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Evaluating the Overall Safety of Glucokinase Activators in Patients with Type 2 Diabetes Mellitus

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Purpose: This study aimed to assess the overall clinical adverse events (AEs) associated with glucokinase activators (GKAs) in patients with type 2 diabetes mellitus (T2DM).

Methods: We searched MEDLINE, EMBASE, Cochrane Library, and ClinicalTrials.gov databases from their dates of inception to June 6, 2023, for randomized controlled trials (RCTs) that reported safety data for GKAs in patients with T2DM. A random-effects model was used to obtain a summary odds ratio (OR) with associated 95% Confidence Intervals (CIs). Pre-specified subgroup analyses were conducted according to individual GKAs (dorzagliatin and all other GKAs), various controls, follow-up duration, mean duration of diabetes, and the location of clinical research.

Results: 17 RCTs enrolling 4,918 patients (3,196 patients received GKAs and 1,722 patients received placebo or other hypoglycemic drugs) were identified. Among the 17 RCTs, dorzagliatin, AZD1656 and MK-0941 in three trials (1,541 patients), five trials (885 patients), and three trials (798 patients), respectively. GKA treatment was associated with a higher risk of any AEs (OR 1.220, 95% CI 1.072–1.389), mild AEs (OR 1.373, 95% CI 1.085–1.738), hyperlipidemia (OR 1.532, 95% CI 1.071–2.189), and hyperuricemia (OR 2.768, 95% CI 1.562–4.903) compared to patients in the control groups. The higher risks of any AEs were mainly attributed to dorzagliatin and MK-0941 and mild AEs mainly attributed to dorzagliatin. Notably, dorzagliatin had significant effects on the occurrence of hyperlipidemia (OR 1.476, 95% CI 1.025–2.126) and hyperuricemia (OR 2.727, 95% CI 1.523–4.883) in the subgroup analyses. No significant effects were detected from other GKAs when regarding hyperlipidemia and hyperuricemia.

Conclusion: The results of our meta-analysis indicated that GKAs were associated with a higher risk of any AEs, mild AEs, hyperlipidemia, and hyperuricemia. Further subgroup analyses revealed that the increased occurrence of hyperlipidemia, and hyperuricemia mainly originated from dorzagliatin treatment.

Plain Language Summary: Glucokinase activators (GKAs) reduce blood glucose by increasing the activity of glucokinase (GK) and are being developed for the treatment of diabetes. Here, we aimed to assess the safety of GKAs in patients with type 2 diabetes. The results showed that GKAs were associated with a higher risk of any AEs, mild AE, hyperlipidemia, and hyperuricemia compared to controls.

Keywords: type 2 diabetes mellitus, safety, randomized controlled trials, systematic review, meta-analysis

Introduction

According to the International Diabetes Federation, approximately 536.6 million individuals (including diagnosed and undiagnosed persons) were living with diabetes in 2021. Among these diabetic individuals, type 2 diabetes mellitus (T2DM) accounts for the largest proportion, representing over 90% of this cohort.[1] T2DM is a chronic metabolic disorder

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characterized by relative insulin deficiency or insulin resistance, resulting in elevated blood glucose levels.[2] The need for new diabetes treatments arises because many patients are not achieving their desired glycated hemoglobin (HbA_{1c}) goals with current therapies. This indicates a lack of effective management strategies. Existing antidiabetic drugs have adverse events that worry patients and healthcare providers, leading to the search for safer alternatives. Also, there is a need for therapies that can restore or preserve β-cell function, which is essential for insulin production. Despite the inclusion of multiple medications with different glucose-lowering mechanisms in the standard treatment pathway for T2DM, only some antidiabetic drugs are beneficial for improving pancreatic β-cell function, and the effects are debated. For example, traditional thiazolidinediones (TZDs) have been widely used to ameliorate insulin resistance; they may increase the risk of heart failure and osteoporosis. Furthermore, literature has reported that metformin exerts a certain degree of beneficial effect on islet β-cell function.[3] In recent years, novel hypoglycemic drugs such as sodium-glucose cotransporter two inhibitors (SGLT2 inhibitor) and glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonist) have also been demonstrated to possess the potential to enhance islet β-cell function.[4–8] However, studies have also indicated that the data on the improvement of islet function by SGLT2 inhibitors are not entirely conclusive, and the efficacy of such improvement varies among individuals.[9]

Therefore, a need for novel medications with new mechanisms of action as treatment still exists. Dorzagliatin, which has been approved for use in adult patients with type 2 diabetes, is more commonly used in combination therapy with other types of antidiabetic drugs for dual or triple therapy and it also can be used as monotherapy in some type 2 diabetes patients. Notably, dorzagliatin is the first glucokinase activator (GKA) diabetes medication in the world to submit a new drug marketing application in China in 2022. Currently, dorzagliatin has not yet been launched in the United States (US), the European Union (EU), the United Kingdom (UK), and other countries and regions, but a Phase I clinical study (HM-002-1005, NCT06498284) was approved in the US in January 2024. Nevertheless, the patient groups receiving dorzagliatin treatment have consistently exhibited elevated levels of liver enzymes, serum triglycerides, and serum uric acid (SUA).[10,11] Glucokinase (GK) is a rate-limiting enzyme of glucose metabolism that is active in the liver and pancreas besides being expressed in the hypothalamus, pituitary gland and intestine.[12] GKAs are a class of small molecules that bind to allosteric sites on GK and enhance its activity. By restoring GK function in patients with T2DM, GKAs act as glucose sensors in the pancreas and as a glucose receptor in the liver, restoring sensitivity to blood glucose fluctuations and balancing insulin, glucagon-like peptide-1, and glucagon levels to achieve blood glucose homeostasis.[13] Multiple GKAs have been developed and evaluated for potential clinical use, including piragliatin, AMG 151, MK-0941, PF-04937319, AZD1656, and TTP399. Several studies have investigated the safety and efficacy of GKAs.[14–16] However, these meta-analyses have focused more on drug efficacy and have not reported comprehensive analyses of overall safety assessment. Meanwhile, multiple GKAs have been developed and evaluated for potential clinical use, and reports have revealed varying levels of safety among these agents. For example, the incidences of hypoglycemia following treatment with either piragliatin, AMG 151, or MK-0941 were high. Treatment with MK-0941, AMG151, and AZD1656 was also associated with an increased risk of hypertriglyceridemia, and piragliatin treatment may result in liver toxicity in patients with T2DM.[13] In a Phase II clinical study (NCT00266240), patients who regularly use piragliatin to treat chronic diseases such as type 2 diabetes may cause liver toxicity.[17] Therefore, the overall safety of GKAs needs to be evaluated urgently.

There has not been a systematic and comprehensive evaluation of the safety outcomes associated with treatment with various GKAs due to their relatively short market time. Hence, the objective of this study was to conduct a systematic review of the literature and assess reported adverse events (AEs) of treatment with GKAs. Additionally, meta-analysis was conducted where feasible to compare the reported effects between GKAs and the control comparator.

