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REVIEW

Cost-Effectiveness of Newer Antidiabetic Drugs as Second-Line Treatment for Type 2 Diabetes: A Systematic Review

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ABSTRACT

Introduction: Evidence from cardiovascular outcome trials (CVOTs) for newer antidiabetic drugs is increasingly influencing revised recommendations for second-line therapy in type 2 diabetes (T2D). This systematic review aimed to compare the cost-effectiveness of newer antidiabetic drugs specified as sodium-glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like peptide 1 receptor agonist (GLP-1RA), and dipeptidyl peptidase 4 inhibitor (DPP-4i) for T2D in a second-line setting.

Methods: A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines, and all relevant published studies were searched comprehensively in electronic databases, including PubMed, Embase, Web of Science, and International Health Technology Assessment database published from April 2023. The quality of the included studies was evaluated using Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 reporting checklists.

Results: We included 28 studies that met the inclusion criteria. Overall reporting of the identified studies largely met CHEERS 2022 recommendations. The CORE and Cardiff models were the most frequently utilized for pharmacoeconomic evaluation in T2D. Four studies consistently discovered that SGLT2i was more cost-effective than GLP-1RA in T2D who were not adequately controlled by metformin monotherapy. Four studies compared GLP-1RA with DPP-4i, sufonylurea (SU), or insulin. Except for one that demonstrated SU was cost-effective, all were GLP-1RA. Five studies revealed that SGLT2i was more cost-effective than DPP-4i or SU. Eleven studies indicated that DPP-4i was more cost-effective than traditional antidiabetic drugs. Four additional studies explored the cost-effectiveness of various antidiabetic drugs as second-line options, indicating that SU, SGLT2i, or meglitinides were more economically advantageous. The most common driven factors were the cost of new antidiabetic drugs.

Conclusion: Newer antidiabetic drugs as second line are the cost-effective option for T2D from the cost-effectiveness perspective, especially SGLT2i.

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Keywords: Cost-effectiveness; Dipeptidyl peptidase 4 inhibitor; Glucagon-like peptide 1 receptor agonist; Second-line treatment; Sodium-glucose transporter 2 inhibitor; Type 2 diabetes

Key Summary Points

Why carry out this study?

The surge in fees of high-cost new antidiabetic drugs will likely pose a challenge for the healthcare system. There are weak supporting evidence and extensive debate regarding the best second-line agent considering long-term efficacy, quality of life, and cost. Therefore, whether new antidiabetic drugs are superior to classic ones remains unclear

This systematic review summarizes the pharmacoeconomic studies thus far performed in newer antidiabetic drugs as second-line treatment for type 2 diabetes and provides further evidence to guide treatment strategies

What was learned from the study?

Newer antidiabetic drugs appear to be generally cost-effective therapy in second-line options with T2D compared to classic antidiabetic drugs

SGLT2i was superior to GLP-1RA and DPP-4i; DPP-4i has a good safety profile and weight neutrality, making it more cost-effective than other classical antidiabetic drugs, but not as favorable as GLP-1RA and SGLT2

With the continued improvement in the accessibility and affordability of newer antidiabetic drugs, SGLT2i can be a preferred option for second-line treatment with a great future

INTRODUCTION

Global diabetes-related health expenditures were approximately US$ 966 billion in 2021 and are projected to reach 1054 billion USD by 2045 [1]. Cardiovascular disease (CVD), a major public health challenge, is one of the primary cost-drivers. Diabetes medication affordability and the combination of cardiovascular protective drugs are independent protective factors against cardiovascular death [2].

Increasing evidence suggests newer hypoglycemic agents, such as sodium-glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like peptide 1 receptor agonist (GLP-1 RA), and dipeptidyl peptidase 4 inhibitor (DPP4i), carry lower risks of hypoglycemia than conventional hypoglycemic agents, such as sulfonylurea (SU) and insulin, promote weight loss, and are weight neutral. Crucially, these agents are beneficial in reducing CVD events and mortality in type 2 diabetes (T2D) patients at increased cardiovascular risk [3, 4]. Therefore, new classes of hypoglycemic agents have been progressively replacing SU as the most common treatment for metformin monotherapy failure [5]. Nevertheless, shifting to newer hypoglycemic agents increases the diabetes treatment cost, which could outweigh savings from cardiovascular benefits [6].

The second-line choice in clinical practice has become more complex and uncertain with the constant updating of evidence and guidelines and the rapid expansion of newer antidiabetic drugs. Given the many therapeutic options with a wide range of costs, a challenge for the health system is the suitable selection as second line in new antidiabetics to ensure maximum benefit and acceptable cost. Although several studies have systematically evaluated that newer antidiabetics, including GLP-1 RA, DPP-4i, and SGLT2i, are more cost-effective than classical antidiabetics, such as insulin, thiazolidinedione (TZD) and SU [7, 8], these studies are not explicitly designed for second-line strategies in T2D.

The latest American Diabetes Association guidelines state that GLP-1 RA and SGLT2i can be used for patients at high risk of CVD, heart

failure, or chronic kidney disease, irrespective of glycemic control and baseline metformin [9]. Thus, this cardiorenal protective effect independent of glycemic control has shifted the paradigm of conventional second-line T2D strategies, resulting in a continued increase in the overall use of these high-cost new antidiabetics. This systematic review aims to evaluate the cost-effectiveness of the newer antidiabetics, including SGLT2i, GLP-1RA, and DPP-4i, as second-line therapy for T2D failed metformin monotherapy to provide a reference for future clinical decision-making.

METHODS

Search Strategy

We conducted a systematic search according to the PRISMA 2020 statement [10]. PubMed, Embase, Web of Science, and International Health Technology Assessment (HTA) databases were searched for eligible articles until April 26, 2023. Search strategies are provided in Supplementary Table S1.

