The efficacy and safety of once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus
A systemic review and meta-analysis

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Abstract
Background: The efficacy and safety of once-weekly dipeptidyl peptidase-4 inhibitor (DPP-4i) omarigliptin as monotherapy or add on to other antihyperglycemic agents (AHAs) in patients with type 2 diabetes mellitus (T2DM) is unclear.

Methods: PubMed, EMBASE, Cochrane library, and ClinicalTrials.gov were searched from the inception to January 24, 2018. Randomized controlled trials comparing omarigliptin with placebo or other AHAs in T2DM patients were included in our meta-analysis. Risk ratio (RR) and mean difference (MD) were used to evaluate the outcomes.

Results: Totally, 11 trials involving 8276 patients were satisfied with our inclusion criteria. Compared with control group, omarigliptin was associated with a significantly stronger reduction in hemoglobin A1c (HbA1c) (MD 0.38%, 95% confidence interval [CI] [0.18, 0.58], P=.0002) and fasting plasma glucose (MD 0.48 mmol/L, 95% CI [0.14 mmol/L, 0.82 mmol/L], P=.006). Omarigliptin increased the number of participants who achieved HbA1c < 7.0% compared with control group (RR 2.03, 95% CI [1.38, 2.98], P=.0003). No significant difference was found in the aspect of adverse events (RR 1.00, 95% CI [0.97, 1.03], P=.99), serious adverse events (RR 1.02, 95% CI [0.91, 1.13], P=.75), hypoglycemic events (RR 0.86, 95% CI [0.48, 1.54], P=.61) between omarigliptin and control group. Omarigliptin has a homologous efficacy and safety background to other AHAs according to the results of subgroup analysis.

Conclusions: This review revealed that omarigliptin had a favorable efficacy and safety as monotherapy or add on to other AHAs in treating T2DM patients. It is a superior choice for T2DM patients who have a poor adherence to daily AHAs.

Abbreviations: AEs = adverse events, AHAs = antihyperglycemic agents, CI = confidence interval, DPP-4i = dipeptidyl peptidase-4 inhibitor, FPG = fasting plasma glucose, GLP-1s = glucagon-like peptide-1 receptor agonists, HbA1c = hemoglobin A1c, MD = mean difference, NCT = National Clinical Trial, RCTs = randomized controlled trials, RR = risk ratio, SAEs = serious adverse events, T2DM = type 2 diabetes mellitus.

Keywords: efficacy, meta-analysis, omarigliptin, safety, type 2 diabetes mellitus

1. Introduction

Diabetes is a worldwide health issue, and the burden of disease is estimated to increase from 425 to 629 million adults between 2017 and 2045.[1,2] Diabetes can lead to extensive damage to the microvascular and macrovascular body systems. Proper management of blood glucose level will delay the progression of the underlying metabolic dysfunction and reduce the risk of diabetic complications.[3,4]

Dipeptidyl peptidase-4 inhibitor (DPP-4i) is a novel series of oral antihyperglycemic agents (AHAs). DPP-4i decreases blood glucose of type 2 diabetes mellitus (T2DM) patients by prolonging the half-life of glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, gut-derived peptides which stimulate insulin secretion and decrease glucagon release in a glucose-dependent manner.[5] Over the past decade, daily-dosed DPP-4i have become an established part of AHAs in the treatment of T2DM.[6] However, a substantial proportion people with T2DM does not take their medication as prescribed.[7,8] Nonadherence and nonpersistence with medications in T2DM are associated with worse outcomes, including poorer glycemic control, more complications, and higher overall costs.[9,10]

Omarigliptin is a selective, oral DPP-4i with a half-life that permits once-weekly dosing.[11] The less medication frequency may contribute to improved compliance and management of blood glucose level in patients with T2DM. Many studies[14–16] which had tested the efficacy and safety of omarigliptin monotherapy or add on to other AHAs in the treatment of T2DM were published recently. Herein, we conducted a systematic review and meta-analysis to present an overview of the efficacy and safety of omarigliptin in patients with T2DM.
2. Methods and materials

Ethical approval and patient consent are not required, as the study is a meta-analysis of previously published studies and not involve direct contact with patients.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting a high-quality meta-analysis\[17,18\] and the Cochrane handbook guidelines.\[19\] This meta-analysis was registered in PROSPERO (CRD42018085310).

