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Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants

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SUMMARY

Background
Gastrointestinal (GI) bleeding is a common complication among anticoagulated patients. Non-vitamin K antagonist oral anticoagulants (NOACs) are associated with increased risk of GI (major and clinically relevant non-major) bleeding. However, more information is needed regarding severe events.

Aim
To evaluate the risk of NOACs major GI bleeding.

Methods
We searched for phase III randomised clinical trials (RCT) evaluating NOACs (apixaban, dabigatran, edoxaban and rivaroxaban) and reporting major GI bleeding events, in MEDLINE, Cochrane Library, SciELO collection and Web of Science databases (July 2015). Meta-analysis was performed to estimate risk ratio (RR) and 95% confidence intervals (95% CIs). Heterogeneity was assessed with the I^2 test.

Results
A total of 23 studies were included. Among patients with atrial fibrillation, the risk of major GI bleeding was not different between NOACs and vitamin K antagonists (VKA) (RR 1.08, 95% CI 0.85–1.36, I^2 = 78%; 5 RCTs) or acetylsalicylic acid (RR 0.78, 95% CI 0.36–1.72; 1 RCT). Similar results were found for patients undergoing orthopaedic surgery and those with venous thromboembolism. NOACs were not found to increase the risk compared to low-molecular-weight heparin (LWMH) alone (RR 1.42, 95% CI 0.55–3.71, I^2 = 7%; 8 RCTs), the sequential treatment with LMWH-VKA (RR 0.77, 95% CI 0.49–1.21, I^2 = 43%; 7 RCTs) or placebo (RR 1.48, 95% CI 0.15–14.84, I^2 = 21%; 2 RCTs).

Conclusion
Despite previous evidence supporting the association of non-vitamin K antagonist oral anticoagulants and overall GI bleeding, non-vitamin K antagonist oral anticoagulants were not associated with increased risk of major GI bleeding compared to other anticoagulant drugs (with known increased risk of these events).

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INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs), also named direct oral anticoagulants (DOACs) or target-specific oral anticoagulants (TSOACs), were recently studied for multiple indications. For patients who require long-term anticoagulation, NOACs (such as apixaban, dabigatran, edoxaban and rivaroxaban) are convenient, dismissing the need of regular checking of haemostatic parameters, unlike the vitamin K antagonists (VKA). Furthermore, NOACs have been shown to reduce the risk of major bleeding in comparison with VKA, in particular intracranial haemorrhage,[1] which is judged by clinicians to be the most serious bleeding adverse event.

Gastrointestinal (GI) bleeding is the most frequent cause of major bleeding accounting for 30–40% of these events[2–5] and some studies have shown an increased risk of GI bleeding among NOAC-treated patients.[6, 7] A previously published systematic review have also associated NOACs with an increased GI major and clinically relevant non-major bleeding risk.[8] However, since further trials have been published, the overall severity of this "class effect" is not known. This requires a comprehensive evaluation of major - rather than clinically relevant - bleeding events. Therefore, we intended to evaluate the risk of major GI bleeding associated with NOACs, through a systematic review with meta-analysis of randomised controlled trials (RCTs).

METHODS

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as per the guidelines.[9] The protocol was published in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) with registration number CRD42015017455.

Eligibility criteria

For this systematic review, we considered the published RCTs which evaluate patients treated with NOACs (also named DOACs or TSOACs), such as dabigatran, apixaban, edoxaban or rivaroxaban, in comparison with any active or placebo control, and reporting major GI bleeding data.

The primary outcome was major GI bleeding, as defined by each trial. When more than one major bleeding definition was available, data using International Society on Thrombosis and Hemostasis (ISTH) definition were used.[10, 11]

We considered all trials, irrespective of patients' baseline disease, comorbidities, background therapy, NOAC treatment duration or follow-up.

Only phase III RCTs were included to obtain robust data without the bias associated with statistical effects of small size underpowered studies on meta-analysis results.[12–15] Furthermore, we were interested in determining the risk associated with approved NOACs and their commonly used doses.

