

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

Diabetes & Vascular Disease Research

May-June 2022: 1–14

© The Author(s) 2022

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/14791641221106866

journals.sagepub.com/home/dvr

SuA Oh¹ , Sujata Purja¹ , Hocheol Shin¹ , Minji Kim¹ and Eunyoung Kim, Ph.D¹

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

¹Data Science, Evidence-Based and Clinical Research Laboratory, Department of Health, Social and Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul, Republic of Korea

Corresponding author:

EunYoung Kim, Data science, Evidence-Based and Clinical Research Laboratory, Department of Health, Social and Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul 06974, Republic of Korea. Email: eykimjcb777@cau.ac.kr



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

variability (GV),³ both of which are related to vascular outcomes.^{4–6} Therefore, TIR and GV should also be considered as additional measures for glycemic control in addition to HbA1c.^{7,8} 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.⁹ 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.¹⁰ Thus, MAGE may be able to better represent glucose fluctuation in this context.^{7,11} 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.^{12–14} Subin Lee et al. reported that DPP-4 inhibitors were effective in GV regulation in a direct analysis comparing DPP-4 inhibitors and oral antihyperglycemic drugs (OAD).¹⁴ In addition, Heeyoung Lee et al. compared and analyzed GLP-1 RAs and SGLT-2 inhibitors.¹¹ According to published studies, SGLT-2 inhibitors, GLP-1 RAs, and DPP-4 inhibitors show pharmacological differences in their mechanisms of action, but effectively reduce glucose levels, complications, and GV in diabetic patients.^{11,14} However, in existing studies, it is difficult to ascertain the differences between individual drugs because direct comparison drugs for each drug pair exist in part. Although there have been indirect studies regarding HbA1c reduction between antidiabetic treatment pairs,¹⁵ there have been no studies on MAGE, which is another parameter that indicates differences between GV fluctuations. Therefore, the purpose of this study was to compare the effect of each drug pair on GV based on HbA1c and MAGE reduction in type 2 diabetes patients.

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](#).

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 (RAs), 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).

Outcome and data analysis

The primary outcome was MAGE in type 2 diabetes mellitus participants, while the secondary outcome was HbA1c. Uncertain information was decided after a discussion between two or more authors. 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. We then performed Markov Chain Monte Carlo simulations using vague priors¹⁶ and a generalized linear model with Gaussian family distribution and an identity link function.^{17,18} The analysis was conducted using 10 000 burn-ins, 100 000 iterations, and 1000 adaptations. The deviance information criterion and individual datapoint posterior mean deviance contribution were used to compare goodness-of-fit between the consistency and inconsistency models. The deviance information criterion was also used to select between a fixed-effects or random-effects model.^{17,18} The outcomes were analyzed using the mean difference (MD) and 95% confidence intervals (CIs). All analyses were generated by R Software with GeMTC package.^{19–21}

The methodological quality assessment was performed by using Cochrane Collaboration’s tool to assess the risk of bias in each trial.²² The evaluation items included in the present study were random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and potential bias. Each item was presented as “low risk,” “some concern,” or “high risk.” The graphs were synthesized by Review Manager version 5.4. The quality of evidence of collective outcomes was

estimated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.²³ Publication bias was also assessed using funnel plots.²⁴

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.²⁵ 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.²⁶ We ranked the interventions according to their surface under the cumulative ranking (SUCRA), which ranged from 0 to 1.²⁷ The SUCRA 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

