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A Systematic Review: Cost-Effectiveness of SGLT2 Inhibitors versus DPP-4 Inhibitors as Add-on to Metformin

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Abstract

Background: *The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) are two second-line therapy alternatives for T2DM patients inadequately controlled with metformin.* ***Objective:*** *This study aimed to systematically review the cost-effectiveness of combining metformin+SGLT2i vs metformin+DPP-4i for T2DM treatment.* ***Methods:*** *A systematic search was conducted in PubMed, Scopus, and ScienceDirect for articles published between 2015-2025, using predefined keywords and following the PRISMA and PICOS frameworks (P: T2DM patients uncontrolled on metformin monotherapy; I: Metformin+SGLT2i therapy; C: Metformin+DPP-4i therapy; O: Cost, clinical outcomes (HbA1c% reduction), Incremental Cost-Effectiveness Ratio (ICER) values, Quality Adjusted Life Years (QALY); S: Study with cost-effectiveness analysis design). Additional studies were identified through reference screening. Eligible articles were independently reviewed and assessed for reporting quality using the CHEERS-2022 standards.* ***Results:*** *Five studies met the inclusion criteria. Considerable heterogeneity was observed with mean patient ages ranging from 55-61 years old and baseline HbA1c levels from 7.9%-9.4%. The studies were conducted in the US, UK, Mexico, and Greece, all funded by the pharmaceutical industry, and used economic models. Despite these differences, all studies consistently demonstrated that combining metformin+SGLT2i was more cost-effective than metformin+DPP-4i. SGLT2i improved the quality of life by 0.032–0.04 QALYs, reduced hypoglycemia, and provided additional benefits for patients with cardiovascular risk, although it was associated with higher initial costs.* ***Conclusion:*** *This review showed that the combination of metformin+SGLT2i was more cost-efficient and effective in managing T2DM than the combination of metformin+DPP-4i.*

Keywords: *cost-effectiveness analysis, diabetes mellitus, DPP-4 inhibitors, metformin, SGLT2 inhibitors*

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INTRODUCTION

Diabetes mellitus is a chronic disease, and the number of patients continues to increase every year. Based on data from the International Diabetes Federation (IDF), there are 589 million adults living with diabetes with an age range of 20-79 years old, of which 20,426 million are from Indonesia. This positioned Indonesia in the 5th position with the most DM patients in the world in 2024 (International Diabetes Federation, 2024). According to the American Diabetes Association (ADA), the annual cost of diabetes in the US will reach $413 billion by 2022, including $307 billion in direct healthcare costs and $106 billion in productivity lost. Diabetes and its associated health complications impose a significant financial burden on individuals and society (American Diabetes Association, 2025).

Metformin is an oral antidiabetic drug (OAD) that is most commonly used to treat type 2 diabetes mellitus (T2DM) (Müller et al., 2018). However, given the progressive nature of T2DM, many patients require additional therapy to maintain adequate glycemic control. The use of a combination of drugs, such as dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium glucose cotransporter 2 inhibitors (SGLT2i), which have complementary mechanisms of action, can help control blood sugar levels and promote weight loss while reducing the risk of hypoglycemia (Hadjadj et al., 2016; Rosenstock et al., 2016).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), introduced in 2012 as the newest class of non-insulin antidiabetic agents, provide glycemic control comparable to that of traditional therapies while offering additional advantages, including a lower risk of hypoglycemia and clinically meaningful weight reduction. Moreover, evidence has demonstrated their ability to decrease major adverse cardiovascular events and mortality, as well as to improve clinical outcomes in patients with chronic kidney disease (Yoshida et al., 2020). SGLT2i and DPP-4i have been shown to have a lower risk of hypoglycemia and are beneficial in reducing CVD events and mortality in patients with type 2 diabetes (T2DM) and cardiovascular risk compared to conventional therapies, such as sulfonylureas (SU) and insulin (Zhu et al., 2023).

To ensure that patients receive the best treatment at the available cost, the clinical benefits of each drug must be compared to the cost impact (Charokopou et al., 2015). Many cost-effectiveness analysis (CEA) studies have shown that SGLT2i are more cost-effective than DPP-4i. Due to differences in settings, healthcare costs, and populations, the results of these studies vary, and there is no clear consensus on which of the two combinations is more cost-effective in T2DM therapy (Peng et al., 2022).

