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First-Line Therapy for Type 2 Diabetes With Sodium–Glucose Cotransporter-2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists:

A Cost-Effectiveness Study

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Abstract

Background: Guidelines recommend sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) receptor agonists as second-line therapy for patients with type 2 diabetes. Expanding their use as first-line therapy has been proposed but the clinical benefits may not outweigh their costs.

Objective: To evaluate the lifetime cost-effectiveness of a strategy of first-line SGLT2 inhibitors or GLP1 receptor agonists.

Design: Individual-level Monte Carlo–based Markov model.

Data Sources: Randomized trials, Centers for Disease Control and Prevention databases, RED BOOK, and the National Health and Nutrition Examination Survey.

Target Population: Drug-naive U.S. patients with type 2 diabetes.

Time Horizon: Lifetime.

Perspective: Health care sector.

Intervention: First-line SGLT2 inhibitors or GLP1 receptor agonists.

Outcome Measures: Life expectancy, lifetime costs, incremental cost-effectiveness ratios (ICERs).

Results of Base-Case Analysis: First-line SGLT2 inhibitors and GLP1 receptor agonists had lower lifetime rates of congestive heart failure, ischemic heart disease, myocardial infarction, and stroke compared with metformin. First-line SGLT2 inhibitors cost $43 000 more and added 1.8 quality-adjusted months versus first-line metformin ($478 000 per quality-adjusted life-year [QALY]). First-line injectable GLP1 receptor agonists cost more and reduced QALYs compared with metformin.

Results of Sensitivity Analysis: By removing injection disutility, first-line GLP1 receptor agonists were no longer dominated (ICER, $327 000 per QALY). Oral GLP1 receptor agonists were not cost-effective (ICER, $823 000 per QALY). To be cost-effective at under $150 000 per QALY, costs for SGLT2 inhibitors would need to be under $5 per day and under $6 per day for oral GLP1 receptor agonists.

Limitation: U.S. population and costs not generalizable internationally.

Conclusion: As first-line agents, SGLT2 inhibitors and GLP1 receptor agonists would improve type 2 diabetes outcomes, but their costs would need to fall by at least 70% to be cost-effective.

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In the United States, type 2 diabetes affects more than 30 million adults (1, 2) and costs approximately $327 billion annually, up from $174 billion in 2007 (3). This dramatic cost increase is partially attributable to the drug classes of sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) receptor agonists (3–7). Large randomized controlled trials of SGLT2 inhibitors (8–10) and GLP1 receptor agonists (11–15) have demonstrated reductions in atherosclerotic cardiovascular disease (ASCVD), microvascular disease, and mortality in addition to improvements in glycated hemoglobin (HbA_{1c}) and cardiovascular risk factors.

Based on these trials and other evidence, the 2020 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines recommended SGLT2 inhibitors or GLP1 receptor agonists as second-line therapy, after lifestyle intervention and metformin, in patients with type 2 diabetes without ASCVD, and as first-line therapy with metformin for patients with coexistent—or high risk for—ASCVD, heart failure, or chronic kidney disease (CKD) (16–19). Some experts have gone further to argue for SGLT2 inhibitors and GLP1 receptor agonists as first-line therapy (before metformin) in high-risk populations (20). Trials investigating safety have also suggested that some SGLT2 inhibitors may reduce heart failure admissions even without metformin (21, 22).

Although clinical trials have demonstrated the clinical effectiveness of these newer drugs, they are hundreds of times more expensive than other oral diabetes drugs. In recognition of their high costs, ADA guidelines do not recommend SGLT2 inhibitors and GLP1 receptor agonists as second-line therapy if “cost is a major issue” (19). In 2019, an Institute for Clinical and Economic Review evaluation not only found GLP1 receptor agonists as an add-on therapy to metformin to be cost-effective but also issued an “affordability alert” signaling that GLP1 receptor agonists put a large strain on payers, particularly state Medicaid programs (23). Importantly, the costs of these drug classes may be declining in the next few years because some SGLT2 inhibitors and GLP1 receptor agonists are scheduled to lose (or already have lost) market exclusivity.

