EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2025;40:258-267
https://doi.org/10.3803/EnM.2024.2120
pISSN 2093-596X · eISSN 2093-5978

# Effectiveness and Safety of Oral Quadruple Combination Therapy in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

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**Background:** Achieving optimal glucose control is essential in the management of type 2 diabetes (T2D). This study aimed to evaluate the effectiveness and safety of oral quadruple combination therapy for the treatment of T2D.

**Methods:** This meta-analysis reviewed original research on oral quadruple combination therapy for T2D, including both experimental and observational studies with a minimum duration of 12 weeks. The primary endpoint was the change in glycated hemoglobin (HbA1c) from baseline to follow-up. The secondary endpoint was the incidence rate of adverse events. Two investigators independently extracted data and assessed the risk of bias. Outcomes were pooled as the standardized mean difference (using Hedge's *g*) and the risk ratio for adverse events in random-effects meta-analyses.

**Results:** The meta-analysis included 17 studies. Oral quadruple combination therapy resulted in an additional mean reduction in HbA1c levels of 1.1% in patients who did not achieve glycemic control with oral triple combination therapy. Compared with switching to injectables, such as insulin or a glucagon-like peptide-1 receptor agonist–containing regimen, this therapy was non-inferior, even demonstrating a slightly superior glucose-lowering effect. Furthermore, it was determined to be safe, with an adverse event rate of 0.25, indicating no significant difference in safety compared with adding a placebo or switching to an injectable-containing regimen.

**Conclusion:** Oral quadruple combination therapy is a valid option for patients with T2D who are unable to achieve glycemic targets with oral triple combination therapy, offering both effective glycemic control and a favorable safety profile.

**Keywords:** Diabetes mellitus, type 2; Hypoglycemic agents; Meta-analysis

## INTRODUCTION

Type 2 diabetes (T2D), a chronic disease with progressive characteristics, arises and progresses through multiple pathological mechanisms [1]. Consequently, it is often challenging to maintain target blood glucose levels with monotherapy alone, and combination therapy involving two or more drugs is typically necessary. When glycemic control is not achieved with combination therapy of two or more oral antidiabetic drugs (OADs), a transition to insulin therapy or glucagon-like peptide-1 receptor

**Received:** 29 July 2024, **Revised:** 1 October 2024, **Accepted:** 5 November 2024

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agonist (GLP-1RA) injection therapy is commonly recommended [2,3]. However, these injection therapies are generally not well accepted by patients, and the gastrointestinal adverse effects of GLP-1RAs and the increased risk of hypoglycemia associated with insulin therapy amplify this resistance [4].

In Korea, a single health insurance system insures the entire population and typically covers up to three OADs. Transitioning to injection therapy is advised for patients who do not reach target glucose levels with triple combination therapy by the insurance system. However, only 7.5% of adults with previously diagnosed diabetes in Korea were treated with insulin, and the prescription rate for GLP-1RAs was approximately 1% [5], showing the resistance to the transition to injection therapy mentioned above.

Given these challenges, oral quadruple combination therapy presents a viable alternative in the pharmacological treatment of T2D. The development of dipeptidyl peptidase 4 (DPP4) inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors in the 21st century has enriched the available arsenal of safe and effective OADs, enabling the prescription of quadruple combinations suited to individual patient characteristics.

Research on oral quadruple combination therapies has been reported since the mid-2010s [6-22]. The studies have been primarily conducted in Korea, where they are significantly affected by the National Health Insurance system, and have shown that oral quadruple combination therapy can produce excellent blood glucose-lowering effects in patients inadequately controlled with triple OAD treatments. Furthermore, several studies have reported outcomes that are comparable to or even surpass those achieved with therapies including GLP-1RAs or basal insulin [6,7,18].

Despite these promising results, no comprehensive systematic review or meta-analysis has examined the disparate data concerning oral quadruple combination therapy. Therefore, we aimed to conduct a systematic review and meta-analysis to evaluate the effectiveness and safety of oral quadruple combination therapy in managing T2D.