Methods

Data Sources and Searches

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement 2020 checklist and a previous protocol (PROSPERO: CRD42023437027). Three electronic databases, PubMed, EMBASE, and the Cochrane Library, were searched from their dates of inception to June 6,

2023, with English language restrictions. We employed Medical Subject Heading search terms, free-text terms associated with GKAs, and terms related to randomized controlled trials (RCTs). To identify additional clinical trials, we checked the references of the included studies, review articles, and meta-analyses. The search terms were as follows: glucokinase activators, glucokinase activator, GKAs, dorzagliatin, HMS5552, piragliatin, RO4389620, AMG 151, ARRY-403, AZD1656, AZD6370, TMG-123, MK-0941, TTP399, SY004, GKM001, LY2599506, PF-04937319, PF-04991532, PB-201. Details of the study search strategies are presented in Table S2.

Study Selection and Outcomes

The inclusion criteria were as follows: (1) study type: RCT; (2) study population: patients with type 2 diabetes; (3) study phase: phase II or III clinical trial; (4) study drugs: any GKAs; and (5) study results including overall AEs (at least including AEs such as any AEs, serious AEs, AEs leading to discontinuation, AEs related to study drugs, and death-associated AEs) or specified safety outcomes.

To date, dorzagliatin has been approved for use in China (approved by the Chinese National Medical Products Administration on Sep 30, 2022), whereas AZD1656, MK-0941, piragliatin, PF-04937319, AMG 151, TTP399, PF-04991532, and other agents have not been approved. Nevertheless, we were able to obtain data related to their use from clinical trials (http://www.clinicaltrials.gov).

Observational studies, summary analyses, abstracts, and letters were excluded from this meta-analysis. Two authors (TTL and MJC) independently reviewed the titles and abstracts, evaluated the full text of the retrieved articles, and resolved differences by consulting with the corresponding authors (FHS and LFG). The outcomes of this study included safety indices and clinical AEs.

Clinically interesting AEs referred to AEs reported in > 3% of the total cases. In total, we assessed four aspects of AEs involving infections, gastrointestinal disorders, neurological disorders, metabolism and cardiovascular system. Infections included upper respiratory tract infections, nasopharyngitis, influenza, and urinary tract infections. Gastrointestinal disorders encompassed diarrhea, nausea, vomiting, and constipation. Neurological disorders comprised headaches and dizziness. Metabolism and cardiovascular system defects included hyperlipidemia, hypertriglyceridemia, hyperuricemia, hypertension, and hypokalemia.

Data Extraction

The data were independently extracted by two authors (TTL and MJC) using a previously designed table,[18] including research characteristics, patient demographics, and clinical characteristics. If there were multiple publications of a specific RCT, data were only extracted from the publication with the most prolonged follow-up duration. For example, regarding the AE of severe hypoglycemia, we extracted the number of patients with severe hypoglycemia and the total number of individuals and obtained an odds ratio (OR) as a binary variable.

Quality and Bias Assessment

The quality of data was evaluated using the RCT bias risk assessment tool recommended by the Cochrane Handbook, involving random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. The risk of bias was graded as unclear, high, moderate, or low. If all the content of the study was grade L, the bias was deemed to be low risk. If part of the study content was grade M, the bias was denoted as medium risk. If part of the study content was graded H, the bias was deemed to be high risk.

For instance, some studies were single-blind trials, so the blinding of participants and personnel items was assessed as moderate risk. Therefore, the studies were judged to have a moderate risk of bias. Some studies were open-label trials, so the blinding of participants and personnel items was assessed as high risk; these studies were considered to have a high risk of bias.

Data Analysis

The results were analyzed by using a forest plot, and the Odds Ratio (OR) and relevant 95% confidence intervals (CIs) were calculated by a random effects model. The heterogeneity between studies was explored using the I^2 statistic (I^2 > 50% significance).[19] Prescribed subgroup analyses were performed according to individual GKAs (dorzagliatin and all

other GKAs), various controls, follow-up duration, mean duration of diabetes, and the location of clinical research. The publication bias was evaluated through quantitative analysis of the visual funnel plot, Begg's test, and Egger's test. Statistics were carried out with STATA software, and a *P*-value < 0.05 was considered statistically significant.

Results

Study Selection and Patient Characteristics

Using a variety of search strategies, we retrieved a total of 598 articles. After screening the titles and abstracts, 581 articles were excluded. Further evaluation was conducted on 116 records. Out of these, 99 studies were excluded for the following reasons: reviews or protocols (n=4), no reporting of primary outcomes (n=17), duplicated or sub-analysis (n=28), not RCTs (n=8), single-arm studies (n=4), and phase I or II studies (n=38). Finally, 17 RCTs were included in this meta-analysis that reported the most common AEs related to treatment with GKAs. The study identification and selection process are shown in Figure 1. Randomized controlled trials excluded from the meta-analysis with reasons for exclusion are shown in Table S1.

The characteristics of the included trials are presented in Table S3. A total of 4,918 patients were involved, with 3,196 patients prescribed GKA considered as the experimental group and 1,722 patients in the control group. Among the 17 RCTs included in this meta-analysis, Dorzagliatin was studied in three RCTs (1,541 patients), AZD1656 in five RCTs (885 patients), MK-0941 in three RCTs (798 patients), PF-04991532 in two RCTs (572 patients), while piragliatin, PF-04937319, AMG 151, and TTP399 were studied in one RCT each. The patients had a similar age range of 50.8–64.3 years. However, the shortest follow-up duration was only 1 week, and the most prolonged follow-up duration was 42 weeks. These studies were published between 2009 and 2022.

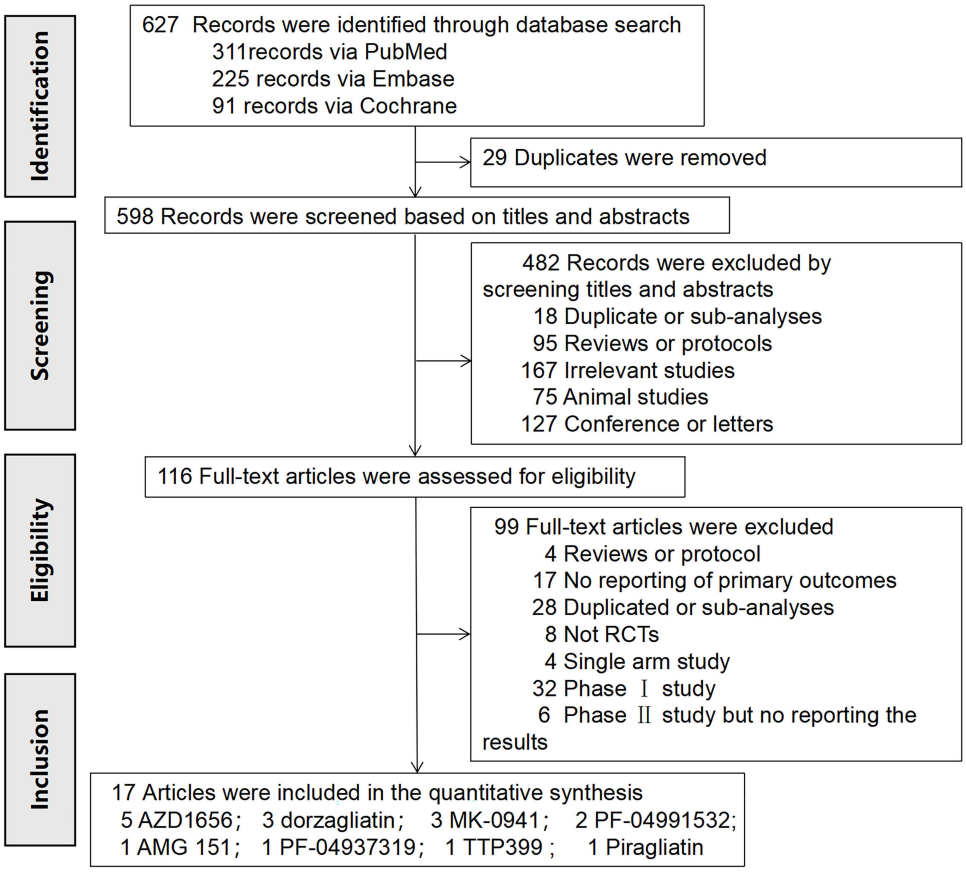

Figure 1 Flow diagram for the selection of eligible randomized clinical trials (RCTs).

