Modeling the Efficiency of Reaching a Target Intermediate End Point: A Case Study in Type 2 Diabetes in the United States

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ABSTRACT

Objective: The objective of this study was to describe an approach to modeling the efficiency of an intervention by focusing on an established intermediate end point directly. A case study addresses the economic efficiency of obtaining dual glycemic control over time, according to initial choice of treatment.

Methods: From the perspective of a payer in the United States, instead of the usual approach of basing the model on projecting long-term diabetic complications from glycemic control, this model focuses directly on glycemic control. Treatment changes and associated health-care utilization needed to address postprandial glucose. After assigning each of 10,000 drug-naïve patients, HbA1c, age, race, and sex based on distributions from a randomized clinical trial, the model applies the efficacy of nateglinide compared to metformin. Sensitivity analyses were carried out for all parameters. Costs are reported in year 2000 US dollars and discounted at 3%.

Results: In the base case, starting on nateglinide and increasing the time in dual glycemic control over 3 years by 2.4 months led to savings of US $295 compared to starting on metformin. Savings increased with stricter treatment criteria but decreased if glycemic control was better initially.

Conclusions: This study illustrates the use of an efficiency model that focuses directly on the relevant short-term end point: glycemic control. Starting patients with nateglinide is shown to be an efficient way of obtaining dual glycemic control during the first 3 years of treatment.

Keywords: modeling, diabetes, glycemia, economic.

Introduction

For most chronic diseases, it is not practical to repeatedly conduct studies that quantify the effects of treatments on the long-term outcomes that are ultimately of interest. Although it is usually those very outcomes that are the reason for treatment, the time and effort required and the lack of timeliness of the resulting information tend to be prohibitive. Moreover, to monitor the disease and treatments in actual practice, clinicians need measures that reflect the long-term prognosis but are obtainable in the real time of practice and are sensitive enough to guide therapy. Accordingly, an indicator of therapeutic effect has been developed in most chronic diseases. This indicator is distinguished by strong prognostic ability in absolute terms: the capacity to reflect risk changes owing to modifications in value, though often unproven, sensitivity to treatment, and relative ease of measurement. The lipid profiles, glycemic levels, blood pressure, and the mini-mental status exam are all examples.

For obvious reasons, clinical trials tend to use these intermediate indicators as the primary end points. For economic modeling these are viewed as problematic, however. Cost-effectiveness ratios expressed in terms of cost per unit change in an intermediate indicator are not comparable among diseases and are not even very meaningful within a specific disease area. Thus, the tendency has been to use their predictive ability to “translate” the short-term results of the trials to meaningful long-term outcomes. These types of models, however, are fraught with difficult-to-support assumptions, extend well beyond the time horizons of relevance to most decision-makers—both clinical and administrative—and go counter to developing regulatory opinion that claims regarding health outcomes that have not been studied should not be “created” by a
model. Thus, although technically reasonable and interesting, these long-term prediction models may not have the authority to inform decisions and hence the weight to significantly sway those who take them.

In this article, we describe a different approach that, although not entirely novel, has not been commonly used. Rather than projecting the intermediate indicator values over the long term, we suggest that they themselves be the focus—just as they are in actual clinical practice. To avert meaningless outcomes, however, we avoid building what amount to simply short-term versions of the long-term models. Instead, we think that the short-term model should examine the efficiency of getting patients to the target values of the indicator: what proportion achieves the goal in the near term, how long do they stay at goal, what does it take to get them there, and how much does it cost? The outcomes are compared between current management where the new drug or intervention is not available and what it would be like if it were offered. These efficiency models must allow for realistic treatment changes and should try to reflect actual practice. Accordingly, they should be flexible to permit custom application to a given setting. We illustrate this type of model with an example from diabetes.

