Second-line Agents for Glycemic Control for Type 2 Diabetes: Are Newer Agents Better?

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OBJECTIVE

While metformin is generally accepted as the first-line agent in treatment of type 2 diabetes, there are insufficient evidence and extensive debate about the best second-line agent. We aimed to assess the benefits and harms of four commonly used antihyperglycemia treatment regimens considering clinical effectiveness, quality of life, and cost.

RESEARCH DESIGN AND METHODS

We developed and validated a new population-based glycemic control Markov model that simulates natural variation in HbA_{1c} progression. The model was calibrated using a U.S. data set of privately insured individuals diagnosed with type 2 diabetes. We compared treatment intensification of metformin monotherapy with sulfonylurea, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, or insulin. Outcome measures included life-years (LYs), quality-adjusted life-years (QALYs), mean time to insulin dependence, and expected medication cost per QALY from diagnosis to first diabetes complication (ischemic heart disease, myocardial infarction, congestive heart failure, stroke, blindness, renal failure, amputation) or death.

RESULTS

According to our model, all regimens resulted in similar LYs and QALYs regardless of glycemic control goal, but the regimen with sulfonylurea incurred significantly lower cost per QALY and resulted in the longest time to insulin dependence. An HbA_{1c} goal of 7% (53 mmol/mol) produced higher QALYs compared with a goal of 8% (64 mmol/mol) for all regimens.

CONCLUSIONS

Use of sulfonylurea as second-line therapy for type 2 diabetes generated glycemic control and QALYs comparable with those associated with other agents but at lower cost. A model that incorporates HbA_{1c} and diabetes complications can serve as a useful clinical decision tool for selection of treatment options.

Diabetes is one of the most prevalent and costly chronic medical conditions worldwide, incurring significant burdens on individuals, society, and the health care system. It is currently estimated that 25.8 million Americans, or 8.3% of the population, have diabetes (1). Glucose-lowering therapies are the cornerstone of diabetes management, with multiple epidemiological studies linking glycemic control to a lower risk of diabetes-related complications and mortality. Large randomized controlled trials have demonstrated a reduction in microvascular complications

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with intensive glycemic control, e.g., lowering glycosylated hemoglobin (HbA_{1c}) to <6.5–8.0% (48—64 mmol/mol), depending on the study (2–9). Evidence linking glycemic control to lower macrovascular disease risk and mortality has been less conclusive; lowering HbA_{1c} among younger patients with newly diagnosed diabetes did reduce cardiovascular event rates and mortality in the UK Prospective Diabetes Study (UKPDS) (5,6), but further reductions among people with long-standing diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) studies and Veterans Affairs Diabetes Trial (VADT) did not yield similar results (7–9). The exact glycemic target in the treatment of diabetes therefore remains controversial, with professional groups and regulatory organizations currently recommending lowering HbA_{1c} to <6.5% (48 mmol/mol) (10), 7.0% (53 mmol/mol) (11), or 8.0% (64 mmol/mol) (12), except in patients at high risk for hypoglycemia or those with limited life expectancy or multiple comorbid conditions that preclude safe intensive control.

There are currently 11 classes of approved glucose-lowering medications, and the usage of these medications has varied from 1994 to 2007 (13). The 2011 Centers for Disease Control and Prevention diabetes fact sheet reported that 58% of adults with diabetes are being treated with oral agent(s), 12% with insulin, and 14% with both insulin and oral agent(s) (1). Diabetes medications alone accounted for 11.8% of all prescriptions issued in the U.S. in 2012 at a cost of more than 18.3 billion USD (14). Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and is regarded by most as the primary first-line agent in the treatment of type 2 diabetes (10,11,15). When metformin fails to achieve or maintain glycemic goals, another agent should be added; however, there is no consensus or sufficient empirical evidence supporting the use of one second-line agent over another (16). Over the past decade, the mix of secondary agents used in the treatment of diabetes has changed significantly, with increasing use of newer glucose-lowering agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in place of older and less expensive drugs such as sulfonylureas. This has resulted in a dramatic rise in the cost of diabetes medications and management; yet, the long-term clinical benefit of this shift is uncertain (13).

In the absence of clinical trials directly comparing alternative treatment regimens and considering the high cost and challenges of running any such trials, we developed and validated a new population-based glycemic control model based on a Markov chain to compare the real-world effectiveness and cost of different treatment regimens for individuals newly diagnosed with type 2 diabetes. We used this model to quantify differences among the regimens in terms of life-years (LYs), quality-adjusted life-years (QALYs), and medication cost per QALY necessary to achieve and maintain glycemic control from the time of diagnosis to the development of first major diabetes-related complication, specifically, ischemic heart disease, stroke, blindness, renal failure, amputation, or death from other cause. We specifically chose these micro- and macrovascular complications of diabetes, as they have been used in most large observational and interventional studies of diabetes therapies (5,7–9). Each regimen was tested using the range of currently recommended glycemic control goals between HbA_{1c} 6.5% (48 mmol/mol) and 8% (64 mmol/mol) both to confirm model generalizability and to identify the potential impact of different glycemic control goals on patient health, quality of life, and expenditure.

