THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Thrombotic and Hemorrhagic Adverse Events of Direct Oral Anticoagulants: An Analysis of Sex-Related Differences Using Food and Drug Administration Adverse Event Reporting System

ABSTRACT

Background: Sex-related differences in the safety profiles of direct oral anticoagulants (DOACs) remain insufficiently understood. This study aimed to evaluate sex-specific differences in the most frequently reported hemorrhagic and thrombotic adverse events (AEs) associated with DOAC therapy using data from the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: A retrospective pharmacovigilance analysis was conducted using FAERS reports from each DOAC's approval date through 2024. Only cases in which a single DOAC was designated as the primary suspect and the report was submitted by a healthcare professional were included. Six major AEs were evaluated: gastrointestinal hemorrhage, intracerebral hemorrhage, pulmonary embolism (PE), deep vein thrombosis, ischemic stroke, and myocardial infarction (MI). Dabigatran served as the reference comparator. Reporting odds ratios (RORs) with 95% CIs were calculated to identify disproportionate reporting signals.

Results: Hemorrhagic and thrombotic AE patterns demonstrated notable sex differences. Gastrointestinal hemorrhage risk was higher with apixaban (ROR = 2.32, $P < .001$, 95% CI: 2.20-2.45) and edoxaban (ROR = 2.95, $P < .001$, 95% CI: 2.54-3.42) compared with dabigatran, while female dabigatran users reported these events more frequently ($P < .001$). Intracranial hemorrhage was reported more often among males using dabigatran and rivaroxaban ($P = .003$ and $P = .004$). All DOACs were associated with increased MI reports (e.g., apixaban ROR = 2.37, $P < .001$, 95% CI: 2.08-2.71), particularly among males. Conversely, PE and ischemic stroke were more frequently reported in female rivaroxaban users ($P < .001$ and $P = .018$).

Conclusions: Significant sex-specific differences exist in DOAC safety profiles. Recognizing these patterns may inform individualized anticoagulant selection and enhance pharmacovigilance-driven personalized medicine.

Keywords: Adverse Drug Reaction Reporting Systems, anticoagulants, hemorrhage, sex differences, thrombosis

INTRODUCTION

Anticoagulants play a critical role in the prevention and treatment of thromboembolic disorders. Over the past decade, a new generation of direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban, has gained widespread use in clinical practice owing to their unique pharmacological advantages. Their fixed dosing, lack of routine laboratory monitoring, and broad clinical indications make them appealing alternatives to traditional vitamin K antagonists (VKAs).[1,2] However, serious bleeding events and thrombotic complications remain important safety concerns.[3,4]

Most of the available safety data on DOACs have been derived from clinical trial populations. Randomized trials typically involve selected and homogeneous patient groups. As a result, the findings may not fully reflect sex-related safety differences in real-world settings.[3] The reflection of biological and clinical factors related to sex (e.g. hormone levels, thrombotic and hemorrhagic tendencies,

ORIGINAL INVESTIGATION

Mehmet Şahinbaş[1]
Burcu Şahinbaş[2]
Ezgi Ağadayı[3]

[1]*Department of Cardiology, Sivas Numune Hospital, Sivas, Türkiye*
[2]*Department of Pharmacology, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye*
[3]*Department of Medical Education, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye*

Corresponding author:
Ezgi Ağadayı
✉ drezgiagadayi@hotmail.com

Received: September 19, 2025
Accepted: December 23, 2025
Available Online Date: February 10, 2026

Cite this article as: Şahinbaş M, Şahinbaş B, Ağadayı E. Thrombotic and hemorrhagic adverse events of direct oral anticoagulants: an analysis of sex-related differences using FDA Adverse Event Reporting System. *Anatol J Cardiol.* 2026;XX(X):1-9.

DOI:10.14744/AnatolJCardiol.2025.5827

pharmacokinetic properties) in adverse event (AE) profiles has not been comprehensively explored.[4] Despite this gap, growing evidence suggests that there may be significant sex differences in the efficacy and safety profiles of DOACs.[5] Overall, the available data for sex-specific differences remain fragmentary and are often restricted to subgroup analyses, which limits statistical power and complicates clinical interpretation. In addition to sex-related differences, elderly patients with multiple comorbidities or polypharmacy are often excluded from randomized trials, further contributing to uncertainties about the safety of DOACs in complex clinical populations.[6]

Large-scale pharmacovigilance databases such as the Food and Drug Administration Adverse Event Reporting System (FAERS) involving heterogeneous populations have the potential to reveal sex-specific AE differences with respect to DOACs that may not be noticed in controlled clinical trials.[7,8] Therefore, this study analyzed FAERS data to evaluate the most commonly reported hemorrhagic and thrombotic AEs associated with DOAC use and to investigate potential sex-related differences. The findings provide clinicians with insights that support more individualized anticoagulant selection and contribute to the growing body of pharmacovigilance research in this field.

METHODS

Data Source and Study Design

This retrospective, descriptive data analysis was performed using FAERS data.[9] The FAERS is an open-access database to which patients, pharmaceutical companies, and healthcare professionals voluntarily submit reports of drug-related AEs and product quality issues. The database includes case-level information including the year of reporting, type of reaction, product/generic name, patient age and sex, reporter type/region, event outcome, severity classification, and therapeutic indication. Reported reactions in FAERS represent suspected AEs at the Preferred Term level according to the Dictionary of Medical Regulatory Activities.[10]

HIGHLIGHTS

- Reports from healthcare professionals in the United States Food and Drug Administration Adverse Event Reporting System between 2010 and 2024 were analyzed.
- Direct oral anticoagulants were compared with dabigatran using disproportionality analysis.
- Gastrointestinal hemorrhage was more frequently associated with apixaban and edoxaban, while rivaroxaban showed fewer reports; edoxaban had the highest signal for intracranial hemorrhage.
- Pulmonary embolism and deep vein thrombosis were less common with rivaroxaban, whereas myocardial infarction (MI) and ischemic stroke were more frequent with all agents.
- Gastrointestinal hemorrhage was more often reported in female patients, whereas intracranial hemorrhage and MI were more frequently reported in male patients.

