Individualized Glycemic Control for U.S. Adults With Type 2 Diabetes
A Cost-Effectiveness Analysis

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Background: Intensive glycemic control in type 2 diabetes (glycated hemoglobin [HbA$_{1c}$] level <7%) is an established, cost-effective standard of care. However, guidelines recommend individualizing goals on the basis of age, comorbidity, diabetes duration, and complications.

Objective: To estimate the cost-effectiveness of individualized control versus uniform intensive control (HbA$_{1c}$ level <7%) for the U.S. population with type 2 diabetes.

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

Data Sources: National Health and Nutrition Examination Survey 2011–2012.

Target Population: The approximately 17.3 million persons in the United States with diabetes diagnosed at age 30 years or older.

Time Horizon: Lifetime.

Perspective: Health care sector.

Intervention: Individualized versus uniform intensive glycemic control.

Outcome Measures: Average lifetime costs, life-years, and quality-adjusted life-years (QALYs).

Results of Base-Case Analysis: Individualized control saved $13 547 per patient compared with uniform intensive control

($105 307 vs. $118 854), primarily due to lower medication costs ($34 521 vs. $48 763). Individualized control decreased life expectancy (20.63 vs. 20.73 years) due to an increase in complications but produced more QALYs (16.68 vs. 16.58) due to fewer hypoglycemic events and fewer medications.

Results of Sensitivity Analysis: Individualized control was cost-saving and generated more QALYs compared with uniform intensive control, except in analyses where the disutility associated with receiving diabetes medications was decreased by at least 60%.

Limitation: The model did not account for effects of early versus later intensive glycemic control.

Conclusion: Health policies and clinical programs that encourage an individualized approach to glycemic control for U.S. adults with type 2 diabetes reduce costs and increase quality of life compared with uniform intensive control. Additional research is needed to confirm the risks and benefits of this strategy.

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Diabetes affects 9% of the U.S. population and costs the United States an estimated $245 billion annually (1). Because of the substantial financial and public health burden of diabetes, understanding the cost-effectiveness of treatments is important. More than a decade ago, a cost-effectiveness analysis found that intensive glycemic control (plasma glucose concentration <6 mmol/L [<108 mg/dL]) with glucose-lowering medications was cost-effective, with an incremental cost-effectiveness ratio of $41 384 per quality-adjusted life-year (QALY) compared with conventional control (2). This study provided evidence for the cost-effectiveness of the American Diabetes Association (ADA) recommendations to pursue glycated hemoglobin (HbA$_{1c}$) values less than 7.0% using glucose-lowering medications.

The standards of diabetes care have changed over the past decade. Results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial showed that patients who had or were at high risk for cardiovascular disease had an increased mortality risk with very intensive glycemic control (achieved HbA$_{1c}$ level of 6.4% vs. 7.5%) (3). In addition, several observational studies have revealed a high incidence of severe hypoglycemia (an adverse effect of glucose-lowering

agents) in older Medicare and managed care beneficiaries (4–6). As a result of accumulating evidence for the potential harms of intensive glycemic treatment, in 2012, the ADA and the European Association for the Study of Diabetes (EASD) published a position statement recommending that providers individualize glycemic goals on the basis of several factors, including age, life expectancy, comorbidity, diabetic complication history, diabetes duration, and hypoglycemia risk (7).

These guidelines could have major implications for the U.S. population with type 2 diabetes. It is estimated that more than half of U.S. adults with diabetes have advanced age, high comorbidity, preexisting diabetic complications, or long disease duration (8). However, to date, the clinical implications and economic value of individualizing glycemic goals have not been examined. Also, it is highly unlikely that diabetes trials will be

designed to compare the lifetime effects of individualized versus uniform intensive glycemic control. Without these analyses, the need for policymakers to prioritize individualized diabetes care is uncertain. We sought to examine the cost-effectiveness of individualized glycemic control compared with uniformly applied intensive control (HbA$_{1c}$ level <7.0%) for the U.S. population with type 2 diabetes.

METHODS

Study Model

The U.S. Type 2 Diabetes Policy Model is an individual patient–level, Monte Carlo–based Markov model of the incidence, prevalence, mortality, and costs related to type 2 diabetes among U.S. adults with self-reported disease (**Appendix Figure 1**, available at Annals.org). We integrated the diabetes-related complication and mortality modules from the UKPDS (United Kingdom Prospective Diabetes Study) Outcomes Model version 2 (OM2) (9) with a hypoglycemic event module (10), an ADA/EASD-based diabetes medication algorithm (7), and a module for utility and 2015 U.S. costs.

The equations from the UKPDS OM2 and its predecessor (UKPDS OM1) (11) are used by all major type 2 diabetes simulation models worldwide (12–14). The UKPDS OM2 has been shown to accurately predict results for the population in which it was developed (internally validated) (9) and for other diabetes populations (externally validated) (see the **Appendix**, available at Annals.org, for details) (13). We internally validated our version of the UKPDS OM2 by comparing our results with predicted results for the same UKPDS population. Our model results were within 1% of published results for all complications and within 3% for composite death. The UKPDS OM1 risk equations were used in the prior cost-effectiveness analysis of intensive versus standard glycemic control (2). No other risk equations for diabetic complications and mortality meet these standards, which necessitated our use of the UKPDS OM2 equations. However, it is important to note their limitations. Because the UKPDS OM2 equations predict annual risk for events, they do not account for long-term effects of early intensive glucose control (legacy effect) on cardiovascular and microvascular events and mortality seen in the follow-up of the UKPDS (15), the ACCORD trial (16), and the VADT (Veterans Affairs Diabetes Trial) (17, 18). They also do not include the excess mortality risk observed in the ACCORD trial.

Using 26 individual patient–level characteristics, the UKPDS OM2 predicts lifetime risk for diabetes-related complications (foot ulcer, blindness, renal failure, first and subsequent amputation, first and subsequent myocardial infarction, ischemic heart disease, and first and subsequent stroke) using 13 risk equations and mortality using 4 risk equations. For mortality, the model assumes that all diabetic complications (except foot ulcer and blindness) increase the probability of death. The model predicts both non–diabetes-related and diabetes-related death.

We simulated risk for hypoglycemia based on use of diabetes medications (see the **Appendix** for details) (19). We assumed that severe hypoglycemia was associated with a greater decrease in quality of life (utility) than mild or moderate events and that only severe hypoglycemic events increased the probability of health care use.

We started patients in the model with their self-reported combination of diabetes medications and their measured HbA$_{1c}$ value from NHANES (National Health and Nutrition Examination Survey) 2011–2012 (**Appendix Table 1**, available at Annals.org). We followed the 2015 ADA/EASD algorithm for initiating use of diabetes medications (7). The algorithm includes all medication classes except α-glucosidase inhibitors and meglitinides because neither is recommended by ADA/EASD. The choice of medication was based on the proportion of its use in the United States as a second-line agent from reported literature (20). We assumed that the decision to start or stop use of a diabetes medication depended on the HbA$_{1c}$ value.