RESEARCH DESIGN AND METHODS

Treatment Regimens

We considered four treatment-intensification regimens: metformin, sulfonylurea, and insulin (T1); metformin, DPP-4 inhibitor, and insulin (T2); metformin, GLP-1 agonist, and insulin (T3); and metformin and insulin (T4). In each regimen, patients started metformin monotherapy when HbA_{1c} reached the prespecified glycemic control goal. In T1–T3, treatment was sequentially intensified by addition of a second-line agent other than insulin, and if or when HbA_{1c} again exceeded the glycemic control goal, insulin was initiated (in place of the second-line agent) as the third-line agent in combination with metformin. In T4, treatment was intensified by directly adding insulin once HbA_{1c} exceeded the glycemic control goal. For all regimens, there were no further treatment changes once insulin was initiated, as it was assumed to maintain glycemic control.

Markov Model

The Markov model is based on the 10 discrete HbA_{1c} states presented in Supplementary Tables 1 and 2. Each state is defined by the conditional mean HbA_{1c} in a given interval for a patient newly diagnosed with type 2 diabetes. The mean HbA_{1c} value for each state increases linearly with respect to age according to a linear trend factor. This common assumption, based on other published glycemic control models (17,18), reflects the expected rise in HbA_{1c} with age and anticipated deterioration of glycemic control. At the beginning of each 3-month period, treatment is initiated/intensified if HbA_{1c} exceeds the glycemic control goal. Treatment results in a proportional decrease in HbA_{1c} according to a medication effect estimated from observational data (Table 1). If no diabetes complications or death occurs, patients undergo continued HbA_{1c} state transition based on the 3-month transition probability matrices provided in Supplementary Tables 1 and 2. Each treatment regimen was evaluated using the Markov model by backward induction (29). All analyses were conducted using MATLAB R2012b (MathWorks, Inc., Natick, MA).

Outcome Measures

We considered four outcome measures related to primary prevention: expected LYs, expected QALYs, mean time to insulin dependence, and expected medication cost per QALY for maintaining glycemic control from diagnosis to occurrence of first diabetes-related complication or death. For each period in which no diabetes complications or death occurred, LYs were increased by 3 months, QALYs were adjusted based on the disutility of medications, and the medication cost was calculated based on the sum of the costs of using medications for 3 months discounted at a 3% annual discount rate (30).

Data Sources

A retrospective administrative claims data set that included medical claims, pharmacy claims, laboratory data, and eligibility information from a large, national U.S. health plan was used to estimate 3-month HbA_{1c} state transition probabilities

Table 1—Model parameters for base-case analysis and sensitivity analysis

Parameter (reference no.)	Base-case value (range)
Patient's characteristics	
Diagnosis age (years) (19)	Women 55.2; Men 53.6
Ethnicity	None Afro-Caribbean
BMI (kg/m^2) (20)	32.6
Smoking status	Nonsmoker
Concurrent comorbidity at diagnosis*	No
Blood pressure (mmHg) (11)†	140
Total cholesterol (mg/dL) (21)†	200
HDL (mg/dL) (21)†	40
Glycemic control goals, % (mmol/mol) (10–12)	7 (53), 6.5 (48), 8 (64)
Disutility of hypoglycemia (22)	
Metformin	−0.0002
Sulfonylurea	−0.0064
DPP-4 inhibitor	−0.0002
GLP-1 agonist	−0.0005
Insulin‡	−0.0143
Disutility of weight gain (22)	
Metformin	0
Sulfonylurea	−0.0031
DPP-4 inhibitor	0
GLP-1 agonist§	0.0013
Insulin	−0.0031
Disutility of injectable medication (22)	
Metformin	0
Sulfonylurea	0
DPP-4 inhibitor	0
GLP-1 agonist	−0.0032
Insulin	−0.0032
Month medication cost (USD) (16,23)	
Metformin	81.75 (25.87–181.09)
Sulfonylurea	54.85 (9.31–165.57)
DPP-4 inhibitor	232.84 (227.66–238.01)
GLP-1 agonist	325.97 (165.57–486.37)
Insulin	245.70 (189.39–327.54)
Base-case medication effect||	
Metformin	0.0661 (0.0620–0.0703)
Sulfonylurea	0.0937 (0.0852–0.1022)
DPP-4 inhibitor	0.0520 (0.0378–0.0662)
GLP-1 agonist	0.0558 (0.0472–0.0644)
Insulin	Maintain HbA_{1c} at 7% (53 mmol/mol)
Randomized control trial medication effect	
Sulfonylurea (24,25)	(0.1282–0.2090)
DPP-4 inhibitor (24)	(0.0588–0.1149)
GLP-1 agonist (26,27)	(0.0886–0.1744)

*Concurrent comorbidities include peripheral vascular disease, atrial fibrillation, ischemic heart disease, congestive heart failure, and blindness. †Patients' blood pressure, total cholesterol, and HDL were assumed to be well controlled by antihypertension and antihyperlipidemia medications. ‡The disutility of hypoglycemia associated with insulin is set to be 2.24 times the disutility of hypoglycemia associated with sulfonylurea. This choice is motivated by the incidence rate of severe hypoglycemia among patients using each medication provided in ref. 28. §Weight loss is reflected in terms of gains in quality of life; therefore, it is associated with positive number. ||Values in the range represent the 95% CI of the estimated relative effect in reducing HbA_{1c}. Sample sizes for estimating clinical effect were 2,118 for metformin, 765 for sulfonylurea, 204 for DPP-4 inhibitor, and 477 for GLP-1 agonist.

