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ORIGINAL ARTICLE

Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis

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ABSTRACT

Objective Non-vitamin K antagonist oral anticoagulants (NOACs) are efficacious and safe antithrombotic drugs but the non-availability of an antidote for potential fatal haemorrhagic events is clinically perceived as a strong limitation. We aimed at evaluating the risk of haemorrhage-related fatalities associated with NOACs in patients requiring long-term anticoagulation.

Methods MEDLINE, Cochrane Library and Web of Science databases were searched in November 2014 for atrial fibrillation (AF) or venous thromboembolism (VTE) phase III randomised controlled trials (RCT) comparing NOACs with vitamin K antagonists (VKAs) or low molecular weight heparin (LMWH) followed by VKAs. Pooled OR and 95% CIs were estimated through meta-analysis. Heterogeneity was assessed with the I^2 test.

Results Eleven studies were included: 5 on AF and 6 on VTE. A total of 100 324 patients were evaluated in 4 rivaroxaban, 3 dabigatran, 2 apixaban and 2 edoxaban studies. NOAC-treated patients had a 47% odds reduction compared with VKA (OR 0.53; 95% CI 0.42 to 0.68; I^2=0%; 3 events avoided per 1000 patients) and 64% odds reduction compared with LMWH–VKA (OR 0.36; 95% CI 0.15 to 0.84; I^2=0%; 1 event avoided per 1000 patients) regarding fatal bleeding risk. Case fatality due to major bleeding was lower in NOAC-treated patients both in AF (OR 0.68; 95% CI 0.48 to 0.96; I^2=37%; 1 death avoided per 39 major bleedings) and VTE (OR 0.54; 95% CI 0.22 to 1.32; I^2=0%) patients. AF survivors of major bleeding events treated with NOACs had lower mortality compared with patients treated with VKAs (OR 0.57; 95% CI 0.45 to 0.73; I^2=0%; 78 events avoided per 1000 survivors to major bleeding).

Conclusions These data suggest that NOACs decrease the risk of fatality cases related to major bleeding events, particularly in AF patients. These results support the safety profile of NOACs even without having a widely available drug-specific antidote.

INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs) have granted market authorisation for the prevention of thromboembolic events in patients at high thrombotic risk. There is strong evidence supporting the fact that the efficacy of NOACs compares at least similarly with other drugs considered the standard of care in these conditions.[1–3] The safety profile also exceeds other antithrombotic drugs, namely vitamin K antagonists (VKAs), in the predictability of the dose–response relation, lack of coagulation monitoring and dose adjustment needs, fast onset of action[3] and decreased risk of intracranial haemorrhage.[4]

However, the absence of an antidote for NOACs for emergent haemorrhagic events is considered by many as one of the main drawbacks of this group of drugs and argues against their routine use.[5–7]

Our objective was to evaluate the risk of haemorrhage-related fatalities associated with NOACs in comparison with VKAs or sequential treatment with low molecular weight heparin (LMWH) and VKAs. We reviewed the fatality cases, directly or indirectly related to the major bleeding events, reported in randomised controlled trials (RCTs) of patients requiring long-term anticoagulation.

METHODS

This systematic review followed PRISMA guidelines.[8] Reporting of statistical data followed SAMPL guidelines.[9]

Eligibility criteria

All phase III RCTs comparing NOACs, including inhibitors of IIa (dabigatran) or Xa (apixaban, darexaban, edoxaban, or rivaroxaban), against VKAs or sequential treatment of LMWH and VKAs in patients with atrial fibrillation (AF) or venous thromboembolism (VTE) were included.[4 10] We selected these conditions due to the requirement for medium-term and long-term anticoagulation. Patients with recent hip or knee arthroplasty were excluded because these would only require short-term anticoagulation and the inclusion of such trials would increase bias associated to statistical effects of rare events. Studies comparing NOACs with antiplatelet drugs were also excluded.

Fatal bleeding events are not frequent. Therefore, we considered only phase III RCTs to avoid bias in risk estimation due to statistical effects of small-size underpowered studies on meta-analysis results.[11–14] Furthermore, we were interested in determining the risk associated with

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commonly used doses of NOACs, which are typically used in phase III RCTs.

All published RCTs were considered for inclusion irrespective of background therapy, NOAC treatment duration or follow-up. Only trials reporting fatal and non-fatal bleeding events were included.

Our primary objective was to evaluate overall mortality directly or indirectly associated with major bleeding events. Therefore, our main outcomes were incidence of fatal bleeding, major bleeding case fatality rate and all-cause mortality in major bleeding survivors.

Fatal bleeding events were defined as events in which the cause of death was a direct consequence of a major bleeding event. Major bleeding case fatality rate was defined as the ratio between fatal bleeding and major bleeding events. In patients who survived a major bleeding event we also evaluated the all-cause mortality.

