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A disproportionality analysis of adverse events associated with loop diuretics in the FDA Adverse Event Reporting System (FAERS)

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Abstract

Background Loop diuretics, including furosemide, torsemide, and bumetanide, are widely utilized in the management of volume overload-related conditions. Although previous studies have extensively documented risks such as electrolyte imbalances, ototoxicity, and nephrotoxicity, real-world evidence regarding novel or underrecognized adverse event (AE) signals remains limited and underexplored.

Methods Using data from the Food and Drug Administration Adverse Event Reporting System (FAERS) from the first quarter of 2004 to the third quarter of 2024, we conducted a disproportionality analysis integrating Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Empirical Bayesian Geometric Mean (EBGM), combined with multivariate logistic regression. It is considered a significant signal when one of the four indicators meets the criteria. The temporal characteristics were elucidated via time-to-onset (TTO) analysis.

Results A total of 24,875 AE reports were analyzed, with furosemide accounting for 89.18%, torsemide for 8.33%, and bumetanide for 2.47%. Commonly reported risks included electrolyte imbalances, fluid balance disorders, and nephrotoxicity. Several novel safety signals were identified: furosemide was significantly associated with vitamin B1 deficiency (TTO = 71 days), Wernicke's encephalopathy (TTO = 2167 days), and gastrointestinal mucosal pigmentation (TTO = 549.1 days). Torsemide was associated with palisaded neutrophilic granulomatous dermatitis (TTO = 62.8 days), systemic infection (TTO = 548.3 days), pemphigoid (TTO = 470.6 days), bleeding events (involving the respiratory, gastrointestinal, and urinary tracts), and prolonged prothrombin time (TTO = 159.4 days). Bumetanide was linked to blood ketone body increased (TTO = 9.0 days), metabolic encephalopathy (TTO = 1786.0 days), and immune hypersensitivity reactions (Stevens-Johnson syndrome, pemphigoid, and lip swelling).

Conclusion This study identified both common and drug-specific AEs associated with loop diuretics, particularly focusing on the metabolic and immune risks of long-term use. To enhance patient safety, clinicians are advised to develop personalized monitoring strategies based on individual patient characteristics. For furosemide, monitoring and supplementation of vitamin B1 and magnesium are recommended. For torsemide, attention should be given to coagulation function and delayed hypersensitivity reactions. For bumetanide, close monitoring of metabolic

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disorders and immune-related skin lesions is essential. These findings support individualized therapy and precise pharmacovigilance, ensuring safer and more effective use of loop diuretics.

Keywords Furosemide, Torsemide, Bumetanide, Adverse event, Pharmacovigilance, FAERS

Introduction

Volume overload refers to an increase in extracellular fluid volume caused by sodium and water retention, which is a common pathological feature of various diseases, including congestive heart failure, end-stage liver disease, chronic kidney disease, and nephrotic syndrome [1]. Effective management of volume overload is critical for improving the prognosis of patients with these conditions [2]. Diuretics, as the cornerstone of volume management, play a central role in this process [1]. According to the 2021 European Society of Cardiology (ESC) guidelines, diuretic therapy is classified as a Class I recommendation for patients with heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) who present with symptoms of fluid overload [3]. Additionally, the 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) clinical practice guidelines recommend diuretics, particularly loop diuretics, as the first-line treatment for patients with heart failure with reduced ejection fraction (HFrEF) who have a history of or current volume overload [4]. Loop diuretics are transported to the renal tubular lumen via organic anion transporters (OAT1/2) and multidrug resistance-associated protein 4 (MRP4), where they act on the Na+/K+/2Cl – symporter (NKCC2) in the thick ascending limb of the loop of Henle to inhibit the reabsorption of Na+, K+, and Cl–, thereby promoting the excretion of water and electrolytes [5]. This mechanism not only rapidly corrects volume imbalance but also improves multi-organ function through pathways such as reducing cardiac preload and enhancing renal hemodynamics.

The use of loop diuretics is associated with a range of adverse events (AEs) that encompass multi-system pathological changes. The most common issues include electrolyte imbalances and acid-base disorders, such as hypokalemia, hyponatremia, hypomagnesemia, and metabolic alkalosis [5]. In severe cases, these changes can lead to neuromuscular symptoms like muscle weakness and intestinal paralysis, or even life-threatening arrhythmias [6]. Additionally, loop diuretics may cause dehydration-related complications, such as orthostatic hypotension and syncope, as well as prerenal azotemia [5]. Notably, the nephrotoxic risk may also arise from the inhibition of NKCC2 in the afferent arterioles, a mechanism that can activate the renin-angiotensin-aldosterone system (RAAS), exacerbating renal unit damage and ultimately leading to acute kidney injury (AKI) [7]. Metabolic abnormalities may manifest as disturbances in glucose metabolism (e.g., hyperglycemia), hyperuricemia, and lipid metabolism disorders (e.g., hypertriglyceridemia) [8]. Immune-related adverse reactions include rashes, acute interstitial nephritis, and the rare but potentially fatal conditions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [9]. Furthermore, neurological damage (such as headaches, tinnitus, and hearing loss) and hematological issues (such as thrombocytopenia) have also been reported [10]. Studies indicate that users of loop diuretics have a 40% increased risk of hearing loss over a 10-year period compared to non-users, as well as a 33% higher risk of progression of hearing loss [11].

The U.S. Food and Drug Administration (FDA)-approved loop diuretics comprise furosemide, bumetanide, torsemide, and ethacrynic acid. Given ethacrynic acid's substantial ototoxicity and elevated AE incidence, its clinical application remains strictly restricted [10]. Therefore, this study focuses on furosemide, bumetanide, and torsemide. While these agents share a common mechanism of action via NKCC2 inhibition, they exhibit marked differences in pharmacokinetics, therapeutic efficacy, and safety profiles. Pharmacokinetically, furosemide demonstrates wide interindividual variability in oral bioavailability (10–100%), with approximately 50% renal excretion, resulting in a prolonged elimination half-life (2–3 times the baseline) in cases of renal impairment [12]. In contrast, torsemide and bumetanide exhibit high oral bioavailability (80–100%) and predominantly hepatic metabolism (torsemide: 80%; bumetanide: 50%), maintaining stable clearance in renal dysfunction but necessitating dose adjustments in hepatic insufficiency [12]. In terms of efficacy and safety, each drug has its own characteristics. Furosemide, as a traditional first-line medication, is widely used in the treatment of heart failure and edema but carries a higher risk of ototoxicity [1]. Bumetanide, with 40 times the diuretic potency of furosemide and a stronger affinity for the NKCC2 transporter, can effectively overcome furosemide resistance while significantly reducing the risk of ototoxicity [1, 13]. Torsemide combines diuretic and anti-aldosterone effects, with a longer half-life (3–4 h), providing a more stable diuretic effect. This makes it potentially safer and more effective in heart failure patients, as evidenced by a reduction in hypokalemia (torsemide 12.9% vs. other diuretics 17.9%) and mortality (torsemide 2.2% vs. other diuretics 4.5%) [13, 14]. However, the Torsemide Comparison with Furosemide

for Management of Heart Failure (TRANSFORM-HF) trial failed to demonstrate that torsemide was superior to furosemide in terms of all-cause mortality and readmission rates [15]. This conflicting evidence challenges previous conclusions and underscores the necessity for rigorous comparative safety evaluations among loop diuretics.

Existing observational studies and randomized controlled trials (RCTs) have limitations in assessing drug safety, including insufficient sample sizes, short follow-up periods, and inadequate capacity to capture rare AEs [16]. As one of the largest pharmacovigilance databases globally, the FDA Adverse Event Reporting System (FAERS) provides a unique perspective for analyzing the real-world safety of drugs [17]. The FAERS database contains individual safety reports from around the world, documenting AEs associated with drugs across different patient populations. By conducting disproportionality analysis, potential safety signals can be identified, and the associations between drug-event combinations can be evaluated [18]. This study aims to systematically summarize the adverse reaction profiles of furosemide, torsemide, and bumetanide using the FAERS database, revealing potential or underappreciated new risk signals and exploring their mechanisms and clinical significance to optimize individualized medication decisions.