Study Selection

Economic evaluations were selected using the following search technique based on the PICOS (Participants, Intervention, Comparator, Outcome, Study design) criteria in Supplementary Table S2. Two independent investigators (JZ, YZ) extracted eligible studies and relevant data. A third investigator (QL) resolved the discrepancies between the two investigators and verified for data accuracy. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

- Participants: Adults with T2D.
- Intervention: second-line therapy.
- Outcome: cost, life gain year (LYG), quality-adjusted life year (QALY), incremental cost-effective ratio (ICER), and incremental net monetary benefit (INMB).
- Study design: cost-effectiveness analysis (CEA) and cost-utility analysis (CUA).

Data Extraction and Synthesis Strategy

Data items extracted included study characteristics (e.g. author, year of publication, region, perspective, interventions, modelling approach, time horizon, sensitivity analysis, funding source, etc.) and primary outcomes (ICER and INMB). INMB = ΔQALY * willingness-to-pay thresholds—ΔCost. All costs were converted into 2022 US dollars using the CCEMG-EPPI-Center Cost Converter Version.1.6 via purchasing power parities to make ICER and INMB comparable across studies [11].

Quality Assessment Reporting

Reporting quality was assessed using the 28-item checklist of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) statement [12]. The corresponding scores of every 'Yes' (completely fulfill the items), 'Partly' (partially fulfill), and 'NA' (not applicable) recorded for each item were assigned 1, 0.5, and 0, respectively. The quality of the included studies was ranked as high, moderate, or poor quality depending on the total score: high quality for score $\geq$ 21 (quality percentage score $>$ 75%); moderate quality for score 14–21 (quality percentage score between 50 and 75%); poor quality for score for score $\leq$ 14 (quality percentage score $<$ 50%) [13].

RESULTS

Search Results

Figure 1 presents the literature search strategy and exclusion criteria. The search yielded 218 publications. Following title and abstract screening, 81 potentially relevant articles were evaluated for full-text eligibility. The systematic review evaluated 28 studies based on the inclusion criteria.

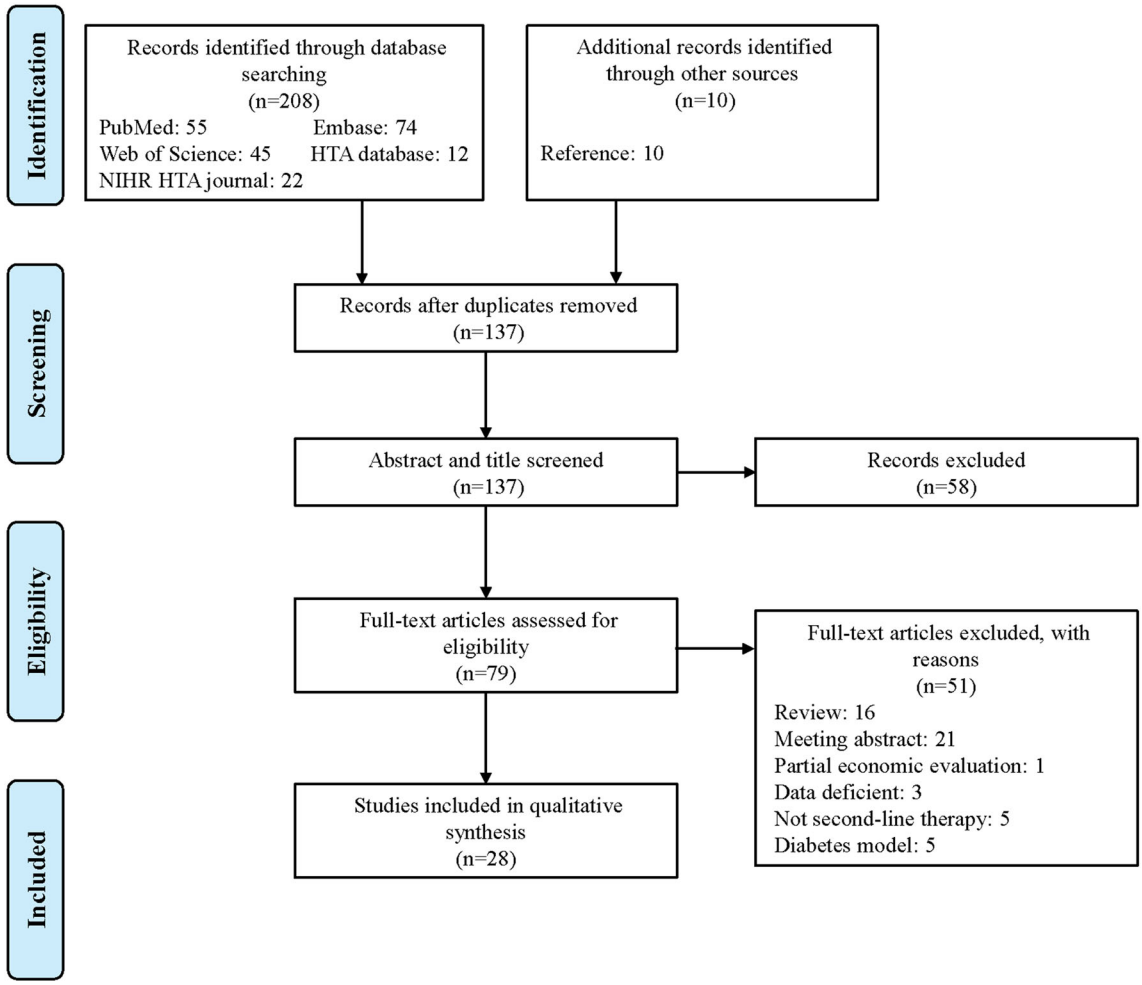

Fig. 1 PRISMA flowchart of study selection

General Characteristics of the Included Studies

Table 1 presents the general characteristics of the included studies. The most studied population was adults with T2D, and a few focused on specific populations, such as established CVD [14] and patients > 65 years old [15]. Two additional studies analyzed subgroups for heart failure [16] as well as gender and smoking status [17]. Among the included second-line comparison, four studies compared GLP-1RA and SGLT2i [14, 16, 18, 19]. The rest were SGLT2i (n = 5) [20–24], GLP-1RA (n = 4) [17, 25–27], and DPP-4i (n = 11) [15, 28–37] compared to other hypoglycemic agents. Four additional studies compared multiple second-line therapies for T2D [38–41].