2.1. Data source and searching

The databases of PubMed, EMBASE, and Cochrane library were systematically searched for eligible studies from the inception to January 24, 2018. We used the combination of following medical subject heading and free-text terms: diabetes, diabetes mellitus, type 2 diabetes mellitus, DM, T2DM, omarigliptin, marizev, MK-3102, dipeptidyl peptidase-4 inhibitor, and DPP-4i. To find out newly developed clinical trials, we searched the ClinicalTrials.gov. Finally, we carried out an additional manual search of the references of included trials, former meta-analyses, and diabetes-related journals to identify other newly published and unpublished studies.

2.2. Study selection

Two researchers independently chose eligible studies which were included in meta-analysis. When there existed a disagreement, they resolved it by consulting another researcher. Inclusion criteria was listed as followings: randomized controlled trials (RCTs); omarigliptin versus placebo or any other AHAs were assessed; treatment duration ≥ 12 weeks; patients involved were with a clinical diagnosis of T2DM; at least one of the following outcomes was reported in trial: reduction in hemoglobin A1c (HbA1c), reduction in fasting plasma glucose (FPG), number of participants achieving HbA1c < 7.0%, adverse events (AEs), serious adverse events (SAEs); hypoglycemic events; eligible participants were ≥ 18 years of age. Papers were excluded if they are non RCTs; data published in the form of abstracts, short communications, or brief reports; trials tested in animals or healthy human subjects; articles that did not report information of interest; and trials whose treatment duration was shorter than 12 weeks. If several papers had been published about 1 trial, the paper which contains more adequate information was included in our meta-analysis.

2.3. Data extraction

We abstracted the information of included studies in 3 aspects: the baseline characteristics of included trials and participants, the basic outcomes, and the quality of included studies. Two independent researchers extracted the needed information; when there existed a disagreement, they reached a consensus by discussing with other researcher. We collected the following information in each trial: first author, publication year, sample size, average age, gender ratio, medications in treatment and control group, National Clinical Trial (NCT) number, treatment duration, duration of diabetes, and baseline HbA1c. We also extracted following outcomes in trials: reduction in HbA1c, reduction in FPG, number of participants achieving HbA1c < 7%, AEs, SAEs, and hypoglycemic events.

2.4. Quality assessment

With the Cochrane Collaboration’s tool, we assessed the risk of bias in the included studies.\[17\] The risk of bias was described and assessed in 7 specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The results of these domains were graded as a “low” risk of bias, a “high” risk of bias, or an “unclear” risk of bias.

2.5. Statistical analysis

Risk ratio (RR) and 95% confidence interval (CI) were applied to dichotomous outcomes, whereas mean difference (MD) and 95% CI were applied to continuous outcomes. Two-tailed, P < .05 was considered statistically significant. Statistical heterogeneity was assessed by Cochrane chi-squared test, P < .10 and I^2 > 50% was considered to be significant heterogeneity. Pooled analyses were conducted using a fixed-effects model, whereas a random-effects model was applied if there was heterogeneity (P < .10 and I^2 > 50%). Publication bias was evaluated with Egger test. Subgroup analysis was performed according to different treatment methods in control group. All the analyses were conducted with R version 3.6.3 and Stata 11.0 (StatCorp, College Station, TX).

3. Results

3.1. Search results

The study identification and selection process were summarized in Fig. 1. Of 128 records identified by initial electronic search, 11 studies\[14–16,20–27\] met our inclusion criteria for the final narrative synthesis with a combined population of 8276 persons with T2DM. No additional study was identified by manual search. The characteristics of the included trials and participants were described in Table 1. All studies were published between 2015 and 2017. The sample size ranged from 203 to 4202. All 11 studies adopted a double-blind design. Only 1 trial\[14\] mostly involved patients with renal impairment (estimated glomerular filtration rate < 60 ml/min per 1.73 m^2). Among 11 trials, 9 trials\[14,15,20,24,26,27\] compared the efficacy and safety of omarigliptin with placebo, 3 trials\[16,20,23\] compared the efficacy and safety of omarigliptin with other AHAs.

