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Research Paper

Cost-effectiveness of Empagliflozin Compared to Liraglutide in Iran Based on Cardiovascular Outcome Trials in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Empagliflozin and liraglutide are anti-hyperglycemic agents with proven cardiovascular benefits in Type 2 Diabetes Mellitus (T2DM) patients with established Cardiovascular (CV) disease. Although both drugs are available in Iran's pharmaceutical market, no local or regional study has analyzed the cost-effectiveness of these drugs in terms of reduction in the rate of CV-related mortality in T2DM patients in this country. In the present study, a one-year Cost-Effectiveness Analysis (CEA) was conducted based on decision-analytic modeling to compare the effectiveness of empagliflozin versus liraglutide in the prevention of CV-related death in T2DM patients in Iran.

Methods: A one-year CEA was performed to compare the effects of empagliflozin in contrast to liraglutide on the prevention of CV-related mortality from the Iranian T2DM payers' perspective. Clinical data were extracted from the results of LEADER and EMPA-REG OUTCOME studies. Economical and cost data were taken from the FDA official website of Iran (http://irc.fda.gov.ir/nfi) and the national book of tariffs. The data then were converted to the 2021-USD using governmental conversion rates and presented in terms of Incremental Cost-Effectiveness Ratio (ICER). In order to assess the robustness of the results, scenario analysis and multiple Deterministic Sensitivity Analysis (DSA) were also performed.

Results: Empagliflozin dominated original brand liraglutide and biosimilar liraglutide with reduced costs in preventing one extra CV-related death in T2DM patients. The annual cost was $30,585 (95%CI: $22,283- $48,745), $736,179 (95%CI: $457,206- $2,286,029), and $445,512 (95%CI: 276,686- 1,383,432) for empagliflozin, original brand liraglutide, and biosimilar liraglutide, respectively. These results were in line with the findings from scenario, base-case and deterministic sensitivity analyses.

Conclusion: Empagliflozin is projected to be highly cost-effective in terms of the prevention of CV-related death compared to liraglutide in Iran.

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Introduction

The economic burden of Type 2 Diabetes Mellitus (T2DM) is substantial. The International Diabetes Federation (IDF) data indicate that the annual global health expenditure on diabetes is estimated to be USD 760 billion [1]. Cardiovascular (CV) events are the main complications in T2DM patients that increase the financial burden on patients, the health care system, and society [2]. In this regard, the prevention of CV-related mortality is one of the ultimate goals in the management of adults with T2DM [3-5]. Iran has a considerable prevalence of T2DM (9.4% in 2019), which is projected to be doubled from 2011 to 2030 [6, 7]. Unlike western countries, in which most T2DM patients are at old age, many cases in Iran and other developing middle eastern countries are middle-aged and economically productive [8]. A prevalence-based cost-of-illness study indicated that T2DM is an expensive medical issue for the Iranian healthcare system and its complications, mainly CV-related, contribute to 53% of added extra costs of the disease [8]. Moreover, available local data showed that better glycemic control resulted in fewer diabetes-related complications and expenditures [9]. Since the rate of patients with diabetes is estimated to be raised constantly, early complications detection and appropriate therapeutic approaches could decrease the disease's economic burden notably in Iran [9].

Although several anti-hyperglycemic therapies are available worldwide, the benefits of decreased CV-related events have been identified only by a few [10, 11]. CV-mortality risk reduction is mainly attributed to empagliflozin, as a Sodium-Glucose cotransporter-2 (SGLT2) inhibitor, and liraglutide, as a Glucagonlike Peptide-1 (GLP-1) receptor agonist. Based on the results of EMPA-REG OUTCOME and LEADER trials, empagliflozin and liraglutide could get FDA (Food and Drug Administration) approval as anti-hyperglycemic agents that can reduce the risk of CV-related death in adult T2DM patients with established CV disease [12, 13]. Although both drugs are available to Iranian patients and are widely used in T2DM pharmacotherapy practice, no study in Iran or any other developing Middle East country has evaluated the comparative cost-effectiveness of the aforementioned pharmaceutical strategies in reducing CV-related mortality in T2DM patients.

The aim of the current study was to conduct a cost-effectiveness analysis to compare empagliflozin and liraglutide in the prevention of CV-related mortality, based on data from EMPA-REG OUTCOME and LEADER trials. This analysis, which is based on decision-analytic modeling, may provide evidence-based information for policy-makers in Iran and other developing Middle Eastern countries and lead to the efficient allocation of healthcare resources in the absence of head-to-head clinical trials.

