# Influence of Diabetes Complications on $HbA_{1c}$ Treatment Goals Among Older U.S. Adults: A Cost-Effectiveness Analysis

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*Diabetes Care 2019;42:1–7 | https://doi.org/10.2337/dc19-0381*


## OBJECTIVE

**Guidelines on the standard care of diabetes recommend that glycemic treatment goals for older adults consider the patient's complications and life expectancy. In this study, we examined the influence of diabetes complications and associated life expectancies on the cost-effectiveness (CE) of $HbA_{1c}$ treatment goals.**

## RESEARCH DESIGN AND METHODS

**We used data from the 2011 to 2016 National Health and Nutrition Examination Survey (NHANES) to generate nationally representative subgroups of older individuals with diabetes with various health states. We used the Centers for Disease Control and Prevention–RTI International diabetes CE model to estimate the long-term consequences of two treatment goals—a stringent control goal ($HbA_{1c}$ <7.5%) and a moderate control goal ($HbA_{1c}$ <8.5%)—on health and cost. Our simulation population represented typical patients, and all individuals in each health subgroup had average characteristics, which did not account for person-level variations. The CE study was conducted from a health system perspective and followed the study samples over a lifetime. We used $50,000 per quality-adjusted life year (QALY) as the incremental CE threshold.**

## RESULTS

**A stringent goal was, on average, cost-effective for individuals with no complications ($10,007 per QALY) or only microvascular complications (excluding renal failure; $19,621 per QALY), but it was not cost-effective for individuals with one or more macrovascular complications (all >$82,413 per QALY). Further, a stringent goal was not cost-effective when an individual had less than 7 years of life remaining.**

## CONCLUSIONS

**Our findings support the guideline recommendation that glycemic goals for older adults should consider the complexity of their complications and their life expectancy from a CE perspective.**


Q:1

Most current clinical diabetes-related guidelines for $HbA_{1c}$ treatment goals recommend $HbA_{1c}$ of ~7% or lower in order to reduce microvascular and macrovascular complications for most nonpregnant adults with diabetes (1–6). Guidelines also recommend more stringent $HbA_{1c}$ goals for individuals with a short duration of

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*Received 22 February 2019 and accepted 21 August 2019*
*This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0381/-/DC1.*

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diagnosed diabetes, long life expectancy, and no cardiovascular disease (7,8). Several recent studies, however, have shown that $HbA_{1c}$ goals below 7% resulted in small or no clinical benefits, as measured in cardiovascular outcomes (9) and microvascular complications (10), with an unexpected escalation in mortality rate (9,11). The benefits of a more stringent glycemic treatment goal were even less certain in relation to preventing cardiovascular complications among an older population (12–14). In light of these study results, many clinical guidelines recommend a less stringent $HbA_{1c}$ goal (e.g., $HbA_{1c}$ <8.0%) for those with advanced complications and limited life expectancy (8).

Despite the widespread emergence of these individualized glycemic targets, no diabetes care guidelines on $HbA_{1c}$ treatment goals formally consider the cost-effectiveness (CE) of recommendations. Patient factors may affect CE, however, and such information can play a vital role in efficiently using limited resources for diabetes care. First, the clinical benefits of the same glycemic control goal may depend on the number and severity of patients' comorbidities. Those with multiple comorbidities are more vulnerable to adverse events such as hypoglycemia than patients with no or few comorbidities (15). In addition, because those with multiple comorbidities tend to have shorter life expectancies, they have fewer years in which to benefit from the long-term health and economic benefits of tighter glycemic control. The benefits of tighter glycemic control may take years to accrue before long-term diabetes-related complications are prevented or delayed.

Older adults (i.e., age ≥65 years) now comprise an important part (40%) of the population with diabetes (16). Older adults incurred ~ $146 billion (61%) of all health care costs attributed to diabetes in 2017 (17). Managing glucose levels in, or setting appropriate $HbA_{1c}$ treatment goals for, older adults is particularly challenging because of diabetes duration, comorbid conditions, acute and chronic microvascular and cardiovascular complications of diabetes, and life expectancy. In this study, we examined how the CE of glycemic control goals relates to complications in and the life expectancy of older U.S. adults at the level of the average population.

