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Title Page

The risk of gastrointestinal bleeding with direct oral anticoagulant medications. A systematic review and network meta-analysis.

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Research in context

Evidence before this study

Direct oral anticoagulants (DOAC) are being increasingly used for all indications for anticoagulation. One of the main complications with DOAC use is gastrointestinal (GI) bleeding. There is conflicting evidence on the risk of GI bleeding with DOACs compared to warfarin and low molecular weight heparin (LMWH).

Added value of this study

This is the largest study to date to analyse the effect of GI bleeding with DOACs and the first network meta-analysis encompassing all indications for anticoagulation. We have shown that there is no difference in association between each class of DOAC, warfarin and low molecular weight heparin and major GI bleeding. Factor Xa inhibitors may be superior to dabigatran and warfarin for all severities of GI bleeding.

Implications of all the available evidence

Projected use of DOACs is likely to continue to increase for all indications due to the ease of dosing and lack of monitoring required. The evidence supports the continued use of DOACs from a GI bleeding perspective.

Abstract

Background – Direct oral anticoagulants (DOAC) are being increasingly used for a wide range of indications. There is conflicting data on the risk of major gastrointestinal (GI) bleeding with these medications. The aim of this study was to compare the risk of GI bleeding with DOAC, warfarin and low molecular weight heparin (LMWH).

Methods - We performed a comprehensive search of the available evidence to April 2016. Prospective and retrospective studies were included reporting on the risk of GI bleeding when using a DOAC compared to warfarin or LMWH for all indications. The primary outcome of interest was the incidence of major GI bleeding with all GI bleeding as a secondary outcome. We performed a Bayesian network meta-analysis to produce incidence rate ratios (IRR) with 95% credible intervals (CrI).

Findings - We included 31 articles reporting on 287, 692 patients exposed to 230, 090 years of anticoagulant medication in our primary analysis. We found no difference in the risk of major GI bleeding when comparing DOAC medications with warfarin and LMWH. This result was sustained on pre-specified sensitivity analyses to test the robustness of the result. When analysing all severities of GI bleeding, we found a reduction in risk when comparing factor Xa inhibitors with warfarin, IRR 0. 0.25 (95% CrI 0·07 – 0·76) and thrombin inhibitors, IRR 0·24 (95% CrI (0·07 – 0·77) respectively.

Interpretation – We have shown no association between the use of DOAC medications and the risk of major GI bleeding compared to warfarin and LMWH. This supports the continued use of DOAC medications from a GI bleeding perspective.

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Introduction

The direct oral anticoagulants (DOACs), previously known as novel oral anticoagulants and non-vitamin k oral anticoagulants(1), are a group of medications that are increasingly being used for the treatment and prevention of thromboembolism. There are several approved medications which comprise inhibitors of thrombin (dabigatran etexilate) and factor Xa (rivaroxaban, apixaban and edoxaban). DOACs have shown non-inferiority when compared to the established treatments for stroke prophylaxis in atrial fibrillation (AF)(2) and prophylaxis against and treatment of venous thromboembolism (VTE).(3) The DOACs are being rapidly incorporated into clinical practice and DOAC prescriptions were similar to warfarin for AF anticoagulation in 2014 in the USA.(4)

Bleeding is the main complication of anticoagulation therapy. Annual rates of major bleeding in patients prescribed warfarin has been shown to be as high as 8%.(5,6) A significant concern when the DOAC medications came into use was the lack of reversal agents but these are now in development and becoming available for both direct thrombin(7) and factor Xa inhibitors.(8)

The gastrointestinal (GI) tract is the most common site for major bleeding with anticoagulant use.(9,10) There is conflicting data from prospective trials and meta-analyses of the risk of major GI bleeding with these medications(9,11) and there is emerging data from population databases on their longitudinal use. This has not been synthesised in the literature to our knowledge, to date. We therefore performed a systematic review of the literature and Bayesian network meta-analysis of the risk of GI bleeding with the use of DOAC medication compared to warfarin and low molecular

weight heparin (LMWH) for all indications. We incorporated observational data and addressed limitations of previous, traditional meta-analyses.

