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High-signal drug assessment for drug-related aortic aneurysm and dissection rupture: Evidence from real-world databases and animal experiments

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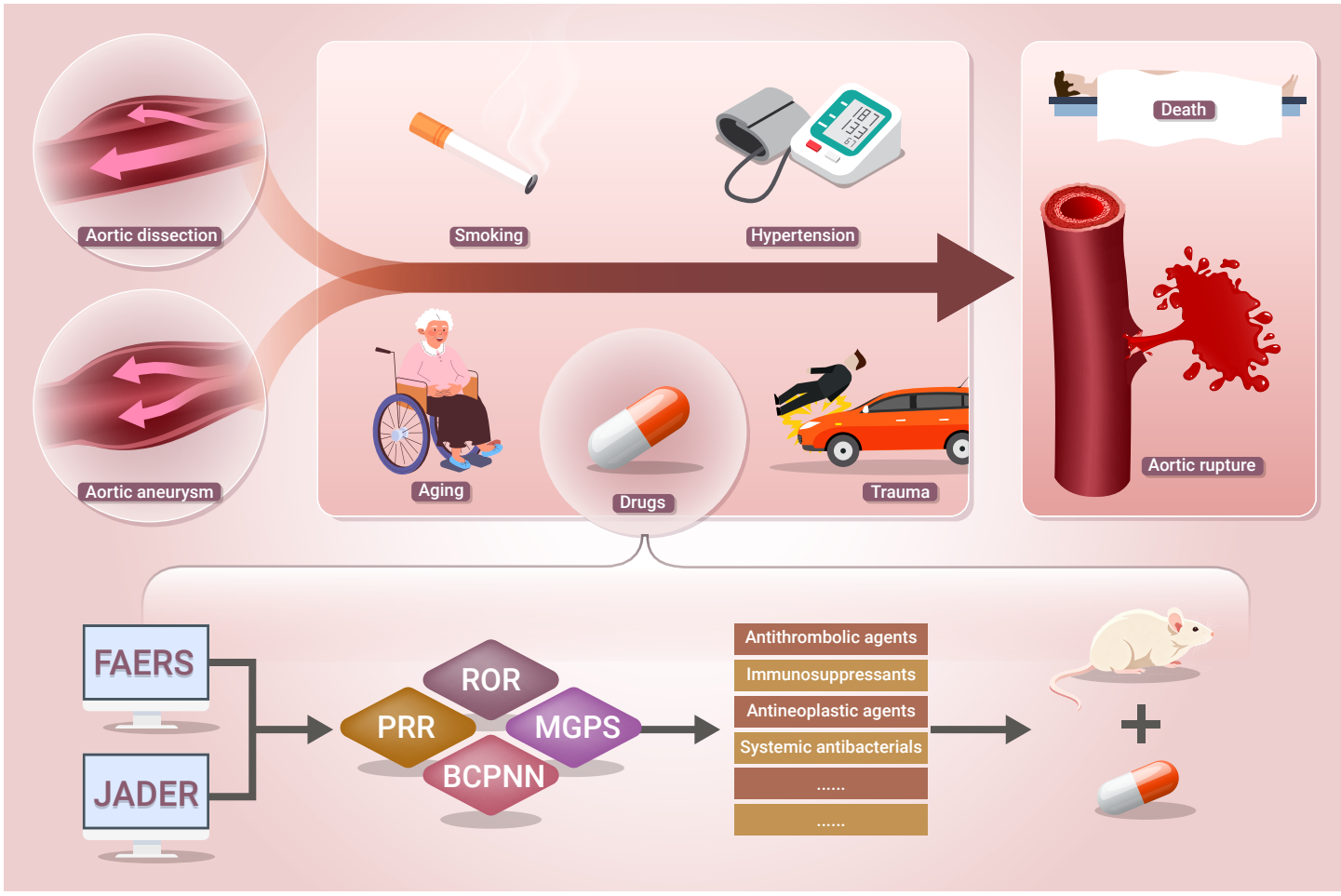
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Aortic aneurysm and dissection may lead to fatal aortic rupture.
- We screened 40 high-signal related drugs from real-world databases and verified the risk with animal models.
- These drug signals do not confirm causality, and further research is needed to guide safe clinical medication.

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High-signal drug assessment for drug-related aortic aneurysm and dissection rupture: Evidence from real-world databases and animal experiments

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Background: Aortic rupture represents the most critical complication of aortic aneurysm and dissection (AAD). Identifying and avoiding drugs associated with increased aortic rupture risk may provide immediate clinical benefits. Methods: Data from the FAERS and JADER databases (2004 Q1–2025 Q2) were analyzed. Clinical characteristics associated with adverse events of aortic rupture were summarized. Four disproportionality methods, reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS), were applied to detect adverse drug reaction signals. Drugs positive in all four methods were classified as high-signal. A time-to-onset analysis was conducted. Rivaroxaban was chosen as a representative drug for further investigation of its impact on aortic rupture risk in an AAD mouse model. Results: FAERS analysis identified 1,313 drug-associated AAD rupture reports involving 333 medications. Antithrombotic agents were most frequently implicated (247 cases, 18.8%), followed by Immunosuppressants (218 cases, 16.6%) and Antineoplastic agents (176 cases, 13.4%). Disproportionality analysis identified 40 drugs with high reporting signals for AAD rupture. Affected individuals were predominantly male (63.8%) and aged ≥65 years (74.0%). Reports and associated fatalities have increased in recent years, although overall mortality has declined. JADER provided 104 reports (17 drugs), consistent with FAERS findings except for the inclusion of SARS-CoV-2 mRNA vaccines. Animal experiments demonstrated that rivaroxaban did not increase AAD incidence but significantly elevated the aortic rupture risk. Conclusion: This study identified 40 high-signal drugs associated with AAD rupture, offering clinical references for safer drug usage. Further studies are necessary to clarify these risks.

INTRODUCTION

Aortic aneurysm and dissection (AAD), major life-threatening cardiovascular conditions in adults, cause approximately 167,400 deaths worldwide each year, with numbers steadily increasing annually.[1] Aortic rupture is the most severe and fatal complication of AAD. Upon rupture, blood progressively penetrates all arterial wall layers, flowing into the thoracic cavity, abdominal cavity, or pericardium, resulting in mortality rates ranging from 60% to 90%.[2,3] Therefore, reducing AAD rupture rates is critically important. Previously, researchers primarily focused on elucidating novel pathogenesis and therapeutic targets for AAD. Although numerous promising results have been reported recently, there remain no clinically available drugs clearly effective in slowing AAD progression.[4,5] However, identifying and avoiding drugs associated with increased aortic rupture risk can immediately benefit patients with AAD.

In recent years, due to the increasing diversity of clinical medications, associations between drugs and cardiovascular toxicity have attracted growing attention.[6,7] Nevertheless, systematic studies on drug-induced AAD rupture remain limited, and identification, reporting characteristics, and potential mechanisms of high-signal drugs in real-world settings have yet to be clarified. Pharmacovigilance databases, such as the Food and Drug Administration Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER), represent valuable resources for real-world drug safety evaluations. These databases provide extensive data support for detecting signals of drug-related AEs.[8,9]

This study analyzed reports of drug-related AAD rupture from the FAERS database. It systematically investigated reporting characteristics and annual trends associated with drug-related AAD rupture. Additionally, key influencing factors, including patient demographics and drug classifications, were identified. Disproportionality methods were employed to screen drugs significantly associated with AAD rupture. Moreover, representative drugs were selected for animal experiments to explore underlying mechanisms involved in inducing or exacerbating AAD rupture. This study aims to clarify high-signal drug categories, reporting trends, and influencing factors. The findings will provide scientific evidence for rational clinical drug use and contribute to reducing AAD rupture risks, offering important clinical insights for optimizing treatment strategies in high-signal AAD populations.

MATERIALS AND METHODS

FAERS data source and selection

Data for this study were obtained from the FDA Adverse Event Reporting System (FAERS) database, covering 2004 Q1 to 2025 Q2. To identify cases of aortic rupture, the Preferred Terms (PTs) "aortic rupture", "ruptured aortic dissection", and "ruptured aortic aneurysm" were selected. These PTs were chosen based on their direct relevance to the target condition, ensuring comprehensive inclusion of aortic rupture-related AE reports.

FAERS data cleaning and standardization

Extracted raw data underwent a strict two-step deduplication procedure following FDA data-cleaning guidelines. Initially, all records marked as "primaryid = 0" were excluded as invalid. Next, among records with identical "caseid", the entry with the latest "fda_dt" was retained. If both "caseid" and "fda_dt" were identical, the entry with the highest "primaryid" was selected, adhering to FDA recommendations.

PTs were standardized using the Medical Dictionary for Regulatory Activities (MedDRA), version 27.1 (September 2024 release). PTs were mapped to corresponding MedDRA hierarchical levels (SOC, HLT). Deprecated terms were harmonized to current equivalents using official mapping files, ensuring data consistency throughout the study period.

FAERS statistical methods

Statistical analyses were performed using R 4.4.2. To identify associations between drugs and AEs, disproportionality analysis was employed. Disproportionally reported signals in this study were defined as a significantly higher frequency of AAD rupture reports linked to a specific drug compared with the baseline reporting frequency of all other adverse events associated with other

drugs in the FAERS database. It should be emphasized that all disproportionality signals only represent statistical reporting imbalance in the spontaneous reporting database, not absolute risk, incidence rate, or causal relationship in the general population. These signals reflect unusual reporting frequency rather than definitive evidence of drug-induced AAD rupture. The same baseline definition was applied to the JADER database analysis.

