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Interaction between dipeptidyl-peptidase-4 inhibitors and drugs acting on renin angiotensin aldosterone system for the risk of angioedema: a pharmacovigilance assessment using disproportionality and interaction analyses

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Abstract

Background Dipeptidyl peptidase-4 inhibitors (DPP-4is) and drugs interfering with the renin-angiotensin-aldosterone system (RAAS) are frequently co-prescribed in type 2 diabetes management. Both drug classes have been independently associated with angioedema, raising concerns about potential interaction risks. This study aimed to evaluate the safety signals and interaction patterns for angioedema associated with DPP-4is alone and in combination with RAAS-interfering drugs.

Methods We conducted a comprehensive pharmacovigilance analysis using the United States Food and Drug Administration Adverse Event Reporting System (USFDA AERS) database. Disproportionality analyses employing both frequentist (Reporting Odds Ratio, Proportional Reporting Ratio) and Bayesian approaches were performed. Drug-drug interactions were assessed using multiplicative drug-drug interaction model. Additionally, we reviewed published case reports of DPP-4i-associated angioedema.

Results Analysis of 29,163,222 reports identified 588 cases of DPP-4i-associated angioedema. Significant safety signals were detected for DPP-4i monotherapies, while combinations with RAAS-interfering drugs demonstrated stronger signals through both frequentist and Bayesian analyses. Significant interaction signals were observed for sitagliptin/irbesartan, sitagliptin/valsartan, linagliptin/valsartan and alogliptin/lisinopril combinations. Alogliptin/lisinopril and sitagliptin/irbesartan combinations showed the highest risk profiles. Angioedema occurred predominantly in elderly patients (> 65 years) and females. Sixteen case reports corroborated the findings from the database assessment. Clinical outcomes were comparable between monotherapy and combination therapy groups.

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Conclusion This pharmacovigilance analysis reveals significant safety signals for angioedema with specific DPP-4i combinations with RAAS-interfering drugs, suggesting potential drug-drug interactions. These findings emphasize the need for careful patient monitoring, particularly in vulnerable populations, when prescribing these combinations. Further prospective studies are warranted to validate these findings and establish definitive causal relationships.

Keywords Sitagliptin, Saxagliptin, Alogliptin, Lisinopril, Valsartan, Irbesartan

Introduction

Dipeptidyl peptidase-4 inhibitors (DPP-4is) represent an innovative class of oral medications for type 2 diabetes that extend beyond mere glucose regulation through incretin hormones. These agents demonstrate remarkable pleiotropic effects, including antihypertensive, anti-inflammatory, antiapoptotic, and immunomodulatory actions on cardiovascular and renal systems, independent of their incretin-related mechanisms [1]. The ubiquitous enzyme DPP-4 plays a pivotal role in glucose homeostasis primarily through the degradation of incretin hormones - glucagon-like peptide-1 and gastric inhibitory polypeptide - which orchestrate insulin release and glucagon suppression [2].

Importantly, DPP-4is also influence the metabolism of vasoactive peptides, particularly bradykinin and substance P. By interfering with the breakdown of these kinins, DPP-4is can potentially trigger angioedema through enhanced vasodilation and increased capillary permeability [3]. Angioedema represents a significant healthcare burden in the United States, with angiotensin-converting enzyme inhibitors (ACEIs) implicated in approximately 25% of hospitalizations related to this condition [4].

In diabetic patients, drugs that modulate the renin-angiotensin-aldosterone system (RAAS), including ACEIs, angiotensin receptor blockers (ARBs), and direct renin inhibitors, are frequently prescribed to counteract the deleterious cardiovascular and renal effects mediated by angiotensin II [5]. The common concurrent prescription of DPP-4is with RAAS-modulating agents raises substantial concerns regarding the potential augmentation of angioedema risk [6].

While angioedema has been traditionally considered a class effect of DPP-4is, emerging evidence suggests potential intraclass variations. A notable case report documented angioedema occurrence with one DPP-4i that resolved upon switching to another agent within the same class [7]. This observation raises intriguing questions about possible differential risks among various DPP-4is. Furthermore, while ACEIs have historically been strongly associated with angioedema, recent evidence has expanded this concern to include ARBs [8].

The United States Food and Drug Administration's Adverse Event Reporting System (USFDA AERS) stands as a cornerstone in pharmacovigilance, offering crucial insights into potential drug safety signals. This comprehensive database incorporates both mandatory manufacturer reports and voluntary submissions from healthcare professionals through spontaneous reporting mechanisms [9]. Disproportionality analysis has emerged as a sophisticated statistical methodology for detecting safety signals within this database, particularly valuable in identifying adverse events that may arise from drug interactions, such as those between DPP-4is and RAAS-modulating agents [10, 11].

Given the limited evidence base regarding angioedema risk arising from potential interactions between DPP-4is and RAAS-modulating agents, we undertook a comprehensive pharmacovigilance investigation. Our study employed disproportionality analysis of the USFDA AERS database complemented by interaction analysis to elucidate this critical safety concern. This investigation aims to provide healthcare providers with essential information for making informed therapeutic decisions when managing patients requiring both classes of medications.

Methods

Data source

Data for this study were retrieved from the USFDA AERS, using the Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query (Narrow) "Angioedema" (MedDRA code: 20000024) [12]. The Preferred Terms included present in this SMQ are listed in the Electronic Supplementary Table 1. Data encompassed adverse event reports submitted to AERS from the first quarter of 2004 through the second quarter of 2024, covering a span of 82 quarterly reports.