A previous systematic review assessed the cost-effectiveness of SGLT2i compared with that of multiple antidiabetic classes, including DPP-4i. However, it did not specifically address SGLT2i versus DPP-4i, despite both being commonly prescribed and frequently considered therapeutic alternatives in routine clinical practice. Therefore, the purpose of this review was to conduct a cost-effectiveness analysis of the combination of metformin + SGLT2i compared to metformin + DPP-4i, especially in T2DM patients.

This study aimed to review and evaluate the data thoroughly to provide a deeper understanding of the economic aspects of the two comparable treatment approaches. The results are expected to serve as a reference for medical personnel and policymakers in making appropriate decisions regarding the management of patients with T2DM. Although these two combinations have been shown to effectively control blood sugar level, cost considerations remain a crucial factor in determining the therapy used. As the burden of healthcare costs increases, economic analysis becomes increasingly important in T2DM management strategies.

METHODS

Search Strategy

The literature search was limited to studies published between 2015 and 2025, considering that SGLT2 inhibitors were first approved by the FDA in 2013 (canagliflozin) and 2014 (dapagliflozin), with relevant publications on clinical effectiveness and cost-effectiveness analyses consistently emerging from 2015 onward. The databases used were from PubMed, ScienceDirect, and Scopus. The search strategy focused on the topic "Cost Effectiveness of metformin+SGLT2i compared to metformin+DPP-4i in patients with type 2 Diabetes Mellitus," using several keywords, namely "Cost Effectiveness," "Diabetes Mellitus," "Dipeptidyl Peptidase-4 Inhibitors," "Metformin," "Sodium Glucose Cotransporter 2 Inhibitors," which were applied to the database. This literature study used a structured search technique that used Boolean operators such as "AND" or "OR."

Inclusion and Exclusion Criteria

The search scheme was adjusted to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021) and Participants,

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Intervention, Comparator, Outcome, and Study Design (PICOS) method (P: Type 2 diabetes mellitus patients inadequately controlled on metformin monotherapy; I: Metformin + SGLT2i therapy; C: Metformin + DPP-4i therapy; O: Cost and clinical outcomes such as HbA1c% reduction, Incremental Cost-Effectiveness Ratio (ICER) values, and quality adjusted life years (QALY); S: studies with cost-effectiveness analysis design). The excluded articles were articles from journals that could not be accessed, written in languages other than English, research protocols, opinions, notes, letters, editorials, books, conference abstracts, and review articles.

Data extraction and analysis

After reviewing, the information obtained will be included in the table: 1) bibliography, including authors, year, and country of publication; (2) study design, including study perspective, time horizon, interventions, type of modeling, costs included in the study, discount rates, clinical outcomes, and sensitivity analysis; (3) results and conclusions, including the incremental cost-effectiveness ratio (ICER) and QALY. Quality assessment was performed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022, which consists of 28 items (Husereau D et al., 2022). Each item with an answer of "yes" was given a score of 1, while the answers of "no" or "not applicable" were given a score of 0. Study quality was classified into three categories: high (scores of 22-28 or more than 75%), moderate (scores of 14-21 or 50% - 75%), and low (scores of <14 or less than 50%).

RESULTS AND DISCUSSION

Search results

From the initial search results, 69 studies were identified. There was one duplicate article, 51 articles had titles that were not in accordance with CEA, two were systematic review articles, and nine articles did not focus on discussing the CEA combination of metformin + SGLT2i compared to metformin + DPP-4i, two articles were not in full text, and one article was not in English. Next, a manual search was conducted, and two articles were obtained. Five articles were included in the final review. The article selection process used PRISMA diagrams (Figure 1).

