The effects and safety of activators of glucokinase versus placebo in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

Hongcui Diao¹, Xiaolong Yu¹, Chengqian Li¹, Yanjun Guo¹, Baoming Shen² and Wenjuan Zhao¹

¹Department of Endocrinology and Metabolism, the Affiliated Hospital of Qingdao University, Qingdao, Shandong, China
²Department of Equipment and Information, the Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

Abstract. We undertook a systematic review and meta-analysis to assess the effects and safety of activators of glucokinase (GKAs) in patients with type 2 diabetes mellitus (T2DM). 11 RCTs, including 2,429 participants, are enrolled in our study. According to different doses, we divided the studies into 3 groups: low-dose group, medium-dose group and high-dose group for subgroup analysis. There were decreases of HbA1c in all dose group (WMD = –0.27, 95%CI (–0.51~ –0.03), Z = 2.17, \( p = 0.03 \); WMD = –0.37, 95%CI (–0.58~ –0.16), Z = 3.41, \( p = 0.0006 \); WMD = –0.60, 95%CI (–0.86~ –0.33), Z = 4.43, \( p < 0.00001 \)). Though the total risk of hypoglycemia is absolutely low, in the high-dose group higher hypoglycemia than the placebo can be observed (RR = 0.03, 95%CI (0.00~0.06), Z = 2.27, \( p = 0.02 \)). In addition, the study found that the drug was less likely to have adverse reactions such as diarrhea, headache and dizziness, nasopharyngitis and upper respiratory tract infection (RR = 0.76, 95%CI (0.36~1.60), Z = 0.73, \( p = 0.47 \); RR = 1.26, 95%CI (0.73~2.17), Z = 0.83, \( p = 0.41 \); RR = 0.71, 95%CI (0.41~1.22), Z = 1.25, \( p = 0.21 \); RR = 1.61, 95%CI (0.77~3.36), Z = 1.26, \( p = 0.21 \)). It concludes that GKAs are relatively effective and safe in the treatment of patients with T2DM, but in consideration of the potential risk of hypoglycemia in the high-dose group, the low-dose and medium-dose group, in the clinical practice, can be an excellent choice.

Key words: Activators of glucokinase, Type 2 diabetes mellitus, Meta-analysis

TYPE 2 DIABETES MELLITUS (T2DM) is a metabolic disorder characterized by elevated blood glucose resulting from deficiencies in insulin secretion/sensitivity and increased hepatic glucose production [1]. Current guidelines suggest metformin as the first-line pharmacological therapy with second-line therapies employing a variety of mechanisms including sulphonylureas or dipeptidyl peptidase-4 inhibitors [2]. In spite of these therapies and several other available classes of agents, only 52.5% of patients achieve glycaemic control [3]. Novel mechanisms that can avoid or reduce the adverse events associated with the available drug classes and delay or avoid the loss of efficacy over time associated with current therapies are needed [4]. Glucokinase is expressed in pancreatic β-cells and the liver, where it catalyses the phosphorylation of glucose to glucose-6-phosphate and is believed to act as a physiological ‘glucose sensor’ [5]. Glucokinase activators (GKAs) may have antihyperglycaemic effects through enhancement of glucose-stimulated insulin secretion and hepatic glucose utilization. Impaired glucokinase function and expression has been found in patients with type 2 diabetes [6-8]. Hepatic glucose sensing is impaired in people with impaired fasting glucose, but can be augmented by pharmacological or environmental glucokinase activators [9]. Therefore, we undertook a meta-analysis to evaluate the safety on glucose control of GKAs treatment in T2DM patients.

Materials and Methods

Data sources and search strategy

This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (Number CRD42020171040).

We searched PubMed, web of science, Embase and the Cochrane Library from inception to November, 2019, as well as grey literature sources, without language restrictions. And because our study is a meta-analysis, there is...
no need for an ethics statement. Two reviewers independently screened titles and abstracts of all records, full texts of potentially eligible studies. Any disagreements were resolved by consensus with a third reviewer. The searching term were “Diabetes Mellitus, Type 2” OR “Diabetes Mellitus, Noninsulin-Dependent” OR “Diabetes Mellitus, Type II” OR “Type 2 Diabetes Mellitus” OR “Type 2 Diabetes” OR “Diabetes, Type 2” OR “Diabetes Mellitus, Adult-Onset” AND “glucokinase activator” OR “glucokinase (GK) activator” OR “GKAs”.