Data processing

The USFDA AERS was systematically searched for reports involving DPP-4is as well as its combinations with drugs interfering with RAAS to ensure comprehensive retrieval of Individual Case Safety Reports (ICSRs) [13]. We excluded cases receiving concomitant metformin as few reports have associated angioedema with this drug [14, 15]. The following DPP-4is were considered: sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin, anagliptin and trelagliptin. Amongst the drugs interfering with RAAS, we have included direct renin inhibitor (aliskiren), ACEIs (benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril and trandolapril), and ARBs (azilsartan, candesartan, eprosartan, irbesartan, losartan,

Olmesartan, telmisartan and valsartan). To avoid duplication, we followed the USFDA's deduplication guidelines, sorting reports in ascending order by Case_IDs and retaining only those with the latest FDA_DT or Individual Safety Report number, representing the most recent entry. Reports were included in the final analysis only if they identified DPP-4i as the "primary suspect" drug in association with angioedema. We restricted our search to non-proprietary drug names for DPP-4i and its combination with drugs interfering with RAAS. The following variables were collected from deduplicated reports: age, gender, report year, and reporting country.

Data mining algorithms

A "case-non-case" disproportionality analysis method was employed to evaluate the association of DPP-4i (and its combinations) with angioedema by comparing the frequency of adverse event reports involving DPP-4i with reports involving all other drugs [16]. Data retrieval and analysis were conducted using the OpenVigil 2.1 platform for DPP-4i-angioedema pairs. We used two frequentist and two Bayesian data mining algorithms to detect potential safety signals for angioedema.

In the frequentist approach, we calculated the Reporting Odds Ratio (ROR) and the Proportional Reporting Ratio (PRR). The ROR for a particular drug and the associated angioedema is estimated as the number of reports pertaining to this drug-angioedema pair in comparison to the total number of reports for all other adverse events related to that same drug. This ratio is then analyzed alongside a similar ratio for all other drugs to compute the ROR [17]. In contrast, the PRR is determined by comparing the proportion of angioedema cases linked to the drug of interest with the proportion of angioedema cases linked to all other drugs [17]. Signal detection criteria adhered to Evans' standards, which include a minimum of three reports, a PRR > 2, and a chi-square (χ^2) statistic > 4 for each DPP-4i-angioedema pair [18]. A 95% confidence interval (CI) was calculated for both ROR and PRR, with a signal identified if the lower limit of the ROR CI exceeded 1.

Bayesian analysis was conducted using the Bayesian Confidence Propagation Neural Network (BCPNN). The BCPNN is a model that combines neural networks with Bayesian inference to enhance the estimation of parameters and uncertainty in predictions that utilizes a probabilistic approach to improve the reliability of the results [19]. For BCPNN, signal detection was determined by the Information Component (IC), defined as the logarithmic ratio of the observed co-occurrence of DPP-4i and angioedema relative to the expected frequencies in the database. An IC-based signal was detected if the lower bound of the 95% CI (IC025) exceeded zero [20]. The formula for estimating the frequentist and Bayesian signal detection measures is outlined in the Electronic Supplementary Table 2.

Interaction signal assessment

The interaction strength between DPP-4is and ACEIs/ARBs was evaluated using multiplicative drug-drug interaction model [21]. The formula used for assessing potential interaction is outlined in Table 1. Both log-linear and logistic regression analyses were employed and $e^{\beta 12}$ (log of risk of angioedema with DPP-4i-RAAS-i drug combinations) and $e^{\gamma 12}$ (logit of risk of angioedema with DPP-4i-RAAS-i drug combinations) were estimated. A potential interaction for the risk of angioedema was detected when $e^{\beta 12}$ or $e^{\gamma 12}$ exceeds 1 [21].

Outcomes assessed

For the DPP-4i and DPP-4i combination-angioedema pairs, the primary outcomes evaluated included death, life-threatening events, and hospitalization (initial or prolonged).

Compliance with reporting standards

This study adheres to the guidelines outlined in the Reporting of a Disproportionality Analysis for drUg

Table 1 Signal detection measure used for DPP-4i-RAAS-i drug interaction for the risk of angioedema

	Angioedema	All adverse events except angioedema	Total
DPP-4i with RAAS-i drug	n_{111}	n_{110}	n_{11+}
DPP-4i without RAAS-i drug	n_{101}	n_{100}	n_{10+}
RAAS-i drug without DPP-4i	n_{011}	n_{010}	n_{01+}
Neither DPP-4i nor RAAS-i drug	n_{001}	n_{000}	n_{00+}
Total	n_{++1}	n_{++0}	n_{+++}
Signal detection for DPP-4i -RAAS-i drug interaction for the risk of angioedema			
	DPP-4i	**RAAS-i drugs**	
DPP-4i	p_{11} ($=n_{111}/n_{11+}$)	p_{10} ($=n_{101}/n_{10+}$)	
RAAS-i drugs	p_{01} ($=n_{011}/n_{01+}$)	p_{00} ($=n_{001}/n_{00+}$)	
Log-linear regression for the risk of angioedema ($e^{\beta 12}$): $(p_{11} \times p_{00})/(p_{10} \times p_{01})$			
Logistic regression for the risk of angioedema ($e^{\gamma 12}$): $[p_{11}/(1-p_{11}) \times p_{00}/(1-p_{00})]/[p_{10}/(1-p_{10}) \times p_{01}/(1-p_{01})]$			

n: number of reports; p: proportion of reports; DPP-4i: Dipeptidyl peptidase 4 inhibitor; and RAAS-i drugs: Renin-angiotensin aldosterone system interfering drugs

Safety signal detection using spontaneously reported adverse events in Pharmacovigilance (READUS-PV) [22].