We assumed that HbA$_{1c}$ values would increase annually, based on an equation from UKPDS OM1 (11). We also assumed that patients' medications would change in the year after their HbA$_{1c}$ value increased above (or decreased >1% below) their goal and that each medication reduced the HbA$_{1c}$ level by 1% (21–23). Under the individualized strategy, as patients developed complications and aged, their goals increased (for example, from an HbA$_{1c}$ level <6.5% to a level <7.0% to a level <8.0%). When the individualized HbA$_{1c}$ goal decreased and this resulted in an HbA$_{1c}$ level that was more than 1% below the goal, the last medication added would be removed the next year (see the **Appendix** for details).

Model Inputs

We used data from individual participants with self-reported diabetes in NHANES 2011–2012 (**Appendix Table 1**). We included adults who answered "yes" to the question, "[Other than during pregnancy,] have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?" To identify patients with likely type 2 diabetes, we included only those who were aged 30 years or older at diagnosis. For missing values that were necessary for the model, we used the average of 5 values generated using Markov-chain Monte Carlo multiple imputation (see the **Appendix** and **Appendix Table 2** [available at Annals.org] for details). We excluded participants with 4 or more missing model inputs or unidentifiable diabetes medication data (**Appendix Figure 2**, available at Annals.org). Characteristics were similar between included and excluded participants (**Appendix Table 1**).

Individual characteristics were used as baseline data. Baseline variables included age, sex, race/ethnicity, smoking status, diabetes duration, and self-reported medical conditions (coronary heart disease, angina, heart failure, myocardial infarction, stroke, dialysis in the previous year, retinopathy, lung disease, rheumatoid arthritis, liver disease, and cancer [exclud-

ing skin cancer]). Measured values included HbA$_{1c}$ level, body mass index, estimated glomerular filtration rate, low-density lipoprotein and high-density lipoprotein cholesterol levels, hemoglobin level, leukocyte count, heart rate, systolic blood pressure, and albuminuria. History of peripheral vascular disease, atrial fibrillation, amputation, blindness, and neuropathy were not available in NHANES. The age- and sex-based probabilities of having peripheral vascular disease or atrial fibrillation were imputed on the basis of published literature (24, 25). We assumed that no patients had amputations, blindness, or neuropathy at baseline.

Costs and Health Utility

Costs associated with complications, hospital use, medication use, and self-monitoring (testing and supplies) were included. Medication costs were calculated using the average wholesale price across drug classes (26). Generic prices were used when available. All costs were from a health care sector perspective and were in 2015 U.S. dollars (Appendix Table 3, available at Annals.org) (27). The Impact Inventory is provided in Appendix Table 4 (available at Annals.org).

An annual health utility was calculated to estimate QALYs. Health utilities are used to value health states, with 0 equal to death and 1 equal to perfect health. Using established utilities in the literature, we accounted for the independent quality-of-life effects of each diabetic complication, hypoglycemia, and routine use of glucose-lowering medications (oral agents and

insulin) (Appendix Table 3) (28, 29). The multiplicative method, which entails multiplying all utility values within a patient cycle, was used to combine utilities (30).

Statistical Analysis

For NHANES participants with self-reported diabetes in 2011 to 2012, we compared the strategies suggested by the ADA: individualized glycemic goals and a uniform intensive goal (HbA$_{1c}$ level <7.0%). For individualized goals, the guidelines specify more and less stringent goals than an HbA$_{1c}$ level less than 7.0%. We assumed that the more stringent HbA$_{1c}$ goal was less than 6.5% and the less stringent goal was less than 8.0%. To operationalize these goals, we used age, complication history, comorbidity status, and diabetes duration because these are objective measures included in recommendations from the ADA and the EASD (see the footnote to Table 1) (7, 31). The individualized goals were at the patient level and were updated in the model every year. To define complication history, we considered a patient-reported history of any of the following: angina pectoris, myocardial infarction, stroke, coronary heart disease, congestive heart failure, retinopathy, dialysis in the past year, an albumin–creatinine ratio greater than 300 mg/g, or development of a diabetic complication during the simulation. Comorbidity status was calculated using a weighted combined Charlson Comorbidity Index score based on the patient's baseline self-report of myocardial infarction,

Table 1. Incremental Cost-Effectiveness of a Strategy of Individualized Versus Uniform Intensive Glycemic Control for U.S. Adults With Diabetes Diagnosed at Age ≥30 Years (*n* = 569)*

Variable	Mean (95% CI)		Incremental Difference†
	Uniform Intensive Control	**Individualized Control**	
Lifetime costs, $‡			
Medications	48 763 (41 660 to 55 867)	34 521 (28 908 to 40 133)	−14 242
Complications	55 459 (35 302 to 75 616)	56 920 (37 642 to 76 198)	1461
Hypoglycemia	1040 (529 to 1550)	760 (331 to 1190)	−280
Office visits	10 307 (9349 to 11 264)	10 174 (9225 to 11 123)	−133
Self-management	3285 (2897 to 3672)	2932 (2597 to 3267)	−353
Total	118 854 (96 312 to 141 395)	105 307 (84 443 to 126 172)	−13 547
Life expectancy, y§	20.73 (18.77 to 22.69)	20.63 (18.67 to 22.58)	−0.10
Change in QALYs‖			
Medications	−0.62 (−0.55 to −0.70)	−0.45 (−0.38 to −0.52)	0.17
Complications	−0.08 (−0.06 to −0.10)	−0.09 (−0.07 to −0.11)	−0.01
Hypoglycemia	−0.20 (−0.17 to −0.23)	−0.15 (−0.12 to −0.18)	0.05
Total QALYs	16.58 (14.99 to 18.18)	16.68 (15.08 to 18.29)	0.10

HbA$_{1c}$ = glycated hemoglobin; QALY = quality-adjusted life-year.
* These participants represent about 17.3 million U.S. adults aged ≥30 y with self-reported diabetes. Individualized glycemic goals were assigned annually to patients on the basis of their age, history of complications, comorbidity level, and diabetes duration. An HbA$_{1c}$ goal <6.5% was assigned to patients aged 30–44 y who did not have a history of diabetic complications or high comorbidity. An HbA$_{1c}$ goal <7.0% was assigned to patients aged 30–44 y with a history of diabetic complications and low comorbidity, those aged 45–64 y without a history of complications or high comorbidity, and those aged 65–75 y without a history of complications or high comorbidity and diabetes duration <10 y. All other patients were assigned an HbA$_{1c}$ goal <8.0%.
† *P* < 0.001 for all values.
‡ Expressed in 2015 U.S. dollars and discounted at 3% per year. Negative incremental costs indicate cost savings from individualized vs. uniform intensive control.
§ Not discounted.
‖ Quality-adjusted life expectancy was discounted at 3% per year. The changes in QALYs due to medications, complications, and hypoglycemia do not sum to the total incremental difference in quality-adjusted life expectancy because QALYs were combined annually using the multiplicative method (30).

heart failure, stroke, lung disease, rheumatoid arthritis, liver disease, diabetes, or cancer or development of these complications during the simulation. A score less than 5 (vs. ≥5) indicated low (vs. high) comorbidity status (32).

