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Hemorrhage risk associated with triple antithrombotic therapy: a focused real-world pharmacovigilance disproportional analysis study

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Abstract

Background Triple antithrombotic therapy (TAT), combining dual antiplatelet therapy (DAPT) with oral anticoagulants, is commonly used in patients requiring long-term anticoagulation following acute coronary syndrome or percutaneous coronary intervention. However, TAT may increase the risk of hemorrhage. There is a dearth of data regarding the risks of bleeding with various oral anticoagulants in TAT in comparison with DAPT and individual anticoagulants and antiplatelets due to which we carried out the present study examining the real-world pharmacovigilance data.

Methods Data were extracted from the USFDA Adverse Event Reporting System (AERS) from March 2004 to June 2024 using the Standardized MedDRA Query (SMQ) code for "haemorrhages." We employed the "case-non-case" approach in disproportionality analysis to detect safety signals for hemorrhage among anticoagulant, antiplatelet, dual antiplatelet and triple antithrombotic combinations. Reports including combinations of DAPT (acetylsalicylic acid and clopidogrel) with oral anticoagulants (acenocoumarol, apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin) were analyzed. Signal detection used both frequentist (reporting odds ratio [ROR], proportional reporting ratio and Bayesian (Bayesian Confidence Propagation Neural Network, Multi-Item Gamma Poisson Shrinker algorithms. The lower limit of 95% confidence interval of ROR above 1 indicates higher reporting risk of bleeding. Following outcomes were evaluated for each TAT: death, disability and hospitalization.

Results Of 20,626 unique reports, 812 involved TAT, 3,820 DAPT, and 15,995 individual antiplatelets. Most cases occurred in elderly patients (age ≥ 65 years) with a predominance of male patients. Rivaroxaban combined with DAPT presented the highest hemorrhage signal (ROR: 82.84; 95% CI, 60.77–112.92), while apixaban showed the lowest (ROR: 13.11; 95% CI, 9.39–18.3) and the other anticoagulants are as follows: warfarin (ROR: 15.96; 95% CI: 18.36), dabigatran (ROR: 27.32; 95% CI: 20.03–37.26) and acenocoumarol (ROR: 43.98; 95% CI: 17.21–112.4). Mortality and hospitalization rates varied significantly among treatments, with rivaroxaban linked to the highest mortality.

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Conclusion This study highlights the elevated hemorrhage risk associated with TAT, particularly with rivaroxaban, while apixaban appears safer in terms of bleeding and mortality. These findings underscore the need for cautious monitoring of bleeding outcomes with anticoagulant regimens, particularly rivaroxaban combinations for optimizing patient outcomes. However, the signals obtained in this study need to be validated in future trials.

Keywords Warfarin, Apixaban, Aspirin, Clopidogrel, Dabigatran, Dipyridamole, Cilostazol

Introduction

Dual antiplatelet therapy, typically involving acetylsalicylic acid and clopidogrel, is commonly administered to patients, especially those undergoing percutaneous coronary intervention (PCI) which has been shown to reduce risks of stent thrombosis and major adverse cardiovascular events [1]. In patients undergoing PCI who also have atrial fibrillation, anticoagulants are often necessary to prevent stroke [2]. According to the 2020 American College of Cardiology (ACC) expert consensus on antiplatelet and anticoagulant therapy, clopidogrel is recommended for use with anticoagulants due to its relatively lower bleeding risk among thienopyridine antiplatelet drugs, with acetylsalicylic acid not to exceed a daily dose of 100 mg [3, 4]. The combination of an anticoagulant with dual antiplatelet therapy is known as "triple antithrombotic therapy" [5].

However, while effective, triple antithrombotic therapy carries a heightened risk of bleeding due to which they are limited for a shorter duration of one week [6]. In a large study on the Danish population ($n = 118{,}606$), the hazard ratio (95% confidence interval) for bleeding risks was 0.93 (0.88–0.98) with acetylsalicylic acid, 1.06 (0.87–1.29) with clopidogrel alone, 1.66 (1.34–2.04) with both, 1.83 (1.72–1.96) for warfarin with acetylsalicylic acid, 3.08 (2.32–3.91) for warfarin with clopidogrel, and 3.70 (2.89–4.76) for triple therapy (warfarin, aspirin, clopidogrel) [7]. Additionally, a recent meta-analysis of randomized clinical trials comparing dual therapy (an anticoagulant plus an antiplatelet) with triple therapy revealed significantly lower bleeding risks in the dual therapy group (746/5470 vs. 950/4710; odds ratio: 0.59, 95% CI 0.53–0.65; number needed to harm for triple therapy was 16) [8]. However, this meta-analysis only included four trials, each involving a different direct oral anticoagulant (DOAC), such as rivaroxaban, dabigatran, edoxaban, or apixaban, versus warfarin. Another study involving 575 patients with drug-eluting coronary stents found that bleeding was significantly more common with triple therapy compared to dual antiplatelet therapy (38.0% vs. 12.8%), with major bleeding also higher in the triple therapy group (18.0% vs. 2.7%) [9]. In contrast, a randomized clinical trial comparing edoxaban with vitamin K antagonists demonstrated a non-inferior bleeding rate with no significant differences in ischemic events [10]. The 2023 European Society of Cardiology (ESC) guidelines emphasize that decisions regarding antithrombotic therapy should be guided by a careful assessment of the balance between antithrombotic benefits and bleeding risks [11].