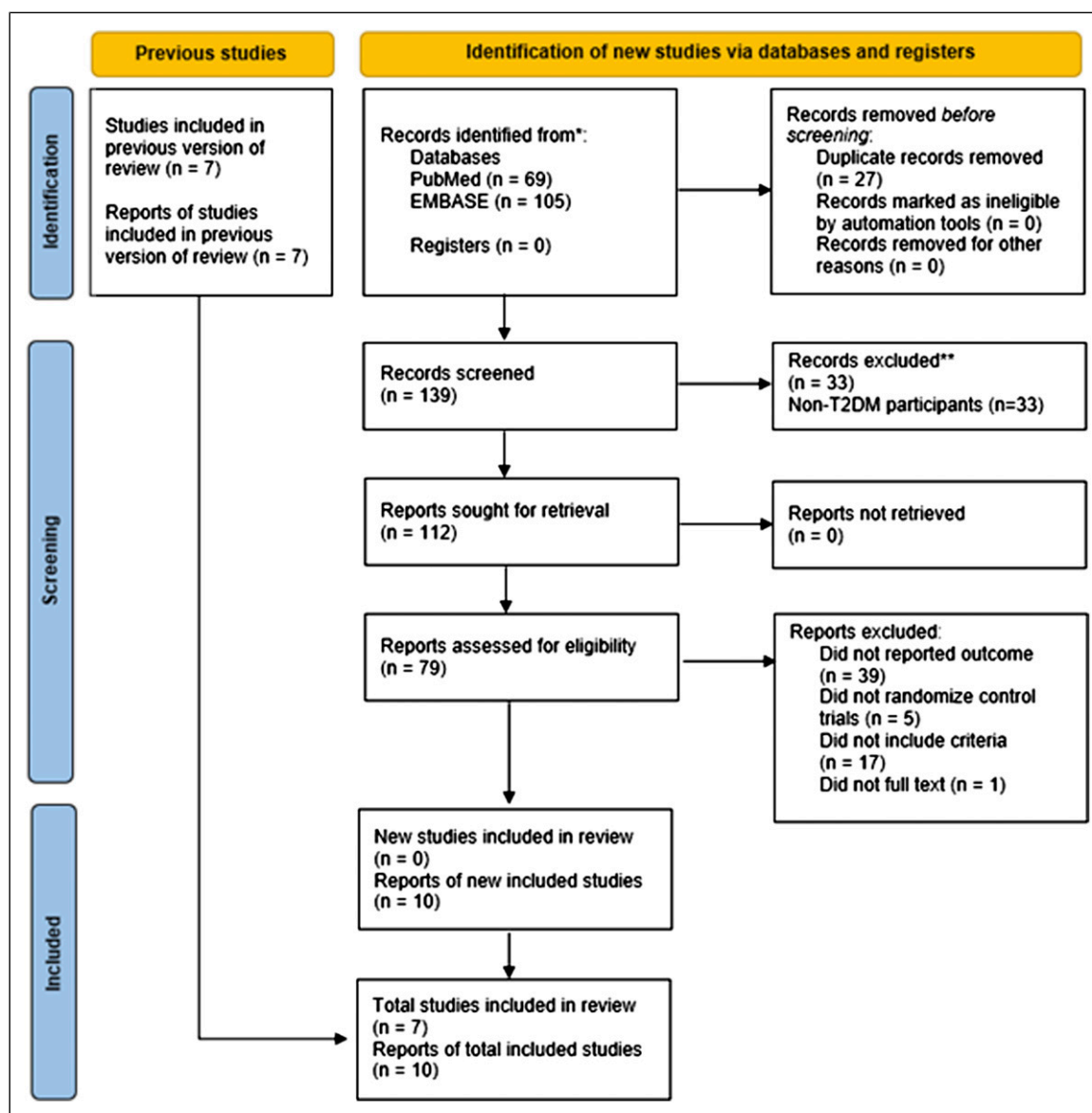


Figure 1. Flow chart of articles search and screening process.

Table 1. Characteristics of studies included in the network meta-analysis.

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 ⁴⁹	UMIN000028014	RCT	Dapagliflozin (168)	Gliclazide (163)	57.8	60.1	27.85	6.4	331	N/A	7.8	N/A	HbA1c reduction
Frias 2017 ⁵⁰	NCT02288273	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 2018-1 ⁵¹	NCT02429258	RCT	Dapagliflozin and metformin (23)	Placebo and metformin (25)	54.6	52.26	32.45	16.2	48	1 week	8.125	94.1 (mg/dL)	MAGE reduction
Henry 2018-2 ⁵¹	NCT02429258	RCT	Dapagliflozin and insulin (27)	Placebo and insulin (25)	59.05	50.07	35	29.5	52	1 week	8.535	116.1 (mg/dL)	MAGE reduction
Kim G 2017 ⁵²	NCT01404676	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)	MAGE reduction
Kim HS 2013 ⁵³	NCT00699322	RCT	Sitagliptin and metformin (16)	Glimepiride and metformin (17)	57.7	58.09	25.55	10.7	33	4 weeks	7.15	5.3 (mmol/L)	MAGE reduction
Kim NH 2017 ⁵⁴	NCT01339143	RCT	Vildagliptin and metformin (14)	Pliglitazone and metformin (11)	56	NA	26.6	NA	25	16 weeks	7.3	96.25 (mg/dL)	MAGE reduction
Kwak 2020 ⁵⁵	NCT03202563	RCT	Dapagliflozin and metformin (36)	Gemigliptin and metformin (34)	52.05	65.52	25.8	5.7	70	N/A	7.9	89.1 (mg/dL)	MAGE reduction
Lee 2020 ⁵⁶	NCT02459353	RCT	Dapagliflozin 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 ⁵⁷	MB102055	RCT	Dapagliflozin (18)	Placebo (10)	60	40.5	NA	NA	28	N/A	N/A	5.85 (mmol/L)	MAGE reduction
Li 2017 ⁵⁸	ChiCTR-PPR-15007045	RCT	Exenatide and insulin (18)	Placebo and insulin (18)	48.74	NA	26.42	NA	36	N/A	9.255	6.13 (mmol/L)	MAGE reduction

(continued)

Table 1. (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 ⁵⁹	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 ⁶⁰	UMIN000015033	RCT	Dapagliflozin 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 ⁶¹	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 ⁶²	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 ⁶²	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 ⁶³	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 ⁶⁴	NCT02925559	RCT	Dapagliflozin (45)	Gliclazide (52)	57.8	56.26	30.9	8	97	24 h	8.4	6.9 (mmol/L)	MAGE reduction
Xiao 2016 ⁶⁵	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 anti-diabetic 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.

