The risk of gastrointestinal hemorrhage with non-vitamin K antagonist oral anticoagulants
A network meta-analysis

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Abstract

Background: Non-vitamin K antagonist oral anticoagulants (NOACs) have been widely used for stroke prevention in atrial fibrillation (AF) and the treatment and prevention of venous thromboembolism. There is an issue with safety, especially in clinically relevant bleeding. We performed a network meta-analysis to evaluate the risk of major gastrointestinal (GI) bleeding associated with NOACs.

Methods: Interventions were warfarin, enoxaparin, apixaban, dabigatran, edoxaban, and rivaroxaban. The primary outcome was the incidence of major GI bleeding. A subgroup analysis was performed according to the following indications: AF, deep venous thrombosis/pulmonary embolism, and postsurgical prophylaxis.

Results: A total of 29 randomized controlled trials (RCTs) and 4 large observation population studies were included. Compared with warfarin, apixaban showed a decreased risk of major GI bleeding (relative risk [RR] 0.54, 95% confidence interval [CI] 0.25–0.78), and rivaroxaban tended to increase this risk (RR 1.40, 95% CI 1.06–1.85). Dabigatran (RR 1.25, 95% CI 0.98–1.60), edoxaban (RR 1.07, 95% CI 0.69–1.65), and enoxaparin (RR 1.24, 95% CI 0.63–2.43) did not significantly increase the risk of GI bleeding than did warfarin. In the subgroup analysis, according to indications, apixaban showed a decreased risk of major GI bleeding (RR 0.50, 95% CI 0.34–0.74) than did warfarin in AF studies. Dabigatran (RR 2.36, 95% CI 1.55–3.60), and rivaroxaban (RR 1.75, 95% CI 1.10–6.41) increased the risk of major GI bleeding than did apixaban. An analysis of studies on venous thromboembolism or pulmonary embolism showed that no individual NOAC or enoxaparin was associated with an increased risk of major GI bleeding compared to warfarin.

Conclusion: Individual NOACs had varying profiles of GI bleeding risk. Results of analyses including only RCTs and those including both RCTs and population studies showed similar trends, but also showed several differences.

Abbreviations: AF = atrial fibrillation, CI = confidence intervals, GI = gastrointestinal, NOAC = non-vitamin K antagonist oral anticoagulant, RCT = randomized controlled trial, RR = relative risks, VKA = vitamin K antagonist, VTE = venous thromboembolism.

Keywords: apixaban, direct factor Xa inhibitor, edoxaban, network meta-analysis, novel oral anticoagulants, rivaroxaban, warfarin

1. Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) that inhibit thrombin or activated factor X were developed and approved for stroke prevention in atrial fibrillation (AF) and for the treatment or prevention of venous thromboembolism.[1] Recently, NOACs are also safe to use in patients with cancer-associated VTE and also AF-associated HF.[2–4] These drugs, including apixaban, dabigatran, edoxaban, and rivaroxaban,
were shown to be as effective as traditional anticoagulation therapy.\textsuperscript{[7–11]} In addition, unlike the vitamin K antagonists (VKAs), NOACs have rapid onset and termination of action, fewer drug interactions, lack of dietary vitamin K intake interaction, and no need for drug monitoring, which led to rapid adoption in clinical practice worldwide.\textsuperscript{[12]}

Although NOACs have been widely used due to efficacy and compliance, the issue of safety has arisen, especially with respect to clinical relevant bleeding.\textsuperscript{[13,14]} For decades, gastrointestinal bleeding has been a serious medical condition that causes considerable morbidity and mortality (5%–15%).\textsuperscript{[11]} In addition, GI bleeding in patients with anticoagulants has significant impacts.\textsuperscript{[16]} including the requirement to alter or discontinue anticoagulant agents, activation of inflammation states, and paradoxical thromboembolic events. Furthermore, in contrast with the traditional VKA, no clinically tested antidote is currently available for NOACs, except for dabigatran. Various randomized controlled trials and large population studies have been carried out, and some studies reported an increased GI bleeding risk in patients with NOACs. Recently, population based observation studies reported that individual NOACs are associated with various risks of GI bleeding compared to warfarin. Traditional pair-wise meta-analysis can only answer questions about pairs of drugs; therefore, they cannot determine which among several drugs is the safest. A network meta-analysis is a useful statistical method for comparing the GI bleeding risk of multiple drugs.

Therefore, we evaluate the risk of major GI bleeding associated with NOACs using a network meta-analysis of randomized controlled trials (RCTs) and observation studies.

