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The Net Monetary Benefit of Introducing Sodium-Glucose Cotransporter-2 Inhibitors in Middle-Income Countries

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Introduction

- An estimated 422 million people have diabetes globally, the majority of which live in low- and middle-income countries (MICs).[1]
- There is a 'cost of not' managing diabetes optimally, with both payer-perspective and societal-perspective cost consequences. Complications associated with poorly managed diabetes can significantly impact patient outcomes and increase healthcare costs.
- Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are an established treatment option for the management of type 2 diabetes mellitus (T2DM).[2]
  - Three key placebo-controlled cardiovascular outcome trials (CVOTs) demonstrated that adding individual SGLT2i to background therapy reduced cardiovascular (CV) complications and delayed renal complications versus placebo.[3,4,5]
  - Real-world evidence from the Comparative Effectiveness of CV Outcomes in New Users of SGLT2i (CVD-REAL) 1 and CVD-REAL 2 studies demonstrated that T2DM patients who initiated SGLT2i had lower risks for hospitalization for heart failure (hHF), myocardial infarction (MI), stroke, and death versus those who initiated other glucose-lowering drugs (oGLD).[6,7]
- SGLT2i are often not accessible or available in middle-income countries (MICs).[8]

Objectives

- The objective of this study was to quantify the economic value of short- and long-term reductions in CV and renal complications associated with the introduction of SGLT2i for the treatment of T2DM in six (6) selected MICs: Argentina, Brazil, Egypt, Malaysia, Mexico, and Turkey.

Methods

- A cohort-level partitioned survival model (PSM) estimated the economic and clinical outcomes of introducing SGLT2i (canagliflozin, empagliflozin, or dapagliflozin) versus other glucose lowering drugs (oGLD) or placebo in patients with T2DM.
  - The original model was developed for six high-income country settings, including the United States and the five leading European economies (EU5).[9]
  - We have made local adaptations using this model for settings in the 6 MICs.
- Two model populations corresponded with the SGLT2i-eligible T2DM population, as defined in CVOTs (CANVAS, EMPA-REG, DECLARE-TIMI 58)[3,4,5] and in CVD-REAL 1 & 2.[7,8]
- Clinical inputs from CVD-REAL 1&2 and a meta-analysis of CVOTs[10] enabled comparison of SGLT2i with oGLD and placebo, respectively (Table 1).
  - Baseline risks for hHF, MI, stroke, and all-cause mortality (ACM) were estimated as best-fitting statistical distributions applied to Kaplan-Meier (KM) curves for CVOT placebo arms and for oGLD patients from CVD-REAL 1&2.
  - Mean eGFR per cycle was estimated by applying an annual rate of eGFR decline to initial mean eGFR of CVOT placebo patients and CVD-REAL 1&2 oGLD patients.
  - Hazard ratios from CVOTs and CVD-REAL 1&2 were applied to estimate reduced complication risks for SGLT2i versus placebo or oGLD, respectively.

Table 1. Clinical parameters, CVD-REAL 1&2 and CVOTs.

Population	Parameter	HHF	MI	Stroke	ACM	ESRD
CVD-REAL: oGLD	Survival distribution	Log-normal, shape = 3.5199, scale = 8.6693	Exponential, rate = 0.0029	Log-logistic, shape = 0.8707, scale = 338.7169	Exponential, rate = 0.0066	Exponential, rate = 0.0007
	Baseline events / 1,000 patient-years	1.14	0.58	1.12	1.32	1.32
CVD-REAL: SGLT2i	HR	0.68	0.86	0.79	0.52	0.38
CVOTs: placebo	Survival distribution	Weibull, shape = 0.9484, scale = 250.8635	Weibull, shape = 0.9509, scale = 172.4838	Weibull, shape = 0.8765, scale = 413.5888	Weibull, shape = 1.2602, scale = 65.5742	Exponential, rate = 0.0004
	Baseline events / 1,000 patient-years	9.99	14.30	8.84	20.21	0.88
CVOTs: SGLT2i	HR	0.69	0.89	1*	0.85	0.50

*HR not found to be statistically significant; presented as 1.