## RESEARCH DESIGN AND METHODS

### National Representative Simulation Samples

We used data from the 2011 to 2016 National Health and Nutrition Examination Survey (NHANES) to generate nationally representative simulation samples of individuals aged 65 years or older with diagnosed diabetes and varying health status. Diabetes status was identified by self-report or by an $HbA_{1c}$ laboratory result >6.5%. Our simulation population represented typical patients, and all individuals in each health subgroup had average characteristics, which did not account for person-level variations.

In this study, we evaluated two alternative glycemic goals that guidelines often recommend for adults aged ≥65 years with type 2 diabetes: a stringent glycemic goal ($HbA_{1c}$ <7.5%) and a moderate treatment goal ($HbA_{1c}$ <8.5%) (5,8). We quantified the complexity of complications by the number of macrovascular conditions, including stroke, angina, myocardial infarction (MI), and congestive heart failure (CHF). Microvascular complications included retinopathy and nephropathy. Macrovascular complications and retinopathy were identified by using a self-reported questionnaire. Nephropathy was identified on the basis of an estimated glomerular filtration rate <60 mL/min/1.73 $m^2$, which was calculated by using the MDRD study equation (18).

On the basis of diabetes complication status, we generated six nationally representative study samples: *1*) no microvascular/macrovascular complications; *2*) only microvascular complications, including nephropathy and retinopathy (end-stage renal disease was excluded because of the limited number of events); *3*) history of stroke; *4*) history of angina; *5*) history of MI; and *6*) history of CHF. During the simulation we estimated the life expectancy for each simulation sample on the basis of mortality rates from a U.S. life table among various age groups (Supplementary Appendix 3). We further adjusted these mortality rates by health conditions among the simulated individuals.

### Simulation Flow

The flow of the study design is summarized in Fig. 1. To estimate the CE of stringent glycemic control among adults older than 65 years with various health states, we applied the Centers for Disease Control and Prevention–RTI International type 2 diabetes CE simulation model (19) to each simulation sample. This model is an incorporated Markov cohort simulation model for diabetes progression and is widely applied in CE analysis of various interventions for populations with prediabetes (20–22) and diabetes (19). The model has been validated against 24 clinical trials and cohort studies, several of which focused mostly on the elderly population (23). More details regarding the structure of the simulation model can be found in Supplementary Appendices 2 and 3.

For each of the six simulation samples, the CE model simulated the progression of diabetes and calculated the lifetime costs and health benefit gained by two alternative glycemic control targets ($HbA_{1c}$ <7.5% or <8.5%). We conducted the simulation experiment following a classic treat-to-target design in which individuals met their $HbA_{1c}$ target over time by escalating their treatment. In other words, each individual had a constant $HbA_{1c}$ value over time set to the cohort's goal and was assigned a drug escalation pattern, extracted from the NHANES data, in order to maintain that $HbA_{1c}$ goal. We calculated the incremental CE ratio (ICER) as the difference between the lifetime medical costs and the health benefit gained with the two glycemic control goals. In this study we used the Mount Hood Diabetes Challenge Network's checklist for model input to ensure the transparency of the simulation report (24). Details are reported in Supplementary Table 8.

### CE of $HbA_{1c}$ <7.5% vs. <8.5%

We measured the ICER in costs per quality-adjusted life year (QALY). The study examined a lifetime time period to account for the long-term health and economic benefits of the intervention. Costs and QALYs were discounted at 3% annually. We used a conventional $50,000 per QALY as the CE threshold.