3.2. Risk of bias in included studies and quality of evidence

The bias assessment of all 11 trials was detailed in Fig. 2. A total of 8 studies\[14–16,20–22,25,26\] explicitly described the random sequence generation, mainly by an interactive voice response system. Eight studies\[14–16,20–22,25,26\] had used unpredicted methods to generate random sequence which stated a low risk of allocation concealment process, whereas 3 studies\[23,24,27\] which lack random sequence generation method were regarded as having an unclear risk of bias in random sequence generation and allocation concealment. All 11 trials\[14–16,20–27\] indicated that they had adopted a double-blind design. Three trials\[16,22,25\] did not involve a blinded outcome assessment. There was no trial that described neither the number of withdrawal nor loss to follow-up and the reason for these aspects; therefore, all trials were regarded as having a low risk in this domain. There were 11 studies\[14–16,20–27\] which had been registered in ClinicalTrials.gov, and an NCT number was identified. All included studies were considered to have a low risk of bias in selective reporting, according to the review of their protocols. One study\[15\] was
Table 1
The basic characteristics of included studies and participants.

| Trial name          | NCT          | Study arms       | Patients | Age, y | Male, n (%) | Duration of diabetes, y | Baseline HbA1c, % | Treatment duration, wk |
|---------------------|--------------|------------------|----------|--------|-------------|------------------------|-------------------|------------------------|
| Antonio Chacra2017  | NCT01698775  | Omarigliptin 12.5 mg/25 mg Placebo | 107      | 65.9 ± 9.4 | 68 (63.6) | 14.9 ± 8.2 | 8.3 ± 0.8 | 54 |
| Ira Gantz2017-1     | NCT01703208  | Omarigliptin 25 mg + AHA Placebo + AHA | 2100     | 63.7 ± 8.5 | 1461 (69.6) | 12.0 ± 7.6 | 8.0 ± 0.9 | 90 |
| Ira Gantz2017-2     | NCT01703221  | Omarigliptin 25 mg Stagliptin 50 mg Placebo | 166      | 60 ± 9 | 104 (63.7) | 7.4 ± 5.5 | 7.9 ± 0.7 | 52 |
| Ira Gantz2017-3     | NCT01697592  | Omarigliptin 25 mg + AHA Placebo + AHA | 389      | 61 ± 10 | 271 (69.7) | 9.3 ± 3.8 | 8.0 ± 0.7 | 52 |
| Ira Gantz2017-4     | NCT01814748  | Omarigliptin 25 mg Placebo | 102      | 38.8 ± 4.7 | 67 (65.7) | 7.9 ± 0.9 | 8.1 ± 0.9 | 24 |
| Philip Home2017     | NCT01717313  | Omarigliptin 25 mg Placebo | 165      | 57.4 ± 9.2 | 95 (57.6) | 5.4 ± 3.8 | 8.0 ± 0.9 | 54 |
| R. Ravi Shankar2017 | NCT01755156  | Omarigliptin 25 mg + metformin Placebo + metformin | 201      | 57.5 ± 8.1 | 101 (50.2) | 8.2 ± 5.2 | 8.1 ± 0.9 | 104 |
| Ronald Goldenberg2016 | NCT01841697 | Omarigliptin 25 mg + metformin Stagliptin 100 mg + metformin | 322 | 57 ± 10 | 151 (46.8) | 7.0 ± 4.5 | 7.5 ± 0.8 | 24 |
| Saung-Hwan Lee2017  | NCT01704261  | Omarigliptin 25 mg + metformin + sulfonylurea Placebo + metformin + sulfonylurea | 154 | 57.2 ± 8.4 | 151 (46.8) | 9.8 ± 5.3 | 8.5 ± 0.8 | 24 |
| Wayne H.-H. Sheu2015 | NCT01217073  | Omarigliptin 25 mg Placebo | 114      | 55.1 ± 8.8 | 69 (60.5) | 5.9 ± 5.2 | 8.1 ± 1.0 | 78 |
| Yehuda Handelman2017 | NCT01682759  | Omarigliptin 25 mg + metformin Glimepiride + metformin | 376 | 59 ± 10 | 203 (54.0) | 7.6 ± 5.1 | 7.5 ± 0.8 | 54 |

AHA = antihyperglycemic agent, C = control group, HbA1c = hemoglobin A1c, n = number of participants, NCT = National Clinical Trial number, T = treatment group.
prematurely terminated and 2 studies[22,23] had seriously confounding factors in the process of implementation; these trials were considered high risk in other bias.

3.3. Efficacy outcomes

All outcomes were reported in total and subgroup analysis. We made subgroup analysis of both efficacy and safety outcomes according to predefined groups.

