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

*Global Health & Population Project on Access to Care for Cardiometabolic Diseases (HPACC)**

Summary

Background For patients with type 2 diabetes in low-income and middle-income countries (LMICs), access to newer antidiabetic drugs (eg, sodium–glucose co-transporter-2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, and insulin analogues) could reduce the incidence of diabetes-related complications. We aimed to estimate price targets to pursue in negotiations for inclusion in national formularies given the addition of these novel agents to WHO's Essential Medicines List.

Methods We incorporated individual-level, nationally representative survey data (2006–18) from 23 678 people with diabetes in 67 LMICs into a microsimulation of cardiovascular events, heart failure, end-stage renal disease, vision loss, pressure sensation loss, hypoglycaemia requiring medical attention, and drug-specific side-effects. We estimated price targets for incremental costs of switching to newer treatments to achieve cost-effectiveness (ie, <3-times gross domestic product per disability-adjusted life-year averted) or to achieve net cost-savings when including costs of averted complications. We compared switching to SGLT2 inhibitors or GLP-1 receptor agonists in place of sulfonylureas, or insulin analogues in place of human insulin, and also compared a glycaemia-agnostic pathways of adding SGLT2 inhibitors or GLP-1 receptor agonists to existing therapies for people with heart disease, heart failure, or kidney disease.

Findings To achieve cost-effectiveness, SGLT2 inhibitors would need to have a median price of $224 per person per year (a 17·4% cost reduction; IQR $138–359, population-weighted across countries; mean price $257); GLP-1 receptor agonists $208 per person per year (98·3% reduction; $129–488; $240); and glargine insulin $20 per vial (31·0% reduction; $16–42; $28). To achieve net cost-savings, price targets would need to reduce by a further $9–10 to a median cost for SGLT2 inhibitors of $214 (21·4% reduction; $148–316; $245) and for GLP-1 receptor agonists to $199 per person per year (98·4% reduction; $138–294; $228); but insulin glargine remained around $20 per vial (32·4% reduction; $15–37; $26). Using SGLT2 inhibitors or GLP-1 receptor agonists in a glycaemia-agnostic pathway produced a 92% reduction (SGLT2 inhibitors) and 72% reduction (GLP-1 receptor agonists) in incremental cost-effectiveness ratios.

Interpretation Among novel agents, SGLT2 inhibitors hold particular promise for reducing complications of diabetes and meeting common price targets, particularly when used among people with established cardiovascular or kidney disease. These findings are consistent with the choice to include SGLT2 inhibitors in the WHO Essential Medicines List.

Funding Clinton Health Access Initiative.

Lancet Diabetes Endocrinol 2021; 9: 825–36

Published Online October 14, 2021 https://doi.org/10.1016/S2213-8587(21)00240-0

See Comment page 801

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Introduction

As prevalence of type 2 diabetes increases in low-income and middle-income countries (LMICs), a key question is whether—and how—to enhance access to newer pharmacological therapies.[1] Current WHO guidelines (figure 1) recommend sulfonylureas after first-line metformin to minimise costs,[2] noting that "new oral hypoglycaemic 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."[3]

Recent evidence suggests that the risk of atherosclerotic cardiovascular disease events (myocardial infarctions and strokes), heart failure exacerbations, and end-stage renal disease (ESRD) is reduced by sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.[4,5] Updated guidance from the American Diabetes Association (ADA),[6] European Association for the Study of Diabetes (EASD),[7] International Diabetes Federation,[8] and regional entities,[9,10] suggest using SGLT2 inhibitors and GLP-1 receptor agonists instead of sulfonylureas for people with atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, and compelling needs to minimise hypoglycaemia. By contrast, it remains more controversial whether small differences between insulin analogues and human insulins in terms of nocturnal hypoglycaemia are sufficient to warrant the greater cost of insulin analogues.[11–15]

Research in context

Evidence before this study

We searched the PubMed database on May 16, 2021, for original research, systematic reviews, or meta-analyses published between Jan 1, 2000, and May 16, 2021, without language restrictions 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". 61 results were retrieved, of which 15 were judged relevant to the current study. The relevant studies revealed lower rates of myocardial infarction and stroke among patients receiving sodium-glucose co-transporter-2 (SGLT2) inhibitor treatment versus other glucose-lowering agents in real-world practice and randomised clinical trials; limited insulin availability and high cost of insulin across formulations in low-income 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; modelling studies indicating that the current WHO 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 WHO 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-income 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 WHO's existing diabetes treatment guidelines to incorporate novel therapeutic agents, and identify which agents might 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 given their recent addition to the WHO's Essential Medicines List. Third, we estimate the comparative benefits and costs of using such novel agents for glucose control versus adopting a glycaemia-agnostic pathway in which SGLT2 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 previous work and the current study are consistent with the recent decision to include novel agents, particular SGLT2 inhibitors, in the WHO's Model Essential Medicines List; that target prices to achieve common thresholds for cost-effectiveness or cost-savings can be achievable with modest price reductions for SGLT2 inhibitors, but would require large price reductions for GLP-1 receptor agonists, glargine insulin, and other newer agents; and that a glycaemia-agnostic approach to including such medicines among people with relevant comorbid conditions, rather than as an alternative to sulfonylureas, could improve incremental benefits and cost-effectiveness.

To improve access to newer pharmacological therapies, government authorities and international organisations negotiate with drug manufacturers and trade organisations for price reductions.[16–19] 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 given their recent addition to the WHO Model Essential Medicines List.

Methods

Study design

We estimated the prices at which SGLT2 inhibitors, GLP-1 receptor agonists, and other alternative agents (namely dipeptidyl peptidase-4 [DPP-4] inhibitors, thiazolidinediones [TZDs], and the long-acting insulin analogue, glargine insulin) would meet each of two thresholds: first, being considered cost-effective by having costs per disability-adjusted life-year (DALY) averted less than three times the national gross domestic product (GDP) per capita (a threshold used by the WHO[20–22]); or second, 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 neutral protamine Hagedorn [NPH] insulin). We used a microsimulation to estimate the risk of DALYs lost from and cost of microvascular and macrovascular complications, heart failure, and hypoglycaemia requiring medical attention for individuals with type 2 diabetes in LMICs, when switching from sulfonylureas to alternative agents or NPH insulin to glargine insulin (figure 1).[6,7] All simulations were performed on the individual level, to account for how individuals who have higher risk would also experience potentially higher benefits from therapy.

See Online for appendix

Data sources

We input data from the WHO STEPwise approach to Surveillance (STEPS) and other, similar, surveys (2006–18) according to previous methods,[23] including adults with diabetes across 67 countries spanning 15 world regions (details of each individual survey are in appendix pp 11–61).