Despite the well-documented bleeding risks of anticoagulants and antiplatelets, limited data exist on bleeding risks with DOACs in triple antithrombotic therapy. The DOACs are more selective to a certain coagulation factor, either thrombin or factor Xa. The lack of real-world evidence on the relative risks of bleeding associated with various anticoagulants used in combination with dual antiplatelet therapies, particularly in high-risk populations such as patients with atrial fibrillation undergoing PCI, poses a significant challenge for physicians and limits informed decision-making [12]. There exist no clear guidelines on the choice of anticoagulant drug to be combined with antiplatelet therapy due to knowledge gap between the risk of bleeding and thrombosis [13].

The United States Food and Drug Administration Adverse Event Reporting System (USFDA AERS) contains a comprehensive collection of adverse event reports, both mandatory manufacturer submissions and spontaneous reports from healthcare providers [14]. This database serves as a crucial resource for identifying safety signals, establishing monitoring strategies, and generating hypotheses for further investigation [15]. Disproportionality analysis, a statistical approach comparing specific adverse event reports associated with drugs against reports for other drugs, is commonly used to detect safety signals [16]. Several studies have leveraged disproportionality analysis within the USFDA AERS to uncover previously unknown drug-adverse event relationships [17]. Adverse events associated with drugs identified through randomized clinical trials are often limited by constraints such as sample size, the duration of participant follow-up, and strict eligibility criteria [18]. In contrast, real-world pharmacovigilance studies, which reflect everyday clinical practice without these restrictions, provide valuable complementary evidence on adverse drug events. These studies play a crucial role in refining therapeutic objectives and enhancing the understanding of drug safety profiles [19]. Given the existing gap in understanding the relative bleeding risks of DOACs compared to warfarin in triple antithrombotic therapy, we conducted this study using USFDA AERS.

Methods

Data source

We obtained relevant data from the USFDA AERS using the Standardized Medical Dictionary for Regulatory Activities Query (SMQ) code 20,000,038 termed "haemorrhages" [20]. This SMQ (broad) has been defined as "*Haemorrhage is defined as the escape of blood from the vessels; bleeding. Small haemorrhages are classified according to size as petechiae (very small), purpura (up to 1 cm), and ecchymoses (larger). A large accumulation of blood within a tissue is called a hematoma*" [20]. The list of preferred terms included in this SMQ are listed in the Electronic Supplementary Table 1. The reports that were collected spanned over 82 quarters, between March 2004 and June 2024.

Data processing

We included individual case safety reports (ICSRs) with the SMQ code for hemorrhage, without restrictions on demographic characteristics. For dual antiplatelet therapy, we focused on the combination of acetylsalicylic acid and clopidogrel. The USFDA approved oral anticoagulants were considered in combination with dual antiplatelet therapy as part of triple antithrombotic therapy: acenocoumarol, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, and warfarin. Reports documenting hemorrhagic events for these dual antiplatelet and anticoagulant combinations were included and compared with those reporting hemorrhage involving acetylsalicylic acid, clopidogrel, or the combined DAPT.

Following USFDA recommendations, we deduplicated reports by first sorting using the Case_ID, arranging them chronologically, and retaining only the latest report with the highest FDA_DT (Individual Safety Report number). Older reports were excluded [21]. In each report, the role of the suspected drug was categorized by the USFDA as either primary suspect, secondary suspect, interacting, or concomitant. Only reports with acetylsalicylic acid and clopidogrel as the primary suspect drugs, and any role for drug combinations, were included. All drug names were specified in non-proprietary format. Deduplication was conducted separately for each anticoagulant and dual antiplatelet pair. Adverse event reporting systems inherently generate duplicate entries due to multiple stakeholders, healthcare providers, patients, and pharmaceutical companies, documenting the same incident. The deduplication methodology mitigated this data redundancy, ensuring more accurate representation of adverse event frequencies and enhancing the reliability of the signal analysis. We extracted the following characteristics for each report: age, gender, year, and country of reporting.

Data mining algorithms

We employed the "case-non-case" approach in disproportionality analysis to detect safety signals for hemorrhage among anticoagulant, antiplatelet, dual antiplatelet and triple antithrombotic combinations [22]. This approach compares the frequency of hemorrhagic events in cases (those exposed to relevant drugs) to non-cases (other events reported for the drugs of interest). The Openvigil 2.1 platform was used to retrieve data on the relevant drug-hemorrhage pairs, including demographic details. We applied both frequentist and Bayesian approaches to signal detection, encompassing four data mining algorithms.

In the frequentist analysis, we calculated the Reporting Odds Ratio (ROR) and the Proportional Reporting Ratio (PRR). The ROR was estimated by the ratio of odds of reporting bleeding with the drug/s of interest upon the odds of all other adverse events with the same drug/s of interest over odds ratio of the same with all other drugs. The PRR was estimated as the proportion of reports with bleeding with drug/s of interest upon the proportion of all other adverse events with the same drug/s of interest upon the same proportion for all other drugs. According to Evan's criteria, a signal was detected if the drug-event combination met the following criteria: at least three reports, PRR ≥ 2, and a Chi-square (χ^2) value ≥ 4 [23].

The Bayesian approach included the Bayesian Confidence Propagation Neural Network (BCPNN) and the Multi-Item Gamma Poisson Shrinker (MGPS). In BCPNN, we calculated the Information Component (IC), representing the logarithmic ratio of the joint probability of anticoagulant or dual antiplatelet and triple antithrombotic combinations with hemorrhage compared to the product of their individual probabilities, based on USFDA AERS data. A signal was identified when the lower 95% CI limit of the IC (IC025) exceeded zero. In MGPS, we used the Empirical Bayes Geometric Mean (EBGM), with a signal identified if the lower 95% CI limit (EBGM05) exceeded 2. According to the recommendations of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII, there are no universally accepted gold-standard methods for signal detection, and Bayesian approaches are considered more effective in reducing false-positive findings [24].

