Hypoglycemic agents and glycemic variability in individuals with type 2 diabetes: A systematic review and network meta-analysis

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Abstract
While hemoglobin A₁c (HbA₁c) is commonly used to monitor therapy response in type 2 diabetes (T2D), GV is emerging as an essential additional metric for optimizing glycemic control. Our goal was to learn more about the impact of hypoglycemic agents on HbA₁c levels and GV in patients with T2D. A systematic review and network meta-analysis (NMA) of randomized controlled trials were performed to assess the effects of glucagon-like peptide 1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter (SGLT)-2 inhibitors, dipeptidyl peptidase (DPP)-4 inhibitors, sulfonylurea and thiazolidinediones on Mean Amplitude of Glycemic Excursions (MAGE) and HbA₁c. Searches were performed using PubMed and EMBASE. A random-effect model was used in the NMA, and the surface under the cumulative ranking was used to rank comparisons. All studies were checked for quality according to their design and also for heterogeneity before inclusion in this NMA. The highest reduction in MAGE was achieved by GLP-1 RAs (SUCRA 0.83), followed by DPP-4 inhibitors (SUCRA 0.72), and thiazolidinediones (SUCRA 0.69). In terms of HbA₁c reduction, GLP-1 RAs were the most effective (SUCRA 0.81), followed by DPP-4 inhibitors (SUCRA 0.72) and sulfonylurea (SUCRA 0.65). Our findings indicated that GLP-1 RAs have relatively high efficacy in terms of HbA₁c and MAGE reduction when compared with other hypoglycemic agents and can thus have clinical application. Future studies with a larger sample size and appropriate subgroup analyses are warranted to completely understand the glycemic effects of these agents in various patients with T2D. The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (CRD42021256363).

Keywords
Type 2 diabetes, glycemic variability, meta-analysis, glucagon-like peptide 1 agonist, sodium-glucose cotransporter 2 inhibitor, dipeptidyl-peptidase 4 inhibitor

Introduction
Diabetes is a serious and chronic disease that affects individuals and families worldwide. In 2019, 537 million adults aged 20–79 years have diabetes, and diabetes reached 10% of total health spending.¹ To date, the main goal of diabetes management is hemoglobin A₁c (HbA₁c) control, which has been the standard parameter for determining the risk of complications in diabetic patients.² However, HbA₁c fails to capture the time spent within the glucose target range (TIR) of 70–180 mg/dL and glucose
variability (GV), both of which are related to vascular outcomes. Therefore, TIR and GV should also be considered as additional measures for glycemic control in addition to HbA1c. Currently, the International Consensus on the Use of Continuous Glucose Monitoring recommends employing the coefficient of variation (CV) of <36% as a key indicator of GV, despite the fact that at least 20 GV metrics have been reported in the literature, each with its own set of advantages and disadvantages. Among these metrics, the mean amplitude of glycemic excursion (MAGE) is one of the most widely used in the literature, and it has a higher potential of capturing glucose swings than CV. Thus, MAGE may be able to better represent glucose fluctuation in this context. Hence, in the current study, we used MAGE as a primary GV metric due to its extensibility.

There is emerging evidence that patients use glucagon-like peptide 1 receptor agonists (GLP-1 RA), dipeptidyl-peptidase 4 (DPP-4) inhibitors, and sodium-glucose co-transporter 2 (SGLT-2) inhibitors can effectively achieve glycemic control. In a direct analysis comparing DPP-4 inhibitors and oral anti-hyperglycemic drugs (OAD), two or more trials available for the studied outcome. All outcomes were calculated as the difference between pre- and post-treatment values.

The evaluation of MAGE and HbA1c outcomes were extracted from the included trials. In this network meta-analysis, we used the random-effects model in Bayesian frameworks. Analyses were only conducted when there were two or more trials available for the studied outcome. The graphs were synthesized by Review Manager version 5.4. Only randomized control trials (RCTs) that evaluated HbA1c and MAGE of type 2 diabetes in participants aged ≥18 years were included. Five anti-diabetes treatments were intervention compared GLP-1 receptor agonists (RA), DPP-4 inhibitor, SGLT-2 inhibitors, sulfonylurea, or thiazolidinediones. Our study assessed HbA1c and MAGE of the anti-diabetes treatment pairs. The intervention was monotherapy or add-on therapy, which included GLP-1 RA, SGLT-2 inhibitors, or DPP-4 inhibitors, and the control was either a placebo or other antidiabetic treatment. We limited the language of the publications to English and excluded publications without MAGE data.