We ran 2500 simulations for the lifetime of each NHANES participant for each strategy (see the **Appendix** for details). To obtain national population estimates, we applied medical examination subsample weights to the model results, which include average per-person lifetime costs, life expectancy, QALYs, and complication and hypoglycemia rates. Differences in results by strategy were compared using general linear models. Costs and QALYs were discounted at 3% annually. We combined annual costs and QALYs by applying the Simpson 1/3 rule (33). The models were run using Microsoft Excel–based @Risk 7.0 software (Palisade Corporation). Analyses were conducted using SAS, version 9.4 (SAS Institute).

Subgroup and Sensitivity Analyses

We analyzed subpopulations defined by age (30 to 44, 45 to 64, 65 to 75, and >75 years), diabetes duration (<10 or ≥10 years), and complication history (present or absent). We also performed 1-way sensitivity analyses on model assumptions. The effectiveness of diabetes medications at decreasing HbA$_{1c}$ level was changed from 1% to 0.8% and 1.2%. We examined our assumptions in the hypoglycemia model by increasing and decreasing the rates of hypoglycemia due to medication use and the rates of severe hypoglycemia–related health care use by 20% each. We also analyzed how results were affected by 20% increases and decreases in costs and utilities related to microvascular and macrovascular complications, hypoglycemia, and diabetes medications. Furthermore, we examined how results changed when receiving diabetes medications was associated with no decrease in utility. Finally, we varied the discount rate to 1% and 5% from its original value of 3% and modeled the additive approach for combining utilities in calculating QALYs (34).

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 2011–2012, there were 569 participants who met inclusion criteria, representing about 17.3 million U.S. adults aged 30 years or older with self-reported diabetes (**Appendix Table 1**). The average age was 61 years, and 50% were female. Participants had diabetes for an average of 10 years; 36% had a history of diabetic complications, and 42% had high comorbidity scores. The most common diabetes medications were metformin (51%), sulfonylureas (33%), and basal insulin (18%).

Individualized glycemic control dominated uniform intensive control (HbA$_{1c}$ level <7%) (**Table 1**). The

Figure 1. Diabetes-related complications (*top*) and hypoglycemic events (*bottom*), by glycemic control strategy.
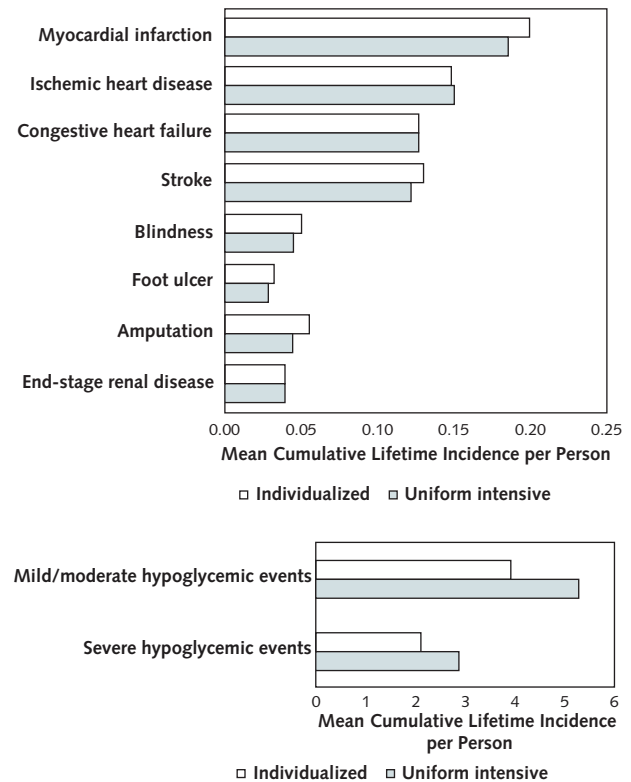
individualized strategy cost $13 547 less per person ($105 307 vs. $118 854), mainly due to differences in medication costs ($34 521 vs. $48 763). This strategy was associated with fewer remaining life-years than uniform intensive control (20.63 vs. 20.73; difference, −0.10 [36 days]) because of a higher rate of diabetic complications (7854 vs. 7456 events per 10 000 patients). However, the individualized strategy was also associated with less medication use (−0.6 medication per year) and fewer hypoglycemic events (−2.1 events). These differences translated into an increase in QALYs due to medications (0.17 QALY) and hypoglycemia (0.05 QALY), which led to slightly improved QALYs relative to uniform intensive control (16.68 vs. 16.58; difference, 0.10 [36 quality-adjusted life-days]).

Complications and Hypoglycemia

Individualized control increased the absolute lifetime risk for myocardial infarction by 1.39%, amputation by 1.05%, and stroke by 0.85% versus uniform intensive control (**Figure 1**). However, individualized control decreased the absolute lifetime risk for mild or moderate (−1.4%) and severe (−0.8%) hypoglycemia compared with uniform glycemic control (5.3 mild or moderate and 2.9 severe hypoglycemic events).

Subpopulations

Among all subgroups analyzed, individualized glycemic control dominated uniform intensive control (Table 2). Individualized control reduced costs the most and yielded the highest increase in QALYs for adults in the youngest age group (30 to 44 years) (−$16 365 and 0.20 QALY) and those with low comorbidity (−$16 540 and 0.11 QALY). The individualized strategy remained cost-saving for the oldest age group (>75 years) but, as expected, reduced costs and increased QALYs by less (−$5401 and 0.05 QALY), with similar findings for adults with high comorbidity (−$8863 and 0.04 QALY). The greatest savings and increase in QALYs occurred for young patients with low comorbidity (−$18 191 and 0.25 QALY), and the smallest savings and increase in QALYs occurred for young patients with complications and low comorbidity (−$7901 and 0.02 QALY) (Table 2).

Sensitivity Analyses

Individualized control was cost-saving in all sensitivity analyses compared with uniform intensive control (savings range, $10 084 to $15 504 per person) (Ap-

pendix Table 5, available at Annals.org). The individualized strategy increased QALYs compared with the uniform intensive strategy in all sensitivity analyses except those that varied medication disutility (the quality-of-life burden from taking medications) (Figure 2). Individualized control remained preferred over uniform intensive control unless the disutility was reduced by at least 60% from our baseline estimate.