### Cost

Because our study took a health care system perspective, when estimating costs we included only intervention costs and direct medical costs associated with treating diabetes and related complications. We used meta-analysis to

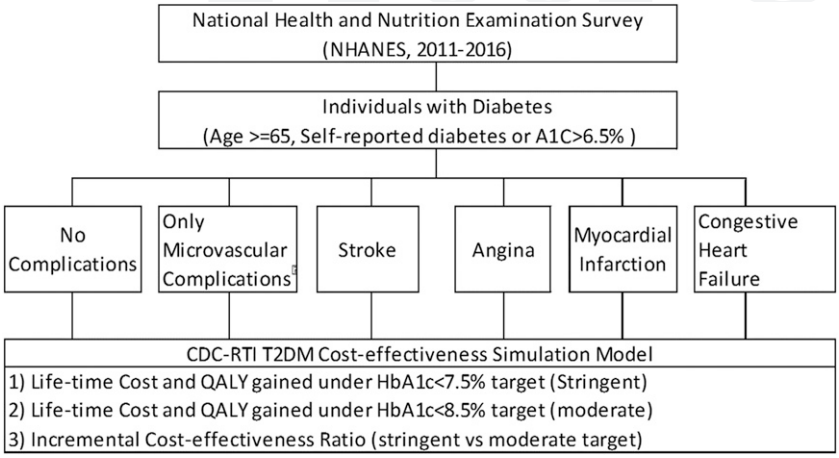



**Figure 1**—Logistic flowchart of study design. CDC-RTI, Centers for Disease Control and Prevention–RTI International; T2DM, type 2 diabetes.

synthesize the costs for angina, MI, CHF, and lower extremity amputation from current literature and from cost records from the Health Care and Utilization Project (2013). We also used meta-analysis to synthesize statistics from published articles to account for annual costs of other health states. Details are summarized in Supplementary Table 1.

The costs of treating diabetes were divided into three components: drug costs, outpatient visit costs, and self-testing costs. For drug costs, we adopted a joint approach using drug use patterns from NHANES data (2011–2014, identified by using Multum therapeutic classification codes) and retail price information from Costco Wholesale Corp. Details are provided in Supplementary Tables 2 and 3. For outpatient visit costs, following Dong et al. (25), we assumed that non–insulin users made four office visits per year when receiving moderate treatment and seven office visits per year when under stringent glycemic control. Insulin users under moderate control made five office visits per year, and those under stringent control made eight office visits per year. The costs of each visit follow the same algorithm we applied in our previous publication using the 2012 Medicare fee schedule, where the cost of a regular visit was estimated to be $58.26 and the cost of an annual visit, $128.17 (26). Thus, the annual cost for visits was $302.95 for a non–insulin user receiving moderate treatment, $477.73 for an insulin user receiving moderate treatment, $361.21 for a non–insulin user under stringent glycemic control, and $535.99 for an insulin user under stringent glycemic control.

In addition, self-testing is an important component of stringent glycemic control in the United States. We used data from the 2012 National Health Interview Survey diabetes supplement to estimate the frequency of self-testing (27). We found that, on average among the population with diabetes, insulin users conducted three self-tests daily and non–insulin users conducted one per day. Self-tests required glucose test strips, lancets, a glucose meter, and batteries. Using the 2018 Medicare fee schedule, we estimated the annual costs for self-testing for a non–insulin user and an insulin user; details can be found in Supplementary Table 4. After estimating costs for drugs, outpatient visits, and self-testing, we summarized those items to calculate the overall costs for treating diabetes in both groups (Supplementary Table 5). All costs were expressed in 2017 U.S. dollars and adjusted for inflation by using the Consumer Price Index.

### QALYs

Lifetime health benefits gained that were associated with each glycemic goal were measured in QALYs, which is a generic measure of both quality and quantity of life lived and is widely used in economic evaluations. We used the health utility values estimated by Herman and colleagues (28) to calculate QALYs in this study. Details of the equation have been described previously (28).