Outcomes in each unique report were categorized as death, disability, or hospitalization (initial or prolonged). These indices and outcomes were also calculated for DAPT, and for acetylsalicylic acid and clopidogrel individually, to enable comparative analysis. All study methods adhered to the Reporting of a Disproportionality analysis for drUg Safety signal detection using spontaneously reported adverse events in Pharmacovigilance (READUS-PV) guidelines [25].

Statistical analysis

Descriptive statistics were used for representing demographic variables. Means (SD) were used for calculating numerical variables, while proportions (%) were used for categorical variables. Volcano plots were generated by plotting the log2(ROR) on x-axis and -log10(*P*-values) on y-axis for identifying the hemorrhage risk with various triple anti-thrombotic therapies. The Chi-square test was employed for assessing the significance of outcome distributions across dual antiplatelet/anticoagulant combinations for hemorrhage. The statistical analyses were performed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.).

Results

Search results

The initial search identified a total of 29,153,222 reports in the USFDA AERS database, of which 20,626 unique reports met the inclusion criteria and were used in the final analysis (Fig. 1). These reports included 812 involving anticoagulant combinations with dual antiplatelet therapy, 3,820 for dual antiplatelet therapy alone, and 15,995 involving aspirin or clopidogrel alone. There were no reports of hemorrhage associated with betrixaban in combination with dual antiplatelet therapy, and only one report involved edoxaban. Key demographic and clinical characteristics of the included reports for anticoagulant combinations with dual antiplatelet therapy, dual antiplatelet therapy alone, and individual aspirin or clopidogrel cases are summarized in Table 1. Most cases occurred in elderly patients (age ≥ 65 years) with a predominance of male patients, and most reports originated from the United States.

Signal detection measures with aspirin and clopidogrel alone, and dual antiplatelet combinations

Among all adverse event reports, the proportion of hemorrhage reports was 0.2 for acetylsalicylic acid, 0.5 for clopidogrel, and 0.3 for dual antiplatelet therapy. Signal detection, as measured by the ROR with 95% CI, showed elevated signals for hemorrhage: ROR [95% CI] for acetylsalicylic acid was 4.2 [4.0, 4.3], for clopidogrel was 17.6 [17.1, 18.0], and for dual antiplatelet therapy was 6.4 [6.2, 6.7]. Additional frequentist and Bayesian signal detection measures, as outlined in Table 2, indicated positive hemorrhage signals for these therapies.

Signal detection measures for triple antithrombotic therapies

The proportion of hemorrhage reports relative to total adverse event reports for each dual antiplatelet-anticoagulant combination are depicted in Fig. 2. Among triple antithrombotic therapies, the combination of dual antiplatelet therapy with rivaroxaban showed the highest proportion of hemorrhage reports, followed by acenocoumarol combinations while the least was observed with apixaban combination. Both frequentist and Bayesian analyses indicated hemorrhage signals across all combinations of anticoagulants with dual antiplatelet therapy (Table 2). The highest number of reports was associated with warfarin in combination with dual antiplatelet therapy, followed by rivaroxaban. ROR values for each dual antiplatelet-anticoagulant combination are plotted

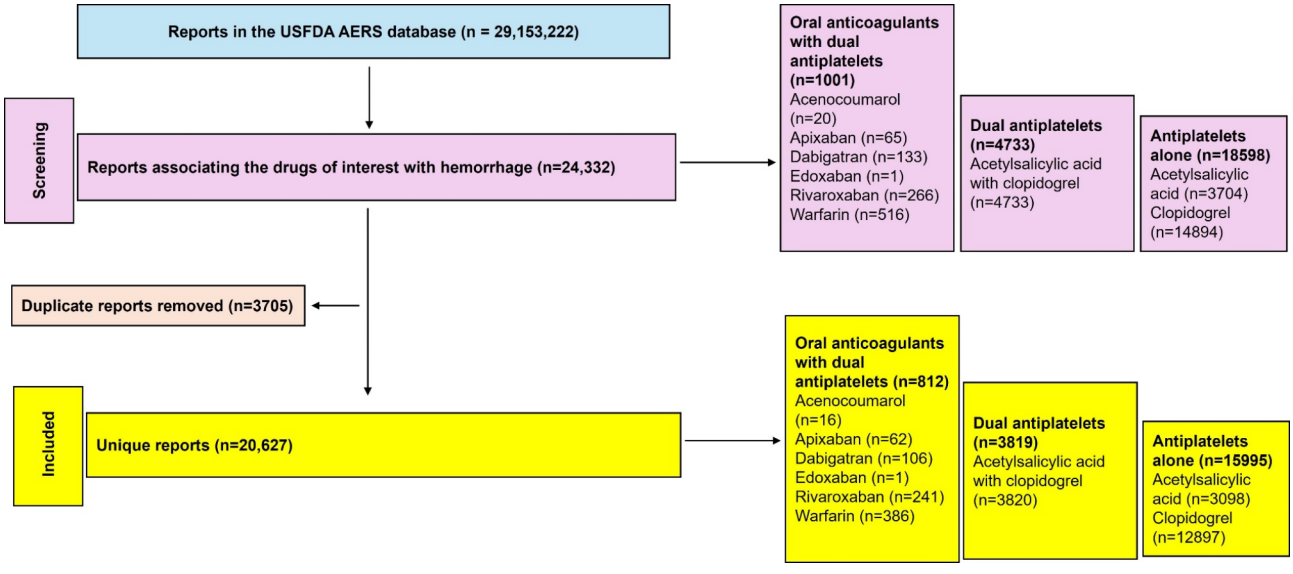

Fig. 1 Study flow diagram
A total of 20,627 unique reports were included in this study analyzing the risk of hemorrhage with anticoagulant/dual antiplatelets, dual antiplatelets, aspirin and clopidogrel alone