Methods

We followed a pre-specified and peer reviewed PRISMA extension guideline and checklist for reporting systematic reviews and network meta-analyses.(12)

Data Sources and Searches

Separate electronic database searches were performed on MEDLINE (1946 – April 2016) and EMBASE (1947 – April 2016) for retrospective and prospective studies reporting on DOAC with GI bleeding as an outcome. Further searches were conducted on The Cochrane Library for systematic reviews and assessment evaluations, the National Health Service (UK) Economic Evaluation Database to April 2016 and ISS Web of Science to capture conference abstracts and proceedings. The search terms used were “apixaban”, “edoxaban”, “rivaroxaban”, “dabigatran”, “direct oral anticoagulant”, “novel oral anticoagulant” and “non-vitamin K antagonist oral anticoagulant”. Medical subject heading (MeSH), free text terms and variations were used including the trade names of each medication. No further limits or language restrictions were applied to maximise the yield. We performed a recursive search of the literature by reviewing the bibliographies of the relevant articles identified from the search strategy. Two independent reviewers (NB and AC) assessed the eligibility of each study for inclusion with any disagreements being resolved by consensus decision. We also attempted to contact authors of studies with missing or incomplete data to include in our analyses. The search strategy and results are detailed in the supplementary appendix. A data flow diagram is shown in figure 1.

Prospective or retrospective studies comparing DOAC use with VKA or LMWH for all indications, and reporting on GI bleed incidence were eligible for inclusion. We did not include studies that compared licensed DOACs against placebo, other oral

anticoagulants or antiplatelet medications. After screening relevant titles, we excluded studies with no information on the duration of follow up, studies with no comparator group, studies with a placebo comparator, studies which only presented adjusted or corrected results and studies using an unlicensed DOAC medication.

Data extraction and quality assessment

Two researchers (NB & KL) independently extracted data on study design, study populations, indication for anticoagulation, dose and duration of medications, and the type and definition of GI bleeding. Our study outcomes were:

Primary outcome

- Major GI bleeding, defined as a fall in haemoglobin level of 20g/L (1·24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells according to International Society on Thrombosis and Haemostasis (ISTH) criteria(13) for RCTs and International Classification of Diseases, 9th revision codes (ICD-9) for major GI bleeding for observational studies.

Secondary outcome

- All GI bleeding, defined as the total number of GI bleeds reported in each study. This included major, clinically relevant non-major bleeding (CRNM) and minor bleeding events combined or the total number of GI bleeding events where there were no details given on the severity of bleeding. Studies where bleed location was not reported for all patients were excluded from this analysis.

We excluded oropharyngeal bleeding and separated upper and lower GI bleeding. Data was compared for accuracy and any disagreements were resolved by consensus decision. The quality of the studies was assessed by the JADAD score(14) for prospective RCTs and the Newcastle-Ottawa scale (NOS) for case-control and cohort studies.(15)

Data synthesis and analysis

We produced a pooled incidence rate ratio (IRR) of the number of major GI bleeds per patient year exposed to each medication. We performed a series of sensitivity analyses to test the robustness of the primary hypothesis. We compared study design (RCT vs. observational), indication for DOAC use, the dose of DOAC used (prophylactic vs. therapeutic) and separated out studies which used bridging therapy with either a higher dose of DOAC or LMWH as this may alter the bleeding risk. To account for potential differences in patient groups, medication regimes and patients characteristics in different geographical populations we excluded studies from North America and then studies from Asia and repeated the primary analyses. We performed an indirect comparison of each specific medication instead of grouping them by class. We also repeated analysis for studies reporting on all GI bleeding events.