2. Methods

This study was exempted from institutional review board review because it did not involve human subjects.

2.1. Search strategy

This systematic review and network meta-analysis was conducted and reported based on the guidelines and recommendations for network meta-analysis. PubMed-Medline, EMBASE, Cochrane Library and Web of Science searches were performed on July 1, 2018 using key terms (“apixaban,” “rivaroxaban,” “dabigatran,” “edoxaban,” and “bleeding”). The detailed search strategies in each database are presented in Supplemental Table 1, http://links.lww.com/MD/F935. All trials had to be randomized, double-blinded, and controlled to ensure a minimum high level of quality. We checked the reference lists of all potentially eligible studies and reviewed papers to find additional relevant publications.

2.2. Study selection

We considered all full-text RCTs and population studies that investigated patients treated with NOACs or conventional coagulation therapy (vitamin K antagonist and low molecular weighted heparin) for approved indications such as the prevention of stroke or systemic embolism in patients with AF, reporting major GI bleeding, without limitation of study size. Among observational studies, we included studies of clear comparisons with propensity scoring matched controls or nested case controls to minimize bias.

The exclusion criteria included the following:
1. non-English publications;
2. abstract-only publications or unpublished studies inclusion of nonhuman subjects;
3. failure to include major GI bleeding as a specified outcome; and
4. trials assessing NOACs for unapproved indications.

Concerning population studies, we excluded single-arm observational studies without comparisons, including case series, case reports, and medical chart review studies. Studies were also excluded if there were insufficient data for determining the hazard risks, relative risks (RR) or odds ratios with 95% confidence intervals (CIs).

Two reviewers (HJO and BHY) independently evaluated the studies for eligibility and resolved any disagreements through discussion and consensus. If no agreement could be reached, a third reviewer (KHR) determined eligibility. The Cochrane risk of bias assessment tool was used for assessing the risk of bias individual studies.

2.3. Data extraction and outcome measure

Two reviewers (HJO and BHY) independently classified the data from included studies as indications. NOACs was classified as apixaban, rivaroxaban, dabigatran, and edoxaban. Conventional anticoagulation was divided by vitamin K antagonist, and low molecular weighted heparin or heparin. The primary outcome was major GI bleeding as defined by the International Society on Thrombosis and Hemostasis.\textsuperscript{[17]} Other GI bleeding events, not referred or classified as major bleeding, were not included.

2.4. Subgroup and sensitivity analysis

The subgroup analysis was done according to the indication: AF, deep venous thrombosis/pulmonary embolism, and postsurgical prophylaxis. There are several limitations in studies based on large observational data such as nonstandardized follow-up and outcome evaluation. Therefore, we performed a sensitivity analysis by excluding 4 large cohort observational studies.

2.5. Statistical analysis

Direct meta-analysis was conducted to calculate pooled RRs with 95% CIs for each pairwise comparison across NOACs and conventional anticoagulant therapy. Taking a conservative approach, we used a random-effects model, which produces wider CIs than a fixed effect model. Statistical heterogeneity was assessed using $I^2$ statistics, with values $>50\%$ suggestive of significant heterogeneity. $P$ values $<.05$ were assumed to indicate statistical significance. The tests for funnel plot asymmetry were not conducted when there were fewer than 10 included studies for each pair-wise comparison.

In order to combine indirect and direct comparisons, we performed a network meta-analysis to determine comparative safety among the 6 treatments. This type of analysis allowed us to utilize results from 2 drugs compared to the same third drug for indirect comparisons. For example, 2 treatments (apixaban and dabigatran) had trial data compared to warfarin. The network meta-analysis application allows for the comparison between these 2 treatments using the evidence for each non-operative treatment and provides indirect evidence of the comparative
effects between the treatment modalities. All analyses were performed using the “mvmeta” command of STATA (version 14.0; Stata Corporation, College Station, TX, USA).

Corresponding 95% credible intervals (CrIs) were obtained using the 2.5th and 97.5th percentiles of the posterior distribution.

2.6. Quality of evidence

Two investigators (HJO and BHY) independently performed quality assessments using the risk of bias assessment tool, which was described in the Cochrane Handbook for Systematic Reviews of Interventions.