For hemorrhagic events, the terms "cerebral hemorrhage" and "intracranial hemorrhage" were used to describe intracranial bleeding, and "gastrointestinal hemorrhage" was used to define gastrointestinal bleeding. Thrombotic events consisted of deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, and myocardial infarction (MI); only the terms "myocardial infarction" and "acute myocardial infarction" were used to define MI. The AE records were retrieved by querying the database using the relevant generic name: "dabigatran," "dabigatran etexilate," "dabigatran etexilate mesylate," "rivaroxaban," "apixaban," "edoxaban," "edoxaban tosylate," and "edoxaban tosylate monohydrate."

In this study, predefined inclusion and exclusion criteria were applied. The AEs reports associated with DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) were evaluated for the period from each drug's FDA approval date to the end of 2024. Betrixaban was excluded from the study due to its limited number of reports (n = 35). Only records in which the DOAC was designated as the primary suspect were included; concomitant medications were not considered in this analysis. Records in which the DOAC was coded as a secondary suspect or concomitant agent were excluded. Only AEs submitted by healthcare professionals were included (Figure 1). Cases with missing sex information were included in the overall analysis but excluded from sex-specific subgroup assessments. Duplicate reports were addressed according to the FDA-recommended procedures.[11] Among entries sharing the same case identifiers (CASEID), the version with the latest FDA receipt date (FDA_DT) was retained.

Disproportionality Analysis and Statistical Analysis

Annual AE reporting rates were calculated by dividing the total number of AEs by the number of years each drug had been listed in the FAERS database. Demographic characteristics were summarized descriptively. For comparative analyses, each Factor Xa inhibitor (rivaroxaban, apixaban, and edoxaban) was compared with dabigatran. Reporting odds ratios (RORs) for each AE were calculated using a 2×2 contingency table. A potential safety signal indicating a disproportionate association between a drug and a specific AE was identified by an ROR exceeding 1.[12] The chi-square test was used to evaluate sex-based differences for each of the 6 AEs. All statistical analyses and graphical visualizations were conducted using SPSS versions 23.0 and GraphPad Prism version 10.4.1. A P value of $<.05$ was considered statistically significant.

RESULTS

After applying the inclusion and exclusion criteria to 30 179 725 AE reports in the FAERS database through 2024, a total of 37 537 dabigatran, 61 983 rivaroxaban, 43 930 apixaban, and 5040 edoxaban cases were included in the final analysis (Figure 1). Among DOACs, apixaban accounted for the highest number of primary-suspect AE reports, whereas rivaroxaban had the highest number of AEs reported specifically by healthcare professionals. Annual AE counts, thrombotic and hemorrhagic events, annual death totals, and the study periods for each DOAC are shown in Figure 2. Apixaban