Methods

The Example

Type 2 diabetes is a serious, prevalent chronic disease that comprises more than 90% of the estimated 15 million diabetes cases identified in the United States [1-3]. Because most of its devastating health and economic [4-9] impact is a direct result of hyperglycemia, the cornerstone of therapy is glycemic control. Current guidelines of the American Diabetes Association (ADA) recommend the use of glycosylated hemoglobin (HbA1c) to monitor this control [10] and physician adherence to these clinical practice guidelines is growing [11]. This is important because it has been shown that an increase of 1% in HbA1c is associated with a 28% increase in the risk of death independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking in men with diabetes [12]. Moreover, it has been established that achieving reductions in HbA1c decreases the risk of macrovascular complications [13,14,15].

Recently, the ADA recommended including postprandial glucose (PPG) monitoring as well [16], based on growing evidence of the association between PPG and macrovascular complications [16-20]. Therefore, new therapies that modify PPG and thereby reduce HbA1c, such as the recently introduced nateglinide, could be valuable for meeting the challenge of improving the management of diabetes [21].

The insulin secretagogue nateglinide (Starlix®) is effective in controlling PPG and reducing HbA1c [22,23]. It has been approved for use in the United States as monotherapy or in combination with other drugs [23]. Like all new drugs entering the market, it is important to assess not only its health benefits, but also its economic implications. Previous economic models in diabetes have focused on long-term complications [5,7,8,24,25], but these require numerous assumptions and do not address the clinically important issue of the efficiency with which it can bring patients to target levels in the near term. Therefore, a short-term efficiency model was developed to examine the direct medical costs of managing type 2 diabetes, according to the initial choice of treatment based on the notion that it is desirable to attain dual (both HbA1c and PPG) glycemic control.

Efficiency Model

Structure. The model (Fig. 1) is a discrete event simulation of the therapeutic process aimed at gaining dual glycemic control. The model considers four main health states: glycemic control, uncontrolled glycemia, failure of oral therapy, and death. Dual glycemic control is defined in terms of both HbA1c and PPG, according to the ADA guidelines. Uncontrolled glycemia occurs when either measure is outside the range specified in the guidelines. Failure is defined as persistent lack of glycemic control with combination therapy. The model estimates the proportion of patients achieving dual control at various points in time as well as the costs of getting patients

![Figure 1](schematic_representation_of_the_us_diabetes_economic_model.png)

Figure 1 Schematic representation of the US diabetes economic model.
to that goal. Time is advanced in monthly fixed increments within a maximum time frame of 3 years. Random sampling of prespecified distributions is used to assign patient characteristics and to simulate the management of each individual.

The model starts with a patient whose diabetic state is defined by an HbA\(_1c\) value sampled from a distribution. This derivation is based on regression equations that take into account the baseline value, the direction of change, and the type of treatment in patients who failed dietary treatment and who received antidiabetics for first time (“drug naïve”). Age, race, and sex are also assigned by weighted random sampling of distributions [23]. These characteristics help determine cholesterol, smoking status, body mass index, and systolic blood pressure values, all of which are sampled from conditional distributions [26,27]. These attributes play a role in longer-term simulations but not in the analyses carried out here.

The management of this patient, along with resulting changes in glycemic control, is then simulated under a current treatment strategy and in one where the new drug is available and used first. For each initial treatment, the resulting HbA\(_1c\) is calculated and referred to a desired range to determine if control has been achieved. Flexibility was built into the use of different guidelines (e.g., ADA, Joslin Clinic) for determining control. If HbA\(_1c\) control (HbA\(_1c\) ≤ 8.0\%, according to the ADA guidelines) is attained, it is assumed, consistent with current practice, that this measure is given more importance and thus outweighs PPG control; the model considers the PPG by applying the treatment-specific probability of reducing PPG to the desired range. If dual control is achieved, then treatment with the same drug(s) is continued at the same dose(s) and the implications of dual control are tallied. For these analyses, the implication is that the physician visit rate is changed to every 6 months. If the PPG is not controlled, then the implications of lack of dual control are tallied (time with uncontrolled glycemia is incremented) but treatment is continued unchanged (i.e., the model assumes that current practice is not to make changes in treatment if HbA\(_1c\) is under control).

