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Expanding access to newer medicines for people with type 2 diabetes mellitus in low- and middle-income countries: a cost-effectiveness and price target analysis

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Abstract

Background: Newer type 2 diabetes medicines, including sodium–glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin analogues, offer clinical benefits as second-line therapies after metformin, yet their costs pose barriers to wider use. As type 2 diabetes increases in prevalence in low- and middle-income countries (LMICs), we asked what price targets to pursue in price negotiations, if such therapies were incorporated into national formularies or the World Health Organization's (WHO) Essential Medicines List.

Methods: We estimated price targets to achieve thresholds of either three times gross domestic product (GDP) per capita per disability-adjusted life-year (DALY) averted (a threshold used by the WHO), or net cost-savings when including costs of averted complications. We incorporated individual-level, nationally-representative cross-sectional survey data from people with diabetes mellitus in LMICs (N = 23,678 individuals in 67 countries, 2006-2018) into a microsimulation of atherosclerotic cardiovascular disease, congestive heart failure, end-stage renal disease, vision loss, pressure sensation loss, hypoglycemia requiring medical attention, and drug-specific side-effects. We compared use of SGLT-2 inhibitors and GLP-1 receptor agonists as substitutes for sulfonylureas, or use according to a 'glycemia-agnostic' pathway in which they are added to existing medicines for people with a history of atherosclerotic heart disease, heart failure, or chronic kidney disease. Costs and DALYs were computed over a 10-year planning horizon, discounted at 3% annually.

Findings: To achieve costs per DALY averted less than three times the GDP per capita, SGLT-2 inhibitors would need to have a median price of $224 per person per year (IQR: $138, $359, population-weighted across countries; mean $257); GLP-1 receptor agonists $208 per person per year (IQR: $129, $335; mean $240); and glargine insulin $20 per vial (IQR: $16, $42; mean $28). Price targets to achieve net cost-savings were $9-$10 per person per year lower for SGLT-2 inhibitors or GLP-1 receptor agonists, but remained near $20 per vial for insulin glargine. Using SGLT-2 inhibitors or GLP-1 receptor agonists in a glycemia-agnostic pathway had a fourfold greater benefit in DALYs than applying them as substitutes for sulfonylureas, with a

92% reduction (SGLT-2 inhibitors) and 72% reduction (GLP-1 receptor agonists) in incremental cost-effectiveness ratios.

Implications: Among novel agents, SGLT-2 inhibitors hold particular promise for reducing complications of diabetes, particularly when used among people with established cardiovascular disease, heart failure, or kidney disease, and modest price reductions may achieve common thresholds for consideration in national formularies or the WHO Essential Medicines List.

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Research in context

Evidence before this study

The NCBI PubMed database was searched on May 16, 2021 for original research, systematic reviews, or meta-analyses published between January 2000 and May 2021 in any language using the query: (((((((sodium glucose transporter 2 inhibitors) OR (glucagon-like peptide 1 receptor analogues)) OR (dipeptidyl peptidase 4 inhibitors)) OR (thiazolidinediones)) OR (insulin, long acting) OR (guidelines AND (diabetes mellitus))) AND (countries, developing)) AND (cost))). Sixty-one results were retrieved, of which fifteen were judged relevant to the current study. The relevant studies revealed lower rates of myocardial infarction and stroke among patients receiving sodium glucose transporter-2 (SGLT-2) inhibitor treatment versus other glucose-lowering agents in real-world practice and randomized trials; limited insulin availability and high cost of insulin across formulations in low- and middle-income countries; two model-based estimates suggesting that insulin detemir and biphasic insulin aspart were cost-effective versus no insulin therapy in five developing countries; modeling studies indicating that the current World Health Organization diabetes treatment cascades were cost-effective when including blood pressure and statin therapy alongside glucose lowering medicines (metformin, sulfonylureas, and Neutral Protamine Hagedorn [NPH] insulin); descriptive data showing low rates of screening, treatment, and control per World Health Organization definitions among people with diabetes in various countries; and studies showing cost-effectiveness of community health worker-led, pharmacist-led, or nurse-led medication adherence support programs for people with diabetes. A systematic review done in 2018 noted the lack of adequate data on cost or cost-effectiveness of novel diabetes agents in low- and middle-income countries, along with lack of clear guidelines for practitioners in such countries on whether, when and how to use such agents.

Added value of this study

Our study adds three contributions to existing evidence. First, using individual-level, nationally-representative data, we fill the stated evidence gap by estimating the incremental cost-effectiveness of altering the World Health Organization's existing diabetes treatment guidelines to incorporate novel therapeutic agents, and identify which agents may be particularly helpful to improve incremental disability-adjusted life-years when prescribed as alternatives or as

supplements to standard second-line sulfonylurea therapy or (in the case of analogue insulins) to NPH insulin therapy. Second, we estimate price targets to achieve common thresholds for considering inclusion of the novel agents in country formularies or in the World Health Organization's Essential Medicines List. Third, we estimate the comparative benefits and costs of using such novel agents for glucose control versus adopting a glycemia-agnostic pathway in which SGLT-2 inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists are prescribed to individuals with relevant comorbidities regardless of their glucose control status.

Implications of all the available evidence

The combined evidence from prior work and the current study indicate that it is reasonable to include novel agents, particular SGLT-2 inhibitors, in country formularies and the World Health Organization's Model Essential Medicines List; that target prices to achieve common thresholds for cost-effectiveness or cost-savings may be achievable with modest price reductions for SGLT-2 inhibitors, but would require large price reductions for GLP-1 receptor agonists, glargine insulin, and other newer agents; and that a glycemia-agnostic approach to including such medicines among people with relevant co-morbid conditions, rather than as an alternative to sulfonylureas, may improve incremental benefits and cost-effectiveness.