Materials and methods

Data source and study design

This study conducted a retrospective pharmacovigilance analysis by querying the FAERS database from the first quarter (Q1) of 2004 to the third quarter (Q3) of 2024. FAERS is a publicly accessible post-marketing safety monitoring database that primarily collects AE reports submitted by healthcare professionals, pharmaceutical companies, patients, and others. It includes seven types of files: Demographic and Administrative Information (DEMO), Drug Information (DRUG), Adverse Events (REAC), Patient Outcomes (OUTC), Report Source (RPSR), Drug Therapy Start and End Dates (THER), and Indications (INDI). Each file is linked through the "caseid" and "primaryid," allowing us to obtain information about patients and AEs. The "drug_seq" variable in the DRUG and THER files records drug usage and treatment information. The FAERS dataset is available for download on the FDA website (https://fis.fda.gov/extensions/FPDQDE-FAERS/FPD-QDE-FAERS.html). Since the data in FAERS is anonymous and publicly available, the requirement for informed consent and approval from an institutional review board is waived. This research adheres to the READUS-PV guidelines for disproportionality analysis of drug safety signals based on individual case safety reports in pharmacovigilance [18]. The target drugs are three classic loop diuretics (furosemide, torsemide, and bumetanide), with all FAERS drugs serving as the background to identify potential AE signals related to loop diuretics.

Data extraction

This study downloaded ASCII report files from the FAERS database and then imported and processed the data using R Studio (version 4.2.2). Identify the target loop diuretics in the DRUG file by utilizing both generic names and brand names, including furosemide (Lasix, Furix, Seguril), torsemide (Torasemide, Demadex, Torem), and bumetanide (Bumex, Burinex, Bumetadine). More detailed and comprehensive information is provided in Supplementary Table S1. Files such as DEMO, DRUG, REAC, and INDI related to the same case were merged based on "primaryid" and "caseid," duplicate data were removed, and only the most recent reports were retained based on the date. To enhance the accuracy of the association between drugs and AEs, the analysis was limited to drug records in the DRUG file where "role_cod" was designated as "primary suspect (PS)." AEs related to the target drugs were standardized and classified according to the Preferred Terms (PTs) and System Organ Classes (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA). The data extraction process is illustrated in Fig. 1.

Descriptive analysis

This study conducted a descriptive analysis of reports related to furosemide, torsemide, and bumetanide in the FAERS database. Demographic characteristics included patient age, gender, country of report, reporter, report date, indication, and outcomes. We plotted the trend of AE reports associated with loop diuretics by year and quarter. The time to onset (TTO) of loop diuretic-related AEs was defined as the interval between the date of AE onset (EVENT_DT) and the date of drug initiation (START_DT). Records with inaccurate or missing dates, as well as cases where the AE onset date was earlier than the loop diuretic initiation date, were excluded. Additionally, for the new risk signals identified through proportional imbalance analysis, we calculated the mean TTO in days corresponding to each PT and plotted a distribution chart to illustrate the occurrence timing of adverse reactions [19].

Disproportionality analyses

Disproportionality analysis is a commonly used method for monitoring AEs. We employed Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Empirical Bayes Geometric Mean (EBGM) to detect the signal strength of loop diuretics at the SOC and PT levels in the FAERS database [16]. The equations for the four

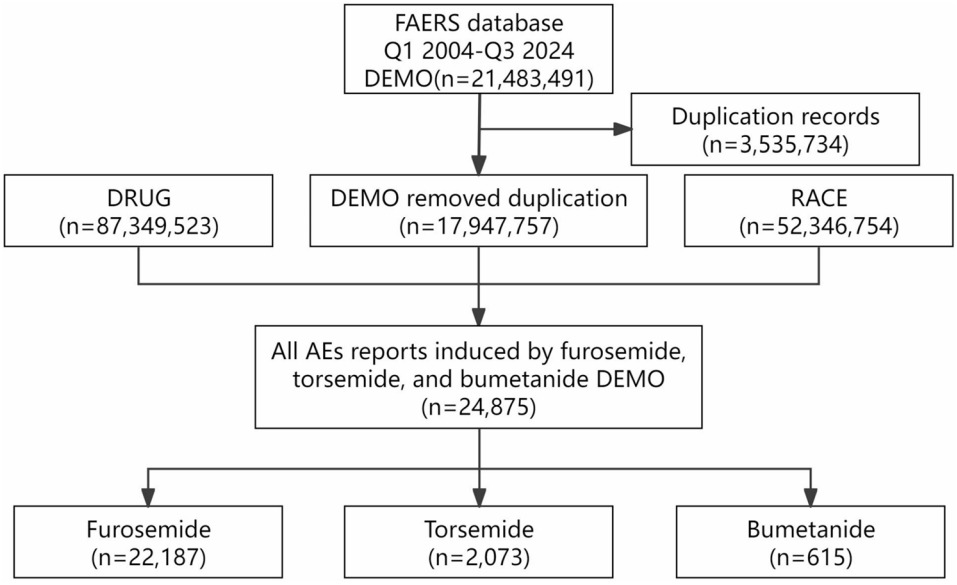

Fig. 1 Flowchart for selecting AEs related to furosemide, torsemide, and bumetanide from the FAERS database

Table 1 Algorithms and thresholds for signal detection

Algorithms	Equation	Threshold
ROR	$ROR = ad/bc$ $95\%CI = e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)\text{^}0.5}$	$a \geq 3$ ROR > 1 95%CI (lower limit) > 1
PRR	$PRR = a\,(c+d)/c/\,(a+b)$ $\chi^2 = [(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]$	$a \geq 3$ PRR ≥ 2 95%CI (lower limit) > 1
BCPNN	$IC = \log_2 a(a+b+c+d)(a+c)(a+b)$ $95\%\ CI = e^{\ln(IC)\pm1.96(1/a+1/b+1/c+1/d)\ \text{^}\ 0.5}$	IC025 > 0
EBGM	$EBGM = a(a+b+c+d)/(a+c)/(a+b)$ $95\%\ CI = e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)\text{^}0.5}$	EBGM05 > 2

Notes: a, the number of reports that simultaneously include the suspect drug and the suspect adverse drug reaction; b, the number of reports that include the suspect adverse drug reaction but are related to other medications (excluding the drug of interest); c, number of reports containing the suspect drug with other adverse drug reactions (except the event of interest); d, number of reports containing other medications and other adverse drug reactions

algorithms are detailed in Table 1. ROR, by introducing a continuity correction factor, adjusts for small sample bias and has high sensitivity, while PRR, through constructing a statistical model of observed-to-expected ratios, provides higher specificity [20, 21]. BCPNN and EBGM optimize the detection of low-frequency events by correcting with Bayesian prior distributions, making them effective for identifying rare event signals [22]. The synergistic integration of these algorithms achieves optimized signal discrimination through complementary error control mechanisms and adaptive data harmonization, thereby significantly enhancing the sensitivity and specificity of pharmacovigilance signal detection. A significant signal was considered when any one of the four criteria was met, indicating a potential association between the drug and the AE.

Statistical analysis

Descriptive statistics were employed to summarize the clinical characteristics of reports related to loop diuretics, including patient demographic information, geographical distribution, clinical outcomes, and sources of reporting. For continuous variables such as age, the median and interquartile range (IQR) were calculated. The distribution of categorical variables was summarized using frequencies and percentages. The results of the statistical analysis were presented using Microsoft Excel 2021. For potential AEs, univariate analysis was first conducted to screen for PTs that met the criteria of ROR with a 95% confidence interval (CI) lower limit > 1 and p-adjusted < 0.01. Subsequently, for the PTs with p-values less than 0.01 from the univariate analysis, a multivariate logistic regression analysis was performed to further clarify and refine the new potential AEs that may exist for the three drugs [23]. Finally, TTO analysis was performed

on the identified key AE signals to further elucidate their temporal characteristics.

