



Original article

Economic analysis of glucagon like peptide-1 receptor agonists from the Saudi Arabia payer perspective



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ABSTRACT

Objectives: To perform a cost of control analysis of glucagon like peptide-1 receptor agonists (GLP1RA) in Saudi Arabia (SA) and determine the economic impact of adopting GLP1RAs.

Methods: A budget impact model that captures the cost of control model was constructed to simulate hypothetical patient on six treatment options: a current mix of 60% liraglutide and 40% dulaglutide, semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide. We estimated the relative amounts of SAR spend to achieve HbA1c targets ($\leq 6.5\%$ or $< 7.0\%$). For each treatment option, annual treatment cost, proportion of patients achieving HbA1c targets, and cost to treat major adverse cardiovascular events (MACE) were aggregated to estimate the cost of control per patient per year (CCPPPY) over 5-year horizon (2021–2025). Probabilistic sensitivity analysis (PSA) was performed as a confirmatory analysis.

Results: The CCPPPY to achieve HbA1c $\leq 6.5\%$ / $< 7.0\%$ using current mix, semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide were SAR 17,097/SAR 14,113, SAR 12,889/SAR 11,123, SAR 15,594/SAR 12,892, SAR 19,184/SAR 15,940, SAR 580,211/SAR 380,936, and SAR 246,570/SAR 143,759, respectively. The relative amounts of SAR spend to achieve HbA1c $\leq 6.5\%$ / $< 7.0\%$ relative to 1 SAR on semaglutide in case of adopting current mix, liraglutide, dulaglutide, exenatide, and lixisenatide were SAR 1.42/SAR 1.18, SAR 1.30/SAR 1.07, SAR 1.60/SAR 1.33, SAR 48.33/SAR 31.73, and SAR 20.54/SAR 11.97, respectively. These results were confirmed in the PSA.

Conclusions: Semaglutide 1 mg once weekly was the most economically favorable GLP1RA; associated with the least CCPPPY, and amount of SAR spent to achieve HbA1c of $\leq 6.50\%$ / $< 7.00\%$ versus all other GLP1RAs.

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1. Introduction

Globally, the estimated number of adults (20–79 years) living with diabetes mellitus (DM) has soared to 463 million in 2019 (“International Diabetes Federation Atlas, 9th Edition,” 2019). This number is projected to increase to 700 million by 2045 (“International Diabetes Federation Atlas, 9th Edition,” 2019). Based on data from the International Diabetes Federation (IDF), type 2 diabetes mellitus (T2DM) accounts for 91% of total number of DM cases (“International Diabetes Federation Atlas, 9th Edition,” 2019). With this in mind, the estimated economic burden of DM

was US\$ 760 billion in 2019 (“International Diabetes Federation Atlas, 9th Edition,” 2019). In addition, the direct cost of T2DM in high-income countries is higher than in low-to middle income countries (Alzaid et al., 2020; “International Diabetes Federation Atlas, 9th Edition,” 2019; Xu et al., 2018).

In high-income countries, healthcare decision makers are trying to reduce the economic burden of T2DM, and its related micro- and macro-vascular complications (Alhowaish, 2013) by considering different measures like adopting innovative and efficacious treatments that showed clinical superiority over the conventional treatments. Glucagon like peptide-1 receptor agonists (GLP1RAs) are innovative T2DM therapies which can reduce bodyweight, optimize HbA1C readings, minimize the risk of hypoglycemia, and control blood pressure and serum lipid levels (Araki et al., 2020; Igarashi et al., 2020). In general, GLP1RAs are effective in reducing the cardiovascular risks in T2DM patients (Zafeiropoulos et al., 2021).

Saudi Arabia (SA) is a high-income country with a gross domestic product (GDP) of US\$ 793 billion in 2019 (The World Bank, 2021) and has one of the highest T2DM prevalence globally (Alanzi, 2018). The estimated prevalence of DM among Saudi adults is 18.3% in 2020 (~6,443,731 patient) (“International Diabetes Federation Atlas, 9th Edition,” 2019). This prevalence is projected to increase to 20.60% by 2030 (~8,454,337 patient) (“International Diabetes Federation Atlas, 9th Edition,” 2019). From an economic point of view, the World Health Organization (WHO) reported that people diagnosed with diabetes in SA, on average, have medical healthcare expenditures that are ten times higher than what expenditures would be in the absence of diabetes (US\$ 3686 versus US\$ 380) (Alhowaish, 2013; Mathers et al., 2003; Organization et al., 2005).