Table 1 Demographic characteristics of patients in the reports

Variables		Triple anti-thrombotic therapies (*n* = 812)	Dual antiplatelets (*n* = 3820)	Acetylsalicylic acid (*n* = 3098)	Clopidogrel (*n* = 12897)
Age categories [n (%)]	≤ 17 years	None	5 (0.1)	36 (1.2)	15 (0.1)
	18–64 years	157 (19.3)	945 (24.7)	768 (24.8)	2179 (16.9)
	≥ 65 years	504 (62.1)	2018 (52.8)	1602 (51.7)	6284 (48.7)
	Not reported	151 (18.6)	852 (22.3)	692 (22.3)	4419 (34.3)
Mean (SD) age (years)		70.9 (10.9)	69 (12.6)	67.8 (16.9)	71.8 (12.6)
Median (range) age (years)		72 (31–100)	70 (1-100)	71 (0-100)	74 (0-103)
Gender distribution [n (%)]	Male	507 (61.2)	2211 (57.9)	1562 (50.4)	6036 (46.8)
	Female	256 (31.5)	1366 (35.7)	1256 (40.5)	3885 (30.1)
	Unknown	59 (7.3)	243 (6.4)	280 (9.1)	2976 (23.1)
Year of receiving the report [n (%)]	2004–2008	177 (21.8)	1551 (40.6)	1168 (37.7)	694 (5.4)
	2009–2012	314 (38.7)	1621 (42.4)	1009 (32.6)	570 (4.4)
	2013–2016	62 (7.6)	174 (4.6)	163 (5.3)	4758 (36.9)
	2017–2020	196 (24.1)	306 (8)	602 (19.4)	4052 (31.4)
	2021–2024 (June)	63 (7.8)	166 (4.3)	156 (5)	2823 (21.9)
Top reporting countries [n (%)]	USA	568 (70)	2117 (55.4)	1727 (55.7)	5928 (46)
	Others	254 (30)	1703 (45.6)	1371 (44.3)	6969 (54)

Table 2 Signal detection measures for the drugs of interest

Anticoagulants and antiplatelets	RRR	PRR	95% Lower limit PRR	95% Upper limit PRR	Signal by frequentist approach	Number of reports	IC025	EBGM05	Signal by Bayesian approach
Antiplatelet drugs alone									
Acetylsalicylic acid	3.5	3.5	3.4	3.6	Positive	3098	1.7	3.4	Positive
Clopidogrel	8.9	9.1	9	9.2		12,897	3.1	8.7	
Dual antiplatelets									
Acetylsalicylic acid with clopidogrel	4.9	4.9	4.8	5.1	Positive	3820	2.2	4.7	Positive
Triple antithrombotic therapies (with acetylsalicylic acid and clopidogrel)									
Acenocoumarol	12.7	12.7	9.9	16.4	Positive	16	1.4	5	Positive
Apixaban	7.7	7.7	6.4	9.3		62	2.1	5.6	
Dabigatran	10.9	10.9	9.7	12.3		106	2.5	8	
Rivaroxaban	14.1	14.1	13.3	14.9		241	2.9	10.6	
Warfarin	8.6	8.6	8.1	9.2		386	2.7	7.5	

PRR: Proportional reporting ratio; RRR: Relative reporting ratio; IC: Information component; and EBGM: Empirical Bayes geometric mean

in Fig. 3, revealing that apixaban had the lowest ROR (13.11; 95% CI: 9.39–18.3), followed by warfarin (15.96; 95% CI: 13.88–18.36), while rivaroxaban (82.84; 95% CI: 60.77-112.92) showed the highest ROR among the anticoagulants studied. Volcano plot also reveals that the maximum risk of hemorrhage with rivaroxaban amongst the triple anti-thrombotic therapies (Fig. 4). Male predominance, particularly among the elderly, was evident across all anticoagulant and antiplatelet drug combinations (Electronic Supplementary Table 2).

Comparison of reported outcome measures

The distribution of reported outcomes, including death, life-threatening events, and hospitalizations, is summarized in Table 3. Statistically significant differences in outcome distributions were observed across antiplatelets and their combinations with oral anticoagulants. Among dual antiplatelet-anticoagulant combinations, the highest mortality was observed with rivaroxaban, while acenocoumarol and apixaban showed the lowest mortality rates.

