

Evaluation of Rivaroxaban- and Dabigatran-Associated Hemorrhagic Events Using the FDA-Adverse Event Reporting System Database (FAERS)

Mingxing Guo

Beijing Friendship Hospital

Sydney Thai

University of North Carolina at Chapel Hill Gillings School of Global Public Health

Junwen Zhou

Aix-Marseille Universite

Jingkai Wei

Milken Institute School of Public Health

Ying Zhao

Beijing Friendship Hospital

Wanyi Xu

Beijing Friendship Hospital

Tiansheng Wang

University of North Carolina at Chapel Hill Gillings School of Global Public Health

Xiangli Cui (✉ cui10@163.com)

Beijing Friendship Hospital

Research Article

Keywords: Rivaroxaban, Dabigatran, Hemorrhagic events, FAERS

Posted Date: February 24th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-242485/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Rivaroxaban and dabigatran are non-vitamin K antagonist oral anticoagulants that are widely used for treatment and prevention of venous thrombo-embolism and prevention of stroke in patients with atrial fibrillation.

Objective To estimate and compare hemorrhagic events reported for rivaroxaban and dabigatran.

Setting FDA Adverse Event Reporting System (FAERS) database.

Methods The reporting odds ratio (ROR) was used to analyze the reporting of hemorrhagic events.

Main outcome measure The overall hemorrhagic events and hemorrhagic events in different physiological systems and indications.

Results A total of 53,085 reports of hemorrhage related to rivaroxaban, accounting for 49.79% of all rivaroxaban-related ADR reports and 13151 hemorrhagic reports related to dabigatran, accounting for 38.51% of all dabigatran-related ADR reports. The overall ROR (95% CI) for hemorrhagic event reporting for rivaroxaban compared with dabigatran was 1.58 (95% CI 1.54-1.62). The RORs (95% CI) in gastrointestinal systems, nervous system, renal and urinary system, skin and subcutaneous tissue, and eye system were 1.38 (1.34-1.42), 0.94 (0.90-0.98), 1.07 (1.01-1.13), 0.80 (0.70-0.90), and 1.38 (1.19-1.60), respectively. The RORs (95% CI) for hemorrhagic events in patients with atrial fibrillation, pulmonary embolism and deep vein thrombosis comparing rivaroxaban with dabigatran were 1.85 (1.79-1.91), 2.02 (1.67-2.47) and 2.17 (1.82-2.59).

Conclusions Overall, a moderate signal for hemorrhage associated with rivaroxaban use was observed when compared with dabigatran. Hemorrhagic events in different physiological systems were not have a higher risk in case reports of rivaroxaban compared to dabigatran. But for the treatment of patients with pulmonary embolism or deep vein thrombosis, rivaroxaban are associated with more hemorrhagic events compared to dabigatran.

Impacts On Practice

- Compared with dabigatran, rivaroxaban is associated with slightly higher reported hemorrhagic events.
- Patients with pulmonary embolism or deep vein thrombosis and on rivaroxaban are associated with more hemorrhagic events compared to dabigatran.
- Patients using rivaroxaban to treat pulmonary embolism or deep vein thrombosis who experience symptoms related to hemorrhage should be closely monitored and advised to adhere to an appropriate regimen.

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly considered as the preferred anticoagulation treatment to prevent stroke for patients with nonvalvular atrial fibrillation (NVAF) and to prevent and treat deep vein thrombosis (DVT) and pulmonary embolism (PE), particularly for anticoagulant-naïve patients [1–3]. NOACs have a better risk-benefit profile than vitamin K antagonists (VKAs) for management of NVAF and are better than low-molecular-weight heparin (LMWH) for treatment and prevention of DVT and PE [4, 5]. However, the extensive clinical application of NOACs has raised concerns on bleeding risk. Pivotal efficacy randomized controlled trials (RCTs) have documented an increased risk of gastrointestinal bleeding and a decreased risk of intracranial hemorrhage for NOACs compared with warfarin [6, 7].

Rivaroxaban and dabigatran are the most commonly used NOACs, and they have different anticoagulation mechanisms. Rivaroxaban binds reversibly to the factor Xa (the common factor between intrinsic and extrinsic coagulation pathways). A major benefit of using direct factor Xa inhibitors is that they can inactivate prothrombinase activity in addition to clot bound or free factor Xa. Dabigatran can competitively bind to the active site of thrombin (downstream of the coagulation pathway). In doing so, dabigatran prevents thrombin from converting fibrinogen to its active form of fibrin, and thereby inhibits thrombus development [8]. Because they act on different coagulation pathway sites, rivaroxaban and dabigatran may have different levels of anticoagulant effects and consequently may confer different risks for adverse events (e.g. major bleeding). Estimation of such differences requires an appropriate assessment of the drug exposure and the anticoagulant effect. The current evidence base for the safety of NOACs does not include any head-to-head trials that directly compare the different NOACs [9–11].

