ECONOMIC IMPLICATIONS of PATIENT-RELATED FACTORS in DIABETES CARE

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Economic Implications of Patient-related Factors in Diabetes Care

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Economische implicaties van patiënt-gerelateerde factoren in de diabeteszorg

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To my family,
David Swezey, Karen, and Heather

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Chapter 1

General Introduction

Introduction

Diabetes mellitus is a chronic disease characterized by high blood sugar levels with serious complications, particularly if it is not adequately treated. It is increasingly prevalent and burdensome from both a health and economic standpoint globally, amounting to hundreds of billions of dollars in expenditure each year [1,2]. Also increasing are the numbers and types of pharmaceutical interventions being introduced to treat this disease. Over the next decade, numerous diabetes compounds currently in development are expected to be commercialized, making it essential for the most robust and accurate evidence to be available to healthcare decision-makers [3].

Approximately 90% of people with diabetes are diagnosed as Type 2 (T2D), most often in adulthood [4]. In contrast, Type 1 diabetes (T1D) patients are commonly diagnosed as juveniles, but live well into adulthood with effective treatment [4]. Consequently, adult patients with diabetes, namely T2D, are responsible for most of the health and economic burden of this disease. Therefore, much of the effort to improve outcomes and reduce costs in diabetes concentrates on this population.

The goal of diabetes treatment has remained to control glycated hemoglobin (HbA1c) while reducing the risk of adverse events (e.g., hypoglycemia). However, recent international guidelines emphasize an individualized, patient-centered approach to setting treatment targets given the many unique clinical, social, and environmental risk profiles, rather than establishing a single target for all patients (e.g., HbA1c < 7.0%) [5]. For T1D, an unpreventable autoimmune disorder causing destruction of pancreatic beta cell activity, the treatment requirement is exogenous insulin over a lifetime [5].

The underlying causes and treatment options are more complex for T2D, which is a metabolic disorder associated with a combined effect of reduced ability to properly absorb sugar (insulin resistance) and loss of normal beta cell function (relative insulin deficiency) [5-7]. Its onset may be influenced by a multitude of factors – lack of exercise, a diet high in saturated fats (obesity), medical conditions such as hypertension and hypercholesterolemia, and inheritable genetics [6,7]. Initial treatment commonly begins with diet and exercise, followed by one or multiple oral anti-diabetic drugs (OADs), and later may include insulin or other injectable medication as disease progresses [5]. As the prevalence of T2D and its associated economic impact are much higher than with T1D, this thesis focuses predominantly on adult T2D patients, although a modeling application of insulin treatments among adult T1D patients is found in Chapter 3.

However, irrespective of diabetes type, an important part of tailoring treatment involves the consideration of not only the biological factors of care, but also the non-biological. It is important to account not only for how a patient's body will respond to a specific compound, but how likely the patient will comply with and remain on therapy [5]. As such, unique product features potentially impacting a patient's satisfaction with and preference for treatment are relevant [5].

As treatments for diabetes continuously evolve, it's become ever more difficult to consistently demonstrate improved clinical efficacy at historical rates – earlier compounds have more readily been able to demonstrate significant HbA1c reductions, as they've competed with older, less potent therapies at time of their launch [3,8]. The challenge of distinguishing modern products on biological grounds has led to intense efforts by manufacturers to differentiate therapies by highlighting non-biological product features, while only meeting minimum efficacy requirements. Indeed, as it pertains to clinical efficacy and safety, critics have defined the current era of diabetes drug development as *me too*, citing the manufacturers' increased replacement of head-to-head superiority trials with non-inferiority designs [3,8].

Non-biological product innovations in diabetes have predominantly been patient-centered and aim at making products less intrusive and easier to use (e.g., alleviating problems with needle phobia). These innovations may influence patients' perceptions of treatment, and can thereby improve their ability and willingness to properly self-manage and maintain therapy [9]. Improved handling and device ergonomics for injecting insulin, reduced dosages, and less frequent, simpler routes of drug administration are all non-biological product characteristics that have been progressively refined specifically to increase the preference for and satisfaction with treatment. [3,5]. Patient preferences in diabetes are economically important for a wide range of reasons pertaining to both biological and non-biological factors, and their importance is only rising for decision-makers [10,11].

A substantial amount of originality and diversity surrounding non-biological product features is being introduced into the diabetes market, and healthcare payers and decision-makers have struggled with assigning value to these product features. This is because the methods they currently have for doing so are largely focused on clinical changes (HbA1c) only [12]. In this expanding, complex market environment, the question remains, "do current methods of economic evaluation used to make decisions on patient access and reimbursement reflect the rapidly evolving nature of diabetes products in the real world? Have methodologies adequately kept pace with innovations in non-biological product development?" Current studies suggest that historical approaches at economic evaluation in diabetes, in particular for cost-effectiveness analyses (CEAs), are not able to fully capture the value of non-biological, yet economically important, features of modern products [12]. This may lead to a misinformed and incomplete foundation for decision-making in coming years.

In context of the need to ensure that payers and decision-makers are well-equipped when considering future products, this thesis addresses two overarching themes: (1) the increased diversity of non-biological diabetes product features; and (2) the patient-centered, economically relevant outcomes they impact. To this end, the specific objectives herein are to examine the broad, multifaceted relationships between patient-centered, clinical, and cost outcomes associated with diabetes treatment, and to propose new methods which better incorporate these relationships in CEAs used for reimbursement and policy decision-making in the real world. The emphasis of this

introductory section is to provide a working definition of terms, describe the general framework for the thesis, and outline the individual contribution of each chapter.

Defining economically relevant patient-centered outcomes

Several terms are used throughout this thesis to describe patient-centered outcomes which become important when proposing novel frameworks of economic evaluation. These include self-reported outcomes depicting experiences with treatment, as well as calculated metrics acting as surrogate measures to illustrate patient behaviors.

The manner and context in which these outcomes were analyzed vary by chapter, spanning retrospective, observational to prospective, controlled research designs. Although there is some overlap, these outcomes generally fall within three categories: those that are (1) patient-reported; (2) measures of medication self-management; and (3) intrinsically relevant to economic analyses.

The patient-reported outcomes (PROs), or perceptions of care, examined in this thesis are Patient Preference and Treatment Satisfaction, measured with validated instruments and specific to diabetes (e.g., *ITSQ – Insulin Treatment Satisfaction Questionnaire*). For the purposes of this thesis, patient preference is considered to be a measurement of the comparative desirability of treatments, or the extent to which a patient chooses or otherwise endorses the use of one treatment over another based on actual as well as perceived attributes [13]. Treatment Satisfaction is regarded as the measurement of a patient's approval, or contentment, with the treatment process and its associated outcomes based on predefined criteria [14]. Conceptually, the objective for both is to quantify a patient's subjective, personal sentiment toward treatment in order to better understand the impact that it can have on observed behavior, such as medication adherence and persistence [13,14].

To that end, several chapters focus on generating and applying proxy indicators for adherence and persistence by utilizing healthcare claims databases to calculate Medication Possession Ratios (MPRs) and number-of-days covered. The MPR is a common metric intended to describe the proportion of time that a patient is covered by, or in possession of, the correct supply of their medication. It is often calculated as the sum of the days' supply of a drug divided by the number of days between the first fill and the last refill, plus the days' supply of the last refill [15]. Number of days covered is simply the time from drug initiation (index date) to discontinuation (defined by a period of absence of refill activity).

Using those standards to calculate MPR and days covered, it becomes apparent how they relate to adherence and persistence. Medication adherence, which is a synonym for compliance, refers to a patient's conformity to healthcare providers' recommended or prescribed timing, dosage, and frequency of medication taking [16]. Similarly, yet distinct, persistence is defined as the duration of time from treatment initiation to discontinuation [16]. More simply, adherence may be viewed as the extent to which a patient follows the prescribed interval and dosage of their medication, and persistence

only relates to the length of time a patient continues to take any amount of their medication [16]. Operationally, both adherence and persistence are measured with units of time. However, adherence is reported as a percentage of time while persistence is described in units of total time [16].

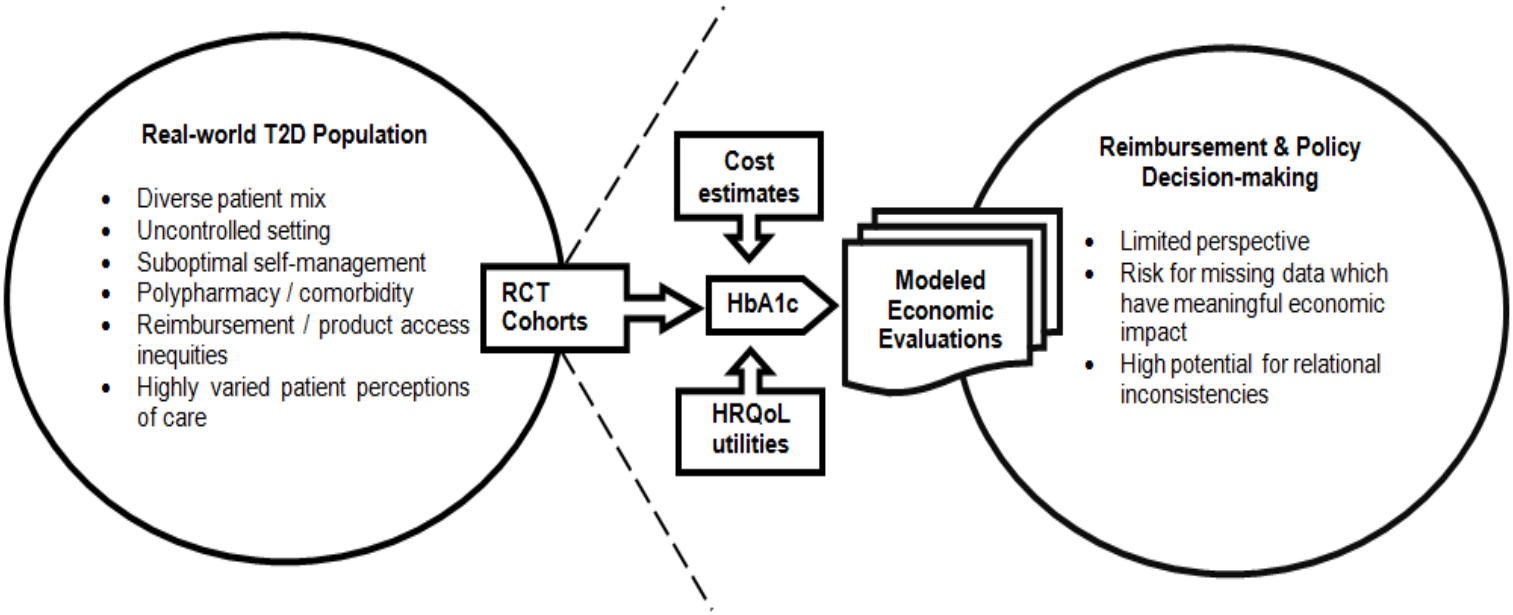
The culminating effort for this thesis is aimed at improving upon methods used in the economic evaluation of treatments for diabetes, and T2D in particular. Although Chapter 3 examines the cost-effectiveness of insulin treatments in adult T1D patients, the primary aim for purposes of this thesis was to build on Chapter 2 by demonstrating that modeling is sensitive to treatment-specific differences in HbA1c and hypoglycemia. The ultimate aim for each patient-centered outcome was to examine its relationship to costs. The outcomes previously mentioned – preference, satisfaction, adherence and persistence – have a downstream effect on pharmacy and medical costs. Others, such as Health-related Quality of Life (HRQoL), are more inherently linked to economic evaluations through their association with actual health benefit and not just costs, and therefore deserve careful consideration.

Measures of HRQoL may be broadly defined as a patient's appraisal of their level of functioning and health while on treatment in comparison to what they perceive to be ideal or more desirable without it [17]. They begin as preference-based PROs, but may be expressed mathematically in the form of utility scores calculated from patient responses to HRQoL instruments. Utilities are valuable for CEAs since they make it possible to compare the ability of treatments to impact not only survival, but also quality of life. Quality-adjusted life-years (QALYs), the combination of life-years lived with the quality of that life, represent an important health outcome used in many cost-effectiveness analyses. For chronic diseases like diabetes, the inclusion of utilities in CEAs is particularly important since patients tend to remain in various health states with a reduced quality of life for a prolonged period of time.

The historical paradigm and new dynamic of economic evaluation in diabetes

The majority of CEAs comparing diabetes treatments have taken an *inside-out* approach. Incremental Cost-effectiveness Ratios (ICERs) that are intended to facilitate decision-making in the real world have instead been calculated extensions of clinical efficacy and safety observed within rigidly defined clinical trial populations of limited sample size [Figure 1]. The primary driver of modeled health events, resource use, and costs in these CEAs are intermediate levels of HbA1c based first and foremost on RCT results. Although supplemental information from large epidemiological studies, healthcare claims and registry databases, and general population surveys are routinely incorporated, this is done on a secondary basis after the impact of treatment on HbA1c been applied. This often produces only isolated, or indirect, effects on health state transition probabilities, cost estimates, and utilities.

Figure 1. Historical *inside-out* paradigm of economic evaluation in the context of real-world application for decision-making in diabetes



The core of this historical approach at economic evaluation is flawed for making decisions in the real world due in part to the structural makeup of RCTs. This flaw largely excludes the impact of non-biological product features [12,18]. The main purpose of a RCT is to test the efficacy and safety of a chemical entity on a disease in a controlled setting among restricted types of patients, not to serve as the foundation for health economic analyses.

Additionally, non-structural biases inherent to RCTs further limit their applicability for economic evaluations used in real world reimbursement decision-making. For example, this includes the tendency of study investigators, intentionally or unintentionally, to selectively enroll patients with greater likelihood of attending routine follow-up visits and taking medication according to study protocol. Furthermore, the requirement of informed consent may predispose enrolled patients to achieve much higher levels of adherence than they might otherwise if they were not actively watched, or did not feel they were being relied upon as part of a scientific study [12,19]. Both forms of bias may mean that the RCT results provide no indication of the impact of non-biological product features on patient behavior, and may therefore overestimate what may be expected for non-selected patients in uncontrolled, real world settings.

Still, RCTs will always remain an essential component for economic evaluation, as they are a rich source of the requisite comparative clinical information. The key for developing novel approaches at CEA is not to change this fact, but rather to enhance their usefulness by: (1) identifying all non-biological factors that have a direct or indirect economic impact and may be captured outside the RCT setting; (2) measuring how much

they affect economic outcomes; and (3) testing the application of additional knowledge in new analytic frameworks. Without these augmentations, the absence of real-world influences on patient perceptions of care and self-management would prevent CEAs from revealing the true value of many forthcoming diabetes products.

CEA as a primary means for economic evaluation in diabetes

The purpose of CEA, and more broadly, health technology assessment (HTA), is to aid healthcare decision-making, rather than be a statement of fact; in other words, it's a means and not an end in itself [[18,19]. As such, the more accurate and relevant a CEA, the better its results serve decision-makers [18,19]. Although specific methodologies for CEA may differ, the basic intent remains to generate an ICER that describes the potential value for money of using one healthcare intervention versus another. In order to understand how CEAs are meaningful in diabetes (and to establish it as a method of economic evaluation that would be most appropriate to target for revision), we first had to (1) identify a suitable clinical marker to serve as the main driver of modeled results, and (2) test its ability to differentiate health outcomes and costs in relevant patient populations.

The primary methodological construct for CEAs within this thesis is the Markov / Monte-Carlo simulation (M/MC). The Markov component is used to illustrate the structural approach for a given CEA, where the general flow of health states in which modeled patients may transition over time is portrayed [12,18,19]. Each potential health state is coupled to a transition probability (derived from literature), resulting in adjustment of HR-QoL and costs for patients with applicable risk factors [12,18,19]. The Monte-Carlo component may be thought of as the mathematical engine allowing transition probabilities to be applied, at either the individual patient or cohort level [12,18,19]. It also facilitates sensitivity analyses, where the uncertainty in transition rates and other parameters may be applied to reveal the possible range of ICERs given changing assumptions. The M/MC approach has historically been considered optimal for simulating diabetes and other chronic diseases, as it can accommodate the numerous health states which are impacted and also allow for complex sensitivity analyses [12,18,19].

The second chapter of this thesis aims to establish the applicability of M/MC simulations for CEA in diabetes, starting with a demonstration of how HbA1c may be used as the clinical marker of modeled disease progression. If modeled changes in HbA1c, regardless of treatment, were not able to successfully differentiate outcomes and costs over time, then it would not make sense to move forward in applying specific treatment effects and costs directly or indirectly related to HbA1c control, including non-biological and real-world factors. The rationale for choosing HbA1c stemmed from (1) its widespread availability as a primary measure of efficacy or effectiveness in diabetes clinical studies, (2) its rising importance in not only monitoring disease progression, but in screening for and diagnosing diabetes, and (3) the high likelihood that it will remain a core marker of disease progression for the foreseeable future [20].

Within a validated M/MC model, we hypothesized that pre-defined, incremental improvements in HbA1c could be used to differentiate disease progression and costs over the long-term, natural course of diabetes. Three separate HbA1c thresholds were specified, realistic to what could be achieved in the real world – reductions from (1) 9.5% to 8.0%; (2) 7.9% to 7.0%; and (3) 6.9% to 6.5% – and all were compared to no reductions (e.g., remain at 9.5%, 7.9%, and 6.9%, respectively). This *difference in differences* approach allowed us to isolate the impact of step-wise improvements in HbA1c, and evaluate whether reasonable changes in HbA1c are sensitive enough within M/MC simulations to detect gains in health and economic benefit.

Treatment-specific Markov / Monte-Carlo modeling

Building on this, the next stage entailed demonstrating the ability to include treatment-specific effects on HbA1c as well as direct pharmacy costs. In doing so, we would ensure that diabetes treatments with varying degrees of HbA1c control and safety could be differentiated in terms of ICER results. Applying two separate RCTs comparing a total of three types of insulin within the same validated M/MC model, we hypothesized that because of improved HbA1c and reduced side effects (e.g., lower hypoglycemia), insulin detemir (IDet) would be cost-effective compared to both insulin glargine (IGlarg) and neutral protamine Hagedorn insulin (NPH). Specifically, this would occur because of reductions in modeled adverse events (i.e., poor health states) resulting in improved HRQoL, and less resource use and costs.

Chapters 2 and 3 first explore concepts and assumptions in existing modeling approaches. In order to propose new methods of CEA which may accommodate non-biological and real-world characteristics of diabetes treatment, it is important to demonstrate that disease and treatment effects, independently, have the potential to result in meaningful CEA results. Next, this initial groundwork is then revised to include non-biological and real-world factors, as generated from observational research evidence.

The role of PROs in relation to clinical and non-biological treatment attributes

A primary methodological concentration of this thesis is in PROs, with T2D as the main area of application. Having demonstrated that CEAs in diabetes can accommodate clinical changes (HbA1c) imparted by natural disease progression as well as individual treatments, attention could be placed on creating a foundation for describing the impact of non-biological aspects of therapy. Specifically, PROs such as patient preferences and treatment satisfaction have been noted as being sensitive to both clinical and non-biological treatment attributes, and therefore are potentially important when predicting future health outcomes and costs in real-world populations [11].

To maintain consistency between chapters, variation in patient preferences and treatment satisfaction was investigated among patients specifically taking insulin. Insulin became a central therapy in this thesis because each of the non-biological innovations in modern products are relevant – device ergonomics (handling), medication timing and dosage, and route of administration (injectable, inhaled, etc.) [9,10]. Any important changes in

preference and satisfaction associated with treatment were more likely to be captured with insulin than with oral medication. For this reason, the effect of preference and satisfaction were first assessed among insulin patients.

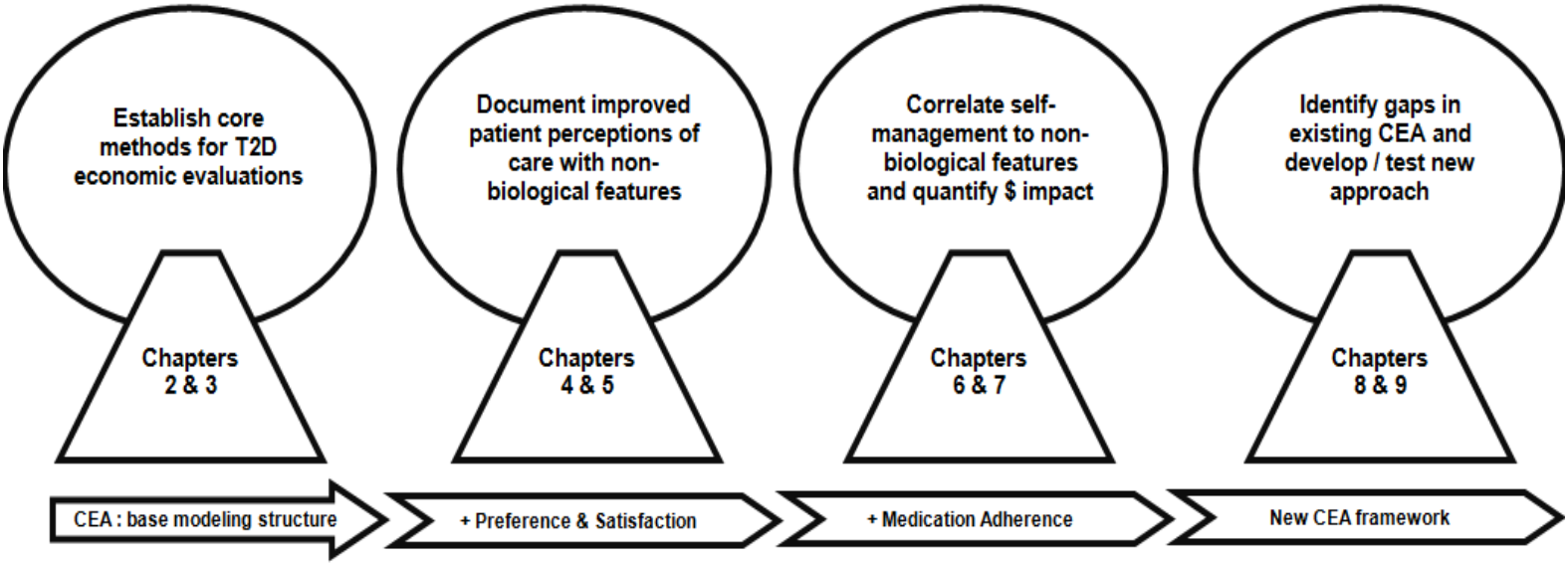
We used a prospective, open-label RCT design to investigate potential differences in preference and treatment satisfaction among patients injecting insulin with a vial/syringe compared to a pre-filled handheld device. The type of insulin did not differ between cohorts (cross-over design), only the method of injection, thus making it possible to isolate the influence of non-biological product attributes on PROs. These attributes may cause the pen device to be less burdensome due to improved handling (device flexibility), a less painful gauge and shorter needle, less complicated administration process (no need to manually fill syringe), and more accurate dosing. As such, it was expected that both preference and satisfaction would be significantly improved when using the device.

Still, in order to weave a common thread warranting inclusion of non-biological treatment characteristics back into CEA, it was necessary to extend the hypothesis that a pen device could improve PROs by addressing possible correlations between PROs and actual clinical efficacy and safety. In other words, the next step was to evaluate whether or not PROs (treatment satisfaction in our case), which are sensitive to non-biological product features, could also be linked to changes in clinical outcomes that serve as the primary driver of modeled results in CEAs. It could therefore be seen that non-biological product features influence patient perceptions of care, which then may play a part in determining the likelihood of achieving HbA1c control, and therefore should be included as a primary consideration in CEA. We used a retrospective analysis of a multi-center RCT in which both clinical and PRO measures were captured to investigate the extent to which these correlations may exist. Specific domains of, and overall, treatment satisfaction were expected to improve as insulin patients' HbA1c improved, and as certain side effects were reduced, namely those relevant to non-biological product features (e.g., neuropathy (injection site pain), retinopathy (visual acuity needed to properly fill syringe and accurately inject)).

Insight from these complimentary analyses can be used as evidence that PROs may be the facilitating outcome measure between non-biological and clinical factors of treatment (with insulin as our example). Through its impact on PROs, which then may influence clinical markers applied in CEA, the relevancy of non-biological treatment factors in CEA can be established.

The first half of this thesis intended to establish the relevancy of CEA and M/MC modeling in diabetes, and to evaluate interrelations between PROs, non-biological product features, and clinical changes. The remaining chapters aim to (1) assess real-world factors such as treatment-specific levels of patient self-management, (2) inquire the extent to which medication adherence and persistence impact resource use and costs, and (3) develop and test new ways of incorporating this information back into CEA (Figure 2).

Figure 2. Development of conceptual framework and innovative approach at CEA in diabetes, by chapter and topic



Associations of patient self-management with health economic outcomes

The immediate effects of sub-optimal medication adherence seem obvious – pharmacy costs go down due to lowered utilization, yet the disease is undertreated and risk increases for poor health outcomes and a subsequent rise in resource use and medical costs. This was a core assumption underpinning our hypotheses for Chapters 6 and 7. However, several questions remained to actually quantify these relationships in a manner appropriate for inclusion in CEA, such as: (1) what ranges exist for levels of adherence among different diabetes treatment types? (e.g., oral vs. injectable); (2) to what extent does sub-optimal adherence impact resource use and costs, and for which types of health events?; and (3) are non-biological treatment factors involved in determining medication adherence?

The answers to these questions were essential in developing and testing new frameworks for CEA in diabetes, as it was expected that they would provide information to create reasonable effect sizes (on resource use and costs) and ranges for sensitivity analysis when incorporating, for example, the real-world influence of medication adherence. Additionally, if non-biological product features inherent to various treatments were found to be significantly associated with adherence, further rationale would exist for including adherence in modeling. In order to begin obtaining these estimates, a systematic literature review was performed to assess current evidence on the overall prevalence and cost consequences of medication adherence for various diabetes treatments.

Once it was confirmed that medication adherence in diabetes varies widely between treatments and may heavily influence healthcare costs in general, a follow-up analysis

was conducted at a more granular level to assess whether specific treatments with important differences in non-biological features would differ in adherence, and if these differences correlated to differences in health outcomes and costs in the real world. Utilizing a large database of administrative healthcare claims, several cohorts of insulin patients were analyzed retrospectively, hypothesizing that patients converting to injection of insulin with a pre-filled handheld injection device (from vial/syringe) would exhibit greater adherence, and that there would be observed correlations to improved health outcomes, lower resource use, and costs. In doing so, non-biological product features associated with handheld injection devices could be correlated to measures of self-management and costs, and in turn, become relevant for inclusion in CEA.

Novel framework and methods for application of CEA to modern treatments

Having established broad and individual treatment-specific correlations between medication adherence and health economic outcomes, and assessing the relationship that non-biological treatment factors may have on self-management, it became important to critically evaluate current methods and published examples of economic models in diabetes, specifically T2D. The primary goal of Chapter 8 was to investigate whether current modeling approaches adequately address issues of self-management that are important for determining the true economic impact seen in real-world patient populations. Secondly, if current methods did not adequately incorporate these relationships, our goal was to propose a novel framework of interactions for PROs, measures of self-management, clinical changes (HbA1c), resource use, and costs.

Chapter 9 builds on the novel framework of these interrelations by developing a unique M/MC model with structural and mathematical components incorporating the real-world impact of self-management on clinical changes, resource use, and costs. Two separate CEAs were conducted, one which served as a base case analysis ignoring medication adherence, and a second which incorporated adherence to adjust results. Simulated treatments were those with very distinct differences in non-biological product features (oral vs. injectable), and commonly used by T2D patients. The corresponding ICERs could then be compared, and an estimate of the impact of real-world adherence on calculated cost-effectiveness obtained.

The overarching aim of this thesis is to propose new, enhanced means for CEA in diabetes in order to ensure that modeled results used in decision-making are more relevant for real-world populations. As modern treatments increasingly focus on non-biological product innovations directly aimed at improving patient perceptions of care and, subsequently, self-management, the importance of continuously adapting and improving CEA per these parameters will remain.

Non-biological treatment attributes may impact patient perceptions of care (PROs), which can then influence whether or not a patient is willing or able to properly self-manage. They have become an important part of the patient-centered approach to tailoring therapy and achieving individualized HbA1c targets, and are central to successfully implementing prescribed therapy in the real world. Medication adherence is

able to impact HbA1c, which will influence whether or not a patient experiences poor health outcomes, and increased resource use and costs. Moving forward, decision-makers will be able to better understand these relationships and be equipped with the tools to generate more accurate estimates of the cost-effectiveness of modern therapies. This should help to ensure that patients receive more appropriate access to care in the most efficient way possible.

References

1. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. Diabetes Care 2008; **31**(3):596-615.
2. World Health Organization. The Economic Burden of Diabetes. Available from http://www.who.int/mediacentre/factsheets/fs312/en/, accessed 27 August 2007.
3. HauberA, Gale E. The market in diabetes. Diabetologia 2006; **49**(2):247-252.
4. World Health Organisation Department of Noncommunicable Disease Surveillance. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. 1999.
5. American Diabetes Association Executive Committee. Standards of Medical Care in Diabetes – 2011. Diabetes Care. 2011; **34**(1): S11-S61.
6. Steinberger J, Moran A, Hong CP, Jacobs DR, Sinaiko AR (2001). "Adiposity in childhood predicts obesity and insulin resistance in young adulthood". J Pediatr **138**(4): 469–73.
7. Mozaffarian D, Kamineni A, Carnethon M, Djoussé L, Mukamal KJ, Siscovic, D (April 2009). "Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study". Arch of Internal Medicine **169**(8): 798–807.
8. H King, R E Aubert and W H Herman. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; **21**(9):1414-1431.
9. Guimarães C, Marra CA, Gill S, Simpson S, Meneilly G, Queiroz RH, Lynd LD. A discrete choice experiment evaluation of patients' preferences for different risk, benefit, and delivery attributes of insulin therapy for diabetes management. Patient Prefer Adherence. 2010; **8**(4):433-440.
10. Ryan M, Ferrar S. Using conjoint analysis to elicit preferences for health care. BMJ. 2000; **320**(7248):1530-1533.
11. Ryan M. Using conjoint analysis to take account of patient preferences and go beyond health outcomes: an application to in vitro fertilisation. Soc Sci Med. 1999; **48**(4):535-546.
12. Cobden DS, Niessen LW, Barr CE, Rutten FF, Redekop WK. Relationships among self-management, patient perceptions of care, and health economic outcomes for decision-making and clinical practice in type 2 diabetes. Value Health. 2010; **13**(1):138-47.
13. Flatley-Brennan P, Strombom I. Improving Health Care by Understanding Patient Preferences: The Role of Computer Technology. J Am Med Inform Assoc. 1998; **5**(3): 257–262.
14. Weaver M, Patrick DL, Markson LE, Martin D, Frederic I, Berger M: Issues in the measurement of satisfaction with treatment. Am J Man Care 1997; **3**:579-594.

15. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. JAMA 1998; **279**:1458–62.
16. Cramer JA, Roy A, Burrell A, et al. Medication Compliance and Persistence: Terminology and Definitions. Value Health 2008; **11**:44-47.
17. Cella DF, Tulsky DS. Measuring quality of life today: methodological aspects. Oncology 1990; **4**(5):29-38; discussion 69.
18. Banta HD, Luce BR. Health Care Technology and its Assessment: An International Perspective. New York: Oxford University Press; 1993.
19. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, Luce BR. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health. 2003; **6**(1):9-17.
20. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, Phillips LS. Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. Diabetes Care. 2010; **33**(10):2184-2189.

Chapter 2

Modeling incremental HbA1c targets in Type 2 diabetes

Adapted from: Valentine WJ, Palmer AJ, Nicklasson L, Cobden D, Roze S. Improving Life Expectancy and Decreasing the Incidence of Complications Associated with Type 2 Diabetes: A Modelling Study of HbA1c Targets. *International Journal of Clinical Practice*. 2006; **60**(9):1138-45.

Summary

The purpose of this chapter was to project the long-term clinical and cost outcomes that accompany pre-defined improvements in glycaemic control in patients with Type 2 diabetes (T2D). A peer-reviewed, validated, non-product-specific Markov model of T2D was used to project the long-term clinical and cost outcomes associated with three HbA1c reduction scenarios (vs. no reduction): (i) decreasing mean HbA1c from 9.5% to 8.0%; (ii) from 8.0% to 7.0%; and (iii) from 7.0% to 6.5%. A typical baseline U.S. T2D cohort derived from National Health and Nutrition Examination Survey (NHANES) data was simulated over a lifetime horizon (35 years). Incidence of diabetes-related complications and costs (2005 USD) were accounted based on published data. Discount rates (3% per annum) were applied to clinical benefits and costs. Sensitivity analyses were performed.

Stepwise reductions in HbA1c as an independent variable correlated with delayed time to diabetes-related complications and a reduced cumulative incidence of complications, including cardiovascular, renal and neurologic comorbidities. Related costs also decreased. Reductions in both poorly- (9.5–8.0%) and better-controlled (7.0–6.5%) patients produced incremental gains in undiscounted life expectancy (LE) [1.06 (0.31) and 0.32 (0.34) years [mean (SD)], respectively]. Similar improvement patterns were observed in quality-adjusted life expectancy (QALE). Benefits from sequential reduction scenarios, when aggregated, exhibited the most dramatic effect. Improved glycaemic control was associated with reductions in complication rates and costs, as well as increased LE and QALE among T2D patients. These data illustrate the long-term importance of reaching normoglycaemia and support intensified HbA1c control as a cornerstone of effective long-term T2D management.

Introduction

Glycaemic control is of fundamental importance in the management of diabetes [1]. Landmark clinical and epidemiological studies have provided evidence that improved glycaemic control is associated with decreased incidence of diabetes-related complications, including nephropathy, retinopathy, neuropathy and cardiovascular disease (CVD) [2–7]. The United Kingdom Prospective Diabetes Study 33 (UKPDS) reported that intensive treatment [mean glycosylated haemoglobin (HbA1c) 7.0%] resulted in a 12% lower risk of experiencing any diabetes-related complication and a 10% lower risk of diabetes-related death compared with conventional treatment (mean HbA1c 7.9%) [3]. The importance of effective glycaemic control has been recognised in several publications of guidelines for the treatment of diabetes. The International Diabetes Federation (IDF) and American Association of Clinical Endocrinologists (AACE) guidelines recommend a target HbA1c level of 6.5% for adults [8,9]. More recently, the American Diabetes Association (ADA) published Clinical Practice Recommendations in which a target level for HbA1c of 7.0% was recommended for non-pregnant adults [1].

Other risk factors included blood pressure (target 130/80 mmHg) and lipid levels (target low-density lipoprotein cholesterol 100 mg/dl, high-density lipoprotein cholesterol (HDL) 140 mg/dl and triglycerides 150 mg/dl). A recent modeling study investigated the relative

impact of these risk factors by simulating independent variations in each among a cohort of patients with newly-diagnosed T2D [10]. A 10% improvement from baseline in HbA1c, systolic blood pressure (SBP), HDL or total cholesterol was simulated over patients' lifetimes. The study concluded that of these four risk factors, glycaemic control defined by HbA1c level has the greatest impact on long-term health outcomes.

Although the evidence supporting tight glycaemic control in T2D is very strong, the mean HbA1c of T2D patients is increasing in the U.S. According to the NHANES 1999–2000 report, average HbA1c in 2000 was 7.9%, an increase of 0.3% compared with the period 1988–1994, and this despite an increase in use of prescription medication [11]. With the treatment emphasis being placed upon reaching recommended goals of HbA1c 7.0%, patients often become de-motivated despite achieving a significant reduction when they fail to reach these targets. However, as noted by Gaede and Pederson [12], a target is not an all-or-nothing phenomenon; evidence from the UKPDS suggested that any reduction in glycaemia will be beneficial in clinical terms.

