The Evaluation of Clinical and Cost Outcomes Associated with Earlier Initiation of Insulin in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND: The treatment for patients with type 2 diabetes mellitus (T2DM) follows a stepwise progression. As a treatment loses its effectiveness, it is typically replaced with a more complex and frequently more costly treatment. Eventually this progression leads to the use of basal insulin typically with concomitant treatments (e.g., metformin, a GLP-1 RA [glucagon-like peptide-1 receptor agonist], a TZD [thiazolidinedione] or a DPP-4i [dipeptidyl peptidase 4 inhibitor]) and, ultimately, to basal-bolus insulin in some forms. As the cost of oral antidiabetics (OADs) and noninsulin injectables have approached, and in some cases exceeded, the cost of insulin, we reexamined the placement of insulin in T2DM treatment progression. Our hypothesis was that earlier use of insulin produces clinical and cost benefits due to its superior efficacy and treatment scalability at an acceptable cost when considered over a 5-year period.

OBJECTIVES: To (a) estimate clinical and payer cost outcomes of initiating insulin treatment for patients with T2DM earlier in their treatment progression and (b) estimate clinical and payer cost outcomes resulting from delays in escalating treatment for T2DM when indicated by patient hemoglobin A1c levels.

METHODS: We developed a Monte Carlo microsimulation model to estimate patients reaching target A1c, diabetes-related complications, mortality, and associated costs under various treatment strategies for newly diagnosed patients with T2DM. Treatment efficacies were modeled from results of randomized clinical trials, including the time and rate of A1c drift. A typical treatment progression was selected based on the American Diabetes Association and the European Association for the Study of Diabetes guidelines as the standard of care (SOC). Two treatment approaches were evaluated: two-stage insulin (basal plus antidiabetics followed by biphasic plus metformin) and single-stage insulin (biphasic plus metformin). For each approach, we analyzed multiple strategies. For each analysis, treatment steps were sequentially and cumulatively removed from the SOC until only the insulin steps remained. Delays in escalating treatment were evaluated by increasing the minimum time on a treatment within each strategy. The analysis time frame was 5 years.

RESULTS: Relative to SOC, the two-stage insulin approach resulted in 0.10% to 1.79% more patients achieving target A1c (<7.0%), at incremental costs of $95 to $3,267. (The ranges are due to the different strategies within the approach.) With the single-stage approach, 0.50% to 2.63% more patients achieved the target A1c compared with SOC at an incremental cost of -$1,642 to $1,177. Major diabetes-related complications were reduced by 0.38% to 17.46% using the two-stage approach and 0.72% to 25.92% using the single-stage approach. Severe hypoglycemia increased by 17.97% to 60.43% using the two-stage approach and 6.44% to 68.87% using the single-stage approach.

In the base case scenario, the minimum time on a specific treatment was 3 months. When the minimum time on each treatment was increased to 12 months (i.e., delayed), patients reaching A1c targets were reduced by 57%, complications increased by 13% to 76%, and mortality increased by 8% over 5 years when compared with the base case for the SOC. However, severe hypoglycemic events were reduced by 83%.

CONCLUSIONS: As insulin was advanced earlier in therapy in the two-stage and single-stage approaches, patients reaching their A1c targets increased, severe hypoglycemic events increased, and diabetes-related complications and mortality decreased. Cost savings were estimated for 3 (of 4) strategies in the single-stage approach.

Delays in treatment escalation substantially reduced patients reaching target A1c levels and increased the occurrence of major nonhypoglycemic diabetic complications. With the exception of substantial increases in severe hypoglycemic events, earlier use of insulin mitigates the clinical consequences of these delays.

J Manag Care Pharm. 2014;20(9):968-84

What is already known about this subject

- American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines on treatment of type 2 diabetes mellitus (T2DM) follow a stepwise progression that escalates treatment according to the hemoglobin A1c levels.
- Oral antidiabetics and noninsulin injectable treatments, such as metformin, GLP-1 RAs, and DPP-4is, are subject to eventual loss of effectiveness that is known as A1c drift.
- Research shows that the average time from the initiation of T2DM treatment to the initiation of insulin therapy is approximately 8 years, long after indicated by A1c levels.

What this study adds

- Using the ADA and EASD treatment guidelines, this study created a Monte Carlo simulation model to estimate the clinical and cost outcomes of patients with T2DM over a 5-year period.
- When compared with current real-world practices, earlier initiation of insulin increased the number of patients reaching A1c targets, decreased diabetic complications and mortality, but increased hypoglycemic events. In some cases, the earlier initiation of insulin was cost saving.
- Delays in treatment escalation substantially increase diabetic complications and mortality.

Current treatment guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[1] focus on achieving and maintaining tight control of hemoglobin A1c for patients with type 2 diabetes mellitus (T2DM). Numerous studies have established that reductions in A1c levels decrease both macro- and microvascular complications.[2-4]

The ADA-EASD treatment guidelines follow a stepwise additive progression, based on changes to patient A1c levels over 3-month intervals.[1] Typically, the first step is metformin; the second step is metformin + sulfonylurea; and the third step adds an oral therapy (a dipeptidyl peptidase 4 inhibitor [DPP-4i] or a thiazolidinedione [TZD]) or a noninsulin injectable (glucagon-like peptide-1 receptor agonist [GLP-1 RA]). When the third step fails to achieve or maintain the desired A1c level, the fourth step adds basal insulin and removes sulfonylurea. Fourth-step failure leads to step 5, which is metformin + basal + prandial (bolus) insulin.[1]

Oral antidiabetics (OADs) and noninsulin injectables, although initially efficacious, are not a durable solution for most patients. Multiple studies[5-8] show a pattern of efficacy for OADs and noninsulin injectables characterized by the following: (a) an initial precipitous drop in A1c postinitiation; (b) a brief plateau in A1c, followed by (c) a gradual increase in A1c (referred to as A1c drift). A1c drift occurs because of loss of β cell function (see Kahn et al. 2006[9]) or insulin sensitivity. This A1c drift exposes the patient to elevated risks of macrovascular and microvascular complications.

The A1c drift that occurs with an appropriately titrated dosage of basal insulin + OADs or noninsulin injectables is typically less than with OADs and/or noninsulin injectables (see Appendix A). With appropriate monitoring and titration, basal + bolus insulin therapy should be subject to even less or no A1c drift so that the risk of complications may be ameliorated.

The primary objective of this study was to estimate the clinical and cost outcomes of initiating insulin treatment for T2DM patients earlier in their treatment progression. Our secondary objective was to determine how HbA1c drift combined with delays in treatment escalation affect clinical outcomes and payer costs. The hypothesis was that earlier use of insulin may produce benefits due to its efficacy and treatment scalability at an acceptable cost when considered over a 5-year period.

Methods

Model Overview

We developed a Monte Carlo microsimulation model to estimate clinical and cost outcomes for patients newly diagnosed with T2DM under various treatment strategies. The simulated population was a heterogeneous cohort of patients in the United States with respect to initial age (> aged 20 years), gender, ethnicity, and diabetes complication history. Model outputs included the number of patients reaching target A1c, major T2DM complications, mortality, and costs (total, pharmacy, and direct medical). The model time frame was 5 years (60 months) with a 1-month fixed time cycle length. Model input data and sources are listed in Appendix A.

