

Modeling the economic impact of medication adherence in type 2 diabetes: a theoretical approach

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Aims: While strong correlations exist between medication adherence and health economic outcomes in type 2 diabetes, current economic analyses do not adequately consider them. We propose a new approach to incorporate adherence in cost-effectiveness analysis.

Methods: We describe a theoretical approach to incorporating the effect of adherence when estimating the long-term costs and effectiveness of an antidiabetic medication. This approach was applied in a Markov model which includes common diabetic health states. We compared two treatments using hypothetical patient cohorts: injectable insulin (IDM) and oral (OAD) medications. Two analyses were performed, one which ignored adherence (analysis 1) and one which incorporated it (analysis 2). Results from the two analyses were then compared to explore the extent to which adherence may impact incremental cost-effectiveness ratios.

Results: In both analyses, IDM was more costly and more effective than OAD. When adherence was ignored, IDM generated an incremental cost-effectiveness of \$12,097 per quality-adjusted life-year (QALY) gained versus OAD. Incorporation of adherence resulted in a slightly higher ratio (\$16,241/QALY). This increase was primarily due to better adherence with OAD than with IDM, and the higher direct medical costs for IDM.

Conclusions: Incorporating medication adherence into economic analyses can meaningfully influence the estimated cost-effectiveness of type 2 diabetes treatments, and should therefore be considered in health care decision-making. Future work on the impact of adherence on health economic outcomes, and validation of different approaches to modeling adherence, is warranted.

Keywords: economics, modeling, adherence, diabetes, cost-effectiveness

Introduction

Type 2 diabetes (T2D) presents a substantial health economic burden globally, and its prevalence and costs are only forecasted to increase in the coming years.^{1–3} Medication adherence, especially for patients with chronic diseases such as T2D, has long been viewed as a critical lever for improving outcomes and containing costs. Recent studies conclude that more than \$100 billion is spent each year in the US on hospitalizations that could have been avoided with optimal medication adherence.⁴ Indeed, growing evidence suggests that suboptimal T2D medication adherence eventually results in higher HbA_{1c} levels, complication rates, and costs. Conceptual frameworks have been developed to describe these interrelations and their effect on reimbursement policies.^{5–8}

In order to make appropriate judgments about resource allocation and cost-sharing (namely involving pharmaceuticals), decision-makers have progressively relied on health technology assessment and economic evaluation. The long-term impact of

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diabetes treatment on clinical outcomes, health events, quality-of-life (QoL), and costs is often mathematically modeled since notable complications may occur years after onset of diabetes.⁹ However, current models used in T2D economic analysis do not adequately address or explain incorporation of real-world factors which influence medication adherence. These factors are wide-ranging and include patient preferences and behaviors, health care system factors, practice guidelines and patterns, and treatment characteristics.^{8,10} The exclusion of these factors can lead to inaccurate estimates on the cost-effectiveness of diabetes therapies, and thereby result in misinformed reimbursement decisions affecting patient access to treatment.

Several diabetes medications now in development have been criticized for being too similar to each other and not offering significant clinical benefit over existing therapies.¹¹ However, most of these new therapies and delivery systems differ greatly in other “nonclinical” ways, such as their route of administration, dosing schedule/convenience, and device ergonomics, all of which may influence patient preferences and behaviors (hence, medication adherence).^{5,6,8} This highlights the increasingly important role that adherence could play in the health technology assessment of new anti-T2D therapies as they reach the market. In particular, this is noteworthy for injectable diabetes medications (IDM) (ie, insulin) versus oral antidiabetic (OAD) medications, since needle phobia, multiple daily injections, and varied dosing schedules (eg, meal timing) are inherently associated with IDM and may adversely affect adherence.⁵

There is substantial opportunity to improve the methods used to estimate the cost-effectiveness of T2D medications by considering medication adherence.^{8,9} The objective of this study was to develop and apply an approach to integrate adherence in an economic model of diabetes.⁸ In doing so, we compared the cost-effectiveness of IDM versus OAD before and after adjustment for adherence, hypothesizing that incorporation of medication adherence would reduce the cost-effectiveness of IDM versus OAD, since patients on IDM generally exhibit poorer adherence than OAD patients.

