists (VKA) (RR 0.44; 95 % CI 0.36–0.54; $I^2 = 37$ %; NNT: 137 during 2 years) and to sequential treatment with low molecular weight heparin and VKA (RR 0.28; 95 % CI 0.12–0.65; $I^2 = 0$ %; NNT: 463 patients during 7 months). Compared to placebo, NOACs were associated with an increased ICH risk (RR 3.31; 95 % CI 1.59–6.90; $I^2 = 0$ %; NNH: 433 during 1 year). Results were similar for the different NOAC drugs and across the different clinical conditions. In patients requiring anticoagulation treatment, the risk of ICH is about half with the NOACs in comparison to standard antithrombotic treatment. This safer profile found in RCTs should be confirmed in real-world database studies.

Keywords Intracranial hemorrhages · Anticoagulants · Meta-analysis

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Introduction

Oral anticoagulants are the corner stone therapeutic option for the prevention and/or treatment of venous thromboembolism and atrial fibrillation. The so-called new oral anticoagulants (NOACs) or non-vitamin K oral anticoagulants selectively inhibit factors IIa or Xa. These drugs have overcome some limitations associated with the

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traditional oral and parenteral anticoagulants. In randomized controlled trials (RCTs), it has been shown that NOACs' efficacy across a whole spectrum of prothrombotic conditions is, at least, non-inferior to the standard care [1].

Regarding safety, it is not surprising that anticoagulants pose an increased risk of bleeding [2]. Among the many possible different bleeding events, both in terms of location and severity, intracranial hemorrhage (ICH) is by far the most feared due to the increased morbidity and lethality [3, 4]. In RCTs, NOACs' risk of major bleeding events has been heterogeneous [5, 6], and uncertainty exists regarding a putative "protective" effect of NOACs in comparison to other antithrombotic drugs through all indications, as well as the clinical relevance of this effect. Therefore, we aimed to evaluate these questions by performing a systematic review of RCTs evaluating NOACs ICH risk irrespective of the indications under study.

Methods

Guidelines

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) framework guidelines were used for reporting guidance [7].

Studies' eligibility criteria

For this review, we included all phase III RCTs comparing NOAC, namely direct inhibitors of IIa (dabigatran) or Xa (apixaban, darexaban, edoxaban, or rivaroxaban), with any other control group (placebo, no-treatment or standard care, non-pharmacological interventions or any drug), reporting data for ICH events. We selected only phase III RCTs because we were interested in determining the risk associated with the approved and commonly used doses of the NOACs. Furthermore, we wanted to avoid bias in risk estimation due to statistical effects of rare events and the impact of small-size underpowered studies on meta-analysis results [8–11]. All RCTs were considered for inclusion irrespective of patients' indications for anticoagulation.

Search method

Investigators retrieved potential-eligible studies through an electronic search in Medline (via OVID) and Cochrane Library, performed in April 2014. Search strategy is detailed in supplementary online. There were no language restrictions. Additionally, we checked the references of retrieved systematic reviews and meta-analyses that evaluated NOAC, as well as the reference list of each included study. When data for the intended outcome were not available from published articles, we looked at the available public reports of these drugs from the European Medicine Agency and Food and Drug Administration websites.

Data extraction, evaluation and synthesis

Titles and abstract of obtained records were screened independently by two authors. Doubts and disagreements were solved by consensus. Selected studies were assessed in full-text to determine the appropriateness for inclusion in the systematic review. Study characteristics and outcomes were extracted independently by two authors.

Appraisal of methodological bias was done according to the Cochrane Collaboration's tool for assessing risk of bias [12]. Studies were not excluded a priori based on their quality of reporting.