Background

As type 2 diabetes mellitus prevalence increases in low- and middle-income countries (LMICs), a critical question is whether--and how--to enhance access to newer pharmacological therapies.[1] Current World Health Organization (WHO) guidelines for the pharmacological treatment of diabetes focus on reducing microvascular complications (nephropathy, retinopathy, and neuropathy) with metformin, sulfonylureas, and human insulins (typically, Neutral Protamine Hagedorn, or NPH insulin) by reaching target fasting blood glucose or hemoglobin A1c levels (**Figure 1**).[2] The guidelines specifically recommend sulfonylureas after first-line metformin to minimize costs,[2] noting that "new oral hypoglycemic agents are currently substantially more expensive compared to sulfonylureas, and that the modest clinical benefit...does not sufficiently outweigh the current price difference in the context of a public health approach," though reconsiderations can be made if prices fall.[3]

Newer evidence suggests that the risk of atherosclerotic cardiovascular disease events (myocardial infarctions and strokes), heart failure exacerbations, and end-stage renal disease is reduced by sodium glucose transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists.[4,5] Additionally, food insecurity can increase the risk of hypoglycemia, particularly in the setting of sulfonylurea use, prompting consideration to switch to newer alternatives.[6] In this context, updated guidance from the American Diabetes Association (ADA),[7] European Association for the Study of Diabetes (EASD),[8] International Diabetes Federation,[9] and regional entities,[10,11] suggest using SGLT-2 inhibitors and GLP-1 receptor agonists instead of sulfonylureas for people with atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, and compelling needs to minimize hypoglycemia. By contrast, it remains more controversial whether small differences between insulin analogues and human insulins in terms of nocturnal hypoglycemia--but not severe hypoglycemia--are sufficient to warrant the greater cost of insulin analogues.[12–16]

To improve access to newer pharmacological therapies, government authorities and international organizations negotiate with drug manufacturers and trade organizations through mechanisms such as volume guarantees for price reduction.[17–20] We sought to estimate price targets to pursue in price negotiations for novel diabetes therapies, to inform decisions about their inclusion in LMIC government formularies or the WHO Model Essential Medicines List.

Methods

Methods overview

We estimated the prices at which SGLT-2 inhibitors, GLP-1 receptor agonists, and other alternative agents--dipeptidyl peptidase 4 (DPP-4 inhibitors), thiazolidinediones (TZDs), and glargine insulin (a long-acting insulin analogue)--would meet each of two thresholds: (i) being considered cost-effective by having costs per DALY averted less than three times national GDP per capita (a threshold used by the WHO[21–23]), or (ii) being considered cost-saving, by having the drug cost plus averted complications costs be lower for the novel agents than for the current standard alternatives (sulfonylureas and NPH insulin). We used a microsimulation to perform three sequential calculations, estimating: (i) first, the risk of microvascular and macrovascular complications, heart failure, and hypoglycemia requiring medical attention for individuals with type 2 diabetes mellitus in LMICs; (ii) second, the incremental change in disability-adjusted life-years (DALYs) lost to these diabetes complications, and the incremental change in costs of treatment including management of complications, when switching from sulfonylureas to alternative agents or NPH insulin to glargine insulin; and (iii) third, the prices necessary to achieve each of the above two cost-thresholds (cost-effectiveness and cost-savings). In part (ii), we specifically compared DALYs and costs between the current 2020 WHO Package of Essential Noncommunicable (PEN) disease guidelines to a revision of the guidelines that incorporates key elements of the 2020 ADA and EASD guidelines, among other national and international guidelines (**Figure 1**).[7,8]

Data Sources

We input data from the World Health Organization (WHO) STEPwise approach to Surveillance (STEPS) and other, similar, surveys (2006-2018; see methodology[24] and Appendix for individual survey details) including adults with diabetes mellitus (defined as fasting blood glucose $\geq$126 mg/dL [7 mmol/L], random blood glucose $\geq$200 mg/dL [11.1 mmol/L], hemoglobin A1c (HbA1c) $\geq$ 6.5% [48 mmol/mol], or taking a glycemic control medicine including insulin) across 67 countries spanning 15 world regions. We assumed 95% of these adults would have type 2 mellitus.[25] To be included in the analysis, surveys needed to have been performed at the

individual level, be nationally-representative in demographics with intentional stratified sampling of community-dwelling participants, have been conducted on or after 2008, been performed in a low- or middle-income country as defined by the World Bank in the year of the survey, collected sufficient data for diabetes diagnosis, and provided information on current medications and glycemic control (fasting plasma glucose or hemoglobin A1c; details of each individual survey are in the **Appendix**).

Outcomes

We estimated the 10-year risk for each of the following key health outcomes, conditional on medication choices: (i) atherosclerotic cardiovascular events, defined as fatal or non-fatal myocardial infarctions or strokes; (ii) heart failure with reduced ejection fraction resulting in hospital admission (ejection fraction of <40%, with New York Heart Association class III or IV functional limitations); (iii) end-stage renal disease (ESRD), defined as estimated glomerular filtration rate <15 mL/min/1.73m^2 or needing dialysis or transplant; (iv) retinopathy with severe vision loss (<20/200 visual acuity by Snellen chart); (v) neuropathy with pressure sensation loss by Semmes-Weinstein 5.07/10 gram monofilament exam; or (vi) hypoglycemia requiring medical attention, defined as emergency medical services, emergency department visit, or hospitalization. We estimated baseline cardiovascular disease risk using region-specific 2019 WHO cardiovascular disease risk equations (using laboratory-based estimates for countries with lipid measurement available in the surveys, and clinic-based estimates otherwise),[26] and the risks of other outcomes using the Risk Equations for Complications of type 2 Diabetes (RECODe; equations in **Appendix Tables 1 and 2**),[27–29] incorporating age-specific mortality and outcome-specific fatality rates to account for competing risks (Appendix Table 6).(GBD Compare)