## METHODS

This systematic review and meta-analysis have been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1) [23,24]. This review has been registered in the International Prospective Register of Systematic Reviews (CRD42024581404).

### Literature search and study selection

We systematically searched PubMed and the Cochrane Library for all relevant studies that were published up to January 2024. The search strategy is provided in Supplemental Tables S1, S2. After removing duplicates, the titles and abstracts of the search results were screened for relevance. Case reports, review articles, editorials, and studies that were not original research or lacked results were excluded. The full texts of the remaining results were independently assessed in duplicate by two authors (J.B. and M.H.Y.) for inclusion based on predetermined criteria. The final list of included studies was decided through discussion between the authors, with full agreement required for inclusion. Disagreements were resolved through discussion or by a third reviewer (B.W.L.).

Studies were considered eligible for inclusion if they (1) enrolled participants with T2D; (2) included patients on oral quadruple combination therapy; (3) had a follow-up period of at least 12 weeks; (4) included glycated hemoglobin (HbA1c) data; and (5) included only adult subjects (age ≥18 years).

### Data extraction and quality assessment

We extracted basic information about the studies, such as the authors, research design, publication year, study drug, follow-up duration, and number of participants. For glucose-lowering effectiveness, we extracted data on the change in HbA1c from baseline to follow-up as the primary outcome. When available, we also extracted data on all reported adverse events to evaluate the safety of oral quadruple combination therapy.

Study quality was evaluated using the Cochrane risk of bias (ROB) tool for randomized controlled trials (RCTs) and the Newcastle Ottawa scale (NOS) for non-RCTs and cohort studies (Supplemental Tables S3, S4) [25,26]. When evaluating studies with the ROB tool, if mentioned in the paper, the study was judged to have a low ROB and rated as 'low.' If not mentioned or ambiguously expressed in the literature, it was considered 'unclear.' If not conducted or conducted using inappropriate methods according to the literature, it was judged to have a high ROB and rated as 'high.' The evaluation using the NOS was conducted by assigning each study a score between 0 and 9; the average score of the selected studies for the final analysis was 8.43.

### Statistical analysis

The baseline to follow-up difference in HbA1c was calculated using the standardized mean difference (SMD; Hedge's g) with 95% confidence interval (CI). Adverse event rates were calcu-

lated as relative risk values with 95% CIs to compare quadruple combination therapy with other treatments. We used the $I^2$ statistic to quantify the degree of heterogeneity among the studies in each meta-analysis. The random-effects model was incorporated to derive the overall estimates in all meta-analyses to account for potential heterogeneity between studies. Publication bias was assessed through Egger's tests. As a sensitivity analysis, we performed a trim-and-fill analysis when publication bias was suggested. We used R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) for data analysis. Two-sided $P$ values less than 0.05 were considered statistically significant.

## RESULTS

### Selection and characteristics of studies

Fig. 1 provides a flow chart illustrating the inclusion and exclusion of studies. A total of 29,161 studies were initially identified from the PubMed and Cochrane databases. Out of these, 3,179 were removed as duplicates through automatic filtering by Endnote software. Subsequently, 25,982 studies were screened based on their title and abstract; the full manuscript was reviewed when necessary. From these, 35 records related to quadruple combination therapy were identified and subjected to further review. At this stage, we excluded six clinical registry records, four conference abstracts, one epidemiologic study not addressing clinical outcomes, and one study that only included quadruple combination therapy as a factor in regression analysis. The 23 remaining studies investigated the effectiveness or safety of quadruple combination therapy in T2D. In the final review process, we excluded one article that incorporated insulin into the quadruple therapy regimen, two articles with unclear study designs, and three articles that did not have designs that switched from the oral triple combination therapy to oral quadruple combination therapy in patients with T2D. As a result, 17 studies were finally included in our meta-analysis.