This study was prepared according to the PRISMA extension statement for network meta-analyses guidelines (Supplementary Table S1). The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (CRD42021256363).

**Methods**

**Search strategy and selection criteria**

For this systematic review and network meta-analysis, we searched MEDLINE, Embase from database inception through to 28 June 2021. Database search was performed using medical subject heading (MeSH) terms “glycemic variability,” “glycemic fluctuations,” “mean amplitude of glycemic excursions,” in combination with “Diabetes Mellitus, Type 2” “dipeptidyl-peptidase 4 inhibitors”. Terms related to DPP-4 inhibitor, GLP-1 RA and SGLT-2 inhibitor are shown in Supplementary Table S2.
estimated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Publication bias was also assessed using funnel plots.

The consistency of network meta-analysis was assessed using the node-splitting models to detect whether the results of the direct and indirect comparisons were in agreement within treatment loops. Also, we used the analysis of heterogeneity to quantify the degree of heterogeneity using the $I^2$ calculation. Values of $I^2 > 50\%$ were considered heterogeneous across the trials. We ranked the interventions according to their surface under the cumulative ranking (SUCRA), which ranged from 0 to 1. The SUCRAs is based solely on the point estimates and standard errors of the network estimates and measure the mean extent of the network estimates and the mean extent of certainty that one intervention is superior to another averaged over all competing interventions.

**Results**

Systematic searching through 28 June 2021, identified 139 studies, of which 17 were included in the final analysis. The flow diagram for the results of the electronic search is described in Figure 1.

The characteristics of the included studies are shown in Table 1. The mean age of the 1218 participants was 56.8 years old, and the proportion of males was 58%. All studies were...
| Study            | ClinicalTrials.gov identifier | Study design | Treatment arm (n) | Control arm (n) | Mean age (years) | Male (%) | Mean BMI | Mean duration of diabetes (years) | Total subject | Follow-up Period | Baseline HbA1c | Baseline MAGE | Primary outcome |
|------------------|--------------------------------|--------------|-------------------|----------------|------------------|----------|---------|-------------------------------|--------------|----------------|----------------|---------------|----------------|
| Fuchigami 2020  | UMIN000028014 RCT             | RCT          | Dapagliptin (168) | Gliclazide (163) | 57.8             | 60.1     | 27.85   | 6.4                           | 331           | N/A             | 7.8            | N/A           | HbA1c reduction |
| Frias 2017      | NCT02288273 RCT               | RCT          | Exenatide and metformin (60) | Placebo and metformin (56) | 55.5             | 56.07    | 31.8    | 19                           | 116           | 4 weeks         | 8.1            | 5.035         | MAGE reduction  |
| Henry 2018      | NCT02429258 RCT               | RCT          | Dapagliptin and metformin (23) | Placebo and metformin (25) | 54.6             | 52.26    | 32.45   | 16.2                          | 48            | 1 week          | 8.125          | 94.1          | (mg/dL)         |
| Henry 2018      | NCT02429258 RCT               | RCT          | Dapagliptin and insulin (27) | Placebo and insulin (25) | 59.05            | 50.07    | 35      | 29.5                          | 52            | 1 week          | 8.535          | 116.1         | (mg/dL)         |
| Kim G 2017      | NCT01404676 RCT               | RCT          | Vildagliptin and metformin (17) | Glimepiride and metformin (17) | 55.95            | 58.82    | 25.9    | 12.2                          | 34            | N/A             | 7.55           | 91.4          | (mg/dL)         |
| Kim HS 2013     | NCT00699322 RCT               | RCT          | Sitagliptin and metformin (16) | Glimepiride and metformin (17) | 57.7             | 58.09    | 25.55   | 10.7                          | 33            | 4 weeks         | 7.15           | 5.3           | MAGE reduction  |
| Kim NH 2017     | NCT01339143 RCT               | RCT          | Vildagliptin and metformin (14) | Pioglitazone and metformin (11) | 56               | NA       | 26.6    | NA                           | 25            | 16 weeks        | 7.3            | 96.25         | (mg/dL)         |
| Kwak 2020       | NCT03202563 RCT               | RCT          | Dapagliptin and metformin (36) | Gemiglptin and metformin (34) | 52.05            | 65.52    | 25.8    | 5.7                           | 70            | N/A             | 7.9            | 89.1          | (mg/dL)         |
| Lee 2020        | NCT02459353 RCT               | RCT          | Dapagliptin and insulin and/or OADs (41) | Placebo and insulin and/or OADs (43) | 58.7             | 41.66    | 26.95   | 30.2                          | 84            | N/A             | 8.275          | N/A           | MAGE reduction  |
| Li 2016         | MB102055 RCT                  | RCT          | Dapagliptin (18) | Placebo (10) | 60               | 40.5     | NA      | NA                           | 28            | N/A             | N/A            | 5.85          | (mmol/L)        |
| Li 2017         | ChiCTR-PPR-15007045 RCT       | RCT          | Exenatide and insulin (18) | Placebo and insulin (18) | 48.74            | NA       | 26.42   | NA                           | 36            | N/A             | 9.255          | 6.13          | MAGE reduction  |