Four metrics were applied to quantify disproportionality: ROR, PRR, BCPNN, and EBGM. Formulas and criteria for signal positivity are provided in Tables S1-S2. In this study, high-signal drugs for AAD rupture reporting were defined as those with positive signals identified concurrently by four disproportionality methods. This strict intersection approach prioritizes high specificity over sensitivity, reducing false positives and ensuring only the most robust signals are classified as high-signal drugs. This enhances the clinical credibility of the findings.

JADER database

Data were retrieved from the Japanese Adverse Drug Event Report (JADER) database for the period 2004 Q1 to 2025 Q2. Analytical methods were identical to those described in sections 2.1–2.3.

Animals and mouse model

This study was approved by the Animal Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (approval No. KS2024114). Three-week-old male C57BL/6J mice were obtained from Beijing Weishang Lide Biotechnology Co., Ltd. To establish the aortic dissection model, mice received drinking water containing 0.3% β-aminopropionitrile (BAPN) for 28 consecutive days. Successful model formation was confirmed by aortic dilation and dissection formation. Specifically, after two weeks of BAPN administration, rivaroxaban (15 mg/kg/day) was administered intragastrically during the subsequent intervention period. The control group received an equal volume of PBS throughout the experiment.

Coagulation function and D-dimer in mouse model

Serum coagulation parameters, including prothrombin time-sensitive (PT-S), fibrinogen (FIB), activated partial thromboplastin time (APTT), thrombin time (TT), and D-dimer, were measured. Blood samples were collected from the heart after deep anesthesia with isoflurane. Whole blood was immediately mixed with 3.2% sodium citrate anticoagulant at a 9:1 ratio, followed by centrifugation at 3000 rpm for 10 minutes at room temperature (25°C). Supernatants were analyzed using a Toshiba 120FR automated coagulation analyzer (Toshiba Corporation, Japan) following the manufacturer's instructions.

Hematoxylin & eosin staining and elastic fiber staining

At the end of the experiment, abdominal aortic segments were promptly excised. The segments with the maximum aneurysm diameter were collected, fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned (3 μm thickness) for histological analysis. Hematoxylin & eosin (HE) staining and elastic-Van Gieson (EVG) staining were performed strictly following reagent suppliers' protocols.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 9.0, and results were presented as mean ± standard deviation (SD). The Student's t-test was used for comparisons between two groups. Comparisons among three or more groups were performed using one-way analysis of variance (ANOVA). Statistical significance was set at $P \leq 0.05$.

RESULTS

Clinical characteristics of drug-related AAD rupture reports

A total of 1,313 reports of drug-related AAD rupture were identified from the FAERS database (2004 Q1–2025 Q2) after screening and excluding duplicates, aberrant data, and reports lacking suspected drug information (Figure 1). The annual number of reports and mortality rates exhibited dynamic changes over time (Figure 2). Reports gradually increased from 2004, peaked in 2018, then stabilized at approximately 75 cases annually. Conversely, the overall mortality rate declined from nearly 100% to approximately 50%. This

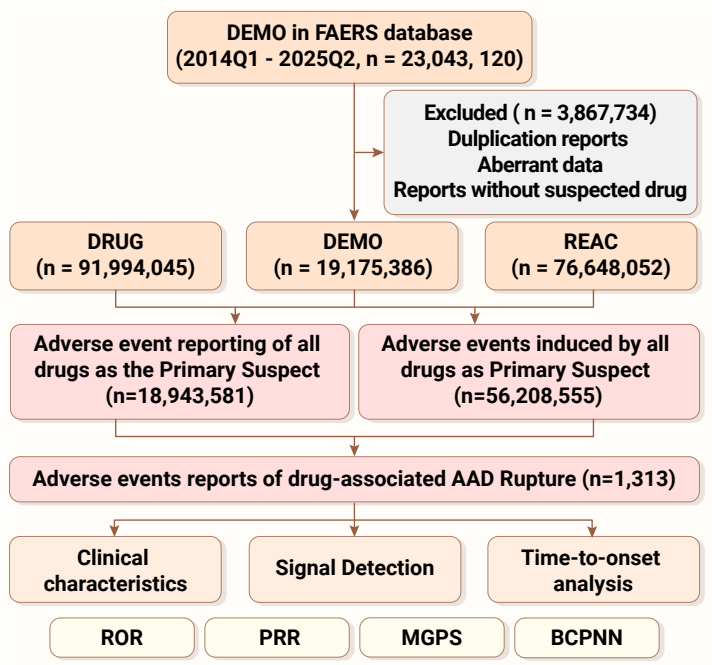

Figure 1. Study flow chart Reports associated with AAD ruptures were screened in the database and subsequently analyzed further by drug type FAERS, FDA Adverse Event Reporting System. AAD, Aortic aneurysm and dissection; DEMO, Demographics; REAC, Adverse Drug Reaction Information; DRUG, Drug information; ATC, Anatomical Therapeutic Chemical Classification System; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; MGPS, multi-item gamma Poisson shrinker; BCPNN, Bayesian Confidence Propagation Neural Network.

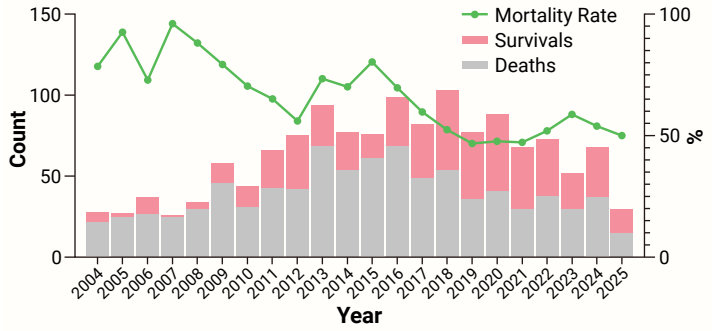

Figure 2. Annual report distribution of drug-related AAD rupture and line chart of mortality rate from 2004Q1 to 2025Q2.

downward trend in mortality is closely associated with the continuous advancement of clinical diagnosis and treatment, as well as the improved risk stratification and standardized management of underlying diseases in high-risk populations for AAD.

Demographic and reporting characteristics are summarized in Table 1. The median age of patients was 73.0 years (range, 0.8–95.0 years); 74.04% of patients were aged ≥65 years, while only 0.64% were younger than 18 years. Reports involved 63.8% male patients, surpassing females (36.2%). Physicians submitted 43.4% of reports, consumers 27.6%, and the leading reporting countries were the United States (31.47%), Japan (21.06%), and the United Kingdom (8.96%). The median interval from drug exposure to AAD rupture was 135 days (range, 1–5,114 days). Common indications included rheumatoid arthritis (8.1%), atrial fibrillation (5.9%), and cerebrovascular accident prophylaxis (2.7%). None of these drugs had approved indications for aortic dissection or aneurysm.

Distribution of drug classes and individual drugs linked to AAD rupture

Analysis of the 1,313 reports using the Anatomical Therapeutic Chemical (ATC) Classification System (Level 2) identified the top 10 drug classes ranked by report frequency (Figure 3A): antithrombotic agents (B01, n=247),

immunosuppressants (L04, n=218), antineoplastic agents (L01, n=176), systemic antibacterials (J01, n=85), Immunostimulants (L03, n=33), analgesics (N02, n=32), systemic corticosteroids (L03, n=31), psycholeptics (N05, n=24), calcium homeostasis (H05, n=24), bone metabolism drugs (M05, n=23), drugs for obstructive airway diseases (R03, n=22) and antiinflammatory (M01, n=22).

At the individual drug level, the highest reported cases (Figure 3B) involved rivaroxaban (n=68), adalimumab (n=64), dabigatran (n=53), levofloxacin (n=40), apixaban (n=35), ciprofloxacin (n=33), bevacizumab (n=23), infliximab (n=21), tocilizumab (n=20), alteplase (n=18), etanercept (n=18) and acetylsalicylic acid (n=17).

A volcano plot was generated to identify drugs potentially linked to AAD rupture (Figure 3C). Notable examples included antithrombotic agents (rivaroxaban, dabigatran), thrombolytic agents (apixaban, alteplase), antibacterials (levofloxacin, ciprofloxacin), biological agents (adalimumab, infliximab, tocilizumab), antineoplastic agents (bevacizumab), and hormonal drugs (prednisolone). These drugs showed high log ROR and -log10 (adjusted p-value) values and substantial case numbers. Additionally, ferumoxytol, despite fewer cases, displayed a very high log ROR, indicating a potential safety signal. All drugs in the baseline reference group are listed in Table S3.

High-signal drugs associated with AAD rupture identified via four disproportionality analyses

Drugs positive across all four disproportionality metrics were classified as high-signal (Figure 4). Among these, the top five drugs by report count were rivaroxaban (ROR = 8.47; 95% CI: 6.63–10.81), dabigatran (ROR = 13.02; 95% CI: 9.89–17.14), levofloxacin (ROR = 18.25; 95% CI: 13.32–25.01), apixaban (ROR = 3.66; 95% CI: 2.62–5.12), and ciprofloxacin (ROR = 15.2; 95% CI: 10.75–21.47). Conversely, the drugs with the highest ROR values were ticlopidine (ROR = 28.34; 95% CI: 41.13–400.45), dacarbazine (ROR = 88.1; 95% CI: 32.92–235.79), cilostazol (ROR = 17.99; 95% CI: 21.49–107.15), tenecteplase (ROR = 9.01; 95% CI: 15.76–152.46), and rofecoxib (ROR = 4.47; 95% CI: 2.47–8.09).