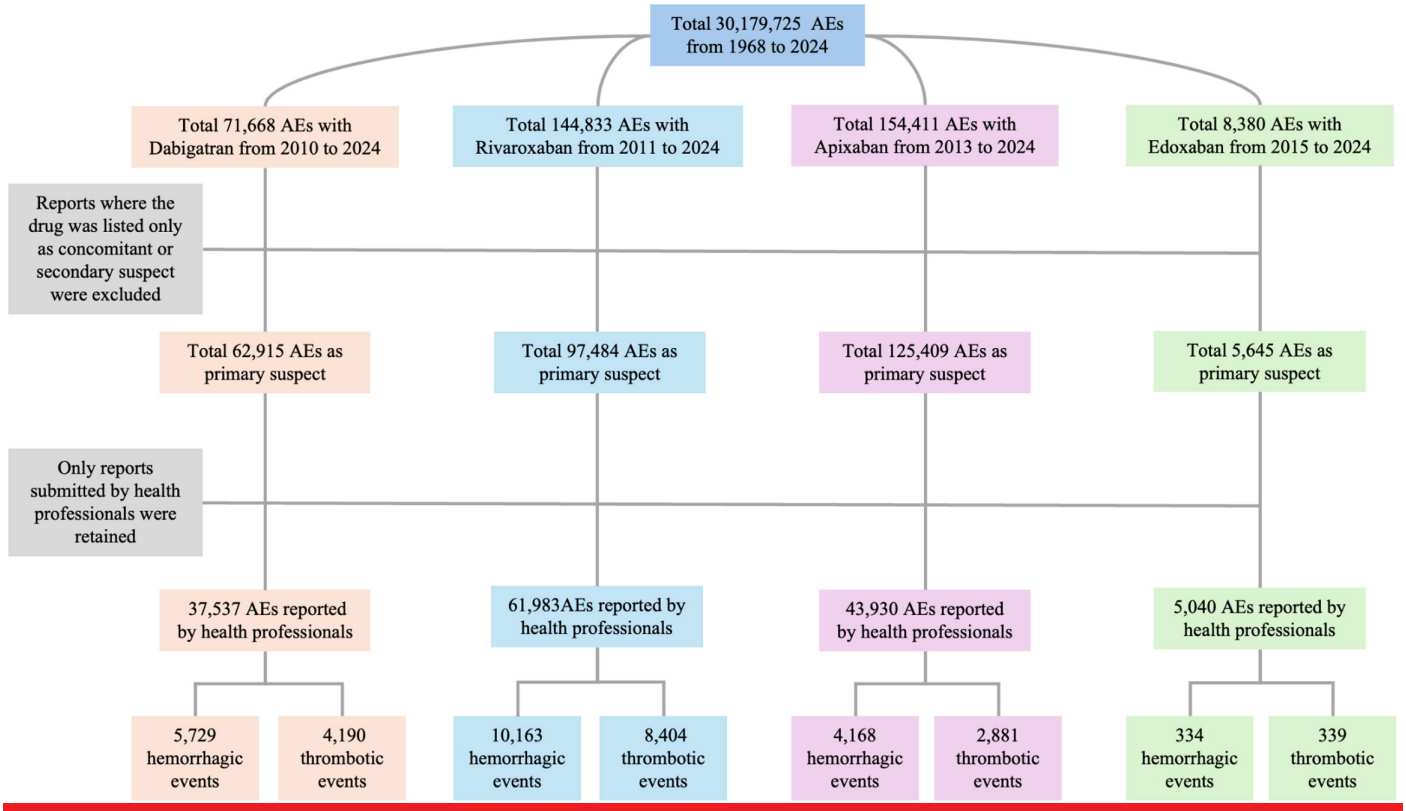

Figure 1. Flowchart of adverse events reported to the FAERS with DOACs. AEs, Adverse events.

exhibited the highest annual number of reported deaths, while edoxaban showed the lowest annual AE counts, reflecting its comparatively lower usage. Demographic characteristics of patients experiencing hemorrhagic and thrombotic disorders related to DOAC use are presented in Table 1. For all DOACs, these AEs were most reported in individuals aged 65-85 years. When overall hemorrhagic and thrombotic AEs were evaluated, male patients receiving dabigatran and apixaban demonstrated a significantly higher reporting frequency ($P < .001$; Figure 3).

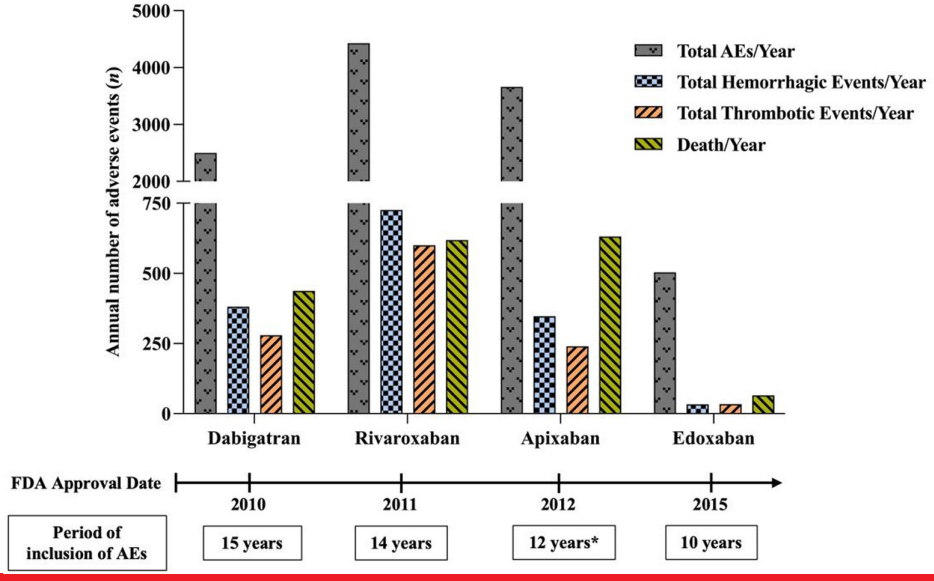

Figure 2. Annual number of adverse events reported with DOACs as the primary suspect. Hemorrhagic, thrombotic, and death-related events are shown on the graph together with annualized total AE numbers. Each drug's FDA approval date served as the basis for calculating the inclusion period (in years). *Apixaban was approved on December 28, 2012; hence, the year 2012 was excluded from the period used to calculate annual averages. AEs, Adverse events.

Table 1. Demographics of Reported Selected Thrombotic and Hemorrhagic AEs with DOACs