Of the 17 articles, four were experimental, three of which were RCTs. Five articles were observational, prospective cohort

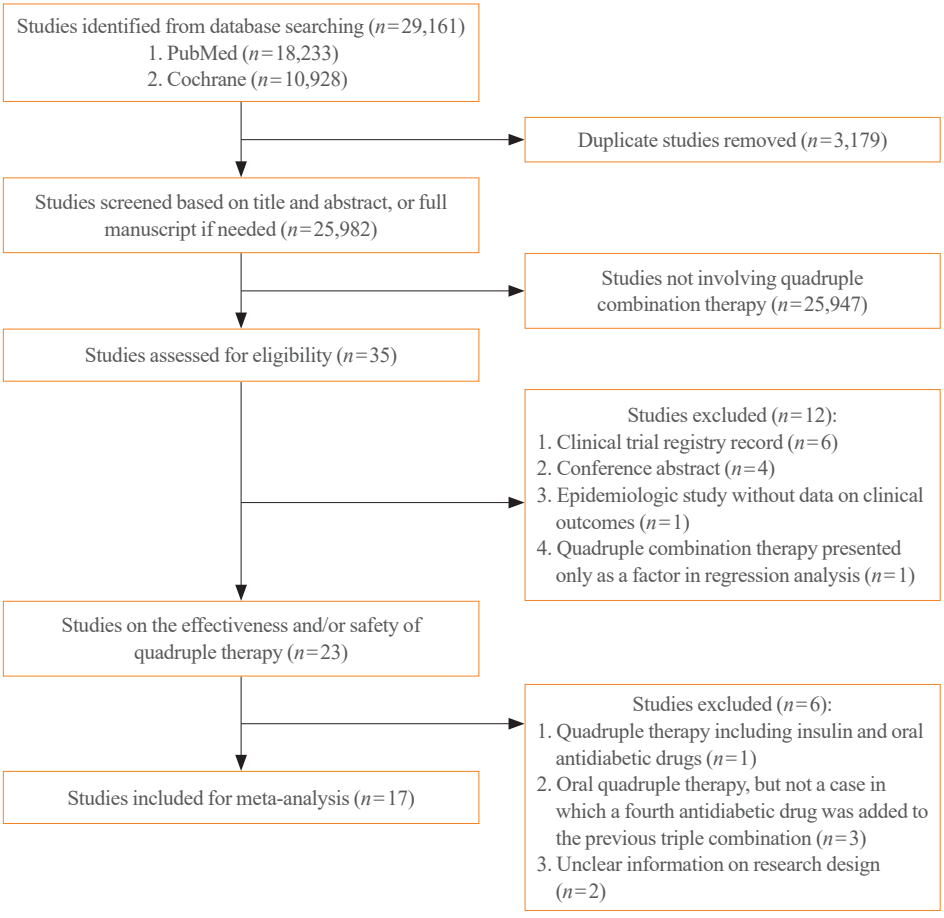


**Fig. 1.** Flow diagram of study selection for the current systematic review.

studies, and the remaining eight were observational, retrospective studies. The mean observation period was approximately 46 weeks. Altogether, the 17 articles included 22 treatment groups with 3,511 total patients receiving various forms of oral quadruple combination therapy, which were analyzed for their glucose-lowering effects, the primary outcome of this study. The characteristics of the included studies are summarized in Supplemental Table S5.

### Glucose-lowering effects of oral quadruple combination therapy

All 17 articles provided data on changes in HbA1c following the addition of a fourth OAD to triple combination therapy, initiating oral quadruple combination therapy.