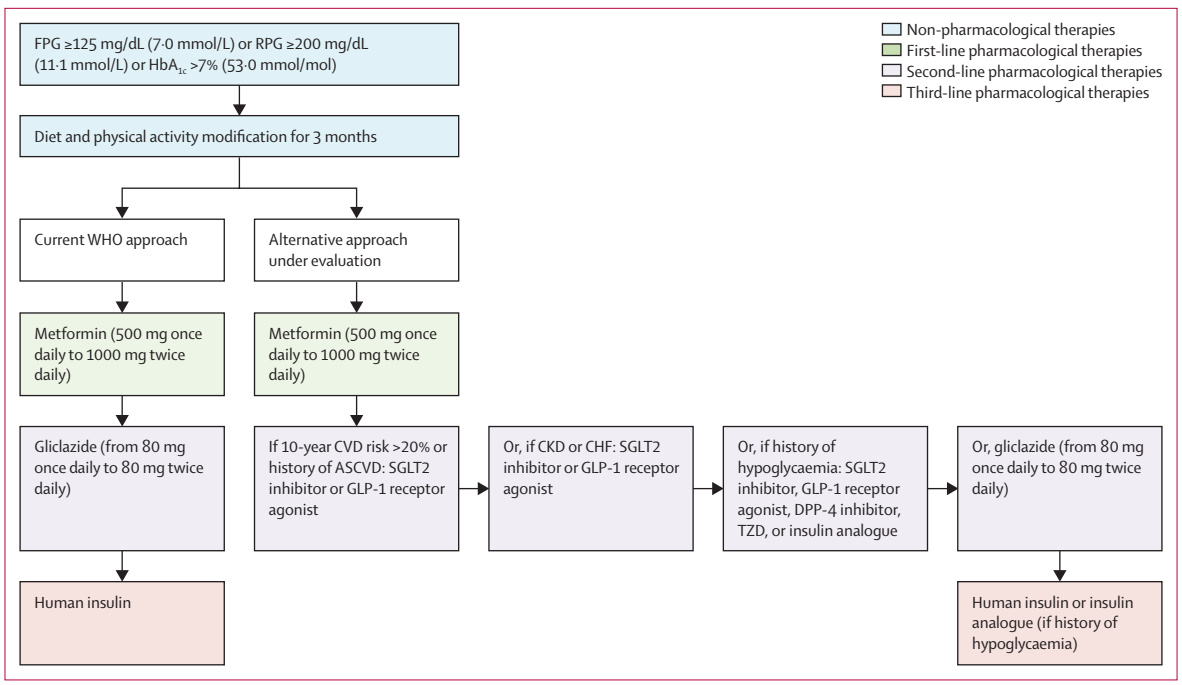

Figure 1: **Approaches to pharmacological treatment of diabetes.**
ASCVD=atherosclerotic cardiovascular disease. CHF=congestive heart failure. CKD=chronic kidney disease. DPP-4=dipeptidyl peptidase-4. FGP=fasting plasma glucose. RPG=random blood glucose. SGLT2=sodium–glucose co-transporter-2. TZD=thiazolidinedione.

Outcomes

We estimated the 10-year risk, conditional on medication choices, for atherosclerotic cardiovascular events, defined as fatal or non-fatal myocardial infarctions or strokes; 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); ESRD, defined as estimated glomerular filtration rate of less than 15 mL/min per 1·73 m² or needing dialysis or transplantation; retinopathy with severe vision loss (<20/200 visual acuity by Snellen chart); neuropathy with pressure sensation loss by Semmes-Weinstein 5·07/10 g monofilament examination; or hypoglycaemia requiring medical attention, defined as emergency medical services, emergency department visit, or hospitalisation. We estimated baseline cardiovascular disease risk using region-specific 2019 WHO cardiovascular disease risk equations (laboratory-based estimates for countries with lipid measurement available in the surveys, and clinic-based estimates otherwise),[24] and the risks of other outcomes using the Risk Equations for Complications of type 2 Diabetes (RECODe; appendix pp 67–68),[25–27] incorporating age-specific mortality and outcome-specific fatality rates to account for competing risks (appendix pp 85–86).[28]

Analytic approach

We sampled—using survey weights to account for the probabilities of survey receipt and non-response—the age, sex, blood pressure, lipid profile, medication history, cardiovascular event history, and smoking history of each adult with diabetes (previously diagnosed or un-diagnosed) in the survey data, of whom we assumed 95% would be type 2 diabetes,[29] to construct the simulated

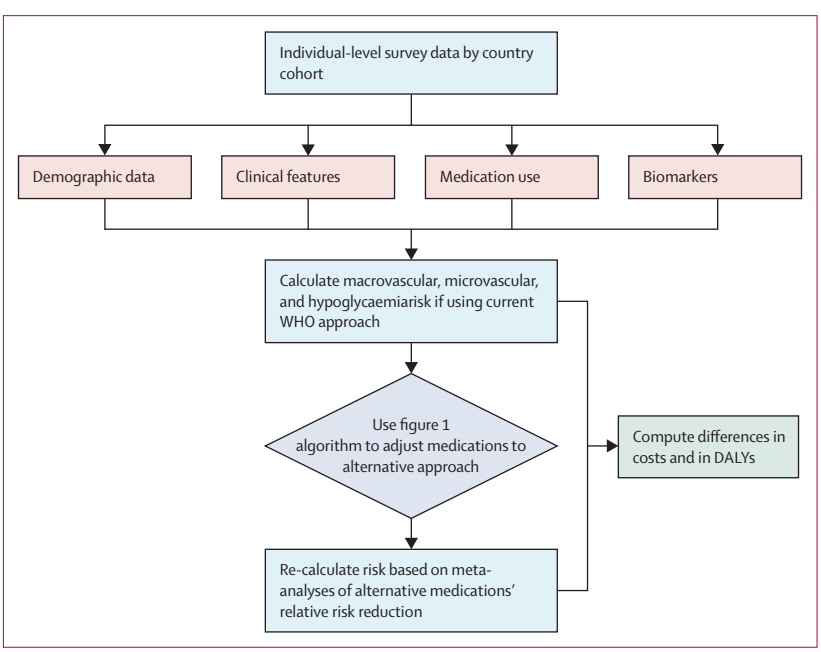

Figure 2: **Model diagram**
DALY=disability-adjusted life-year.

population of adults with type 2 diabetes in each surveyed country and simulated their history of atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, or hypoglycaemia requiring medical attention based on the previously mentioned equations (figure 2, appendix pp 68–70). 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-line and third-line agents,[2,31] and an alternative incorporating recommendations from the ADA and EASD (figure 1).[6,7] We first back-calculated the baseline levels of HbA_{1c} given the survey data on current treatment and meta-analytic estimates of the impact of each therapy on HbA_{1c} (appendix p 79). 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 once-daily, titrated up to 80 mg twice-daily, followed by NPH insulin treatment if needed to achieve a fasting plasma glucose of lower than 125 mg/dL (<7·0 mmol/L) or HbA_{1c} of 7% or lower (≤53 mmol/mol). Simultaneously, we simulated blood pressure treatment (starting with enalapril 20 mg once-daily for systolic blood pressure ≥130 mm Hg or diastolic blood pressure of ≥80 mm Hg) and statin treatment (simvastatin 20 mg once daily for individuals aged ≥40 years 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 package of essential non-communicable (PEN) disease guidelines, along with the novel SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. Specifically, we evaluated the individual and combined impact of prescribing, after metformin: first, an SGLT2 inhibitor with cardiovascular benefit (eg, empagliflozin) for individuals 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 (eg, liraglutide) if stage 4 or beyond (ie, estimated glomerular filtration rate <30 mL/min per 1·73 m²; second, any of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, or (if no history of heart failure) TZDs for individuals with a history of hypoglycaemia needing medical attention; and third, glargine insulin (U100) instead of NPH insulin for those requiring insulin and having a history of hypoglycaemia needing medical attention. The novel agents were continued at the rates of self-reported adherence to diabetes drugs from the survey. Given available evidence of efficacy and LMIC market availability, we focused our analysis on empagliflozin as the SGLT2 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.[6,7] The estimated change in HbA_{1c} for each of the oral medicines is provided in appendix (p 79).[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 randomised trials and meta-analyses of the effect of each drug on each outcome, as well as on the risk of adverse events (appendix pp 3–5).