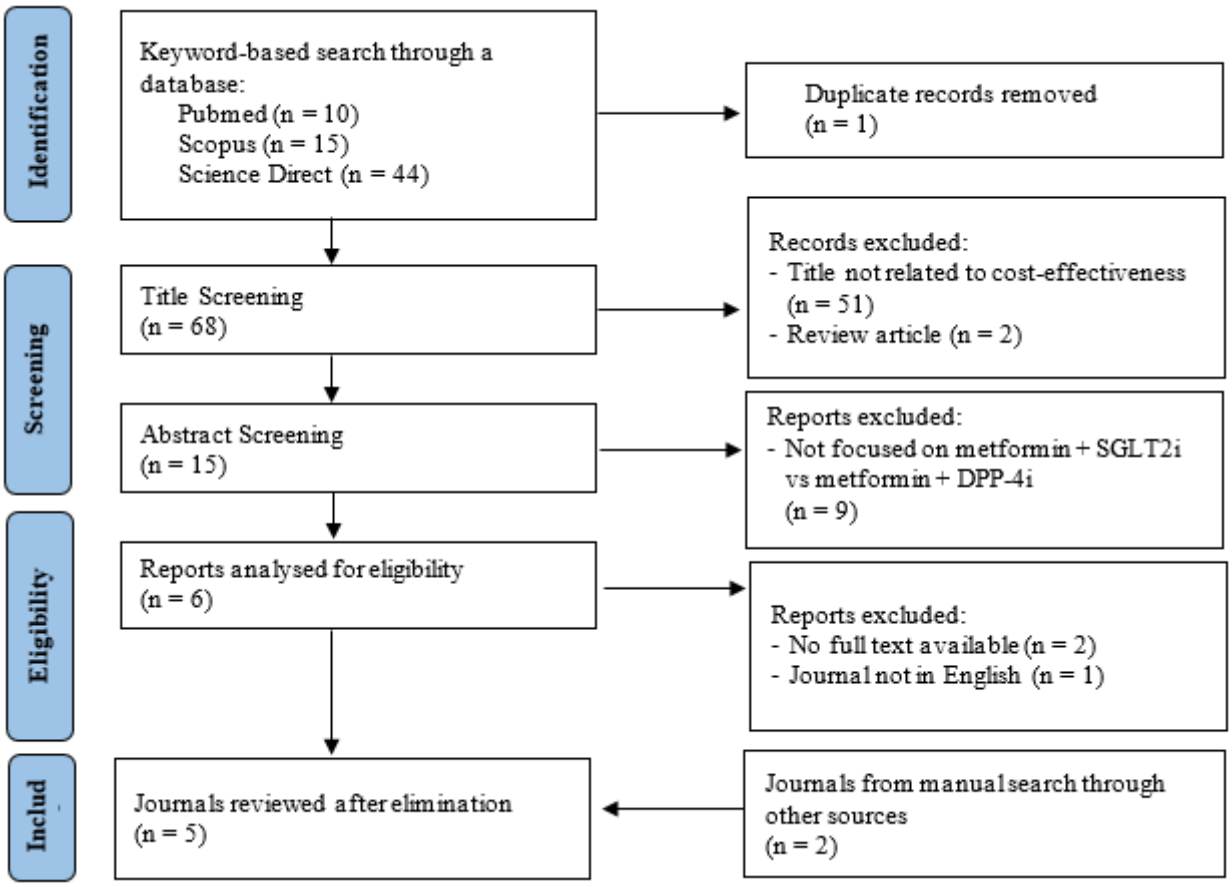

Figure 1. The source search flow using the PRISMA method is cost-effectiveness of Metformin+ SGLT2i compared to Metformin+ DPP-4i

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Table 1. General characteristics of the included studies