### The extent of the glucose-lowering effect with oral quadruple combination therapy

In a meta-analysis that included 22 oral quadruple combination therapy groups from 17 experimental and observational studies, quadruple therapy achieved a reduction in HbA1c of 1.11%, with a 95% CI ranging from −1.22% to −0.99% (Fig. 2). The sensitivity analysis using the trim-and-fill technique showed a similar result (SMD, −0.89; 95% CI, −1.03 to −0.75). This glucose-lowering effect was consistent across various study designs, including experimental, prospective observational, and retrospective observational studies, as shown in Supplemental Fig. S1. In addition, this effect was consistently observed in the subgroup analysis based on an HbA1c level of 9.0% ($P$=0.19) (Supplemental Fig. S2), and the result remained similar when a meta-analysis was conducted by study (17 studies) rather than by treatment groups (Supplemental Fig. S3) [27].

### Comparison of oral quadruple combination therapy with regimens including injectables

We identified two previous studies—one experimental RCT [6] and one observational retrospective cohort [8]—that compared the glucose-lowering effects of transitioning to oral quadruple combination therapy versus switching to a regimen of GLP-1RA and two OADs in patients with T2D who failed to achieve glycemic control with triple combination therapy. The transition from oral triple combination therapy to oral dual combination therapy with GLP-1RA reflects the reimbursement standards in Korea. The meta-analysis results did not show the significant differences between oral quadruple combination therapy and a regimen of GLP-1RA (SMD, −0.18; 95% CI, −0.41 to 0.05) (Fig. 3A). However, in the RCT, oral quadruple combination therapy was shown to be superior, exhibiting an SMD of −0.26 (95% CI, −0.50 to −0.02). Conversely, the observational retrospective study reported similar glucose-lowering effects between the therapies (SMD, 0.0; 95% CI, −0.40 to 0.40).

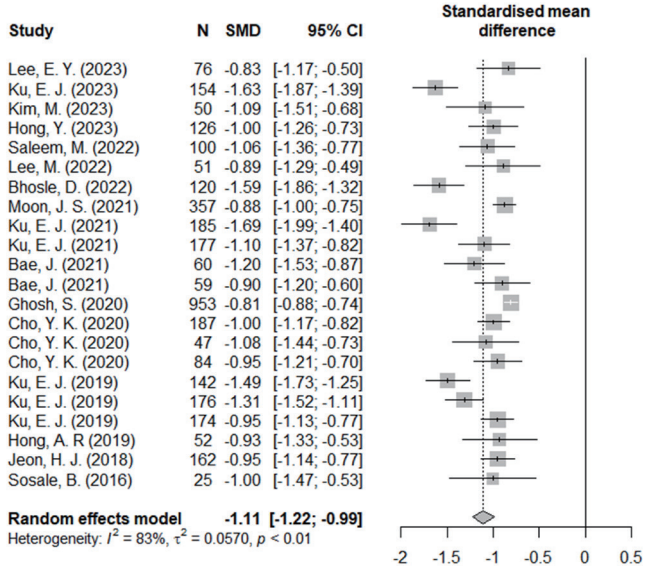


Fig. 2. Meta-analysis of the glucose-lowering effects of oral quadruple combination therapy in all 22 groups in 17 studies. SMD, standardized mean difference; CI, confidence interval.

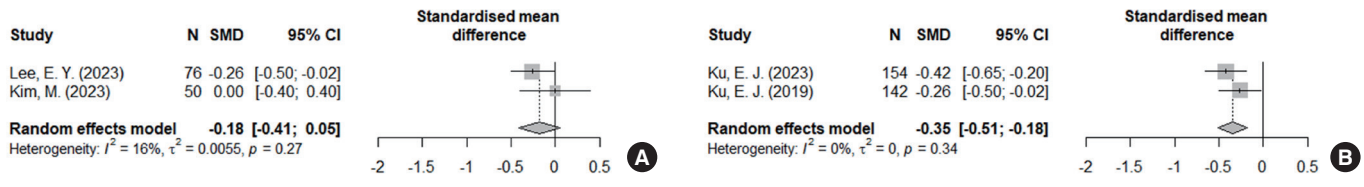


Fig. 3. Meta-analysis comparing the glucose-lowering effects between oral quadruple combination therapy and regimens including injectable agents in patients with type 2 diabetes who did not achieve adequate blood glucose levels: (A) comparison between adding a fourth oral antidiabetic drug (OAD) for oral quadruple combination therapy and switching to a combination of two OADs and glucagon-like peptide-1 receptor agonist, and (B) comparison between oral quadruple therapy and adding basal insulin to previous triple therapy. SMD, standardized mean difference; CI, confidence interval.