Risk of Bias

The risk of bias assessment is shown in Table S4. All the items in 15 trials were low risk and were judged to have a low risk of bias. Two studies were assessed as medium-risk because they were single-blind trials. Among the 17 trials included in this meta-analysis, eight provided details of the randomization sequence generation method, and these studies used a computerized randomization sequence or a random number table. Only four studies referred to allocation concealment. Most of the studies did not describe the methods of allocation concealment and blinding of outcome assessment used in their research. These studies were judged as unclear. There were two studies that were single-blinded, so they were defined as having a moderate risk.

Safety Outcomes: Overall Safety

The results of overall safety outcomes are summarized in Figure 2, including any AEs, mild AEs (the appearance of signs or symptoms, but can be easily tolerated), moderate AEs (obvious discomfort interfering normal daily activities), AEs

	No.s	Experimental	Control	OR	95%CI	I^2(%)	P interaction
All AEs							
Any AEs	16	1657/3096 (53.52)	878/1707 (51.44)	1.220	(1.072 - 1.389)	0	0.003
Any AEs-Mild	3	614/897 (68.45)	379/591 (64.13)	1.373	(1.085 - 1.738)	3.7	0.008
Any AEs-Moderate	3	55/897 (6.13)	43/591 (7.28)	0.818	(0.534 - 1.254)	0	0.357
AEs leading to discontiuation	7	27/1822 (1.48)	12/869 (1.38)	0.767	(0.354 - 1.664)	0	0.503
AEs leading to withdrawal from study	4	6/832 (0.72)	8/647 (1.24)	0.656	(0.225 - 1.912)	0	0.440
Any serious AEs	13	79/2675 (2.95)	64/1410 (4.54)	0.762	(0.526 - 1.103)	0	0.149
Any serious AEs-death	2	5/464 (1.08)	9/459 (1.96)	0.616	(0.105 - 3.594)	30.7	0.590
Any serious AEs-Other serious AEs	13	74/2675 (2.77)	55/1410 (3.90)	0.811	(0.553 - 1.188)	0	0.281
Metabolism and cardiovascular system							
Hyperlipidemia	5	104/1461 (7.12)	51/932 (5.47)	1.532	(1.071 - 2.189)	0	0.019
Hypertriglyceridemia	3	25/956 (2.62)	13/674 (1.93)	1.693	(0.859 - 3.336)	0	0.128
Hyperuricemia	3	56/992 (5.65)	16/672 (2.38)	2.768	(1.562 - 4.903)	0	0.000
Hypertension	6	35/1823 (1.92)	11/891 (1.23)	1.559	(0.787 - 3.088)	0	0.203
Hypokalaemia	2	5/487 (1.03)	1/308 (0.32)	2.122	(0.151 - 29.735)	41.4	0.576
Gastrointestinal disorders							
Diarrhea	10	74/1881 (3.93)	27/974 (2.77)	1.435	(0.904 - 2.275)	0	0.125
Nausea	5	24/562 (4.27)	10/399 (2.51)	1.519	(0.602 - 3.832)	20.4	0.376
Vomiting	3	16/840 (1.90)	4/523 (0.76)	2.381	(0.778 - 7.284)	0	0.128
Constipation	2	2/34 (5.88)	0/13 (0.00)	1.254	(0.119 - 13.161)	0	0.850
Neurological disorders							
Headache	10	75/1843 (4.07)	26/937 (2.77)	1.377	(0.838 - 2.260)	0	0.207
Dizziness	5	24/870 (2.76)	10/398 (2.51)	0.933	(0.301 - 2.887)	24.1	0.904
Infections and infestation							
Upper respiratory tract infection	10	186/2411 (7.71)	103/1304 (7.90)	1.126	(0.862 - 1.470)	0	0.383
Nasopharyngitis	10	83/2086 (3.98)	41/1048 (3.91)	0.901	(0.489 - 1.659)	32.6	0.737
Influenza	3	30/1036 (2.90)	1/456 (0.22)	4.881	(1.083 - 22.004)	0	0.039
Urinary tract infection	9	88/2046 (4.30)	46/1316 (3.50)	1.054	(0.609 - 1.825)	45.1	0.851
Hypoglycemia							
Severe hypoglycemia	2	4/748 (0.53)	1/297 (0.34)	1.031	(0.136 - 7.842)	0	0.976
Clinically significant hypoglycemia	9	138/2392 (5.77)	37/1265 (2.92)	1.198	(0.510 - 2.812)	61	0.679
Mild hypoglycemia	8	105/1766 (5.95)	36/1074 (3.35)	1.406	(0.639 - 3.091)	59.1	0.397
Any hypoglycaemic events	11	383/1996 (19.19)	123/1027 (11.98)	1.123	(0.649 - 1.943)	67.5	0.678
Drop out due to hypoglycemia	2	12/674 (1.78)	0/149 (0.00)	2.594	(0.333 - 20.184)	0	0.363

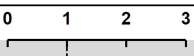

Figure 2 Main adverse events of glucokinase activators.
Abbreviations: AEs, adverse events; I^2, heterogeneity; No. s, numbers of studies; OR, odds ratio; CIs, Confidence Intervals; NR, no reported.

leading to discontinuation, AEs leading to withdrawal from the study, serious AEs (incapacitating, and cannot perform normal daily activities), serious AEs resulting in death, and other serious AEs. The results of the subgroup analyses in all AEs are summarized in Figure 3 and Table S8. Compared with sulfonylureas and sitagliptin, GKA users had a similar risk of overall safety (Tables S6 and S7). For the extent of AEs, 16 trials, including 4,803 patients, provided information about the risk of any AEs in patients treated with GKAs. Compared to the control group, GKAs increased the risk of any AEs (OR 1.220, 95% CI 1.072–1.389, I^2 0%, $P < 0.05$). Moreover, subgroup analyses showed that the risk of any AEs was significantly increased among patients on GKAs, compared with placebo (OR 1.275, 95% CI 1.102–1.474, I^2 0%, $P < 0.05$). Additionally, subgroup analyses also indicated that the increase in the risk of any AEs caused by GKAs was driven by dorzagliatin (OR 1.427, 95% CI 1.122–1.815, I^2 0%) and MK-0941 (OR 1.421, 95% CI 1.022–1.976, I^2 0%) treatment. Notably, the incidence of any AEs caused by MK-0941 was 58.13% (336/578), significantly higher than the control group incidence rate of 44.55% (98/220). We also found that there were significant differences in mild AEs (OR 1.373, 95% CI 1.085–1.738, I^2 3.7%). Further analysis found that the incidence rate of any mild AE was 68.45% (614/897) for dorzagliatin compared to 64.13% (379/591) for the placebo, indicating that dorzagliatin had a higher risk (OR 1.373, 95% CI 1.085–1.738, I^2 3.7%), while there was no significant difference in the incidence of moderate AEs (OR 0.818, 95% CI 0.534–1.254, I^2 0%). A higher risk for mild AEs was observed in the location of clinical research in Asia (OR 1.373, 95% CI 1.085–1.738, I^2 3.7%) and groups with follow-ups of greater than 12 weeks and less than or equal to 24 weeks (OR 1.373, 95% CI 1.085–1.738, I^2 3.7%).