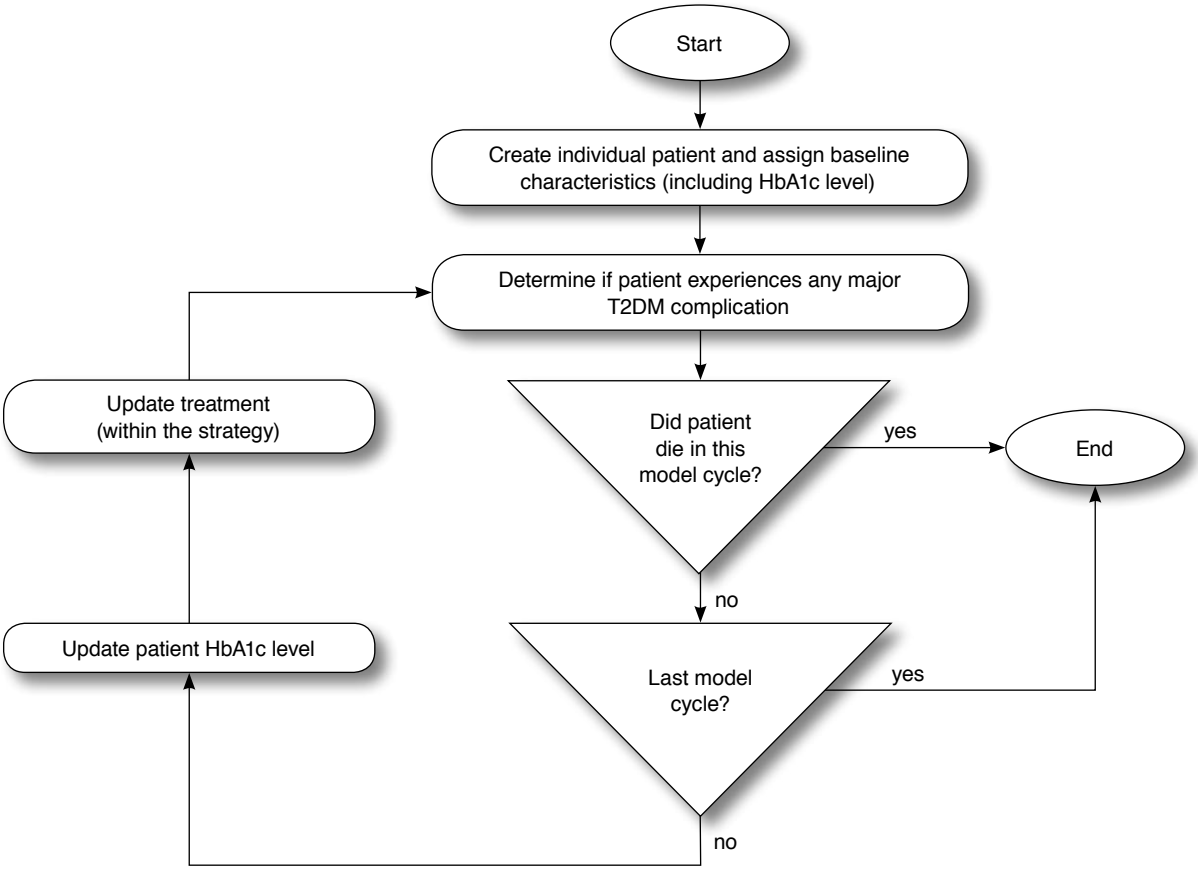
An overview of the model structure and flow is presented in Figure 1. First, the model creates an individual simulated patient and assigns baseline demographic and clinical characteristics. Next, the model determines whether in the current model cycle the patient experiences a major T2DM complication event. These events are severe hypoglycemia, myocardial infarction (MI), stroke, blindness, lower extremity amputation (LEA), and end-stage renal disease (ESRD). The event determination involves comorbidity submodels for nephropathy, neuropathy, retinopathy, stroke, coronary heart disease (CHD), and hypoglycemia. The submodels were adapted from models originally developed by the CDC Diabetes Cost-effectiveness Group.[10] The model then determines whether the patient dies in the current cycle. The probability that a patient dies in a particular cycle is a function of the patient's comorbidity-related mortality and overall natural mortality. If the patient dies during a particular cycle, then the patient exits the model.

If the patient does not die during a particular cycle, the model checks to see if the model time frame has expired. If not, the patient's A1c level is updated. This is determined by the patient's A1c level from the previous cycle, the patient's current treatment, and whether the patient has achieved durable control of A1c. Durable control is defined as the ability to maintain an A1c level below the target (7% for these analyses). The ADA-EASD guidelines recommend lowering A1c to < 7.0% in most patients.[1] They note that more/less stringent A1c targets be considered in patients based on their disease duration, life expectancy, diabetes-related complications, and other factors.

Next, the model determines whether the patient's treatment within a strategy is updated (escalated). Patients not achieving durable A1c control are subject to A1c drift after a specific period of time on treatment (a treatment modifiable model input). Once a patient's A1c fails to decline or remain below the A1c target for a prescribed amount of time (treatment specific), the patient will advance to the next step in the treatment progression (e.g., from metformin to metformin + sulfonylurea). This completes the patient cycle.

During a model run, each of the patients were cloned *n* times to correspond to *n* treatment strategies being compared, i.e., identical patients were simulated for each treatment strategy. Common random numbers were used with each cloned patient between treatment strategies to reduce extraneous sampling variation.[11]

FIGURE 1 Model Structure and Flow



HbA1c = hemoglobin A1c; T2DM = type 2 diabetes mellitus.

Treatment Strategies

In the model, we defined the T2DM standard of care (SOC) as the treatment progression presented in the first column in Table 1. Consistent with the ADA-EASD guidelines,[1] we defined 2 insulin-related steps within the SOC: the use of basal insulin with metformin plus DPP-4i, and the use of biphasic insulin with metformin. Alternatively, we could have chosen basal-bolus as the terminal insulin treatment. Biphasic insulin efficacy data was sourced from the 2007 Holman et al. study, which was a randomized, large (N = 708), and relatively long-term (1 year) study.[12] Furthermore, multiple studies have shown biphasic insulin to be as efficacious as basal-bolus insulin in reducing A1c in T2DM patients.[13-16]

Our selection of the SOC treatment pattern was taken from the ADA-EASD and American Association of Clinical Endocrinologists-American College of Endocrinology (AACE-ACE) guidelines.[1,17] It was intended to be representative of, rather than inclusive of, all possible T2DM treatment patterns referenced in the guidelines. Other treatment patterns using GLP-1s or TZDs, rather than DPP-4s, could have been evaluated as well. We chose DPP-4s because they represent the largest noninsulin treatment in sales volume for T2DM. The goal for this analysis was to base the SOC treatment strategy on a typically used pattern so the implications of earlier insulin usage could be examined in the most general context possible.

The treatment strategies simulated in the model are variations of the 5-step escalation pattern of the SOC. Two treatment strategy approaches were used (see Table 1). In Approach 1, steps 3, 2, and 1 were sequentially and cumulatively removed from the SOC, effectively moving the later (insulin) steps earlier in treatment pattern, that is, steps 1,2,3,4,5 (SOC); 1,2,4,5; 1,4,5; and 4,5. This is referred to as the two-stage insulin approach (steps 4 and 5). In Approach 2, step 4 (basal insulin) is excluded from all the strategies, that is, steps 1,2,3,5; 1,2,5; 1,5; and 5. The second approach is referred to as the single-stage insulin approach (step 5).