As our survey data provided information on whether a person was on oral glycaemic agents 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 utilised insulin at a typical weight-based dosing of 0·64 IU/kg/day (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 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 simulated the switch from NPH to glargine insulin if the person had a history of hypoglycaemia, was also already on an insulin, and still needed insulin to achieve a fasting plasma glucose <125 mg/dL (<7·0 mmol/L) or HbA_{1c} ≤7% (≤53 mmol/mol) after titration of both second-line and third-line oral medicines as listed above.

Costs and DALYS

We estimated target prices for each medicine to cost less than three-times GDP per DALY averted or to 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 pp 102–08).

We included costs for medicines, treatment of diabetes complications, adverse events and their management, and equipment and devices (eg, needles) using the WHO OneHealth tool and literature reviews (appendix pp 80–84). Costs were expressed in 2020 International Dollars.

We obtained DALY disutility weights for each outcome from international preference elicitation surveys.[33] We included the most common or most serious adverse events from the newer medicines and the disutility of injection therapy for GLP-1 receptor agonists (appendix pp 85–86).

We computed costs and DALYs over a 10-year policy planning time horizon at a 3% annual discount rate. We comported with the Consolidated Health Economic

Evaluation Reporting Standards (CHEERS) guideline (appendix pp 87–89).

Sensitivity analyses

We noted that the ADA recommends that SGLT2 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 glycaemic status. Hence, we simulated a glycaemia-agnostic pathway in which SGLT2 inhibitors or GLP-1 receptor agonists were prescribed to all people with diabetes with these comorbidities, regardless of their HbA_{1c} (ie, in addition to metformin alone, in addition to metformin and sulfonylurea therapy, or in addition to metformin and insulin therapy). Additionally, we estimated the incremental cost-effectiveness of empagliflozin if lower-limb amputation risk were not a class effect in being applicable to all SGLT2 inhibitors (ie, 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 SGLT2 inhibitors.[34]

	Overall	Africa				Asia			
		ESSA	NAME	SSSA	WSSA	CASIA	EASIA	SASIA	SEASIA
Survey data									
Participants	23 678	1274	5777	964	1526	1740	648	1018	2315
Female	15 394 (65·0%)	768 (60·3%)	4659 (80·6%)	703 (72·9%)	810 (53·1%)	1025 (58·9%)	300 (46·3%)	543 (53·3%)	1538 (66·4%)
Age, years	53·00 (42·00–61·00)	48·00 (36·00–58·00)	54·00 (44·00–62·00)	56·00 (47·00–63·00)	40·00 (30·00–50·00)	54·00 (43·00–61·00)	59·80 (50·18–69·02)	47·00 (37·00–55·00)	53·00 (44·00–60·00)
Previous diabetes diagnosis	13 372 (56·5%)	416 (32·7%)	5182 (89·7%)	442 (45·9%)	120 (7·9%)	765 (44·0%)	232 (35·8%)	437 (42·9%)	1264 (54·6%)
HbA_{1c}, %	7·50 (6·60–9·30)	7·30 (6·50–8·90)	7·60 (6·60–9·30)	7·20 (6·60–9·00)	7·10 (6·50–8·63)	7·53 (6·60–9·30)	6·90 (5·90–8·43)	7·40 (6·60–9·30)	7·42 (6·62–9·30)
HbA_{1c}, mmol/mol	58·47 (48·63–78·14)	56·28 (47·54–73·77)	59·56 (48·63–78·14)	55·19 (48·63–74·86)	54·10 (47·54–70·80)	58·80 (48·63–78·14)	51·91 (40·98–68·58)	57·38 (48·63–78·14)	57·65 (48·81–78·14)
Fasting blood glucose, mmol/L	8·28 (7·20–10·99)	7·91 (7·17–9·80)	8·32 (7·15–11·06)	8·08 (7·11–10·90)	9·01 (7·46–10·39)	8·20 (7·20–11·10)	8·00 (7·27–10·18)	8·39 (7·33–11·06)	8·21 (7·10–10·90)
BMI, kg/m²	27·78 (24·07–32·02)	23·49 (20·29–27·56)	28·37 (25·00–32·04)	30·12 (25·25–34·33)	22·86 (20·23–27·64)	29·30 (25·71–33·61)	25·05 (22·64–27·72)	24·60 (21·99–27·50)	24·77 (21·89–27·89)
On any glucose-lowering medicine	10 669 (45·1%)	296 (23·2%)	4401 (76·2%)	396 (41·1%)	89 (5·8%)	617 (35·5%)	213 (32·9%)	329 (32·3%)	1082 (46·7%)
On insulin	4011 (16·9%)	152 (11·9%)	1393 (24·1%)	162 (16·8%)	55 (3·6%)	209 (12·0%)	54 (8·3%)	105 (10·3%)	194 (8·4%)
Diagnosed with hypertension	10 205 (43·1%)	288 (22·6%)	3537 (61·2%)	491 (50·9%)	182 (11·9%)	834 (47·9%)	211 (32·6%)	337 (33·1%)	964 (41·6%)
Has hypertension on examination or taking medicines	14 444 (61·0%)	562 (44·1%)	4744 (82·1%)	690 (71·6%)	636 (41·7%)	1100 (63·2%)	359 (55·4%)	500 (49·1%)	1270 (54·9%)
Systolic blood pressure, mm Hg	134·00 (121·00–151·00)	130·67 (117·00–148·00)	136·67 (123·33–152·00)	143·50 (127·50–163·50)	130·00 (118·50–147·00)	136·33 (123·00–155·38)	131·00 (121·00–148·00)	128·67 (118·33–143·00)	133·00 (121·00–150·33)
Diastolic blood pressure, mm Hg	82·00 (74·00–90·33)	82·00 (74·00–91·00)	81·50 (73·67–89·50)	83·83 (76·25–93·50)	82·00 (74·33–90·00)	87·00 (78·50–95·50)	82·00 (79·00–90·00)	85·00 (77·33–92·33)	83·67 (76·00–92·00)
On blood pressure medicines	6977 (29·5%)	143 (11·2%)	2516 (43·6%)	396 (41·1%)	107 (7·0%)	614 (35·3%)	181 (27·9%)	204 (20·0%)	551 (23·8%)
Total cholesterol, mmol/L	4·58 (3·84–5·40)	4·36 (3·57–5·20)	4·34 (3·57–5·15)	4·50 (3·77–5·40)	4·20 (3·52–5·15)	4·79 (4·00–5·57)	5·12 (4·42–5·84)	4·76 (4·09–5·56)	4·63 (3·80–5·48)
Total cholesterol, mg/dL	177·00 (148·49–208·82)	168·74 (138·25–201·00)	167·87 (138·00–199·00)	174·00 (145·69–208·82)	162·41 (136·22–199·00)	185·23 (154·68–215·39)	197·99 (170·92–225·93)	184·00 (158·00–215·00)	179·00 (146·95–211·91)
High-density lipoprotein cholesterol, mmol/L	1·06 (0·88–1·30)	1·08 (0·86–1·36)	1·03 (0·85–1·25)	1·09 (0·90–1·33)	1·14 (0·88–1·44)	1·12 (0·94–1·40)	1·23 (1·04–1·49)	0·96 (0·85–1·14)	1·08 (0·88–1·32)
High-density lipoprotein cholesterol, mg/dL	41·15 (34·00–50·32)	41·76 (33·29–52·49)	40·00 (33·00–48·34)	42·00 (34·80–51·43)	44·00 (34·01–55·68)	43·31 (36·35–54·14)	47·56 (40·22–57·71)	37·00 (32·74–44·00)	41·76 (34·00–51·00)
Self-reported history of myocardial infarction	2738 (11·6%)	83 (6·5%)	822 (14·2%)	103 (10·7%)	74 (4·8%)	402 (23·1%)	45 (6·9%)	113 (11·1%)	277 (12·0%)
On statin	2655 (11·2%)	34 (2·7%)	1351 (23·4%)	87 (9·0%)	37 (2·4%)	133 (7·6%)	31 (4·8%)	55 (5·4%)	261 (11·3%)
Current smoker	3755 (15·9%)	122 (9·6%)	1002 (17·3%)	86 (8·9%)	101 (6·6%)	297 (17·1%)	173 (26·7%)	195 (19·2%)	363 (15·7%)