Inclusion and exclusion criteria
Eligible trials were listed and assessed independently by 2 reviewers using predefined inclusion criteria. Studies were included if they met the following criteria: (1) randomized controlled design; (2) type 2 diabetic patients; (3) patients 18 years or older; (4) the intervention group received GKAs; (5) the comparison group received placebo; (6) reported at least one outcome of interest. There were no restrictions on length of follow-up. The exclusion criteria were as follows: (1) animal studies, case reports and review; (2) non-randomized design; (3) patients with diabetes other than Type 2 or patients with underlying debilitating conditions; (4) articles that provided inadequate information of interest or primary data.

Quality assessment
The quality of eligible study was assessed using the Cochrane Collaboration’s risk-of-bias assessment tool [10], which included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personal (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential sources of bias. The judgment for each entry involves answering a question, with ‘Yes’ indicating low risk of bias, ‘No’ indicating high risk of bias, and unclear indicating lack of information or uncertainty about the possibility of bias.

Data synthesis and statistical analysis
For each outcome measure of interest, the WMD (weighted mean difference) and its 95% CI were applied for continuous variables while RR and its 95% CI were used for dichotomous outcomes. Considering the differences in baseline participants characteristics and drug administration, a random effects model was selected for analyses regardless of heterogeneous. A p-value <0.05 for any test or model was considered statistically significant. The degree of between-study variability attributable to heterogeneity beyond chance was calculated using the I² statistic and Q statistic. 10 Outcomes with I² levels from 0% to 40% were considered lower heterogeneous, while I² >50% was considered an indication of statistically significant heterogeneity among included studies.

Results

Search results and study characteristics
According to the literature inclusion and exclusion criteria, the final study included a total of 11 literatures. The study flow diagram is available in Supplementary Fig. 1. The basic information and related data of the 11 documents are detailed in Table 1.

Quality evaluation of selected studies
11 RCTs random methods were correct, 11 studies reported the generation of random sequences in detail, 5 studies had complete outcome data, 9 studies used the correct method of allocation concealment, 9 studies used blind methods for the participants and personnel, and no reported bias or other known bias existed in each study (Supplementary Fig. 2).

The effects of GKAs on HbA1c in patients with T2DM
According to the treatment dose of GKAs, we divided the studies into 3 groups: low-dose group, medium-dose group and high-dose group for subgroup analysis. Compared with placebo, the reduction in the HbA1c level of all dose group could be observed (WMD = –0.27, 95%CI (-0.51~ –0.03), Z = 2.17, p = 0.03; WMD = –0.37, 95%CI (-0.58~ –0.16), Z = 3.41, p = 0.0006; WMD = –0.60, 95%CI (-0.86~ –0.33), Z = 4.43, p < 0.0001; Fig. 1). And the difference between these three groups were statistically significant (p = 0.0009), indicating that the group method of data handling was significant. The heterogeneity test showed that the heterogeneity of the middle-dose and high-dose group obvious (I² = 62, p = 0.03; I² = 75, p = 0.001), indicating relatively high heterogeneity.

The safety of GKAs in patients with T2DM
The incidence of hypoglycemia
A total of nine studies reported the risk of hypoglycemia after treatment. The meta-analysis showed that there was no difference between the GKAs group and the placebo group (RR = 1.36, 95%CI 0.83~2.24; Z = 1.22, p = 0.22; Fig. 2). The heterogeneity test showed that I² = 0, indicating good stability.

Then, according to different doses of GKAs, we compared the incidence of hypoglycemia in low, medium and high-dose groups. Compared with placebo, initial decrease in HbA1c was observed with GKAs high-dose group (RR = 0.03, 95%CI (0.00~0.06), Z = 2.27, p = 0.02; Fig. 3).
And we didn’t observe any significant difference between the low-dose and medium-dose group compared to the placebo group (RR = 0.04, 95%CI (–0.01~0.09), Z = 0.47, p = 0.63, I² = 0; RR = 0.02, 95%CI (–0.02~0.06), Z = 0.83, p = 0.41; Fig. 3).