Analytic approach

We sampled--using survey weights to account for the probabilities of survey receipt and non-response--from the age, sex, blood pressure, lipid profile, medication history, cardiovascular event history, and smoking history of each adult with diabetes (previously diagnosed or undiagnosed) in the survey data, of whom we assumed 95% would be type 2,[25] to construct the simulated population of adults with type 2 diabetes mellitus in each surveyed country and simulated their history of atherosclerotic cardiovascular disease, heart failure, chronic kidney

disease, or hypoglycemia requiring medical attention based on the above-mentioned equations (Figure 2). We describe the distributions of these risk factors and simulated histories at the regional level in **Table 1** and at the individual country level in **Appendix Table 3**. Missing data were imputed using multiple imputation with chained equations (using the age, sex, blood pressure, lipid profile, medication history, cardiovascular event history, smoking history, and diabetes diagnosis history as imputation variables) with a classification and regression tree algorithm to account for the complex covariation among data elements, before conducting the sampling.[30]

After the sampling, we compared the outcome rates under two different approaches for pharmacologic treatment of diabetes: the WHO PEN and associated WHO guidelines for use of second- and third-line agents,[2,31] and an alternative incorporating recommendations from the ADA and EASD (**Figure 1**).[7,8] We first back-calculate the baseline levels of hemoglobin A1c given the survey data on current treatment and meta-analytic estimates of the impact of each therapy on hemoglobin A1c (Appendix Table 4). Then, in the first approach, individuals with type 2 diabetes would begin lifestyle modification followed by metformin at 500 mg once daily, titrated up to 1000 mg twice daily, then gliclazide at 80 mg daily, titrated up to 80 mg twice daily, followed by NPH insulin treatment if needed to achieve a fasting plasma glucose <125 mg/dL (7 mmol/L) or hemoglobin A1c $\leq$7% (53 mmol/mol). Simultaneously, we simulated blood pressure treatment (starting with enalapril 20 mg once daily for systolic blood pressure $\geq$130 mmHg or diastolic $\geq$80 mmHg) and statin treatment (simvastatin 20 mg once daily for those aged 40 years or older or having an estimated 10-year cardiovascular risk >20%) at the reported rates of prescribing and adherence in each survey.

In the alternative approach (**Figure 1**), we substituted sulfonylureas with alternatives for both second-line (after metformin) and third-line (before insulin) therapies, and enabled access to insulin glargine as an alternative to NPH insulin. We included all drug classes included in the current WHO PEN guidelines, along with the novel SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. Specifically, we evaluated the individual and combined impact of prescribing, after metformin: (i) a SGLT-2 inhibitor with cardiovascular benefit (e.g., empagliflozin) for those with a history of atherosclerotic cardiovascular events, heart failure, or chronic kidney disease of stages 1 through 3,or a GLP-1 receptor agonist with cardiovascular benefit (e.g., liraglutide) if stage 4 or beyond, i.e., estimated glomerular filtration rate [eGFR]

<30 mL/minute/1.73 m^2; (ii) any of: SGLT-2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, or (if no history of heart failure) TZDs for those with a history of hypoglycemia needing medical attention; and (iii) glargine insulin (U100) instead of NPH insulin for those requiring insulin and having a history of hypoglycemia needing medical attention. The novel agents were continued at the rates of self-reported adherence to diabetes drugs from the survey. While history of myocardial infarction was available in the surveys, the other histories of prior stroke, heart failure, chronic kidney disease, or hypoglycemia were estimated by calculating the RECODe equations for each of these risks at the starting point of the microsimulation and using a binomial probability function to estimate which persons would likely have a prior history of these conditions (Appendix Table 2). Given available evidence of efficacy and LMIC market availability, we focused our analysis on empagliflozin as the SGLT-2 inhibitor of choice, liraglutide as the GLP-1 receptor agonist of choice, sitagliptin as the DPP-4 inhibitor of choice, pioglitazone as the TZD of choice, and glargine U100 as the insulin analogue of choice.[7,8] As our survey data provided information on whether a person was on oral glycemic agents and/or on insulin, but did not provide specific drugs or dosages, we simulated the current WHO PEN guidelines--assuming those on insulin were previously titrated on maximum dose metformin and sulfonylureas before insulin, and utilized insulin at a typical weight-based dosing of 0.64 IU/kg/day (interquartile range [IQR]: 0.37, 0.84).[32] We also simulated those not on insulin as being sampled from a uniform distribution of metformin and sulfonylurea dosing along the spectrum of possible dosing combinations described above and shown in **Figure 1**. We then simulated the switch from second-line sulfonylureas to an alternative agent(s) based on the alternative algorithm shown in **Figure 1**; we also then simulated the switch from NPH to glargine insulin if the person had a history of hypoglycemia, was also already on an insulin, and still needed insulin to achieve a fasting plasma glucose <125 mg/dL (7 mmol/L) or hemoglobin A1c $\leq$7% (53 mmol/mol) after titration of both second- and third-line oral medicines as listed above. The estimated change in hemoglobin A1c for each of the oral medicines is provided in **Appendix Table 4**.[5]

To reflect the change in risk for each outcome associated with each type of therapeutic switch (sulfonylurea to alternative, and NPH to glargine), we used results from randomized trials and meta-analyses of the effect of each drug on each outcome, as well as on the risk of adverse events (**Appendix**).

Costs and DALYs

We estimated target prices for each medicine to cost less than three-times GDP per DALY averted or be net cost-saving. We compared the target prices to the 2020 estimated price --including generics--from an international drug price database in 2020 International Dollars (**Appendix Figure 1**).