Case review

We conducted a comprehensive literature review in PubMed, Cochrane CENTRAL, and Google Scholar to identify case reports of angioedema occurring with DPP-4is. The search terms used were "("sitagliptin"[Title/Abstract] OR "saxagliptin"[Title/Abstract] OR "linagliptin"[Title/Abstract] OR "alogliptin"[Title/Abstract] OR "vildagliptin"[Title/Abstract] OR "anagliptin"[Title/Abstract] OR "trelagliptin"[Title/Abstract] OR "DPP 4 inhibitors"[Title/Abstract] OR "dipeptidyl peptidase 4 inhibitors"[Title/Abstract]) AND "angioedema"[Title/Abstract]". For each case, the following details were extracted: patient age, gender, concomitant drugs with potential link to angioedema, DPP-4i dosage, onset time of angioedema from initiating DPP-4i, outcome, and interpretation of the causality assessment using the Naranjo algorithm. The causality assessment scores were categorized as definite (>9), probable (5–8), possible (1–4), and doubtful (<0) [23].

Statistical analysis

Descriptive statistics were used to summarize demographic variables, presenting numerical variables as means (SD) and categorical variables as proportions (%) from the AERS ICSRs and published case reports. Volcano plots were generated with log2(ROR) on the X-axis and -log10(*P*-values) on the Y-axis, indicating the significance of DPP-4i (alone and in combination) associations with angioedema. All statistical analyses were performed in SPSS© (IBM SPSS Statistics for Windows, Version 27.0; IBM Corp., Armonk, NY), with VolcaNoseR© used for volcano plots [24].

Results

Search results

A comprehensive review of the USFDA AERS database yielded 29,163,222 reports, of which 588 met the predefined inclusion criteria and underwent detailed analysis (Fig. 1). Among DPP-4i monotherapies, sitagliptin emerged as the predominant contributor to adverse event reports, followed by linagliptin. No adverse event reports were documented for anagliptin and trelagliptin, while vildagliptin monotherapy generated no angioedema-specific reports. In the context of DPP-4i combinations with RAAS-interfering drugs, the sitagliptin-lisinopril combination, followed by sitagliptin-valsartan, demonstrated the highest reporting frequency. Combinations with fewer than three reports were excluded from the primary analysis but are comprehensively documented in Electronic Supplementary Table 3.

Demographic analysis (Table 2) revealed a predominant occurrence of DPP-4i-associated angioedema in the elderly population (>65 years), consistently observed across both monotherapy and combination therapy with RAAS-interfering agents. A notable gender disparity was observed, with female predominance across all DPP-4is except alogliptin.

Signal detection analysis

The reporting rates for DPP-4i-associated angioedema (Fig. 2) demonstrated a consistently higher frequency for

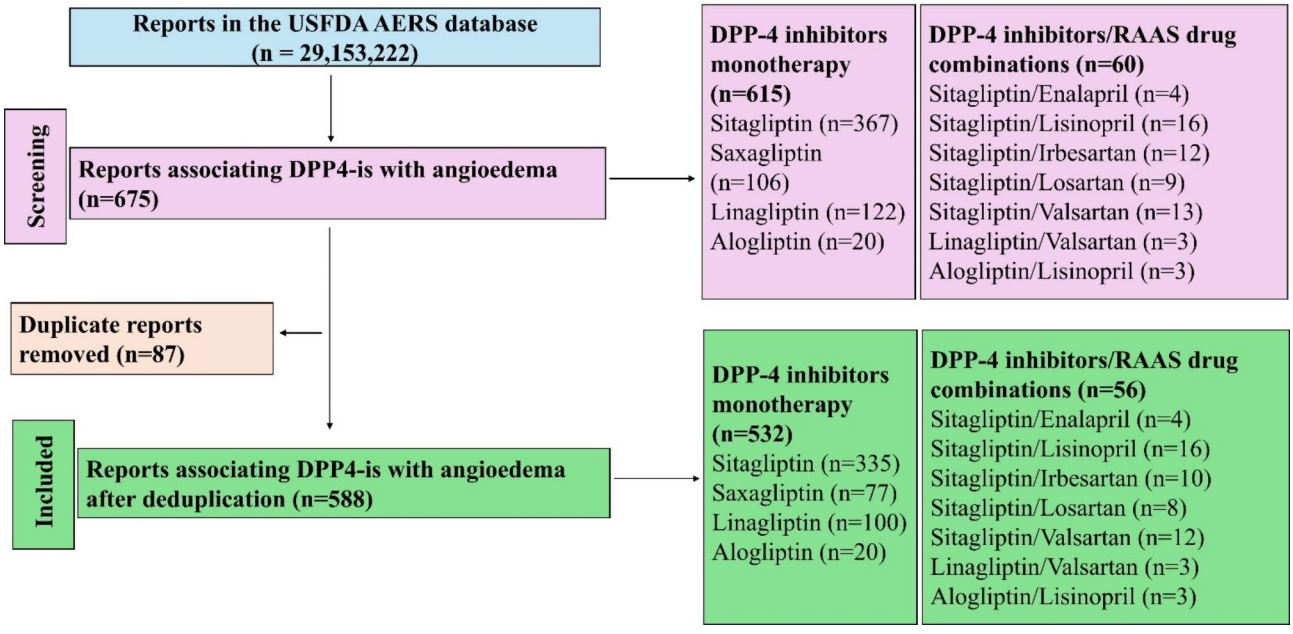

Fig. 1 Study flow diagram. A total of 588 unique reports were included in the final analysis for DPP-4i-associated angioedema

Table 2 Summary of demographic characteristics for patients with DPP-4i-associated angioedema