The purpose of this study was to simulate the long-term effects on costs and clinical outcomes of improving glycaemic control in T2D patients. This was performed by applying three pre-defined HbA1c thresholds to T2D patients presenting baseline characteristics derived from NHANES data and simulating the costs and effects of reaching each target in a stepwise manner. A computer modeling approach was used to examine the impact of changing HbA1c levels independently of changes in other risk factors [lipid profiles, blood pressure, body mass index (BMI)] over patient lifetimes.

Methods

Overview

A previously published and validated computer simulation model of diabetes was used to project the long-term clinical and cost outcomes of improving HbA1c levels in three separate glycaemic scenarios among a typical T2D cohort (base case analysis). Patients were assumed to progress from the preceding scenario to the next, with the resulting benefits of the improved glycaemic control then modeled over time. Patients in the simulation received hypothetical interventions to perform the following comparisons:

- Scenario 1: reduction in mean HbA1c from 9.5% to 8.0% vs. no reduction (patients remained at an HbA1c level of 9.5%). The starting value of 9.5% was based on several recent prospective, cross-sectional analyses in poorly controlled T2D patients that focused on the extent to which intensification of glycaemic control improved outcomes [13–15]. These studies were designed to include patients with mean baseline HbA1c levels between 9.0% and 9.5%, corresponding to the definition of poor glycaemic control in adults by the National Quality Measures Clearinghouse of the Agency for Healthcare Research and Quality.

- Scenario 2: reduction in mean HbA1c from 8.0% to 7.0% (ADA recommended target HbA1c level) vs. no reduction (patients remained at an HbA1c level of 8.0%).

- Scenario 3: reduction in mean HbA1c from 7.0% to 6.5% (IDF and AACE recommended target HbA1c level) vs. no reduction (patients remained at an HbA1c level of 7.0%).

Reductions in mean HbA1c level associated with the hypothetical interventions in this study were applied at the start of the simulation. HbA1c levels in all simulated patients, including those in the 'no reduction' treatment groups, then followed a pre-defined progression based on published long-term data from the UKPDS [3,4,16]. To assess the impact of lowering HbA1c in isolation, no treatment effects were applied to other risk factors such as SBP, BMI and lipid levels in the simulated cohorts. These parameters followed a natural progression over time as previously described by Palmer et al. [16]. Improvements in complication rates, life expectancy (LE) and quality-adjusted life expectancy (QALE) associated with decreasing HbA1c levels were reported for each of the three scenarios to provide a measure of the anticipated clinical benefits associated with tight glycaemic control. The cost of diabetes-related complications over patients' lifetimes was also assessed.

Model

The analysis was performed using a published, peer-reviewed, validated, non-product-specific model of T2D [17,18]. It is an interactive computer simulation model designed to project the long-term health outcomes and economic consequences of different clinical policies or treatment interventions. The model performs real-time simulations to evaluate the incidence of complications, LE, QALE and total costs within defined populations and has been extensively validated against 'real life' data from published prospective clinical and epidemiological studies of diabetes [18].

Simulation Cohort

A hypothetical patient cohort was created for the analysis with the aim of mimicking a typical U.S. T2D population. Baseline demographic data was based on information from the NHANES database collected between 1999 and 2000 [19] (Table 1). Much of the necessary information on baseline complication rates was not available from NHANES (only data on previous myocardial infarction and heart failure were found), making it necessary to supplement this cohort with recently published characteristics from Initiation of Insulin to reach A1c Target (INITIATE), a randomised, controlled clinical trial in 233 patients with T2D in the U.S. (20) (Table 1). Current patient management data specific to the U.S. setting were derived from several published sources [21–24] (Table 1).

Table 1. Baseline demographics, complications, relevant concomitant medications and management of patients in the simulated cohort

Characteristics	*Model simulation population*	*Source*
Sex (% male)	49.3	NHANES, 2002 (19)
Ethnic origin (%)		
Caucasian	62.1	NHANES, 2002 (19)
Hispanic	15.4	NHANES, 2002 (19)
Black	17.4	NHANES, 2002 (19)
Other	5.1	NHANES, 2002 (19)
Age (years), mean (SD)	59	NHANES, 2002 (19)
BMI (kg/m^2), mean (SD)	32.0	NHANES, 2002 (19)
Duration of diabetes (years), mean (SD)	12	NHANES, 2002 (19)
Hypertensive heart disease (assumed LVH)	0	INITIATE study (20)
Angina pectoris (%)	1.72	INITIATE study (20)
Myocardial infarction (%)	10.8	NHANES, 2002 (19)
Heart failure (%)	8.2	NHANES, 2002 (19)
Cardiac dysrhythmia (assumed atrial fibrillation) (%)	1.29	INITIATE study (20)
Stroke (%)	8.8	INITIATE study (20)
Peripheral vascular disease (%)	0.86	INITIATE study (20)
Peripheral neuropathy (%)	23.2	INITIATE study (20)
Foot ulcer/amputation (%)	0.43/0.43	INITIATE study (20)
Microalbuminuria (%)	4.0	INITIATE study (20)
Gross proteinuria (%)	4.0	INITIATE study (20)
Background diabetic retinopathy (%)	8.5	INITIATE study (20)
Proliferative diabetic retinopathy (%)	0	INITIATE study (20)
Blindness and low vision (%)	0	INITIATE study (20)
Cataract (%)	4.3	INITIATE study (20)
Macula oedema (%)	0	INITIATE study (20)
Taking ACE-I/ARB (%)	41.0	21
Taking statins (%)	45.0	22
Taking aspirin (%)	45.6	23
Screened for retinopathy (assumed treated with laser if detected) (%)	55.0	24
Screened for renal disease (assumed treated with ACE-I or ARB if detected) (%)	74.0	24
Proportion on foot ulcer prevention program (%)	86.0	24

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; LVH, left ventricular hypertension; SD, standard deviation.

Costs

U.S.-specific cost data were collected from numerous sources [25–30] and have been described previously [16]. All costs were inflated to 2005 values and are expressed in U.S. dollars ($). The present analysis takes into account the cost of complications associated with T2D in the simulated cohort. Treatment costs were not included in the study as the interventions commonly used to yield such HbA1c reductions are subject to significant variation and are often adjusted.

Discounting, Time Horizon and Perspective

In the base case analysis, undiscounted LE, QALE discounted at 3% per annum and direct costs discounted at 3% per annum were presented. The process of discounting clinical and economic outcomes is designed to weight gains that are obtained sooner more favourably than those achieved later. It is a common established practice in economic analyses. The discount rates applied are country specific (U.S.). Undiscounted cumulative incidence rates for diabetes-related complications were presented. A patient lifetime horizon was used (35 years). Complication costs were accounted from a third party, U.S.-payer perspective.

Sensitivity Analyses

Sensitivity analyses were performed to investigate the impact of varying discount rates and time horizon on simulation outcomes. Discount rates on clinical outcomes (LE and QALE) were varied between 0% and 6% and discount rates on costs were varied between 3% and 6% per annum. Time horizon was varied between 0 and 35 years to evaluate the impact of improvements in HbA1c over shorter time periods. Cost and clinical outcomes at 2-, 5- and 10-year time horizons, as well as the 35-year base case values were reported in this study.

Statistical Approach

For each simulation performed in the present study (base case and sensitivity analyses), 1000 patients were run 1000 times through the model and mean results and standard deviations (SD) were generated using a non-parametric bootstrapping approach [31]. Mean and SD values were presented for LE, QALE, cumulative incidence of complications and the costs of complications in the base case analysis. For the sensitivity analyses, only the differences between mean (and SD) values in the ‘reduced HbA1c’ and ‘no reduction’ groups were presented for LE, QALE and total complications costs.

Results

Long-term Clinical Benefits of Improved Glycaemic Control: LE and QALE

The base case analysis demonstrated that reductions in HbA1c were associated with improvements in undiscounted LE in all three base case scenarios (Table 2). The greatest

improvement in LE was observed in scenario 1, where baseline HbA1c was reduced from 9.5% to 8% and undiscounted LE was extended by 1.11 years compared with no HbA1c change. When baseline HbA1c was lowered from 8.0% to 7.0% in scenario 2, the improvement in undiscounted LE was 0.72 years vs. no change. The smallest improvement in undiscounted LE was observed in scenario 3, where baseline HbA1c was reduced from 7.0% to 6.5% and there was an increase of 0.33 years. A similar pattern was observed in the QALE endpoint, which was discounted at 3% per annum in line with current recommendations for analyses in the U.S. settings (Table 2).

Table 2 Summary of base case results

Characteristics	*HbA1c reduced*	*No change*	*Difference*
Scenario 1: HbA1c reduced from 9.5% to 8.0%			
Undiscounted life expectancy (years)	13.35 (0.17)	12.24 (0.16)	1.11
Quality-adjusted life expectancy (QALYs)*	6.86 (0.12)	6.29 (0.10)	0.58
Total lifetime cost of complications*	67,420 (2583)	72,629 (2497)	−5209
Outcome/ICER	Reducing HbA1c from 9.5% to 8.0% was dominant to no change		
Scenario 2: HbA1c reduced from 8.0% to 7.0%			
Undiscounted life expectancy (years)	14.07 (0.17)	13.35 (0.17)	0.72
Quality-adjusted life expectancy (QALYs)*	7.24 (0.12)	6.86 (0.12)	0.38
Total lifetime cost of complications*	64,322 (2498)	67,420 (2583)	−3099
Outcome/ICER	Reducing HbA1c from 8.0% to 7.0% was dominant to no change		
Scenario 3: HbA1c reduced from 7.0% to 6.5%			
Undiscounted life expectancy (years)	14.40 (0.18)	14.07 (0.17)	0.33
Quality-adjusted life expectancy (QALYs)*	7.42 (0.13)	7.24 (0.12)	0.18
Total lifetime cost of complications*	62,684 (2333)	64,322 (2498)	−1637
Outcome/ICER	Reducing HbA1c from 7.0% to 6.5% was dominant to no change		

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio. The values shown are means with standard deviation in parentheses. *Discounted at 3% per annum.

In scenario 1 (9.5–8.0%), mean QALE was increased by just over half a quality-adjusted life year (QALY) compared with no HbA1c reduction (0.58). In scenario 2 (8.0–7.0%), the improvement associated with reduced HbA1 was 0.38 QALYs, and in scenario 3 (7.0–6.5%) it was 0.18 QALYs.

Complication Rates and Costs of Complications

The cumulative incidence of diabetes-related complications was projected to decrease over patient lifetimes with improved glycaemic control (Figure 1). For example, the cumulative incidence of end-stage renal disease (ESRD) was reduced from 13.2% (1.1%) to 7.9% (0.9%) with improved glycaemic control in scenario 1 (9.5–8.0%). In scenario 2 (8.0–7.0%), the corresponding decrease was from 7.9% (0.9%) to 5.3% (0.7%) and in scenario 3 (7.0–6.5%) a reduction from 5.3% (0.7%) to 4.2% (0.6%) was exhibited. A similar pattern was observed with the cumulative incidence of retinopathy, neuropathy, other nephropathy and most CVD complications (Figure 1).

Interestingly, an exception to this pattern was observed with stroke, where the cumulative incidence increased from 12.1% (1.1%) in patients with HbA1c remaining at 9.5% (scenario 1) to 15.1% (1.1%) in patients treated to target HbA1c of 6.5% (scenario 3). This effect was mirrored by the cumulative incidence of non-specific mortality. Both may be due to the survival paradox, where patients receiving a more efficacious intervention generally experience fewer complications and therefore live longer. As the population grows older, the likelihood of experiencing stroke or death because of other causes (non-specific mortality) increases relative to other complications/diabetes-related mortality.

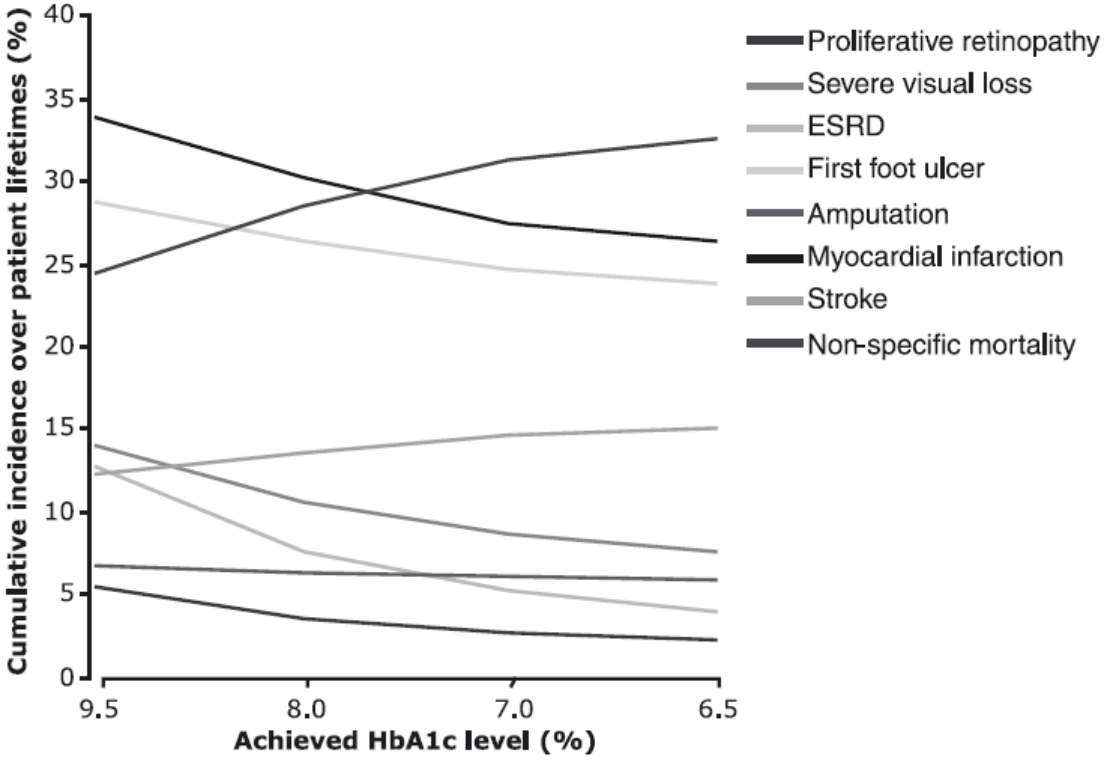
The improvements in the cumulative incidence rates of diabetes-related complications were reflected in the total lifetime costs of complications (Table 2). The most substantial cost savings were projected in scenario 1 (9.5–8.0%) where mean total lifetime costs of $72,629 (2497) per patient were reduced to $67,420 (2583) with the hypothetical intervention, a savings of $5209 per patient. In scenario 2, the hypothetical intervention further reduced the total cost of complications to $64,322 (2498), corresponding to a savings of $3099. In scenario 3, reducing HbA1c to 6.5% decreased total lifetime complication costs to $62,684 (2333), saving $1637 per patient compared with no HbA1c change.

Time to Onset of Complications

In the base case analysis, reductions in HbA1c were associated with increased periods free of diabetes-related complications. For example, in scenario 1 (9.5–8.0%), the mean time alive and free of any complications was increased from 1.4 years in the no reduction group to 2.1 years with HbA1c reduction. In scenario 3 (7.0–6.5%), this value improved from 2.6 to 3.0 years with HbA1c reduction. A similar pattern of delayed time to onset was observed across the range of diabetes-related complications including retinopathy, nephropathy, neuropathy, lower extremity amputation and CVD. For example, mean time to onset of ESRD was delayed from 12.0 years to 13.2 years in scenario 1 (9.5–8.0%) and from 14.0 to 14.3 years in scenario 3 (7.0–6.5%). Similarly, the mean time to onset of

first myocardial infarction was delayed by just over 1 year in scenario 1 (from 10.1 to 11.3 years) and by approximately 0.4 years in scenario 3 (from 12.1 to 12.5 years).

Figure 1 Cumulative incidence of complications over patient lifetimes at target HbA1c levels



Sensitivity Analyses

Sensitivity analyses were performed to investigate the impact of discount rates and time horizon. In the base case analysis, LE was presented with no discounting applied. QALE and costs of complications were discounted at 3% per annum. In the first sensitivity analysis, a discount rate of 0% was applied to all clinical benefits. This decreased the projected QALE values from the base case and led to smaller improvements associated with the hypothetical interventions. Improvements in QALE ranged between 0.90 QALY in scenario 1 (9.5–8.0%) and 0.29 QALY in scenario 3 (7.0–6.5%) for hypothetical intervention vs. no HbA1c reduction.

When a discount rate of 3% per annum was applied to all clinical benefits, in line with current recommendations for the U.S. setting, projected LE was lower than in the base case. Improvements in LE associated with treatment to target HbA1c levels were between 0.58 years (scenario 1, 9.5–8.0%) and 0.18 years (scenario 3, 7.0–6.5%). Increasing the discount rates on costs and clinical benefits to 6% per annum decreased LE and QALE

projections and the improvements associated with decreasing HbA1c. Similarly, projections of mean total lifetime costs of complications were lower, with decreased cost savings associated with improved glycaemic control. Sensitivity analysis on the time horizon showed that clinical benefits associated with reduced HbA1c levels were evident after only 2 years. For example, QALE was increased by 0.01 QALY with HbA1c reduction in scenario 1 (9.5–8.0%) compared with no reduction. In scenario 3 (7.0–6.5%), an improvement of 0.004 QALY was projected.

After 10 years, QALE was improved by 0.19 QALYs with HbA1c reduction in scenario 1 (9.5–9.0%) and in scenario 3 (7.0–6.5%), this value was 0.05 years. Notable savings in the costs of complications were projected at the 10-year time horizon. A savings of $4041 per patient was associated with improved glycaemic control in scenario 1 (9.5–8.0%), representing approximately 78% of the total per patient savings reported in the base case analysis. However, cost benefits took longer to accumulate with the other HbA1c reductions investigated. For instance, in scenario 3 (7.0–6.5%), cost savings of $723 were reported at the 10-year time horizon, accounting for only 44% of the base case savings associated with improved HbA1c.

Discussion

This modeling study is the first to report the long-term clinical benefits associated with a range of pre-defined, stepwise improvements in HbA1c independently of other risk factors in patients with T2D. Whilst the UKPDS study results demonstrated a direct relationship between glycaemia and the risk of microvascular complications over the 6 year study period, we have quantified the clinical and economic impact of incremental improvements when viewed over a patient's lifetime. Our simulations indicated that improved glycaemic control was associated with substantial improvements in undiscounted LE and QALE, reduced cumulative incidence and costs of diabetes-related complications, and increased time to onset of complications in a typical cohort of patients with T2D.

In the simulated patient group, the increase in LE over the lifetime period was considerable [32–34]. The gain associated with decreasing HbA1c values from 9.5% to 8.0% was 1.11 years and decreasing from 7% to 6.5% was associated with a gain of 0.3 years of life. These improvements compare favourably with other medical interventions such as quitting smoking (for a 35-year-old man, mean improvement in LE is 0.83 years); routine beta-blocker therapy (for 55-year-old men who have survived a myocardial infarction, improvement of 0.1–0.47 years); chemotherapy for patients with advanced non-small cell lung cancer (improvement of 0.15–0.24 years); reduction of diastolic blood pressure (from 95 mmHg to 88 mmHg in 35-year-old men results in an improvement of 1.08 years); and reduction in cholesterol (from 239 to 200 mg/dl results in an improvement of 0.5 years) or thrombolytic therapy with recombinant tissue plasminogen activator during suspected myocardial infarction (improvement of 1.25 years) [33].

The most substantial improvements in clinical outcomes were observed in the hypothetical treatment groups where the greatest improvements in HbA1c were simulated (i.e. scenario 1 > scenario 2 > scenario 3). Perhaps the main strength of the present analysis is that it provides an illustration of the anticipated benefits associated with treating patients to a range of HbA1c targets that are realistic for the majority of T2D patients. As there are individual differences in the risks of hypoglycaemia, weight gain and other adverse effects which are vital considerations when intensifying the treatment of type 2 patients, it is important to estimate the incremental difference between HbA1c goals. A limitation of currently recommended glycaemic goals is that they often do not provide detailed, comparative, differential data, but rather set a generic target which may be inappropriate for certain patients with specific baseline risk factors. In addition to this, many interventions such as patient education [35,36] and self-monitoring of blood glucose [37] amongst type 2 diabetics achieve moderate improvements in glycaemic control and patient quality of life. Therefore patients beginning with higher HbA1c levels, although achieving improvement in glycaemic control, are unlikely to reach recommended targets based solely on these interventions. Evaluation of such interventions requires an appreciation for the long-term clinical and economic benefits that incremental improvements in HbA1c can yield.

The results presented here provide a reference against which to consider the costs of such interventions when provided to patients with differing baseline levels of glycaemic control. Although the present study indicates that improved glycaemic control with conservative HbA1c targets (9.5% and 8.0%) can lead to substantial clinical benefits, it indicates that more aggressive HbA1c targets (7.0% and 6.5%) provide the greatest benefits in patient health, cost containment, quality of life and LE, allowing clinicians to compare these outcomes and assess the appropriateness of instituting a more rigorous treatment approach.

Improvements in HbA1c have been studied in isolation. Some may argue that this is not a completely accurate reflection of a patient's clinical progression. However, this was an exploratory analysis specifically designed to assess only the impact of HbA1c improvements with other clinical considerations pre-defined. If there were data pertaining to simulated improvements in a range of risk factors in the present study, it would have become very difficult to conclusively identify drivers of long-term clinical benefits. As a result, the present study may underestimate the clinical benefits of a multifactorial approach to the management of patients with T2D including proactive treatment of other risk factors such as SBP and lipid levels. Indeed, as new clinical knowledge and best practices are continuously evolving, the importance of SBP, lipids, and inflammatory processes on diabetes outcomes are becoming more apparent. However, it should be noted that the present modeling simulation did not ignore the treatment of hypertension or hyperlipidaemia, but applied published data on patient management in the U.S. to accurately simulate the treatment of a typical U.S. cohort [21,23,24,38].

A potential shortcoming of the present study was that, because the interventions used to reduce HbA1c levels were hypothetical, the simulation did not take into account any negative effects associated with currently available treatments (i.e., weight gain and/or

elevated risk of hypoglycaemia). This may have led to an overestimation of the clinical benefits associated with these treatments in relation to real-life interventions used to treat patients to target HbA1c. However, the simulation did take into account hypoglycaemia, with an annual probability of severe hypoglycaemic events of 3% applied to all of the hypothetical treatments, in line with published observations in T2D patients from the UKPDS [3].

Conclusions

This modeling study provides evidence that improvements in glycaemic control over a range of HbA1c values between 9.0% and 6.5% are associated with substantial improvements in long-term clinical outcomes in patients with T2D. Improved glycaemic control, independent of improvements in other risk factors such as blood pressure or lipid levels, was associated with extended LE and time to complications, improvements in QALE, and a reduced cumulative incidence of complications over patient lifetimes. These findings reinforce the idea that intensified therapy aimed at optimising glycaemic control should be the foundation of effective long-term management of type 2 patients.

References

1. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2004; **27** (Suppl. 1): S15–35.
2. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; **329**: 977–986.
3. The UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; **352**: 837–53.
4. The UK Prospective Diabetes Study Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; **352**: 854–865.
5. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; **342**: 381–389.
6. Lawson ML, Gerstein HC, Tsui E, Zinman B. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. A systematic review and meta-analysis. Diabetes Care 1999; **22** (Suppl. 2): B35–9.
7. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; **321**: 405–12.
8. International Diabetes Federation. IDF Guidelines for Diabetes Care. http://www.d4pro.com/diabetesguidelines/. Accessed January 13, 2005.
9. American Association of Clinical Endocrinologists. Medical Guidelines for the Management of Diabetes Mellitus. Endocrine Practice 2002; **8** (Suppl. 1): 40–82.

10. Palmer AJ, Roze S, Valentine WJ et al. Impact of changes in HbA(1c), lipids and blood pressure on long-term outcomes in type 2 diabetes patients: an analysis using the CORE diabetes model. Curr Med Res Opin 2004; **20**: 53–8.
11. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004; **27**:17–20.
12. Gaede P, Pedersen O. Intensive integrated therapy of type 2 diabetes: implications for long-term prognosis. Diabetes 2004; **53** (Suppl. 3): S39–47.
13. Abraira C, Duckworth W, McCarren M et al. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. J.Diabetes Complications 2003; **17**: 314–322.
14. Gitter J, Langefeld CD, Rich SS, Pedley CF, Bowden DW, Freedman BI. Prevalence of nephropathy in black patients with type 2 diabetes mellitus. Am J Nephrol 2002; **22**:35–41.
15. McBean AM, Huang Z, Virnig BA, Lurie N, Musgrave D. Racial variation in the control of diabetes among elderly medicare managed care beneficiaries. Diabetes Care 2003; **26**:3250–3256.
16. Palmer AJ, Roze S, Valentine WJ et al. Diabetes model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin 2004; **20**: 5–26.
17. Palmer AJ, Roze S, Valentine W et al. The CORE diabetes model: projecting long term clinical outcomes, costs and cost effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision making. Curr Med Res Opin 2004; **20**: S6–26.
18. Palmer AJ, Roze S, Valentine W et al. Validation of the CORE diabetes model against epidemiological and clinical studies. Curr Med Res Opin 2004; **20**: S27–40.
19. National Center for Health Statistics, Centers for Disease Control and Prevention. NHANES 1999–2000 Dataset: Diabetes Survey. 2002.
20. Raskin P, Allen E, Hollander P et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005; **28**: 260–265.
21. Hueston WJ, Scibelli S, Mainous AG III. Use of microalbuminuria testing in persons with type 2 diabetes: are the right patients being tested? J Fam Pract 2001; **50**: 669–673.
22. Massing MW, Foley KA, Sueta CA et al. Trends in lipid management among patients with coronary artery disease: has diabetes received the attention it deserves? Diabetes Care 2003; **26**: 991–997.
23. McFarlane SI, Jacober SJ, Winer N et al. Control of cardiovascular risk factors in patients with diabetes and hypertension at urban academic medical centers. Diabetes Care 2002; **25**:718–723.
24. Miller CD, Phillips LS, Tate MK et al. Meeting American Diabetes Association guidelines in endocrinologist practice. Diabetes Care 2000; **23**: 444–448.
25. O'Brien JA, Patrick AR, Caro J. Estimates of direct medical costs for microvascular and macrovascular complications resulting from type 2 diabetes mellitus in the United States in 2000. Clin Ther 2003; **25**: 1017–1038.
26. DRG Guidebook. A comprehensive resource to the DRG classification system. St. Anthony Publishing, Eden Prairie, MN, USA, 2001.

27. Shearer A, Scuffham P, Gordois A, Oglesby A. Predicted costs and outcomes from reduced vibration detection in people with diabetes in the U.S. Diabetes Care 2003; **26**: 2305–2310.
28. 2000 Drug Topics Red Book. Medical Economics Company, Montvale, NJ, 2000.
29. Golan L, Birkmeyer JD, Welch HG. The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. Ann Intern Med 1999; **131**: 660–667.
30. Kantor J, Margolis DJ. Treatment options for diabetic neuropathic foot ulcers: a cost-effectiveness analysis. Dermatol Surg 2001; **27**: 347–351.
31. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997; **6**: 327–340.
32. Detsky AS, Redelmeier DA. Measuring health outcomes – putting gains into perspective. N Engl J Med 1998; **339**: 402–404.
33. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions – standardizing data on outcomes. N Engl J Med 1998; **339**: 380–386.
34. Naimark D, Naglie G, Detsky AS. The meaning of life expectancy: what is a clinically significant gain? J Gen Intern Med 1994; **9**: 702–707.
35. Keers JC, Groen H, Sluiter WJ, Bouma J, Links TP. Cost and benefits of a multidisciplinary intensive diabetes education programme. J Eval Clin Pract 2005; **11**: 293–303.
36. Banister NA, Jastrow ST, Hodges V, Loop R, Gillham MB. Diabetes self management training program in a community clinic improves patient outcomes at modest cost. J Am Diet Assoc 2004; **104**: 807–810.
37. Welschen LM, Bloemendal E, Nijpels G et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care 2005; **28**:1510–1517.
38. Weinstein MC, O'Brien B, Hornberger J et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices – modeling studies. Value Health 2003; **6**: 9–17.

Chapter 3

Cost-effectiveness of basal insulin in the U.S. health system

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Summary

The purpose of this study was to compare in clinical and economic terms the long-acting insulin analogue detemir with intermediate-acting Neutral Protamine Hagedorn (NPH) insulin and with long-acting insulin glargine. We used the validated Center for Outcomes Research (CORE) Diabetes Model to project clinical and cost outcomes over a 35-year base case time horizon; outcome data were extracted directly from randomized, controlled trials designed to compare detemir with NPH and with insulin glargine. Modeled patient characteristics were derived from corresponding trials, and simulations incorporated published quality-of-life utilities with cost data obtained from a Medicare perspective.

Detemir, when compared with NPH, increased quality-adjusted life expectancy by 0.698 quality-adjusted life-years (QALYs). Lifetime direct medical costs were increased by $10,451 per patient, although indirect costs were reduced by $4688. On the basis of direct costs, the cost per QALY gained with detemir was $14,974. In comparison with glargine, detemir increased quality-adjusted life expectancy by 0.063 QALYs, reduced direct medical costs by $2072 per patient, and decreased indirect costs by $3103 (dominant). Reductions in diabetes-related comorbidities were also associated with detemir in both instances, most notably in the complications of retinopathy and nephropathy. Relative reductions in rates of complications were greatest in the comparison of detemir with NPH. Results were most sensitive to variation in hemoglobin A1c (HbA1c) levels. However, variation among any of the key assumptions, including HbA1c, did not alter the relative results. Detemir represents an attractive clinical and economic intervention in the U.S. health care setting compared with both NPH insulin and insulin glargine.

Introduction

The landmark Diabetes Control and Complications Trial (DCCT) of insulin treatment in type 1 diabetes (T1D) clearly demonstrated that intensive insulin therapy administered over a 6.5 year period significantly reduces the incidence and progression of diabetic complications [1]. On the basis of the DCCT findings, current diabetes guidelines issued by the American Association of Clinical Endocrinologists recommend intensive insulin therapy for all patients with T1D [2]. However, the DCCT also showed that intensive insulin therapy was associated with an increased incidence of hypoglycemia and weight gain [3,4]. The occurrence of hypoglycemia is largely due to the pharmacodynamics of commonly used human insulin preparations. Intermediate acting insulins, such as Neutral Protamine Hagedorn (NPH) insulin, are characterized by a 12-hour duration of action that peaks approximately 5 hours after injection; patient absorption rates are highly variable [5]. Consequently, NPH must be injected twice daily by most patients, and it often fails to mimic physiologic insulin activity in that it begins more slowly, peaks later, and lasts longer than the endogenous insulin response.

In an attempt to overcome these drawbacks, long-acting insulin analogues have recently been developed that exhibit a more rapid onset of action with a 24 hour duration and peak-less activity, resulting in a near-physiologic basal level of insulin between meals [6].

In numerous randomized clinical trials of long-acting insulin analogues, insulin detemir (IDet) and insulin glargine (IGlarg) have demonstrated at least equivalent or moderately improved glycemic control compared with NPH [7-13]. It is important to note, however, that treatment with IDet was associated with less weight gain, reduced within-patient variability, and decreased rates of nocturnal and major hypoglycemia when compared with NPH insulin [7,9,10,14]. The clinical efficacy and cost-effectiveness of IDet were recently highlighted in a combined clinical trial meta-analysis and economic cost-effectiveness evaluation of IDet versus NPH conducted in the United Kingdom [15]. On the basis of a meta-analysis of 4 relevant randomized studies, it was concluded that treatment with IDet (similar to IGlarg) results in modest improvements in glycemic control, reduced hypoglycemia, and less patient weight gain compared with NPH. In the long-term economic analysis, this translated into reduced complications and improved quality of life; these outcomes represent excellent value for money spent [15].

However, because of differences in health care and treatment costs between countries, investigators must evaluate the cost-effectiveness of treatments in a country-specific manner. For this reason, and on the basis of findings of a randomized, controlled trial reported by Hermansen et al. [7], this report presents a discussion of the cost-effectiveness of IDet compared with that of NPH within the United States. In a second and separate analysis that is presented in the following report, IDet is directly compared with IGlarg. This comparison has been made possible by the recent completion of a 26 week, multicenter, randomized trial of IDet and IGlarg administered in conjunction with the rapid-acting insulin aspart [16]. In this head-to-head comparison, it was found that although improvements in glycemic control were comparable, adverse events such as risk for major and nocturnal hypoglycemia were significantly less frequent with IDet treatment. The more predictable glucose-lowering effect of IDet compared with both NPH and IGlarg has been previously suggested on the basis of pharmacodynamic and pharmacokinetic studies conducted in patients with T1D [17]. For the first time, it is now possible to directly compare these 2 long-acting insulin analogues from a clinical and an economic perspective on the basis of randomized clinical trial data.

In the following report, the validated Center for Outcomes Research (CORE) Diabetes Model is used to project the long-term clinical and economic benefits that might be anticipated with IDet treatment (either as a replacement for NPH or as an alternative to IGlarg) in the U.S. health system setting. Because currently available clinical data for these new long-acting insulin analogues have been generated from trials of less than 12 months' duration, the use of a computer simulation modeling approach is one of the few ways by which the long-term impact can be taken into consideration. By applying clinical trial results to simulation cohorts that closely resemble patients included in the trials, realistic assessments can be made in a defined cost setting. The following report represents a first attempt to predict the long-term clinical and economic potential of IDet in the U.S. diabetes market.

Methods

Two separate analyses were undertaken and are included in this report. The first analysis modeled the impact of IDet usage compared with NPH insulin. Data were extracted from an 18 week, open-label, randomized trial that compared treatment with twice-daily IDet given in conjunction with mealtime insulin (aspart) versus treatment with twice-daily NPH supplemented with human soluble insulin 30 minutes before meals [7]. In total, 598 patients with T1D were randomized and monitored for changes in glycemic control, insulin dose, body weight, and adverse events. The latter cost-effectiveness analysis, reported here, compares the long-acting insulins IDet and IGlarg. Model projections have been based on results generated in a recently completed head-to-head, randomized trial of IDet and IGlarg, in which IDet was administered twice-daily in combination with premeal insulin aspart (IAsp), and IGlarg was given once daily in combination with premeal IAsp [16]. Subjects were monitored over a 26 week period of treatment (6 weeks' titration and 20 weeks' maintenance); changes in glycosylated hemoglobin (HbA1c) and body weight, hypoglycemic events, and other adverse events were recorded.

Model Description

Through the CORE Diabetes Model, the short-term clinical effects of IDet versus NPH and IDet versus IGlarg were simulated over a long-term horizon (35 years) from the U.S. health system perspective. The CORE Diabetes Model has been previously published in considerable detail [18]. Briefly, it is an interactive computer simulation model of diabetes that investigators developed for the purpose of determining the long-term health outcomes and economic consequences of interventions in type 1 or type 2 diabetes. Comprising 15 interdependent sub-models, the model simulates the diabetic complications of angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy, end-stage renal disease, neuropathy, foot ulcer, amputation, and nonspecific mortality.

Each sub-model is a Markov model that uses time-, state-, and diabetes-type dependent probabilities derived from published sources; these are interconnected with the use of tracker variables. Patient cohorts can be defined in terms of age, sex, baseline risk factors, and preexisting complications, and disease management components can be altered in a disease management module. Similarly, economic data can be altered in an appropriate module that reflects the required setting. The CORE Diabetes Model thereby allows comparison of different patient populations in a variety of realistic clinical settings to yield long-term health and economic outcomes. Extensive validation of this model to ensure reliability of reported outcomes has been established in 66 separate analyses [19].

Simulation Cohorts

Two separate simulation cohorts were defined according to the corresponding clinical trial from which clinical outcomes data were derived. Baseline characteristics of the 2 treatment arms within a given clinical trial were pooled to generate an appropriate

simulation cohort; no statistical differences in baseline patient characteristics were noted between arms in either trial. The first cohort was based on a randomized, 18 week, multicenter clinical trial undertaken to compare IDet with NPH insulin in 595 patients with T1D [7] (Table 1). The second cohort was modeled on the 26 week, randomized, multicenter clinical trial recently presented by Pieber et al. [16]. In that trial, the long-acting insulin analogues IDet and IGlarg (both given in combination with rapid-acting insulin aspart) were compared in intensively treated subjects with T1D (Table 1).