Whenever possible, we used the International Society of Thrombosis and Haemostasis (ISTH) definition for major bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.[15] We were not restrictive and other definitions were allowed when ISTH major bleeding outcome was not available.

Information sources and search method

Records of potentially eligible studies were identified through an electronic search of bibliographic databases from inception to November 2014 (MEDLINE, CENTRAL at Cochrane Library and Web of Science). Search strategy details are provided in the online supplementary data. No language restrictions were applied. We screened and cross-checked identified systematic reviews and meta-analyses evaluating NOACs, as well as reference lists of reports of potential eligible studies.

Study selection and data collection process

Titles and abstract of records obtained in the search process were screened by two investigators. Doubts and disagreements were solved by consensus. Whenever needed, a third element was consulted. Selected studies were assessed in full text to determine its appropriateness for inclusion. Data from included studies were independently extracted by three authors to an electronic form. Retrieved data items were study design, year of publication, patients' characteristics and drugs used, outcomes of studies, data of required outcomes and estimates adjustments. Data were double-checked for software entry before analyses by an additional author.

Should the studies present different estimates of the outcomes of interest, estimates reporting the most precise or adjusted measures of association were used. Otherwise, we used crude OR or derived it from raw data.

Quality of reporting was independently analysed by two authors using the Cochrane Collaboration Risk of Bias Tool to assess risk bias and to evaluate reporting.[16] Arbitrarily, we classified the overall risk of bias as low (if ≥80% of all analysed items in all included studies had a low bias risk), moderate (if this percentage ranged between 50% and 80%) and high (if this percentage was below 50%). Doubts or disagreements were solved through consensus or a third element. Risk-of-bias graphs were derived from this tool.

Data analysis

We used RevMan V.5.3.3 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.

Outcomes data were summarised as dichotomous data. We compared NOACs with VKAs (with or without an initial period using concomitantly LMWH) through random effects meta-analysis weighted by the inverse-variance method to estimate pooled OR and 95% CIs. The effect measurement estimate chosen was OR because relative estimates are more similar across studies with different designs, populations and lengths of follow-up than absolute effects.[17]

Heterogeneity measured as the percentage of total variation between studies due to heterogeneity was assessed through the χ^2 and I^2 tests.[18] We used a random effects model independently of the existence ($I^2 \geq 50\%$, $P_{heterogeneity} < 0.05$ in χ^2 test) or absence of substantial heterogeneity between the results of studies because we pooled results of studies with different designs and patients' characteristics. When significant differences were found we determined the number of events avoided per 1000 treated patients with NOACs, using as baseline risk the event rate reported in the control group (VKAs or LWMH–VKAs). For case fatality of major bleeding, in case of significant differences, the absolute risk measure reported was the number needed to treat, that is, the number of patients needed to experience a major bleeding event with NOACs required to avoid one bleeding fatality compared with VKAs.

Results were stratified according to indication for anticoagulation (AF or VTE) to explore differences in outcome estimates. Differences between subgroups were evaluated through random effects model due to the lower risk of false-positive results.[19]

In order to minimise the risk of type I errors, trial sequential analyses (TSA) were performed using TSA V.0.9 β (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011). TSA evaluated whether cumulative data were adequately powered to evaluate the outcomes.[20] The required information size (and the O'Brien-Fleming adjacent trial sequential α spending monitoring boundaries) was calculated based on a two-sided 5% risk of a type I error, 20% risk of a type II error (power of 80%), risk reduction based on the pooled analysis and the incidence of events in the control group. Results were considered adequately powered if significance is reached with either minimum sample size or crossing trial sequential α spending monitoring boundary.

Publication bias was assessed through visual inspection of funnel plots asymmetry and Egger's and Peters' regression tests.[21 22] The latter evaluates the linearity of effect estimate with sample size.

RESULTS

After reviewing all potentially eligible reports for appropriateness for inclusion, 11 studies[23–30 S1–S3] were included: 5 studies on AF[23 25 26 29 S2] and 6 studies on VTE.[24 27 28 30 S1 S3]

A flowchart of study selection phases is depicted in online supplementary figure S1.

All included studies were international multicentre double-blinded RCTs with the exception of one Japanese study[29] and three open-label studies.[23 27 28] Three post hoc analyses of RCTs were also included as these provided the required data.[S4–S6] RE-LY additional major bleeding events were considered for analysis.[S7] Characteristics of included studies are summarised in table 1.