Materials and Methods

Base case study design

In the present study, a cost-effectiveness analysis was performed to compare the cost per one extra CV-related death prevention with empagliflozin and liraglutide from the Iranian T2DM payers' perspective. This analysis was based on one-year decision-analytic modeling to assess the value for money and financial consequences of a new health intervention in the absence of head-to-head clinical trials.

Model inputs

Clinical data: Clinical data were extracted from LEADER [14] and EMPA-REG OUTCOME [15] placebo-controlled phase-III randomized clinical trials on liraglutide and empagliflozin, respectively. Both trials reported significant superiority of drug arms in CV-related death, non-fatal stroke, and non-fatal Myocardial Infarction (MI) reduction vs. the placebo. Because the primary outcome was a decrease in the risk of CV-related death (P-value <0.007 and <0.001 for liraglutide and empagliflozin, respectively), the focus of the present single clinical outcome economic analysis was on this outcome. The number of prevented cardiovascular death was determined based on the translation of the risk reduction into hazard ratio under the context of each study's results. This method was also used by Arbel et al. [16].

Costs: Direct medical costs as drug acquisition costs were included in the current study. Unit costs were adopted from the official FDA website of Iran on June 2020 [17] and converted to the 2020 US Dollars (USD); the governmental conversion rate was 42,000 Iranian Rial Rates (IRR) per one USD [18]. Because the economic shocks, in the long run, may alter the exchange rate, purchasing power parity (PPP) was also used in the sensitivity analysis [19]. Based on the latest data from the World Bank in 2018, the ratio of PPP conversion factor to exchange rate 16,951 IRR/USD [20]. Because the governmental exchange rate was consistent from 2018 to 2020, the 2018 ratio was used in the sensitivity analysis.

Both 10 mg and 25 mg dosage forms of empagliflozin were used in the EMPA-REG OUTCOME trial [15]; there-

fore, the average price of both mentioned forms was adopted. This approach was justified by empagliflozin's Defined Daily Dose (DDD), which is 17.5 mg per day [21]. Although the allotted daily dose of liraglutide in the LEADER trial was 1.8 mg, the reported DDD is 1.2 mg/day [22]. Since clinical outcomes were presented for the 1.8 mg/day dosage [23], this dosage was used for cost calculations.

Because Iran is not a member of the World Trade Organization (WTO), it does not comply with intellectual property laws, naming pharmaceutical patents [24]; thus, pharmaceutical products could be available in an Original Brand (OB), Generics (Gx), and Biosimilar (BS) forms. The available OB and BS forms of liraglutide (6 mg/ml, 3 ml prefilled pen) were in unit prices of 72.79$ and 44.05$, respectively. Gx forms were the only available forms of empagliflozin in Iran their unit prices were 0.65$ for 10 mg and 0.81$ for 25 mg tablets.

Model outputs

The primary outcome of the current study was Incremental Cost-Effectiveness Ratio (ICER), which indicated the extra cost of pharmacological treatment needed to prevent one additional CV-related death, as designated clinical outcome, in a 3.5-year time horizon. The following formula was used: ICER=(cost of the intervention- the cost of the comparator)/(number of deaths prevented when using intervention – number of deaths prevented when using comparator).

Scenario analysis

Due to the lack of head-to-head clinical trials and differences between the designs of LEADER and EMPA-REG trials, a scenario analysis was performed (Table 1). This analysis could determine the simulation of each comparator's effect on the other comparator's trial.

Another scenario analysis also was conducted to select defined daily doses as the base of annual cost calculations. By this approach, 17.5 mg per day was selected for empagliflozin (as in the base case) and an average price for 10 and 25 mg dosage forms was obtained. For liraglutide, on the other hand, a 1.2 mg dosage was chosen for DDD; however, in clinical outcomes, 1.8 mg/day was used.

Deterministic Sensitivity Analysis (DSA)

To assess the robustness of the achieved results, the one-way deterministic sensitivity analysis was also performed, as explained below:

1. Risk reduction variation is assessed by comparing the best case (higher interval) of each to the worst-case (lower interval) of the comparator

2. Cost variation (±20%)

3. Purchasing power parity, instead of governmental exchange rate

Results

The rate of cardiovascular-related death per 100 patient-years for liraglutide was 1.2 and 1.6 for the placebo in the LEADER trial and 2.02 for empagliflozin versus 1.24 for the placebo in the EMPA-REG trial. Based on the results of the LEADER trial, Risk Reduction (RR) of treatment with liraglutide versus Standard of Care (SOC) was 0.22 (95% Confidence Interval [CI]: 0.07-0.34) and therefore, 59 (95%CI: 19-95) CV-related deaths were prevented in 16,338 patient-years, whereas in EMPA-REG trial, RR was 0.38 (95% CI: 0.23-0.51) and the number of CV-related death prevented in 5,833 patient-years was 51 (95% CI: 32-70). Annual costs for Gx empagliflozin, OB liraglutide, and BS liraglutide were 267.42$, 2,658.5$, and 1,608.8$, respectively.