Information sources

MEDLINE, Cochrane Library, SciELO collection and Web of Science databases (inception to July 2015) were used. MEDLINE and Cochrane Library were searched through OVID interface. SciELO collection and Web of Science databases were searched through Web of Science platform. Search strategy is outlined in the Supplementary Online.

Reference lists of systematic reviews, as well as the reference list of included studies were comprehensively searched. As a conventional search may not detect GI bleeds because they may not be mentioned in the title or abstract in the electronic record (although they appear in the full report),[16, 17] we sought for bleeding data in all published phase III RCTs and available public reports of these drugs in the websites of regulatory entities (U.S. Food and Drug Administration, European Medicines Agency and Australian Therapeutic Goods Administration)[18, 19] irrespective of the initial search.

Study selection

After excluding duplicated records obtained in the electronic search, the references were screened independently by two authors through title and abstract for full-text assessment eligibility.

Study characteristics and results were extracted into a standardised form. Included studies were appraised for methodological bias risk with Cochrane Collaboration's Risk of Bias Tool outcomes.[20] Studies were not excluded *a priori* on the basis of quality reporting assessment.

Outcome measures

The primary outcome was GI major bleeding as defined by the ISTH.[10, 11] Other GI bleeding events, not referred or classified as major bleeding, were not included. Outcome data were summarised as dichotomous data.

Data analysis

We used RevMan 5.3.5 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for statistical

analysis and to derive forest plot showing the results of individual studies and pooled analysis. Intention-to-treat samples were used for this purpose.

We compared NOACs with controls (active drugs or placebo) through random effects meta-analysis to estimate pooled risk ratio (RR) and 95% confidence intervals (95% CIs). The effect measurement estimate chosen was RR because relative measures are more similar across studies with different designs, populations and lengths of follow-up compared to absolute measures, such as risk difference.[21]

Heterogeneity was determined through the chi-squared test. The results were considered heterogeneous if $P < 0.10$. Heterogeneity was further quantified as the percentage of total variation between studies due to heterogeneity through the I^2 test.[22] We used random effects model irrespective of the existence of substantial heterogeneity between study results ($I^2 \geq 50\%$) because we pooled results of studies with different designs and patient characteristics. When significant differences were found, we also determined the number needed to treat or harm (NNT/NNH) and 95% CI, taking into account the control baseline risk. A subgroup analysis was performed with patients who required VKA irrespective of the low-molecular-weight heparin (LMWH) need. Such analysis included patients with atrial fibrillation (AF) and venous thromboembolism (VTE). Pooled estimates for each single NOAC were also retrieved.

Publication bias was assessed through Egger's and Peters' regression tests.[23, 24] Visual evaluation of funnel plot asymmetry was also performed.

RESULTS

Results of the search and included studies

A total of 23 studies fulfilled the eligibility criteria.[6, 7, 20, 25–44] The flowchart of study selection is depicted in Figure S1. Included studies evaluated the risk of major GI bleeding associated with NOACs against VKA ($n = 5$), acetylsalicylic acid (ASA) ($n = 1$), LMWH and VKA ($n = 7$), LMWH alone ($n = 8$) and placebo ($n = 2$).

Risk of major GI bleeding was assessed through ISTH criteria in patients with AF ($n = 6$), VTE ($n = 9$) and patients undergoing total knee replacement ($n = 8$), in a total of 139 585 patients with a mean age ranging from 55 to 73 (Table 1).

Most of the studies included in the analysis were classified as having an overall low risk of bias. However, a few studies (the EINSTEIN acute DVT, the EINSTEIN-PE and the RE-LY study) were open-label RCTs, and consequently allocation concealment procedures and blinding of participants and study personnel items were considered to be of high risk of bias (Figure S2).

Main analyses

Six RCTs evaluated patients with AF, five of which compared NOACs with VKA[6, 7, 25, 27, 28] in 72 961 patients, and one compared NOAC (apixaban) with ASA[26] in 5599 patients. NOACs were not associated with an increased risk of major GI bleeding in comparison with VKA (RR 1.08, 95% CI 0.85–1.36, $P_{\text{heterogeneity}} = 0.001$, $I^2 = 78\%$) and ASA (RR 0.78, 95% CI 0.36–1.72).