Table 1 Characteristics of included studies

Year	Study acronym	Mean/ median age	Active group	Control group	Follow-up	Primary outcome
Atrial fibrillation						
2011	ARISTOTLE	70	9088 patients Apixaban 5 mg BID	9081 patients dose adjusted Warfarin	1.8 years	Stroke or systemic embolism
2009	RE-LY	71	6015 patients Dabigatran 110 mg BID; 6076 patients Dabigatran 150 mg BID	6022 patients Warfarin OD Target INR 2.0–3.0	2 years	Stroke or systemic embolism
2009	ENGAGE-AF	72	7035 patients Edoxaban 60 mg OD; 7034 patients Edoxaban 30 mg OD	7036 patients Warfarin OD Target INR 2.0–3.0	2.8 years	Stroke or systemic embolism
2011	ROCKET-AF	73	7131 patients Rivaroxaban 20 mg OD	7133 patients Warfarin OD Target INR 2.0–3.0	1.9 years	Stroke or systemic embolism
2011	J-ROCKET	71	639 patients Rivaroxaban 15 mg OD	639 patients Warfarin ODTarget INR 2.0–3.0; except >70 years INR 1.6–2.6	>1 year	Stroke or systemic embolism
Venous thromboembolism						
2013	Hokusai-VTE	56	4118 patients Edoxaban 60 mg OD or 30 mg OD if CrCl 30–50 mL/min or <60 kg	4122 patients Warfarin OD Target INR 2.0–3.0	8.2 months	Recurrent symptomatic VTE
2010	EINSTEIN Acute DVT	56	1731 patients Rivaroxaban 15 mg BID for 3 weeks and 20 mg OD afterwards	1718 patients Enoxaparin and VKA OD Target INR 2.0–3.0	According to intended treatment duration: 3 months (12%), 6 months (63%) and 1 year (25%)	Recurrent VTE events
2009	RE-COVER	55	1273 patients Dabigatran 150 mg BID	1266 patients Warfarin OD Target INR 2.0–3.0	30 days	VTE events and thromboembolic-related death
2013	RE-MEDY	55	1430 patients Dabigatran 150 mg BID	1426 patients Warfarin OD Target INR 2.0–3.0	6 months	VTE or VTE-related death associated with VTE
2012	EINSTEIN–PE	58	2420 patients Rivaroxaban given 15 mg BID for 3 weeks, followed by 20 mg OD	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
2013	AMPLIFY	57	2691 patients Apixaban 10 mg BID for 7 days, and then 5 mg BID for 6 months	2704 patients with subcutaneous enoxaparin, followed by VKA	6 months	VTE events or VTE-related death

AF, atrial fibrillation; BID, twice daily; DVT, deep vein thrombosis; INR, international normalised ratio; OD, once daily; VKA, vitamin K antagonist; VTE, venous thromboembolism.

A total of 100 324 patients were included (72.73% with AF) with a mean age of 71 years for AF patients and 56 years for VTE patients. Mean follow-up period ranged from 1 to 2.8 years for AF trials, and most of VTE patients had 6 months follow-up. RE-COVER[24] was the only trial having 30 days of follow-up.

Among all included patients, 56.5% were treated with NOACs: 11 799 patients treated with apixaban (2 RCTs), 14 794 patients treated with dabigatran (3 RCTs), 18 187 patients treated with edoxaban (2 RCTs) and 11 921 patients treated with rivaroxaban (4 RCTs). A total of 302 fatal bleeding events among 4291 major bleeding events were reported in these RCTs.

Overall, the risk of bias of included studies was low to moderate (78% of the bias items were rated as having a low bias risk, as depicted in online supplementary figure S2). Although three studies had an open-label design, we considered it appropriate to include these trials because lack of blinding is not associated with over or sub-estimates of objective outcomes in clinical trials, in particular mortality.[S8] Despite the availability of adjusted estimates for postbleeding mortality in RE-LY[23] and ARISTOTLE,[25] none of the other studies provided adjusted estimates for fatal bleeding or case fatality rate of major bleeding. Therefore, we considered all trials to be at high risk of bias regarding this characteristic (last column in the online supplementary figure S2).

Fatal bleeding

The 11 RCTs included reported data on fatal bleeding. In AF patients, NOACs were associated with a 47% odds reduction in the risk of fatal bleeding (OR 0.53, 95% CI 0.42 to 0.68; $I^2=0\%$, $\chi^2=3.85$, $P_{heterogeneity}=0.43$). The number of fatal bleeding events avoided per 1000 patients treated with NOACs was 3 (95% CI 2.7 to 3.5) in a period of 1–2.8 years.

TSA showed that cumulative evidence is adequately powered (sample size >24 760 patients) and that statistical significance was reached after the third published trial with a cumulative sample size over the minimum required (see online supplementary figure S3).