We included costs for medicines, treatment of diabetes complications, adverse events and their management, and equipment and devices (e.g., needles). Costs for treatment of complications were obtained from the WHO OneHealth Tool, which included costs for clinical visits for diabetes control or management of complications at primary, secondary, or tertiary facilities, and costs of tests (e.g., serum creatinine). Costs of most procedures were not available in WHO OneHealth tool, and were based on literature reviews (**Appendix Table 5**). Because we only simulated the switch from NPH to glargine insulin among people already on insulin, we did not compute any differential costs between NPH and glargine insulin for glucose monitoring or insulin delivery supplies (e.g., glucometer device, glucometer test strips, lancets, or needles). Costs were expressed in 2020 International Dollars.

We obtained DALY disutility weights for each outcome from international preference elicitation surveys (**Appendix Table 6**).[33] We included the most common or most serious adverse events from the newer medicines, including genitourinary tract infections, diabetic ketoacidosis, gastrointestinal distress, and lower-extremity amputations. We simulated a switch back to sulfonylurea therapy if these side-effects occurred. We included the disutility of injection therapy for GLP-1 receptor agonists.

We computed costs and DALYs over a 10-year policy planning time horizon at a 3% annual discount rate, simulating with a one-year discrete time increment with age- and sex-specific updates to the biomarkers to reflect the linear rate of change observed with age in each sex group in the data, and simulating the lifecourse or people alive or borne during the 10-year period. We sampled with replacement 10,000 times from the empirical distributions of each input variable in the survey data to construct credible intervals around each of the outcome metrics. We comported with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline (**Appendix Table 7**).

Sensitivity analyses

We performed two sensitivity analyses. First, we noted that ADA recommends that SGLT-2 inhibitors or GLP-1 receptor agonists be considered for patients with a history of atherosclerotic cardiovascular events, heart failure or chronic kidney disease regardless of glycemic status. Hence, we simulated a glycemia-agnostic pathway in which SGLT-2 inhibitors or GLP-1 receptor agonists were prescribed to all persons with diabetes with these above comorbidities, regardless of their hemoglobin A1c (i.e., in addition to metformin alone, in addition to metformin and sulfonylurea therapy, or in addition to metformin and insulin therapy). Second, we estimated the incremental cost-effectiveness of empagliflozin if lower-limb amputation risk were not a class effect in being applicable to all SGLT-2 inhibitors (i.e., did not apply to empagliflozin and only applied to canagliflozin), as it remains controversial whether increased lower-limb amputations observed in a canagliflozin trial are indicative of all SGLT-2 inhibitors.[34]

Results

Descriptive statistics on the study population

The surveys we used for 67 countries included 23,678 people with diabetes mellitus (**Table 1**). Less than 7% of any included variable was missing prior to imputation. Among participants with diabetes mellitus, the median age was 53.0 years (interquartile range [IQR] 42.0, 61.0), a majority were female (59.6%), 51.8% reported being previously diagnosed with diabetes before the survey, the median haemoglobin A1c was 7.5% (IQR: 6.6%, 9.3%; 58.5 mmol/mol), and 41.3% reported taking an oral diabetes medicine while 15.5% reported use of insulin. The estimated risks of diabetes complications are also shown in **Table 1** (at the regional level) and **Appendix Table 3** (at the country level). The median risk of atherosclerotic cardiovascular disease events, taking into account current treatment rates, was 10.0% over 10 years (IQR: 4.0%, 17.0%), of congestive heart failure hospitalization was 2.6% over 10 years (IQR: 1.2%, 5.3%), of ESRD was 7.2% over 10 years (IQR: 5.6%, 9.4%), of retinopathy was 6.0% over 10 years (IQR: 4.2%, 8.6%), of neuropathy was 7.8% over 10 years (IQR: 5.0%, 11.8%), and of hypoglycemia requiring medical attention was 7.3% over 10 years (IQR: 3.8%, 22.5%).

Cost of therapies

We estimated that the median cost of a year's supply of metformin among the studied countries at the typical starting dose of 500 mg once daily was $24 (IQR: $20, $28; mean $45), for a sulfonylurea (gliclazide 80mg daily) was $26 (IQR: $16, $67; mean $37) for an SGLT-2 inhibitor (empagliflozin 5mg daily) was $271 (IQR: $168, $370; mean $294), for a GLP-1 receptor agonist (liraglutide 1.2mg daily) was $12,378 (IQR: $10,963, $13,641; mean $12,819), for a DPP-4 inhibitor (sitagliptin 100mg daily) was $148 (IQR: $77, $208; mean $143), for a thiazolidinedione (pioglitazone 15mg daily) was $84 (IQR: $37, $92; mean $99), for NPH insulin was $10 per 10mL vial of 100IU/mL (IQR: $9, $17; mean $13), and for glargine insulin was $29 per 10mL vial of 100IU/mL (IQR: $17, $54; mean $37).

Incremental cost-effectiveness for alternative therapies

The incremental changes in intermediating outcomes (e.g., atherosclerotic cardiovascular events), and associated DALYs and costs of switching from sulfonylureas to each of SGLT-2 inhibitors, GLP-1 receptor analogues, DPP-4 inhibitors, or thiazolidinediones, and of switching from NPH to glargine insulin (following the algorithms in **Figure 1**) are shown in **Table 2**. We include medians and interquartile ranges alongside means and standard deviations for each outcome, due to the right-skewed distributions of risk for many outcomes, and the observation that many treatments only affected those at high risk for the outcome.