Seven RCTs evaluated a total of 29 829 patients with VTE and compared NOACs to VKA (with or without the initial treatment with LMWH). Major GI bleeding risk was not different between NOACs and LMWH-VKA (RR 0.77, 95% CI 0.49–1.21, $P_{\text{heterogeneity}} = 0.11$, $I^2 = 43\%$).

Eight RCTs compared NOACs with LMWH in 27 371 patients undergoing major orthopaedic surgery (hip or knee replacement) for the prevention of thrombotic events. Major GI bleeding risk of NOACs was not significantly different from LMWH (RR 1.42, 95% CI 0.55–3.71, $P_{\text{heterogeneity}} = 0.37$, $I^2 = 7\%$).

Compared to placebo in the extended period of VTE trials (3825 patients), the GI bleeding risk was also not different (RR 1.48, 95% CI 0.15–14.84, $P_{\text{heterogeneity}} = 0.27$, $I^2 = 21\%$).

Figure 1 shows the results of the pooled analysis of major GI bleeding risk associated with NOACs, according to the indication for anticoagulation and control group.

Secondary analyses

NOACs vs. VKA (with or without LMWH). Overall, NOACs were compared to VKA (± LMWH) in 12 RCTs enrolling 102 729 patients with AF or VTE, without differences in the pooled major bleeding risk (RR 0.97, 95% CI 0.78–1.21, $P_{\text{heterogeneity}} < 0.001$, $I^2 = 66\%$; Figure 2).

Risk of major GI bleeding with individual NOACs. Figure 3 shows the results for each individual NOAC according to the control group. None of the NOACs individually were associated with an increased risk of major GI bleeding.

Publication bias

Asymmetry of study distribution suggested increased risk of publication bias, detrimental to NOAC results