DISCUSSION

Because of the large economic burden of diabetes in the United States, the need to reduce treatment costs is a public health and health policy priority. Our study found that individualized glycemic control for U.S. adults with type 2 diabetes was cost-saving (−$13 547 per person), mainly due to reductions in medication costs (−$14 242 per person). Overall, individualized glycemic control resulted in a slight improvement in quality of life (0.10 year) that more than offset a slight decrease in length of life (−0.10 year) due to an expected decrease in quality of life from ad-

Table 2. Incremental Cost-Effectiveness of Individualized Versus Uniform Intensive Glycemic Control for Subpopulations of U.S. Adults With Diabetes Diagnosed at Age ≥30 Years

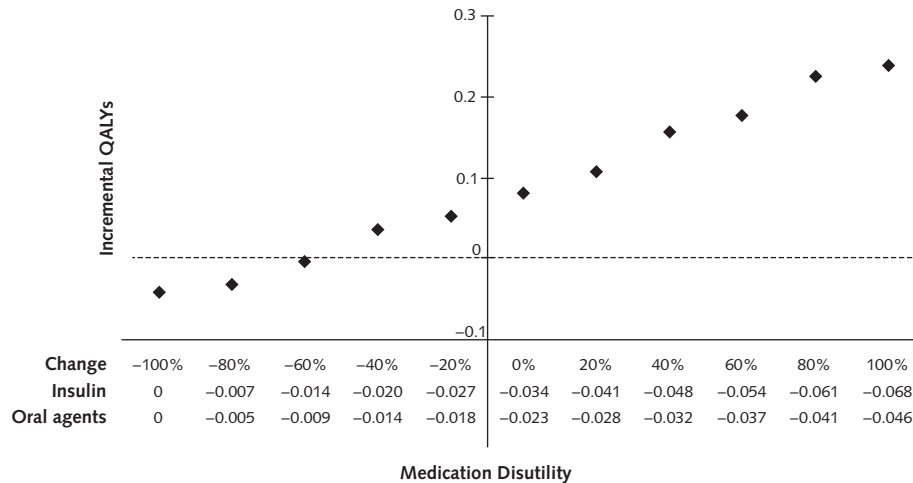| Patient Characteristic	NHANES Population (95% CI), %	Incremental Lifetime Costs, $*	Incremental Life-Years	Incremental QALYs
Age				
30−44 y	9 (6 to 13)	−16 365	−0.10	0.20
45−64 y	48 (44 to 52)	−16 315	−0.17	0.09
65−75 y	26 (21 to 31)	−11 692	−0.10	0.04
>75 y	17 (14 to 19)	−5401	−0.09	0.05
Complications†				
No	64 (58 to 70)	−14 885	−0.14	0.10
Yes	36 (30 to 42)	−10 452	−0.11	0.04
Comorbidity status‡				
Low	58 (53 to 63)	−16 540	−0.13	0.11
High	42 (37 to 47)	−8863	−0.13	0.04
Diabetes duration				
<10 y	44 (38 to 50)	−14 508	−0.14	0.10
≥10 y	56 (50 to 62)	−11 735	−0.11	0.05
Age 30−44 y				
Without complications, with low comorbidity	7 (3 to 11)	−18 191	−0.08	0.25
With complications and low comorbidity	2 (0 to 4)	−7901	−0.11	0.02
Age 45−64 y, without complications, with low comorbidity	35 (32 to 39)	−14 961	−0.16	0.09
Age 65−75 y, without complications, with low comorbidity and diabetes for <10 y	5 (3 to 7)	−10 131	−0.10	0.08
All other patients§	50 (48 to 53)	−11 982	−0.12	0.05

NHANES = National Health and Nutrition Examination Survey; QALY = quality-adjusted life-year.
* Expressed in 2015 U.S. dollars. Negative values indicate cost savings from individualized vs. uniform intensive control.
† Self-reported history of angina pectoris, myocardial infarction, stroke, coronary heart disease, congestive heart failure, or retinopathy; receipt of dialysis in previous year; or measured albumin–creatinine ratio >300 mg/g.
‡ Calculated by using a weighted combined Charlson Comorbidity Index score based on the patient's self-report of myocardial infarction, heart failure, stroke, lung disease, rheumatoid arthritis, liver disease, diabetes, and cancer (excluding skin cancer). A score <5 (vs. ≥5) indicated low (vs. high) comorbidity status.
§ Those aged 30−44 y with complications and high comorbidity, those aged 45−75 y with complications, all patients aged >75 y, and all patients with high comorbidity.

Figure 2. Sensitivity analysis of medication disutility.

Change	−100%	−80%	−60%	−40%	−20%	0%	20%	40%	60%	80%	100%
Insulin	0	−0.007	−0.014	−0.020	−0.027	−0.034	−0.041	−0.048	−0.054	−0.061	−0.068
Oral agents	0	−0.005	−0.009	−0.014	−0.018	−0.023	−0.028	−0.032	−0.037	−0.041	−0.046

Medication Disutility

QALY = quality-adjusted life-year.
* Represents difference between individualized vs. uniform intensive glycemic goals.

verse effects of taking more diabetes medications, including hypoglycemia.

Our major finding was that individualized glycemic control in the United States would be cost-saving compared with uniform intensive glycemic control. Across the remaining life of the U.S. diabetes population, the lifetime cost savings ($13 547 per person) would total $234 billion. In contrast, a previous cost-effectiveness analysis of standard versus intensive glycemic control showed that intensive control was cost-effective but not cost-saving, mostly because of an increase in treatment costs (2). Because individualized control shifts patients from very intensive to less intensive control over their lifetime, our finding that the major source of cost savings was decreased use of diabetes medications rather than complication-related costs is not surprising. The prospect of reducing costs by using fewer medications (−0.6 per person per year) and not substantially worsening patient outcomes is appealing, especially given that many patients prefer to avoid diabetes medications if they can do so safely (35). Our finding agrees with a study in low- and middle-income countries, which found that treatment based on risk for diabetic complications was cost-effective compared with a uniform goal of an HbA_{1c} level less than 7% (36).

Our finding that individualized control is cost-saving and increases quality of life compared with uniform intensive control is conservative because we made model assumptions that favored uniform control. Findings of observational studies (37) and the ACCORD trial (38) have suggested a relationship between severe hypoglycemia and mortality that seemed to be independent of treatment intensity. For example, in the ACCORD trial, a relationship between severe hypoglycemia and mortality was found among patients in the control group but not among those in the intensive treatment group. On the basis of this evidence, we linked the risk for hypoglycemia to the intensification of

medication use but assumed no association between severe hypoglycemia and mortality. These assumptions may have resulted in underestimation of the harms of hypoglycemia. In addition, we used the UKPDS OM2 equations because they have been validated (39) and are widely used in analyses for diverse populations throughout the world (12, 14). However, the equations are based on epidemiologic associations and have limitations, as noted in the Methods. As a result of these limitations, the long-term effects of early, very intensive glycemic control (HbA_{1c} level <6.5%), which is possible with the individualized strategy, may have been underestimated. Also, the UKPDS OM2 is unlikely to account for harms associated with intensive glycemic control in patients with cardiovascular disease (16), which explains why we found decreased life expectancy overall and decreased quality of life among the subgroup with preexisting diabetic complications in our model.