Additionally, no significant differences were observed between GKAs and controls in terms of AEs leading to discontinuation of treatment, AEs leading to withdrawal from the study, any serious AEs, any serious AEs leading to death, and other serious AEs. As for individual GKAs, the location of clinical research, mean duration of diabetes, and follow-up time, the results were consistent with the primary analyses without finding a significant difference ($P >0.05$ for each outcome; Figures 2, 3 and Table S8). It is noteworthy that the incidence of any serious AEs for treatment with AZD1656 was 3.85% (21/546), significantly lower than that of the control group of 10.34% (33/319). Notably, AZD1656 treatment reduced the risk of any serious AE (OR 0.433, 95% CI 0.234–0.801, I^2 0%) and other serious AEs (OR 0.505, 95% CI 0.259–0.986, I^2 0%). In general, the heterogeneity of the included RCTs was relatively low (I^2 <50%).

Specified Safety

For analyzing safety with respect to metabolism and the cardiovascular system, we included hyperlipidemia, hypertriglyceridemia, hyperuricemia, hypertension, and hypokalemia. The risk of hyperlipidemia was higher in patients treated with GKAs than controls (OR 1.532, 95% CI 1.071–2.189, I^2 0%, $P < 0.05$, Figure 2). However, no significant difference was observed between GKAs and controls in terms of hypertriglyceridemia. The total incidence of hyperuricemia was 5.65% (56/992) in patients treated with GKAs and 2.38% (16/672) in the control group, indicating a significantly higher risk associated with GKAs (OR 2.768, 95% CI 1.562–4.903, I^2 0%, $P < 0.001$). In comparison, the incidence of hypertension was not significantly different between patients on GKAs and those in the control group ($P > 0.05$). The results of the subgroup analyses with respect to metabolism and the cardiovascular system are summarized in Figure 4 and Table S8. Notably, the risk of hyperlipidemia (OR 1.476, 95% CI 1.025–2.126, I^2 0%) and hyperuricemia (OR 2.727, 95% CI 1.523–4.883, I^2 0%) was significantly increased in patients treated with dorzagliatin. Compared with the placebo group, the risk of hyperlipidemia (OR 1.488, 95% CI 1.041–2.127, I^2 0%) and hyperuricemia (OR 2.699, 95% CI 1.523–4.781, I^2 0%) was significantly increased in patients treated with GKAs. Compared with participants in the placebo groups or other interventions, those in the GKA treatment group had a similar risk of hypertriglyceridemia and hypertension ($P > 0.05$), and the results were consistent with the primary analyses. Compared with sulfonylureas and sitagliptin, GKA users had a similar risk of metabolism and the cardiovascular system (Tables S6, and S7). Elevated risks for hyperlipidemia and hyperuricemia were observed in groups where the clinical research was conducted in Asia, with a mean duration of diabetes exceeding 60 months and a follow-up period ranging from more than 12 weeks to 24 weeks or less (Table S8). Additionally, we found that hypokalemia risks were not significantly different between GKAs and controls.

For gastrointestinal disorders and neurological disorders, there was no significant difference in the incidence of diarrhea, nausea, vomiting, constipation, headache, and dizziness (Figures 2, S1, S2 and Tables S6–S8). For infection and

All AEs			No.s	Experimental	Control	OR	95%CI	I^2(%)	P interaction
Any AEs	Drug	Dorzagliatin	3	651/897 (72.58)	408/591 (69.04)	1.427	(1.122 - 1.815)	0	0.003
		AZD1656	5	273/561 (48.66)	148/324 (45.68)	1.186	(0.889 - 1.581)	0	
		MK-0941	3	336/578 (58.13)	98/220 (44.55)	1.421	(1.022 - 1.976)	0	
		PF-04937319	1	166/405 (40.99)	99/234 (42.31)	0.947	(0.683 - 1.313)	NR	
		AMG 151	1	68/202 (33.66)	11/34 (32.35)	1.061	(0.489 - 2.304)	NR	
		TTP399	1	47/93 (50.54)	59/97 (60.82)	0.658	(0.370 - 1.170)	NR	
		PF-04991532	2	116/360 (32.22)	55/207 (26.57)	1.349	(0.922 - 1.974)	0	
	Control	PLA	15	1625/3024 (53.74)	705/1273 (55.38)	1.275	(1.102 - 1.474)	0	0.004
		AHA	6	475/1206 (39.39)	173/434 (39.86)	1.046	(0.794 - 1.379)	24.8	
Any AEs-Mild	Drug	Dorzagliatin	3	614/897 (68.45)	379/591 (64.13)	1.373	(1.085 - 1.738)	3.7	0.008
	Control	PLA	3	614/897 (68.45)	379/591 (64.13)	1.373	(1.085 - 1.738)	3.7	0.008
Any AEs-Moderate	Drug	Dorzagliatin	3	55/897 (6.13)	43/591 (7.28)	0.818	(0.534 - 1.254)	0	0.357
	Control	PLA	3	55/897 (6.13)	43/591 (7.28)	0.818	(0.534 - 1.254)	0	0.357
AEs leading to	Drug	Dorzagliatin	3	4/897 (0.45)	5/591 (0.85)	0.386	(0.082 - 1.822)	0	0.503
discontiuation		AZD1656	2	5/251 (1.99)	3/129 (2.33)	0.932	(0.208 - 4.170)	0	
		MK-0941	1	16/472 (3.39)	3/115 (2.61)	1.310	(0.375 - 4.574)	NR	
		AMG 151	1	2/202 (0.99)	1/34 (2.94)	0.330	(0.029 - 3.743)	NR	
	Control	PLA	7	27/1822 (1.48)	12/869 (1.38)	0.767	(0.354 - 1.664)	0	0.503
AEs leading to	Drug	Dorzagliatin	2	1/692 (0.14)	4/538 (0.74)	0.268	(0.041 - 1.766)	0	0.440
withdrawal from		Piragliatin	1	1/47 (2.13)	0/12 (0.00)	0.806	(0.031 - 21.028)	NR	
study		TTP399	1	4/93 (4.30)	4/97 (4.12)	1.045	(0.254 - 4.306)	NR	
	Control	PLA	4	6/832 (0.72)	5/598 (0.84)	0.662	(0.178 - 2.465)	0	0.438
		AHA	1	4/93 (4.30)	3/49 (6.12)	0.689	(0.148 - 3.210)	NR	
Any serious AEs	Drug	Dorzagliatin	3	34/897 (3.79)	26/591 (4.40)	0.943	(0.557 - 1.596)	0	0.149
		AZD1656	4	21/546 (3.85)	33/319 (10.34)	0.433	(0.234 - 0.801)	0	
		MK-0941	3	16/578 (2.77)	3/220 (1.36)	1.827	(0.441 - 7.567)	0	
		Piragliatin	1	1/47 (2.13)	0/12 (0.00)	0.806	(0.031 - 21.028)	NR	
		PF-04937319	1	6/405 (1.48)	2/234 (0.85)	1.744	(0.349 - 8.713)	NR	
		AMG 151	1	1/202 (0.50)	0/34 (0.00)	0.514	(0.021 - 12.867)	NR	
	Control	PLA	10	67/1922 (3.49)	56/923 (6.07)	0.731	(0.489 - 1.093)	0	0.131
		AHA	1	1/72 (1.39)	1/71 (1.41)	0.986	(0.060 - 16.074)	NR	
Any serious AEs-	Drug	Dorzagliatin	1	1/382 (0.26)	0/385 (0.00)	3.031	(0.123 - 74.648)	NR	0.590
death		AZD1656	1	4/82 (4.88)	9/74 (12.16)	0.370	(0.109 - 1.258)	NR	
	Control	PLA	2	5/464 (1.08)	9/459 (1.96)	0.616	(0.105 - 3.594)	30.7	0.590
Any serious AEs	Drug	Dorzagliatin	3	33/897 (3.68)	26/591 (4.40)	0.908	(0.535 - 1.544)	0	0.281
-Other serious AEs		AZD1656	4	17/546 (3.11)	24/319 (7.52)	0.505	(0.259 - 0.986)	0	
		MK-0941	3	16/578 (2.77)	3/220 (1.36)	1.827	(0.441 - 7.567)	0	
		Piragliatin	1	1/47 (2.13)	0/12 (0.00)	0.806	(0.031 - 21.028)	NR	
		PF-04937319	1	6/405 (1.48)	2/234 (0.85)	1.744	(0.349 - 8.713)	NR	
		AMG 151	1	1/202 (0.50)	0/34 (0.00)	0.514	(0.021 - 12.867)	NR	
	Control	PLA	12	73/2603 (2.80)	50/1129 (4.43)	0.808	(0.543 - 1.204)	0	0.227
		AHA	2	6/348 (1.72)	4/165 (2.42)	0.631	(0.174 -2.287)	0	