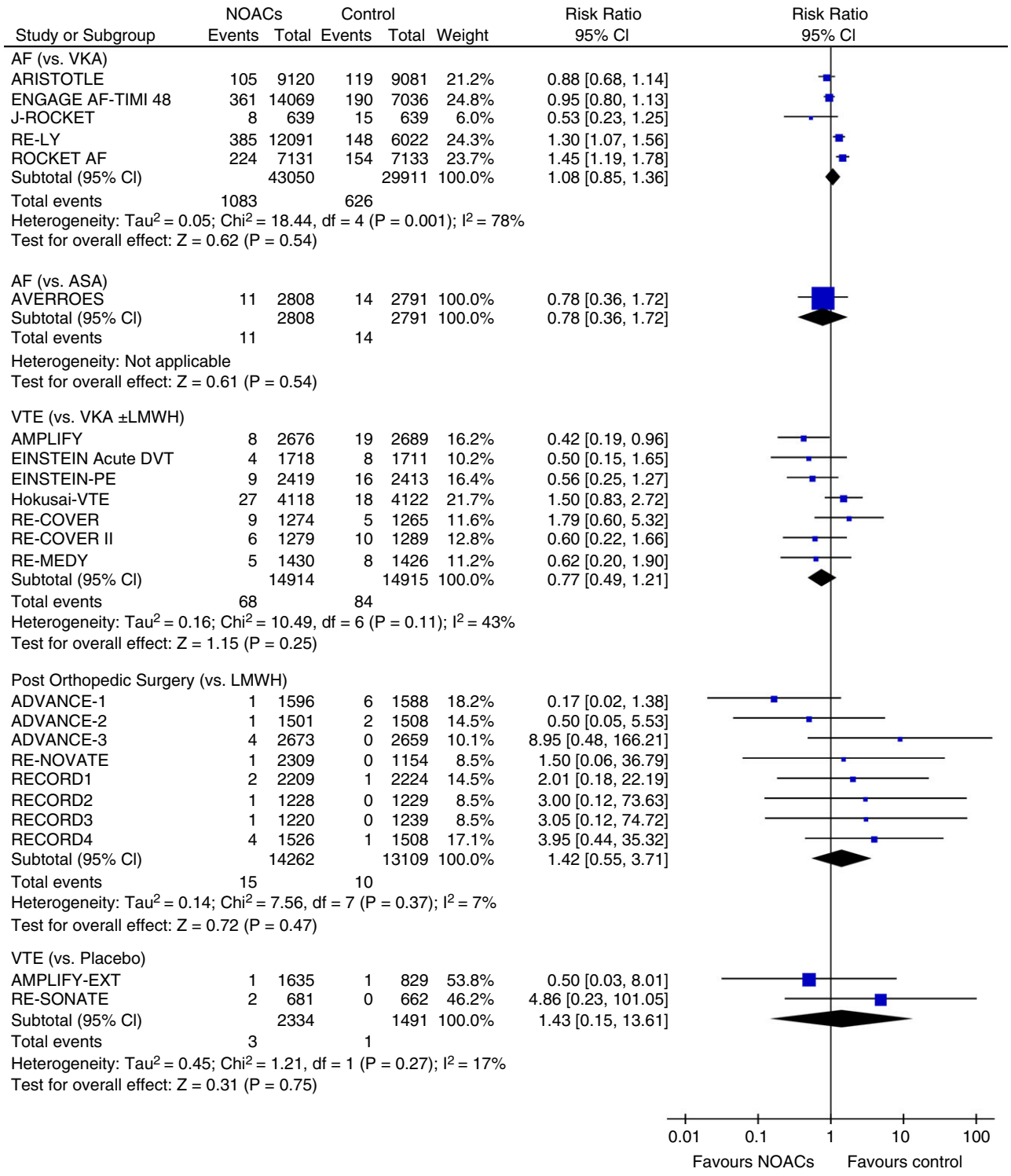

Figure 1 | Forest plot with the results of the pooled analysis for major gastrointestinal bleeding risk associated with non-vitamin K antagonist oral anticoagulants (NOACs), according to the indication and control group. Squares represent the point estimates for individual trials and diamonds represent the results of the meta-analysis. The horizontal lines and the width of the diamond represent the confidence intervals of individual studies and pooled estimates respectively.

Table 1 | Global characteristics of included studies according to clinical indication

Study acronym	Mean age	NOAC group	Control group	Follow-up	Primary outcome
Atrial fibrillation					
ARISTOTLE[27]	70	9120 patients Apixaban 5 mg b.d.	9081 patients dose-adjusted warfarin o.d. Target INR 2.0–3.0	1.8 years	Stroke or systemic embolism
AVERROES[26]	70	2808 patients Apixaban 5 mg b.d.	2791 patients ASA 81–324 mg/day	1.1 years	Stroke or systemic embolism
ENGAGE-AF[28]	72	7035 patients Edoxaban 60 mg o.d.; 7034 patients Edoxaban 30 mg o.d.	7036 patients Warfarin o.d. Target INR 2.0–3.0	2.8 years	Stroke or systemic embolism
J-ROCKET[25]	71	639 patients Rivaroxaban 15 mg o.d.	639 patients Warfarin o.d. Target INR 2.0–3.0; except >70 years INR 1.6–2.6	30 days	Stroke or systemic embolism
RE-LY [6]	72	6015 patients Dabigatran 110 mg b.d.; 6076 patients Dabigatran 150 mg b.d.	6022 patients Warfarin o.d. Target INR 2.0–3.0	2 years	Stroke or systemic embolism
ROCKET-AF [7]	73	7131 patients Rivaroxaban 20 mg o.d.	7133 patients Warfarin o.d. Target INR 2.0–3.0	23 months	Stroke or systemic embolism
Venous thromboembolism					
AMPLIFY[29]	57	2676 patients Apixaban 10 mg b.d. for 7 days, and then 5 mg b.d. for 6 months	2689 patients Enoxaparin, followed by VKA Target INR 2.0–3.0	6 months	Symptomatic recurrent VTE or VTE-related death
AMPLIFY-EXT[44]	57	840 patients Apixaban 2.5 mg b.d.; 813 patients Apixaban 5 mg b.d.	829 patients Placebo	1 year	Symptomatic recurrent VTE or VTE-related death
EINSTEIN Acute DVT[31]	56	1718 patients Rivaroxaban given 15 mg b.d. for 3 weeks, followed by 20 mg o.d.	1711 patients Enoxaparin and VKA Target INR 2.0–3.0	According to intended treatment duration: 3 months (12%), 6 months (63%) and 1 year (25%)	1 Recurrent VTE
EINSTEIN–PE[30]	58	2419 patients Rivaroxaban given 15 mg b.d. for 3 weeks, followed by 20 mg o.d.	2413 patients Enoxaparin and VKA Target INR 2.0–3.0	According to intended treatment duration: 3 months (5%), 6 months (57%) and 1 year (38%)	Symptomatic recurrent VTE
Hokusai-VTE[34]	56	4118 patients Edoxaban 60 mg o.d. or 30 mg o.d. if CrCl 30–50 mL/min or <60 kg	4122 patients Warfarin o.d. Target INR 2.0–3.0	A safety follow-up visit approximately 1 month after the last study drug dose	Recurrent symptomatic VTE
RE-COVER[32]	55	1274 patients Dabigatran 150 mg b.d.	1265 patients Warfarin o.d. Target INR 2.0–3.0	30 days	6-month incidence of recurrent symptomatic VTE and VTE-related death