(continued)
| Study          | ClinicalTrials.gov identifier | Study design | Treatment arm (n)                        | Control arm (n) | Mean age (years) | Male (%) | Mean BMI | Mean duration of diabetes (years) | Total subject | Follow-up Period | Baseline HbA1c | Baseline MAGE | Primary outcome                      |
|---------------|-------------------------------|--------------|-----------------------------------------|-----------------|------------------|-----------|----------|-------------------------------|----------------|-----------------|----------------|--------------|--------------------------------------|
| Li 2019       | NCT01644500                   | RCT          | Dulaglutide (13)                        | Glimepiride (10) | 54.03            | 56.93     | 24.38   | 4                             | 23             | 26 weeks        | 8.145         | 5.92 (mmol/L) | MAGE reduction                        |
| Nomoto 2017   | UMIN000015033                 | RCT          | Dapagliplon and insulin (14)            | DPP-4 and insulin (5) | 61.5            | 59.52     | 26.1    | 31.9                          | 29             | N/A             | 7.25          | 87.9 (mg/dL)  | MAGE reduction                        |
| Park KS 2017  | NCT01812122                   | RCT          | Vildagliptin and metformin (16)         | Glimepiride and metformin (16) | 60              | 31.25     | 25.5    | 14.8                          | 32             | N/A             | 8.4           | N/A (log data) | Risk factor for cardiovascular disease MAGE reduction (secondary) |
| SE Park 2017-1| NCT01890689                   | RCT          | Gemigliptin and metformin (24)          | Glimepiride and metformin (21) | 50.2            | 71        | 26.3    | 2.1                           | 45             | N/A             | 9.6           | 99 (mg/dL)    | MAGE reduction                        |
| SE Park 2017-2| NCT01890689                   | RCT          | Sitagliptin and metformin (21)          | Glimepiride and metformin (21) | 50.55           | 73.5      | 25.95   | 3.47                          | 42             | N/A             | 9.4           | 95.5 (mg/dL)  | MAGE reduction                        |
| Suzuki 2018   | NCT02318693                   | RCT          | Sitagliptin (26)                        | Glibenclamide (26) | 59.85           | 98.1      | 24.5    | 16.3                          | 52             | N/A             | 7.8           | 6.18 (mmol/L) | MAGE reduction                        |
| Vianna 2019   | NCT02925559                   | RCT          | Dapagliplon (45)                        | Gliclazide (52)  | 57.8            | 56.26     | 30.9    | 8                             | 97             | 24 h            | 8.4           | 6.9 (mmol/L)  | MAGE reduction                        |
| Xiao 2016     | KLS12185                      | RCT          | Sitagliptin and metformin (23)          | Glimepiride and metformin (18) | 68.9            | 56.04     | 28.13   | NA                            | 41             | 24 weeks (evaluated at 4, 8, 12, and 24 weeks) | N/A           | 8.165 (mmol/L) | MAGE reduction                        |
studies were RCTs. There were 12 trials with add-on treatment, whereas 5 trials used monotherapy. Figure 2 shows the network plots of the eligible comparisons for type 2 diabetes treatments. There were five pairs of antidiabetic agents (DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors, sulfonylureas, and thiazolidinediones) and a placebo.