Reduction in HbA1c is the primary outcome in this meta-analysis. Eleven trials[14–16,20–27] reported data on reduction in HbA1c (Fig. 3). The pooled evidence showed that compared with placebo or other AHAs, omarigliptin had further reduced the level of HbA1c in T2DM patients (MD 0.38%, 95% CI [0.18, 0.58], \( P = .0002 \)). There existed a significantly statistical heterogeneity between included studies (\( P < .00001, I^2 = 96\% \)).

Information regarding reduction in FPG was reported in 10 trials[14,16,20–27]. The pooled evidence showed that compared with control group, omarigliptin decreased the level of FPG by 0.48 mmol/L (MD 0.48 mmol/L, 95% CI [0.14 mmol/L, 0.82 mmol/L], \( P = .006 \)). Random-effects model was adopted because there existed a significantly statistical heterogeneity between included studies (\( P < .00001, I^2 = 87\% \)) (Fig. 4).

Totally 9 trials[14,16,20,21,23–27] reported the outcome of number of participants achieving HbA1c < 7.0% (Fig. 5). Pooled evidence indicated that compared with control group, omarigliptin increased number of participants achieving HbA1c < 7.0% by 103% (RR 2.03, 95% CI [1.38, 2.98], \( P = .0003 \)). For the significantly statistical heterogeneity between included studies, we adopted random-effects model in the analysis of this outcome.

Figure 2. Risk of bias graph and summary for included studies.

Figure 3. Individual and summary MD with 95% CI of reduction in HbA1c. CI = confidence interval, HbA1c = hemoglobin A1c, MD = mean difference.
Figure 4. Individual and summary MD with 95% CI of reduction in FPG. CI = confidence interval, FPG = fasting plasma glucose, MD = mean difference.

Figure 5. Individual and summary RR with 95% CI of number of participants achieving HbA1c < 7.0%. CI = confidence interval, HbA1c = hemoglobin A1c, RR = risk ratio.
3.4. Safety outcomes

The safety endpoints were AEs, SAEs, and hypoglycemic events. Totally 11 trials\(^{14-16,20-27}\) reported values on AEs. As shown in Fig. 6, there was no significant difference in the risk of AEs between omarigliptin and control group (RR 1.00, 95% CI [0.97, 1.03], \(P = .99\)). All 11 trials\(^{14-16,20-27}\) had reported information regarding SAEs (Fig. 7). The pooled evidence indicated that compared with control group, omarigliptin led to a slightly increase in this domain (RR 1.02, 95% CI [0.91, 1.13], \(P = .75\)). The hypoglycemic events was available on 10 trials\(^{14-16,21-27}\); the hypoglycemic events in omarigliptin are not more than that in control group (RR 0.86, 95% CI [0.48, 1.54], \(P = .61\)) (Fig. 8).

3.5. Subgroup analysis and publication bias

By dividing control group into placebo-controlled group and active-controlled group, we made subgroup analysis of all 6 outcomes. Compared with other AHAs, omarigliptin had similar results in reduction in HbA1c (MD \(-0.04\%\), 95% CI \([-0.18, 0.09]\), \(P = .54\)), reduction in FPG (MD \(-0.06\ mmol/L\), 95% CI \([-0.44 \ mmol/L, 0.32 \ mmol/L]\), \(P = .75\)), and the number of participants achieving HbA1c < 7.0% (RR 1.00, 95% CI [0.8, 1.25], \(P = 1.00\)). Patients in omarigliptin group had a stronger reduction HbA1c (MD 0.53%, 95% CI [0.36, 0.73], \(P < .00001\)), FPG (MD 0.78 mmol/L, 95% CI [0.54 mmol, 1.02 mmol], \(P < .00001\)), and more participants achieving HbA1c < 7.0% (RR 2.92, 95% CI [1.78, 4.79], \(P < .0001\)) compared to patients in placebo-controlled group. No difference was found in the incidence of AEs (RR 1.02, 95% CI [0.98, 1.05], \(P = .30\)) and SAEs (RR 1.00, 95% CI [0.90, 1.12], \(P = .96\)) between omarigliptin and placebo-controlled group, and omarigliptin slightly increased the risk of hypoglycemic events (RR 1.14, 95% CI [1.03, 1.27], \(P = .01\)). All outcomes of subgroup analysis were listed in Table 2.