(Supplementary Data), to estimate the medication effect on reducing HbA_{1c} (Supplementary Data), and to calibrate and validate our model (Supplementary Data). The individuals covered by this health plan are geographically diverse across the U.S. with greatest representation in the south and midwest U.S. census regions. The plan provides fully insured coverage for professional (e.g., physician), facility (e.g., hospital), and outpatient prescription medication services. Medical (professional, facility) claims include ICD-9, Clinical Modification (ICD-9-CM) diagnosis codes, ICD-9 procedure codes, *Current Procedural Terminology*, version 4 procedure codes, Healthcare Common Procedure Coding System procedure codes, site of service codes, provider specialty codes, and health plan and patient costs. Outpatient pharmacy claims provide National Drug Codes for dispensed medications, quantity dispensed, drug strength, days' supply, provider specialty code, and health plan and patient costs. Laboratory results linked to the administrative claims data are available for a subset of these patients. All study data were accessed using techniques that are in compliance with the Health Insurance Portability and Accountability Act of 1996, and no identifiable protected health information was extracted during the course of the study. Because this study involved analysis of preexisting, de-identified data, it was exempt from institutional review board approval.

The population meeting criteria for our study (37,501 individuals) were age of at least 40 years, diagnosis with type 2 diabetes between 1995 and 2010, prescription for their first noninsulin glucose-lowering medication at least 6 months after enrollment, and at least 5 years of continuous enrollment with at least two HbA_{1c} records and complete pharmacy claim data. Type 2 diabetes was defined using the Healthcare Effectiveness Data and Information Set criteria (31). Healthcare Effectiveness Data and Information Set requirements for pharmacy data include at least one antihyperglycemia medication prescription and, for claim encounter data, the presence of at least one diabetes-specific ICD-9 diagnosis codes 250.XX (exclude 250.X1 and 250.X3), 357.2X, 362.0X, or 366.41 with two annual face-to-face outpatient encounters with different dates of service or one face-to-face in

an acute inpatient or emergency department encounter.

Model Parameters for Base-Case and Sensitivity Analysis

Model parameters, including base-case values and ranges for sensitivity analysis, are shown in Table 1. We assumed a diagnosis age of 55.2 years for women and 53.6 years for men based on the median age at time of diagnosis of diabetes in the U.S. as of 2011 (19). The initial HbA_{1c} state distributions for men and women are shown in Supplementary Tables 1 and 2. Treatment regimens were assumed to be fixed for patients living beyond 100 years, and future life expectancy at age 100 years was assumed to be 2.24 years for women and 2.05 years for men based on a 2008 U.S. life table (32).

The probabilities of diabetes complications were determined by a patient's age, sex, ethnicity (Afro-Caribbean or not), smoking status, BMI, HbA_{1c}, systolic blood pressure, total cholesterol, and HDL cholesterol; history of peripheral vascular disease, atrial fibrillation, ischemic heart disease, and congestive heart failure; and blindness at diagnosis using the UKPDS outcomes model (33). Probability of death from other cause was estimated based on the Centers for Disease Control and Prevention 2007 mortality tables (34).

The cost of medications other than insulin was based on the Federal median price for generic agents and the average wholesale price for brand name agents provided by the Agency for Healthcare Research and Quality Evidence Practice Centers (16). The cost of insulin therapy, including the cost related to self-monitoring of blood glucose, insulin, and insulin-related supplies, was taken from Yeaw et al. (23). All costs were inflation adjusted to 2013 dollars using the consumer price index method (35). For medications other than insulin, the base-case cost was the mean price of all brand name and generic (if available) medicines, and the cost in the range represents the least and the most expensive medicines. The base-case cost for insulin was the mean cost of all insulin regimens including basal insulin regimens, premixed insulin regimens, and basal-bolus insulin regimens. The cost in the range represents the average cost for basal insulin therapy (the least expensive insulin therapy) and the average cost for basal-bolus insulin therapy (the most expensive insulin therapy), respectively.

Medication effect (other than for insulin) was estimated based on HbA_{1c} changes seen with use of these agents by patients included in the data set and is presented as the relative reduction in HbA_{1c} observed during each 3-month treatment interval.

Model Calibration and Validation

To calibrate and validate the model, we used all available HbA_{1c} pairs at least for 3.5 months to ensure at least one 3-month transition, as long as the patient was not on insulin during that time period. This provided a total of 97,667 pairs of HbA_{1c} test results. The linear trend factor was varied from 0 to 0.25 to estimate the trend factor that minimized the mean of the sum of the squared errors (SSE) between the observed HbA_{1c} state distribution (determined by the second HbA_{1c} value in each pair) and the model-generated HbA_{1c} state distributions. The optimal trend factor was 0.1075 for men (mean SSE of 0.0022) and 0.105 for women (mean SSE of 0.0015). Additional details of the model calibration and validation can be found in Supplementary Data.