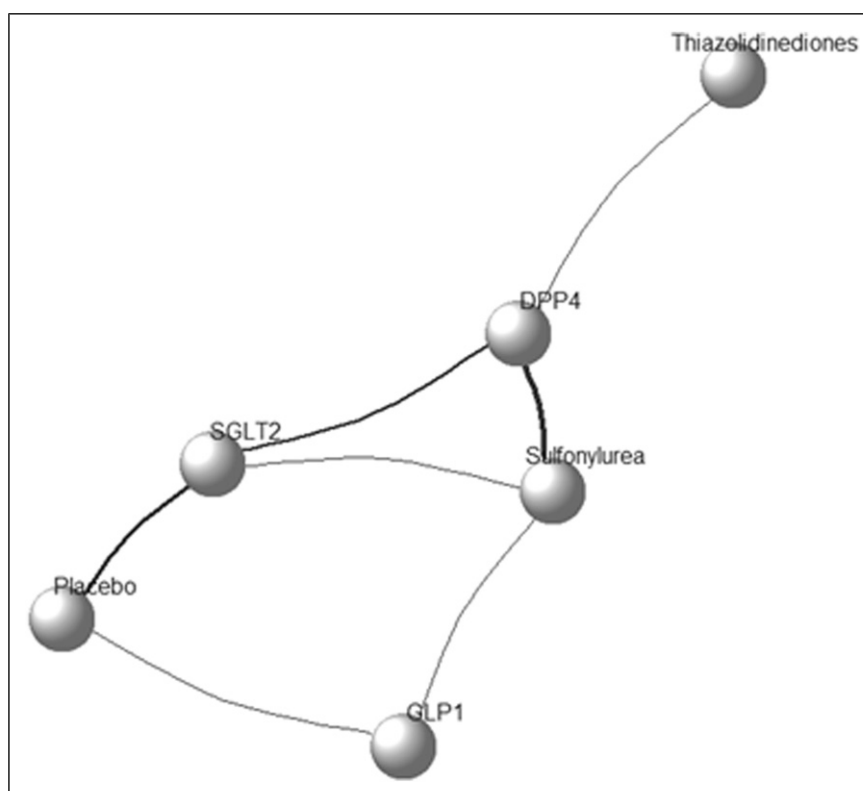


Figure 2. Network plot of HbA1c and MAGE. The size of the nodes is proportional to the number of subjects (sample size) randomized to receive the therapy. The width of the lines is proportional to the number of trials comparing each pair of treatments. GLP-1 = Glucagon-like-peptide-1 receptor agonists; DPP-4 = dipeptidyl-peptidase 4 inhibitor; SGLT-2 = Sodium-glucose cotransporter 2 inhibitors.

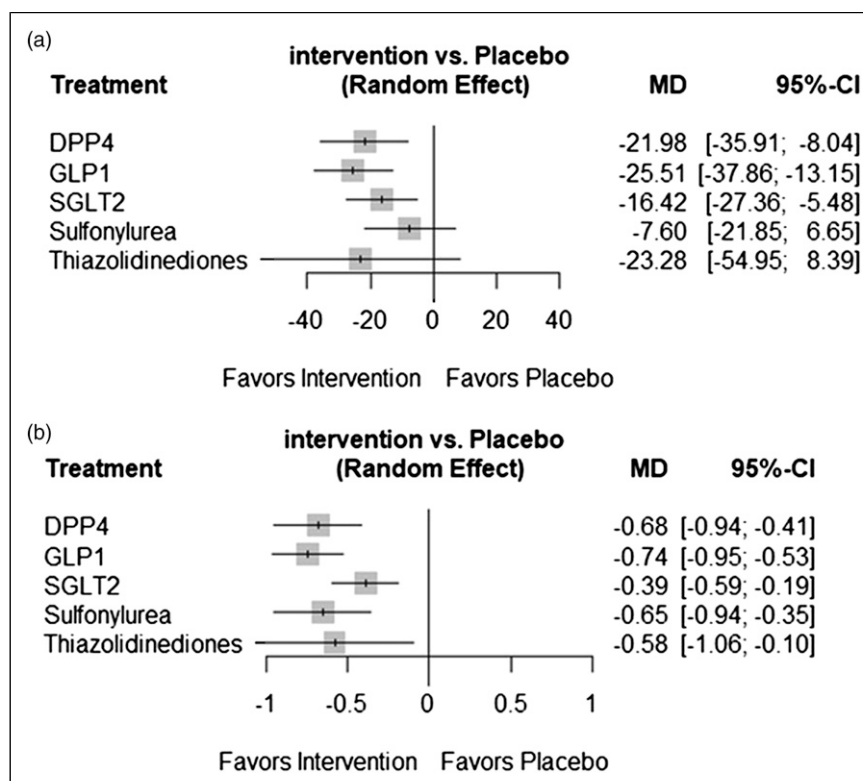


Figure 3. Forest plot between antidiabetic treatment for (a) MAGE, (b) HbA1c in type 2 diabetes patients. HbA1c = hemoglobin A1c; MAGE = timing of mean amplitude of glycemic excursion; MD = mean difference; CI = confidence interval; GLP-1 = Glucagon-like-peptide-1 receptor agonists; DPP-4 = dipeptidyl-peptidase 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.⁷ 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.^{6,28–30} The most known GV parameters, such as

SD, CV, MAGE, are the most relevant metrics to assess glycemic control.⁶ Although the clinical significance of intra-day and inter-day blood glucose variability for chronic complications is still controversial,⁶ 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 inhibitors) and SGLT-2 inhibitors have high efficacies in GV reduction since their glucose-lowering mechanisms do not contribute to an increased risk of hypoglycemia.^{31,32} 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.³³ DPP-4 inhibitors rely on endogenous GLP-1 synthesis by increasing its half-life, but GLP-1RAs are resistant to DPP-4 degradation and provides super physiologically stimulate GLP-1 receptors.^{34,35} SGLT-2 inhibitors act by reducing the rate of renal tubular glucose reabsorption, which reduces blood glucose levels without