Results

Basic information on adverse event reports

From Q1 2004 to Q3 2024, the FAERS database contained a total of 21,483,491 records. After removing duplicate entries, 17,947,757 records were retained. The total number of DRUG records amounted to 87,349,523, while the total number of REAC records reached 52,346,754. Among these, 86,635 AEs induced by loop diuretics were identified, with 24,875 AE reports explicitly associated with loop diuretics as the "PS". Basic information regarding the AE reports is presented in Fig. 2; Table 2. Among these, furosemide constituted 22,187 AE reports, representing 89.18% of the total. The majority of the reported patients were female (42.94%) and aged 65 years or older (52.13%). In terms of clinical outcomes, the hospitalization rate was 46.72%, and the proportion of death or life-threatening events was 12.72%. The primary sources of reports were France (19.80%) and the United States (19.25%), with peak reporting years in 2020 (2,538 cases) and 2021 (2,563 cases). Torsemide accounted for 2,073 AE reports, representing 8.33% of the total. Patients aged 65 years or older made up the largest proportion (70.48%), and the gender distribution was approximately equal (47.76% female, 48.67% male). Regarding clinical outcomes, the hospitalization rate was 59.71%, and death or life-threatening events accounted for 12.23%. The majority of reports originated from Germany (42.55%), with peak reporting years in 2020 (266 cases) and 2022 (276 cases). Bumetanide accounted for 615 AE reports, representing 2.47% of the total. A high proportion of reports lacked age data (47.15%), and the percentage of male patients (39.67%) slightly exceeded that of female patients (33.82%). In terms of clinical outcomes, the hospitalization rate was 46.77%, and death or life-threatening events accounted for 12.90%. Most reports originated from the United States (63.90%), with a peak reporting year in 2018 (92 cases). For all three drugs, more than half of the reports were submitted by healthcare professionals, with torsemide having the highest proportion of reports from healthcare professionals (80.90%).

Disproportionality analysis of adverse events based on system organ classification

The study employed the signal detection method to identify the SOC characteristics of AEs associated with three loop diuretics, as presented in Fig. 3 and Supplementary Table S2. The results indicated that the SOCs with significant signals shared by all three drugs (meeting at least one criterion) included metabolism and nutrition disorders, renal and urinary disorders, cardiac disorders, vascular disorders, investigations, ear and labyrinth disorders, and respiratory, thoracic, and mediastinal disorders. Among these, bumetanide demonstrated the strongest association with investigations and ear and labyrinth disorders, whereas furosemide exhibited the most significant associations with the remaining SOCs. The SOCs jointly associated with furosemide and torsemide included endocrine disorders, hepatobiliary disorders, and blood and lymphatic system disorders. Further analysis revealed that furosemide displayed stronger signal intensity in endocrine disorders, while torsemide showed stronger associations with hepatobiliary disorders and blood and lymphatic system disorders. Specific association analyses identified SOCs uniquely associated with each drug. For torsemide, these included congenital, familial, and genetic disorders as well as gastrointestinal disorders. In contrast, bumetanide was uniquely

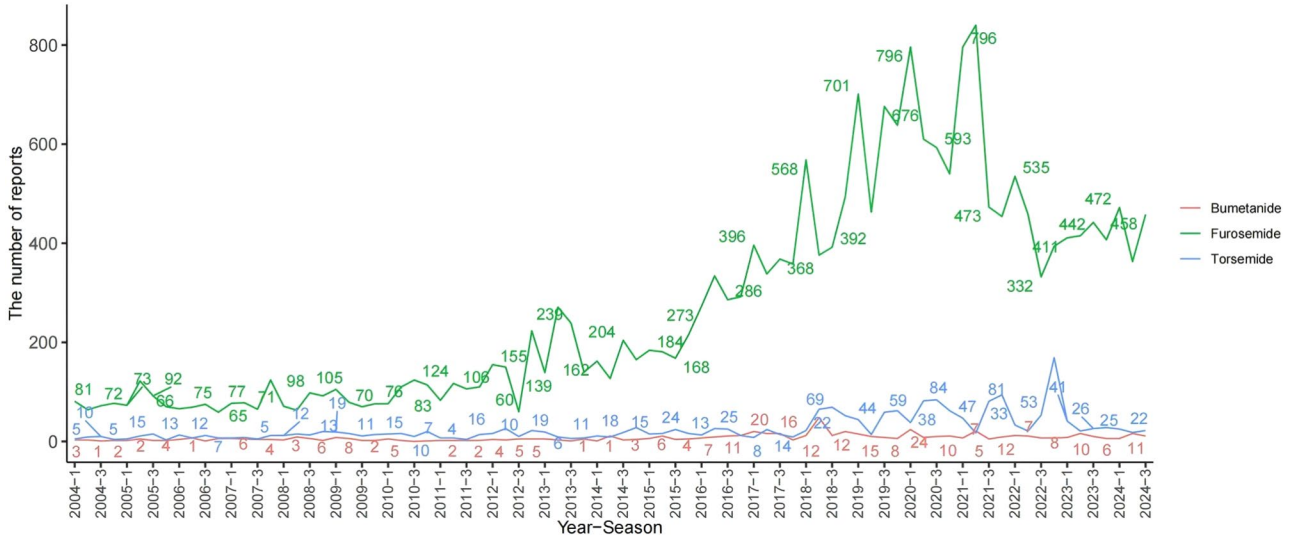

Fig. 2 Trends in reporting of furosemide, torsemide, and bumetanide

Table 2 Clinical characteristics of Furosemide, torsemide, and bumetanide reports

	Furosemide *n* (%)	Torsemide *n* (%)	Bumetanide *n* (%)
Number of reports	22,187	2073	615
Gender			
Female	9528(42.94)	990(47.76)	208(33.82)
Male	8252(37.19)	1009(48.67)	244(39.67)
Unknown	4407(19.86)	74(3.57)	163(26.50)
Age			
Median (interquartile)	74.00(62.00,84.00)	77.00(68.00,84.00)	72.00(62.00,80.00)
<18	580(2.61)	13(0.63)	4(0.65)
18～65	4147(18.69)	351(16.93)	100(16.26)
>=65	11,566(52.13)	1461(70.48)	221(35.93)
Unknown	5894(26.57)	248(11.96)	290(47.15)
Reported countries			
France	4393(19.80)	0	
United States	4272(19.25)	366(17.66)	393(63.90)
Italy	2257(10.17)		
United Kingdom	2065(9.31)		68(11.06)
Germany	386(1.74)	882(42.55)	
Other countries	8814(39.73)	825(39.80)	154(25.04)
Reporter			
Healthcare professionals	17,682(79.70)	1677(80.90)	405(65.85)
Non-healthcare professionals	3296(14.86)	322(15.53)	184(29.92)
Unknown	1209(5.45)	74(3.57)	26(4.23)
Outcomes			
Hospitalization	12,948(46.72)	1460(59.71)	261(46.77)
Other serious	10,709(38.64)	634(25.93)	192(34.41)
Death	1868(6.74)	147(6.01)	46(8.24)
Life threatening	1658(5.98)	152(6.22)	26(4.66)
Disability	355(1.28)	33(1.35)	12(2.15)
Required intervention	139(0.50)	9(0.37)	21(3.76)
Congenital anomaly	38(0.14)	10(0.41)	
Indications			
Hypertension	3152(14.11)	170(8.13)	0
Cardiac failure	2755(12.34)	160(7.66)	99(15.62)
Oedema or swelling	2552(11.43)	82(3.92)	37(5.84)
Kidney disease	317(1.42)	0	0
Others	3494(15.64)	303(14.50)	189(29.81)
Unknown	10,064(45.06)	1375(65.79)	309(48.74)

associated with skin and subcutaneous tissue disorders, immune system disorders, and musculoskeletal and connective tissue disorders. This revised version ensures clarity, academic rigor, and smooth flow while maintaining the original meaning.