In 2014, the Saudi Ministry of Health spent around SAR 25 billion on direct management of all types of DM (Aitken, 2016). For T2DM only, the mean annual economic costs associated with T2DM complications were captured and projected from 2015 to 2025 at SAR 25.7 billion (Aitken, 2016). However, the avoidable complication cost due to the sub-optimal control was estimated at SAR 3.9 billion (Aitken, 2016). In 2014, different measures were taken by the Saudi government to improve patients' outcomes through delivering novel treatments and self-management technologies (Alanzi, 2018). Liraglutide once daily (QD) was approved by the Saudi Food and Drug Authority (SFDA) in 2014, followed by other GLP1RAs: exenatide twice daily (BID), dulaglutide once weekly (OW), lixisenatide QD, and lastly semaglutide QW in 2020. These GLP1RAs are recommended in health care settings, like in the health system in Saudi Arabia, in which the sub-optimal control of T2DM is frequently seen in DM clinics, and prevalence of overweight is high (36.9% of Saudi population) (Mohan et al., 2020; SS, 2016). Also, antidiabetic treatments are associated with risk of major adverse cardiovascular events (MACE). Such events are associated with high cost that may affect the decision making of antidiabetic treatments.

Although better glycemic control, reduction in patients' weight, and reduced risk of major adverse cardiovascular events (MACE) remain essential aspects of GLP1RAs, patient access and treatment costs are major limiting factors (Nauck et al., 2021; Stegbauer et al., 2020). Therefore, economic evaluation of GLP1RAs in SA is needed to inform decisions that can reduce the national burden of T2DM. Such economic evaluation has not been performed yet. In this study, we aimed to perform a budget impact analysis that captures the T2DM-based cost of control analysis per patient per year (CCPPPY) from the Saudi Arabia payer perspective. This cost of control is over 5-year time horizon (2021–2025) in which we captured and compared the costs attributed to the uptake of all approved GLP1RAs in the Saudi market.

2. Methods

2.1. Overview

In this study, we developed a cost of control model that compared the cost of control of a current mix scenario (60% uptake of liraglutide 1.8 mg QD and 40% dulaglutide 1.5 mg QW) with full-uptake scenarios of GLP1RAs in SA: semaglutide 1 mg QW, liraglutide 1.8 mg QD, dulaglutide 1.5 mg QW, exenatide 10 µg BID, and lixisenatide 20 µg QD. This cost of control model was constructed over 5-year time horizon, from 2021 to 2025, and costs were expressed in 2021 Saudi Arabian Riyal (SAR). The cost of control was evaluated for two treatment targets for routine practice: HbA1c ≤ 6.50% and HbA1c < 7.00%. These two targets were recommended by the American Diabetes Association (ADA) (American Diabetes Association, 2021) and the American Association of Clinical Endocrinologists (AACE) (Garber et al., 2020).

This analysis was aimed to capture the 5-year aggregated cost of control for an eligible cohort of T2DM patients in SA. To do so, we used a prevalence-based approach. In which, we multiplied the cost of control per patient per year by the number of eligible T2DM patients in Saudi Arabia. Then, head-to-head cost comparisons and assessment to patient access to GLP1RAs were performed, and relative amounts of SAR to spend to achieve targets of HbA1c were estimated.

2.2. Patient and public involvement

The economic model did not use patient level data. The inputs for the model were obtained from literature and the SFDA website.

2.3. Model inputs

Model inputs used in our analysis are shown in Table 1. The proportions of patients achieving the HbA1c targets, ≤ 6.50% and <7.00%, were obtained from a network meta-analysis (NMA) (Nuhoho et al., 2019). Our analysis used the median proportion for the base case results, reported in this study, and the credible intervals for probabilistic sensitivity analysis (PSA). The rate of MACE for each treatment arm was retrieved from a published network meta-analysis (NMA) (Table 1) (Alfayez et al., 2020).