If the HbA\(_1c\) is not controlled according to the guidelines in force, or if it increased because response to treatment was altogether negative, then the model considers whether the HbA\(_1c\) has reached the level required to take action—a level also determined according to the chosen guideline, ADA for the base case [32]. If it has not reached that level, the treatment continues unchanged but the implications of no control are tallied; time with uncontrolled glycemia is incremented. If the HbA\(_1c\) level indicates a need for treatment change, the next therapeutic action in a predetermined sequence is considered at the time of the next visit to the health-care provider. This may include a titration to a higher dose, an addition of another drug or a switch to another drug depending on what treatment the patient has been on, and how many visits with uncontrolled glycemia have occurred. The model also allows for imperfect clinical action either in detection of the lack of control or in taking action, but in the analyses presented here it is assumed that practice is optimal in this regard. The implications of the treatment change are then tallied. Before proceeding to the next monthly cycle, if there has been no treatment change, the model applies upward drift to the HbA\(_1c\) based on the results observed in the UKPDS study [28–30]. If the treatment has changed, then the effect of that treatment is applied using the same technique (though different, treatment-specific equations) as for the initial treatment. At the start of each monthly cycle, the model checks whether the simulated patient has survived to that point. The risk of death was obtained by adjusting the general age- and sex-dependent mortality hazard by the relative risk associated with diabetes [31]. It was assumed that over the short term, treatment did not change this hazard.

The assumptions made in developing the treatment pathways and determining the resource use and costs associated with the algorithms in each arm of the model were tested using an expert panel of seven physicians (two endocrinologists, two internists, and three family physicians), who concurred with them [1].

**Default Inputs.** There were two types of inputs specified: one applied to all treatments compared and the other particular to each treatment. The general set of inputs involved the distributions of initial HbA\(_1c\), age, race, and sex; the mortality hazard equations; the frequency of physician visits according to the patient’s status; the criteria for considering control and treatment changes; the upward drift in HbA\(_1c\); the unit costs and resource use profiles (for physician visits, laboratory tests, and other studies); and the discount rate. The treatment-specific inputs involved dosing, efficacy in terms of lowering the HbA\(_1c\), and in terms of bringing the PPG within the controlled range, the risk of hypoglycemia, any additional monitoring, and drug costs.
For the base case, the distribution of initial HbA1c, age, sex, and race were obtained from a randomized clinical trial that compared nateglinide to metformin monotherapy and the combination of the two [23]. There were 3.4% of patients whose HbA1c was 8.0, 45.9% between 8.1 and 9.0, 36.2% from 9.1 to 10.0, 12.9% from 10.1 to 11.0, and 1.6% above that. The proportion of men was 62.2%, and 80.6% of patients were white whereas 11.8% were black, 1.6% were Asian, and 6% were other. The mean age was 58.3 $\pm$ 10.9 years (Table 1).

The routine frequency of physician visits was assigned to each patient based on a distribution that allowed for practice variations. Base case analyses used the ADA guidelines [32] that patients should be seen at least quarterly until achievement of treatment goals. Once a patient reaches glycemic control, it was assumed that the visit frequency decreased to biannual. A visit was also assumed to take place when the dose was titrated up or when treatment was changed. In the base case, the cutoff points to consider HbA1c controlled or to take an action were defined using the ADA guidelines: $\leq$ 7.0% for control and $\geq$ 8.0% to change treatment. From 7.0% to 8.0%, glycemia was considered neither controlled nor high enough to warrant action. In sensitivity analyses, the criteria of the Joslin Clinic, which require a tighter glycemic control (7.5% to take action compared to 8.0% of ADA), were used. As observed in the UKPDS [28–30], it was estimated that the HbA1c would drift upward on average 0.15% per year.