(Table 1 continues on next page)

	Overall	Africa				Asia			
		ESSA	NAME	SSSA	WSSA	CASIA	EASIA	SASIA	SEASIA
(Continued from previous page)									
Model-based prevalence estimates									
History of chronic kidney disease, stage 1–4	101 364 (7·9%)	4914 (7·7%)	29247 (7·4%)	3341 (6·9%)	6688 (8·8%)	6925 (8·0%)	2029 (6·3%)	4157 (8·2%)	8996 (7·8%)
History of hypoglycaemia requiring medical attention	247 925 (19·2%)	11336 (17·8%)	74831 (18·9%)	9352 (19·4%)	11115 (14·6%)	16594 (19·1%)	4439 (13·7%)	9257 (18·2%)	22399 (19·4%)
History of CHF hospitalisation	57 434 (4·4%)	1638 (2·6%)	19260 (4·9%)	2634 (5·5%)	1307 (1·7%)	4665 (5·4%)	1447 (4·5%)	1523 (3·0%)	4548 (3·9%)
History of ASCVD events	273 464 (21·2%)	8075 (12·7%)	99215 (25·1%)	9701 (20·1%)	7000 (9·2%)	30554 (35·1%)	7658 (23·6%)	8672 (17·0%)	22926 (19·8%)
Estimated 10-year risks									
ASCVD	10·00% (4·00–17·00)	6·00% (0·00–11·00)	15·00% (8·13–22·91)	10·00% (5·00–16·00)	2·00% (0·00–8·00)	12·29% (5·00–24·00)	17·00% (10·00–25·00)	6·00% (0·00–10·00)	8·00% (4·00–12·00)
CHF hospitalisation	2·58% (1·21–5·29)	1·59% (0·75–3·10)	2·91% (1·44–5·94)	3·24% (1·48–6·73)	0·91% (0·50–1·83)	3·04% (1·28–6·50)	2·87% (1·31–5·57)	1·84% (1·02–3·71)	2·54% (1·35–4·87)
ESRD	7·23% (5·59–9·42)	7·24% (5·72–9·13)	6·79% (5·32–8·88)	6·20% (4·86–8·02)	8·16% (6·49–10·42)	7·38% (5·79–9·32)	5·67% (4·53–7·36)	7·72% (6·09–9·70)	7·04% (5·45–9·23)
Retinopathy	5·98% (4·22–8·62)	4·65% (3·18–6·65)	6·23% (4·44–8·67)	6·35% (4·34–9·00)	3·85% (2·82–5·55)	6·52% (4·62–9·49)	6·66% (4·84–9·28)	5·00% (3·72–6·97)	6·04% (4·36–8·46)
Neuropathy	7·79% (5·04–11·77)	5·87% (3·63–9·17)	8·02% (5·31–11·84)	8·14% (5·21–12·11)	4·66% (3·08–7·10)	8·33% (5·56–12·70)	8·91% (5·94–13·19)	6·73% (4·52–9·99)	7·46% (5·13–10·88)
Hypoglycaemia requiring medical attention	7·27% (3·80–22·46)	6·25% (3·64–18·20)	7·73% (3·86–22·56)	6·61% (4·10–19·93)	5·25% (3·17–14·19)	7·42% (3·92–22·50)	5·05% (2·69–14·08)	6·25% (3·61–22·44)	6·94% (3·81–22·89)

Data are n, n (%), or median (IQR). Data are for the subset of people with diabetes (defined as fasting blood glucose >126 mg/dL [>7 mmol/L], random blood glucose >200 mg/dL [>11·1 mmol/L], HbA_{1c} ≥6·5% [≥48 mmol/mol], or taking a glycaemic control medicine including insulin). Country-specific statistics are in the appendix pp 71–78. ASCVD=atherosclerotic cardiovascular disease. CASIA=Central Asia. CHF=congestive heart failure. EASIA=East Asia. ESRD=end-stage renal disease. ESSA=Eastern Sub-Saharan Africa. NAME=North Africa and the Middle East. Neuropathy=loss of pressure sensation by monofilament test. Retinopathy=severe vision loss by Snellen chart. SASIA=South Asia. SEASIA=Southeast Asia. SSSA=Southern Sub-Saharan Africa. WSSA=Western Sub-Saharan Africa.

Table 1: **Study sample characteristics overall and for Africa and Asia**

Results

The surveys we used for 67 countries included 23 678 people with diabetes (tables 1, 2). Less than 7% of any included variable was missing before imputation. Among participants with diabetes, the median age was 53·0 years (IQR 42·0–61·0), 15 394 (65·0%) were female, 13 372 (56·5%) reported being previously diagnosed with diabetes before the survey, median HbA_{1c} was 7·5% (IQR 6·6–9·3; 58·5 mmol/mol [IQR 48·6–78·1]), and 10 669 (45·1%) reported taking an oral diabetes medicine while 4011 (16·9%) reported use of insulin (table 1). The estimated risks of diabetes complications are also shown at the regional level in tables 1 and 2 and at the country level in appendix pp 71–78.

We estimated that, among the studied countries, the median cost of a year's supply of metformin at the typical starting dose of 500 mg once daily was $24 (IQR $20–28; mean $45), of a sulfonylurea (gliclazide 80 mg once-daily) was $26 ($16–67; $37), of an SGLT2 inhibitor (empagliflozin 5 mg once-daily) was $271 ($168–370; $294), of a GLP-1 receptor agonist (liraglutide 1·2 mg once-daily) was $12 378 ($10 963–13 641; $12 819), of a DPP-4 inhibitor (sitagliptin 100 mg once-daily) was $148 ($77–208; $143), of a thiazolidinedione (pioglitazone 15 mg once-daily) was $84 ($37–92; $99), of NPH insulin was $10 per 10 mL vial of 100 IU/mL ($9–17; $13), and of glargine insulin was $29 per 10 mL vial of 100 IU/mL ($17–54; $37; appendix pp 102–108).

Switching from a sulfonylurea to an SGLT2 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. At a population level, the switch to SGLT2 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 3), and to lower the risk of heart failure hospitalisation, ESRD, hypoglycaemia, and BMI, while increasing the risk of genito-urinary infections, lower-extremity amputation, and ketoacidosis. 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 1000 people (IQR 63–92), at a median incremental discounted cost of $558 817 per 1000 people ($493 711–1 172 238) over the same time period, for a median incremental cost-effectiveness ratio of $10 696 per DALY averted ($7072–15 780) over sulfonylurea treatment (table 3,

figure 3, appendix pp 109–10). 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 1000 (64–93), median incremental cost would be $557 816 per 1000 ($492 648–1 170 986), and the median incremental cost-effectiveness ratio would be $10 503 per DALY averted ($6962–15 569; figure 3).