TABLE 1 Modeled Comparator Approaches—Approach 1: Two-Stage Insulin and Approach 2: Single-Stage Insulin

Standard of Care	Approach 1: Two-Stage Insulin[a]	Approach 2: Single-Stage Insulin[a]
1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	1. metformin 2. metformin + sulfonylurea 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 5. metformin + biphasic insulin
	1. metformin 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	1. metformin 2. metformin + sulfonylurea 5. metformin + biphasic insulin
	4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	1. metformin 5. metformin + biphasic insulin
		5. metformin + biphasic insulin

[a]*For Approach 1 and Approach 2, the numbering of the steps within a specific strategy is consistent with the numbering for the standard of care.*
DPP-4i = dipeptidyl peptidase 4 inhibitor.

Sources of Model Parameters

Demographic and Clinical. The model estimated the T2DM population by age (20-39, 40-64, and 65 or greater); race (non-Hispanic white, non-Hispanic black, Hispanic, and other); and gender. The general population demographic data came from the 2008 Current Population Survey.[18] T2DM prevalence data for the age, race, and gender groups came from National Health and Nutrition Examination Survey Data (NHANES)[19] and Danaei et al. (2009).[20] The primary source for major T2DM nonhypoglycemia complications was Valentine et al. (2006).[21] Data for estimating severe hypoglycemia came from Curkendall et al. (2011).[22]

Diabetic Comorbidity Submodels. The submodels for the T2DM comorbidities came from the CDC Diabetes Cost-effectiveness Group.[10] The submodels for CHD and stroke were adapted using transition probabilities from the United Kingdom Prospective Diabetes Study.[23] Relative risk reductions resulting from comorbidity treatments were based on data for nephropathy,[2,24] neuropathy and retinopathy,[2] stroke,[2,25] and coronary heart disease.[2,25-27]

Treatment. T2DM treatment efficacies used in the model were obtained from published randomized clinical trial data (see Appendix A). After initiation of a particular treatment (e.g., metformin + sulfonylurea), we split T2DM treatment efficacy into 2 segments. In the first segment, the A1c level decreases at a given rate for a specified time. In the second segment, the treatment becomes less efficacious and the patient's A1c level drifts upward. For each treatment, the model has distinct inputs for efficacy per month, months until A1c drift onset, and A1c drift per month.

The model allows the user to specify a minimum number of months on each treatment used. This represents the time a physician will allow a patient to remain on a specific treatment before considering an escalation. We used a minimum time on each treatment of 3 months in the base case analysis from the ADA-EASD guidelines (Inzucchi et al. 2012).[1]

Treatment adherence by ethnicity for T2DM was sourced from Suh et al. (2010)[28] and Rajagopalan et al. (2003).[29] Additionally, the first time a patient's A1c reached the defined target, the model probabilistically determined whether they will remain at target, that is, achieve durable control. This determination is based on probabilities by ethnicity from Suh et al.[28]

Associated with each treatment are an annual percentage of severe hypoglycemic events. Incidence and cost data for severe hypoglycemia events was sourced from Curkendall et al.[22] These events were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes from an analysis of commercial and Medicare databases. The severe hypoglycemia event costs used in the model were the weighted average of event-related costs for inpatient, emergency room plus inpatient, emergency room, and outpatient services.

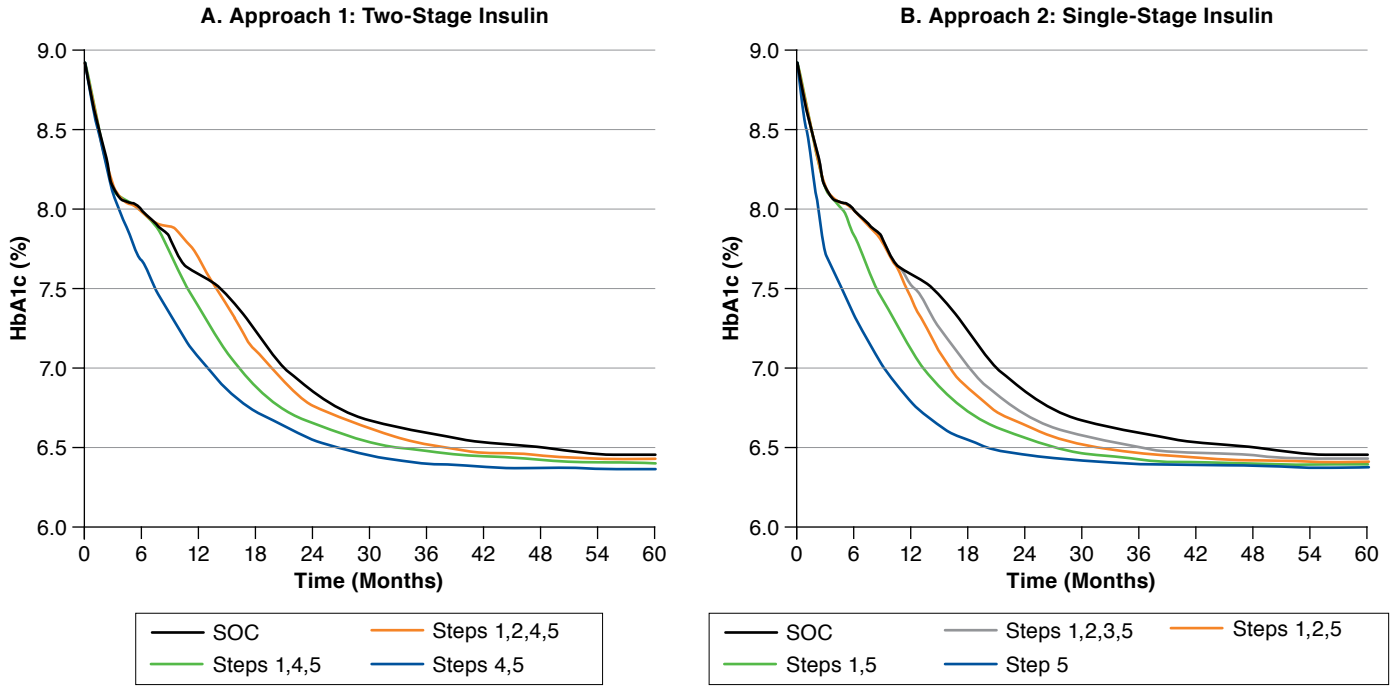
Costs related to nonhypoglycemic complications (e.g., nephropathy, neuropathy, and retinopathy) were based on direct medical costs using a model from Brandle et al. (2003).[30] The Brandle model uses a base cost and multipliers associated with identified patient characteristics. Annual direct medical costs for major events such as MI, stroke, and LEA were also taken from Brandle et al.[30] Annual drug costs were obtained from the Redbook[31] for each treatment. Where applicable, cost data were inflated to 2013 values.[32] Costs for physician visits were not included in the model. These costs would have been equal for both SOC and comparator treatments and thus would not have affected the incremental costs that were the focus of our analyses.

Results

Base Case

Table 2 and Table 3 present model clinical and cost outcome results. The results are presented as differences between SOC (steps 1,2,3,4,5) and each comparator strategy for simulated patients. The comparator strategies are grouped by Approach 1 (two-stage insulin, steps 4,5) and Approach 2 (single-stage insulin, step 5).

FIGURE 2 A1c Levels of SOC and Strategies in Approach 1 and Strategies in Approach 2 over Time



HbA1c = hemoglobin A1c; SOC = standard of care.