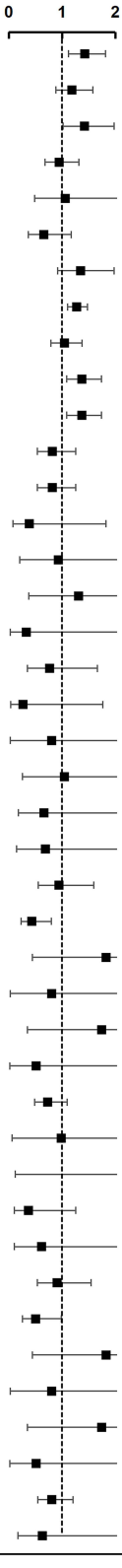

Figure 3 Subgroup analysis of overall adverse events of different glucokinase activators.
Abbreviations: AEs, adverse events; I^2, heterogeneity; No. s, numbers of studies; OR, odds ratio; PLA, placebo; AHA, antihyperglycaemic agent.

Metabolism and cardiovascular system			No.s	Experimental	Control	OR	95%CI	I^2(%)	P interaction
Hyperlipidemia	Drug	Dorzagliatin	3	95/897 (10.59)	50/591 (8.46)	1.476	(1.025 - 2.126)	0	0.019
		PF-04937319	1	4/405 (0.99)	1/234 (0.43)	2.324	(0.258 - 20.918)	NR	
		PF-04991532	1	5/159 (3.14)	0/107 (0.00)	7.654	(0.419 - 139.868)	NR	
	Control	PLA	5	104/1461 (7.12)	51/762 (6.69)	1.488	(1.041 - 2.127)	0	0.019
		AHA	2	9/564 (1.60)	0/170 (0.00)	3.187	(0.404 - 25.128)	0	
Hypertriglyceridemia	Drug	Dorzagliatin	1	21/382 (5.50)	11/385 (2.86)	1.978	(0.940 - 4.161)	NR	0.128
		AZD1656	1	2/169 (1.18)	0/55 (0.00)	1.657	(0.078 - 35.035)	NR	
		PF-04937319	1	2/405 (0.49)	2/234 (0.85)	0.576	(0.081 - 4.114)	NR	
	Control	PLA	3	25/956 (2.62)	13/558 (2.33)	1.173	(0.344 - 3.997)	37.8	0.347
		AHA	1	2/405 (0.49)	0/116 (0.00)	1.444	(0.069 - 30.281)	NR	
Hyperuricemia	Drug	Dorzagliatin	2	53/587 (9.03)	16/438 (3.65)	2.727	(1.523 - 4.883)	0	0.000
		PF-04937319	1	3/405 (0.74)	0/234 (0.00)	4.078	(0.210 - 79.299)	NR	
	Control	PLA	3	56/992 (5.65)	16/556 (2.88)	2.699	(1.523 - 4.781)	0	0.001
		AHA	1	3/405 (0.74)	0/116 (0.00)	2.026	(0.104 - 39.506)	NR	
Hypertension	Drug	Dorzagliatin	1	16/310 (5.16)	6/153 (3.92)	1.333	(0.511 - 3.479)	NR	0.203
		AZD1656	1	1/276 (0.36)	1/182 (0.55)	0.658	(0.041 - 10.590)	NR	
		MK-0941	1	2/472 (0.42)	0/115 (0.00)	1.227	(0.059 - 25.741)	NR	
		PF-04937319	1	7/405 (1.73)	2/234 (0.85)	2.040	(0.420 - 9.903)	NR	
		PF-04991532	2	9/360 (2.50)	2/207 (0.97)	2.525	(0.533 - 11.965)	0	
	Control	PLA	6	35/1823 (1.92)	10/577 (1.73)	1.227	(0.615 - 2.445)	0	0.384
		AHA	4	17/1041 (1.63)	1/314 (0.32)	1.803	(0.427 - 7.602)	0	
Hypokalaemia	Drug	AZD1656	1	4/82 (4.88)	0/74 (0.00)	8.541	(0.452 - 161.389)	NR	0.576
		PF-04937319	1	1/405 (0.25)	1/234 (0.43)	0.577	(0.036 - 9.264)	NR	
	Control	PLA	2	5/487 (1.03)	1/192 (0.52)	1.519	(0.055 - 41.824)	62.8	0.824
		AHA	1	1/405 (0.25)	0/116 (0.00)	0.864	(0.035 - 21.351)	NR	

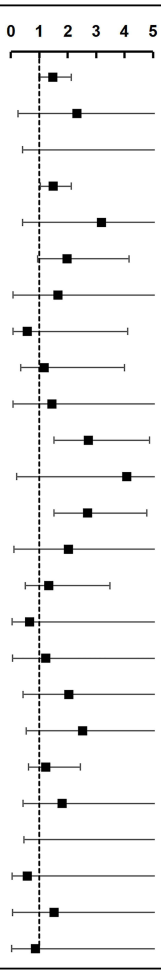

Figure 4 Subgroup analysis of metabolism and cardiovascular system of different glucokinase activators.
Abbreviations: I^2, heterogeneity; No. s, numbers of studies; OR, odds ratio; PLA, placebo; AHA, antihyperglycaemic agent.

infestation, no statistical difference was found in the incidence of upper respiratory tract infections, nasopharyngitis, and urinary tract infections ($P > 0.05$, Figures 2, S3 and Tables S6–S8); GKAs were associated with a higher risk of influenza as compared to control (2.90% vs 0.22%), with a corresponding OR of 4.881 (95% CI 1.083 to 22.004, I^2 0%, $P < 0.05$). However, the result was only reported in three trials. After further analyses, we found that the incidence risk of influenza in patients receiving MK-0941, PF-04937319, or PF-04991532 did not significantly increase ($P > 0.05$).