In VTE patients, NOACs were also associated with a significant 64% odds reduction in the risk of fatal bleeding (OR 0.36; 95% CI 0.15 to 0.84; $I^2=0\%$, $\chi^2=1.91$, $P_{heterogeneity}=0.86$). Despite not reaching the minimum required sample size (79.0% of the required information size), TSA showed that sufficient evidence was established to show a risk reduction with NOACs regarding fatal bleeding, with crossing of the upper boundary of

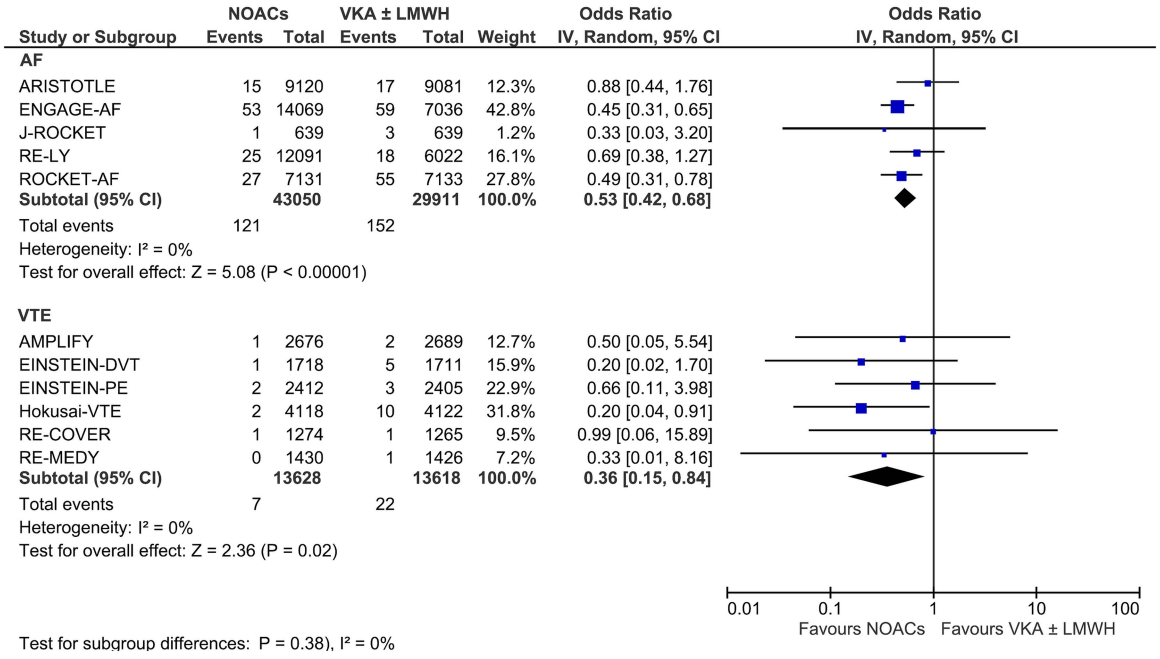

Figure 1 Forest plot of fatal bleeding incidence in comparison with controls according to condition. AF, atrial fibrillation; LMWH, low molecular weight heparin; NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist; VTE, venous thromboembolism.

the trial sequential α spending monitoring (see online supplementary figure S4).

The number of fatal bleeding events avoided per 1000 patients treated with NOACs was 1 (95% CI 0.2 to 1.4) in an average period of 6 months. Figure 1 shows the forest plot for this outcome.

Major bleeding case fatality rate

Case fatality rate was lower for AF patients treated with NOACs. Pooled analysis showed a significant 32% odds reduction (OR 0.68, 95% CI 0.48 to 0.96; I^2=37%, χ^2=6.38, $P_{heterogeneity}$=0.17) (figure 2). For each 39 patients (95% CI 24 to 322) experiencing a major bleeding event with NOACs, one bleeding fatality is avoided compared with VKAs. Regarding VTE, NOACs did not significantly reduce major bleeding case fatality rate (OR 0.54; 95% CI 0.22 to 1.32; I^2=0%, χ^2=4.05, $P_{heterogeneity}$=0.54) (figure 2).

For both AF and VTE patients, the estimates for major bleeding case fatality were underpowered (72.5% and 33.3% of the required information size for respectively, AF and VTE) (see online supplementary figures S5 and S6). Despite reaching statistical significance, the major bleeding case fatality rate with

