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Review Article

Efficacy and safety of glucokinase activators for type 2 diabetes mellitus: A systematic review

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ABSTRACT

Glucokinase activators (GKAs) are newly drug class proposed for diabetes treatment. This systematic review aimed to assess the efficacy and safety of GKAs in type 2 diabetes mellitus (T2DM) compared to placebo for their readiness in clinical practice and future development. Systematic review on online databases including CINAHL, the Cochrane Library, EMBASE, MEDLINE, Scopus, Web of Science, and ClinicalTrials.gov was conducted with inception until December 2018. Randomized-controlled trials (RCTs) reported in English were assessed in terms of study quality, placebo-corrected efficacy on glycemic control, and list of safety issues. Thirteen studies were included comprising of eight candidates for GKAs namely AMG 151 (ARRY-403), AZD1656, dorzagliatin, MK-0941, PF-04937319, PF-04991532, RO4389620 (piragliatin), and TTP399. Of the promising GKAs, efficacy on glycemic control was demonstrated on HbA1c reduction more than fasting plasma glucose (FPG) and 2-hours post prandial glucose (2h PPG). Compared to placebo, GKAs contributed to significant HbA1c decrease up to 0.7-0.8%. Direct GKAs revealed great potency, but more selective GKAs offered certain moderation. This was due to some raised concerns such as hypoglycemia, triglyceride alteration, and adverse events leading to discontinuation. Regardless of limited data, some factors might influence the effects of GKAs in T2DM, for example, structure-molecular aspect, varied trial settings, and diversity in participants' background. These findings shed light in diabetes management. However, mechanisms towards the unmet benefits of GKAs in T2DM should be tackled. Large clinical trials with longer duration are also still needed.

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder presenting uncontrolled glycemic level. The prevalence had been estimated rising from 8.8% in 2017 to be 9.9% in 2045 around the world[1]. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes. This type is related to the lack of insulin secretion due to progressive loss of pancreatic β-cell on the background of insulin resistance[2]. The development of these conditions is recently found to be determined by genes and environment as β-cell function was claimed heritable[3]. There is evidence that genetic polymorphism of glucokinase might become one

of the risk factors associated with increased susceptibility to T2DM[4].

Glucokinase is a key enzyme involved in glucose homeostasis by acting as glucose sensor in pancreatic β-cells as well as a rate limiting step of glucose metabolism and glucose storage in the liver[5]. This monomeric enzyme was also found having allosteric site which can be activated by small molecule causing positive glucose cooperativity mechanism in glucose metabolic regulation[6]. Regarding this concept, it seems that modulation of glucokinase activity might contribute to glucose maintenance in order to remain in the normal level. Hence, some decades have been eagerly being spent to develop glucokinase activators (GKAs). This development highlights the potential of GKAs to meet the challenge in the emergence of T2DM in which the glucokinase also plays role[7].

The first published GKA was in 2003, tested in rodent models of T2DM. The results showed it lowering blood glucose levels, improving the results of glucose tolerance tests, and increasing hepatic glucose uptake accordingly[8]. This finding led the high interest in the development of many other GKAs to become rising. It was recorded later that almost one hundred applications of patent were competitively proposed, including some candidates to enter clinical phase[9,10]. Until now, the results of clinical trials are available and have been published[11-20]. In addition, based on pharmacokinetics-pharmacodynamic (PK-PD) findings, certain GKAs showed more promising efficacy due to their selective action[11,16,19,20]. However, the systematic review focusing on the efficacy of GKAs to control blood glucose and their safety is limited. Therefore, we reviewed the efficacy and safety of GKAs compared to placebo from randomized-controlled trials (RCTs) in T2DM to justify whether GKAs are worthwhile to be applied in clinical practice.

2. MATERIALS AND METHODS

We conducted a systematic review following the PRISMA guidelines[21]. Our framework was based on the following methodology.

2.1. Eligibility criteria

The eligible studies had to meet the inclusion criteria as follows: RCTs comparing GKAs with placebo; patients with T2DM; and studies reporting at least one outcome of interest for both efficacy and safety. Efficacy outcomes included effects on glycemic control such as glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), or 2-hours post prandial glucose (2h PPG). Safety outcomes included adverse events (AEs), serious adverse events (SAEs), and hypoglycemic events (HEs). There was no restriction regarding race, age of participants, and duration of treatment. Pharmacokinetics and pharmacodynamics (PK-PD) studies were considered when they met all of the above-mentioned criteria. If PK-PD studies provided the effects on glycemic parameters in standard unit for clinical setting declared by American Diabetes Association (ADA) (FPG, 2h PPG: mg/dL or mmol/L; HbA1c: % or mmol/mol)[2] or at least, percentage of changes in the desired outcomes, the studies were accepted. We sought both published studies and studies in clinical trial registry with summary estimate. In case of duplication, published study would be prioritized, unless the records with more information were available.

Studies were excluded if they were not reported in English. Protocols for ongoing studies were not accepted. Studies which did not report the results completely, for example, abstract without particular results, outcomes without baseline data, or incomplete data in the absence of supplementary files, were not eligible.

2.2. Data sources and search strategy

We independently performed systematic literature search by using electronic databases such as the Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (EMBASE), MEDLINE (PubMed), Scopus, Web of Science, and Clinical-Trials.gov (http://clinicaltrials.gov) to identify clinical trial reports with inception until the end of December 2018. Single search term or numerous combinations of keywords and medical subject headings (MeSH) were used as follows: diabetes mellitus, type 2 (population), glucokinase activator (intervention), blood glucose, hemoglobin A glycosylated, hypoglycemia, hyperglycemia, glycemic control, efficacy, safety (outcomes), and randomized controlled trial. These were followed by search terms to proceed. For example, we carried out the

following search strings in PubMed: ("glucokinase activator") AND (diabetes mellitus, type 2 OR NIDDM OR hyperglycemia OR hypoglycemia) AND (glycosylated hemoglobin OR blood glucose OR fasting plasma glucose OR efficacy OR safety). Manual search of reference list based on relevant articles was also conducted.

2.3. Study selection

Obtained records were screened based on title and abstract. Only full-text articles of relevant RCTs were included for in-depth review. Identified records were evaluated and reviewed for eligibility by NS. PDMK identified records and extracted the data. Conflicts over inclusion were resolved by discussion between the two authors.

2.4. Data collection and quality assessment

Data from eligible studies were extracted including: studies' characteristics (author, year of publication, study design, location, interventions, background therapy, study duration, inclusion criteria, type of outcomes), baseline characteristics (number of participants, age, baseline value of desired outcomes), outcome of interest (efficacy outcomes were adjusted to placebo; safety outcomes were presented in rate), and methodological quality. Outcome values were pooled manually or converted to standard unit if applicable. We provided efficacy outcomes in placebo-corrected change in least square means (LSM) with 95% confidence interval (CI), unless otherwise stated. Methodological assessment was evaluated based on the risk of bias in individual studies by using Cochrane Risk of Bias Tool[22]. We generated the risk of bias graph and the risk of bias summary by using The Review Manager Software (RevMan 5.3)[23].

3. RESULTS

Electronic databases and hand search identified 332 articles. Based on the full-text screening of 40 relevant RCTs, 13 studies met the inclusion criteria (Figure 1).