Characteristics		DPP-4i monotherapy				DPP-4i combinations with drugs interfering RAAS ($n=56$)
		Sitagliptin ($n=335$)	Saxagliptin ($n=77$)	Linagliptin ($n=100$)	Alogliptin ($n=20$)	
Age group [n (%)]	< 40	3 (0.9)	1 (1.3)	1 (1)	1 (5)	Nil
	≥ 40 to < 65	62 (18.5)	23 (29.9)	16 (16)	4 (20)	17 (30.4)
	≥ 65	98 (29.3)	29 (37.7)	34 (34)	6 (30)	25 (44.6)
	Not specified	172 (51.3)	24 (31.2)	49 (49)	9 (45)	14 (25)
Quantitative age (years)	Mean (SD)	66.8 (12.4)	65.8 (12.4)	67.1 (11.8)	62.2 (14.1)	68.9 (11.4)
	Median (range)	68 (36–91)	65 (36–87)	68 (25–85)	65 (33–78)	68.5 (43–87)
Gender [n (%)]	Male	98 (29.3)	27 (35.1)	26 (26)	11 (55)	17 (30.4)
	Female	190 (56.7)	40 (51.9)	63 (63)	7 (35)	38 (67.9)
	Unknown	47 (14)	10 (13)	11 (11)	2 (10)	1 (1.7)
Reporting year [n (%)]	2004–2008	114 (34)	Nil			18 (32.1)
	2009–2012	108 (32.2)	66 (85.7)	47 (47)	Nil	21 (37.5)
	2013–2016	62 (18.5)	4 (5.2)	34 (34)	8 (40)	8 (14.3)
	2017–2020	33 (9.9)	6 (7.8)	12 (12)	5 (25)	3 (5.4)
	2021–2024 (June)	18 (5.4)	1 (1.3)	7 (7)	7 (35)	6 (10.8)
Reporting top countries	USA	299 (89.3)	56 (72.7)	71 (71)	18 (90)	46 (82.1)
	Others and unknown	36 (10.7)	24 (27.3)	29 (29)	2 (10)	10 (17.9)

DPP-4i: Dipeptidyl peptidase-4; RAAS: Renin angiotensin aldosterone system; USA: The United States of America

combinations with RAAS-interfering drugs compared to DPP-4i monotherapy. Signal detection analysis, incorporating both frequentist and Bayesian methodologies (Table 3), revealed interesting patterns. While DPP-4i monotherapies generated significant frequentist signals, combination therapies demonstrated more robust safety signals across both analytical approaches. Particularly strong signals emerged for sitagliptin/irbesartan, sitagliptin/valsartan, and alogliptin/lisinopril combinations. Risk assessment through RORs identified alogliptin/lisinopril and sitagliptin/irbesartan as combinations associated with the highest risk profiles (Fig. 3), a finding further validated through volcano plot analysis (Fig. 4).

Interaction signal analysis

Evaluation of interaction signals revealed statistically significant drug-drug interactions for specific combinations (Table 4). Notable interactions were documented for sitagliptin/irbesartan, sitagliptin/valsartan, linagliptin/valsartan and alogliptin/lisinopril combinations, suggesting potential synergistic effects in angioedema development.

Clinical outcome analysis

The distribution of clinical outcomes associated with DPP-4i-related angioedema (Fig. 5) showed no statistically significant differences between monotherapy and combination therapy with RAAS-interfering agents (χ^2: 1.2; df: 2; p-value: 0.5), suggesting comparable clinical severity regardless of therapeutic approach.

Literature review of case reports

A systematic literature search identified 25 articles, of which 16 specifically reported DPP-4i-associated angioedema [7, 25–39]. The case distribution included nine reports involving sitagliptin, two each for saxagliptin and vildagliptin, and single reports for alogliptin, anagliptin, and trelagliptin. The affected population spanned ages 32–83 years, with a male-to-female ratio of 10:6 (Table 5). Equal numbers of patients (seven each) were receiving concurrent RAAS-interfering agents or metformin. All documented cases achieved complete resolution without permanent sequelae. Causality assessment using the Naranjo algorithm classified one case as "probable," with the remaining cases designated as "possible," highlighting the challenges in establishing definitive causal relationships in spontaneous reporting systems.

Discussion

Key findings

This comprehensive pharmacovigilance analysis of the USFDA AERS database reveals several important findings regarding DPP-4i-associated angioedema. First, while DPP-4i monotherapy demonstratedsignificant risk for angioedema, the combination of DPP-4is with