Patient-centered care involves accounting for patient preferences and quality of life, and such individualization has been found to be more valuable than uniform care (40). Likewise, we found that the superiority of individualized glycemic control depended on the decrement in quality of life associated with taking diabetes medications. Previous studies have also found that decrements in quality of life due to diabetes treatments can be large (41), with significant individual-level variation (42). In our study, we assumed that the routine task of receiving diabetes medications was associated with a decrement in quality of life above and beyond their relationship with hypoglycemia risk. We know that diabetes agents have adverse effects apart from hypoglycemia and that the route of delivery (injectable or oral) affects patient quality of life (43). Another decision analysis also found that the net benefit of diabetes treatment may be especially sensitive to decrements in quality of life due to diabetes treatment in patients with an HbA_{1c} level less than 9% (44). The collective findings

of our analyses along with prior literature suggest that intensive glycemic control may still be preferred for individual patients who do not object to receiving diabetes medications. This consideration is especially important for adults aged 30 to 44 years with diabetic complications because for this population, individualized glycemic control was less cost-saving and had marginal quality-of-life benefits.

Our study had additional limitations. First, we assumed that all diabetes medications included in the ADA/EASD algorithm decreased HbA_{1c} levels by 1%. This assumption is based on a systematic review of the effects of first- and second-line diabetes medications (21). However, evidence suggests that the effectiveness of diabetes medications at decreasing HbA_{1c} levels depends on the HbA_{1c} level. We did not examine this scenario because this evidence is based on meta-regressions that include results from trials of α-glucosidase inhibitors and meglitinide (45, 46), and our model excluded these drug classes because they are not recommended by the ADA/EASD. Future diabetes care guidelines may prioritize sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 (GLP-1)–receptor agonists because they have been found to reduce cardiovascular outcomes (47–49). These benefits have been identified in patients with high risk for or preexisting cardiovascular disease, and the mean trial HbA_{1c} values were greater than 8.0%. If future diabetes medication algorithms prioritize these new drug classes, costs of diabetes care will increase dramatically, but the question of the cost-effectiveness of different glycemic control strategies will remain. Second, our analysis did not include harmful but more distal effects of hypoglycemia, such as falls and cognitive impairment (50, 51). Third, we did not account for lifestyle interventions and patient adherence, but the degree to which these differ across treatment groups is unclear. Fourth, we did not model treatment inertia, which was examined in a previous study. That study compared the cost-effectiveness of intensifying treatments at guideline-recommended HbA_{1c} levels (range, <6.5% to ≤8.5%) versus actual levels seen in clinical practice (range, <8.75% to <9.0%) (52) and found that adhering to the guideline-recommended levels was more cost-effective than current clinical practice. However, we did conduct sensitivity analyses on all major assumptions, including rates of hypoglycemia due to medication use and hypoglycemia-related health care use, costs, and utilities, and found minimal effects on our main conclusions.

In summary, we found that individualized glycemic control for U.S. adults with diabetes diagnosed at age 30 years or older would be cost-saving due to decreased medication costs and would slightly improve quality of life compared with uniform intensive control. The dominance of individualized glycemic control over uniform intensive control was sensitive to patient preferences against receiving diabetes medications. Additional research is needed to understand how glycemic control affects outcomes differently over the disease course and the pleiotropic effects of newer diabetes agents in order to develop diabetes simulation models that can better inform future strategies in diabetes management and health care policy.

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APPENDIX: METHODS

UKPDS OM2 Internal and External Validation

The UKPDS OM2 has been internally and externally validated (9, 13). Internal validation is the performance of a predictive model in a population similar to that from which the sample originated. The UKPDS OM2 was developed based on patient-level data from 5102 UKPDS participants with newly diagnosed type 2 diabetes mellitus who were aged 25 to 65 years and were recruited between 1977 and 1991 (9). The internal validation of the model compared its predictive accuracy for patient-level outcomes at 25 years for the same UKPDS participants. The predicted failure curves for diabetes outcomes and mortality were within the 95% CI of the actual cumulative failure curves for all events and death.

The UKPDS OM2 was externally validated in a study of the Swedish Institute for Health Economics Cohort Model of Type 2 Diabetes (13). This study included data from 12 clinical trials and observational studies. The UKPDS OM2 slightly underestimated diabetes outcomes, especially macrovascular events, compared with the UKPDS OM1 (slope, 0.899 vs. 0.996, where 1 indicates perfect prediction). The correlation between predicted and actual events was high (>0.96).

Hypoglycemia Module

We assumed that diabetes medications were associated with an increased annual risk for mild or moderate and severe hypoglycemia events, based on published literature (19). Patients receiving insulin (medium, combination, short, or long-acting) were assumed to have a 52% probability of a mild or moderate hypoglycemic event and a 21% risk for a severe hypoglycemic event each year. Patients receiving sulfonylureas were assumed to have a 33% risk for a mild or moderate hypoglycemic event and a 5% risk for a severe hypoglycemic event each year. Patients receiving other diabetes medications were assumed to have a 5% risk for a severe hypoglycemic event each year. Patients were assumed to have no more than 1 mild or moderate hypoglycemic event and 1 severe hypoglycemic event per year and could have multiple hypoglycemic events during their lifetime.

On the basis of published literature, we assumed that a severe hypoglycemic event would result in physician visits 96.5% of the time, emergency department visits 2.6% of the time, and hospitalizations 0.9% of the time (10). The costs associated with these visits are provided in **Appendix Table 3**.

Diabetes Medication Algorithm

We assumed that HbA_{1c} values would drift upward over time to create a need for additional medications over the patient's lifetime and in keeping with the known natural history of diabetes [53]. We used a risk equation from the UKPDS OM1 to model the change in HbA_{1c} level over time [11]. For patients who had HbA_{1c} values above their glycemic goal, medications were added sequentially. Each addition of a medication class was assumed to decrease HbA_{1c} level by 1.0% [21–23]. Only 1 medication class was added per year. Medication classes were added on the basis of guidelines from ADA/EASD [7]. These guidelines include metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1–receptor agonists, basal insulin, and bolus insulin as medication options. We followed all recommended combinations and restrictions. Insulin was dosed at 0.3 unit per kilogram of the patient's measured weight; if patients were receiving combination basal and bolus insulin, it was assumed that they required an additional 0.3 unit per kilogram and that 50% of their dose was basal insulin and 50% was bolus insulin. It was also assumed that patients would be started on analogue insulins with syringes (not pens, which would have increased uniform intensive control costs more than the individualized control strategy). If patients developed end-stage renal disease or had it at baseline, use of all noninsulin medications was discontinued.

Second- and third-line medication classes were added in proportions equivalent to those reported in a national study of diabetes medication use that was based on data from NAMCS (National Ambulatory Medical Care Survey) 2012 [20]. The NAMCS paper includes the number and percentage of visits with 2 or more diabetes medication classes used in the United States. We used these percentages as the basis for the probability that use of each medication class could be started. To use an example from NAMCS, among visits where 2 or more medications were used, metformin was used in combination with sulfonylureas in 30.6% of visits, thiazolidinediones in 10.1% of visits, DPP-4 inhibitors in 20.4% of visits, GLP-1–receptor agonists in 3.3% of visits, and basal insulin in 11.0% of visits. To determine the second medication that would be started, we adjusted the percentages to total 100% for each medication class (for example, for metformin, sulfonylureas would be started 40.6% of the time, thiazolidinediones would be started 13.4% of the time, DPP-4 inhibitors would be started 27.0% of the time, GLP-1–receptor agonists would be started 4.4% of the time, and basal insulin would be started 14.6% of the time).