All results of publication bias for each outcome were listed in Table 3. Except for the funnel plot of number of participants achieving HbA1c < 7.0% (Egger test: \(P = .002\)), all funnel plot did not reveal any asymmetry in any other outcomes.

4. Discussion

The meta-analysis of 8276 participants provided evidence about the efficacy and safety of omarigliptin in treating patients with T2DM. This meta-analysis confirmed that patients treated with omarigliptin had a significantly greater reduction in HbA1c, FPG, and a significantly stronger increase in the number of participants achieving HbA1c < 7.0% than patients treated with placebo or other AHAs. Pooled evidence indicated that there was no significant difference between omarigliptin and control group in terms of AEs, SAEs, and hypoglycemic events. In the subgroup analysis of placebo-controlled or active-controlled trials, we found that compared with placebo, omarigliptin had significantly reduced the level of HbA1c, FPG, and increased the number of participants achieving HbA1c < 7.0%. Omarigliptin had similar effects in HbA1c level, FPG level, number of participants achieving HbA1c < 7.0%, the prevalence of AEs, SAEs, and hypoglycemic events when compared with other AHAs.

Diabetes is a metabolic disease, mainly manifested as chronic hyperglycemia, abnormal metabolism of serum lipids and protein, whose complications seriously affect the quality of life...
**Figure 7.** Individual and summary RR with 95% CI of serious adverse events. CI = confidence interval, RR = risk ratio.

**Figure 8.** Individual and summary RR with 95% CI of hypoglycemic events. CI = confidence interval, RR = risk ratio.
of diabetic patients. Among all complications of diabetes, foot ulcers occupied the primary cause in the hospitalization of diabetic patients, and approximately 20% to 40% medical resources were used in the treatment of diabetic foot ulcers.[28,29] Nevertheless, related studies have shown that the incidence of diabetic foot ulcers was increasing at an annual rate of 5.8%. About 15% of these patients suffer from amputation, which not only reduces the quality of life, but also shortens their lifespan.[30]

Recently, several studies[31–33] had justified that DPP-4i might diminish scar formation by blocking DPP-4 activity. Long et al.[33] found that DPP-4i can improve diabetic wound healing by promoting the migration and epithelial–mesenchymal transition of keratinocytes in diabetic mice. Long et al.[33] also conducted a randomized clinical trial involving 67 patients with type 2 diabetes to further confirm the effects of DPP-4i on diabetic wound healing. The results indicated that DPP-4i accelerated diabetic wound healing at different phases of the wound repair process. All of these findings support the application of DPP-4i in the treatment of diabetic patients with ulcers.

Incretin-based therapies include glucagon-like peptide-1 receptor agonists (GLP-1s) and DPP-4i. GLP-1s and DPP-4i both directly and indirectly strengthen the function of glucagon-like peptide-1 which stimulates insulin secretion and decreases glucagon release in a glucose-dependent manner.[31] Elashoff et al.[34] reported that increased risks of both pancreatitis and pancreatic cancer were associated with the use of incretin drugs. Meta-analysis conducted by Wang et al.[35] included 79,971 T2DM patients of 33 trials; the results showed that the overall pancreatitis risk was not increased in the incretin group compared with the control group (odds ratio 1.12, 95% CI [0.85, 1.47]). All 11 included trials concerning omarigliptin referred to the information on pancreatitis, and we analyzed the risk of pancreatitis in these trials. The outcome indicated that there was no difference in the risk of pancreatitis between omarigliptin and control group (RR 0.78, 95% CI [0.29, 2.09]); this result was in accordance with the conclusions obtained by Wang et al.[35]

The issue of nonadherence to AHAs is an enormous challenge in T2DM patients.[8,9,36] Nonadherence and nonpersistence with medications in T2DM are associated with worse outcomes, including poorer glycemic control, more complications, and higher overall costs.[9–12] Mody et al.[37] had discovered that long-acting AHAs such as dulaglutide had a good adherence and improved all selected glycemic control metrics such as mean HbA1c, proportion of patients with HbA1c <7%. At present, once-weekly DPP-4i like omarigliptin and trelagliptin and GLP-1s like albiglutide, dulaglutide, and exenatide had been developed, which can overcome the challenge of nonadherence to long-term medication to some degree.[9,38] This series of long-acting AHAs may contribute to improve the degree of blood glucose control in T2DM.