Research design and methods

We developed a novel approach to modeling medication adherence among T2D patients using conventional health economic techniques and software (Microsoft Excel and TreeAge Pro 2009). To test our approach, 2 separate economic analyses were conducted in a Markov/Monte Carlo format to provide a preliminary estimate of the impact of medication adherence on incremental cost-effectiveness ratios (ICERs):

- Analysis 1: Base-case modeling of IDM vs OAD
- Analysis 2: Adherence-adjusted modeling

Markov modeling in health care consists of developing a structure of a specified number of health states related to a given disease. Over time, patients will have a certain chance (or transition probability) to move from one health state to another.¹² This approach is particularly well suited for modeling chronic diseases, such as T2D, where numerous health states/complications exist and are repeatable, previous history of complications may impact future events, and where a long-term perspective for downstream outcomes is relevant. Monte Carlo simulations commonly serve as the analytic/mathematic engine to a Markov structure, as was done in our analyses. This allows for transition probabilities into and out of health states to be applied, including sensitivity analysis, whereby assumptions on reasonable variation for transition probabilities and the effects of random error may be accounted for.¹³

Base case model

The model we developed consists of major health states that define the natural history of T2D and are consistent with those seen in previous models (see Figure 1).^{10,14} These states include the various diabetes complications, such as end-stage renal disease (ESRD), lower-extremity amputation, cardiovascular and coronary artery disease (CVD/CAD), nephropathy, stroke, neuropathy, retinopathy, and major hypoglycemia.

In this model, patients receive either IDM (insulin in our example) or OADs, chosen as mutually exclusive comparators because of the inherent differences between them which readily impact adherence. Patients on both therapies begin at a baseline HbA_{1c} that is either <7% or ≥7%, and through subsequent annual iterations, may (1) remain in a ‘healthy’ state with controlled (<7%) or uncontrolled (≥7%) HbA_{1c}, (2) progress between T2D complication states (with controlled or uncontrolled HbA_{1c}), or (3) die. Probabilities for patients to move from one complication state to another are based on HbA_{1c} over time, since patients with controlled HbA_{1c} are much less likely to develop complications.^{10,14} Treatment effects (mean of -1.2% HbA_{1c} and -0.8% HbA_{1c} for IDM and OAD, respectively, to reflect greater potency of insulin use) were applied to assumed baseline HbA_{1c} means of 8.1% and 6.8% for patients modeled to HbA_{1c} ≥7% and <7%, respectively.^{14,15} An annual increase in HbA_{1c} – or “creep up” effect – of +0.14% per year was applied to initial levels of glycemic control to reflect the natural progression of underlying biological