Notably, discrepancies between report frequency and ROR rankings indicated that some drugs (e.g., rivaroxaban, levofloxacin) had high reporting rates, whereas others (e.g., ticlopidine, dacarbazine) demonstrated stronger statistical risk signals despite lower report numbers. This highlights the necessity of integrating multiple metrics in pharmacovigilance assessments. Additionally, the onset time after drug discontinuation varied: for example, rivaroxaban had a median onset of 0.5 days, tocilizumab 17.5 days, levofloxacin 19 days, and cinacalcet 285.5 days. These variations may reflect differences in pharmacological mechanisms or physiological responses post-discontinuation, warranting further exploration of AE timing among these high-signal drugs.

Identification of suspected drugs linked to AAD rupture in the JADER database

In addition to FAERS analysis, the JADER database was screened to identify drugs associated with AAD rupture (Figure 5). In the JADER database, the SARS-CoV-2 mRNA vaccine had the highest report count (a = 28), with an ROR of 5.83 (95% CI: 3.89–8.73). Other high-signal drugs included prednisolone (a = 13, ROR = 2.67; 95% CI: 1.52–4.69), edoxaban silate hydrate (a = 12, ROR = 17.35; 95% CI: 9.65–31.2), dabigatran etexilate methanesulfonate (a = 8, ROR = 12.59; 95% CI: 6.19–25.61), and levofloxacin hydrate (a = 8, ROR = 7.39; 95% CI: 3.64–15.03). Drugs such as edoxaban silate hydrate, dabigatran etexilate methanesulfonate, and cilostazol exhibited notably high ROR values, indicating strong statistical signals of risk.

Comparisons between JADER and FAERS revealed both consistencies and discrepancies. Consistent high-signal signals appeared for antithrombotic agents (edoxaban, rivaroxaban, dabigatran), fluoroquinolone antibiotics (levofloxacin hydrate), glucocorticoids (prednisolone), and immunosuppressants (tocilizumab, etanercept) in both databases, highlighting robust associations across different pharmacovigilance systems. However, JADER uniquely flagged the SARS-CoV-2 mRNA vaccine, suggesting possible regional differences in patient demographics, reporting practices, or drug utilization patterns between FAERS and JADER.

Table 1. General information on drug-related AAD rupture in real-world reports from FAERS database.

Characteristics	Available number	Drug-related AAD Rupture (N=1,313)
Age (years)	936	
Median (range)		73.0 (0.8, 95.0)
Age_group, n %	936	
<18		6 (0.64%)
18-45		55 (5.88%)
45-65		185 (19.76%)
≥65		693 (74.04%)
Gender	1,217	
Female		441 (36.2%)
Male		776 (63.8%)
Weight (Kg)	358	
Median (range)		71.0 (34.0, 204.0)
Time-to-onset (day)	514	
Median (range)		135 (1-5,114)
Occupation of the reporter	1,289	
Physician		560 (43.4%)
Pharmacist		67 (5.2%)
Health Professional		76 (5.9%)
Other Health Professional		223 (17.3%)
Lawyer		7 (0.5%)
Consumer		356 (27.6%)
Country of the reporter (top three)	1,306	
UNITED STATES		411 (31.47%)
JAPAN		275 (21.06%)
UNITED KINGDOM		117 (8.96%)
Indications (top three)	1,269	
Rheumatoid arthritis		103(8.1%)
Atrial fibrillation		75(5.9%)
Cerebrovascular accident prophylaxis		34(2.7%)

Available number denotes the number of reports used for analysis after excluding missing values. All analyses were performed on data without missing values. Abbreviation: AAD, aortic aneurysm and dissection.

Rivaroxaban increases the risk of AAD rupture

Findings from FAERS and JADER required preliminary validation through animal experiments. Considering that rivaroxaban prominently ranked by report frequency and ROR value, and given limited existing evidence regarding its effect on AAD rupture risk and underlying mechanisms, it was chosen for further verification. A mouse model susceptible to AAD was established using 0.3% BAPN in drinking water, with interventions involving oral administration of rivaroxaban or PBS control (Figure 6A). Representative aortic photographs revealed that mice treated with rivaroxaban exhibited wider areas of aortic intimal tear, involving both thoracic and suprarenal abdominal aorta (Figure 6B).

Experimental outcomes indicated that rivaroxaban significantly aggra-

Figure 3. Drugs associated with AAD rupture from FAERS were classified by ATC Level 2, with the top 10 drug classes (A) and individual drugs (B) ranked by report number. Volcano plot (C) showing drug signals for AAD rupture, with the display of drugs with positive ROR signals X-axis: log-transformed reporting odds ratio (log ROR); Y-axis: -log10(p-adjust). Color indicates log(number of cases). Dashed lines mark thresholds for significant association (log ROR > 1, -log10(p-adjust) > 2).

vated AAD pathology. Compared with controls, although the incidence of AAD was not significantly altered in the rivaroxaban group, the rupture rate notably increased (Figure 6C), and survival rates markedly decreased (Figure 6E, n=20 per group, log-rank test p=0.02). These findings suggest rivaroxaban elevates AAD rupture risk by promoting progression of aortic lesions.

Coagulation function tests showed that in the rivaroxaban-treated group, plasma prothrombin time (PT) (11.74 vs. 23.08, p=0.01) and activated partial thromboplastin time (APTT) (36.56 vs. 63.28, p=0.01) were significantly

ATC_L2	Drug	a	PRR (χ^2)	EBGM (EBGM05)	IC(IC025)	ROR(95%CI)	Median TTR	Median Onset Time
B01	Rivaroxaban	68	8.46 (424.41)	8.08 (6.58)	3.01 (1.35)	8.47 (6.63 - 10.81)	148	0.5
B01	Dabigatran	53	13.01 (563.96)	12.53 (9.95)	3.65 (1.98)	13.02 (9.89 - 17.14)	947	2
J01	Levofloxacin	40	18.23 (631.65)	17.71 (13.6)	4.15 (2.48)	18.25 (13.32 - 25.01)	23	19
B01	Apixaban	35	3.66 (65.85)	3.59 (2.71)	1.84 (0.18)	3.66 (2.62 - 5.12)	514.5	0.5
J01	Ciprofloxacin	33	15.18 (426.21)	14.83 (11.1)	3.89 (2.22)	15.2 (10.75 - 21.47)	4	0.5
L01	Bevacizumab	23	5.24 (77.59)	5.17 (3.66)	2.37 (0.7)	5.24 (3.47 - 7.92)	68	3.5
L04	Tocilizumab	20	5.03 (63.53)	4.97 (3.43)	2.31 (0.64)	5.03 (3.23 - 7.82)	128	17.5
B01	Alteplase	18	21.28 (343.12)	21 (14.23)	4.39 (2.72)	21.31 (13.38 - 33.94)	0.5	0.5
N02	Acetylsalicylic acid	17	9.93 (134.72)	9.81 (6.57)	3.29 (1.63)	9.93 (6.15 - 16.03)	0.5	0.5
H02	Prednisolone	17	8.73 (114.94)	8.63 (5.79)	3.11 (1.44)	8.74 (5.42 - 14.1)	22	13
S01	Ranibizumab	15	10.12 (121.91)	10.02 (6.54)	3.32 (1.66)	10.13 (6.09 - 16.85)	1065	0.5
B01	Clopidogrel	14	5.35 (48.93)	5.3 (3.41)	2.41 (0.74)	5.35 (3.16 - 9.05)	211	0.5
L04	Tacrolimus	14	4.04 (31.71)	4.01 (2.58)	2 (0.34)	4.04 (2.39 - 6.85)	344	0.5
B01	Warfarin	14	5.32 (48.54)	5.27 (3.39)	2.4 (0.73)	5.32 (3.14 - 9.01)	58	0.5
M05	Zoledronic acid	12	3.98 (26.51)	3.95 (2.46)	1.98 (0.31)	3.98 (2.25 - 7.03)	-	-
B01	Edoxaban	11	39.15 (405.55)	38.83 (23.62)	5.28 (3.61)	39.25 (21.67 - 71.12)	198.5	0.5
M01	Rofecoxib	11	4.47 (29.35)	4.44 (2.7)	2.15 (0.48)	4.47 (2.47 - 8.09)	326	-76
L01	Carboplatin	10	3.55 (18.2)	3.53 (2.1)	1.82 (0.15)	3.55 (1.91 - 6.62)	41	18
L04	Ciclosporin	10	5.76 (39.07)	5.73 (3.4)	2.52 (0.85)	5.77 (3.09 - 10.74)	0.5	-20
L01	Sunitinib	10	4.26 (24.8)	4.24 (2.52)	2.08 (0.42)	4.27 (2.29 - 7.95)	52	1
B03	MPG-Epo	9	14.78 (114.87)	14.69 (8.48)	3.88 (2.21)	14.8 (7.68 - 28.51)	345	-96
L01	Lenvatinib	7	4.36 (18.04)	4.34 (2.33)	2.12 (0.45)	4.36 (2.08 - 9.17)	7	-9
B01	Cilostazol	6	47.83 (273.87)	47.62 (24.31)	5.57 (3.9)	47.99 (21.49 - 107.15)	12	1
L01	Nintedanib	6	4.24 (14.79)	4.22 (2.16)	2.08 (0.41)	4.24 (1.9 - 9.46)	349.5	-14.75
N01	Fentanyl	5	7.93 (30.16)	7.9 (3.79)	2.98 (1.31)	7.93 (3.3 - 19.09)	4	0.5
V03	Sevelamer	5	39.72 (188.01)	39.57 (18.96)	5.31 (3.64)	39.83 (16.53 - 95.96)	1131	-73
R06	Cetirizine	4	5.91 (16.26)	5.89 (2.59)	2.56 (0.89)	5.91 (2.21 - 15.78)	-	-
H05	Cinacalcet	4	30.95 (115.59)	30.86 (13.56)	4.95 (3.28)	31.02 (11.61 - 82.85)	413.5	285.5
L01	Dacarbazine	4	87.57 (341.31)	87.31 (38.31)	6.45 (4.78)	88.1 (32.92 - 235.79)	208	5
N07	Fampridine	4	12.61 (42.65)	12.58 (5.53)	3.65 (1.98)	12.62 (4.73 - 33.7)	-	-
B01	Fondaparinux	4	12.47 (42.06)	12.43 (5.47)	3.64 (1.97)	12.48 (4.67 - 33.31)	4.5	-3.5
V08	Iopamidol	4	51.09 (195.85)	50.94 (22.37)	5.67 (4)	51.27 (19.18 - 137.04)	0.5	0.5
A03	Metoclopramide	4	5.37 (14.2)	5.36 (2.36)	2.42 (0.75)	5.38 (2.01 - 14.35)	-	-
L02	Apalutamide	3	5.49 (10.99)	5.48 (2.12)	2.45 (0.79)	5.49 (1.77 - 17.05)	-	-
J01	Daptomycin	3	8.29 (19.2)	8.28 (3.21)	3.05 (1.38)	8.3 (2.67 - 25.77)	-	-
N06	Galantamine	3	20.94 (56.82)	20.89 (8.09)	4.38 (2.72)	20.96 (6.75 - 65.14)	-	-
B01	Prasugrel	3	7.8 (17.74)	7.78 (3.02)	2.96 (1.29)	7.8 (2.51 - 24.23)	-	-
B01	Tenecteplase	3	48.85 (140.3)	48.74 (18.86)	5.61 (3.94)	49.01 (15.76 - 152.46)	1	0.5
B01	Ticlopidine	3	127.22 (374.85)	126.93 (48.98)	6.99 (5.31)	128.34 (41.13 - 400.45)	2	-0.25
L02	Triptorelin	3	27.95 (77.79)	27.89 (10.8)	4.8 (3.13)	28 (9.01 - 87.03)	-	-