RESULTS

Base-Case Results

The Markov model–based results showed that the expected LYs and QALYs from diagnosis to first event produced by the four treatment regimens were similar (Table 2). The maximum difference among regimens in the expected LYs to first event, specifically, the difference between T4 and T1, was 0.03 years (12.73 days) for women and 0.03 years (11.06 days) for men. Similarly, the maximum difference among regimens in the expected QALYs to the first event, specifically, the difference between T4 and T1, was 0.04 QALYs (16.12 quality-adjusted days) for women and 0.04 QALYs (14.20 quality-adjusted days) for men. The observed differences in expected LYs and QALYs among regimens were primarily the result of different expected durations of sustained glycemic control with the three second-line agents (in combination with metformin). The mean time elapsed between failure of metformin monotherapy and the need for insulin initiation was 1.05 years (381.99 days) for women and 1.0 year (364.65 days) for men using T1, 0.62 years (224.50 days) for women and 0.53 years (194.84 days) for men using T2, and 0.68 years (247.96 days) for women and 0.62 years (225.46 days) for men using T3.

Significant differences were observed in the expected medication cost per QALY incurred by the four treatment regimens. Compared with using sulfonylurea as a second-line agent, which was the least expensive treatment regimen, use of DPP-4 inhibitor (T2) was associated with a mean per-person additional medication cost of 141 USD per QALY for women and 160 USD per QALY for men. Use of GLP-1 agonist (T3) incurred a mean additional medication cost of 191 USD per QALY for women and 216 USD per QALY for men compared with T1, and use of insulin as a second-line agent (T4) incurred a mean additional medication cost of 150 USD per QALY for women and 170 USD per QALY for men compared with T1.

Sensitivity Analyses

For any fixed glycemic control goal ranging between 6.5% (48 mmol/mol) and 8.0% (64 mmol/mol), use of sulfonylurea as the second-line agent incurred

Table 2—Base-case comparison of four treatment regimens

	Women				Men			
Treatment regimen	T1	T2	T3	T4	T1	T2	T3	T4
Expected LYs	68.66	68.63	68.64	68.63	64.58	64.55	64.55	64.54
Expected QALYs	68.41	68.39	68.39	68.37	64.38	64.35	64.35	64.34
Expected medication cost (USD) per QALY	2,600	2,741	2,791	2,750	2,675	2,835	2,891	2,845
Mean time to use insulin (years)	2.76	2.33	2.40	1.72	2.59	2.13	2.21	1.59

Comparison of the expected LYs, expected QALYs, expected medication cost per QALY, and mean time from diagnosis to insulin initiation for men and women. Four treatment regimens are T1, metformin plus sulfonylurea plus insulin; T2, metformin plus DPP-4 inhibitor plus insulin; T3, metformin plus GLP-1 agonist plus insulin; and T4, metformin plus insulin.

the lowest expected medication cost per QALY, and GLP-1 agonist use incurred the highest expected medical cost per QALY, among both men and women (Fig. 1). Targeting a treatment goal of 6.5% (48 mmol/mol) vs. 7% (53 mmol/mol) incurred significantly higher expected medication cost per QALY and a small reduction in the expected QALYs for all treatment regimens (Fig. 1). All treatment regimens resulted in increased expected QALYs and increased medication cost per QALY when targeting a treatment goal of 7% (53 mmol/mol) compared with 8% (64 mmol/mol) (Fig. 1).

The expected medication cost per QALY of each of the four treatment regimens varied significantly (Fig. 2) as a result of differential costs incurred by generic (metformin, sulfonylurea) compared with brand name (DPP-4, GLP-1) medications and basal insulin compared with basal plus bolus insulin regimens. T3 exhibited the largest variation in the expected medication cost per QALY (503 USD per QALY difference for women and 453 USD per QALY difference for men), while T2 was associated with the smallest variation in the expected medication cost per QALY (291 USD for women and 261 USD for men).

When the effects of sulfonylurea, DPP-4 inhibitor, and GLP-1 agonist on HbA_{1c} were simultaneously set to be the lower bound or upper bound of the randomized control trial (RCT) results on the efficacy of medications (Table 1**)**, the four treatment regimens still resulted in similar expected LYs and QALYs from diagnosis to first event. The treatment regimen with sulfonylurea as the second-line agent resulted in the lowest cost per QALY (2,537 USD per QALY for women and 2,612 USD per QALY for men at lower bound and 2,388 USD per QALY for women and 2,454 USD per QALY for men at upper bound), while the treatment regimen with GLP-1 agonist as the second-line agent still produced the highest cost per QALY (2,809 USD per QALY for women and 2,911 USD per QALY for men at lower bound and 2,867 USD per QALY for women and 2,971 USD per QALY for men at upper bound).

CONCLUSIONS

The conclusions drawn from this study are based on a model and therefore may not be a perfect representation of what would be observed in practice. Direct comparison of four different diabetes treatment regimens by the Markov model developed and validated in this study demonstrated that all four treatment regimens resulted in similar expected benefits in LYs and QALYs irrespective of glycemic control goal. However, for all glycemic control goals ranging between the currently recommended targets of HbA_{1c} 6.5% (48 mmol/mol) and 8% (64 mmol/mol), the use of sulfonylurea as the second-line agent incurred the lowest expected medication cost per QALY. These findings hold for both observed effects of medications from real-world data and randomized control trial results. The differences in cost per patient among the four treatment regimens were substantial and thus of potential importance to patients as well as health care providers and payers. In addition, the treatment regimen with a sulfonylurea as the second-line agent resulted in the longest time of insulin independence compared with all other regimens—an important factor to be considered by patients who wish to delay insulin initiation as long as possible. Conversely, the more expensive treatment options that use a DPP-4 inhibitor or a GLP-1 agonist as the second-line agent were associated with slightly less expected benefit in terms of both LYs and QALYs, and a shorter time of insulin independence, compared with the use of sulfonylurea. Use of insulin as the second-line agent resulted in the shortest time to insulin dependence, and was also significantly more expensive than using sulfonylurea with no added benefit in terms of LYs or QALYs.

