

DIABETES MEDICATIONS AS MONOTHERAPY OR METFORMIN - BASED COMBINATION THERAPY FOR TYPE 2 DIABETES : A SYSTEMATIC REVIEW

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Abstract

Introduction: Early combination therapy may reduce glucotoxicity. This method may improve insulin sensitivity and preserve β -cell bulk and function. 10 Early combination therapy with several antihypertensive agents may increase costs and patient compliance due to the number of pills, but a fixed-dose medication combination can help.

The aim: This article compared monotherapy or metformin - based combination therapy for type 2 diabetes medications.

Methods: By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Result: In the PubMed database, the results of our search brought up 88 articles, whereas the results of our search on SagePub brought up 56 articles. The results of the search conducted for the last year of 2013 yielded a total 42 articles for PubMed and 31 articles for SagePub. In the end, we compiled a total of 11 papers, 7 of which came from PubMed and four of which came from SagePub. We included three research that met the criteria.

Conclusion: Initiation of the AHA combination of metformin and other drugs may provide better results in diabetes control. In addition, the combination of two and three drugs did not show significantly different results.

Keyword: Blood sugar; Metformin; Monotherapy; Type 2 diabetes medications

INTRODUCTION

Diabetes Mellitus (DM) refers to a collection of metabolic disorders characterized by elevated levels of blood glucose. Elevated blood glucose levels can arise due to dysfunctions in either insulin synthesis, insulin action, or a combination of both factors. Diabetic chronic hyperglycemia has been associated with many adverse effects on glandular function, particularly in the eyes, kidneys, nerves, heart, and blood vessels. These effects manifest as long-term damage, malfunctioning, and failure of the aforementioned glands.¹

The determination of the incidence of DM presents complications due to the variability in the diagnostic criteria utilized for identifying the condition. Diabetes mellitus affects an estimated population of approximately 10.2 million individuals residing inside the United States. The estimated prevalence of diabetes mellitus (DM) among individuals aged over 15 years in Indonesia ranges from 1.5% to 2.3%. It is worth mentioning that in the Manado region, the prevalence of diabetes mellitus (DM) is shown to be 6.1%. The incidence of Type 2 diabetes mellitus is higher in females in comparison to males.²⁻⁴

The therapy of type 2 diabetes mellitus (T2DM) focuses on preventing or delaying micro- and macrovascular consequences, limiting acute metabolic decompensation, and reducing premature death while maintaining quality of life. The pharmacological method to treating T2DM consists of either a stepwise approach or starting with a combination of anti-hyperglycemic agent (AHA). In the absence of sufficient evidence for early combination therapy supported by the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) consensus protocol, the stepwise method of adding AHA progressively was the usual practice until recently.⁵

Step-by-step addition of AHA for the treatment of T2DM has been recommended in many Asian guidelines, including those from Japan, Korea, Hong Kong, Taiwan, and China. Monotherapy with metformin alone at the time of type 2 diabetes mellitus (T2DM) diagnosis alleviates concerns regarding hypoglycemia and potential side effect escalation in comparison to early combination therapy. However, due to the intricate pathophysiological characteristics of T2DM, it is improbable for monotherapy to consistently sustain the desired glycated hemoglobin (HbA1c) target.^{6,7}

Metformin enhances insulin sensitivity within the body, hence necessitating the presence of insulin for its pharmacological effects to manifest. The primary mechanism of action involves the inhibition of liver gluconeogenesis, primarily through the suppression of mitochondrial oxidative phosphorylation and mitochondrial glycerophosphate dehydrogenase.⁸ It also has some effect on the body's ability to get rid of glucose. Metformin, unlike phenformin, is not broken down in the body. Instead, the kidneys get rid of it all. It is removed from the blood by glomerular filtration and, to a greater extent, by tubular release through a number of transporters. Even though it is spread around a lot, its half-time of elimination is only about 2.7 hours.⁹

Furthermore, the implementation of combination therapy in the early stages of the disease may offer prospective benefits in terms of mitigating the harmful effects of glucotoxicity. This approach has the potential to not only retain the mass and functionality of β -cells, but also lead to a substantial enhancement in insulin sensitivity.¹⁰ Although the utilization of early combination therapy including several antihypertensive agents may incur higher costs and perhaps result in decreased patient compliance due to the requirement of taking many pills, this challenge can be partially mitigated through the implementation of a fixed-dose medication combination.¹¹⁻¹³

This study compared monotherapy or metformin - based combination therapy for type 2 diabetes medications.

METHODS

In keeping with the guidelines specified in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the researcher of this study implemented procedures to ensure rigorous compliance with these criteria. The use of this strategy is intended to ensure the accuracy of the results obtained from the investigation. The primary aim of this literature review was to compare monotherapy or metformin - based combination therapy for type 2 diabetes medications. The primary objective of this work is to demonstrate the importance of the aforementioned challenges discussed inside the text.