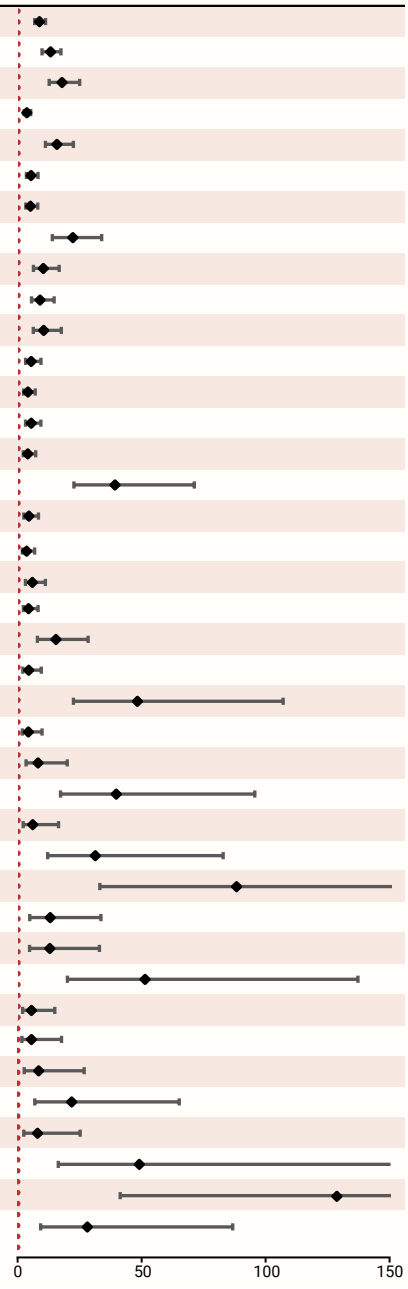

Figure 4. Disproportionality analysis in FAERS database High-signal drugs were defined as those with positive signals in all four disproportionality analyses. The forest plot shows reporting odds ratio (ROR) with 95% confidence intervals (CIs) for high-signal drugs associated with drug-related AAD rupture. Abbreviation: AAD, aortic aneurysm and dissection; ATC_L2, Anatomical Therapeutic Chemical Classification System Level 2; a, Number of reports; PRR (χ^2), Proportional Reporting Ratio (Chi-square value); EBGM (EBGM05), Empirical Bayes Geometric Mean (EBGM 5% quantile) ; IC (IC025)：Information Component (IC 2.5% quantile); Median TTR (d): Median time to AAD rupture; Median Onset Time (d): Median Onset Time Post Drug Discontinuation(positive values indicate adverse events (AEs) occurring post drug discontinuation, negative values indicate AEs occurring pre drug discontinuation, and absolute values < 1 mean AEs developed during drug use with immediate discontinuation); MPG-EPO: methoxy-polyethylene glycol-epoetin beta.

prolonged. Fibrinogen (FIB) levels slightly decreased (2.08 vs. 1.61, p=0.28), whereas D-dimer levels slightly increased (0.08 vs. 0.10, p=0.34) (Figure 6E, n=5 per group). These results suggest rivaroxaban interferes with coagulation-dependent vascular repair mechanisms after injury, exacerbating AAD progression and increasing rupture likelihood.

Pathological staining (Figure 6F) showed more severe structural damage to thoracic aortic tissue in rivaroxaban-treated mice, characterized by elastic fiber rupture and smooth muscle layer disruption. Although thoracic aortic dissection also occurred in the PBS group, extensive blood clotting facilitated repair processes, including intimal thickening and substantial fibrin deposition in adventitial tissue. In contrast, lesions in the rivaroxaban group extended to the suprarenal abdominal aorta, forming false lumens and further elevating rupture risk.

In conclusion, following aortic intimal injury, activation of endogenous coagulation processes normally facilitates repair. However, rivaroxaban interrupts the coagulation cascade by inhibiting factor X activation, impairing effective thrombus formation at the injury site. This effect exacerbates AAD progression, ultimately increasing rupture risk (Figure 6G). Thus, coagulation inhibition represents a crucial mechanism by which rivaroxaban promotes AAD rupture.

DISCUSSION

In recent years, animal studies on AAD have achieved numerous breakthroughs,[10,11] successfully uncovering several key pathogenic mechanisms

ATC_L2	Drug	a	PRR (χ^2)	EBGM (EBGM05)	IC(IC025)	ROR(95%CI)	p_value
J07	SARS-CoV-2 mRNA vaccine	28	5.83 (94.28)	5.06 (3.61)	2.34 (0.66)	5.83 (3.89 - 8.73)	<0.001
H02	Prednisolone	13	2.67 (12.53)	2.54 (1.59)	1.35 (-0.33)	2.67 (1.52 - 4.69)	<0.001
B01	Edoxabant silate hydrate	12	17.3 (171.86)	16.2 (9.91)	4.02 (2.34)	17.35 (9.65 - 31.2)	<0.001
B01	Dabigatran etexilate methanesulfonate	8	12.57 (81.34)	12.04 (6.65)	3.59 (1.91)	12.59 (6.19 - 25.61)	<0.001
R03	Levofloxacin hydrate	8	7.39 (42.18)	7.1 (3.92)	2.83 (1.15)	7.39 (3.64 - 15.03)	<0.001
L04	Tocilizumab	8	6.31 (34.13)	6.07 (3.35)	2.6 (0.92)	6.31 (3.11 - 12.84)	<0.001
B01	Clopidogrel sulfate	8	5.74 (29.92)	5.53 (3.05)	2.47 (0.79)	5.75 (2.83 - 11.68)	<0.001
B01	Warfarin potassium	8	8.08 (47.41)	7.76 (4.29)	2.96 (1.28)	8.09 (3.98 - 16.45)	<0.001
B01	Aspirin	7	3.76 (13.65)	3.66 (1.94)	1.87 (0.19)	3.77 (1.77 - 8.02)	<0.001
B01	Rivaroxaban	6	4.61 (16.37)	4.48 (2.27)	2.16 (0.48)	4.61 (2.04 - 10.41)	<0.001
B01	Cilostazol	5	9.91 (38.95)	9.66 (4.59)	3.27 (1.59)	9.93 (4.08 - 24.18)	<0.001
L04	Etanercept	4	4.62 (11.1)	4.54 (1.98)	2.18 (0.5)	4.62 (1.72 - 12.47)	<0.001
L04	Aflibercept	3	11.34 (27.81)	11.17 (4.29)	3.48 (1.8)	11.36 (3.62 - 35.61)	<0.001
B01	Alteplase	3	8.9 (20.67)	8.76 (3.37)	3.13 (1.45)	8.91 (2.84 - 27.92)	<0.001
L01	Enzalutamide	3	6.67 (14.22)	6.57 (2.53)	2.72 (1.04)	6.68 (2.13 - 20.92)	<0.001

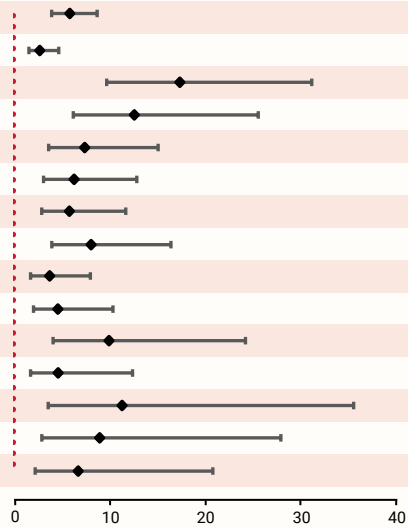

Figure 5. Disproportionality analysis in JADER database High-signal drugs were defined as those with positive signals in all four disproportionality analyses. The forest plot shows reporting odds ratio (ROR) with 95% confidence intervals (CIs) for high-signal drugs associated with drug-related AAD rupture. Abbreviation: AAD, aortic aneurysm and dissection; ATC_L2, Anatomical Therapeutic Chemical Classification System Level 2; a, Number of reports; PRR (χ^2), Proportional Reporting Ratio (Chi-square value); EBGM (EBGM05), Empirical Bayes Geometric Mean (EBGM 5% quantile) ; IC (IC025)：Information Component (IC 2.5% quantile).

and providing potential intervention targets and drug candidates for clinical use. However, these candidate drugs have yet to undergo successful clinical translation or application, and effective alternatives to surgical treatment for AAD remain unavailable. Therefore, accurately identifying drug-related risks and developing scientific avoidance strategies hold substantial clinical importance and practical value for reducing AAD mortality and enhancing medication safety.