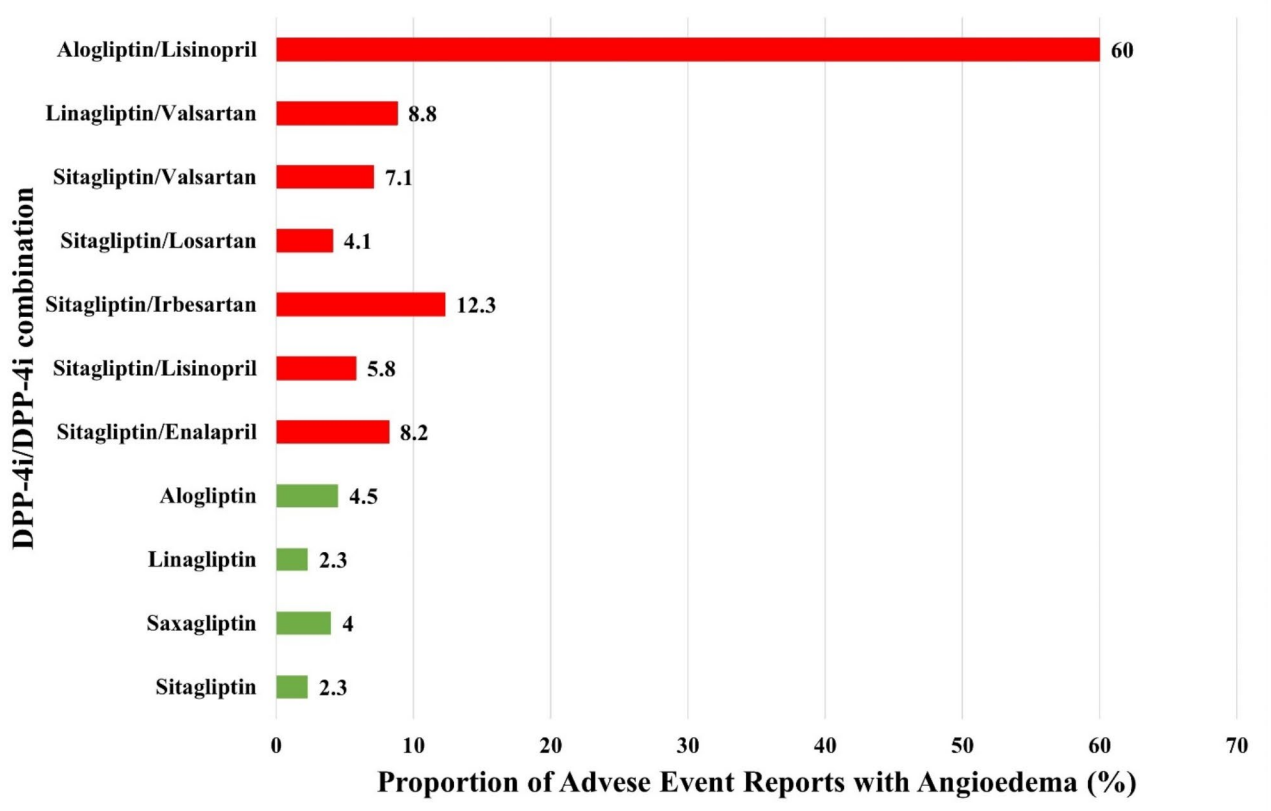

Fig. 2 Rate of reporting of angioedema with DPP-4is. The horizontal bars represent the rates of reporting angioedema amongst the total reports for DPP-4is and their combinations with drugs interfering with RAAS. The green bars represent DPP-4i monotherapy and red bars represent DPP-4i combinations

Table 3 Signal detection measures for the risk of angioedema with DPP-4is

Drugs	PRR	Lower limit 95% CI of PRR	Upper limit 95% CI of PRR	RRR	χ2	Number of reports	IC025
Monotherapy							
Sitagliptin	1.3	1.2	1.4	1.3	23.1	335	0.3
Saxagliptin	2.3	1.8	2.9	2.3	55.7	77	1
Linagliptin	1.3	1.1	1.6	1.3	6.3	100	0.3
Alogliptin	2.5	1.6	3.9	2.5	17.3	20	0.9
Combination therapy							
Sitagliptin/Enalapril	4.6	1.8	11.9	4.6	8.2	4	0.8
Sitagliptin/Lisinopril	3.3	2.1	5.3	3.3	23.9	16	1
Sitagliptin/Irbesartan	7	3.9	12.5	7	46.5	10	1.4
Sitagliptin/Losartan	2.3	1.2	4.6	2.4	5	8	0.6
Sitagliptin/Valsartan	4.1	2.4	7	4.1	25.1	12	1.1
Linagliptin/Valsartan	5	1.7	14.8	5	6.1	3	0.7
Alogliptin/Lisinopril	34.1	16.7	69.7	34.1	67.2	3	0.9

RRR: Relative reporting ratio; PRR: Proportional reporting ratio; χ2: Chi-square test statistics; and IC: Information component.

RAAS-interfering drugs generated stronger safety signals across both frequentist and Bayesian analyses. Second, significant drug-drug interactions were identified for specific combinations, notably sitagliptin/irbesartan, sitagliptin/valsartan, linagliptin/valsartan and alogliptin/lisinopril suggesting potential synergistic effects in angioedema development. Third, demographic analysis revealed a predominant occurrence in elderly patients (>65 years) and a general female preponderance. Fourth, the combination of alogliptin/lisinopril and sitagliptin/irbesartan demonstrated the highest risk profiles based on reporting odds ratios. Importantly, while the clinical outcomes did not significantly differ between monotherapy and combination therapy groups, these findings suggest the need for heightened vigilance when prescribing