To reflect the direct economic burden of diabetes management from the perspective of a comprehensive health-care payer, we considered costs associated with the drugs, medical doctor visits, other professional services (e.g., dietician), laboratory tests, and home monitoring supplies. In the base case, the laboratory testing profiles at the annual visit and at monitoring visits were based on the recommendations made in the ADA guidelines [32] and set identically for all treatments, except insulin, which was assumed to incur an additional electrocardiogram annually. Unit costs were obtained from national fee schedules [33], the Redbook [34], and other published data. The unit costs for monitoring visits included a urine dipstick ($4.35), a fasting plasma glucose ($5.41), and an HbA1c determination ($13.23) [33]. For the annual visit, a lipid panel ($17.98), a test for albumin in urine ($5.47), a plasma albumin ($7.69), a plasma creatinine ($7.05), and a basic metabolic profile ($11.34) were added [33]. The cost of a regular physician visit for monitoring was set at $33.19 and for the annual comprehensive visit at $53.69; for a dietician the annual visit was set at $48.48; the cost of a monitoring visit, including all the laboratory tests and professional fees, was $62; and the annual comprehensive visit was $176. The unit cost of metformin was based on the average wholesale price: $0.65 for 500-mg tablets, $1.09 for 850-mg tablets, and $1.33 for 1000-mg tablets [34]. The unit cost for nateglinide was $0.96 per 120-mg tablet. For the combination, the cost was the sum ($4.83). All costs are reported in year 2000 US dollars (no adjustment for medical inflation was necessary). Discounting (3% per year) was applied to the costs and to time in control that accrued beyond the first month.

### Treatments Compared

In these analyses, efficacy data from the nateglinide clinical trial were the basis for comparison of nateglinide with metformin monotherapy as initial choices patients with type 2 diabetes. The base case examined 120 mg nateglinide and 500 mg metformin, both three times daily. Metformin can be increased progressively up to 2550 mg per day with titrations every 2 weeks, according to the HbA1c levels.

For both treatments, the first treatment change, other than titration, was to the combination of 120 mg nateglinide and 500 mg metformin taken three times daily. If combination treatment failed,

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### Table 1 Inputs for the base case analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (%)</td>
<td></td>
</tr>
<tr>
<td>29–40</td>
<td>5.3</td>
</tr>
<tr>
<td>41–52</td>
<td>24.3</td>
</tr>
<tr>
<td>53–64</td>
<td>41.0</td>
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<td>65–76</td>
<td>25.3</td>
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<tr>
<td>&gt;77</td>
<td>3.9</td>
</tr>
<tr>
<td>Men (%)</td>
<td>62.2</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
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</tr>
<tr>
<td>Black</td>
<td>11.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.0</td>
</tr>
<tr>
<td>Asian</td>
<td>1.6</td>
</tr>
<tr>
<td>Natives</td>
<td>3.0</td>
</tr>
<tr>
<td>Mean HbA1c Initial (%)</td>
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</tr>
<tr>
<td>Upward drift (%/year)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean decrease in HbA1c level</td>
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</tr>
<tr>
<td>Monotherapy</td>
<td>-0.82</td>
</tr>
<tr>
<td>Combination</td>
<td>-2.13</td>
</tr>
<tr>
<td>Mean initial 2-hour PPG (mg/dl)</td>
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</tr>
<tr>
<td>Guidelines</td>
<td></td>
</tr>
<tr>
<td>American Diabetes Association</td>
<td></td>
</tr>
<tr>
<td>Model time horizon (years)</td>
<td>3</td>
</tr>
<tr>
<td>Discount rate (%)</td>
<td>3</td>
</tr>
<tr>
<td>Physician visit, routine rate</td>
<td>One visit/quarter</td>
</tr>
<tr>
<td>Nateglinide price (cost/day)</td>
<td>$2.88</td>
</tr>
<tr>
<td>Metformin price</td>
<td>$1.95</td>
</tr>
</tbody>
</table>