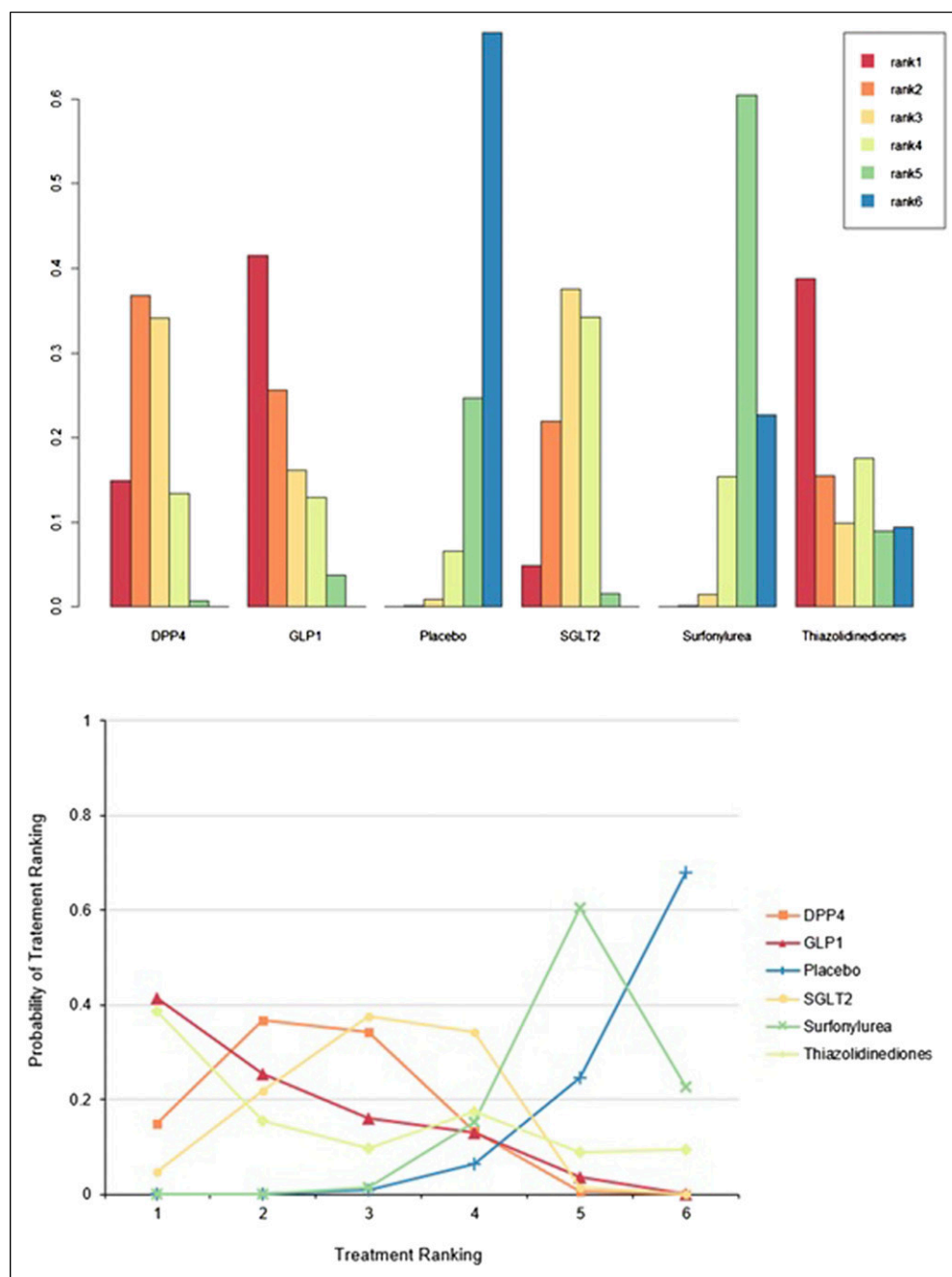


Figure 4. Cumulative rank probabilities for MAGE between antidiabetic treatment in type 2 diabetes patients. Changes in the rank of treatments across different MAGE scores. Cumulative rank probabilities for each treatment were estimated using surface under the cumulative rank curve (SUCRA). SUCRA provided 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. MAGE 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.

stimulating insulin release.³⁶ 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-

