LETTERS TO THE EDITOR

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Gastrointestinal Safety Profiles Differ Among Non–Vitamin K Antagonist Anticoagulants?

Dear Editor:

The article by Miller et al[1] published in the April 2017 issue of *Clinical Gastroenterology and Hepatology* deals with the important topic of non–vitamin K antagonist anticoagulants (NOACs). In this regard, Miller et al[1] conducted a pairwise meta-analysis to evaluate the gastrointestinal (GI) bleeding risk of 4 NOACs (rivaroxaban, dabigatran, apixaban, and edoxaban).

The investigators concluded that rivaroxaban and dabigatran were associated with an increased risk of major GI bleeding compared with conventional anticoagulants (odds ratio [OR], 1.40; 95% confidence interval, 1.15–1.70; OR, 1.27; 95% confidence interval, 1.04–1.55, respectively). Nevertheless, the pairwise meta-analysis failed to evaluate the comparative effectiveness among the individual NOACs because no head-to-head randomized control trials were available.

Thus, it can be resolved by using a network meta-analysis, which is a widely used statistical methodology. A network meta-analysis allows for indirectly comparing 2 treatments through a common comparator, and then obtains estimates of the relative treatment effects within a single analysis. For instance, by obtaining information from a trial comparing the effectiveness of rivaroxaban with warfarin, and another trial comparing the effectiveness of dabigatran with warfarin, an indirect estimate on the comparison of rivaroxaban vs dabigatran can be obtained. Therefore, we performed a complementary network meta-analysis to evaluate the GI bleeding risk in treating patients with NOACs, based on the source literature identified used by Miller et al.[1]

We excluded studies with zero events in both groups because this comparison provided no information on the treatment effect. The end point was an incidence of major GI bleeding, which was defined as per the International Society of Thrombosis and Haemostasis as a drop in hemoglobin of 2g/dL or requiring two or more units of pack red blood cells. The network meta-analysis was performed using a fixed Bayesian model account for the rarity of events.[2] All outcomes were expressed as the OR and corresponding 95% credible interval (CrI). The model fit was based on the residual deviance,[3] and the analyses were performed using the Markov chain Monte Carlo method.[4] We used noninformative uniform distributions to generate the posterior distributions of the model parameters and fitted 4 chains, yielding 400,000 iterations (100,000 per chain). Convergence was assessed using the Brooks et al[5] diagnostic, and global heterogeneity was assessed by the I^2 statistic.[6] The Bayesian frame network meta-analysis was conducted using gemtc and rjags in R software, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

The results are shown in Table 1. Relative to apixaban, rivaroxaban (OR, 1.74; 95% CrI, 1.28–2.37) and dabigatran (OR, 1.57; 95% CrI, 1.16–2.14) were associated with an increased risk of major GI bleeding. Similarly, rivaroxaban (OR, 1.53; 95% CrI, 1.17–1.98) and dabigatran (OR, 1.38; 95% CrI, 1.06–1.79) were associated with a higher major GI bleeding risk than edoxaban. When rivaroxaban and dabigatran were compared with conventional anticoagulants, the pooled results were favorable for conventional anticoagulants (OR, 1.40; 95% CrI, 1.15–1.71; OR, 1.26; 95% CrI, 1.04–1.54, respectively). No difference was observed between rivaroxaban and dabigatran (OR, 0.90; 95% CrI, 0.68–1.20). Similarly, no difference was found between apixaban and edoxaban (OR, 1.14; 95% CrI, 0.85–1.53). The global heterogeneity parameter I^2 value was 32.1%, suggesting moderate heterogeneity in the network.