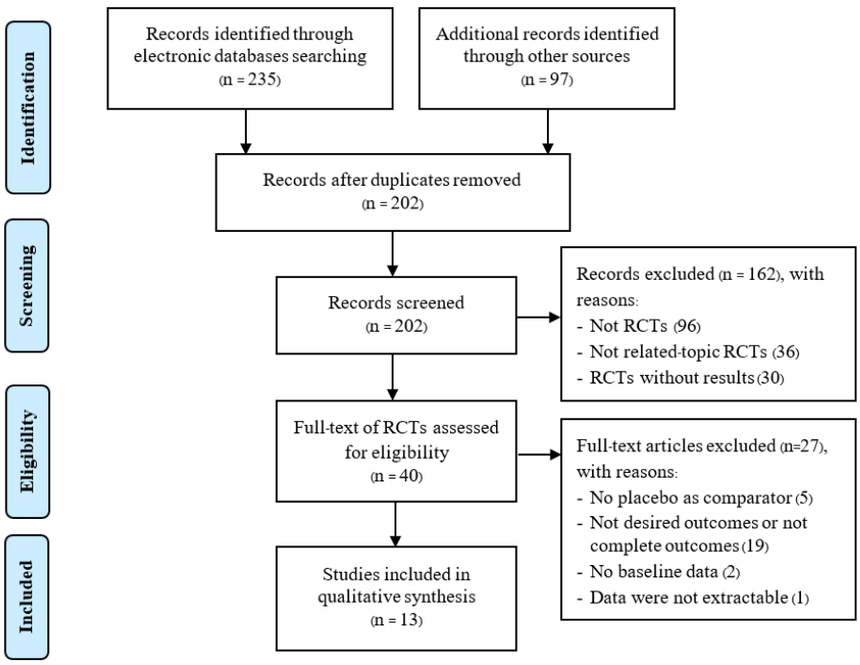

Figure 1. PRISMA flow chart of study selection process
RCT = randomized-controlled trial

3.1. Study characteristics and study quality

The characteristics of included studies and participants are summarized in Table 1 and Table 2. All the included studies reported trial results of eight GKAs namely AMG 151 (ARRY-403)[12], AZD1656[13,15,17], dorzagliatin (HMS5552)[24], MK-0941[14], PF-04937319[11,25,26], PF-04991532[27,28], piragliatin[18], and TTP399[16]. All of the studies had been published, except two studies of which the results were collected from clinical trial records[25,26]. Two studies[27,28] had been published as abstracts in conference[19,20], but the results were considerably taken from clinical trial records for more complete data. Two studies[13,26] recruited only Japanese populations and one study[24] enrolled Chinese patients. All studies represented either phase 1 trials[15,18,25,26] or phase 2 trials[11-14,16,17,24,27,28] with study duration not longer than four months. Majority of the studies were conducted as parallel design and as add-on therapy to metformin. Outcomes reported for glycemic parameters were mostly HbA1c and FPG. Only two studies reported 2h PPG[14,24].

Most studies are either of low risk of bias or unclear risk of bias. Some studies minimized the risk of selection bias, performance bias, attrition bias, and reporting bias. Only one study addressed the allocation concealment and blinding of outcome assessment. Methodological evaluation for the included studies is presented in the risk of bias graph (Figure 2) and the risk of bias summary (Figure 3).

3.2. Efficacy outcomes on glycemic control

Overall, based on the placebo-corrected values, GKAs reduced HbA1c significantly within range 0.24% to 0.81% (Table 3). The highest HbA1c reduction up to 0.81% was represented by titrated dose of 10-140 mg AZD1656 as add-on to metformin ($p<0.001$)[17]. The other add-on dose of titrated 20-200 mg AZD1656 as well as thrice-daily dose of 30 mg and 40 mg MK-0941 offered similar efficacy on HbA1c by only one point lower than the highest reduction (0.80%, $p<0.001$)[14,17]. Additionally, significant effect with slight difference to the highest HbA1c reduction was observed in 75 mg dorzagliatin given twice daily (0.77%, $p<0.0001$)[24]. All drugs, except AZD1656, reduced HbA1c in dose-dependent manner. Reduction pattern on HbA1c of AMG 151 was similar between the frequency given either as once-daily dose or twice-daily dose. However, PF-04937319 administered in dose 50 mg once daily in two studies by Amin et al. (B1621002 and B1621007) demonstrated different points of HbA1c reduction, although both values were not significant[11]. Inconsistent results were presented by two studies of PF-04991532. A total daily dose of 150 mg PF-04991532 could increase HbA1c by 0.08% ($p=0.68$) when given as single dose, but decrease HbA1c by 0.28% ($p=0.027$) when administered as 75 mg-twice-daily dose,[27,28].

The efficacy of GKAs on HbA1c over time from all drugs in the phase 2 trials were reported, except AMG 151[11-14,16,17,24,27,28]. The effects of some GKAs on HbA1c in this review started immediately after given, but did not sustain until the end of study. For example, efficacy of AZD1656 monotherapy tested in Japanese population started declining after two months[13]. MK-0941 also demonstrated maximum efficacy for not more than ten weeks[14]. Furthermore, PF-04991532 was reported with sustained efficacy only until eight weeks, instead of lasted at the end of the twelfth week[27,28]. GKAs' sustainability on HbA1c reduction until the end of study was represented by the rest GKAs. The HbA1c reduction of dorzagliatin[24], PF-04937319[11], and TTP399[16] lasted until the final week of the trial. In addition, AZD1656 prolonged the effect on HbA1c reduction up to three months when given as add-on to metformin[17]; however, it failed to show as monotherapy[13].

Unlikely the effects on HbA1c, effects of GKAs on FPG showed non-dose dependent pattern for most of the drugs, as well as the effects on 2h PPG (Table 4 and Table 5). However, AMG 151 twice daily groups[12], AZD1656[15], and PF-04937319 in PK-PD study with Japanese [26] indicated the trend of FPG reduction in dose-dependent manner. All GKAs studied approximately one to two weeks were reported decreasing FPG significantly within 0.68 to 6.2 mmol/L (12.25 to 111.71 mg/dL). The highest value was contributed by PF-04937319 300 mg once daily and it was known causing hypoglycemia[25]. Longer period of GKAs trials within four to 16 weeks revealing significant FPG reduction from 0.85 to 1.38 mmol/L (15.32 to 24.99 mg/dL). Of these, the highest FPG reduction was given by AMG 151 (200 mg) twice daily. Both dorzagliatin and MK-0941 reported the effect on 2h PPG, reduction

Table 1. Characteristics of included studies

Study, year	Location	Study design	Interventions	Background therapy	Study duration (weeks)	Key inclusion criteria[b]	Outcomes assessed[c]
Amin *et al*., 2015[11] Pooled studies: B1621002 & B1621007	Multicentre (10 countries: US, Canada, Europe, Asia, South Africa)	RCT, DB, DD, P	PF-04937319 (systemic partial activator); PCB; sitagliptin; glimepiride	Metformin	12	Age 18-70 years, T2DM >5 years (B1621002), age 18-55 years, T2DM ≤5 years (B1621007), HbA1c 7.0-11.0% (on metformin), HbA1c 6.5-9.5% (on metformin + 1 OAD except TZD), FPG <15 mmol/L	HbA1c, FPG, fasting insulin, insulin, pro-insulin, postprandial glucose after OGTT, c-peptide, safety
B1621003, 2017[25] (NCT01272804)[a]	Multicentre (US)	RCT, DB, P	PF-04937319 (systemic partial activator); PCB	-	2	M/F non-childbearing potential, age 18-70 years, on stable metformin, BMI 18.5-45.0 kg/m^2, TBW >50 kg, HbA1c 7.0-10.0%	PK-PD, AUC (glucose, insulin, c-peptide), average plasma glucose, FPG, lactate, safety
B1621018, 2016[26] (NCT02292433)[a]	Single centre (Japan)	RCT, DB, C	PF-04937319 (systemic partial activator); PCB	-	1 (8 days)	Japanese, M/F non-childbearing potential, age 20-64 years, on diet/exercise therapy only or background therapy with 1 OAD (except TZD)	PK-PD, WMDG, FPG, pre-meal insulin, pre-meal C-peptide, safety
B2611002, 2013[27] (NCT01336738)[a]	Multicentre (7 countries: US, Canada, Hungary, Korea, Mexico, Slovakia, Taiwan)	RCT, DB, P, DD	PF-04991532 (hepatoselective activator); PCB; sitagliptin	Metformin	12	Age 18-70 years, on stable background medicines for diabetes, BMI 22.5-45.5 kg/m^2	HbA1c, FPG, BW, safety
B2611003, 2013[28] (NCT01338870)[a]	Multicentre (6 countries: Canada, Hungary, Mexico, Slovakia, Taiwan, US)	RCT, DB, P, DD	PF-04991532 (hepatoselective activator); PCB; sitagliptin	Metformin	12	Age 18-70 years, on stable background medicines for diabetes, BMI 22.5-45.5 kg/m^2	HbA1c, FPG, BW, safety

Table 1. Characteristics of included studies (cont.)