Statistical analysis

We aimed to estimate the incidence of ICH (primary outcome), defined as any intra-axial or extra-axial hemorrhage diagnosed and reported by investigators as such. Data from each study were treated as dichotomous data. Risk ratio (RR) and 95 % confidence interval (95 % CI) were used to report data from pooled results because relative measurements, such as RR, are more similar across studies with different designs, populations, baseline risk and lengths of follow-up, than absolute measurements of treatment effect [13]. In the presence of significant differences between groups, we also calculated the number needed to treat/harm (NNT/NNH) and 95 % CI taking into account the baseline risk (weighted proportion of bleeding event rate in control group) because of possible differences in the predicted absolute effect of treatment according to variation in baseline risk between groups [14, 15].

Software Review Manager 5.2.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to obtain the estimates of individual studies, pooled analysis and to retrieve the forest plots. Heterogeneity was assessed with the I^2 test, which measures the percentage of total variation attributed to inter-study heterogeneity rather than random [16]. The inverse of variance method with random effects' model was used by default independently of the existence ($I^2 \geq 50$ %) or not of substantial heterogeneity between studies' results.

We assumed that the risk of ICH is above all a direct consequence of the drug itself (described in clinical trials as treatment-emergent or treatment-related adverse events), and therefore, NOAC-associated ICH risk should not be significantly different across the clinical conditions in which these drugs are used. Consequently, in the primary

analysis we decided to pool the data for NOAC according to the control group used (active drug or placebo/no-treatment) and not according to the clinical condition in which they were evaluated. However, to explore whether the ICH risk was different across individual NOACs and in particular clinical conditions, we performed a subgroup analysis based on each individual NOAC and clinical conditions, irrespectively of the presence or not of significant heterogeneity found in the primary analysis.

Publication bias was assessed through visual inspection of funnel plot asymmetry and with Egger's and Peters' regression tests [17, 18].

Results

The study selection for this review returned 18 RCTs reporting at least one ICH event (supplementary Fig. 1) [19–36]. The included trials evaluated NOAC among different clinical conditions and settings: patients with venous thromboembolic disease (VTD) ($n = 6$ RCTs), non-valvular atrial fibrillation (NVAF) ($n = 6$ RCTs), acute coronary syndrome ($n = 2$ RCTs), patients that underwent orthopedic surgery ($n = 2$ RCTs) and patients hospitalized for medical illnesses ($n = 2$ RCTs).

These 18 studies evaluated a total of 148,149 patients with a mean age ranging from 55 to 73 years. The comparators were different according to the different settings: low molecular weight heparin (LMWH) after orthopedic surgery ($n = 2$ RCTs), LMWH–VKA sequential combination in VTD disease ($n = 4$ RCTs), VKA ($n = 6$ RCTs) and acetylsalicylic acid (ASA) ($n = 1$ RCT) in NVAF, LMWH–placebo in patients with medical illnesses ($n = 2$ RCTs), and placebo in acute coronary syndrome (ACS) and VTD trials ($n = 3$ RCTs).

Overall, the risk of bias of included studies was considered to be low (supplementary Fig. 2).

ICH risk associated with NOACs in comparison to controls

The forest plot with the pooled analysis of ICH risk associated with NOACs according to each control group is illustrated in Fig. 1.

NOACs were compared to LMWH in two RCTs evaluating apixaban and rivaroxaban on 6,218 patients that underwent surgery (knee or hip). ICH risk was similar between NOAC and LMWH with an RR of 0.33 (95 % CI 0.03–3.18; $I^2 = 0$ %; Fig. 1) during a mean treatment period of 1.5 months.

In comparison to sequential treatment with LMWH and VKA among patients with VTD ($n = 4$ RCTs; 20,961 patients), NOACs were associated with a significant 72 % risk reduction of ICH risk (95 % CI 35–88 %; Fig. 1), without statistical heterogeneity ($I^2 = 0$ %). NNT to prevent one ICH compared to LMWH–VKA was 463 patients during an average of 7 months.