The results from the network meta-analysis were consistent with the pairwise meta-analysis conducted by Miller et al,[1] which showed that rivaroxaban and dabigatran were associated with an increased major GI bleeding risk compared with the conventional anticoagulants. In addition, the network meta-analysis also indirectly compared the bleeding outcome between individual NOACs. The results suggested that the major GI bleeding risk was different among the NOACs. The previous studies were performed to evaluate the effectiveness of individual NOACs on GI bleeding. Abraham et al[7] performed a large retrospective propensity-matched study, including 31,574 patients, comparing the GI bleeding risk between rivaroxaban, dabigatran, and apixaban. The results showed that apixaban was associated with a lower risk of GI bleeding than rivaroxaban and dabigatran. These results were similar to the findings from network meta-analysis. Although the pooled result favored dabigatran when compared with rivaroxaban in that study, the confidence interval was close to the 1. In the network meta-analysis, we found no different GI bleeding risk between these 2 therapy options. Furthermore, in that study, they failed to add edoxaban to the comparator set because of the complexity of pharmacoepidemiologic studies. In this

Table 1. Estimated Relative Treatment Effects as OR and its Corresponding 95% CrIs

Comparison	Apixaban	Edoxaban	Rivaroxaban	Dabigatran	Conventional anticoagulants	Placebo
Apixaban	—	1.14 (0.85–1.53)	1.74 (1.28–2.37)[a]	1.57 (1.16–2.14)[a]	1.24 (0.99–1.57)	0.22 (0.01–1.52)
Edoxaban	0.88 (0.65–1.17)	—	1.53 (1.17–1.98)[a]	1.38 (1.06–1.79)[a]	1.09 (0.92–1.29)	0.19 (0.01–1.34)
Rivaroxaban	0.57 (0.42–0.78)[a]	0.65 (0.50–0.86)[a]	—	0.90 (0.68–1.20)	0.71 (0.58–0.87)[a]	0.12 (0–0.88)[a]
Dabigatran	0.64 (0.47–0.86)[a]	0.73 (0.56–0.95)[a]	1.11 (0.84–1.47)	—	0.79 (0.65–0.96)[a]	0.14 (0–0.98)[a]
Conventional anticoagulants	0.80 (0.64–1.01)	0.92 (0.77–1.09)	1.40 (1.15–1.71)[a]	1.26 (1.04–1.54)[a]	—	0.17 (0.01–1.22)
Placebo	4.64 (0.66–125.39)	5.28 (0.75–145.5)	8.08 (1.14–220.58)[a]	7.29 (1.02–202.66)[a]	5.77 (0.82–156.63)	—

NOTE. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining treatment and the row-defining treatment. An OR value higher than 1 favors the column-defining treatment. An OR value less than 1 favors the row-defining treatment.
[a]Statistically significant.

network meta-analysis, 4 NOACs were added in the synthesis set. The results suggested that dabigatran and rivaroxaban also were associated with a higher risk of GI bleeding than edoxaban. In addition, the GI bleeding risk was similar between apixaban and edoxaban.

Overall, based on the evidence from network meta-analysis, the GI bleeding risk was different among the individual NOACs. In addition, rivaroxaban and dabigatran have the least favorable GI safety profile, which should be taken into account in clinical practice.

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Conflicts of interest
The authors disclose no conflicts.

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Reply. We thank Guo and Li[1] for their interest in our systematic review and meta-analysis examining the risk of gastrointestinal (GI) bleeding associated with non–vitamin K antagonist oral anticoagulants (NOACs) compared with conventional anticoagulation.[2] We are in agreement that network meta-analysis is a potentially useful tool to estimate the comparative effects of multiple interventions indirectly in the absence of head-to-head randomized controlled trial data.[3] In light of results from our subgroup analyses that suggested variability across NOACs, we believe a properly conducted network meta-analysis may contribute valuable data by indirectly comparing NOACs with each other.

The correspondence by Guo and Li[1] includes a "complementary network meta-analysis…based on the source literature" identified in our study. They provide results that include increased odds of major GI bleeding associated with dabigatran and rivaroxaban compared with apixaban, edoxaban, and conventional anticoagulants. They found no statistically significant difference between either dabigatran and rivaroxaban, or apixaban and edoxaban.

Although these results are interesting, we are concerned about the lack of reported methodology in the letter. It is unknown what crude bleeding data or what exact statistical methodology were used for their analyses, rendering it difficult to interpret and impossible to reproduce their results. Furthermore, the number of trials informing each comparison was unstated, preventing readers from estimating the strength of each comparison. As a result, readers such as ourselves are unable to evaluate the significance of these results critically and meaningfully.

In summary, we believe that the consequential issue of NOAC-associated GI bleeding indeed can be elucidated further by means of a thoroughly executed network meta-analysis, but only if fully reported with explicit and transparent methodology.

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