The incidence of other adverse events

We did not observe significant difference in the incidence of diarrhea, headache, dizziness, nasopharyngitis and upper respiratory tract infection (RR = 1.26, 95%CI (0.73~2.17), Z = 0.83, p = 0.41, I² = 0; RR = 0.71, 95%CI (0.41~1.22), Z = 1.25, p = 0.21, I² = 0; RR = 1.61, 95%CI (0.77~3.36), Z = 1.26, p = 0.21, I² = 0).

Assessment of publication bias

Funnel diagrams were used to test the 9 studies included in the meta-analysis reporting the occurrence of hypoglycemia. The inverted funnel diagrams showed basic symmetry, suggesting a lower risk of publication bias in the included literature (Fig. 4). Because of less than 8 studies were included in the HbA1c group, we did not present the evaluation of publication bias in this group.

Sensitivity analysis

In addition, we further performed sensitivity analysis on the data by eliminating the literature one by one, and we have found that if the results of MK0941 is excluded, the heterogeneity of the middle-dose and high-dose group can be lowered drastically (I² = 0, p = 0.76; I² = 0, p = 0.43), that may because the objects of this study is much more than any other study.

Discussion

The results of this study show that GKAs treatment can effectively control HbA1c level in patients with T2DM, and current studies have found that high-dose treatment group increase the risk of hypoglycemia.

The meta-analysis shows that low-dose, medium-dose and high-dose treatment can reduce HbA1c level in patients with T2DM to some extent (WMD = –0.27 mmol/L, –0.37 mmol/L, –0.60 mmol/L). Glucokinase (GK) is one of a family of isoenzymes that catalyze the metabolism of glucose to glucose-6-phosphate [5, 11]. GK acts as a molecular sensor of whole-body glucose homeostasis due to its location and activity in pancreatic β-cells [12], regulating insulin secretion in b-cells in response to increased glucose levels, and controlling the rate of glucose conversion to glycogen in the liver [13, 14]. In hepatic cells, GK catalyzes the first step in glucose metabolism and, by this mechanism, determines the rate of glucose use glycogen formation by the liver and influences circulating glucose levels [15].

Fig. 1 The effects of GKAs on HbA1c level.
activities confer on GK a central role in the regulation of normal glucose metabolism [12, 16]. GK activation has, therefore, been proposed as a therapeutic target as it offers the potential for dual effects in correcting two underlying defects in T2DM: impaired insulin secretion and excessive hepatic glucose output [4].

The study also finds that patients have better overall tolerance for taking GKAs and meta-analysis found that the drug was less likely to have adverse reactions such as diarrhea, headache and dizziness, nasopharyngitis and upper respiratory tract infection (all \( p > 0.05 \)). And the total incidence of hypoglycemia is low, but it has a slightly higher incidence of high-dose treatment group than in the placebo group (RR = 0.03, \( p < 0.05 \)), which is in accordance to Meininger GE and Wilding J’s results [17, 18]. This may because of the glucose-lowering