The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System Database (FAERS) is a spontaneous reporting system and common pharmacovigilance tool that collects case reports of suspected adverse drug reactions. With disproportionality analysis methods, FAERS can be used to assess relative differences in the reporting of common adverse events between case reports listing rivaroxaban and reports listing dabigatran. FAERS has been used to evaluate hemorrhage risk associated with dabigatran and/or rivaroxaban [12–14]. However, most studies focused on comparing hemorrhagic reporting between warfarin and NOACs. To our knowledge, no FAERS studies have directly compared hemorrhagic reporting between different NOACs. However, this is an important consideration for the clinical choice between NOACs.

Aim of the study

The objective of this study was to compare hemorrhagic event reporting between case reports listing rivaroxaban and reports listing dabigatran in the FAERS database and analyze the reporting of hemorrhagic events overall and hemorrhagic events in different physiological systems and indications.

Ethics approval

The ethics approval for this study was not applicable. However, necessary permission for utilization of FAERS data was obtained.

Methods

Intervention

The interventions of interest were dabigatran and rivaroxaban. All records in the FAERS database (<https://open.fda.gov/data/faers/>) from 1 January 2014 to 31 December 2019 were included in this study. The FAERS Public Dashboard was searched with the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms: “dabigatran”, “dabigatran etexilate”, “dabigatran etexilate mesylate”, “pradaxa”, “rivaroxaban”, and “xarelto”.

Outcome

The outcome of interest was hemorrhagic event. The primary outcome was overall hemorrhagic event. The secondary outcomes were hemorrhagic events in cases affecting the top 5 physiological systems: gastrointestinal (GI), nervous, renal and urinary, skin and subcutaneous tissue, and eye system. At the same time, secondary outcomes also included hemorrhagic events in different indications. The hemorrhagic events were identified from case reports listing the interventions of interest by searching the following preferred terms: “bleed”, “bleeding”, “haemorrhagic”, “haematoma”, “hemorrhage” and “haemorrhage”. Hemorrhagic events in specific systems were identified using MedDRA classifications of the side effect.

Statistical analysis

Disproportionality analysis was conducted using the reporting odds ratio (ROR) and 95% confidence intervals (CIs) to compare the proportional reporting of hemorrhagic events for rivaroxaban and dabigatran. The ROR was calculated by dividing the odds of hemorrhagic event reporting for the drug of interest by the odds of hemorrhagic event reporting for the comparison drug. The odds of hemorrhagic event reporting for a drug were calculated by dividing the number of drug case reports listing “hemorrhagic events” by the number of drug case reports listing all other adverse events. In this study, rivaroxaban was the drug of interest and dabigatran was the comparison drug. A signal was defined as $ROR \geq 2.0$ [15]. ROR between 1 and 2 is considered as a moderate signal.

Subgroup analyses were performed for the primary outcome by gender, age, year of reporting, and severity of adverse event. The severity of adverse events was classified as death, life-threatening, disabling, hospitalization, requiring intervention and others. We additionally evaluated nervous system hemorrhagic events in different reporting years to assess deviations and heterogeneity.

Results

Overall hemorrhagic event

Overall, 106,671 reports listing rivaroxaban and 34,154 reports listing dabigatran were identified. The number of hemorrhagic event reports was 53,085 (49.79%) for rivaroxaban and 13,151 (38.51%) for

dabigatran. The ROR for hemorrhagic events comparing rivaroxaban with dabigatran was 1.58 (95% CI: 1.54–1.62) (Fig. 1).

Hemorrhagic event by physiological systems

When comparing rivaroxaban with dabigatran, there was no strong signals for increased hemorrhage risk across the 5 physiological systems. The RORs (95% CI) in GI, nervous system, renal and urinary system, skin and subcutaneous tissue, and eye system were 1.38 (1.34–1.42), 0.94 (0.90–0.98), 1.07 (1.01–1.13), 0.80 (0.70–0.90), and 1.38 (1.19–1.60), respectively (Fig. 2).

Hemorrhagic event by indications

The RORs (95% CI) for hemorrhagic events in patients with atrial fibrillation, PE or DVT comparing rivaroxaban with dabigatran were 1.85 (1.79–1.91), 2.02 (1.67–2.47) and 2.17 (1.82–2.59). There were signals for the risk of hemorrhage with the use of rivaroxaban compared with dabigatran in patients with PE or DVT (Fig. 3). However, no signal of increased bleeding risk were found in GI and nervous system under different indications.