In the glycaemia-agnostic pathway, the median incremental reduction in DALYS would be 310 DALYs per 1000 (IQR 280–348), median incremental cost would be $140 952 per 1000 people as greater drug costs were more than offset by greater reduction in cardiovascular disease event management costs ($124 235–586 878), and median cost-effectiveness ratio would be $829 per DALY averted ($199–1571; figure 3).

Switching from a sulfonylurea to a GLP-1 receptor agonist among individuals with a relevant indication (figure 1) was estimated to affect 8·8% of the total

	Europe		Latin America				Oceania
	CEUR	EEUR	ALA	CAR	CLA	SLA	OCN
Survey data							
Participants	256	586	341	493	3075	538	3127
Female	107 (41·8%)	380 (64·8%)	194 (56·9%)	358 (72·6%)	1986 (64·6%)	317 (58·9%)	1706 (54·6%)
Age, years	63·00 (53·00–70·00)	58·00 (51·00–64·00)	52·00 (43·00–60·00)	55·00 (46·00–65·00)	57·00 (47·00–67·00)	61·00 (51·25–70·00)	48·00 (38·00–56·00)
Previous diabetes diagnosis	198 (77·3%)	356 (60·8%)	161 (47·2%)	349 (70·8%)	2109 (68·6%)	333 (61·9%)	1008 (32·2%)
HbA_{1c}, %	6·55 (5·70–7·60)	7·20 (6·50–8·97)	7·70 (6·62–9·40)	8·00 (6·70–9·70)	7·90 (6·60–9·80)	7·40 (6·60–9·03)	7·50 (6·60–9·30)
HbA_{1c}, mmol/mol	48·09 (38·80–59·56)	55·19 (47·54–74·59)	60·66 (48·81–79·24)	63·93 (49·73–82·51)	62·84 (48·63–83·61)	57·38 (48·63–75·21)	58·47 (48·63–78·14)
Fasting blood glucose, mmol/L	7·78 (7·06–9·31)	7·70 (7·00–9·80)	8·11 (7·11–11·50)	8·61 (7·10–11·89)	8·11 (6·61–11·94)	7·94 (7·21–10·88)	8·60 (7·48–11·80)
BMI, kg/m^2	30·78 (27·96–34·58)	31·09 (26·99–35·51)	28·87 (25·31–32·60)	29·31 (25·79–33·61)	29·38 (26·18–33·32)	29·82 (26·30–34·10)	29·31 (25·46–34·15)
On any glucose-lowering medicine	37 (14·5%)	293 (50·0%)	144 (42·2%)	299 (60·6%)	1728 (56·2%)	246 (45·7%)	499 (16·0%)
On insulin	12 (4·7%)	95 (16·2%)	37 (10·9%)	49 (9·9%)	1049 (34·1%)	46 (8·6%)	399 (12·8%)
Diagnosed with hypertension	162 (63·3%)	389 (66·4%)	121 (35·5%)	262 (53·1%)	1440 (46·8%)	314 (58·4%)	673 (21·5%)
Has hypertension on examination or taking medicines	120 (46·9%)	471 (80·4%)	126 (37·0%)	301 (61·1%)	1867 (60·7%)	334 (62·1%)	1364 (43·6%)
Systolic blood pressure, mm Hg	138·00 (125·38–151·00)	150·50 (134·08–170·00)	125·33 (116·00–137·33)	134·50 (119·50–150·00)	131·50 (119·00–151·00)	137·50 (125·50–154·50)	131·00 (119·00–146·00)
Diastolic blood pressure, mm Hg	80·50 (74·50–87·50)	91·33 (82·00–99·00)	77·67 (71·33–84·33)	80·00 (71·50–87·50)	79·00 (70·00–87·00)	78·25 (70·50–87·50)	81·33 (73·00–89·50)
On blood pressure medicines	0 (0·0%)	297 (50·7%)	71 (20·8%)	186 (37·7%)	1212 (39·4%)	166 (30·9%)	333 (10·6%)
Total cholesterol, mmol/L	4·99 (4·16–5·80)	5·00 (4·30–5·80)	4·91 (4·06–5·84)	4·78 (3·98–5·69)	4·89 (4·22–5·56)	4·97 (4·17–5·76)	4·60 (3·93–5·37)
Total cholesterol, mg/dL	193·00 (161·00–224·25)	193·35 (166·38–224·29)	190·00 (157·00–226·00)	185·00 (154·00–220·00)	189·00 (163·00–215·00)	192·00 (161·16–222·84)	177·88 (151·97–207·49)
High-density lipoprotein cholesterol, mmol/L	1·22 (0·98–1·43)	1·25 (1·01–1·57)	1·09 (0·88–1·30)	1·18 (0·94–1·48)	1·03 (0·88–1·22)	1·04 (0·90–1·27)	1·06 (0·80–1·33)
High-density lipoprotein cholesterol, mg/dL	47·00 (38·00–55·25)	48·34 (39·06–60·71)	42·00 (34·00–50·27)	45·63 (36·50–57·40)	40·00 (34·00–47·00)	40·30 (34·70–49·00)	40·99 (30·94–51·43)
Self-reported history of myocardial infarction	18 (7·0%)	148 (25·3%)	38 (11·1%)	58 (11·8%)	232 (7·5%)	67 (12·5%)	258 (8·3%)
On statin	13 (5·1%)	62 (10·6%)	24 (7·0%)	40 (8·1%)	350 (11·4%)	61 (11·3%)	116 (3·7%)
Current smoker	48 (18·8%)	85 (14·5%)	44 (12·9%)	21 (4·3%)	315 (10·2%)	117 (21·7%)	786 (25·1%)
Model-based prevalence estimates							
History of chronic kidney disease, stage 1–4	744 (5·8%)	2095 (7·2%)	1583 (9·3%)	1689 (6·9%)	13411 (8·7%)	2116 (7·9%)	13429 (8·6%)
History of hypoglycaemia requiring medical attention	1165 (9·1%)	5003 (17·1%)	3684 (21·6%)	5582 (22·6%)	37595 (24·5%)	5255 (19·5%)	30318 (19·4%)
History of congestive heart failure hospitalisation	418 (3·3%)	1791 (6·1%)	635 (3·7%)	1285 (5·2%)	9982 (6·5%)	1850 (6·9%)	4451 (2·8%)
History of atherosclerotic cardiovascular disease events	3397 (26·5%)	12185 (41·6%)	2768 (16·2%)	5120 (20·8%)	25018 (16·3%)	6709 (24·9%)	24466 (15·6%)

(Table 2 continues on next page)