Treatment Effects

Treatment effects were extracted from the corresponding randomized clinical trials and were adjusted for baseline HbA1c. The between–treatment group difference in HbA1c was significant — a decrease of 0.5% versus 0.28% — with IDet versus NPH after 18 weeks, respectively [7]. The risk of hypoglycemia was 21% lower with IDet than with NPH ($p<0.036$), and the risk of major hypoglycemia (defined as requiring third-party medical assistance) was non-significantly reduced at an event rate of 58 per 100 patient-years with IDet versus 66 per 100 patient-years with NPH. Nocturnal hypoglycemia and major nocturnal hypoglycemia, however, were significantly reduced in the IDet arm by 55% and 83%, respectively (both, $p<0.008$). Furthermore, a significant difference in body weight was observed after 18 weeks of treatment; the adjusted weight change was 1 kg lower in the IDet treatment group than in the NPH group ($p<0.001$).

In the randomized trial that compared IDet with IGlarg, HbA1c decreased from 8.76% to 8.16% (–0.71% points) and from 8.70% to 8.19% (–0.62% points), respectively—a nonsignificant between–treatment group difference [16]. However, a significant reduction in major hypoglycemic events (72%) favored IDet; an event rate of 6.5 per 100 patient-years contrasted with a rate of 24.5 per 100 patient-years reported in the IGlarg treatment group ($p<0.05$). Episodes of nocturnal hypoglycemia were also significantly reduced in the IDet arm (32% lower; $p<0.05$). A nonsignificant difference in weight gain was also observed, although IDet was associated with a lower increase in body weight (0.52 kg) compared with the IGlarg group (0.96 kg). Although variation in the stability of glucose profiles was observed between arms in both trials, IDet-based treatment consistently exhibited reduced intra-day variability of fasting glucose levels compared with both NPH and IGlarg; these data were not included in the current analysis.

Costs

Cost analyses from a societal perspective within the U.S. health care system were performed, and both direct and indirect costs were taken into account. Direct costs, which were regarded as the sum of treatment, complication, and medication costs as listed by Medicare, were inflated to 2005 values (as previously reported) [20]. Indirect costs included those incurred through lost productivity; these were based on U.S.-specific data on average salaries, retirement age, and days of work missed because of complications (data taken from the U.S. Department of Labor, Bureau of Labor Statistics). All costs and clinical benefits were discounted at an annual rate of 3.0%, in accordance with recommendations for the U.S. setting [21]. Acquisition costs of insulin were based on

Table 1. Baseline demographics, complications, relevant concomitant medications, and management of patients in the simulated cohort

	Model Simulation Population IDet vs NPH	Model Simulation Population IDet vs IGlarg
Demographics		
Sex, % male	63	51.3
Ethnic origin, %		
Caucasian	99.8	95.3
Other	0.2	4.7
Mean age, y	39	40.2
BMI, kg/m²	24.9	25.5
Mean duration of diabetes, y	15	17
Risk factors		
Glycosylated hemoglobin (HbA_{1c}), % points	8.38	8.84
Systolic blood pressure, mm Hg	124	127.9
Total cholesterol, mg/dL	208	208
High-density lipoprotein cholesterol, mg/dL	56.1	56.1
Low-density lipoprotein cholesterol, mg/dL	131.6	131.6
Triglycerides, mg/dL	97.4	97.4
Proportion smokers, %	20	19.6
Complications, %		
Left ventricular hypertrophy	1.2	0.5
Angina pectoris	0.5	2.4
Myocardial infarction	0	0.3
Heart failure	0.2	0.3
Atrial fibrillation	0.5	0.5
Stroke	0	0.4
Peripheral vascular disease	0	0.4
Neuropathy	0.3	1.5
Foot ulcer/amputation	0.2	0.2
Microalbuminuria	27.2	27.2
Gross proteinuria	9.6	9.6
Background diabetic retinopathy	42	24.0
Proliferative diabetic retinopathy	3.7	2.4
Severe vision loss	0.2	0.6
Cataract	1.7	2.8
Macular edema	9.2	9.2
Management, %		
Taking ACE-I/ARB	41.0	67.0
Taking statins	60.0	9.8
Taking aspirin	7.7	17.2
Screened for retinopathy (assumed treated with laser if detected)	48.2	75.0
Screened for renal disease (assumed treated with ACE or ARB if detected)	60	75.0
Proportion on foot ulcer prevention program	37.3	30.0

BMI=body mass index; ACE-I=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker.

mean end-of-study dosing, and published Average Wholesale Price cost data (*2005 Drug Red Book;* Medical Economics Co., Inc., Montvale, NJ, USA) were used.

Quality-of-Life Utilities

Quality-of-life utilities were derived as previously described [18] with the exception of utilities associated with hypoglycemic events. For major hypoglycemic events, an event disutility of –0.0121 quality-adjusted life-years (QALYs) was assumed on the basis of recently published data [22]; for all other hypoglycemic events, a value of –0.0052 QALYs was applied [23] Event disutilities are applied in the model to the 1 year period in which the event occurred, as previously outlined by Palmer et al. [18]. Subsequent state disutilities are applied for non-transient events that affect quality of life over a longer period.

Sensitivity Analysis

Sensitivity analysis was performed on key assumptions and variables used in the base case analysis: change in HbA1c, discount rate, duration of treatment effect, and costs for insulin and management of hypoglycemia. The impact of changes in HbA1c within the model was evaluated under 2 assumptions: (1) that improvements in HbA1c were identical in the 2 treatment groups, and (2) that they persisted for only 5 years. Through assignment of a variable annual discount rate of between 0% and 6%, the impact of this variable on costs and clinical benefits was assessed relative to the base case rate of 3.0% used in the simulation. Similarly, the time horizon was varied from the base case setting of 35 years to 5 and 10 year time horizons. Insulin detemir acquisition costs were varied by ±15% so that the impact of potential contractual rebate adjustments reflected within the U.S. setting could be assessed; sensitivity to costs associated with major hypoglycemic events was assessed through application of the confidence intervals associated with the base cost as reported by Bullano et al. [24].

Statistical Approach

Analysis was performed by means of a nonparametric bootstrapping approach, in which the progression of diabetes was simulated in 1000 patients passed through the model 1000 times for calculation of the mean and standard deviations of life expectancy; quality-adjusted life expectancy and costs were derived through second-order Monte Carlo simulation [25]. A total of 1000 mean values (each of 1000 patients) for incremental costs and incremental effectiveness in terms of quality-adjusted life expectancy were plotted (scatter plots) on the cost-effectiveness plane, and these data were used to generate an acceptability curve through calculation of the proportion of points below a range of willingness-to-pay thresholds.

Results

IDet versus NPH: Life Expectancy, Quality-Adjusted Life Expectancy, and Cost-Effectiveness

Long-term projections indicated that treatment with IDet compared with NPH was associated with improvements in life expectancy and quality-adjusted life expectancy (Table 2). Life expectancy (discounted by 3.0%) was improved by 0.168 QALYs with IDet compared with NPH insulin. Quality-adjusted life expectancy increased with IDet by 0.698 QALYs; average values consisted of 8.0 QALYs (±0.09) and 7.32 QALYs (±0.08) for IDet and NPH, respectively. Direct medical costs increased by $10,451 in the IDet treatment group relative to the NPH group; however, this was partially balanced by reduced indirect costs of $4688 to yield a total lifetime cost increase of $5763 among those using IDet. In the final cost-effectiveness analysis, treatment with IDet was associated with an incremental cost-effectiveness ratio (ICER) of $14,974 per QALY gained versus NPH on the basis of direct costs.

IDet versus NPH: Incremental Cost-Effectiveness Scatter Plot

In the base case analysis, most points in the incremental cost-effectiveness scatter plot (Figure 1) fell within the upper right quadrant, indicating that treatment with IDet was both more effective and more costly than NPH-based therapy. When this was converted to an acceptability curve, it could be seen that in the base case analysis, IDet-based treatment was associated with a 100% likelihood that it would be cost-effective versus NPH, if the willingness to pay was $50,000 per QALY gained.

Table 2. Summary of Base Case Results: IDet versus NPH

IDet vs NPH	IDet	NPH	Difference
Clinical outcomes, all settings			
Undiscounted life expectancy, y	21.346 (0.162)	21.026 (0.167)	
Discounted life expectancy, y	14.869 (0.162)	14.701 (0.167)	0.168
Quality-adjusted life expectancy, QALYs	8.018 (0.087)	7.32 (0.083)	0.698
Cost outcomes, US$			
Direct medical costs	118,746 (2805)	108,295 (2942)	+10,451
Indirect costs	141,809 (5034)	146,497 (5214)	−4688
Total lifetime costs	260,555 (7839)	254,792 (8156)	+5763
Outcome/ICER		14,974	

Values shown are means with standard deviations in parentheses. Values are expressed as means from 1000 cohorts, each of 1000 patients.

IDet versus NPH: Diabetes-Related Complications

Treatment with IDet compared with NPH resulted in an overall reduction in diabetes-related complications, most notably in retinopathy and nephropathy (Table 3). The greatest absolute reductions were projected for the cumulative incidences of proliferative diabetic retinopathy (PDR), end-stage renal disease (ESRD), microalbuminuria, and gross proteinuria, with values 0.8%, 0.8%, 2.1%, and 2.8% lower than those resulting from NPH treatment, respectively. Cardiovascular complication rates were generally similar between treatment groups, with the exception of myocardial infarction, for which the cumulative incidence was reduced by 0.7% with IDet compared with NPH.

Sensitivity Analysis

Sensitivity analysis revealed that the ICER for IDet versus NPH was most sensitive to changes in HbA1c. However, even when no difference in efficacy with respect to HbA1c was assumed between treatment groups, IDet was associated with an ICER of $20,386 per QALY gained versus NPH (Table 4). As would be expected, reducing the time horizon increased the ICER, because benefits that result from improvements in glycemic control tend to occur later rather than earlier. Nevertheless, variations in key assumptions (including price of IDet, discount rate, and cost of managing hypoglycemia) had no impact on the relative results and yielded ICERs below the $25,000 per QALY gained threshold used to define “attractive” diabetes interventions [26].

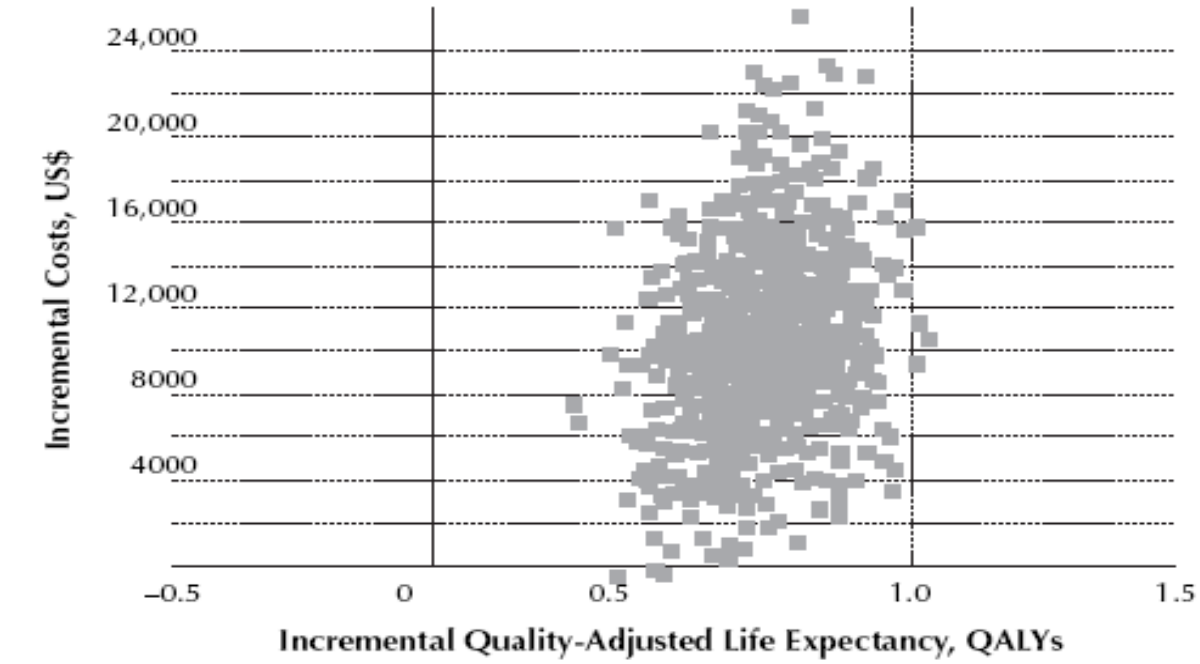
IDet versus IGlarg: Life Expectancy, Quality-Adjusted Life Expectancy, and Cost-Effectiveness

Treatment with IDet was associated with lower direct medical and indirect costs, as well as improved quality of life and life expectancy, when compared with treatment with IGlarg (Table 5). Discounted life expectancy was improved by 0.087 years and quality-adjusted life expectancy by 0.063 years with IDet. For IDet relative to IGlarg, direct medical costs were reduced by $2072 and indirect costs were reduced by $3103 per patient, resulting in overall lifetime cost savings of $5174 per patient from a societal perspective. In the cost-effectiveness analysis, IDet was therefore a dominant treatment option.

IDet versus IGlarg: Incremental Cost-Effectiveness Scatter Plot

In the base case analysis for IDet versus IGlarg, the incremental cost-effectiveness scatter plot (Figure 2) demonstrated that most points fell within the lower right quadrant, indicating that treatment with IDet was more effective and less costly than IGlarg-based therapy. However, there were a number of points in the upper right and lower left quadrants; when this plot was converted to an acceptability curve, it could be seen that in the base case analysis, IDet-based treatment had an 80% probability that it would be cost-effective, if the willingness to pay was $50,000 per QALY gained.

Figure 1. Scatter plot and acceptability curve for IDet versus NPH (Base case scatter plot of 1000 samples of mean incremental costs plotted against mean incremental effectiveness (quality-adjusted life-years gained) generated for 1000 patients for IDet therapy versus NPH-based therapy)



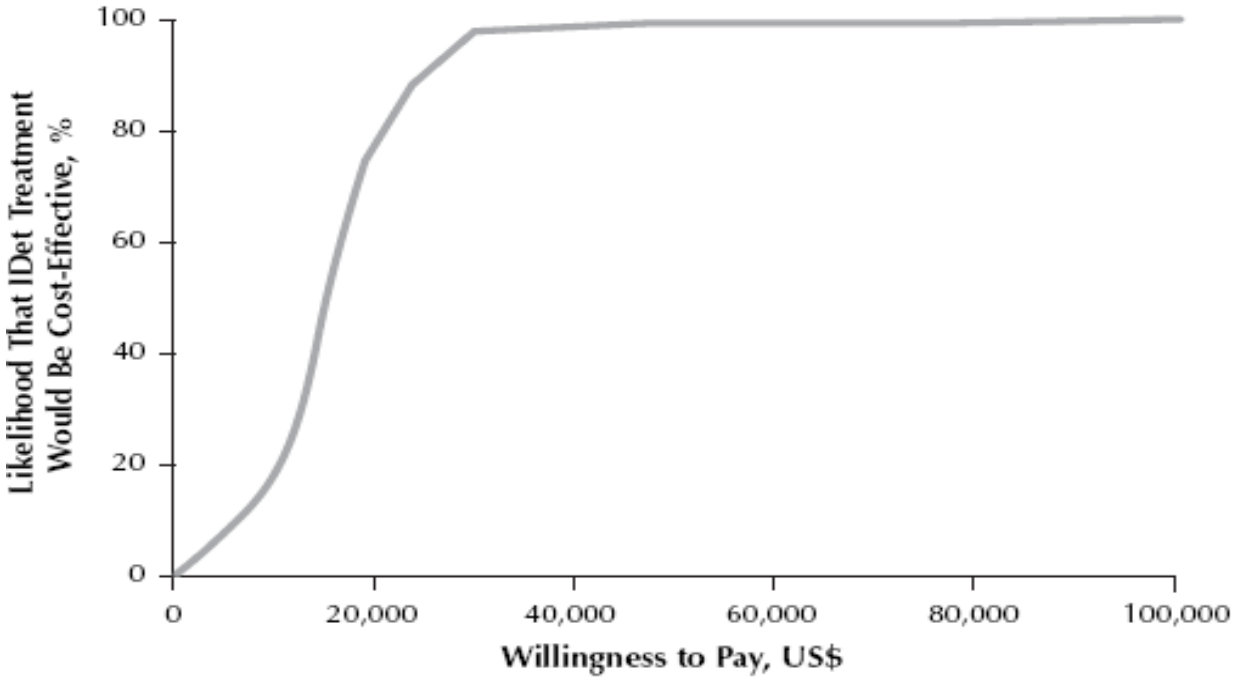


Table 3. Cumulative incidence of diabetes-related complications: IDet vs NPH and IDet vs IGlarg

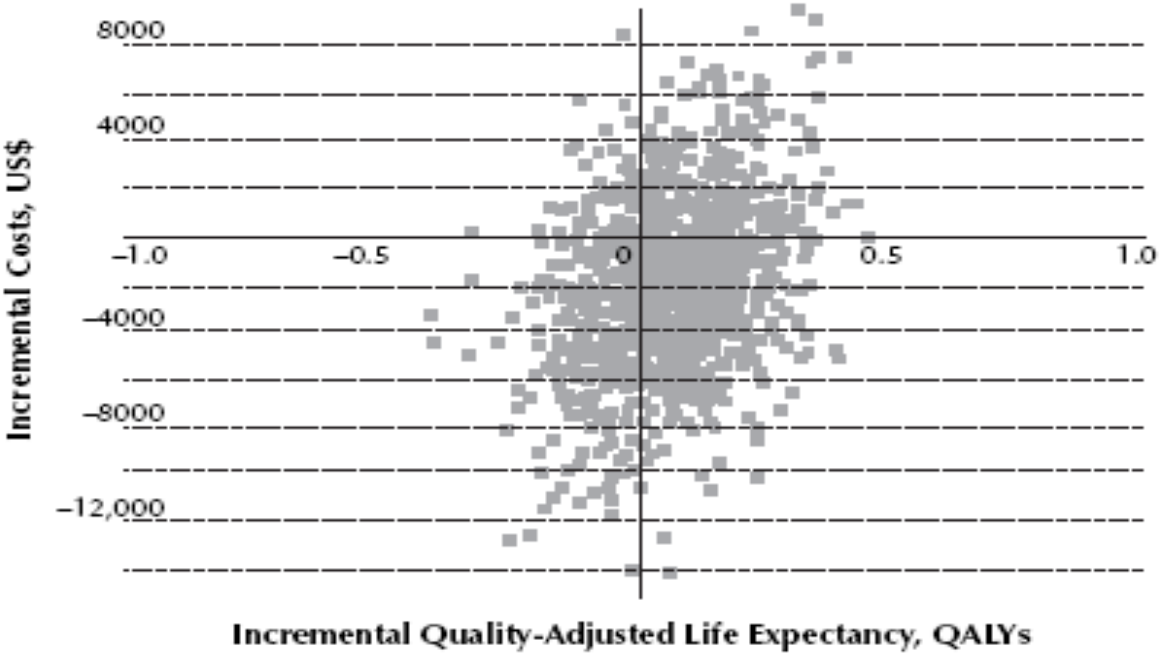
Complication	Cumulative Incidence, % (SD)*			Cumulative Incidence, % (SD)*		
	IDet	NPH	Difference	IDet+IAsp	IGlarg+IAsp	Difference
Proliferative diabetic retinopathy	19.6 (1.2)	20.4 (1.3)	–0.8	18.13 (1.3)	18.93 (1.28)	–0.8
Severe vision loss	27.3 (1.4)	27.8 (1.4)	–0.5	23.9 (1.29)	23.6 (1.4)	+0.3
Microalbuminuria	67.0 (2.0)	69.1 (1.9)	–2.1	70.6 (1.8)	71.5 (1.8)	–0.9
Gross proteinuria	50.2 (1.8)	53.0 (1.7)	–2.8	53.4 (1.7)	54.7 (1.6)	–1.3
End-stage renal disease	19.2 (1.3)	20.0 (1.3)	–0.8	20.1 (1.3)	20.6 (1.3)	–0.5
First foot ulcer	49.3 (1.6)	49.6 (1.5)	–0.3	49.4 (1.5)	49.8 (1.6)	–0.4
First amputation due to an ulcer	14.9 (1.3)	15.2 (1.3)	–0.3	15.2 (1.3)	15.1 (1.4)	+0.1
Congestive heart failure	24.7 (1.3)	24.4 (1.3)	+0.3	27.4 (1.4)	27.2 (1.4)	+0.2
Myocardial infarction	36.0 (1.5)	36.7 (1.5)	–0.7	37.6 (1.5)	37.9 (1.5)	–0.3
Stroke	9.3 (0.9)	9.1 (0.9)	+0.2	9.0 (0.8)	9.1 (1.0)	–0.1

*Cumulative incidence of complications over patient lifetimes expressed as mean percentage (standard deviation) from 1000 cohorts, each of 1000 patients.

Table 4. Sensitivity analysis on the direct incremental costs per QALY

Assumption	Costs/QALY, $	
	IDet vs NPH	IDet vs IGlarg
Base case (assuming that HbA_{1c} improvements, decreased BMI, and decreased major hypoglycemia event rates occur simultaneously, 35-year horizon)	14,947	Dominant
5-year horizon	17,040	Dominant
10-year horizon	15,439	Dominant
Discount rate of 0%	14,910	Dominant
Discount rate of 6%	14,970	Dominant
Cost per major hypoglycemic event low	15,957	Dominant
Cost per major hypoglycemic event high	13,993	Dominant
IDet cost –15%	12,180	Dominant
IDet cost +15%	17,771	1126
No change in HbA_{1c}	20,386	Dominant
Change in HbA_{1c} lasts for only 5 years	16,781	Dominant

Figure 2. Scatter plot and acceptability curve for IDet versus IGlarg (Base case scatterplot of 1000 samples of mean incremental costs plotted against mean incremental effectiveness (quality-adjusted life-years gained) generated for 1000 patients for IDet therapy versus IGlarg-based therapy)



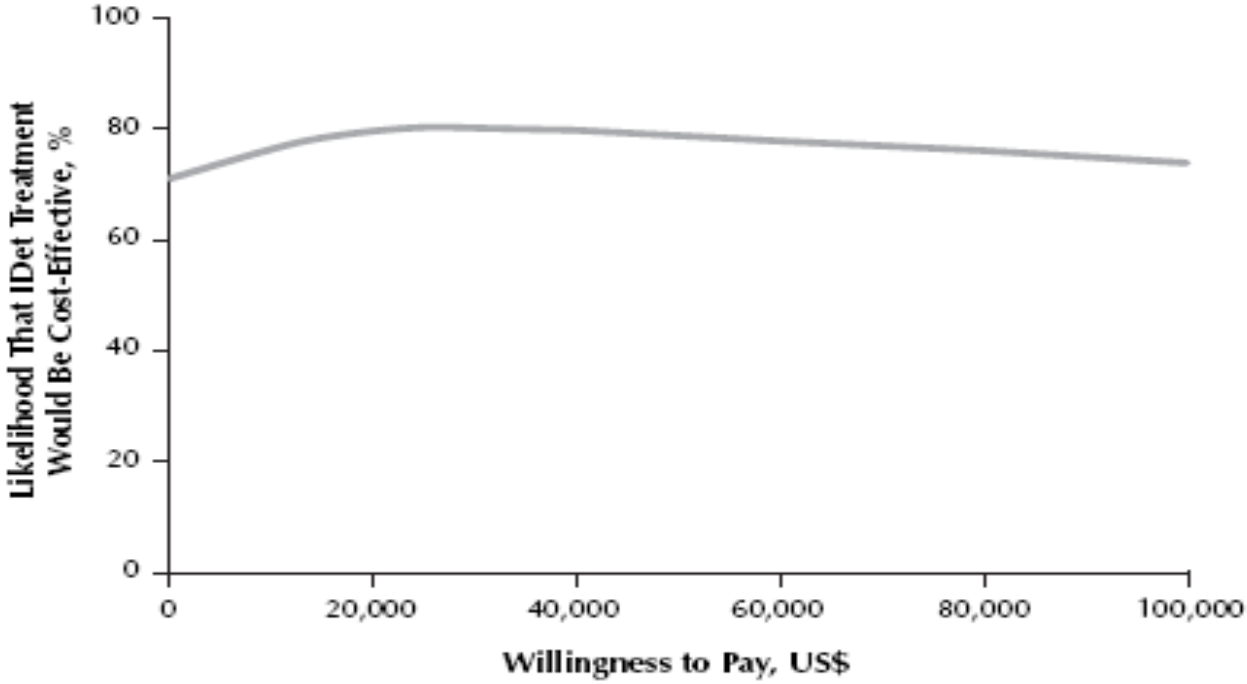


Table 5. Summary of Base Case Results: IDet vs IGlarg

IDet vs IGlarg	IDet + IAsp	IGlarg + IAsp	Difference
Clinical outcomes (all settings)			
Undiscounted life expectancy, y	20.12 (0.182)	19.958 (0.174)	
Discounted life expectancy, y	14.231 (0.182)	14.144 (0.174)	0.087
Quality-adjusted life expectancy, QALYs	7.242 (0.094)	7.179 (0.089)	0.063
Cost outcomes, US$			
Direct medical costs	108,208 (2768)	110,280 (2691)	2072
Indirect costs	144,145 (5456)	147,248 (5168)	3103
Total lifetime costs	252,354 (8225)	257,528 (7859)	5174
Outcome/ICER		Dominant	

Values shown are means with standard deviations in parentheses. Values are expressed as means from 1000 cohorts, each of 1000 patients.

IDet versus IGlarg: Diabetes-Related Complications

IDet treatment was associated with a reduced cumulative incidence of diabetes-related complications, particularly of retinopathy and nephropathy, when compared with IGlarg (Table 3). The corresponding absolute reductions in cumulative incidence of PDR, ESRD, microalbuminuria, and gross proteinuria were 0.8%, 0.5%, 0.9%, and 1.3%, respectively, for IDet versus IGlarg.

Sensitivity Analysis

When IDet was compared with IGlarg, results were most sensitive to changes in pharmacy acquisition costs, with an ICER of $1126 for a 15% increase in the cost of IDet. However, variation in the other key assumptions had no impact on relative results, and IDet remained dominant in the U.S. setting (Table 1).

Discussion

We have used the validated CORE Diabetes Model to analyze long-term economic and clinical outcomes that can be expected with uptake of the long-acting insulin detemir into the intensive treatment regimen of patients with T1D within the United States. Compared with both intermediate-acting NPH insulin and an alternative long-acting insulin, IGlarg, model projections indicate that use of IDet is associated with improvements in life expectancy, quality-adjusted life expectancy, and cumulative incidence of diabetes-related complications. In economic terms, IDet represents a very attractive alternative to both NPH and IGlarg according to generally accepted standards.

Long-acting insulin analogues have been developed in response to high rates of major and minor hypoglycemia, both daytime and nocturnal, experienced by patients with diabetes who use NPH. The occurrence of hypoglycemia is a frequent complication among intensively treated patients with T1D; it affects overall patient quality of life and has the potential to be a life-threatening event [27]. Weight gain associated with insulin use is also a considerable problem for patients with diabetes. Apart from negative effects on blood pressure and lipid levels [28,29], which exacerbate diabetic complications, increased weight often has an adverse effect on patient quality of life [30].

Randomized clinical trials comparing IGlarg with NPH have demonstrated improved or at least equivalent glycemic control, reduced incidence of hypoglycemia, and reduced weight gain with the former. Additionally, recent retrospective assessments of Medicaid claims in the United States reported that patients who used IGlarg, when compared with matched reference patients with diabetes, recorded lower event rates of hypoglycemia or greater reductions in event rates, as well as reduced treatment costs [24,31]. These early data suggest that the potential benefits exhibited by long-acting insulin analogues within controlled settings are already being realized in clinical practice. Before IDet was approved by the U.S. Food and Drug Administration (FDA) in 2005, IGlarg was the only long-acting insulin analogue available in the United States. Preliminary trials directly comparing IDet and IGlarg for within-subject variability found that IDet had a significantly more predictable glucose-lowering effect than IGlarg, which, it was postulated, should result in fewer hypoglycemic events [17]. Indeed, a recently reported 26 week long, head-to-head trial of IDet and IGlarg found a significant reduction in major hypoglycemic events associated with the use of IDet [16].

To gain an appreciation for the long-term potential offered by IDet, we have used the CORE Diabetes Model to project over 35 years the short-term benefits observed with IDet versus NPH or IGlarg treatment in randomized clinical trials. Treatment with IDet has resulted in increased life expectancy, improved quality of life, and reduced complication rates compared with NPH; costs associated with these improvements are well within the limits of general acceptability at an ICER of $14,974 based on direct costs. According to Klonoff and Schwartz [26], an ICER that is less than $25,000 should be considered a very attractive diabetes intervention.

In the comparison of IDet with IGlarg, although both are long-acting insulin analogues, IDet was shown to result in cost savings and an improved patient quality of life, making it a dominant option to IGlarg treatment. The between-group difference in complication event rates was, as anticipated, less than that seen for IDet versus NPH. Nevertheless, over a 35-year time projection, these differences translated into meaningful clinical and economic benefits favoring IDet. Because long-acting insulin analogues offer relevant improvements and flexibility in diabetes care, both clinically and in terms of patient quality of life, interest in and uptake of these new insulins by clinicians are on the rise. For this reason, it becomes necessary to make timely clinical and economic decisions regarding their short- and long-term potential. Because the available trial data are based on relatively short periods of observation, use of appropriate and validated disease models to project long-term clinical and economic outcomes represents the best currently

available approach by which clinicians can make evidence-based decisions on the basis of long-term assessments.

The present modeling study was based on randomized clinical studies conducted predominantly within European health care settings. Extrapolation of these findings to a U.S. setting has permitted the prediction of likely economic and clinical outcomes in a U.S. diabetes population. However, the necessity of confirming these short-term clinical outcomes in a typical U.S. diabetes cohort of representative ethnic diversity is acknowledged. With the recent completion (late in 2005) of a United States–based randomized trial of IDet versus IGlarg, new data can be used to further elucidate the relative merits of the conclusions presented here.

Conclusions

Among patients with insulin-dependent diabetes, basal bolus therapy with detemir was projected to yield improvements in life expectancy and quality-adjusted life expectancy when compared with either NPH or IGlarg. IDet was also associated with a reduced cumulative incidence of diabetes-related complications and consequently represents a clinically and economically attractive treatment option from a societal and reimbursement perspective in the U.S. setting.

References

1. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; **329**:977-986.
2. American Association of Clinical Endocrinologists. Medical Guidelines for the Management of Diabetes Mellitus. Jacksonville, Fla: AACE; 2002.
3. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med. 1991; **90**:450-459.
4. The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complications trial. Diabetes Care. 1988; **11**:567-573.
5. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. Diabetes Care. 1984; **7**:188-199.
6. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care. 2005; **28**:1107-1112.
7. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia. 2004; **47**:622-629.
8. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabet Med. 2005; **22**:850-857.

9. Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care. 2004; **27**:1081-1087.
10. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. Clin Ther. 2004; **26**:724-736.
11. Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. Intern Med J. 2005; **35**:536-542.
12. Fischer JS, McLaughlin T, Loza L, Beauchamp R, Schwartz S, Kipnes M. The impact of insulin glargine on clinical and humanistic outcomes in patients uncontrolled on other insulin and oral agents: an office-based naturalistic study. Curr Med Res Opin. 2004; **20**:1703-1710.
13. Home PD, Rosskamp R, Forjanic-Klapproth J, Dressler A. A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. Diabetes Metab Res Rev. 2005; **21**:545-553.
14. Linkeschova R, Raoul M, Bott U, Berger M, Spraul M. Less severe hypoglycaemia, better metabolic control, and improved quality of life in Type 1 diabetes mellitus with continuous subcutaneous insulin infusion (CSII) therapy: an observational study of 100 consecutive patients followed for a mean of 2 years. Diabet Med. 2002; **19**:746-751.
15. Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Curr Med Res Opin. 2004; **20**:1729-1746.
16. Pieber TR, Treichel H-C, Robertson LI, Mordhorst L, Gall M-A. Insulin detemir plus insulin aspart is associated with less risk of major as well as nocturnal hypoglycaemia than insulin glargine plus insulin aspart at comparable levels of glycaemic control in type 1 diabetes [abstract]. Diabetologia. 2005; **48** (suppl 1):A92.
17. Heise T, Nosek L, Ronn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes. 2004; **53**:1614-1620.
18. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin. 2004; **20** (8 suppl):5-26.
19. Palmer AJ, Roze S, Valentine W, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin. 2004; **20** (suppl 1):S27-S40.
20. Ray J, Valentine WJ, Roze S, et al. Insulin therapy in type 2 diabetes patients failing oral agents: cost-effectiveness of biphasis insulin aspart 70/30 versus insulin glargine in the US. Diabetes Obes Metab. In press.
21. Tarn T, Smith M. Pharmacoeconomic guidelines around the world. ISPOR Connections. 2004:15-18.
22. Davies R, Wittrup-Jensen KU, Peters JR, Morrissey M, Currie CJ. The Impact on Health-Related Quality of Life (EQ-5D Index) in People With Type 1 Diabetes Who

Experience Severe Hypoglycaemia. Dusseldorf, Germany: European Association for the Study of Diabetes; 2005.
23. National Institute for Clinical Excellence. Technology Appraisal Guidance. No. 53. Guidance on the Use of Long-Acting Insulin Analogues for the Treatment of Diabetes—Insulin Glargine. London, UK: NICE; 2002.
24. Bullano MF, Al Zakwani IS, Fisher MD, Menditto L, Willey VJ. Differences in hypoglycemia event rates and associated cost-consequence in patients initiated on long-acting and intermediate-acting insulin products. Curr Med Res Opin. 2005; **21**:291-298.
25. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ. 1997; **6**:327-340.
26. Klonoff DC, Schwartz DM. An economic analysis of interventions for diabetes. Diabetes Care. 2000; **23**:390-404.
27. Nordfeldt S, Ludvigsson J. Fear and other disturbances of severe hypoglycaemia in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2005; **18**: 83-91.
28. Purnell JQ, Hokanson JE, Marcovina SM, Steffes MW, Cleary PA, Brunzell JD. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial. JAMA. 1998; **280**:140-146.
29. De Block CE, De Leeuw IH, Van Gaal LF. Impact of overweight on chronic microvascular complications in type 1 diabetic patients. Diabetes Care. 2005; **28**:1649-1655.
30. Lee AJ, Morgan CL, Morrissey M, Wittrup-Jensen KU, Kennedy-Martin T, Currie CJ. Evaluation of the association between the EQ-5D (health-related utility) and body mass index (obesity) in hospital-treated people with type 1 diabetes, type 2 diabetes and with no diagnosed diabetes. Diabet Med. 2005; **22**:1482-1486.
31. Zhang Q, Menditto L. Incremental cost savings 6 months following initiation of insulin glargine in a Medicaid fee-for-service sample. Am J Ther. 2005; **12**:337-343.

Chapter 4

Evaluating patient preferences for an insulin delivery system

Adapted from: Stockl K, Ory C, Vanderplas A, Nicklasson L, Lyness W, Cobden D, Chang E. An Evaluation of Patient Preference for an Alternative Insulin Delivery System compared to Standard Vial and Syringe. *Current Medical Research & Opinion*. 2007 Jan;23(1):133-46.