Study, year	Location	Study design	Interventions	Background therapy	Study duration (weeks)	Key inclusion criteria[b]	Outcomes assessed[c]
Katz *et al.*, 2016[12]	Multicentre (4 countries: US, Czech Republic, Poland, Estonia)	RCT, DB, P	AMG 151 (ARRY-403) (direct activator); PCB	Metformin	4	Age 18-75 years, stable on metformin, BMI 25-45 kg/m^2, HbA1c 7.5-11.0%	FPG, AUC (glucose after OGTT), safety
Kiyosue *et al.*, 2013[13]	Multicentre (Japan)	RCT, DB, P	AZD1656 (direct activator); PCB	-	16	Japanese, age ≥20 years, HbA1c 7.5-10.0% (Naïve) or 7.5-9.5% (on ≤ 2 OADs), BMI 19-42 kg/m^2	HbA1c, FPG, fasting insulin, c-peptide, hs-CRP, safety
Meininger *et al.*, 2011[14]	Multicentre (27 countries: US, Latin America, Europe, Asia, Africa, New Zealand)	RCT, DB, P	MK-0941 (direct activator); PCB	Insulin or insulin + metformin	14	Age 21-70 years, HbA1c 7.5-11.0%, taking insulin or insulin + OAD(s), except TZD	HbA1c, 2-h PPG, FPG, safety
Morrow *et al.*, 2012[15] (Part A & B)	Single centre (US)	RCT, SB, MAD	AZD1656 (direct activator); PCB	-	1 (8 days)	M/F non-childbearing potential, on ≤2 OADs (except TZD), BMI 19-40 kg/m2, HbA1c ≤10.5%, FPG 7.0-13.0 mmol/L	PK-PD, AUC (glucose, s-insulin, c-peptide), post-meal GLP-1, post-meal GIP, FPG, safety
Valcarce *et al.*, 2014[16]	Multicentre (US)	RCT, DB, P	TTP399 (hepatoselective activator); PCB	Metformin	6	NA	MDG, HbA1c, lactate, insulin, c-peptide, safety
Wilding *et al.*, 2013[17]	Multicentre (11 countries: UK, Europe, Latin America)	RCT, DB, DD, P, Op	AZD1656 (direct activator); PCB	Metformin	16	M/F non-childbearing potential, age ≥18 years, BMI 18-42 kg/m^2, stable on metformin	HbA1c, FPG, c-peptide, safety

2-h PPG 2-hours postprandial glucose, *AUC* area under curve, *BMI* body mass index, *BW* body weight, *C* crossover design, *DB* double blind, *DD* double dummy, *FPG* fasting plasma glucose, *GIP* gastric inhibitory polypeptide, *GLP-1* glucagon-like peptide-1, *GKA* glucokinase activators, *HbA1c* glycosylated haemoglobin, *HOMA-IR* homeostasis model assessment of insulin resistance, *hs-CRP* high sensitivity C-reactive protein, *M/F* male/ female, *MAD* multiple ascending dose, *MDG/WMDG* mean/ weighted mean daily glucose, *OAD* oral antidiabetic drugs, *OGTT* oral glucose tolerance test, *Op* open-label, *P* parallel, *PCB* placebo, *PK-PD* pharmacokinetic-pharmacodynamics parameters, *RCT* randomized-controlled trial, *TZD* thiazolidinedione (pioglitazone, etc.), *UK* United Kingdom, *US* United State of America

[a] Unpublished studies were obtained from trial records.

[b] All participants were diagnosed with type 2 diabetes mellitus (T2DM).

[c] Safety outcomes were varied: adverse events, serious adverse events, vital sign, electrocardiogram (ECG) measure, laboratory parameters, lipid profiles (triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), hypoglycemic events, etc.

Table 2. Pooled baseline characteristics of study population

Study, year	Total N (% M/F)	Age (mean, years)	BW (mean, kg)	BMI (mean, kg/m²)	Duration of DM (mean, years)	HbA1c (mean, %)	FPG (mean, mmol/L)[b]	2h PPG (mean, mmol/L)[b]
Amin *et al.*, 2015[11] Pooled studies: B1621002 & B1621007	B02: 304 (57.2%/ 42.8%) B07: 335 (57.33%/ 42.67%)	B02: 55.40 B07: 47.67	B02: 89.60 B07: 47.67	NA	B02: 6.90 B07: 2.65	B02: 7.98 B07: 8.07	B02: 9.24 B07: 9.07	NA
B1621003, 2017[25] (NCT01272804)[a]	61 (70.5%/ 29.5%)	54.4	NA	NA	NA	NA	9.93	NA
B1621018, 2016[26] (NCT02292433)[a]	12 (100%/ 0%)	51.8	NA	NA	NA	NA	8.89	NA
B2611002, 2013[27] (NCT01336738)[a]	266 (64.7%/ 35.3%)	55.9	88.5	NA	NA	8.2	9.36	NA
B2611003, 2013[28] (NCT01338870)[a]	301 (56.15%/ 43.85%)	56.6	88.45	NA	NA	7.98	9.25	NA
Katz *et al.*, 2016[12]	236 (54.9%/ 45.1%)	NA	NA	NA	7.14	8.64	10	NA
Kiyosue *et al.*, 2013[16]	224 (85.7%/ 14.3%)	56	NA	25.93	6.15	8.65	9.58	NA
Meininger *et al.*, 2011[14]	587 (48.75%/ 51.25%)	56.16	NA	30.28	12.02	9	8.47	15.29
Morrow *et al.*, 2012 (Part A & B)[15]	52 (78.85%/ 21.15%)	51.73	NA	31.1	NA	7.32	9.3	NA
Valcarce *et al.*, 2014[16]	120 (NA)	57	NA	31	NA	8.2	NA	NA
Wilding *et al.*, 2013[17]	DB: 458 (48.47%/ 51.53%), OP: 72 (51.4%/ 48.6%)	56.67	NA	31.08	6.12	8.33	8.97	NA
Zhi *et al.*, 2016[18]	59 (86.6%/ 13.4%)	56.57	89.97	29.89	7.26	7.56	9.2	NA
Zhu *et al.*, 2018[24]	258 (59.22%/ 40.78%)	55.86	NA	24.99	3.22	8.38	9.52	17.51

2h PPG 2-hours postprandial plasma glucose, *BW* body weight, *BMI* body mass index, *DM* diabetes mellitus, *FPG* fasting plasma glucose, *HbA1c* glycosylated haemoglobin, *M/F* male/ female, *NA* not available

[a] Unpublished studies were obtained from trial records.

[b] Values can be converted to mg/dl (multiplied by 18.0182).