As an example, if a hypothetical patient in the model was receiving metformin in year 1 and their HbA_{1c} level increased above the goal in year 5, use of a second medication would be started in year 6. According to the 2015 ADA/EASD guidelines, the medication class options for this patient should be sulfonylureas, thiazolidinediones, DPP-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, GLP-1–receptor agonists, or basal insulin. Given the prevalence of medication use, this hypothetical patient would have a 40.6% probability of starting a sulfonylurea, a 13.4% probability of starting a thiazolidinedione, a 27.0% probability of starting a DPP-4 inhibitor, a 4.4% probability of starting a GLP-1–receptor agonist, and a 14.6% probability of starting basal insulin.

Imputation of Missing Data

To include NHANES participants with missing data, we used multiple imputation using multivariate normal distribution (Markov-chain Monte Carlo) to impute missing data. We chose this method because almost all of our variables of interest were continuous [54]. We used the variables that were necessary for the simulation model as the variables for the imputation models (age, sex, race/ethnicity, age at diabetes diagnosis, duration of diabetes, body mass index, estimated glomerular filtration rate, hemoglobin level, HbA_{1c} level, leukocyte count, high-density lipoprotein and low-density lipoprotein cholesterol level, heart rate, systolic blood pressure, and smoking status). The proportion of missing observations for each variable was as follows: body mass index, 2% ($n = 12$); HbA_{1c} level, 0.3% ($n = 2$); high-density lipoprotein cholesterol level, 3% ($n = 19$); low-density lipoprotein cholesterol level, 52% ($n = 294$); heart rate, 3% ($n = 15$); systolic blood pressure, 3% ($n = 18$); and smoking status, 49% ($n = 276$). The following variables had no missing data: age, sex, race/ethnicity, age at diabetes diagnosis, duration of diabetes, hemoglobin level, leukocyte count, and estimated glomerular filtration rate. We used the average of 5 imputed values to estimate missing data (**Appendix Table 2**). The imputation was conducted using SAS, version 9.4.

For peripheral vascular disease and atrial fibrillation, we used the prevalence of these conditions to determine their event probabilities by age and sex. Then, for each model iteration, we compared the age- and sex-based probability to a random number from a uniform distribution between 0 and 1, and if the number was less than the probability, the iteration was assumed to have the condition (Monte Carlo simulation).

Number of Model Iterations

To determine the number of iterations per participant, we assessed the number of iterations needed for the major outcomes of total costs, life-years, and QALYs. We used the convergence feature in @Risk to assess the number of iterations needed for our outcome. We set parameters of a 3% convergence tolerance and a 95% confidence level. Convergence was achieved at 2400 iterations for total costs and 1000 iterations for life-years and QALYs. We chose to model 2500 iterations per participant.

Appendix Figure 1. U.S. Type 2 Diabetes Policy Model.
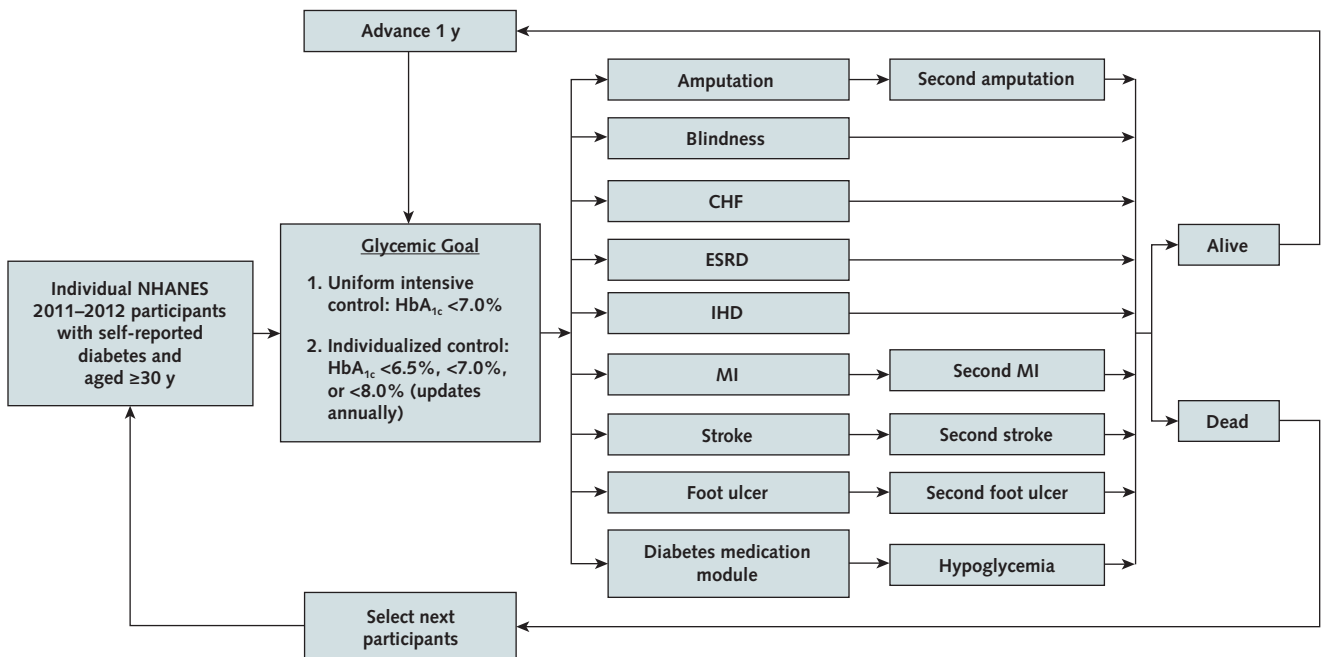
All individual NHANES participants were simulated to receive both glycemic interventions, and 2500 independent simulation replications were performed for each patient. CHF = congestive heart failure; ESRD = end-stage renal disease; HbA$_{1c}$ = glycated hemoglobin; IHD = ischemic heart disease; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey.