	Europe		Latin America				Oceania
	CEUR	EEUR	ALA	CAR	CLA	SLA	OCN
(Continued from previous page)							
Estimated 10-year risks							
ASCVD	20·00% (11·00–31·00)	22·00% (14·00–31·00)	5·17% (3·00–8·00)	8·87% (4·43–15·00)	8·00% (4·00–14·00)	13·00% (7·00–20·00)	7·00% (0·00–12·00)
CHF hospitalisation	2·56% (1·32–4·11)	3·75% (1·70–7·97)	2·54% (1·32–4·82)	3·17% (1·61–5·68)	3·87% (1·88–7·99)	4·32% (2·21–7·96)	1·83% (0·94–3·53)
ESRD	5·55% (4·66–7·10)	6·58% (5·11–8·58)	8·76% (6·95–11·41)	5·97% (4·68–8·05)	7·96% (6·02–10·62)	7·32% (5·86–9·78)	8·05% (6·47–10·21)
Retinopathy	7·20% (4·84–9·50)	7·93% (5·53–11·12)	5·69% (4·13–7·76)	6·01% (4·18–8·44)	7·14% (5·06–10·39)	7·42% (5·38–10·76)	5·56% (3·95–7·71)
Neuropathy	9·22% (6·44–13·14)	9·60% (6·50–13·99)	7·83% (5·15–11·17)	7·82% (5·19–11·86)	9·80% (6·49–14·81)	10·42% (7·24–15·31)	7·01% (4·59–10·42)
Hypoglycaemia requiring medical attention	4·59% (2·49–9·49)	6·47% (3·46–19·02)	7·54% (4·00–23·91)	10·68% (4·40–29·51)	10·57% (4·29–34·16)	7·65% (4·20–21·99)	7·30% (3·87–22·28)

Data are n, n (%), or median (IQR). Data are for the subset of people with diabetes (defined as fasting blood glucose >126 mg/dL [>7 mmol/L], random blood glucose >200 mg/dL [>11·1 mmol/L], HbA_{1c} ≥6·5% [≥48 mmol/mol], or taking a glycaemic control medicine including insulin). Country-specific statistics are in the appendix pp 71–78. ALA=Andean Latin America. ASCVD=atherosclerotic cardiovascular disease. CAR=Caribbean. CEUR=Central Europe. CHF=congestive heart failure. CLA=Central Latin America. EEUR=Eastern Europe. ESRD=end-stage renal disease. Neuropathy=loss of pressure sensation by monofilament test. OCN=Oceania. Retinopathy=severe vision loss by Snellen chart. SLA=Southern Latin America.

Table 2: **Study sample characteristics for Europe, Latin America, and Oceania**

population of people with diabetes. 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 3). The switch would be expected to lower the risk of ESRD, hypoglycaemia, and BMI, while increasing the risk of serious gastrointestinal distress. Overall, GLP-1 receptor agonists had an expected median incremental reduction in discounted DALYs by 56 per 1000 (IQR 47–67), at a median incremental discounted cost of $55 462 510 per 1000 ($32 303 607–70 492 510) over 10 years, producing a median incremental cost-effectiveness ratio of $910 076 per DALY averted ($589 313–1 295 277). In the glycaemia-agnostic pathway, the median incremental reduction in DALYS would be 209 per 1000 (IQR 208–267), median incremental cost would be $55 478 291 per 1000 due to increased savings from complications offsetting increased drug costs ($32 233 171–70 296 903), and the median incremental cost-effectiveness ratio would be $252 186 per DALY averted ($101 871–349 848; table 3, figure 3, appendix pp 109–10).

Results for SGLT2 inhibitors and GLP-1 receptor agonists together, and for DPP-4 inhibitors and thiazolidinediones, are presented in appendix pp 9–10.

If people taking basal insulin and having a history of hypoglycaemia requiring medical attention (4·7% of the overall population with diabetes) were switched from NPH to glargine insulin, the population level risk of hypoglycaemia would be expected to reduce (mean 10-year risk of hypoglycaemia reducing from 19·2% to 17·7% and median from 7·3% to 6·9%; table 3). The availability of glargine would in turn have an expected median incremental reduction in discounted DALYs by 13 DALYs per 1000 (IQR 6–19) over 10 years, at a median incremental discounted cost of $450 771 per 1000 ($83 004–995 829) over the same time period, producing a median incremental cost-effectiveness ratio of $20 544 per DALY averted ($2992–64 161) over NPH insulin (table 3, figure 3, appendix pp 109–10).

In terms of cost targets for alternative therapies, three-times GDP per capita had a median value of $14 258 across the studied countries (IQR $5435–30 532). SGLT2 inhibitors were below the threshold for incremental cost-effectiveness among 51 (76%) of 67 countries in the sample, GLP-1 receptor agonists among one (1%, and analogue insulins among 42 (63%). SGLT2 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 (98·3% reduction; $129–488; $240); and glargine insulin $20 per vial (31·0% reduction; $16–42; $28) to have incremental cost-effectiveness less than three-times GDP per capita (table 4; appendix pp 90–92). In a glycaemia-agnostic pathway, an SGLT2 inhibitor would need a median target price of $271 per person per year (no price reduction; IQR $161–370; mean $294), and a GLP-1 receptor agonist $252 per year (98·0% reduction; $150–345; $274; appendix pp 93–95).

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, SGLT2 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 (98·4% reduction; $138–294; $228); and insulin glargine to $20 per vial (32·4% reduction; $15–37; $26; table 4, appendix pp 96–98). In a glycaemia-agnostic pathway, the SGLT2 inhibitors would need to achieve