Discussion

Key findings

In this study, we analyzed 20,626 unique adverse event reports from the USFDA AERS related to anticoagulant and dual antiplatelet therapies. Most reports originated from the United States, with predominant elderly, male patient demographic. A signal detection analysis revealed elevated hemorrhage signals for acetylsalicylic acid, clopidogrel, dual antiplatelet therapy, and triple antithrombotic therapies. When dual antiplatelets were combined

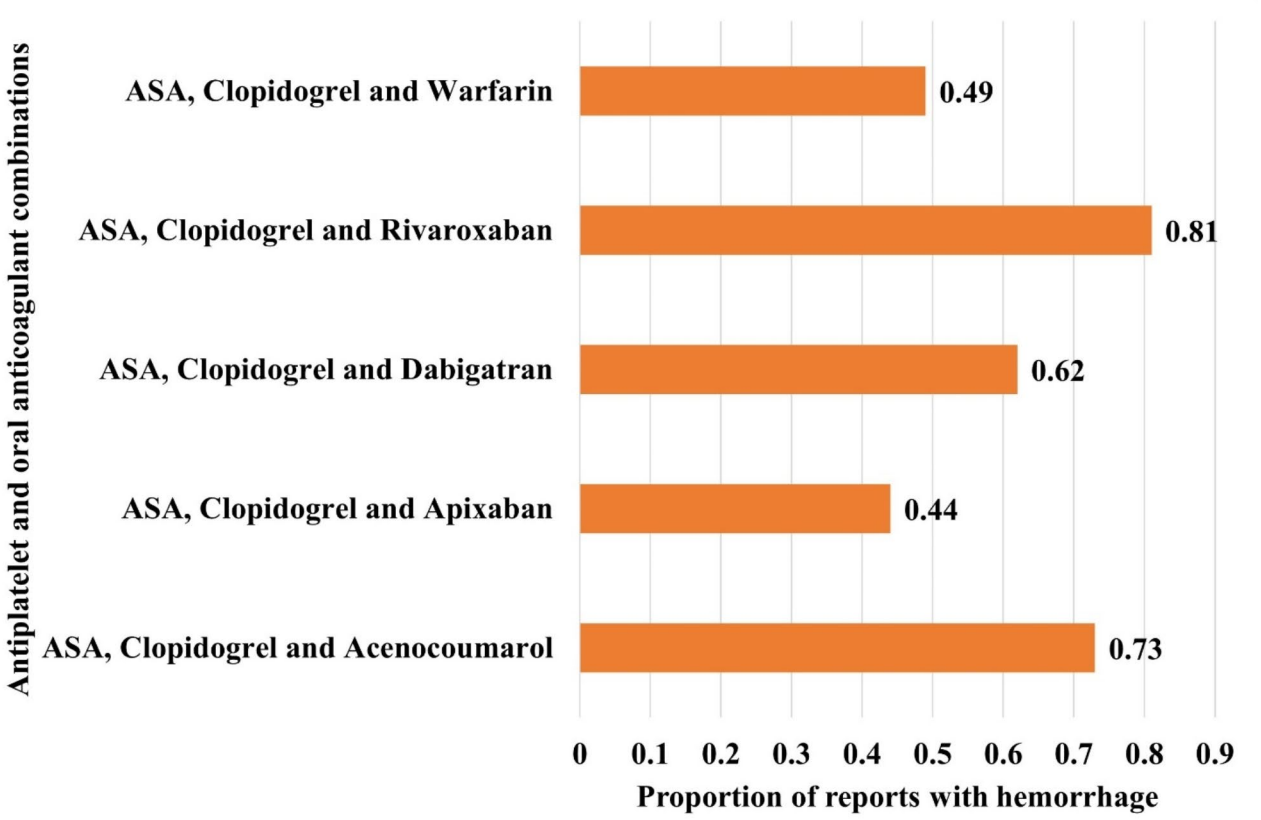

Fig. 2 Proportion of reports with hemorrhage associated with triple anti-thrombotic therapy
ASA: Acetylsalicylic acid
The horizontal bars represent the proportions of reports with hemorrhage compared to total reported adverse events with various triple anti-thrombotic therapies

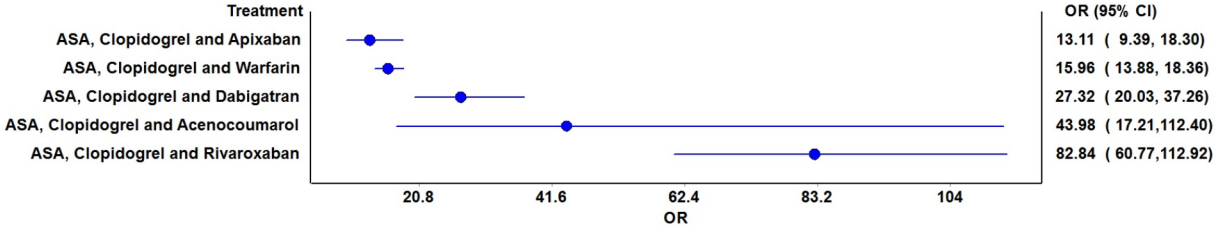

Fig. 3 Reporting odds ratios of various triple anti-thrombotic therapies
ASA: Acetylsalicylic acid
The blue circles represent the reporting odds ratio (ROR) and the horizontal blue lines represent the 95% CI for ROR

with oral anticoagulants, rivaroxaban demonstrated the highest hemorrhage signal, while apixaban showed the lowest. Moreover, mortality and hospitalization rates varied significantly across treatments, with rivaroxaban demonstrating the highest mortality among combined therapies, while acenocoumarol and apixaban showed relatively lower risks.