Characteristics	Dabigatran (n = 9619)	Rivaroxaban (n = 17806)	Apixaban (n = 6844)	Edoxaban (n = 657)
Serious type				
Serious, n (%)	9530 (99.07)	17755 (99.71)	6755 (98.69)	626 (95.28)
Non-serious, n (%)	89 (0.92)	51 (0.28)	89 (1.30)	31 (4.71)
Sex				
Female, n (%)	3829 (39.80)	7867 (44.18)	2649 (38.70)	160 (24.35)
Male, n (%)	4366 (45.38)	7677 (43.11)	3072 (44.88)	155 (23.59)
Not specified, n (%)	1424 (14.80)	2262 (12.70)	1123 (16.40)	342 (52.05)
Age group				
<18, n (%)	9 (0.09)	18 (0.10)	3 (0.04)	1 (0.15)
18-64, n (%)	1041 (10.82)	3808 (21.38)	833 (12.17)	33 (5.02)
65-85, n (%)	4500 (46.78)	7568 (42.50)	2866 (41.87)	165 (25.11)
>85, n (%)	1030 (10.70)	1396 (7.84)	918 (13.41)	67 (10.19)
Not specified, n (%)	3039 (31.59)	5016 (28.17)	2222 (32.46)	391 (59.51)
Outcome of event				
Died, n (%)	2271 (23.60)	3522 (19.77)	1184 (17.29)	120 (18.26)
Life-threatening, n (%)	1379 (14.33)	1301 (7.30)	887 (12.96)	92 (14.00)
Hospitalized, n (%)	6515 (67.73)	11172 (62.74)	3129 (45.71)	424 (64.53)
Disabled, n (%)	354 (3.68)	388 (2.17)	194 (2.83)	26 (3.95)
Congenital anomaly, n (%)	2 (0.02)	1 (0.00)	2 (0.02)	0 (0.00)
Required intervention, n (%)	52 (0.54)	54 (0.30)	136 (1.98)	2 (0.30)
Other, n (%)	3273 (34.02)	7784 (43.71)	5774 (84.36)	311 (47.33)
Case priority				
Direct, n (%)	572 (5.94)	741 (4.16)	842 (12.30)	11 (1.67)
Expedited, n (%)	7192 (74.76)	11404 (64.04)	5305 (77.51)	615 (93.60)
Non-expedited, n (%)	1855 (19.28)	5661 (31.79)	693 (10.12)	31 (4.71)

Events include gastrointestinal hemorrhage, intracranial hemorrhage, pulmonary embolism, deep vein thrombosis, myocardial infarction, and ischemic stroke.

Hemorrhagic Adverse Events

For gastrointestinal hemorrhage, apixaban (ROR = 2.32, $P < .001$, 95% CI: 2.20-2.45) and edoxaban (ROR = 2.95, $P < .001$, 95% CI: 2.54-3.42) were associated with significantly higher reporting risk compared with dabigatran. In contrast, rivaroxaban demonstrated a significantly lower risk of gastrointestinal hemorrhage (ROR = 0.86, $P < .001$, 95% CI: 0.82-0.89; Table 2). In the sex-based assessment, reports of gastrointestinal hemorrhage were more frequent in females receiving rivaroxaban and edoxaban, although these differences did not reach statistical significance ($P = .949$ and $P = .908$, respectively). However, this difference was significantly in favor of females for dabigatran ($P < .001$; Figure 4).

For intracranial hemorrhage, edoxaban (ROR = 1.76, $P < .001$, 95% CI: 1.49-2.09) and rivaroxaban (ROR = 1.09, $P = .007$, 95% CI: 1.02-1.15) were associated with significantly increased risks compared with dabigatran. The modest increase

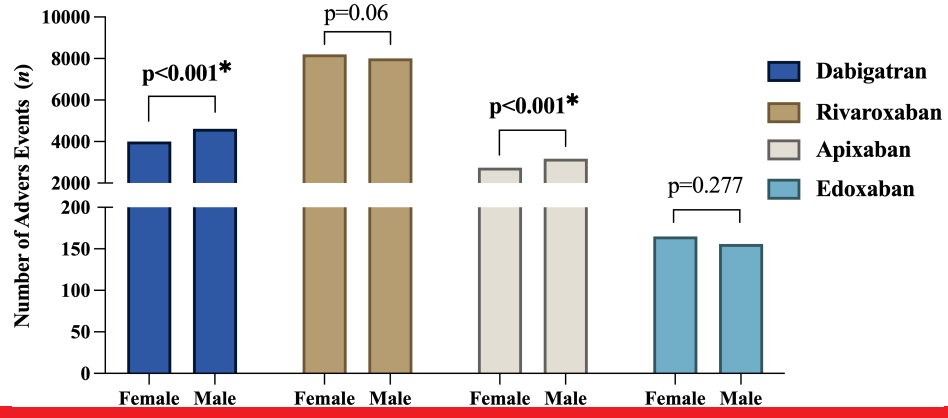

Figure 3. Sex differences of total hemorrhagic and thrombotic adverse events with DOACs. *$P < .05$.

observed with apixaban was not statistically significant ($P = .186$). In sex-stratified analyses, intracranial hemorrhage was reported significantly more frequently in males receiving dabigatran and rivaroxaban ($P = .003$ and $P = .004$, respectively).

Thrombotic Adverse Events

For PE, rivaroxaban (ROR = 0.40, $P < .001$, 95% CI: 0.38-0.44) and apixaban (ROR = 0.91, $P = .039$, 95% CI: 0.83-0.99) were associated with significantly fewer reports than dabigatran. No significant difference was observed for edoxaban ($P = .996$; Table 2). In sex-stratified analyses, PE was reported significantly more often in females receiving rivaroxaban ($P < .001$; Figure 4).

For DVT, rivaroxaban demonstrated a significantly lower reporting risk (ROR = 0.41, $P < .001$, 95% CI: 0.38-0.44), whereas edoxaban was associated with a higher risk (ROR = 1.63, $P < .001$, 95% CI: 1.27-2.09). The difference for apixaban did not exceed the statistical limit ($P = .066$). In sex-based assessments, DVT was reported more frequently in male patients receiving dabigatran, rivaroxaban, and apixaban; however, this difference was statistically significant only for rivaroxaban ($P = .019$).

With respect to MI, all DOACs showed a significantly higher reporting risk than dabigatran: rivaroxaban (ROR = 1.92, $P < .001$, 95% CI: 1.71-2.14), apixaban (ROR = 2.37, $P < .001$, 95% CI: 2.08-2.71), and edoxaban (ROR = 2.51, $P < .001$, 95% CI: 1.81-3.54). When stratified by sex, MI AEs were more frequently reported in male patients for all DOACs. This difference was statistically significant for dabigatran ($P < .001$), rivaroxaban ($P < .001$), and apixaban ($P = .001$) but not significant for edoxaban ($P = .481$).