Disproportionality analysis of adverse events based on preferred terms

Through systematic signal mining at the PT level of the MedDRA® classification system, this study identified distinct PT-specific AE profiles associated with three loop diuretics. The signal detection results revealed that furosemide, torsemide, and bumetanide exhibited 159, 161, and 58 positive signals at the PT level, respectively, with detailed information provided in Supplementary Table S3. Among these, 28 PT signals were shared by all three drugs, and all simultaneously met the criteria of the four algorithms, as detailed in Table 3. As expected, these shared signals were all documented in the current drug labels and were primarily related to electrolyte imbalances, fluid balance abnormalities, and nephrotoxicity. Signal intensity analysis revealed that metabolic alkalosis presented the highest risk association for furosemide (ROR = 152.39) and torsemide (ROR = 50.85), while the strongest signal for bumetanide was polyuria (ROR = 50.76). The distribution of case numbers further indicated that the top three high-frequency AEts for furosemide were hyponatremia (n = 1,655), hypokalemia (n = 1,646), and hypotension (n = 1,550). For torsemide, the most common events were dehydration (n = 230),

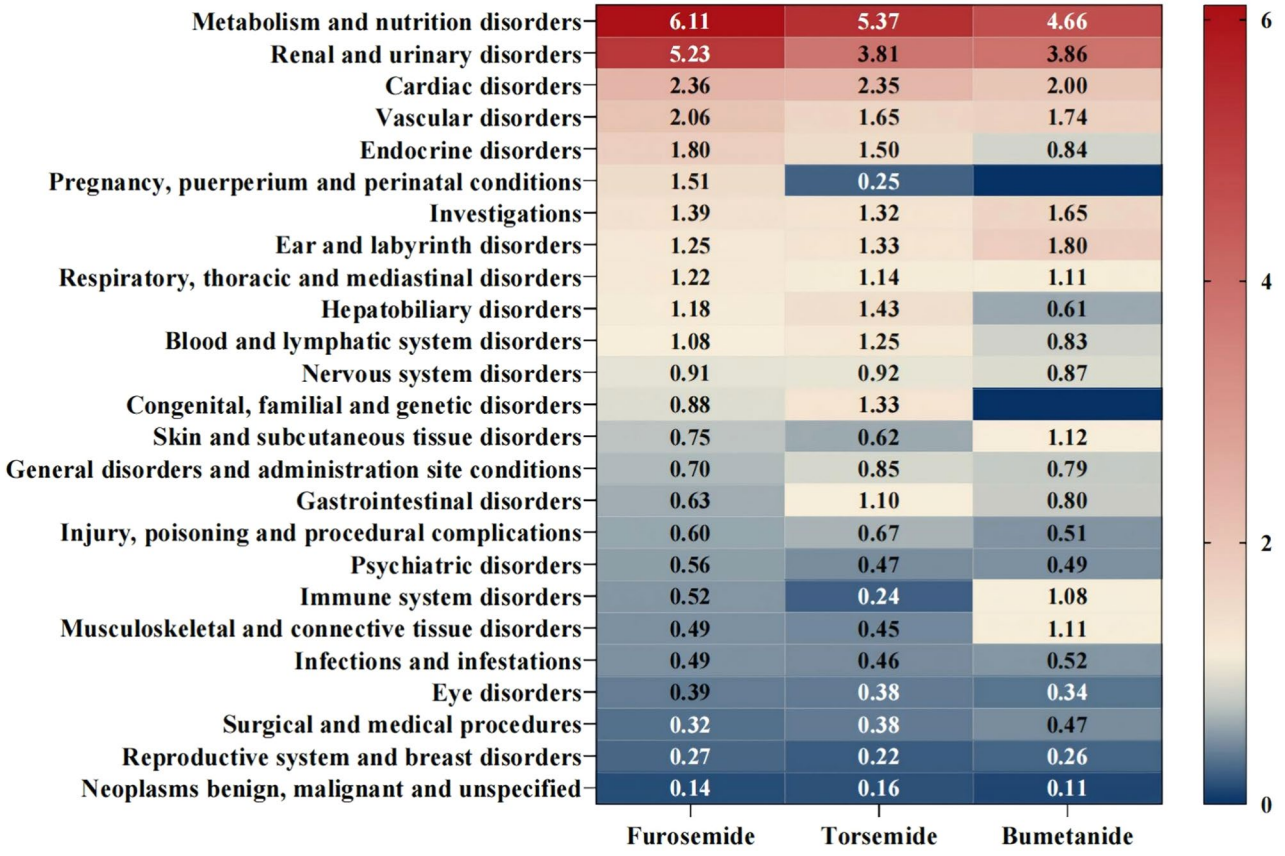

Fig. 3 Signal strength at the SOC level for furosemide, torsemide, and bumetanide. The heatmap shows the ROR values for AEs in the FAERS database under different loop diuretic treatment strategies

hypokalemia ($n = 143$), and hyponatremia ($n = 133$). For bumetanide, the most frequent events were hypotension ($n = 42$), dehydration ($n = 39$), and hypokalemia ($n = 25$).

By employing four disproportionality analysis methods combined with a multivariate logistic regression model, this study unexpectedly identified several potential AEs with significant statistical associations. The detailed results are presented in Table 4 and Supplementary Table S4. Signal strength was classified as strong ($IC025 > 3.0$) or moderate ($1.5 < IC025 \leq 3.0$). For furosemide, three strong signals were identified: vitamin B1 deficiency, gastrointestinal tract mucosal pigmentation, and Wernicke's encephalopathy. Torsemide showed five strong signal associations, including palisaded neutrophilic granulomatous dermatitis, systemic infection, respiratory tract haemorrhage, coarctation of the aorta, and pemphigoid. Notably, although signals for haematochezia ($n = 45$, $p < 0.01$), haematemesis ($n = 19$, $p < 0.01$), haematuria ($n = 18$, $p < 0.01$), TEN ($n = 8$, $p < 0.01$), and prothrombin time prolonged ($n = 7$, $p < 0.01$) did not rank among the strongest, their relatively high reporting frequency ($n \geq 3$) and significant associations in multivariate logistic regression analysis suggest potential specific links. For bumetanide, two strong signals were detected: blood ketone body increased and metabolic encephalopathy. Additionally, cases of lip swelling ($n = 6$, $p < 0.01$), SJS ($n = 4$, $p < 0.01$), and pemphigoid ($n = 3$, $p < 0.01$) were observed, all reaching statistical significance.

Time-to-onset analysis of new signals at the preferred term level

To further elucidate the temporal characteristics of the newly identified AE signals, this study conducted a TTO analysis at the PT level, with the results presented in Fig. 4 and Supplementary Table S5. The results showed that for furosemide-specific PTs, the mean TTO days from highest to lowest were as follows: Wernicke's encephalopathy (2,167.0 days), gastrointestinal tract mucosal pigmentation (549.1 days), and vitamin B1 deficiency (71.0 days). For torsemide-specific PTs, the top three PTs with the longest average TTO days were haematuria (2,868.0 days), respiratory tract haemorrhage (2,004.0 days), and haematemesis (1,406.0 days), while the bottom three were TEN (33.8 days), palisaded neutrophilic granulomatous dermatitis (62.8 days), and coarctation of the aorta (77.0 days). In the bumetanide group, a polarized trend was observed: metabolic encephalopathy had the latest onset (1,786.0 days, approximately 4.9

Table 3 Signal strength of shared adverse events at the PT level for Furosemide, torsemide, and bumetanide