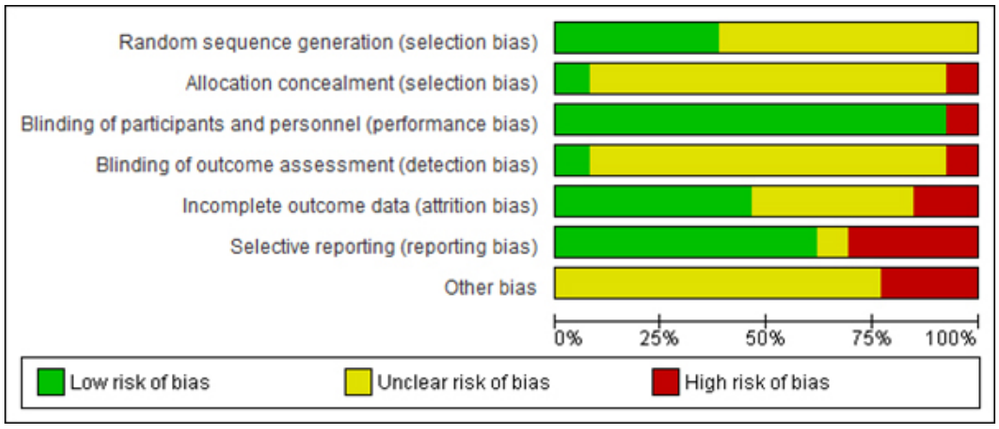

Figure 2. Risk of bias graph

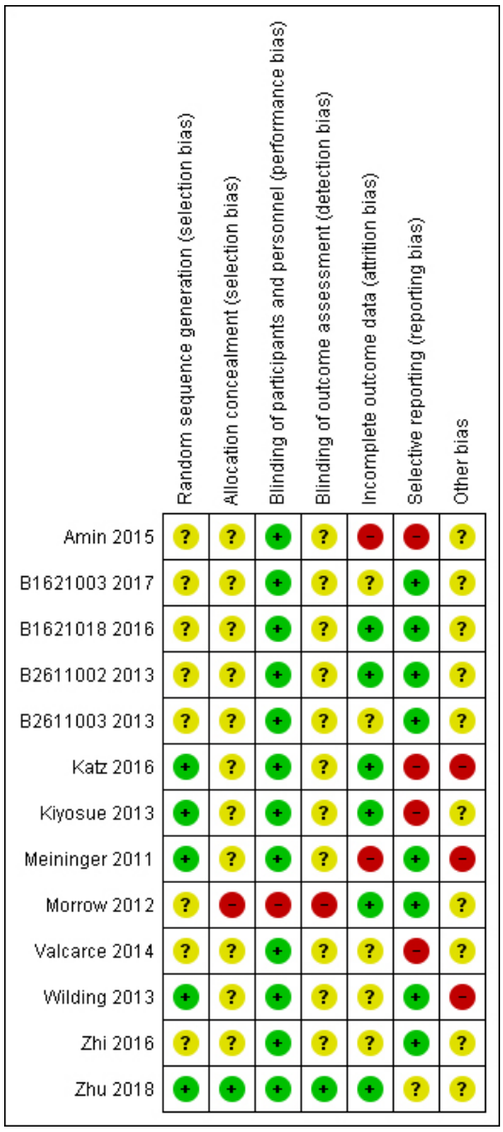

Figure 3. Risk of bias summary
(+) low risk of bias; (-) high risk of bias; (?) unclear risk of bias

Table 3. Efficacy comparison of glucokinase activators (GKAs) on glycosylated haemoglobin (HbA1c)

Drugs (study duration, week), *remark*	Study arms (mg, frequency)	No. of patients	Baseline (%, SD)	Placebo-adjusted change from baseline at study end (%, LSM, 95% CI)	p-value
AMG 151 (4 w)[12]	50 mg, BID	33	8.8 (1.0)	-0.15 (-0.43, 0.13)[b]	NS (NR)
Add-on to metformin	100 mg, OD	32	8.8 (1.0)	-0.15 (-0.43, 0.13)[b]	NS (NR)
	100 mg, BID	33	8.8 (1.3)	-0.25 (-0.53, 0.03)[b]	NS (NR)
	200 mg, OD	34	8.4 (0.9)	-0.20 (-0.48, 0.08)[b]	NS (NR)
	200 mg, BID	34	8.6 (1.0)	-0.45 (-0.73, -0.17)[b]	S (0.008)[*]
	400 mg, OD	35	8.6 (1.2)	-0.40 (-0.68, -0.12)[b]	S (0.001)[*]
AZD1656 (16 w)[13]					
Monotherapy in Japanese	10-80 mg, BID[a]	54	8.9 (1.0)	-0.05 (-0.48, 0.38)	NS (0.817)
	20-140 mg, BID[a]	58	8.6 (0.9)	-0.47 (-0.89, -0.05)	S (0.027)
	40-200 mg, BID[a]	55	8.7 (1.0)	-0.22 (-0.65, 0.20)	NS (0.301)
AZD1656 (16 w)[17]					
Add-on to metformin	20 mg, BID[a]	34	8.2 (0.9)	-0.16 (-0.60, 0.28)	NS (0.480)
	40 mg, BID[a]	47	8.4 (0.7)	-0.22 (-0.62, 0.17)	NS (0.264)
	10-140 mg, BID[a]	82	8.4 (0.9)	-0.81 (-1.14, -0.47)	S (<0.001)[*]
	20-200 mg, BID[a]	80	8.4 (0.8)	-0.80 (-1.14, 0.46)	S (<0.001)[*]
Dorzagliatin (12 w)[24]	75 mg, OD	53	8.4 (0.8)	-0.04 (-0.37, 0.30)	NS (0.83)
Monotherapy in Chinese	100 mg, OD	50	8.3 (0.6)	-0.30 (-0.64, 0.04)	NS (0.085)
	50 mg, BID	50	8.3 (0.7)	-0.44 (-0.78, -0.10)	S (0.0104)[*]
	75 mg, BID	49	8.5 (0.7)	-0.77 (-1.11, -0.43)	S (<0.0001)[*]
MK-0941 (14 w)[14]	10 mg, TID	112-118	9.1 (1.1)	-0.50 (-0.80, -0.20)	S (≤ 0.001)[*]
Add-on to insulin or insulin + metformin	20 mg, TID	113-117	8.9 (0.9)	-0.60 (-0.90, -0.40)	S (≤ 0.001)[*]
	30 mg, TID	113-117	9.0 (0.9)	-0.80 (-1.10, -0.50)	S (≤ 0.001)[*]
	40 mg, TID	113-118	9.0 (1.1)	-0.80 (-1.00, -0.50)	S (≤ 0.001)[*]
PF-04937319 (12 w)[11]	3 mg, OD	52	8.0 (1.1)	0.01 (-0.21, 0.23)[c]	NS (NR)
B1621002 (B02), B1621007 (B07) Add-on to metformin	10 mg, OD	53	8.0 (0.9)	-0.02 (-0.21, 0.17)[c]	NS (NR)
	20 mg, OD	45	7.9 (1.1)	-0.17 (-0.40, 0.05)[c]	NS (NR)
	50 mg, OD (B02)	53	8.0 (1.0	-0.30 (-0.48, -0.11)[c]	NS (NR)
	50 mg, OD (B07)	52	8.2 (1.0)	-0.17 (-0.39, 0.05)[c]	NS (NR)
	100 mg, OD (B02)	54	7.9 (1.0	-0.47 (-0.65, -0.28)[c]	NS (NR)
	100 mg, OD (B07)	50	8.3 (1.1)	-0.45 (-0.68, -0.23)[c]	S (0.005)[**]
PF-04991532 (12 w)[26,27]	25 mg, BID	37	7.9 (0.9)	0.10 (-0.08, 0.29)[c]	NS (0.761)
Add-on to metformin (2 studies sorted by doses)	75 mg, BID	39	7.9 (1.0)	-0.28 (-0.46, -0.09)[c]	S (0.027)[**]
	150 mg, OD	44	8.3 (0.9)	0.08 (-0.13, 0.29)[c]	NS (0.680)
	150 mg, BID	40	7.9(1.0)	-0.24 (-0.42, -0.06)[c]	S (0.044)[**]
	450 mg, OD	44	8.2 (0.9)	-0.49 (-0.71, 0.28)[c]	S (0.017)[**]
	300 mg, BID	46	8.0 (1.1)	-0.53 (-0.71, -0.36)[c]	S (<0.001)[**]
	750 mg, OD	43	8.0 (1.0)	-0.58 (-0.80, -0.36)[c]	S (<0.001)[**]
TTP399 (6 w)[16]	800 mg, OD	8	7.2	-0.25[d]	NA
Add-on to metformin	400 mg, BID	7	7.3	-0.45[d]	NA
	800 mg, BID	7	7.2	-0.65[d]	NA

BID twice daily, *HbA1c* glycosylated haemoglobin, *LSM* least square mean difference, *NA* not available, *NR* not reported, *NS* not significant, *OD* once daily, *S* significant, *SD* standard deviation, *TID* thrice daily, *w* weeks

[a] Given twice daily in split dose

[b] Estimated from graph with placebo correction and recalculated to mean difference with 95% CI