ICER, indicating the cost per one CV-related death prevention, for empagliflozin, BS liraglutide and OB liraglutide was $30,585 (95%CI: $22,283-$48,745), $445,512 (95%CI: 276,686-1,383,432), and $736,179 (95%CI: $457,206-$2,286,029), respectively. Consequently, cost-saving with empagliflozin in preventing one extra CV-related death was $705,594 (95%CI: $434,929-$2,237,284) or 95.85% compared to OB liraglutide and $414,927 (95% CI: $254,403-$1,334,688) or 93.13%, compared to BS liraglutide. Moreover, the results of scenario analysis revealed the superiority of cost-savings with empagliflozin versus liraglutide in treated patients. Base-case and scenario analysis results are shown in Table 2.

One-way DSA results also showed that comparing low-interval RR of empagliflozin (the worst case for Empagliflozin) with high interval RR of BS and OB liraglutide (the best case for Liraglutide) would be associated with 89.70% and 93.77% cost-savings in favor of empagliflozin compared to BS and OB forms of liraglutide. In addition to RR variations, all cost variations indicated the favorable cost-saving of empagliflozin as well. Using PPP instead of exchange rate did not change the results since both arms were equally affected. DSA outcome is presented in Table 3.

Table 1. Differences in design and patient characteristics of LEADER and EMPA-REG trials

Variables	LEADER	EMPA-REG
Patient population	T2DM ≥50 years old:+ ≥1: existing CV condition or ≥ 60 years old: + ≥1: CV risk factor; HbA1c ≥7%: whether or not used any drug	T2DM ≥18 years old, BMI ≤45, eGFR>30 ml/min/1.73m^2, If no glucose-lowering drug was used in last 12 weeks: HbA1c of ≥7%-<9%, and if used: ≥7%-<10%.
Intervention	Liraglutide (1.8 mg/day or max. tolerated dose)	Empagliflozin (10 & 25 mg)
Primary outcome	A composite of time to death from a CV event, non-fatal stroke or MI	A composite of time to death due to a CV event, non-fatal stroke, or MI
Secondary outcome	A composite of CV event, death due to any cause, a composite of renal and retinal microvascular outcome, neoplasms, and pancreatitis	A composite of primary outcome + hospitalization for unstable angina
Sample number	9,340	7,020
Follow-up period (years, mean)	3.8	3.2
Women/men ratio	0.56	0.38
Age (years, mean)	64	63
BMI (kg/m^2, mean)	32.5	30.6
HbA1c (mmol/mol, at Baseline)	8.7	8.1
Prior CV condition	81%	99%
eGFR< 60 ml/min/1.73 m^2	25%	26%

BMI: Body Mass Index; CV: Cardiovascular; eGFR: estimated Glomerular Filtration Rate; MI: Myocardial Infarction.

Discussion

Based on the results of the current one-year projections of clinical and cost outcomes, empagliflozin was identified as the most cost-effective treatment strategy versus liraglutide, in the context of the Iranian healthcare sector. The results of this study also showed that empagliflozin is associated with 95.85% cost savings in the prevention of one extra CV-related death compared to the original brand and 93.13% in comparison to biosimilar liraglutide.

Our findings were in line with another CEA study, which was performed based on the EMPA-REG or LEADER trial outcomes. In the mentioned study, empagliflozin was also highly cost-effective in the prevention of CV-related death in T2DM patients with CV disease risk factors compared to liraglutide [25]. The results of this study showed that the cost of preventing one CV-related death with empagliflozin in EMPA-REG OUTCOME trial would be 0.77% lower than liraglutide's cost in LEADER trial [$2,575,312 (95%CI: $1,607,526- $7,807,986) versus $569,526 (95%CI: $415,713-$921,798)] [25]. Empagliflozin has also been shown a cost-effective and cost-saving strategy in other studies with different comparator arms [24-26]. According to the results of a discrete-event simulation model study in the UK, which was performed based on the data from the EMPA-REG OUTCOME trial, empagliflozin was a cost-saving strategy compared to the placebo, when added to the standard of care in T2DM patients with established CV disease in the lifetime horizon. The authors of the mentioned study claimed that empagliflozin increased costs but was associated with increased quality-adjusted life years (QALY=1.0). Besides, ICER was lower than the UK national cost-effectiveness threshold (£4083/QALY) [25]. The data from another CEA study in the US revealed that adding empagliflozin to the standard of care in patients with T2DM and Heart Failure (HF) at baseline was associated with increased life span (+1.2) and QALY (+0.67). In this lifetime horizon study, empagliflozin was cost-effective with a probability of 87% in the US national cost-effectiveness threshold [26]. Empagliflozin was estimated to have a 100% probability of being cost-effective compared to the standard of care in a CEA study in Greece, which is a developing country with a lower threshold of cost-effectiveness willingness to pay [24].