No studies compared patients who did not achieve glycemic targets with oral triple combination therapy and then switched to a combination of two OADs and insulin against those who transitioned to oral quadruple combination therapy. However, two observational cohorts [7,18] compared the addition of basal insulin to the existing triple therapy versus oral quadruple combination therapy. These studies demonstrated that oral quadruple combination therapy had a significantly better glucose-lowering effect compared with adding basal insulin to triple combination therapy (SMD, −0.35; 95% CI, −0.51 to −0.18) (Fig. 3B).

### Comparison of oral quadruple combination therapies based on their drug composition

The oral quadruple combination therapy in previous studies can be classified into three categories based on which class of OAD was added as the fourth medication.

The first category added an SGLT2 inhibitor. Except for Bhosle et al. [12], all studies in this category added an SGLT2 inhibitor to triple combination therapy consisting of metformin, sulfonylurea, and a DPP4 inhibitor [6,7,9,10,14,15,17-22]. In the study by Bhosle et al. [12], the composition of the triple combination therapy regimens before adding the SGLT2 inhibitor was heterogeneous. When studies in this category added an SGLT2 inhibitor as the fourth drug, it reduced the HbA1c by 1.17% (Supplemental Fig. S4).

The second category added thiazolidinedione (TZD) as the fourth OAD. The two studies in this category added TZD to triple combination therapy consisting of metformin, sulfonylurea, and a DPP4 inhibitor [15,17], which showed a reduction in HbA1c of 0.97%.

Lastly, three studies added a DPP4 inhibitor [11,16,17] to different triple combination regimens: metformin+sulfonylurea+SGLT2 inhibitor, metformin+sulfonylurea+α-glucosidase inhibitor, or metformin+sulfonylurea+TZD. In these studies, the meta-analysis showed a reduction in HbA1c of 0.82%.

We found a statistically significant difference ($P<0.01$) in the glucose-lowering effects across these three categories of oral quadruple therapy: SGLT2 inhibitors showed the most potent effect when added as the fourth OAD, followed by TZD and DPP4 inhibitors.

### Safety data of oral quadruple combination therapy

Among the 17 articles included in the meta-analysis for glycemic effectiveness, eight articles provided data on adverse events across 11 treatment groups [6,8,11,14,15,18,19,21]. The safety meta-analysis of these 11 treatment groups showed an adverse event rate of 0.24 (Supplemental Fig. S5).

One study compared the adverse event rate of oral quadruple combination therapy with a placebo group [11], two studies compared it with a GLP-1RA group [6,8], and two studies compared it with an insulin group [18,21]. In the study comparing the oral quadruple combination therapy with the placebo group, patients with T2D who were on triple combination therapy of metformin, sulfonylurea, and SGLT2 inhibitor were given either a placebo or a DPP4 inhibitor (teneligliptin). The most commonly observed adverse events in the quadruple combination therapy group were hypoglycemia and gastrointestinal disorder, but the percentage was not statistically different. In studies comparing oral quadruple combination therapy with regimens including GLP-1RA or insulin, the adverse events occurred at expected levels for the added medications. For instance, when the SGLT2 inhibitor was added as the fourth OAD, genitourinary infections were more common; when switched to GLP-1RA, gastrointestinal disorders were predominant; and when switched to insulin regimen, hypoglycemia was the main adverse event observed.

There were no statistically significant differences in the rates of adverse events between oral quadruple combination therapy and the comparator groups in our meta-analysis (Fig. 4).