Subgroup analysis for hemorrhagic events

Across gender and age groups, there were no strong signals of increased hemorrhagic reporting comparing rivaroxaban with dabigatran (Fig. 1). In the subgroup analyses by severity of adverse events, there were signals of increased hemorrhagic event reporting among case reports associated with hospitalization (2.08, 2.01–2.12) and other severity events (3.03, 2.82–3.28).

In the subgroup analysis by year of reporting, compared with dabigatran, rivaroxaban showed a signal of increased hemorrhagic event reporting in 2016 (3.54, 3.31–3.79) (Fig. 1). In order to assess whether the case report year influenced the reporting of rivaroxaban- and dabigatran-associated neurological hemorrhagic events, secondary analyses of neurological hemorrhagic events were conducted by the year of reporting (Fig. 4). The only ROR (95% CI) greater than 1.0 was for 2014 (1.79, 1.59–2.01). No signals were detected for years 2015 to 2019, which was consistent with the secondary analyses in nervous system.

Discussion

We compared hemorrhagic event reporting between case reports listing dabigatran and reports listing rivaroxaban in the FAERS database including 53,085 hemorrhagic event reports for rivaroxaban and 13,151 hemorrhagic event reports for dabigatran from 2014 to 2019. We used disproportionality analysis to assess the reporting of hemorrhagic events overall and hemorrhagic events in different physiological systems. We found there was a moderate signal for hemorrhage associated with rivaroxaban use compared with dabigatran (ROR 1.58, 1.54–1.62) (Fig. 1). In adverse event cases involving gastrointestinal systems, nervous systems, renal and urinary systems, skin and subcutaneous tissue, or eye systems, hemorrhagic events were not have a higher risk in case reports of rivaroxaban compared to

dabigatran (Fig. 2). It is worth noting that the RORs were increased for the risk of hemorrhage with the use of rivaroxaban compared with dabigatran in patients with PE or DVT (Fig. 3).

Hemorrhage is the most common complication of anticoagulants. There are no head-to-head randomized clinical trials to investigate the hemorrhage risk of different NOACs. Up to now, several studies have been conducted to assess the bleeding risk of NOACs using some spontaneous reporting systems (14,16–17). It should be noted that they all use warfarin or all other drugs present in the database for the reference drug to disproportionality analysis. In this study, we directly use rivaroxaban and dabigatran for comparison. Thus making the baseline characteristics of the study population more consistent.

Overall, we observed a moderate signal for hemorrhagic events associated with rivaroxaban compared with dabigatran (ROR 1.58, 1.54–1.62) (Fig. 1). Patrick et al. compared rivaroxaban with dabigatran at standard and reduced doses in a propensity-score-matched cohort study and found that different doses of dabigatran had lower bleeding risk (dabigatran vs. rivaroxaban hazard ratio, HR, 95% CI: standard dose HR 0.59, 0.39–0.90, reduced dose HR 0.74, 0.57–0.96) [18]. Douros et al. compared the risk of major bleeding between rivaroxaban and dabigatran through a meta-analysis that included 6 studies. The result showed that there was an increased bleeding risk for rivaroxaban versus dabigatran (HR 1.33; 95% CI: 1.20–1.47) [19].

We compared hemorrhagic event reporting between rivaroxaban and dabigatran by different physiological systems. GI hemorrhage and intracranial hemorrhage are the two main adverse reactions that clinicians focus on. A meta-analysis showed rivaroxaban, but not dabigatran, was associated with an increased risk for major GI hemorrhage (RR 1.39; 95% CI, 1.17–1.65 and HR 1.14; 95% CI, 1.04–1.23) [20]. In our study, compared with hemorrhagic event reporting for dabigatran, there was a moderate signal of hemorrhage for rivaroxaban with the ROR (95% CI) in GI was 1.38 (1.34–1.42). For intracranial hemorrhage, some large clinical trials have reported the bleeding event rates per. Rates of intracranial bleeding with the 110-mg dose of dabigatran was 0.23% and the 150-mg dose of dabigatran was 0.30% [6], rates of intracranial bleeding with the rivaroxaban was 0.50% [7]. Since it is not a head-to-head study, no clinical conclusion can be drawn from it. We evaluated nervous system hemorrhage as intracranial hemorrhage. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. There was not a signal of hemorrhage for rivaroxaban in nervous system compared with dabigatran with the ROR (95% CI) in nervous system was 0.94 (0.90–0.98). In adverse event cases involving GI systems, nervous systems, renal and urinary systems, skin and subcutaneous tissue, or eye systems, hemorrhagic events were not have a higher risk in case reports of rivaroxaban compared to dabigatran (Fig. 2).