[c] Estimated in 80% CI

[d] Estimated from graph with placebo correction, only for well-controlled subject with HbA1c ≤7.5%

[*] Significant in 95% CI, [**] Significant in 80% CI

Table 4. Efficacy comparison of glucokinase activators (GKAs) on fasting plasma glucose (FPG)

Drugs (study duration, week), *remark*	Study arms (mg, frequency)	No. of patients	Baseline (mmol/L), SD)	Placebo-adjusted change from baseline at study end (mmol/L, LSM, 95% CI)[f]	p-value
AMG 151 (4 w)[12]	50 mg, BID	33	10.3 (2.6)	0.20 (-0.96, 1.35)	NS
Add-on to metformin	100 mg, OD	32	10.0 (2.5)	-0.22 (-1.33, 0.89)	NS
	100 mg, BID	33	10.2 (2.7)	-0.97 (-2.08, 0.14)	NS
	200 mg, OD	34	9.8 (2.8)	-0.76 (-1.86, 0.35)	NS
	200 mg, BID	34	10.1 (2.9)	-1.38 (-2.52, -0.25)	S (0.017)*
	400 mg, OD	35	10.2 (2.6)	-0.60 (-1.71, 0.51)	NS
AZD1656 (1 w)[15]	7 mg, BID	6	9.1 (1.7)	-4 (-22, 18)[b]	NS
PK-PD multiple	20 mg, BID	6	9.1 (1.7)	-6 (-25, 15)[b]	NS
ascending dose study	40 mg, BID	6	9.1 (1.7)	-12 (-29, 8)[b]	NS
	80 mg, BID	6	9.1 (1.7)	-21 (-38, -4)[b]	S (0.020)*
	up to 45 mg, BID[a]	14	9.8 (1.7)	-19 (-39, 3)[b]	NS
AZD1656 (16 w)[13]	10-80 mg, BID[a]	56	10.1 (1.8)	-0.61 (-1.40, 0.19)	NS (0.137)
Monotherapy in	20-140 mg, BID[a]	58	9.5 (1.8)	-0.49 (-0.27, 0.29)	NS (0.214)
Japanese	40-200 mg, BID[a]	55	9.5 (2.1)	-0.35 (-1.14, 0.44)	NS (0.379)
AZD1656 (16 w)[17]	20 mg, BID[a]	39	8.8 (2.3)	0.21 (-0.74, 1.15)	NS (0.669)
Add-on to metformin	40 mg, BID[a]	49	9.3 (2.6)	0.22 (-0.65, 1.10)	NS (0.617)
	10-140 mg, BID[a]	87	8.9 (2.3)	-0.90 (-1.64, -0.16)	S (0.018)
	20-200 mg, BID[a]	90	8.9 (2.0)	-0.64 (-1.37, 0.10)	NS (0.090)
Dorzagliatin (12 w)[24]	75 mg, OD	53	9.9 (2.3)	0.46 (-0.31, 1.24)	NS (0.24)
Monotherapy in Chinese	100 mg, OD	50	9.1 (1.5)	0.39 (-0.40, 1.18)	NS (0.33)
	50 mg, BID	50	9.4 (1.5)	0.03 (-0.76, 0.81)	NS (0.95)
	75 mg, BID	49	9.9 (2.0)	-0.56 (-1.36, 0.23)	NS (0.16)
MK-0941 (14 w)[14]	10 mg, TID	112-118	8.4 (2.4)	0.10 (-0.64, 0.84)	NS
Add-on to insulin or	20 mg, TID	113-117	8.2 (2.4)	0.57 (-0.15, 1.29)	NS
insulin + metformin	30 mg, TID	113-117	8.8 (2.5)	-0.52 (-1.25, 0.22)	NS
	40 mg, TID	113-118	8.6 (2.3)	0.37 (-0.37, 1.11)	NS
PF-04937319 (1 w)[26]	50 mg + 50 mg	12	9.1 (1.8)	-0.68 (-0.95, -0.40)[c]	S (<0.001)**
PK-PD study in Japanese	100 mg + 150 mg	12	8.7 (2.1)	-1.43 (-1.71, -1.16)[c]	S (<0.001)**
PF-04937319 (2 w)[25]	10 mg, OD	8	9.9 (1.8)	-1.38 (0.38, 2.38)	S (0.009)
PK-PD multiple dose	30 mg, OD	9	10.1 (2.8)	-0.55 (-1.62, 0.52)	NS (0.278)
study	50 mg, OD	9	10.6 (1.9)	-0.69 (-2.16, 0.79)	NS (0.289)
	100 mg, OD	9	10.8 (2.5)	-1.81 (-2.68, -0.94)	S (<0.001)*
	300 mg, OD	7	9.0 (2.8)	-6.2 (-2.78, -0.45)	S (0.006)
PF-04937319 (12 w)[12]	3 mg, OD	53	9.0 (2.4)	0.07 (-0.39, 0.52)[d]	NS
B1621002 (B02),	10 mg, OD	54	9.5 (2.6)	-0.45 (-0.89, 0.00)[d]	NS
B1621007 (B07)	20 mg, OD	47	8.8 (2.6)	0.00 (-0.47, 0.47)[d]	NS
Add-on to metformin	50 mg, OD (B02)	54	9.7 (2.0)	-0.61 (-1.06, -0.16)[d]	NS
	50 mg, OD (B07)	52	9.2 (2.4)	-0.23 (-0.69, 0.23)[d]	NS
	100 mg, OD (B02)	55	8.9 (2.1)	-0.83 (-1.27, -0.38)[d]	NS
	100 mg, OD (B07)	51	9.2 (2.3)	0.50 (0.04, 0.96)d	NS
PF-04991532 (12 w)[27,28]	25 mg, BID	37	9.3 (2.9)	0.36 (-0.32, 1.04)	NS (0.296)
Add-on to metformin	75 mg, BID	38	9.0 (2.4)	-0.54 (-1.21, 0.13)	NS (0.116)
(2 studies sorted by doses)	150 mg, OD	45	9.6 (2.2)	-0.11 (-0.87, 0.65)	NS (0.772)
	150 mg, BID	40	9.1 (2.5)	0.26 (-0.40, 0.93)	NS (0.441)
	450 mg, OD	44	9.4(2.3)	-0.04 (-0.80, 0.73)	NS (0.920)
	300 mg, BID	46	9.4 (2.6)	-0.85 (-1.49, -0.20)	S (0.010)*
	750 mg, OD	44	8.8 (2.5)	-0.09 (-0.85, 0.68)	NS (0.818)

Table 4. Efficacy comparison of glucokinase activators (GKAs) on fasting plasma glucose (FPG) (cont.)

Drugs (study duration, week), *remark*	Study arms (mg, frequency)	No. of patients	Baseline (mmol/L), SD)	Placebo-adjusted change from baseline at study end (mmol/L, LSM, 95% CI)[f]	p-value
Piragliatin (1 w)[18]	10 mg, BID	7	9.1 (NA)	-7.10 (-14.66, 0.46)[e]	NS (0.154)
PK-PD multiple	25 mg, BID	8	8.4 (NA)	-5.50 (-15.20, 4.20)[e]	NS (0.299)
ascending dose study	50 mg, BID	8	9.9 (NA)	-11.80 (-19.42, -4.18)[e]	S (0.018)*
	100 mg, BID	7	9.2 (NA)	-16.00 (-26.90, -5.10)[e]	S (0.011)*
	200 mg, BID	6	9.3 (NA)	-33.40 (-45.82, -20.98)[e]	S (<0.001)*
	200 mg, OD	7	8.9 (NA)	-15.10 (-26.38, -3.82)[e]	S (0.016)*

BID twice daily, *LSM* least square mean difference, *NA* not available, *NS* not significant, *OD* once daily, *PK-PD* pharmacokinetics-pharmacodynamics, *S* significant, *SD* standard deviation, *TID* thrice daily, *w* weeks

[a] Given twice daily in split dose

[b] Estimated from graph of mean difference in % placebo-corrected change

[c] Estimated in 90% CI

[d] Estimated in 80% CI

[e] Estimated from graph with placebo correction and recalculated to mean difference with 95% CI, in % reduction