To date, there has been no comprehensive side-by-side evaluation of the clinical benefits, effects on quality of life, and costs incurred by different

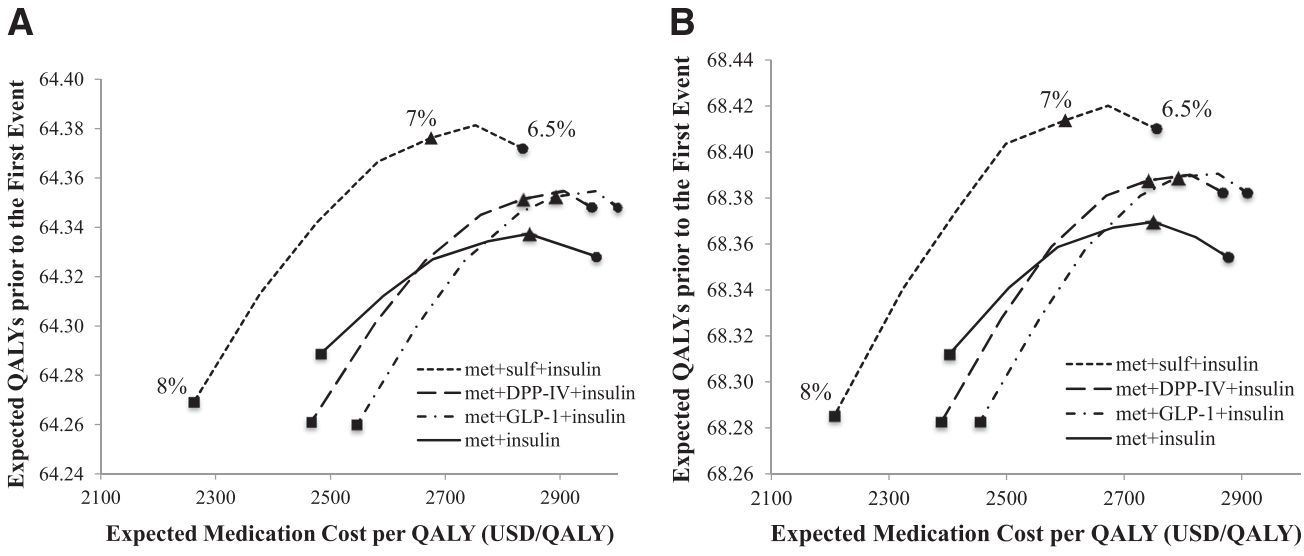

Figure 1—QALYs versus cost incurred by the four different treatment regimens as a function of glycemic control goal. Comparison of the expected QALYs versus the expected medication cost per QALY incurred from diagnosis to first event (diabetes-related complication or death) for men (*A*) and women (*B*). Each of the four treatments is compared as the glycemic control goal is varied from 6.5% (48 mmol/mol) to 8% (64 mmol/mol). Results are presented using HbA_{1c} of 6.5% (48 mmol/mol) (●), 7% (53 mmol/mol) (▲), and 8% (64 mmol/mol) (■) as the glycemic control goal.

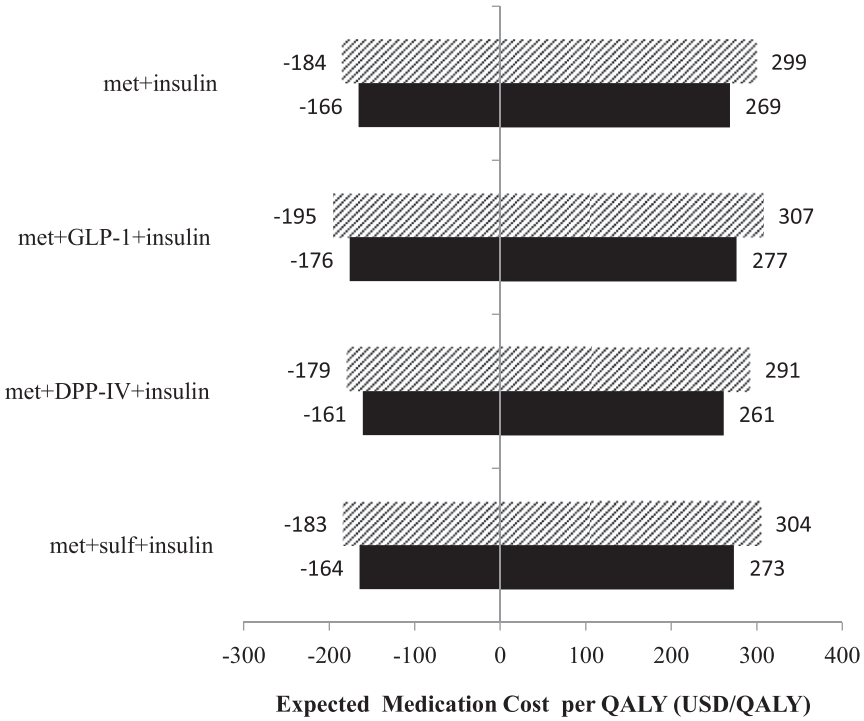

Figure 2—Sensitivity analysis on the medication cost. The *x*-axis represents the difference in the expected medication cost per QALY from the base-case cost: metformin costs 81.75 USD per month, sulfonylurea costs 54.85 USD per month, DPP-4 inhibitor costs 232.84 USD per month, GLP-1 agonist costs 325.97 USD per month, and insulin therapy costs 245.70 USD per month. The *y*-axis represents the treatment regimen. The solid bar represents men, and the hatched bar represents women. met, metformin; sulf, sulfonylurea.