Bayesian network meta-analysis is an increasingly popular method for indirect analysis. It performs multiples of pairwise analyses across a range of treatments based on direct and indirect evidence. Even when the direct evidence appears conclusive the network analysis can produce a more precise level of treatment effect.(16) We performed a Bayesian random effects (chosen a priori) regression model with vague priors for heterogeneity variances as a conservative approach.(17) A further analysis using informative priors was performed as a sensitivity test.(18) We

produced an evidence network of drug class with results grouped for; thrombin inhibitors (dabigatran), factor Xa inhibitors, warfarin and LMWH. We used adjusted continuity corrections of 0·5 to account for studies with no events.(19) To estimate the effect of DOAC on the risk of GI bleed we calculated IRR, with 95% credible intervals, based on the number of patient years exposed to the medication. The credible interval (CrI) is a Bayesian analog of the 95% confidence interval used in traditional meta-analyses(20). We used the Markov Chain Monte Carlo method(21) to obtain pooled effect sizes, considering the result statistically significant if it did not include the value 1. The relative effects of each medication were converted to a probability that one of the specific treatments caused less GI bleeds, and then ranked the medications in order with “best” to “worst” creating a league table.

Inconsistency test

Inconsistency in network meta-analysis can be viewed as an extension to heterogeneity across studies using different comparisons(22) and refers to the variability in the effect size caused by differences in characteristics and effect modifiers from study to study. (22,23) A test for inconsistency is important in network meta-analysis as it estimates the discrepancy between the direct and indirect evidence(24) We produced an inconsistency plot and repeated the primary analysis after removing outlier studies to assess the robustness of our results.

All analyses were performed using WinBUGS software (MRC Biostatistics unit)(25) using the visual basics applications tool NetMetaXL.(23)

Results

The results from the literature search and fate of articles screened for inclusion are shown in figure 1. We included 38 articles (25 RCTs(26–50) and 13 observational studies in our analyses(51–63), reporting on 501, 224 patients exposed to 418, 446 years of anticoagulant medication. The key characteristics of each study and the extracted data used in the analyses are displayed in the supplementary material (supplementary tables 1 & 2). The overall quality of the included studies was high with all RCTs having a JADAD score of five and all observational studies having a NOS of >six (supplementary table 3).

We contacted 20 authors of relevant articles, of which six replied, but they were unable to provide any additional study data.

Major GI bleeding

The evidence network for the primary analysis (figure 2) included 31 studies (25 RCTs(26–50) and six observational studies(52,55–58,62)) reporting on 287, 692 patients exposed to 230, 090 years of anticoagulant medication. We were unable to separate out upper and lower GI bleeds as most of the studies did not include this information. On indirect comparison of all of the anticoagulant medications there was no difference in the IRR of major GI bleeds (figure 3). We ranked the anticoagulants in order of the IRR of major GI bleed in a league table (table 1. A). Factor Xa inhibitors are in the top left position as it has the lowest IRR of causing a major GI bleeding and dabigatran is in the bottom right as it has the highest, bearing in mind that these results did not reach statistical significance on indirect comparison.

Inconsistency plot and sensitivity analyses

We performed an inconsistency plot to examine discrepancy between direct and indirect evidence from our network (supplementary figure 1). There were two outlying studies(32,55). These studies were removed from the network and the primary outcome analysis was repeated. There was no change in the overall effect, or indeed change in the order and ranking in the league table.

We performed a series of subgroup analyses as sensitivity tests of the primary outcome (table 2). There was no change in the effect estimate when removing observational studies, analysing according to the indication for anticoagulation, examining therapeutic anticoagulation only and when removing studies which using a higher dose of DOAC or LMWH as bridging therapy. We excluded studies from North America and Asia in turn from the primary analysis and there was no change in the associations. We also stratified each medication separately in a further sensitivity analysis to examine for a class effect (supplementary figure 2). This network analysis showed that edoxaban had a significant reduction in major GI bleeding when compared to dabigatran (IRR 0·15, 95% CrI, 0·02 – 0·66).

All GI bleeding

Thirteen studies (4 RCTs(34,45,47,49) and nine observational studies(51,53,54,58–63)) reporting on 220, 997 patients exposed to 191, 117 years of anticoagulant medication were included in the analysis. We found a significant difference in the risk of all GI bleeding when comparing factor Xa inhibitors and warfarin (IRR 0·25, 95% Cr 0·07 – 0·76) and factor Xa inhibitors with dabigatran (IRR 0·24, 95% CrI 0·07 – 0·77). There was no significant difference with all GI bleeding events between factor Xa inhibitors and LMWH (IRR 0·63, 95% CrI 0·10 – 3·41). There was no significant difference in risk seen with the indirect comparisons between dabigatran, warfarin, and

LMWH (figure 4). As for major GI bleeds we arranged the treatments in order of the greatest impact on all GI bleeding creating a league table (table 1. B.). The ranking produced the same order as the primary outcome of major GI bleeding, showing that factor Xa inhibitors had the least effect, in the top left of the table, with dabigatran having the greatest. The only results that reached statistical significance were for direct factor Xa antagonists versus both dabigatran and warfarin.