For ischemic stroke, all DOACs were associated with higher AE reporting compared with dabigatran: apixaban (ROR = 5.12, $P < .001$, 95% CI: 4.62-5.69), rivaroxaban (ROR = 2.35, $P < .001$, 95% CI: 2.19-2.53), and edoxaban (ROR = 2.09, $P < .001$, 95% CI: 1.74-2.51). In sex-based analyses, ischemic stroke was reported significantly more frequently in female patients using rivaroxaban ($P = .018$).

DISCUSSION

This study comprehensively evaluated sex-based differences in hemorrhagic and thrombotic AEs associated with DOACs by analyzing data from the FAERS database. Among DOACs, rivaroxaban accounted for the highest overall number of

Table 2. The Comparison Between Hemorrhagic and Thrombotic Disorder Adverse Events of DOACs as a Primary Suspect Medication

Type of Reaction	DOACs	Cases	Non-cases	ROR (95% CI)	*P*
Gastrointestinal hemorrhage	*Dabigatran*	*3856*	*33681*		
	Rivaroxaban	7305	54678	0.86 (0.82-0.89)	<.001***
	Apixaban	2064	41866	2.32 (2.20-2.45)	<.001***
	Edoxaban	188	4852	2.95 (2.54-3.42)	<.001***
Intracranial hemorrhage	*Dabigatran*	*1873*	*35664*		
	Rivaroxaban	2858	59125	1.09 (1.02-1.15)	.007**
	Apixaban	2104	41826	1.04 (0.98-1.11)	.186
	Edoxaban	146	4894	1.76 (1.49-2.09)	<.001***
Pulmonary embolism	*Dabigatran*	*842*	*36695*		
	Rivaroxaban	3324	58659	0.40 (0.38-0.44)	<.001***
	Apixaban	1082	42848	0.91 (0.83-0.99)	.039*
	Edoxaban	113	4927	1.00 (0.82-1.22)	.996
Deep vein thrombosis	*Dabigatran*	*799*	*36738*		
	Rivaroxaban	3140	58843	0.41 (0.38-0.44)	<.001***
	Apixaban	1019	42911	0.92 (0.83-1.01)	.066
	Edoxaban	66	4974	1.63 (1.27-2.09)	<.001***
Myocardial infarction	*Dabigatran*	*665*	*36872*		
	Rivaroxaban	578	61405	1.92 (1.71-2.14)	<.001***
	Apixaban	332	43598	2.37 (2.08-2.71)	<.001***
	Edoxaban	36	5004	2.51 (1.81-3.54)	<.001***
Ischemic stroke	*Dabigatran*	*1884*	*35653*		
	Rivaroxaban	1362	60621	2.35 (2.19-2.53)	<.001***
	Apixaban	448	43482	5.12 (4.62-5.69)	<.001***
	Edoxaban	124	4916	2.09 (1.74-2.51)	<.001***

*$P < .05$ **$P < .01$ ***$P < .001$; *Dabigatran* was used as the reference among DOACs. Other medications include all non-DOAC primary suspect reports within the same adverse event category. RORs were calculated with 95% CI.
DOAC, direct oral anticoagulant; ROR, reporting odds ratio.
*$P < .05$.
**$P < .01$.
***$P < .001$.