Author/ Year	Population	Perspectives	Cost	Interventions & Comparisons	Model	Time Horizon	Discount Rate (%)	Funding Sources
UK, Charokopou et al., 2015	Average age: 58 years old Average HbA1c: 8.05% Patients who failed to achieve adequate control on previous metformin monotherapy and require modifications to their treatment regimen	UK national health services	Direct medical costs: micro- and macrovascular complications (IHD, MI, CHF, stroke, amputation, ESRD, blindness), CV death, non-CV death, hypoglycemia, adverse events	MET+DAPA, MET+DPP4i	Cardiff diabetes model	40 years (Lifetime)	3.5	Bristol-Myers Squibb and AstraZeneca
Mexico, Neslusan et al., 2015	Average age: 55 years old Average HbA1c: 7.9% Patients with T2DM inadequately controlled on metformin monotherapy	Third-party payer in the US healthcare system	Direct costs: drug costs, complications (MI, stroke, nephropathy, neuropathy, retinopathy), adverse events (genital infections, dehydration, etc.), long-term management costs	MET+Canagliflozin 300mg, MET+Sitagliptin	Economic and Health Outcomes Model of T2DM (ECHO-T2 DM)	30 years	5	Janssen Global Services, LLC.
Greece, Tzanetakos et al., 2016	Average age: 58 years old Average HbA1c: 7.98% T2DM patients inadequately controlled with metformin monotherapy	Greece healthcare system	Direct costs: drugs, micro- and macrovascular complications (DM, MI, CHF, stroke, amputation, ESRD, blindness); Costs of hypoglycemia, Adverse events	MET+DAPA, MET+DPP-4i	Cardiff diabetes model	40 years	3.5	AstraZeneca
US, Chakravarty et al., 2018	Average age: 57 years old Average HbA1c: 7.98% Patients with T2DM treated with DAPA vs other glucose-lowering therapy classes added as add-on therapy to metformin.	US third-party payer perspective	Direct medical costs: related to changes in HbA1c, weight, blood pressure, and risk of hypoglycemia; drug costs (wholesale prices); and medical costs (visit, hospitalization, lab)	MET+DAPA, MET+DPP-4i	A short-term economic model (1year)	1 year	-	AstraZeneca
US, Reifsnider et al., 2021	Average age: 61 years old Average HbA1c: 9.4% T2DM patients with or with out CVD on metformin plus empagliflozin or metformin plus sitagliptin	*US healthcare payer perspective*	Direct medical costs: medication, diabetes complications: CVD, kidney failure, stroke, amputation, neuropathy, blindness; Adverse events; Therapy escalation costs.	MET+Empagliflozin, MET+Sitagliptin	Individual patient-level simulation model	10 years	3	Boehringer Ingelheim Pharma-ceuticals Inc. of Ridgefield, CT, USA

Description: DAPA: dapagliflozin, MET: metformin, SITA: sitagliptin

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Table 2. CHEERS assessment result

Author/ Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	%
UK, Charokopou et al., 2015	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	-	✓	✓	✓	-	✓	✓	✓	89
Mexico, Neslusan et al., 2015	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	-	✓	✓	✓	-	✓	✓	✓	89
Greece, Tzanetakos et al., 2016	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	-	✓	✓	✓	-	✓	✓	✓	89
US, Chakravarty et al., 2018	✓	✓	✓	-	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	-	✓	✓	✓	-	✓	✓	✓	86
US, Reifsnider et al., 2021	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	-	✓	✓	✓	-	✓	✓	✓	89

Table 3. The economic outcomes of the literature study analysis of Metformin+ SGLT2i compared with Metformin+ DPP-4i

Country, Author, Year	Sensitivity Analysis	Clinical Outcomes/ QALY	Cost	ICER	WTP Threshold (Cost/ QALY)	Cost Effective
UK, Charokopou et al., 2015	*One way*, PSA	MET+DAPA: 11.86 years MET+DPP4i: 11.83 years	MET+DAPA : £13,809 MET+DPP4i: £13,593	MET+DAPA vs MET+DPP4i: £6,761/ QALY	£20,000/QALY	MET+DAPA
Mexico, Neslusan et al., 2015	*One way,* PSA	MET+Canagliflozin 300mg: 6.35 years MET+Sitagliptin: 6.19 years	MET+Canagliflozin 300mg: MXP 330,087 Sitagliptin MET: MXP 328,290	MET+Canagliflozin 300mg vs MET+Sitagliptin: MXP 11,210/QALY	MXP 141,200/QALY	MET+Canagliflozin 300mg
Greece, Tzanetakos et al., 2016	PSA	MET+DAPA:12.24 years MET+DPP-4i: 12.19 years	MET+DAPA : €25,088 MET+DPP-4i: €24,332	MET+DAPA vs MET+ DPP-4i: €17,695/QALY	€34,000/QALY	MET+DAPA
US, Chakravarty et al., 2018	*One way* and *PSA*	MET+DAPA : +0.0587	MET+DAPA:-$795	MET+DAPA Dominates	$50,000/QALY	MET+DAPA
US, Reifsnider et al., 2021	DSA and PSA	MET+Empagliflozin: 8.85 years MET+Sitagliptin: 8.66 years	MET+Empagliflozin: $89,436 Sitagliptin MET: $88,118	MET+Empagliflozin VS MET+Sitagliptin: $6967/QALY	$50,000/QALY	MET+Empagliflozin