In different indications, we found a increased risk of hemorrhage with the use of rivaroxaban compared with dabigatran in patients with PE or DVT (ROR 2.02, 95% CI: 1.67–2.47 in PE and ROR 2.17, 95% CI: 1.82–2.59 in DVT) (Fig. 3). No direct head-to-head comparisons are available for NOACs in venous thrombo-embolism (VTE) treatment. A network meta-analysis, on the basis of indirect comparison of NOACs for the treatment of VTE, revealed a relative risk for a major or clinically relevant nonmajor

bleeding 1.50 (95% CI: 1.17–1.92, $p = 0.001$) for rivaroxaban versus dabigatran [21]. Those findings suggest that VTE treatment including DVT or PE with rivaroxaban is associated with more bleeding compared to administration of dabigatran.

Furthermore, we performed subgroup analyses for the primary outcome by conducting the disproportionality analysis by gender, age, year of reporting, and severity of adverse event. For the secondary analyses, there was a moderate signal for rivaroxaban-associated hemorrhage among case reports of patients over 65 years old (ROR 1.95, 1.89–2.02). Our results are consistent with a previous study on elder patients (> 80 years) with nonvalvular atrial fibrillation [22] which showed dabigatran was associated with a lower risk of major bleeding (HR 0.77, 0.67–0.90) compared with rivaroxaban. For subgroup analyses by reporting year (Fig. 1), the strikingly low ROR for 2014 may be partly due to the increasing number of patients using rivaroxaban. A study based on IMS Health National Disease and Therapeutic Index found that rivaroxaban treatment visits increased from 2011 Q4 to 2014 Q4, while dabigatran treatment visits remained relatively stable since 2011 Q4 [23].

The major strength of this study was to provide a head-to-head assessment of hemorrhagic event reporting between rivaroxaban and dabigatran in large pharmacovigilance database and assessed the association in different physiological systems and indications. Certainly there are several limitations. First, FAERS data is prone to reporting biases and missing data, and we were unable to fully control for confounding. Second, because the data lacks a meaningful denominator for causal analyses, we cannot assess incidence and make causal inferences from FAERS data. Third, drug-drug interactions documented in “Reaction” variable of FAERS case reports may not represent all potential interactions as drug-drug interaction may not be reported as an adverse event. And we are not restricted to hemorrhagic drug-drug interaction case reports that have drugs of interest listed as primary or secondary suspect. Lastly, we did not consider the effect of drugs dosage due to missing data, and this could be an important factor in bleeding events.

Conclusions

In conclusion, this study found a moderate signal for hemorrhage associated with rivaroxaban compared to dabigatran. The signals for bleeding events varied in subgroup analyses. In reported cases involving GI systems, nervous systems, renal and urinary systems, skin and subcutaneous tissue, or eye systems, we saw no signal of increased bleeding risk in rivaroxaban compared to dabigatran. But when treating patients with PE or DVT, rivaroxaban had a higher bleeding risk compared with dabigatran. Patients with rivaroxaban to treat VTE or PE who experience symptoms related to hemorrhage should be closely monitored and advised to adhere to an appropriate care plan.

Declarations

Acknowledgements

The authors were involved at all stages of manuscript development. The authors received no direct compensation related to the development of the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of Interest

The authors report no conflict of interest relevant to the subject of this article.

Contributions

(I) Conception and design: M Guo, T Wang, X Cui; (II) Administrative support: X Cui; (III) Collection and assembly of data: M Guo, Y Zhao, W Xu; (IV) Data analysis and interpretation: All authors; (V) Manuscript writing: All authors; (VI) Final approval of manuscript: All authors.

References

1. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-52.
2. Enea I, Roncon L, Gulizia MM, Azzarito M, Becattini C, Bongarzoni A, et al. [ANMCO](#) Position Paper: the use of non-vitamin K dependent new oral anticoagulant(s) in pulmonary embolism therapy and prevention. *Eur Heart J Suppl*. 2017;19(Suppl D):D293-D308.
3. January CT, Wann LS, Calkins H, Field ME, Chen LY, Furie KL, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation*. 2019;140(2):e125–51.
4. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-62.
5. Yao X, Abraham NS, Alexander GC, Crown W, Montori VM, Sangaralingham LR, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2):e003074.
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-51.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-91.
8. Kapil N, Datta YH, Alakbarova N, Bershada E, Selim M, Liebeskind DS, et al. Antiplatelet and anticoagulant therapies for prevention of ischemic stroke. *Clin Appl Thromb Hemost*. 2017;23(4):301-18.