- All cost inputs were collected in local currencies; here, we present costs in 2021 USD equivalents, using the official exchange rates at the time (Table 2).
  - Direct cost inputs included SGLT2i treatment (market share for canagliflozin, empagliflozin, or dapagliflozin adjusted per MIC setting) and costs of T2DM complications.
  - Indirect costs included workforce productivity losses from disability, assuming that MI, hHF, stroke, and ESRD cause 100% productivity loss.
- The model estimated outcomes from a societal perspective, using 6-month Markov time cycles. The base case included a 20-year time horizon, although 5-year and 10-year time horizons were also estimated.
  - Clinical outcomes included CV events (hHF, MI, stroke), chronic kidney disease (CKD) progression to end-stage renal disease occurrence (ESRD), and all cause-mortality.
  - Economic outcomes included direct and indirect costs, quality-adjusted life year (QALY) gains, and net monetary benefit (NMB).
  - Willingness-to-pay (WTP) thresholds were defined as one Gross Domestic Product (1 GDP) per capita for Brazil, and three (3 GDP) per capita for other MICs.
  - WTP and discount rates were obtained from each country's HTA guidelines.

Table 2. Direct cost estimates (USD) per 6-month model cycle.

	Mexico	Malaysia	Turkey	Brazil	Egypt	Argentina
Drug costs (Mean ±SE USD)**						
SGLT2i treatment cost*†	81 ±8	89 ±9	63 ±6	74 ±7	105 ±11	374 ±37
Complication costs (Mean ±SE USD)**						
Heart failure hospitalization event (HHF)	9,435 ±943	2,044 ±204	173 ±17	491 ±49	1,410 ±141	2,459 ±246
Heart failure (HF) maintenance	791 ±79	790 ±79	248 ±25	95 ±9	715 ±72	665 ±67
Myocardial infarction (MI) event	17,896 ±1,790	4,626 ±463	192 ±19	1,750 ±175	1,567 ±157	2,018 ±202
MI maintenance	2,104 ±210	1,788 ±179	145 ±14	107 ±11	191 ±19	605 ±61
Stroke event	2,492 ±249	882 ±88	1,103 ±110	1,203 ±120	1,286 ±129	3,954 ±395
Stroke maintenance	2,008 ±201	561 ±56	496 ±50	54 ±5	153 ±15	1,186 ±119
Chronic kidney disease (CKD)						
No CKD - stage 1	0	0	83 ±8			
CKD stage 2	0	127 ±13	88 ±9	12 ±1	32 ±3	0
CKD stage 3	1,395 ±140	163 ±16	125 ±12	38 ±4	32 ±3	893 ±89
CKD stage 4	2,654 ±265	252 ±25	179 ±18	420 ±42	302 ±30	957 ±96
End stage renal disease - ESRD	4,024 ±402	10,110 ±1,011	1,913 ±191	5,211 ±521	1,391 ±139	6,541 ±654

*SGLT2i: sodium-glucose cotransporter; †Market share-weighted average cost of authorized SGLT2i treatments per MIC;
**SE: standard error.

Results

- The base case model estimated incremental QALY gains for all countries, whether clinical inputs were from CVOTs or CVD-REAL (Table 3).
  - QALY gains accrue partly from an estimated 35% reduction in new ESRD cases and a 30% reduction in hHF, whether CVOTs or CVD-REAL are used as clinical inputs.
  - CVOTs and CVD-REAL inputs yielded more variable risk reduction estimates for other complications, including MI (10-13%), mortality (12-45%), and stroke (20% from CVD-REAL only).
- Incremental costs were positive in all countries and settings, except in Mexico using CVOT inputs.

Table 3. Cost and effectiveness estimates for SGLT2i, per MIC.

	Incremental cost [USD]	Incremental [QALY]	ICER [USD/QALY]	WTP [USD]	20-Year NMB [USD]
SGLT2i versus placebo using data from CVOTs					
Mexico	-6,578	0.2957	SGLT2i dominates*	27,679	15,029
Malaysia	265	0.3724†	710	29,875	11,685
Turkey	1,045	0.2957	3,533	22,963	3,811
Brazil	893	0.2957	3,019	20,847	1,477
Egypt	1,751	0.2957	5,922	9,112	1,561
Argentina	3,417	0.2957	11,557	15,402	2,138
SGLT2i versus oGLD using data from CVD-REAL 1&2					
Mexico	497	0.5021	990	27,679	13,796
Malaysia	139	0.6283†	221	29,875	19,985
Turkey	1,231	0.5021	2,451	22,963	7,328
Brazil	1,038	0.5021	2,067	20,847	2,918
Egypt	2,131	0.5021	4,243	9,112	3,469
Argentina	7,842	0.5021	15,617	15,402	1,571

*SGLT2i dominates placebo because it was associated with QALY gain and lower costs compared with placebo; †Malaysia recommended discount rate of 3% (vs. 5% for other MICs) led to higher estimated incremental QALY gains.