To the best of our knowledge, there is 1 recently published meta-analysis[40] which has mentioned the efficacy and safety of once-weekly DPP-4i for T2DM patients. They also recommended omarigliptin for T2DM which is consistent with our results. Compared with this analysis, first we focused on the efficacy and safety of omarigliptin as monotherapy or add on to other AHAs in patients with T2DM. Second, we included 8276 patients in 11 trials which are far more than 5173 patients they have included in omarigliptin’s study. Third, the quality of the all included studies in our meta-analyses were assessed with Cochrane Collaboration’s tool, whereas overall risk of bias was unclear in most studies which were included in analysis conducted by Stoinenis et al.[40] Moreover, we have made subgroup analysis for omarigliptin according to different treatment methods in control group (placebo-controlled and active-controlled).

Cardiovascular safety is an important safety index which was required to be tested by US Food and Drug Administration for new therapies. Gantz et al.[15] had tested the cardiovascular safety of omarigliptin in 4202 patients with T2DM. The results indicated that compared with placebo, omarigliptin did not increase the risk of major adverse cardiovascular safety event (the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and hospitalization for heart failure, which are

### Table 2
Summary of subgroup analyses for type 2 diabetes mellitus patients.

| Outcomes                      | Subgroup                  | Included studies | Included patients | Statistical method | RR/MD (95% CI) | P for interaction |
|-------------------------------|---------------------------|------------------|-------------------|--------------------|----------------|------------------|
| Reduction in HbA1c            | Placebo controlled        | 9                | 6704              | MD (I-V, random, 95% CI) | 0.55 (0.36, 0.73) | <.00001          |
|                               | Active controlled         | 3                | 1722              | MD (I-V, random, 95% CI) | 0.91 (0.83, 1.00) | .35              |
| Reduction in FPG              | Placebo controlled        | 8                | 2512              | MD (I-V, random, 95% CI) | 0.78 (0.54, 1.02) | .003             |
|                               | Active controlled         | 3                | 1722              | MD (I-V, random, 95% CI) | 0.38 (0.09, 1.53) | .12              |
| Number of participants        | Placebo controlled        | 7                | 2309              | RR (M-H, random, 95% CI) | 2.92 (1.78, 4.79) | .0001            |
| achieving HbA1c <7.0%         | Active controlled         | 3                | 1722              | RR (M-H, random, 95% CI) | 1.00 (0.8, 1.25) | .03              |
| Adverse events                | Placebo controlled        | 9                | 6704              | RR (M-H, random, 95% CI) | 1.02 (0.98, 1.05) | .00001           |
|                               | Active controlled         | 3                | 1722              | RR (M-H, fixed, 95% CI) | 0.91 (0.83, 1.00) | .35              |
| Serious adverse events        | Placebo controlled        | 9                | 6704              | RR (M-H, fixed, 95% CI) | 1.00 (0.90, 1.12) | .35              |
|                               | Active controlled         | 3                | 1722              | RR (M-H, fixed, 95% CI) | 1.26 (0.70, 2.02) | .12              |
| Hypoglycemic events           | Placebo controlled        | 8                | 6456              | RR (M-H, fixed, 95% CI) | 1.14 (1.03, 1.27) | .00001           |
|                               | Active controlled         | 2                | 1392              | RR (M-H, random, 95% CI) | 0.38 (0.09, 1.53) | .12              |

CI = confidence interval, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, MD = mean difference, RR = risk ratio.

### Table 3
Results of P value for Egger test.

| Outcomes                      | Included studies | P for Egger test |
|-------------------------------|------------------|-----------------|
| Reduction in HbA1c            | 11               | .848            |
| Reduction in 2 h PMG          | 5                | .637            |
| Reduction in FPG              | 10               | .298            |
| Number of participants        | 9                | .002            |
| achieving HbA1c <7.0%         | 11               | .871            |
| Serious adverse events        | 11               | .625            |
| Adverse events                | 10               | .481            |
| Hypoglycemic events           | 10               | .481            |

FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, PMG = postmeal plasma glucose.
consistent with daily DPP-4 inhibitors. Therefore, omarigliptin is generally well tolerated in patients with T2DM and established cardiovascular disease in terms of cardiovascular safety.