[f] Values can be converted to mg/dl (multiplied by 18.0182)

* Significant in 95% CI, ** Significant in 90% CI

Table 5. Efficacy comparison of glucokinase activators (GKAs) on 2-hours postprandial plasma glucose (2h PPG)

Drugs (study duration, week), *remark*	Study arms (mg, frequency)	No. of patients	Baseline (mmol/L), SD)	Placebo-adjusted change from baseline at study end (mmol/L, LSM, 95% CI)[a]	p-value
Dorzagliatin (12 w)[24]					
Monotherapy in Chinese	75 mg, OD	53	18.0 (3.3)	-2.91 (-4.33, -1.49)	S (<0.0001)*
	100 mg, OD	50	17.4 (3.2)	-3.33 (-4.72, -1.95)	S (<0.0001)*
	50 mg, BID	50	17.2 (3.1)	-2.30 (-3.69, -0.90)	S (0.0014)*
	75 mg, BID	49	17.9 (3.1)	-3.02 (-4.40, -1.63)	S (<0.0001)*
MK-0941 (14 w)[14]	10 mg, TID	112-118	15.6 (3.5)	-2.03 (-3.09, -0.97)	S (≤ 0.001)*
Add-on to insulin or	20 mg, TID	113-117	15.1 (3.2)	-1.48 (-2.52, -0.45)	S (≤ 0.05)*
insulin + metformin	30 mg, TID	113-117	15.4 (3.2)	-1.94 (-3.00, -0.89)	S (≤ 0.001)*
	40 mg, TID	113-118	15.3 (3.2)	-2.05 (-3.10, -0.99)	S (≤ 0.001)*

BID twice daily, LSM least square mean difference, NA not available, NS not significant, OD once daily, S significant, SD standard deviation, TID thrice daily, w weeks

[a] Values can be converted to mg/dL (multiplied by 18.0182)

* Significant in 95% CI

was seen significantly from 1.48 to 3.33 mmol/L (26.67 to 60.00 mg/dL)[14,24]. The most superior value of 3.33 mmol/L (60.00 mg/dL) was provided by dorzagliatin 100 mg as once-daily treatment exceeding the reduction by the rest of dorzagliatin's groups either once daily or twice daily and all groups of MK-0941 thrice daily.

The reports of the GKAs' efficacy on FPG over time were available from phase 1 trials and phase 2 trials in this systematic review. The trend

of FPG reduction around one until two weeks for piragliatin and PF-04937319 based on their PK-PD studies demonstrated preserved effect until the end of the studies[18,25]. The study of piragliatin had been suspended, so sustainability effect could not be observed in longer period of study. Whereas, PF-04937319 as add-on to metformin in the phase 2 trial within 12 weeks presented rapid onset on FPG reduction. Moreover, the effect persisted until the end of trial, except for the highest dose group which declined after eight weeks[11]. Another agent PF-04991532 in two studies showed varied onset from two to eight weeks, but the effect started declining around the fourth to the twelfth weeks[27,28]. Similar effect deterioration occurred in 4-week-study with AMG 151. Although the onset initiated since the beginning of the trial, FPG reduction remained only until the middle of the trial[12]. Lastly, AZD1656 as monotherapy in Japanese and add-on to metformin started decreasing FPG immediately, but declined after two months[13,17]. No report of 2h PPG over the time was noticed.

The pattern of the reduction on glycemic parameters regarding the intervention frequency could be noticed from available data. Based on the significant changes on HbA1c, FPG, and 2h PPG, GKAs appeared to work better as twice-daily dose. AMG 151, dorzagliatin monotherapy, and PF-04991532 as add-on to metformin provided the evidence of preferable dose given twice a day[12,24,27,28]. Furthermore, AMG 151 and piragliatin showed more effective results on FPG by twice-daily dose[12,18]. On contrary to the evidence for HbA1c and FPG, once-daily dose of dorzagliatin monotherapy seemed to perform better than its twice daily dose on 2h PPG.

3.3. Safety outcomes

GKAs groups and placebo groups generally shared similar ranges of any adverse events (AEs) rate (Table 6). Only two small studies conducted in short duration (PF-04937319 with total daily dose of 10-300 mg and 100-250 mg) revealed the gap of rate between GKAs groups and placebo groups[11,26]. Frequent and similar types of AEs between GKAs groups and placebos were headache, nasopharyngitis, nausea, upper respiratory tract infection/ inflammation (URTI), and diarrhea. Drug-related serious adverse events (SAEs) were only noticed in two studies involving AZD1656 and MK-0941. Musculoskeletal chest pain was reported in one patient using MK-0941 40 mg thrice daily. This symptom was considered drug-related as it disappeared after drug discontinuation[14]. Another discontinuation happened in study with dorzagliatin given 50 mg twice daily. One patient experienced eyelid edema which was not claimed serious, but this was a drug-related adverse event[24].

Table 6. Drug-related adverse events rate per study

Drugs	Doses range in groups of each study[a]	N (range, drug groups vs PCB)	Any AEs rate (range, drug groups vs PCB)	Any SAEs rate (range, drug groups vs PCB)	Any HEs rate (range, drug groups vs PCB)
AMG 151[12]	100-400 mg	32-35/34	23.5-42.4%/32.4%	0%/0%	18.2-52.9%/33.7%
AZD1656[13,15,17]	10-200 mg	55-58/55	39.7-50.0%/41.8%	0%/0%	0-0.01%/0%
	14-160 mg	6-15/5-8	50.0-80.3%/ 60.0-75.0%	0%/0%	0-33.3%/0-7.7%
	20-200 mg	40-92/87	31.0-44.4%/36.8%	1.1-2.5%/3.4%	2.0-12.2%/0%
Dorzagliatin[24]	75-150 mg	50-53/53	47-62%/51%	0-2.0%/0%	4.0-8.0%/0%
MK-0941[14]	30-120 mg	117-119/118	16.8-30.8%/14.8%	0-0.8%/0.2%	38.7-53.4%/34.8%
PF-04937319[11,25,26]	3-100 mg	117-171/118	4.3-7.6%/11.9%	0%/0%	1.8-6.0%/2.5%
	10-300 mg	9/16	33.3-88.9%/31.3%	0%/0%	22.2-66.7%/0%
	100-250 mg	12/12	8.3-50.0%/8.3%	0%/0%	8.3-33.3%/0%
PF-04991532[27,28]	50-600 mg	49-52/50	22.0-32.7%/28.0%	0%/0%	0-2.0%/0%
	150-750 mg	52-54/53	32.7-43.4%/30.2%	0%/0%	0-3.7%/1.9%
Piragliatin[18]	20-400 mg	6-8/12	<0.38%	0%/0%	0-25.0%/0%
TTP399[16]	800-1600 mg	29-31/30	NA	NA	No increase rate or severity vs PCB

AE adverse events, *HE* hypoglycemic events, *SAE* serious adverse events, *PCB* placebo

[a] Shortened as the number of doses which were received daily in each group, regardless as once daily, twice daily, or as split dose.