Seventeen studies were conducted in Europe, including six in the UK [8, 16, 21, 22, 25, 30], three in Sweden [17, 26, 31], two in Denmark [14, 18], and two in Greece [24, 35]; the rest were in Poland [32], Germany [29], Portugal [37], and Europe [36]. Six were conducted in North America (two in Canada [40, 41] and three in the USA [19, 23, 27]) and one in South America (Argentina [28]). Five additional studies were from Asia (four in China [33, 34, 38, 39] and one in India [20]). All studies adopted the model-based simulation approach using data predominately derived from clinical trials or literature, except for one based on real-world data.

Table 1 Characteristics of the included studies

Author, year	Region	Perspective	Interventions	Model	Time horizon	Discount rate	Sensitivity analysis	Funding
GLP-1RA vs. SGLT2i								
Ehlers et al., 2022 [18]	Denmark	Payer	Semaglutide (sc) vs. empagliflozin	CORE	50Y	4%	Scenario, DSA and PSA	Industry
Ehlers et al., 2021 [14]	Denmark	Healthcare	Liraglutide vs. empagliflozin	CORE	50Y	4%	Scenario, DSA and PSA	Industry
Ramos et al., 2020 [16]	UK	Payer	Semaglutide (po) vs. empagliflozin	CORE	50Y	3.5%	Scenario and PSA	Industry
Reifsnider et al., 2022 [19]	USA	Payer	Liraglutide vs. empagliflozin	DICE	Lifetime	3%	Scenario, DSA and PSA	Industry
GLP-1RA vs. others[a]								
Steen Carlsson et al., 2014 [17]	Sweden	Societal	Liraglutide vs. Glimepiride or Sitagliptin	IHECM	40Y	3%	Scenario and PSA	Industry
Davies et al., 2012 [25]	UK	Payer	Liraglutide vs. sitagliptin or glimepiride	CORE	50Y	3.5%	DSA and PSA	Industry
Sinha et al., 2010 [27]	USA	Healthcare	Exenatide (daily) vs. sitagliptin or glyburide	UKPDS	Lifetime	3%	DSA	Industry
Kiadaliri et al., 2014 [26]	Sweden	Societal	GLP-1RA vs. DPP-4i or NPH insulin	IHECM	35Y	3%	DSA and PSA	Public funding
SGLT2i vs. others[b]								
Reifsnider et al., 2021 [23]	USA	Payer	Empagliflozin vs. sitagliptin	DICE	Lifetime	3%	Scenario, DSA and PSA	Industry

Table 1 continued

Author, year	Region	Perspective	Interventions	Model	Time horizon	Discount rate	Sensitivity analysis	Funding
Charokopou et al., 2015 [22]	UK	Healthcare	Dapagliflozin vs. sitagliptin	Cardiff	40Y	3.5%	Scenario, DSA and PSA	Industry
Bagepally et al., 2021 [20]	India	Payer	Dapagliflozin vs. SU	Markov	Lifetime	3%	DSA and PSA	Public funding
Charokopou et al., 2015 [21]	UK	Healthcare	Dapagliflozin vs. SU	Cardiff	40Y	3.5%	Scenario, DSA and PSA	Industry
Tzanetakos et al., 2016 [24]	Greece	Payer	Dapagliflozin vs. DPP-4i or SU	Cardiff	40Y	3.5%	Scenario, DSA and PSA	Industry
DPP-4i vs. others[c]								
Gu et al., 2015 [33]	China	Payer	Saxagliptin vs. glimepiride	Cardiff	40Y	3%	DSA and PSA	Industry
Elgart et al., 2013 [28]	Argentina	Payer	Saxagliptin vs. SU	Cardiff	20Y	3.5%	DSA and PSA	Industry
Granström et al., 2012 [31]	Sweden	Not specified	Saxagliptin vs. glipizide	Cardiff	40Y	3%	DSA and PSA	Not specified
Erhardt et al., 2012 [29]	Germany	Payer	Saxagliptin vs. glipizide	Cardiff	40Y	3%	DSA and PSA	Industry
Grzeszczak et al., 2012 [32]	Poland	Payer	Saxagliptin vs. NPH insulin	Cardiff	40Y	3.5%	Scenario, DSA and PSA	Industry
Kousoulakou et al., 2017 [35]	Greece	Payer	Vildagliptin vs. glimepiride	UKPDS	Lifetime	4%	DSA	Industry