Summary

Diabetes mellitus (DM) affects over 18.2 million Americans and diabetes-related medical costs exceed 132 billion dollars per year, totaling more than 12% of the United States healthcare budget. The Diabetes Control and Complications Clinical Trial demonstrated that intensive insulin therapy and the control of plasma glucose can significantly reduce the incidence of late diabetic complications and delay the progression of existing conditions in type 1 diabetes (T1D). Optimal glycemic control often requires intensive insulin therapy to maintain a hemoglobin A1C (A1C) of less than 7% as recommended by the American Diabetes Association. It is estimated that more than half of the approximately 7 million Americans using insulin do so with suboptimal treatment and while administering one or two insulin injections per day. Non-adherence may be a contributing factor in suboptimal treatment. For a variety of reasons, many patients diagnosed with diabetes and treated with insulin are non-adherent.

The primary objective of this study was to evaluate preference for an insulin delivery system comparing a disposable doser (InnoLet) to the standard vial/syringe. In a prospective, randomized, open-label, two-period, crossover study, 260 patients were enrolled (age ≥ 18 years, with type 1 or 2 diabetes, and receiving NPH or regular or 70/30 insulin for at least 6-months). A total of 162 patients completed both treatment arms. Excluded were those unable to read/write English or administer their own injections, pregnant/lactating women, those using antipsychotics, and those with a history of alcohol abuse or cognitive impairment. Patients completed the eight-item Diabetes Fear of Self-Injection Questionnaire at baseline, week 12 and week 24. Items were rated on a 4-point Likert scale (1 = almost never; 4 = almost always) with a maximum fear score of 32. At week 24, patients completed a preference survey.

Of the 162 patients completing both treatment arms, 89 (55.0%) were in the vial/syringe to disposable doser treatment arm, 50% were female and mean age was 60 ± 11 years. Patients in both treatment arms displayed little significant differences in baseline characteristics. Patients reported significantly lower fear of self-injection after using the disposable doser compared to vial/syringe (mean ± SEM: 9.5 ± 0.2 vs. 11.2 ± 0.4; $p<0.0001$). Most patients (71.5%) indicated a preference for the disposable doser compared to the vial/syringe method ($p<0.0001$).

The majority of patients preferred the disposable doser, and reported significantly less fear of self-injection using this delivery system. There are some potential limitations to consider. A randomization bias may have been present, patients who enrolled in this study were those who were actively seeking medical treatment for diabetes, insulin pens and cartridges are not available for all types of insulin regimens, pre-filled pens and cartridges may not be altered and, in general, alternative insulin delivery systems tend to be more costly than insulin sold in traditional vials. However, insulin may have greater patient acceptance and less psychological distress when administered via an alternative delivery system.

Introduction

Diabetes mellitus (DM) affects over 18.2 million Americans and diabetes-related medical costs exceed 132 billion dollars per year, totaling more than 12% of the United States healthcare budget [1,2]. A portion of this budget is used to treat complications associated with diabetes, primarily among those whose diabetes is poorly controlled. The Diabetes Control and Complications Clinical Trial [3] demonstrated that intensive insulin therapy and the control of plasma glucose can significantly reduce the incidence of late diabetic complications and delay the progression of existing conditions in T1D. Optimal glycemic control often requires intensive insulin therapy to maintain a hemoglobin A1C (A1C) less than 7% as recommended by the American Diabetes Association [4]. It is estimated that more than half of the approximately 7 million Americans using insulin do so with suboptimal treatment and while administering one or two insulin injections per day [5,6]. Non-adherence may be a contributing factor in suboptimal treatment. For a variety of reasons, many patients diagnosed with diabetes and treated with insulin are non-adherent. Lack of diabetes education, poverty, stigma and fear associated with needles, denial, and lifestyle all contribute to non-adherence with insulin injections and poor glycemic control.

In 1987, insulin pens were introduced in the United States and, through the years, additional alternative insulin delivery systems have become available. The development of alternative insulin delivery systems have offered patients improved flexibility, more accurate dosing, convenience and improved social acceptability with administration of their insulin regimen. Moreover, these benefits may have improved patients' adherence to their insulin regimen. Two multicenter surveys of 1310 insulin users showed that 77% of patients found insulin adherence to be easier with the use of an insulin pen, and 85% of insulin pen users never missed a scheduled injection, as compared to 73% of the vial and syringe users [7]. In 1993, Plevin and Sadur [8] assessed patient acceptance of insulin pens and found that 98% of the patients reported that the insulin pen was easier to use and 91% preferred to continue using the pen. Recognizing the increasing importance of patient preference, we investigated through a multicenter, randomized, cross-over trial whether patients diagnosed with diabetes and treated with insulin therapy would prefer the disposable doser (InnoLet, Novo Nordisk Inc., Princeton, NJ) over the standard vial and syringe, as has been found among patients using insulin pens. The disposable doser is similar to an insulin pen in that it is a pre-filled disposable insulin delivery system. It has a large dial that is easy to read, with audible clicks to help patients select the correct dose of insulin. To use the system, patients set their dose, insert the needle and press a button.

Methods

Study design

This was a randomized, open-label, two-period cross-over study conducted at 50 physician offices within Arizona, California, Colorado, Oregon, Texas, Washington and Wyoming with patient enrollment occurring from August 1, 2003 through May 5,

2004. The majority of physician investigators who participated specialized in internal medicine (54.0%), followed by family medicine (36.0%), endocrinology (8.0%), and general medicine (2.0%). Conduct of this trial conformed to the human experimentation guidelines of the Declaration of Helsinki and title 21 parts 50 and 56 of the United States Code of Federal Regulations [9,10]. An institutional review board for each clinical center approved the protocol, and all study participants gave written informed consent.

Patients

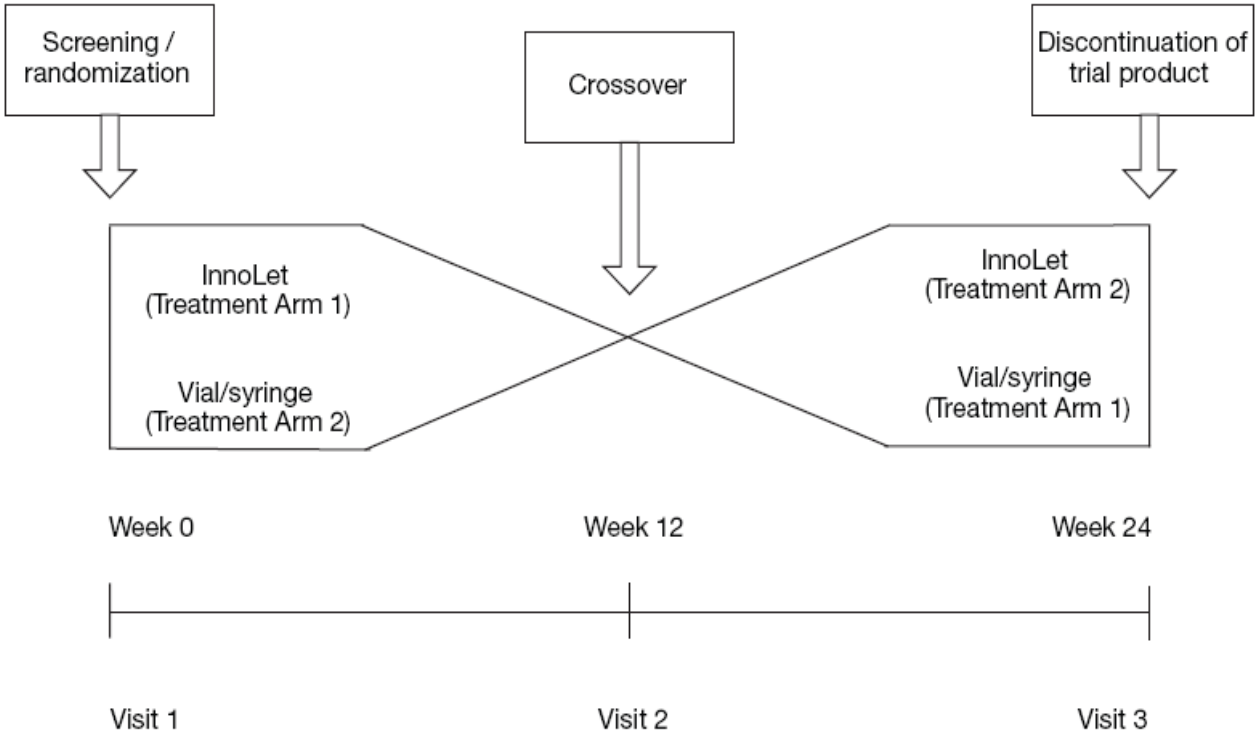
Patients were eligible for inclusion if they were at least 18 years of age at the time of enrollment, diagnosed with type 1 or 2 DM and had an A1C value of ≤ 10%. Patients were required to use at least one daily injection of neutral protamine hagedorn (NPH), regular or 70/30 insulin, and to have been using insulin for at least 6 months. Patients were excluded if they were unable to read or write English, were unable to administer their own injections, had used an alternative insulin delivery system during the 6 months prior to enrollment, were pregnant or lactating (or had the intention of becoming pregnant), or were using antipsychotics. Patients were also excluded if they had any form of cognitive impairment or a history of alcohol abuse.

Organization of the study

All patients were identified during routine physician office visits. Three study visits were performed: visit 1 at baseline (week 0), visit 2 for treatment crossover (week 12), and visit 3 for the final visit (week 24). Patients were randomized to either the disposable doser or vial/syringe for approximately 12 weeks and then 'crossed over' to the alternate treatment for an additional 12 weeks (Figure 1). At visit 1 (week 0), patients who enrolled were randomly assigned to receive the disposable doser or vial/syringe on the basis of a computer-generated randomization scheme. If randomized to the disposable doser, the investigator, or trained staff, taught the patients how to use it. Patients were required to demonstrate proficiency in the use of the delivery system. In addition, the patients were given written instructions on the use of the device. At each visit, A1C testing was performed at the site using a disposable monitor, which had been waived by the Clinical Laboratory Improvement Amendments (CLIA) and certified by the National Glycohemoglobin Standardization Program (NGSP).

Patients also completed the following questionnaires: Diabetes Fear of Self-Injection [11], Thoughts about Taking Insulin, Insulin Treatment Satisfaction Questionnaire (ITSQ) [12], and Problem Areas in Diabetes (PAID) [13,14] (Appendix A). During visit 3, patients also completed the Insulin Device Preference Questionnaire (Appendix A). Patients were required to complete the questionnaires in the exam room prior to leaving the site. To obtain study medication, patients were given a pharmacy purchase card to present to their community pharmacy. Therefore, all patients received study medication, delivery systems and supplies at no charge. In addition, after each visit, patients were compensated for their time with a gift card of a nominal amount to redeem at a national chain retail store.

Figure 1. Treatment schedule



Efficacy assessments

The primary efficacy endpoint was patient preference of an insulin delivery system: disposable doser or vial/syringe as measured by the Insulin Device Preference Questionnaire. Secondary measures included patient responses to the following questionnaires: Diabetes Fear of Self Injection [11], Thoughts about Taking Insulin, ITSQ [12], and PAID [13,14] (Appendix A). To assess delivery system preference and patients' thoughts about taking insulin, the Device Preference and Thoughts About Taking Insulin Questionnaires were developed. In addition, baseline demographics and clinical characteristics of patients were evaluated to describe the population, and to determine if there were any differences in study outcomes based on patients' characteristics. The demographics evaluated included age, gender, body mass index, and race. The clinical characteristics evaluated included type of diabetes, duration of diabetes, and duration of insulin use, Charlson Co-morbidity Index (CCI), and A1C values. The CCI for each patient was calculated from the patient's concomitant illnesses and was used as a measure of co-morbidity [15]. The CCI contains 17 categories of diseases, each assigned an associated weight based on the adjusted risk of one-year mortality [16]. The overall score reflects the cumulative increased likelihood of one-year mortality. The higher the score, the more severe the burden of comorbidity [15,16].

Statistical analysis

Due to the non-systematic distribution of missing data across study variables, the number of patients with missing data for each study variable is reported. All data are presented as mean ± standard error of the mean (SEM) or *N* (%; percent) and stratified by either treatment arm or treatment response (completion of disposable doser or vial/syringe use) as appropriate for the data. To compare baseline demographic and clinical characteristics between treatment arms, *t*-test and chi-square analyses were performed on non-missing data. Patient preference rates for each of the survey questionnaires were reported from the questionnaires completed during visit 2 and visit 3. To test the preference rates, a one-sample test of proportions was used. Proportions were compared to a baseline value of 0.50 (ie, no preference).

To compare treatment effect, only non-missing pairs (ie, for patients with non-missing data upon completion of each treatment arm) were included in the analysis. The mean treatment effect was first determined within each treatment arm among non-missing pairs, then the un-weighted average of the two treatment arms was calculated as the overall treatment effect. The *t*-test or Wilcoxon signed rank was used to compare the treatment effect for continuous or ordinal variables. Logistic regression was performed to identify potential factors that influence a patient's preference for the disposable doser versus no preference for the disposable doser. The no-preference category included patients who reported no preference plus those who reported preference for vial/syringe. Variables entered into the model included: age at enrollment, gender, diabetes type and treatment arm. Two-way interaction terms were checked for significance and included in the final model if significant. Reported *p*-values for the preference survey questionnaire are one-sided, all other reported *p*-values are two-sided. An alpha level of 0.05 was used for all statistical analyses.

Results

A total of 260 patients were enrolled in the study. To be included in the primary analysis, a patient had to have met all inclusion and exclusion criteria, completed all study visits within the designated timeframe and completed the preference outcome (n = 162). Patient demographics are displayed in Table 1. Ninety-eight patients failed to meet these requirements and were excluded for the following reasons: one patient (0.4%) used insulin for less than 6 months prior to enrollment, 53 (20.4%) were lost to follow-up, 32 (12.3%) were exposed to either delivery system for less than 9 weeks or had greater than a 15-week gap between visit dates, seven (2.7%) had a serious adverse event (all were deemed unrelated to study treatment), two (0.7%) did not complete the preference outcome, and three (0.7%) had a history of alcohol abuse or dementia.

Delivery system preference

Of the entire cohort, 71.5% of the patients reported an overall preference for the disposable doser ($p<0.0001$; Table 2). Patients reported that the disposable doser was a more convenient method for the administration of insulin (74.1%, $p<0.0001$), an easier

Table 1. Baseline demographic and clinical characteristics

	Randomized group		Overall (n = 162)
	Arm 1 Disposable doser to vial/syringe (n = 73)	Arm 2 Vial/syringe to disposable doser (n = 89)	
Age in years (mean ± SD)	59.6 ± 10.2	59.9 ± 11.2	59.8 ± 10.7
Men (%)	53.4	47.2	50.0
Race (%)			
American Indian	1.4	0	0.6
Asian/Pacific Islander	1.4	2.3	1.9
Black/African American	5.5	15.7	11.1
White/Caucasian	69.9	58.4	63.6
White/Hispanic	19.2	22.5	21.0
Other	2.7	1.1	1.9
Type of DM (%)			
Type 1	12.3	10.1	11.1
Type 2	87.7	89.9	88.9
Duration of diabetes (%)			
< 5 years	11.0	12.4	11.7
5–10 years	26.0	19.1	22.2
11–15 years	24.7	28.1	26.5
15+ years	38.4	39.3	38.9
Duration of insulin use (%)			
6 months – 1 year	11.0	4.5	7.4
1 – < 2 years	8.2	13.5	11.1
2 – < 3 years	4.1	5.6	4.9
3 – < 4 years	5.5	9.0	7.4
4 – < 5 years	4.1	12.4	8.6
5+ years	67.1	55.1	60.5
BMI (%)			
Normal: 18.5–24.9	9.6	11.2	10.5
Overweight: 25–29.9	28.8	19.1	23.5
Obesity: ≥ 30	61.6	69.7	66.1
A1C* (mean ± SD)	7.2 ± 1.3	7.8 ± 1.3	7.5 ± 0.1
Charlson Co-morbidity Index (mean ± SD)	3.0 ± 2.0	2.8 ± 2.1	2.9 ± 2.0

* $p < 0.05$ for the comparison between treatment arms
SD = Standard deviation

method for insulin administration (75.2%, p<0.0001), was more comfortable to use in public (72.3%, p<0.0001), was the least unpleasant method to use (67.9%, p<0.0001), made it easier to take all of their daily insulin doses (62.3%, p=0.0006), and made life

with diabetes easier (62.2%, p=0.0007; Table 3). Although not statistically significant, a slightly higher percentage of patients reported that the disposable doser allowed a more enjoyable social life (52.5%, p=0.2658), was the method of insulin administration that least interfered with daily activities (51.5%, p=0.3569), and provided an overall better quality of life (55.6%, p=0.0763).

No statistical test was performed on the questions for preference of the disposable doser providing a more flexible method to deliver insulin, a method of insulin administration that provides better control over blood sugar, and a method of insulin administration that makes them less dependent on others, because the proportion of patients who selected the disposable doser as the preferred method was less than the baseline comparison value of 0.50 (ie, no preference). The degree of patient preference (slight, some, strong, very strong) was examined for each subset: those who preferred the disposable doser and those who preferred the vial/syringe. Of the subset of patients who preferred the disposable doser (n = 117), 78.6% (n = 92) had a strong or very strong preference for this delivery system. Of the subset of patients who preferred vial/syringe (n = 36), 66.7% (n = 24) had a strong or very strong preference for this delivery system. Factors that influenced preference for the disposable doser included age and treatment arm. For each additional year of age increased, patients reported a decrease in their preference for the disposable doser (odds ratio [OR], 0.948; 95% CI 0.911–0.986). Those who were randomized to arm 2 (vial/syringe to disposable doser) preferred the disposable doser more than those who were randomized to arm 1 (disposable doser to vial/syringe) (OR, 2.170; 95% CI 1.051–4.478).

Fear of Self-Injection Questionnaire

Results for all of the eight items, as well as the summary score, on the Fear of Self-Injection Questionnaire showed a statistically significant difference, where after using the disposable doser, patients reported a lower fear of self-injection ($p<0.05$; Table 4). The summary score for overall fear of self-injection was lower after using the disposable doser than after using vial/syringe (mean ± SEM: 9.5 ± 0.2 vs. 11.2 ± 0.4).

Thoughts About Taking Insulin Questionnaire

Results for six of the seven items, as well as the summary score, on the Thoughts About Taking Insulin Questionnaire showed a statistically significant difference, where after using the disposable doser, patients reported a lower degree of non-compliance ($p<0.05$; Table 5). The summary score for overall degree of non-compliance was lower after using the disposable doser than after using vial/syringe (mean ±SEM: 10.3 ± 0.3 vs. 12.0 ± 0.5).

Insulin Treatment Satisfaction Questionnaire (ITSQ)

There was a statistically significant difference in all transformed score categories of the ITSQ, as well as the overall summary score ($p<0.05$; Table 6). After using the

Table 2. Patient preference for insulin administration delivery system stratified by randomization

	Randomized group		Overall *n* (%)
	Arm 1 Disposable doser to vial/syringe *n* (%)	Arm 2 Vial/syringe to disposable doser *n* (%)	
Total in each arm	73 (45.06)	89 (54.94)	162 (100.00)
Choice of disposable doser versus vial/syringe as preferred method of insulin use?			
Disposable doser	47 (64.38)	70 (78.65)	117 (72.22)
Vial/syringe	20 (27.40)	16 (17.98)	36 (22.22)
No difference	6 (8.22)	3 (3.37)	9 (5.56)
Which method is more convenient to use?			
Disposable doser	50 (68.49)	71 (79.78)	121 (74.69)
Vial/syringe	14 (19.18)	12 (13.48)	26 (16.05)
No difference	9 (12.33)	6 (6.74)	15 (9.26)
Which method is easier to use?			
Unknown/missing	0 (0)	1 (1.12)	1 (0.62)
Disposable doser	50 (68.49)	72 (80.90)	122 (75.31)
Vial/syringe	15 (20.55)	11 (12.36)	26 (16.05)
No difference	8 (10.96)	5 (5.62)	13 (8.02)
Which method is offers greater flexibility?			
Unknown/missing	2 (2.74)	1 (1.12)	3 (1.85)
Disposable doser	33 (45.21)	45 (50.56)	78 (48.15)
Vial/syringe	8 (10.96)	6 (6.74)	14 (8.64)
No difference	30 (41.10)	37 (41.57)	67 (41.36)
Which method is more comfortable to use in public?			
Unknown/missing	1 (1.37)	2 (2.25)	3 (1.85)
Disposable doser	47 (64.38)	69 (77.53)	116 (71.60)
Vial/syringe	8 (10.96)	6 (6.74)	14 (8.64)
No difference	17 (23.29)	12 (13.48)	29 (17.90)
Which method allows a more enjoyable social life?			
Unknown/missing	1 (1.37)	1 (1.12)	2 (1.23)
Disposable doser	33 (45.21)	52 (58.43)	85 (52.47)
Vial/syringe	9 (12.33)	6 (6.74)	15 (9.26)
No difference	30 (41.10)	30 (33.71)	60 (37.04)
Which method least interferes with daily activities?			
Unknown/missing	1 (1.37)	1 (1.12)	2 (1.23)
Disposable doser	34 (46.58)	49 (55.06)	83 (51.23)
Vial/syringe	7 (9.59)	4 (4.49)	11 (6.79)
No difference	31 (42.47)	35 (39.33)	66 (40.74)
Which method provides better control over blood sugar?			
Unknown/missing	1 (1.37)	4 (4.49)	5 (3.09)
Disposable doser	27 (36.99)	40 (44.94)	67 (41.36)
Vial/syringe	12 (16.44)	9 (10.11)	21 (12.96)
No difference	33 (45.21)	36 (40.45)	69 (42.59)
Which method is least unpleasant to use?			
Unknown/missing	1 (1.37)	1 (1.12)	2 (1.23)
Disposable doser	43 (58.90)	67 (75.28)	110 (67.90)
Vial/syringe	9 (12.33)	12 (13.48)	21 (12.96)
No difference	20 (27.40)	9 (10.11)	29 (17.90)

Table 2. (Continued)

	Randomized group		Overall *n* (%)
	Arm 1 Disposable doser to vial/syringe *n* (%)	Arm 2 Vial/syringe to disposable doser *n* (%)	
Which method makes it easier to take all of your daily insulin doses?			
Unknown/missing	1 (1.37)	1 (1.12)	2 (1.23)
Disposable doser	39 (53.42)	62 (69.66)	101 (62.35)
Vial/syringe	13 (17.81)	10 (11.24)	23 (14.20)
No difference	20 (27.40)	16 (17.98)	36 (22.22)
Which method makes you less dependent on others?			
Unknown/missing	1 (1.37)	3 (3.37)	4 (2.47)
Disposable doser	30 (41.10)	48 (53.93)	78 (48.15)
Vial/syringe	6 (8.22)	5 (5.62)	11 (6.79)
No difference	36 (49.32)	33 (37.08)	69 (42.59)
Which method makes life with diabetes easier?			
Unknown/missing	0 (0)	1 (1.12)	1 (0.62)
Disposable doser	41 (56.16)	60 (67.42)	101 (62.35)
Vial/syringe	10 (13.70)	6 (6.74)	16 (9.88)
No difference	22 (30.14)	22 (24.72)	44 (27.16)
Which method provides an overall better quality of life?			
Unknown/missing	0 (0)	2 (2.25)	2 (1.23)
Disposable doser	35 (47.95)	55 (61.80)	90 (55.56)
Vial/syringe	10 (13.70)	5 (5.62)	15 (9.26)
No difference	28 (38.36)	27 (30.34)	55 (33.95)

disposable doser, patients had higher insulin treatment satisfaction in the areas of convenience of regimen ($p<0.0001$), lifestyle flexibility ($p=0.0006$), glycemic control ($p<0.0001$), hypoglycemic control ($p<0.0001$), insulin delivery system satisfaction ($p<0.0001$) and overall satisfaction ($p<0.0001$) compared to after using vial/syringe. The transformed summary score for overall insulin treatment satisfaction was higher after using the disposable doser than after using the vial/syringe (mean ± SEM: 79.0 ± 1.3 vs. 70.4 ± 1.7; Table 7).

Problem Areas in Diabetes (PAID)

Results for 17 of the 20 items, as well as the summary score, on the PAID questionnaire showed a statistically significant difference, where after using the disposable doser, patients reported a lower amount of problem areas in diabetes ($p<0.05$; Table 8). The summary score for the overall problem areas in diabetes was lower after using the disposable doser than after using the vial/syringe (mean ± SEM: 20.8 ± 1.5 vs. 26.1 ± 1.9).

Table 3. Comparison* of overall preference for the disposable doser upon study completion

Patient preference for insulin device	*n*	Percent of cohort that preferred disposable doser	*p*-value
Disposable doser for administration of insulin	162	71.51	<0.0001
Disposable doser as the more convenient method for administration of insulin	162	74.13	<0.0001
Disposable doser as the easier method for administration of insulin	161	75.15	<0.0001
Disposable doser as the more flexible method for administration of insulin	159	48.80	N/A
Disposable doser as the method of administration for insulin that is more comfortable to use in public	159	72.29	<0.0001
Disposable doser as the method of administration for insulin that allows a more enjoyable social life	160	52.46	0.2658
Disposable doser as the method of administration for insulin that least interferes with daily activities	160	51.45	0.3569
Disposable doser as the method of administration for insulin that provides better control over blood sugar	157	42.27	N/A
Disposable doser as the method of administration for insulin that is least unpleasant to use	160	67.92	<0.0001
Disposable doser as the method of administration for insulin that makes it easier to take all of their daily insulin doses	160	62.31	0.0006
Disposable doser as the method of administration for insulin that makes them less dependent on others	158	48.74	N/A
Disposable doser as the method of administration for insulin that makes life with diabetes easier	161	62.17	0.0007
Disposable doser as the method of administration for insulin that provides an overall better quality of life	160	55.58	0.0763

*Comparisons performed on non-missing data only

Table 4. Responses to Diabetes Fear of Self-Injection Questionnaire upon completion of disposable doser versus vial/syringe

Question: *When I have to inject an insulin dose…*	Scoring scale	Completed disposable doser		Completed vial/syringe	
		No. of patients	Mean (SEM)	No. of patients	Mean (SEM)
I become restless	1 (almost never) to 4 (almost always)	160	1.23 (0.04)	162	1.41 (0.06)
I feel tense	1 (almost never) to 4 (almost always)	160	1.28 (0.04)	162	1.57 (0.06)
I feel afraid	1 (almost never) to 4 (almost always)	160	1.08 (0.02)	162	1.29 (0.05)
I worry about it	1 (almost never) to 4 (almost always)	160	1.19 (0.04)	161	1.42 (0.06)
I feel nervous	1 (almost never) to 4 (almost always)	159	1.18 (0.03)	162	1.43 (0.06)
I brood about it	1 (almost never) to 4 (almost always)	160	1.18 (0.04)	162	1.36 (0.06)
I try to postpone it	1 (almost never) to 4 (almost always)	160	1.21 (0.04)	161	1.39 (0.06)
I get angry	1 (almost never) to 4 (almost always)	160	1.14 (0.03)	162	1.36 (0.06)
Overall Fear of Insulin Injection score	Max score = 32	159	9.47 (0.21)	161	11.23 (0.39)

Table 5. Responses to Thoughts About Taking Insulin Questionnaire upon completion of disposable doser versus vial/syringe

Question:	Scoring scale	Completed disposable doser		Completed vial/syringe	
During the past 4 weeks, how often did you…		No. of patients	Mean (SEM)	No. of patients	Mean (SEM)
Think about postponing your insulin dose to a more convenient time?	1 (never) to 6 (always)	160	1.65 (0.07)	162	1.98 (0.10)
Think about skipping or not taking your insulin dose?	1 (never) to 6 (always)	160	1.43 (0.06)	162	1.65 (0.09)
Postpone taking your insulin until a more convenient time?	1 (never) to 6 (always)	160	1.68 (0.07)	162	1.98 (0.10)
Miss an insulin dose on purpose?	1 (never) to 6 (always)	160	1.29 (0.05)	161	1.46 (0.07)
Miss an insulin dose because you forgot to take it?	1 (never) to 6 (always)	159	1.71 (0.07)	162	1.90 (0.08)
Miss an insulin dose because you forgot your insulin supplies?	1 (never) to 6 (always)	160	1.36 (0.05)	162	1.61 (0.08)
Miss an insulin dose because you wanted to avoid the hassle of injecting?	1 (never) to 6 (always)	160	1.20 (0.05)	162	1.43 (0.07)
Overall score for Thoughts About Taking Insulin Questionnaire	Max score = 42	159	10.33 (0.31)	161	12.03 (0.49)

Table 6. Responses to Insulin Treatment Satisfaction Questionnaire upon completion of disposable doser versus vial/syringe

Question:	Scoring scale	Completed disposable doser		Completed vial/syringe	
		No. of patients	Mean (SEM)	No. of patients	Mean (SEM)
How convenient is it for you to take all you daily insulin doses as prescribed?	1 (extremely convenient) to 7 (not convenient at all)	161	2.24 (0.12)	161	2.86 (0.14)
How much of a bother is it for you to take all your daily insulin doses as prescribed?	1 (no bother at all) to 7 (a tremendous bother)	161	2.12 (0.11)	161	2.77 (0.14)
How much does your current insulin treatment interfere with you ability to enjoy social or leisure activities?	1 (does not interfere at all) to 7 (interferes tremendously)	161	2.00 (0.09)	161	2.65 (0.14)
How much does your current insulin treatment interfere with your work or school activities?	1 (does not interfere at all) to 7 (interferes tremendously)	161	1.85 (0.10)	162	2.35 (0.13)
How much do you have to plan the timing of your meals or snacks around the insulin you currently use?	1 (no planning at all) to 7 (a tremendous amount of planning)	160	2.59 (0.13)	162	3.10 (0.13)
How much do you have to plan what you eat with your current insulin treatment?	1 (no planning at all) to 7 (a tremendous amount of planning)	159	2.99 (0.14)	162	3.21 (0.13)
How much do you have to plan your physical activities (such as exercise or strenuous household chores) around your current insulin treatment?	1 (no planning at all) to 7 (a tremendous amount of planning)	161	2.45 (0.13)	162	2.75 (0.13)
How confident are you that you can avoid symptoms of low blood sugar (such as sweating, trembling, dizziness, blurred vision) with your current insulin treatment?	1 (extremely confident) to 7 (not at all confident)	160	2.45 (0.11)	162	3.00 (0.13)
How confident are you that you can avoid severe episodes of low blood sugar that result in loss of consciousness (fainting or passing out) with the insulin you currently use?	1 (extremely confident) to 7 (not at all confident)	160	1.93 (0.10)	161	2.42 (0.12)
In general, how bothered are you by symptoms of low blood sugar (such as sweating, trembling, dizziness, blurred vision) due to the insulin you currently use?	1 (no bother at all) to 7 (a tremendous bother)	161	2.32 (0.10)	162	2.85 (0.12)
How much do you feel that the insulin you are currently using increases the chances that you will experience low blood sugar?	1 (not at all) to 7 (extremely)	161	1.99 (0.09)	162	2.43 (0.11)
How worried are you about experiencing low blood sugars during the night with the insulin you currently use?	1 (not worried at all) to 7 (extremely worried)	161	2.11 (0.10)	162	2.66 (0.13)
How confident are you that you can avoid symptoms of *high* blood sugar (such as dry mouth, thirst, frequent urination, fatigue, increased appetite) with your current insulin treatment?	1 (extremely confident) to 7 (not at all confident)	161	2.54 (0.10)	162	2.88 (0.13)
How satisfied are you with the stability of your blood sugar levels with your current insulin treatment?	1 (extremely satisfied) to 7 (not at all satisfied)	159	2.50 (0.12)	161	2.85 (0.13)

Question:	Scoring scale	Completed disposable doser		Completed vial/syringe	
		No. of patients	Mean (SEM)	No. of patients	Mean (SEM)
How time consuming is it for you to manage your current insulin treatment?	1 (not at all time consuming) to 7 (extremely time consuming)	160	2.24 (0.11)	161	2.73 (0.13)
Overall, how pleased are you with the blood sugar control you achieve with your current insulin treatment?	1 (extremely pleased) to 7 (not at all pleased)	160	2.53 (0.12)	161	2.77 (0.12)
In general, how stressful is it for you to manage taking your current insulin treatment?	1 (not at all stressful) to 7 (extremely stressful)	159	2.06 (0.10)	161	2.63 (0.13)
How burdensome is it for you to manage your current insulin treatment?	1 (not at all burdensome) to 7 (extremely burdensome)	159	2.10 (0.10)	161	2.75 (0.14)
To what extent do you sometimes feel down or depressed because of your current insulin treatment?	1 (not at all down or depressed) to 7 (extremely down or depressed)	160	2.13 (0.10)	161	2.69 (0.13)
How easy is it for you to take the correct amount of insulin each time with your current method of taking insulin?	1 (extremely easy) to 7 (not easy at all)	159	1.64 (0.10)	162	2.40 (0.13)
How convenient is your current method of taking insulin when you are away from home?	1 (extremely convenient) to 7 (not convenient at all)	160	2.11 (0.12)	162	3.46 (0.16)
How much pain or other physical discomfort do you experience with your current method of taking insulin?	1 (no pain or discomfort) to 7 (a tremendous amount of pain or discomfort)	159	1.81 (0.09)	162	2.60 (0.12)

Table 7. Mean difference comparisons* of transformed scored responses to Insulin Treatment Satisfaction Questionnaire upon completion of disposable doser versus vial/syringe

Question topic	*n*	Disposable doser to vial/syringe		*p*-value
		Mean difference	SEM	
Inconvenience of regimen (transformed score)	161	8.595	1.811	<0.0001
Lifestyle flexibility (transformed score)	161	6.556	1.884	0.0006
Glycemic control (transformed score)	161	6.832	1.633	<0.0001
Hypoglycemic control (transformed score)	161	7.323	1.557	<0.0001
Insulin delivery device satisfaction (transformed score)	161	12.62	2.030	<0.0001
Overall summary score (transformed score)	161	8.385	1.489	<0.0001

*Comparisons performed on non-missing pairs only

Table 8. Responses to Problem Areas in Diabetes questionnaire upon completion of disposable doser versus vial/syringe

Question:	Scoring scale	Completed disposable doser		Completed vial/syringe	
Which of the following diabetes issues are currently problems for you?		No. of patients	Mean (SEM)	No. of patients	Mean (SEM)
Not having clear and concrete goals for your diabetes care?	0 (not a problem) to 4 (serious problem)	159	0.67 (0.07)	162	0.94 (0.08)
Feeling discouraged with your diabetes treatment plan?	0 (not a problem) to 4 (serious problem)	159	0.65 (0.07)	161	0.91 (0.08)
Feeling scared when you think about living with diabetes?	0 (not a problem) to 4 (serious problem)	159	0.98 (0.09)	161	1.24 (0.10)
Uncomfortable social situations related to your diabetes care (e.g., people telling you what to eat)?	0 (not a problem) to 4 (serious problem)	159	0.78 (0.08)	162	1.11 (0.09)
Feelings of deprivation regarding food and meals?	0 (not a problem) to 4 (serious problem)	159	0.92 (0.08)	161	1.21 (0.09)
Feeling depressed when you think about living with diabetes?	0 (not a problem) to 4 (serious problem)	159	0.96 (0.08)	162	1.23 (0.10)
Not knowing if your mood or feelings are related to your diabetes?	0 (not a problem) to 4 (serious problem)	157	1.03 (0.08)	161	1.24 (0.10)
Feeling overwhelmed by your diabetes?	0 (not a problem) to 4 (serious problem)	158	0.84 (0.08)	161	1.11 (0.10)
Worrying about low blood sugar reactions?	0 (not a problem) to 4 (serious problem)	159	1.01 (0.08)	160	1.19 (0.09)
Feeling angry when you think about living with diabetes?	0 (not a problem) to 4 (serious problem)	158	0.72 (0.08)	160	0.94 (0.10)
Feeling constantly concerned about food and eating?	0 (not a problem) to 4 (serious problem)	159	1.05 (0.08)	162	1.30 (0.10)
Worrying about the future and the possibility of serious complications?	0 (not a problem) to 4 (serious problem)	159	1.65 (0.10)	161	1.80 (0.11)
Feelings of guilt or anxiety when you get off track with your diabetes management?	0 (not a problem) to 4 (serious problem)	158	1.33 (0.09)	162	1.41 (0.10)
Not 'accepting' your diabetes?	0 (not a problem) to 4 (serious problem)	161	0.56 (0.07)	162	0.73 (0.08)
Feeling unsatisfied with your diabetes physician?	0 (not a problem) to 4 (serious problem)	160	0.11 (0.03)	162	0.21 (0.05)
Feeling that diabetes is taking up too much of your mental and physical energy every day?	0 (not a problem) to 4 (serious problem)	161	0.69 (0.07)	160	0.93 (0.09)
Feeling alone with your diabetes?	0 (not a problem) to 4 (serious problem)	157	0.60 (0.07)	161	0.72 (0.08)
Feeling that your friends and family are not supportive of your diabetes management efforts?	0 (not a problem) to 4 (serious problem)	161	0.38 (0.06)	161	0.52 (0.07)
Coping with complications of diabetes?	0 (not a problem) to 4 (serious problem)	160	1.03 (0.08)	162	1.21 (0.10)
Feeling 'burned out' by the constant effort needed to manage diabetes?	0 (not a problem) to 4 (serious problem)	160	0.85 (0.08)	162	1.21 (0.10)
Overall Score for Problem Areas in Diabetes Questionnaire	Max. Score = 100	150	20.76 (1.46)	151	26.10 (1.86)

Discussion

The primary objective of this study was to evaluate patients' preference for an insulin delivery system by comparing a disposable insulin doser to standard vial and syringe. We have shown that in the real world setting, after using both delivery systems, patients reported a greater preference for the disposable insulin doser. The goal of insulin therapy is to return blood glucose levels to normal or near-normal levels. It has been extensively documented that glycemic control may prevent both short-term and long-term effects of poorly controlled blood glucose [1–3]. However, for long-term regimens, such as insulin therapy, to be effective, patients must be willing to adhere to their treatment plan. While there are many factors that affect adherence, factors that may enhance patients' willingness to adhere include ease and convenience of administration, minimization of lifestyle disruptions, and the ability to be confident in the skills necessary to manage the regimen.