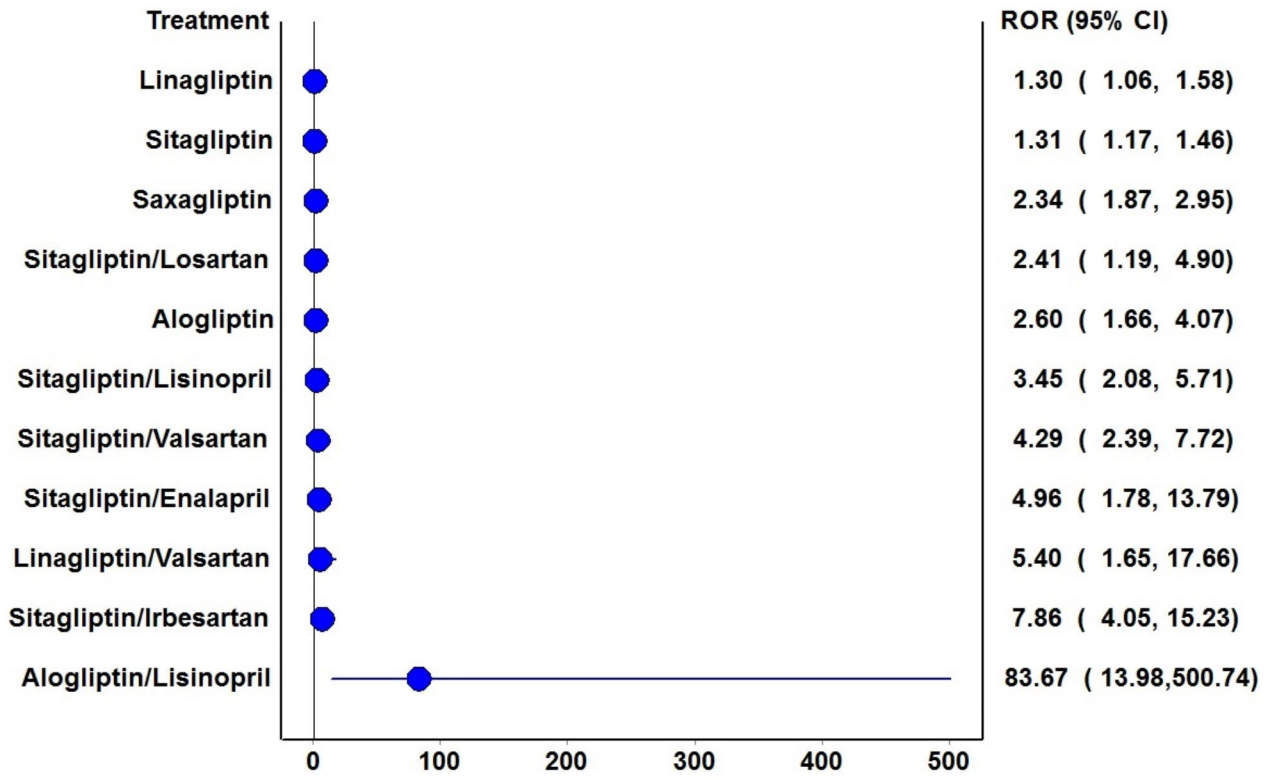

Fig. 3 Reporting odds ratios for the risk of angioedema with DPP-4i as monotherapy and in combinations with drugs interfering with RAAS. The blue circles represent the point estimates, and the horizontal lines represent the 95% CI of RORs. Vertical black line represents the line of no difference in the risk of angioedema

certain DPP-4i combinations with RAAS-interfering drugs, particularly in vulnerable populations.

Comparison with existing literature

Previous studies have explored the risk of angioedema associated with DPP-4 inhibitors (DPP-4is). One such study found no overall association between the DPP-4i class and angioedema but noted significant risks in specific subgroups, such as females in their 60s and males aged ≥ 80 years, with a potential link to linagliptin [40]. However, this study had several limitations: it did not exclude patients receiving ARBs, direct renin inhibitors, or metformin, all of which are independently associated with angioedema risk. Furthermore, the study lacked robust signal detection criteria and did not evaluate differences in risk across various DPP-4i and ACEI/ARB combinations. Additionally, potential differences within the ACEI class, previously identified by another pharmacovigilance study, were not explored [41]. A separate analysis using VigiBase, a global database for adverse event reporting, examined 19,997 angioedema cases linked to ACEIs and found that virtually all except three reports were associated with ACEIs [42]. Among these, 677 cases involved concomitant DPP-4i use. While individual DPP-4is were not directly associated with angioedema, co-administration with ACEIs was implicated in 345 cases, yielding a robust ROR of 42.77 (95% CI, 36.93–49.53) [42]. However, this study also failed to differentiate risks among individual DPP-4i and RAAS-interfering drug combinations or assess within-class differences for DPP-4is and ARBs. Our study addresses these gaps by evaluating the differential risk of angioedema across specific DPP-4i combinations with ACEIs and ARBs. We observed significant positive signals for sitagliptin combined with ARBs, particularly irbesartan and valsartan, indicating both signal strength and interaction effects. Also, interaction signals were identified for linagliptin/valsartan that aligns with case reports indicating that linagliptin may cause acute renal failure with hypotension and hyperkalemia in patients on ACE inhibitors. Moreover, in silico and in vivo studies demonstrate that linagliptin can inhibit ACE at therapeutic concentrations, likely contributing to angioedema via dual enzyme inhibition of bradykinin and substance P degradation [43, 44].

Importantly, significant signals for angioedema were predominantly observed with sitagliptin combinations in our study, suggesting potential intraclass differences in both DPP-4 and ACE inhibition profiles [44]. Additionally, we found that females and elderly patients were most