Table 1 continued

Author, year	Region	Perspective	Interventions	Model	Time horizon	Discount rate	Sensitivity analysis	Funding
Viriato et al., 2014 [37]	Portugal	Healthcare	Vildagliptin vs. SU	UKPDS	40Y	5%	Scenario, DSA and PSA	Industry
Gordon et al., 2016 [30]	UK	Not specified	Alogliptin vs. glipizide	CORE	50Y	3.5%	Scenario, DSA and PSA	Industry
Schwarz et al., 2008 [36]	Europe	Not specified	Sitagliptin vs. rosiglitazone or SU	JADE	Lifetime	3%-6%	DSA	Not specified
Gu et al., 2016 [34]	China	Payer	Saxagliptin vs. acarbose	Cardiff	40Y	3%	DSA and PSA	Industry
Gordon et al., 2017 [15]	UK	Payer	DPP-4i vs. SU or TZD	CORE	50Y	3.5%	PSA	Industry
Multiple antidiabetic drugs								
CADTH, 2017 [40]	Canada	Healthcare	SU, DPP-4i, SGLT2i, GLP-1RA, basal insulin or biphasic insulin	UKPDS	40Y	NA	Scenario, DSA and PSA	Public funding
Klarenbach et al., 2011 [41]	Canada	Payer	Metformin, SU, Meglitinide, AGI, TZD, DPP-4i, basal insulin or biphasic insulin	UKPDS	40Y	5%	DSA	Public funding
Chien et al., 2020 [39]	Taiwan	Payer	SU, SGLT2i, GLP-1RA, DPP-4i or insulin	Cardiff	40Y	3%	Scenario, DSA and PSA	Public funding

Table 1 continued

Author, year	Region	Perspective	Interventions	Model	Time horizon	Discount rate	Sensitivity analysis	Funding
Gu et al., 2020 [38]	China	Healthcare	SU, TZD, AGI, meglitinide or DPP-4i	Cardiff	40Y	3%	Scenario, DSA and PSA	No funding

AGI α-glucosidase inhibitors, *CADTH* Canadian Agency for Drugs and Technologies in Health, *CORE* Centre for Outcomes Research Diabetes Model, *DICE* discretely integrated condition event, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *DSA* deterministic sensitivity analysis, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *IHECM* Swedish Institute for Health Economics Cohort Model, *JADE* Januvia Diabetes Economic Model, *NPH* neutral protamine Hagedorn, *PSA* probabilistic sensitivity analysis, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *SU* sulfonylurea, *TZD* thiazolidinedione, *UKPDS* UK prospective diabetes study outcomes

[a]GLP-1RA vs. DPP-4i, SU or insulin

[b]SGLT2i vs. DPP-4i or SU

[c]DPP-4i vs. SU, TZD, AGI or insulin

The most frequently used models in order were Cardiff (n = 11) [21, 22, 24, 28, 29, 31–34, 38, 39], CORE diabetes model (n = 6) [14–16, 18, 25, 30], UK Prospective Diabetes Study Outcomes (UKPDS) (n = 5), discretely integrated condition event (DICE) (n = 2) [19, 23], Swedish Institute for Health economics cohort model (IHECM) (n = 2) [17, 26], Januvia Diabetes Economic (JADE) (n = 1) [36], and Markov (n = 1) [20].

More than half (57.1%, 16/28) of the studies examined the payer perspective [15, 16, 18–20, 23–25, 28, 29, 32–35, 39, 41]. Only two studies adopted societal [17, 26], the remaining seven were healthcare [14, 21, 22, 27, 37, 38, 40], and three were unspecified [30, 31, 36]. The most reported funding was sponsored by pharmaceutical companies (71.4%, 20/28) [14–19, 21–25, 27–30, 32–35, 37], five were public funding [20, 26, 39–41], one was no funding [38], and two were not stated [31, 36].

Quality of the Included Studies

Figure 2 presents the quality assessment results of the design and performance of pharmacoeconomic analysis of second-line therapies for T2D using the CHEERS guideline. According to the quality assessment, approximately 70% (20/28) of studies met the high-quality criteria (Supplementary Table S3). The most frequently unreported were item 21, "Approach to engagement with patients and others affected by the study," and item 25, "Effect of engagement with patients and others affected by the study."

Pharmacoeconomics Evaluation Results

Tables 2 and 3 summarize the economic outcomes of the included studies.

GLP-1 RA vs. SGLT2i

Four studies compared the cost-effectiveness of GLP-1 RA and SGLT2i as second-line treatments, with SGLT2i consistently indicating greater cost-effectiveness [14, 16, 18, 19]. Three studies agree that SGLT2i conferred more