Table 1 | (Continued)

Study acronym	Mean age	NOAC group	Control group	Follow-up	Primary outcome
RE-COVER II[33]	55	1279 patients Dabigatran 150 mg b.d.	1289 patients Warfarin o.d. Target INR 2.0–3.0	30 days	6-month incidence of recurrent symptomatic VTE and VTE-related death
RE-MEDY[35]	55	1430 patients Dabigatran 150 mg b.d.	1426 patients Warfarin o.d. Target INR 2.0–3.0	6 months	Recurrent symptomatic VTE or VTE-related death
RE-SONATE[35]	56	681 patients Dabigatran 150 mg b.d.	662 patients Placebo	18 months	Recurrent symptomatic VTE or VTE-related death or all-cause mortality
Post-surgical prophylaxis of VTE					
ADVANCE-1[36]	66	1596 patients Apixaban 2.5 mg of b.d.	1588 patients Enoxaparin 30 mg b.d.	60 days after anticoagulation period	DVT, nonfatal pulmonary embolism, and all-cause mortality
ADVANCE-2[37]	67	1501 patients Apixaban 2.5 mg of b.d.	1508 patients Enoxaparin 40 mg o.d.	60 days after anticoagulation period	DVT, non-fatal pulmonary embolism, and all-cause mortality
ADVANCE-3[38]	61	2673 patients Apixaban 2.5 mg of b.d.	2659 patients Enoxaparin 40 mg o.d.	60 days after anticoagulation period	DVT, non-fatal pulmonary embolism or all-cause mortality
RECORD1[40]	63	2209 patients Rivaroxaban 10 mg o.d.	2224 patients Enoxaparin 40 mg o.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism or all-cause mortality
RECORD2[41]	62	1228 patients Rivaroxaban 10 mg o.d.	1229 patients Enoxaparin 40 mg o.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism, and all-cause mortality
RECORD3[42]	68	1220 patients Rivaroxaban 10 mg o.d.	1239 patients Enoxaparin 40 mg o.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism or all-cause mortality
RECORD4[43]	65	1526 patients Rivaroxaban 10 mg o.d.	1508 patients Enoxaparin 30 mg b.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism or all-cause mortality
RE-NOVATE [39]	64	1146 patients Dabigatran 220 mg of o.d.; 1163 patients Dabigatran 150 mg o.d.	1154 patients Enoxaparin 40 mg o.d.	60 days after coagulation period	VTE events and VTE-related death

AF, atrial fibrillation; ASA, acetylsalicylic acid; b.d., twice daily; CrCl, creatinine clearance; DVT, deep-vein thrombosis; INR, international normalised ratio; o.d., once daily; VKA, vitamin K antagonists; VTE, venous thromboembolism.

(Figure S3). A balanced funnel plot would further favour results towards a decreased risk of major GI bleeding with NOACs which is supportive of the safety of these drugs. Nevertheless, Egger ($P = 0.47$) and Peters' ($P = 0.11$) tests do not support increased risk for publication bias.