Description: Euro (€), Pound (£), US Dollar ($), Mexican Peso (MXP), DAPA: DAPAGLIFLOZIN, MET: metformin, SITA: sitagliptin, WTP: willingness to pay

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Characteristics of the study

An analysis of the characteristics of the five studies is presented in Table 1. All five studies used economic models to evaluate the cost-effectiveness of SGLT2i in T2DM patients. The most widely used model is the Cardiff Diabetes Model, which has been previously validated and shown to be able to project key clinical endpoints related to the natural course of T2DM, therapeutic effects, and their impact on patient cost and quality of life over the long term (Charokopou et al., 2015). In addition to the Cardiff Diabetes Model, three other models are used: echo-T2DM, a short-term decision-analytic model (1 year), and an individual patient-level simulation model using a discretely integrated condition event (DICE). Each model has a different structure and assumptions, which may affect the results of the cost-Effectiveness evaluation. The pharmacoeconomic perspective is one of the considerations in pharmacoeconomic research. Pharmacoeconomic perspectives are used to consider who pays the costs and who receives the benefits. Of the five studies, most were conducted from the payer's perspective (three studies), and two were conducted from the healthcare perspective.

Most studies used a lifetime horizon to capture the long-term benefits of SGLT2i therapy. However, there is one study that uses short-term models that are considered more suitable for estimating costs and benefits in a short period (Chakravarty et al., 2018). Although a lifetime time horizon is generally used, the time horizon is limited to 20-40 years; this is because the range represents the remaining life expectancy of T2DM patients and is sufficient to capture all relevant benefits and costs (Reifsnider et al., 2021).

The variation in discount rates (3%, 3.5%, and 5%) influences the valuation of future costs and health outcomes in the present (Andayani, 2013). A higher discount rate undervalues long-term benefits, potentially making preventive or chronic disease interventions appear less cost effective. In comparison, a lower rate gives greater weight to the future outcomes. Even small differences in discount rates can meaningfully shift incremental cost-effectiveness ratios (ICERs), particularly when the results are close to the willingness-to-pay thresholds (Kemenkes, 2013). For the study using a one-year horizon, discounting was not applied because it is only relevant for longer timeframes.

The participants in this study were T2DM patients who did not achieve optimal glycemic control with metformin monotherapy, thus requiring second- or third-line additional therapy. All studies involved adults aged > 55 years, in accordance with data from the IDF, which states that in 2024, there will be 589 million adults aged 20-79 years with T2DM (International Diabetes Federation, 2024). The average Body Mass Index of the five studies was above 30 kg/m2. According to the WHO, the ideal BMI classification is in the range of 18.5-24.9 kg/m2; therefore, it is included in class 1 obesity. The HbA1c levels in the five studies ranged from 7.5% to 9.4%.

Quality assessment

All studies in this review showed a high quality of reporting based on the CHEERS checklist, with a score of more than 80%. All studies conducted a sensitivity analysis, including univariate analysis, one-way sensitivity analysis, and Probabilistic Sensitivity Analysis (PSA), and the results obtained were assessed as consistent or stable. The reporting quality of the studies is presented in Table 2.

Document evaluation

The results of the analysis of the cost-effectiveness literature study of metformin + SGLT2i compared with metformin + DPP-4i (Table 3) showed that in the UK, dapagliflozin resulted in an increase in QALY with ICER £ 6.761/ QALY, and a cost-effective probability of 85% at a threshold of £20,000 (Charokopou et al., 2015). In a study in Mexico, canagliflozin (300 mg) showed an ICER well below the national WTP limit and was very cost-effective, mainly due to its impact on blood sugar, body weight, and blood pressure (Neslusan et al., 2015). In a Greek study, dapagliflozin provided additional QALY and remained cost-effective (ICER € 17.695/QALY) compared to the €34,000 threshold (Tzanetakos et al., 2016). In studies conducted in the US (two studies), dapagliflozin and empagliflozin were more cost-effective than DPP-4i and sitagliptin, with lower costs or higher clinical benefits. Empagliflozin is particularly beneficial in patients at risk of CVD, as it reduces CVD mortality and extends CVD-free life (Chakravarty et al., 2018; Reifsnider et al., 2021).