9. Fontaine GV, Mathews KD, Woller SC, Stevens SM, Lloyd JF, Evans RS. Major bleeding with dabigatran and rivaroxaban in patients with atrial fibrillation: A real-world setting. *Clin Appl Thromb Hemost.* 2014;20(7):665-72.
10. Graham DJ, Reichman ME, Wernecke M, Hsueh YH, Izem R, Southworth MR, et al. Stroke, bleeding, and mortality risks in elderly medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med.* 2016;176(11):1662-71.
11. Prins MH, Bauersachs R, Bellen B, Bellen B, Bounameaux H, Brighton TA, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J.* 2013;11(1):21.
12. Abe J, Umetsu R, Kato Y, Ueda N, Nakayama Y, Suzuki Y, et al. Evaluation of dabigatran- and warfarin-associated hemorrhagic events using the FDA-adverse event reporting system database stratified by age. *Int J Med Sci.* 2015;12(4):312-21.
13. Alshammari TM, Ata SI, Mahmoud MA, Alhawassi TM, Aljadhey. Signals of bleeding among direct-acting oral anticoagulant users compared to those among warfarin users: analyses of the post-marketing FDA adverse event Reporting system (FAERs) database, 2010-2015. *Ther Clin Risk Manag.* 2018;14:803-9.
14. DeLoughery EP, Shatzel JJ. A comparative analysis of the safety profile of direct oral anticoagulants using the FDA adverse event reporting system. *Eur J Haematol.* 2019;103(1):43-6.
15. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf.* 2004;13(8):519-23.
16. Shimada K, Hasegawa S, Nakao S, Mukai R, Sasaoka S, Ueda N, et al. Adverse reaction profiles of hemorrhagic adverse reactions caused by direct oral anticoagulants analyzed using the Food and Drug Administration Adverse Event Reporting System (FAERS) database and the Japanese Adverse Drug Event Report (JADER) database. *Int J Med Sci.* 2019;16(9):1295-303.
17. Yokoyama S, Tanaka Y, Nakagita K, Hosomi K, Takada M. Bleeding risk of warfarin and direct oral anticoagulants in younger population: A historical cohort study using a Japanese Claims Database. *Int J Med Sci.* 2018;15(14):1686-93.
18. Patrick B, Caroline DP, Yves C, Jacques B, Patrick M, Abdelilah A, et al. Comparative effectiveness and safety of standard or reduced dose dabigatran versus rivaroxaban in non-valvular atrial fibrillation. *Clin Pharmacol Ther.* 2019;105(6):1439-55.
19. Douros A, Durand M, Doyle CM, Yoon S, Reynier P, Filion KB. Comparative effectiveness and safety of direct oral anticoagulants in patients with atrial fibrillation: A systematic review and meta-analysis of observational studies. *Drug Saf.* 2019;42(10):1135-48.
20. Gu ZC, Wei AH, Zhang C, Wang XH, Zhang L, Shen L, et al. Risk of major gastrointestinal bleeding with new vs conventional oral anticoagulants: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2020;18:792-9.
21. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. *J Thromb Thrombolysis.* 2015;39:155-65.

22. Deitelzweig S, Keshishian A, Li XY, Kang A, Dhamane AD, Luo XM, et al. Comparisons between oral anticoagulants among older nonvalvular atrial fibrillation patients. *J Am Geriatr Soc.* 2019;67(8):1662-71.
23. Barnes GD, Lucas E, Alexander GC, Goldberger National trends in ambulatory oral anticoagulant use. *Am J Med.* 2015;128(12):1300-5.e2.