- The model also estimated positive NMBs in all 6 countries, whether clinical inputs were from CVOTs (Figure 1) or CVD-REAL (Figure 2). NMB estimates increase monotonically from 5-year to 20-year time horizons.
- The positive NMBs mean that the Incremental Cost Effectiveness Ratios (ICER) in Table 2 are within each the WTP threshold of each MIC. SGLT2i can be regarded as a cost-effective strategy in the 6 MICs.

Figure 1. NMB over 5, 10, and 20 years, per MIC, CVOT clinical inputs.

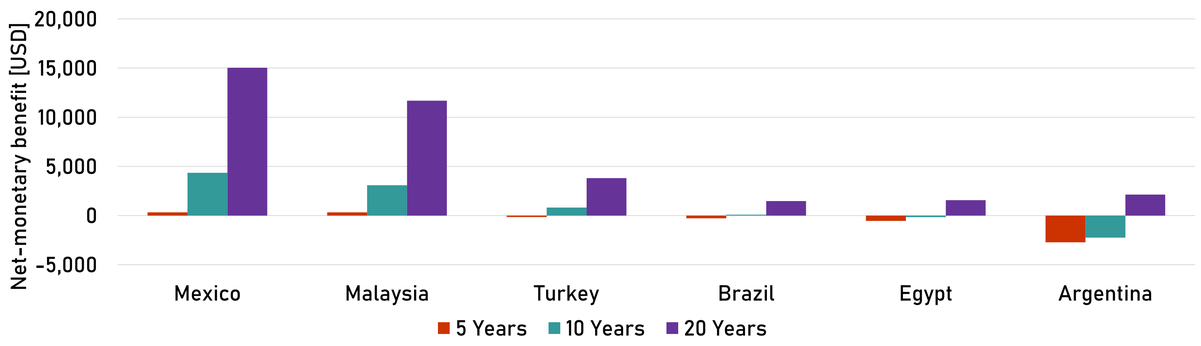
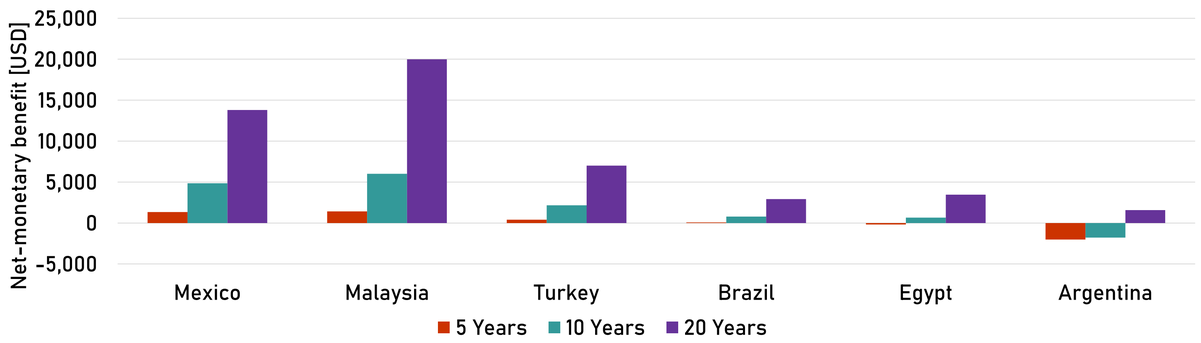


Figure 2. NMB over 5, 10, and 20 years, per MIC, CVD-REAL 1&2 clinical inputs.



Conclusions

- Introduction of SGLT2i treatment for T2DM patients, either as an add-on therapy or to replace existing treatment options (oGLD), demonstrated cost-effectiveness in all evaluated middle income countries.
- Cost-effectiveness estimates resulted from reductions in cardiovascular and renal complications associated with T2DM.
- More frequent consideration of SGLT2i treatment could minimize the 'cost of not' managing TDM2 optimally in MICs.

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