Real-world data indicated that drugs such as antithrombotic agents, immunomodulators, antineoplastic agents, and certain antibacterial drugs are closely associated with an increased risk of AAD rupture. Disproportionality analyses confirmed that drugs such as rivaroxaban, dabigatran, and levofloxacin exhibited prominent reporting frequency and strong risk signals, categorizing them as high-signal drugs associated with AAD rupture. Statistical analysis of reported populations demonstrated that elderly men constituted the primary affected group, with those aged ≥65 years accounting for 74.04% and males representing 63.8%. Notably, experiments using a BAPN-induced mouse model of AAD showed that rivaroxaban could inhibit the coagulation cascade by blocking coagulation factor Xa activation, significantly increasing AAD rupture rates and reducing mouse survival rates.

Antithrombotic drugs (including antiplatelet agents, anticoagulants, and fibrinolytic agents) rank first among high-risk drugs potentially inducing aortic rupture, warranting particular attention. Antiplatelet agents (e.g., aspirin, clopidogrel, ticagrelor) inhibit platelet aggregation and activation to reduce thrombosis, and are widely used in atherosclerotic cardiovascular disease (ASCVD) prevention and treatment, as well as in post-interventional antiplatelet therapy.[12] However, the role of aspirin in primary cardiovascular prevention has declined in recent years, as multiple large-scale studies show that its absolute benefits are largely offset by bleeding risks.[13-15] Thus, guidelines issued by ACC/AHA, ADA, and ESC no longer recommend aspirin for primary prevention in low-to-moderate ASCVD-risk populations, particularly those aged >70 years.[16-18] Recent evidence also shows no significant difference in bleeding risk between clopidogrel and aspirin in patients with coronary heart disease after >5 years of follow-up.[19] Although aortic dissection and aneurysm formation are closely associated with vascular inflammation and platelet activation,[20] the role of antiplatelet agents in primary prevention of aortic dissection remains unclear. Aspirin is contraindicated in the acute phase of aortic dissection due to bleeding risk from intimal tearing.[4] Clinical findings regarding aspirin and aortic diseases remain inconsistent: a Danish case-control study (n=8,020) reported no association between pre-admission aspirin use and abdominal aortic aneurysm (AAA) rupture risk, but noted a potentially worse prognosis after rupture,[21] whereas another cohort study (n=3,435) suggested aspirin may reduce aneurysm expansion or rupture risk in specific populations (males and non-smokers).[22] In summary, aspirin's effects in aortic-related diseases remain controversial, varying by population and disease stage, and require further targeted investigation.

Anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, heparin, argatroban) inhibit coagulation factors to delay clot formation and prevent thrombosis.[23] The pathophysiology of AAD is closely related to coagulation dysfunction: patients with aortic dissection often show activation and consumption of coagulation factors due to blood flow through the non-endothelialized false lumen, which activates the coagulation system.[24,25] Intraluminal thrombus (ILT), a key feature of aortic aneurysms, has a controversial role. Some studies suggest that ILT creates an inflammatory microenvironment rich in neutrophils, cytokines, proteases, and reactive oxygen species, while long-term hypoxia and parenchymal cell apoptosis weaken aortic wall strength.[26] Other studies argue that ILT provides mechanical support, reducing wall stress and thereby decreasing AAA rupture risk.[27,28] Whether anticoagulants increase the clinical rupture rate of AAD remains unclear. On one hand, patients treated with factor Xa inhibitors exhibit a higher risk of perioperative complications, longer hospital stays, and higher mortality during emergency cardiovascular surgery.[29] On the other hand, in vitro experiments show that rivaroxaban inhibits vascular smooth muscle cell migration, proliferation, and the production of inflammatory cytokines (IL-1β, TNFα).[30] However, our study found that anticoagulants accounted for the largest number of drug-related aortic rupture reports. Further animal experiments confirmed that rivaroxaban widened the extent of AAD lesions and increased acute rupture risk, likely by inhibiting factor Xa activation and blocking the protective effect of the coagulation cascade against acute aortic rupture. Although our study provides initial confirmation through real-world data and animal evidence, the association between anticoagulants and AAD rupture requires validation through additional randomized clinical trials.

Fibrinolytic agents (e.g., t-PA, streptokinase, urokinase, tenecteplase) are used to lyse thrombi in acute myocardial infarction, pulmonary embolism, and cerebral infarction.[17,31] These agents activate plasminogen to dissolve ILT associated with aortic aneurysms, potentially influencing aneurysm progression. Guidelines clearly indicate that aortic dissection is a contraindication for thrombolytic therapy,[32,33] yet evidence regarding the benefits or risks of fibrinolytic drugs in patients with aortic aneurysms remains insufficient. A 2025 retrospective study of 16 acute ischemic stroke patients receiving thrombolysis after prior aneurysm repair reported 1 case of aneurysm rupture.[34] Based on FAERS data, we observed that fibrinolytic agents may increase the risk of aortic aneurysm rupture. Alteplase and tenecteplase were identified as high-