Preferred Term (PT)	Furosemide		Torsemide		Bumetanide	
	N	ROR (95CI lower limit)	*N*	ROR (95CI lower limit)	*N*	ROR (95CI lower limit)
Metabolic alkalosis	250	152.39(132.87)	12	50.85(28.79)	3	50.02(16.1)
Hypovolaemia	228	31.23(27.35)	23	25.48(16.91)	11	48.49(26.8)
Hypokalaemia	1646	29.89(28.44)	143	20.92(17.73)	25	14.38(9.69)
Hyponatraemia	1655	23.92(22.77)	133	15.58(13.13)	14	6.43(3.8)
Hyperkalaemia	962	22.56(21.15)	78	14.9(11.92)	18	13.59(8.55)
Acute kidney injury	3448	19.53(18.86)	200	9.08(7.89)	66	11.85(9.27)
Orthostatic hypotension	398	17.99(16.29)	18	6.66(4.2)	10	14.7(7.9)
Pemphigoid	142	16.82(14.24)	15	14.63(8.81)	3	11.5(3.71)
Hypomagnesaemia	252	14.9(13.15)	12	5.84(3.32)	11	21.27(11.76)
Polyuria	127	12.16(10.2)	14	11.11(6.57)	16	50.76(31.02)
Electrolyte imbalance	145	10.3(8.74)	65	38.77(30.35)	5	11.68(4.86)
Blood urea increased	191	8.48(7.35)	12	4.43(2.51)	13	19.18(11.12)
Hypocalcaemia	193	8.15(7.07)	18	6.33(3.98)	6	8.35(3.75)
Cardiac failure acute	63	7.69(6)	8	8.15(4.07)	5	20.13(8.37)
Dehydration	1216	7.17(6.78)	230	11.44(10.03)	39	7.62(0.55)
Brain natriuretic peptide increased	28	7.12(4.9)	4	8.49(3.18)	3	25.29(8.15)
Syncope	824	6.43(6)	104	6.78(5.59)	24	6.2(4.15)
Hypotension	1550	6.15(5.85)	153	5.05(4.3)	42	5.5(4.05)
Cardiac failure	614	6(5.54)	83	6.79(5.47)	17	5.5(3.41)
Bradycardia	383	5.52(4.99)	60	7.24(5.62)	10	4.77(2.56)
Blood creatinine increased	434	5.1(4.64)	40	3.92(2.88)	25	9.8(6.6)
Renal impairment	489	4.69(4.29)	116	9.37(7.8)	21	6.68(4.35)
Glomerular filtration rate decreased	63	4.4(3.43)	7	4.09(1.95)	3	6.94(2.23)
Rash maculo-papular	114	4.12(3.42)	12	3.63(2.06)	5	5.99(2.49)
Fluid retention	247	3.75(3.31)	24	3.05(2.05)	20	10.15(6.54)
Oedema peripheral	552	3.41(3.14)	127	6.63(5.56)	20	4.18(2.69)
Pancreatitis acute	86	3.08(2.49)	15	4.51(2.72)	6	7.21(3.24)
Right ventricular failure	29	3.03(2.1)	5	4.38(1.82)	4	13.9(5.21)

Table 4 New signal strength at the PT level for Furosemide, torsemide, and bumetanide

Drug	Preferred Term (PT)	*N*	ROR (95% CI)	*p*
Furosemide	Vitamin b1 deficiency	65	156.59(119.63, 204.97)	<0.01
	Gastrointestinal tract mucosal pigmentation	38	145.61(102.63, 206.59)	<0.01
	Wernicke's encephalopathy	41	64.48(46.82, 88.81)	<0.01
Torsemide	Palisaded neutrophilic granulomatous dermatitis	6	1592.54(645.57, 3928.58)	<0.01
	Systemic infection	28	108.04(74.3, 157.1)	<0.01
	Respiratory tract haemorrhage	3	31.55(10.14, 98.15)	<0.01
	Coarctation of the aorta	5	31.39(13.03, 75.61)	<0.01
	Haematochezia	45	5.52(4.11, 7.39)	<0.01
	Haematemesis	19	4.81(3.06, 7.54)	<0.01
	Haematuria	18	3.34(2.1, 5.31)	<0.01
	Pemphigoid	15	14.63(8.81, 24.3)	<0.01
	Toxic epidermal necrolysis (TEN)	9	3.97(2.07, 7.64)	<0.01
	Prothrombin time prolonged	7	7.01(3.34, 14.72)	<0.01
Bumetanide	Blood ketone body increased	3	109.76(35.28, 341.5)	<0.01
	Metabolic encephalopathy	4	34.77(13.03, 92.8)	<0.01
	Lip swelling	6	4.73(2.12, 10.54)	<0.01
	Stevens-Johnson syndrome (SJS)	4	4.62(1.73, 12.32)	<0.01
	Pemphigoid	3	11.5(3.71, 35.71)	<0.01

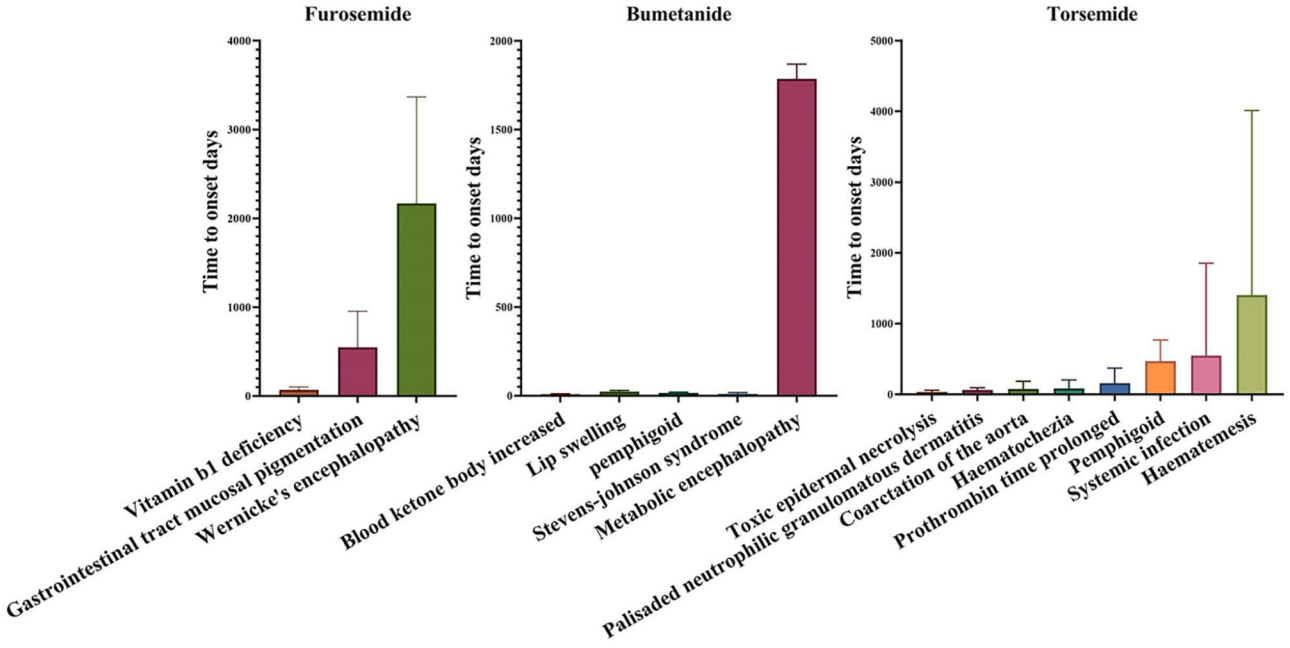

Fig. 4 Mean time to onset of new adverse event signals for furosemide, torsemide, and bumetanide

years), while immune-related reactions such as blood ketone body increased (9.0 days) and SJS (11.1 days) had the fastest onset.