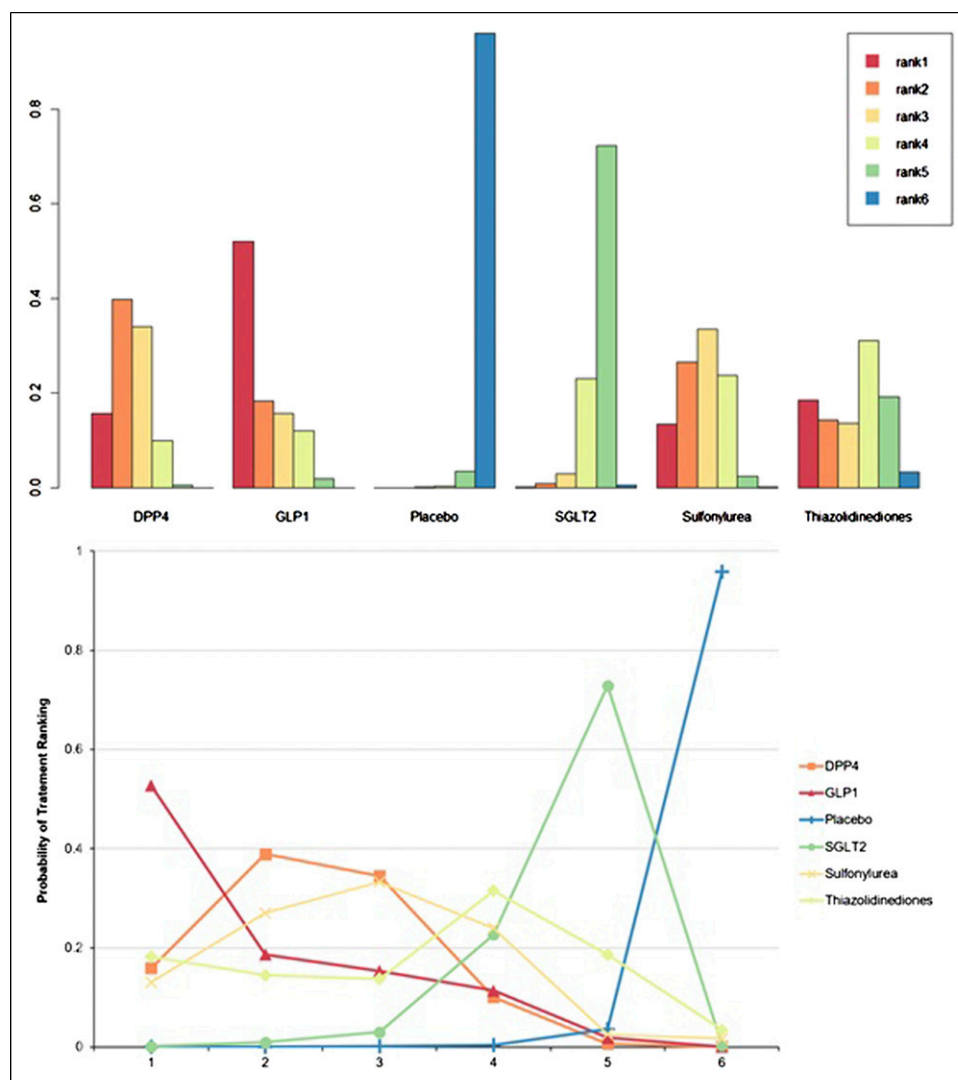


Figure 5. Cumulative rank probabilities for HbA1c between antidiabetic treatment in type 2 diabetes patients. Changes in the rank of treatments across different HbA1c scores. Cumulative rank probabilities for each treatment were estimated using surface under the cumulative rank curve (SUCRA). SUCRA provided 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.

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

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 ^a	Not serious	Serious	Not serious	⊕⊕○○ Low

^aDowngraded 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 I² 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 Puhon 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.³⁹ They also specify that while selecting additional medications for patients with type2 diabetes, the risk of cardiovascular disease and the possibility of related diseases must be considered.^{40,41} 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.^{42,43} 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.⁴⁴ 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.⁴⁵ 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.⁶ 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.⁴⁶ However, network meta-analysis provides useful evidence, including direct and indirect comparisons to carefully select the best treatment.⁴⁷ However, 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.⁴⁸ 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

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science and ICT, MICT) (NRF2021R1F1A1062044), and by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (Grant Number 2021R1A6A1A03044296), which had no further role in the study design, data collection, analysis, and interpretation, the writing of the report, or in the decision to submit the paper for publication.

Data availability statement

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

ORCID iDs

SuA Oh  <https://orcid.org/0000-0001-5682-4066>

Sujata Purja  <https://orcid.org/0000-0001-6507-915X>

Hocheol Shin  <https://orcid.org/0000-0002-7835-6838>

Minji Kim  <https://orcid.org/0000-0002-1464-9017>

Eunyoung Kim  <https://orcid.org/0000-0003-3525-8805>

Supplemental Material

Supplemental material for this article is available online.

References

1. Federation ID. IDF diabetes atlas. 2019. <https://www.diabetesatlas.org/en/>
2. Association AD. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2019. *Diabetes Care* 2019; 42: S61–S70, doi:10.2337/dc19-S006
3. Yoo HE and Kim JH. Time in range from continuous glucose monitoring: a novel metric for glycemic control. *Diabetes Metab J* 2020; 44: 828–839. DOI: 10.4093/dmj.2020.0257

4. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care* 2019; 42: 400–405. DOI: [10.2337/dc18-1444](https://doi.org/10.2337/dc18-1444)
5. Smith-Palmer J, Brändle M, Trevisan R, et al. Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. *Diabetes Res Clin Pract* 2014; 105: 273–284. DOI: [10.1016/j.diabres.2014.06.007](https://doi.org/10.1016/j.diabres.2014.06.007)
6. Zhou Z, Sun B, Huang S, et al. Glycemic variability: adverse clinical outcomes and how to improve it? *Cardiovasc Diabetol* 2020; 19: 102. DOI: [10.1186/s12933-020-01085-6](https://doi.org/10.1186/s12933-020-01085-6)
7. Suh S and Kim JH. Glycemic variability: how do we measure it and why is it important? *Diabetes Metab J* 2015; 39: 273–282. DOI: [10.4093/dmj.2015.39.4.273](https://doi.org/10.4093/dmj.2015.39.4.273)
8. DeVries JH. Glucose variability: where it is important and how to measure it. *Diabetes* 2013; 62: 1405–1408. DOI: [10.2337/db12-1610](https://doi.org/10.2337/db12-1610)
9. Draznin B, Aroda VR, Bakris G, et al. 6. Glycemic targets: standards of medical care in diabetes-2022. *Diabetes Care* 2022; 45: S83–S96. DOI: [10.2337/dc22-S006](https://doi.org/10.2337/dc22-S006)
10. Siegelaar SE, Holleman F, Hoekstra JB, et al. Glucose variability; does it matter? *Endocr Rev* 2010; 31: 171–182. DOI: [10.1210/er.2009-0021](https://doi.org/10.1210/er.2009-0021)
11. Lee H, Park SE and Kim EY. Glycemic variability impacted by SGLT2 inhibitors and GLP 1 agonists in patients with diabetes mellitus: a systematic review and meta-analysis. *J Clin Med* 2021; 10: 4078. DOI: [10.3390/jcm10184078](https://doi.org/10.3390/jcm10184078)
12. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2018; 319: 1580–1591. DOI: [10.1001/jama.2018.3024](https://doi.org/10.1001/jama.2018.3024)
13. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA* 2016; 316: 313–324. DOI: [10.1001/jama.2016.9400](https://doi.org/10.1001/jama.2016.9400)
14. Lee S, Lee H, Kim Y, et al. Effect of DPP-IV inhibitors on glycemic variability in patients with T2DM: a systematic review and meta-analysis. *Sci Rep* 2019; 9: 13296. DOI: [10.1038/s41598-019-49803-9](https://doi.org/10.1038/s41598-019-49803-9)
15. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. *Ann Intern Med* 2020; 173: 278–286. DOI: [10.7326/m20-0864](https://doi.org/10.7326/m20-0864)
16. van Valkenhoef G, Lu G, de Brock B, et al. Automating network meta-analysis. *Res Synth Methods* 2012; 3: 285–299. DOI: [10.1002/jrsm.1054](https://doi.org/10.1002/jrsm.1054)
17. Shim SR, Kim SJ, Lee J, et al. Network meta-analysis: application and practice using R software. *Epidemiol Health* 2019; 41: e2019013. DOI: [10.4178/epih.e2019013](https://doi.org/10.4178/epih.e2019013)
18. Béliveau A, Boyne DJ, Slater J, et al. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. *BMC Med Res Methodol* 2019; 19: 196. DOI: [10.1186/s12874-019-0829-2](https://doi.org/10.1186/s12874-019-0829-2)
19. Röver C. Bayesian random-effects meta-analysis using the bayesmeta R Package. *J Stat Softw* 2020; 93(6): 1–51.
20. Lunn DJ, Thomas A, Best N, et al. WinBUGS - A Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000; 10: 325–337. DOI: [10.1023/A:1008929526011](https://doi.org/10.1023/A:1008929526011)
21. Shim SR, Kim SJ, Lee J, et al. Network meta-analysis: application and practice using R software. *Epidemiol Health* 2019; 41: e2019013–e2019013. DOI: [10.4178/epih.e2019013](https://doi.org/10.4178/epih.e2019013)
22. Higgins JP, Altman DG, Gøtzsche PC, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928. DOI: [10.1136/bmj.d5928](https://doi.org/10.1136/bmj.d5928)
23. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014; 349: g5630. DOI: [10.1136/bmj.g5630](https://doi.org/10.1136/bmj.g5630)
24. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; 343: d4002. DOI: [10.1136/bmj.d4002](https://doi.org/10.1136/bmj.d4002)
25. van Valkenhoef G, Dias S, Ades AE, et al. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods* 2016; 7: 80–93. DOI: [10.1002/jrsm.1167](https://doi.org/10.1002/jrsm.1167)
26. Thorlund K, Imberger G, Johnston BC, et al. Evolution of heterogeneity (I²) estimates and their 95% confidence intervals in large meta-analyses. *PLoS One* 2012; 7: e39471–e39471. DOI: [10.1371/journal.pone.0039471](https://doi.org/10.1371/journal.pone.0039471)
27. Salanti G, Ades AE and Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163–171. DOI: [10.1016/j.jclinepi.2010.03.016](https://doi.org/10.1016/j.jclinepi.2010.03.016)
28. Hirakawa Y, Arima H, Zoungas S, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. *Diabetes Care* 2014; 37: 2359–2365. DOI: [10.2337/dc14-0199](https://doi.org/10.2337/dc14-0199)
29. Folli F, Corradi D, Fanti P, et al. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular complications: avenues for a mechanistic-based therapeutic approach. *Curr Diabetes Rev* 2011; 7: 313–324. DOI: [10.2174/157339911797415585](https://doi.org/10.2174/157339911797415585)
30. Bruginski D, Précoma DB, Sabbag A, et al. Impact of glycemic variability and hypoglycemia on the mortality and length of hospital stay among elderly patients in Brazil. *Curr Diabetes Rev* 2020; 16: 171–180. DOI: [10.2174/1573399815999190619141622](https://doi.org/10.2174/1573399815999190619141622)