We found factors that contributed to patients' preference for the disposable doser included its convenience, ease of use, comfort of use in public and social settings, lessening fear of self-injection, lessening feeling of being overwhelmed by diabetes and making life with diabetes easier. Our findings of 71.5% overall preference for the disposable doser are consistent with the results of a previous clinical trial that showed patients' preference for use of an alternative insulin delivery system over vial and syringe [7,8]. Furthermore, a two-sided test was conducted and there was no significant difference in the study findings. While we found many factors that may contribute to patients being more adherent to their insulin treatment regimen, we did not find a significant difference in A1C concentrations between the two treatment groups during the study observation period. While a few of the patients had a change in their insulin regimen between study visits, the majority did not and generally, patients switched their insulin delivery system rather than the type, frequency and/or dose of insulin.

The design of this study required that patients used insulin therapy for at least 6 months; however, the majority of patients had been using insulin therapy for 5 or more years. Therefore, it is reasonable to assume that these patients had mastered the manual dexterity and hand–eye coordination necessary to administer insulin via vial and syringe. However, patients reported that using the disposable doser to administer insulin consumed even less time, made it easier to give the correct amount of insulin, caused less pain, and postponed or missed insulin doses occurred less often. These enhanced efficiencies may result in greater patient acceptance of insulin therapy, more accurate insulin administration, fewer insulin administration errors and missed doses, and thereby may delay or prevent the onset of long-term complications of diabetes.

Limitations

There are some study limitations to consider. Although patients were randomized, there were some differences in baseline characteristics between the patients within the two treatment arms. Therefore, logistic regression was performed to adjust for age, gender, type of diabetes, and treatment arm. For the majority of patients, only the delivery system

changed so any potential drug or efficacy bias that would affect preference was removed. However, a randomization bias may have been present. To correct this potential bias, Koch's method was used when performing tests of treatment effect; however, one cannot be certain if it was completely eliminated. While our findings were statistically significant, we cannot be certain that patients' preference for an insulin delivery system would result in an improvement in their clinical status. Additional research exploring the clinical significance of each of the delivery systems would be helpful.

In addition, patients who enrolled in this study were those who were actively seeking medical treatment for diabetes. It is not known if these findings would be similar for the general population of patients treated for diabetes. This study had a large proportion of patients with T2D. Therefore, our study finding may not be generalizable to the entire insulin-dependent population. Finally, some disadvantages exist with the use of alternative insulin delivery systems. Insulin pens and cartridges are not available for all types of insulin regimens, pre-filled pens and cartridges may not be altered and, in general, alternative insulin delivery systems tend to be more costly than insulin sold in traditional vials.

Conclusions

In real-world clinical practice settings, after using both the disposable doser and vial and syringe, patients in this study preferred the disposable doser to administer their insulin therapy. The importance of patient preference should not be underestimated. When prescribing insulin therapy, physicians may consider asking patients which delivery system they would prefer. An alternative insulin delivery system may offer greater patient acceptance of insulin therapy and, as was found in our study, improved treatment satisfaction. These findings may be clinically significant, given the potential health gains that can be obtained through improved diabetes self-management. Further research is needed to examine long-term use of the alternative insulin delivery systems.

References

1. American Diabetes Association. Economic costs of diabetes in the US in 2002. *Diabetes Care* 2003; **26**:917-932
2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet [online]. Atlanta, GA.; Available at: http://www.cdc.gov/diabetes/pubs/estimates.htm#incidence. [last accessed 4 Oct 2005]
3. Diabetes Control and Complication Trial Research Group. The effects of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; **329**:977-986
4. American Diabetes Association. Clinical practice recommendations 2005. *Diabetes Care* 2005;28 (Suppl 1): S1-79
5. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus. JAMA 2003; **289**:2254-2264

6. Tabak AG, Tamas G, Zgibor J, et al. Targets and reality. *Diabetes Care* 2000; **23**:1284-1289
7. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther 2004; **26**:1498-1505
8. Costa S, Brackenridge B, Hicks D. A comparison of insulin pen use in the United States and the United Kingdom. Diabetes Educator 2002; **28**:52-56
9. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Amended by 48th General Assembly, Somerset West, Republic of South Africa, October 1996. JAMA 1997; **277**(11).
10. International Conference on Harmonisation (ICH) Topic E6. Harmonised Tripartite Guideline for Good Clinical Practice. Step 5, Consolidated Guideline 1 May 1996
11. Mollema E, Snoek FJ, Pouwer F, et al. Diabetes fear of injecting and self testing questionnaire: a psychometric evaluation. Diabetes Care 2000; **23**:765-769
12. Anderson RT, Skovlund SE, Marrero D, et al. Development and validation of the Insulin Treatment Satisfaction Questionnaire. Clin Ther 2004; **26**:565-578
13. Welch G, Weinger K, Anderson B, Polnsky WH. Responsiveness of the Problem Areas in Diabetes (PAID) questionnaire. Diabetes Medicine 2003; **20**:69-72
14. Snoek FJ, Pouwer F, Welch G, Polonsky WH. Diabetes-related emotional distress in Dutch and US diabetic patients. Diabetes Care 2000; **23**:1305-1309
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; **40**:373-383
16. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; **45**:613-619

Chapter 4 – Appendix A – Study Questionnaires

Insulin Treatment Satisfaction Questionnaire

This questionnaire consists of two parts with a total of 22 items. Each item has a range of 1 (highest satisfaction) to 7 (lowest satisfaction). A summary score for the ITSQ was calculated by grouping the original 22 items into six scales. The scale categories were: inconvenience of regimen, lifestyle flexibility, glycemic control, hypoglycemic control, insulin device satisfaction and an overall summary score. Raw scores for each individual item were first transformed to a 0–100 scale where higher scores indicated better satisfaction. The transformed score was calculated as (7 minus the raw score) divided by 6 (i.e. 7 minus 1), multiplied by 100. The final transformed score for each of the scale categories was calculated as the mean of the non-missing transformed items used to define each scale.

Diabetes Fear of Self-Injection Questionnaire

This questionnaire consists of eight items. The range of each item is 1 (Never) to 4 (Always). A summary score was calculated for each patient by taking the sum of all eight items, 8 representing the lowest amount of fear and 32 representing the highest amount of fear. If a response to any of the eight items was missing, then no summary score could be calculated and was reported as a missing value.

Thoughts about Taking Insulin Questionnaire

This questionnaire consists of seven items. Each item has a range of 1 (Never) to 6 (Always). A summary score was calculated for each patient by taking the sum of all seven items, 7 representing the lowest amount of noncompliance and 42 representing the highest amount of noncompliance. If a response to any of the seven items was missing, then no summary score could be calculated and was reported as a missing value.

Problem Areas in Diabetes

This questionnaire consists of 20 items. The range of each item is 1 (not a problem) to 4 (serious problem). A summary score was calculated for each patient by taking the sum of all 20 items and multiplying this total by 1.25 to achieve a scale of 0 (lowest amount of problems) to 100 (highest amount of problems). If a response to any of the 20 items was missing, then no summary score could be calculated and was reported as a missing value.

Insulin Device Preference Questionnaire

This questionnaire consists of two parts with a total of 14 items. The first part determined which device the patient preferred overall (or if there was no preference for either device) and how strong their preference was for the device if the disposable doser or vial/syringe was chosen. The second part asked which device was preferred (or if there was no preference) on a series of questions ranging from convenience of use to providing an overall better quality of life.

Chapter 5

Examining correlates of treatment satisfaction for insulin

Adapted from: Brod M, Cobden D, Lammert M, Bushnell D, Raskin P. Examining Correlates of Treatment Satisfaction for Injectable Insulin in Type 2 Diabetes: Lessons Learned from a Clinical Trial comparing Biphasic and Basal Analogues. *Health & Quality of Life Outcomes*. 2007. Feb 7;5:8.

Summary

Successfully managing diabetes is a complex process that includes addressing issues of drug efficacy, safety and treatment satisfaction. Additionally, the combined impact of patient/disease characteristics and treatment outcomes on treatment satisfaction is not well understood. The purpose of this study was to examine the impact of age, weight, gender, co-morbid conditions, diabetes history, treatment burden, efficacy (HbA1c) and side effects (weight gain, hypoglycemic events) on patients' appraisal of treatment satisfaction using linear regression models. Data from a multi-center, randomized clinical trial comparing the efficacy/safety of biphasic insulin aspart 70/30 (BIAsp 70/30) vs. glargine (Glar) among insulin naïve type 2 patients were analyzed. Subjects were between ages 18–75, with baseline HbA1c > 8% and BMI ≤ 40 kg/m2 (N = 233). Treatment satisfaction was assessed by the Insulin Treatment Satisfaction Questionnaire (ITSQ).

When factors were examined independently, multiple significant relationships (age, comorbidity, hypoglycemic events, and weight gain) with overall and/or domains of treatment satisfaction were found. However, when all significant relationships were examined together, only neuropathy, treatment efficacy, and number of hypoglycemic events maintained their previous significance. By examining predictors independently, significant relationships were identified. However, not all findings remained significant when examined in combination with each other. Thus, to more accurately characterize the impact of factors on treatment satisfaction, a more comprehensive approach may be necessary. By improving patient treatment satisfaction, the efficacy of treatments, as well as critical treatment outcomes such as compliance and cost of care should be improved.

Introduction

Successfully managing diabetes is a complex process and must address not only issues of drug efficacy and safety but also treatment satisfaction. Weaver and colleagues [1] defined treatment satisfaction as the patient's view of the treatment process and its associated outcomes based on predefined criteria. Treatment satisfaction is a key patient-reported outcome as it has been found to impact patient compliance [2,3], cost of care [4,5], and self-management behaviors [6]. Treatment satisfaction has also been shown to significantly differ between the array of drug treatment options available to clinicians for a given patient [7,8]. It may at times be more sensitive to change than quality of life, and has the ability to distinguish treatments with equivalent efficacy [9]. Persons with diabetes who perceive injecting insulin as burdensome may experience more negative health outcomes [10], whereas patients who are satisfied with their treatments are more likely to maintain positive physical and psychological health [11].

Understanding the elements of treatment satisfaction for diabetes is especially important, given the ever increasing range of treatment options for diabetes patients as treatment satisfaction expectations have been shown to be dynamic and changing with the introduction of new therapies [12]. Overall treatment satisfaction in diabetes consists of the patient's appraisal of 3 main treatment-related parameters: side effects,

burden/inconvenience, and efficacy [13,14]. In diabetes, appraisal of side effects may predominantly include factors such as weight gain or the occurrence of hypoglycemic events. Appraisal of inconvenience or burden may take into consideration number of injections or type of delivery device. The gold standard for assessing efficacy is generally considered to be improvement in HbA1c level, although it is unclear if diabetes patients are aware of their exact values when not enrolled in a clinical trial. Additionally, patient and disease characteristics such as age, gender, time with diabetes, and prevalence and incidence of co-morbid conditions may act as mediators that influence these appraisals. Static factors such as patient and disease characteristics are generally constant or fixed at any given point in time. Characteristics such as age, gender, level of education, ethnicity and duration of diabetes have been shown to account for some of the differences in patients' treatment satisfaction with their diabetes care when provided by endocrinologists compared to generalists [15].

However, data on the relationship of these factors to treatment satisfaction is oftentimes conflicting, and many significant relationships do not endure when examined in combination with other important factors. For example, studies have found that greater satisfaction is associated with decreasing age, while others have indicated that younger patients are less satisfied with their treatment [16-18]. The occurrence of diabetes-related complications has been found to be associated with lower treatment satisfaction with diabetes medication, however, this association was no longer found when age, therapy and HbA1c level were also taken into consideration [17]. Insulin-treated patients have been found to have significantly greater treatment satisfaction than non-insulin treated patients with diabetes, though this significant difference was also lost after adjustments were made for age, gender, body mass index and duration of diabetes [19]. When examining treatment outcome factors which influence the appraisal of treatment satisfaction in diabetes, the most universal finding is that treatment satisfaction has generally been shown to be greater for those treatments that are most efficacious [13,17,20]. Additionally, clinical wisdom assumes that patients prefer treatments with few injections and few side effects such as weight gain or hypoglycemic events, although the data supporting these assumptions is not extensive and is contradictory [1].

For treatments with equal efficacy and no significant differences in weight gain or occurrence of hypoglycemic events, significant differences in treatment satisfaction have not been found [21]. Despite significant improvement in treatment satisfaction after 7 months of efficacious treatment (improved HbA1c) with decreased hypoglycemic events and increased weight, a significant relationship between weight gain, HbA1c and treatment satisfaction has not been found [22]. Interestingly, fewer number of daily injections has been shown both to improve treatment satisfaction and to have no impact on treatment satisfaction [23,24]. Further, continuous subcutaneous insulin infusion has been shown to be both superior to multiple daily injections, as well as to have no impact in determining patient treatment satisfaction [25,26]. Thus, it remains unclear what part of our beliefs about the relationships between patient/disease characteristics, clinical wisdom and treatment satisfaction in diabetes is myth versus reality.

The purpose of this study was to examine, in the context of a randomized clinical trial (RCT), the correlative relationship between treatment satisfaction, patient/disease characteristics, and key treatment outcomes that impact the appraisal of treatment satisfaction. By understanding the myths versus the realities of these relationships, clinicians will be in a better position to identify patients at risk for decreased treatment satisfaction and tailor treatment plans to maximize treatment satisfaction. By improving patient treatment satisfaction, the efficacy of diabetes treatments as well as other critical treatment outcomes such as compliance and cost of care is likely to be improved.

Methods

Procedures

Baseline and end of study (28 weeks) data from the INITIATE trial, a multi-center (25 U.S. sites) open-label RCT comparing the efficacy and safety of twice-daily (BID) biphasic insulin aspart 70/30 (BIAsp 70/30) vs. once-daily, bedtime (QD) glargine (Glar) among insulin naïve type 2 diabetes (T2D) patients failing oral medication were analyzed. Eligible subjects had T2D inadequately treated, controlled on oral antidiabetic agents (OADS), were insulin naïve, and male or female between the ages of 18–75 with baseline HbA1c > 8% and BMI ≤ 40 kg/m2. Patients with a history of recurrent, severe hypoglycemia, hepatic or renal insufficiency, cardiac disease, acute or chronic metabolic acidosis, active proliferative retinopathy or intolerance to metformin were excluded from the study.

The first phase of the study was a 4 week run-in period with metformin with patients with a fasting blood glucose level of ≤ 140 mg/dL, or any single value ≤ 170 mg/dL considered a run-in failure. Patients who successfully completed the run-in period were then randomized to receive equal doses of BIAsp 70/30 within 15 minutes before breakfast and dinner in addition to their current metformin, or Glar at bedtime in addition to their current metformin treatment. Subjects were told to perform daily blood glucose self-monitoring before breakfast and dinner. Insulin doses were titrated weekly for the first 12 weeks, then every 2 weeks thereafter according to a predefined titration algorithm based on blood glucose levels for the 3 days preceding a visit. Post-randomization, subjects were seen in the office weekly for the first month, and then again at weeks 8, 12, 16, 20, 24 and 28. Phone visits were conducted for weeks in which there was no office visit. Patients in the INITIATE trial signed informed consent forms and the study complied with FDA Good Clinical Practices. The study protocol had IRB approval.

Measures

The following data were derived from and/or generated during the trial and were used for the present analyses:

- Patient characteristics and diabetes history including age (as a continuous variable), sex, ethnic group, time with diabetes (at baseline as a continuous variable), body mass index (BMI) and co-morbid conditions (classified as

diabetes-related condition and as total number of conditions). These data were collected at the baseline visit.

- The Insulin Treatment Satisfaction Questionnaire (ITSQ) [11]: a validated measure consisting of 22 items that comprehensively assess treatment satisfaction for persons with diabetes on insulin. The measure was developed as a patient-reported outcome based on interviews with patients and clinical experts regarding treatment satisfaction as well as information in the literature. Satisfactory factor structure and internal consistency as well as adequate test-retest reliability, construct and discriminant validity for the ITSQ have been demonstrated [11]. In addition to an Overall score, the items make up five domains of satisfaction: Inconvenience of Regimen (IR-5 items), Lifestyle Flexibility (LF-3 items), Glycemic Control (GC-3 items), Hypoglycemic Control (HC-5 items) and Insulin Delivery Device (DD-6 items). All items are scored on a seven-point Likert-like response scale ranging from "not at all" to "extremely" (as worded appropriately for item). Items in the Glycemic and Hypoglycemic Control subscales are worded so that the respondent is asked about the relevant symptoms of their control such that a clinical understanding of either is not required. The ITSQ is scored by transforming all items to a scale of 0–100 with the higher score indicating better treatment satisfaction. For each subscale, the sum score is divided by number of items. Missing values are imputed based on the mean of the non-missing items. The ITSQ was administered after 28 weeks of treatment.

- Diabetic treatment effect status assessed after 28 weeks of treatment:

  - HbA1c level

  - Hypoglycemic episodes classified as total number, by timing of event (classified as day or night), and by type of event (classified as symptomatic or not)

  - BMI classified as BMI group (< 25 as normal, between 25 and 29.9 as overweight, and ≥ 30 as obese) and by absolute value change (classified as improved or worsened)

Statistical strategy

According to an a priori statistical analysis plan, for each statistical test performed, the relationship between the factors of interest, overall satisfaction and satisfaction within each domain of the ITSQ was examined by linear regression with list-wise entry (all variables entered as a block to test interaction with treatment satisfaction as the dependent variable). Statistical significance was considered to be achieved with a minimum p value of 0.05.

Examining the relationship between patient and disease characteristics and treatment satisfaction

First, in order to confirm successfully randomized cohorts, differences between treatment groups for baseline patient and disease characteristics were examined by ANOVA or chi square as appropriate for each characteristic. Next, a list-wise linear regression analysis was performed to examine baseline predictors of treatment satisfaction assessed at week 28. The model included all demographic and diabetes history variables collected at baseline (age, gender, ethnicity, duration of diabetes diagnosis, BMI, and number/type of diabetes-related co-morbid conditions). Independent linear regression models were assessed for each of the ITSQ subscales and the Overall score. The relationship of total number of co-morbid conditions and treatment satisfaction (each subscale and Overall) was examined by Pearson correlations. Additionally, the relationship between types of diabetes-related co-morbid conditions and treatment satisfaction was examined by independent linear regression (list-wise) analyses of the diabetes-related co-morbid conditions found in this sample and treatment satisfaction.

Examining the relationships between treatment outcomes and treatment satisfaction

The relationship between the number of minor hypoglycemic events and treatment satisfaction was assessed by Pearson correlation (2-tailed). Type of event (symptomatic or not) and time of event (day or night), cumulative over the treatment period, and treatment satisfaction were examined by linear regression analyses independently for each subscale and Overall ITSQ score. The relationship between BMI change during treatment and treatment satisfaction (Overall and all subscales) was first examined by performing an ANOVA, controlling for baseline weight, using change in BMI group from baseline to week 28. An independent ANOVA, controlling for baseline weight, examined the relationship between absolute changes in BMI, comparing those who had improved BMI to those whose BMI had worsened over the 28 weeks. The relationship between HbA1c levels at week 28 and treatment satisfaction was examined by Pearson correlation coefficients. The relationship between treatment group and treatment satisfaction was examined by ANOVAs for the total ITSQ score and each of its domains.

Examining the combined impact of significant factors

Lastly, as outlined in the statistical analysis plan, to understand the larger picture of the impact of demographic and treatment effect variables on treatment satisfaction, a regression analysis was performed on all of the above factors that were found to have a significant relationship to treatment satisfaction at week 28. Variance and goodness-of-fit was examined by the R^2.

Results

Sample description

A total of 233 patients with T2D, a slight majority of which were male (52.9%) and Caucasian (51.7%) with an average age of 52.15 (± 10.34) years, were randomized into the INITIATE study. Two hundred and nine (209) of these subjects had treatment effect data and 197 of these completed the ITSQ and were included in these analyses. The average duration of diabetes diagnosis was 8.29 years (± 5.24), and mean baseline HbA1c was 9.71% (± 1.47%).

Statistical findings

INITIATE trial clinical results

The INITIATE trial demonstrated that patients receiving BIAsp 70/30 were significantly more likely to have achieved HbA1c targets vs. Glar (66% vs. 40% of patients to HbA1c $< 7\%$, $p<0.01$, and 42% vs. 28% of patients to HbA1c $\leq 6.5\%$, $p<0.05$, respectively), and significantly improving total HbA1c reduction (-0.43%; $p<0.01$ between arms). Post-prandial glucose excursions at lunch and supper were also significantly more tightly controlled ($p<0.05$), though an increase in minor hypoglycemia and weight gain occurred (both $p<0.05$) [27].

Examining the relationship between patient and disease characteristics and treatment satisfaction

There were no significant differences found between treatment groups for any of the baseline patient or disease characteristics, indicating that randomization of subjects to treatment groups used in the present analyses was successful. As shown in Table 1, presence of diabetes-related co-morbid conditions at baseline was significantly predictive of overall treatment satisfaction as well as for Lifestyle Flexibility and in the Hypoglycemic and Glycemic Control subscales. Age was also predictive of treatment satisfaction related to Lifestyle Flexibility. The number of total co-morbid conditions in the sample ranged from 0 to 7 with a mean of 1.70 (± 1.50) and a median of 1.00. The diabetes-related co-morbid conditions identified in this sample were retinopathy, nephropathy, neuropathy, and macro-angiopathy. There were no significant relationships between total number of co-morbid conditions and treatment satisfaction. However, neuropathy was a significant predictor of treatment satisfaction (overall and in all subscales), indicating that pain is broadly associated with satisfaction outcomes. One other noted predictor was retinopathy, which was significant for the Device Satisfaction subscale. The relationship between types of diabetes-related co-morbid condition and treatment satisfaction is shown in Table 2.

Table 1: Impact of Demographics and Diabetes History on Insulin-related Treatment Satisfaction

	ITSQ Overall (n = 197)	ITSQ IR (n = 196)	ITSQ LF (n = 196)	ITSQ HC (n = 197)	ITSQ GC (n = 197)	ITSQ DD (n = 197)
	Coefficient (t-ratio)					
Intercept	72.42*** (6.54)	74.63*** (5.89)	68.90*** (4.95)	67.67*** (4.83)	82.53*** (6.32)	73.68*** (6.32)
Age	0.21 (1.51)	0.23 (1.43)	0.35* (2.00)	0.22 (1.24)	0.17 (1.05)	0.14 (0.92)
Gender (0 = M, 1 = F)	-2.30 (-0.87)	0.45 (0.15)	0.23 (0.07)	-6.42 (-1.92)	-4.43 (-1.43)	-1.95 (-0.70)
Ethnicity (1 = C, 0 = Other)	-0.99 (-0.36)	-0.19 (-0.06)	-2.80 (-0.81)	-1.44 (-0.42)	-2.35 (-0.73)	0.90 (0.31)
Length of time with diabetes (↑ longer)	-0.17 (-0.66)	-0.09 (-0.32)	-0.06 (-0.17)	-0.42 (-1.30)	-0.13 (-0.42)	-0.17 (-0.61)
Weight-BMI	0.17 (0.66)	0.01 (0.04)	-0.23 (-0.70)	0.50 (1.53)	0.10 (0.31)	0.23 (0.83)
Number of diabetes related co-morbid conditions	-3.93* (-2.15)	-2.33 (-1.10)	-5.68* (-2.46)	-5.08* (-2.19)	-5.48* (-2.54)	-1.93 (-1.00)
	F = 1.195	F = 0.538	F = 1.812	F = 1.918	F = 1.497	F = 0.534
	R^2 = 0.036	R^2 = 0.016	R^2 = 0.053	R^2 = 0.056	R^2 = 0.044	R^2 = 0.016
	Adj R^2 = 0.006	Adj R^2 = -0.014	Adj R^2 = 0.024	Adj R^2 = 0.027	Adj R^2 = 0.015	Adj R^2 = -0.014

• * p < 0.05, ** p < 0.01, *** p < 0.001
• IR = Inconvenience of Regime subscale, LF = Lifestyle Flexibility subscale, HC = Hypoglycemic Control subscale, GC = Glycemic Control subscale, DD = Device Delivery subscale

Table 2: Impact of Diabetic-related Co-morbid Conditions on Treatment Satisfaction

	ITSQ Overall (n = 197)	ITSQ IR (n = 196)	ITSQ LF (n = 196)	ITSQ HC (n = 197)	ITSQ GC (n = 197)	ITSQ DD (n = 197)
	Coefficient (t-ratio)					
Intercept	84.11*** (56.89)	87.24*** (51.36)	78.85*** (41.72)	81.75*** (42.67)	86.43*** (49.64)	84.79*** (54.58)
Retinopathy (N = 0, Y = 1)	7.29 (1.50)	8.94 (1.60)	0.95 (0.15)	2.31 (0.37)	10.17 (1.78)	10.90* (2.13)
Nephropathy (N = 0, Y = 1)	2.08 (0.40)	-0.61 (-0.10)	3.68 (0.55)	3.79 (0.56)	-2.57 (-0.42)	3.94 (0.71)
Neuropathy (N = 0, Y = 1)	-10.56*** (-3.53)	-8.81* (-2.54)	-12.42** (-3.22)	-10.80** (-2.79)	-13.43*** (-3.82)	-8.00* (-2.54)
Macro Angiopathy (N = 0, Y = 1)	-5.18 (-1.09)	-1.16 (-0.21)	-4.58 (-0.76)	-5.63 (-0.92)	-5.93 (-1.06)	-6.44 (-1.29)
	F = 3.622**	F = 1.888	F = 2.943*	F = 2.280	F = 4.281**	F = 2.789*
	R^2 = 0.069	R^2 = 0.037	R^2 = 0.057	R^2 = 0.044	R^2 = 0.080	R^2 = 0.054
	Adj R^2 = 0.050	Adj R^2 = -0.018	Adj R^2 = 0.038	Adj R^2 = 0.025	Adj R^2 = 0.062	Adj R^2 = -0.035

• * p < 0.05, ** p < 0.01, *** p < 0.001
• IR = Inconvenience of Regime subscale, LF = Lifestyle Flexibility subscale, HC = Hypoglycemic Control subscale, GC = Glycemic Control subscale, DD = Device Delivery subscale

Examining the relationships between treatment outcomes on treatment satisfaction

A total of 1,073 hypoglycemic events, of which 1,072 were minor events, were reported over the 28 weeks of treatment. Hence, the analysis is based on minor hypoglycemic

events only. The number of minor hypoglycemic events per patient was found to be significantly associated only with the Hypoglycemic Control subscale ($r = -0.263$, $p<0.001$). However, as shown in Table 3, the time of a hypoglycemic event was found to be highly predictive of overall treatment satisfaction and for each subscale, with daytime events resulting in decreased treatment satisfaction. There were no significant impacts for the type of hypoglycemic event. The majority of patients (81%) did not change BMI group (normal, overweight or obese) during the treatment period, and no significant relationships between BMI group change and treatment satisfaction were found. The absolute BMI change ranged from -2.57 (decrease) to +6.83 (mean 1.61 ± 1.62) with the majority of the population (85.5%) increasing in BMI levels.

For those 14.5 % of patients who had a decrease in BMI, there was a systematic improvement in treatment satisfaction across all scores, although only the difference for the Lifestyle Flexibility subscale was significant ($p<0.05$). The lack of statistical significance may be due to the small number of patients who did change BMI group power (19%). Pearson correlation coefficients showed a significant relationship between HbA1c and treatment satisfaction. While associations were low, the relationship of HbA1c level to treatment satisfaction was significant for the Overall score ($r = -0.16$, $p<0.05$), Inconvenience of Regimen ($r = -0.15$, $p<0.05$), Glycemic Control ($r = -0.23$, $p<0.001$), and Device Satisfaction ($r = -0.17$, $p<0.05$). No significant differences were found in the total ITSQ score or any of the domains during comparisons between treatment groups, indicating in part the potential that an increase in number of daily injections (BID vs. QD) may not negatively affect treatment satisfaction.

Table 3: Impact of Hypoglycemic Events on Treatment Satisfaction

	ITSQ Overall (n = 197)	ITSQ IR (n = 196)	ITSQ LF (n = 196)	ITSQ HC (n = 197)	ITSQ GC (n = 197)	ITSQ DD (n = 197)
	Coefficient (t-ratio)					
Intercept	*92.74*** (12.96)*	*96.72*** (12.54)*	*85.36*** (8.46)*	*86.42*** (8.50)*	*95.64*** (10.88)*	*96.55*** (12.63)*
Time of event (1 = Active, 7 AM-11 PM; 0 = Sleeping, 11 PM-7 AM)	-5.47*** (-4.52)	-5.13*** (-4.52)	-10.63*** (-6.22)	-4.39** (-2.55)	-2.98** (-2.00)	-5.26*** (-4.06)
Type of event (1 = Symptomatic, 0 = Not symptomatic)	-11.18 (-1.56)	-7.73 (-1.00)	-6.54 (-0.65)	-15.02 (-1.47)	-12.39 (-1.41)	-12.25 (-1.60)
	F = 11.854***	F = 8.454***	F = 19.837***	F = 4.555***	F = 3.164***	F = 9.929***
	R^2 = 0.026	R^2 = 0.018	R^2 = 0.042	R^2 = 0.010	R^2 = 0.007	R^2 = 0.022
	Adj R^2 = 0.023	Adj R^2 = 0.016	Adj R^2 = 0.040	Adj R^2 = 0.008	Adj R^2 = 0.005	Adj R^2 = 0.019

- ** $p < 0.01$, *** $p < 0.001$
- IR = Inconvenience of Regime subscale, LF = Lifestyle Flexibility subscale, HC = Hypoglycemic Control subscale, GC = Glycemic Control subscale, DD = Device Delivery subscale

Examining the combined impact of significant factors

As shown in Table 4, when all previously identified significant relationships were examined together, neuropathy continued to have the broadest impact on treatment satisfaction (Overall and in all 5 subscales). Improved treatment efficacy (HbA1c) maintained the previously identified significant impacts on overall treatment satisfaction and in 3 subscales. The number of hypoglycemic events remained significant only for the Hypoglycemic Control subscale, however the timing of the hypoglycemic event significantly impacted overall satisfaction and 3 subscales rather than the previous 5 (Glycemic Control and Inconvenience of Regimen were no longer significant). The impact of age, weight gain and the number of co-morbid conditions were no longer significant. The R^2 for the model was 0.123, suggesting that these combined factors account for 12% of possible variance of factors that may impact treatment satisfaction.

Table 4: Impact of Significant Treatment Variables on Treatment Satisfaction

	ITSQ Overall (n = 197)	ITSQ IR (n = 196)	ITSQ LF (n = 196)	ITSQ HC (n = 197)	ITSQ GC (n = 197)	ITSQ DD (n = 197)
			Coefficient (t-ratio)			
Intercept	108.93*** (13.06)	110.62*** (11.53)	62.46*** (7.52)	84.27*** (43.10)	124.26*** (12.73)	108.68*** (12.34)
Age			0.32* (2.04)			
Neuropathy (N = 0, Y = 1)	-11.91** (-2.79)	-7.97* (-2.38)	-11.65* (-2.14)	-12.36* (-2.26)	-13.42** (-2.69)	-8.63** (-2.79)
Retinopathy (N = 0, Y = 1)						9.36 (1.86)
Change in weight (BMI)			7.40 (1.69)			
Co-morbid conditions (number of diabetic related)	1.43 (0.55)		-0.22 (-0.01)	1.83 (0.56)	0.04 (0.01)	
HbA_{1c} Level (week 28)	-3.29** (-2.88)	-3.19* (-2.43)			-5.17*** (-3.87)	-3.19** (-2.65)
Number of hypoglycemic events during day (active 7 am-11 pm)	-0.53** (-2.72)	-0.29 (-1.28)	-0.70** (-2.86)	-0.81** (-3.26)	-0.34 (-1.47)	-0.42* (-2.06)
Number of hypoglycemic events during night (sleep 11 pm-7 am)	0.29 (0.72)	0.53 (1.14)	0.71 (1.41)	-0.27 (-0.53)	0.15 (0.32)	0.36 (0.84)
	F = 65.351***	F = 3.177*	F = 4.571***	F = 5.657***	F = 6.093***	F = 4.027**
	R^2 = 0.123	R^2 = 0.062	R^2 = 0.125	R^2 = 0.103	R^2 = 0.138	R^2 = 0.095
	Adj R^2 = 0.100	Adj R^2 = 0.043	Adj R^2 = 0.098	Adj R^2 = 0.085	Adj R^2 = 0.115	Adj R^2 = 0.072

- * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
- IR = Inconvenience of Regime subscale, LF = Lifestyle Flexibility subscale, HC = Hypoglycemic Control subscale, GC = Glycemic Control subscale, DD = Device Delivery subscale

Discussion

Clinical wisdom and common sense would presume, and research has at times supported the idea, that there is a negative impact of unfavorable treatment characteristics, burden of treatment and side effects on patient-reported treatment satisfaction. However, we did not find a significant relationship between the number of minor hypoglycemic events, weight gain or treatments with 1 vs. 2 daily injections with overall treatment satisfaction. The relationship of weight gain to treatment satisfaction was restricted only to Lifestyle Flexibility. This significant finding may be due to the nature of the items in the Lifestyle Flexibility domain, as 2 of the 3 items in that subscale concern eating times and meals. The timing of the hypoglycemic event (minor hypoglycemic events that occurred during the day vs. nocturnal episodes) did have a significantly negative impact on overall treatment satisfaction. However, it should be noted that it remains unclear if daytime hypoglycemic events are also more "feared" or problematic for patients, as nighttime events may be more difficult to identify or respond to and if they are major events they may have a greater potential for serious health consequences. It may also be noteworthy that minor diurnal events may be more bothersome to daily functioning, and therefore more negatively influence treatment satisfaction. On the contrary, minor nocturnal events such as patients' activity levels are likely to be higher during daytime hours. As there was only 1 severe hypoglycemic event during the study, we were not able to examine the relationship between major events and treatment satisfaction.