**Mean amplitude of glycemic excursions (the mean amplitude of blood glucose fluctuations)**

Seventeen RCTs were included in MAGE analysis, and 3 pairs were significantly more effective than placebo (DPP-4 [MD: −21.98, 95% CI: −35.91 to −8.04], GLP-1 [MD: −25.51, 95% CI: −37.86 to −13.15], and SGLT-2 [MD: −16.42, 95% CI: −27.36 to −5.48]) (Figure 3(a) and Supplementary Table S4). The network-estimated effect size between antidiabetic classes is shown in Table S7. There was no inconsistency between the direct and indirect comparisons of node-splitting analysis (Supplementary Table S5-6). In the heterogeneity analysis, the global $I^2$ did not identify any heterogeneity across the studies (Supplementary Table S5, global $I^2 = 46.45$%). Figure 4 shows the cumulative rank probability plot. GLP-1 RAs ranked highest (SUCRA 0.83), followed by DPP-4 inhibitors (SUCRA 0.72), thiazolidinediones (SUCRA 0.69), SGLT-2 inhibitors (SUCRA 0.51), and sulfonylurea (SUCRA 0.20). Table S9 details the results.

**Hemoglobin A1c**

Hemoglobin A1c was assessed in 12 RCTs. All interventions significantly decreased HbA1c more than when a placebo was used. (DPP-4 [MD: −0.68, 95% CI: −0.94 to −0.41]; GLP-1 [MD: −0.74, 95% CI: −0.95 to −0.53]; sulfonylurea [MD: −0.65, 95% CI: −0.94 to −0.35]; thiazolidinediones [MD: −0.58, 95% CI: −1.06 to −0.10]; and SGLT-2 [MD: −0.39, 95% CI: −0.59 to −0.19]) (Figure 3(a) and Table S4). HbA1c fluctuation was also conducted between anti-diabetes treatments (Supplementary Table S7). There was no inconsistency between the form of direct and indirect comparisons of node-splitting analysis (Supplementary Tables 5-6, $p$-value = 0.72). In the heterogeneity analysis, the global $I^2$ did not identify any heterogeneity across the studies (Table S5, global $I^2 = 28.00$%). Figure 5 shows the cumulative rank probability plot.

**Figure 2.** Network plot of HbA1c and MAGE. The size of the nodes is proportional to the number of subjects (sample size) randomized to receive the therapy. The width of the lines is proportional to the number of trials comparing each pair of treatments. GLP-1 = Glucagon-like-peptide-1 receptor agonists; DPP-4 = dipeptidyl-peptidase 4 inhibitor; SGLT-2 = Sodium-glucose cotransporter 2 inhibitors.
GLP-1 RAs ranked highest (SUCRA 0.81), followed by DPP-4 inhibitors (SUCRA 0.72), sulfonylurea (SUCRA 0.65), thiazolidinediones (SUCRA 0.55), and SGLT-2 inhibitors (SUCRA 0.26). More detail is reported in Supplementary Table S9.

The overall risk of bias was low and unclear, except for one study. Figure S1 illustrates the quality of evidence using ROB2. The summary of GRADE is reported in Table 2. The results of the funnel plot in assessing publication bias are shown in Figure S2.

Discussion

In this systematic review and network meta-analysis, we compared and evaluated the relative effects of each treatment on GV reduction among patients with type 2 diabetes. Maintaining a normal glycemic level is crucial for preventing or minimizing complications in the treatment of type 2 diabetes. The results of our study revealed that GLP-1 RA was relatively associated with decreased MAGE and HbA1c levels compared with other treatments.

High GV is associated with an increased risk of diabetic macrovascular and microvascular complications, hypoglycemia, mortality, and other adverse clinical outcomes. The most known GV parameters, such as SD, CV, MAGE, are the most relevant metrics to assess glycemic control. Although the clinical significance of intra-day and inter-day blood glucose variability for chronic complications is still controversial, it is expected that the development of CGMS and the development of drugs to improve blood glucose variability will reveal the clinical significance and mechanism in the future. In this NMA, GLP-1 RAs had a relatively greater effect on MAGE reduction than other therapeutic agents, followed by DPP-4 inhibitors and SGLT-2 inhibitors. When compared with SU, both incretin-based therapy (GLP-1 RAs and DPP-4 inhibitor) and SGLT-2 inhibitors have high efficacies in GV reduction since their glucose-lowering mechanisms do not contribute to an increased risk of hypoglycemia. Incretin is a hormone released by the intestines in response to food consumption. Incretin medication, such as GLP-1 RA or DPP-4 inhibitor, controls meal-related glycemic excursions through augmentation of insulin and inhibition of glucagon secretion. DPP-4 inhibitors rely on endogenous GLP-1 synthesis by increasing it’s half-life, but GLP-1RAs are resistant to DPP-4 degradation and provides super physiologically stimulate GLP-1 receptors. SGLT-2 inhibitors act by reducing the rate of renal tubular glucose reabsorption, which reduces blood glucose levels without...
stimulating insulin release. However, because the majority of the studies included in this NMA are short-term, the long-term effects of each treatment on MAGE reduction remain unknown. Therefore, a prospective, multicenter study is warranted to investigate whether a drug or a class of drugs could provide better long-term GV control and whether treatment-mediated GV reduction can minimize the risk of hypoglycemia or vascular complications.