For Approach 1, relative to SOC, moving the two-stage insulin (steps 4,5) earlier in the treatment progression increased pharmacy and total costs (Table 3). It also increased severe hypoglycemic events (Table 2). However, it resulted in additional patients reaching target A1c, reductions in all major T2DM complications (i.e., MIs, strokes, blindness, LEAs, ESRD), and reductions in all-cause deaths. The incremental total cost per patient (%) was $95 (0.26%) for strategy I (steps 1,2,4,5); $1,164 (3.32%) for strategy II (steps 1,4,5); and $3,267 (9.05%) for strategy III (steps 4,5).

For Approach 2, step 4 (metformin + DPP-4i + basal insulin) was removed from all 4 strategies and the single-stage insulin (step 5) was moved progressively earlier in treatment. As steps 3, 2, and 1 are incrementally removed from the strategies, relative to SOC, there was an increase in the number of patients reaching target A1c, major T2DM complications prevented, and all-cause deaths prevented. Conversely, severe hypoglycemic events increased.

In Approach 2, relative to SOC, there were negative incremental total costs per patient (%), that is, cost savings—for strategies IV (steps 1,2,3,5); V (steps 1,2,5); and VI (steps 1,5)—of -$1,642 (-4.55%), -$1,602 (-4.44%), and -$612 (-1.70%), respectively. These savings were the result of lower pharmacy costs and reductions in nonhypoglycemic major T2DM complications. These reductions in complications occurred due to lower A1c levels resulting from initiating biphasic insulin (step 5) earlier in the treatment progression. Nevertheless, when the strategy consisted of only step 5 (metformin + biphasic insulin), there was a cost increase of $1,177 (3.26%). This was due to the increased number of severe hypoglycemic events and the use of the more expensive biphasic insulin at the start of treatment.

Recall that Approach 1 utilized two-stage insulin (steps 4 and 5) and Approach 2 utilized single-stage insulin (step 5). Accordingly, Approach 1's strategies I, II, and III are analogous to Approach 2's strategies V, VI, and VII, respectively (see Table 1 and Table 2). Approach 2's strategy IV is not analogous to any strategy in Approach 1. When comparing analogous strategies between Approach 1 and Approach 2, Approach 2 is superior in terms of patients reaching target A1c, nonhypoglycemic major T2DM complications prevented, and all-cause deaths prevented. Conversely, in each analogous case, Approach 2 is inferior in terms of additional severe hypoglycemic events.

Figure 2 displays the A1c curves versus time comparing the strategies within Approach 1 (Figure 2A, using two-stage insulin) and Approach 2 (Figure 2B, using single-stage insulin) to the SOC strategy. The horizontal axis represents the model time frame (60 months). Whether Approach 1 or Approach 2 is employed, the earlier insulin is initiated in the treatment

TABLE 2 Clinical Outcome Model Results: Patients Reaching Target A1c, Major T2DM Complications, and Mortality[a]

	Comparator Strategy	Patients Reaching Target A1c	Severe Hypoglycemic Events	MIs	Strokes	Blindness	LEAs	ESRD	All-Cause Deaths
	Standard of Care	**Base Case**							
0.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	93,905	21,570	7,154	2,644	3,547	3,900	88	21,407
	Approach 1: Two-Stage Insulin	**Incremental to Base Case**							
I.	1. metformin 2. metformin + sulfonylurea 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	93 (0.10%)	3,876 (17.97%)	-30 (-0.42%)	-10 (-0.38%)	-30 (-0.85%)	-32 (-0.82%)	-1 (-1.14%)	-20 (-0.09%)
II.	1. metformin 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	788 (0.84%)	6,976 (32.34%)	-101 (-1.41%)	-29 (-1.10%)	-190 (-5.36%)	-310 (-7.95%)	-5 (-5.68%)	-66 (-0.31%)
III.	4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	1,677 (1.79%)	13,034 (60.43%)	-190 (-2.66%)	-54 (-2.04%)	-413 (-11.64%)	-681 (-17.46%)	-12 (-13.64%)	-128 (-0.60%)
	Approach 2: Single-Stage Insulin	**Incremental to Base Case**							
IV.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 5. metformin + biphasic insulin	468 (0.50%)	1,390 (6.44%)	-62 (-0.87%)	-19 (-0.72%)	-113 (-3.19%)	-196 (-5.03%)	-4 (-4.55%)	-43 (-0.20%)
V.	1. metformin 2. metformin + sulfonylurea 5. metformin + biphasic insulin	721 (0.77%)	5,237 (24.28%)	-97 (-1.36%)	-33 (-1.25%)	-187 (-5.27%)	-290 (-7.44%)	-4 (-4.55%)	-69 (-0.32%)
VI.	1. metformin 5. metformin + biphasic insulin	1,486 (1.58%)	8,340 (38.66%)	-178 (-2.49%)	-46 (-1.74%)	-344 (-9.70%)	-584 (-14.97%)	-11 (-12.50%)	-119 (-0.56%)
VII.	5. metformin + biphasic insulin	2,470 (2.63%)	14,856 (68.87%)	-283 (-3.96%)	-76 (-2.87%)	-622 (-17.54%)	-1,011 (-25.92%)	-19 (-21.59%)	-194 (-0.91%)

[a]*Results presented as difference between SOC (steps 1,2,3,4,5) and each comparator strategy per 100,000 patients over a 5-year period. The percentages given represent the relative increase/decrease from the associated base case value.*

A1c = hemoglobin A1c; DPP-4i = dipeptidyl peptidase 4 inhibitor; ESRD = end-stage renal disease; LEA = lower extremity amputation; MI = myocardial infarction; SOC = standard of care; T2DM = type 2 diabetes mellitus.

progression, the quicker a steady-state A1c level is achieved at or below target. Reduction in time to target results in fewer nonhypoglycemic complications and reduced mortality (see Table 2).

Effects of Delaying Treatment Escalation

In the base case, we set a patient's minimum time on a particular treatment within a strategy to 3 months. In practice, however, for many patients with T2DM, the interval between treatment changes is substantially longer.[33-36] To examine the effects of these longer intervals, we estimated clinical and cost outcomes associated with minimum time on a treatment of 6 and 12 months.

The associated clinical outcomes of this sensitivity analysis are presented in Table 4. These outcomes show that as the time interval between treatment escalations within a strategy increases, the estimated number of T2DM major complications, except severe hypoglycemic events, increases. These increases are the result of longer periods of A1c drift and subsequent longer periods of recovery (from that drift) after the next treatment within a strategy is initiated.

As presented in Table 2 and Table 4, for the SOC treatment, the number of patients reaching the target A1c level is reduced by 57% with a minimum time on a treatment of 12 months versus 3 months. The complications associated with a 12-month minimum time on treatment also increased by 13% to 76% (depending on the complication). Severe hypoglycemic events, as expected, decreased substantially (83%) due to higher A1c levels.

Using the SOC, the model estimated 7,154 MIs at 3 months and 8,333 MIs at 12 months, respectively, of minimum time on treatment. As an example using Approach 1 and strategy I (steps 1,2,4,5), the model estimated 7,124 MIs at 3 months and 7,994 MIs at 12 months. Using Approach 1 and strategy III (steps 4,5), the model estimated 6,964 MIs at 3 months and 7,150 at 12 months. As insulin is applied earlier in each respective approach and strategy, the effects of delays in treatment escalation are mitigated, with the exception of major hypoglycemic events.