Also, contrary to common wisdom, no significant differences in treatment satisfaction were found between treatment groups despite the fact that BIAsp 70/30 was administered twice a day (with a pen device) and Glar was administered once a day (with a syringe) as a fixed characteristic of the treatment arm. This finding suggests that number of daily injections may not impact overall treatment satisfaction. However, due to the design of this study, it is difficult to separate out the effect of the number of daily injections versus the delivery device itself. It may be that the increased number of daily injections required for BIAsp 70/30 is balanced by a reported preference for the pen device over syringe [28-30]. It may also be that having 1 vs. 2 injections per day is not as important a factor of treatment satisfaction as the distress experienced by patients going from being insulin naïve (0 injections per day) to having begun injections on a daily basis [31]. Given that there is evidence suggesting that BIAsp 70/30 is also efficacious with once-daily injections [32], additional research should continue to examine the impact of once-daily injections with a pen versus syringe on overall satisfaction, as well as specifically for device satisfaction.

Regarding the belief that treatment efficacy is the primary driver of treatment satisfaction, BIAsp 70/30 was found to have superior efficacy (improvement in HbA1c) to Glar in the INITIATE trial, evidence that is supported in a subsequent clinical trial [33]. Although there is no data available to confirm that patients knew their HbAlc levels, doses were regularly titrated based on blood glucose levels and patients self-monitored their blood glucose levels twice daily. Further, HbAlc level was found to be significantly related to Overall Satisfaction suggesting that subjects were aware of treatment efficacy either by information from the physician or by how they felt. Thus, it is highly likely that

the patients were aware of their HbA1c values, and able to use this factor when appraising their treatment satisfaction.

Despite superior efficacy, treatment satisfaction was equivalent between the 2 treatment groups. This finding may be explained by the Decisional Balance Model of Treatment Satisfaction, whereby Overall treatment satisfaction is determined by the balance between the positive value of treatment and the negative harms and inconveniences of the medication [3]. Thus, the appraisal of treatment satisfaction for a treatment such as BIAsp 70/30, with superior efficacy when compared to Glar, but increased minor hypoglycemia and weight gain, may be equivalent. The Balance Theory model and our findings in the present analysis are supported by those in recent trials where competing insulin preparations which demonstrate disparate side effect and efficacy profiles have caused non-significant differences in treatment satisfaction [34]. The Balance Theory model may also help explain the lack of significant differences in overall treatment satisfaction in pen vs. syringe device studies, even when there is clearly stated preference for the pen device, if treatments have equivalent efficacy and safety [28]. It should be noted that the ITSQ overall score is not a truly independent rating of overall treatment satisfaction as it is the sum of the subscale items rather than a separate item assessing overall satisfaction. Post-hoc analyses with this study data have shown that the correlations between subscales and the overall score are all above 0.77 and a regression analysis of subscales on the Overall score, found all subscales were significantly associated with the Overall score at the 0.01 level, indicating a balance of the subscale weights contributing to the Overall score.

We believe that in order to fully understand the impact of variables on treatment satisfaction, the impact on both subscales and Overall treatment satisfaction should be identified. Understanding the relative weight of subscales in the overall assessment may be valuable as this can help identify subscales of greater importance given a particular treatment or patient characteristic. Future studies may find it helpful to include a truly independent measure of overall satisfaction to further understand the contribution of subscales to overall satisfaction. In this study we have examined both "simple" regression models looking at similar types of factors (e.g. demographic and patient characteristics) as well as more "complex" multivariate models allowing us to test if significance of variables from the like factor model is maintained when "competing" against a wide spectrum of influences. This incremental approach to the importance of factors provides a more compressive picture of these factors and allows us to refine our understanding of their influence treatment satisfaction.

It should be noted that although statistically significant relationships were identified in the study, the amount of variance accounted for in some of the models was small to moderate. Further, as with all statistical significance, it is unclear what the relationship is between the statistical and clinical significance of the findings and it is often difficult to separate out the unique contributions of variables which may be related, such as age and co-morbidity. Older T2D patients are more likely to have diabetes related co-morbid conditions and these conditions may negatively impact a patient's ability to self-manage their disease, creating a barrier to positive outcomes. Thus, it is important to understand

the unique contributions of each of these factors to overall as well as domains of satisfaction. For example, although age did not have a significant impact on Overall satisfaction, neuropathy – a painful diabetes related condition – was the strongest predictor for decreased treatment satisfaction overall and across subscales. Although it may be difficult for physicians to reduce neuropathy-related pain in diabetes, lessening of pain has been found to play only a partial role in explaining treatment satisfaction for people with chronic pain. Several studies have found that provider-patient interaction factors such as confidence, trust and positive communications are also important for improving satisfaction [35-37]. Thus, improving provider-patient relationships for persons with diabetes and neuropathy may help improve their treatment satisfaction in general and lead to improved outcomes. This study did not examine the impact of non-diabetes related co-morbid conditions on treatment satisfaction and we suggest that this relationship be examined in future studies.

Diabetes related retinopathy was also a significant indicator for the Device Delivery subscale, indicating that visual impairments and the sensory experience should be taken into consideration in choosing an insulin delivery device for a given patient. When pen devices have been compared head-to-head (FlexPen vs. Humalog Pen vs. syringe), significant improvements in patient preferences have been found in favor of the devices which improve the readability of the dose scale and user confidence [28,38]. The auditory feature of pen devices has also been shown to affect the patient's confidence in selecting the correct dose [39], suggesting that auditory impairments also be considered when exploring treatment options. These findings may also help clinicians identify patients who are most at risk for poor treatment satisfaction, so that the clinicians can develop targeted treatment plans for these patients. Certainly, patients with neuropathy or frequent daytime hypoglycemic events should be targeted for a discussion regarding their potential dissatisfaction with treatment. Additionally, their compliance and diabetes self-management behavior, critical factors for diabetes treatment success, should be assessed to identify if these behaviors have been negatively affected by their dissatisfaction.

Finally, although cost of treatment was not examined in this study, it should be noted that biphasic insulin has been projected to be cost-effective therapy vs. basal insulin alone for long-term treatment [40,41]. Given the superior efficacy and equivalent patient-reported treatment satisfaction between these treatments, it may be reasonable for clinicians to consider the estimated improvements in quality-adjusted life expectancy along with potential cost savings associated with complication reductions. Understanding the complex and multidimensional nature of treatment satisfaction as well as the interaction between factors that may impact how persons with diabetes appraise their treatments is still evolving. This study has begun to examine factors that may impact these relationships; considerably more research will be required to further unravel the myths and the realities of treatment satisfaction in diabetes.

There are some shortcomings of this study that should be noted so that future research can address these issues. First, although satisfaction with previous treatments may significantly impact satisfaction with new treatments [42], the reality is that it is often difficult or unfeasible to assess. The lack of baseline treatment satisfaction also prevents

the assessment of responsiveness of a measure to differences in treatment. These methodological challenges present limitations both in the broader treatment satisfaction literature and in this study. As the subjects were insulin naïve at baseline, previous insulin treatment satisfaction could not be measured. However, the absence of any differences in baseline demographic or health characteristics in the sample in combination with the study entry criteria requiring all subjects to have failed OADs, suggests that baseline differences in treatment satisfaction would not have been significant. Furthermore, a 4 week run-in period prior to the addition of the study insulin ensured that all randomized subjects were stabilized on an identical OAD regimen at baseline.

It is also known that RCT populations are generally not representative of the entire population. Therefore, it would be very informative to examine these relationships in a more representative diabetic population such as in a clinic-based study. Additionally, although this study examined potential baseline patient/disease characteristics and key treatment outcomes that may influence treatment satisfaction, data on other important ongoing treatment factors such as burden and compliance were not collected. There may also be other diabetes as well as non diabetes related co-morbid conditions not reported in this sample, which may impact treatment satisfaction. These additional influences should be considered when looking at the broader spectrum of variables that may or may not impact treatment satisfaction. Inclusion of these variables or other potential drivers of treatment satisfaction may have increased the amount of variance in predicting treatment satisfaction in this study.

Conclusions

Using baseline and end of study treatment effect data from a randomized controlled trial comparing the efficacy of BIAsp 70/30 (administered BID via pen device) and Glar (administered QD via syringe), and by correlating it to measured responses in the ITSQ, we examined the relationship between treatment satisfaction, patient/disease characteristics, treatment outcomes, and treatment groups. By assessing these factors independently, certain significant relationships were identified. However, not all of these significant findings survived when examined in combination with each other. Thus, in order to more accurately characterize the impact of patient/disease characteristics and treatment outcomes on treatment satisfaction, a more comprehensive approach at capturing data on all potentially relevant variables is necessary. This approach can enhance our understanding of factors that exert enduring or broader impacts on treatment satisfaction.

The perfect drug for diabetes would improve efficacy with no side effects, and the perfect patient with diabetes would be otherwise healthy. However, given the real world, clinicians will need to balance the advantages and disadvantages of various treatments and patient types, and aim to more fully understand the myths and realities of patient-reported treatment satisfaction to identify the optimal treatment for a given patient.

References

1. Weaver M, Patrick DL, Markson LE, Martin D, Frederic I, Berger M: Issues in the measurement of satisfaction with treatment. Am J Man Care 1997, **3**:579-594.
2. Albrecht G, Hoogstraten J: Satisfaction as determination of compliance. Community Dent Oral Epidemiol 1998, **26**:139-146.
3. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL: Hierarchical construct validity of the treatment Satisfaction Questionnaire for Medication (TSQM Version ll) among outpatient pharmacy consumers. Value Health 2005, **8**:S9-S24.
4. Menzin J, Langley-Hawthorne C, Friedman M, Boulanger L, Cavanaugh R: Potential short-term economic benefits of improved glycemic control: a managed care perspective. Diabetes Care 2001, **24**:51-55.
5. Hogan P, Dall T, Nikolov P, American Diabetes Association: Economic Costs of Diabetes in the U.S. in 2002. Diabetes Care 2003, **26**:917-932.
6. Anderson RT, Marrero D, Skovlund SE, Cramer J, Schwartz S: Selfreported compliance with insulin injection therapy in subjects with type 1 and 2 diabetes. Diabetologia 2003, **46**:A275.
7. Rosenstock J, Cappelleri JC, Bolinder B, Gerber RA: Patient satisfaction and glycemic control after 1 year with inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes. Diabetes Care 2004, **27**:1318-1323.
8. Clark CM Jr, Snyder JW, Meek RL, Stutz LM, Parkin CG: A systematic approach to risk stratification and intervention within a managed care environment improves diabetes outcomes and patient satisfaction. Diabetes Care 2001, **24**:1079-1086.
9. Colman SS, Brod MI, Krishnamurthy A, Rowland CR, Jirgens KJ, Gomez-Mancilla B: Treatment satisfaction, functional status and health related quality of life of patients with migraine randomly assigned to almotriptan or aumatriptan. Clin Ther 2001, **23**:127-145.
10. Weijman I, Ros WJ, Rutten GE, Schaufeli WB, Schabracq MJ, Winnubst JA: Frequency and perceived burden of diabetes self-management activities in employees with insulin-treated diabetes: relationships with health outcomes. Diabetes Res Clin Pract 2005, **68**:56-64.
11. Anderson RT, Skovlund SE, Marrero D, Levine DW, Meadows K, Brod M, Balkrishnan R: Development and validation of the insulin treatment satisfaction questionnaire. Clin Ther 2004, **26**:565-578.
12. Testa M: Improving diabetes therapy: improving satisfaction. Diabetes Voice 2003, **48**:23-25.
13. Brod M, Skovlund SE, Wittrup-Jensen KU: Measuring the impact of diabetes through patient report of treatment satisfaction, productivity and symptom experience. Qual Life Res 2006, **15**:481-491.
14. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR: Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004, **2**:12.
15. Greenfield S, Kaplan SH, Kahn R, Ninomiya J, Griffith JL: Profiling care provided by different groups of physicians: effects of patient case-mix (bias) and physician-level clustering on quality assessment results. Ann Intern Med 2002, **136**:111-121.

16. Cappelleri JC, Gerber RA, Kourides IA, Gelfand RA: Development and factor analysis of a questionnaire to measure patient satisfaction with injected and inhaled insulin for type 1 diabetes. Diabetes Care 2000, **23**:1799-1803.
17. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GE, Wolffenbuttel BH, Niessen LW: Health-related quality of life and treatment satisfaction in Dutch patients with Type 2 diabetes. Diabetes Care 2002, **25**:458-463.
18. Taylor MD, Frier BM, Gold AE, Deary IJ, Edinburgh Prospective Diabetes Study: Psychosocial factors and diabetes-related outcomes following diagnosis of type 1 diabetes in adults: the Edinburgh prospective diabetes study. Diabet Med 2003, **20**:135-146.
19. Petterson T, Lee P, Hollis S, Young B, Newton P, Dornan T: Wellbeing and treatment satisfaction in older people with diabetes. Diabetes Care 1998, **21**:930-935.
20. Bech P, Moses R, Gomis R: The effect of prandial glucose regulation with repaglinide on treatment satisfaction, wellbeing and health status in patients with pharmacotherapy naïve Type 2 diabetes: a placebo-controlled, multicentre study. Qual Life Res 2003, **12**:413-425.
21. Herman WH, Ilag LL, Johnson SJ, Martin CL, Sinding J, Al Harthi A, Plunkett CD, LaPorte FB, Burke R, Brown MB, Halter JB, Raskin P: A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care 2005, **28**:1568-1573.
22. Wilson M, Moore MP, Lunt H: Treatment satisfaction after commencement of insulin in Type 2 diabetes. Diabetes Res Clin Pract 2004, **66**:263-267.
23. Brod M, Lammert M, Raskin P: Comparison of treatment satisfaction of twice-daily BIAsp 70/30 with once-daily insulin glargine in patients with type 2 diabetes. Poster presented at the 65th Scientific Session of the American Diabetes Association Meeting – San Diego, California, 2005. of the American Diabetes Association Meeting – San Diego, California 2005.
24. Bradley C, Plewe G, Kliebe-Frisch : Treatment satisfaction with a basal insulin added to oral agents versus twice-daily premixed insulin alone in patients with Type 2 diabetes. Diabetes 2005, **54**:A304.
25. Raskin P, Bode PW, Marks JB, Hirsch IB, Weinstein RL, McGill JB, Peterson GE, Mudaliar SR, Reinhardt RR: Continuous subcutaneious insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24 week study. Diabetes Care 2003, **26**:2598-2603.
26. Hoogma RP, Spijker AJ, van Doorn-Scheele M, van Doorn TT, Michels RP, van Doorn RG, Levi M, Hoekstra JB: Quality of Life and metabolic control in patients with diabetes mellitus type 1 treated by continuous subcutaneous insulin infusion of multiple daily insulin injections. Neth J Med 2004, **62**:383-387.
27. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A, INITIATE Study Group: Initiating insulin therapy in type 2 diabetes. Diabetes Care 2005, **28**:260-265.
28. Korytkowski M, Bell D, Jacobsen C, Suwannasari R, FlexPen Study Team: A multicenter, randomized open-label comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clin Ther 2003, **25**:2836-2848.

29. Rubin RR, Peyrot M: Quality of life, treatment satisfaction and treatment preference associated with use of a pen device delivering a pemixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. Diabetes Care 2004, **27**:2495-2497.
30. Summers KH, Szeinbach SL, Lenox SM: Preference for insulin delivery systems among current users and nonusers. Clin Ther 2004, **26**:1498-1505.
31. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, Landgraf R, Kleinebreil L, The International DAWN Advisory Panel: Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005, **28**:2673-2679.
32. Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, Jain R: Attainment of glycaemic goals in type 2 diabetes with once, twice, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab 2006, **8**:58-66.
33. Kann P, Wascher T, Zackova V, Moeller J, Medding J, Szocs A, Mokan M, Mrevlje F, Regulshki M: Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin Aspart 30 plus metformin versus once-daily insulin glargine plus glimepiride. Exp Clin Endocrinol Diabetes 2006, **114** (9):527-32.
34. Goudswaard AN, Stolk RP, Zuithoff P, de Valk HW, Rutten GE: Starting insulin in type 2 diabetes: continue oral hypoglycemic agents? A randomized trial in primary care. The J Fam Pract 2004, **53**:393-399.
35. Shaw WS, Zaia A, Pransky G, Winters T, Patterson WB: Perceptions of provider communication and patient satisfaction for treatment of acute low back pain. J Occup Environ Med 2005, **47**:1036-1043.
36. Hirsh AT, Atchison JW, Berger JJ, Waxenberg LB, Lafayette-Lucey A, Bulcourf BB, Robinson ME: Patient satisfaction with treatment for chronic pain: predictors and relationship to compliance. Clin J Pain 2005, **21**:302-310.
37. McCracken LM, Klock PA, Mingay DJ, Asbury JK, Sinclair DM: Assessment of satisfaction with treatment for chronic pain. J Pain Symptom Manage 1997, **14**:292- 299.
38. Niskanen L, Jensen EJ, Rastam J, Nygaard-Pedersen L, Erichsen K, Vora JP: Randomized, multinational open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispor 25 and pen devices in adult patients with Type 2 diabetes mellitus. Clin Ther 2004, **26**:531-540.
39. Asakura T, Seino H: Assessment of dose selection attributes with audible notification in insulin pen devices. Diabetes Technol Ther 2005, **7**:620-626.
40. Ray JA, Valentine J, Nicklasson L, Cobden D, Raskin P, Garber A, Palmer AJ: Insulin therapy in type 2 diabetes patients failing oral agents: cost-effectiveness of biphaic insulin aspart 70/30 vs. insulin glargine in the US. Diabetes Obes Metab 2007, **9**:103-113.
41. Valentine WJ, Palmer AJ, Lammert M, Nicklasson L, Foos V, Roze S: Long-term clinical and cost outcomes of treatment with biphasic insulin aspart 30/70 versus insulin glargine in insulin naïve type 2 diabetes patients: cost-effectiveness analysis in the UK setting. Curr Med Res Opin 2005, **21**:2063-2071.
42. Hurwitz EL, Morgenstern , Yu F: Satisfaction as a predictor of clinical outcomes among chiropractic and medical patients enrolled in the UCLA low back pain study. Spine 2005, **30**:2121-2128.

Chapter 6

Prevalence and economic consequences of adherence in diabetes

Adapted from: Lee WC, Balu S, Cobden D, Joshi AV, Pashos C. Prevalence and Economic Consequences of Medication Adherence in Diabetes: A Systematic Literature Review. *Managed Care Interface*. 2006 Jul;19(7):31-41.

Summary

We conducted a systematic literature review using a comprehensive list of relevant search terms (1990–2005) to identify studies on adherence among patients with diabetes, and its economic effect. A lack of adequate treatment adherence (36%–87%) among patients with diabetes was confirmed, primarily measured by medication possession ratio (MPR). Adherence varied among oral agent−only (36%–87%) versus concomitant or insulin-only (54%–81%) regimens. Economic consequences of adherence were a decrease in health care costs, ranging from 8.6% to 28.9%, with an approximate 10% increase in MPR, mostly in the form of a 4.1% to 31.0% decrease in hospitalization. Increased cost sharing was associated with a 9% to 23% decline in medication use.

Introduction

Diabetes is a chronic medical condition that currently affects nearly 21 million people in the United States, comprising 7% of the entire population [1]. Commensurate with this high prevalence rate and its increasing trend, the national economic burden of treating diabetes in 2002 was approximately $132 billion, representing 19% of total personal health care expenditures in the United States [2]. This figure represents a significant and steady increase in diabetes-attributable health care costs; the corresponding figure in 1997 was just $44 billion. In light of the rising health care costs for management of diabetes, numerous studies demonstrate the benefit of improving glycemic control in the form of increased cost savings. The decrease in overall health care costs is largely attributable to the benefits of improved health by lowering or normalizing blood glucose levels [3−7].

The goal of effective diabetes management, according to the American Diabetes Association (Alexandria, VA), is to achieve tight glycemic control, characterized as a hemoglobin A1c level of less than 7% [8]. Studies have shown that effective management of diabetes rests heavily on adequate adherence to treatment therapy [9−21]. The present study sought to synthesize and analyze published levels of adherence with diabetes medications including oral anti-diabetic drugs (OADs) and insulin, and to report the effect of adherence on overall health care costs through a systematic literature review. A secondary goal was to identify information gaps and areas of research where additional work would contribute to the literature.

Methods

Literature Search

A systematic literature search was conducted to identify articles containing information on adherence to diabetes treatment regimens primarily among patients with Type 2 diabetes (T2D), and its association with relevant health care costs. To this end, electronic MEDLINE and PubMed searches were conducted in various phases. Such important factors contributing to diabetes medication adherence as patient preference, mode of

administration, and medication copayment were included in the search strategy, as were searches on the effect of adherence and clinical and economic outcomes.

For adherence data, search terms included: "diabetes" combined with "adherence," "compliance," "persistence" or "nonadherence."

For costs associated with diabetes medication compliance, search terms included: "diabetes" combined with "adherence," "compliance," "persistence," or "nonadherence" in combination with "costs," "economics," "resource utilization," "hospitalizations," "physician visits," "direct costs," "indirect costs," or "cost analyses."

For identifying articles examining the effect of cost sharing on diabetes medication adherence, search terms included: "diabetes" combined with "adherence," "compliance," "persistence," or "nonadherence" in combination with "cost sharing" or "copayments."

All search terms were limited to Medical Subjects Headings (MESH) terms, English-language abstracts, human subjects, and the years 1990 to 2005. From the initial electronic search, 975 article abstracts were screened, comprising 139 article abstracts for costs associated with nonadherence, 832 article abstracts for adherence/compliance data, and four articles related to cost sharing. In addition to the MESH term search, a keywords search was conducted using "diabetes," "epidemiology," "prevalence," "incidence," "compliance," "costs," "economics," "cost sharing," and "copayments." A total of 1,216 articles were identified with these keywords.

Supplemental searches were conducted with additional resources, including E-medicine along with comprehensive Internet searches using well-known search engines (e.g., Google). The search through these additional resources yielded 20 articles. All abstracts and articles were imported into a master reference database after eliminating duplicate references. Of the total 2,211 articles identified (975 studies identified through the electronic searches with MESH terms described above, 1,216 identified with the keywords, and 20 articles found through additional search engines), 21 papers that met the subject criteria were retrieved and included for the literature review. Although the search terms were as thorough as possible, several relevant articles that were additionally identified from these 21 papers were missing in this electronic search. In addition to the electronic searches, six articles were identified by manual review of the bibliographies of the references retrieved, thereby yielding the total number of 27 references.

Results

The results of the review were disaggregated into three categories for analysis: (1) quantitative and qualitative information on adherence to diabetes medications (N = 13), [9–21]; (2) the effect of adherence on overall health care costs (N = 7) [5, 22−27]; and (3) the effect of medication copayment on levels of adherence and overall health care costs (N = 7) [28−34]. Descriptive statistics (e.g., means, ranges) and the results of inferential analysis (e.g., odds ratio, hazard ratio, and regression coefficients) were identified from

the studies and presented wherever appropriate, and analysis was performed by class of medication (OAD, insulin) to the extent possible.

Adherence to Oral Anti-diabetic Drugs and Insulin Therapy

A total of 13 papers were identified and included for analysis in this section. Excluding one literature review paper [35], which reported adherence rates of 20 papers from 1993 to 2003, and one quantitative review paper [36], which compared adherence levels of diabetes with those of other chronic diseases, most studies on drug adherence in diabetes were conducted on OADs (N = 8) [9,12,13,15−19]. In addition, four articles (30.8%) addressed individuals who were taking either OADs or insulin therapy [11,14,20,21].

Morris and colleagues [10] described adherence rate of insulin therapy alone. A systematic literature review by Cramer [35] summarized oral as well as insulin medication adherence rates. The paper identified research addressing the association between adherence rates and glycemic control. Much attention was given to studies that focused on and supported electronic monitoring tools to estimate levels of adherence; therein resides the difference between their review and this study's examination of levels of adherence. The present review extends Cramer [35] by including two additional studies (Guillausseau and colleagues [18], and Hertz and co-workers [20]), by focusing the analysis on both retrospective and prospective studies, by comparing adherence rates of OADs with those of insulin, and by presenting a comprehensive review of the economic consequences of suboptimal adherence and the effect of cost sharing on adherence (in T2D patients only). To reiterate, the review of these papers was conducted specifically to provide background information for the primary research goal, which was to identify, synthesize, and analyze published literature that discussed the effect of levels of adherence to diabetes medications on overall health care costs, and to then identify key areas of future research.

Follow-up period in these 13 studies varied greatly, ranging from two to 120 months. The mean ages of the study populations were greater than 50 years, indicative of a Type 2 population. Adherence rates among the retrospective studies (N = 8) for OADs ranged from 36% to 87% (Table 1). Of note, this range is similar to that (36%−93%) estimated by Cramer [35]. A recent meta-analysis identified in the literature search offered an overview of 569 studies conducted from 1948 to 1998 reporting adherence levels to medical treatments for a variety of conditions including diabetes [36]. The composite score of the average adherence level in patients with diabetes was obtained from 23 studies and was reported at 67.5% (95% confidence interval [CI], 58.5%–75.8%). This was a substantially lower rate than those found in other medical conditions, including: human immunodeficiency virus (88.3%), arthritis (81.2%), gastrointestinal disorders (80.4%), and cancer (79.1%) [36]. Adherence to medical treatments prescribed by non-psychiatrist physicians was measured and performed using such techniques as pill counts, medical record/chart, self-report, physical test, and electronic monitoring. This meta-analysis underscores two points of interest: (1) although their reported adherence of these medications all reside somewhere in the upper range of 36% to 87% found in the review

of individual papers, (2) diabetes was isolated as the condition with the most suboptimal rate, suggesting the presence of unique barriers to adherence in these patients.

The lower boundary rate estimate of adherence of 36% was observed by Dailey and associates [9]. This adherence rate was defined as the total days of drug supply during the follow-up period divided by the number of days in the follow-up period. This low number may be explained by two factors: (1) the study population consisted of Medicaid enrollees initiating diabetes medication treatments and (2) the study focused on patients receiving multiple drugs from two or more classes of anti-diabetic medications, or poly-pharmacy. In comparison with the 36% adherence observed in patients with poly-pharmacy, adherence among patients receiving monotherapy (drug regimen with a single class of anti-diabetic medication) was 49% [9]. In confirmatory data reported by Donnan and colleagues [16], 35% of patients with diabetes receiving single drug regimens were greater than 90% adherent, whereas the corresponding figure was only 27% for patients with diabetes receiving poly-pharmacy. However, Melikian and co-workers [19] found no statistically significant difference in adherence rates between patients on monotherapy and poly-therapy. This lack of difference may again be attributable to the study population selected for the study, which was a newly diagnosed subject group having a follow up of only six months. It is not surprising that patients in both groups would have been optimally adherent to their prescribed medications at the initiation period of diabetes treatment. Furthermore, the relatively short follow-up may not have fully captured the effect of any occurrence of chronic complications that might affect medication adherence; that is, factors that commonly generate differences in adherence rates between these two groups may not yet have developed.

An average adherence rate, defined by medication possession ratio (MPR), was estimated to be 79.2% among patients with diabetes prescribed OADs for the first time (N = 85,888) [13]. The most interesting and notable result emerging from this study was the decline in adherence rate as length of therapy increased, indicating that long-term adherence with diabetes oral medication therapy is low. Once-daily diabetes medication regimens were associated with a higher adherence level compared with twice-daily treatment regimens (61% vs. 52%, respectively) [15]. Even though the once-daily patient cohort exhibited a greater number of mean pills per day, adherence was 8.5% higher than the twice-daily patient cohort; adherence was found to be more strongly associated with an easier-to-maintain/schedule dosing regimen rather than the number of tablets per dose. Guillausseau [18] reported adherence rates of 46% among patients with T2D (N = 11,896) treated with OADs in a prospective analysis. Adherence was estimated using self reports through data collection with a questionnaire and was categorized into three levels: (1) no omission, (2) omission one to three times a month, and (3) omission once a week. The study found that once-daily therapy was associated with an approximate 60% adherence rate as compared with 48% for twice-daily, which further fell to 38% when medications were administered 3x. A prospective study by Winkler and co-workers [17] measured adherence through self-reports, pill counts, and a medication event–monitoring system among 19 patients with T2D. Adherence was defined as the percentage of days in which the dose was taken as prescribed. Results showed an overall adherence rate of 78.6%, though again, once-daily regimens exhibited better adherence as compared with

Table 1: Studies of patient adherence to oral anti-diabetic agents

Study (Type)	Country and/or Source of Population	Number	Follow-up Period (mo)	Medication Type	Mean Age (yr)	Adherence Rate (%)	Adherence Measure
Guillausseau[16] (prospective)	France	11,896	N/A	Sulfonylureas, metformin, or alpha-glucosidase inhibitors	N/A	46%	Self-reported adherence using questionnaire
Donnan et al[16] (retrospective)	Scotland	2,849	12	Single OAD (sulfonylurea or metformin)	68	35%	Percent of patients with adherence > 90%
		2,849		Multiple OADs (sulfonylureas or metformin)	68	27%	Percent of patients with adherence > 90%
Dezii et al[15] (retrospective)	U.S. PBM	746	12	Glipizide qd	54	61%	MPR*
		246		Glipizide bid	56	52%	MPR*
Evans et al[12] (retrospective)	Scotland	2,537	6	Sulfonylurea	67	87%	MPR*
		1,519		Metformin	64	83%	MPR*
Melikian et al[19] (retrospective)	U.S. PBM	105	6	Single antidiabetic drug (metformin or glyburide)	67	54%	MPR*
		105		Single (metformin or glyburide) to combination OAD regimens (metformin and glyburide)	67	77%	MPR*
		59		Multiple drugs (metformin and glyburide)	63	71%	MPR*
		59		Multiple drugs (metformin and glyburide) to fixed-dose combination therapy (glyburide/metformin)	63	87%	MPR*
Winkler et al[17] (prospective)	Switzerland	19	2	Sulfonylurea	> 65	79%	MPR*
Boccuzzi et al[13] (retrospective)	U.S. PBM	79,498	12	OAD (metformin, sulfonylureas, troglitazone, alphaglucosidase inhibitors, and repaglinide)	60	79%	MPR*
Dailey et al[9] (retrospective)	U.S. Medicaid	29,560	18	Single OADs (sulfonylurea or metformin)	N/A	49%	MPR*
		1,406		Multiple OADs (sulfonylurea and metformin)	N/A	36%	MPR*

*Medication possession ratio (MPR) = Sum of number of days supply on all but the last prescription/number of days in treatment interval.
N/A = Not available; OAD = oral antidiabetic drug; PBM = pharmacy benefit management organization.

more frequent dosing (93.6% vs. 57.8%, respectively). Overall, these findings illustrate the critical importance of convenience and ease of drug administration in improving adherence rates of OADs.

Four studies examining adherence levels among patients with diabetes who were prescribed either oral medications or insulin therapy reported adherence rates ranging from 54% to 81%, excluding one persistence study that reported a rate of 27% (Table 2)

[11,14,20,21]. Schetman and associates [14] reported that medication type, be it insulin or OADs, was not correlated with adherence after adjusting for age, race, income, frequency of glucose testing, and frequency of visits in their regression model. A retrospective study found a mean adherence rate of 62% to 81% for a large cohort (N = 199,000) of patients with diabetes initiating treatment with either oral medications or insulin [11]. Adherence, measured by MPR, was found to be higher among oral medication patients (N = 52,469; 81%) as compared with patients taking insulin (N = 27,274; 62%). Brown and associates [21] estimated persistence rather than adherence and demonstrated the persistence rate for each subsequent year post-diagnosis among a large cohort of patients with diabetes (N = 693) for a period of 10 years. Persistence in this study was calculated by the number of times that each member changed his or her drug regimen, which was considered a modification of the regimen, during the nine years after the year of diagnosis. The persistence rate was 27.3%. Mean adherence (88.3% [95% CI, 85.9%–90.6%]) among patients previously taking oral medications (i.e., sulfonylureas) who then switched to insulin was slightly higher than that of patients taking sulfonylureas alone (87.4% [95% CI, 86.7%–88.2%]) [12].

Hertz and colleagues' [20] findings are somewhat at odds with this study, as adherence was found to be lower among patients using insulin compared with those taking OADs (30.8% for insulin vs. 63.9% for sulfonylurea users, 63.8% for biguanides, and 67.1% for thiazolidinedione users) (OR = 3.00; 95% CI, 2.30–3.91). They found the overall adherence rate, estimated using MPR, among patients with either medication type to be 53.8%. This study population, however, was treatment-naïve, with patients newly prescribed anti-diabetic medications over three years (1997–2000). Three forces may explain the contrasting results observed in these two studies: (1) medication-naïve patients initiating insulin may have experienced a more inconvenient mode of administration, leading to inadequate adherence levels; (2) variation in disease severity among patients requiring insulin therapy versus OADs alone may indicate that patients were either more motivated to be adherent or they were less able to adhere consistently; and (3) patients taking OADs commencing insulin therapy are likely to experience tighter glucose control versus continued OAD-only therapy, which may improve health-related quality of life and increase willingness to comply.

The lone study estimating adherence rate of insulin alone was, not surprisingly, conducted among young Scottish patients (N = 89; mean age, 16 yr) with T1D. In this study, an adherence index was created using the insulin dose and cumulative supply of insulin preparations [10]. This adherence index, similar to MPR, calculated the days of insulin coverage using two variables: (1) medically recommended insulin dose and (2) cumulative supply of insulin prescriptions. The latter variable was obtained from data that have an actual purchased amount of insulin. Based on the calculated days of supply, the study found the adherence rate to be 72% (i.e., 28% of the 89 study patients obtained less insulin than the prescribed doses). Adherence rates of OADs and insulin therapy have varied, because of a difference of applied methods among very diverse study populations. Only four studies [11,14,20,21] comparatively assessed adherence rates of OADs and insulin therapy on similar populations, and just one study was performed solely on patients with diabetes treated with insulin [10]. Whether the adherence level of

patients to insulin therapy after previous use of oral medications is higher or lower than that of patients to OADs is largely inconclusive and requires further inquiry. Studies estimating adherence for diabetes have so far relied mainly on such techniques as MPR, whereas a few have reported persistence rates, defined as switch or discontinuation of initial medication.

Table 2: Retrospective Database Studies of Patient Adherence to Oral Anti-diabetic Medications or Insulin

Study	Number	Source of Population	Mean Age (yr)	Medication Type	Follow-up Period (mo)	Adherence Rate	Adherence Measure
Brown et al[21]	102	HMO	N/A	Sulfonylurea, insulin, or metformin	120	27%	Persistence*
Rajagopalan et al[11]	27,274	PBM	53	Pioglitazone, insulin, metformin, or rosiglitazone	24	81%	MPR†
Hertz et al[20]	6,090	Administrative claims database	51.0‡	Sulfonylureas, biguanides, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, or insulin	12	54%	MPR†
Schectman et al[14]	810	Primary care practice site	50	Sulfonylureas, metformin, alpha-glucosidase inhibitors, thiazolidinediones, or insulin	15	80%	MPR†

*Persistence = Percent of patients who do not modify treatment regimen.
†Medication possession ratio (MPR) = Sum of number of days supply on all but the last prescription/number of days in treatment interval.
‡Median.
N/A = Not available; PBM = pharmacy benefit management organization.