In order to meet the eligibility requirements for participation in the study, researchers were required to satisfy the following criteria: The composition of the article should be in the English language and its focus compared monotherapy or metformin - based combination therapy for type 2 diabetes medications. In order to meet the requirements for publishing, the paper must fulfill both of these criteria. A number of the examined articles were published throughout the period spanning from 2013 to the pre-established timeframe deemed pertinent for this systematic review. The following are considered prohibited: editorials, submissions without a Digital Object Identifier (DOI), review articles that have already been published, and entries that are essentially duplicates of previously published journal papers.

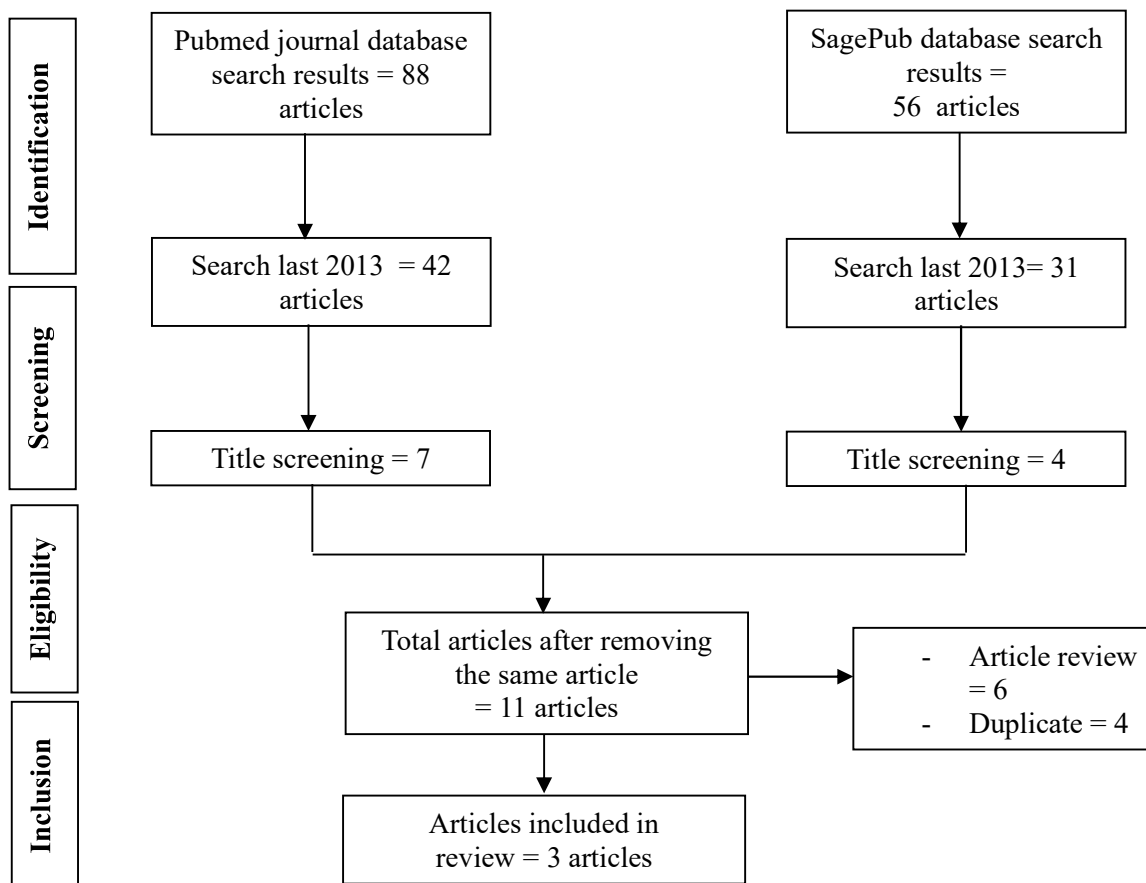


Figure 1. Article search flowchart

We used “monotherapy”; “metformin - based combination therapy”; and “type 2 diabetes” as keywords. The search for studies to be included in the systematic review was carried out from August, 9th 2023 using the PubMed and SagePub databases by inputting the words: (*"monotherapies"[All Fields] OR "monotherapy"[All Fields]*) AND (*"metformin"[Supplementary Concept] OR "metformin"[All Fields] OR "metformin"[MeSH Terms] OR "metformine"[All Fields] OR "metformin s"[All Fields] OR "metformins"[All Fields]*) AND (*"based"[All Fields] OR "basing"[All Fields]*) AND (*"combined modality therapy"[MeSH Terms] OR ("combined"[All Fields] AND "modality"[All Fields] AND "therapy"[All Fields]) OR "combined modality therapy"[All Fields] OR ("combination"[All Fields] AND "therapy"[All Fields]) OR "combination therapy"[All Fields]*) AND (*"diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "type 2 diabetes"[All Fields]*) used in searching the literature.