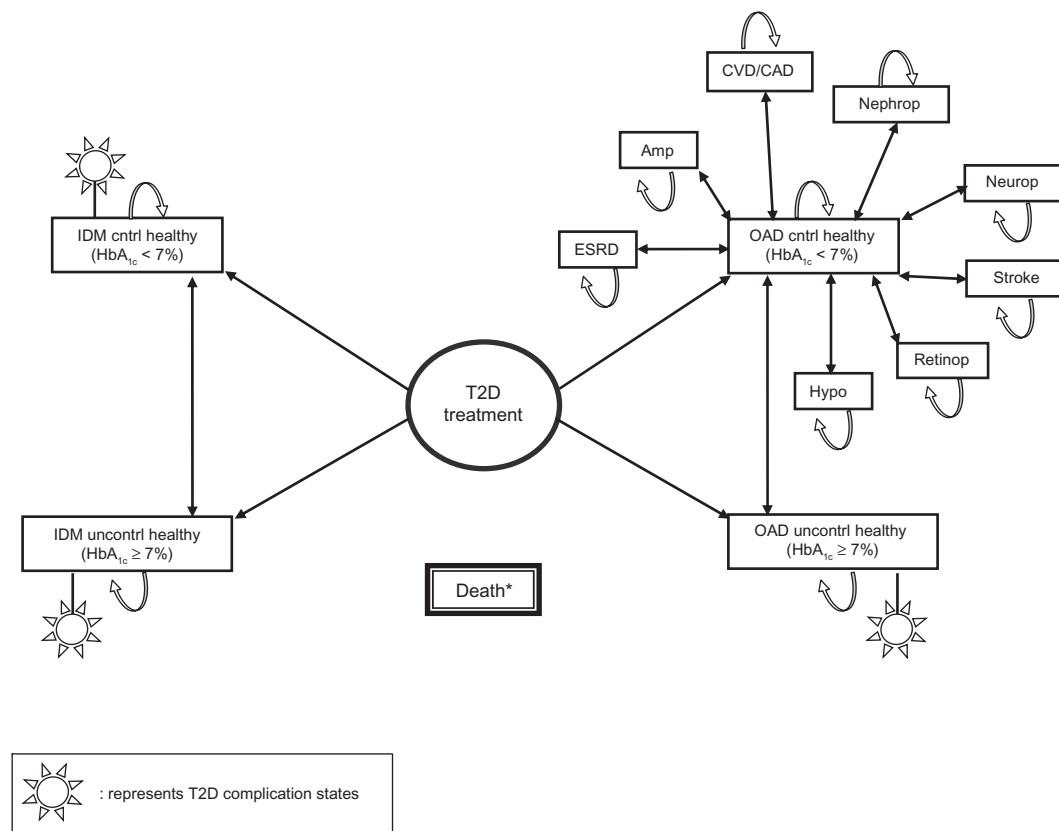


Figure 1 Base case model of fundamental T2D health states.

Notes: *Death = All-cause mortality adjusted for T2D/CVD severity.

Abbreviations: IDM, injectable diabetes medication; OAD, oral antidiabetic drug; CVD, cardiovascular disease; CAD, coronary artery disease; ESRD, end-stage renal disease.

mechanisms affecting glycemic control over time, such as beta-cell loss and reduced insulin sensitivity.^{10,14} In the base case scenario, approximately 50% fewer IDM patients were, on average, likely to have baseline HbA_{1c} <7% versus OAD patients, as those who are prescribed IDM frequently have further progressed, and/or more difficult to control, T2D.^{14–16} In both analysis 1 and analysis 2, the Death state may be transitioned to after any/all previous health state(s) and reflects all-cause mortality as well as adjustment for severity of T2D/CVD risk over time.

A lifetime (up to 35-year horizon), US third-party payer perspective was taken starting from the time of T2D treatment initiation.¹⁰ Cohort characteristics and transition probabilities were derived from large epidemiologic studies, clinical trials, and recent national surveillance data.^{10,14,15} Modeled output included life expectancy (LE), quality-adjusted life expectancy (QALE), cumulative incidence of T2D complications, direct medical and pharmacy costs, total lifetime costs, and ICERs.

Simulated cohorts and assumptions

The demographic and clinical characteristics used in the patient cohorts reflected those of typical US

T2D populations, including the percentage of patients receiving specific OADs and IDM, the percentage of patients with baseline HbA_{1c} <7% (for OADs 46.6%, for IDM 26.8%), age (mean of 51.1 years), gender (51.6% male), race/ethnicity (62.1% white, 17.4% black, 15.4% Hispanic, 5.1% other), presence of risk factors (eg, smokers 18.8%), and presence of preexisting complications.^{10,14–16}

The magnitude and duration of mean treatment effects remained consistent among IDM and OAD subclasses, and were extracted from large, long-term epidemiologic studies and literature reviews.^{10,14,15} Applied risk factors included BMI, total cholesterol, systolic blood pressure, triglycerides, and smoking.¹⁰