Discussion

This real-world evidence study not only confirmed the common risks outlined in loop diuretic labels but also uncovered distinct drug-specific safety profiles and novel risk signals. Key findings revealed: Furosemide accounted for the predominant share (89.18%) of AE reports, reflecting its status as the first-approved and most widely used agent in this class [6]. A significant age-related pattern was observed, with patients aged ≥ 65 years accounting for more than 50% of cases across all three drugs. This demographic correlation aligns with the higher prevalence of heart failure and chronic kidney disease in the elderly population [24]. Geographically, the United States, as the primary data source, contributed the majority of reports, while Germany and France, with their well-established medical monitoring systems and high levels of aging populations (over 20% aged 65 and above), jointly facilitated the identification and reporting of AEs [25, 26]. Notably, more than half of the AE reports were submitted by healthcare professionals, underscoring the pivotal role of clinician-driven surveillance in pharmacovigilance. In terms of common safety signals, high-frequency AEs such as metabolic disturbances and acute kidney injury were consistent with the pharmacological mechanisms and established safety profiles of loop diuretics [6]. However, newly identified signals not documented in drug labels revealed distinct risk characteristics for each drug. For furosemide, novel risks included metabolic accumulation issues, such as vitamin B1 deficiency, Wernicke's encephalopathy, and gastrointestinal tract mucosal pigmentation. Torsemide was significantly associated with palisaded neutrophilic granulomatous dermatitis, systemic infection, respiratory tract haemorrhage, and coarctation of the aorta. It also frequently presented with coagulation abnormalities (e.g., prothrombin time prolonged and bleeding events) and immune hypersensitivity reactions (e.g., pemphigoid and TEN). Bumetanide, on the other hand, was linked to new metabolism-related signals, such as elevated blood ketones and metabolic encephalopathy, as well as immune hypersensitivity reactions, including pemphigoid, lip swelling, and SJS. These findings provide important evidence for further investigation into the risk-benefit profiles of individual loop diuretics, highlighting the need for tailored safety monitoring and clinical management strategies.

A newly identified AE signal common to all three loop diuretics is pemphigoid. Previous studies on pemphigoid have primarily focused on furosemide, while research and reports on torsemide and bumetanide remain scarce, with no mention of their potential association with pemphigoid in drug labeling [27–29]. Pemphigoid is a common autoimmune blistering disorder characterized by the production of autoantibodies targeting the BP180 and BP230 proteins at the dermal-epidermal junction [30]. These autoantibodies trigger immune responses and proteolysis-induced tissue damage. Previous studies have established a significant association between furosemide

and pemphigoid development, with its pathogenic mechanism potentially linked to the sulfhydryl group in its molecular structure, which may induce autoantibody production [29, 31, 32]. Our study demonstrated that torsemide and bumetanide are also associated with the occurrence of pemphigoid. Moreover, recent research has shown that in patients with type 2 diabetes treated with dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., gliptins), the concurrent use of loop diuretics significantly increases the risk of drug-induced pemphigoid [33]. Although drug-induced pemphigoid is generally mild and typically resolves rapidly after discontinuation of the causative drug, it is often overlooked or misdiagnosed as other dermatological conditions, potentially delaying proper diagnosis and treatment [27, 28]. Therefore, this AE warrants greater clinical attention.

Long-term use of furosemide necessitates careful monitoring for vitamin B1 (thiamine) deficiency and its associated secondary neurological risks. Thiamine, a critical coenzyme in glucose metabolism, is essential for maintaining normal cellular function, and its deficiency can lead to multisystem damage and potentially life-threatening outcomes [34]. Both animal studies and clinical observations have demonstrated that furosemide increases urinary thiamine excretion, resulting in reduced plasma thiamine levels [35, 36]. In patients with heart failure, prolonged use of furosemide (80–240 mg/day) significantly elevates urinary thiamine excretion, with excretion rates positively correlated with urine output [37]. However, the dose-dependency of this effect remains controversial. For instance, Zenuk et al. [38] reported that 96% of patients receiving high-dose furosemide (≥ 80 mg/day) experienced severe thiamine deficiency compared to 57% in the low-dose group, whereas Teigen et al. [39] did not observe a clear dose-response relationship. Although thiamine deficiency may not be a specific AE of diuretics, this study observed a significant safety signal predominantly in furosemide-related AEs. Further analysis revealed a mean TTO of 71.0 days, underscoring the importance of routine monitoring and thiamine supplementation in furosemide users. Of greater concern is the progression of thiamine deficiency to Wernicke's encephalopathy, a neurological disorder characterized by altered consciousness, ophthalmoplegia, and ataxia. This condition may be exacerbated by concurrent magnesium deficiency [40, 41]. Notably, long-term furosemide use has been shown to increase magnesium excretion by up to 400%, which not only impairs the conversion of thiamine to its active form but also directly contributes to neurotoxicity, such as cerebellar vermis abnormalities, thereby worsening the symptoms of Wernicke's encephalopathy [42]. Studies have further indicated that patients with Wernicke's encephalopathy complicated by magnesium deficiency may not respond adequately to thiamine supplementation alone, with symptoms often improving only after magnesium levels are corrected [43]. Notably, while this study observed a mean TTO of 2,167.0 days for Wernicke's encephalopathy, once the condition manifests, it can rapidly progress to irreversible damage [40]. Therefore, for patients on long-term furosemide therapy, routine monitoring and combined supplementation of thiamine and magnesium are strongly recommended. This dual approach may mitigate cascading metabolic and neurological damage associated with these deficiencies.

Compared to other loop diuretics, torsemide demonstrates more pronounced drug safety signals related to bleeding, including respiratory tract, gastrointestinal, and urinary tract bleeding, as well as prothrombin time prolonged. However, potential confounding factors must be carefully considered. Mechanistic studies suggest that torsemide may activate the RAAS system, enhance angiotensin II signaling, and upregulate angiopoietin-2 (Ang-2) expression. These changes may lead to abnormal angiogenesis and the formation of arteriovenous malformations, providing a pathological basis for gastrointestinal bleeding [44–46]. Clinical feature analysis indicates that torsemide is primarily prescribed for patients with furosemide resistance, refractory edema, and cardiorenal syndrome. These populations are often characterized by increased vascular fragility and microcirculatory dysfunction, which predispose them to bleeding. Furthermore, the co-administration rate of torsemide with anticoagulants is relatively high, and studies have shown that polypharmacy significantly increases the risk of gastrointestinal bleeding. Underlying diseases, such as pulmonary edema (which may cause respiratory tract bleeding) or renal disease (associated with hematuria), can further amplify the intensity of these bleeding signals [10]. TTO analysis revealed that haematochezia (83.4 days) and prothrombin time prolonged (159.4 days) tend to occur relatively early, whereas haematemesis (1,406 days) and haematuria (2,868 days) are characterized by delayed onset. Additionally, the study also identified a potential association between torsemide and TEN, though confounding factors such as concomitant medications (e.g., allopurinol and other known TEN-inducing agents) cannot be excluded [47]. Although only sporadic case reports have documented torsemide-induced TEN to date, heightened vigilance remains imperative given that TEN represents one of the most severe delayed-type drug-induced hypersensitivity reactions [48]. Caution is warranted during its clinical use. Other signals, such as systemic infection and coarctation of the aorta, may also be amplified by the underlying diseases or complications associated with torsemide's indications. Based on these findings, it is recommended that patients on long-term torsemide therapy undergo regular monitoring of

bleeding-related parameters (including coagulation function and occult blood tests), assess the risks associated with polypharmacy, and remain alert to potential drug hypersensitivity reactions.