Discussion

We have shown that there is no increase in major GI bleeding when comparing DOACs to warfarin and LMWH for each indication for anticoagulation. The result for major GI bleeding was sustained when comparing clinical trial data and data from observational studies. When examining the data on all GI bleeding we found a reduced risk of GI bleeding with the use of factor Xa inhibitors compared to both warfarin and dabigatran. It is important to note that there were only 13 studies in this analysis as we were unable to include studies that did not report on bleeding location for clinically relevant non-major or minor bleeding events. There are plausible hypotheses for these potential associations. Excess bleeding risk with warfarin could be due to variations in drug levels and subsequent international normalised ratio (INR), reflecting anticoagulant effect, which are seen with this medication. Increases in INR can potentiate bleeding from the GI mucosa which resolves when warfarin is withdrawn or reversed with the addition of vitamin K or prothrombin complexes. Dabigatran is administered as a pro-drug (dabigatran etexilate) that is activated through absorption through the GI mucosa.(64) Non-bleeding GI side effects with the use of dabigatran were reported in 16·9% of patients in a follow up analysis of a prospective randomised trial.(65) Oesophageal mucosal injury is also being seen with dabigatran treatment.(66) Oesophagitis can predispose to minor GI bleeding especially in anticoagulated patients.(67) This potential effect should be considered by clinicians prescribing these medications and thorough documentation of GI side effects should be recorded in future studies on anticoagulants.

In a further sensitivity analysis, analysing each individual DOAC, edoxaban was associated with a significant reduction in the risk of major GI bleeding compared to dabigatran (figure s3). We cannot account for the difference in association seen with

edoxaban compared to the other factor Xa antagonists rivaroxaban and apixaban. Possible explanations could be that the difference is due to unaccounted heterogeneity between the studies or that there are different pharmacokinetics and anticoagulant effects with the different drugs. More corroborative evidence should be sought before drawing definitive conclusions.

Comparison with previous research

A potential increased risk of GI bleeding was reported in 2013 by Holster et al(68) with an increase in the odds (OR 1·58, 95% CI 1·29 - 1·93) when comparing DOAC to all other medications. This study also reported an increase in the odds of GI bleeding with rivaroxaban (OR 1·48, 95% CI 1·21 - 1·82). This was a standard, pairwise meta-analysis which only included prospective randomised controlled trials, included some placebo controlled studies, did not include observational studies, and did not perform indirect comparisons. They also did not account for duration of follow up which is important for an outcome such as GI bleeding where longer duration and exposure to potential risk may account for increased incidence of bleed. We were able to account for duration of exposure by calculating patient years of medication use. We also have included more studies, with 30 studies in our primary analysis compared to 17 in this earlier study. These reasons may account for our differing results.

A head to head systematic review and meta-analysis of 23 trials was performed by Caldeira et al. in 2015(11). This showed that there was no difference in the major GI bleeding rate when comparing DOAC with VKA, LMWH, or acetylsalicylic acid separately. In this study all of the DOAC medications were grouped together which includes 2 classes of medications namely factor Xa inhibitors and direct thrombin inhibitors. We have stratified the different DOACs and also shown no difference in

association with the different DOAC classes and a potential significant difference between factor Xa inhibitors and dabigatran in studies examining all GI bleeding.

There is ongoing work on the long term effects of DOAC medications and the results of the ORBIT-AF registry(69) and ORANGE study(70) are expected in the near future. These large-scale, population based observational studies will give further information on the use of these medications outside of controlled clinical trials.