For the cost estimates, the retail prices of GLP1RAs which represent the ceiling prices determined by the SFDA were obtained for all concentrations and retrieved from the SFDA website (Saudi Food and Drug Authority, 2021). The average cost of treating one case of MACE in SA was retrieved from a published article (Mokdad et al., 2015). The estimate was SAR 43,901 per an event, captured in 2014; we applied inflation rate to this estimate based on inflation rates estimated by the world bank and specified for Saudi Arabia (Statista, 2021). That is, this estimate was inflated based on 2021 SAR at SAR 48,464 per one case of MACE. Table 1 shows number of eligible patients to receive GLP1RAs in Saudi Arabia over five years from 2021 to 2025. We provided all statistical numbers and projections to estimate the prevalence of T2DM over the 5-year period (2021 to 2025) in the supplemental material.

As shown in the Table S1, the 5-year population in Saudi Arabia was obtained from published resources (Worldmeter, 2021). The 5-year estimated prevalence of DM (Type 1, Type 2, and other sub types) was obtained from published reports (“International Diabetes Federation Atlas, 8th Edition,” 2018, “International Diabetes Federation Atlas, 9th Edition,” 2019). Given that these estimates were for all types of DM, we aimed to estimate only T2DM population from these estimates by considering that 91% of all DM patients are T2DM as per published reports (“International Diabetes Federation Atlas, 8th Edition,” 2018).

Table 1
Input tables.

Input	Estimate		Reference
	HbA1c ≤ 6.50% % (95% CI)	HbA1c < 7.00% % (95% CI)	
Proportion of patients achieving HbA1c targets			
Semaglutide 1 mg QW	65.30% (50.40–77.50)	79.80% (69.30–87.40)	Nuhoho, 2019
Liraglutide 1.8 mg QD	45.80% (33.90–58.30)	64.60% (53.50–74.40)	Nuhoho, 2019
Dulaglutide 1.5 mg QW	49.00% (35.20–63.50)	64.70% (51.90–75.90)	Nuhoho, 2019
Exenatide 10 µg BID	29.20% (18.30–43.70)	44.70% (31.30–59.20)	Nuhoho, 2019
Lixisenatide 20 µg QD	23.50% (15.90–33.70)	41.10% (31.00–51.90)	Nuhoho, 2019
Current mix ¹	47.08% (34.42–60.38)	64.64% (52.86–75.00)	Weighted
MACE rate	Rate % (95% CI)		
Semaglutide 1 mg QW	6.55% (5.41% – 7.86%)		Alfayez , 2020
Liraglutide 1.8 mg QD	13.02% (10.07% – 14.02%)		Alfayez , 2020
Dulaglutide 1.5 mg QW	12.00% (11.11% – 12.94%)		Alfayez , 2020
Exenatide 10 µg BID	11.41% (10.69% – 12.15%)		Alfayez , 2020
Lixisenatide 20 µg QD	13.38% (12.19% – 14.64%)		Alfayez , 2020
Current mix ¹	12.61% (11.69% – 13.59%)		Estimated
GLP1RAs in Saudi Arabia	Retail price SAR²		
Semaglutide (QW): 0.25 mg (1.5 mg pen), 0.5 mg (1.5 mg pen), 1 mg (3 mg pen)	SAR 381		Saudi Food and Drug Authority, 2021. Drug List.
Liraglutide (QD): 6 mg/ml in 3 ml (2 pens)	SAR 397		Saudi Food and Drug Authority, 2021. Drug List.
Dulaglutide (QW): 0.75 mg, 1.5 mg (4 pens)	SAR 504		Saudi Food and Drug Authority, 2021. Drug List.
Exenatide (BID): 5 mcg, 10 mcg	5 mcg: SAR 161 10 mcg: SAR 236		Saudi Food and Drug Authority, 2021. Drug List.
Lixisenatide (QD): 10 mcg, 20 mcg (1 pen)	SAR 155		Saudi Food and Drug Authority, 2021. Drug List.
Cost of MACE management (per case)³	SAR 48,464		Saudi Food and Drug Authority, 2021. Drug List.
Number of eligible patients to receive GLP1RA in Saudi Arabia⁴	Number of patients (based on 1% of total T2DM cases in SA)		
2021	58,638		Estimated
2022	60,464		Estimated
2023	62,200		Estimated
2024	63,960		Estimated
2025	65,743		Estimated