3. Results

3.1. Included studies

A total of 29 RCTs and 4 of large observation population studies were included. The flowchart of study selection is shown in Figure 1. All included studies evaluated the risk of major GI bleeding associated with NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, warfarin, and enoxaparin. Twenty nine RCTs included a total of 121,246 patients with indication of AF (n = 8, 15–19, 21–22) venous thromboembolism (VTE) or pulmonary embolism (n = 11, 23–31) and postsurgical prophylaxis of VTE (n = 11) (Fig. 2). Table 1 summarizes the characteristics of included studies. We analyzed an additional 4 population studies including 265,948 patients with AF (33–36). All population observational studies were retrospective cohort studies with propensity matching. Regarding comparative efficacy for early postpolypectomy bleeding, there was no inconsistency between direct and indirect estimates in all 6 comparisons (Table 2).

3.2. The risk of GI bleeding

Compared with warfarin, apixaban showed a lower risk of major GI bleeding (RR 0.54, 95% CI 0.25–0.76, P < .001), and rivaroxaban showed a higher risk (RR 1.40, 95% CI 1.06–1.85, P = .017). The other 2 NOACs, dabigatran (RR 1.25, 95% CI 0.98–1.60, P = .076) and edoxaban (RR 1.07, 95% CI 0.69–1.65, P = .776), and enoxaparin (RR 1.24, 95% CI 0.63–2.43, P = .536) did not significantly increase the risk of GI bleeding than that with warfarin (Fig. 3). Compared to apixaban, the remaining NOACs (dabigatran, edoxaban, and rivaroxaban) and enoxaparin were associated with increased risk of major GI bleeding.

3.3. Subgroup analysis according to the indications

Eight RCTs and 4 population observation cohort studies with AF were analyzed for risk of major GI bleeding associated with
individual NOACs and warfarin in 352,058 patients. Compared with warfarin, apixaban showed a lower risk of major GI bleeding (RR 0.50, 95% CI 0.50–0.50, P = .001), and the other individual NOACs showed no differences in the risk compared to apixaban, dabigatran (RR 2.36, 95% CI 1.55–3.60, P = .037) and rivaroxaban (RR 1.75, 95% CI 1.10–6.41, P = .014) were associated with greater risk of major GI bleeding (Fig. 4A).

Analysis of studies of VTE or PE (11 RCTs, 26,739 patients) revealed that no individual NOAC or enoxaparin was associated with increased risk of major GI bleeding compared to warfarin. Overall, there was no difference in major GI bleeding rates comparing each individual NOAC (Fig. 4B).

Analysis of studies of post-surgical prophylaxis of VTE (11 RCTs, 28,766 patients) showed no significant differences of major GI bleeding risk among individual NOACs and enoxaparin (Fig. 4C).

### 3.4. Sensitivity analysis and quality assessment

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 deep vein thrombosis, the EINSTEIN-PED 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 (Supplemental Fig. 1, http://links.lww.com/MD/F936). As with the sensitivity analysis, we performed meta-analysis of 29 RCTs after excluding 4 large observation population studies; the plot showed a similar trend with the plot of analysis including all RCTs and population study biases (Supplemental Fig. 2, http://links.lww.com/MD/F937).

### 4. Discussion

GI bleeding is a representative complication of NOAC use; this complication has been a matter of controversy in many RCTs and observation studies. Although NOACs have favorable safety profiles, efficacy, compliance, and convenience compared to conventional anticoagulation, GI bleeding is a fatal disadvantage. Previous RCTs and meta-analyses showed increased risk of GI bleeding with NOACs such as rivaroxaban or dabigatran, than that with conventional therapy. Recently, many large RCTs and meta-analyses addressed the risk of increased GI bleeding with NOACs than with conventional therapy. Recently published population-based observational studies demonstrated variable risk of GI bleeding among each individual NOACs through direct and indirect comparisons. Graham et al reported that, in patients with AF, rivaroxaban increased risk of GI bleeding than did dabigatran. Other studies by Abraham showed equivalent risks between rivaroxaban and dabigatran, and apixaban decreased the risk of GI bleeding compared to rivaroxaban and dabigatran. A recent propensity matched cohort study (YAO) in patients with AF reported increased, equivalent, and decreased GI bleeding risks associated with rivaroxaban, dabigatran, and apixaban, respectively, compared to warfarin. In this network meta-analysis, we assessed major GI bleeding data of 30 RCTs and 4 observation population studies with updated and approved indications, including nonvalvular AF, VTE or PE, and postsurgical prophylaxis of VTE comparing individual NOACs and conventional anticoagulation therapy. We found that each individual NOAC had a different profile of GI bleeding. Overall, apixaban significantly decreased the risk of GI bleeding, and rivaroxaban increased the risk than those with other individual NOACs and conventional therapy. Among other individual NOACs (dabigatran, edoxaban, and rivaroxaban) and conventional therapy, there were no significant associations with major GI bleeding. When we analyzed only RCTs, the plot showed a similar trend. However, some differences were noted:

1. Compared to warfarin, dabigatran significantly increased the risk of major GI bleeding, rather than rivaroxaban.
2. Among individual NOACs, dabigatran showed increased risk of major bleeding, and the other individual NOACs showed no difference between one another.