diabetes treatment regimens for glycemic control. Our model fills this gap by integrating real-world knowledge of treatment costs, benefits, and harm, thereby allowing clinicians, payers, and patients to directly compare treatment regimens to select the one that is best suited for each individual patient given his/her specific glycemic control goal, cost sensitivity, and preference. Given that >25 million patients have been diagnosed with type 2 diabetes in the U.S., the potential policy implications of these differences uncovered by our model are also significant.

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), which is in the recruitment phase now, seeks to compare the same treatment regimens using a prospective clinical trial design; however, our model is significantly different from that of GRADE in that our results compare QALYs and costs for newly diagnosed patients and because our treatment efficacy is based on data that captures long-term adherence effects that are typically much smaller in clinical trials.

Several models have been developed to predict the natural history of diabetes-related complications progression and to gauge their sequelae on patient quality of life (17,18,36–38); however, none of these models were based on real-world data describing the rate of and variations in HbA_{1c} progression caused by both biological changes and patient behavior with and without different treatment modalities. Moreover, none of the previous published models explicitly compared and contrasted different treatment regimens with regard to their practical efficiency, cost, and clinical benefit based on real-world inputs rather than clinical trial data or select observational study population groups. To our knowledge, this study is the first to develop and validate a glycemic control model that takes into consideration the known adverse effects of treatment, such as hypoglycemia, current medication cost, and various suggested glycemic control goals.

Our model can serve as an adjunctive decision aid to facilitate treatment selection for people newly diagnosed with type 2 diabetes in a way that trades off health and economic implications for patients. It can also be used by health care providers and payers to determine whether a particular treatment option is consistent with the goal of high-value care, e.g., providing a clinically justified benefit given the incurred cost. While no clinical study has yet definitively established the clinical benefit of using incretins in place of sulfonylureas as second-line agents and there is increasing concern regarding sulfonylurea use owing to its association with severe hypoglycemia (10), our model, which considers the side effect of severe hypoglycemia, suggests that for a glycemic control goal of 6.5% (48 mmol/mol) or 7% (53 mmol/mol), sulfonylureas provide higher value than incretin. Indeed, use of incretins as second-line agents (treatment regimens T2 and T3) resulted in significantly higher cost but slightly less clinical benefit as measured by LYs and QALYs to first incident diabetes-related complication or death. However, ultimate value will depend on patient preference.

Our study has several limitations. First, the results presented in this manuscript are based on a Markov model rather than a clinical trial, and no model can provide a perfect representation of reality. Specifically, our model assumes that HbA_{1c} varies among discrete states

and at discrete 3-month time intervals rather than continuously; furthermore, transitions among states are assumed to depend only on the most recent HbA_{1c} state. For addressing these limitations, the assumptions were carefully validated based on real patient data. Treatment regimens were designed as sequential one-by-one additions of different classes of antihyperglycemic medications, while in clinical practice patients may start two or more drugs at the same time. We also assumed that insulin would replace the previously used second-line drug, as recommended by most clinical practice guidelines, but it is possible for patients to continue using two or more noninsulin agents in conjunction with insulin. We assumed that insulin will ultimately result in achievement of the glycemic goal; this is an idealized assumption that is based on the physiology of insulin action, and there is likely to be substantial variation among patients in whether they achieve and maintain their glycemic goal over time. Finally, the model is based on data that represents a privately insured population. Therefore, it is possible that these results may not be generalizable to the Medicare and Medicaid populations.

Several features that were not incorporated into the current model are due to insufficient evidence in literature such as the potential variability in how medications influence HbA_{1c} trajectory, the potential variability in the duration of observing the effect of medications, and the potential indirect pleiotropic effects of these medications not mediated by their glucose-lowering properties. Medication disutility values were based on limited empirical data because definitive evidence is not yet available. Our analyses were focused on primary prevention of the most common micro- and macrovascular complications of diabetes, and patients included were treatment naïve and newly diagnosed with diabetes. To the extent possible, we have used previously published data on the utility decrements for complications and treatments; however, utility estimates are limited in that they represent an average measure and do not reflect individual patients' well-being. To address this, we performed sensitivity analysis on the utility estimates. Finally, not all known adverse medication effects were included in the model. We did not consider severe nausea and other gastrointestinal side effects of metformin or DPP-4 inhibitors (16), since these symptoms and availability of alternatives would likely cause the medication to be discontinued. We did not consider pancreatitis risk from the new agents due to the uncertainty of this evidence (39,40). Ultimately, however, our proposed model is sufficiently versatile to allow for easy integration of newly acquired clinical knowledge and its continued refinement.