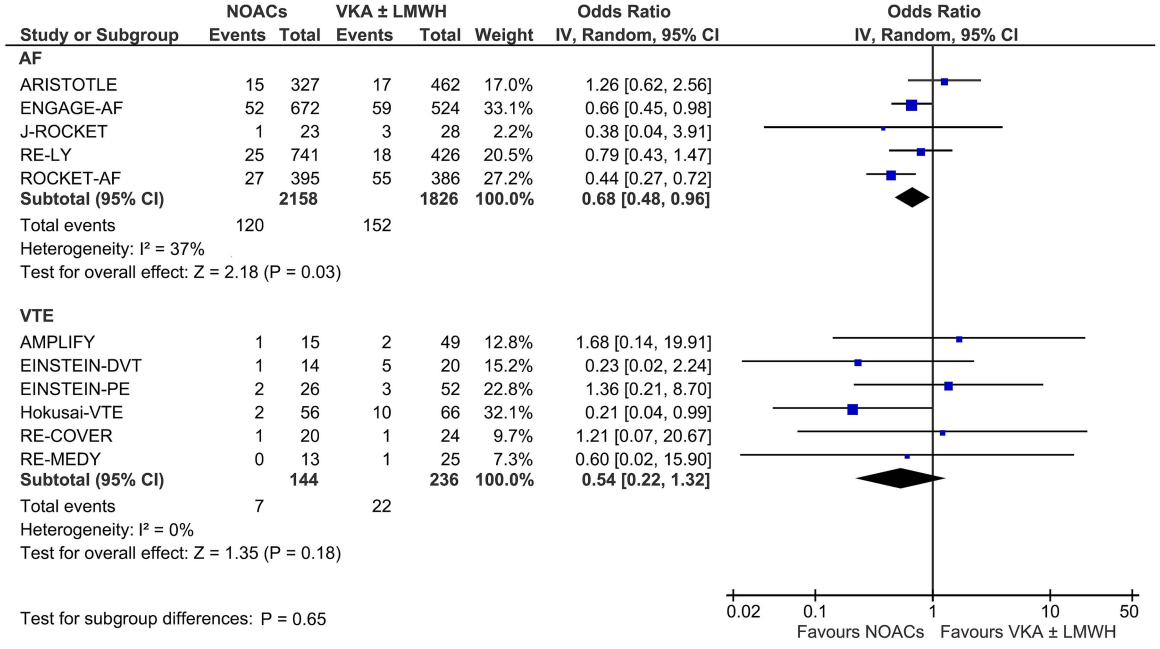

Figure 2 Forest plot of case fatality rate in comparison to controls according to indication. AF, atrial fibrillation; LMWH, low molecular weight heparin; NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist; VTE, venous thromboembolism.

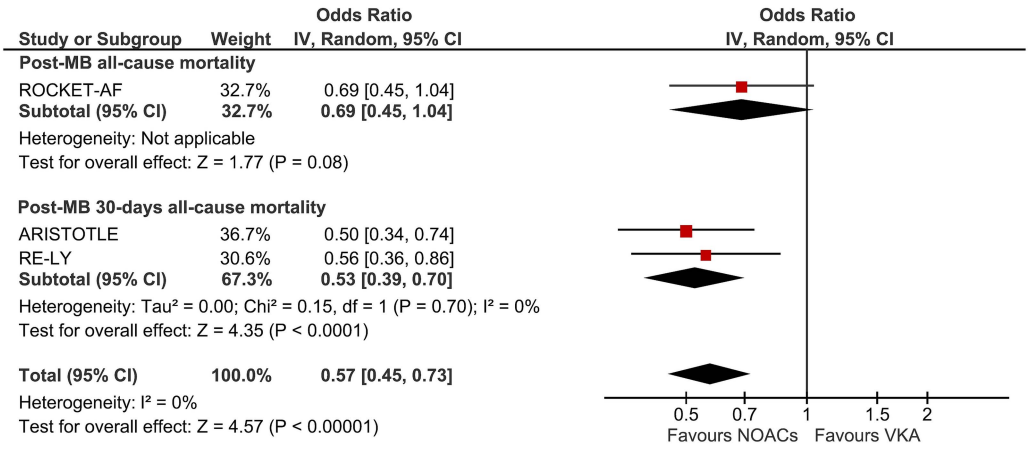

Figure 3 Forest plot of all-cause mortality in major bleeding survivors. NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist.

NOACs in AF did not cross the trial sequential α spending monitoring boundaries.

Post-major bleeding all-cause mortality

Only AF studies presented data for all-cause mortality following major bleeding events. RE-LY (dabigatran vs VKA)[23] and ARISTOTLE (apixaban vs VKA)[25] provided 30 days post-major bleeding mortality, while ROCKET AF (rivaroxaban vs VKA)[26] data were not limited to the 30 days post-index event. Except for ROCKET AF, data were adjusted for multiple variables. Pooled analysis of these trials showed a significant 43% odds reduction in the risk of all-cause mortality in major bleeding survivors (OR 0.57, 95% CI 0.45 to 0.73; I^2=0%, χ^2=1.22, $P_{heterogeneity}$=0.54) (figure 3). Adjusting the data to the 30 days mortality rate reported by Majeed and colleagues,[S4] 78 deaths (95% CI 63 to 98) would have been avoid per 1000 patients surviving a major bleeding event treated with NOACs compared with VKAs. TSA determined that the minimum information size was 921 patients, and the three trials had 2007 patients experiencing major bleeding events, favouring the robustness of the results.