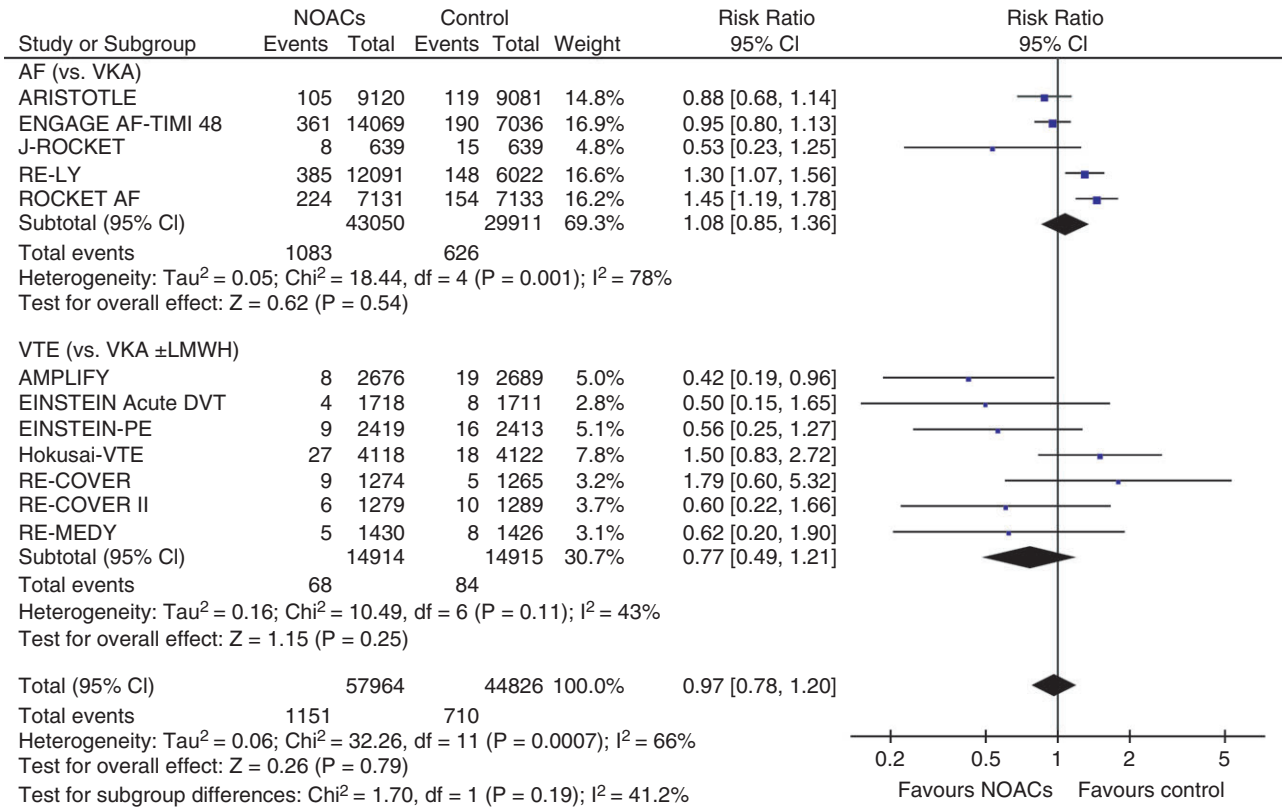

Figure 2 | Forest plot with the results of the pooled analysis for major gastrointestinal bleeding risk associated with non-vitamin K antagonist oral anticoagulants (NOACs) vs. vitamin K antagonists (VKA) [with or without low-molecular-weight heparin (LMWH)]. Squares represent the point estimates for individual trials and diamonds represent the results of the meta-analysis. The horizontal lines and the width of the diamond represent the confidence intervals of individual studies and pooled estimates respectively.

DISCUSSION

The main conclusion of this systematic review is that NOACs, overall, did not increase the risk of major GI bleeding. Even with the established proneness to GI bleeding associated with NOACs, our data suggest that it is not due to severe events. This conclusion derives from phase III randomised controlled data. This is a considerable contribution to previously published data[8] due to the inclusion of more recent trials, and restriction of analysis to major GI bleeding.