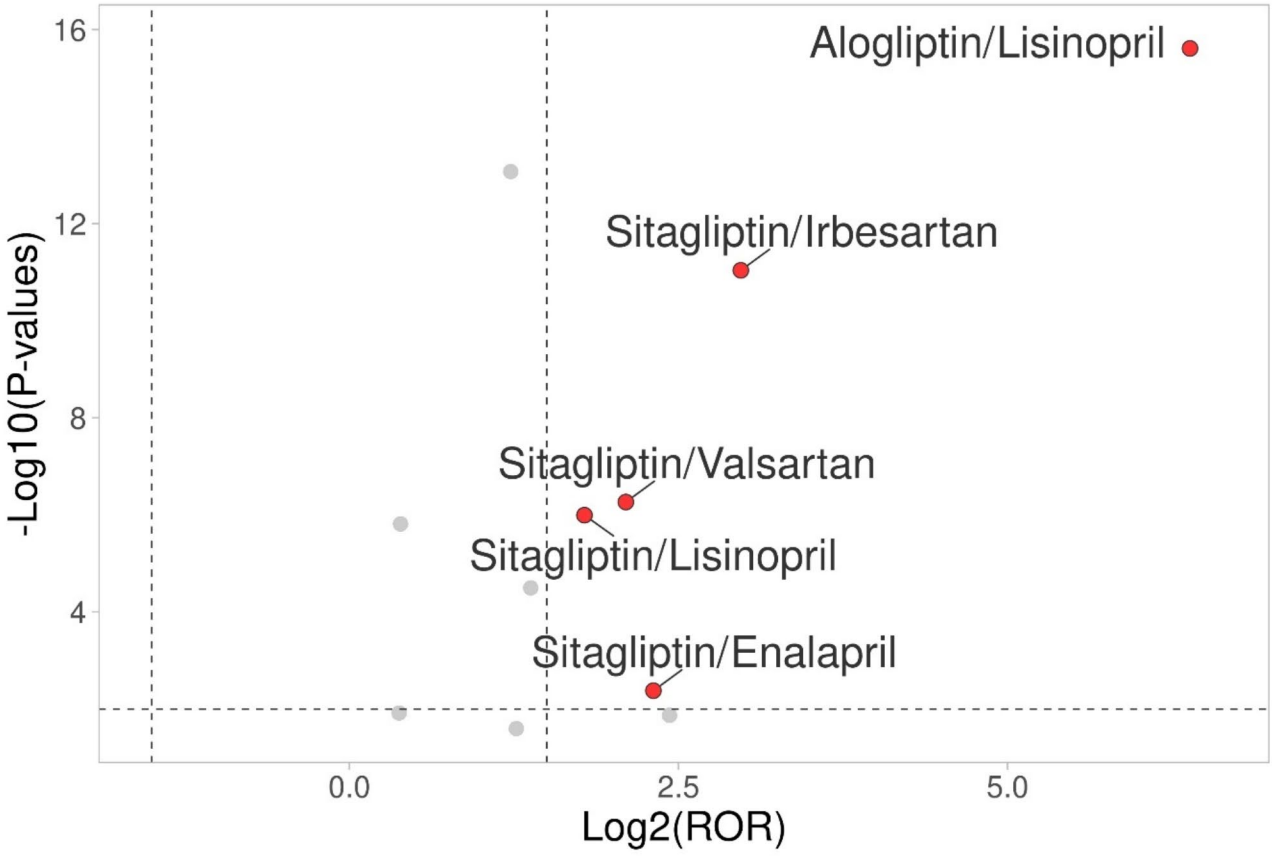

Fig. 4 Volcano plots for the risk of angioedema with DPP-4i combinations. The red circles represent DPP-4i combinations and as farther they lie on both the x- and y-axes, more significant is the association of the drug with the risk of angioedema

Table 4 Interaction analysis between DPP-4i and RAAS-i drugs for the risk of angioedema

DPP-4i-RAAS-i combinations	$e^{\beta 12}$	$e^{\gamma 12}$
Sitagliptin/Enalapril	0.3	0.3
Sitagliptin/Lisinopril	0.1	0.1
Sitagliptin/Irbesartan	2.3*	2.5*
Sitagliptin/Losartan	0.5	0.5
Sitagliptin/Valsartan	3.2*	3.4*
Linagliptin/Valsartan	4*	4.3*
Alogliptin/Lisinopril	0.7	1.1*

RAAS-i drugs: Renin angiotensin aldosterone system drugs; $e^{\beta 12}$: log (risk of angioedema with DPP-4i-RAAS-i drug combinations); $e^{\gamma 12}$: logit (risk of angioedema with DPP-4i-RAAS-i drug combinations); and *: Statistically significant interactions

frequently affected by DPP-4i-associated angioedema, a finding consistent with previous research [45]. These observations underscore the importance of tailoring therapeutic decisions based on individual patient characteristics and potential drug interactions.

Strengths, limitations and way forward

Our study presents several notable strengths, including the utilization of a large-scale, real-world pharmacovigilance database, the application of both frequentist and Bayesian analytical approaches, and the novel examination of drug-drug interactions through sophisticated interaction signal analyses. This is the first study evaluating the intraclass differences within DPP-4is and ACEIs/ARBs for the risk of angioedema. However, several limitations warrant consideration when interpreting these findings. First, the inherent limitations of spontaneous reporting systems, including potential underreporting, reporting bias, and the inability to establish true causality, must be acknowledged [46]. Second, the absence of precise denominator data (total number of patients exposed to these medications) precludes the

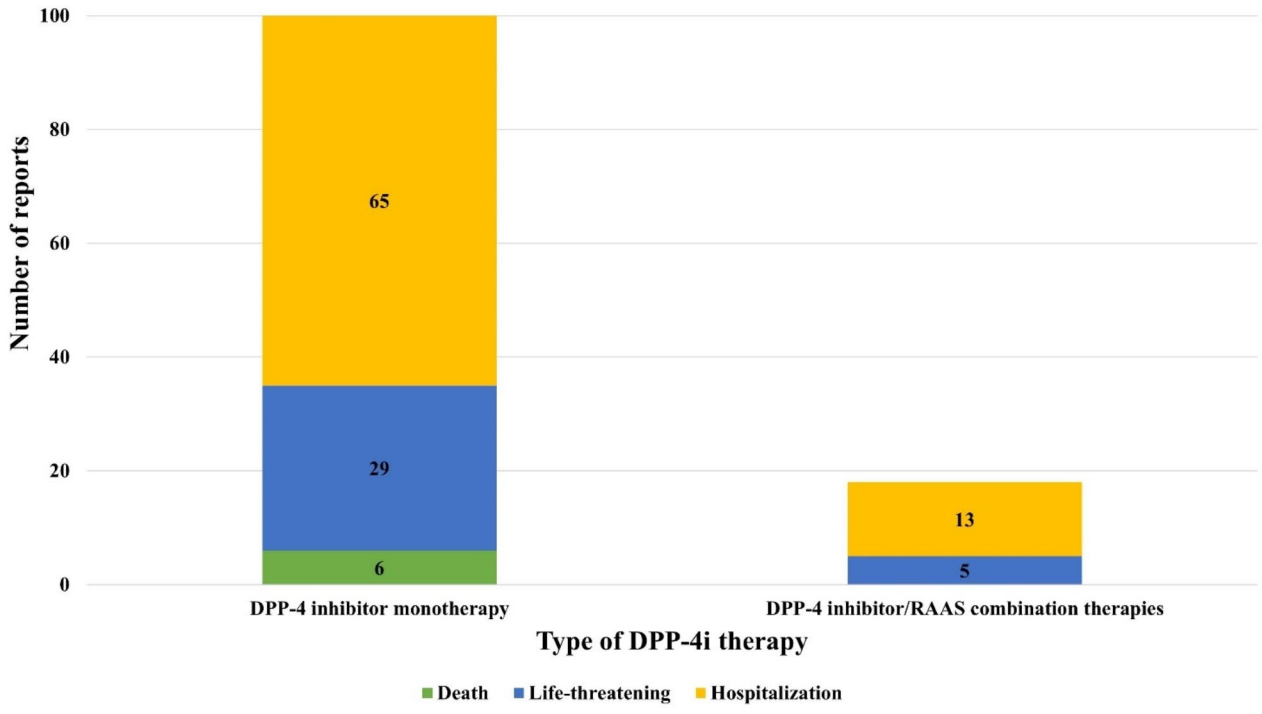

Fig. 5 Comparison of outcomes between DPP-4is monotherapy and in combination with drugs interfering RAAS. The stacked bar charts depict the reported outcomes between angioedema associated with DPP-4i monotherapy and in combination with drugs interfering with RAAS