### Sensitivity Analysis

We performed a one-way sensitivity analysis to test the effect of parameter uncertainty on the lifetime costs and estimated QALYs gained. Each cost parameter in this study varied from 50 to 150% of its base case value (Supplementary Table 7). In addition, we tested whether differences in the risk of hypoglycemia between the two groups would influence our CE results. We assigned to the intensive treatment arm an incremental hypoglycemia frequency of 2.1% annually (observed from the Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial [29]). We extracted the QALY decrement for each hypoglycemic episode from the Health Utility Index diabetes complication equation (30), and we estimated the cost parameter from the study by Curkendall et al. (31). Moreover, we replaced Q:7 the QALY decrements for each complication used in the base case with the Health Utility Index diabetes complication equation; this allowed us to examine whether different QALY equations influence the CE results. Last, we assigned an additional 0.004 QALY decrement to insulin therapy, which is associated with potential weight gain estimated from a meta-analysis conducted by Deng et al. (32).

## RESULTS

### Main Analysis

Demographic characteristics and history of complications among the simulation samples are summarized in Supplementary Table 6. The CE of $HbA_{1c}$ <7.5% vs. <8.5% was associated with the patients' complication status (Table 1). For individuals without a history of microvascular or macrovascular complications, an $HbA_{1c}$ goal <7.5% was associated with a $2,900 incremental cost and 0.288 incremental QALY gained, which resulted in an ICER of $10,000 per QALY. For those with a history of microvascular events, an $HbA_{1c}$ goal <7.5% resulted in a $4,700 incremental cost and 0.238 incremental QALY, with an ICER of $19,600 per QALY. For those with a history of angina, the corresponding incremental cost was $3,600; for MI the cost was $1,600, for CHF, $1,500; and for stroke, $10,600. The corresponding incremental QALYs were 0.046, 0.012, 0.010, and 0.065, respectively. $HbA_{1c}$ <7.5% yielded an ICER of

**Table 1—Results of a CE analysis among subpopulations with various health states**

| | Total cost (2017 US$) | Total QALYs gained | ICER (cost [$] per QALY) |
|---|---|---|---|
| No complications | | | |
| Moderate (A1C <8.5%) | 49,200 | 4.135 | 10,000 |
| Stringent (A1C <7.5%) | 52,100 | 4.423 | |
| Incremental* | 2,900 | 0.288 | |
| Microvascular complications | | | |
| Moderate (A1C <8.5%) | 63,600 | 3.728 | 19,600 |
| Stringent (A1C <7.5%) | 68,300 | 3.966 | |
| Incremental | 4,700 | 0.238 | |
| Angina history | | | |
| Moderate (A1C <8.5%) | 46,300 | 3.215 | 82,400 |
| Stringent (A1C <7.5%) | 49,200 | 3.250 | |
| Incremental | 2,900 | 0.035 | |
| MI history | | | |
| Moderate (A1C <8.5%) | 15,600 | 1.746 | 266,800 |
| Stringent (A1C <7.5%) | 18,000 | 1.755 | |
| Incremental | 2,400 | 0.009 | |
| CHF history | | | |
| Moderate (A1C <8.5%) | 29,100 | 1.559 | 336,000 |
| Stringent (A1C <7.5%) | 31,400 | 1.565 | |
| Incremental | 2,300 | 0.007 | |
| Stroke history | | | |
| Moderate (A1c <8.5%) | 123,500 | 2.968 | 104,100 |
| Stringent (A1c <7.5%) | 130,200 | 3.033 | |
| Incremental | 6,700 | 0.065 | |
| Two Macrovascular complications | | | |
| Moderate (A1C <8.5%) | 47,000 | 1.434 | 658,000 |
| Stringent (A1C <7.5%) | 49,700 | 1.438 | |
| Incremental | 2,700 | 0.004 | |
| Three Macrovascular complications | | | |
| Moderate (A1C <8.5%) | 51,100 | 1.108 | 1,365,600 |
| Stringent (A1C <7.5%) | 53,600 | 1.110 | |
| Incremental | 2,500 | 0.002 | |

*Incremental: stringent–moderate.

$82,400 per QALY for angina, $266,800 per QALY for MI, $336,000 per QALY for CHF, and $104,100 per QALY for stroke. For those with two or three macrovascular complications, the ICER of $HbA_{1c}$ <7.5% was $658,000 per QALY, and that for $HbA_{1c}$ <8.5% was $1,365,600 per QALY.