The authors examined the abstract and title of each study to determine whether or not it met the inclusion criteria. The authors then determined which previous studies would serve as sources for the article and chose those studies. This conclusion was reached after analyzing numerous studies that all appeared to indicate the same trend. All submissions must be written in English and must be previously unpublished. For the systematic review, only publications meeting all inclusion criteria were considered. This narrows the search results to only those that are pertinent to your search. We disregard the findings of any study that does not meet our criteria. The research findings will then be analyzed in depth.

The research conducted for this study revealed the following information: names, authors, publication dates, location, study activities, and parameters. Each author conducted independent research on the research included in the publication's title and abstract prior to deciding which publications to investigate further. The next stage is to evaluate all of the articles that meet the review's inclusion criteria. Then, based on the findings, we will choose which articles to include in the review. This criterion is used to select documents for further analysis. To facilitate the selection of papers for evaluation as much as feasible. This section discusses the prior studies conducted and the aspects of those studies that made their inclusion in the review appropriate.

RESULT

In the PubMed database, the results of our search brought up 88 articles, whereas the results of our search on SagePub brought up 56 articles. The results of the search conducted for the last year of 2013 yielded a total 42 articles for PubMed and 31 articles for SagePub. In the end, we compiled a total of 11 papers, 7 of which came from PubMed and four of which came from SagePub. We included three research that met the criteria.

Table 1. The literature include in this study

Author	Origin	Method	Sample Size	Intervention	Result
Lin, 2022¹⁴	Taiwan	Randomised, double-blind trial	60 patients	Metformin plus linagliptin (DPP-4 inhibitor) or dapagliflozin (SGLT2 inhibitor)	The combination of metformin and linagliptin in dual therapy demonstrates comparable efficacy in glycemic control when compared to triple therapy. In the realm of metformin combination triple therapy, it is plausible that the glycemic control efficacy of triple therapy involving empagliflozin and linagliptin surpasses that of dual therapy only comprising linagliptin. Furthermore, it is possible that the combination of dapagliflozin and saxagliptin in triple therapy may exhibit superior lipid management capabilities compared to the dual therapy involving dapagliflozin alone.
Matthews, 2019¹⁵	United State of America	Randomised, double-blind trial	2,001 participants	Vildagliptin plus metformin	The implementation of an early intervention strategy including a combination therapy consisting of vildagliptin and metformin yields superior and sustained long-term advantages when compared to the conventional approach of initiating treatment with metformin alone for those recently diagnosed with type 2 diabetes.
Henry, 2018¹⁶	United State of America	Randomised, double-blind trial	571 participants	QD placebo (PBO); QD Metformin DR 600, 900, 1200, or 1500 mg; or to single-blind BID Metformin immediate-release (IR) 1000 mg	The extended-release formulation of Metformin (Metformin DR) demonstrated superior effectiveness in relation to the concentration of the drug in the bloodstream when compared to the immediate-release formulation of Metformin (Metformin IR). Subsequent investigations will undertake an assessment of the impact of Metformin DR on individuals diagnosed with type 2 diabetes and exhibiting advanced renal dysfunction.

Lin, et al (2022)¹⁴ showed combination of metformin with DPP4 and SGLT2 inhibitor medication shown a greater efficacy in reducing LDL-C levels (p = 0.016) compared to metformin monotherapy. The administration of a combined treatment of metformin, DPP4 inhibitors, and SGLT2 inhibitors shown a greater efficacy in enhancing total cholesterol (p = 0.049) and HDL-C levels compared to the use of metformin alone (p = 0.037). The combination of metformin and linagliptin as a dual therapy demonstrated superior efficacy compared to metformin alone in decreasing levels of HbA1C (p = 0.011).

The study found that patients who were administered a combination of linagliptin and empagliflozin had a statistically significant decrease in their fasting blood glucose (p = 0.019), HbA1c (p = 0.036), and Chol (p = 0.010) levels in comparison to patients who received linagliptin dual therapy. In addition, it was observed that individuals who were administered a combination of metformin, dapagliflozin, and saxagliptin exhibited a statistically significant decrease in Chol levels (p = 0.011) and LDL-C levels (p = 0.035) as compared to those who received a combination of metformin and dapagliflozin.¹⁴

Matthews, et al (2019)¹⁵ conducted a study with 2,001 eligible individuals were selected at random to be allocated to one of two groups: the early combination treatment group (n = 998) or the first metformin monotherapy group (n = 1003). A total of 1598 patients, accounting for 79.9% of the sample, successfully completed the 5-year trial. Among them, 811 patients (81.3%) were assigned to the early combination therapy group, while 787 patients (78.5%) were assigned to the monotherapy group. During period 1, the combination treatment group exhibited an incidence of initial treatment failure in 429 patients, accounting for 43.6% of the group. In contrast, the monotherapy group had initial treatment failure in 614 patients, representing 62.1% of the group.