Outcome results according to NOAC

NOACs were comparable as far as risk of fatal events associated with major bleeding is concerned, either for AF or VTE. The odds reductions for all the outcomes presented above were similar among the different NOACs (figure 4).

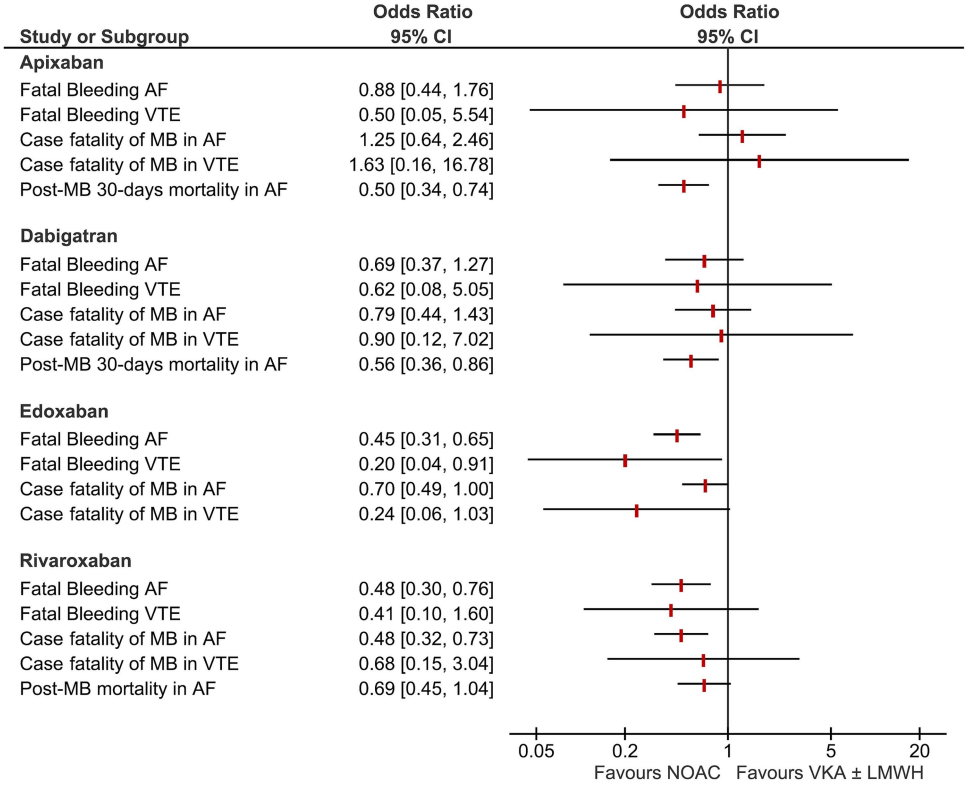

Figure 4 Risk of bleeding-related fatal events according to each NOAC. AF, atrial fibrillation; LMWH, low molecular weight heparin; MB, major bleeding; NOAC, non-vitamin antagonist K oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Publication bias

Visual inspection of funnel plot for fatal haemorrhage outcome does not suggest publication bias (see online supplementary figure S7). Egger and Peters regression tests also do not suggest the presence of publication bias in AF population (Egger p=0.60; Peters p=0.71), VTE population (Egger p=0.40; Peters p=0.45) or overall population (Egger p=0.74; Peters p=0.46). For case fatality rates calculation, major bleeding events were used as denominator. Therefore, publication bias evaluation was not reliable. Since only three studies reported postbleeding all-cause mortality, evaluation of the risk of publication bias was not possible for this outcome.

DISCUSSION

The main finding of our study is that NOACs are not associated with an increased mortality. In fact, based on published random controlled data, NOACs decrease the risk of fatal events directly or indirectly related to major bleeding, particularly in AF patients. The figures for VTE failed to reach statistical significance but shared the same trend. Smaller sample sizes and shorter follow-up periods lessen the captured number of major bleeding and fatal events, which probably justifies the lack of significant differences in VTE trials.

Concerns have been raised against NOACs due to the absence of an antidote to reverse anticoagulation in patients with major bleeding events.[S9] In an individual patient the lack of an antidote may interfere with the clinician's perception of available therapeutic options, but most of the studies show that the majority of major bleeding events were managed solely with supportive therapy or red cell transfusion.[23 S4 S5] VKA reversal with vitamin K (used in one-third of major bleeding cases on RE-LY and ROCKET AF trials), fresh frozen plasma (used in 30% and 20% of major bleeding events in RE-LY and ROCKET AF, respectively), prothrombin complex concentrates or recombinant factor VIIa were not frequently used.[23 S4 S5] The underuse of rapid reversal agents raised some concerns as these patients could have been through a suboptimal management, thus resulting in worse outcomes.[S4] These sort of interventions may decrease international normalised ratio (INR) values in VKA-anticoagulated patients, but the best available evidence about the overall effect on active bleeding patients' prognosis lacks robustness.[S10–S12]