Strengths

There are several strengths to this study. By combining the available evidence through indirect analysis we have been able to report on over half a million patients followed up for over 400, 000 years. We also included data from observational studies to obtain a real world estimate of the potential risk with these medications. Prospective randomised trials often have stringent inclusion and exclusion criteria which can limit their applicability. Importantly, patients with prior GI bleeding are excluded which means that the pre-selected cohort are likely to have a much lower GI bleeding risk than the general population. Time exposure is an important consideration when considering outcomes using anticoagulant medication as these medications are often prescribed for many years. We controlled for time exposure by using the IRR as the risk estimate in our analyses. Observational studies tend to give data covering a longer period of time which is especially important when reporting on rare events such as GI bleeding. This data has not been previously included in direct meta-analyses investigating the safety of these medications.

Limitations

It is important to consider that the different study patients may have different GI bleeding risks, depending on the indication for anticoagulation. There are likely to be

different, important characteristics between patients for each indication including age, co-morbidity, renal function and concomitant medication use. To try and account for these differences we performed pre-planned sensitivity analyses of the different indications for DOAC therapy (table 3). Unfortunately, due to a paucity of available data, we were unable to produce results for some of the comparisons. There are various treatment doses of the DOACs available and different dosing regimens used worldwide. We did not account for the different doses of medications here as it would have markedly extended the data network and also reduced the sample size in each treatment arm. This could have some bearing as bleeding risk increases with higher doses(71). We performed a subgroup analysis of therapeutic and prophylactic doses of DOAC (table 3) and found no change in the association with no significant differences between the medication classes. To account for potential variation in dosing or patient characteristics seen in different countries we performed subgroup analyses after excluding patients from North America and then Asia in turn. Again there was no change in the overall effect estimates. Whilst higher doses of each individual medication may pose additional major GI bleeding risk we haven't found a difference in the association at prophylactic or therapeutic doses.

The definitions of GI bleeding were not consistent between all of the studies identified from our search. This is a potential bias with meta-analyses as there is a danger of comparing different clinical outcomes. To account for this potential effect we used strict definitions of major GI bleeding for our primary analysis, namely ISTH criteria for randomised trials and ICD-9 admission codes for the observational studies. The ICD-9 codes have been validated for anticoagulant associated GI bleeding and have >90% sensitivity and >83% specificity for any GI bleeding and major GI bleeding.(72)

We have not been able to differentiate between upper and lower GI bleeds in our network meta-analysis because this detail was not available for most of the included studies. This data should be captured in future studies. There is ongoing research from anticoagulant registries which will hopefully report on the specific bleed locations.(73) Concomitant use of medications such as non-steroidal anti-inflammatory medications and antiplatelets can increase the GI bleeding risk (74) and gastroprotective medications such as proton pump inhibitors may reduce the bleeding risk. We were unable to investigate these potential effects in this study although we would not expect there to be a differential effect for each class of anticoagulant.

Implications for clinical practice

The DOACs are increasingly being used, largely due to the lack of dose adjustments and drug level monitoring which is required with traditional medications. Although warfarin therapy has been widely used and effective for over 60 years it requires regular therapeutic monitoring. Previous work has shown that the “time in therapeutic range” for warfarin patients is only 50 to 70%(75) which makes DOAC medications an attractive alternative.

Clinicians withhold anticoagulants due to a perceived bleeding risk but those at higher risk for bleeding are also those at highest risk for thromboembolic events due to their co-morbidities.(76) In patients with higher bleeding risk a common occurrence is for aspirin to be prescribed instead of warfarin due to a perceived lower risk of bleeding. A study in 2007 showed no significant difference in major bleeding between warfarin and aspirin in patients >75 years with AF.(77) We are now reporting no difference in major GI bleeding between DOAC medications and warfarin.

GI bleeding remains a serious side effect of anticoagulant use. DOACs are already used by a large numbers of patients and as expected adherence to guidelines continues this use could increase exponentially. It is therefore important to have robust data on the risk profiles of these medications. In this study we found no difference in the risk of major GI bleeding when comparing DOAC, warfarin and LMWH anticoagulation medications which supports their use for a range of anticoagulant indications. We have shown a potential association with a decreased risk of all GI bleeding events with the use of factor Xa inhibitors when compared to warfarin and direct thrombin inhibitors. Further work is needed but this may help with clinical decisions when selecting an anticoagulant.

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