Economic Consequences of Suboptimal Levels of Diabetes Medication Adherence

Seven studies were identified that elucidate increased health care costs owing to patients' inability to adhere to prescribed diabetes medications [5,22–27]. They were exclusively retrospective database studies, including a longitudinal cohort investigation. A summary of these studies is provided in Table 3. An administrative claims data study revealed an association between levels of adherence to OADs and subsequent hospitalization among individuals with T2D [22]. Approximately 29% of patients who were prescribed an anti-hyperglycemic agent were nonadherent. Nonadherence was defined as a MPR of less than 80%. When the MPR dropped below 80% of that observed in the preceding year, the rate of hospitalizations related to diabetes significantly increased, specifically from 4.1% to 14.8% in response to a decrease of adherence rate from 100% to less than 40%. The results of this study suggest that the effect of suboptimal adherence substantially increases diabetes-related hospitalization in the following year and adversely affects the quality of life of these patients. A further study compared two distinct populations: (1) individuals with T2D alone and (2) those with both diabetes and diagnosed

cardiovascular disease (CVD), a population more prone to substantial health care utilization. Patients with diabetes alone who were no more than 75% and 76% to 95% adherent had a 31% and 19% greater chance of a hospital/ emergency room (ER) admission than those with greater than 95% adherence, respectively [23]. However, patients who were no greater than 75% and 76% to 95% adherent in the diabetes plus CVD cohort exhibited a 44% and 51% greater chance of ER/hospital admission, respectively, as compared with those with better than 95% adherence. Although the difference between these two cohorts was expected, the results between levels of adherence within the cohort of patients having diabetes plus CVD were surprising; this outcome could be explained by the possibility that patients who were no greater than 75% adherent in this cohort may have had an increased susceptibility to further co-morbidities unrelated to medications captured in the study. Still, this study confirms a lower level of adherence among patients with concomitant co-morbidity than that among patients with diabetes alone, creating a negative effect on overall health care costs and suggesting the importance of achieving tight glycemic control to inhibit the negative effect of uncontrolled diabetes on CVD.

Outcome measures, such as health care costs and utilization, were found to commonly be measured after a lag time of 360 days from the date the patient was identified. Where medication adherence rates initially increase, one might expect that medication costs would also initially rise. Hepke and co-workers [24] reported that medical care costs steadily increased at an adherence level of 20% to 39%; however, once this level was reached, overall medical care utilization started to decrease through reduced use of ER and hospital inpatient resources. A shortcoming of using a one-year lag time in patients with diabetes is that the effect of co-morbidity is readily missed, owing to the fact that diabetes is a chronic medical condition, and most complications develop over time. Sokol and co-workers [25] compared a diabetes population with three stratified cohorts, each having a different chronic medical condition, such as hypertension, hypercholesterolemia, and congestive heart failure. Among these conditions, only for diabetes and hypercholesterolemia was a high level of medication adherence associated with lower overall costs for the one-year period after patient identification. The short-term increase in medication costs related to a higher adherence level was offset by the increased savings in overall health care costs for these two medical conditions. This analysis differed, however, from Hepke and colleagues' [24] study examining the quantity of overall health care cost savings achieved through increased adherence (a difference in total costs at the 80%–100% adherence level of $2,830, $4,570 for the study by Sokol and co-workers [25], and $7,400 for that by Hepke and associates [24]). The investigation by Sokol's group [25] examined those who were receiving prolonged medication before the analysis period and thus demonstrated a higher cost savings because of the cumulative effects of maintained adherence.

Adherence and its effect on overall health care costs were also studied among a low-income population (North Carolina Medicaid program). Patients receiving thiazolidinedione (TZD) therapy, who had better treatment adherence calculated using MPR in comparison with patients receiving other OADs (13% increase in MPR, $p<0.01$), experienced a 16.1% decrease in total annual health care costs ($p<0.01$) in the post-

medication start year [26]. A period of 365 days was used as the lag time for the analyses. Interestingly, adherence rates in this population were substantially lower than the general population; 60% for the TZD group versus 50% for other OADs was found to be lower than the rates reported in other studies. A five-year retrospective longitudinal cohort study using prescription refill patterns as a major outcome measure of adherence confirmed the findings obtained from the above five short-term database studies [27]. A random-effects log linear regression model was employed to observe the association between mean adherence and a host of confounders including categorical MPR. Other predictor variables included: age, gender, Charlson co-morbidity index, total health care costs, smoking status, and total days in hospital. Increased anti-diabetic MPRs proved to be the strongest predictor of decreased total annual health care costs (i.e., 8.6%–28.9% decrease in annual costs with every 10% increase in MPR).

The above six studies illustrate that higher levels of medication adherence result in increased cost savings accrued because of decreased hospitalizations. Interestingly, one study revealed cost savings to be associated with a decrease in primary care and specialist physician visits rather than a decrease in hospitalizations/ER visits, though this was likely because of the length of the follow-up (5 years), where reduced specialty visits may have arisen because of reductions in co-morbidity associated with improved glycemic control [5]. This study demonstrated higher hospitalization rates only among higher levels of adherence; the primary outcome measure was the number of primary care and specialty visits among patients with improved and unimproved glycemic control, without ascertaining whether higher levels of adherence to treatments directly improved glycemic control. Economic consequences of suboptimal adherence levels to diabetes were found to be significant, with increasing overall health care costs in the form of higher hospitalization and ER visit rates.

Effect of Medication Copayment on Medication Adherence among Patients with Diabetes

Few studies have shown the effect of copayment alone for prescription medications on patient treatment adherence among patients with diabetes, though several have shown that greater cost-sharing reduces spending on prescription drugs (Table 4) [28−34]. Each of these studies covers either the general population regardless of specific disease or patients with diabetes. None of the studies narrowly focus on patients undergoing insulin treatments. A recent assessment of 528,969 individuals enrolled in health insurance plans found that doubling copayments reduced the use of nonessential medications (including antihistamines and anti-inflammatories) and, to a lesser extent, essential medications used to treat chronic diseases including diabetes [31]. With regard to diabetes medications, a 25% decrease in response to copayment doubling was observed. These results suggest more essential drugs are less price sensitive, providing a reference figure for price sensitivity of insulin therapy. As this study did not assess insulin, one may posit that the price sensitivity of insulin treatment would actually be lower than the 25% decrease seen with oral medication. Similarly, the effect of prescription drug cost sharing on use of essential and less essential drugs among elderly patients (N = 93,950) and welfare recipients (N = 55,333) was studied in Canada, whereby the rate of adverse events associated with discontinuation or reductions in drug use owing to increased cost sharing

Table 3: The Effect of Levels of Patient Adherence on Health Care Costs

Study	Design (N)	Measures	Adherence Measure and Rate	Study Result
Sokol et al[25]	Retrospective cohort (N = 137,277)	Diabetes, hypercholesterolemia, hypertension, and CHF-related and all-cause medical costs, drug costs, and hospitalization risk	Not available	Diabetes and hypercholesterolemia showed associations between high levels of adherence and low health care costs; this association was not seen in patients with hypertension and CHF
Lau et al[22]	Retrospective administrative claims data analysis (N = 900)	Nonadherence, subsequent hospitalization	28.9% Nonadherent	Increase in rate of hospitalizations was associated with a decrease in adherence level
White et al[23]	Retrospective analysis (N = 67,029)	Medication adherence, total health care costs, and utilization	75%, > 75%– 95%, > 95% Adherence	Annual costs of $5,706, $5,314, and $4,835, respectively
Balkrishnan et al[26]	Retrospective cohort design (N = 3,483)	Differences in total health care costs, medication adherence, and persistence among patients on thiazolidinedione as compared with other oral hypoglycemics	13% Increase in MPR and 10% increase in persistence index ($P < .001$), 16.1% lower total annual health care costs ($P < .01$)	Improved treatment adherence and persistence was associated with lower annual health care costs
Balkrishnan et al[27]	Longitudinal cohort study (N = 775)	Antidiabetic medication adherence and health care service utilization	10% Increase in MPR	Decrease in 8.6% to 28.9% in annual cost
Wagner et al[5]	Historical cohort study (N = 4,744)	Total health care costs, percentage hospitalized	Not available	Improved glycemic control led to decrease in primary care and specialist visits but hospitalization rates were not different compared with patients with unimproved glycemic control
Hepke et al[24]	Retrospective cohort design using insurance claims (N = 57,687)	Level of adherence, utilization, and medical costs	Threshold level of adherence was identified	Decreased use of medical care services, but not with lower medical costs

N = Number; CHF = congestive heart failure; MPR = medication possession ratio.

was estimated [32]. Increased cost sharing resulted in reduced utilization of essential medications, including those for diabetes, and a subsequent higher rate of serious adverse events and ER visits. Interrupted time-series analysis of data for a period of 17 months after introduction of medication coinsurance and cost sharing for the year 1996 was performed. The results showed a decrease in use of essential drugs by 9.1% (95% CI, 8.7%–9.6%) among elderly persons and by 14.4% (95% CI, 13.3%–15.6%) among Medicaid beneficiaries, respectively. Rate of serious adverse events, estimated per 10,000

person-months, increased from 5.8 before introduction of the cost-sharing policy to 12.6 post-introduction among elderly persons, compared with 14.7 to 27.6, respectively, among welfare recipients. Similarly, an increase in ER visits owing to reductions in use of essential drugs was also noticed between both cohorts (from 32.9 to 47.1 / 10,000 person-mo. among elderly persons, and from 69.6 to 123.8 / 10,000 person-mo. among welfare recipients).

Decreased medication utilization and expenditures were noted as a result of a three-tier prescription copay [33]. An increase in copayments from 20% to 30% yielded a significant decrease in medication adherence (83.7% vs. 66.7%, respectively) among patients with diabetes (N = 66). However, this decrease did not compromise any other complications [30]. One primary reason was that the copayment change explored in this study was not sufficient to trigger a substantial decrease in medication utilization which would increase any complications. Finally, lack of insurance coverage for patients with diabetes (N = 405) for their testing supplies led to underuse of diabetes medications, thereby leading to poorer glycemic control (HbA1c 7.1% vs. 7.4%; p=0.03) [34]. However, these results should be treated with caution because of the cross-sectional nature of the study, thus limiting inferences on causal associations.

A patient survey reported less use of diabetic medications because of varied insurance, linked with different cost-sharing levels [28]. Nine percent of Veterans Administration (VA) patients showed an underuse of medications compared with other sources of insurance, including private insurance (18%), Medicare (25%), and no insurance (40%) ($p<0.0001$). These results are significant, because patients enrolled in the VA had relatively comprehensive drug coverage as compared with some private insurances and Medicare. Lack of medication coverage, thereby generating increased out-of-pocket expenditures on medications, led patients to discontinue buying their prescribed medications, ultimately resulting in low adherence. These studies were characterized by the absence of an income variable; the majority of patients included in these studies would likely have been less affluent and therefore more price sensitive. After adjusting for levels of income, the effect of copayment on resource utilization in a general population may have been lessened. Financial constraints on patients in terms of increased medication copayments have been found to reduce patients' ability to adhere to diabetes medications.

Discussion

This systematic review confirms that adherence rates to diabetes medications — OADs and insulin — are suboptimal among patients with diabetes. Only one study, which was focused on T1D in adolescent patients, reported an adherence level of 72%, though factors facilitating this adherence rate remain unverified. It is perhaps equally as influential that these patients likely received strong parental monitoring, that exogenous insulin is an absolute necessity for them, and that copayment/cost sharing is generally a more indirect factor in adherence for these patients. Whether adherence level of patients to insulin therapy is higher or lower than that of patients to OADs was found to be

Table 4: Effect of Cost-Sharing on Patient Medication Adherence and Overall Health Care Costs

Study	Design	Measures	Effect
Roblin et al[29]	Quasi-experimental	Effect of small, moderate, and large cost sharing in oral hypoglycemic use	Cost-sharing increases > $10 led to drastic underuse of oral hypoglycemics as compared with moderate or no cost sharing
Babazono et al[30]	Retrospective administrative claims data analysis	Effect of increase in copayments from 20%–30% on use of hypertension and diabetes medications	In patients with diabetes without complications, compliance rate was 83.7% and 66.7% preincrease and postincrease in copayment
Goldman et al[31]	Retrospective analysis of pharmacy claims data	Relative change in drug days supplied after doubling of payments	Decrease in overall days supplied for antidiabetics (25%); use of antidiabetic drugs decreased by 23%
Piette et al[28]	Patient survey linked to insurance and clinical data	Self-reported medication underuse, physical and mental functioning scores through SF-12 instrument	Fewer VA patients reported cost-related medication underuse (9%) than patients with private insurance (18%), Medicare (25%), Medicaid (31%), or no health insurance (40%)
Tamblyn et al[32]	Interrupted time series analysis of Quebec drug policy data	Effect of prescription cost sharing on use of essential and less-essential drugs	Use of essential drugs including diabetes drugs decreased by 9.1% in elderly persons and 14.4% in welfare recipients
Bowker et al[34]	Randomized controlled trial with a baseline survey	Effect of insurance for testing supplies on glycemic control	Patients with insurance had lower blood glucose levels than those without (7.1% vs. 7.4%, $P = .03$)

SF = Short form; VA = Veterans Affairs.

inconclusive, although all studies concluded the significantly negative effect of suboptimal adherence levels to diabetes medications, as well as the financial constraints imposed by increased copayments, on overall health care costs. Results of adherence rates to both OADs and insulin varied owing to a diversity of applied methods, with differing follow-up periods among study populations. One study reported a persistence rate (27.3%) that was lower than the lowest adherence rate (36%) obtained in the present literature review. This low persistence rate resulted from a different method of calculation of therapy persistence compared with traditional estimation of adherence. The results of the present review are consistent with those of other surveys, where adherence to medications for different medical conditions have been found to be approximately 75% [39–41].

Studies targeting younger populations are almost completely lacking in the literature. One might expect research to be focused on adults with T2D, who are more prone to costly co-morbidities and who constitute the majority of the population with diabetes (and are therefore most burdensome for providers). Analyses in which the mean age of the study population was 50 to 59 years revealed adherence levels between 61% and 80% [11,14,15,20], whereas those whose study populations had a mean age of 60 to 68 years

demonstrated adherence rates between 54% and 79% [12,13,16,17,19]. These results suggest that age is a critical demographic variable in predicting adherence and that future studies focusing on younger populations may have adherence rates similar to or higher than 61% to 80%. Nichols and co-workers [42] demonstrated this strong association between age and adherence to diabetes medications. This is significant, because diabetes is more prevalent among elderly patients who are more prone to have multiple medical conditions for which they receive numerous concomitant medications. Multiple co-morbidities, which collaboratively may exacerbate disease progression, and an aging body (presence of ocular and visual disease, arthritis, and other disorders afflicting manual dexterity, etc.) may have a bearing on the level of adherence. Access to therapies and modes of administration aiming to ease burden of care and self-management in these patients may prove valuable in improving outcomes.

A shortcoming concerning adherence estimates was that most of the studies on adherence to diabetes medications have classified adherence levels based on prescription refill patterns or MPRs using claims data. Different categories or levels of medication adherence have been defined based on MPR (e.g., > 80%, 20%–80% and < 20%). Although MPRs provide an intensity measure of drug utilization over a certain period, it fails to assess therapy duration. For example, it is possible that with a higher MPR, one group may have a shorter time to treatment discontinuation compared with another group. Therefore, more sophisticated methods of defining medication adherence, including survival analyses — such as time to treatment discontinuation — have the potential to complement adherence studies that use MPR. Measuring adherence and persistence through these sophisticated methods was lacking in the literature review. These studies most commonly divided the adherence rates calculated by MPR into different categories, estimating the health care costs and utilization in each category. Across several studies, MPRs greater than 80% were used to define adherent patients [9,10−13,15], whereas others employed a separate threshold (e.g., 90%, categorization into 3 levels, etc.) [16,18]. Of note, Wagner and colleagues [5] found cost savings only in sub-populations exhibiting improved glycemic control, rather than on an aggregate level; however, the sources of improved glycemic control were unclear in the study.

Findings from the literature illustrated that savings are significantly different between patients with the lowest adherence rates and patients with the highest adherence rates. Studies determining the effect of adherence over a longer period of time on subsequent health care costs are generally lacking in the literature, as effect of adherence over a period of one year after patient identification was the common finding, perhaps because of limitations of available longitudinal databases. An increase in cost-sharing as a result of copayment or other changes in insurance status triggered a decrease in use of even essential medications such as diabetes, thereby leading to increased adverse events and subsequent health care costs. Particularly, low income patients and patients suffering several co-morbidities are most vulnerable to experience devastating effects on their drug utilization in response to an increase in copayments or any other cost-sharing program.

It is commonly held by providers that oral medications, because of their ease of administration, would induce better adherence levels compared with injection-based

insulin therapy, potentially delaying insulin prescriptions. In the long run, it may well serve patients if this perception is taken more in balance with clinical evidence establishing that insulin therapies, when taken correctly, pose the greatest potential for pharmaceutical intervention to more tightly control hyperglycemia and curb advanced co-morbidity through inhibiting disease progression, in addition to data showing that adherence may actually be improved after initiating insulin among patients taking OADs [12,37,38,46–48]. The literature review shows that as patients are prescribed increasing numbers of OADs and/or are kept on OAD therapy for prolonged periods, adherence is increasingly suboptimal without any beneficial effect on disease progression [46]. A sensible approach might constitute initiating insulin sooner to improve glycemic control, delay disease progression, and thereby increase the probability of better outcomes leading to overall cost reductions. Furthermore, as improved glycemic control has been shown to benefit health-related quality of life among patients with T2D [49], potential improvement in willingness to adhere is an additional factor for consideration.

Injectable insulin is recognized as inconvenient to administer because of fear of self administration/needle phobia [43] and because insulin treatment regimens may range from one to four daily doses (or more), depending on severity and type of disease, and the capability of the patient to manage his or her dosing schedule [44,45]. The review showed no stark differences in comparative adherence rates between patients treated with insulin and with OADs. They do indicate that, as with OADs, adherence to conventional insulin therapy may be characterized as suboptimal, and its attributes mentioned above may contribute to many of the poor outcomes observed in patients with T2D. Adopting modes of insulin administration that ease the burden of injections, increase patient preference and satisfaction, and reduce time of self-management instruction (decreased provider burden) may present a promising approach at diminishing costly outcomes.

As insulin pens have been shown to improve patient satisfaction and treatment preference leading to improved quality of life, they may represent a specific method to improve adherence [50,51]. Studies that assess persistence and adherence to insulin pens and related economic consequences are lacking in the literature, and thus, future studies comparatively evaluating these outcomes among patients receiving oral medications and insulin administered by syringe would contribute considerably to this field of literature.

The results of this systematic review should be interpreted carefully, with the following three caveats: (1) the data on medication adherence are predominantly applied to specific adult populations; (2) several studies have analyzed prevalent populations of patients with diabetes with longer disease duration as opposed to newly diagnosed populations; the former population typically incurs higher resource utilization and health care costs because of more advanced disease progression, coupled with other co-morbidities; and (3) adherence was measured in disparate fashion, often with a threshold of 80% MPR defining adherence, categorizing adherence levels into several classes, whereas other studies used a persistence measure (i.e., percentage of patients who switched or discontinued).

Conclusions

Poor adherence among patients with diabetes is a major and established problem in contrast with other chronically managed diseases including arthritis, and gastrointestinal diseases [36], and costs associated with nonadherence to diabetes medications are similarly significant. This review on the effect of suboptimal levels of diabetes adherence on overall health care costs showed that patients adhering to prescribed therapy (OADs and insulin) incurred fewer overall health care costs. The consequences of suboptimal adherence to diabetes medications are of critical importance, both from a clinical and an economic standpoint.

According to the Centers for Disease Control and Prevention, the number of Americans with T2D that cannot be controlled by exercise and a healthy diet has increased significantly from 5.8 million in 1980 to 18.2 million in 2005 [52]. A high number of these patients will eventually require treatment with medications accompanied by reasonable access and sustained self-management in order for success to be realized in controlling the progression of this debilitating disease.

References

1. Total prevalence of diabetes in the United States, All ages, 2005. National Diabetes Statistics, (diabetes.niddk.nih.gov/dm/pubs/statistics/#7), March 2006.
2. Hogan P, Dall T, Nikolov P, et al: Economic costs of diabetes in the U.S. in 2002. Diabetes Care 2003; **26**:917-932 .
3. Brown JB, Pedula KL, Bakst AW: The progressive cost of complications in type 2 diabetes mellitus. Arch Intern Med 1999; **159**:1873-1880.
4. Menzin J, Langley-Hawthorne C, Friedman M, et al: Potential short-term economic benefits of improved glycemic control: A managed care perspective. Diabetes Care 2001; **24**:51-55.
5. Wagner EH, Sandhu N, Newton KM, et al: Effect of improved glycemic control on health care costs and utilization. JAMA 2001; **285**:182-189.
6. Gray A, Clarke P, Farmer A, et al: United Kingdom Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; **352**:837-853.
7. The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; **329**:977-986.
8. Harris MI, Flegal KM, Cowie CC, et al: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey (NHANES) 1988–1994. Diabetes Care 1998; **21**:518-524.
9. Dailey G, Kim MS, Lian JF: Patient compliance and persistence with anti-hyperglycemic drug regimens: Evaluation of a Medicaid patient population with type 2 diabetes mellitus. Clin Ther 2001; **23**:1311-1320.
10. Morris AD, Boyle DI, McMahon AD, et al: Adherence to insulin treatment,

glycemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside, Scotland. Medicines Monitoring Unit. Lancet 1997; **350**:1505-1510.
11. Rajagopalan R, Joyce A, Ollendorf D, et al: Medication compliance in type 2 diabetes patients: Retrospective data analysis (Abstract). Value Health 2003; **6**:328.
12. Evans JM, Donnan PT, Morris AD: Adherence to oral hypoglycemic agents prior to insulin therapy in type 2 diabetes. Diabet Med 2002; **19**:685-688.
13. Boccuzzi SJ, Wogen J, Fox J, et al: Utilization of oral hypoglycemic agents in a drug-insured U.S. population. Diabetes Care 2001; **24**:1411-1415.
14. Schectman JM, Nadkarni MM, Voss JD: The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care 2002; **25**:1015-1021.
15. Dezii CM, Kawabata H, Tran M: Effects of once-daily and twice-daily dosing on adherence with prescribed glipizide oral therapy for type 2 diabetes. South Med J 2002; **95**:68-71.
16. Donnan PT, MacDonald TM, Morris AD: Adherence to prescribed oral hypoglycemic medication in a population of patients with type 2 diabetes: A retrospective cohort study. Diabet Med 2002; **19**:279-284.
17. Winkler A, Teuscher AU, Mueller B, et al: Monitoring adherence to prescribed medication in type 2 diabetic patients treated with sulfonylureas. Swiss Med Wkly 2002; **132**:379-385.
18. Guillausseau PJ: Influence of oral anti-diabetic agents in type 2 diabetes: A survey in general practice. Diabetes Metab 2003; **29**:79-82.
19. Melikian C, White J, Vanderplas A, et al: Adherence to oral anti-diabetic therapy in a managed care organization: A comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 2002; **24**:460-467.
20. Hertz RP, Unger AN, Lustik MB: Adherence with pharmacotherapy for type 2 diabetes: A retrospective cohort study of adults with employer-sponsored health insurance. Clin Ther 2005; **27**:1064-1073.
21. Brown JB, Nichols GA, Glauber HS, et al: Ten-year follow-up of anti-diabetic drug use, nonadherence, and mortality in a defined population with type-2 diabetes mellitus. Clin Ther 1999; **21**:1045-1057.
22. Lau DT, Nau DP: Oral anti-hyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. Diabetes Care 2004; **27**: 2149-2153.
23. White TJ, Vanderplas A, Chang E, et al: The costs of nonadherence to oral anti-hyperglycemic medication in individuals with diabetes mellitus and concomitant diabetes mellitus and cardiovascular disease in a managed care environment. Disease Management and Health Outcomes 2004; **12**:181-188.
24. Hepke KL, Martus MT, Share DA: Costs and utilization associated with pharmaceutical adherence in a diabetic population. Am J Manag Care 2004; **10**:144-151.
25. Sokol MC, McGuigan KA, Verbrugge RR, et al: Impact of medication adherence on hospitalization risk and health care cost. Med Care 2005; **43**:521-530.
26. Balkrishnan R, Rajagopalan R, Shenolikar RA, et al: Health care costs and prescription adherence with introduction of thiazolidinedione therapy in Medicaid type 2 diabetic patients: A retrospective data analysis. Curr Med Res Opin 2004; **20**:1633-1640.

27. Balkrishnan R, Rajagopalan R, Camacho FT, et al: Predictors of medication adherence and associated health care costs in an older population with type 2 diabetes mellitus: A longitudinal cohort study. Clin Ther 2003; **25**:2958-2971.
28. Piette JD, Wagner TH, Potter MB, et al: Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. Med Care 2004; **42**:102-9.
29. Roblin DW, Platt R, Goodman MJ, et al: Effect of increased cost-sharing on oral hypoglycemic use in five managed care organizations: How much is too much? Med Care 2005; **43**:951-959.
30. Babazono A, Miyazaki M, Imatoh T, et al: Effects of the increase in co-payments from 20 to 30 percent on the compliance rate of patients with hypertension or diabetes mellitus in the employed health insurance system. Int J Technol Assess Health Care 2005; **21**:228-233.
31. Goldman DP, Joyce GF, Escarce JJ, et al: Pharmacy benefits and the use of drugs by the chronically ill. JAMA 2004; **291**:2344-2350.
32. Tamblyn R, Laprise R, Hanley JA, et al: Adverse events associated with prescription drug cost-sharing among poor and elderly persons. JAMA 2001; **285**:421-429.
33. Motheral B, Fairman KA: Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. Med Care 2001; **39**:1293-1304.
34. Bowker SL, Mitchell CG, Majumdar SR, et al: Lack of insurance coverage for testing supplies is associated with poorer glycemic control in patients with type 2 diabetes. CMAJ 2004; **171**:39-43.
35. Cramer JA: A systematic review of adherence with medications for diabetes. Diabetes Care 2004; **27**:1218-1224.
36. DiMatteo MRP: Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. Medical Care 2004; **42**:200-209.
37. Marre M: Before oral agents fail: The case for starting insulin early. Int J Obes 2002; **26**(Suppl 3):25-30.
38. Owens DR, Zinman B, Bolli GB: Insulins today and beyond. Lancet 2001; **358**:739-746.
39. Dunbar-Jacob J, Mortimer-Stephens MK: Treatment adherence in chronic disease. J Clin Epidemiol 2001; **54**(suppl 1):57-60.
40. Haynes RB, McDonald H, Garg AX, et al: Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev 2002; **2**:CD 000011.
41. Roter DL, Hall JA, Merisca R, et al: Effectiveness of interventions to improve patient compliance: A meta-analysis. Med Care 1998; **36**:1138-1161.
42. Nichols GA, Hillier TA, Javor K, et al: Predictors of glycemic control in insulinusing adults with type 2 diabetes. Diabetes Care 2000; **23**:273-277.
43. Zambanini A, Newson RB, Maisey M, et al: Injection related anxiety in insulin-treated diabetes. Diabetes Res Clin Pract 1999; **46**:239-246.
44. Glasgow RE: Compliance to diabetes regimens: Conceptualization, complexity, and determinants, in Cramer JA, Spilker B, (eds): Patient Compliance in Medical Practice and Clinical Trials. New York, Raven Press, 1991; 209-224.
45. Anderson EA, Usher JA: Understanding and enhancing adherence with medications for diabetes. Curr Diab Rep 2003; **3**:141-148.

46. Raz I, Stranks S, Filipczak R, et al: Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: An 18-week, randomized, openlabel study. Clin Ther 2005; **27**:1432-1443.
47. Rolla AR, Rakel RE: Practical approaches to insulin therapy for type 2 diabetes mellitus with premixed insulin analogues. Clin Ther 2005; **27**:1113-1125.
48. Riddle MC, Rosenstock J, Gerich J: The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; **26**:3080-3086.
49. Testa MA, Simonson DC: Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: A randomized, controlled, double-blind trial. JAMA 1998; **280**:1490-1496.
50. Korytkowski M, Bell D, Jacobsen C, et al: A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clin Ther 2003; **25**:2836-2848.
51. Rubin RR, Peyrot M: Quality of life, treatment satisfaction, and treatment preference associated with use of a pen device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. Diabetes Care 2004; **27**:2495-2497.
52. National diabetes fact sheet, 2005. Centers for Disease Control and Prevention (www.cdc.gov/diabetes), January 2006.

Chapter 7

Health and economic impact of conversion to an insulin analog pen

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Summary

The purpose of this study was to evaluate claims-related treatment adherence, health care resource utilization, and associated costs of therapy conversion from an insulin vial and syringe to a premixed biphasic insulin analog pen device among privately insured patients with Type 2 diabetes mellitus (T2D). A retrospective, longitudinal, intrapatient (before and after) analysis was conducted within the *PharMetrics* database of medical and pharmaceutical claims from 57 commercial health plans across the United States. A total of four hundred eighty-six adult patients with a confirmed diagnosis of T2D who converted from an insulin analog vial and syringe (233 patients) or a human insulin vial and syringe (253 patients) to a biphasic insulin analog pen device between July 1, 2001 and December 31, 2002 were included. All patients had no previous use of the pen device. Primary endpoints were medication possession ratio (MPR), a measure of adherence; hypoglycemic events; associations between treatment adherence and hypoglycemic events, and adherence and all-cause health care costs; and all-cause–attributable, hypoglycemia-attributable, and other diabetes-attributable costs.

After conversion to the pen device, MPR increased significantly from 59% to 68% ($p<0.01$). A significant decrease in the likelihood of experiencing a hypoglycemic event was also observed after conversion (odds ratio [OR] 0.40, 95% confidence interval [CI] 0.27–0.61, $p<0.05$), with hypoglycemic occurrences reduced nearly two thirds among subjects with optimal adherence indicated by an MPR of 80% or greater (incidence rate ratio [IRR] 0.36, 95% CI 0.11–0.76, $p<0.05$). Significant decreases in hypoglycemia-attributable emergency department visits (OR 0.36, 95% CI 0.16–0.84, $p<0.05$) and physician visits (OR 0.39, 95% CI 0.20–0.77, $p<0.05$) were observed. Total mean all-cause annual treatment costs were reduced by $1748/patient ($p<0.01$), hypoglycemia-attributable costs were reduced by $908/patient ($p<0.01$), and other diabetes-attributable costs were reduced by $643/patient ($p<0.01$). Patients with an MPR of 80% or greater were associated with significant reductions in all-cause health care costs (OR 0.55, 95% CI 0.31–0.80, $p<0.05$).

Our study demonstrated that privately insured patients with T2D may exhibit considerable improvements in clinical and economic outcomes after insulin therapy conversion from vial and syringe to a premixed biphasic insulin analog pen device.

Introduction

In 2005, an estimated 21 million people across the United States were affected by diabetes mellitus, a chronic medical condition characterized by elevated blood glucose levels [1]. Its worldwide prevalence is expected to approach 366 million, or 4.4% of the global population, by 2030 [2], with T2D constituting greater than 90% of all diagnosed cases [1]. The national economic burden of treating diabetes was estimated at $132 billion in 2002, with direct medical costs representing nearly 70%, or $92 billion, of the total cost [1]. Diabetes-related health outcomes and complication events, having the potential for substantial financial consequences, may be significantly influenced by level of glycemic control, differences in the safety profiles of appropriate treatments, access to

therapy per health plan benefit designs, and issues related to proper self-management over the long-term duration of the disease [3–10]. In particular, recent reports have identified hypoglycemia, an acute complication and safety concern commonly associated with intensive diabetes care, as a major contributor to elevated diabetes-related costs for patients treated in public and private managed care settings [11,12].

Although glycemic control has been established as the cornerstone of successful diabetes treatment, most patients with T2D in the United States are not achieving recommended hemoglobin A1c (A1C) targets, despite advancements in insulin molecular design, delivery systems, and recommendations for antidiabetic therapy [13–15]. To this end, adequate patient self-management has been identified as a critical component for successful short- and long-term treatment of diabetes and its complications [16–19], including the acute and potentially fatal complication of hypoglycemia [16]. Recent health policy initiatives and recommendations aiming to curb the progression of T2D have included earlier initiation of either premixed biphasic or basal insulin (human or analog) for patients with T2D who have failed diet and exercise as well as oral anti-diabetic therapy [18,20–23]. Insulin administration has traditionally occurred through the use of a vial and syringe; however, several disadvantages with this therapeutic approach have been noted. These include difficulty of transportation, intimidation of use with regard to anxiety about self-injection, fear of injection (needle phobia) and associated pain, lengthy training time on initiation, and social embarrassment. These factors have all been suspected to impact lifestyle flexibility and to negatively influence treatment adherence, patient self-management behavior, and achievement of euglycemia [24–26].

Insulin delivery systems, including pen devices, may be useful tools for clinicians aiming to overcome the barriers to treatment adherence for patients using a vial and syringe. Most pen devices are structured such that the insulin cartridge and syringe are combined in a single unit, which has led to reported improvements in portability, dosing accuracy, mealtime flexibility, and convenience of delivery [25,27]. Increased patient preference and treatment satisfaction, which may be particularly important due to their demonstrated impact on patient compliance [28], cost of care [6,29], patient self-management behaviors [30], and adherence to treatment, have also been reported for pen devices, including modern premixed insulin analog pens [24,28,31–36]. Furthermore, patients who perceive their insulin injection to be burdensome may experience more negative health outcomes than those who do not feel such burden [37], and those who are satisfied are more likely to maintain positive physical and psychological health [38]. Additional advantages of prefilled insulin pens include improved user confidence, ease of training, patient acceptance of therapy, and greater stability during injection (handling) [25,27,39–41].

Considering these positive effects, the increasing use of insulin pens as opposed to traditional insulin delivery devices may lead to better health-related quality of life [42,43]. Effective and safe long-term treatment of diabetes may depend a great deal on patients' adherence to drug therapy and level of proper self-management, particularly as modern and novel class therapies become available and are increasingly used [44]. As recent, randomized, controlled, clinical trials support the efficacy and safety of modern insulin analog therapies, including premixed insulin, versus preexisting human and basal

insulin treatments [45–48], and given that significant differences for patient-reported outcomes exist among anti-diabetic therapies, potentially influencing adherence and subsequent health outcomes, it is important to evaluate the real-life effectiveness and economic impact of therapy conversion among such therapies. This may be especially noteworthy in the established framework of a strong correlation between poor diabetes treatment adherence and an increased risk for hospitalizations and associated costs, with claims-related hypoglycemic event rates having already been found to significantly vary for conventional versus modern insulin formulations [49–51].

To this end, and to the best of our knowledge, this study is a first attempt to evaluate the impact that conversion to a premixed biphasic insulin analog pen from preexisting insulin preparations administered with vial and syringe may have on health and economic outcomes in routine clinical practice. The study is intended to be an in-depth follow-up analysis to previously reported data [52] that examined a similar range of primary endpoints among patients with T2D who were converting to insulin pen delivery devices. However, the present analysis extends the methodological and statistical approach to include an assessment of the potential correlation of diabetes treatment adherence to an impact on patient health care costs, and specifically evaluates a subset of patients converting to the biphasic insulin aspart (BIAsp) 70/30 pen device from a more refined and transparent set of pre-conversion insulin formulations.

Methods

Data Source

This study used the *PharMetrics* Database (PharMetrics, Inc., Watertown, MA), which contains a fully integrated and adjudicated set of medical and pharmaceutical claims for all covered services for more than 40 million lives from 57 commercial health plans across the United States (at the time of data acquisition). It is composed of a broad, representative sample of national, commercially-insured health care beneficiaries on a variety of measures, including geographic dispersion, age, sex, and health plan structure. As the database includes a continuously enrolled managed care population, longitudinal retrospective assessment of medical practice patterns and health care resource utilization is permissible. Descriptive information on patients' dates of coverage, sex, geographic region, and age is included in the enrollment file, whereas the medical file contains details on claims for physician office visits, outpatient services, and hospital stays.

Specifically, the information available includes dates of service, medical diagnoses, and procedures performed, coded using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *Current Procedural Terminology Version 4* codes. Documentation of each prescription filled, including records of the dispensing date, National Drug Code, quantity of drug, and number of days supplied, is contained in the outpatient pharmacy file. Each of these files is linked through a unique patient identification number, allowing integration of individual patient records across the entire analytic file to create episodes of care over time. The database is fully compliant with the Health Insurance Portability and Accountability Act of 1996 [53].

Study Design and Cohort Selection

This was a retrospective, longitudinal, intra-patient (before and after) analysis similar to that used in recently published database research aimed at assessing the clinical and health outcomes, as well as costs, of various therapy conversions from a third-party payer perspective [52,54,55]. A cohort of patients with a confirmed diagnosis of T2D who converted to the BIAsp 70/30 pen device (contains 70% insulin aspart protamine suspension and 30% insulin aspart injection) (NovoLog Mix 70/30 FlexPen; Novo Nordisk Inc., Princeton, NJ) for the first time (i.e., index event) and who had previously been treated with either human or analog insulin administered by vial and syringe were identified as the study group.