For hypoglycemia, there was no significant difference between GKAs and controls in terms of severe hypoglycemia (hypoglycemia with severe cognitive impairment requiring external assistance for recovery), clinically significant hypoglycemia (≤3.0 mmol/l), mild hypoglycemia (>3.0 and≤3.9 mmol/l), any hypoglycemic event (severe hypoglycemia or a blood glucose level≤3.9 mg/dl), or dropout due to hypoglycemia ($P > 0.05$, Figure 2). The results of the subgroup analyses in hypoglycemia are summarized in Figure 5. Notably, compared with the control group, MK-0941 (OR 2.120, 95% CI 1.026–4.378, I^2 NR) and AMG 151 (OR 8.404, 95% CI 1.116–63.272, I^2 NR) increased the risk of clinically significant hypoglycemia events, while PF-04937319 reduced the risk (OR 0.257, 95% CI 0.109–0.606, I^2 NR). The risk of clinically significant hypoglycemia in GKAs was notably higher than that in the placebo group (OR 2.219, 95% CI 1.271–3.875, I^2 0%). However, there was a significantly lower risk for GKA treatment (OR 0.255, 95% CI 0.096–0.677, I^2 48.2%) compared to other interventions. Additionally, for mild hypoglycemia, dorzagliatin significantly increased the risk of its occurrence (OR 5.371, 95% CI 1.713–16.842, I^2 0%), while PF-04937319 decreased the risk (OR 0.253, 95% CI 0.087–0.739, I^2 NR). Furthermore, regarding any hypoglycemic event, MK-0941 increased the risk of its occurrence (OR 1.584, 95% CI 1.104–2.272, I^2 0%), while PF-04937319 reduced the risk (OR 0.255, 95% CI 0.126–0.518, I^2 NR).

Hypoglycemia			No.s	Experimental	Control	OR	95%CI	I^2(%)	P interaction
Severe hypoglycemia	Drug	AZD1656	1	1/276 (0.36)	1/182 (0.55)	0.658	(0.041 - 10.590)	NR	0.976
		MK-0941	1	3/472 (0.64)	0/115 (0.00)	1.722	(0.088 - 33.572)	NR	
	Control	PLA	2	4/748 (0.53)	0/203 (0.00)	1.317	(0.149 - 11.654)	0	0.783
		AHA	1	1/276 (0.36)	1/94 (1.06)	0.338	(0.021 - 5.461)	NR	
Clinically significant	Drug	Dorzagliatin	3	6/897 (0.67)	0/591 (0.00)	2.494	(0.424 - 14.679)	0	0.679
hypoglycemia		AZD1656	1	6/276 (2.17)	6/182 (3.30)	0.652	(0.207 - 2.053)	NR	
		MK-0941	1	72/472 (15.25)	9/115 (7.83)	2.120	(1.026 - 4.378)	NR	
		Piragliatin	1	2/47 (4.26)	0/12 (0.00)	1.374	(0.062 - 30.498)	NR	
		PF-04937319	1	8/405 (1.98)	17/234 (7.26)	0.257	(0.109 - 0.606)	NR	
		AMG 151	1	41/202 (20.30)	1/34 (2.94)	8.404	(1.116 - 63.272)	NR	
		TTP399	1	3/93 (3.23)	4/97 (4.12)	0.775	(0.169 - 3.560)	NR	
	Control	PLA	9	138/2392 (5.77)	13/1006 (1.29)	2.219	(1.271 - 3.875)	0	0.736
		AHA	3	17/774 (2.20)	24/259 (9.27)	0.255	(0.096 - 0.677)	48.2	
Mild hypoglycemia	Drug	Dorzagliatin	2	26/587 (4.43)	3/438 (0.68)	5.371	(1.713 - 16.842)	0	0.397
		AZD1656	2	23/445 (5.17)	13/237 (5.49)	1.119	(0.558 - 2.244)	0	
		MK-0941	1	8/34 (23.53)	4/34 (11.76)	2.308	(0.623 - 8.554)	NR	
		PF-04937319	1	5/405 (1.23)	11/234 (4.70)	0.253	(0.087 - 0.739)	NR	
		AMG 151	1	43/202 (21.29)	4/34 (11.76)	2.028	(0.678 - 6.071)	NR	
		TTP399	1	0/93 (0.00)	1/97 (1.03)	0.344	(0.014 - 8.552)	NR	
	Control	PLA	8	105/1766 (5.95)	14/815 (1.72)	2.284	(1.142 - 4.570)	18.8	0.632
		AHA	2	27/681 (3.96)	22/210 (10.48)	0.304	(0.087 - 1.068)	72.2	
Any hypoglycaemic	Drug	AZD1656	4	43/392 (10.97)	18/269 (6.69)	2.365	(0.699 - 8.002)	44.2	0.678
event		MK-0941	2	252/544 (46.32)	63/186 (33.87)	1.584	(1.104 - 2.272)	0	
		PF-04937319	1	12/405 (2.96)	25/234 (10.68)	0.255	(0.126 - 0.518)	NR	
		AMG 151	1	67/202 (33.17)	6/34 (17.65)	2.316	(0.915 - 5.865)	NR	
		TTP399	1	3/93 (3.23)	5/97 (5.15)	0.613	(0.142 - 2.642)	NR	
		PF-04991532	2	6/360 (1.67)	6/207 (2.90)	0.571	(0.182 - 1.795)	0	
	Control	PLA	10	355/1924 (18.45)	55/593 (9.27)	1.795	(1.277 - 2.522)	0	0.932
		AHA	6	73/1206 (6.05)	68/434 (15.67)	0.438	(0.184 - 1.044)	76.5	
Drop out due	Drug	MK-0941	1	4/472 (0.85)	0/115 (0.00)	2.219	(0.119 - 41.504)	NR	0.363
to hypoglycemia		AMG 151	1	8/202 (3.96)	0/34 (0.00)	3.015	(0.170 - 53.453)	NR	
	Control	PLA	2	12/674 (1.78)	0/149 (0.00)	2.594	(0.333 - 20.184)	0	0.363

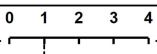

Figure 5 Subgroup analysis of hypoglycemia of different glucokinase activators.
Abbreviations: I^2, heterogeneity; No. s, numbers of studies; OR, odds ratio; PLA, placebo; AHA, antihyperglycaemic agent.

Compared with sulfonylureas, the incidence of clinically significant hypoglycemia was significantly lower in patients receiving GKAs (OR 0.131, 95% CI 0.024–0.725, I^2 81.7%, $P < 0.05$, Table S6). In comparison, the incidence of hypoglycemia events was not significantly different between GKAs and sitagliptin ($P > 0.05$, Table S7). As for the location of clinical research, mean duration of diabetes, and follow-up time, the hypoglycemia results were also in accordance with the primary analyses ($P > 0.05$ for each outcome; Table S8).