Two key factors that were not explicitly incorporated into the model are medication adherence and lifestyle modifications, both of which are known to improve glycemic control, particularly in early stages of diabetes. However, this is alleviated by our use of real-world observational data for patients who adhere to their treatments and lifestyle recommendations with the frequency expected from any general population among which such therapies are to be deployed. This affords our model an aspect of generalizability and validity that makes it attractive and relevant to patients, health care providers, and payers.

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SUPPLEMENTARY DATA

Appendix A. HbA_{1c} Transition Probability Matrix Estimation

To estimate the 3-month HbA_{1c} transition probabilities, we selected all pairs of HbA_{1c} records from the 37,501 eligible patients such that the period between tests was between 2.5 and 3.5 months and the patient was not on insulin during that time period. This resulted in 30,249 pairs (multiple pairs permitted per patient). Using the observed HbA_{1c} value, $h_{i,t}$, of patient i at time epoch t, the corresponding natural HbA_{1c} value (without medication), $h^n_{i,t}$, was estimated as:

$$h^n_{i,t} = h_{i,t}\frac{1}{1-\omega(m_{i,t})}, \quad \forall i,t$$

Where $m_{i,t}$ denotes patient i's current treatment regimen and $\omega(m_{i,t})$ is the estimated relative reduction in HbA_{1c} when patient i is using treatment regimen $m_{i,t}$ at time period t (**Table 1**). We discretized all natural HbA_{1c} values into 10 HbA_{1c} states as defined in **Supplement Table s1** and **Supplement Table s2**. For any two HbA_{1c} states, a and b, we denoted the total number of transitions from state a to state b as n_{ab}. The maximum likelihood estimate of the transition probability from state a to state b was estimated as:

$$q_a(b) = \frac{n_{ab}}{\sum_{b\in\mathcal{L}} n_{ab}}, \quad \forall a \in \mathcal{L}$$

where $\mathcal{L}$ is the set of HbA_{1c} states.

Appendix B. Treatment Effect Estimation

Five classes of glucose-lowering medications were considered: metformin, sulfonylurea, DPP-IV inhibitor, GLP-1 agonist, and insulin. We assumed that once insulin was initiated, HbA_{1c} would be maintained at a predefined level (it is set to be 7% in our numerical experiments). We also assumed that medications other than insulin had additive effect in reducing HbA_{1c} (1); therefore, each medication effect was estimated independently.

For each medication other than insulin, we selected patients who had at least one HbA_{1c} record within 3 months before and after its initiation, and who were treated with this medication for at least 3 consecutive months. For each selected patient, we calculated the pre-treatment HbA_{1c} and the post-treatment HbA_{1c} by taking the mean of his/her HbA_{1c} records during the 3-month intervals before and after the date of initiation, respectively. The medication effect shown in **Table 1** was then calculated as the overall mean relative change between the pre-treatment HbA_{1c} and the post-treatment HbA_{1c} of all the selected patients.

Appendix C. Model Calibration and Validation

To calibrate and validate the model we used all HbA_{1c} pairs of the eligible 37,501 patients such that the period between HbA_{1c} tests was greater than or equal to 3.5 months (in order to have at least one 3-month transition) and the patient was not on insulin during that time period. This resulted in 97,667 pairs.

For each value of the linear trend factor, β, between 0 and 0.25, and for each initial test result in each pair, we simulated the second test result in the pair 100 times using the 3-month HbA_{1c} transition probability matrix (**Supplement Table s1** and **Supplement Table s2**) and the number of transitions, t_k, determined by the time interval between the two HbA_{1c} tests of each pair k. Using the model-generated natural HbA_{1c} state, $\theta^k(t_k)$, for each pair k, we calculated the model-generated HbA_{1c} value, $h_{k,t_k}(\theta^k(t_k))$ with medications initiated during the time interval as follows:

$$h_{k,t_k}(\theta^k(t_k)) = h^n\left(\theta^k(t_k)\right) + \beta \times t_k - \omega(m_{k,t_k}) \times h^n\left(\theta^k(t_k)\right),$$

where $h^n\left(\theta^k(t_k)\right)$ is the mean natural HbA_{1c} value of being in the HbA_{1c} state $\theta^k(t_k) \in \mathcal{L}$ at diagnosis (**Supplement Table s1** and **Supplement Table s2**) and $\omega(m_{k,t_k})$ is the medication effect of using medications

m_{k,e_R}. Finally, we determined the model-generated HbA_{1c} state for that pair based on the model-generated HbA_{1c} value.

Given the 100 model-generated 97,667 HbA_{1c} pairs, we calculated the mean of the sum of the squared errors (SSE) between the model-generated HbA_{1c} state distribution and the observed HbA_{1c} state distribution as:

$$F(\beta) = \frac{\sum_{i=1}^{n} (\pi - p^i(\beta))^T (\pi - p^i(\beta))}{n}$$

where $\pi = (\pi(e_1), \pi(e_2), \ldots, \pi(e_{10}))$ represents the observed HbA_{1c} state probability distribution (based on the second HbA_{1c} values in all pairs) and the vector $p^i(\beta)$ represents the model-generated HbA_{1c} state probability distribution for the i^{th} simulation with a fixed linear trend value β. The best linear trend was selected as the one that minimizes the mean of the SSE.

We found that the optimal trend factor was 0.1075 for men (mean SSE of 0.0022) and 0.105 for women (mean SSE of 0.0015) with the median difference between the observed HbA_{1c} distribution and the simulated HbA_{1c} distribution of 0.0096 (minimum: 0.0027, maximum 0.0271) for men and 0.0055 (minimum: 0.0000, maximum: 0.0197) for women.