QoL utilities and disutilities for T2D health states were derived from previous studies.^{10,14} Mean pharmacy costs based on average 30-day wholesale price, and direct medical costs such as hospitalizations, were collected from published data and inflated to 2009 USD.^{5,6,10,15,17} Of the patients who received IDM, it was assumed that 70% of them were given human insulin and 30% analog insulin. Within the OAD cohort, 70% of the patients were assumed to receive generic

metformin ± sulfonylurea, and 30% nongeneric thiazolidinediones. This was done in analyses 1 and 2 to incorporate consistency for drug costs, and to approximate the use of generics in a real-world US scenario.^{18,19} A 3% discount rate for future costs and health was applied as a base case assumption; however, a range of 0%–6% was allowed during sensitivity analyses to address a range of variation in present value of benefits over time.¹⁰

Adherence-adjusted model and theoretical approach

As depicted in Figure 2, adjustments for adherence involved revisions to the degree of modeled glycemic control, risks of subsequent diabetes complications, and costs using current evidence on the impact of real-world medication adherence. Applied rates of adherence were primarily determined using medication possession ratios (MPR), and were derived from large observational studies.^{5–7,18–22} Just as the target of HbA_{1c} <7% was applied to model the impact of glycemic control in analysis 1, MPR (≥80%) was added and applied to model the influence of optimal versus suboptimal (MPR < 80%) adherence in analysis 2. New health states were created, where categorical levels of MPR were combined with categorical HbA_{1c} control, thereby enabling MPR to directly influence the likelihood of a patient moving to, and

remaining in, either of the HbA_{1c} categories (HbA_{1c} < 7% or HbA_{1c} ≥ 7%), and hence experience downstream T2D complications and costs. For example, recent data suggest that OAD and IDM patients with MPR ≥ 80% are more likely to achieve HbA_{1c} < 7%, have reduced incidence of hypoglycemia and related resource use, and incur lower health care costs.^{5,7,18–22}

Specifically, revised transition probabilities in the adherence-adjusted model include means and distributions regarding adherence to anti-T2D treatment, likelihood of achieving HbA_{1c} < 7%, and likelihood of major hypoglycemia. Up to 13% and 6% of patients on OADs and IDM, respectively, were allowed to exhibit MPR ≥ 80% (ranges: 36%–93% OADs, 54%–86% IDM). The chance of achieving target HbA_{1c} was approximately 28% greater for patients with MPR ≥ 80%, and the chance of major hypoglycemia was 64% lower for patients with MPR ≥ 80% (74% chance overall, but only 47% chance for optimal adherence; OR: 0.36, *P* < 0.01).^{5,7,18–22} Medication adherence in both groups was modeled to worsen over time, at –0.3% per year.^{6,14}

Statistical and sensitivity analyses

Probabilistic sensitivity analyses, wherein a range of distributions (uncertainty) for values of all input parameters are applied simultaneously, were conducted using cohort-level Monte Carlo