Sensitivity Analysis

To investigate the impact of each study on the overall effect size estimate and identify those with significant influence, meta-analyses were conducted using the leave-one-out method, where one study was systematically excluded from each analysis.

The sensitivity analysis outcomes did not reveal any influence on the primary results of each study and thus confirmed the robustness of the results, as shown in Table S5.

Publication Bias

As shown in Figure S4A–O, we did not observe any publication bias by qualitative funnel plots, Begg's test, and Egger's test.

Discussion

This study is a meta-analysis aimed at comprehensively evaluating the safety of GKAs and included 17 clinical trials involving eight different GKAs for the treatment of patients with T2DM, with a total of 4,918 patients being involved. In this study, we selected RCTs to assess the overall AEs for treatment with GKAs compared to other drug treatment groups. Although there have been some meta-analyses related to GKAs, this is the first meta-analysis focusing on the safety of GKAs among patients with T2DM. We found that GKAs may increase the risk of any AEs. Interestingly, further subgroup analyses revealed that the increased occurrence of any AEs were mainly derived from dorzagliatin and MK-0941. The higher incidence of mild AEs specifically was attributed to dorzagliatin treatment alone. Meanwhile, treatment with GKAs showed a higher risk of hyperlipidemia and hyperuricemia. In addition, we also found that GKAs may increase the risk of influenza, but due to limited inclusion in studies, the result of subgroup analysis did not support this view.

Our results demonstrate that compared to the control group, treatment with GKAs led to a 22.0% and 37.3% increase in the risk of any AEs and mild AEs, respectively. Subgroup analysis based on treatment with various GKAs showed that dorzagliatin increased the risk of any AEs, with an increased risk of 42.7%. This result is consistent with previous meta-analysis results where the patients receiving dorzagliatin were associated with a nearly 43% increased risk of any AEs.[20] Besides, dorzagliatin also increased the risk of mild AEs to 37.3%. Most AEs were mild (including gastrointestinal reactions or rashes) and were effectively relieved during treatment. Furthermore, MK-0941 was also associated with a 42.1% increased risk of any AEs. The incidence of any AEs was modestly higher with MK-0941 than placebo, primarily due to the increased incidence of hypoglycemia.[21] Also, AZD1656 was linked to a 56.7% risk reduction of any serious AEs and a 49.5% decreased risk of other serious AEs. The ARCADIA trial data may be driving these results. It is worth noting that previous reports have studied the therapeutic immunomodulatory effect of AZD1656 in hospitalized patients with diabetes and Corona Virus Disease 2019 (COVID-19). AZD1656 was associated with a decrease in deaths and a reduction in the duration of hospitalization compared to placebo. We speculate that this may be the main reason for the reduced risk of serious AEs associated with AZD1656 treatment.[22]

Specific Safety: Metabolism and the Cardiovascular System

Compared with placebo groups, treatment with GKAs was associated with a statistically significant 53.2% increase in the risk of hyperlipidemia. Our findings substantiate the concern that GKAs, primarily dorzagliatin, are associated with a 47.6% increased risk of hyperlipidemia. Consistent with our results, the meta-analysis by Yang et al also found that the incidence of hyperlipidemia events during dorzagliatin treatment was higher, with a nearly 50% increased risk than in placebo.[15] Stratified analysis of the location of clinical research, mean duration of diabetes, and follow-ups presented similar results. Hyperlipidemia and hepatic steatosis may be due to the disruption of normal glucokinase-glucokinase regulatory protein (GKRP) interactions.[23] The exact mechanism of this effect is unknown, and it has to be thoroughly assessed in future RCTs.

Interestingly, we found that GKAs did not increase the risk of hypertriglyceridemia in patients with T2DM. This result is inconsistent with the previous meta-analysis, where the use of GKAs in patients was shown to be associated with a higher elevation (0.322 mmol/L) in triglyceride concentration.[15] These differences may be due to variations in study inclusion or assessment criteria. Notably, it has been reported that MK-0941, AZD1656, and dorzagliatin have shown slight elevation in triglyceride levels.[21,24,25] Moreover, hypertriglyceridemia played a significant role in the discontinuation of research and development efforts for AMG 151.[26] Due to the lack of data, the safety profiles of MK-0941 and AMG151 for hypertriglyceridemia were not included in our meta-analysis. The differences in the outcomes regarding hypertriglyceridemia may be attributed to the variations in the included studies, or the deviation in results could be due to the smaller sample size of hypertriglyceridemia cases in our study. Two pathophysiologic mechanisms may explain hypertriglyceridemia. Firstly, overstimulation of hepatic GK leads to excessive glucose-6-phosphate (G-6-P) buildup, activating glycolysis facilitated by fructose 2,6-bisphosphate. Secondly, GK mRNA expression is linked to new lipid

production and triglyceride accumulation in the liver.[27] Therefore, our results regarding the safety outcomes with respect to triglycerides during GKA treatment should be interpreted with caution. Further verification of these results by undertaking high-quality large-sample studies is warranted.

Regarding hyperuricemia, the GKA treatment group showed a significant difference with an ~170% increased risk compared with controls, although only three studies reported this outcome. A stratified analysis examining the location of clinical research, the mean duration of diabetes, and follow-ups yielded comparable results. Previous meta-analyses have reported that patients receiving dorzagliatin showed a higher elevation (29.07 mmol/L) in SUA concentration in comparison with placebo.[15] The exact mechanism of this effect is unknown. However, several pathophysiologic mechanisms might explain the reason for the high risks of hyperuricemia by GKAs. Genome-wide association studies indicate that glucokinase regulator protein and single-nucleotide polymorphisms may be linked to an increased risk of gout and higher levels of SUA.[28–30] Moreover, continuous activation of GK can increase the lactate level rise and thus interfere with uric acid excretion. Additionally, elevated uric acid levels may also result from the participation of glucose-6-phosphate in the hexose monophosphate shunt, increasing uric acid precursors and raising uric acid production through phosphoribosyl pyrophosphate.[31] More research is needed to confirm this finding and its underlying mechanism.

From the perspective of metabolism and cardiovascular protection, in light of the risks associated with GKAs potentially causing hyperlipidemia, hypertriglyceridemia, and hyperuricemia, and given that both GLP-1 receptor agonists and SGLT2 inhibitors have demonstrated efficacy in reducing uric acid levels and blood lipids, the combination therapy of GKAs with either GLP-1 receptor agonists or SGLT2 inhibitors may present a more optimized treatment option. Moreover, in patients with hyperuricemia, moderate or severe hepatic impairment, and hyperlipidemia, the use of GKAs should be used with caution, and lipid and uric acid levels should be monitored regularly.

Gastrointestinal Disorders, Neurological Disorders, and Infection

In the present meta-analysis, we demonstrated that the use of GKAs was not associated with increased risk for gastrointestinal disorders, neurological disorders, and infection. Gastrointestinal-related AEs included nausea, diarrhea, vomiting, and constipation. AEs associated with neurological disorders encompassed headache and dizziness. The infection category included upper respiratory tract infection, nasopharyngitis, and urinary tract infections. Our findings are in accordance with previous meta-analyses.[16,32] Additionally, we found that constipation risks were not significantly different between GKAs and controls. Our results confirmed an increased risk of influenza with GKAs. However, further subgroup analyses revealed that the incidence risk of influenza did not significantly increase in patients receiving MK-0941, PF-04991532, or PF-04937319. Only three trials reported influenza as an AE. Therefore, additional randomized controlled trials or real-world studies are needed to gain further insights.