31. Eriksson JW, Bodegard J, Nathanson D, et al. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. *Diabetes Res Clin Pract* 2016; 117: 39–47. DOI: [10.1016/j.diabres.2016.04.055](https://doi.org/10.1016/j.diabres.2016.04.055)
32. Chen Z and Li G. Sodium-glucose co-transporter 2 inhibitors compared with sulfonylureas in patients with type 2 diabetes inadequately controlled on metformin: a meta-analysis of randomized controlled trials. *Clin Drug Investig* 2019; 39: 521–531. DOI: [10.1007/s40261-019-00781-w](https://doi.org/10.1007/s40261-019-00781-w)
33. Bourdel-Marchasson I, Schweizer A and Dejager S. Incretin therapies in the management of elderly patients with type 2 diabetes mellitus. *Hosp Pract* 2011; 39: 7–21. DOI: [10.3810/hp.2011.02.369](https://doi.org/10.3810/hp.2011.02.369)
34. Mentis N, Vardarli I, Köthe LD, et al. GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes. *Diabetes* 2011; 60: 1270–1276. DOI: [10.2337/db10-1332](https://doi.org/10.2337/db10-1332)
35. Mentlein R, Gallwitz B and Schmidt WE. Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum. *Eur J Biochem* 1993; 214: 829–835. DOI: [10.1111/j.1432-1033.1993.tb17986.x](https://doi.org/10.1111/j.1432-1033.1993.tb17986.x)
36. Hsia DS, Grove O and Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2017; 24: 73–79. DOI: [10.1097/med.0000000000000311](https://doi.org/10.1097/med.0000000000000311)
37. Wang Z, Sun J, Han R, et al. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors as monotherapy or add-on to metformin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab* 2018; 20: 113–120. DOI: [10.1111/dom.13047](https://doi.org/10.1111/dom.13047)
38. Hirst JA, Farmer AJ, Dyar A, et al. Estimating the effect of sulphonylurea on HbA1c in diabetes: a systematic review and meta-analysis. *Diabetologia* 2013; 56: 973–984. DOI: [10.1007/s00125-013-2856-6](https://doi.org/10.1007/s00125-013-2856-6)
39. Association AD. Standards of medical care in diabetes—2022 abridged for primary care providers. *Clin Diabetes* 2022; 40: 10–38. DOI: [10.2337/cd22-as01](https://doi.org/10.2337/cd22-as01)
40. Hur KY, Moon MK, Park JS, et al. 2021 clinical practice guidelines for diabetes mellitus of the Korean diabetes association. *Diabetes Metab J* 2021; 45: 461–481. DOI: [10.4093/dmj.2021.0156](https://doi.org/10.4093/dmj.2021.0156)
41. American Diabetes Association. 9. pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. *Diabetes Care* 2021; 44: S111–S124. DOI: [10.2337/dc21-S009](https://doi.org/10.2337/dc21-S009)
42. Gerbaud E, Darier R, Montaudon M, et al. Glycemic variability is a powerful independent predictive factor of mid-term major adverse cardiac events in patients with diabetes with acute coronary syndrome. *Diabetes Care* 2019; 42: 674–681. DOI: [10.2337/dc18-2047](https://doi.org/10.2337/dc18-2047)
43. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the american college of cardiology solution set oversight committee. *J Am Coll Cardiol* 2020; 76: 1117–1145. DOI: [10.1016/j.jacc.2020.05.037](https://doi.org/10.1016/j.jacc.2020.05.037)
44. Johansen NJ, Dejgaard TF, Lund A, et al. Efficacy and safety of meal-time administration of short-acting exenatide for glycaemic control in type 1 diabetes (MAG1C): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2020; 8: 313–324. DOI: [10.1016/S2213-8587\(20\)30030-9](https://doi.org/10.1016/S2213-8587(20)30030-9)
45. Riggs K, Ali H, Taegtmeier H, et al. The use of SGLT-2 inhibitors in type 2 diabetes and heart failure. *Metab Syndr Relat Disord* 2015; 13: 292–297. DOI: [10.1089/met.2015.0038](https://doi.org/10.1089/met.2015.0038)
46. Esterhuizen TM and Thabane L. Con: meta-analysis: some key limitations and potential solutions. *Nephrol Dial Transpl* 2016; 31: 882–885. DOI: [10.1093/ndt/gfw092](https://doi.org/10.1093/ndt/gfw092)
47. Li T, Puhan MA, Vedula SS, et al. Network meta-analysis: highly attractive but more methodological research is needed. *BMC Med* 2011; 9: 79. DOI: [10.1186/1741-7015-9-79](https://doi.org/10.1186/1741-7015-9-79)
48. Lo M, Owens D, Colette C, et al. Glycaemic variabilities: key questions in pursuit of clarity. *Diabetes Metab* 2021; 47: 101283. DOI: [10.1016/j.diabet.2021.101283](https://doi.org/10.1016/j.diabet.2021.101283)
49. Fuchigami A, Shigiyama F, Kitazawa T, et al. Efficacy of dapagliflozin versus sitagliptin on cardiometabolic risk factors in Japanese patients with type 2 diabetes: a prospective, randomized study (DIVERSITY-CVR). *Cardiovasc Diabetol* 2020; 19: 1. DOI: [10.1186/s12933-019-0977-z](https://doi.org/10.1186/s12933-019-0977-z)
50. Frias JP, Nakhle S, Ruggles JA, et al. Exenatide once weekly improved 24-hour glucose control and reduced glycaemic variability in metformin-treated participants with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab* 2017; 19: 40–48. DOI: [10.1111/dom.12763](https://doi.org/10.1111/dom.12763)
51. Henry RR, Strange P, Zhou R, et al. Effects of dapagliflozin on 24-hour glycemic control in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Technol Ther* 2018; 20: 715–724. DOI: [10.1089/dia.2018.0052](https://doi.org/10.1089/dia.2018.0052)
52. Kim G, Oh S, Jin SM, et al. The efficacy and safety of adding either vildagliptin or glimepiride to ongoing metformin therapy in patients with type 2 diabetes mellitus. *Expert Opin Pharmacother* 2017; 18: 1179–1186. DOI: [10.1080/14656566.2017.1353080](https://doi.org/10.1080/14656566.2017.1353080)
53. Kim HS, Shin JA, Lee SH, et al. A comparative study of the effects of a dipeptidyl peptidase-IV inhibitor and sulfonylurea on glucose variability in patients with type 2 diabetes with inadequate glycemic control on metformin. *Diabetes Technol Ther* 2013; 15: 810–816. DOI: [10.1089/dia.2013.0038](https://doi.org/10.1089/dia.2013.0038)
54. Kim NH, Kim DL, Kim KJ, et al. Effects of vildagliptin or pioglitazone on glycemic variability and oxidative stress in