calculation of true incidence rates. Third, the database lacks comprehensive information about potential confounding factors such as comorbidities, concomitant medications beyond those studied, and detailed clinical parameters. Also, another RAAS-interfering class of drugs include aldosterone antagonist, which has rarely been reported with angioedema, particularly in combination with ACEIs or ARBs [47]. Also, the mechanisms underlying potential spironolactone-associated angioedema remain unclear and we acknowledge the possibility of this association and shall be explored in future studies. There are several other signal detection measures, including omega measures for interaction analysis, that could be considered in future studies [48]. Lastly, although we adhered to standard deduplication methods, residual duplicates may persist. Moving forward, several research directions deserve attention. Large-scale prospective cohort studies or nested case-control studies using electronic health records could help validate these findings and better quantify the absolute risks. Mechanistic studies investigating the molecular basis of the observed drug-drug interactions, particularly for combinations showing strong signals, could provide valuable insights for drug development and clinical practice. Additionally, studies focusing on specific patient subgroups, especially elderly females who showed increased susceptibility, could help develop more targeted risk mitigation strategies. The development of prediction models incorporating clinical and genetic factors could also aid in identifying high-risk patients before initiating combination therapy. Finally, real-world effectiveness studies comparing different DPP-4i agents in combination with RAAS-interfering drugs could help optimize therapeutic choices in clinical practice.

Conclusion

This comprehensive pharmacovigilance analysis provides important insights into the risk of angioedema associated with DPP-4i therapy, particularly when combined with RAAS-interfering drugs. Our findings demonstrate significant safety signals for specific drug combinations, notably sitagliptin/irbesartan, sitagliptin/valsartan, linagliptin/valsartan, and alogliptin/lisinopril, with evidence of potential drug-drug interactions. The predominant occurrence in elderly patients and females, along with varying risks among different DPP-4i agents, suggests the need for individualized risk assessment in clinical practice. While these medications remain valuable therapeutic options for type 2 diabetes management, healthcare providers should exercise increased vigilance when prescribing certain combinations, particularly in vulnerable populations. Regular monitoring, early recognition of

Table 5 Characteristics of patients reported in the published case reports with DPP-4i-associated angioedema

Report ID	Age (years)	Gender	Concomitant drugs with potential link to angioedema	Name and dose of DPP-4i	Onset of angioedema from initiation of DPP-4is	Outcome	Causality assessment
Arcani 2017 [25]	59	Male	Metformin	Sitagliptin: 50 mg/day	3 months	Recovered	Possible
Beaudouin 2014 [26]	56		Lisinopril, Metformin	Sitagliptin: 100 mg/day	1 year		
Ejikeme 2021 [27]	69		Not mentioned (But there was no ACE inhibitor drug)	Sitagliptin: Not mentioned	Not mentioned		
Gabb 2013 [28]	66		Candesartan, Metformin	Saxagliptin: Not mentioned	6 months		
Gosmanov 2012 [29]	46	Female	Metformin, Losartan	Sitagliptin: 50 mg/day	1 week		
Hahn 2017 [30]	83		Ramipril	Saxagliptin: 5 mg/day	Not mentioned		
Hamasaki 2013 [31]	60	Male	Not mentioned	Anagliptin: 200 mg/day			
Hermanrud 2017 [32]	Middle-aged Caucasian		Ramipril	Sitagliptin: Not mentioned			
Millot 2012 [33]	67		Perindopril, Metformin	Sitagliptin: Not mentioned	2 months		
Poddar 2024 [34]	32	Female	None	Vildagliptin: Not mentioned	10 days		
Saisho 2013 [7]	69	Male	None	Vildagliptin: 50 mg twice daily	Not mentioned		
Schneider 2019 [35]	67	Female	None	Sitagliptin: 100 mg/day			
Sharma 2022 [36]	50		Metformin, Levetiracetam	Sitagliptin: Not mentioned			
Skalli 2010 [37]	79		Irbesartan	Sitagliptin: Not mentioned			Probable
Sungworn 2023 [38]	60	Male	Sulfamethoxazole-Trimethoprim	Trelagliptin: 100 mg/day			Possible
Yeddi 2022 [39]	67		Metformin	Alogliptin: 12.5 mg twice daily			

RAAS: Renin-angiotensin-aldosterone system; ACE: Angiotensin converting enzyme

symptoms, and careful patient selection become crucial when initiating combination therapy with DPP-4is and RAAS-interfering drugs. These findings could inform clinical decision-making and future research directions, ultimately contributing to safer medication use patterns and improved patient outcomes. Further prospective studies are warranted to validate these findings and establish definitive causal relationships, enabling the development of evidence-based risk mitigation strategies.

Abbreviations

ACEIs	Angiotensin converting enzyme inhibitors
AERS	Adverse event reporting system
ARBs	Angiotensin receptor blockers
CI	Confidence interval
DPP-4is	Dipeptidyl peptidase-4 inhibitors
EBGM	Empirical bayes geometric mean
IC	Information component
INTSS	Interaction signal scores
MedDRA	Medical dictionary for regulatory activities
MGPS	Multi-item gamma poisson shrinker
PRR	Proportional reporting ratio
RAAS	Renin-angiotensin-aldosterone system
ROR	Reporting odds ratio
USFDA	United states food and drug administration

Supplementary Information

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Supplementary Material 1

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