	Reference agents	Alternative agents made available						
	Sulfonylurea and NPH insulin if needed	SGLT2 inhibitor instead of sulfonylurea if ASCVD, CHF, CKD or hypoglycaemia	GLP-1 receptor agonist instead of sulfonylurea if ASCVD, CHF, CKD or hypoglycaemia	SGLT2 inhibitor (if low eGFR), GLP-1 receptor agonist instead of sulfonylurea if ASCVD, CHF, CKD or hypoglycaemia	DPP-4 inhibitor instead of sulfonylurea if hypoglycaemia	TZD instead of sulfonylurea if hypoglycaemia and no CHF	Glargine insulin instead of NPH insulin if hypoglycaemia	All agents available
ASCVD event, %	11·78% (10·29); 10·00% (4·00–17·00)	11·62% (10·16); 10·00% (4·00–17·00)	11·68% (10·21); 10·00% (4·00–17·00)	11·62% (10·16); 10·00% (4·00–17·00)	11·78% (10·29); 10·00% (4·00–17·00)	11·58% (10·13); 10·00% (4·00–17·00)	11·78% (10·29); 10·00% (4·00–17·00)	11·62% (10·16); 10·00% (4·00–17·00)
CHF hospitalisation, %	4·47% (5·79); 2·58% (1·21–5·29)	4·23% (5·29); 2·52% (1·19–5·10)	4·47% (5·79); 2·58% (1·21–5·29)	4·24% (5·30); 2·52% (1·19–5·11)	4·47% (5·79); 2·58% (1·21–5·29)	4·75% (6·54); 2·62% (1·22–5·47)	4·47% (5·79); 2·58% (1·21–5·29)	4·24% (5·30); 2·52% (1·19–5·11)
ESRD, %	7·90% (3·24); 7·23% (5·59–9·42)	7·70% (3·21); 7·05% (5·45–9·22)	7·72% (3·21); 7·07% (5·47–9·23)	7·70% (3·21); 7·04% (5·44–9·21)	7·90% (3·24); 7·23% (5·60–9·43)	7·89% (3·24); 7·23% (5·59–9·42)	7·90% (3·24); 7·23% (5·59–9·42)	7·70% (3·21); 7·04% (5·44–9·21)
Retinopathy leading to severe vision loss, %	6·92% (3·88); 5·98% (4·22–8·62)	6·93% (3·89); 5·99% (4·22–8·64)	6·87% (3·85); 5·94% (4·20–8·56)	6·93% (3·89); 5·99% (4·22–8·63)	6·93% (3·89); 5·99% (4·22–8·63)	6·91% (3·88); 5·98% (4·22–8·61)	6·92% (3·88); 5·98% (4·22–8·62)	6·93% (3·89); 5·99% (4·22–8·63)
Neuropathy leading to loss of pressure sensation, %	9·28% (6·09); 7·79% (5·04–11·77)	9·29% (6·10); 7·80% (5·05–11·79)	9·24% (6·05); 7·76% (5·03–11·71)	9·28% (6·09); 7·80% (5·04–11·79)	9·28% (6·09); 7·80% (5·04–11·79)	9·27% (6·08); 7·79% (5·04–11·77)	9·28% (6·09); 7·79% (5·04–11·77)	9·28% (6·09); 7·80% (5·04–11·79)
Hypoglycaemia requiring medical attention, %	19·21% (25·46); 7·27% (3·80–22·46)	17·74% (24·45); 6·67% (3·57–19·57)	17·97% (24·34); 6·92% (3·67–20·36)	17·69% (24·39); 6·68% (3·56–19·47)	17·88% (24·34); 6·87% (3·65–20·10)	18·11% (24·36); 6·98% (3·69–20·67)	17·72% (23·37); 6·92% (3·67–20·71)	17·64% (24·41); 6·61% (3·54–19·47)
Genito-urinary infection, %	4·35% (0·00); 4·35% (4·35–4·35)	4·75% (1·33); 4·35% (4·35–4·35)	4·35% (0·00); 4·35% (4·35–4·35)	4·73% (1·23); 4·35% (4·35–4·35)	4·35% (0·00); 4·35% (4·35–4·35)	4·35% (0·00); 4·35% (4·35–4·35)	4·35% (0·00); 4·35% (4·35–4·35)	4·73% (1·23); 4·35% (4·35–4·35)
Diabetic ketoacidosis, %	0·07% (0·00); 0·07% (0·07–0·07)	0·09% (0·04); 0·07% (0·07–0·07)	0·07% (0·00); 0·07% (0·07–0·07)	0·09% (0·04); 0·07% (0·07–0·07)	0·07% (0·00); 0·07% (0·07–0·07)	0·07% (0·00); 0·07% (0·07–0·07)	0·09% (0·04); 0·07% (0·07–0·07)	0·09% (0·04); 0·07% (0·07–0·07)
Lower extremity amputation, %	0·35% (0·00); 0·35% (0·35–0·35)	0·38% (0·09); 0·35% (0·35–0·35)	0·35% (0·00); 0·35% (0·35–0·35)	0·38% (0·09); 0·35% (0·35–0·35)	0·35% (0·00); 0·35% (0·35–0·35)	0·35% (0·00); 0·35% (0·35–0·35)	0·38% (0·09); 0·35% (0·35–0·35)	0·38% (0·09); 0·35% (0·35–0·35)
Severe gastrointestinal distress, %	0·00% (0·00); 0·00% (0·00–0·00)	0·00% (0·00); 0·00% (0·00–0·00)	8·82% (28·36); 0·00% (0·00–0·00)	0·06% (0·19); 0·00% (0·00–0·00)	0·00% (0·00); 0·00% (0·00–0·00)	0·00% (0·00); 0·00% (0·00–0·00)	0·00% (0·00); 0·00% (0·00–0·00)	0·06% (0·19); 0·00% (0·00–0·00)
Change in BMI, kg/m^2	0·16 (0·32); 0·00 (0·00–0·00)	0·03 (0·49); 0·00 (0·00–0·00)	0·00 (0·56); 0·00 (0·00–0·00)	0·03 (0·47); 0·00 (0·00–0·00)	0·10 (0·34); 0·00 (0·00–0·00)	0·27 (0·51); 0·00 (0·00–0·00)	0·16 (0·32); 0·00 (0·00–0·00)	0·03 (0·47); 0·00 (0·00–0·00)
Cost-effectiveness								
DALYs per 1000 people, n	2657 (404); 2729 (2329–3026)	2582 (399); 2654 (2237–2962)	2598 (398); 2674 (2262–2978)	2580 (399); 2652 (2235–2960)	2642 (401); 2714 (2308–3011)	2654 (402); 2727 (2324–3021)	2645 (400); 2716 (2322–3006)	2579 (399); 2651 (2234–2959)
Costs per 1000 people, INT$*	$3 854 819 (1 378 248); 3 385 351 (3 133 716–4 554 518)	$4 713 909 (1 805 339); 3 944 168 (3 627 427–5 726 756)	$57 595 315 (27 426 008); 58 847 862 (35 437 323–75 047 134)	6 908 961 (2 807 409); 6 035 194 (5 111 336–8 150 939)	4 433 162 (1 744 939); 3 952 796 (3 428 213–5 372 135)	4 205 632 (1 760 027); 3 547 007 (3 208 081–4 737 100)	4 143 205 (1 492 683); 3 836 123 (3 216 720–4 850 649)	7 014 318 (2 856 292); 6 067 413 (5 239 192–8 340 048)
Incremental cost-effectiveness ratio, INT$/DALY averted	Reference group	12 425 (7434); 10 696 (7072–15 779)	984 995 (496 886); 910 075 (589 313–1 295 276)	41 883 (16 478); 40 286 (27 943–53 919)	57 289 (67 060); 25 002 (19 054–68 482)	562 753 (904 448); 70 882 (12 887–643 130)	103 019 (234 895); 20 543 (2992–64 161)	42 995 (16 902); 40 469 (28 489–55 048)

Data are mean (SD); median (IQR). ASCVD=atherosclerotic cardiovascular disease. CHF=congestive heart failure. CKD=chronic kidney disease. DALY=disability-adjusted life-year. DPP-4=Dipeptidyl peptidase-4. eGFR= estimated glomerular filtration rate. ESRD=end-stage renal disease. GLP-1=glucagon-like peptide-1. INT$=international $. NPH=neutral protamine Hagedorn. SGLT2=sodium-glucose co-transporter-2. TZD=thiazolidinedione. *Including medications and treatment of complications.

Table 3: **Estimated 10-year risks of diabetes complications and associated DALYs and costs (2020 INT$) when adopting alternatives to sulfonylureas or NPH insulin per the alternative treatment algorithm shown in figure 1**

median target price of $224 per person per year (a 17·3% reduction; IQR $161–343; mean $263), and GLP-1 receptor agonists $208 per person per year (98·3% reduction; $150–319; $245; appendix pp 99–101).

Discussion

We found that among novel agents, SGLT2 inhibitors hold particular promise for reducing complications of diabetes and meeting common price targets. Consistent with this finding, SGLT2 inhibitors were recently included in the WHO's Essential Medicines List, which provides opportunity for their price reduction and inclusion in national formularies in many LMICs. SGLT2 inhibitors would require price reductions by approximately 17%, 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. Achieving net cost-savings required further reductions off current prices. The incremental cost-effectiveness of SGLT2 inhibitors and GLP-1 receptor agonists improved when adopting a glycaemia-agnostic pathway (where these medicines were added to existing therapies among people with a history of heart or kidney disease). The glycaemia-agnostic pathway produced a four-fold greater impact on DALYs compared with the use of these novel agents simply as substitutes for sulfonylureas, with a 92% reduction (SGLT2 inhibitors) and 72% reduction (GLP-1 receptor agonists) 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.