Because of the tradeoffs between the clinical benefits of SGLT2 inhibitors and GLP1 receptor agonists and their currently high, but potentially falling, U.S. costs (20), we evaluated the cost-effectiveness of SGLT2 inhibitors and GLP1 receptor agonists as first-line therapies for U.S. patients with type 2 diabetes, compared with metformin as first-line therapy, to inform future clinical guidelines.

Methods

We used an individual patient-level Monte Carlo–based Markov model to simulate the lifetime incidence, prevalence, mortality, and costs associated with a U.S.-representative population with type 2 diabetes not being treated with diabetic medications (24). We compared first-line therapy metformin with using either SGLT2 inhibitors or injectable GLP1 receptor agonists as first-line treatment before metformin for drug-naive patients with type 2 diabetes. We compared drug class-level effects and not individual drug effects because ADA/EASD guidelines specify class level and not individual drug recommendations, and because insurance formularies usually do not cover all SGLT2 inhibitors or GLP1 receptor agonists.

Baseline Strategy: First-Line Metformin (ADA/EASD Guideline Strategy)

The baseline strategy followed the 2021 ADA/EASD guideline (Figure). Whenever HbA_{1c} was at least 7.0%, treatment progression consisted of 1) initial metformin; 2–3) SGLT2 inhibitors or GLP1 receptor agonists with equal probability as second- or third-line options; 4–6) add-on sulfonylureas, thiazolidinediones, or dipeptidyl peptidase-4 inhibitors with a uniform distribution probability (that is, 33% with 3 options) until all recommended combinations were used (dipeptidyl peptidase-4 inhibitors and GLP1 receptor agonists were not combined); 7) add-on basal insulin and discontinued sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors; and 8) prandial insulin with HbA_{1c} assumed to remain stable.

For people developing ASCVD or CKD during follow-up, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors were discontinued, and whenever HbA1c was at least 7.0%, treatment progression consisted of 1–2) SGLT2 inhibitors and GLP1 receptor agonists with 50/50 probability until both were used; 3–4) sulfonylureas or thiazolidinediones (with 50/50 probability) until both options were used; and 5) insulin following the ADA/EASD guideline strategy. In all scenarios, an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 would lead to SGLT2 inhibitor discontinuation, and end-stage renal disease would lead to discontinuation of all medications except insulin.

First-Line SGLT2 (SGLT2 Strategy)

For comparison, whenever HbA_{1c} was at least 7.0% (Figure), treatment progression consisted of an initial SGLT2 inhibitor and then metformin followed as described in the baseline strategy without subsequent SGLT2 inhibitors. For patients with or developing ASCVD or CKD and HbA_{1c} of at least 7.0%, SGLT2 inhibitors would be added and progression consisted of 1) metformin, 2) GLP1 receptor agonists, and 3) treatment options following the remaining ADA/EASD guideline strategy for patients with ASCVD.

First-Line Injectable GLP1 (Injectable GLP1 Strategy)

Whenever HbA_{1c} increased to at least 7.0% (Figure), treatment consisted of initial GLP1 receptor agonists and then metformin followed as described in the baseline strategy without subsequent GLP1 receptor agonists. For patients with HbA_{1c} of at least 7.0% or developing ASCVD or CKD, GLP1 receptor agonists would be started, followed by 1) metformin, 2)

SGLT2 inhibitors, and 3) the remaining ADA/EASD guideline strategy for patients with ASCVD.

Population Simulation Model

Our model was based on diabetes-related complication and mortality modules from the United Kingdom Prospective Diabetes Study Outcomes Model version 2 (UKPDS OM2) (Supplement Figure 1, available at Annals.org) with additional hypoglycemic event, quality of life (utility), and U.S. cost modules (25–29). Used in nearly all major type 2 diabetes simulation models (27–29), the UKPDS outcomes model equations have been internally (26) and externally validated (28).

Based on 26 individual-level characteristics, our model predicts the lifetime risk for diabetes-related microvascular complications (foot ulcer, blindness, renal failure, first and subsequent amputation) and macrovascular complications (first and subsequent myocardial infarction, ischemic heart disease, first and subsequent stroke) using 13 risk equations, and mortality using 4 risk equations. The UKPDS OM2 assumes that the mortality risk increases after all diabetic complications (except foot ulcer and blindness). The model predicts nondiabetes-related and diabetes-related death. We have internally validated our version of the UKPDS OM2 (24).