TABLE 3 Cost Outcome Model Results: Pharmacy Costs, Direct Medical Costs, and Total Costs[a]

Comparator Strategy		Pharmacy Costs Per Patient	Direct Medical Costs Per Patient	Total Costs Per Patient
	Standard of Care	**Base Case**		
0.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	$11,062	$25,028	$36,090
	Approach 1: Two-Stage Insulin	**Incremental to Base Case**		
I.	1. metformin 2. metformin + sulfonylurea 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	$89 (0.80%)	$6 (0.02%)	$95 (0.26%)
II.	1. metformin 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	$1,400 (12.66%)	-$235 (-0.94%)	$1,164 (3.23%)
III.	4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	$3,782 (34.19%)	-$515 (-2.06%)	$3,267 (9.05%)
	Approach 2: Single-Stage Insulin	**Incremental to Base Case**		
IV.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 5. metformin + biphasic insulin	-$1,478 (-13.36%)	-$165 (-0.66%)	-$1,642 (-4.55%)
V.	1. metformin 2. metformin + sulfonylurea 5. metformin + biphasic insulin	-$1,385 (-12.52%)	-$217 (-0.87%)	-$1,602 (-4.44%)
VI.	1. metformin 5. metformin + biphasic insulin	-$134 (-1.21%)	-$478 (-1.91%)	-$612 (-1.70%)
VII.	5. metformin + biphasic insulin	$1,996 (18.04%)	-$819 (-3.27%)	$1,177 (3.26%)

[a]*Results presented as difference between SOC (steps 1,2,3,4,5) and each comparator strategy per patient over a 5-year period. The percentages given represent the relative increase/decrease from the associated base case value.*

DPP-4i = dipeptidyl peptidase 4 inhibitor; SOC = standard of care.

Figure 3 shows the plots of A1c versus time for both Approach 1 (two-stage insulin) and Approach 2 (single-stage insulin) as the minimum time on a treatment is extended to 6 and 12 months, respectively. Comparing these plots to those in Figure 2, note that the time required to reach target A1c (7%) is substantially increased. When the minimum treatment duration of 3 months was used, the SOC reached the target A1c at approximately 22 months (Figure 2A). When the minimum time on a treatment of 6 and 12 months was simulated, the time to reach target for SOC increased to approximately 32 months and more than 60 months, respectively.

When the minimum time on treatment is set to 6 months, the escalation from metformin to metformin + sulfonylurea occurs at 6 months, and the escalation from metformin + sulfonylurea to metformin + sulfonylurea + DPP-4i occurs at 12 months (Figure 3A). The starting and ending mean A1c levels for metformin + sulfonylurea are 8.2% and 8.2%, respectively. With the minimum time on treatment set to 12 months, the metformin + sulfonylurea treatment starts at 12 months and ends at 24 months with mean A1c levels at 8.4% and 8.9%, respectively (Figure 3C). In both cases, the effectiveness of the treatment is lost due to the failure to escalate treatment to the next step in a timely manner (i.e., 3 months), allowing A1c drift to continue.

In Approach 1, the steps 4,5 treatment strategy takes 14, 15, and 22 months to reach the target A1c with a minimum time on treatment of 3, 6, and 12 months, respectively. In Approach 2, the treatment strategy step 5 takes 10 months to reach the target without regard to minimum time on treatment. Both strategies take substantially shorter time than SOC regardless of the delay of treatment escalation. As insulin is initiated earlier, the accumulated nonhypoglycemic complication risks associated with A1c drift in the SOC are reduced.

The cost outcomes estimated for the minimum time on treatment analyses are found in Appendix B. These cost outcomes follow the same general pattern. As delays in switching treatment increase, earlier use of insulin reduces T2DM complication costs because lengthy periods of A1c drift are eliminated (see Figure 3). These reductions offset the higher pharmacy costs of using insulin earlier in the treatment pattern and, in 11 of 14 cases, result in total cost savings.

TABLE 4 For Minimum Step Treatment Duration of 6 and 12 Months, Clinical Outcome Model Results: Patients Reaching Target A1c, T2DM Complications, and Mortality over a 5-Year Period[a]

	Comparator Strategy	Minimum Step Treatment Duration	Patients Reaching Target A1c	Severe Hypoglycemic Events	MIs	Strokes	Blindness	LEAs	ESRD	All-Cause Deaths
	Standard of Care	**Base Case**								
0.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 months	90,790	19,394	7,381	2,713	4,190	5,368	119	21,630
		12 months	59,700	11,758	8,333	3,032	7,278	16,396	351	23,203
	Approach 1: Two-Stage Insulin	**Incremental to Base Case**								
I.	1. metformin 2. metformin + sulfonylurea 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 months	1,116 (1.23%)	4,007 (20.66%)	-82 (-1.11%)	-30 (-1.11%)	-190 (-4.53%)	-438 (-8.16%)	-12 (-10.08%)	-76 (-0.35%)
		12 months	19,392 (32.48%)	5,410 (46.01%)	-339 (-4.07%)	-119 (-3.92%)	-1,092 (-15.00%)	-4,701 (-28.67%)	-103 (-29.34%)	-684 (-2.95%)
II.	1. metformin 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 months	2,844 (3.13%)	8,012 (41.31%)	-235 (-3.18%)	-74 (-2.73%)	-579 (-13.82%)	-1,286 (-23.96%)	-27 (-22.69%)	-214 (-0.99%)
		12 months	29,190 (48.89%)	12,077 (102.71%)	-848 (-10.18%)	-285 (-9.40%)	-2,631 (-36.15%)	-9,753 (-59.48%)	-209 (-59.54%)	-1,404 (-6.05%)
III.	4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 months	4,359 (4.80%)	14,900 (76.83%)	-381 (-5.16%)	-115 (-4.24%)	-949 (-22.65%)	-1,968 (-36.66%)	-40 (-33.61%)	-324 (-1.50%)
		12 months	33,586 (56.26%)	21,768 (185.13%)	-1,183 (-14.20%)	-391 (-12.90%)	-3,608 (-49.57%)	-12,115 (-73.89%)	-257 (-73.22%)	-1,765 (-7.61%)
	Approach 2: Single-Stage Insulin	**Incremental to Base Case**								
IV.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 5. metformin + biphasic insulin	6 months	1,136 (1.25%)	1,595 (8.22%)	-101 (-1.37%)	-33 (-1.22%)	-212 (-5.06%)	-490 (-9.13%)	-13 (-10.92%)	-85 (-0.39%)
		12 months	17,918 (30.01%)	1,752 (14.90%)	-299 (-3.59%)	-95 (-3.13%)	-909 (-12.49%)	-4,041 (-24.65%)	-93 (-26.50%)	-587 (-2.53%)
V.	1. metformin 2. metformin + sulfonylurea 5. metformin + biphasic insulin	6 months	2,272 (2.50%)	5,630 (29.03%)	-193 (-2.61%)	-66 (-2.43%)	-455 (-10.86%)	-989 (-18.42%)	-21 (-17.65%)	-173 (-0.80%)
		12 months	27,277 (45.69%)	7,470 (63.53%)	-674 (-8.09%)	-232 (-7.65%)	-2,075 (-28.51%)	-8,189 (-49.95%)	-175 (-49.86%)	-1,180 (-5.09%)
VI.	1. metformin 5. metformin + biphasic insulin	6 months	4,004 (4.41%)	9,835 (50.71%)	-363 (-4.92%)	-105 (-3.87%)	-853 (-20.36%)	-1,782 (-33.20%)	-36 (-30.25%)	-301 (-1.39%)
		12 months	32,864 (55.05%)	14,501 (123.33%)	-1,115 (-13.38%)	-371 (-12.24%)	-3,384 (-46.50%)	-11,672 (-71.19%)	-245 (-69.80%)	-1,700 (-7.33%)
VII.	5. metformin + biphasic insulin	6 months	5,585 (6.15%)	17,032 (87.82%)	-510 (-6.91%)	-145 (-5.34%)	-1,265 (-30.19%)	-2,479 (-46.18%)	-50 (-42.02%)	-417 (-1.93%)
		12 months	36,675 (61.43%)	24,668 (209.80%)	-1,462 (-17.54%)	-464 (-15.30%)	-4,353 (-59.81%)	-13,507 (-82.38%)	-282 (-80.34%)	-1,990 (-8.58%)