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For the base case, the distribution of initial HbA1c, age, sex, and race were obtained from a randomized clinical trial that compared nateglinide to metformin monotherapy and the combination of the two [23]. There were 3.4% of patients whose HbA1c was 8.0, 45.9% between 8.1 and 9.0, 36.2% from 9.1 to 10.0, 12.9% from 10.1 to 11.0, and 1.6% above that. The proportion of men was 62.2%, and 80.6% of patients were white whereas 11.8% were black, 1.6% were Asian, and 6% were other. The mean age was 58.3 $\pm$ 10.9 years (Table 1).
then the next change was to insulin, which was considered a “failure,” although the costs continued to accrue.

Hypoglycemia was the only side effect considered, based on the trials [23]: 0.46 confirmed episodes per patient-month with nateglinide and 0.16 with metformin. Given that no severe episodes requiring medical intervention occurred, the cost consisted only of the use of one extra glucose strip and the glucometer, $2.48.

**Analyses**

The main measure of effectiveness was the time in dual control and the proportion of patients achieving the dual control. Other outcomes included were time spent on each treatment, number of physician visits, number of treatment changes, cumulative costs after 3 years, and costs by type of resource. Incremental cost per month with dual control was also calculated, where appropriate. Sensitivity analyses were performed for all model parameters and various combinations of these.

**Results**

**Base Case**

In the base case, the patients stayed on monotherapy for 27 months, on average; 14% eventually required combination therapy, and 19% switched to insulin. Patients starting on nateglinide had an additional 2.5 months with dual control (17.8 months compared to 15.3 months with initial metformin) and only 11.6 physician visits compared to 16.4. Metformin leads to an average 3-year cost of $5826 per patient—the majority attributable to the drug itself (73%). Patients who achieved control on the initial dose of metformin were the least expensive (mean $5321). Nateglinide resulted in an average cost of $5531 (Fig. 2). Thus, nateglinide would be expected to be more efficient at attaining therapeutic goals by increasing the time with dual control and reducing costs in doing so. In this context, an incremental cost-effectiveness ratio was not calculated. The average cost-effectiveness ratio (i.e., compared to no treatment at all) for nateglinide was $311 per month with dual control compared to $379 for metformin.

**Sensitivity Analyses**

Extensive sensitivity analyses were carried out and the results are summarized in Figure 3. The HbA1c cutoff point to take an action is a key input: with the stricter Joslin Clinic guideline, the number of treatment changes, as well as physician visits, increases for both treatments but the savings with nateglinide grow to $487 because of fewer titrations. If titration required a physician visit only every other titration, the savings with nateglinide would drop to $166, and if no visits were required, the costs would increase to a net of $61, producing an incremental cost-effectiveness ratio of $17 per additional month with dual control (Table 2). In patients with borderline elevations of initial HbA1c (6% and 7%), metformin had lower net costs because more patients remained on the lowest dose without having to titrate up. In contrast, patients with initial HbA1c greater than 8.0% had better results with nateglinide.

**Figure 2** Total costs at the end of 3-year period by components for patients with initial HbA1c of 8.0.

**Figure 3** Sensitivity analyses of net costs (nateglinide minus metformin) versus net time with dual control. Points in the bottom right quadrant indicate nateglinide dominance.
Discussion

In this article, we present an approach to economic modeling of a chronic disease based on established intermediate end points. This approach has the advantages of requiring fewer assumptions; making no projections over long periods of time; focusing on end points of direct relevance to clinicians, patients, and administrators; and not creating efficacy purely as a result of the model itself. Thus, this kind of model accords with the clinical trial evidence that is usually available—it makes no demands for data that will not be available for a long time, if ever—and should be able to inform decisions about management of the disease in real time and actual practice.