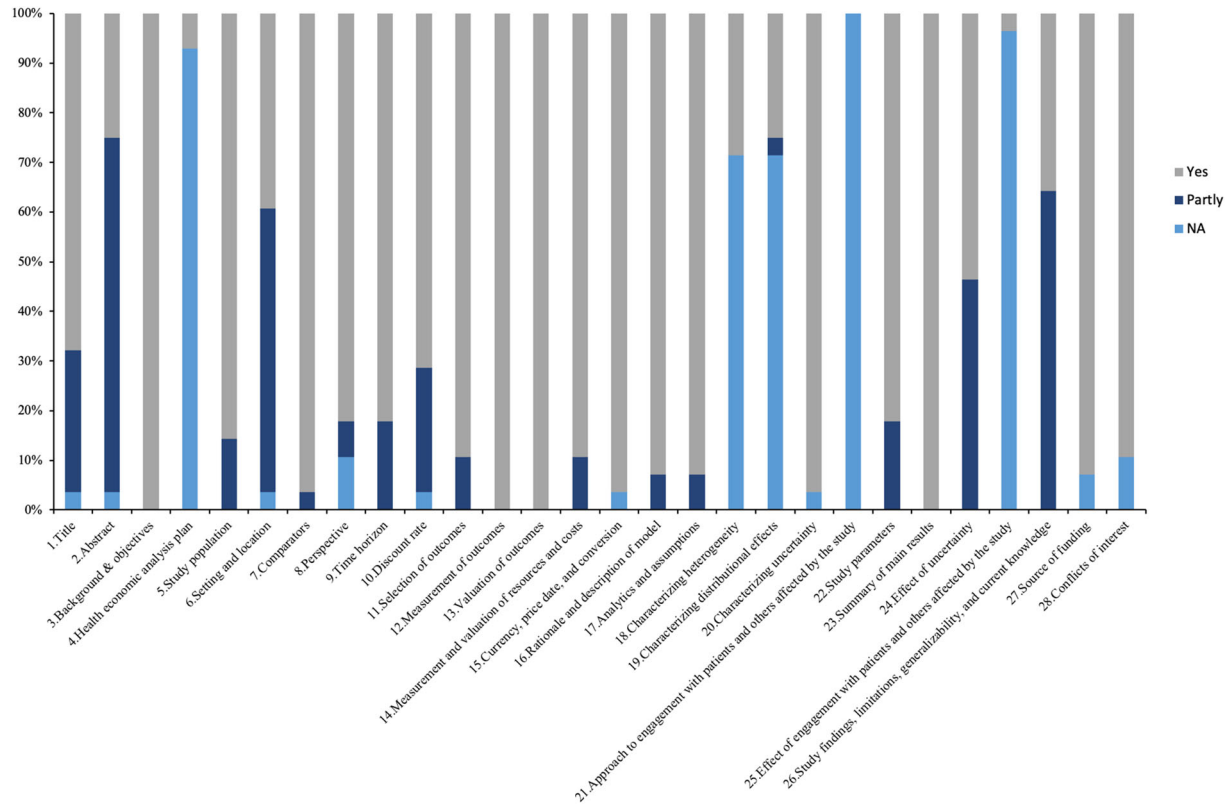

Fig. 2 Quality evaluation result based on CHEERS 2022

QALYs at less cost than GLP-1RA, making it an economically dominant treatment strategy [14, 16, 19]. Sensitivity analysis revealed that the main driver of cost-effectiveness was drug price, with the average annual treatment costs for GLP-1RA (oral/subcutaneous semaglutide or liraglutide) being two to three times that of SGLT2i (empagliflozin) (Supplementary Table S4). One of the studies performed a subgroup analysis based on the inclusion or exclusion of the effect of treatment on heart failure [16]. After excluding the effect on heart failure, empagliflozin plus metformin continued to dominate oral semaglutide plus metformin.

GLP-1 RA vs. Others

Two cost-utility studies based on LEAD-2 [42] and 1860-LIRA-DPP-4 [43] trial indicated that liraglutide combined with metformin monotherapy was a highly cost-effective second-line strategy for treating T2D versus sitagliptin or glimepiride, respectively [17, 25]. Similar conclusions were also observed in a cost-utility analysis of GLP-1 RA compared to DPP-4i or neutral protamine Hagedorn insulin in Sweden [26]. However, short-acting exenatide and sitagliptin as second-line therapy for new-onset diabetes in the USA have cost-effectiveness ratios that exceed the threshold, making them expensive [27].

SGLT2i vs. Others

Two studies compared SGLT2i to DPP-4i [22, 23], two studies compared SGLT2i to SU [8, 21], and one study compared SGLT2i to both DPP-4i and SU [24]. The cost-effectiveness analysis consistently revealed that SGLT2i was more cost-effective than DPP-4i or SU over a range of values for the accepted cost-effectiveness threshold. Although SGLT2i has higher therapy costs than DPP4i or SU, the cost may be partially counterbalanced by the lower total cost of diabetes-related complications and managing severe hypoglycemia due to the

Table 2 Base case analyses of newer antidiabetic drugs combined with metformin as second-line treatment

Author	Currency year	Interventions	Comparator	ICER[a]		INMB[b]		Cost-effectiveness
				Original	2022 US dollars	Original	2022 US dollars	
GLP-1RA vs. SGLT2i								
Ehlers et al. [18]	2019	Semaglutide 1 mg/week	Empagliflozin 25 mg/day	DKK 745,561	USD 108,332	DKK -50,500	USD -7338	SGLT-2i
Ehlers et al. [14]	2019	Liraglutide 1.8 mg/day	Empagliflozin 25 mg/day	Dominated		DKK -88,420	USD -12,848	SGLT-2i
Ramos et al. [16]	NA	Semaglutide 14 mg/day	Empagliflozin 25 mg/day	Dominated		GBP -6648	USD -9940	SGLT-2i
Reifsnider et al. [19]	2019	Liraglutide 1.8 mg/day	Empagliflozin 25 mg/day	Dominated		USD -27,244	USD -28,978	SGLT-2i
GLP-1RA vs. others[c]								
Steen Carlsson et al. [17]	2013	Liraglutide 1.2 mg/day	Glimepiride 4 mg/day	SEK 226,047 to 255,121[f]	USD 30,563 to 34,494[f]	SEK 77,765 to 99,642[f]	USD 10,514 to 13,472 [f]	GLP-1RA
		Liraglutide 1.2 mg/day	Sitagliptin 100 mg/day	SEK 148,766 to 160,827 [f]	USD 20,114 to 21,745 [f]	SEK 113,102 to 133,377[f]	USD 15,292 to 18,034 [f]	
Davies et al. [25]	2008	Liraglutide 1.2/1.8 mg/day	Glimepiride 4 mg/day	GBP 9449/16,501	USD 17,337/30,275	GBP 3397/1,112	USD 12,104/7,361	GLP-1RA
		Liraglutide 1.2/1.8 mg/day	Sitagliptin 100 mg/day	GBP 9851/10,465	USD 18,074/19,201	GBP 1758/2776	USD 6528/10,598	
Sinha et al. [27]	2008	Exenatide 20 µg/d	Glyburide 7.5 mg/d	USD 278,935	USD 353,523	USD -14,253	USD -18,064	SU
		Sitagliptin 100 mg/day	Glyburide 7.5 mg/day	USD 169,572	USD 214,916	USD -19,574	USD -24,808	
		Exenatide 20 µg/d	Sitagliptin 100 mg/d	Dominated		USD -5321	USD -6744	