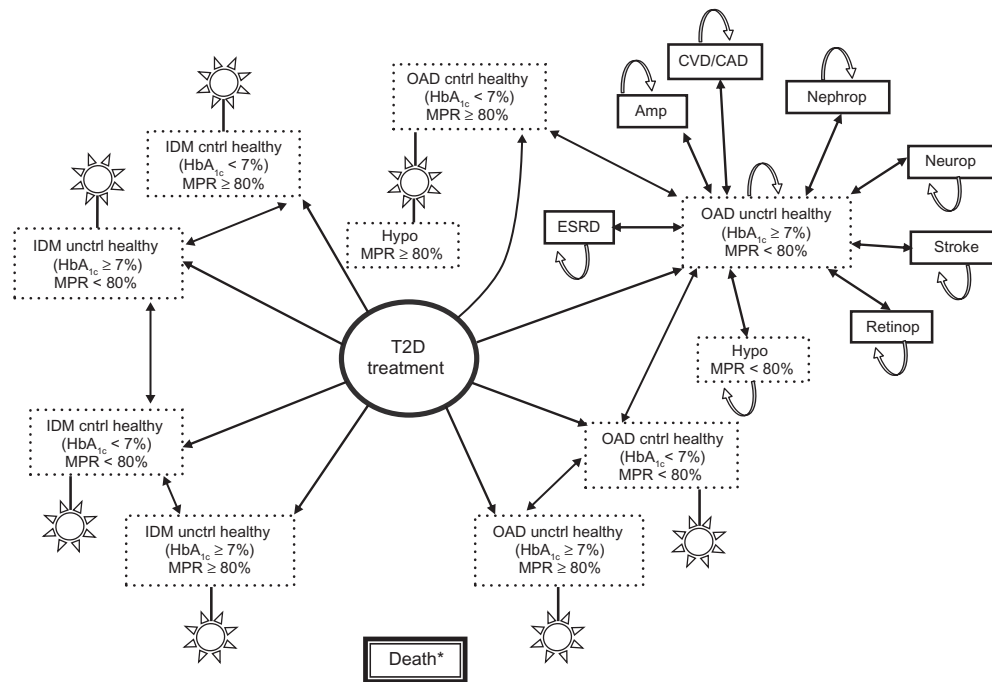


Figure 2 Adherence-adjusted approach at modeling T2D.

Notes: *Death = All-cause mortality adjusted for T2D/CVD severity.

Abbreviations: IDM, injectable diabetes medication; OAD, oral antidiabetic drug; CVD, cardiovascular disease; CAD, coronary artery disease; ESRD, end-stage renal disease; MPR, medication possession ratios.

simulation and bootstrapping. The progression of T2D was simulated in a 1000×1000 manner (each cohort of 1000 patients was simulated 1000 times), producing individual candidate bootstrap samples. The average costs and health for each cohort were first calculated, followed by an analysis of the 1000 average values (one per cohort). This resulted in means and standard deviations of the incremental costs, complication incidences, LE, and QALE for both IDM and OAD. Lastly, these means and standard deviations were calculated and compared for IDM versus OAD.

Results

Base case scenario: analysis 1

IDM use resulted in a longer LE (+0.56 years) and QALE (+0.92 years) than OAD use (Table 1). IDM also reduced

the rates of major hypoglycemia, ESRD, CVD/CAD, nephropathy, and neuropathy.

Although IDM resulted in greater clinical effectiveness, IDM patients also incurred higher costs (by \$11,166) than OAD patients, with pharmacy costs accounting for the majority (\$8,768) of this difference. The ICER for IDM versus OAD was \$12,097 per quality-adjusted life-year (QALY) gained, using total health care costs.

Adherence-adjusted model: analysis 2

After adjustment for adherence, IDM still led to a longer LE and QALE than OADs by +0.331 and +0.675 years, respectively, although the differences observed between IDM and OADs were smaller than without adjustment for adherence.