Pharmacovigilance data for bumetanide reveal novel AE signals, primarily characterized by metabolic disturbances and immune-mediated hypersensitivity reactions. Notably, although bumetanide received FDA approval a decade earlier than torsemide (1983 vs. 1993), the available safety data for bumetanide are significantly limited, which may introduce analytical bias and compromise the robustness of conclusions [49]. Regarding metabolic toxicity, current prescribing information lacks explicit warnings about elevated blood ketone levels and metabolic encephalopathy. The underlying mechanisms may involve multiple pathophysiological pathways: potent diuretic effects-induced volume depletion could reduce insulin levels, thereby promoting accelerated lipolysis, while altered renal perfusion may further exacerbate ketone accumulation, ultimately leading to chronic metabolic derangements and metabolic encephalopathy [6]. TTO analysis indicates that hyperketonemia occurs rapidly (9 days), whereas metabolic encephalopathy exhibits a markedly delayed onset (1786 days), suggesting distinct pathological processes—acute metabolic imbalance versus long-term cumulative damage. In terms of immune-related risks, lip swelling, as a localized manifestation of angioedema, has not been explicitly reported in association with bumetanide or other diuretics. However, given the established link between angiotensin-converting enzyme inhibitors (ACEIs) and angioedema, this signal requires vigilance regarding confounding effects from concomitant medications (e.g., ACEIs) [50]. Additionally, SJS, a fatal T-cell-mediated hypersensitivity reaction, may be triggered by the sulfonamide moiety of bumetanide, particularly in patients with a history of sulfonamide allergy [9, 51]. Nevertheless, while multiple cases of SJS have been documented with furosemide and torsemide, no direct clinical evidence currently links bumetanide to SJS, necessitating cautious interpretation and further case validation [9, 48, 52]. In conclusion, bumetanide's pharmacovigilance data highlight potential novel risk signals. Although some signals lack robust literature support, the plausible pathophysiological mechanisms and observed correlations underscore the critical need for targeted studies to establish causality.

From a clinical perspective, the use of loop diuretics necessitates a careful consideration of their common and specific risks. All three agents—furosemide, torsemide, and bumetanide—have the potential to induce immune-related adverse events, such as pemphigus. However, long-term use of furosemide requires vigilance for Wernicke's encephalopathy, which can result from deficiencies in thiamine and magnesium. Therefore, regular monitoring and supplementation of these nutrients are recommended. Torsemide is significantly associated with an increased risk of bleeding, particularly when used in combination with anticoagulants, which necessitates enhanced monitoring of coagulation parameters. Bumetanide, on the other hand, may lead to metabolic disturbances, such as elevated ketone bodies, as well as immune-mediated hypersensitivity reactions, including SJS. This underscores the importance of monitoring metabolic indicators and reviewing patients' allergy histories. In the general population, extrapolating these risks requires careful consideration of factors such as patient heterogeneity, polypharmacy, and adherence to monitoring protocols. Clinicians should select medications and develop targeted monitoring strategies based on individual patient characteristics, focusing on aspects such as nutritional status, coagulation function, and metabolic indicators. Future research should aim to validate the extrapolation of these risks in the general population through real-world studies. Additionally, interventional trials, such as those investigating preventive nutritional supplementation, and mechanistic studies exploring the metabolic toxicity pathways of bumetanide, are essential for optimizing risk stratification management and enhancing medication safety.

This study has the following limitations: First, with respect to data sources, the FAERS database, a voluntary reporting system, is inherently susceptible to underreporting and selection bias. Additionally, the lack of certain key parameters (e.g., drug dosage) affects the determination of dose-response relationships. In particular, the relatively low number of AE reports related to bumetanide may result in the underdetection of rare or severe AEs, thereby reducing statistical power. Second, regarding controlling for confounding factors, indication bias (e.g., underlying conditions such as heart failure and nephrotic syndrome) and the interference of concomitant medications are particularly prominent. Three key issues are noteworthy: (1) Drug interactions may alter the pharmacodynamic/toxicological characteristics of diuretics; (2) Dose adjustments and changes in patient adherence due to combination therapy may affect efficacy evaluations; (3) The synergistic effects of underlying diseases and concomitant medications increase the complexity of causal inference. Although multivariate logistic regression was used for adjustment, residual confounding may still affect the reliability of the results. Third, methodologically, disproportionality analysis can only suggest statistical associations, and experimental studies are needed to verify causal mechanisms. Based on these limitations, future studies should prioritize: (1) Conduct prospective cohort studies to improve the collection of drug usage parameters and comorbidity data; (2) Perform pharmacological mechanism experiments

to validate newly identified AE signals; (3) Establish long-term drug monitoring systems, including dynamic monitoring of electrolytes, coagulation function, and metabolic indicators; (4) Integrate multimodal data such as electronic medical records and biomarkers to develop individualized drug prediction models, advancing precision pharmacovigilance.

Conclusion

This study systematically evaluated the safety profiles of three loop diuretics using data from the FAERS database. The common AE signals were primarily associated with electrolyte imbalances, volume depletion, and acute kidney injury, consistent with the pharmacological mechanisms of these drugs. Additionally, the study identified several novel adverse reactions not currently included in the drug labels: Long-term use of furosemide was significantly associated with vitamin B1 deficiency, Wernicke's encephalopathy, and gastrointestinal tract mucosal pigmentation, highlighting the need for coordinated supplementation of thiamine and magnesium. Torsemide showed bleeding-related risks (e.g., respiratory tract haemorrhage, coagulation abnormalities) and immune hypersensitivity reactions (e.g., palisaded neutrophilic granulomatous dermatitis), which may be linked to RAAS activation and the context of polypharmacy. Bumetanide indicated signals of metabolic disturbances, such as metabolic encephalopathy and elevated blood ketones, while immune-mediated lip swelling and SJS warrant caution. These findings provide clinical recommendations, emphasizing the need to balance efficacy and risks based on individual patient characteristics and to establish long-term monitoring systems to optimize safety management. Specifically: Patients on long-term furosemide therapy should monitor thiamine and magnesium levels. Regular coagulation function tests are recommended during torsemide use. Bumetanide requires vigilance for metabolic disturbances and hypersensitivity reactions.

Supplementary Information

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Supplementary Material 1

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Author contributions
LX Yu contributed to the experimental design and financial support for this study. ZH Xue, X Liu and QF Liu carried out the experimental design and data analysis and wrote the paper. ZH Xue and XM Yang performed the data of this article. LX Yu and QF Liu completed data proofreading. All authors read and approved the final manuscript.

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Data availability
All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

Declarations

Ethics approval and consent to participate
Anonymized data were collected from a publicly available database (FAERS database, https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html), the need for ethics approval and consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Novak JE, Ellison DH. Diuretics in States of volume overload: core curriculum 2022. Am J Kidney Dis. 2022;80:264–76.
2. Ezekowitz J, Alemayehu W, Edelmann F, Ponikowski P, Lam CSP, O'Connor CM, et al. Diuretic use and outcomes in patients with heart failure with reduced ejection fraction: insights from the VICTORIA trial. Eur J Heart Fail. 2024;26:628–37.
3. Authors/Task Force Members, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) with the special contribution of the heart failure association (HFA) of the ESC. Eur J Heart Fail. 2024;26:5–17.
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American college of cardiology/american heart association joint committee on clinical practice guidelines. Circulation. 2022;145:e895–1032.
5. Cuthbert JJ, Clark AL. Diuretic treatment in patients with heart failure: current evidence and future Directions – Part I: loop diuretics. Curr Heart Fail Rep. 2024;21:101–14.
6. Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug–Nutrient interactions with chronic use of commonly prescribed medications: an update. Pharmaceutics. 2018;10:36.
7. Hirai T, Kondo Y, Sakazaki Y, Seki A, Ishitsuka Y, Iwamoto T. Drug-drug interaction signals between loop diuretics and Teicoplanin during acute kidney injury evaluated using Japanese spontaneous adverse drug event reports. Sci Rep. 2023;13:13989.
8. Kelly L, Almutairi MM, Kursan S, Pacheco R, Dias-Junior E, Castrop H, et al. Impaired glucose tolerance, glucagon, and insulin responses in mice lacking the loop diuretic-sensitive Nkcc2a transporter. Am J Physiol Cell Physiol. 2019;317:C843–56.
9. Abulatan IT, Ben-David SG, Morales-Colon LA, Beason E, Fakoya AO. A compilation of drug etiologies of Stevens-Johnson syndrome and toxic epidermal necrolysis. Cureus. 2023;15:e48728.
10. Maideen NMP, Balasubramanian R, Muthusamy S. A comprehensive review of the Pharmacologic perspective on loop diuretic drug interactions with therapeutically used drugs. Curr Drug Metab. 2022;23:188–99.
11. Joo Y, Cruickshanks KJ, Klein BEK, Klein R, Hong O, Wallhagen MI. The contribution of ototoxic medications to hearing loss among older adults. J Gerontol Biol Sci Med Sci. 2020;75:561–6.