Table 7. Adverse events summary

Drugs	Doses range in groups of each study[a]	Most commonly reported AEs (rate ≥5 %, drug groups vs PCB)	Lipid Profiles	Important remarks (physical finding, body weight, vital sign, laboratory finding, etc.)
AMG 151[12]	100-400 mg	Headache (5.0)/none	Non-dose-dependent increases in TG in twice daily group after placebo correction (15-23%)	Number of patients with increased ≥10 mmHg in BP was similar to PCB
			Similar % patients having >30% increases in TG to PCB	Four patients in some AMG 151 groups had ≥2 grade shifts in ALT level
AZD1656[13,15,17]	10-200 mg	Nasopharyngitis (≤16.1)/ nasopharyngitis (20.0)	Increases in TC, TG, LDL-C, HDL-C in all groups (not significant compared to placebo)	Minor individual increases in LFT indicators in all groups, increase of hs-CRP (WNL) in AZD1656 groups
	14-160 mg	Headache, constipation, URTI (≤33.3), pain in extremity ≤20.0), diarrhoea, nausea, dizziness (≤16.7)/headache (≤40.0), dizziness (≤20.0), constipation, diarrhoea, nausea (≤12.5)	None	None
	20-200 mg	Nasopharyngitis, vomiting (≤10.0), nausea (≤8.0), diarrhoea (≤7.8), gastritis, gastroenteritis (≤5.0)/ nasopharyngitis (6.9)	Dose-dependent increase in TG (5-23%) after placebo correction	Non-dose-related pattern in BP change, increase of 4.4 mmHg in 40 mg fixed-dose group only in 4 months
Dorzagliatin[24]	75-150 mg	Dizziness (≤18.0), hyperuricaemia, URTI (≤12.0), proteinuria, UTI, WBC urine positive, abnormal hepatic function, ventricular extrasystole, nasopharyngitis (≤6.0%)	HDL decreased with rate of 0-8%, but no clinically significant effect on TG	None
MK-0941[14]	30-120 mg	Headache (≤8.5), nasopharyngitis (≤7.7), influenza (≤6.8), cataracts (≤6.7), URTI (≤6.0), diarrhoea (≤5.0)/ none	There was significant increase from baseline after placebo correction in TG (12.7%), BW (0.8 kg), and SBP (3.7 mmHg) in 40 mg group. TG also significantly increased 19.3% in 20 mg group.	None
PF-04937319[11,25,26]	3-100 mg	None/none	Non-dose-dependent change in fasting TG (both studies) after PCB correction (-2.15 to 14.70%), significant in 10 mg group (14.70%) and 20 mg group (-9.5%)	A marginal (<1 kg) placebo-adjusted increase in body weight was observed.

Table 7. Adverse events summary (cont.)

Drugs	Doses range in groups of each study[a]	Most commonly reported AEs (rate ≥5 %, drug groups vs PCB)	Lipid Profiles	Important remarks (physical finding, body weight, vital sign, laboratory finding, etc.)
PF-04937319 [11,25,26]	10-300 mg	Headache, dyspepsia (≤22.22), epistaxis, micturition urgency, muscle spasm, contusion, URTI, viral URTI, acute sinusitis, diarrhoea, abdominal distention, conjunctivitis, vertigo, hyperglycaemia (≤11.11)/skin irritation, skin disorder, skin rash, anxiety, muscle spasm, nausea, dyspepsia, anaemia (6.25)	Significant decrease in TC, LDL-C in low dose groups (10-50 mg) in day 16, but not in F/U period, non-related dose pattern	None
	100-250 mg	Increased blood uric acid, haemoglobin decreased (≤8.33)/diarrhoea (8.33)	NA	None
PF-04991532[27,28]	50-600 mg	Hyperglycaemia (≤10.20), headache (≤8.16), pharyngitis (≤7.69), URTI (≤6.00), dizziness (≤6.12), diarrhoea, UTI (≤6.00), HT (≤5.77) / UTI (10.00), URTI, hyperglycaemia (6.0)	NA	None
	150-750 mg	Diarrhoea (≤13.21), (≤9.26), nausea (≤7.55), hyperglycaemia (≤5.77), nasopharyngitis, headache, HT (≤5.66)/ none	NA	None
Piragliatin[18]	20-400 mg	None/none	No clinically significant abnormality in biochemical parameters	None
TTP399[16]	800-1600 mg	NA	No increase in fasting TG and TC compared to placebo	No increase in lactate, insulin, or C-peptide, compared to placebo

AE adverse events, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *F/U* follow-up, *hs-CRP* high sensitivity C-reactive protein, *HT* hypertension, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *NA* not available, *PCB* placebo, *SB/BP* systolic/blood pressure, *TC* total cholesterol, *TG* triglyceride, *URTI* upper respiratory tract infection/ inflammation, *UTI* urinary tract infection, *WNL* within normal limit

[a] Shortened as the daily doses received in each group, regardless as once daily, twice daily, or as split dose.

Hypoglycemic events (HEs) occurred in all studies. AMG 151 and MK-0941 presented higher HEs rate than placebo (Table 6). One out of two patients treated by these agents might experience hypoglycemia[12,14]. Higher HEs rate than placebo was also found in studies involving AZD1656, piragliatin, and PF-04937319[15,18,25,26]. However, larger clinical trials to the referred drugs, except piragliatin, had further confirmed that the HEs rate was comparable to that of the placebo groups[11,13,17]. The other drugs such as dorzagliatin, PF-04991532, and TTP399 might offer lower risk of hypoglycemia[16,24,27,28].

Lipid profile assessment was varied among the included studies (Table 7). Some studies did not carry out the assessment[26-28]. There was tendency of lipid profile change, especially the increase in triglyceride (TG) level involving AMG 151, AZD1656, MK-0941, PF-04937319, and PF-04991532[11-14,17,20]. Other parameters for safety issues in overall studies showed no significant change in laboratory or physical findings. Important remarks were found in study involving AMG 151 in which some of the participants experienced elevated blood pressure, but it was similar to placebo[12]. Blood pressure increase was also an issue in AZD1656, but it was observed only at the last month of 40 mg group[17]. Change in liver function with rising alanine aminotransferase (ALT) level was again noticed in AMG 151 and in the other study of AZD1656, but it was minor and comparable to placebo[12,13].

4. DISCUSSION

There were several GKAs having been tested in clinical phase for T2DM during this systematic review process. These agents were AMG 151 (ARRY-403)[12], AZD1656[13], AZD6370[30], GKM-001[31], HMS5552 (dorzagliatin)[32], LY2599506[29], LY2608204[34], MK-0941[14], PF-04937319[11], PF-04991532[27], RO4389620 (piragliatin)[18], TMG-123[33], and TTP399[16]. However, we included the drugs which met our eligibility criteria. We included studies involving placebo to see the effects of GKAs from the treatment after adjustment to placebo. GKAs appeared to offer positive efficacy on glycemic parameters towards patients with T2DM. GKAs performed well as both monotherapy and additional drug in patients using metformin. GKAs tend to be responded better in Naïve T2DM. This application yielded GKAs' effects on HbA1c control and sustainability. For example, monotherapy of dorzagliatin and PF-04937319 added on metformin in T2DM patients with shorter disease duration (study B07) proved better effects compared to the other agents tested in populations with longer experience of T2DM such as MK-0941[11,14,24]. Patients in more advanced level of T2DM might have taken more oral antidiabetic drugs or insulin. Hence, we should also concern the influence of the other antidiabetic agents in the GKAs trial to any substantial reduction on glycemic parameters.

Another factor of better GKAs' efficacy towards mild T2DM patients is the concept of glucokinase expression. Haeusler et al. investigated the expression of hepatic glucokinase derived from T2DM subjects. T2DM subjects represented glucokinase expression about half lower compared to normal subjects. In addition, higher HbA1c level in T2DM expressed less glucokinase activity than of T2DM with lower HbA1c[35]. In consequence, there is possibility of requiring more effort to activate the glucokinase expression in progressive T2DM than in mild stage. In fact, the available evidence has not attained to this extent. Either long term use of GKAs or higher effective dose in the treatment might be encouraged to verify this prediction, especially for broader scope in T2DM therapy.

In spite of the favorable findings on glycemic control, there was difficulty to determine the direction of GKAs providing more benefits among HbA1c, FPG, or 2h PPG. The overall evidence seemed to point the benefit of GKAs on substantial HbA1c reduction more than on FPG. However, the efficacy of GKAs on HbA1c should be acceptable in the sufficient length of study lasting more than eight weeks. This is because the difference on HbA1c after treatment change could be well observed within period of 8-12 weeks[36]. Hence, the reliable results should be interpreted from GKAs studied within such duration mentioning AZD1656[13,17], dorzagliatin[24], MK-0941[14], PF-04937319[11], and PF-04991532[27,28]. Accordingly, the trend of significant decrease on FPG was only noticed predominantly in PK-PD studies of no longer than two weeks[15,18,25,26]. GKAs improving 2h PPG was also significant, but the data were lacking. At this stage, GKAs in this systematic review have represented their positive light on HbA1c in T2DM.