Table 1 Summary of modeled results: IDM vs OADs*

IDM vs OADs	IDM	OADs	Difference
Analysis 1			
Clinical outcomes, years			
Life expectancy (discounted)	16.376 (0.18)	15.815 (0.17)	0.561 (0.01)
Quality-adjusted life expectancy	10.554 (0.10)	9.631 (0.09)	0.923 (0.01)
Complication rates, cumulative incidence, % (SD)			
End-stage renal disease	17.6 (1.1)	18.1 (1.2)	-0.5 (0.1)
Amputation	13.4 (1.1)	13.8 (1.0)	-0.4 (0.1)
CVD/CAD	22.1 (1.3)	22.7 (1.5)	-0.6 (0.2)
Nephropathy	36.3 (1.6)	37.2 (1.6)	-0.9 (0.0)
Stroke	9.1 (0.9)	9.4 (1.0)	-0.3 (0.1)
Neuropathy	46.3 (1.6)	47.8 (1.5)	-1.5 (0.1)
Retinopathy	19.9 (1.3)	19.8 (1.3)	0.1 (0.0)
Major hypoglycemia	63.8 (1.9)	55.5 (1.8)	8.3 (0.1)
Cost outcomes, US\$			
Direct medical costs	241,304 (8122)	238,906 (8218)	2,398 (96)
Pharmacy costs	60,551 (2231)	51,783 (2004)	8,768 (227)
Total lifetime costs	301,855 (8933)	290,689 (8690)	11,166 (243)
\$/QALY (IDM vs OADs)	12,097		
Analysis 2			
Clinical outcomes, years			
Life expectancy (discounted)	16.562 (0.18)	16.231 (0.17)	0.331 (0.01)
Quality-adjusted life expectancy	10.848 (0.10)	10.173 (0.01)	0.675 (0.09)
Complication rates, cumulative incidence, % (SD)			
End-stage renal disease	17.0 (1.1)	17.3 (1.0)	-0.3 (0.1)
Amputation	13.3 (1.0)	13.6 (1.2)	-0.3 (0.2)
CVD/CAD	21.9 (1.4)	22.1 (1.3)	-0.2 (0.1)
Nephropathy	34.7 (1.4)	35.0 (1.4)	-0.3 (0.0)
Stroke	8.8 (0.8)	8.9 (0.8)	-0.1 (0.0)
Neuropathy	45.8 (1.7)	46.6 (1.7)	-0.8 (0.0)
Retinopathy	18.5 (1.2)	18.2 (1.1)	0.3 (0.1)
Major hypoglycemia	59.8 (1.8)	48.4 (1.6)	11.4 (0.2)
Cost outcomes, US\$			
Direct medical costs	244,112 (8034)	241,037 (8026)	3,075 (8)
Pharmacy costs	62,788 (2319)	54,900 (1996)	7,888 (323)
Total lifetime costs	306,900 (9155)	295,937 (8716)	10,963 (439)
\$/QALY (IDM vs OADs)	16,241		

Abbreviations: IDM, injectable diabetes medication; OAD, oral antidiabetic drug; CVD, cardiovascular disease; CAD, coronary artery disease; QALY, quality-adjusted life-year.

* Means with standard deviations (SD) from 1000 patients in each of 1000 cohort simulations are provided.

While gaps between IDM and OADs in the incidence rates of some complications shrank, the rate of major hypoglycemia increased.

Total costs remained higher for IDM than for OAD (+\$10,963) after incorporating adherence. The ICER of IDM versus OAD increased to \$16,241 per QALY gained, again using total costs.

Impact of adherence on modeled output

Adjustment for adherence affected the differences between IDM and OAD treatment in a number of ways, including (1) generating smaller differences in LE and QALE; (2) smaller differences in all complication rates except for major hypoglycemia, which increased by 3.1%; and (3) a 34.3% higher ICER for IDM versus OADs (\$16,241/QALY versus \$12,097/QALY).

Comparing analysis 2 with analysis 1, LE and QALE for OADs improved 45% and 54% more than for IDM, and the relative difference in rates of ESRD, amputation, and neuropathy between IDM and OADs narrowed by 40%, 25%, and 53%, respectively, and CVD/CAD, nephropathy, and stroke by 2/3 each.

Sensitivity analyses

Probabilistic simulations did not meaningfully alter ICERs for IDM versus OADs in analysis 1 or 2, indicating a sufficient approach at limiting modeled uncertainty. Our base case model generated a range of ICERs from \$7,155 to \$18,300/QALY, and our revised model generated a range of \$11,217 to \$23,892/QALY.

Discussion

Utilizing a Markov model of fundamental T2D health states, we specifically aimed to (1) describe a new approach for modeling medication adherence, and (2) illustrate its impact on estimated cost-effectiveness. Our simulations demonstrated that adherence may be meaningfully incorporated into comparative economic analysis through its associations with level of glycemic control, which has an important impact on the risk of downstream diabetes complications (eg, major hypoglycemia) and costs.