The monotherapy group exhibited a median observed time to treatment failure of 36.1 months (interquartile range [IQR] = 15.3-NR), but the median time to treatment failure for individuals receiving early combination therapy was anticipated to exceed the study period at 61.9 months (IQR = 29.9-NR). During the 5-year research period, the early combination treatment group exhibited a noteworthy decrease in the relative risk for time to initial treatment failure compared to the monotherapy group (hazard ratio [HR] = 0.51 [95% CI = 0.45-0.58]; $p < 0.001$). Both treatment modalities demonstrated a high level of safety and tolerability, as evidenced by the absence of any unforeseen or novel safety concerns, as well as the absence of any treatment-related fatalities.¹⁵

DISCUSSION

The conventional strategy for managing T2DM, in the absence of osmotic symptoms or severe hyperglycemia, has been to implement lifestyle adjustments in conjunction with metformin monotherapy, unless the patient is intolerant to or has a contraindication for metformin. The 2019 guidelines of the European Society of Cardiology (ESC) advocate for utilization of newer antihyperglycemic agents, specifically sodium-glucose cotransporter-2 inhibitors (SGLT-2Is) or glucagon-like peptide-1 receptor agonists (GLP-1RAs), as initial pharmacological treatment for T2DM in individuals with atherosclerotic cardiovascular disease (ASCVD) or elevated cardiovascular (CV) risks.¹⁷

Both the ADA/EASD and the American Association of Clinical Endocrinologists (AACE) advocate for the intensification of treatment by adding an additional antihyperglycemic agent (AHA) when monotherapy fails to achieve or sustain the desired HbA1c target within a period of 3 months. However, the AACE specifically recommends combination therapy involving metformin and another AHA when the HbA1c level is 7.5% or higher (≥ 59 mmol/L), even at the time of T2DM diagnosis.^{5,18,19}

In Taiwan, it is advised to initiate metformin-based combination therapy when the HbA1c level is equal to or greater than 8.5% (equivalent to 69 mmol/mol). In Korea and Hong Kong, on the other hand, the recommended threshold for initiating this medication is a HbA1c level of equal to or greater than 7.5% (equivalent to 59 mmol/mol) at the time of type 2 diabetes mellitus diagnosis. The Canadian Diabetes Association recommends initiating combination therapy in patients whose HbA1c level exceeds 8.5%.^{5,18,19}

Sulfonylureas were found to be linked to a heightened risk of severe hypoglycemia when used as a standalone treatment (in comparison to metformin or thiazolidinedione), as well as when used in combination with metformin (in comparison to metformin plus a DPP-4 inhibitor or metformin plus an SGLT-2 inhibitor). The utilization of sulfonylureas, both as standalone treatment and in conjunction with metformin, has been found to elevate the likelihood of experiencing mild, moderate, or complete hypoglycemia.^{15,20}

Given the intricate pathophysiology associated with T2D, it may be more suitable to employ a strategy that involves the combination of various medication classes exhibiting synergistic effects. The concurrent administration of metformin with a DPP4 inhibitor has been shown to effectively inhibit hepatic glucagon synthesis. Furthermore, the use of a DPP4 inhibitor has the additional benefit of enhancing prandial insulin release. Additionally, it has been demonstrated that metformin has the ability to elevate the levels of GLP-1 in the bloodstream. This effect can be enhanced by inhibiting the breakdown of GLP-1 through the use of a DPP4 inhibitor. The co-administration of DPP-4 inhibitors and GLP-1 receptor agonists has been observed to mitigate the heightened glucagon levels caused by SGLT2 inhibitors.²¹

In relation to safety, the early combination of metformin with a sulfonylurea (SU) is associated with a higher likelihood of hypoglycemia as compared to metformin monotherapy.¹¹ In contrast, the coadministration of metformin with a DPP4 inhibitor or SGLT2 inhibitor demonstrates a comparable likelihood of hypoglycemia when compared to the use of metformin alone. Nevertheless, the initiation of combination therapy at an early stage may potentially hinder patient adherence due to the perceived complexity of multi-drug regimens. This challenge, however, can be addressed by implementing a fixed-dose drug combination approach.²²

CONCLUSION

Initiation of the AHA combination of metformin and other drugs may provide better results in diabetes control. In addition, the combination of two and three drugs did not show significantly different results.

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