There are some important drawbacks to this approach. Though highly practical and relevant, it is not entirely in agreement with current guidelines for economic analyses of health-care interventions [35]. In particular, it deliberately fails to extend the time horizon “long enough to reflect important and valued differences between the long-run consequences and costs . . . ” This, in turn, means that the results that it produces are not comparable with those of the models that do engage in long-term predictions and, thus, those benchmarks (e.g., $50,000 per QALY gained) are meaningless and comparisons with other health care interventions may be difficult or impossible. Moreover, by failing to extend the time horizon to cover long-term consequences, important savings that may help justify the intervention, or costs that may bury it, are ignored.

It is our contention, however, that these disadvantages pale beside the pragmatic value of this type of model to actual decision-makers concerned with providing quality care consistent with extant clinical guidelines. In this situation, meeting short-term goals is exactly what is sought, and evaluating the efficiency of doing so is the issue.

In these analyses, the early management of type 2 diabetes to address the efficiency with which various treatment strategies achieve glycemic control, in terms of both HbA1c and PPG, consistent with current guidelines. Given the growing appreciation of the relation of glycemic control to the occurrence of macrovascular and other diabetic complications, one may question the period of time covered in the model, but meeting short-term treatment objectives for patients with type 2 diabetes is a prerequisite for successful reduction of complications. This model had some limitations apart from the short time horizon. The total costs have been underestimated as hospitalizations are not included, but this is conservative because it reduces the advantage of attaining glycemic control faster. Another limitation is that diabetes management is driven by current guidelines—it is possible that less aggressive or consistent approaches exist in actual practice. The effect of such variations on the comparative results is unclear and while they may lower short-term costs, they will also lead to poorer control. Furthermore, hypoglycemia was the only adverse event included; yet gastrointestinal events are more frequent with metformin [23]. Therefore, it is possible that we underestimated the costs of metformin treatment.

Over the 3 years modeled, these patients are predicted to remain on monotherapy the majority of the time. This is consistent with the results reported by the UKPDS, where at the end of 3 years, 76% to 81% of patients were still receiving monotherapy [36]. The costs of diabetes management over these 3 years were approximately $5000 per patient, depending on the level of glycemic control and other factors. Other studies [9,37] have found similar costs.

The insulin secretagogue nateglinide is predicted to increase dual control while leading to a savings of about $300. Improving glycemic control has been shown in other studies to decrease costs. One cohort study showed that costs increased significantly for every percentage point increase above an HbA1c of 7% [38], and another [39] found that the charges went from $970 in those with good control to $1380 with fair control and $3040 with poor control. This relationship of cost to glycemic control was confirmed in another recent study.
Efficiency of Reaching Intermediate End Point

Indeed, in our model, patients who achieved dual control on monotherapy were the least expensive to manage. The savings with nateglinide were higher in patients who started with worse control and attenuate when initial glycemia was near normal. This is not surprising because the model “enforces” action when glycemic control is poor and these actions have a cost; but this is consistent with the idea that the decision-maker wants optimal practice.

The focus of this model on both HbA1c and PPG in the short term is novel. Previous guidelines and recommendations advise monitoring fasting plasma glucose (FPG) and HbA1c [32]. FPG, however, does not address the contribution of the postprandial rise in glucose to overall control, and HbA1c does not address the daily oscillations in glucose, because it only reflects average glycemia [41,42]. We added PPG to the criteria for glycemic control because the treatment goal for patients with type 2 diabetes should be to achieve the best possible glycemic control by restoring a normal, physiologic insulin response to feeding and by decreasing late postprandial insulin levels and chronic hyperinsulinemia [43]. In addition, PPG levels may more closely reflect the metabolic processes involved in the pathogenesis of type 2 diabetes—increased hepatic glucose output, impaired insulin secretion, and insulin resistance [44,45]. Indeed, several studies have shown a better correlation between 2-hour PPG and the risk of cardiovascular disease [43,46–50] and atherosclerosis risk factors [51] than with either FPG or HbA1c.

This case study illustrates the modeling of efficiency of reaching a target intermediate end point and indicates that starting drug-naïve patients on nateglinide is an efficient way of obtaining dual glycemic control during the first 3 years of treatment.

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