The inclusion of SGLT2 inhibitors in the WHO Essential Medicines List provides an opportunity for country ministers to include the medicines in their national formularies and negotiate prices of those medicines while doing so. We note that often several generic entrants are needed in a market to push prices down, and generic entry is country-dependent, varying with quality standards and regulatory or prequalification requirements, regionalised market dynamics, and marginal commercial value.[35] Our results should therefore be viewed in the context of

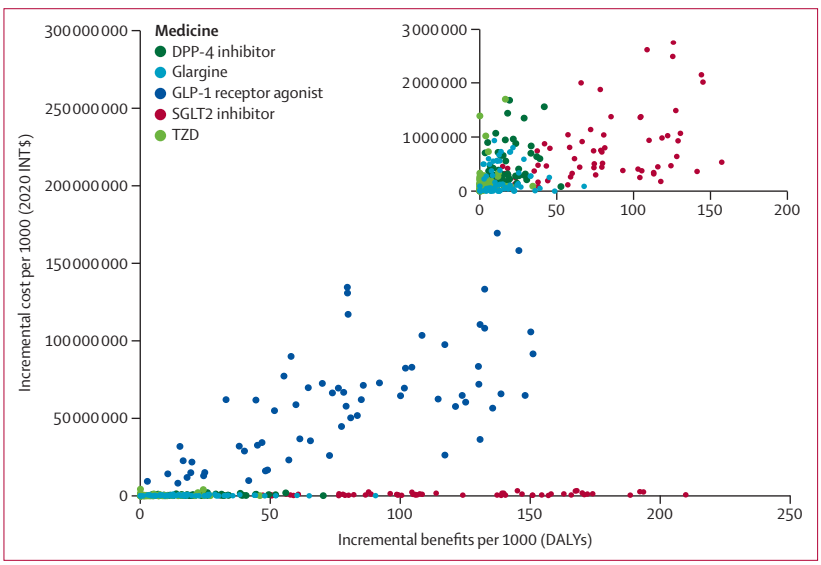

Figure 3: **Cost-effectiveness plane**
Incremental DALYs and costs per 1000 people with diabetes, when adopting alternatives to sulfonylureas or NPH insulin per the alternative treatment algorithm displayed in figure 1. Each dot represents the mean estimate for one country in the dataset. DALY=disability-adjusted life-year. DPP-4=Dipeptidyl peptidase-4. GLP-1=glucagon-like peptide-1. INT$=international $. SGLT2=sodium–glucose co-transporter-2. TZD=thiazolidinedione.

	SGLT2 inhibitor	GLP-1 receptor agonist	DPP-4 inhibitor	TZD	Glargine insulin
Cost-effectiveness threshold of <3×GDP per capita*					
Low-income countries (n=11)	158·64 (115·77–192·55, 30·6%)	147·69 (107·78–179·26, 98·6%)	28·09 (17·22–60·45, 56·4%)	17·81 (9·18–32·93, 59·0%)	17·88 (14·75–31·66, 46·4%)
Lower-middle-income countries (n=28)	234·69 (198·14–359·29, 14·8%)	218·49 (184·47–334·49, 97·7%)	74·16 (36·74–113·17, 42·2%)	24·24 (6·48–49·14, 64·5%)	17·95 (15·89–21·46, 8·96%)
Upper-middle-income countries (n=28)	234·73 (115·77–359·29, 3·3%)	218·53 (107·78–334·49, 98·2%)	80·74 (59·64–183·17, 19·3%)	33·10 (1·67–83·94, 61·1%)	36·21 (17·44–51·53, 30·9%)
Overall (n=67)	223·89 (138·34–359·29, 17·4%)	208·44 (128·79–488·08, 98·3%)	73·07 (51·88–127·86, 50·7%)	27·66 (5·57–61·84, 66·6%)	19·96 (15·79–42·11, 31·0%)
Cost-savings when including cost of complications averted†					
Low-income countries (n=11)	207·94 (141·85–419·30, 8·2%)	193·59 (132·06–390·36, 86·9%)	78·20 (64·20–143·50, 4·4%)	81·30 (32·30–83·25, 4·1%)	20·60 (17·01–35·69, 22·2%)
Lower-middle-income countries (n=28)	268·51 (182·19–317·95, 19·3%)	249·98 (169·62–296·01, 99·3%)	135·00 (74·80–172·66, 10·8%)	79·57 (47·30–90·30, 13·3%)	16·60 (13·34–19·08, 22·6%)
Upper-middle-income countries (n=28)	196·58 (109·78–311·98, 17·3%)	183·02 (102·20–290·45, 99·3%)	142·50 (57·08–207·75, 14·2%)	79·15 (35·40–107·25, 26·1%)	34·52 (19·84–41·90, 39·6%)
Overall (n=67)	213·90 (148·12–315·69, 21·4%)	199·14 (137·90–293·90, 98·4%)	132·51 (65·56–192·62, 10·5%)	80·02 (35·44–90·99, 4·7%)	19·60 (14·70–36·84, 32·4%)

Data are median (IQR, % reduction). INT$=international $. DALY=disability-adjusted life-year. DPP-4=Dipeptidyl peptidase-4. GDP=gross domestic product. GLP-1=glucagon-like peptide-1. NPH=neutral protamine Hagedorn. SGLT2=sodium-glucose co-transporter-2. TZD=thiazolidinedione. *WHO threshold. †Lower cost *vs* standard alternatives (sulfonylureas or NPH insulin; ignoring DALYs and focusing only on costs for a fixed budget decision maker).

Table 4: **Estimated goal drug price in 2020 INT$ per person per year, at the typical starting dose or per-vial quantity**

ongoing initiatives aimed at scaling up proven therapies for diabetes and cardiovascular disease prevention.[36,37] Although insulin glargine was also included in the recent update to the WHO Essential Medicines List, our findings suggested little incremental benefit to glargine at a population level, with a large incremental price increase.

Our assessments are subject to several limitations. First, we utilised 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. Second, our data do not distinguish between type 1 and type 2 diabetes, such that we simulated only a 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.[38] 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 analogues generally remain high-priced in LMICs, with biosimilars often having low uptake.[39–41] Our estimates of microvascular complications are also based on the RECODe equations derived and validated in US populations, which might underestimate or overestimate complications among other populations. Our estimates of effect size are from randomised trials that might overstate long-term real-world effectiveness. Next, the cost-effectiveness threshold we used in this assessment (of three-times GDP), while commonly used, is subject to instability as drug prices vary across time and space, and numerous factors affecting payers' willingness and ability to pay for products.[42–45] Although 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 policy makers, for whom cost has been cited as a key barrier to the inclusion of SGLT2 inhibitors and GLP-1 receptor agonists in treatment guidelines.[3] Our findings support the broader inclusion of such therapies in practice, particularly through a glycaemia-agnostic treatment pathway. As SGLT2 inhibitors have been included in the WHO Essential Medicines List, policymakers within LMICs can now consider their inclusion within national formularies and the negotiation of lower drug prices for these medicines.

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Contributors

SB conducted the analysis and authored the first draft of the paper. The conceptualisation of the paper was formulated by SB, CB, DB, DF, JS, JM-G, JM, JSY, JD, KL, and PD. Revising of the paper was conducted by DB, DF, JSY, JD, KL, and SB. Data collection, cleaning, and curation was conducted by AS, CH, DF, DL, FF, JS, JM-G, JD, KA, MEM, MM, MT, PG, RA, SSM, SV, and TB. 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 Centres for Disease Control and Prevention, consulting fees from the Clinton Health Access Initiative and from the University of California San Francisco, a US patent pending for "Multi-model patient outreach system", unpaid leadership roles at the La Scuola International School Board and the Board of Advisors for the Global Research Analytics for Population Health Center at Columbia University, and stock options in Collective Health. All other authors declare no competing interests.

Data sharing

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

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