Table 2 continued

Author	Currency year	Interventions	Comparator	ICER[a]		INMB[b]		Cost-effectiveness
				Original	2022 US dollars	Original	2022 US dollars	
Kiadaliri et al. [26]	2013	GLP-1RA	DPP-4i	SEK 353,172	USD 47,752	SEK 15,135	USD 2046	GLP-1RA
		GLP-1RA	NPH insulin 40 IU/day	SEK 160,618	USD 21,717	SEK 84,198	USD 11,384	
		DPP-4i	NPH insulin 40 IU/day	SEK 36,050	USD 4874	SEK 69,063	USD 9338	
SGLT2i vs. others[d]								
Reifsnider et al. [23]	2018	Empagliflozin 10–25 mg/day	Sitagliptin 50–100 mg/day	USD 6967	USD 7542	USD 8182	USD 8858	SGLT-2i
Charokopou et al. [22]	2011	Dapagliflozin 10 mg/day	Sitagliptin 100 mg/day	GBP 6761	USD 11,797	GBP 424	USD 740	SGLT-2i
Bagepally et al. [20]	2017	Dapagliflozin 10 mg/day	SU	INR 106,133	USD 6596	USD 87,061	USD 5410	SGLT-2i
Charokopou et al. [21]	2011	Dapagliflozin 10 mg/day	SU	GBP 1246	GBP 2671	GBP 7954	USD 13,878	SGLT-2i
Tzanetakos et al. [24]	2015	Dapagliflozin 10 mg/day	DPP-4i	EUR 17,695	USD 32,665	EUR 944	USD 1743	SGLT-2i
			SU	EUR 10,623	USD 19,610	EUR 11,518	USD 21,262	
DPP-4i vs. others[e]								
Gu et al. [33]	2014	Saxagliptin 5 mg/day	Glimepiride 2.8 mg/day	Dominate		CNY 88,136	USD 28,697	DPP-4i
Elgart et al. [28]	2009	Saxagliptin	SU	USD 7374	USD 11,666	USD 45	USD 2	DPP-4i
Granström et al. [31]	2008	Saxagliptin 5 mg/day	Glipizide 14.7 mg/day	SEK 91,260	USD 13,184	SEK 40,516	USD 5853	DPP-4i
Erhardt et al. [29]	2009	Saxagliptin	Glipizide	EUR 13,931	USD 22,199	NA	NA	DPP-4i

Table 2 continued

Author	Currency year	Interventions	Comparator	ICER[a]		INMB[b]		Cost-effectiveness
				Original	2022 US dollars	Original	2022 US dollars	
Grzeszczak et al. [32]	2009	Saxagliptin 5 mg/day	NPH insulin 25 IU/day	PLN 27,454	USD 19,245	PLN 9336	USD 6544	DPP-4i
Kousoulakou et al. [35]	2014	Vildagliptin	Glimepiride	Dominate		EUR 1561	USD 2872	DPP-4i
Viriato et al. [37]	2013	Vildagliptin	SU	EUR 9072	USD 17,291	EUR 2679	USD 5106	DPP-4i
Gordon et al. [30]	2015	Alogliptin 12.5/25 mg/day	Glipizide 5 mg/day	GBP 10,959/7217	USD 18,092/11,915	GBP 1989/3218	USD 3284/5313	DPP-4i
Schwarz et al. [36]	2007	Sitagliptin	Rosiglitazone	Dominate to EUR 4766	Dominate to USD 6918	NA	NA	DPP-4i
		Sitagliptin [g]	SU [g]	EUR 5949 to 20,350	USD 11,923 to 31,880	NA	NA	
		Sitagliptin[h]	SU[h]	EUR 6029 to 13,655	USD 12,084 to 21,392	NA	NA	
Gu et al. [34]	2014	Saxagliptin 5 mg/day	Acarbose 150 mg/day	Dominate		CNY 41,304	USD 12,927	DPP-4i

Table 2 continued

Author	Currency year	Interventions	Comparator	ICER[a]		INMB[b]		Cost-effectiveness
				Original	2022 US dollars	Original	2022 US dollars	
Gordon et al. [28]	2015	DPP-4i	SU	GBP 18,680	USD 30,839	GBP 531	USD 877	DPP-4i
			TZD	GBP 15,343	USD 25,480	GBP 1431	USD 2362	

DPP-4i dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *ICER* incremental cost-effectiveness ratio; *INMB* incremental net monetary benefit, *NPH* neutral protamine Hagedorn, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *SU* sulfonylurea, *TZD* thiazolidinedione

[a]If ICER > WTP, indicated intervention is not cost-effective; if ICER < WTP, indicated intervention is cost-effective; if ΔCost < 0 and ΔQALY > 0, indicated intervention is dominant (cheaper and more effective); if ΔCost > 0 and ΔQALY < 0, indicated intervention is dominated (costly and less effective)

[b]If INMB > 0, indicated intervention is cost-effective; if INMB < 0, indicated intervention is not cost-effective

[c]GLP-1RA versus DPP-4i, SU, or Insulin

[d]SGLT2i versus DPP-4i or SU

[e]DPP-4i versus SU, TZD, AGI, or insulin

[f]Subgroup analyses stratified according to gender and smoking status

[g]Metformin combined with basal insulin as third line

[h]Metformin combined with rosiglitazone as third line

Table 3 Base case analyses of multiple antidiabetic drugs combined with metformin as second-line treatment