Table 1 Characteristics of trials included in the present analysis

| Author (year)          | Name     | No. of patients | Mean Age (years) | Mean course (years) | Mean HbA1c (%) | Trial duration (weeks) | Intervention                  | Comparator     |
|------------------------|----------|-----------------|------------------|---------------------|----------------|------------------------|-------------------------------|---------------|
| A. Kiyosue (2013)      | AZD1656  | 224             | 56               | 5                   | 7.5–10.0       | 12                     | 40–200 mg, 20–140 mg, 10–80 mg QD | Placebo       |
| Adrian Vella (2019)    | TTP399   | 189             | 55               | 8                   | 7.0–9.5        | 24                     | 400 mg, 800 mg QD             | Placebo       |
| Bonadonna RC (2010)    | RO4389620| 15              | 51               | 4                   | 6.1            | 1 day                  | 25 mg, 100 mg QD              | Placebo       |
| Dalong Zhu (2018)      | HMS5552  | 255             | 58               | 8                   | 7.5–10.5       | 16                     | 75 mg, 100 mg QD, 50 mg, 75 mg BID | Placebo       |
| Gary E. Meininger (2011)| MK-0941 | 587             | 56               | 12                  | 7.5–11.0       | 54                     | 10 mg, 20 mg, 30 mg, 40 mg QD  | Placebo       |
| J.P.H. Wilding (2013)  | AZD1656  | 530             | 56               | 9                   | 7.5–12.0       | 16                     | 20 mg, 40 mg, 10–140 mg, 20–200 mg QD | Placebo       |
| Katz L (2016)          | AMG 151  | 236             | 54               | 7                   | 7.5–11.0       | 4                      | 100 mg, 200 mg, 400 mg QD, 50 mg, 100 mg, 200 mg BID | Placebo       |
| L.A. Morrow (2012)     | AZD1656  | 32              | 51               | —                   | 6.0–10.5       | 1                      | 7 mg, 20 mg, 40 mg, 80 mg BID | Placebo       |
| N.B. Amin (2015)       | PF-04937319| 304        | 55               | 9                   | 7.0–11.0       | 12                     | 10 mg, 50 mg, 100 mg QD       | Placebo       |
| William S. Denney (2016)| PF-04937319| 33             | 57               | 8                   | 6.5–11.0       | 6                      | 150 + 100 mg QD, 300 mg QD    | Placebo       |
| Xiaoxue Zhu (2018)     | HMS5552  | 24              | 52               | 6                   | 7.4–10.6       | 4                      | 75 mg BID, 75 mg QD           | Placebo       |

Fig. 2 The incidence of hypoglycemia.
The effects of GKAs are considered to be glucose-dependent [14], increasing the affinity of glucokinase for glucose, and thus enabling the enzyme to function at lower glucose concentrations. It is theoretically possible that a large dose of a GKA can reduce the glucose threshold for glucokinase activation markedly [13], potentially lowering P-glucose levels into the hypoglycemic range. To address the side-effects of hypoglycemia, chemists have developed liver-selective partial activators, which should control changes in GK kinetic parameters to avoid hypoglycemia.

This study provides new hypoglycemic choice guid-

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| Study or Subgroup | Experimental Events | Control Events | Total Events | Risk Difference M-H, Random, 95% CI | Risk Difference M-H, Random, 95% CI |
|------------------|---------------------|----------------|-------------|--------------------------------------|--------------------------------------|
| **3.1.1 Low dose** |                     |                |             |                                      |                                      |
| Dalong Zhu HM55552 | 3                   | 53             | 56          | 7.2%                   0.08 [0.01, 0.13] |                                      |
| Katz L AMG AZID1656 | 26                  | 65             | 91          | 0.9%                   0.08 [0.12, 0.27] |                                      |
| L.A. Morrow AZID1656 | 1                   | 6              | 7           | 0.3%                   0.04 [0.33, 0.42] |                                      |
| N.B.Amin PF-04037319 | 3                   | 54             | 57          | 5.0%                   0.00 [0.08, 0.09] |                                      |
| SubTotal (95% CI) | 178                 | 152            | 330         | 13.4%                  0.04 [-0.91, 0.99] |                                      |
| Total events     | 33                  | 15             |             |                                      |                                      |

Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 3 (P = 0.77); I² = 0%

Test for overall effect: Z = 1.42 (P = 0.15)

| **3.1.2 Middle dose** |                     |                |             |                                      |                                      |
| Adriane Vella TTP399 | 0                   | 50             | 50          | 7.9%                   -0.04 [-0.11, 0.03] |                                      |
| Dalong Zhu HM55552 | 5                   | 101            | 106         | 13.9%                  0.05 [-0.00, 0.10] |                                      |
| J.P.H.Widig AZID1656 | 1                   | 40             | 41          | 10.1%                  0.03 [-0.03, 0.06] |                                      |
| Katz L AMG AZID1656 | 21                  | 67             | 88          | 1.0%                   -0.01 [-0.20, 0.18] |                                      |
| L.A. Morrow AZID1656 | 2                   | 6              | 8           | 0.2%                   0.21 [-0.23, 0.65] |                                      |
| N.B.Amin PF-04037319 | 3                   | 61             | 64          | 6.1%                   0.00 [-0.08, 0.08] |                                      |
| SubTotal (95% CI) | 10                  | 31             | 41          | 0.8%                   0.17 [0.05, 0.38] |                                      |
| Total events     | 42                  | 21             |             |                                      |                                      |