We modified the model in several ways. In addition to updating the medication module (30), we added the effects of GLP1 receptor agonists or SGLT2 inhibitors on systolic blood pressure, low-density lipoprotein, and weight (Table 1) and also added GLP1 receptor agonist effects on heart rate and SGLT2 inhibitor effects on eGFR. These estimated changes in cardiovascular risk factors were based on findings from our meta-analyses of these drugs versus placebo (28 trials for SGLT2 inhibitors; 17 trials for GLP1 receptor agonists) (31, 32). We assumed that these cardiovascular risk factor changes would only be present while patients were taking these medications. Because patients in our meta-analyses and in the UKPDS were already taking additional cardiovascular medications, we did not incorporate additional changes in cardiovascular risk factors for patients taking other diabetic drugs (for example, metformin, sulfonylureas) to avoid double-counting benefit. Third, our model includes GLP1 receptor agonists (31, 32) or metformin treatment discontinuation using predictive models based on our meta-analysis results for diabetic ketoacidosis and genital infections for SGLT2 inhibitors and gastrointestinal events (nausea, vomiting, or diarrhea).

Model Inputs

We created a nationally representative sample of persons with diabetes eligible to start first-line therapy using participants who self-reported diabetes or had HbA_{1c} of more than 6.5% within the National Health and Nutrition Examination Survey (NHANES) from 2013 to 2016 (Supplement Figure 2, available at Annals.org) (33). We excluded participants with suspected autoimmune diabetes (for example, age at diagnosis <18 years or started insulin within 1 year of diagnosis). We only included participants who were not taking diabetes medications. For missing values that were necessary for the model, we took the average of 5 values generated using Markov chain Monte Carlo multiple imputation (34).

Medical examination subsample weights were used to obtain national population estimates. We excluded participants with 4 or more missing model inputs.

Individual descriptive characteristics from NHANES were used as baseline data, which included age, sex, race, smoking status, diabetes duration, and self-reported medical conditions (coronary heart disease, angina, heart failure, myocardial infarction, stroke, dialysis in the last year, and retinopathy). Biomarkers included HbA_{1c}, systolic blood pressure, eGFR, low-density lipoprotein, high-density lipoprotein, body mass index, hemoglobin, leukocyte count, heart rate, and albuminuria. For medical histories unavailable in NHANES (history of peripheral vascular disease, atrial fibrillation, amputation, blindness, and peripheral neuropathy), we imputed age- and sex-based probabilities for peripheral vascular disease and atrial fibrillation (35, 36) and assumed that no persons had amputations, blindness, or peripheral neuropathy at baseline.

Costs and Health Utility

We calculated costs associated with medication use, complications, hospital utilization, and self-monitoring (testing and supplies) (37–39). Medication costs were calculated using publicly available Medicare costs across drug classes (40). All costs were from a health care sector perspective and in 2019 U.S. dollars (Supplement Table 1, available at Annals.org).

To account for quality-of-life reductions due to complications from disease or treatment, we calculated quality-adjusted life expectancy (QALE) using a health utility assessment where 0 equates to death and 1 equates to perfect health. Using established utility reductions in the literature, the model incorporated quality-of-life reductions for any diabetic complication and use of glucose-lowering medications (oral and injectable) as quality-adjusted life-years (QALYs) (Supplement Table 1) (41–51). For persons developing more than 1 complication, we multiplied all utility values for that year when calculating the QALY (52).

Main Analysis

For the 3 initial treatment approaches—metformin, SGLT2 inhibitors, and injectable GLP1 receptor agonists, the model ran 2500 microsimulations for each NHANES participant and captured the average population lifetime diabetic complications rates, life expectancy, QALYs, and costs. Costs and QALYs were discounted at 3% annually. An efficiency frontier was also constructed.