SGLT-2 inhibitors. Switching from a sulfonylurea to an SGLT-2 inhibitor among those with a relevant indication to switch (**Figure 1**) was estimated to affect 7.9% of the total population of people with diabetes, given an estimated 20.7% of the population on a sulfonylurea of whom 38.4% had an indication for being switched to a SGLT-2 inhibitor (history of atherosclerotic cardiovascular disease, chronic kidney disease, heart failure, or hypoglycemia, with estimated glomerular filtration rate (eGFR) >30 mL/minute/1.73 m^2). At a population level, the switch to SGLT-2 inhibitors would be expected to reduce the mean risk of atherosclerotic cardiovascular disease events (from 11.8% to 11.6% over 10 years) but not the median risk (which remained at 10.0%; IQR: 4.0%, 17.0%; **Table 2**); to lower the risk of heart failure hospitalization over 10 years from a mean of 4.5% to 4.2% and median from 2.6% to 2.5% (IQR: 1.2%, 5.1%); ESRD from a mean of 7.9% to 7.7% and median from 7.2% to 7.1% (IQR: 5.1%, 11.8%); hypoglycemia from a mean of 19.2% to 17.7% and median from 7.3% to 6.7% (IQR: 3.6%, 19.6%); and body mass index (BMI; mean change of -0.13 kg/m^2; median change of 0.0 kg/m^2; IQR: 0.0, 0.0 kg/m^2). The switch to SGLT-2 inhibitors would be expected to increase the risk of genitourinary tract infections (mean risk increase from 4.4% to 4.8% over 10 years; median unchanged at 4.4%; IQR: 4.4%, 4.4%), lower-extremity amputation (mean risk increase from 0.07% to 0.09% over 10 years; median unchanged at 0.07%; IQR: 0.07%, 0.07%), and ketoacidosis (mean risk increase from 0.07% to 0.12%; median unchanged at 0.07%; IQR: 0.07%, 0.07%). The net effect of changes in both diabetes complications and adverse event rates would be an expected median incremental reduction in discounted DALYs by 75 per 1,000 people (IQR: 63, 92), at a median incremental discounted cost of $558,817 per 1,000 people (IQR: $493,711, $1,172,238) over the same time period, for a median incremental cost-effectiveness ratio of $10,696 per DALY averted (IQR: $7,072, $15,780) over sulfonylurea treatment (Table 2, Figure 3, Appendix Figure 2). If lower-limb amputation risk were not a class

effect and did not apply to empagliflozin, the median incremental reduction in DALYS would be 77 per 1,000 (IQR: 64, 93), median incremental cost would be $557,816 per 1,000 ($492,648, $1,170,986), and the median incremental cost-effectiveness ratio would be $10,503 per DALY averted (IQR: $6,962, $15,569).

In the glycemia-agnostic pathway (providing SGLT-2 inhibitors to people with a history of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease independent of glycemic status, subject to eGFR > 30 mL/minute/1.73 m^2, treating 26.8% of people), the median incremental reduction in DALYS would be 310 DALYs per 1,000 (IQR: 280, 348), median incremental cost would be $140,952 per 1,000 people as greater drug costs were more than offset by greater reduction in cardiovascular disease event management costs (IQR: $124,235, $586,878), and median cost-effectiveness ratio would be $829 per DALY averted (IQR: $199, $1,571; Figure 3).

GLP-1 receptor agonists. Switching from a sulfonylurea to an GLP-1 receptor agonist among those with a relevant indication (**Figure 1**) was estimated to affect 8.8% of the total population of people with diabetes (slightly larger than the SGLT-2 population given the exclusion of low eGFR populations from SGLT-2 inhibitors). At a population level, the switch to GLP-1 receptor agonists would be expected to reduce the mean risk of atherosclerotic cardiovascular disease (from 11.8% to 11.7% over 10-years) but not the median risk (which remained at 10.0%; IQR: 4.0%, 17.0%; **Table 2**). The switch would be expected to lower the mean risk of ESRD from 7.9% to 7.7% and median from 7.2% to 7.1% (IQR: 5.5%, 9.2%), hypoglycemia from mean of 19.2% to 18.0% and median from 7.3% to 6.9% (IQR: 3.7%, 20.4%), and BMI (mean change of -0.2 kg/m^2; median change of 0.0 kg/m^2; IQR: 0.0, 0.0 kg/m^2). Adverse effects of switching from sulfonylureas to GLP-1 receptor agonists would be expected to increase the risk of serious gastrointestinal distress (mean risk increase from 0.0% to 8.8% over 10 years; median unchanged at 0.0%; IQR: 0.0%, 0.0%). Overall, GLP-1 receptor agonists had an expected median incremental reduction in discounted DALYs by 56 per 1,000 (IQR: 47, 67), at a median incremental discounted cost of $55,462,510 per 1,000 (IQR: $32,303,607, $70,492,510) over 10 years, producing a median incremental cost-effectiveness ratio of $910,076 per DALY averted (IQR: $589,313, $1,295,277). In the glycemia-agnostic pathway, the median incremental reduction in DALYS would be 209 per 1,000 (IQR: 208, 267), median incremental cost would be $55,478,291 per 1,000 due to increased savings from

complications offsetting increased drug costs (IQR: $32,233,171, $70,296,903), and the median incremental cost-effectiveness ratio would be $252,186 per DALY averted (IQR: $101,871, $349,848; Table 2, Figure 3, Appendix Figure 2).

Having both SGLT-2 inhibitors and GLP-1 receptor analogues available would enable use of SGLT-2 inhibitors with sufficiently high eGFR and GLP-1 receptor agonists for the population with very low eGFR (4.1% of the population). The ratio of SGLT-2 inhibitor use to GLP-1 receptor agonist in this scenario was 90:10 across countries. The treatments in this scenario produced a median incremental reduction in discounted DALYs by 78 DALYs per 1,000 (IQR: 66, 93) over 10 years, at a median incremental discounted cost of $2,649,843 per 1,000 (IQR: $1,977,621, $3,596,420) over the same time period, producing a median incremental cost-effectiveness ratio of $40,286 per DALY averted (IQR: $27,943, $53,919) over sulfonylurea treatment. In the glycemia-agnostic pathway, both medicines together would be expected to produce a median incremental reduction in DALYs by 317 per 1,000 people (IQR: 285, 354) at a median incremental cost of $2,289,018 per 1,000 (IQR: 1,529,840, $3,468,503) for a median incremental cost-effectiveness ratio of $7,750 per DALY averted (IQR: $3,749, $12,767).