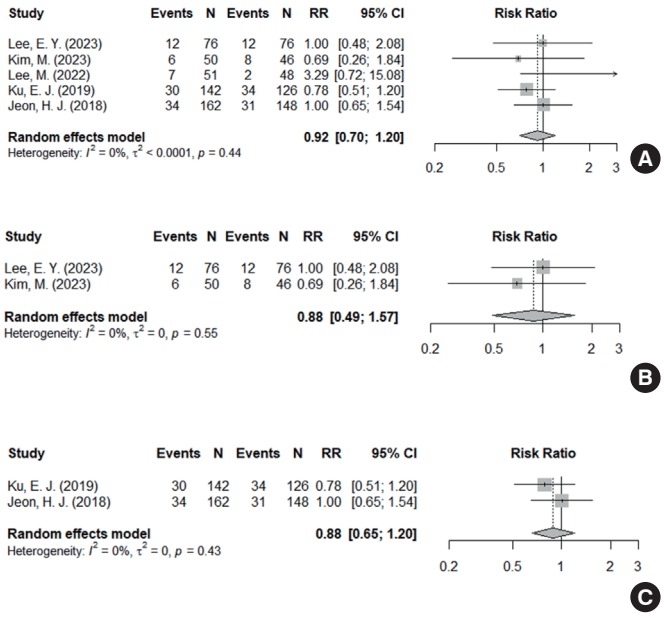


**Fig. 4.** Meta-analysis of the incidence rate of adverse events of oral quadruple combination therapy versus comparator groups that received (A) placebo and injectables, (B) glucagon-like peptide-1 receptor agonist, and (C) insulin. RR, relative risk; CI, confidence interval.

## DISCUSSION

We derived four significant findings from this systematic review and meta-analysis. First, the addition of a fourth OAD to patients with T2D who did not achieve glycemic control (mean HbA1c, 8.88%; 95% CI, 8.56% to 9.21%) with oral triple combination therapy led to a further mean reduction in HbA1c levels of 1.1%. This finding suggests that transitioning from a triple to quadruple combination therapy provides a significant glucose-lowering effect, considering the usual efficacy of single OADs [28]. Second, oral quadruple combination therapy was not inferior to the addition of basal insulin or switching from oral triple combination therapy to a combination of oral dual therapy and GLP-1RA. In this meta-analysis, oral quadruple combination therapy was more effective than adding basal insulin, and the results of an RCT indicated a stronger glucose-lowering effect compared with a GLP-1RA–containing regimen. These results suggest that oral quadruple combination therapy could be a valid option for patients with T2D who do not achieve glycemic targets with oral triple combination therapy. Third, when choosing the fourth OAD for patients with T2D on oral triple combination therapy, SGLT2 inhibitors, if not previously used, appear to be the most effective for glycemic reduction. Although patients' characteristics and prior medication history should be considered, our meta-analysis ranked SGLT2 inhibitors as the most potent addition, followed by TZD and DPP4 inhibitors. Finally, oral quadruple combination therapy was found to be safe, with an adverse event rate of 0.25, indicating relative safety with no significant difference compared with adding a placebo, switching to a GLP-1RA–containing regimen, or adding basal insulin to the previous oral triple combination therapy. This finding supports the notion that oral quadruple combination therapy balances effectiveness and safety.

T2D is a chronic metabolic disease that develops and progresses through complex pathophysiological processes affecting various organs [29,30]. Combining OADs with four different mechanisms of action is considered beneficial for patients with T2D because they simultaneously control multiple pathological pathways, which aligns with previous studies on early combination therapies [31-33]. In particular, as with the general principles of combination therapy for T2D [2,28], adding a fourth OAD without delay for patients who do not achieve their glycemic target with triple combination therapy is expected to yield a favorable long-term prognosis.

Nonetheless, certain patients with T2D might need to transition to injectable therapies, such as GLP-1RAs and insulin. For example, some patients require a swift transition to GLP-1RA–containing regimens due to their pronounced glucose-lowering efficacy, weight loss benefits, cardiovascular benefits, and renoprotective effects [2,28]. In addition, prompt initiation of insulin therapy is crucial for patients with severe hyperglycemia with catabolic features or other typical symptoms, especially for those with a prolonged history of T2D who may require multiple insulin injections.