Abbreviations: QW: once weekly; QD: once daily; BID: twice daily; MACE: major adverse cardiovascular events; GLP1RAs: glucagon like peptide-1 receptor agonists; T2DM: type II diabetes mellitus; CI = credible interval; SA: Saudi Arabia.

¹ At assumed uptakes of 60% from liraglutide and 40% from dulaglutide.

² Probabilistic sensitivity analysis used variations of ±10% of retail estimates.

³ Inflated as per 2021 prices in Saudi Arabia.

⁴ Estimated from projections that assumed 1% of T2DM prevalence as eligible cohort.

2.4. Assumptions

As shown in Table S2 of the supplemental material, we made three assumptions: first, we assumed that the GLP1RA market uptake involves a current mix of 60% for liraglutide 1.8 mg QD and 40% for dulaglutide 1.5 mg QW based on an expert opinion in Saudi market (Alkhatib N); second, because data on number of eligible patients for GLP1RAs in Saudi Arabia are lacking, we assumed that 1% of total T2DM patients are eligible to receive GLP1RAs; third, based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) principles of good practice, we assumed that the time horizon for such cost of control analysis is 5 years and no discount rates are applied (Sullivan et al., 2014).

2.5. Analysis

We simulated a single hypothetical patient in each treatment scenario for 1 year of uptake and estimated the cost of control per patient per year (CCPPPY). This was calculated by dividing the combined cost of treating MACE and the annual treatment cost by the proportion of patients achieving targets of HbA1c (≤6.50% and < 7.00%). Subsequently, the CCPPPY was multiplied by the eligible number of patients (1% of T2DM patients) specified for the

years 2021 to 2025 to estimate the 5-year horizon total cost of control.

We performed head-to-head cost comparisons between treatment options by estimating the difference in the 5-year horizon total cost of control. We estimated the savings achieved (from switching to a lower-cost alternative). Importantly, in case of treatment switching, we assessed the increase in percentage of patient access resulted from switching between treatments. For example, Y is a treatment with a given cost of SAR 10 and this is less expensive than X with a given cost of SAR 20; if X will be fully replaced with Y, this will yield savings of 100% in the resources which may be relocated to get an additional patient access to treatment Y (two patients can be treated with Y versus one patient can be treated with X at a neutral budget). In other words, this will yield a potential increase in patient access by 100%. Upon this, we estimated the increase in percentage of patient access when complete switching between higher-cost treatments and lower-cost treatments takes place. The calculation for the assessment of patient access relied on the median of 5-year total cost of control to achieve the two HbA1c targets.

We estimated relative amounts of SAR to spend to achieve the two targets of HbA1c. This was performed by estimating the median cost of control to achieve HbA1c ≤ 6.50% and HbA1c < 7.00% for all treatment options; and estimating the relative amount of SAR

Table 2
The annual cost of GLP1RAs and the cost of control per patient per year (CCPPPY).

GLP1RAs	Annual cost (per patient)	Cost of control per patient per year (CCPPPY)	
		HbA1c ≤ 6.50%	HbA1c < 7.0%
Semaglutide 1 mg QW	SAR 6,343	SAR 12,889	SAR 11,123
Liraglutide 1.8 mg QD	SAR 4,252	SAR 15,594	SAR 12,892
Dulaglutide 1.5 mg QW	SAR 6,551	SAR 19,184	SAR 15,940
Exenatide 10 µg BID	SAR 167,807	SAR 580,211	SAR 380,936
Lixisenatide 20 µg QD	SAR 56,420	SAR 246,570	SAR 143,759
Current mix	SAR 5,171	SAR 17,097	SAR 14,113

Abbreviations: QW: once weekly; QD: once daily; BID: twice daily; GLP1RAs: glucagon like peptide-1 receptor agonists; Current mix: 60% liraglutide and 40% dulaglutide.

which is the quotient of dividing the median of cost of control of a treatment over median of cost of another treatment. The analysis was performed in Microsoft® Excel® 365 MSO supporting visual basic coding for applications. We performed a PSA as a confirmatory analysis using Monte Carlo Simulation and the credible intervals around clinical estimates. The PSA results were reported in the supplemental material.