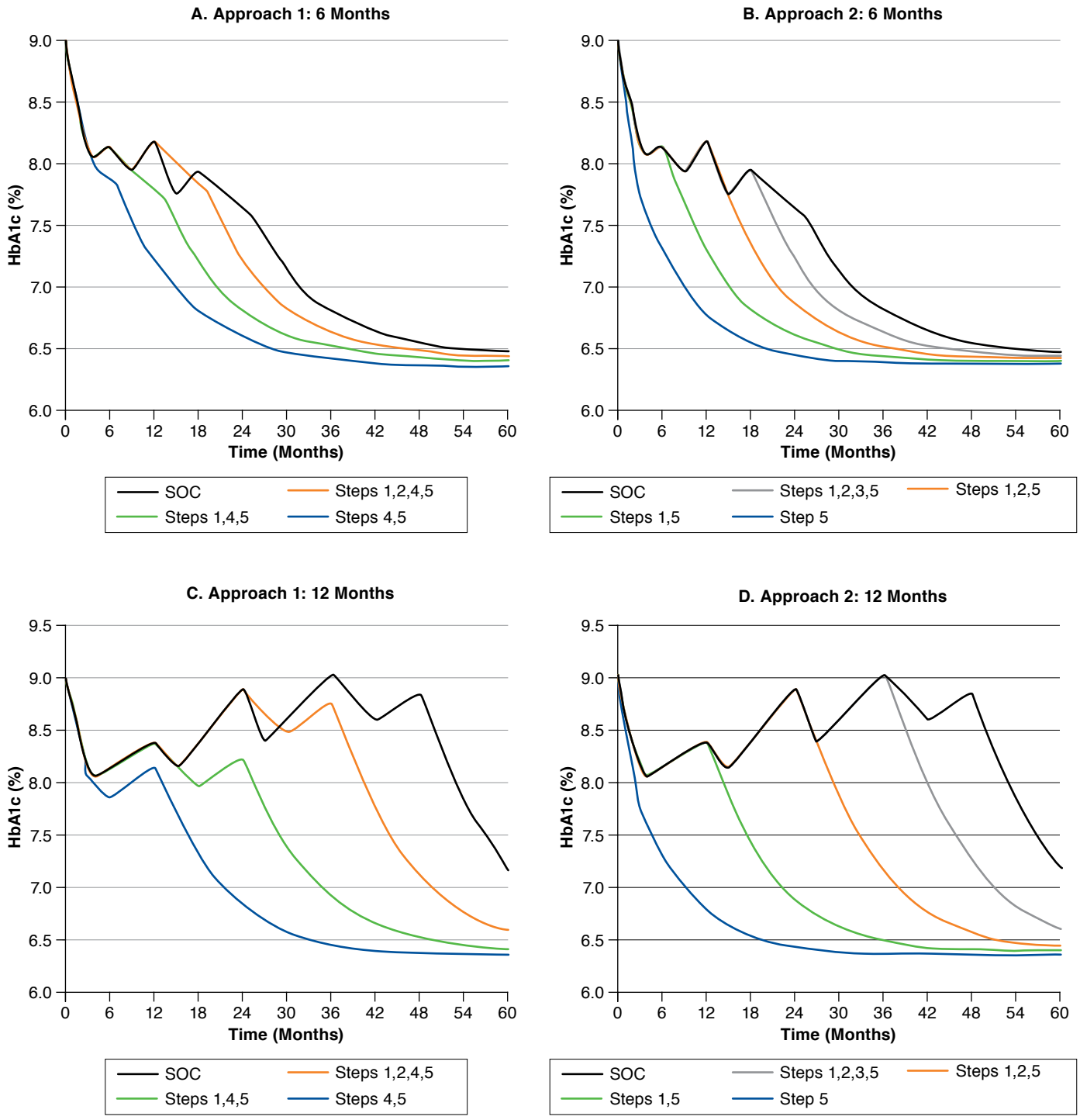
[a]*Results presented as difference between SOC (steps 1,2,3,4,5) and each comparator strategy per 100,000 patients over a 5-year period. The percentages given represent the relative increase/decrease from the associated base case value.*

A1c = hemoglobin A1c; DPP-4i = dipeptidyl peptidase 4 inhibitor; ESRD = end-stage renal disease; LEA = lower extremity amputation; MI = myocardial infarction; SOC = standard of care; T2DM = type 2 diabetes mellitus.

Discussion

The ADA-EASD[1] and the earlier AACE-ACE treatment guidelines[17] suggest that the initial treatment with insulin of T2DM patients with high A1c levels at diagnosis is a viable care option. Our analysis looked at the clinical and cost outcomes of that option, as well as the earlier use of insulin within ADA-EASD guidelines.[1] Treatment costs, efficacy, and estimated A1c drift for all treatments referenced in this study may be found in Appendix A. The costs of third-line noninsulin antidiabetics (e.g., DPP-4is, also GLP-1s and TZDs [not modeled]) are approaching and in some cases exceeding that for analog insulin treatments. Furthermore, these treatments lack insulin's efficacy, are subject to A1c drift, and do not have insulin's ability to have the dose precisely tailored. These factors motivated our interest in analyzing the outcomes of using insulin therapies earlier in T2DM treatment.

FIGURE 3 A1c Levels of SOC and Strategies in Approach 1 and Approach 2 with Minimum Time on a Treatment of 6 and 12 Months



HbA1c = hemoglobin A1c; SOC = standard of care.

Our results indicate that earlier use of insulin in patients with T2DM may provide significant clinical benefits through reductions in nonhypoglycemic major complications compared with the SOC treatment pattern examined. In some cases, by reducing such complications, the earlier use of insulin can save total costs in a 5-year period.

We selected well-documented studies with relatively similar trial populations across treatments to estimate treatment efficacy. Our choice of biphasic analog insulin as the basal-bolus treatment was based on data from Holman et al.[12] Other options, such as using basal and bolus insulin requiring separate injections[37] or use of a pump, are viable but not included in this analysis. The primary reason for the selection of data from Suh et al.,[28] Rajagopalan et al.,[29] and Curkendall et al.[22] was their use of large data sets (respectively, NHANES, Pharmetrics Patient Centric Database, and Thomson Reuters MarketScan) to generate estimates for critical parameters to our model.

We elected to use the 2007 Holman et al. study for the efficacy of metformin + biphasic insulin even though the vast majority of patients (over 90%) in the study used metformin + sulfonylurea + biphasic insulin. This decision was made for several reasons: (a) the Holman et al. study presented results for 1 year, providing a longer period to identify any potential for treatment-related A1c drift, which is considered a critical issue in our study; (b) the duration of diabetes in Holman et al. was 9 years, so the efficacy of sulfonylurea (or metformin) except for new users would have waned (and would have been countered with up titrated insulin); and (c) the length of the Holman et al. study allowed for time to titrate insulin dosage providing for a better estimation of insulin use.