The modeling incorporated patient-level heterogeneity as a first-order Monte Carlo, that is, accounting for the entire distribution of patient risk factors and their potential nonlinear effects on model outcomes. As such, the results reflect stochastic uncertainty (2500 runs for each person) and methodological uncertainty (threshold and scenario and sensitivity analyses, described in the next section) but not distributions of uncertainty around cost or utility variables or the risk equation coefficients in the UKPDS OM2 risk equations (53). Models were run using R 4.0.0 (54). The NHANES analyses were conducted using SAS version 9.4 (55). The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and impact inventory are available in Supplement Tables 2 and 3 (available at Annals.org).

Statistical Analysis

Threshold and Scenario Analyses—The robustness of results was evaluated using several additional analyses.We performed a threshold analysis to determine the hypothetical medication costs required for a strategy to become cost-effective assuming a willingness-to-pay threshold of under $150 000 per QALY.

We conducted many additional scenario analyses including the following.

Maximal Treatment Benefits.: Our base case assumes that risk factor improvements mediate event rate reductions, so in this scenario, we assumed additional reductions in events according to our drug versus placebo meta-analyses, potentially double-counting benefits (Table 1)(30, 31).

No Medication Disutility.: In this scenario analysis, we assumed no disutility from taking any diabetes medications when estimating quality of life.

Orally Administered GLP1 Receptor Agonists.: For oral semaglutide, we assumed that the effectiveness and adverse events were identical to injectable GLP1 receptor agonists but included its higher cost and excluded the injection-associated disutility.

Medication cost estimates from the Federal Supply Schedule (FSS) (56) and Average Wholesale Price (AWP) with a 15% discount (39) were also included. Cost inputs are available in Supplement Table 4 (available at Annals.org).

Sensitivity Analyses—One-way deterministic sensitivity analyses were performed to analyze the effects of changes in discount rate (0% or 6%) and cost (±25%) variables, HbA_{1c} thresholds for changing treatment (<6.5% or <8%), and the upper and lower bounds of medication effects (Table 1) on cardiovascular risk factors.

Role of the Funding Source

The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Results

In NHANES 2013 to 2016, 493 participants met inclusion and exclusion criteria, representing about 7.3 million U.S. adults aged 18 years and older with likely type 2 diabetes and not reporting any diabetes medications (Supplement Table 5, available at Annals.org). The average age was 55 years and 50% were female. Participants had diabetes for an average of 4.2 years; 36% had a history of diabetic complications.

In the lifetime simulation modeling, the first-line metformin strategy had a cumulative absolute reduction in macrovascular complications (congestive heart failure, ischemic heart disease, myocardial infarction, and stroke) of 4.4% to 5.2% for SGLT2 inhibitors and GLP1

receptor agonists (Table 2) but only a 0.1% benefit in reduced microvascular outcomes. The unweighted results are available in Supplement Table 6 (available at Annals.org).

First-line SGLT2 inhibitors or GLP1 receptor agonists increased undiscounted life expectancy by 3.0 months and 3.4 months, respectively, versus first-line metformin (Table 3). The first-line SGLT2 inhibitor increased discounted QALE by 33 days, but GLP1 receptor agonists decreased discounted QALE by 22 days, respectively, versus first-line metformin, due to discounting and treatment-associated disutility.

First-line metformin had the lowest average per-person lifetime cost and GLP1 receptor agonists the highest (Table 3) with 60% to 70% of the cost difference being due to medication costs (initial metformin: $92 000 vs. $135 000 for the SGLT2 inhibitor and $141 000 for the GLP1 receptor agonist). Stroke complications represented 10% to 14% of costs (about $20 000) for each strategy. The incremental cost-effectiveness ratio (ICER) of SGLT2 inhibitors was $478 000 per QALY gained compared with metformin, and injectable GLP1 receptor agonists cost more and shortened QALE (that is, was inferior to metformin) (Table 3).

An efficiency frontier identifies the most efficient use of resources when considering first-line metformin, SGLT2 inhibitor, and injectable and oral GLP1 receptor agonist (Supplement Figure 3, available at Annals.org). Beyond metformin, no strategies fell below the willingness-to-pay threshold of $150 000 per QALY. The SGLT2 inhibitors had an ICER of $478 000 per QALY compared with metformin; oral GLP1 receptor agonists had an ICER of $1 024 000 per QALY compared with SGLT2 inhibitors. First-line injectable GLP1 receptor agonists cost more and yielded lower QALYs.