3. Results

The annual cost of GLP1RAs and the CCPPPY to achieve either HbA1c target of HbA1c ≤ 6.50% or HbA1c < 7% are shown in Table 2. Among all GLP1RA, liraglutide was associated with the lowest annual cost per patient at SAR 4,252 while exenatide was associated with the highest annual cost at SAR 167,807 (Table 2). In terms of the CCPPPY, semaglutide was associated with the lowest cost to bring one patient to HbA1c ≤ 6.50% at SAR 12,889 and SAR 11,123 to achieve HbA1c < 7%. Whereas exenatide was associated the highest CCPPPY to achieve HbA1c ≤ 6.50% at SAR 580,211 and SAR 380,936 to achieve HbA1c < 7%.

Fig. 1 shows the aggregated 5-year horizon cost of control for the eligible 1% of T2DM patients in SA based on the two HbA1c targets. The lowest aggregated 5-year horizon costs of control to bring 1% of T2DM patients in SA to the targets HbA1c ≤ 6.50% or < 7.00% were observed on treatment with semaglutide at SAR 4,008,395,903, and SAR 3,459,439,832, respectively. The treatment with exenatide was associated with highest costs at SAR 180,448,685,790 and SAR 118,473,332,928, respectively.

As shown in Table 3, the switching from one GLP1RA to another can result in a need for some cost saving. The switching from the exenatide to semaglutide leads to the most cost saving at both HbA1c targets (SAR 176,440,289 for HbA1c ≤ 6.50% / SAR 115,013,893,096 for HbA1c < 7.00%). Whereas the switching from the current mix to liraglutide only leads to the lowest cost saving at both HbA1c targets (SAR 467,440,099 for HbA1c ≤ 6.50% / SAR 379,656,616 for HbA1c < 7.00%). The head-to-head comparisons between the GLP1RAs alternatives were reported based on the 5-year cost of control to achieve either HbA1c targets for the eligible 1% of T2DM patients in SA and the cost differences (saving) from all head-to-head comparisons are shown in Table 3.

Besides the cost saving that could result from switching from one GLP1RA to another, the switching from one GLP1RA to lower-cost alternatives at a neutral budget can result in a corresponding increase in percentages of patient access to these alternatives. The switching from exenatide to semaglutide leads to the largest increases in patients' access to semaglutide by 4501.77% and 3324.64% to achieve HbA1c ≤ 6.50% and < 7.00%, respectively. Whereas the switching from current mix to liraglutide leads to the lowest increase in patients access to GLP1RAs by 9.64% and 9.47% to achieve HbA1c ≤ 6.50% and < 7.00%, respectively. The results from the head-to head comparison represented by the increase in patients' access to GLP1RAs are presented in Table 4.

In our analysis, semaglutide was associated with the least amount of SAR spent to achieve both HbA1c targets. The relative amount spent to achieve HbA1c ≤ 6.50% target relative to SAR 1 spent on once weekly semaglutide ranged between SAR 1.30 if liraglutide was adopted to SAR 48.33 if exenatide was adopted. Likewise, the relative amount spent to achieve HbA1c < 7.00% target relative to SAR 1 spent on once weekly semaglutide ranged between SAR 1.07 if liraglutide was adopted to SAR 31.73 if ex-