Appendix Table 1. Characteristics of U.S. Adults Aged ≥30 Years With Self-Reported Diabetes, NHANES 2011–2012 (*n* = 569)

Characteristic	Included Participants (*n* = 569)		Included Participants (*n* = 17.3 million)		Excluded Participants (*n* = 57)		P Value
	Mean (SD)	Number (Percentage)	Weighted Mean (SD)	Percentage (95% CI)	Mean (SD)	Number (Percentage)	
Age, *y*	63.1 (11.6)	–	61.0 (0.6)	–	65.9 (12.0)	–	0.09
Age group							
30–44 y	–	45 (8)	–	9 (6–13)	–	3 (5)	–
45–64 y	–	265 (56)	–	48 (44–52)	–	21 (37)	0.14
65–75 y	–	153 (27)	–	26 (21–31)	–	15 (26)	–
75 y	–	106 (19)	–	17 (14–19)	–	19 (32)	–
Female	–	265 (47)	–	50 (45–55)	–	34 (60)	0.06
Black race	–	199 (35)	–	17 (8–25)	–	25 (44)	0.18
HbA$_{1c}$ level, %	7.5 (1.8)	–	7.4 (0.1)	–	7.2 (1.6)	–	0.71
Duration of diabetes, *y*	10.4 (9.1)	–	9.7 (0.4)	–	14.2 (10.1)	–	0.004
Duration of diabetes <10 y	–	261 (46)	–	44 (38–50)	–	38 (67)	0.003
Current smoker	–	93 (16)	–	17 (13–21)	–	5 (9)	0.18
Body mass index, *kg/m^2*	31.9 (7.4)	–	32.8 (0.5)	–	32.0 (9.5)	–	0.95
Low-density lipoprotein cholesterol level, *mmol/L*	2.6 (1.0)	–	2.6 (0.1)	–	4.0 (0)	–	0.16
High-density lipoprotein cholesterol level, *mmol/L*	1.2 (0.3)	–	1.2 (0.02)	–	1.6 (0.4)	–	0.16
Hemoglobin level, *g/dL*	13.5 (1.6)	–	13.7 (0.01)	–	12.9 (1.4)	–	0.29
Leukocyte count, *× 1000 cells/µL*	7.2 (2.0)	–	7.5 (0.1)	–	7.8 (2.1)	–	0.34
Heart rate, *beats/min*	73.1 (13.2)	–	73.4 (1.0)	–	70.9 (12.0)	–	0.38
Systolic blood pressure, *mm Hg*	131.3 (18.9)	–	129.9 (0.9)	–	131.5 (23.8)	–	0.97
Estimated glomerular filtration rate, *mL/min/1.73 m^2*	78.6 (28.1)	–	78.8 (1.1)	–	88.5 (35.4)	–	0.62
Albuminuria	–	139 (24)	–	19 (13–24)	–	7 (12)	0.047
History of diabetic complications	–	225 (40)	–	36 (30–42)	–	26 (46)	0.37
Macrovascular events	–	157 (28)	–	28 (23–33)	–	22 (39)	0.09
Microvascular events	–	110 (19)	–	14 (10–18)	–	14 (25)	0.35
High comorbidity*	–	269 (47)	–	42 (37–47)	–	36 (63)	0.02
Medications							
Metformin	–	275 (44)	–	51 (42–60)	–	18 (32)	0.02
Sulfonylurea	–	168 (29)	–	33 (25–42)	–	11 (19)	0.26
Thiazolidinedione	–	37 (6)	–	7 (4–11)	–	7 (12)	0.10
Dipeptidyl peptidase-4 inhibitor	–	31 (5)	–	7 (4–10)	–	1 (2)	0.23
Glucagon-like peptide-1–receptor agonist	–	5 (1)	–	0.4 (0–1)	–	0 (0)	0.48
Meglitinide	–	7 (1)	–	2 (0–4)	–	1 (2)	0.74
α-Glucosidase inhibitor	–	5 (1)	–	1 (0–2)	–	0 (0)	0.47
Insulin							
Basal	–	91 (16)	–	18 (12–23)	–	7 (12)	0.74
Short-acting bolus	–	14 (2)	–	2 (0.3–3)	–	2 (4)	0.63
Medium-acting bolus	–	66 (12)	–	11 (8–13)	–	8 (14)	0.64

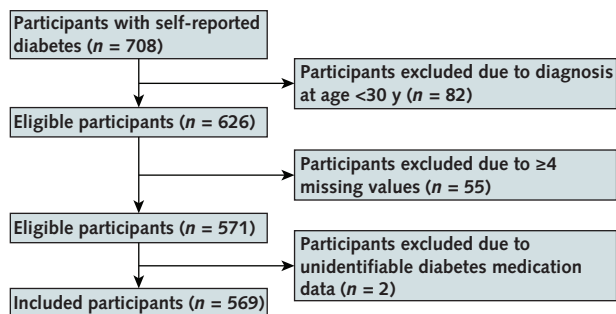HbA$_{1c}$ = glycated hemoglobin; NHANES = National Health and Nutrition Examination Survey.
* Comorbidity status was calculated by using a weighted combined Charlson Comorbidity Index score based on the patient's self-report of myocardial infarction, heart failure, stroke, lung disease, rheumatoid arthritis, liver disease, diabetes, and cancer (excluding skin cancer). A score <5 (vs. ≥5) indicated low (vs. high) comorbidity status (28).

Appendix Table 2. Comparison of Patient Characteristics From Multiple Imputation Data Sets

Variable	Imputation 1		Imputation 2		Imputation 3		Imputation 4		Imputation 5	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age, y	61.99	0.63	61.99	0.63	61.99	0.63	61.99	0.63	61.99	0.63
Female, %	0.50	0.02	0.50	0.02	0.50	0.02	0.50	0.02	0.50	0.02
Black race, %	0.17	0.04	0.17	0.04	0.17	0.04	0.17	0.04	0.17	0.04
HbA$_{1c}$ level, %	7.39	0.10	7.38	0.10	7.38	0.10	7.39	0.10	7.39	0.10
Duration of diabetes, y	9.71	0.42	9.71	0.42	9.71	0.42	9.71	0.42	9.71	0.42
Current smoker, %	0.17	0.02	0.17	0.02	0.17	0.02	0.17	0.02	0.17	0.02
Body mass index, kg/m^2	32.78	0.54	32.77	0.53	32.77	0.54	32.81	0.55	32.82	0.53
Low-density lipoprotein cholesterol, mmol/L	2.59	0.06	2.53	0.06	2.63	0.05	2.59	0.05	2.58	0.05
High-density lipoprotein cholesterol, mmol/L	1.20	0.01	1.20	0.01	1.19	0.02	1.19	0.01	1.19	0.02
Hemoglobin level, g/dL	13.72	0.12	13.72	0.12	13.72	0.12	13.72	0.12	13.72	0.12
Leukocyte count, × 1000 cells/μL	7.45	0.14	7.45	0.14	7.45	0.14	7.45	0.14	7.45	0.14
Heart rate, beats/min	73.15	0.94	73.11	0.96	73.27	0.96	73.38	0.97	73.19	0.96
Systolic blood pressure, mm Hg	130.12	0.89	129.82	0.89	129.76	0.92	129.60	0.89	129.72	0.93
Estimated glomerular filtration rate, mL/min/1.73 m^2	78.51	1.02	78.84	1.09	78.71	1.08	79.05	1.30	78.55	1.03
Albuminuria, %	0.19	0.03	0.19	0.03	0.19	0.03	0.19	0.03	0.19	0.03
Metformin, %	0.56	0.04	0.56	0.04	0.56	0.04	0.56	0.04	0.56	0.04
Sulfonylurea, %	0.35	0.04	0.35	0.04	0.35	0.04	0.35	0.04	0.35	0.04
Thiazolidinedione, %	0.08	0.02	0.08	0.02	0.08	0.02	0.08	0.02	0.08	0.02
Dipeptidyl peptidase-4 inhibitor, %	0.09	0.02	0.09	0.02	0.09	0.02	0.09	0.02	0.09	0.02
Glucagon-like peptide-1 receptor agonist, %	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Meglitinide, %	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01
α-Glucosidase inhibitor, %	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00
Insulin, %										
Basal	0.18	0.03	0.18	0.03	0.18	0.03	0.18	0.03	0.18	0.03
Short-acting bolus	0.11	0.01	0.11	0.01	0.11	0.01	0.11	0.01	0.11	0.01
Medium-acting bolus	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01

HbA$_{1c}$ = glycated hemoglobin.