Table 2. Base-case and scenario analysis results

Comparator	Trial	Patient Year	Number of CV Death Prevented	Annual Cost ($)	Cost per One Death Prevented ($)	Cost Difference With Empagliflozin ($)
Base-Case Analysis Results, cost per one CV-related death prevention:						
Empagliflozin	EMPA-REG	5,833	51 (32-70)	267.42	30,585 (22,283- 48,745)	-
Liraglutide (OB)	LEADER	16,338	59 (19-95)	2,658.50	736,179 (434,929- 2,237,284)	705,594 (434,929-2,237,284)
Liraglutide (BS)	LEADER	16,338	59 (19-95)	1,608.84	445,512 (276,686- 1,383,432)	414,927 (254,403-1,334,688)

Comparator	Trial	Patient Year	Number of CV Death Prevented	Annual Cost ($)	Cost per One Death Prevented ($)	Cost Difference With Empagliflozin ($)
Scenario Analysis Results, cost per one CV-death prevention when simulating each comparator in others' trials:						
Empagliflozin	EMPA-REG	5,833	51 (32-70)	267.4	30,585 (22,283- 48,745)	-
Empagliflozin	LEADER	16,338	106 (64-142)	267.4	41,218 (17,115- 37,397)	-
Liraglutide (OB)	LEADER	16,338	59 (19-95)	2,658.5	736,179 (434,929-2,237,284)	-
Liraglutide (OB)	EMPA-REG	5,833	29 (10-47)	2,658.5	534,705 (1,550,702- 329,937)	-
Liraglutide (BS)	LEADER	16,338	59 (19-95)	1,609.8	445,778 (276,852- 1,384,259)	-
Liraglutide (BS)	EMPA-REG	5,833	29 (10-47)	1,609.8	323,792 (199,786- 938,996)	-

BS: Biosimilar; CV: Cardiovascular; OB: Original Brand.

The lack of direct comparisons between active therapies is the main limitation of the current study. In the present study, data from two separate clinical trials with different patient populations, demographic characteristics, and attributed methods were compared. However, the scenario analysis was performed to overcome the mentioned limitation.

Moreover, considering the reduction in CV mortality risk as the only outcome of interest instead of Major Adverse Cardiac Events (MACE) could be another limitation. Since the main clinical outcome in both LEADER and EMPA-REG trials was CV mortality risk reduction, this limitation was justified. Because both medications had the same and non-statistically meaningful risk reduction in MI and stroke, considering MACE would have not to burden a significant influence on the results.

Conclusion

Overall, the extrapolation of LEADER and EMPA-REG outcome trial data, using one-year decision-analytic

Table 3. One-way sensitivity analysis results

Factor	Value Range (95%CI or±20%)	Annual Cost to Prevent One Death ($)		
		Base Case	Low-Value	High-Value
RR of CV death prevented vs SOC (Empagliflozin arm)	0.38 (0.23- 0.51)	30,585	48,745	22,283
RR of CV death prevented vs SOC (Liraglutide OB arm)	0.22 (0.07- 0.34)	736,179	2,286,029	457,206
RR of CV death prevented vs SOC (Liraglutide BS arm)	0.22 (0.07- 0.34)	445,512	1,383,432	276,686
Annual Cost of Therapy (Empagliflozin arm)	267 (214- 321)	30.585	24,468	36,702
Annual Cost of Therapy(OB Liraglutide arm)	2,658 (2,127- 3,190)	736,179	588,943	883,414
Annual Cost of Therapy(BS Liraglutide arm)	1,609 (1,287- 1,931)	445,512	356,410	534,615

BS: Biosimilar; CV: Cardiovascular; OB: Original Brand; RR: Risk Reduction; SOC: Standard of Care.

modeling, suggests that EMPAGLIFLOZIN is highly cost-effective compared to liraglutide when comparing CV-related mortality prevention in T2DM patients with established CV disease in Iran. Identifying a treatment strategy, which is not only effective in all health outcomes but also is affordable and decreases the disease's economic burden may guide policy-makers and healthcare providers in Iran and other developing Middle Eastern countries in reaching evidence-based decisions regarding treatment strategy selection and scares healthcare resource allocation.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

All authors equally contributed to preparing this article.

Conflict of interest

NA and SL are employees of Abidi pharmaceutical company, Tehran, Iran. AE has no relevant financial contribution and disclosed that would present talks involving all T2DM treatments.

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