In subgroup analysis according to indications, in cases of AF, apixaban significantly decreased the risk of GI bleeding than did other individual NOACs, and warfarin. Indirect comparison showed that, with respect to VTE or PE, no individual NOAC, enoxaparin, and warfarin were associated with increased risk of major GI bleeding. In cases of postsurgical prophylaxis of VTE, no significant difference in major GI bleeding was shown among individual NOACs and enoxaparin.

Taken together, analysis including only RCTs and analysis including both RCTs and population studies showed similar trends, but several differences. According to indications, there were several differences regarding results as well. We found that rivaroxaban increased the risk of GI bleeding in the analysis of RCTs and population studies, while dabigatran increased the risk of GI bleeding in the analysis of only the RCTs. This might be due to study-related differences, including patient criteria and baseline demographic characteristics. Compared with the population cohort study, RCT studies included patients with high CHADS scores who had risk factors for bleeding, including old age and diabetes mellitus. By contrast, population studies included patients with renal dysfunction or liver dysfunction who were excluded from RCTs. Plasma levels of dabigatran and rivaroxaban are elevated in renal dysfunction patients because of their prolonged excretion rates. The recommendation of creatinine clearance (CrCl) range for dabigatran and rivaroxaban were different, 15 to 30 ml/minute/1.73 m² and 15 to 50 ml/minute/1.73 m², respectively. Different ranges of CrCl...
Table 1

Baseline characteristics and results of included trials.

| Study (patients) | Study design | Source of participant | Study Period | Intervention | Conventional treatment | Major GI bleeding, n/N | NOAC vs n/N conventional treatment group |
|------------------|--------------|-----------------------|--------------|--------------|------------------------|------------------------|------------------------------------------|
| Atrial Fibrillation (11 studies) | | | | | | | |
| Granger 2011 | Double blind randomized | North America, South America, Europe, Asia | 2006–2010 | Apixaban (2.5 mg twice) | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Giugliano 2013 | Double blind randomized | North America, South America, Europe, Asia | 2008–2010 | Edoxaban (60 mg, 30 mg) | Warfarin | 361/14069 vs 180/7038 | 361/14069 vs 180/7038 |
| Hori 2013 | Double blind randomized | Asia | 2007–2010 | Rivaroxaban (15 mg) | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Connolly 2009 | Open-label randomized | North America, South America, Europe, Asia | 2005–2007 | Dabigatran (150 mg, 110 mg) | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Patel 2011 | Double blind randomized | North America, South America, Europe, Asia | 2006–2009 | Rivaroxaban (20 mg) | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Connolly 2011 | Double blind randomized | North America, South America, Europe, Asia, South Africa | 2007–2009 | Apixaban (2.5 mg twice) | Aspirin (81–324 mg) | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Chung 2011 | Double blind randomized | Asian countries (Taiwan, South Korea, Hong Kong and Singapore) | 2007–2008 | Edoxaban (60 mg, 30 mg) | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Ogawa 2011 | Double blind randomized | Japan | 2007–2008 | Apixaban (2.5 mg twice) | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Abraham 2017 | Retrospective, propensity matched cohort study. | US, Optum Data Warehouse | 2010–2015 | Dabigatran, 150 mg, twice daily; Rivaroxaban, 20 mg, once daily. | Warfarin | 18/7429 vs 22/7429 | 14/7307 vs 23/7307 |
| Abraham 2015 | Retrospective, propensity matched cohort study. | US, Optum Data Warehouse | 2007–2015 | Dabigatran, 150 mg, twice daily; Rivaroxaban, 20 mg, once daily. | Warfarin | 15/5166 vs 16/5166 | 15/5166 vs 16/5166 |
| Graham 2016 | Retrospective, propensity matched cohort study. | US, fee-for-service Medicare | 2011–2014 | Dabigatran, 150 mg, twice daily; Rivaroxaban, 20 mg, once daily. | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |
| Yao 2016 | Retrospective, propensity matched cohort study. | US insurance database | 2010–2015 | Dabigatran, 150 mg, twice daily; Rivaroxaban, 20 mg, once daily. | Warfarin | 0/31 vs 15/31 | 361/14069 vs 180/7038 |