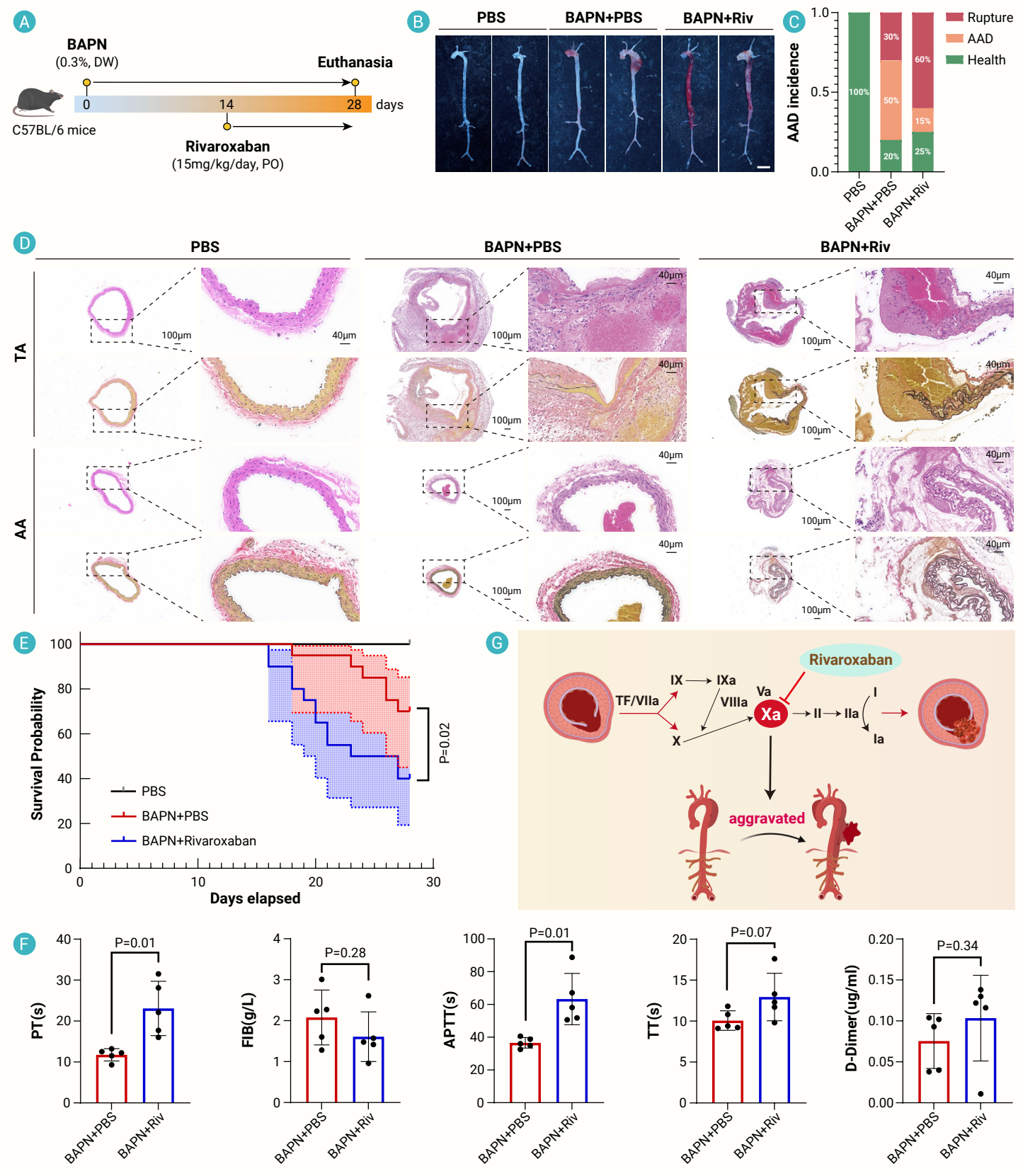

Figure 6. Rivaroxaban aggravates the progression and rupture of aortic dissection by inhibiting the coagulation process (A) Schematic illustration showing the induction process of AAD mouse model using BAPN and the timing of rivaroxaban administration. (B) Representative aortic photographs from control mice, PBS-treated AAD mice, and rivaroxaban-treated AAD mice (Scale bar, 1 cm). (C) Incidence and rupture rate of AAD. (D) Representative HE and EVG staining images of thoracic and abdominal aortas from the three groups (Scale bars: left, 100 μm; right, 40 μm). (E) Survival probability of AAD mice orally administered with PBS or rivaroxaban was estimated by the Kaplan–Meier method and compared using the log-rank test (n=20 per group; p=0.02). (F) Showing plasma PT, FIB, APTT, TT and D-Dimer levels in AAD mice 1 hour after oral administration of PBS or rivaroxaban (n=5 per group). G, Diagram of rivaroxaban aggravating AAD. Tear of the aortic intima activates the coagulation process, and rivaroxaban blocks the subsequent coagulation cascade by inhibiting the activation of factor X, which is an important mechanism contributing to the progression of AAD. Studies have shown that avoiding the use of rivaroxaban in AAD mouse models can alleviate AAD progression, reduce the risk of aortic rupture, and prolong the survival time of the model mice.

risk drugs for AAD rupture, potentially due to ILT disruption and reduced aneurysm stability. Some studies suggest that although antithrombotic therapy may reduce proteolytic injury, it could also impair aneurysm stability.[35] In summary, thrombolytic therapy in patients with prior aneurysm repair should be determined individually based on clinical urgency and patient status. Larger studies are recommended to further evaluate the safety of fibrinolytic therapy in this context.

In addition to antithrombotic agents, fluoroquinolone antibiotics were frequently reported and closely linked to the development of AAD, warranting particular attention. Multiple longitudinal observational and cohort studies have confirmed these risks. A Taiwanese study demonstrated that fluoroquinolone exposure was associated with a more than twofold increased risk of AAD within 60 days, and the risk correlated positively with treatment duration.[36] A Canadian study involving over 1.74 million elderly individuals aged ≥ 65 years showed a significantly elevated risk of aortic aneurysm within 30 days (HR=2.24; 95% CI, 2.02–2.49), comparable to hypertension-related risks and notably higher than with amoxicillin (HR=1.50; 95% CI, 1.32–1.70).[37] A nationwide, propensity score-matched cohort study from Sweden similarly indicated a 66% increased risk of AAD within 60 days among adults aged ≥50 years taking fluoroquinolones compared with amoxicillin (HR=1.66; 95% CI, 1.12–2.46).[38] Consequently, the FDA and EMA have issued safety warnings highlighting the strong association between fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and AAD.[39] Our analysis also identified levofloxacin and ciprofloxacin as high-signal drugs associated with AAD rupture based on four disproportionality signals, consistent with previous studies and verifying the reliability of our findings. Future research and clinical practice should closely monitor these drugs' effects on AAD, with long-term safety evaluations required for newly developed fluoroquinolones.

Cardiotoxicity is a common adverse effect of antitumor therapy, including hypertension, arrhythmia, heart failure, thrombotic microangiopathy, and venous thrombosis.[40] Among antitumor agents, drugs targeting vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are widely utilized clinically and have distinct mechanisms of action. Bevacizumab neutralizes VEGF-A;[41] sunitinib and lenvatinib, as multitarget tyrosine kinase inhibitors,[42,43] inhibit multiple angiogenesis-related receptors; nintedanib blocks angiogenesis by inhibiting multiple kinases, including VEGFR, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR).[44] Robust evidence links these agents to AAD risk. A large-scale retrospective cohort study in 2024 revealed a significant increase in aortic dissection risk associated with VEGF inhibitors.[45] Additionally, WHO adverse reaction database data indicated that bevacizumab had the strongest association with aortic dissection (222 cases, 44.9%).[46] Based on these results, we classified bevacizumab, sunitinib, lenvatinib, and nintedanib as high-signal drugs for AAD rupture. The underlying risk mechanism is established: VEGF/VEGFR inhibitors initially decrease nitric oxide synthase and prostacyclin synthesis in endothelial cells, causing vasoconstriction and hypertension. Additionally, they impair endothelial repair functions, both recognized risk factors for AAD rupture.[47] To minimize drug-related risks, screening for aortic aneurysms before initiating VEGF/VEGFR-targeted antitumor therapy is advisable, and treatment should only commence after excluding such risks.

Our findings suggest that some glucocorticoids may increase AAD rupture risk. Notably, glucocorticoids have shown inconsistent clinical effects, sometimes with opposing outcomes. Some studies reported protective effects: by reducing tumor necrosis factor-α (TNF-α) secretion and elevating free TNF-sRII, glucocorticoids may inhibit aortic dissection formation and actively facilitate vascular remodeling.[48] Conversely, more evidence highlights potential risks: oral steroid usage correlates positively with aneurysm expansion,[49] and a 2020 study further demonstrated a dose-dependent association between oral glucocorticoids and increased AAA risk, even at low doses.[50] Consequently, our research classifies prednisone as a high-signal drug for AAD rupture. The dual effects of glucocorticoids may relate closely to dose, duration, and underlying vascular conditions (e.g., atherosclerosis or pre-existing lesions). Short-term, low-dose glucocorticoids could beneficially influence vascular remodeling through anti-inflammatory actions; in contrast, prolonged or high-dose therapy may elevate AAD occurrence and rupture risk by inducing hypertension, impairing vascular wall collagen metabolism, and reducing vascular elasticity.[51,52] Clinically, glucocorticoid treatment should balance therapeutic necessity with vascular risks, favor minimal effective doses, shorten therapy duration, and avoid unnecessary prolonged exposure. For patients requiring long-term glucocorticoid use, regular aortic screening (e.g., ultrasound) is recommended, alongside improved management of underlying conditions (hypertension, dyslipidemia) and vascular risk monitoring to minimize AAD occurrence and rupture probability.

Besides the aforementioned high-signal medications, other identified drugs contribute directly or indirectly to accelerated aortic lesion progression through mechanisms including elevated blood pressure, disrupted lipid metabolism, aortic calcification, or vascular inflammation, each warranting careful clinical consideration. Drugs increasing blood pressure include immunosuppressants (tacrolimus, cyclosporine), erythropoietin analogs (methoxy polyethylene glycol epoetin beta), and the bisphosphonate amrinone. Chronic uncontrolled hypertension raises aortic wall stress, impairing vascular mechanical stability and accelerating aneurysm expansion or dissection rupture.[53] Drugs inducing dyslipidemia include tacrolimus, which elevates total and low-density lipoprotein cholesterol, and the atypical antipsychotic olanzapine, which exacerbates aortic atherosclerosis by altering hepatic lipid metabolism.[54,55] Dyslipidemia promotes unstable atherosclerotic plaque formation, further damaging the aortic wall. Medications potentially increasing aortic calcification include the parathyroid hormone analog teriparatide (associated with vascular lesions in high-dose rodent studies) and bisphosphonate zoledronic acid. Although direct clinical evidence is lacking, their regulation of calcium-phosphorus metabolism and frequent co-occurrence of aortic calcification and aneurysms justify vigilance. Calcification reduces vascular elasticity and compliance, increasing rupture risk.

Additionally, drugs such as calcineurin inhibitors (e.g., tacrolimus) may elevate vascular inflammation, activating the TLR4 signaling pathway and downstream MyD88/TRIF-mediated responses. This process triggers NF-κB activation and ROS production, leading to upregulated inflammatory factors and adhesion molecules in vascular endothelial and smooth muscle cells.[56] Such inflammation disrupts vascular homeostasis and exacerbates remodeling, indirectly raising aneurysm incidence and rupture risks.

Myocarditis and pericarditis have been established as rare but serious adverse events associated with SARS-CoV-2 mRNA vaccines.[57] The incidence is approximately 13 per million doses in individuals aged 6 months to 64 years, with a predilection for young males aged 12 to 39 years.[58] Symptoms typically manifest within 24 to 72 hours post-vaccination.[59] It is hypothesized that inflammation from vaccine-associated histiocytic pericarditis can extend to the adjacent aortic wall. This extension may compromise aortic wall integrity through elastic fiber disruption and increased wall fragility. When combined with vaccine-associated transient hypertension,[60] this vascular vulnerability may predispose individuals to the development or even rupture of aortic dissection.[61] Despite the high efficacy of COVID-19 mRNA vaccines in preventing severe disease and mortality, continued safety surveillance, individualized risk assessment, and the formulation of rapid response strategies for adverse events remain critically important.

Despite identifying multiple previously underrecognized high-signal drugs associated with AAD rupture, this study has several unavoidable limitations. First, the data were obtained from FAERS, a voluntary reporting system in which adverse drug reaction (ADR) reports may be submitted by healthcare professionals, patients, or consumers. This contributes to potential underreporting and inherent reporting bias. Second, many reports lack key information (e.g., drug dosage, treatment duration, administration frequency, and concurrent medications) and do not include patients' baseline health status or lifestyle factors (e.g., smoking, alcohol consumption), all of which may influence ADR risk.