Hypoglycemia

According to the present meta-analysis, the overall risk of hypoglycemia during GKA treatment was similar to that of patients in the control group. However, compared with placebos, GKAs increased the risk of clinically significant hypoglycemia events, mild hypoglycemia events, and any hypoglycemia events. These findings are in accordance with previous meta-analyses.[32] GKAs increase the risk of hypoglycemia, possibly due to the GK overstimulation and subsequent disruption of the glucose-stimulated insulin secretion (GSIS) threshold.[13,15] Notably, the individual GKA subgroup analysis showed a 112.0% increased risk of clinically significant hypoglycemia events and a 58.4% increased risk of any hypoglycemic events in patients administered MK-0941. MK-0941 is a pancreas-liver dual GKA activator with 100-fold selectivity over other hexokinase isoforms.[21] Moreover, MK-0941 may cause the overstimulation of GK and the subsequent disruption of the threshold for glucose-stimulated insulin secretion.[13,33–35] As for dorzagliatin, we found that it was associated with a 437.1% increased risk of mild hypoglycemia compared with placebo, without significant differences in clinically significant hypoglycemia or severe hypoglycemia events. Studies have shown that the most significant characteristic of dorzagliatin is the activation of increased pancreatic and hepatic GK activity during hypoglycemia without enhancing insulin secretion, thereby avoiding the escalation of hypoglycemic symptoms.[25] Conversely, we found that PF-04937319 was associated with a nearly 75% risk reduction of clinically significant hypoglycemia events, mild hypoglycemia events, and any hypoglycemic events because of liver-selective GKAs.[13] Of

note, the incidence of hypoglycemia with PF-04937319 was found to be high, and the results may be overestimated because of the study design and surveillance bias with regard to monitoring blood glucose.[36] In addition, piragliatin is the inaugural GKA to have entered the clinical study phase, yet the high incidence of hypoglycemia hindered its progression to the clinical phase.[31] Interestingly, a few trials have shown a decreased incidence of clinically significant hypoglycemia events in patients receiving GKAs compared to sulfonylureas. However, clinically significant hypoglycemia events were not significantly different between GKAs and sitagliptin. Due to the limited data from the included studies, more research is needed to confirm these findings.

Additionally, apart from the adverse reactions we summarized, other adverse reactions either occur with a relatively low frequency or some GKAs are still in the research phase, lacking adequate clinical experience and long-term observation. In some reviews or meta-analyses, it is summarized that GKA may also lead to elevated liver enzymes, fatty liver, lactic acidosis, renal insufficiency, bradycardia, and cardiovascular disorders.[15,23,31,37] Nevertheless, outcomes based on a few studies should be interpreted cautiously. In the future, it may be necessary to examine the long-term safety of GKAs in the real-world study. Also, it is just as crucial that CYP3A4 inducers can decrease the exposure of dorzagliatin, while potent or moderate CYP3A4 inhibitors (such as ketoconazole, atazanavir, clarithromycin, and indinavir) can increase its exposure. Therefore, caution should be exercised when dorzagliatin is combined with CYP3A4 inducers and potent or moderate CYP3A4 inhibitors.

Apart from adverse effects, GKAs also face a challenge with diminished long-term treatment efficacy and failure to improve fasting glucose. MK-0941 lost its hypoglycemic effect at week 30. A possible explanation for the observed lack of sustained impact of MK-0941 is the inclusion of patients with long disease duration and severely impaired pancreatic beta cells.[15,21,31,37] Similarly, AZD1656 failed in the hypoglycemic effect in phase II clinical trials. It was hypothesized that the persistent chronic activation of GK in pancreatic beta cells gave rise to glucolipotoxicity, which in turn led to a decrease in glucose-responsive islets.[15,24,31,37] Lack of long-term glycemic control may also be responsible for the clinical termination of AZD6370.[31] Moreover, dorzagliatin has failed to produce a significant improvement in fasting blood glucose.[31,38] The failure of GKAs to improve fasting blood sugar and waning therapeutic efficacy in long-standing diabetes needs validation from more extensive future studies.

Strengths and Limitations

The major advantage of this meta-analysis lies in its comprehensive and meticulous evaluation of the safety of GKAs. Our meta-analysis boasts several strengths: (1) Our research question specifically targets the AEs associated with GKAs; (2) This is the first meta-analysis to assess the comparative safety of GKAs across all AEs; (3) AEs occurring in >3% of patients have been systematically identified; (4) Subgroup analyses have been conducted for individual GKAs, different control groups, follow-up duration, mean duration of diabetes, and the location of clinical research.

Indeed, this study also has several limitations. First, we did not evaluate AEs with low incidence rates (<3% of patients). Second, most trials, particularly those involving MK-0941 and PF-04937319, are unlikely to report specific AEs in their complete publications. Nevertheless, we obtained additional data from the US National Library of Medicine website (ClinicalTrials.gov) to minimize the risk of reporting bias. Third, while differences in background therapies and patient characteristics across RCTs may lead to heterogeneity, we found low statistical heterogeneity in this meta-analysis. Fourthly, hyperlipidemia included type IIb and type IV hyperlipidemia. This may also introduce bias in this study. Finally, we excluded all phase I clinical trials and research with no results on GKAs, so our results do not include GKAs drugs such as LY 2608204 (Globalagliatin) and AZD6370. Studies have reported that globalagliatin may trigger bradycardia.

Conclusion

In conclusion, treatment with GKAs for patients with T2DM appears to be relatively safe. However, GKAs were associated with a higher risk of any AEs, mild AEs, hyperlipidemia, and hyperuricemia. The results of increased risk of hyperlipidemia and hyperuricemia mainly come from dorzagliatin. Therefore, caution is advised when using GKAs to treat patients with T2DM who have comorbidities involving hyperlipidemia or hyperuricemia. Further clinical studies are warranted to assess the long-term safety of GKAs fully.

Abbreviations

AEs, adverse events; GKAs, glucokinase activators; T2DM, type 2 diabetes mellitus; HbA_{1c}, glycated hemoglobin; TZDs, thiazolidinediones; SGLT2 inhibitors, sodium-glucose cotransporter two inhibitors; GLP-1 receptor agonists, glucagon-like peptide-1 receptor agonists; GKA, glucokinase activator; US, the United States; EU, the European Union; UK, the United Kingdom; SUA, serum uric acid; GK, glucokinase; AEs, adverse events; RCTs, randomized controlled trials; OR, odds ratio; CIs, confidence intervals; GKRP, glucokinase regulatory protein; GSIS, glucose-stimulated insulin secretion; G-6-P, glucose-6-phosphate; COVID-19, Corona Virus Disease 2019.

Data Sharing Statement

The raw data supporting the conclusion of this article will be made available by the authors to related qualified researchers.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Shi and Gu are the guarantors of the entire manuscript. Liang and Cao contributed to the study conception and design, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. Wang, Zou, and Yang contributed to the data acquisition, analysis, and interpretation.

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Disclosure

The authors have declared no conflicts of interest for this article.

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