Venous thromboembolism or Pulmonary embolism (11 studies)

| Study (patients) | Study design | Source of participant | Study Period | Intervention | Conventional treatment | Major GI bleeding, n/N | NOAC vs n/N conventional treatment group |
|------------------|--------------|-----------------------|--------------|--------------|------------------------|------------------------|------------------------------------------|
| Bauersachs 2010 | Double blind randomized | North America, South America, Europe, Asia | 2007–2009 | Apixaban (5 mg twice) | Placebo | 3/994 vs 5/994 | 3/994 vs 5/994 |
| Buller 2012 | Double blind randomized | North America, South America, Europe, Asia | 2008–2011 | Apixaban (5 mg twice) | Placebo | 3/994 vs 5/994 | 3/994 vs 5/994 |
| Schulman 2009 | Double blind randomized | Europe, North America | 2006–2008 | Dabigatran (150 mg twice) | Warfarin | 53/16175 vs 40/16175 | 53/16175 vs 40/16175 |
| Schulman 2013(RE-MEDY) | Double blind randomized | North America, South America, Europe, Asia | 2006–2010 | Dabigatran (150 mg twice) | Warfarin | 5/14307 vs 8/14307 | 5/14307 vs 8/14307 |
| Schulman 2013(RE-SONATE) | Double blind randomized | North America, South America, Europe, Asia | 2007–2010 | Dabigatran (150 mg twice) | Placebo | 2/662 vs 0/662 | 2/662 vs 0/662 |

(continued)
### Table 1 (continued)

| Major GI bleeding, n/N | NOAC vs n/N conventional treatment group |
|------------------------|------------------------------------------|
|                        | Conventional                              |
|                        | Study (patients) Study design Source of participant Study Period Intervention |
|                        | Post-surgical prophylaxis of venous thromboembolism (11 studies) |
|                        | Lassen 2009 Double blind randomized Europe NA Apixaban (2.5 mg twice) Enoxaparin (30mg) 1/1596 vs 6/1588 |
|                        | Lassen 2010K Double blind randomized Europe 2007–2008 Apixaban (2.5 mg twice) Enoxaparin (40mg) 2/1501 vs 2/1508 |
|                        | Lassen 2010H Double blind randomized Europe 2007–2009 Apixaban (2.5 mg twice) Enoxaparin (40mg) 4/2673 vs 0/2659 |
|                        | Fuji 2014K Double blind randomized Japan 2009 Edoxaban (30mg) Enoxaparin (2000IU) 1/354 vs 0/349 |
|                        | Fuji 2015 Double blind randomized Japan 2009–2010 Edoxaban (30mg) Enoxaparin (2000IU) 0/303 vs 2/301 |
|                        | Fuji 2014H Double blind randomized Japan 2008–2009 Edoxaban (30mg) Enoxaparin (2000IU) 1/59 vs 0/29 |
|                        | Eriksson 2007 Double blind randomized Europe 2004–2006 Dabigatran (150 mg or 220mg) Enoxaparin 1/2309 vs 0/1154 |
|                        | Eriksson 2008 Double blind randomized Europe 2006–2007 Rivaroxaban (10mg) Enoxaparin (40mg) 2/2209 vs 1/2224 |
|                        | Kakkar 2008 Double blind randomized Europe 2006–2007 Rivaroxaban (10mg) Enoxaparin (40mg) 1/1228 vs 0/1229 |
|                        | Turpie 2009 Double blind randomized North America, Europe 2006–2007 Rivaroxaban (10mg) Enoxaparin (30mg) 1/1526 vs 0/1508 |
|                        | Lassen 2008 Double blind randomized Europe Rivaroxaban 10mg Enoxaparin (40mg) 7/1220 vs 6/1123 |

NA = non-available.

6.

As the HAS-BLED score[65] are needed, as are recommendations of individual NOACs to increase risk of GI bleeding. Therefore, creation and validation of individual NOACs had various comorbidities that are known and population studies showed slight differences. In addition, NOACs had various GI bleeding profiles depending on creatinine clearance. Other risk stratification tools for GI bleeding would be useful, as NOACs need further study.