Author	Currency year	Second line	QALYs	Total costs		Rank of cost-effectiveness
				Original	2022 US dollar	
CADTH [40]	2016	**SU**	8.8784	CAD 39,251	USD 35,219	**1**
		Metformin	8.8369	CAD 37,648	USD 33,780	2
		SGLT2i	8.9530	CAD 49,308	USD 44,242	3
		DPP-4i	8.8998	CAD 48,859	USD 45,674	4
		Basal insulin	8.8998	CAD 54,852	USD 51,276	5
		GLP-1RA	8.9894	CAD 55,946	USD 52,299	6
		Biphasic insulin	8.9340	CAD 63,719	USD 59,565	7
Klarenbach et al. [41]	2009	**SU**	8.72	CAD 40,669	USD 42,318	**1**
		AGI	8.77	CAD 42,797	USD 44,532	2
		Meglitinide	8.78	CAD 42,269	USD 43,983	3
		Metformin	8.72	CAD 39,924	USD 41,543	4
		TZD	8.78	CAD 46,202	USD 48,075	5
		DPP-4i	8.78	CAD 47,191	USD 49,104	6
		Basal insulin	8.78	CAD 47,348	USD 49,268	7
		Biphasic insulin	8.77	CAD 52,367	USD 54,490	8
Chien et al. [39]	2019	**SGLT2i (SU as third line)**	12.483	NTD 283,709	USD 7593	**1**
		SGLT2i (DPP-4i as third line)	12.548	NTD 287,891	USD 7705	2
		SU (SGLT2i as third line)	11.943	NTD 249,626	USD 6681	3
		DPP-4i (SGLT2i as third line)	12.345	NTD 282,722	USD 7566	4
		DPP-4i (SU as third line)	11.931	NTD 270,820	USD 7248	5
		GLP-1RA (SU as third line)	12.453	NTD 452,043	USD 12,098	6
		SU (DPP-4i as third line)	11.469	NTD 246,858	USD 6607	7
		Insulin (SU as third line)	11.064	NTD 278,502	USD 7453	8
Gu et al. [38]	2019	**Meglitinide (Insulin as third line)**	14.085	CNY 55,729	USD 16,872	**1**
		AGI (Insulin as third line)	14.019	CNY 60,741	USD 18,390	2
		DPP-4i (insulin as third line)	14.051	CNY 69,467	USD 21,031	3
		Meglitinide (GLP-1RA as third line)	14.117	CNY 85,142	USD 25,777	4
		SU (insulin as third line)	13.965	CNY 52,923	USD 16,023	5
		TZD (INS as third line)	13.978	CNY 56,374	USD 17,067	6
		AGI (GLP-1RA as third line)	14.053	CNY 89,690	USD 27,154	7
		DPP-4i (GLP-1RA as third line)	14.084	CNY 98,597	USD 29,850	8
		SU (GLP-1RA as third line)	13.997	CNY 81,569	USD 24,695	9
		TZD (GLP-1RA as third line)	14.011	CNY 85,095	USD 25,763	10

AGI α-glucosidase inhibitors, *CADTH* Canadian Agency for Drugs and Technologies in Health, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *ICER* incremental cost-effectiveness ratio, *NPH* neutral protamine Hagedorn, *QALYs* quality adjusted life years, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *SU* sulfonylurea, *TZD* thiazolidinedione

lower cumulative incidence of these events. One study analyzed the baseline presence or absence of cardiovascular disease and payer perspectives on health insurance type (commercial or Medicare) using scenario analysis. The cost per QALY ranged between USD 3589 and USD 12,577, below the USD 50,000 willingness to pay (WTP) threshold commonly suggested for health intervention cost-effectiveness [23].

DPP-4i vs. Others

Eleven studies compared cost-utility in DPP-4i and conventional oral hypoglycemic agents [α-glucosidase inhibitors (AGI), TZD, SU] or NPH insulin as second-line therapy added to metformin in T2D, more than half of which were saxagliptin [28, 29, 31–34], one of them was DPP-4i [15], and the rest were two vildagliptin [35, 37], one alogliptin [30], and one sitagliptin [36]. These results consistently indicated that DPP-4i was cost-effective. Sensitivity analysis exhibited that DPP-4i had fewer hypoglycemia adverse effects and a weight-neutral profile than traditional antidiabetic drugs. The resulting health and economic benefits offset the overall increased costs associated with managing diabetes-related complications and purchasing medications. This conclusion was validated in economic assessment based on a real-world observational study in the older population with T2D [15].

Multiple Antidiabetic Drugs

Four studies conducted a cost-utility analysis of multiple second-line T2D treatment strategies (Supplementary Table S5). One study excluded SGLT2i and GLP-1RA from the comparative analysis because they were commercially unavailable at the start of this study. Two Canadian cost-effectiveness studies comparing multiple antidiabetic agents as second-line treatment options indicated that SU was the most cost-effective choice [40, 41]. The other two studies evaluating the cost-utility of different hypoglycemic agent classes combined with second-line escalation therapies [38, 39] reached contradictory results. SGLT2i as the second line and DPP-4i as the third line were the most cost-effective in Chinese Taiwan. However, meglitinide as the second line and insulin as the third line were the most cost-effective in China.

Overall, these results demonstrated that SU was still highly cost-effective in second-line antidiabetic drugs when antidiabetic drug availability was poor or the WTP cost threshold was low. Otherwise, SGLT2i was more cost-effective because of weight loss, resulting in lower follow-up treatment costs and greater utility.

DISCUSSION

The present study systematically reviewed the cost-effectiveness of second-line antidiabetic therapy in T2D, including newer (GLP-1RA, SGLT2i and DPP-4i) and traditional hypoglycemic agents (SU, TZD, AGI, and insulin). The Cardiff and CORE models are the most commonly suggested health economic model of T2D. Based on the CHEERS checklist, most reviewed studies have good quality.