Our results highlight the safety of NOACs. These drugs showed inferior rates of fatal bleeding, a lower major-bleeding case fatality rate and a decreased all-cause mortality in bleeding survivors, particularly AF patients. One possible explanation is that the lower mortality is a direct consequence of the reduced risk of intracranial haemorrhage with NOACs—the most feared type of major bleeding event due to its associated morbidity and mortality.[S13 S14] Cerebral vessels haemostasis is likely to be highly dependent on the tissue factor/factor VIIa interaction to primarily initiate the coagulation process. Unlike VKAs, which block the carboxylation process and inhibit the production of functional factor VII, among other coagulation factors, NOACs directly and selectively inhibit factor IIa or Xa without interfering with the primary haemostatic mechanism of cerebral vessels.

Unfortunately, the causes of death among major bleeding event survivors were not ascertained in the clinical trials. Early anticoagulation resumption was associated with a significant decrease of mortality risk in a retrospective cohort of AF patients after a major gastrointestinal bleeding event.[S15] Furthermore, a nested case–control study suggested that early initiation of warfarin was associated with a significant increased risk of stroke during the first 30 days of treatment, probably associated with inadequate anticoagulation.[S16] Owing to the predictability, effectiveness and faster onset of action, patients taking NOACs are probably less likely to experience thrombotic events.[S17] Taking these arguments together, it is reasonable to expect that it contributes to a significantly lower mortality after a major bleeding event.[S17]

Nonetheless, despite the magnitude of the relative risk differences found in our study for the mortality risk reduction, it is important to highlight that fatal bleeding events are uncommon, which translates into low net absolute benefits—one to three events avoided per 1000 treated patients.

For safety concerns, observational studies may be more adequate than RCTs to evaluate safety and drug adverse events, as these may include patients that are usually excluded from RCTs (impaired renal and/or hepatic function) and the follow-up may be longer, enabling the unveiling of unknown adverse events. A retrospective evaluation of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database revealed that warfarin bleeding reports were more frequent than dabigatran reports, but 15% of dabigatran's bleeding reports were fatal compared with 7.1% of warfarin.[S18] While unadjusted for a balanced comparison, these data are subject to a significant bias of reporting (and adverse events are frequently under-reported). This is particularly relevant in the case of dabigatran and warfarin. Dabigatran is a recent drug and stakeholders are encouraged and motivated to report adverse events in order to increase the knowledge of this drug in real-world conditions. Furthermore, the possibility exists that, in real-world conditions, NOACs may be used in patients significantly different from those included in phase III RCTs. On the other hand, the knowledge of warfarin and its safety profile is well established, which may lead to an under-reporting of these events.

Other observational studies did not report data about bleeding-related fatalities. Regarding major bleeding outcomes, only intracranial haemorrhage risk reduction by dabigatran is supported by real-world data.[S19 S20] The results concerning the risk of overall major bleeding are divergent;[S19 S20] nevertheless, no sign of increased overall mortality was found.[S20] Data about rivaroxaban and apixaban are still scarce, with the follow-up being short and/or inconclusive.[S21–S23]

The most important message of our study relies on the safety of NOACs and the putative protective association regarding major bleeding-related fatality. Therefore, no alert sign of an increased risk of major bleeding-related mortality can be raised.

Limitations

It must be acknowledged that this review includes a meta-analysis of RCTs instead of individual patient data—generating a potential source of bias.

Additionally, heterogeneity of clinical characteristics and interventions/controls across studies should be considered despite the absence of significant statistical heterogeneity and consistency in results. The clinical management of active bleeding patients treated with VKAs had infrequent and suboptimal administration of rapid reversal agents which could have biased the results towards NOACs.

At outcome level, particularly major bleeding case fatality, selective reporting bias is our main concern as NOACs and VKA bleeders have different clinical characteristics and the estimates reported here are unadjusted. Again, it would be necessary to have individual patient data to perform such an analysis. Furthermore, the amount of information/sample size (number

of major bleeders) necessary to adequately evaluate such outcome in a powered fashion was not adequate.

Also for analysis purposes we considered OR to be similar to adjusted HRs assuming a constant rate of events in both arms.

Nevertheless, and despite all limitations, we consider our results robust enough to support the conclusion of the absence of an increased risk of fatal bleeding among NOAC-treated patients.

CONCLUSIONS

Pooled analysis from randomised controlled data shows that NOACs—apixaban, dabigatran, edoxaban, rivaroxaban—significantly decreased the risk of fatal bleeding in patients with AF and VTE compared with VKAs or LMWH followed by VKAs. In patients with AF these drugs were also associated with a significant decreased risk of all-cause mortality in major bleeding survivors. Major bleeding case fatality was also significantly reduced in this context but estimates may be underpowered as the required information size was not reached (72.5% of the required information size).