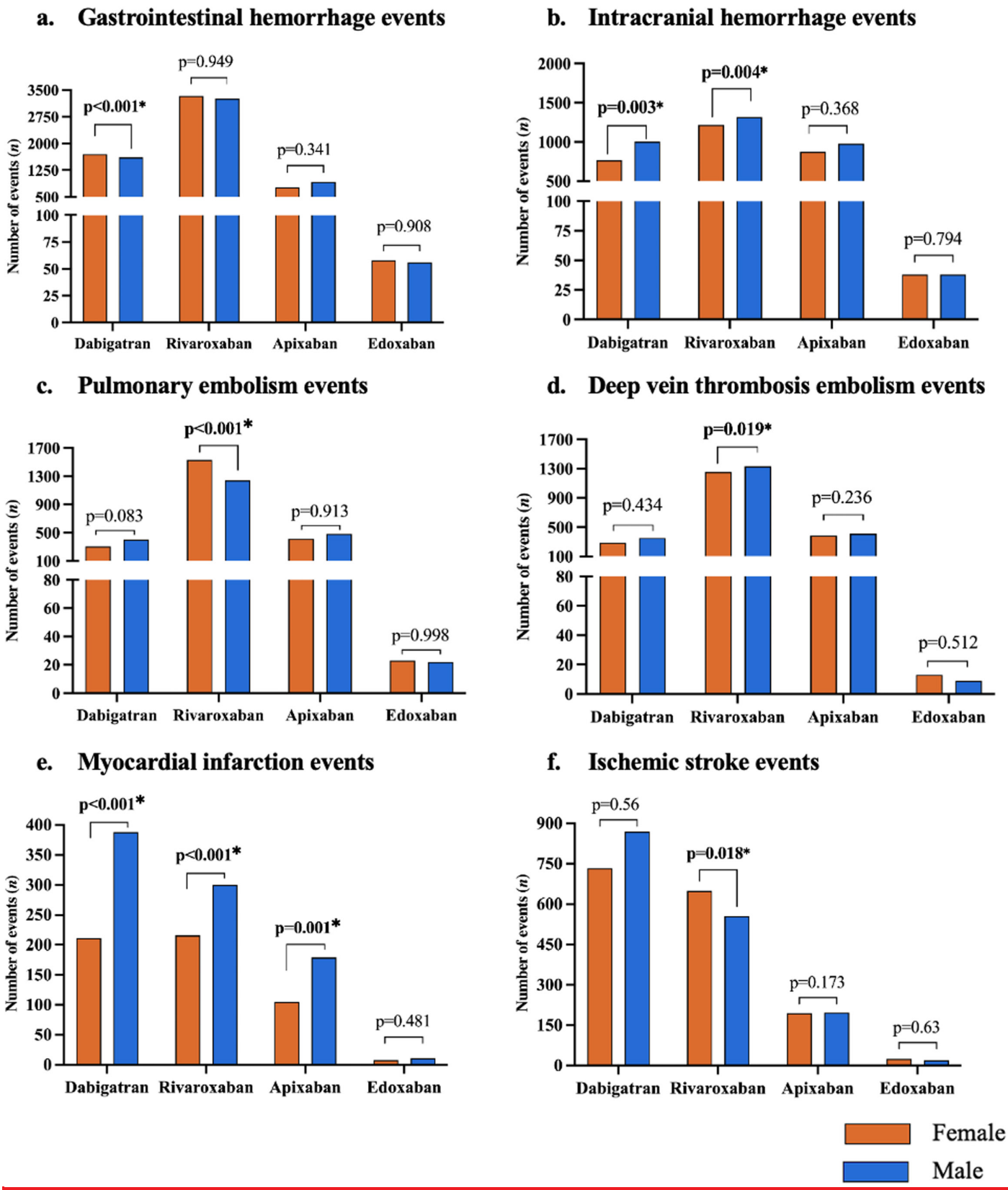

Figure 4. Sex-based differences in hemorrhagic and thrombotic adverse events reported with DOACs. a. Gastrointestinal hemorrhage events, b. Intracranial hemorrhage events, c. Pulmonary embolism events, d. Deep vein thrombosis events, e. Myocardial infarction events, f. Ischemic stroke events. *$P < .05$.

AE reports, whereas apixaban was most frequently associated with fatal outcomes. The most notable finding of this study is the clear sex-specific divergence in AE patterns. Hemorrhagic events were more commonly reported in females, whereas thrombotic events predominated in males. Gastrointestinal hemorrhage was dominant in females, while intracranial hemorrhage was more prominent in males. Additionally, MI and DVT were more frequently observed in males, whereas PE and rivaroxaban-associated ischemic stroke were more prominent in females. These findings suggest that DOAC-related AEs may exhibit sex-specific patterns, potentially influenced by biological differences or pharmacokinetic variability between males and females.

Dabigatran was selected as the reference drug based on its distinct mechanism of action, its status as the first approved drug in this class, and the high number of AE reports available. This approach enabled a structured comparison of the safety profiles of Factor Xa inhibitors versus Factor IIa inhibitor dabigatran. The VKAs were not included due to their longstanding use and well-characterized safety profiles, as well as the increased likelihood of underreporting due to their frequent use.

In the study, rivaroxaban was the DOAC most frequently associated with hemorrhagic AEs, particularly gastrointestinal and intracranial hemorrhages. However, its risk of gastrointestinal hemorrhage was significantly lower compared with dabigatran. This finding contradicts several FAERS-based analyses but aligns more closely with data from the EudraVigilance system.[13,14] Additionally, recent data from Türkiye suggests that low-dose rivaroxaban may be associated with adverse outcomes, highlighting the importance of individualized dosing strategies.[15] Edoxaban demonstrated higher reporting rates for both gastrointestinal and intracranial hemorrhages, consistent with previously published DOAC studies.[16] However, this increase may partly reflect its relatively recent introduction and the greater sensitivity associated with drugs prescribed at lower volumes.[1,17] The frequency of gastrointestinal hemorrhage was significantly increased for apixaban compared to dabigatran, but no significant difference was found regarding intracranial hemorrhage. This result contradicts retrospective studies and pharmacovigilance analyses, in which apixaban was typically associated with a lower risk of bleeding.[14,17] Declining prescription rates and dose adjustments for dabigatran in recent years may partially account for this discrepancy.[18]

Sex-stratified analyses revealed that gastrointestinal hemorrhage was more frequently reported in females, whereas intracranial hemorrhage was significantly more common in males. This suggests that bleeding patterns may be influenced by biological sex. Females exhibit higher rates of gastrointestinal comorbidities such as irritable bowel syndrome and more frequent use of gastro-toxic medications, including SSRIs and NSAIDs, and hormonal differences in mucosal integrity may increase susceptibility to gastrointestinal hemorrhage.[19,20] In addition, slower gastric emptying in females and differences in anticoagulant absorption or metabolism may further increase local gastrointestinal exposure, potentiating the risk.[21] In contrast, intracranial hemorrhage in males may be attributable to a higher prevalence of cerebrovascular risk modifiers such as hypertension, smoking, and alcohol consumption, as well as sex-specific differences in vascular structure and cerebral autoregulation.[22] Clinically, these observations highlight the importance of tailoring anticoagulation management not only according to overall bleeding risk but also to sex-specific bleeding patterns. Enhanced vigilance for gastrointestinal hemorrhage, particularly in older, multimorbid, or polypharmacy-exposed female patients, and stricter monitoring for intracranial complications in males may meaningfully improve the safety of DOAC therapy.