Figure 2 shows the ICER of $HbA_{1c}$ <7.5% vs. <8.5% associated with various life expectancies. We found that the ICER escalated exponentially as life expectancy decreased, and we fitted an exponential curve through observed data points to represent the corresponding relationship. The ICER exceeded the $50,000 per QALY threshold when the life expectancy decreased below 7 years.

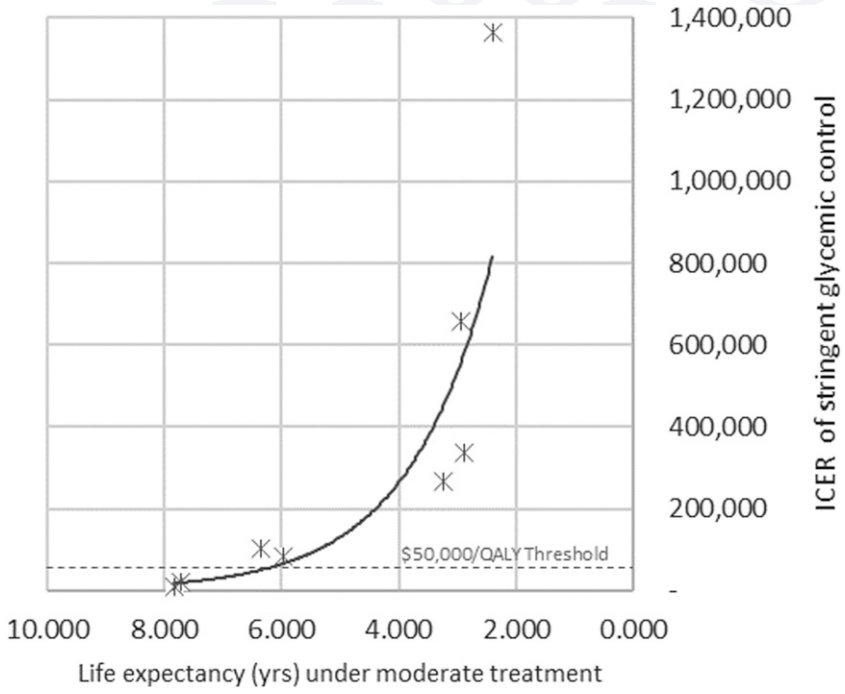
Using the threshold of $50,000 per QALY, a goal of $HbA_{1c}$ <7.5% was cost-effective among an older population with no or mild microvascular complications, but it was not cost-effective among those with any established macrovascular complications, including angina, MI, CHF, and stroke. We also found that a goal of $HbA_{1c}$ <7.5% was cost-effective only among those with a life expectancy more than 7 years.

### Sensitivity Analysis

Figure 3 summarizes the results of a one-way sensitivity analysis in six tornado diagrams for six corresponding subpopulations. We ranked variables from high to low according to their effect on the ICER; the blue bars represent the upper bounds of the results and the orange bars represent the lower bounds. Among all the separate analyses, our estimation of the annual drug costs had the highest impact on the ICER estimation. For a goal of $HbA_{1c}$ <7.5% for individuals without complications, 50% of base case cost estimation could potentially lead to a cost-savings scenario. We also found that a 50% reduction of base case drug costs could bring the ICER below the $50,000 per QALY threshold for individuals with a history of angina. Besides those two specific scenarios, our conclusion is robust to all other parameter estimates.

## CONCLUSIONS

Our study applied CE analysis to explore how the CE of glycemic goals changes with individuals' history of complications and life expectancy. We found that the CE of more stringent glycemic control depends on the number and severity of a patient's morbidity, conditions, and the Q:8 expected number of years to live. The goal of $HbA_{1c}$ <7.5% was cost-effective for patients with no diabetes-related complications or with only one microvascular complication (other than renal failure). The <7.5% goal was not cost-effective among patients with one or more macrovascular complications (all >$82,400 per QALY). Further, the




Q:14

**Figure 2**—Trend of ICERs (asterisks) among subgroups with various life expectancies. The curve was fitted on the basis of an exponential function of life expectancy on the ICER.

goal of $HbA_{1c}$ <7.5% was not cost-effective when the patient's life expectancy was less than 7 years. Thus, when setting glycemic control goals, and in order to efficiently use limited health care resources, those who guide diabetes treatment decisions need to consider the patient's number and severity of complications, and their life expectancy. This conclusion is better applied to individuals with average characteristics among each subgroup and might be influenced by other individualized characteristics. Because the CE results are estimated on the basis of model assumptions, they need to be interpreted carefully when being used to guide clinical practice.