We opted to use insulin studies where dosage was titrated, since rapid and controllable titration is a valuable benefit of insulin use. We elected not to use insulin studies with starting A1c levels higher than 9.0. The insulin studies we reviewed generally showed a higher efficacy in lowering A1c as the starting A1c level rose (see, for example, Kahn et al. 2006[9] or Kvapil et al. 2006[38]).

We used the minimum time on treatment as a proxy to estimate the impact of (patient and physician) controllable delays in escalating treatment of T2DM. Our results demonstrate that even a 3-month delay (from 3 to 6 months) in escalating treatment changes can have substantial clinical impact. Previous studies have suggested that these delays on any specific treatment can be as much as 3 years.[36] Our results indicate that the importance of reducing delays in modifying or changing treatments for T2DM patients is at least as important as treatment efficacy in improving patient outcomes. Insulin use is not subject to the eventual loss of effectiveness and subsequent A1c drift associated with other treatments and, hence, is less affected by these delays.

The number of patients reaching the target A1c level of < 7% over 5 years is important, but the time required for these patients to reach the target is equally critical to their accumulated risk for having major nonhypoglycemic diabetic complications. Reaching the target earlier substantially lessens the occurrence of these complications.

Subsequent to this analysis, the AACE released its most recent diabetic management algorithm.[39] The AACE treatment algorithm contains several differences to the ADA/EASD guidelines, most notably (with respect to the base case scenario evaluated here) the place and use of sulfonylureas in treatment. Regardless of which set of treatment recommendations or specific strategies are evaluated, the effects of A1c drift and the timing of treatment escalation affect clinical outcomes. The decision not to use a sulfonylurea after metformin would increase SOC costs as well as improve the clinical results for SOC for the base case.

Caution should be exercised when generalizing these results. We recognize that barriers to insulin use exist, which include cost, poor compliance with proper glucose monitoring, and aversion to self-injection.[40,41] For example, a patient not comfortable with insulin injections and/or maintaining a pattern of glucose self-monitoring would likely not be a good candidate for insulin use until it is clinically required. Patients unwilling or unable to work regularly with a treating physician to modify dosing as required might also not benefit from more immediate insulin therapy.

Limitations

As with all models, our model is an approximation of the real system and should serve as a supplement to, and not a replacement for, the knowledge of established relevant experts. Our model was based on large, long-term studies with designs reflective of the current standards of care. Study length of at least 24 weeks was especially important in the estimation of A1c drift for noninsulin treatments and the quantity of insulin used. We chose not to estimate efficacy based on a meta-analysis because a review of the literature found only a handful of studies with adequate length and similarity in baseline patient A1c levels across treatments. Such an approach always carries the risk of publication bias—that is, only studies with positive results of newer treatments are published and indeterminate or negative results are not published.

Our analysis did not account for every cost or clinical factor. The value of reduced mortality (end of life cost) or estimated added life years was not included in the model. We did not estimate a cost or savings associated with weight gain or loss on a specific treatment. Clinical benefits in the model were expressed in terms of complications and mortality. Our analysis did not apply any utility metric (e.g., quality adjusted life years) to patient events or outcomes.

Conclusions

Our analysis suggests that earlier insulin use has favorable clinical benefits and may reduce costs in specific cases. Our results also show that delays in making treatment changes as soon as indicated from patient A1c levels have significant clinical consequences. The earlier use of insulin will substantially reduce these consequences because it has very little or no A1c drift when properly titrated. The favorable profile we estimate from using insulin earlier in treatment can only be achieved for patients who can adapt to the discipline required by its use. As pointed out in both the ADA-EASD[1] and AACE-ACE[17] treatment guidelines, that determination requires thoughtful engagement by both the treating physician and the patient.

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DISCLOSURES

The model development and analysis reported in this article was funded by Eli Lilly & Company (Lilly). Medical Decision Modeling Inc. (MDM) does not have any contractual obligation to submit this manuscript to Lilly for prepublication approval. Lilly has reviewed this manuscript solely to ensure that no confidential information was disclosed. The model, analyses, and conclusions presented in this manuscript were developed solely by the authors.

MDM is a contract research organization that performs pharmacoeconomic research to evaluate current and prospective treatments for medical conditions. Smolen is President and CEO and a stockholder of MDM. Curtis is a current employee and stockholder of Eli Lilly and Company.

Concept and design for this study were contributed by Smolen, Murphy, and Curtis. Yu and Gahn collected the data, assisted by Murphy, and Gahn, Murphy, and Yu were responsible for interpretation. The manuscript was written by Smolen, Murphy, and Yu and revised by Smolen, Curtis, and Murphy.

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APPENDIX A Model Input Data

Parameter	Value			References
Patient demographic data				
Male (%)	49			19, 20
Age	**20-39 (%)**	**40-64 (%)**	**≥ 65 (%)**	
Male	8	57	35	
Female	7	53	40	
Non-Hispanic white male	58	68	77	
Non-Hispanic black male	16	14	11	
Hispanic male	21	14	9	
Other male	5	4	3	
Non-Hispanic white female	58	66	75	
Non-Hispanic black female	18	16	13	
Hispanic female	19	13	9	
Other female	5	5	3	
Lifestyle and disease management (%)				
Smoker	16			42
Outpatient diabetes management training	66			43
Type 2 diabetes-related medications (%)				
Antihypertensive agents	51			9
ACE inhibitor	41			21
Statin (lipid-lowering agents)	45			21
Cohort A1c				
Target A1c	≤ 7.0%			User input
A1c at diagnosis	**Mean (%)**	**Minimum (%)**	**Maximum (%)**	
Non-Hispanic white	8.9	6.5	15.2	28, 44
Non-Hispanic black	9.8	6.5	17.0	
Hispanic	9.8	6.5	17.0	
Other	9.9	6.5	17.1	
Clinical data	**Mean**	**Minimum**	**Maximum**	
Systolic blood pressure (mmHg)	135	110	190	45
Total cholesterol (mg/dL)	209	120	400	
High-density lipoprotein (mg/dL)	41	25	80	
Body mass index (kg/m^2)	32	20	50	21
Hypertensive (%)	40			46
Cohort initial diabetic-related complications (%)				
Retinopathy				21
No retinopathy	91			
Photo coagulation	9			
Blind	0			
Nephropathy				21
No nephropathy	92			
Microalbuminuria	4			
Clinical nephropathy	4			
End-stage renal disease	0			
Neuropathy				21
No neuropathy	76			
Peripheral neuropathy	23			
LEA	1			
Coronary heart disease				21
No CHD	87			
Angina	2			
History of MI/CA	11			
Stroke				
No stroke	91			
History of stroke	9			
Atrial fibrillation	7.6			47