Heterogeneity: Tau² = 0.00; Chi² = 7.70, df = 6 (P = 0.26); I² = 22%

Test for overall effect: Z = 0.96 (P = 0.34)

| **3.1.3 High dose** |                     |                |             |                                      |                                      |
| A. Kyooue AZID1656 | 1                   | 55             | 56          | 15.0%                  0.02 [-0.03, 0.07] |                                      |
| Adriane Vella TTP399 | 3                   | 42             | 45          | 3.9%                   0.03 [-0.07, 0.13] |                                      |
| Dalong Zhu HM55552 | 3                   | 51             | 54          | 6.8%                   0.06 [-0.01, 0.13] |                                      |
| J.P.H.Widig AZID1656 | 1                   | 50             | 51          | 14.9%                  0.02 [-0.03, 0.07] |                                      |
| Katz L AMG AZID1656 | 21                  | 69             | 90          | 1.0%                   -0.02 [-0.21, 0.17] |                                      |
| L.A. Morrow AZID1656 | 1                   | 6              | 7           | 0.3%                   0.04 [-0.33, 0.42] |                                      |
| N.B.Amin PF-04037319 | 7                   | 61             | 68          | 3.8%                   0.07 [-0.03, 0.16] |                                      |
| William S.Denney PF-04037319 | 13                  | 30             | 43          | 0.7%                   0.28 [-0.05, 0.50] |                                      |
| Xieouze Zhu HM55552 | 2                   | 12             | 14          | 0.3%                   -0.00 [-0.41, 0.24] |                                      |
| SubTotal (95% CI) | 376                 | 384            | 760         | 46.6%                  0.63 [0.00, 0.68] |                                      |
| Total events     | 52                  | 24             |             |                                      |                                      |

Heterogeneity: Tau² = 0.00; Chi² = 7.87, df = 8 (P = 0.45); I² = 0%

Test for overall effect: Z = 2.27 (P = 0.02)

Total (95% CI) 910 853 100.0% 0.03 [0.01, 0.05]

Total events 127 60

Heterogeneity: Tau² = 0.00; Chi² = 17.18, df = 19 (P = 0.50); I² = 0%

Test for overall effect: Z = 2.67 (P = 0.004)

Test for subgroup differences: Chi² = 0.48, df = 2 (P = 0.79), I² = 0%

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**Fig. 3** The incidence of hypoglycemia of difference groups.

**Fig. 4** The funnel diagrams testing the 9 studies reporting the occurrence of hypoglycemia.
ance for patients with diabetes, and provides evidence-based medical basis for further clinical trials. However, there are some limitations in this study: 1) The search language of this study is limited to English and Chinese, and the majority of the population included are European and American, a small number are Asian, but the pharmacokinetics of different ethnic groups may be different, there is a certain bias. 2) The clinical studies included in this study do not take blood pressure and cardiovascular events as the observation endpoints and do not analyze the occurrence of such adverse reactions. 3) We have found that in the trial of AZD1656 and MK-0941, loss of efficacy of the drug over time was observed. But the reasons for this are currently unclear, and it is uncertain whether this is a general class property of GKAs or if it is particular to AZD1656 and MK-0941. It is possible that sustained administration with a GKA may induce some physiological changes. So further studies are warranted to explore this. 4) It should be noted that in one trial of MK-0941, one of the GKAs, an increase of the serum triglyceride levels was observed, which at least in part led to termination of this particular trial, leading to an increase of lipid storage in liver. But in the several studies we have searched, it was only mentioned in this article. Therefore, the conclusions of this study need larger sample and higher quality studies to prove it.

**Disclosure**

**Statement of ethics**

Because our study is a meta-analysis, there is no need for an ethics statement.

**Disclosure statement**

The authors have no conflicts of interest to declare.

**Funding sources**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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