Patients in 7 studies of 15, 16, 23, 24, 26 out of all 11 included studies used other kinds of antidiabetic drugs except for omarigliptin. Meformin, sulfonylurea, sitagliptin, pioglitazone, and sodium-glucose co-transporter 2 inhibitors were major hypoglycemic drugs used in T2DM patients included in our study. For different hypoglycemic mechanisms, when combined with omarigliptin, meformin, sulfonylurea, pioglitazone, and sodium-glucose co-transporter 2 inhibitors usually have better efficacy than they use alone in T2DM patients.

We noted several limitations in this study. First, the power of our analysis may be restricted because of the limited study numbers and population sizes. Second, Ira Gantz201701 [15] is a large trial which account about 50% of participants in the meta-analysis, therefore its results drove much of the findings. Third, there was significant heterogeneity in some outcomes. Our research is a study-level meta-analysis; studies varied in relation to the study population, combined treatment method, and treatment duration. All of these confounding factors may contribute to heterogeneity in some outcomes. Finally, only published data were included, which may lead to a reporting bias by overestimating the effect of omarigliptin. This study also had some advantages. The general quality of the included trials was good. Furthermore, this is the first meta-analysis which has evaluated the efficacy and safety of once-weekly DPP-4i omarigliptin in T2DM patients.

In conclusion, omarigliptin had a favorable efficacy and safety as monotherapy or add on to other AHAs in treating T2DM patients. It maybe a superior choice for T2DM patients who have a poor adherence to daily AHAs or T2DM patients with ulcers. Omarigliptin has obviously better efficacy than placebo and similar safety profile to placebo. Omarigliptin is noninferior to other AHAs in improving glycemic control and is generally well tolerated.

Author contributions

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References

[1] International Diabetes Federation. Diabetes Atlas. 8th ed. International Diabetes Federation, Brussels, Belgium 2017.
[2] Mukerji I, Iro D, Jaspers L, et al. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. Eur J Epidemiol 2015;30:251–77.
[3] Matter J, Malik V, Wedick NM, et al. Reducing the global burden of type 2 diabetes: a collaborative review and planning exercise. The Global Nutrition and Epidemiologic Transition Initiative. Global Health 2015;11:23.
[4] Garber AJ, Abrahamson MJ, Bazzarly JR, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2017 executive summary. Endocr Pract 2017;23:207–38.
[5] Pratley RE, Salasi A. Inhibition of DPP-4: a new therapeutic approach for the treatment of type 2 diabetes. Curr Med Res Opin 2005;21:919–31.
[6] Inuzuchi N, Bergenthal L, Rose JB, et al. Management of hypergylcaemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–79.
[7] McGovern A, Hinton W, Calderara S, et al. A class comparison of medication persistence in people with type 2 diabetes: a retrospective observational study. Diabetes Ther 2018;9:229–42.
[8] Iglyk K, Carrier SE, Rosen VM, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. Curr Med Res Opin 2015;31:1283–96.
[9] Egede LE, Gebregziabher M, Dismuke CE, et al. Medication non-adherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. Diabetes Care 2012;35:2533–9.
[10] McGovern A, Tippu Z, Hinton W, et al. Systematic review of adherence rates by medication class in type 2 diabetes: a study protocol. BMJ Open 2016;6:e010469.
[11] Currie CJ, Peyrot M, Morgan CLL, et al. The impact of treatment noncompliance on mortality in people with type 2 diabetes. Diabetes Care 2012;35:1279–84.
[12] Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. Clin Ther 2011;33:74–109.
[13] Bifro T, Sinha-Roy R, Chen P, et al. Omarigliptin (MK-3102): a novel long-acting DPP-4 inhibitor for once-weekly treatment of type 2 diabetes. J Med Chem 2014;57:3205–12.
[14] Chacra A, Gantz I, Mendizabal G, et al. A randomised, double-blind, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Curr Med Res Opin 2017;33:1861–8.
[15] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[16] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
[17] Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated September 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
[18] Gantz I, Okamoto T, Ino Y, et al. A randomized, placebo- and sitagliptin-controlled trial of the safety and efficacy of omarigliptin, a once-weekly DPP-4 inhibitor, or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Curr Med Res Opin 2017;33:1861–8.
[19] Handelsman Y, Laurant B, Gantz I, et al. A randomized, double-blind, non-inferiority trial evaluating the efficacy and safety of omarigliptin, a once-weekly DPP-4 inhibitor, or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Curr Med Res Opin 2017;33:1861–8.
[20] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[21] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
[22] Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated September 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
[23] Gantz I, Okamoto T, Ino Y, et al. A randomized, placebo- and sitagliptin-controlled trial of the safety and efficacy of omarigliptin, a once-weekly dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes. Diabetes Obes Metab 2017;19:1602–9.
[24] Gantz I, Okamoto T, Ino Y, et al. A randomized, placebo-controlled trial evaluating the safety and efficacy of adding omarigliptin to antihyperglycemic therapies in Japanese patients with type 2 diabetes and inadequate glycemic control. Diabetes Ther 2017;8:793–810.
[25] Gantz I, Sokolova I, Lai J, et al. Use of prohibited medication, a potentially overlooked confounder in clinical trials: omarigliptin (once-weekly DPP-4 inhibitor) monotherapy trial in 18- to 45-year-olds. Clin Ther 2017;39:2024–37.
[26] Homs P, Ravi Shankar R, Gantz I, et al. A randomized, double-blind trial evaluating the efficacy and safety of monotherapy with the once-weekly dipeptidyl peptidase-4 inhibitor omarigliptin in patients with type 2 diabetes. Diabetes Res Clin Pract 2018;138:253–61.
inadequately controlled on metformin monotherapy. Curr Med Res Opin 2017;33:1853–60.