VKA were the comparators of choice in almost all RCTs evaluating patients with NVAF and in one RCT in patients with VTE [28]. Pooled analysis ($n = 6$ RCTs; 75,649 patients) showed a significant 56 % ICH risk reduction (95 % CI 46–64 %; Fig. 1), with low-to-moderate statistical heterogeneity ($I^2 = 37$ %). NNT was 137 patients during 2.1 years on average. Sensitivity analysis by excluding RE-MEDY trial (which enrolled patients with VTE) yielded similar results (RR 0.44; 95 % CI 0.35–0.55; $I^2 = 49$ %; Fig. 1) [28].

AVERROES was the only RCT that compared NOAC (apixaban) with ASA in patients with atrial fibrillation unsuitable for VKA treatment [21]. This trial included 5,599 patients and the ICH RR reported in the trial was 0.84 (95 % CI 0.38–1.87; Fig. 1).

Two RCTs evaluated NOACs in 14,399 patients that were hospitalized with medical illnesses and used a short course of LMWH followed by placebo as comparator arm [25, 36]. The use of NOACs in this context was not associated with an increased risk of ICH (RR 1.01, 95 % CI 0.04–23.36; $I^2 = 53$ %; Fig. 1).

NOACs were compared against placebo in one extended study period of an apixaban RCT in patients with post-VTE [24], and in two RCTs with ACS patients [20, 34]. Overall these studies included 25,323 patients. The pooled analysis of these three placebo-controlled trials (ACS and post-VTE setting) showed a significant increase in ICH risk with NOAC (RR 3.31; 95 % CI 1.59–6.90; $I^2 = 0$ %). NNH was 433 patients during approximately 1 year on average.

ICH risk associated with each individual NOAC and clinical condition

Table 1 shows the main results for the subgroup analysis considering each individual NOAC and clinical condition. In comparison to controls, the ICH risk was similarly lower for all individual NOACs and across all studied populations. The only exception was the case of rivaroxaban in medically ill patients [36]. Magellan trial was not powered to evaluate the impact of NOACs in ICH risk on medically ill patients. Study's population also includes patients with very heterogeneous conditions [36]. Furthermore, the bleeding risk in medically ill patients is not well defined, and clinical characteristics could not have been adequately balanced between groups.

For each individual NOAC, the ICH risk reduction was similar across the different populations in which they have