Figures

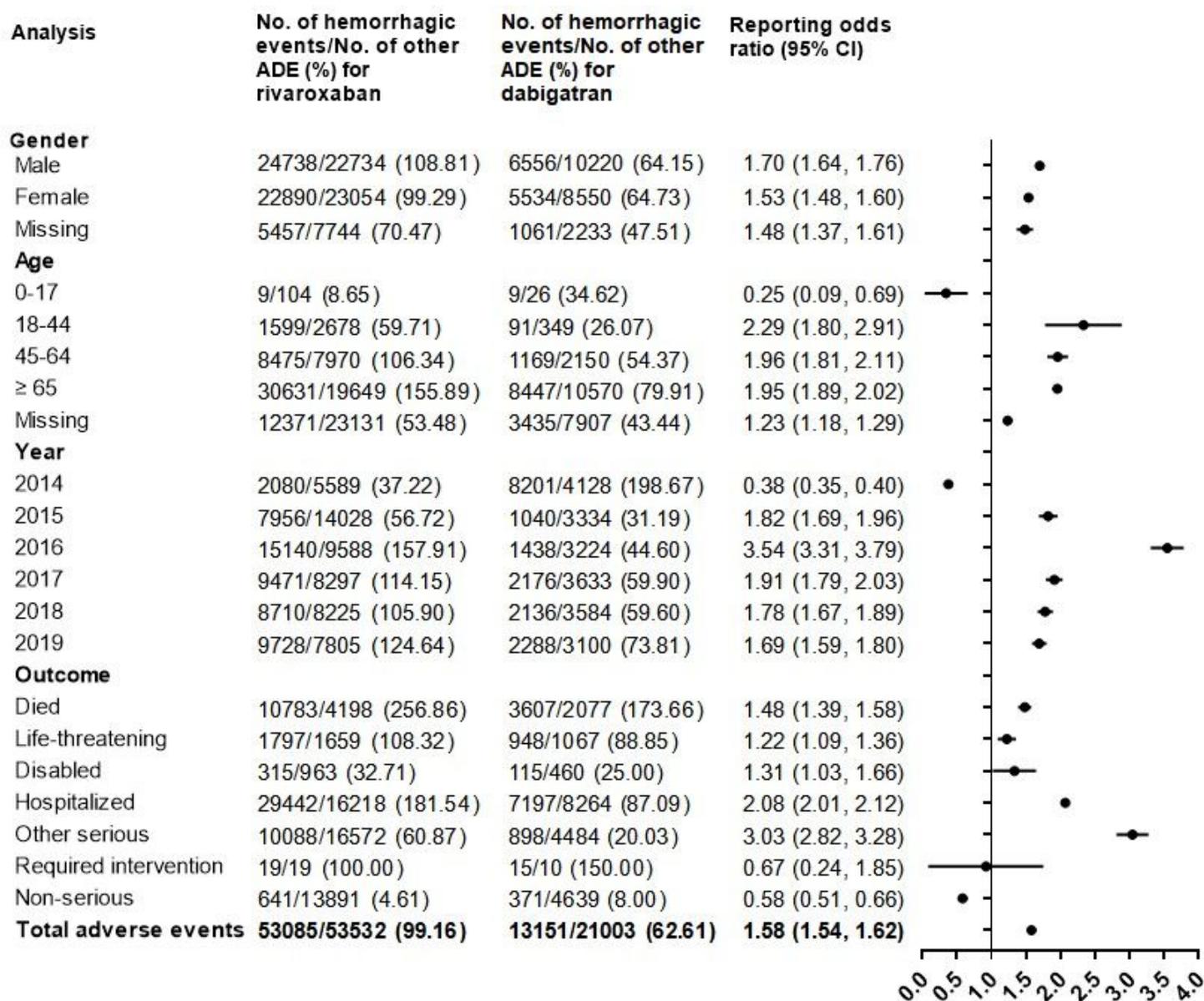


Figure 1

Subgroup analysis of patients with rivaroxaban and dabigatran associated hemorrhagic events. CI confidence interval, ROR reporting odds ratio