Threshold Analyses

Based on a willingness-to-pay threshold of under $150 000 per QALY, SGLT2 inhibitors and oral GLP1 receptors would become cost-effective at $1800 per year ($5 per day) and $2100 per year ($6 per day), respectively, requiring cost reductions of at least 70% for SGLT2 inhibitors and at least 90% for oral GLP1 receptor agonists.

Scenario Analyses

The oral GLP1 receptor agonist (semaglutide) increased QALE by 3 months but had an ICER of $823 000 per additional QALY gained versus metformin (Table 3). Excluding medication disutility, first-line SGLT2 inhibitors or GLP1 receptor agonists remained expensive with ICERs exceeding $300 000 per QALY (Table 3). When adding beneficial changes in event rates, first-line SGLT2 inhibitors or injectable GLP1 receptor agonists increased QALY versus metformin by 2.8 months and 1.6 months, respectively, but ICERs versus metformin remained high at $361 000 per QALY for SGLT2 inhibitors and $815 000 per QALY for GLP1 receptor agonists (Table 3). With either the lower FSS or discounted AWP costs, first-line injectable GLP1 receptor agonists remained more expensive with a lower QALY. First-line SGLT2 inhibitors versus metformin using FSS or discounted AWP yielded ICERs of $316 000 and $296 000 per QALY gained, respectively (Table 3).

Sensitivity Analyses

In all sensitivity analyses, ICERs for SGLT2 inhibitors exceeded $200 000 per QALY compared with metformin even when reducing the discount rate to 0%, the SGLT2 inhibitor costs by 25%, or varying SGLT2 inhibitor effectiveness to its upper bound. The GLP1 receptor agonists were either dominated or had ICERs under $150 000.

Discussion

Our model results suggest that first-line SGLT2 inhibitors and GLP1 receptor agonists are not cost-effective for the U.S. population, compared with the 2021 ADA/EASD guidelines, primarily due to their high medication costs. The model projected improved life expectancy by 3.0 months to 3.4 months due to reduced rates of macrovascular disease from first-line SGLT2 inhibitors and GLP1 receptor agonists (24.4% to 25.2% cumulative absolute reduction). However, the current drug costs would be too high to encourage their adoption as first line for usual clinical practice, requiring a price reduction of 70% for SGLT2 inhibitors and 90% for oral GLP1 receptor agonists. Based on our scenario analyses, eliminating the injection disutility for oral GLP1 receptor agonists, eliminating medication disutilities, modeling maximal treatment benefits, or identifying alternative medication price sources did not alter the absence of cost-effectiveness conclusions.

Diabetes drug prices, including generic prices for newer drugs, have been increasing (3, 57). Our threshold analyses suggest that the cost of the SGLT2 inhibitors and oral GLP1 receptor agonists must be reduced at least 70% and 90% to become cost-effective at a willingness-to-pay threshold of $150 000 per QALY. Generic SGLT2 inhibitors could enter the market (1 of 2 dapagliflozin patents died in October 2020) and approval for generic alternatives has been sought from the U.S. Food and Drug Administration. Although promising, it may take decades for medication prices to drop low enough to become affordable. For example, a generic GLP1 receptor agonist became available in 2017, but its costs remain high. Without external incentives, limited access to these drug classes will likely persist (for example, due to higher copays or requirements for prior authorizations) (58), as will further diabetes disparities—for decades into the future—because of differential access to care due to insurance (for example, private vs. public), which often tracks race and ethnicity (59–61).

The results of our simulation model and subgroup analyses provide greater clarity about the driving forces of the cost-effectiveness of the various treatment options. The major driving factors were their high costs and a decrease in quality of life associated with injections. The first-line SGLT2 inhibitor strategy and GLP1 receptor agonist strategies (both oral and injectable) had greater efficacy in terms of life expectancy and QALE compared with the first-line metformin strategy. Specifically, GLP1 receptor agonists were the most effective strategy to maximize life expectancy, but the injectable form of GLP1 receptor agonists reduced QALE. Our main analysis included the injection disutility as a nontrivial source of concern from the patients' perspective (62).