- patients with type 2 diabetes inadequately controlled with metformin monotherapy: a 16-week, randomised, open label, pilot study. *Endocrinol Metab (Seoul)* 2017; 32: 241–247. DOI: [10.3803/EnM.2017.32.2.241](https://doi.org/10.3803/EnM.2017.32.2.241)
55. Kwak SH, Hwang YC, Won JC, et al. Comparison of the effects of gemigliptin and dapagliflozin on glycaemic variability in type 2 diabetes: a randomized, open-label, active-controlled, 12-week study (STABLE II study). *Diabetes Obes Metab* 2020; 22: 173–181. DOI: [10.1111/dom.13882](https://doi.org/10.1111/dom.13882)
 56. Lee SH, Min KW, Lee BW, et al. Effect of dapagliflozin as an add-on therapy to insulin on the glycemic variability in subjects with type 2 diabetes mellitus (dive): a multicenter, placebo-controlled, double-blind, randomized study. *Diabetes Metab J* 2021; 45: 339–348. DOI: [10.4093/dmj.2019.0203](https://doi.org/10.4093/dmj.2019.0203)
 57. Li FF, Gao G, Li Q, et al. Influence of dapagliflozin on glycemic variations in patients with newly diagnosed type 2 diabetes mellitus. *J Diabetes Res* 2016; 2016: 5347262. DOI: [10.1155/2016/5347262](https://doi.org/10.1155/2016/5347262)
 58. Li FF, Jiang L, Fu L, et al. Exenatide add-on to continuous subcutaneous insulin infusion therapy reduces bolus insulin doses in patients with type 2 diabetes: a randomized, controlled, open-label trial. *Diabetes Ther* 2017; 8: 177–187. DOI: [10.1007/s13300-016-0222-7](https://doi.org/10.1007/s13300-016-0222-7)
 59. Li H, Xu X, Wang J, et al. A randomized study to compare the effects of once-weekly dulaglutide injection and once-daily glimepiride on glucose fluctuation of type 2 diabetes mellitus patients: a 26-week follow-up. *J Diabetes Res* 2019; 2019: 6423987. DOI: [10.1155/2019/6423987](https://doi.org/10.1155/2019/6423987)
 60. Nomoto H, Miyoshi H, Sugawara H, et al. A randomized controlled trial comparing the effects of dapagliflozin and DPP-4 inhibitors on glucose variability and metabolic parameters in patients with type 2 diabetes mellitus on insulin. *Diabetol Metab Syndr* 2017; 9: 54. DOI: [10.1186/s13098-017-0255-8](https://doi.org/10.1186/s13098-017-0255-8)
 61. Park KS, Kwak S, Cho YM, et al. Vildagliptin reduces plasma stromal cell-derived factor-1 α in patients with type 2 diabetes compared with glimepiride. *J Diabetes Investig* 2017; 8: 218–226. DOI: [10.1111/jdi.12572](https://doi.org/10.1111/jdi.12572)
 62. Park SE, Lee BW, Kim JH, et al. Effect of gemigliptin on glycaemic variability in patients with type 2 diabetes (STABLE study). *Diabetes Obes Metab* 2017; 19: 892–896. DOI: [10.1111/dom.12869](https://doi.org/10.1111/dom.12869)
 63. Suzuki R, Eiki JI, Moritoyo T, et al. Effect of short-term treatment with sitagliptin or glibenclamide on daily glucose fluctuation in drug-naïve Japanese patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2018; 20: 2274–2281. DOI: [10.1111/dom.13364](https://doi.org/10.1111/dom.13364)
 64. Vianna AGD, Lacerda CS, Pechmann LM, et al. Improved glycaemic variability and time in range with dapagliflozin versus gliclazide modified release among adults with type 2 diabetes, evaluated by continuous glucose monitoring: a 12-week randomized controlled trial. *Diabetes Obes Metab* 2020; 22: 501–511. DOI: [10.1111/dom.13913](https://doi.org/10.1111/dom.13913)
 65. Xiao X, Cui X, Zhang J, et al. Effects of sitagliptin as initial therapy in newly diagnosed elderly type 2 diabetics: a randomized controlled study. *Exp Ther Med* 2016; 12: 3002–3008. DOI: [10.3892/etm.2016.3729](https://doi.org/10.3892/etm.2016.3729)