12. J G F C JJC. Diuretic treatment in patients with heart failure: current evidence and future Directions-Part II: combination therapy. Curr Heart Fail Rep. 2024;21:115–30.
13. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC State-of-the-Art review. J Am Coll Cardiol. 2020;75:1178–95.
14. Cosín J, Díez J. TORIC investigators. Torasemide in chronic heart failure: results of the TORIC study. Eur J Heart Fail. 2002;4:507–13.
15. Krim SR, Anand S, Greene SJ, Chen A, Wojdyla D, Vilaro J, et al. Torsemide vs Furosemide among patients with New-Onset vs worsening chronic heart failure: A substudy of the TRANSFORM-HF randomized clinical trial. JAMA Cardiol. 2024;9:182–8.
16. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10:796–803.
17. Liu H, Yang Q, Li Z, Yan S, Ming S. Systematic analysis of sugammadex-related adverse drug reaction signals using FAERS database. Int J Surg. 2025;111:1988–94.
18. Fusaroli M, Salvo F, Begaud B, AlShammari TM, Bate A, Battini V, et al. The reporting of a disproportionality analysis for drug safety signal detection using individual case safety reports in pharmacovigilance (READUS-PV): development and statement. Drug Saf. 2024;47:575–84.
19. Zou F, Cui Z, Lou S, Ou Y, Zhu C, Shu C, et al. Adverse drug events associated with linezolid administration: a real-world pharmacovigilance study from 2004 to 2023 using the FAERS database. Front Pharmacol. 2024;15:1338902.
20. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13:519–23.
21. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10:483–6.
22. Dumouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat. 1999;53:177–90.
23. Zhang X, Jiang Y, Guo Y, Zhou W, Qiao W, Zhu H, et al. Safety evaluation of Ceftazidime/avibactam based on FAERS database. Infection. 2024. https://doi.org/10.1007/s15010-024-02248-3.
24. Wehling M. Morbus diureticus in the elderly: epidemic overuse of a widely applied group of drugs. J Am Med Dir Assoc. 2013;14:437–42.
25. Schröder L, Seifert R. The 10 top prescribed medicines in Germany from 1985 to 2022: Pharmacological analysis. Naunyn Schmiedebergs Arch Pharmacol. 2024. https://doi.org/10.1007/s00210-024-03615-5.
26. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet. 2009;374:1196–208.
27. Boulinguez S, Bernard P, Bedane C, le Brun V, Bonnetblanc JM. Bullous pemphigoid induced by bumetanide. Br J Dermatol. 1998;138:548–9.
28. Ambur AB, Nathoo R, Saeed S. A case of Drug-Induced bullous pemphigoid with an isomorphic response and updated review of koebnerization in bullous diseases. Cureus. 2021;13:e20647.
29. Lee JJ, Downham TF. Furosemide-induced bullous pemphigoid: case report and review of literature. J Drugs Dermatol. 2006;5:562–4.
30. de Nicolas-Ruanes B, Ballester-Martinez A, Garcia-Mouronte E, Berna-Rico E, Azcarraga-Llobet C, Fernandez-Guarino M. From molecular insights to clinical perspectives in Drug-Associated bullous pemphigoid. Int J Mol Sci. 2023;24:16786.
31. Lloyd-Lavery A, Chi C-C, Wojnarowska F, Taghipour K. The associations between bullous pemphigoid and drug use: a UK case-control study. JAMA Dermatol. 2013;149:58–62.
32. Panayiotou BN, Prasad MV, Zaman MN. Frusemide-induced bullous pemphigoid. Br J Clin Pract. 1997;51:49–50.
33. Shalmon D, Bar-Ilan E, Peled A, Geller S, Bar J, Schwartz N, et al. Identification of risk factors for Gliptin-associated bullous pemphigoid among diabetic patients. Acta Derm Venereol. 2024;104:26663.
34. Smith TJ, Johnson CR, Koshy R, Hess SY, Qureshi UA, Mynak ML, et al. Thiamine deficiency disorders: a clinical perspective. Ann N Y Acad Sci. 2021;1498:9–28.
35. Yui Y, Itokawa Y, Kawai C. Furosemide-induced thiamine deficiency. Cardiovasc Res. 1980;14:537–40.
36. Rieck J, Halkin H, Almog S, Seligman H, Lubetsky A, Olchovsky D, et al. Urinary loss of thiamine is increased by low doses of Furosemide in healthy volunteers. J Lab Clin Med. 1999;134:238–43.
37. Seligmann H, Halkin H, Rauchfleisch S, Kaufmann N, Motro M, Vered Z, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term Furosemide therapy: a pilot study. Am J Med. 1991;91:151–5.
38. Zenuk C, Healey J, Donnelly J, Vaillancourt R, Almalki Y, Smith S. Thiamine deficiency in congestive heart failure patients receiving long term Furosemide therapy. Can J Clin Pharmacol. 2003;10:184–8.
39. Teigen LM, Twernbold DD, Miller WL. Prevalence of thiamine deficiency in a stable heart failure outpatient cohort on standard loop diuretic therapy. Clin Nutr. 2016;35:1323–7.
40. Cantu-Weinstein A, Branning R, Alamir M, Weleff J, Do M, Nero N, et al. Diagnosis and treatment of Wernicke's encephalopathy: A systematic literature review. Gen Hosp Psychiatry. 2024;87:48–59.
41. Flink EB. Role of magnesium depletion in Wernicke-Korsakoff syndrome. N Engl J Med. 1978;298:743–4.
42. McLean J, Manchip S. Wernicke's encephalopathy induced by magnesium depletion. Lancet. 1999;353:1768.
43. Baroncini D, Annovazzi P, Minonzio G, Franzetti I, Zaffaroni M. Hypomagnesaemia as a trigger of relapsing non-alcoholic Wernicke encephalopathy: a case report. Neurol Sci. 2017;38:2069–71.
44. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J. 1987;57:17–22.
45. Kawanami S, Egami Y, Sugae H, Ukita K, Kawamura A, Nakamura H, et al. Predictors of bleeding events in acute decompensated heart failure patients with antithrombotic therapy: AURORA study. ESC Heart Fail. 2022;10:1114–21.
46. Houston BA, Schneider ALC, Vaishnav J, Cromwell DM, Miller PE, Faridi KF, et al. Angiotensin II antagonism is associated with reduced risk for Gastrointestinal bleeding caused by arteriovenous malformations in patients with left ventricular assist devices. J Heart Lung Transpl. 2017;36:380–5.
47. Yang L, Shou Y-H, Li F, Zhu X-H, Yang Y-S, Xu J-H. Retrospective study of 213 cases of Stevens-Johnson syndrome and toxic epidermal necrolysis from China. Burns. 2020;46:959–69.
48. Reddy S, Aron BK, Stewart J. A Life-Threatening case of Torsemide-Induced toxic epidermal necrolysis associated with the treatment of Anasarca. Cureus. 2022;14:e22895.
49. Ward A, Heel RC, Bumetanide. A review of its pharmacodynamic and Pharmacokinetic properties and therapeutic use. Drugs. 1984;28:426–64.
50. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology and incidence of ACE inhibitor angioedema utilizing a large electronic health record. J Allergy Clin Immunol Pract. 2017;5:744–9.
51. Bassir F, Varghese S, Wang L, Chin YP, Zhou L. The use of electronic health records to study Drug-Induced hypersensitivity reactions from 2000 to 2021: A systematic review. Immunol Allergy Clin North Am. 2022;42:453–97.
52. Godfrey H, Jedlowski P, Thiede R. Medication associations with severe cutaneous adverse reactions: A Case/Non-Case analysis using the FDA adverse event reporting system. J Cutan Med Surg. 2024;28:51–8.

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