NOACs have an oral route of administration and, with the exception of dabigatran, all of them may have their anticoagulant effect directly in the mucosa of the gut. Dabigatran etexilate is a prodrug, and is converted into the active metabolite by esterases present in the gut, plasma and liver. Moreover, dabigatran's oral route bioavailability is 7% and the remainder may act locally in the absorption site.[45] Therefore, dabigatran can also have a direct anticoagulant effect in the mucosa, but these pathophysiologic mechanisms require scientific support.

Different from NOACs, LMWH have a parenteral route and do not have a tropism for or a direct effect on the GI tract. VKAs have an oral route but the anticoagulant effect is dependent on the hepatic inhibition of vitamin K epoxide reductase, to block the function of coagulation factor II, VII, IX and X.[46] This means that both LMWH and VKA would concurrently need other conditions to provoke a major GI bleed. Our data emphasise the safety of NOACs in terms of major GI bleeding compared to VKA[47] and other anti-thrombotic drugs.

Trials with AF patients had higher incidence of GI bleeding (major GI bleeding incidence with NOACs in patients with AF was 2.5%, while 0.5% of VTE patients experienced this event) compared to other conditions evaluated here. These data are concordant with the comment of Beyer-Westendorf which claimed that AF patients are known to have higher bleeding rates, because they are older, have more comorbidities and concomitant anti-platelet drugs, and AF trials are

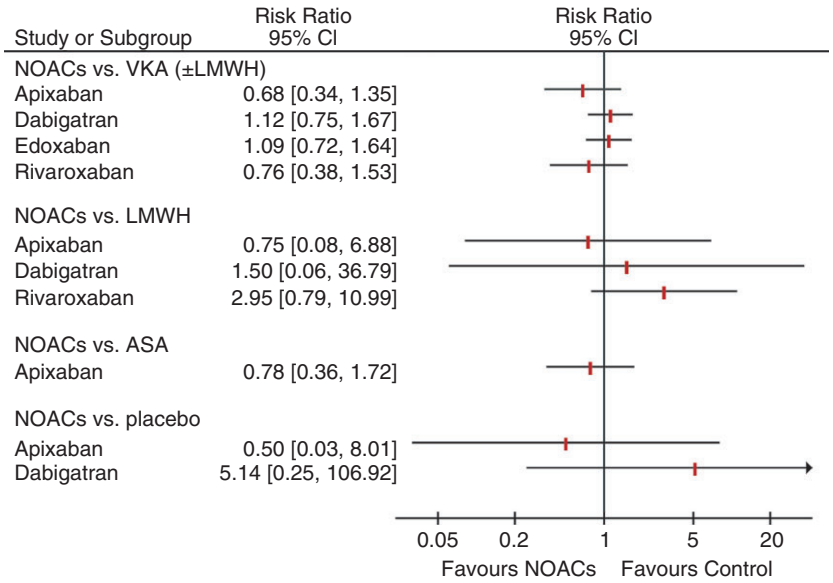

Figure 3 | Results of pooled analyses according to each individual non-vitamin K antagonist oral anticoagulant (NOAC). The central markers represent the point estimates the meta-analysis for each NOAC according to comparator, irrespective of the baseline condition.

generally longer than VTE trials, increasing the probability to capture more events.[48]

Therefore, the main studies to understand the details involved in major GI bleeding are those with AF patients. The RE-LY trial, which evaluated dabigatran vs. warfarin in patients with AF, was the most comprehensive regarding GI adverse events.[49] In a *post hoc* evaluation, dabigatran showed an increased risk of non-bleeding upper GI adverse events, but no difference from warfarin was found in terms of any severe GI adverse events. In fact, dabigatran had numerically less severe adverse events than warfarin. These upper GI symptoms were present in one-third of GI bleeding events. The gastroduodenal injury on endoscopy was expectably associated with increased risk of bleeding (RR 6.92, 95% CI 5.49–8.72). Oesophageal injury should also be considered as 20% of patients treated with dabigatran with GI symptoms referred to endoscopy, may have oesophageal mucosal ulceration.[50] Data for proton pump inhibitors (PPI) used to improve GI care in patients treated with NOACs are heterogeneous. In RE-LY, PPI were not associated with a decrease in the risk of these events, possibly due to previous GI symptoms that required these drugs.[49] However, gastroprotective drugs (41% treated with PPI) were associated with decreased GI bleeding risk in a retrospective cohort with approximately 5000 patients treated with dabigatran.[51] As expected, ASA or non-steroidal anti-inflammatory drugs (NSAIDs) were associated with major bleeding events, irrespective of the anticoagulant treatment (NOAC or VKA).[4, 52] Therefore, drugs that have potential pharmacodynamic interactions with anticoagulants, such as ASA or NSAIDs, should be withdrawn whenever possible.