In the study, PE reports were most frequently observed among individuals using dabigatran. The use of dabigatran at lower doses in clinical practice due to bleeding concerns suggests that this finding may be related to relatively reduced anticoagulant efficacy.[18] Among the DOACs, edoxaban had the highest reporting rate for MI. Comparative studies in the literature indicate that edoxaban carries an MI risk similar to warfarin.[23] All DOACs demonstrated an increased signal for MI AEs compared with dabigatran, a finding that is inconsistent with clinical trials conducted in atrial fibrillation (AF) populations.[24] This discrepancy may stem from the fact that the study, unlike clinical trials, evaluated all AEs without any distinction of age, indication, or comorbidity. National registry studies such as the TRAFFIC registry from Türkiye are expected to contribute to the interpretation of these findings, providing more contemporary insights into AF management and anticoagulant safety.[25] Ischemic stroke was most reported in patients using apixaban and rivaroxaban. However, previous clinical trials suggest that both drugs reduce the risk of ischemic stroke and improve prognosis compared to warfarin.[26]

Sex-based assessments revealed that DVT was reported significantly more often in males, whereas PE was more commonly reported in females among patients using rivaroxaban. Males have a greater disposition to DVT, while females exhibit a comparatively higher incidence of PE due to hormonal factors. Furthermore, the elevated PE reporting rate among females may be partially related to suboptimal anticoagulation, given the tendency in clinical practice to prescribe lower anticoagulant doses to females.[27] There were no significant sex differences for PE and DVT reporting with the other DOACs. Across all DOACs, MI AEs were reported more frequently in male patients, a trend consistent with overall clinical observations in the literature.[28] In contrast, it is noteworthy that ischemic stroke was more frequently reported in female patients using rivaroxaban. Rivaroxaban is largely excreted by the renal route, suggesting that pharmacokinetic differences between the sexes may contribute to this pattern. Reduced creatinine clearance, particularly common in older females, may impair drug elimination, potentially leading to subtherapeutic anticoagulation and an increased risk of thromboembolic events.[29] These findings suggest that sex-specific differences should be considered in anticoagulant therapy and dosage adjustments should be based on an individualized approach.

It is important to recognize that the sex-related differences in AE reporting observed in this study may reflect not only underlying biological mechanisms but also variations in prescribing practices, dose selection, treatment intensity, or comorbidity patterns across sexes. Such clinical practice-related trends may influence the apparent dominance of certain AEs in 1 sex. By examining sex-based safety patterns among DOACs using FAERS data up to 2024, this study provides a novel and timely contribution to the literature.

Study Limitations

This study has several limitations inherent to disproportionality analyses based on ROR methodology. Such analyses are subject to reporting biases, incomplete or missing data, exclusion of healthy populations, lack of denominator information, and potential confounding factors. Although reliance on healthcare professional reports may reduce bias, indication-specific information for DOAC use was missing in many cases. Moreover, because prescription data were not available, AE reports could not be normalized to the actual number of drug users. Furthermore, the sex of patients was not specified in more than 50% of edoxaban reports, a limitation that substantially restricted sex-based subgroup analyses for this agent. Finally, the ROR provides only an approximate estimate of disproportionality intended to generate hypotheses regarding potential safety signals; it does not allow for causal interference or direct comparison of risk between drugs.

CONCLUSION

In this study, gastrointestinal hemorrhage emerged as the most frequently reported hemorrhagic AE, particularly among females using dabigatran, whereas intracranial hemorrhage was more commonly reported in males, especially those treated with dabigatran and rivaroxaban. Among thrombotic events, MI and DVT were reported more often in males, while PE and ischemic stroke were reported at higher rates in females, particularly those receiving rivaroxaban. These findings indicate that the evaluation of AE profiles associated with DOACs by sex, organ systems, and other factors may enhance the clinical decision-making process. When developing individualized anticoagulant therapy regimens, physicians may benefit from considering the relationship between sex and system-specific AEs.

Data Availability Statement: The data underlying this article are publicly available from the FDA Adverse Event Reporting System (FAERS): https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard (Accessed August 31, 2025)

Ethics Committee Approval: Not applicable. This study was based on publicly available, de-identified data from a spontaneous reporting system and did not involve human or animal research requiring ethical approval.

Informed Consent: As this research is based on publicly available, de-identified data obtained from the FAERS spontaneous reporting system, it does not involve direct patient participation. Therefore, obtaining verbal or written informed consent from patients is not required.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Ş., E.A.; Design – M.Ş., B.Ş.; Supervision – E.A., M.Ş.; Resources – B.Ş., E.A.; Materials – M.Ş., B.Ş.; Data Collection and/or Processing – M.Ş., B.Ş.; Analysis and/or Interpretation – M.Ş., E.A.; Literature Search – M.Ş., B.Ş.; Writing – M.Ş., E.A.; Critical Review – E.A., B.Ş.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

Statement on Use of AI-Assisted Technologies: Artificial intelligence tools (ChatGPT, OpenAI) were used solely for grammar and language editing. All content was reviewed and verified by the authors, who take full responsibility for the manuscript.