DPP-4 inhibitors. If a DPP-4 inhibitor was used as an alternative to a sulfonylurea for those with a history of hypoglycemia requiring medical attention (19.2% of the population), the risk of hypoglycemia would be lower (mean 10-year risk of hypoglycemia reducing from 19.2% to 17.9%, median from 7.3% to 6.9%: IQR: 3.7%, 30.7%; **Table 2**), and BMI would be lower (mean change of -0.3 kg/m^2; median change of 0.0 kg/m^2; IQR: 0.0, 0.0 kg/m^2). The DPP-4 inhibitor would avert 16 DALYs per 1,000 (IQR: 15, 20) over 10 years, at a median incremental discounted cost of $567,445 (IQR: $294,498, $817,616) over the same time period, producing a median incremental cost-effectiveness ratio of $25,002 per DALY averted (IQR: $19,054, $68,482; n.b., because of the long right-hand tail of DPP-4 inhibitor costs across countries, the mean incremental cost-effectiveness ratio was much higher than the median, with a mean of $57,289 per DALY averted; Table 2, Figure 3, Appendix Figure 2).

TZDs. By contrast, if a thiazolidinedione was available as an alternative to a sulfonylurea for those with a history of hypoglycemia but not having a prior history of heart failure (17.8% of the population), the population risk of heart failure hospitalization would be expected to increase from a mean of 4.5% to 4.8% over 10 years over 10-years (median remaining at 2.6%; IQR:

1.2%, 5.5%; **Table 2**). The risk of hypoglycemia would be expected to decrease (mean from 19.2.% to 18.1%, median from 7.3% to 7.0%; IQR: 3.7%, 20.7%), while BMI would be expected to increase (mean change of +0.4 kg/m^2; median change of 0.0 kg/m^2; IQR: 0.0, 0.0 kg/m^2). The thiazolidinedione would in turn have an expected median incremental reduction in discounted DALYs by 3 DALYs per 1,000 (IQR: 2, 5) over 10 years, at a median incremental discounted cost of $161,656 (IQR: $74,365, $182,581) over the same time period, producing a median incremental cost-effectiveness ratio of $70,882 per DALY averted (IQR: $12,888, $643,130) over sulfonylureas (Table 2, Figure 3, Appendix Figure 2.

Glargine insulin. If people taking basal insulin and having a history of hypoglycemia requiring medical attention (4.7% of the overall population with diabetes) were switched from NPH to glargine insulin, the population level risk of hypoglycemia would be expected to reduce (mean 10-year risk of hypoglycemia reducing from 19.2% to 17.7% and median from 7.3% to 6.9%; IQR: 3.7%, 20.7%; **Table 2**). The availability of glargine would in turn have an expected median incremental reduction in discounted DALYs by 13 DALYs per 1,000 (IQR: 6, 19) over 10 years, at a median incremental discounted cost of $450,771 per 1,000 (IQR: $83,004, $995,829) over the same time period, producing a median incremental cost-effectiveness ratio of $20,544 per DALY averted (IQR: $2,992, $64,161) over NPH insulin (Table 2, Figure 3, Appendix Figure 2).

We simulated the case where all agents considered in this assessment were available; any individual with a simulated history of atherosclerotic cardiovascular disease, heart failure, chronic kidney disease or hypoglycemia requiring medical attention received a SGLT-2 inhibitor (unless they had low GFR, in which case they received a GLP-1 receptor agonist), and those on insulin and with a history of hypoglycemia were switched from NPH to glargine insulin. Overall, the approach averted 78 DALYs per 1,000 (IQR: 66, 94) over 10 years, at a median incremental discounted cost of $2,682,061 (IQR: $2,105,476, $3,785,529) over the same time period, producing a median incremental cost-effectiveness ratio of $40,470 per DALY averted (IQR: $28,490, $55,049; **Table 2**) over the current WHO approach depicted in **Figure 1**.

Cost targets for alternative therapies

We computed the price target to reach: (i) incremental cost-effectiveness less than three times GDP per capita, or (ii) drug cost plus averted complications cost lower for the newer agents than their standard alternatives (sulfonylureas or NPH insulin; **Table 3**).

Three times GDP per capita had a median value of $14,258 across the studied countries (IQR: $5,435, $30,532). SGLT-2 inhibitors were below the threshold for incremental cost-effectiveness among 76.1% of countries in the sample. GLP-1 receptor agonists among 1.5%, DPP-4 inhibitors among 41.8%, thiazolidinediones among 29.9%, and analogue insulins among 62.7%. SGLT-2 inhibitors across all countries would need to have a median cost of $224 per person per year (a 17.4% cost reduction; IQR: $138, $359; mean $257); GLP-1 receptor agonists $208 per person per year (a 98.3% reduction; IQR: $129, $335; mean $240), DPP-4 inhibitors $73 per person per year (a 50.7% reduction; IQR: $52, $127; mean $93), thiazolidinediones $28 per person per year (a 67.1% reduction; IQR: $6, $62; mean $37), and glargine insulin $20 per vial (a 31.0% reduction; IQR: $16, $42; mean $28) to have incremental cost-effectiveness less than three times GDP per capita (**Table 3**; **Appendix Table 8**). In a glycemia-agnostic pathway, a SGLT-2 inhibitor would need a median target price of $271 per person per year (i.e., no price reduction; IQR: $161, $370; mean $294), and a GLP-1 receptor agonist $252 per year (a 98.0% reduction; IQR: $150, $345; mean $274; **Appendix Table 9**).