The findings of this study underscore the importance of individualized antithrombotic therapy, particularly in elderly or renally impaired patients who are at higher risk of adverse outcomes. Clinicians should carefully weigh the risks and benefits of antithrombotic regimens, prioritizing therapies with lower hemorrhage signals and mortality risks when appropriate. For instance, apixaban, which demonstrated the lowest hemorrhage signal and relatively favorable mortality outcomes in combination therapies, may be a potentially safer option in vulnerable populations. Conversely, the elevated hemorrhage signal and higher mortality associated with rivaroxaban highlight the need for cautious use, particularly in high-risk groups. Furthermore, dual or triple antithrombotic therapies should be employed judiciously, with

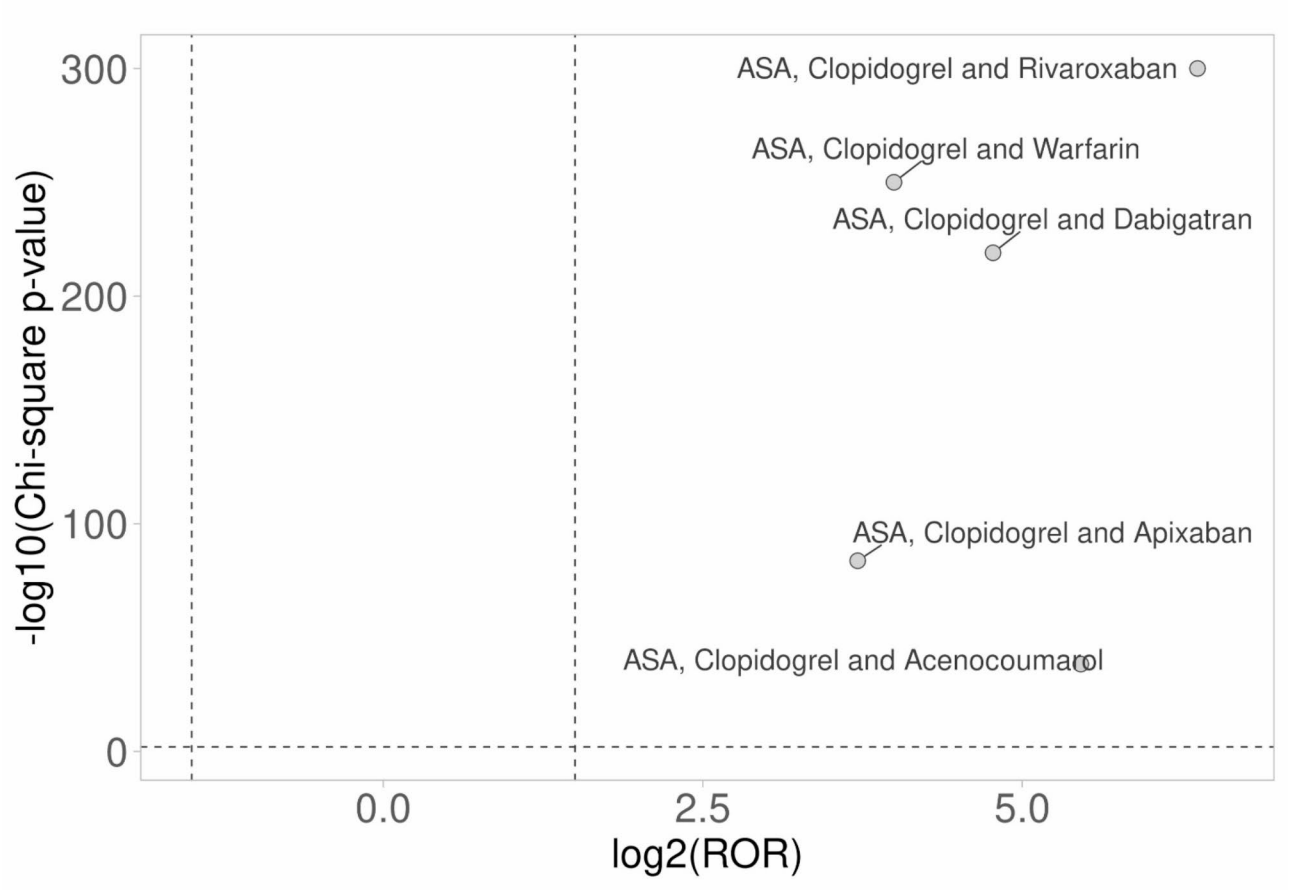

Fig. 4 Volcano plots for ranking the risk of hemorrhage with triple anti-thrombotic therapies
The grey circles represent the significance of hemorrhage risk with each anti-thrombotic therapy, and as farther they lie on both the x- and y-axes, more significant is the association of triple anti-thrombotic therapy with the risk of hemorrhage

Table 3 Comparison of the key reported outcomes between the antiplatelet drugs, dual antiplatelet therapy and triple anti-thrombotic therapies

Drugs	Death [*n* (%)]	Life threatening [*n* (%)]	Hospitalization [*n* (%)]	Statistical significance
ASA	480 (15.5)	230 (7.4)	1843 (59.5)	$\chi 2$: 94.8; df: 14; $p < 0.0001$
Clopidogrel	1538 (11.1)	1059 (8.2)	6446 (50)	
ASA and Clopidogrel	673 (17.6)	383 (10)	2209 (57.8)	
ASA, Clopidogrel and Acenocoumarol	None	1 (4.5)	15 (68.2)	
ASA, Clopidogrel and Apixaban	6 (4.3)	13 (9.3)	29 (20.7)	
ASA, Clopidogrel and Dabigatran	32 (18.8)	6 (3.5)	86 (50.6)	
ASA, Clopidogrel and Rivaroxaban	63 (21.1)	8 (2.7)	206 (68.9)	
ASA, Clopidogrel and Warfarin	56 (7.1)	19 (2.4)	255 (32.5)	

ASA: Acetylsalicylic acid

close monitoring for bleeding complications. This study emphasizes the critical role of tailoring antithrombotic strategies to patient-specific factors, such as age, renal function, and comorbidities, to optimize safety and therapeutic outcomes.