Applying a more stringent glycemic control goal, such as $HbA_{1c}$ <7.5%, yields a more favorable cost-effective outcome among older adults with fewer complications or longer life expectancy, for two reasons. First, the incremental QALYs gained from stringent glycemic control need to accumulate over time and thus are closely associated with an individual's life expectancy. For example, the QALYs gained from an $HbA_{1c}$ control goal of <7.5% were estimated to be less than $10,000 per QALY among those with a life expectancy more than 7 years, but more than $20,000 per QALY among those with a life expectancy less than 5 years. In addition, applying an $HbA_{1c}$ control goal of <7.5% would yield a gain of 0.28 QALY among individuals without any complications and only 0.065 QALY among individuals with a macrovascular condition. Because macrovascular complications have larger effects on life expectancy than microvascular complications, those with a history of macrovascular complications had a shorter life expectancy than those with a history of only microvascular complications. Thus stringent glycemic control is preferred for individuals with no or only microvascular complications. Second, the savings from treating diabetes-related complications through tighter $HbA_{1c}$ control are higher among patients with fewer complications and a longer life expectancy.

Q:9

Our findings add CE data to strengthen further the current diabetes care guidelines for glycemic control among older U.S. adults, most of which also recognize less stringent glycemic targets among the older population and populations with complex health states. For example, a recent consensus report from the American Diabetes Association indicated that the 7.5% $HbA_{1c}$ target was applicable only to those with fewer than three comorbidities. For those with more complex health states, a less intensive treatment target (e.g., $HbA_{1c}$ <8.0% or 8.5%) should be applied (33). The Department of Veterans Affairs/Department of Defense guidelines recommend that the $HbA_{1c}$ target be based on life expectancy: individuals with a life expectancy more than 10 years, with or without mild

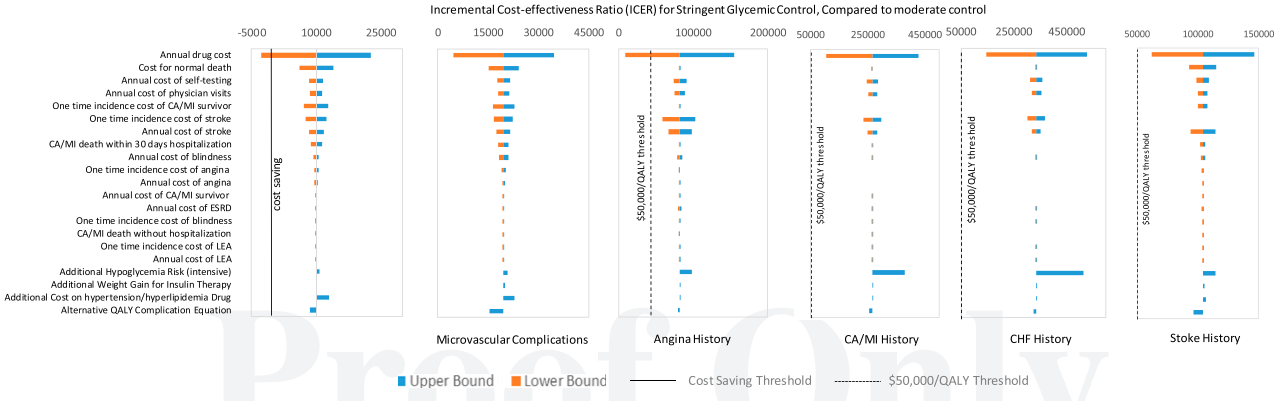



**Figure 3**—Results of a one-way sensitivity analysis of subpopulations with varying health states. CA, cardiac arrest; ESRD, end-stage renal disease; LEA, lower extremity amputation.