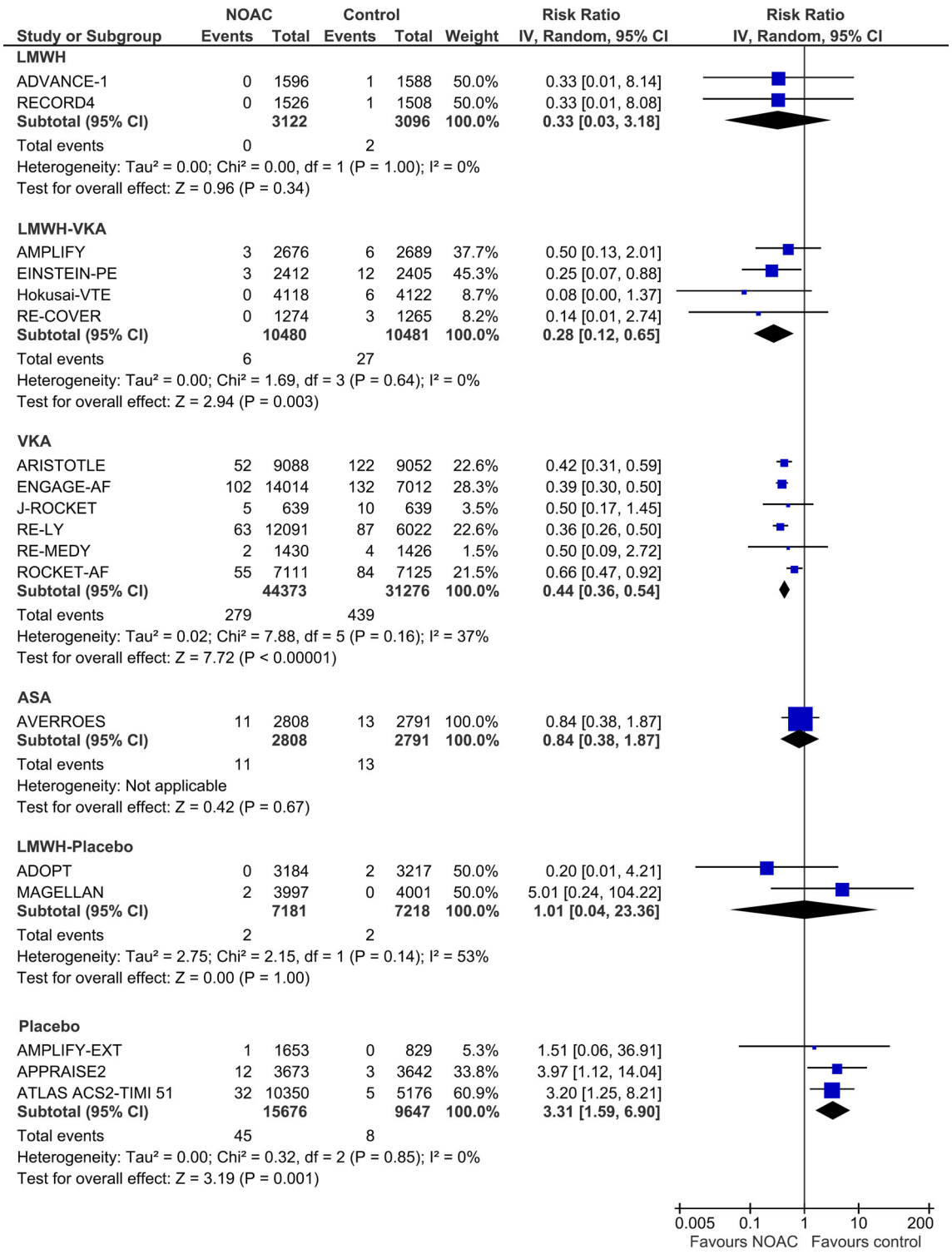

Fig. 1 Risk of intracranial hemorrhage with NOACs in comparison to controls

been tested ($p > 0.25$ for all subgroup differences according to the clinical condition under evaluation; Table 1). In addition, no significant differences existed in ICH risk reduction when considering the different subgroups according to the active control (LMWH, LMWH–VKA, VKA, ASA) ($p = 0.30$ for subgroup differences). Taken together, these findings suggest a drug-class effect and corroborate our initial presupposition that NOAC-

Table 1 Risk of ICH associated with the different NOACs (versus active controls) and clinical conditions

Population	Apixaban			Dabigatran			Edoxaban			Rivaroxaban		
	Studies	RR [95 % CI]	I^2	Studies	RR [95 % CI]	I^2	Studies	RR [95 % CI]	I^2	Studies	RR [95 % CI]	I^2
Medical III patients	1 study 6,401 pts	0.20 [0.01, 4.21]	NA	–	–	–	–	–	–	1 study 7,998 pts	5.01 [0.24, 104.2]	NA
Post-surgical prophylaxis	1 study 3,184 pts	0.33 [0.01, 8.14]	NA	–	–	–	–	–	–	1 study 3,034 pts	0.33 [0.01, 8.08]	NA
VTE	1 study 5,365 pts	0.50 [0.13, 2.01]	NA	2 studies 5,395 pts	0.37 [0.08, 1.59]	0 %	1 study 8,240 pts	0.08 [0.00, 1.37]	NA	1 study 4,817 pts	0.25 [0.07, 0.88]	NA
AF	2 studies 2,373 pts	0.54 [0.28, 1.02]	0 %	1 study 18,113 pts	0.36 [0.26, 0.50]	NA	1 study 21,026 pts	0.39 [0.30, 0.50]	NA	2 studies 15,514	0.64 [0.46, 0.88]	0 %
Pooled	5 studies 38,689 pts	0.46 [0.35, 0.62]	0 %	3 studies 23,508 pts	0.36 [0.26, 0.49]	0 %	2 studies 29,266 pts	0.33 [0.14, 0.83]	0 %	5 studies 31,363 pts	0.60 [0.41, 0.87]	5 %
p value for differences across conditions with the same NOAC	0.93			0.99			0.27			0.26		