To our knowledge, no other studies have compared the cost-effectiveness of using GLP1 receptor agonists or SGLT2 inhibitors as first-line therapy versus the 2021 ADA guidelines. Other recently published U.S. cost-effectiveness analyses have examined drug classes rather

than medication algorithms (63–65). Therefore, our conclusions that SGLT2 inhibitors and GLP1 receptor agonists as first-line therapy may not be cost-effective despite improved clinical outcomes solely reflect the incremental benefit of using the newer agents as first-line agents rather than second-line, that is, a delayed use of the newer agents.

Our modeling analysis has limitations. First, there are known limitations of the UKPDS model, which include the overestimation of macrovascular complications (66–68). This limitation could potentially lead to an artificial increase in the costs and disutilities associated with these complications. However, these issues are present in all comparisons, which minimize their effect. Second, incomplete demographic and heart failure history and a limited sample of NHANES participants precluded additional analyses. In addition, the NHANES population not currently receiving diabetic medications is a mixed population of newly diagnosed diabetes and diabetes for approximately 10 years. The latter population, with an extensive history of diabetes without self-reported diabetes medication, may be a socioeconomically disadvantaged group, which could affect the generalizability of not only our results but also a population of interest given the economic barrier to adequate treatment. Furthermore, the use of Medicare drug costs biases the analysis against the SGLT2 inhibitor and the GLP1 receptor agonist drug classes (Table 3). However, the SGLT2 inhibitor and GLP1 receptor agonist strategies remained not cost-effective regardless of the medication cost source in our scenario analyses. Lastly, our analyses focus on the U.S. population and costs and cannot be generalized to other countries.

Due to their associated lower risk for macrovascular events, SGLT2 inhibitors and GLP1 receptor agonists are potentially effective first-line agents to treat type 2 diabetes. However, these drug classes are not cost-effective at their current costs. In the interest of improving access to high-quality care in the United States, our study results indicate the need to reduce SGLT2 inhibitor and GLP1 receptor agonist medication costs substantially for patients with type 2 patients to improve health outcomes and prevent exacerbating diabetes health disparities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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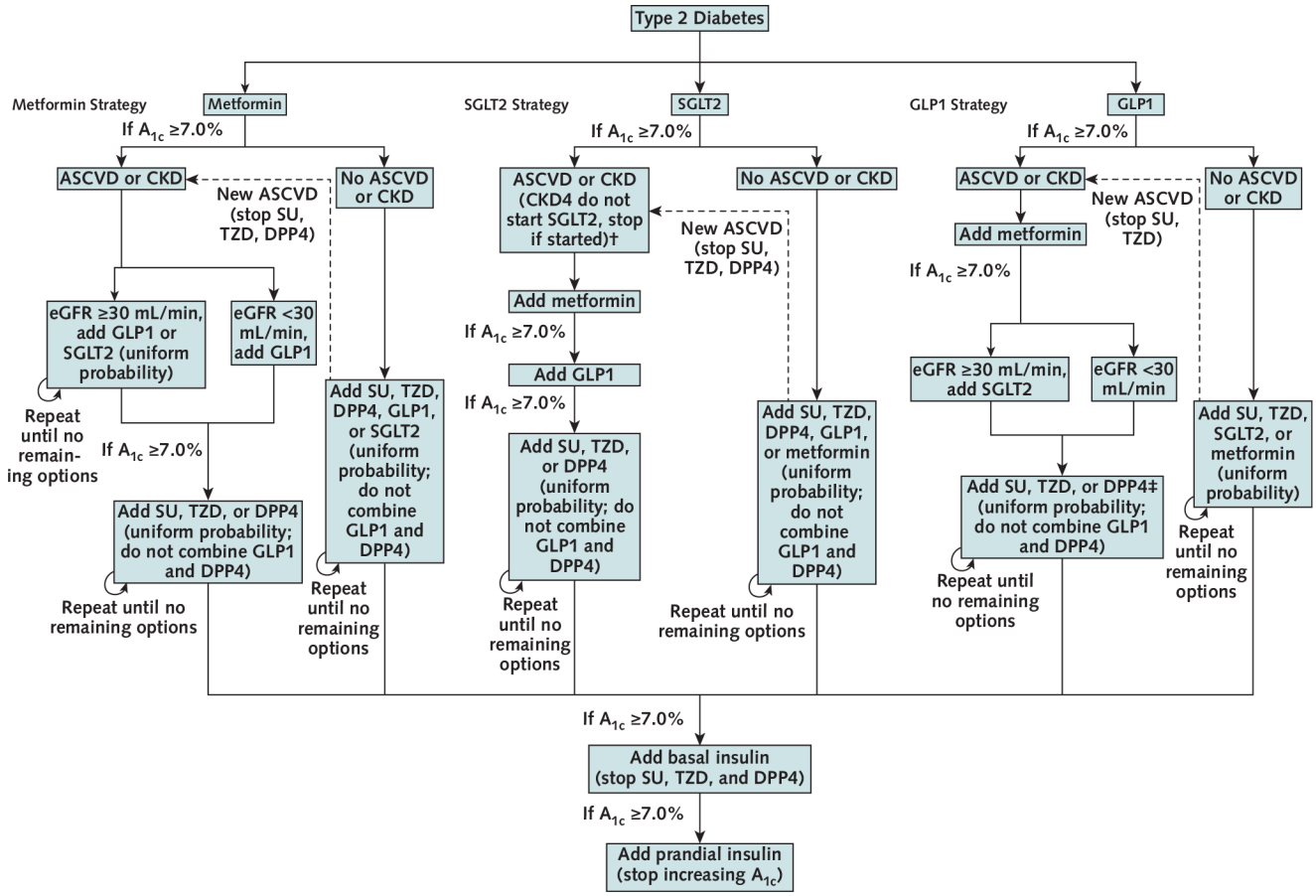