Regarding HbA1c reduction, all antidiabetic drugs exhibited a similar effect, with the exception of SGLT2-
inhibitors, which were comparatively less effective. The relatively poor efficacy of SGLT2-inhibitors is likely due to the fact that this NMA included only a few small studies with heterogenous baseline characteristics and background therapy. Consequently, our study’s results may differ from those of other studies with larger sample sizes and adjustment for these confounders.15,37 Intriguingly, the reducing effect of SU on HbA1c observed in the current study is relatively weak, especially when compared with earlier studies.32,38 This is likely due to the fact that all the included studies that used SU as a comparator focused primarily on MAGE as a primary outcome rather than HbA1c reduction. Therefore, the results of our study regarding the HbA1c reduction efficacy should be interpreted with caution.

In terms of GV and HbA1c reduction, our study indicated that incretin-based therapy, including GLP-1RAs and DPP-4 inhibitors, is more beneficial than SGLT-2 inhibitors, SU, and TZD. However, before prescribing antidiabetic medications to a patient, several factors must be considered, including cardiovascular and renal comorbidities, body weight, hypoglycemia risk, cost and accessibility, and patient preference.39 The latest diabetes guidelines recommend that patients who are unable to achieve their glycemic goal with oral antihyperglycemic drugs and require more aggressive glycemic control to

Figure 5. Cumulative rank probabilities for HbA1c between antidiabetic treatment in type 2 diabetes patients. Changes in the rank of treatments across different HbA1c scores. Cumulative rank probabilities for each treatment were estimated using surface under the cumulative rank curve (SUCRA). SUCRA provided a single summary estimate of relative treatment efficacy by taking the average of cumulative rank probabilities of treatment GLP-1 being ranked 1st best among diabetes treatments. HbA1c is best almost surely when the SUCRA index equals 1 and the worst if equals 0. GLP-1 = Glucagon-like-peptide-1 receptor agonists; DPP-4 = Dipeptidyl-peptidase 4 inhibitor; SGLT-2 = Sodium-glucose cotransporter 2 inhibitors.
Table 2. Certainty of evidence evaluated with GRADE framework.

| Comparisons (vs. Placebo) | Study no. | Effect size (95% CI) | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | GRADE |
|---------------------------|-----------|----------------------|--------------|--------------|---------------|--------------|--------------|-----------------|--------|
| HbA1c, mean difference    |           |                      |              |              |               |              |              |                  |        |
| DPP-4 inhibitor           | 7         | -0.68 (-0.94, -0.41) | RCT          | Serious      | Not serious   | Not serious  | Not serious  | Not serious     | Moderate |
| GLP-1 agonist             | 2         | -0.74 (-0.95, -0.53) | RCT          | Not serious  | Not serious   | Not serious  | Not serious  | Not serious     | High    |
| SGLT-2 inhibitor          | 5         | -0.39 (-0.59, -0.19) | RCT          | Not serious  | Not serious   | Not serious  | Not serious  | Not serious     | High    |
| Sulfonylurea              | 6         | -0.65 (-0.94, -0.35) | RCT          | Not serious  | Not serious   | Not serious  | Not serious  | Not serious     | High    |
| Thiazolidinediones        | 1         | -0.58 (-1.06, -0.10) | RCT          | Not serious  | Serious\(^a\) | Not serious  | Not serious  | Not serious     | Moderate |
| MAGE, mean difference     |           |                      |              |              |               |              |              |                  |        |
| DPP-4 inhibitor           | 10        | -21.98 (-35.91, -8.04) | RCT          | Serious      | Not serious   | Not serious  | Not serious  | Not serious     | Moderate |
| GLP-1 agonist             | 2         | -25.51 (-37.86, -13.15) | RCT          | Not serious  | Not serious   | Not serious  | Not serious  | Not serious     | High    |
| SGLT-2 inhibitor          | 7         | -16.42 (-27.36, -5.48) | RCT          | Not serious  | Not serious   | Not serious  | Not serious  | Not serious     | High    |
| Sulfonylurea              | 8         | -7.60 (-21.85, 6.65)  | RCT          | Not serious  | Not serious   | Not serious  | Serious      | Not serious     | Moderate |
| Thiazolidinediones        | 1         | -23.28 (-54.95, 8.39) | RCT          | Not serious  | Serious\(^b\) | Not serious  | Serious      | Not serious     | Low     |

\(^a\)Downgraded by one when unable to evaluate inconsistency/heterogeneity due to lack of sufficient data (a single study).