APPENDIX A Model Input Data *(continued)*

Parameter	Value				References
Treatment effectiveness					
Treatment	**Efficacy (% per Month)**	**Months Until Drift Starts**	**Drift Rate (Absolute % per Month)**	**Annual Probability of Severe Hypoglycemia (%)**	
Metformin	1.86	4	0.0231	0.300	5, 22
Metformin + sulfonylurea	1.96	3	0.1036	0.896	7, 22
Metformin + DPP-4i	2.93	3	0.0200	1.862	22, 48
Metformin + GLP-1 RA	4.81	4	0.0271	1.862	5, 22
Metformin + basal insulin	1.45	6[a]	0.0245[a]	6.303	22, 49, 12[a]
Metformin + sulfonylurea + DPP-4i	3.60	3	0.0804	1.862	6, 22
Metformin + sulfonylurea + GLP-1 RA	4.94	4	0.1367	3.921	7, 22
Metformin + sulfonylurea + basal insulin	3.68	4	0.0546	7.263	7, 22
Metformin + DPP-4i + basal insulin	2.65	6	0.0200[b]	6.303	8, 22, 48[b]
Metformin + GLP-1 RA + basal insulin	5.71	4	0.0318	6.303	22, 50
Metformin + biphasic insulin	5.32	1,000[c]	0.0	8.790	12, 22
Metformin + basal + bolus insulin	5.55	1,000[c]	0.0	8.790	22, 37
Treatment adherence and diabetes management and control					
Probability adherent	**Non-Hispanic White (%)**	**Non-Hispanic Black (%)**	**Hispanic (%)**	**Other (%)**	28, 29
Any OAD	81	58	58	54	
Any insulin	62	45	45	42	
Patients with durability after reaching target	46	33	33	31	28
Multiplicative complications costs					
Annual direct medical costs (per patients)	$2,716				30
Cost multipliers					
Female	1.25				
BMI [=input^(BMI-30)]	1.01				
Antihypertensive agents	1.24				
Microalbuminuria	1.17				
Proteinuria	1.30				
End-stage renal disease	10.53				
Treatment of stroke	1.30				
Treatment of angina	1.73				
History of MI	1.90				
Peripheral vascular disease	1.31				
Annual costs (per patients)					
Antidiabetes agents	**Active Ingredient, Drug Name**	**Dosage (Unit/Day)**	**Annual Cost ($)**		
Metformin	Metformin, Metformin	1	72		31 (WACs)
Sulfonylurea	Glyburide, Teva	1	100		
DPP-4i	Sitagliptin Phosphate, Januvia	1	2,992		
GLP-1 RA	Exenatide, Byetta	1	5,979		
Basal insulin	Insulin detemir, (Levemir FlexPen)	55[d]	3,338		
Biphasic insulin	Insulin Aspart/Insulin Aspart Protamine, (Novolog Mix 70/30 FlexPen)	48[e]	3,452		
Basal + bolus insulin	Insulin glargine + Insulin glulisine, (Lantus solostar + apidra solostar)	49 + 49[f]	6,068		

APPENDIX A Model Input Data *(continued)*

Parameter	Value	References
Event costs		30
Acute stroke event cost	$42,907	
Acute MI/CA event cost	$39,520	
Acute LEA event cost	$60,651	
Adverse event costs		
Severe hypoglycemia	$1,165	22
Weight gain (at least 5 kg)	$0	
A1c and treatment-related relative risks		
Retinopathy		
A1c-related relative risk	37% decrease per 1% reduction in A1c	2
Nephropathy		
Hypertension treatment relative risk	52% if on an ACE inhibitor	24
A1c-related relative risk	37% decrease per 1% reduction in A1c	2
Neuropathy		
A1c-related relative risk (microvascular disease)	37% decrease per 1% reduction in A1c	2
A1c-related relative risk (peripheral vascular disease)	43% decrease per 1% reduction in A1c	2
CHD		
Cholesterol-controlled relative risk (first incidence of CHD)	69% if on a statin	26
Cholesterol-controlled relative risk (subsequent CHD)	75% if on a statin	27
Hypertension treatment relative risk	79% if on antihypertensive agent	25
A1c-related relative risk	14% decrease per 1% reduction in A1c	2
Stroke		
Hypertension treatment relative risk	56% if on antihypertensive agent	25
A1c-related relative risk	12% decrease per 1% reduction in A1c	2

[a]*Use metformin + sulfonylurea + basal insulin data.*
[b]*Use metformin + DPP-4i data.*
[c]*No effective drift.*
[d]*Dosage obtained from Hollander et al. 2011.*[8]
[e]*Dosage obtained from Holman et al. 2007.*[12]
[f]*Dosage obtained from Fritsche et al. 2010.*[37]

ACE inhibitor = angiotensin-converting enzyme inhibitor; A1c = hemoglobin A1c; BMI = body mass index; CHD = coronary heart disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; kg = kilogram; kg/m^2 = kilogram per square meter; LEA = lower extremity amputation; mg/dL = milligram per deciliter; MI/CA = myocardial infarction/cardiac arrest; mm Hg = millimeter of mercury; OAD = oral antidiabetes drugs; WAC = wholesale acquisition cost.

APPENDIX B Cost Outcome Model Results: Total Costs, Pharmacy Costs, and Direct Medical Costs[a]

Comparator Strategy		Minimum Time on Treatment	Pharmacy Costs Per Patient	Direct Medical Costs Per Patient	Total Costs Per Patient
	Standard of Care	**Baseline**			
0.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 Months	$10,489	$26,216	$36,705
		12 Months	$8,352	$33,995	$42,347
	Approach 1: Two-Stage Insulin	**Incremental to Baseline**			
I.	1. metformin 2. metformin + sulfonylurea 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 Months	$176 (1.68%)	-$312 (-1.19%)	-$136 (-0.37%)
		12 Months	$462 (5.53%)	-$3,122 (-9.18%)	-$2,660 (-6.28%)
II.	1. metformin 4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 Months	$2,078 (19.81%)	-$1,007 (-3.84%)	$1,071 (2.92%)
		12 Months	$3,648 (43.68%)	-$6,787 (-19.96%)	-$3,139 (-7.41%)
III.	4. metformin + DPP-4i + basal insulin 5. metformin + biphasic insulin	6 Months	$4,716 (44.96%)	-$1,541 (-5.88%)	$3,175 (8.65%)
		12 Months	$7,671 (91.85%)	-$8,582 (-25.24%)	-$912 (-2.15%)
	Approach 2: Single-Stage Insulin	**Incremental to Baseline**			
IV.	1. metformin 2. metformin + sulfonylurea 3. metformin + sulfonylurea + DPP-4i 5. metformin + biphasic insulin	6 Months	-$1,654 (-15.77%)	-$387 (-1.48%)	-$2,041 (-5.56%)
		12 Months	-$1,798 (-21.53%)	-$2,711 (-7.97%)	-$4,509 (-10.65%)
V.	1. metformin 2. metformin + sulfonylurea 5. metformin + biphasic insulin	6 Months	-$1,550 (-14.78%)	-$759 (-2.90%)	-$2,309 (-6.29%)
		12 Months	-$1,635 (-19.58%)	-$5,595 (-16.46%)	-$7,230 (-17.07%)
VI.	1. metformin 5. metformin + biphasic insulin	6 Months	$94 (0.90%)	-$1,436 (-5.48%)	-$1,342 (-3.66%)
		12 Months	$1,071 (12.82%)	-$8,271 (-24.33%)	-$7,200 (-17.00%)
VII.	5. metformin + biphasic insulin	6 Months	$2,569 (24.49%)	-$2,007 (-7.66%)	$562 (1.53%)
		12 Months	$4,706 (56.35%)	-$9,786 (-28.79%)	-$5,080 (-12.00%)

[a]*Results presented as difference between SOC (steps 1,2,3,4,5) and each comparator strategy per patient over a 5-year period. The percentages given represent the relative increase/decrease from the associated base case value.*

DPP-4i = dipeptidyl peptidase 4 inhibitor; SOC = standard of care.