Notably, our disproportionality analysis was based on the adverse event reporting distribution in FAERS/JADER, rather than real-world drug utilization or population exposure data. Thus, the FAERS database cannot establish a direct causal relationship between the identified drugs and AAD rupture. Furthermore, most drugs with prominent signals are frequently prescribed to elderly patients and those with cardiovascular comorbidities—groups with an inherently higher baseline risk of AAD rupture, which inevitably introduces certain indication confounding.

Furthermore, defining high-signal drugs as the intersection of all four disproportionality methods may lead to the loss of potential meaningful

signals for AAD rupture reporting. Valid association signals of sparsely reported drugs or those with rare AAD rupture events detected by individual or partial methods were excluded for failing to meet the full overlap criteria. This conservative strategy enhances signal detection specificity at the cost of reduced sensitivity, potentially causing underidentification of relevant drug-related risks. To address this limitation, future studies could adopt a hierarchical signal classification strategy (high-signal for four-method overlap, moderate-signal for 2–3 methods, low-signal for single method) and integrate real-world population exposure data to verify these excluded signals, enabling more comprehensive screening of drug-related AAD rupture risks.

The rivaroxaban animal experiment is presented here not to confirm the risk of other high-signal drugs, but to demonstrate a validatable paradigm for translating real-world pharmacovigilance signals into preclinical investigation. This study only verifies that our screening framework can identify drugs with biologically plausible risks (as exemplified by rivaroxaban's effect on AAD rupture), but these findings cannot be extrapolated to other high-signal agents. Future research will need to independently validate each drug class using targeted preclinical models (e.g., bevacizumab for antineoplastics, levofloxacin for fluoroquinolones) and diverse animal systems (e.g., Ang II-induced AAD model, LDLR-/- knockout mouse model) to confirm individual drug risks. Meanwhile, advancements in cardiovascular organoid models may provide a more humane and scalable approach to implement this paradigm for broader drug safety assessment.

Accordingly, high-risk drugs identified in this study therefore require further validation through comprehensive clinical assessments (e.g., evaluation of temporal associations, drug withdrawal and rechallenge responses), epidemiological investigations (e.g., case–control studies, cohort studies, or meta-analyses), and laboratory verification (e.g., biomarker detection, pathological biopsy).

CONCLUSION

In summary, based on data from the FAERS/JADER databases, this study identified 40 high-signal drugs potentially associated with AAD rupture. For patients with AAD or those at high risk, the use of these drugs should follow the principle of "priority risk assessment-stratified medication management-full-course monitoring and intervention." Treatment necessity should be assessed first, and alternative drugs with lower risk should be selected whenever possible. If the use of high-risk drugs is unavoidable, clinicians should perform aortic structural screening (e.g., ultrasound, CTA) and assess relevant indicators such as blood pressure, blood lipids, and calcium–phosphorus metabolism before initiating therapy. During treatment, changes in these indicators should be monitored regularly, underlying diseases (e.g., hypertension, dyslipidemia) should be actively managed, and drug dosage or treatment duration should be adjusted promptly when necessary to reduce the risk of drug-related aortic lesion progression and rupture. Further research is required to clarify the associated risks more comprehensively.

REFERENCES

1. GBD 2023 Causes of Death Collaborators. (2025). Global burden of 292 causes of death in 204 countries and territories and 660 subnational locations, 1990-2023: a systematic analysis for the Global Burden of Disease Study 2023. *Lancet (London, England)* **406**:1811–1872. DOI:10.1016/s0140-6736(25)01917-8
2. Fukui T. (2018). Management of acute aortic dissection and thoracic aortic rupture. *J. Intensive Care* **6**:15. DOI:10.1186/s40560-018-0287-7
3. Pape L. A., Awais M., Woznicki E. M., et al. (2015). Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the international registry of acute aortic dissection. *J. Am. Coll. Cardiol.* **66**:350–358. DOI:10.1016/j.jacc.2015.05.029
4. Mazzolai L., Teixido-Tura G., Lanzi S., et al. (2024). 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur. Heart J.* **45**:3538–3700. DOI:10.1093/eurheartj/ehae179
5. Isselbacher E. M., Preventza O., Hamilton Black Iii J., et al. (2022). 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: A report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **80**:e223–e393. DOI:10.1016/j.jacc.2022.08.004
6. Peng L., Yang D. and Weng C. (2024). Sintilimab and cardiovascular toxicity. *JAMA* **331**:1333–1334. DOI:10.1001/jama.2024.0673
7. Cirmi S., El Abd A., Letinier L., et al. (2020). Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: An analysis of the FDA adverse event reporting system database (FAERS). *Cancers* **12**:826. DOI:10.3390/cancers12040826
8. Joshi A., Gawey L., Saadi C., et al. (2025). Postmarketing safety surveillance of adalimumab, secukinumab, and infliximab in hidradenitis suppurativa: An analysis of the FDA adverse events reporting system (FAERS) database. *J. Am. Acad. Dermatol.* **92**:1434–1435. DOI:10.1016/j.jaad.2025.02.031
9. Zhu Z., Li Y., Zhu C., et al. (2025). Disproportionality analysis of interstitial lung disease associated with novel antineoplastic agents during breast cancer treatment: A pharmacovigilance study. *EClinicalMedicine* **82**:103160. DOI:10.1016/j.eclinm.2025.103160
10. Tang Y., Zhang J., Fang Y., et al. (2025). Correcting mitochondrial loss mitigates NOTCH1-related aortopathy in mice. *Nat. Cardiovasc. Res.* **4**:235–247. DOI:10.1038/s44161-024-00603-z
11. Rochano-Ortiz A., San Sebastián-Jaraba I., Zamora C., et al. (2025). Excessive glycosylation drives thoracic aortic aneurysm formation through integrated stress response. *Eur. Heart J.* **46**:4988–5005. DOI:10.1093/eurheartj/ehaf556
12. Knuuti J., Wijns W., Saraste A., et al. (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* **41**:407–477. DOI:10.1093/eurheartj/ehz425
13. Wolfe R., Broder J. C., Zhou Z., et al. (2025). Aspirin, cardiovascular events, and major bleeding in older adults: Extended follow-up of the ASPREE trial. *Eur. Heart J.* **46**:4410–4422. DOI:10.1093/eurheartj/ehaf514
14. Bowman L., Mafham M., Wallendszus K., et al. (2018). Effects of aspirin for primary prevention in persons with diabetes mellitus. *N. Engl. J. Med.* **379**:1529–1539. DOI:10.1056/NEJMoa1804988
15. Gaziano J. M., Brotons C., Coppolecchia R., et al. (2018). Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): A randomised, double-blind, placebo-controlled trial. *Lancet (London, England)* **392**:1036–1046. DOI:10.1016/s0140-6736(18)31924-x
16. Arnett D. K., Blumenthal R. S., Albert M. A., et al. (2019). 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **74**:e177–e232. DOI:10.1016/j.jacc.2019.03.010
17. Visseren F. L. J., Mach F., Smulders Y. M., et al. (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* **42**:3227–3337. DOI:10.1093/eurheartj/ehab484
18. American Diabetes Association Professional Practice Committee. (2022). 10. Cardiovascular disease and risk management: Standards of medical care in diabetes-2022. *Diabetes Care* **45**:S144-s174. DOI:10.2337/dc22-S010.
19. Valgimigli M., Choi K. H., Giacoppo D., et al. (2025). Clopidogrel versus aspirin for secondary prevention of coronary artery disease: A systematic review and individual patient data meta-analysis. *Lancet (London, England)* **406**:1091–1102. DOI:10.1016/s0140-6736(25)01562-4
20. Zhang X., Gong Z., Shen Y., et al. (2025). Author Correction: Alkaline ceramidase 1-mediated platelet ceramide catabolism mitigates vascular inflammation and abdominal aortic aneurysm formation. *Nat. Cardiovasc. Res.* **4**:1206. DOI:10.1038/s44161-025-00720-3
21. Wemmelund H., Jørgensen T. M., Høgh A., et al. (2017). Low-dose aspirin and rupture of abdominal aortic aneurysm. *J. Vasc. Surg.* **65**:616–625.e614. DOI:10.1016/j.jvs.2016.04.061
22. Hariri E., Matta M., Layoun H., et al. (2023). Antiplatelet therapy, abdominal aortic aneurysm progression, and clinical outcomes. *JAMA Netw. Open* **6**:e2347296. DOI:10.1001/jamanetworkopen.2023.47296
23. Lyon A. R., López-Fernández T., Couch L. S., et al. (2022). 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur. Heart J.* **43**:4229–4361. DOI:10.1093/eurheartj/ehac244
24. Paparella D., Rotunno C., Guida P., et al. (2011). Hemostasis alterations in patients with acute aortic dissection. *Ann. Thorac. Surg.* **91**:1364–1369. DOI:10.1016/j.athoracsur.2011.01.058
25. Guan X., Li J., Gong M., et al. (2016). The hemostatic disturbance in patients with acute aortic dissection: A prospective observational study. *Medicine* **95**:e4710. DOI:10.1097/md.0000000000004710
26. Haller S. J., Crawford J. D., Courchaine K. M., et al. (2018). Intraluminal thrombus is associated with early rupture of abdominal aortic aneurysm. *J. Vasc. Surg.* **67**:1051–1058.e1051. DOI:10.1016/j.jvs.2017.08.069
27. Riveros F., Martufi G., Gasser T. C., et al. (2015). On the impact of intraluminal thrombus mechanical behavior in AAA passive mechanics. *Ann. Biomed. Eng.* **43**:2253–2264. DOI:10.1007/s10439-015-1267-x
28. Manils J., Marruecos L. and Soler C. (2022). Exonucleases: Degrading DNA to deal with genome damage, cell death, inflammation and cancer. *Cells* **11**:2157. DOI:10.3390/cells11142157
29. Røed-Undlien H., Schultz N. H., Husebråten I. M., et al. (2024). Apixaban removal during emergency surgery for type A acute aortic dissection: A prospective cohort study. *Int. J. Surg. (London, England)* **110**:7782–7790. DOI:10.1097/js9.0000000000002137
30. Hara T., Fukuda D., Tanaka K., et al. (2018). Inhibition of activated factor X by rivaroxaban attenuates neointima formation after wire-mediated vascular injury. *Eur.*