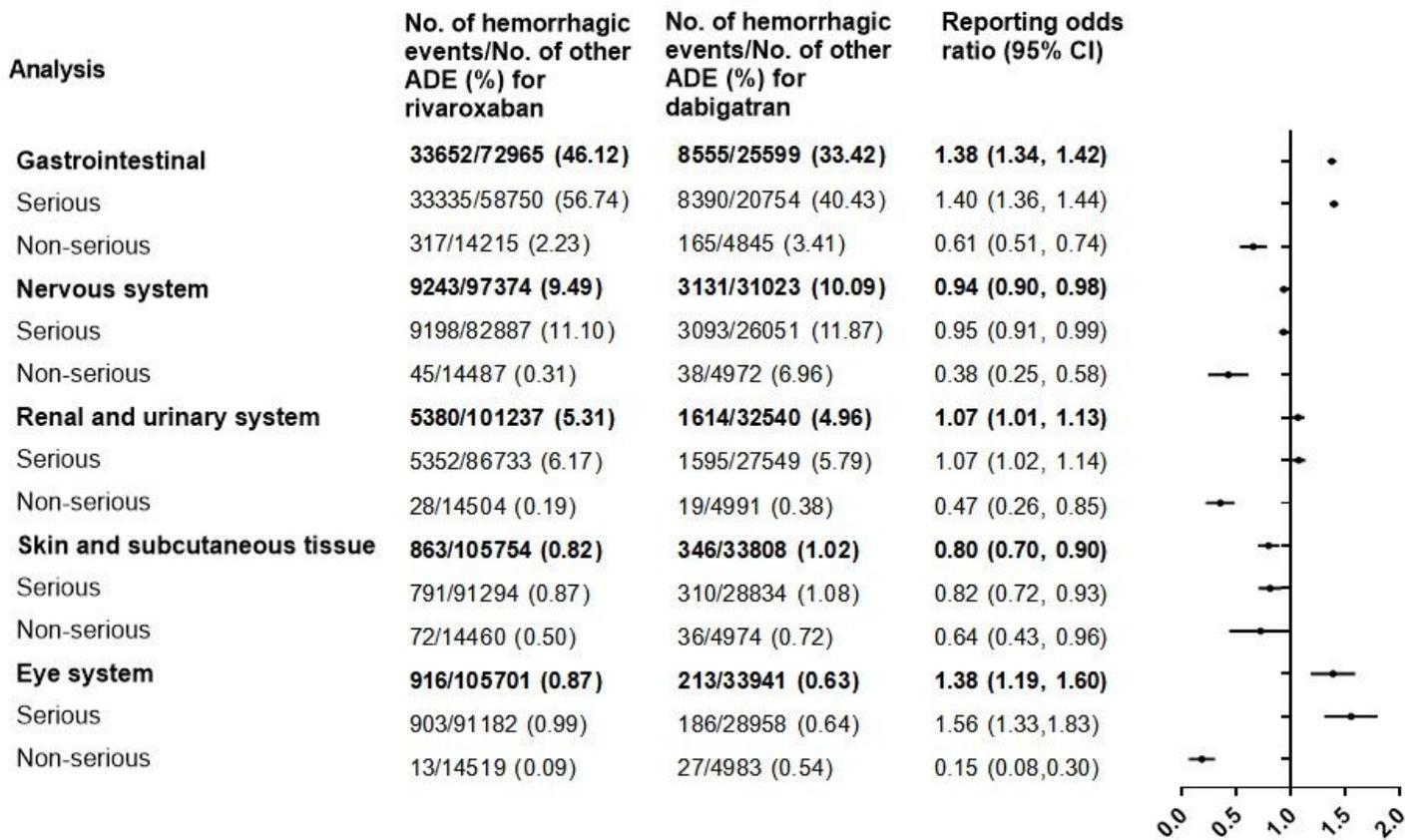


Figure 2

Hemorrhagic signals and ROR in different physiological systems. CI confidence interval, ROR reporting odds ratio