REFERENCES

1. Chen A, Stecker E, A Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. *J Am Heart Assoc*. 2020;9(13):e017559. [CrossRef]
2. Margetić S, Goreta SŠ, Ćelap I, Razum M. Direct oral anticoagulants (DOACs): from the laboratory point of view. *Acta Pharm*. 2022;72(4):459-482. [CrossRef]
3. Bejjani A, Bikdeli B. Direct oral anticoagulants: quick primer on when to use and when to avoid. *Thromb Haemost*. 2025;125(7):611-617. [CrossRef]
4. Ruff CT, Giugliano RP, Braunwald E, 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(9921):955-962. [CrossRef]
5. Raccah BH, Perlman A, Zwas DR, et al. Gender differences in efficacy and safety of direct oral anticoagulants in atrial fibrillation: systematic review and network meta-analysis. *Ann Pharmacother*. 2018;52(11):1135-1142. [CrossRef]
6. Kitapçı MT, Karakuş O, İşli F, Aksoy M, Güvel MC, Uluoğlu C. Evaluation of the potentially inappropriate cardiovascular medication prescription in elderly: a nationwide study in turkey. *Anatol J Cardiol*. 2023;27(6):328-338. [CrossRef]
7. Suvarna V. Phase IV of drug development. *Perspect Clin Res*. 2010;1(2):57-60. [CrossRef]
8. Van Gelder IC, Rienstra M, Bunting KV, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45(36):3314-3414. [CrossRef]
9. United States Food and Drug Administration. FDA Adverse Event Reporting System (FAERS). U.S. Food and Drug Administration. 2025. Available at: https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. .Accessed August 31, 2025.
10. Zhang YJ, Duan DD, Tian QY, Wang CE, Wei SX. A pharmacovigilance study of the association between proton pump inhibitors and tumor adverse events based on the FDA adverse event reporting system database. *Front Pharmacol*. 2024;15:1524903. [CrossRef]
11. Zhao K, Zhao Y, Xiao S, Tu C. Assessing the real-world safety of tralokinumab for atopic dermatitis: insights from a comprehensive analysis of FAERS data. *Front Pharmacol*. 2024;15:1458438. [CrossRef]
12. Van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for

adverse drug reactions. *Pharmacoepidemiol Drug Saf*. 2002;11(1):3-10. [CrossRef]
13. di Biase L, Bonura A, Pecoraro PM, Di Lazzaro V. Real-world safety profile of direct oral anticoagulants (DOACs): disproportionality analysis of major bleeding events. *J Stroke Cerebrovasc Dis*. 2025;34(2):108173. [CrossRef]
14. Moudallel S, van den Eynde C, Malý J, Rydant S, Steurbaut S. Retrospective analysis of gastrointestinal bleedings with direct oral anticoagulants reported to EudraVigilance. *Naunyn Schmiedebergs Arch Pharmacol*. 2023;396(6):1143-1153. [CrossRef]
15. Özlek B. Can differences in non-vitamin K antagonist oral anticoagulant preferences result in varying clinical outcomes in patients with atrial fibrillation? *Anatol J Cardiol*. 2024;28(1):68-69. [CrossRef]
16. Neha R, Subeesh V, Beulah E, Gouri N, Maheswari E. Existence of notoriety bias in FDA Adverse Event Reporting System database and its impact on signal strength. *Hosp Pharm*. 2019;56(3):152-158. [CrossRef]
17. Shimada K, Hasegawa S, Nakao S, 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):1295-1303. [CrossRef]
18. Wheelock KM, Ross JS, Murugiah K, Lin Z, Krumholz HM, Khera R. Clinician trends in prescribing direct oral anticoagulants for US medicare beneficiaries. *JAMA Netw Open*. 2021;4(12):e2137288. [CrossRef]
19. De Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. *Arch Gen Psychiatry*. 2008;65(7):795-803. [CrossRef]
20. Heitkemper M, Jarrett M. Irritable bowel syndrome: does gender matter? *J Psychosom Res*. 2008;64(6):583-587. [CrossRef]
21. Anderson GD. Gender differences in pharmacological response. *Int Rev Neurobiol*. 2008;83:1-10. [CrossRef]
22. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-123. [CrossRef]
23. Liang X, Xie W, Lin Z, Liu M. The efficacy and safety of edoxaban versus warfarin in preventing clinical events in atrial fibrillation: a systematic review and meta-analysis. *Anatol J Cardiol*. 2021;25(2):77-88. [CrossRef]
24. Grajek S, Kałużna-Oleksy M, Siller-Matula JM, Grajek M, Michalak M. Non-vitamin K antagonist oral anticoagulants and risk of myocardial infarction in patients with atrial fibrillation with or without percutaneous coronary interventions: a meta-analysis. *J Pers Med*. 2021;11(10):1013. [CrossRef]
25. Karabay CY, Taşolar H, Ülgen Kunak AÜ, et al. Turkish real life atrial fibrillation in clinical practice: TRAFFIC study. *Anatol J Cardiol*. 2024;28(2):87-93. [CrossRef]
26. Chun KH, Lee H, Hong JH, Seo KD. Prognosis of patients with ischemic stroke with prior anticoagulant therapy: direct oral anticoagulants versus warfarin. *J Am Heart Assoc*. 2024;13(15):e034698. [CrossRef]
27. Wiegers HMG, van Es J, Pap ÁF, Lensing AWA, Middeldorp S, Scheres LJJ. Sex-specific differences in clot resolution 3 weeks after acute pulmonary embolism managed with anticoagulants—a substudy of the EINSTEIN-PE study. *J Thromb Haemost*. 2021;19(7):1759-1763. [CrossRef]
28. Schulte KJ, Mayrovitz HN. Myocardial infarction signs and symptoms: females vs. males. *Cureus*. 2023;15(4):e37522. [CrossRef]
29. Yong CM, Tremmel JA, Lansberg MG, Fan J, Askari M, Turakhia MP. Sex differences in oral anticoagulation and outcomes of stroke and intracranial bleeding in newly diagnosed atrial fibrillation. *J Am Heart Assoc*. 2020;9(10):e015689. [CrossRef]