J. Pharmacol. **820**:222–228. DOI:10.1016/j.ejphar.2017.12.037
31. Konstantinides S. V., Meyer G., Becattini C., et al. (2020). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur. Heart J.* **41**:543–603. DOI:10.1093/eurheartj/ehz405
32. Rao S. V., O'Donoghue M. L., Ruel M., et al. (2025). 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the management of patients with acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **151**:e771–e862. DOI:10.1161/cir.0000000000001309
33. Warner J. J., Harrington R. A., Sacco R. L., et al. (2019). Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. *Stroke* **50**:3331–3332. DOI:10.1161/strokeaha.119.027708
34. Cameron S. J., Russell H. M. and Owens A. P., 3rd (2018). Antithrombotic therapy in abdominal aortic aneurysm: Beneficial or detrimental? *Blood* **132**:2619-2628. DOI:10.1182/blood-2017-08-743237
35. Duarte-Celada W., Rivas K., Suppakitjanusant P., et al. (2025). Safety of thrombolysis in acute ischemic stroke patients with previous aortic abdominal aneurysm repair. *J. Stroke Cerebrovasc. Dis.* **34**:108421. DOI:10.1016/j.jstrokecerebrovasdis.2025.108421
36. Lee C. C., Lee M. T., Chen Y. S., et al. (2015). Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern. Med.* **175**:1839–1847. DOI:10.1001/jamainternmed.2015.5389
37. Daneman N., Lu H. and Redelmeier D. A. (2015). Fluoroquinolones and collagen associated severe adverse events: A longitudinal cohort study. *BMJ Open* **5**:e010077. DOI:10.1136/bmjopen-2015-010077
38. Pasternak B., Inghammar M. and Svanström H. (2018). Fluoroquinolone use and risk of aortic aneurysm and dissection: Nationwide cohort study. *BMJ (Clinical research ed.)* **360**:k678. DOI:10.1136/bmj.k678
39. Bennett A. C., Bennett C. L., Witherspoon B. J., et al. (2019). An evaluation of reports of ciprofloxacin, levofloxacin, and moxifloxacin-association neuropsychiatric toxicities, long-term disability, and aortic aneurysms/dissections disseminated by the Food and Drug Administration and the European Medicines Agency. *Expert Opin. Drug Saf.* **18**:1055–1063. DOI:10.1080/14740338.2019.1665022
40. Liu X. and Li Z. (2025). The role and mechanism of epigenetics in anticancer drug-induced cardiotoxicity. *Basic Res. Cardiol.* **120**:11–24. DOI:10.1007/s00395-024-01054-0
41. Garcia J., Hurwitz H. I., Sandler A. B., et al. (2020). Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat. Rev.* **86**:102017. DOI:10.1016/j.ctrv.2020.102017
42. Motzer R. J., Escudier B., Gannon A., et al. (2017). Sunitinib: Ten years of successful clinical use and study in advanced renal cell carcinoma. *Oncologist* **22**:41–52. DOI:10.1634/theoncologist.2016-0197
43. Llovet J. M., Ricci S., Mazzaferro V., et al. (2008). Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* **359**:378–390. DOI:10.1056/NEJMoa0708857
44. Roth G. J., Binder R., Colbatzky F., et al. (2015). Nintedanib: From discovery to the clinic. *J. Med. Chem.* **58**:1053–1063. DOI:10.1021/jm501562a
45. Wu C. W., Huang H. Y., Lin S. Y., et al. (2024). Vascular endothelial growth factor inhibitors and the risk of aortic aneurysm and aortic dissection. *JAMA Netw. Open* **7**:e240940. DOI:10.1001/jamanetworkopen.2024.0940
46. Guyon J., Gouverneur A., Maumus-Robert S., et al. (2021). Association between antiangiogenic drugs used for cancer treatment and artery dissections or aneurysms. *JAMA Oncol.* **7**:775–778. DOI:10.1001/jamaoncol.2021.0210
47. Oshima Y., Tanimoto T., Yuji K., et al. (2017). Association between aortic dissection and systemic exposure of vascular endothelial growth factor pathway inhibitors in the Japanese adverse drug event report database. *Circulation* **135**:815–817. DOI:10.1161/circulationaha.116.025144
48. Zhang L., Zhou J., Jing Z., et al. (2018). Glucocorticoids regulate the vascular remodeling of aortic dissection via the p38 MAPK-HSP27 pathway mediated by soluble TNF-RII. *EBioMedicine* **27**:247–257. DOI:10.1016/j.ebiom.2017.12.002
49. Tajima Y., Goto H., Ohara M., et al. (2017). Oral steroid use and abdominal aortic aneurysm expansion - positive association. *Circ. J.* **81**:1774–1782. DOI:10.1253/circj.CJ-16-0902
50. Pujades-Rodriguez M., Morgan A. W., Cubbon R. M., et al. (2020). Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: A population-based cohort study. *PLoS Med.* **17**:e1003432. DOI:10.1371/journal.pmed.1003432
51. Jang Y. H., Choi E. Y., Lee H., et al. (2024). Long-term use of oral corticosteroids and safety outcomes for patients with atopic dermatitis. *JAMA Netw. Open* **7**:e2423563. DOI:10.1001/jamanetworkopen.2024.23563
52. Ko Y. H., Tsai M. S., Lee P. H., et al. (2013). Methylprednisolone stiffens aortas in lipopolysaccharide-induced chronic inflammation in rats. *PloS One* **8**:e69636. DOI:10.1371/journal.pone.0069636
53. Hibino M., Otaki Y., Kobeissi E., et al. (2022). Blood pressure, hypertension, and the risk of aortic dissection incidence and mortality: Results from the J-SCH study, the UK biobank study, and a meta-analysis of cohort studies. *Circulation* **145**:633–644. DOI:10.1161/circulationaha.121.056546
54. Bardou F. N., Guillaud O., Erard-Poinsot D., et al. (2019). Tacrolimus exposure after liver transplantation for alcohol-related liver disease: Impact on complications. *Transpl. Immunol.* **56**:101227. DOI:10.1016/j.trim.2019.101227
55. Chen C. H., Shyue S. K., Hsu C. P., et al. (2018). Atypical antipsychotic drug olanzapine deregulates hepatic lipid metabolism and aortic inflammation and aggravates atherosclerosis. *Cell. Physiol. Biochem.* **50**:1216–1229. DOI:10.1159/000494573
56. Rodrigues-Diez R., González-Guerrero C., Ocaña-Salceda C., et al. (2016). Calcineurin inhibitors cyclosporine A and tacrolimus induce vascular inflammation and endothelial activation through TLR4 signaling. *Sci. Rep.* **6**:27915. DOI:10.1038/srep27915
57. Fanti S., Dyer C., Ingimarsdóttir I. J., et al. (2025). Combined adaptive immune mechanisms mediate cardiac injury after COVID-19 vaccination. *Circulation* **152**:1485–1500. DOI:10.1161/circulationaha.125.074644
58. Witberg G., Barda N., Hoss S., et al. (2021). Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. *N. Engl. J. Med.* **385**:2132–2139. DOI:10.1056/NEJMoa2110737
59. Satyam S. M., El-Tanani M., Bairy L. K., et al. (2025). Unraveling cardiovascular risks and benefits of COVID-19 vaccines: A systematic review. *Cardiovasc. Toxicol.* **25**:306–323. DOI:10.1007/s12012-024-09954-2
60. Meylan S., Livio F., Foerster M., et al. (2021). Stage III hypertension in patients after mRNA-based SARS-CoV-2 vaccination. *Hypertension (Dallas, Tex. : 1979)* **77**:e56-e57. DOI:10.1161/hypertensionaha.121.17316
61. Takahashi M., Kondo T., Yamasaki G., et al. (2022). An autopsy case report of aortic dissection complicated with histiolymphocytic pericarditis and aortic inflammation after mRNA COVID-19 vaccination. *Leg. Med. (Tokyo)* **59**:102154. DOI:10.1016/j.legalmed.2022.102154

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AUTHOR CONTRIBUTIONS

Xuezhen Xuan: Responsible for data extraction from FAERS database, clinical feature analysis, imbalance analysis, high-risk drug screening, and writing of the core content of the manuscript. Xuexing Xuan: Responsible for synchronous data analysis of JADER database, cross-database result verification, and core writing of the manuscript. Jia Li: Responsible for animal experiment-related work including AAD mouse model construction, coagulation function detection, and pathological staining. Xin Guan: Responsible for the collection and visualization of experimental data. Wei Wang: Focused on the risk mechanism analysis of antithrombotic drugs, tumor/antibiotic drugs, and immune/anti-inflammatory drugs. Sichong Qian: Jointly reviewed the scientificity of the manuscript. Hongjia Zhang: Led the overall research design and establishment of scientific issues, determined the research framework. Haiyang Li: Coordinated the result integration and discussion writing of the corresponding research direction, and jointly reviewed the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

This study was approved by the Animal Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (approval No. KS2024114).

DATA AND CODE AVAILABILITY

The data used in this study are publicly available, and permission to use the databases has been obtained.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2026.100225.