Despite the fact that individual NOACs are associated with distinct profiles of GI bleeding, there are no specific screening guidelines and no established risk factor grading system for GI bleeding for individual NOACs. Current guidelines have not definitely addressed the risk of major bleeding risk of GI bleeding with individual NOACs.[64] Although based on insufficient data, American Gastroenterological Association recommended lowering dose of dabigatran and rivaroxaban depending on creatinine clearance. Other risk stratification tools for GI bleeding or specific recommendations for preventing GI bleeding for individual NOACs have not been defined. We found individual NOACs had various GI bleeding profiles, and the results of RCTs and population studies showed slight differences. In addition, patients with NOACs had various comorbidities that are known to increase risk of GI bleeding. Therefore, creation and validation of individual NOAC-specific scoring tools for GI bleeding, such as the HAS-BLED score[65] are needed, as are recommendations of patient screening, selection, and changing of NOACs.

This study has several limitations. First, we could perform network analysis only on studies with AF patients. Other studies with VTE or PE and postsurgery VTE prophylaxis were not subjected to network analysis, because a closed loop was not formed. Second, there was heterogeneity because RCTs as well as observation studies were analyzed. Nevertheless, major confounding factors (including age, use of gastroprotective agents, and ulcerogenic agents (including antplatelet agents, NSAIDs, steroids, and selective serotonin reuptake inhibitors), as well as indications for anticoagulation were evaluated using subgroup and sensitivity analysis. Through analysis of not only RCTs but also observation studies, we recognized differences between which make this study to be relevant. These differences suggest that further studies are needed. Last, all the included studies in this meta-analysis investigated the warfarin and enoxaparin as VKA and low molecular weight heparin group respectively. Further studies accessed other various types of conventional
anticoagulation therapies employed in real clinical world, especially such as dalteparin and nadroparin, are needed.

In conclusion, this network meta-analysis showed that individual NOACs had distinct profiles of GI bleeding risk. Overall, apixaban significantly decreased the risk of GI bleeding, and rivaroxaban increased the risk of GI bleeding than did individual NOACs and conventional therapy. According to the meta-analysis of RCTs, dabigatran increased the risk of GI bleeding. To confirm the clinical relevance and to establish the practical clinical guidelines for tailored therapy, high-quality head-to-head comparison studies are needed.

Table 2
Inconsistency test between direct and indirect treatment comparisons in mixed treatment comparison.

| Side     | Direct Coef | Std. Err | Indirect Coef | Std. Err | Difference Coef | Std. Err | P > |z |
|----------|-------------|----------|---------------|----------|-----------------|----------|-----|---|
| AvsB     | -0.2207917  | 0.1778605| -0.9997044    | 0.189685 | 0.7789127       | 0.2594087| .103|
| AvsC     | 0.1685377   | 0.1590577| 0.5348726     | 0.2327751| -0.1663349      | 0.2814689| .555|
| AvsD     | 0.0609293   | 0.2311838| 0.123441      | 0.101456 | -0.0625117      | 1.038363 | .952|
| AvsE     | 0.1239015   | 0.1858956| 0.0116441     | 0.2010711| -0.4776826      | 0.2742042| .081|
| AvsF     | 0.8642481   | 0.4970639| -0.3319522    | 0.4595372| 1.1962          | 0.6769394| .077|
| BvsC     | 1.312897    | 0.2981637| 0.62859       | 0.2021851| 0.6843069       | 0.3602505| .057|
| BvsD     | 1.300795    | 0.3252648| 0.7915953     | 0.2337526| 0.5092002       | 0.4065131| .21 |
| BvsE     | 0.2263967   | 0.67782   | 1.066951      | 0.4201928| -0.840554       | 0.7972694| .292|
| BvsF     | 0.1977302   | 0.2086055| 0.0180269     | 0.2178189| 0.1797033       | 0.3016484| .551|
| CvsE     | -0.4056616  | 1.655209  | 0.0988333     | 0.3622032| -0.4145148      | 1.694376 | .807|
| CvsF     | 0.0977506   | 0.9423688| 0.1602654     | 0.4362663| -0.0625148      | 1.038363 | .952|
| DvsF     | -0.9106376  | 0.8555769| 0.0362069     | 0.3859908| -0.0468445      | 0.9351117| .313|

A = warfarin, B = apixaban, C = dabigatran, Coef = coefficient, D = edoxaban, E = rivaroxaban, F = enoxaparin, Std. Err = standard error.

Figure 3. The interval plot of the relative risk for the major gastrointestinal bleeding in network meta-analysis including all studies.
Author contributions

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