Varied reduction pattern on glycemic control among the presented GKAs might be influenced by their diverse structures proposed by each responsible company in their development. Basically, common structure of GKAs consists of a center with three attached groups. The center can be a carbon or an aromatic ring such as aryl, pyridine, pyrrole, thiophene, and so forth. Whereas the two attached groups are hydrophobic groups with either one of aromatic ring and heterocyclic amine as H-bond donor-acceptor pair. This kind of formation is responsible for GKAs' activity. Efforts in structure modification approached by different companies affected the drugs' action including GKAs' capability to increase glucokinase-glucose affinity and other kinetic properties of glucokinase[9]. According to the involved eight GKAs, three agents were disclosed having aromatic ring-centered of pyridine; AMG 151, and aryl group; both AZD1656 and MK-0941, respectively[37-39]. Three agents were built with carbon-centered structure (piragliatin, PF-04937319, PF-04991532)[40-42]. Dorzagliatin is likely a carbon-centered GKA[43].

Type of GKAs regarding their target of action might be considered to play a role in the differed pattern. As noted, the role of glucokinase in physiological function of glucose homeostasis involved liver and pancreas[5]. The first class of GKAs is non-selective (direct) activators affecting pancreas to induce insulin secretion and liver to reduce glucose output in glucose metabolism. Concerning these actions on the two main organs, direct GKAs might strongly trigger hypoglycemia. In fact, we found corresponding results to this theory. AMG 151, AZD1656, and MK-0941 as direct activators[44] demonstrated potent efficacy on glycemic control as either monotherapy (AZD1656 in Japanese)[13] or add-on therapy[12,14,17], but also complied with rather high hypoglycemic rate. Even after implementing dose titration in AZD1656 as prevention strategy, suggestive hypoglycemia did not appear to be avoidable. Notwithstanding the less hypoglycemic incidence by the other direct activators, dorzagliatin (dual-acting activator)[24] and piragliatin (mixed-type activator)[18,45], the presence of hypoglycemic events was claimed drug-related. Therefore, the nature of direct activators provoking hypoglycemic trend is likely to represent their one point of weakness.

The other class of GKAs is selective activators. This class was proposed and designed to act on the liver. Synthesis as substrate for transporter-mediated uptake and reduced-passive permeability to peripheral organs had influenced GKAs' selective distribution to the liver. In addition to obtain functional action on the liver, molecules of GKAs were designed to encounter liver-specific metabolic activation and to be involved in the interaction between glucokinase and glucokinase regulatory protein (GKRP)[46]. PF-04937319, PF-04991532, and TTP-399 are hepatoselective GKAs. In preclinical study, PF-04937319 was known efficacious in hyperglycemic state, but less effective in euglycemic state[46]. Therefore, PF-04937319 was unlikely to increase hypoglycemic risk as long as it was not given more than 100 mg a day[11,25,26]. PF-04991532 in two human studies also provided favorable results on glycemic control and low rate of hypoglycemia regardless it had such higher effective dose than PF-04937319[27,28]. Despite preclinical properties of TTP-399 have not been revealed, this agent was convinced to increase neither rate nor severity of hypoglycemia. Winning over hypoglycemic issue towards direct activators, hepatoselective activators may offer promising development of GKAs in the near future.

Lack of glycemic sustainability was another issue observed in most of the GKAs. The average of deterioration starting point was around eight or ten weeks, except dorzagliatin, PF-04937319, and PF 04991532, preserving their effects until the trials lasted[11,24,27,28]. Although study with TTP-399 was not as longer as the previously mentioned studies, TTP-399's glycemic effect could sustain until the end of the study[16]. The underlying mechanism of intermediate efficacy declination is still unclear. Early declination was indeed hypothesized from glucose homeostasis being compromised after exposure of glucokinase activation in certain period of time[47]. Some factors might influence this phenomenon such as GKAs' unique characteristic, varied molecule structures regardless its classification, or varied participants' condition.

Compared to placebo, the overall GKAs were claimed having good tolerability in the trials, but triglyceride (TG) elevation was spotted. This issue appeared in majority of GKAs' trials without respect to either direct or selective activation

mechanism. The obvious change in TG might represent one of GKAs' characteristics. This is explained by the nature of glucokinase activation. Glucokinase is involved in the metabolic cycle in hepatic circulation. It may enter to either lactic cycle or citric cycle, resulting in alteration of liver function or hyperlipidemia[5]. Chemical structure should also be included as influencing factor, but structure similarity among suspected GKAs should not be the only main focus. One chemical study proposed structure-based toxicity pointing thiourea metabolite from piragliatin's parent drug to be responsible in hepatic lipid alteration, although piragliatin shared similar structure with the parent molecule[40]. Hence, understanding structure-activity relationship along with how GKAs move in the body may help for more thorough preparation of the established GKAs in clinical practice.

Some important safety issues in GKAs trials have contributed for the drug discontinuation. Due to serious adverse events (SAEs), MK-0941 and AZD1656 were discontinued during the trials[14,17]. Also, noticeable alteration in liver enzyme or triglyceride appeared to cause termination such as PF-04991532 and piragliatin[10]. Discontinuation toward PF-04991532 took place during the trial. Meanwhile, piragliatin, the first-studied-GKA in human with T2DM, had been long stopped for development. Piragliatin was proved as safe in toxicology-preclinical study and phase 1 trial. Instead, hepatic lipidosis was related to the piragliatin's parent drug which did not progress to clinical phase[18,40]. Regardless of safety concern about serious hypoglycemia in AMG 151, termination of this agent was due to patent right transfer in the responsible company[10]. Resuming to all the discontinued GKAs, we still have some hope from the rest on-going-GKAs including dorzagliatin, PF-04937319, and TTP-399.

In clinical practice, GKAs may be useful for naïve T2DM patients. Considering the potential efficacy, adverse events (AEs), selectivity, and sustainability of GKAs, There would be two options for their application at this level. Firstly, non-selective or direct-type GKAs appeared to be more appropriate as monotherapy agent. For example, dorzagliatin responded well as monotherapy throughout the study yielding favorable control on HbA1c and minimum hypoglycemic events in naïve T2DM[24]. In contrast, earlier direct activator, MK-0941, was obviously leading to high rate of hypoglycemia when it was given as add-on to metformin or insulin in more advanced T2DM[14]. Secondly, partially selective GKAs might support as add-on in T2DM therapy due to its limited data regarding selective GKA only as add-on in the available clinical trials with adequate duration such as PF-0493319[11]. Regardless of the two options considered here, sustainability is another unresolved problem for the application of GKAs. Currently, dosing management might be required to tackle the unsustainability in the practice. However, the uncertainty of their sustainability can be answered by longitudinal studies.

We found some limitations during the process of this systematic review. All of the included studies are clinical trials in either phase 1 or phase 2. The overall studies were conducted in small number of participants. Also, majority of the studies were carried out in duration of no longer than four months. As a result, this evidence may only support the application of GKAs as treatment in T2DM with short-term effects. In addition, some included studies were not peer-reviewed as obtained from clinical trial registry[25-28].

Nevertheless, we may point some suggestions for GKAs future development in T2DM to prevent another failure ended with discontinuation in clinical phase. The effect from glucokinase activation in the nervous system has not been found from the previous trials. However, this might be an example of potential side effect because the role of neuronal glucokinase in glucose sensing and metabolism has been discovered in the complexity of glucokinase expression as a network in body system[48,49].

5. CONCLUSIONS

Constant efforts in the decades of GKAs development should be appreciated. Despite the limitation and the complexity of the available data, the results in this systematic review have represented prospective light to clearly define the image of GKAs. Of the promising GKAs in clinical phase are for example, dorzagliatin and TTP-399. At the present time, GKAs are half-way ready for clinical implementation. This is due to GKAs limited efficacy on HbA1c notwithstanding the significant reduction up to 0.7-0.8%. Some refinement may also

be required for managing the safety issues or potential side effects including hypoglycemia and lipid alteration. Large clinical trials are encouraged to establish benefits of GKAs in T2DM.

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