In the adherence-adjusted model (analysis 2), we observed an increased ICER, resulting from several sources. Most notably, LE and QALE increased by up to 54% more for OADs than for IDM (although both cohorts saw slightly higher values than in analysis 1). The main reason for this effect was the increased number of patients modeled to $HbA_{1c} < 7\%$ after stratifying by MPR, and thus experiencing less T2D complications and associated QoL disutilities

(ie, the range of applied MPR estimates caused up to 13% and 6% more OAD and IDM patients to have greater likelihood of $HbA_{1c} < 7\%$ in analysis 2). Secondly, although the differences for most complication rates between IDM and OADs decreased after adjustment for adherence, the difference in major hypoglycemia rates increased by 37%. Thirdly, a greater proportion of IDM lifetime costs were driven by direct medical costs, as opposed to pharmacy costs, after adjustment for adherence. These changes in modeled results likely occurred because more OAD patients were categorized into $MPR \geq 80\%$ than IDM patients, and they therefore experienced less risk of major hypoglycemia (and related QoL disutility) as well as a greater chance of $HbA_{1c} < 7\%$, resulting in fewer complications and increased QoL over time. Similarly, a higher frequency of $MPR < 80\%$ amongst IDM patients meant a higher risk of hypoglycemia, as well as a higher risk of other complications and higher costs. Furthermore, a balancing effect between greater treatment potency and overall poorer adherence likely occurred for IDM versus OADs. In this way, the greater HbA_{1c} -lowering effect of insulin, which would reduce complication rates and thereby improve health outcomes, may have been partially offset by a higher frequency of $MPR < 80\%$ and $HbA_{1c} \geq 7\%$, and thus a higher starting HbA_{1c} level in the first year of treatment.

It is important to note several limitations to our modeling approach. Although the simulated diabetes population in our analyses was intended to represent a typical US T2D population, our assumptions regarding transition probabilities, actual pharmacy costs, and QoL values may not have fully achieved this. However, it is important to note that the primary goal of this study was to illustrate how adherence may be included in diabetes health economic models, and to then estimate the impact of adherence on ICERs. Our goal was not to evaluate the cost-effectiveness of a specific treatment, nor to focus on a specific population. In keeping the treatments and simulated populations constant between analyses 1 and 2, the isolated effect on cost-effectiveness of modeled adherence was revealed. Although outside the scope of our current analysis, it is important to recognize the increasing evidence that T2D disproportionately affects minority subpopulations in the US. It would therefore be interesting and worthwhile to model the impact of adherence in these subpopulations in a future study. The choice to compare IDM with OADs as hypothetical therapies occurred solely because they clearly differ in treatment modalities which may impact degree of adherence. Although our model could have allowed switches to occur between OADs

and IDM throughout a patient's life, we chose not to allow these switches, since it would have complicated the model and would not have contributed to illustrating the potential effect of incorporating adherence. That is, the incorporation of treatment changes would have generated a "mixed effect" of the impact of medication adherence and the relative effectiveness of different treatment strategies at various points in a patient's disease progression. Thirdly, transition probabilities in the adherence-adjusted model are based largely on observational studies, which provide statistical associations that do not necessarily reflect cause-effect relationships. This underscores the importance of future work aimed at (1) developing more robust evidence on correlations between adherence and T2D outcomes, (2) identifying novel data sources and analytic techniques for observational, real-world research, and (3) further validation of different modeling approaches.

Modeling techniques worth exploring in future analyses include application of differential- and regression-based equations where adherence is a continuous parameter (variable) that influences glycemic control and complication rates over time, as opposed to a categorical approach, as was done in this study. Additionally, deterministic sensitivity analyses using point estimates could be performed to gain more direct insight into how much influence a specific input variable has, as opposed to allowing multiple parameters to vary simultaneously in a probabilistic sensitivity analysis. Lastly, it is important to note that although our adherence-adjusted approach produced an ICER that was approximately 34% higher than the ICER without adherence adjustment, IDM remained well within conventional thresholds of what is considered "good value for money", especially when considering preferences and trade-offs in health care from a US societal perspective (up to \$297,000/QALY).²³

Medication adherence is an important issue in chronic disease and, in particular, diabetes care. However, current economic models of diabetes pay too little attention to adherence, even though it may meaningfully influence the estimated cost-effectiveness of diabetes medicines. As new data and analytic techniques become available, and as new T2D compounds are commercialized, this will become increasingly important to inform health care decision-making for real-world settings.

Disclosure

The authors report no conflicts of interest in this work.

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