Comparison with existing literature

Triple antithrombotic therapy is frequently prescribed for patients with acute coronary syndrome who also require long-term oral anticoagulation. In such cases, DOACs are often preferred for initial therapy [26]. Our findings align with previous studies indicating that apixaban carries a lower risk of hemorrhage and mortality, whereas rivaroxaban is associated with a higher

risk. Lopes et al. observed that in patients with atrial fibrillation undergoing PCI or experiencing ACS, apixaban had a lower incidence of bleeding (10.5% vs. 14.7%) and mortality (23.5% vs. 27.4%) compared to vitamin K antagonists [27]. Another registry-based study in the US revealed that patients on apixaban with acetylsalicylic acid had a relatively lower rate of bleeding compared to rivaroxaban combination (22.5 vs. 39.3/100 patient-years; RR, 0.6; 95% CI, 0.5–0.7) [28]. Further research comparing apixaban and vitamin K antagonists in combination with dual antiplatelet therapy showed a 2.4% absolute risk reduction in bleeding and hospitalization events within the first 30 days post-therapy initiation, with a continued reduced risk up to six months [29]. Additionally, patients with renal impairment have shown increased susceptibility to hemorrhage with TAT, especially with warfarin, which has been linked to a high risk of intracranial and fatal bleeding. As a result, warfarin is frequently discontinued in these patients, with DOACs like apixaban or rivaroxaban often considered safer options due to their reduced renal excretion requirements [9, 30, 31]. Apixaban undergoes elimination by multiple pathways including hepatic metabolism, renal excretion and biliary excretion and only 27% depends on renal excretion [32]. Given these findings and our observations in this study, apixaban appears to be the preferred option for patients with renal dysfunction among TATs.

Our study highlighted a higher risk of bleeding with rivaroxaban when used in combination with dual antiplatelet therapy, consistent with several meta-analyses. One meta-analysis of phase II/III clinical trials on apixaban and rivaroxaban in TATs reported pooled hazard ratios [95% CI] for bleeding of 2.27 [1.28, 4.02] for apixaban and 3.46 [2.09, 5.73] for rivaroxaban at a dose of 2.5 mg twice daily, with further elevation at 5 mg twice daily [33]. Additionally, a large real-world study among 29,338 patients with non-valvular atrial fibrillation found that apixaban presented a lower bleeding risk (adjusted hazard ratio: 0.52, 95% CI: 0.30–0.89) compared to rivaroxaban, which had a similar bleeding risk to warfarin (adjusted hazard ratio: 1.13, 95% CI: 0.91–1.41) [34]. A comprehensive registry analysis evaluated outcomes in 13,435 patients receiving anticoagulation therapy across six Michigan centers [35]. The study population comprised 3,536 apixaban users, 1,395 rivaroxaban users, and 8,504 warfarin users treated for VTE, non-valvular AF, or both conditions. The findings revealed significantly higher bleeding rates with rivaroxaban versus apixaban - both for overall bleeding (37.9 vs. 25.7 events/100 patient years, $p < 0.001$) and major bleeding episodes (4.7 vs. 2.6 events/100 patient years, $p < 0.001$). Rivaroxaban use was also associated with increased emergency department utilization (12.8 vs. 10.1 events/100 patient years, $p = 0.003$) and mortality (3.5 vs. 2.6 deaths/100 patient years, $p = 0.047$) compared to apixaban [35]. In a retrospective analysis of 99,878 patients with atrial fibrillation, apixaban 5 mg twice daily was observed with 12.9 bleeding episodes per 1000 person-years compared to 21.9 per 1000 person-years with rivaroxaban [36]. Another study evaluated gastrointestinal bleeding with various anticoagulants amongst 1.64 million patients (mean age 76.4 years), predominantly for atrial fibrillation (74.9%), rivaroxaban demonstrated the highest risk of upper gastrointestinal bleeding hospitalizations when used without proton pump inhibitor co-therapy [37]. The adjusted incidence rates of upper GI bleeding hospitalizations were notably higher with rivaroxaban (144 per 10,000 person-years) compared to dabigatran (120 per 10,000 person-years), warfarin (113 per 10,000 person-years), and least with apixaban (73 per 10,000 person-years) [37]. In another large retrospective analysis of 581,451 Medicare beneficiaries with atrial fibrillation (mean age 77.0 years, 50.2% women), rivaroxaban use was associated with higher risks compared to apixaban across multiple outcomes during 474,605 person-years of follow-up [38]. The composite of major ischemic and hemorrhagic events occurred more frequently with rivaroxaban (16.1 vs. 13.4 per 1000 person-years; HR 1.18). Rivaroxaban users experienced higher rates of hemorrhagic events (7.5 vs. 5.9 per 1000 person-years; HR 1.26), and notably higher nonfatal extracranial bleeding (39.7 vs. 18.5 per 1000 person-years; HR 2.07) [38]. Mortality outcomes also favored apixaban, with rivaroxaban showing increased rates of fatal extracranial bleeding (1.4 vs. 1.0 per 1000 person-years; HR 1.41), fatal ischemic/hemorrhagic events (4.5 vs. 3.3 per 1000 person-years; HR 1.34), and total mortality (44.2 vs. 41.0 per 1000 person-years; HR 1.06) [38]. The increased risk with rivaroxaban was observed in both standard and reduced dose cohorts, with particularly pronounced differences in the reduced-dose group (primary outcome: 27.4 vs. 21.0 per 1000 person-years; HR 1.28) [38]. Another study has demonstrated a dose-response relationship for bleeding episodes with rivaroxaban, where lower doses (5 mg/day or 2.5 mg/day) were associated with a reduced incidence of bleeding compared to the standard dose (15 mg/day) [39]. Low dose rivaroxaban has also been associated with reduced thrombotic risk when combined with antiplatelet drug and recommended for patients with peripheral arterial disease and coronary artery disease [40]. However, the standard dose is more commonly used in clinical practice, which plausibly explains the increased risk of bleeding observed in this study. However, this finding could not be definitively confirmed due to the underreporting of doses administered to patients. Our study, however, could not examine dose-dependent bleeding risks due to underreporting of dosing regimens within the USFDA AERS dataset. This limitation underscores