Figure.

Medication treatment algorithms.

* A_1c = hemoglobin A_1c; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CKD4 = chronic kidney disease stage 4; eGFR = estimated glomerular filtration rate; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP1 = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylureas; TZD = thiazolidinediones.

* The same population was compared using each of the 3 medication treatment algorithms.

† Patients with CKD4 should not start an SGLT2, and should stop one that has been started; SGLT2 should be stopped and not started.

‡ DPP-4 inhibitors were added in the first-line GLP1 receptor agonist strategy only if the GLP1 receptor agonist was discontinued due to adverse events.

Table 1.

Meta-Analytic[*] Effects of SGLT2 Inhibitors and GLP1 Receptor Agonists on Cardiovascular Risk Factors, Diabetic Complications, Mortality, and Adverse Events[†]

Variable	Mean Difference (95% CI)/Risk Difference (95% CI)	
	SGLT2 Inhibitors vs. Placebo	**GLP1 Receptor Agonistsvs. Placebo**
Cardiovascular risk factors		
Weight, *kg*	−2.02 (−2.22 to −1.82)	−1.84 (−2.37 to −1.30)
Systolic blood pressure, *mm Hg*	−3.62 (−4.22 to −3.01)	−1.75 (−2.14 to −1.35)
Heart rate, *beats/min*	No effect	2.22 (1.69 to 2.75)
Low-density lipoprotein		
mmol/L	No effect	−0.04 (−0.06 to −0.03)
mg/dL	No effect	−1.55 (−2.32 to −1.16)
High-density lipoprotein		
mmol/L	0.05(0.04 to 0.06)	No effect
mg/dL	1.93(1.55 to 2.32)	No effect
eGFR, *mL/min/1.73 m*^{2}	−1.41 (−1.98 to −0.84)	No effect
Macrovascular outcomes		
Stroke	No effect	−0.002 (−0.002 to −0.001)
Any myocardial infarction	−0.001 (−0.002 to −0.00004)	No effect
Heart failure	−0.004 (−0.004 to −0.003)	No effect
Microvascular outcomes		
End-stage renal disease	No effect	−0.003 (−0.003 to −0.002)
Mortality		
All-cause mortality	−0.001 (−0.002 to −0.0006)	−0.002 (−0.004 to −0.001)
Adverse events		
Any gastrointestinal event	No effect	0.031 (0.014 to 0.058)
Severe hypoglycemia	−0.001 (−0.002 to −0.0001)	No effect
Diabetic ketoacidosis	0.0005(0.0001 to 0.001)	No effect
Genital yeast infection	0.043 (0.029 to 0.060)	No effect

eGFR = estimated glomerular filtration rate; GLP1 = glucagon-like peptide-1; SGLT2 = sodium–glucose cotransporter-2.