[25] Goldenberg R, Gantz I, Andryuk PJ, et al. Randomized clinical trial comparing the efficacy and safety of treatment with the once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor omarigliptin or the once-daily DPP-4 inhibitor sitagliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab 2017;19:394–400.

[26] Lee SH, Gantz I, Round EA, et al. A randomized, placebo-controlled clinical trial evaluating the safety and efficacy of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes inadequately controlled by glimepiride and metformin. BMC Endocr Disord 2017;17:70.

[27] Sheu WH, Gantz I, Chen M, et al. Safety and efficacy of omarigliptin (MK-3102), a novel once-weekly DPP-4 inhibitor for the treatment of patients with type 2 diabetes. Diabetes Care 2015;38:2106–14.

[28] Bakker K, Apelqvist J, Schaper NC, et al. Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes Metab Res Rev 2012;28(suppl 1):225–31.

[29] Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, et al. The global burden of diabetic foot disease. Lancet 2005;366:1719–24.

[30] Abbott CA, Vileikyte L, Williamson S, et al. Multicenter study of the incidence and of predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care 1998;21:1071–5.

[31] Rinkevich Y, Walmsey GG, Hu MS, et al. Skin fibrosis. Identification and isolation of a dermal lineage with intrinsic fibrogenic potential. Science 2015;348:aaal2151.

[32] Leavitt T, Hu MS, Marshall CD, et al. Scarless wound healing: finding the right cells and signals. Cell Tissue Res 2016;365:483–93.

[33] Long M, Cai L, Li W, et al. DPP-4 inhibitors improve diabetic wound healing via direct and indirect promotion of epithelial-mesenchymal transition and reduction of scarring. Diabetes 2018;67:518–31.

[34] Elzahho M, Matteyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1 based therapies. Gastroenterology 2011;141:150–6.

[35] Wang H, Liu Y, Tian Q, et al. Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: a meta-analysis of randomised controlled trials. Diabetes Obes Metab 2018;20:910–20.

[36] McGovern A, Tippu Z, Hinton W, et al. Comparison of adherence and persistence by medication class in type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2017;20:1040–5.

[37] Mody R, Grabner M, Yu M, et al. Real-world effectiveness, adherence and persistence among patients with type 2 diabetes mellitus initiating dulaglutide treatment. Curr Med Res Opin 2018;34:995–1003.

[38] Grimshaw CE, Jennings A, Kamran R, et al. Trelagliptin (SYR-472, Zafatek), novel once-weekly treatment for type 2 diabetes, inhibits dipeptidyl peptidase-4 (DPP-4) via a non-covalent mechanism. PLoS ONE 2016;11:e0157509.

[39] Ding L, Lu S, Wang Y, et al. BPI-3016, a novel long-acting hGLP-1 analogue for the treatment of type 2 diabetes mellitus. Pharmacol Res 2017;122:130–9.

[40] Stoimenis D, Karagiannis T, Katsoula A, et al. Once-weekly dipeptidyl peptidase-4 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Expert Opin Pharmacother 2017;18:843–51.