SUPPLEMENTARY DATA

Supplementary Table 1. Glycosylated hemoglobin (HbA_{1c}) used in the Markov model for women. HbA_{1c} range definition at diagnosis, the mean natural HbA_{1c} values for each HbA_{1c} state at diagnosis (prior to initiating medication), the initial HbA_{1c} distributions at diagnosis, and 3-month HbA_{1c} transition probability matrices for men and women.

		HbA_{1c} State									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
HbA_{1c} Range		<6	[6,6.5)	[6.5,7)	[7,7.5)	[7.5,8)	[8,8.5)	[8.5,9)	[9,9.5)	[9.5,10)	≥10
Mean HbA_{1c} value (%)		5.70	6.25	6.74	7.24	7.73	8.23	8.73	9.22	9.72	11.73
Initial HbA_{1c} Distribution		0.0771	0.1543	0.2125	0.1800	0.1105	0.0848	0.0502	0.0350	0.0273	0.0683
Transition Probability Matrix	**HbA_{1c} state 1**	0.6379	0.3042	0.0481	0.0088	0.0010	0.0000	0.0000	0.0000	0.0000	0.0000
	HbA_{1c} state 2	0.1717	0.5086	0.2692	0.0412	0.0064	0.0020	0.0000	0.0000	0.0000	0.0010
	HbA_{1c} state 3	0.0299	0.1731	0.5214	0.2258	0.0374	0.0085	0.0018	0.0004	0.0011	0.0007
	HbA_{1c} state 4	0.0114	0.0538	0.2830	0.4167	0.1716	0.0446	0.0114	0.0029	0.0021	0.0025
	HbA_{1c} state 5	0.0048	0.0240	0.1055	0.2740	0.3329	0.1678	0.0568	0.0199	0.0055	0.0089
	HbA_{1c} state 6	0.0045	0.0116	0.0491	0.1438	0.2482	0.2768	0.1598	0.0661	0.0268	0.0134
	HbA_{1c} state 7	0.0015	0.0120	0.0316	0.0648	0.1687	0.2364	0.2184	0.1370	0.0768	0.0527
	HbA_{1c} state 8	0.0043	0.0065	0.0281	0.0562	0.0864	0.1533	0.1879	0.1965	0.1555	0.1253
	HbA_{1c} state 9	0.0000	0.0166	0.0194	0.0332	0.0831	0.1357	0.1662	0.1717	0.1828	0.1911
	HbA_{1c} state 10	0.0078	0.0111	0.0277	0.0532	0.0831	0.0920	0.0854	0.0976	0.1042	0.4379

SUPPLEMENTARY DATA

Supplementary Table 2. Glycosylated hemoglobin (HbA_{1c}) used in the Markov model for men. HbA_{1c} range definition at diagnosis, the mean natural HbA_{1c} values for each HbA_{1c} state at diagnosis (prior to initiating medication), the initial HbA_{1c} distributions at diagnosis, and 3-month HbA_{1c} transition probability matrices for men and women.

		HbA_{1c} State									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
HbA_{1c} Range		<6	[6,6.5)	[6.5,7)	[7,7.5)	[7.5,8)	[8,8.5)	[8.5,9)	[9,9.5)	[9.5,10)	≥10
Mean HbA_{1c} value (%)		5.69	6.25	6.73	7.24	7.74	8.24	8.74	9.21	9.73	11.59
Initial HbA_{1c} Distribution		0.0694	0.1388	0.1968	0.1626	0.1138	0.0919	0.0619	0.0424	0.0328	0.0896
Transition Probability Matrix	**HbA_{1c} state 1**	0.6244	0.2885	0.0685	0.0093	0.0034	0.0025	0.0008	0.0008	0.0000	0.0017
	HbA_{1c} state 2	0.1574	0.4949	0.2953	0.0402	0.0072	0.0038	0.0004	0.0000	0.0004	0.0004
	HbA_{1c} state 3	0.0349	0.2061	0.4715	0.2279	0.0441	0.0078	0.0024	0.0012	0.0024	0.0018
	HbA_{1c} state 4	0.0130	0.0592	0.2462	0.4014	0.1971	0.0549	0.0166	0.0043	0.0029	0.0043
	HbA_{1c} state 5	0.0098	0.0237	0.1058	0.2606	0.3029	0.1852	0.0686	0.0243	0.0083	0.0108
	HbA_{1c} state 6	0.0058	0.0134	0.0645	0.1335	0.2313	0.2888	0.1514	0.0550	0.0294	0.0268
	HbA_{1c} state 7	0.0104	0.0142	0.0455	0.0796	0.1308	0.2284	0.2351	0.1422	0.0645	0.0493
	HbA_{1c} state 8	0.0111	0.0249	0.0456	0.0526	0.0982	0.1674	0.1840	0.1646	0.1328	0.1189
	HbA_{1c} state 9	0.0125	0.0233	0.0412	0.0376	0.0789	0.1057	0.1595	0.1792	0.1344	0.2276
	HbA_{1c} state 10	0.0098	0.0249	0.0537	0.0688	0.0629	0.0799	0.0911	0.0996	0.1134	0.3958

SUPPLEMENTARY DATA

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