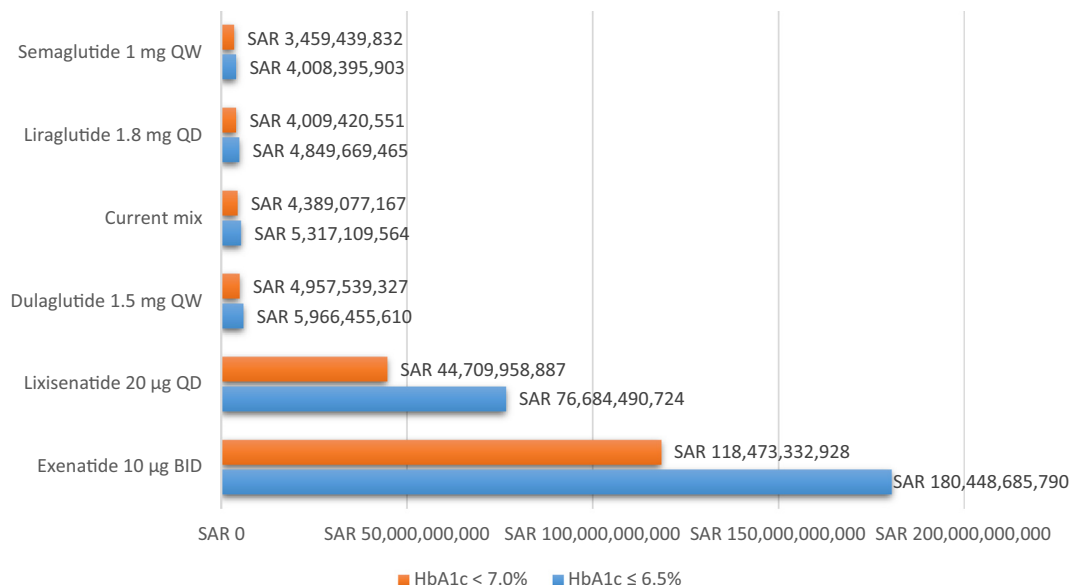


Fig. 1. The 5-year horizon total cost of control for eligible 1% of T2DM patients in Saudi Arabia. Abbreviations: QW: once weekly; QD: once daily; BID: twice daily; Current mix: 60% liraglutide and 40% dulaglutide.

Table 3
Head-to-head cost comparison model: the cost difference (saving) for both HbA1c targets $\leq 6.50\%$ or $< 7.00\%$.

Exenatide 10 µg BID	SAR 73,763,374,041	SAR 113,515,793,601	SAR 114,084,255,761	SAR 114,463,912,376	SAR 115,013,893,096
SAR 103,764,195,066	Lixisenatide 20 µg QD	SAR 39,752,419,560	SAR 40,320,881,720	SAR 40,700,538,335	SAR 41,250,519,055
SAR 174,482,230,180	SAR 70,718,035,114	Dulaglutide 1.5 mg QW	SAR 568,462,160	SAR 948,118,775	SAR 1,498,099,494
SAR 175,131,576,225	SAR 71,367,381,159	SAR 649,346,045	Current mix	SAR 379,656,616	SAR 929,637,335
SAR 175,599,016,324	SAR 71,834,821,258	SAR 1,116,786,144	SAR 467,440,099	Liraglutide 1.8 mg QD	SAR 549,980,719
SAR 176,440,289,887	SAR 72,676,094,821	SAR 1,958,059,707	SAR 1,308,713,662	SAR 841,273,563	Semaglutide 1 mg QW

Abbreviations: QW: once weekly; QD: once daily; BID: twice daily; Current mix: 60% liraglutide and 40% dulaglutide. Numbers above and beneath the diagonal line represent the 5-year cost difference between two GLP1RA alternatives(left column versus right column) to bring eligible patients to the HbA1c $\leq 6.50\%$ target (beneath) or HbA1c $< 7.00\%$ target (above).

Table 4
The increase in patients' access to GLP1RAs for both HbA1c targets $\leq 6.50\%$ or $< 7.00\%$.