Price targets for being cost-saving were different than for cost-effectiveness. The cost-saving metric ignores DALYs, focusing on only the incremental dollars spent, and is therefore not subject to the denominator of incremental DALYs averted. To be cost saving, SGLT-2 inhibitors would need to reduce to a median cost of $214 per person per year across all countries (a 21.4% reduction; IQR: $148, $316; mean $245); GLP-1 receptor agonists to $199 per person per year (a 98.4% reduction; IQR: $138, $294; mean $228); DPP-4 inhibitors to $133 per person per year (a 10.5% reduction; IQR: $66, $193; mean $127); thiazolidinediones to $80 per person per year (a 4.7% reduction; IQR: $35, $91; mean $82); and insulin glargine to $20 per vial (a 32.4% reduction; IQR: $15, $37; mean $26, **Table 3**; **Appendix Table 10**). In a glycemia-agnostic pathway, the SGLT-2 inhibitors would need to achieve median target price of $224 per person per year (a 17.3% cost reduction; IQR: $161, $343; mean $263), and GLP-1 receptor agonists $208 per person per year (a 98.3% reduction; IQR: $150, $319; mean $245; **Appendix Table 11**).

Discussion

We estimated the risk of CVD and microvascular complications of type 2 diabetes in low- and middle-income countries and found that SGLT-2 inhibitors would require price reductions by approximately 13%, and GLP-1 receptor agonists by 98%, to meet a common cost-effectiveness threshold of achieving incremental costs per incremental DALY averted less than three times the GDP per capita over sulfonylurea therapy alone. Cost targets to achieve net cost-savings were lower for these medication classes, requiring further reductions off current prices. The benefits of SGLT-2 inhibitors were notably concentrated among populations at highest risk for cardiovascular events. We observed improvements in the incremental cost-effectiveness of SGLT-2 inhibitors and GLP-1 receptor agonists when adopting a 'glycemia-agnostic' pathway, in which these medicines were added to existing therapies among people with a history of atherosclerotic cardiovascular events, heart failure, and chronic kidney disease. The glycemia-agnostic pathway produced a fourfold greater impact on DALYs compared with the use of these novel agents simply as substitutes for sulfonylureas, with a 92% reduction (SGLT-2 inhibitors), 72% reduction (GLP-1 receptor agonists), and 81% reduction (both) in incremental cost-effectiveness ratios. By contrast, thiazolidinediones in particular were consistently inferior to all other alternatives, and might be discontinued from future iterations of treatment guidelines.

As generic medications increasingly become available in this market, our analysis may help identify target prices for each drug class government ministers. We note that oftentimes several generic entrants are needed in a market to push prices down, and generic entry is country-dependent, varying with quality standards and regulatory/prequalification requirements, regionalized market dynamics, and marginal commercial value.[35] Our findings on the magnitude of necessary cost reductions are notable in the context of knowledge that diabetes may cost approximately 2% of gross domestic product globally by the year 2030 when including both the costs of treatment and the costs of productivity losses from disability.[36] The costs of treatment are generally at the level of the primary health center, versus the costs of complications primarily being at the secondary or tertiary hospital level. It has been noted that including novel agents in treatment guidelines is insufficient to guarantee their accessibility and utilization, however, and thereby reducing cardiovascular and microvascular complications and their costs remains aspirational in many settings. Work from Ministries of Health is required to render agents accessible in terms of cost and market availability, consumer and prescriber understanding of

risks and benefits, and supply chain reliability to ensure treatments are consistently available to those at high risk for disease complications.[37] Our results should be therefore viewed in the context of ongoing global initiatives aimed at scaling-up proven therapies for diabetes and CVD disease prevention.[38,39]

Our assessments, which are based on microsimulation modeling using input data from national community-based surveys, are subject to limitations of the data availability, quality, and modeling exercise itself. First, we utilized price data indicating the lowest available price within a given country for each therapeutic agent, yet within-country variations in both public and private sector prices are important to note when undertaking price negotiations. Second, our data do not distinguish between type 1 and type 2 diabetes, such that we simulated only an adult type 2 diabetes subset. The burden of type 1 diabetes is particularly important to consider when choosing formularies that provide a range of insulin options.[40] Additionally, for insulin pricing, we focused on the price of vials, not of pens or cartridges, which are typically more expensive and less available in LMICs. The prices of biosimilar insulins were not considered here, but overall analogs remain high-priced in low- and middle-income countries, with biosimilars often having low uptake.[41–43] Our estimates of microvascular complications are also based on the RECODe equations that were derived and validated in US populations, and therefore may under- or over-estimate complications among other populations. Our estimates of effect size are from randomized trials that might over-state long-term real-world effectiveness.Next, the cost-effectiveness threshold we used in this assessment (of three times GDP), while commonly used by the WHO, is subject to many limitations, including instability as drug prices vary across time and space, and numerous factors affecting payers' willingness and ability to pay for products.[44–47]

The limitations of the current study highlight the need to identify personalized strategies for applying guidelines to individuals, particularly when calculating the anticipated risk and benefit of each medicine. The financial burdens of diabetes therapies have been repeatedly highlighted in both high- and lower-income countries,[48,49] and investigating how much this burden is reduced by policy efforts will be important to improve equity in diabetes outcomes. While price targets are potentially helpful to government planners, the affordability to the individual at a pharmacy often determines whether or not a patient can access the drug in many LMICs.

Our estimates provide important context and potential targets for policymakers, for whom cost has been cited as a key barrier to the inclusion of SGLT-2 inhibitors and GLP-1 receptor agonists in global diabetes treatment guidelines.[3] Our findings support the broader inclusion of such therapies in practice, particularly through a glycemia-agnostic treatment pathway. As further research defines the optimal personalized use of novel diabetes agents, our results highlight the need to rigorously assess the distribution of risk and benefit in a population and the incremental benefits of reducing risk of both macro- and micro-vascular risk factors when considering the role of novel diabetes agents.

Data sharing statement

De-identified microdata are available from the surveyed countries. Please contact Paul Martin at pmartin@hsph.harvard.edu to request data.