Appendix Figure 2. Participant flow chart.

Participants with self-reported diabetes (n = 708)
→ Participants excluded due to diagnosis at age <30 y (n = 82)
Eligible participants (n = 626)
→ Participants excluded due to ≥4 missing values (n = 55)
Eligible participants (n = 571)
→ Participants excluded due to unidentifiable diabetes medication data (n = 2)
Included participants (n = 569)

Appendix Table 3. Model Cost and Utility Parameters

Definition (Reference)	Value
Medication costs (26)*	
Metformin	$835.18 per year
Sulfonylurea	$526.81 per year
Meglitinide	$3623.41 per year
Thiazolidinedione	$3237.94 per year
Dipeptidyl peptidase-4 inhibitor	$2891.02 per year
Glucagon-like peptide-1 receptor agonist	$4047.43 per year
α-Glucosidase inhibitor	$1124.29 per year
Bolus insulin†	$110.90 per 1000 units (vial) (rapid) $48.18 per 1000 units (vial) (short)
Basal insulin†	$48.18 per 1000 units (vial) (intermediate) $106.86 per 1000 units (vial) (long)
Self-monitoring costs	
Noninsulin (55)	$94 per year
Insulin (26)	$289 per year
Health care use costs	
Outpatient visit: noninsulin (55)	$500.39 per year
Outpatient visit: insulin (56)	$547.60 per year
Complication and hypoglycemia costs	
Nonfatal cardiac arrest or myocardial infarction (27)	$59 212.99 per event
History of cardiac arrest or myocardial infarction (27)	$1997.37 per year
Ischemic heart disease (27)	$22 455.72 per event
History of ischemic heart disease (27)	$1997.37 per year
Congestive heart failure (27)	$24 923.06 per event
History of congestive heart failure (27)	$1997.37 per year
Stroke (27)	$44 184.46 per year
History of stroke (27)	$16 302.06 per year
Amputation (27)	$9484.36 per event
Foot ulcer (27)	$2252.29 per event
Blindness (27)	$3002.35 per year
End-stage renal disease (27)	$82 659.01 per year
Severe hypoglycemic episode requiring emergency department visit (27)	$1375.29 per event
Severe hypoglycemic episode requiring hospitalization (27)	$17 286.06 per event
Severe hypoglycemic episode requiring physician visit (27)	$189.88 per event
Utility	
Diabetes (57)	0.863
Myocardial infarction (29)	0.945
Ischemic heart disease (29)	0.910
Congestive heart failure (29)	0.892
Stroke (29)	0.836
Amputation (29)	0.720
Foot ulcer (58)	0.830
Blindness (29)	0.926
End-stage renal disease with hemodialysis (59)	0.836
End-stage renal disease with peritoneal dialysis (59)	0.796
Mild/moderate hypoglycemia (60)	0.986
Severe hypoglycemia (60)	0.953
Oral diabetes medication (61)‡	0.977
Insulin (61)‡	0.966

* Average wholesale prices inflated to 2015 U.S. dollars (www.bls.gov/data/inflation_calculator.htm). Generic drug prices were used if available; otherwise, brand-name prices were used.
† Basal insulin was assumed to be for partial β-cell replacement at a rate of 0.3 unit per kilogram of body weight per day. Bolus insulin was assumed to be for complete β-cell replacement at a rate of an additional 0.3 unit per kilogram of body weight per day.
‡ A single utility value was used to indicate taking an oral diabetes medication or insulin, regardless of the actual number (or type) of medication being taken.

Type of Impact	Included in This Reference Case Analysis From Each Perspective		Notes on Sources of Evidence
	Health Care Sector	**Societal**	
Formal health care sector			
Health			
Health outcomes (effects)			
Longevity effects	Yes		UKPDS OM2, ADA/EASD guidelines
Health-related quality-of-life effects	Yes		Utilities from published literature
Other health effects	No		
Medical costs			
Paid for by third-party payers	Yes		Costs from published literature
Paid for by patients out of pocket	No		
Future related medical costs	Yes		Costs from published literature
Future unrelated medical costs	No		
Informal health care sector			
Health			
Patient-time costs	No		
Unpaid caregiver-time costs	No		
Transportation costs	No		
Non–health care sectors			
Productivity	No		
Consumption	No		
Social services	No		
Legal or criminal justice	No		
Education	No		
Housing	No		
Environment	No		

ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes; UKPDS OM2 = United Kingdom Prospective Diabetes Study Outcomes Model 2.

Appendix Table 5. One-Way Sensitivity Analyses: Individualized Versus Uniform Intensive Control

Scenario	Incremental Lifetime Costs, $*	Incremental Life-Years	Incremental QALYs
Medication changes HbA$_{1c}$ level			
By 1.2%	−12 574	−0.17	0.06
By 0.8%	−12 520	−0.08	0.14
Medication increases hypoglycemic event rates			
By 20% more	−13 443	−0.11	0.10
By 20% less	−13 376	−0.09	0.10
Severe hypoglycemia increases health care use			
By 20% more	−13 983	−0.16	0.06
By 20% less	−12 911	−0.16	0.06
Costs of microvascular complications			
20% more	−12 993	−0.13	0.07
20% less	−13 228	−0.09	0.11
Costs of macrovascular complications			
20% more	−13 739	−0.14	0.08
20% less	−13 443	−0.10	0.11
Costs of hypoglycemic events			
20% more	−13 675	−0.13	0.08
20% less	−13 182	−0.10	0.10
Costs of diabetes medications			
20% more	−15 504	−0.08	0.12
20% less	−10 084	−0.12	0.09
Disutility due to microvascular complications			
20% more	−13 373	−0.10	0.10
20% less	−13 404	−0.08	0.04
Disutility due to macrovascular complications			
20% more	−13 560	−0.11	0.11
20% less	−13 600	−0.16	0.08
Disutility due to hypoglycemic events			
20% more	−13 295	−0.10	0.10
20% less	−13 134	−0.12	0.10
Discount rate			
1% annually	−13 826	−0.12	0.09
5% annually	−12 563	−0.09	0.11
Combination of utilities: additive method	Not applicable	Not applicable	0.12

HbA$_{1c}$ = glycated hemoglobin; QALY = quality-adjusted life-year.
* Expressed in 2015 U.S. dollars. Negative values indicate cost savings from individualized vs. uniform intensive control.