Direction of complete switching					
Exenatide 10 µg BID	164.98%	2289.76%	2599.28%	2854.87%	3324.64%
135.31%	Lixisenatide 20 µg QD	801.86%	918.66%	1015.12%	1192.40%
2924.39%	1185.26%	Dulaglutide 1.5 mg QW	12.95%	23.65%	43.30%
3293.74%	1342.22%	12.21%	Current mix	9.47%	26.87%
3620.85%	1481.23%	23.03%	9.64%	Liraglutide 1.8 mg QD	15.90%
4401.77%	1813.10%	48.85%	32.65%	20.99%	Semaglutide 1 mg QW

Abbreviations: QW: once weekly; QD: once daily; BID: twice daily; GLP1RAs: glucagon like peptide-1 receptor agonists; Current mix: 60% liraglutide and 40% dulaglutide. Numbers above and beneath the diagonal line represent the increase or decrease in patients' access from switching between two GLP1RA alternatives (left column versus right column) while treating eligible patients to the HbA1c $\leq 6.50\%$ target (beneath) or HbA1c $< 7.00\%$ target (above).

Table 5
Amount spent to achieve target HbA1C relative to 1 SAR spent on once weekly semaglutide.

GLP1RAs	HbA1c $\leq 6.50\%$	HbA1c $< 7.0\%$
Semaglutide 1 mg QW	Reference	Reference
Liraglutide 1.8 mg QD	1.30	1.07
Current mix	1.42	1.18
Dulaglutide 1.5 mg QW	1.60	1.33
Lixisenatide 20 µg QD	20.54	11.97
Exenatide 10 µg BID	48.33	31.73

Abbreviations: QW: once weekly; QD: once daily; BID: twice daily; GLP1RAs: glucagon like peptide-1 receptor agonists; Current mix: 60% liraglutide and 40% dulaglutide.

natide was adopted. The amount spent to achieve either HbA1c targets relative to SAR 1 spent on once weekly semaglutide for other GLP1RAs alternatives are listed in Table 5.

4. Discussion

Five GLP1RAs were approved between 2014 and 2020 in Saudi Arabia. This study showed that semaglutide 1 mg QW was associated with the best economic outcomes versus other GLP1RAs from the payer perspective. While the annual cost of semaglutide was superseded by liraglutide, semaglutide was associated with the lowest rate of MACE. Therefore, semaglutide had the lowest CCPPPY and the lowest relative amount to spend to achieve either HbA1c targets. Exenatide was shown to have the highest CCPPPY and the total 5-year cost of control which resulted in the increase of the patients' access to other GLP1RAs when exenatide is fully replaced with one of the other GLP1RAs. The highest increase in the access was observed when exenatide is fully replaced with semaglutide. In this study, used the once weekly semaglutide as a reference option; that is, decisions to switch toward the once weekly semaglutide from other GLP1RA are informed by the expected increase in patients' access to semaglutide.

The lack of clinical data in some emerging markets would drive some to extrapolate results of clinical trials in international settings and use international guidelines. Importantly, these interna-

tional guidelines, while comprehensive, may not be appropriate for some regions; where epidemiology, patient phenotypes, cultural conditions, and socioeconomic status are different (Mohan et al., 2020). When assessing the efficacy or effectiveness of GLP1RAs in SA, data from clinical trials or real-world evidence are lacking. However, international studies showed that these GLP1RAs offer better delivery systems, efficacy in achieving target HbA1c, and weight reduction than other hypoglycemic agents but at higher costs (Giorgino et al., 2018; Prasad-Reddy and Isaacs, 2015; Sun et al., 2015). Considering lacking of country-specific clinical data, decision makers should carefully consider the cost of GLP1RAs when selecting these innovative agents over other conventional treatments; thus, there is a need to construct a balance between the necessity to achieve optimal glycemic control and the affordability and accessibility to GLP1RAs for eligible patients (Mohan et al., 2020).

The implications of our findings can be utilized in multiple ways. First, while different GLP1RAs were approved in the SA decision makers are in need for economic models, such as this study, to estimate the financial consequences of adopting these innovative agents. Moreover, patients with T2DM in SA may benefit from the clinical advantages that can be achieved by these agents, but no previous economic evaluation on GLP1RAs has been performed from the Saudi payer perspective. Thus, a transparent analysis to evaluate these GLP1RAs was warranted.