Contributions

SB conducted the analysis and authored the first draft of the paper. The conceptualization of the paper was formulated by: Sanjay Basu, Colin Brown, David Beran, David Flood, Jacqueline Seigle, Jen Manne Goehler, Jenna Mezhrahid, John Yudkin, Justine Davies, Kasia Lipska, and Paul Domainico. Revising of the paper was conducted by: David Beran, David Flood, John Yudkin, Justine Davies, Kasia Lipska, and Sanjay Basu. Data collection, cleaning and curation was conducted by: Abla Sibai, Corine Houehanou, David Flood, Demetre Labadarios, Farshad Farzadfar, Jacqueline Seiglie, Jennifer Manne-Goehler, Justine Davies, Krishna Aryal, Maja E. Marcus, Mary Mayige, Michaela Theilmann, Pascal Geldsetzer, Rifat Atun, Sahar Saeedi Moghaddam, Sebastian Vollmer, and Till Bärnighausen. All authors were involved in the critical appraisal and commenting on draft manuscript versions, and all authors agreed to publication.

Declaration of interest

SB reports receiving grants from the US National Institutes of health and US Centers for Disease Control and Prevention, outside the submitted work, consulting fees from the Clinton Global Health Access Initiative related to the submitted work and from the

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Tables and Figures

Table 1: Descriptive statistics on the study sample (*N* = 23,678 individuals in 67 countries, 2006-2018) obtained from the World Health Organization (WHO) STEPwise approach to Surveillance (STEPS) and other, similar, surveys (2006-2018).[24] Legend: ALA = Andean Latin America, CAR = Caribbean; CASIA = Central Asia; CEUR = Central Europe; CLA = Central Latin America; EASIA = East Asia; EEUR = Eastern Europe; ESSA = Eastern Sub-Saharan Africa; NAME = North Africa and the Middle East; OCN = Oceania; SASIA = South Asia; SEASIA = Southeast Asia; SLA = Southern Latin America; SSSA = Southern Sub-Saharan Africa; WSSA = Western Sub-Saharan Africa; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; ESRD = end-stage renal disease; retinopathy = severe vision loss by Snellen chart; neuropathy = loss of pressure sensation loss by monofilament test. Data were from the subset of people with diabetes mellitus (defined as fasting blood glucose >126 mg/dL [7 mmol/L], random blood glucose >200 mg/dL [11.1 mmol/L], hemoglobin A1c $\geq$ 6.5% [48 mmol/mol], or taking a glycemic control medicine including insulin). Country-specific statistics are available in **Appendix Table 3**.

Table 2: Estimated risk of diabetes complications, and associated disability-adjusted life-years (DALYs) and costs (2020 $Int) when adopting alternatives to sulfonylureas or NPH insulin per the alternative treatment algorithm displayed in **Figure 1**.

Table 3: Estimated goal drug price (in 2020 International Dollars, at the typical starting dose or per-vial quantity listed below) across studied countries required to reach each of two metrics: (i) being considered cost-effective in having costs per DALY averted be less than three times the GDP per capita (the threshold used by the World Health Organization[46]), or (ii) being considered cost-saving by having the drug cost plus averted complications costs be lower for the novel agents than for their current standard alternatives (sulfonylureas or NPH insulin; ignoring DALYs and focusing only on costs for a fixed budget decision-maker). The median cost of a year's supply of metformin among the studied countries at the typical starting dose of 500mg once daily was $24 (IQR: $20, $28; mean $45), for a sulfonylurea (gliclazide 80mg daily) was $26 (IQR: $16, $67; mean $37) for an SGLT-2 inhibitor (empagliflozin 5mg daily) was $271

(IQR: $168, $370; mean $294), for a GLP-1 receptor agonist (liraglutide 1.2mg daily) was $12,378 (IQR: $10,963, $13,641; mean $12,819), for a DPP-4 inhibitor (sitagliptin 100mg daily) was $148 (IQR: $77, $208; mean $143), for a thiazolidinedione (pioglitazone 15mg daily) was $84 (IQR: $37, $92; mean $99), for NPH insulin was $10 per 10mL vial of 100IU/mL (IQR: $9, $17; mean $13), and for glargine insulin was $29 per 10mL vial of 100IU/mL (IQR: $17, $54; mean $37).

Figure 1: Alternative approaches to second-line pharmacological treatment of diabetes. We compared the risks of macrovascular, microvascular, and hypoglycemia outcomes among people with diabetes mellitus in low- and middle-income countries under two different approaches for pharmacologic treatment of diabetes: the current WHO PEN guidelines, and an alternative reflecting preferences from the ADA and EASD guidelines.[7,8] Following diet and physical activity modifications, the first line pharmacological treatment (metformin) is in green, followed by second line therapies in yellow and third-line (insulin) in orange.

Figure 2: Model diagram. We estimated the risks of macrovascular, microvascular, and hypoglycemia outcomes among people with diabetes mellitus in low- and middle-income countries based on the current WHO PEN guidelines, then simulated at annual increments their life-course history based on their estimated risk, updating the simulation with age- and sex-specific secular trends to compute disability-adjusted life years (DALYs) and costs. We then re-simulated the population given an alternative reflecting preferences from the ADA and EASD guidelines (see Figure 1),7,8 using estimates from meta-analyses of randomized controlled trials (RCTs) to estimate how much changes to the medication treatment regimen would be expected to change risk and associated DALYs and costs. All simulations are performed on the individual level, to account for how persons who have higher risk would also experience potentially higher benefits from therapy.

Figure 3: Cost-effectiveness plane. Incremental disability-adjusted life-years (DALYs) and costs (2020 $Int) per 1,000 people with diabetes, when adopting alternatives to sulfonylureas or NPH insulin per the alternative treatment algorithm displayed in Figure 1. Each dot represents the mean estimate for one country in the dataset.