In patients who started dabigatran or switched from VKA to dabigatran, the results were heterogeneous.[53, 54] A *post hoc* analysis of RE-LY using the adjusted estimates of the European label for dabigatran showed a trend towards increased risk of GI bleeding.[55]

In a propensity-matched evaluation of dabigatran and warfarin-treated in the Danish Registry,[56] there was an association between dabigatran 110 mg and a lower risk of GI bleeding [hazard ratio (HR) 0.60, 95% CI 0.37–0.93], and risk was similar compared to warfarin with both dosages in patients with exposures >1 year.[56] On the other hand, a Medicare retrospective study showed that dabigatran (without specification of doses) significantly increased risk of any major bleeding irrespective of the bleeding site (HR 1.58, 95% CI 1.36–1.83).[57]

Despite the heterogeneity, three recently published cohort studies did not find any association between NOACs exposure and GI bleeding,[58–60] with the exception of elderly patients in one of the studies.[60]

Thus, the heterogeneity in the results of the current published post-marketing large cohort studies precludes a definite answer for this question.

Limitations

This review includes a meta-analysis of RCTs and not individual patient data, which is a potential source of bias. Search methods are based on published RCTs. Multiple databases were searched, but some like EMBASE were not available to the authors. To partially exceed this limitation, the authors explored all NOAC published phase III RCTs and systematic reviews for data of interest.

Included studies were not powered to detect differences in major GI bleeding risk and the incidence of major GI bleedings was relatively low (<3% in studies with longer follow-up); therefore, results should be interpreted carefully. Despite the potential limitations inherent in the inclusion of phase II trials (mentioned in Methods), their exclusion may increase the risk of bias and should be acknowledged.

Heterogeneity of clinical characteristics and interventions (different NOACs, the same NOAC at different dosages, and the possibility of different co-medications, such as anti-platelet drug which are commonly associated with GI bleeding) across various studies should also be considered. The statistical heterogeneity found in some subgroups defined according to the control group used in the trial is a further limitation. The outcome of interest was major GI bleeding according to the ISTH definition.[10, 11] All trials that were included reported major bleeding events according to the ISTH definition (for medical or surgical conditions, or modified ISTH definitions). Nevertheless, it is not possible to evaluate whether these small variations may have an impact on the final results.

CONCLUSION

In patients requiring anticoagulation, there is no evidence of increased risk for major GI bleeding with the NOACs compared to other anti-thrombotic drugs, which, themselves are associated with a definite risk of major GI bleeding. However, the lack of power of the included studies and the scarcity of events, as well as the possible bias from other concomitant anti-thrombotic drugs, preclude a definitive conclusion. It is particularly important to evaluate as to whether these findings from a random-controlled setting are also documented in real-life post-marketing studies.

AUTHORSHIP

Guarantor of the article: Daniel Caldeira.

Author contributions: DC contributed to the concept and design, data acquisition, data analysis and interpretation of the data, wrote the first draft of the manuscript, and critically revised the manuscript. MB, AF, AR and AA contributed to data acquisition and data analysis, wrote parts of the manuscript and critically revised it. FJP, JC and JJF contributed to the interpretation of data and critically revised the manuscript.

All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Search strategy.

Figure S1. Flowchart of studies selection.

Figure S2. Risk of bias evaluation. The green symbols represent low risk of bias, the yellow symbols represent unclear risk of bias and the red symbols represent high risk of bias.

Figure S3. Funnel plot. Intervention effect estimates from individual studies are plotted against their precision.

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