Therefore, although this meta-analysis supports the use of oral quadruple combination therapy for patients with T2D inadequately controlled by oral triple therapy, it does not suggest that this therapy should universally replace injectable options. Instead, our results indicate that oral quadruple combination therapy is an effective and safe alternative for those unable to meet glycemic targets with oral triple therapy and are either unsuitable for or reluctant to commence injectable treatments

Several limitations of the present meta-analysis should be considered in the interpretation of the results. First, the quality of the studies included in our meta-analysis was not homogeneous, possibly introducing bias. The diversity of the study designs, including only three RCTs and many studies with short observation durations, further complicates the analysis. Additionally, the limited overall number of studies and participants underscores the necessity for more comprehensive RCTs with extended follow-up periods to definitively affirm these findings. Second, the restricted number of studies comparing oral quadruple combination therapy with injectable regimens also constrained the analysis. Third, few studies on oral quadruple combination therapy provided safety data. Lastly, a significant number of the participants included in the study were Korean, limiting the generalizability of these findings to all ethnic groups. This phenomenon is attributed to the region-specific characteristics of Korea, where there is a higher necessity to verity the effectiveness and safety of the oral quadruple therapy for patients with T2D under its unique national insurance system. Further studies that sufficiently include other ethnic groups are needed in the future. Despite these limitations, this study is significant as it is the first meta-analysis to thoroughly evaluate the effectiveness and safety of oral quadruple combination therapy in T2D patients.

In conclusion, oral quadruple combination therapy is a safe and effective treatment option for patients with T2D who fail to achieve adequate glycemic control (mean HbA1c, 8.88%) with oral triple combination therapy. Notably, oral quadruple combination therapy was not inferior to—and was sometimes even more effective than—switching to regimens that include inject-

ables, such as GLP-1RA or insulin. However, further large-scale, long-term studies and subsequent meta-analyses incorporating these studies are needed to validate the long-term effectiveness and safety of oral quadruple combination therapy in patients with T2D.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTIONS

Conception or design: J.B., M.H.Y., B.W.L. Acquisition, analysis, or interpretation of data: J.B., M.H.Y., B.W.L. Drafting the work or revising: J.B., M.H.Y., B.W.L. Final approval of the manuscript: J.B., M.H.Y., M.L., B.S.C., B.W.L.

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**Appendix 1.** PRISMA 2020 Checklist

| Section and topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **Title** | | | |
| Title | 1 | Identify the report as a systematic review. | 1 |
| **Abstract** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 2 |
| **Introduction** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 4–5 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 5 |
| **Methods** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 5–6, Fig. 1 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 5–6 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 5–6, Supplemental Table S1 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 5–6 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 6 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 6, Supplemental Table S4 |
| | 10b | List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 6, Supplemental Table S4 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 6, Supplemental Tables S2, S3 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results. | 7 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]). | 7 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 7 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 7 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 7 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression). | 7 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 7 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 7 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 5–6 |

(*Continued to the next page*)

**Appendix 1.** Continued

| Section and topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **Results** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 7, Fig. 1 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | NA |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 7–8, Supplemental Table S4 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | 6, Supplemental Tables S2, S3 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots. | 7–11, Figs. 2–4 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 7–11, Figs. 2–4 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 7–11, Figs. 2–4 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 8–10 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 9, Fig. 3 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 9 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 6 |
| **Discussion** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 11–14 |
| | 23b | Discuss any limitations of the evidence included in the review. | 13–14 |
| | 23c | Discuss any limitations of the review processes used. | 13–14 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 13–14 |
| **Other information** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 5 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 5 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 14 |
| Competing interests | 26 | Declare any competing interests of review authors. | 14 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | NA |

Adapted from Page et al. [24].
PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; NA, not available.