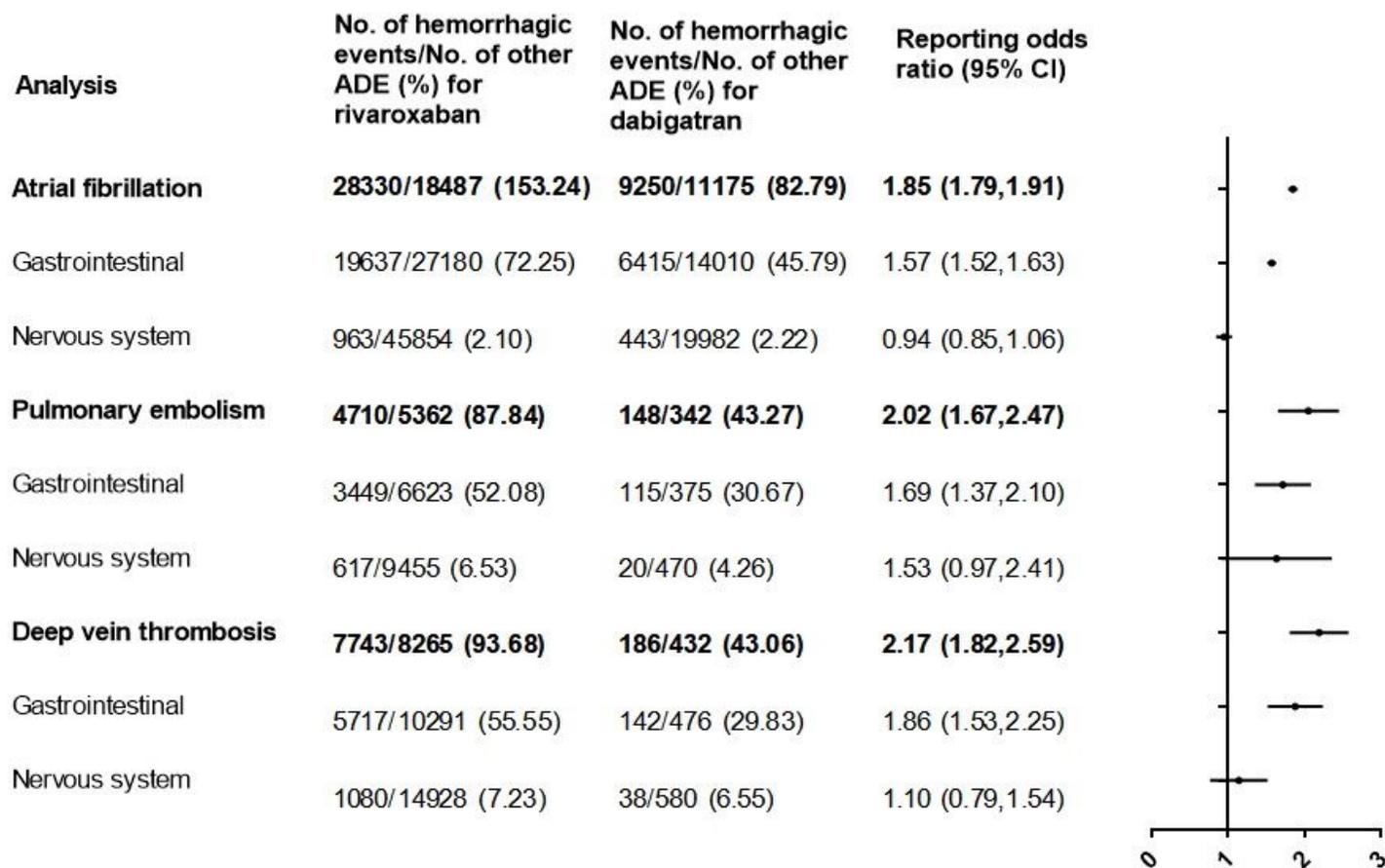


Figure 3

Rivaroxaban and dabigatran associated hemorrhagic events in different indications. CI confidence interval, ROR reporting odds ratio

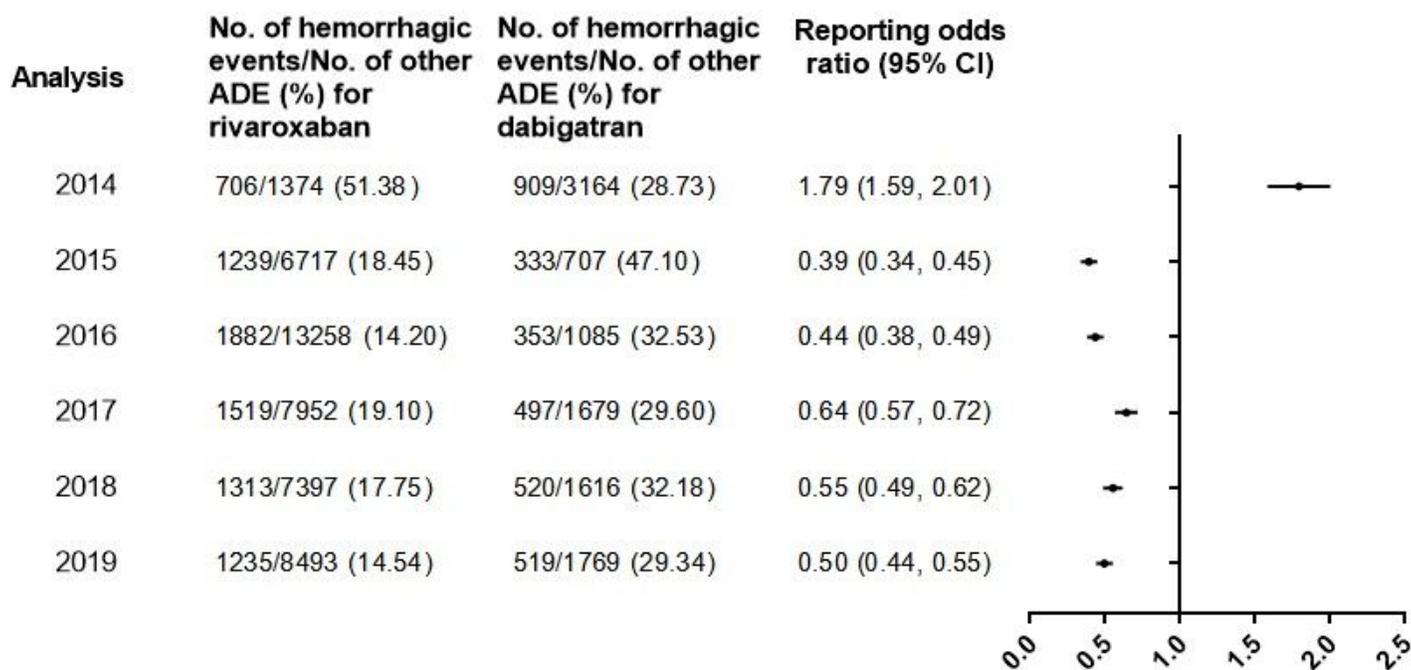


Figure 4

Rivaroxaban and dabigatran associated nervous system hemorrhagic events in different reporting years.
CI confidence interval, ROR reporting odds ratio