The base case analysis indicates that SGLT2i was more cost-effective than GLP-1RA and DPP-4i. GLP-1RA had better cost-effectiveness than DPP-4i and insulin in three evaluations. DPP-4i was cost-effective compared to traditional hypoglycemic agents, consistent with previously reported cost-effectiveness analyses. The remaining four comparative evaluations analyzed multiple strategies that SU or SGLT2i was the preferred second-line option for treatment failure with metformin monotherapy. New hypoglycemic agents have better cost-effectiveness as second-line therapy in treating T2D with the continuous improvement of the accessibility of new hypoglycemic agents, and the efficacy and safety data accumulation, especially the conclusions of cost–benefit advantages of SGLT2i, are mostly consistent.

A systematic review evaluated the cost-effectiveness of SGLT2i for T2D revealed that SGLT2i was more cost-effective than GLP-1RA and classic antidiabetic treatment options among patients who were not meeting HbA1c goals on metformin, especially for elevated CVD risk [7]. A similar study indicated that SGLT-2i and GLP-1RA were more cost-effective than

DPP-4i and conventional hypoglycemic agents as second-line T2D treatment options [44]. Our comprehensive pharmacoeconomic evaluation of second-line treatment options for T2D has yielded some inconsistent results. This may be related to heterogeneity in economic simulation modeling in T2D, simulated treatment pathways and switching thresholds for treatment escalation in the study design, and susceptibility of different ethnicities to T2D.

The Canadian Agency for Drugs and Technologies in Health suggested that replacing SU as the most cost-effective option would result in price reductions of 60% and 70% on SGLT2i and GLP-1RA, respectively. Since the HTA report used the UKPDS model, the independent assessment of SGLT-2 and GLP-1 cardiovascular benefits may have been limited. Furthermore, it was hypothesized that metformin, in combination with a hypoglycemic agent as a long-term treatment for T2D, might not entirely reflect standard clinical practice.

Other cost-utility analyses using the Cardiff model revealed that SGLT2i as second line and DPP-4i as third line were the most cost-effective choices in Chinese Taiwan, but in China, meglitinide sequential add-on insulin was the best in the absence of SGLT2i. There are several potential reasons for this difference. Second-line escalation strategies were set inconsistently. Unlike the second-line setting of GLP-1RA in Chinese Taiwan, GLP-1RA was assumed as the third line in China. However, the efficacy data input models are heterogeneous because they are obtained from different included studies meta-analyzed. According to Gu et al., meglitinide as second line has better weight control, HbA1c reduction, and lower risk of hypoglycemia compared to SU, TZD, AGI, and DPP-4i, contradicting other cost-effective analyses. This may be related to the effect of ethnicity on glucose metabolism and insulin regulation. Compared with Caucasian people, the onset of T2D in the Asian population is characterized by limited β cell reserve, and inability to compensate for the slight decrease in insulin sensitivity, which can lead to β cell dysfunction prior to the decrease in insulin sensitivity and an increased risk for developing T2D [45]. In addition, since the Asian population has a higher carbohydrate content in its diet than the Western population, the glycemic response to the same glycemic load is also greater. Thus, the hypoglycemic regimen is more suitable for insulin secretagogue, which mainly reduces postprandial glycemia.

The current studies have several limitations. First, classical economic evaluation models of diabetes, such as UKPDS, may not meet all requirements because of the unique cardiovascular protective effects of GLP-1RA and SGLT-2i that are independent of their hypoglycemic effects. Therefore, there are growing appeals for encouraging the incorporation of new CVOT data on drug-mediated cardioprotection in the T2D economic model [46, 47]. Second, most clinical trial data of hypoglycemic drugs are currently based on the Caucasian population, and there is a lack of data support for the Asian population. Additional prospective studies are therefore needed to understand better the effects of different ethnic groups on the efficacy and safety of novel hypoglycemic agents. This can provide more personalized and targeted management strategies, especially for Asian populations. Third, in terms of study design, only a few studies have included costs from a societal perspective. An economic and health burden analysis of cardiovascular disease in the T2D population suggested that total healthcare costs were comparable to total lost productivity costs. The productivity loss due to premature mortality accounted for 42.65% of the indirect costs [48]. Hence, omitting the indirect costs is likely to underestimate the cost-effectiveness of SGLT2i in reducing all-cause mortality. In addition, the pharmaceutical industry funded approximately 70% of the included studies, which may cause bias in favor of newer antidiabetic agents' cost-effectiveness.

Despite these limitations, the current studies' findings have important implications for future research and clinical practice, suggesting that the pattern of glucose-lowering drug use has changed substantially, with novel antidiabetic drugs increasingly being used as second-line therapies. The trade-off among efficacy, safety, and cost of novel hypoglycemic drugs underscores the importance of cost-effectiveness analyses in practical clinical practice with

accumulating CVOT evidence for hypoglycemic agents. Although only one second-line study in our systematic review used real-world data, this method of using real-world evidence in pharmacoeconomics will become more mainstream, potentially identifying subgroups that benefit the most from particular interventions to facilitate clinical care and health policy decisions and optimize health care resource allocation.

CONCLUSION

Our systematic review suggests that newer antidiabetic drugs are cost-effective therapy in second-line options following metformin monotherapy with T2D than classic glucose-lowering agents. Cost-effectiveness analysis suggested that SGLT2i was a dominant strategy compared with GLP-1RA as an add-on treatment to metformin. DPP-4i has good safety profiles and weight neutrality, showing predominant cost-effectiveness in relation to other classical antidiabetic drugs but is less favorable than GLP-1RA and SGLT2i. When comparing various classes of antidiabetic drugs, the simulated treatment pathways by different studies and the accessibility and affordability of new antidiabetic drugs in different regions had significant heterogeneity. Therefore, it is difficult to draw definitive conclusions regarding which hypoglycemic agents should be recommended as the preferred second-line treatment from a cost-effectiveness perspective. However, as newer antidiabetic drugs reach patent expiry, SGLT2i may have potential as the preferred second-line treatment after metformin failure in T2D as the potential impact of generics could decrease the economic burden.

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