microvascular complications, should target an $HbA_{1c}$ level from 6 to 7%; individuals with established microvascular or macrovascular disease, or a life expectancy from 5 to 10 years, should target an $HbA_{1c}$ level from 7 to 8.5%; and individuals with a life expectancy less than 5 years should target an $HbA_{1c}$ level from 8 to 9% (4). The American College of Physicians guideline also recommends that for individuals with a life expectancy less than 10 years, clinicians should prioritize minimizing symptoms related to hyperglycemia, instead of targeting $HbA_{1c}$ levels to a specific range, because the negative outcomes of the former outweigh the benefits of the latter in this specific population (5). Our findings generally agree with the recommendations from these main guidelines. Although the base case analysis did not account for the potential escalated risk for hypoglycemia under the stringent A1C goal (compared with the moderate goal), we included this comparison in the sensitivity analysis. Our conclusions are robust for this parameter.

CE analysis can provide valuable information in determining the optimal target glycemic levels for patients with diabetes, especially when considering the continuous increases in the costs of medications used for glycemic control. The increase in the number of oral medications and insulin for glycemic control has made glucose management flexible, more complex, and sometimes controversial (34). Even small changes in recommended treatment targets, such as a 0.5% reduction in $HbA_{1c}$ at a population level, could mean billions of dollars in national health care costs. Our study results can be used to inform future glycemic treatment guidelines for older U.S. adults.

Recent studies have shown additional cardiovascular benefits of newer drugs in addition to lowering A1C. Although they aim at the same $HbA_{1c}$ target, competing drugs may yield different clinical benefits. Future research is warranted in order to explore clinical pathways that yield optimal CE when treating diabetes.

Q:10

Our study has several limitations. First, the simulation results are subject to the assumptions in the model. Because we developed the simulation model on the basis of data from multiple sources, the accuracy of the model relies heavily on the data quality and the techniques researchers applied in each source study. However, our previous validation study showed that the simulation model could achieve reliable prediction accuracy (23). Thus, we believe the economic inference drawn from our analysis is valid. Second, cohort-based data represent only the average effects of interventions among the general population and may not reflect individual-level variations. Individuals with the same demographic characteristics and disease history might have very different life expectancies because of other uncaptured factors such as terminal disease (e.g., cancer), medication choices, access to care, or genetic variations. Clinicians need to consider a patient's unique features when interpreting the results of this study. Third, we conducted the simulation under the assumption that all individuals would adhere to the assigned control level, which might not be true in the real world. Individuals who require stringent A1C control often have lower adherence than those who require moderate control. If that is the case, the estimated CE of stringent control might be even lower when patients drop out of the assigned treatment regimen and cannot achieve the designated clinical benefit. Also, it is critically important to take into account patients' preferences for treatment goals in clinical practice. Even a cost-effective treatment target might not be appropriate if the person is strongly against it. A previous study demonstrated the strong association between patients' characteristics and their preference for intensive care (35). As the older diabetes population is becoming more ethnically and racially diverse, more attention to patients' personal preferences is required when individualizing their treatment goals, because patient preferences substantially influence the CE of a treatment. Fourth, complication costs were estimated on the basis of current health care systems, and we assumed they will be stable in the future. Although this approach has been widely applied by other modeling studies, this assumption can be violated if essential changes emerge from factors such as medical technology. Fifth, because of our computational power constraints, we did not conduct a full probabilistic sensitivity analysis. Ideally, each model parameter would be sampled from the distribution and reflected in calculations of variations in lifetime costs and QALYs. Sixth, the model does not consider the biologic interactions between glycemic treatment and coexisting comorbidities. The simulation-based study is less costly than a clinical trial and provides insights into the lifetime intervention effect that real clinical trials often cannot afford, especially for national-level estimations. Seventh, health statuses for the simulation sample were collected through the use of a self-reported questionnaire. Recall bias might influence the predicted outcomes of the model. Eighth, the estimated life expectancy is endogenous for each complication group. It is possible that for certain patients (especially relatively healthier individuals with a history of only angina), targeting a stringent A1C goal might lengthen their life expectancy long enough to achieve cost-effective outcomes. This further highlights the importance of considering a patient's unique features when interpreting the results of this cohort-level simulation. Instead of providing an actual cut point with which to decide an appropriate treatment target for a patient, our study aims to illustrate how the CE of a stringent A1C goal changes as a patient's health condition declines. Last, the drugs included in this study came from 2011 to 2014 NHANES data. Newer drug classes (e.g., sodium-glucose cotransporter-2 inhibitors) with additional cardiovascular benefits have been introduced since then, and more individuals with diabetes have started to use them. Whether the use of newer drugs can produce cost-effective outcomes requires further exploration among the older population with diabetes.