Despite the absence of specific antidotes, NOACs did not show an increased risk of mortality associated to the bleeding event. Inversely, these drugs were likely to improve these outcomes.

Our results are mere indirect surrogates of the need for NOAC-specific antidotes and studies are ongoing to evaluate the direct efficacy of potential drug-specific antidotes. However, the anticipated cost-effectiveness ratio of these antidotes may preclude its availability in some countries, further making our results relevant for clinical practice.

Key messages

What is already known on this subject?

- Non-vitamin K antagonist oral anticoagulants (NOACs), such as apixaban, dabigatran, edoxaban and rivaroxaban, do not require international normalised ratio (INR) monitoring and are at least as efficacious as vitamin K antagonists (VKAs) in atrial fibrillation (AF) and venous thromboembolism (VTE).
- These drugs decrease the risk of intracranial haemorrhage, but the current lack of availability of a specific antidote is still considered one of the main drawbacks of these drugs.

What might this study add?

- NOACs decrease the risk of fatal bleeding by 47%, major bleeding case fatality (ie, the proportion of fatal events among all major bleeding events) by 32% and all-cause mortality after a bleeding event by 43%.

How might this impact on clinical practice?

- The favourable safety profile and decreased bleeding-related mortality with NOACs compared with VKA anticoagulation support the current approved clinical indications for these medications.

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Contributors DC contributed to the concept and design, data acquisition, data analysis and interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. FR contributed to the interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. MB, ATS, DdA contributed to the data acquisition, data analysis and interpretation of the data; critically revised the manuscript; and gave final approval of the submitted manuscript. NG contributed to the data analysis, and interpretation of the data; critically revised the manuscript; and gave final approval of the submitted manuscript. FJP and JJF contributed to the interpretation of data, critically revised the manuscript and gave final approval of the submitted manuscript. JC contributed to the concept and design, and interpretation of the data; critically revised the manuscript; and gave final approval of the submitted manuscript. DC and JC are the guarantors.

Competing interests JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme; FJP had consultant and speaker fees with Astra Zeneca, Bayer and Boehringer Ingelheim.

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REFERENCES

1 Adam SS, McDuffie JR, Ortel TL, *et al*. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. *Ann Intern Med* 2012;157:796–807.
2 Gomez-Outes A, Terleira-Fernandez AI, Lecumberri R, *et al*. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. *Thromb Res* 2014;134:774–82.
3 Heidbuchel H, Verhamme P, Alings M, *et al*. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;15:625–51.
4 Caldeira D, Barra M, Pinto FJ, *et al*. Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis. *J Neurol* 2015;262:516–22.
5 Veltkamp R, Horstmann S. Treatment of intracerebral hemorrhage associated with new oral anticoagulant use: the neurologist's view. *Clin Lab Med* 2014;34:587–94.
6 Breuer G, Weiss DR, Ringwald J. 'New' direct oral anticoagulants in the perioperative setting. *Curr Opin Anaesthesiol* 2014;27:409–19.
7 Siegal DM, Cuker A. Reversal of novel oral anticoagulants in patients with major bleeding. *J Thromb Thrombolysis* 2013;35:391–8.
8 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
9 Lang TA, Altman DG. *Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines"*. Science Editors' Handbook, European Association of Science Editors, 2013.
10 Caldeira D, Barra M, Santos AT, *et al*. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. *Heart* 2014;100:550–6.
11 Lane PW. Meta-analysis of incidence of rare events. *Stat Methods Med Res* 2013;22:117–32.
12 Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLoS ONE* 2013;8:e59202.
13 Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001;135:982–9.
14 Zhang Z, Xu X, Ni H. Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. *Crit Care* 2013;17:R2.
15 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–4.
16 Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions*. 5.1.0 edn. John Wiley & Sons, 2011.
17 Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* 2002;21:1575–600.
18 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
19 Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med* 2004;23:1663–82.
20 Brok J, Thorlund K, Gluud C, *et al*. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol* 2008;61:763–9.
21 Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54:1046–55.
22 Peters JL, Sutton AJ, Jones DR, *et al*. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;295:676–80.
23 Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
24 Schulman S, Kearon C, Kakkar AK, *et al*. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342–52.

25 Granger CB, Alexander JH, McMurray JJ, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
26 Patel MR, Mahaffey KW, Garg J, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
27 Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-extension study). *Expert Rev Cardiovasc Ther* 2011;9:841–4.
28 Buller HR, Prins MH, Lensin AW, *et al*. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
29 Hori M, Matsumoto M, Tanahashi N, *et al*. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation—the J-ROCKET AF study. *Circ J* 2012;76:2104–11.
30 Agnelli G, Buller HR, Cohen A, *et al*. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799–808.

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