SGLT2 inhibitors are one of the newest classes of antidiabetic drugs that are currently increasingly used as the main choice in T2DM treatment. This is because SGLT2i not only lowers blood glucose levels but also provides protective benefits against cardiovascular and renal complications in T2DM patients (Hsia et al., 2017). However, the prices of drugs in this class are relatively high (Charokopou et al., 2015). Therefore, evaluating the cost-effectiveness of SGLT2i therapy is important. This systematic review shows that SGLT2i is an effective and safe therapeutic option for T2DM patients, especially in patients who have not reached the HbA1c

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target with metformin, because it can reduce blood sugar levels while reducing the risk of cardiovascular complications and mortality.

The results of this systematic review are generally consistent with those of a previous review, which also concluded that SGLT2i is cost-effective. The addition of dapagliflozin to metformin provided a small but significant increase in benefits compared with the addition of DPP-4i, namely an additional life expectancy of 0.01 years and an increase in quality of life of 0.04 QALY during the patient's lifetime in a study conducted in Greece (Tzanetakos et al., 2016). Meanwhile, in the UK, dapagliflozin + metformin increases the quality of life by 0.032 QALY. These differences are mainly due to differences in patient weight, which are known to affect the health-related quality of life (Charokopou et al., 2015). The improvement in QoL was also supported by a decrease in hypoglycemia rates in the dapagliflozin group.

The results of this study align with the Health Technology Assessment (HTA) framework used in various health systems. The economic models used in these studies have generally been validated and used in official HTA assessments, ensuring that their findings have a strong methodological foundation. Furthermore, HTA principles, such as the use of a GDP-based cost-per-QALY threshold and an emphasis on healthcare resource efficiency, were also reflected in the analysis. Consistently, dapagliflozin, compared with DPP-4i, demonstrated more cost-effective results in both short- and long-term models (Chakravarty et al., 2018; Charokopou et al., 2015; Cummins et al., 2012; Neslusan et al., 2015; Tzanetakos et al., 2016).

When interpreting the results of this review, caution is required because of some limitations. First, data on effectiveness are often limited in scope. Efficacy data generally originate from older clinical trials with selected patient populations (Lopez et al., 2015). Second, the wide variation in methodology between studies and in terms of data use, discount rate, modelling, perspective, types of cost, time horizon, and so on, plus differences in population and country contexts, make research results difficult to compare directly and general conclusions are limited (Yoshida et al., 2020). Third, all of the studies analyzed were funded by pharmaceutical companies, which may tend to report more favorable results regarding the cost-effectiveness ratio of recent diabetes therapies such as SGLT2i. The study also did not include non-English-language publications, which could be a source of publication bias. In addition, some paid journals do not provide the full text, which can limit the completeness of the data analyzed.

CONCLUSION

Studies conducted in the UK, Mexico, Greece, and the US found that the combination of metformin with SGLT2i, such as dapagliflozin and empagliflozin, was more cost-effective than metformin and DPP-4i. Despite higher initial costs, SGLT2i improved the quality of life by 0.032–0.04 QALYs, reduced hypoglycemia, and provided additional benefits for patients at cardiovascular risk.

AUTHOR CONTRIBUTIONS

Conceptualization, I.A.H., Y.N..; Methodology, I.A.H., Y.N.; Software, I.A.H.; Validation, I.A.H., A.R.; Formal Analysis, I.A.H., L.; Investigation, I.A.H., L.; Resources, I.A.H.; Data Curation, I.A.H., Y.N., L.; Writing - Original Draft, I.A.H.; Writing - Review & Editing, I.A.H., Y.N., L., A.R.; Visualization, V.; Supervision, I.A.H.; Project Administration, I.A.H.; Funding Acquisition, I.A.H.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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