In summary, our findings support the guideline recommendation that glycemic treatment goals among older adults should consider the complexity of a patient's complications and their life expectancy from a CE perspective. A moderate glycemic target such as $HbA_{1c} < 8.5\%$ might be more appropriate for those with limited life expectancy and complex comorbidities. This cohort-based study represents only the average effects of interventions on the general population; thus, when being used to guide clinical practice, patients' individualized features and preferences should also be considered.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported. Q:15

**Author Contributions.** H.S. analyzed data and prepared the results. H.S. and E.W.G. developed the manuscript. H.S. and P.Z. wrote the manuscript.

J.L., X.Z., and D.B.R. provided statistical support. E.W.G. oversaw the project. H.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Q:11

**Data Availability.** The data sets used for this study are publicly available and can be requested.

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# AUTHOR QUERIES

## PLEASE ANSWER ALL QUERIES 1

Q1: Do edits retain your intended meaning, here and in the first paragraph of the Research Design and methods section? (“Our simulation population represented typical patients, and all individuals in each health subgroup had average characteristics . . .”)

Q2: Do edits retain your intended meaning? (“The benefeits of . . . prevented or delayed.”)

Q3: Original reference 18 was a duplicate of reference 5 and was therefore deleted; the remaining references were renumbered, both in the text and in the reference list. Please verify changes.

Q4: What material does “Appendix 3” refer to? (The supplementary material provided includes one “Appendix” that contains 8 tables, a page of text, and 14 references; nothing seems to be labeled as “Appendix 3.”) Please provide updated files with the appendix material titled appropriately, or adjust to reflect the appropriate titles here.

Q5: What material does “Appendix 2” refer to? (The supplementary material provided includes one “Appendix” that contains 8 tables, a page of text, and 14 references; nothing seems to be labeled as “Appendix 2” or “Appendix 3.”) Please provide updated files with the appendix material titled appropriately, or adjust to reflect the appropriate titles here.

Q6: Please note that, per journal style, all references to “eTables” have been renamed as “Supplementary Tables.”

Q7: The original in-text citation for the reference “Suellen and colleagues (31)” has been changed to “Curkendall et al. (31)” to match the References section. Please check and verify this change.

Q8: What is meant by “the number and severity of a patient’s morbidity”? Do you perhaps instead mean something like “. . . the extent of a patient’s morbidity number and severity of their conditions, and the expected number of years to live”? Please check wording and amend as necessary.

Q9: The sentence “Because macrovascular complications have larger effects . . . only microvascular complications history” seemed to repeat almost verbatim the sentence just above, it has been deleted here.

Q10: Do edits retain your intended meaning? (“Although they aim at the same $HbA_{1c}$ target, competing drugs may yield different clinical benefits.”)

Q11: Please check and verify the listed author contributions are set correctly.

Q12: Please provide source details (e.g., a URL and access date?) for the item cited in reference 27.

Q13: Please provide a page range for the article cited in reference 34, if available.

Q14: In the Fig. 2 legend, please verify that the asterisk-type symbols represent the ICERs.

Q15: Check that the conflict of interest information for each author is presented in full in the Duality of Interest section.

# AUTHOR QUERIES

**PLEASE ANSWER ALL QUERIES** **2**