[*] From references 31 and 32.

[†] Cardiovascular risk factor changes and adverse events were added to the simulation model in the main cost-effectiveness analyses. In sensitivity analyses, additional effects on macrovascular and microvascular events and mortality were added to the simulation modeling to estimate the maximal potential effect of SGLT2 inhibitors and GLP1 receptor agonists.

Table 2.

Estimated Lifetime Complication Rates due to First-Line Metformin, SGLT2 Inhibitor, and GLP1 Receptor Agonist Strategies for the U.S. Population With Type 2 Diabetes

Complication, %	First-Line Metformin	First-Line SGLT2 Inhibitor	First-Line GLP1 Receptor Agonist
Macrovascular outcomes			
Heart failure	14.2	13.2	13.1
Ischemic heart disease	18.8	17.3	17.2
Myocardial infarction	27.0	26.0	25.5
Stroke	17.2	16.3	16.2
Microvascular outcomes			
Amputation	3.5	3.5	3.5
Blindness	11.5	11.4	11.5
End-stage renal disease	2.6	2.6	2.5
Adverse events			
Foot ulcer	2.9	2.9	2.9

GLP1 = glucagon-like peptide-1; SGLT2 = sodium–glucose cotransporter-2.

Table 3.

Comparison of Estimated LE, QALE, Cost, ICER, and Scenario Analyses for First-Line Metformin, SGLT2 Inhibitor, and GLP1 Receptor Agonist Strategies for the U.S. Population With Type 2 Diabetes

Variable	LE, *y*	Incremental LE, *y*	QALE, *y*	Incremental QALE, *y*	Lifetime Cost, *U.S. Dollars*[*]	Incremental Cost, *U.S. Dollars*[*]	ICER vs. Metformin, *U.S. Dollars*[*]
Base case							
Metformin	24.33	-	12.75	-	145 000	-	-
SGLT2	24.58	0.25	12.84	0.09	188 000	43 000	478 000
GLP1	24.61	0.28	12.69	−0.06	194 000	49 000	Inferior[†]
Orallyadministered GLP1 receptor agonists							
Metformin	24.33	-	12.75	-	148 000	-	-
SGLT2	24.58	0.25	12.84	0.09	191 000	43 000	478 000
GLP1	24.61	0.28	13.01	0.26	362 000	214000	823 000
No medication disutility							
Metformin	24.33	-	13.17	-	145 000	-	-
SGLT2	24.58	0.25	13.31	0.14	188 000	43 000	307 000
GLP1	24.61	0.28	13.32	0.15	194 000	49 000	327 000
Additional treatment benefits beyond risk-factor changes							
Metformin	24.90	-	12.98	-	217 000	-	-
SGLT2	25.46	0.56	13.21	0.23	300 000	83 000	361 000
GLP1	25.60	0.7	13.11	0.13	323 000	106 000	815 000
Federal SupplySchedule							
Metformin	24.33	-	12.75	-	135 000	-	-
SGLT2	24.58	0.25	12.84	0.09	167 000	32 000	316 000
GLP1	24.61	0.28	12.69	-0.06	179 000	44 000	Inferior[†]
AverageWholesale Price (15% discount)							
Metformin	24.33	-	12.75	-	99 000	-	-
SGLT2	24.58	0.25	12.84	0.09	132 000	33 000	296 000
GLP1	24.61	0.28	12.69	−0.06	110 000	11 000	Inferior[†]

GLP1 = glucagon-like peptide-1; ICER = incremental cost-effectiveness ratio comparing each strategy to baseline metformin strategy; LE = life expectancy; QALE = quality-adjusted life expectancy; SGLT2 = sodium–glucose cotransporter-2 inhibitor.

* Costs are discounted at 3%, and ICER is based on discounted costs.

† These strategies were dominated because they were more expensive and had lower QALE versus metformin.