the importance of considering individualized dosing strategies, particularly with rivaroxaban, to minimize hemorrhage risks. Further, the bleeding risk must be assessed using validated scales such as HASBLED in clinical practice before initiating antithrombotic drugs. A study revealed that among high-risk patients (HASBLED score ≥ 3), apixaban was associated with a lower incidence of major bleeding compared to rivaroxaban (2.9% vs. 4.2% per year; hazard ratio [HR], 0.69; 95% CI, 0.58–0.81) [41]. Similarly, in low-risk patients, apixaban demonstrated a reduced major bleeding rate (1.8% vs. 2.9% per year; HR, 0.63; 95% CI, 0.56–0.70) [41]. Even among low-risk patients, apixaban appears to be associated with a lower bleeding risk compared to rivaroxaban. However, the comparative bleeding risks across different doses of apixaban and rivaroxaban remain underexplored in the literature. This gap underscores apixaban's potential as a safer alternative, particularly for patients at high risk of bleeding.

The findings of this study underscore the importance of individualized antithrombotic therapy, particularly in elderly or renally impaired patients who are at higher risk of adverse outcomes. Clinicians should carefully weigh the risks and benefits of antithrombotic regimens, prioritizing therapies with lower hemorrhage signals and mortality risks when appropriate. For instance, apixaban, which demonstrated the lowest hemorrhage signal and relatively favorable mortality outcomes in combination therapies, may be a potentially safer option in vulnerable populations. Conversely, the elevated hemorrhage signal and higher mortality associated with rivaroxaban highlight the need for cautious use, particularly in high-risk groups. Furthermore, dual or triple antithrombotic therapies should be employed judiciously, with close monitoring for bleeding complications. This study emphasizes the critical role of tailoring antithrombotic strategies to patient-specific factors, such as age, renal function, and comorbidities, to optimize safety and therapeutic outcomes.

Strength, limitations and way forward

This study has several strengths, including its large sample size and comprehensive use of data from the USFDA AERS, which provides real-world insights into hemorrhage risks associated with anticoagulant and antiplatelet therapies across diverse populations. By focusing on signal detection in a real-world setting, this analysis offers valuable information that may support risk-benefit considerations in clinical decision-making, particularly for elderly patients and those with coexisting renal impairment. However, limitations are inherent to the use of spontaneous reporting systems, including potential underreporting, reporting biases, a lack of detailed data on dosing and patient comorbidities including renal functions, diabetes, and concomitant medications, and overrepresentation of severe cases which can impact the accuracy and generalizability of the findings. Additionally, we were unable to evaluate the clinical significance of bleeding episodes, including the need for intervention or the extent of hemoglobin reduction, as this information was not available in the reports. Similarly, details on the therapeutic efficacy in preventing thrombotic events, as well as the duration of TAT and DAT treatments, were also unavailable. Furthermore, despite following the recommended procedures for deduplication, residual duplicate reports may remain. Since the search was conducted using the non-proprietary names of drugs, reports referring to acetylsalicylic acid as aspirin may not have been captured. To overcome these limitations, future studies should consider integrating real-world evidence from additional databases, applying robust pharmacoepidemiological methods, and exploring dose-dependent effects through well-designed cohort studies. Additionally, leveraging machine learning to predict individualized risk profiles for hemorrhage could refine therapeutic recommendations and improve patient safety in high-risk groups.

Conclusion

In conclusion, we identified significant hemorrhage signals associated with both dual and triple antithrombotic therapies, particularly among elderly patients. The preliminary findings from this study suggest a potentially higher hemorrhage risk and associated mortality with rivaroxaban when combined with dual antiplatelet therapy, while apixaban demonstrated a potentially lower risk profile for bleeding. This suggests that apixaban could likely be a potentially better alternative anticoagulant to rivaroxaban (particularly at high doses) to combine with DAT in clinical practice. For patients with atrial fibrillation and elevated bleeding risk, as determined by validated risk scores and clinical history, apixaban shall be considered as the preferred anticoagulant when DAT is required. The results of this study shall be considered while updating and providing recommendations on various antithrombotic drug combinations by ESC and ACC. Future research that combines spontaneous reporting data with prospective clinical studies could provide further clarity on dose-related hemorrhage risks and support tailored anticoagulation strategies to enhance patient safety.

Supplementary Information

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Supplementary Material 1

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Declarations

Competing interests
The authors declare no competing interests.

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