Second, GLP1RAs are available in different ready-to-use formulations, delivery systems, and dosing frequency. Semaglutide and dulaglutide had the advantage of being used once weekly. While liraglutide and lixisenatide are given once daily and exenatide is given twice daily. Studies performed in non-Saudi settings showed that once-weekly formulations of GLP1RAs were associated with better adherence rate and outcomes over once daily formulations (Giorgino et al., 2018; Qiao et al., 2016; Weeda et al., 2021). If this is the case in SA, semaglutide will be even more favorable over other available GLP1RA formulations from economic point of view.

Third, the methods of our model are reproducible to fit specific settings in SA. We suggested that 1% of T2DM population to be treated with GLP1RA. However, decision makers can easily increase or decrease the percentage of T2DM population who can be treated with GLP1RA and get the corresponding CCPPPY. In

addition, we have used retail prices for GLP1RAs, because tendering prices for public sectors are confidential. However, decision makers from public sectors can adjust the results of this study by applying discounts to retail prices used in this study to make the results more informative for tendering and national procurement commissions in SA.

Fourth, regardless of number of patients being treated, we have highlighted the relative value of one SAR invested on GLP1RAs to achieve two HbA1c targets. Apparently, treating patients to achieve more stringent targets of HbA1c would need more investment. In this study, aiming to achieve stringent HbA1c target of $\leq 6.50\%$ requires more investment by an average of 37% than achieving HbA1c target of $< 7.00\%$. This approach of estimating the relative value of 1 unit of a currency was previously suggested and used by Igarashi et al (Igarashi et al., 2020).

Fifth, the results of our study are consistent with the literature. While the study used the cost of control rather than cost-effectiveness analyses, this was mainly due to the lack of country-specific clinical data from SA. A cost-effectiveness analysis was performed using Japanese estimates to compare semaglutide versus dulaglutide, has shown that semaglutide was associated with better clinical-economic outcomes. The amount spent to achieve the targets of HbA1c relative to one Japanese yen (JPY) spent on semaglutide was 1.6 for dulaglutide (Igarashi et al., 2020). This relative value was same as reported in our study despite the purchasing power parity between the SAR to the JPY. Additionally, a cost of control analysis specified for all the available GLP1RAs in the US market, showed that the once weekly semaglutide was ranked second least cost burden over all other GLP1RAs after the oral semaglutide (Hansen et al., 2020); the latter is not yet available in the SA market.

This study has some limitations that needs to be addressed. Data on comparative efficacy and effectiveness of GLP1RAs specified for the SA population were lacking. Therefore, we conservatively generalized the efficacy data collected and summarized from 27 clinical trials in other settings (Nuhoho et al., 2019) to SA population. In addition, data on rates of MACE in SA are lacking. Thus, we used rates for MACE from an NMA of seven randomized clinical trials (Alfayez et al., 2020). However, the results of the NMA can be informative to the economic model used in this study. Also, we assessed the reliability of estimates by performing probabilistic sensitivity analysis that used ranges and confidence intervals reported in the NMAs. Lastly, we have assumed that the current mix of GLP1RA based on experts' opinion. While this was an assumption, it was validated from clinicians and sales experts in SA. Quality of life associated with the all treatment comparators in this study were not included. This is because efforts in literature to estimate utilities in Saudi Arabia were limited to insulin-based formulations (Jarab et al., 2019).

Further studies are needed to confirm the present findings and reveal the uncertainties associated with clinical and economic costs of GLP1RAs in Saudi Arabia. This study can be considered as a preliminary guidance to inform decisions that can reduce the national burden of T2DM on SA. Also, studies that estimate adherence with different GLP1RAs formulations should be performed for the Saudi perspective to better inform clinical and economic decisions for better understanding of patients' needs and strategizing for the budget efficiently.

5. Conclusion

The findings of this study indicated that the full uptake model of semaglutide 1 mg QW was the most economically favorable model for GLP1RAs in SA. Semaglutide 1 mg QW was associated with the least CCPPPY, and amount of SAR spent to achieve targets HbA1c of $\leq 6.50\%$ and $< 7.00\%$ versus all other GLP1RA. Therefore, the full

uptake of semaglutide 1 mg QW would improve patients' access to the class of GLP1RAs over the 5-year time horizon.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jsps.2022.01.018>.

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