AF atrial fibrillation; *CI* confidence intervals; *NA* not available; *NOAC* non-vitamin K antagonist oral anticoagulant; *pts* patients; *RR* risk ratio; *VTE* venous thromboembolism

associated ICH risk is mainly a consequence of the drug itself and not of the conditions in which they are used.

Risk of publication bias

Funnel plot was not suggestive of publication bias (supplementary Fig. 3), and both Egger ($p = 0.87$) and Peters ($p = 0.66$) test results were also not suggestive of important publication bias.

Discussion

Intracranial hemorrhage is a well-known serious complication of antithrombotic drugs [37, 38]. The most important finding of this review is the safer profile of the new oral anticoagulants regarding this outcome in comparison to standard antithrombotic strategies and across different clinical conditions. This review also showed, as expected, an increased risk of ICH with NOACs when compared with placebo.

In comparison to other anticoagulant regimens (considered the standard of care in each condition), the risk of ICH was reduced to more than an half with the NOACs, particularly against VKA (mostly in AF patients) and LMWH–VKA (VTD patients) regimens, which owe the most robust data of this review. Treatment with VKA requires INR periodical monitoring, and despite the controlled environment of clinical trials the mean time in therapeutic range did not exceed 70 %. The risk reduction here retrieved (about 70 %) was both clinically and statistically significant, without statistical heterogeneity. The evidence carried from other conditions and other comparators, such as LMWH, was not only smaller, with larger CIs, but also overlaps with the other estimates.

The risk of anticoagulation-related ICH has been previously evaluated and the absolute risk reduction of this outcome was not different across clinical conditions [39]. In line with this conclusion, the results here presented showed a consistent decrease of ICH risk with NOACs compared to active controls. Reliable estimates of ICH events are difficult to retrieve from single-trial results as these are relatively rare events. Despite the methodological limitations of this analysis, the inclusion of multiple large-size trials, the absence of subgroup differences and the estimates consistency provide robustness to the findings.

According to a subanalysis of RE-LY, intracerebral and subdural hemorrhages (46 % each) were the most common types of ICH [40]. Dabigatran significantly decreased the risk of both these types of ICH. Dabigatran also decreased the risk of traumatic ICH (most of them with a subdural location) without increasing the case-fatality rate [40]. A post hoc analysis of ROCKET AF confirmed the protective

effect of rivaroxaban concerning overall ICH through a multivariable cox proportional hazards model [41]. However, rivaroxaban did not reduce ICH-related mortality [41].

These results are important to patients, physicians and policy-makers. NOACs are at least as effective as VKA/LMWH in the studied conditions and significantly decreased ICH risk. Furthermore, NOACs do not require regular control of anticoagulation status, like in the case of VKA-treated patients. Treatment with NOACs waives such burden and lightens resources consumption. NOACs are also likely to be cost-effective, which is of extreme importance for policy-makers [42–44].

Limitations

This systematic review with meta-analysis has limitations related to included studies and analysis method, including the fact of being a study-based meta-analysis rather than individual patient data analysis.

Pooling data from studies evaluating patients with different clinical conditions is always a methodological concern and should be considered as a limitation for conclusions. Other potential limitation is the possibility of selection bias because a significant proportion of patients with AF have already been treated with VKA without previous major bleeding events (exclusion criteria of all trials).

Conclusions

In patients requiring anticoagulation treatment, the risk of ICH is about half with the NOACs in comparison to standard antithrombotic treatment.

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