Study design: If randomized trials form the evidence base, the quality rating starts at “high.” If observational studies form the evidence, base the quality rating starts at “low.”

Risk of bias: Downgraded for failure to conceal random allocation or blind participants in randomized controlled trials or failure to adequately control for confounding in observational studies.

Inconsistency: Downgraded if heterogeneity represented by I\(^2\) statistics or global inconsistency (Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random-effects model) was high.

Indirectness: Downgraded when the assumption of transitivity is challenged, or the result is solely derived from indirect comparisons.

Imprecision: Downgraded when confidential interval (CI) is relatively too large compared to other active drugs.

Publication bias: Downgraded when substantial asymmetry is observed in funnel plot or p < 0.05 in the Egger test.

GRADE Definition (suggested by Puhan et al. in “A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis”).

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate, i.e., the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited, i.e., the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate, i.e., the true effect is likely to be substantially different from the estimate of effect.
consider combining GLP-1 RAs with basal insulin. They also specify that while selecting additional medications for patients with type 2 diabetes, the risk of cardiovascular disease and the possibility of related diseases must be considered. Based on this study’s findings, patients with diabetes and acute coronary syndrome as well as a high GV may benefit from GLP-1 RAs for preventing midterm MACE or the addition GLP-1 RAs to basal insulin could help patients achieve optimal glycemic control while minimizing the potential for hypoglycemia. In addition, incretin mimetics (GLP-1 RAs or DPP-4i) treatment would benefit patients dependent on insulin who are experiencing weight gain and hypoglycemia with a high GV profile. However, SGLT-2 inhibitors are recommended for patients with diabetes with or at high risk of HF, diabetic kidney disease, clinically evident atherosclerotic cardiovascular disease, or any combination of these conditions. Importantly, a decreased GV not only affects clinical outcomes. It has the potential to lead to improved treatment continuity, because it is associated with improved treatment satisfaction and quality of life. Therefore, a suitable treatment for diabetes should not rely primarily on MAGE or HbA1c reduction, but should also consider the above mentioned factors.

Direct meta-analysis is limited by the few studies evaluating specific treatment pairs. However, network meta-analysis provides useful evidence, including direct and indirect comparisons to carefully select the best treatment. Our analysis has several limitations. First not all studies reported HbA1c with MAGE, and only 12 studies reported HbA1c in this analysis. Therefore, HbA1c reduction should be carefully interpreted in this NMA. Second, GLP-1 RAs, which were the most effective in reducing HbA1c in this analysis, were not divided into short- and long-acting subclasses; hence, no analysis was conducted between these subclasses. Since previous studies have confirmed that short-acting GLP-1 RAs are more effective for GV than long-acting, a detailed classification of GLP-1 RAs is necessary. Third, this systematic review and NMA included 17 small studies, and subgroup analysis could not be performed due to differences in the baseline characteristics and background treatment among the studies. Therefore, the power of the mean difference between pairwise comparisons is lacking, and heterogeneity may exist. Therefore, caution is needed in the interpretation of the pairwise indirect comparison, and additional research is needed according to the patient’s condition in accordance with the revised guidelines in future studies.

In conclusion, this systematic review and network meta-analysis comprehensively compared various therapeutics for HbA1c reduction as well as GV markers in patients with type 2 diabetes. This study demonstrates that GLP-1 RAs have relatively high efficacy in terms of both HbA1c and MAGE reduction compared to other antidiabetic treatments. To draw clear conclusions about the major clinical benefits and risks of these therapies, additional studies using a larger sample size and presence of classifications according to patient status are recommended.

**Author Contributions**

E. Y designed the study; S.A collected the data; S.A conducted the data analysis; S.A and E. Y interpreted results and drafted the manuscript; S.P, M.K, and H.C supported quality assessment; all authors finalized the manuscript.

**Declaration of conflicting interests**

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**Data availability statement**

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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**Supplemental Material**

Supplemental material for this article is available online.

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