Characteristics of the cohort in the 6-month period before the index event (pre-index period) were compared with those in the 2-year or longer period after the index event (post-index period). The primary study endpoints included treatment adherence and claims-identified hypoglycemic events (i.e., those requiring third-party intervention). Associations between adherence and hypoglycemic events, and the subsequent relationship between health care costs and adherence, were analyzed. The overall study cohort was entirely composed of and divided into four sub-cohorts by type of pre-index drug for further analysis: (1) NPH insulin users, (2) human premix insulin users, (3) insulin glargine users, and (4) premixed analog insulin users. Data were collected for the period from January 1, 2001–April 30, 2005. Patient inclusion criteria consisted of age 18 years or older, multiple diagnostic claims for T2D (i.e., ICD-9-CM code 250.xx, excluding type 1 subcodes), and first use of BIAsp 70/30 pen therapy that started between July 1, 2001, and December 31, 2002. These patients were identified by National Drug Code and assigned an index date (i.e., the date of the first prescription for the pen device).

All patients included in the study were required to have longitudinal data characterized by at least 6 months of continuous enrollment before the index date and at least a 2-year length of follow-up after the index date. First use of BIAsp 70/30 pen therapy was determined by the absence of its prescription during the 6 months before the index date. Data were collected longitudinally from the index date to first occurrence of either discontinuation of the index drug or to the end of the study period (April 30, 2005).

Statistical Analysis

Descriptive statistics were calculated, with categorical variables reported as percentages. Patient demographic and clinical characteristics between groups were analyzed with use of the Pearson x2 test. For continuous variables, means ± SDs and medians (ranges) were generated. The Student *t*-test was used to analyze mean differences among the sub-cohorts. An a priori level of significance of 0.05 was set for all of the analyses. Clinical characteristics (i.e., patient co-morbidities, complications related to diabetes) were assessed over the 6 month pre-index period. Co-morbid conditions and complications associated with diabetes were comprehensively chosen for consideration after having been identified from the literature. Those conditions included cardiovascular disease, diabetes-related infections, other metabolic diseases, nephropathy, neuropathy,

retinopathy, obesity, lower-extremity amputation, depression, and hypoglycemic events. Specifically, metabolic complications such as hypoglycemic coma (ICD-9-CM code 251.0), other specified hypoglycemia (251.1), unspecified hypoglycemia (251.2), postsurgical hypoinsulinemia (251.3), and disturbances of branched-chain amino acid metabolism (270.3) were included. These conditions were tracked by using primary and secondary ICD-9-CM diagnosis codes. Binary indicator variables (1 = yes, 0 = no) were used to signify the presence or absence of these medical conditions during the pre-index period.

Adherence to diabetes treatment before and after the index event was evaluated by using the medication possession ratio (MPR). The MPR, an indicator used commonly in database-related outcomes research to assess levels of optimal or suboptimal adherence [56–58], is defined as the sum of the days' supply of drug divided by the number of days between the first fill and the last refill plus the days' supply of the last refill. This indicator allows for a representation of the proportion of time during the follow-up period that a patient was in possession of a supply of their index drug. This designation of MPR usually results in a ratio of 1 or less, due to time gaps in refilling the drug; MPR values greater than 1 were adjusted to 1. An MPR value of less than 80% was defined as poor adherence (conversely, > 80% was defined as optimal adherence). The statistical significance of differences in MPR between cohorts was assessed with use of a *t*-test.

Annualized odds ratios (ORs), quantities used to compare whether the probability or likelihood of a certain event differs between two groups, were estimated by using person-time and event-time analyses with adjustment for varying lengths of follow-up. Hypoglycemic events before and after the index event were estimated with the OR, including associated data on health care resource utilization (e.g., physician visits, hospitalization, emergency department visits). Having tested for overdispersion of the model (i.e., conditional variance is greater than the mean), Poisson regression was used as an appropriate multivariate regression model for these count data, which followed a Poisson distribution [59–61]. The outcome variable of the Poisson regression model was the count of hypoglycemic events in the post-index period. A stepwise and systematic approach to building the statistical models was taken. Variable advancement in the Poisson regression models was driven on a theoretical background.

In model 1, associations between hypoglycemic count and baseline demographics (age, sex, and geographic region), study cohort, and clinical variables (co-morbid conditions or complications of diabetes) were analyzed. Model 2 involved addition of the main variable (level of adherence). In addition to observing the association between adherence and hypoglycemic count, this model also helped in analyzing the impact of adding the adherence variable on the coefficients of the baseline demographic and clinical variables. The third model (model 3) introduced two variables that are closely related to drug adherence: log-transformed post-index treatment duration and preindex hypoglycemic count. Addition of these two variables helped us in analyzing their impact on the adherence coefficient. Although geographic region was one of the independent variables in all three models, as a location fixed-effect model was considered, estimates for geographic region were not reported. Incident rate ratios (IRRs) were derived by

exponentiating the parameter estimates from the model. Payments made by third-party payers to health care providers for utilization of health care resources (i.e., the actual reimbursement amount) were used to compute total health care costs.

Since administrative claims were collected over several years, all costs were adjusted for inflation to 2005 dollars by using the medical care consumer price index [62]. Hypoglycemia-attributable costs were computed by summing the amounts paid for all claims related to hypoglycemic events (ICD-9-CM codes 250.8, 251.0, 251.1, and 251.2). Other mutually exclusive diabetes-attributable costs were computed by totaling the amounts paid for claims related to T2D (ICD-9-CM codes 250.0x–250.7x and 250.9x, where x = 0 or 2). Overall diabetes-attributable and hypoglycemia-attributable costs were further stratified into emergency department, hospitalization, outpatient visit, physician visit, and pharmacy costs. The Wilcoxon rank sum test was used to test for significance of the cost difference before and after the index event as the cost data gave rise to non-normal and skewed distributions.

For analyzing associations between study sub-cohorts (the main independent variable) and total cost in the post-index period (dependent variable) after adjusting for baseline demographics, clinical co-morbidities, level of adherence, and post-index treatment duration, a generalized gamma regression model was used as an appropriate multivariate regression approach. Stepwise models were created similar to the Poisson regression models described above. Similar to the Poisson regression models, variable advancement in the gamma regression models was driven on a theoretical background. In model 1, associations between total cost in the post-index period and baseline demographic and clinical variables were analyzed. Model 2 of the gamma regression involved the addition of the main variable (level of adherence). In addition to observing the association between adherence and total post-index period cost, this model also helped in analyzing the impact of adding the adherence variable on the coefficients of baseline demographic and clinical variables. Model 2 also included another important variable that is related to drug adherence: log-transformed post-index treatment duration. The third model (model 3) introduced one variable that would have an impact on total post-index cost: total pre-index (baseline) cost. Addition of this variable related to total post-index period cost helped in analyzing the impact of this variable on the adherence coefficient. Although geographic region was one of the independent variables in all three models, since a location fixed-effect model was considered, estimates for geographic region were not reported, as with the Poisson models. Odds ratios with 95% confidence intervals (CIs) were derived from the model and presented. All statistical analyses were performed by using SAS, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

The overall study population consisted of 486 patients newly beginning treatment with the BIAsp 70/30 pen device. Subjects previously treated with an insulin analog vial and syringe (233 patients [47.9%]) and subjects previously treated with human insulin vial

and syringe (253 patients [52.1%]) constituted two general sub-cohorts within this study group. Of those treated with human insulin during the pre-index period, 112 (44.3%) had been prescribed NPH insulin and 141 (55.7%) were prescribed premixed biphasic human insulin. Of patients using an insulin analog vial and syringe during the pre-index period, 132 (56.7%) and 101 (43.3%) were prescribed insulin glargine and a premixed biphasic insulin analog, respectively. The mean ± SD age of the study population was 45.1 ± 13.7 years; most subjects (56.4%) were male (Table 1). Generally, patients had an elevated prevalence of diagnosed co-morbid conditions: metabolic disease (48 [9.9%]), nephropathy (48 [9.9%]), neuropathy (46 [9.5%]), retinopathy (41 [8.4%]), and cardiovascular disease (39 [8.0%]).

Previous insulin analog users were significantly younger than previous human insulin users (mean ± SD age 43.5 ± 14.2 vs. 46.7 ± 13.1 yrs, p=0.04), with the proportion of subjects older than 45 years also significantly lower compared with that age group among the previous human insulin users (47.2% vs. 56.9%, p<0.05). Male subjects constituted a higher proportion of the previous analog insulin vial and syringe sub-cohort than previous human insulin cohort (61.8% vs. 51.4%, p=0.02). However, no significant differences were observed with respect to level of individual co-morbid conditions or diabetes-related complications, with the exception of metabolic diseases (12.9% vs. 7.1%, p=0.04).

Treatment Adherence

Adherence (measured by MPR) increased significantly after conversion to the pen device ((mean ± SD) MPR: 68 ± 31% vs. 59 ± 30%, p<0.01). Furthermore, the percentage of individuals exhibiting an adherence rate of 80% or greater was significantly higher in the post-index period compared with the pre-index period (56.2% vs. 35.4%, p<0.01). These improvements in MPR were also observed across the two general pre-index sub-cohorts (previous insulin analog users MPR 71 ± 32% vs. 59 ± 28%, p<0.01, and previous human insulin users MPR 66 ± 30% vs. 59 ± 29%, p<0.01). Among individuals who were prescribed an insulin analog in the pre-index period, premixed biphasic analog users (MPR 72 ± 33% vs. 60 ± 29%, p<0.01) and insulin glargine users (MPR 68 ± 31% vs. 57 ± 26%, p=0.01) showed a similar increase in treatment adherence after conversion. Among individuals who were prescribed human insulin in the pre-index period, NPH users showed a 6% increase in adherence (MPR 65 ± 29% vs. 59 ± 27%, p=0.03), whereas previous premixed human insulin users showed an 8% increase in adherence (MPR 68 ± 32% vs. 60 ± 28%, p=0.01).

Hypoglycemic Events

Thirty-two subjects were found to have 44 hypoglycemic events during the pre-index period, and 30 individuals had 64 hypoglycemic events during the post-index period (Table 2). The percentage of individuals experiencing a hypoglycemic event, after controlling for differences in length of follow-up, was reduced by 74% (OR 0.26, 95% CI 0.15–0.44, p<0.05).

Table 1. Baseline demographic and clinical characteristics

Characteristic	Previous Insulin Analog Users[a] (n=233)	Previous Human Insulin Users[b] (n=253)	All Patients (n=486)	p Value
Age (yrs)				0.04
Mean ± SD	43.5 ± 14.2	46.7 ± 13.1	45.1 ± 13.7	
Median	45.0	48.0	47.0	
		No. (%) of Patients		
Age group				<0.01
18–30 yrs	48 (20.6)	33 (13.0)	81 (16.7)	
31–45 yrs	75 (32.2)	76 (30.0)	151 (31.1)	
≥ 46 yrs	110 (47.2)	144 (56.9)	254 (52.3)	
Geographic region				0.91
East	18 (7.7)	20 (7.9)	38 (7.8)	
Midwest	51 (21.9)	51 (20.1)	102 (21.0)	
South	43 (18.4)	53 (20.9)	96 (19.8)	
West	121 (51.9)	129 (51.0)	250 (51.4)	
Sex				0.02
Male	144 (61.8)	130 (51.4)	274 (56.4)	
Female	89 (38.2)	123 (48.6)	212 (43.6)	
Comorbid conditions or complications before index event				
Metabolic disease	30 (12.9)	18 (7.1)	48 (9.9)	0.04
Neuropathy	27 (11.6)	19 (7.5)	46 (9.5)	0.16
Retinopathy	20 (8.6)	21 (8.3)	41 (8.4)	0.43
Nephropathy	22 (9.4)	26 (10.3)	48 (9.9)	0.83
Cardiovascular disease[c]	17 (7.3)	22 (8.7)	39 (8.0)	0.22
Infections related to diabetes mellitus	2 (0.8)	1 (0.4)	3 (0.6)	0.11
Depression	2 (0.8)	0 (0.0)	2 (0.4)	0.18
Leg amputation	0 (0.0)	1 (0.4)	1 (0.2)	0.14

[a]Patients who used only an insulin analog vial and syringe before the index event.
[b]Patients who used only human insulin vial and syringe before the index event.
[c]Excluding hypertension.

Table 2. Hypoglycemic events in the 486 patients

Hypoglycemia-Related Health Care Resource Utilization	Preindex Event		Postindex Event
No. of hypoglycemic events			
Previous glargine users	10		12
Previous analog premix users	12		19
Previous NPH users	11		17
Previous human premix users	11		16
Total	44		64
Emergency department visits			
No. (%) of events	10 (22.7)		13 (20.3)
Total person-years	200.7		722.8
OR (95% CI)		0.36 (0.16–0.84)	
Hospitalizations			
No. (%) of events	8 (18.2)		21 (32.8)
Total person-years	200.7		722.8
OR (95% CI)		0.73 (0.32–1.67)	
Physician visits			
No. (%) of events	15 (34.1)		21 (32.8)
Total person-years	200.7		722.8
OR (95% CI)		0.39 (0.20–0.77)	
Outpatient visits			
No. (%) of events	4 (9.1)		6 (9.4)
Total person-years	200.7		722.8
OR (95% CI)		0.42 (0.12–1.49)	
Other[a]			
No. (%) of events	7 (15.9)		3 (4.7)
Total person-years	200.7		722.8
OR (95% CI)		0.12 (0.03–0.46)	

Total person-years = mean annualized sum of treatment duration for all the study patients; OR = odds ratio; CI = confidence interval.

[a]Health care resource utilization that did not have a code for either an emergency department visit, hospitalization, physician visit, or outpatient visit.

Similarly, the likelihood of experiencing a hypoglycemic event was reduced by 60% (OR 0.40, 95% CI 0.27–0.61, $p<0.05$). Model 3 of our Poisson regression estimated that the frequency of hypoglycemic events in subjects with an MPR of 80% or greater decreased by nearly two thirds (IRR 0.36, 95% CI 0.11–0.76, $p<0.05$). Pre-index insulin analog users showed the highest reduction in hypoglycemic events after converting to the BIAsp 70/30 pen device. Previous glargine users and premixed biphasic analog users showed a similar reduction of approximately two thirds of subjects experiencing a hypoglycemic event (OR 0.36, 95% CI 0.15–0.87, $p<0.05$ for previous glargine users, and OR 0.37, 95% CI 0.16–0.82, $p<0.05$ for previous pre-mixed biphasic analog users). Human insulin users in the pre-index period showed a slightly smaller, yet still significant, reduction in hypoglycemic events after conversion. Previous NPH users and premixed human insulin

users showed a comparable 58% reduction in the annual number of subjects experiencing a hypoglycemic event (OR 0.42, 95% CI 0.18–0.95, $p<0.05$ for previous NPH insulin users, and OR 0.43, 95% CI 0.19–0.98, $p<0.05$ for previous pre-mixed human insulin users).

Hypoglycemic events that required resource utilization are summarized in Table 2. Significant decreases in hypoglycemic event–related emergency department visits (OR 0.36, 95% CI 0.16–0.84, $p<0.05$) and physician visits (OR 0.39, 95% CI 0.20–0.77, $p<0.05$) were observed, although hypoglycemic event–related hospitalizations (OR 0.73, 95% CI 0.32–1.67) and outpatient visits (OR 0.42, 95% CI 0.12–1.49) were non-significantly reduced, similar to previous reports [52]. Significant factors were found to be associated with hypoglycemic events in the post-index period examined in a Poisson multivariate context. The full analysis (model 3) revealed no significant difference in the occurrence of hypoglycemic events in the post-index period among individuals who were previously prescribed NPH insulin (IRR 1.00, 95% CI 0.99–1.01), premixed insulin analogs (IRR 0.90, 95% CI 0.58–1.23), and insulin glargine (IRR 0.86, 95% CI 0.55–1.28) when using premixed human insulin vial and syringe users as the baseline comparison group. Several co-morbid conditions and complications did emerge as significant characteristics of subjects experiencing hypoglycemia in the post-index period: neuropathy (IRR 1.93, 95% CI 1.27–3.18, $p<0.05$), nephropathy (IRR 3.53, 95% CI 2.19–5.12, $p<0.05$), cardiovascular events (IRR 1.77, 95% CI 1.12–3.06, $p<0.05$), and other metabolic diseases (IRR 5.47, 95% CI 3.98–8.29, $p<0.05$).

Health Care Costs

Annually adjusted mean all-cause health care costs/patient decreased significantly after conversion to the BIAsp 70/30 pen device ($16,004 vs. $14,256, $p<0.01$; Table 3). Hypoglycemia-attributable costs decreased by $908 from the pre-index period to the post-index period ($1528 vs. $620, $p<0.01$), mainly reflected in significant annualized mean savings in associated emergency department costs of $67 ($95 vs. $28, $p<0.01$), hospitalization costs of $585 ($895 vs. $310, $p<0.01$), physician-visit costs of $96 ($160 vs. $64, $p<0.01$), and pharmacy costs of $177 ($321 vs. $144, $p<0.01$). Reductions in hospitalization and emergency department costs were mainly due to decreases in the mean annual number of associated emergency department visits (7.7 vs. 5.0 visits, $p<0.01$) and hospital length of stay during those visits (9.9 vs. 6.0 days, $p<0.01$).

Other diabetes–attributable costs decreased by $643 in the post-index period compared with the pre-index period ($8699 vs. $8056, $p<0.01$), reflected mainly in mean per-patient reductions of $114 in associated emergency department visits ($276 vs. $162, $p<0.01$), $877 in physician visits ($1522 vs. $645, $p<0.01$), and $433 in pharmacy costs ($4068 vs. $3635, $p<0.01$; Table 3). Similar to the hypoglycemia-attributable emergency department cost reductions, decreases in the cost of diabetes-attributable emergency department resource utilization were driven by a significant annual mean decrease in emergency department visits after conversion (10.1 vs. 7.2 visits, $p<0.01$; Table 3).

Examination of pre-index and post-index diabetes-attributable pharmacy costs, stratified by the cost of insulin and the cost of oral anti-diabetic drugs, revealed a significant increase in the cost of insulin in the overall study cohort ($2278 vs. $2617, p<0.01); however, analyses of each of the individual sub-cohorts did not show significant increases after conversion. During the post-index period, a reduction in the cost of oral anti-diabetic drugs ($772) was observed in the overall cohort ($1790 vs. $1018, p<0.01) as well as within each sub-cohort, significantly so for three of the four groups (previous glargine insulin: $484 vs. $248, p=0.04, premixed biphasic insulin analog: $483 vs. $251, p=0.04, premixed biphasic human insulin: $422 vs. $253, p=0.03, NPH insulin: $401 vs. $266, p=0.06; Table 4).

Factors potentially associated with post-index all-cause total health care costs were examined in a generalized linear gamma regression context (Table 5). Using premixed human insulin as the pre-index baseline sub-cohort comparator, the most extensive model (model 3) revealed significantly lower all-cause health care costs in the post-index period among individuals who had been prescribed insulin glargine (OR 0.81, 95% CI 0.67–0.95) and a premixed insulin analog (OR 0.79, 95% CI 0.68–0.90) during the pre-index period, with previous NPH insulin vial and syringe users showing a non-significant increase in all-cause health care costs (OR 1.20, 95% CI 0.90–1.59). Several co-morbid conditions and complications emerged as significant characteristics of subjects experiencing higher health care costs during the post-index period: neuropathy (OR 1.26, 95% CI 1.11–1.43, p<0.05), nephropathy (OR 1.72, 95% CI 1.51–1.99, p<0.05), cardiovascular events (OR 1.49, 95% CI 1.30–1.51, p<0.05), other metabolic diseases (OR 1.14, 95% CI 1.06–1.24, p<0.05), retinopathy (OR 1.23, 95% CI 1.09–1.38, p<0.05), and depression (OR 1.84, 95% CI 1.68–2.04, p<0.05).

Discussion

Clinicians treating patients with T2D have a wide array of appropriate pharmacotherapeutic options available, with each having individual effects on clinical effectiveness, safety, treatment satisfaction, and other patient-reported outcomes affecting patient self-management behavior [17,24–26,31–34,39]. Therefore, assessing the effects on health and economic outcomes that individual therapy classes may have in routine clinical practice is important. Of particular importance may be distinguishing these outcomes not only among delivery methods but also among classes of anti-diabetic therapies given the current and ever-increasing range of treatment options and given that patient perceptions of care have been shown to be multifactorial and variable between conventional and modern therapies [44].

This study aimed to provide an extended and more focused methodological approach to data recently reported on the health economic sequelae of conversion to insulin pen devices among a larger cohort [52]. We attempted to achieve this first by examining the impact of conversion to the pen device of a specified class of insulin from a refined, stratified variety of pre-existing vial and syringe preparations, and then by including an assessment of the potential impact that treatment adherence with this pen may have on

Table 3. All-cause-attributable, hypoglycemia-attributable, and other diabetes-attributable resource utilization and costs associated with switching to or adding analog insulin pen therapy

	All-Cause Attributable			Hypoglycemia Attributable[a]		
Cost Component	Preindex	Postindex	Difference[c]	Preindex	Postindex	Difference[c]
Total ($)[d]						
Mean ± SD	16,004 ± 20,336	14,256 ± 17,629	-1748 ± 2625	1528 ± 2336	620 ± 899	-908 ± 1396
Median	4992	3100	842	490	142	308
Emergency department ($)						
Mean ± SD	592 ± 1475	244 ± 1752	-348 ± 901	95 ± 534	28 ± 408	-67 ± 368
Median	228	115	137	29	11	26
Emergency department (annual visits)						
Mean ± SD	10.8 ± 21.7	7.1 ± 21.8	-3.7 ± 10.2	7.7 ± 23.6	5.0 ± 18.6	-2.7 ± 8.5
Median	3.7	4.2	1.1	3.8	2.5	1.1
Outpatient visits ($)						
Mean ± SD	1732 ± 7523	1043 ± 3233	-689 ± 1855	57 ± 218	74 ± 337	+17 ± 68
Median	502	421	309	15	27	5
Hospitalization ($)						
Mean ± SD	6426 ± 13,553	5962 ± 10,299	-464 ± 1115	895 ± 13,305	310 ± 8662	-585 ± 13,681
Median	1448	1079	86	342	100	179
Hospital LOS (days)						
Mean ± SD	12.1 ± 38.2	10.1 ± 32.5	-2.0 ± 16.8	9.9 ± 31.2	6.0 ± 26.2	-3.9 ± 15.2
Median	5.9	4.3	0.9	4.8	3.2	1.1
Physician visit ($)						
Mean ± SD	2225 ± 6236	1590 ± 4098	-635 ± 2189	160 ± 569	64 ± 371	-96 ± 240
Median	906	562	441	69	22	31
Pharmacy ($)						
Mean ± SD	5029 ± 11,886	5417 ± 12,583	+388 ± 5268	321 ± 524	144 ± 467	-177 (293)
Median	2442	2864	198	105	84	41

LOS = length of stay.
[a]Primary diagnosis of hypoglycemia.
[b]Primary diagnosis of type 2 diabetes excluding hypoglycemia.
[c]All resource utilization and cost differences were statistically significant at $p<0.01$, with the exception of mean all-cause– and other diabetes-attributable hospital LOS.
[d]Costs (per patient) annualized and adjusted to 2005 dollars.

Table 3. (continued – far right column)

Other Diabetes Attributable[b]		
Preindex	Postindex	Difference[c]
8699 ± 9268 4113	8056 ± 8559 4248	-643 ± 988 351
276 ± 4462 101	162 ± 2352 54	-114 ± 2228 39
10.1 ± 21.2 3.8	7.2 ± 18.4 3.0	-2.9 ± 8.2 0.9
745 ± 11,882 279	772 ± 10,992 371	+27 ± 2146 15
2088 ± 11,046 812	2842 ± 10,663 1142	+754 ± 5776 329
12.0 ± 36.2 4.6	12.4 ± 36.4 5.4	+0.4 ± 2.7 0.1
1522 ± 3138 708	645 ± 4366 272	-877 ± 2358 467
4068 ± 7254 2446	3635 ± 5553 1427	-433 ± 1075 705

Table 4. Comparison of pre-index and post-index diabetes-related pharmacy acquisition costs

	Insulin Costs[a]			Oral Antidiabetic Drug Costs[a]		
Insulin Group	Preindex	Postindex	p Value[b]	Preindex	Postindex	p Value[b]
Overall	2278 ± 1401	2617 ± 1155	<0.01	1790 ± 826	1018 ± 445	<0.01
Glargine	632 ± 558	707 ± 623	0.13	484 ± 306	248 ± 178	0.04
Analog premix	643 ± 488	733 ± 524	0.09	483 ± 343	251 ± 166	0.04
NPH	458 ± 379	526 ± 427	0.14	401 ± 327	266 ± 207	0.06
Human premix	545 ± 385	652 ± 505	0.08	422 ± 319	253 ± 188	0.03

[a]Data are mean ± SD costs (in dollars)/patient/year.
[b]Wilcoxon rank sum test.

Table 5. All-cause-related treatment costs: a generalized linear gamma regression model

	Model 1[a]		Model 2[b]		Model 3[c]	
Variable	Estimate	OR (95% CI)	Estimate	OR (95% CI)	Estimate	OR (95% CI)
Previous glargine users	-0.17[d]	0.84 (0.71–0.96)	-0.21[d]	0.81 (0.66–0.95)	-0.21[d]	0.81 (0.67–0.95)
Previous analog premix users	-0.19[d]	0.83 (0.69–0.95)	-0.23[d]	0.79 (0.69–0.89)	-0.24[d]	0.79 (0.68–0.90)
Previous NPH users	0.21	1.23 (0.92–1.56)	0.19	1.21 (0.90–1.58)	0.18	1.20 (0.90–1.59)
Age 18–30 yrs	-0.22[d]	0.80 (0.72–0.91)	-0.25[d]	0.78 (0.66–0.90)	-0.26[d]	0.77 (0.67–0.90)
Age 31–45 yrs	-0.13	0.88 (0.61–1.09)	-0.17	0.84 (0.55–1.26)	-0.17	0.84 (0.54–1.25)
Male	0.04	1.04 (0.81–1.23)	0.03	1.03 (0.80–1.21)	0.03	1.03 (0.79–1.20)
Cardiovascular events	0.52[d]	1.68 (1.51–1.86)	0.46[d]	1.58 (1.44–1.73)	0.40[d]	1.49 (1.30–1.51)
Infections related to diabetes	0.20[d]	1.22 (1.10–1.33)	0.18[d]	1.20 (1.09–1.32)	0.17[d]	1.19 (1.09–1.29)
Retinopathy	0.27[d]	1.31 (1.18–1.46)	0.24[d]	1.27 (1.11–1.44)	0.21[d]	1.23 (1.09–1.38)
Neuropathy	0.32[d]	1.38 (1.17–1.61)	0.27[d]	1.31 (1.14–1.50)	0.23[d]	1.26 (1.11–1.43)
Leg amputation	-0.72	0.49 (0.11–1.62)	-0.74	0.48 (0.12–1.60)	-0.74	0.48 (0.11–1.57)
Nephropathy	0.66[d]	1.93 (1.72–2.20)	0.60[d]	1.82 (1.68–2.14)	0.54[d]	1.72 (1.51–1.99)
Depression	0.72[d]	2.05 (1.77–2.29)	0.66[d]	1.93 (1.71–2.15)	0.61[d]	1.84 (1.68–2.04)
Other metabolic diseases	0.21[d]	1.23 (1.11–1.34)	0.17[d]	1.19 (1.08–1.31)	0.13[d]	1.14 (1.06–1.24)
MPR ≥ 80%	—	—	-0.58[d]	0.56 (0.32–0.81)	-0.60[d]	0.55 (0.31–0.80)
Postindex treatment duration[e]	—	—	0.19[d]	1.21 (1.10–1.32)	0.18[d]	1.20 (1.09–1.31)
Total baseline cost	—	—	—	—	0.23[d]	1.26 (1.16–1.37)

OR = odds ratio; CI = confidence interval; MPR = medication possession ratio.
Total cost during the follow-up period was used as the dependent variable; reference categories were previous human premix insulin users, age ≥ 46 yrs, female, east region, MPR category < 80%; Pearson χ^2 *df*: 0.74 for model 1, 0.68 for model 2, and 0.66 for model 3. Although this gamma regression model was a location fixed-effect model including geographic region as one of the independent variables in all three models, the results are not shown in the table.
[a]Model 1 includes age, sex, region, insulin cohort, and clinical comorbidities and complications.
[b]Model 2 extends model 1 by adding MPR categories and postindex treatment duration.
[c]Model 3 extends model 2 by adding baseline total cost.
[d]Significant variables ($p<0.05$).
[e]Postindex treatment duration was log transformed.

patient health care costs in a multivariate context of other clinical and patient characteristics. In using a data source providing observational perspective within privately-insured community practice settings, the analytic approach supplements clinical trial data (from a controlled setting) comparing BIAsp 70/30 pen with the defined variety of sub-cohort pre-index insulin formulations in this study. This thereby allowed a first

attempt to offer insight to clinical and policy decision-makers of the potential impact that therapy conversion to a dual-action insulin analog may have on treatment adherence, occurrence of hypoglycemic events, resource utilization, costs, and the correlative effects therein.

Optimal treatment adherence, one of the primary endpoints measured by an MPR of 80% or greater, was significantly improved during the post-index period compared with the pre-index period (68% vs. 59%, $p<0.01$). This positive impact on MPR for conversion to the BIAsp 70/30 pen was more pronounced than was observed in a more general, inclusive insulin pen cohort previously reported [52], highlighting a potentially distinctive benefit associated with the pre-mixed, dual-action insulin analog. Furthermore, the present analysis revealed more prominent all-cause-attributable, hypoglycemia-attributable, and other diabetes-attributable cost reductions on conversion when compared with the larger pen group ($1748 vs. $1590, $908 vs. $788, and $643 vs. $600, respectively) [52]. That hypoglycemia-attributable cost reductions accounted for 58.5% of the total reduction in diabetes-related health care resource use reinforces the notion that hypoglycemia is a major contributor to diabetes-attributable costs, and also suggests that improved adherence associated with reductions in hypoglycemia-attributable events may have a positive influence on total diabetes-attributable resource use in the short term. Hypoglycemia should therefore be an important factor to focus on for improving patient safety and containing costs during medical decision-making.

The number of hypoglycemic events during the post-index period also decreased significantly (OR 0.40, 95% CI 0.27–0.61, $p<0.05$); this reduction, in parallel to the results for MPR and health care costs, was found to be higher than the previously reported [52] OR of 0.50 (95% CI 0.37–0.68, $p<0.05$). The utilization of specific health care resources associated with hypoglycemic events declined: emergency department visits (OR 0.36, 95% CI 0.16–0.84, $p<0.05$) as well as physician visits (OR 0.39, 95% CI 0.20–0.77, $p<0.05$). However, no significant change was noted in hypoglycemia-attributable hospitalizations (OR 0.73, 95% CI 0.32–1.67) or outpatient visits (OR 0.42, 95% CI 0.12–1.49), which were mutually exclusive from the emergency department and physician visits. This may be an indication that patients experiencing hypoglycemia severe enough to warrant third-party intervention may be more prone to receive care specifically within the emergency department or from a physician rather than through treatment provided within other hospital units or settings of outpatient care. These outcomes data specific to use of the BIAsp 70/30 pen device may also reinforce its previously documented benefit in hypoglycemia versus human insulin and may provide impetus to further test for causality regarding improved patient-reported treatment preference and satisfaction and a positive impact on adherence [31,32,42,45–48].

The Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit (DARTS/ MEMO) collaborative study found that the presence of inadequately controlled diabetes-related complications is associated with a negative impact in terms of the acute occurrence of hypoglycemia [63]. Similarly, our findings highlight the significantly negative impact that various diabetes-related co-morbidities and complications may have on hypoglycemic events and costs; patients were significantly more likely to experience

hypoglycemia if they had concomitant metabolic disorders (IRR 5.47, 95% CI 3.98–8.29, p<0.05), nephropathy (IRR 3.53, 95% CI 2.19–5.12, p<0.05), cardiovascular events (IRR 1.77, 95% CI 1.12–3.06, p<0.05), or neuropathy (IRR 1.93, 95% CI 1.27–3.18, p<0.05). Note that although not statistically significant, post-index hypoglycemic event occurrences were lower among subjects who received analog insulin in the pre-index period compared with those who received human insulin.

T2D has a well-established and progressive correlation with many long-term complications, such as dysfunction or failure of the peripheral nerves, vision, and the renal and cardiovascular systems [64,65]. Increased and suboptimally controlled plasma glucose level is a strong indicator of increased risk for these complications [4,8]; however, monitoring patient self-management and hypoglycemia, not only A1C values, should constitute an essential component to diabetes care. Although the present analysis did not evaluate A1C laboratory values as an outcome measure, and therefore no conclusions can be made regarding glycemic control for this study group, previous research suggests that improvements in treatment adherence are significantly correlated to improved glycemic control [66,67] and that this may considerably ameliorate complication events, increased resource utilization, and the financial consequences of T2D [49–51], particularly related to hypoglycemia and hospitalizations. As such, the results in this analysis demonstrating a correlation between increased MPR and reduced hypoglycemia may be hypothesis-generating for future research evaluating a causal relationship between treatment adherence and A1C, data that would represent an important contribution to managing T2D.

Hypoglycemia, one of the primary obstacles to successfully controlling diabetes, is a potentially serious complication that is most often associated with insulin and insulin secretagogues, and may discourage providers from starting more intensive therapy [68,69]. Large epidemiologic studies such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that intensive diabetes care, particularly with insulin, although providing significant improvements in glycemic control, is associated with increased rates of hypoglycemia [70,71]. Without the inclusion of A1C as an outcome measure in the results of the present analysis, it is not possible to conclude whether the reduction in hypoglycemia observed in patients converting to the BIAsp 70/30 pen was correlated to or independent of A1C; however, the possibility exists that a reduction in hypoglycemia was associated with elevated A1C levels (loss of glycemic control). Nevertheless, reductions in hypoglycemic events and the potential benefits therein on health-related quality of life may lead to a reduction in the ensuing fear of recurrent hypoglycemia [72], which may facilitate a greater likelihood of sustained adherence and tighter glycemic control over the course of long-term management of T2D. This too, however, requires further research and confirmation.

Symptoms and levels of severity of hypoglycemia can vary considerably from patient to patient, potentially leading to unreported or unidentified occurrences of the condition [68,69,73]. The coded hypoglycemic events in the claims data used to estimate resource utilization in the present analysis were likely to be of a more severe nature, as some

patients may either not detect or have a higher tolerance for the effects of minor events, which may therefore not require a third party and go unreported. An MPR value of 80% or greater was associated with fewer hypoglycemic events (IRR 0.36, 95% CI 0.11–0.76, $p<0.05$). This result is very similar to that previously observed [52], thereby reinforcing the possible association between improved adherence and reduced hypoglycemia over an annually adjusted time period.

A reduction in diabetes-attributable pharmacy costs in association with an increased level of adherence after conversion to the BIAsp 70/30 pen device was observed, although a significant increase was seen in the contribution that total insulin costs had to overall diabetes-attributable pharmacy costs over time (from 56.0% to 72.0%). It may be noteworthy that beneficiaries' diabetes-attributable pharmacy costs analyzed here were the actual reimbursed amount and that it was not possible to ascertain manufacturer rebates. Future research on the impact of disparities in copayment and rebate levels as they pertain to received health care benefit designs and health economic outcomes may help further create efficiencies and equality in access to care. Nonetheless, the cost for oral anti-diabetic drugs in the present analysis was significantly reduced by $772/patient/year, which was higher than the $664 observed in the more generalized pen cohort [52]. This cost reduction may be an indication that the association between improved MPR and, subsequently, improved short-term outcomes (hypoglycemia) may have led physicians treating patients in the study group to reduce the prescribed number, strength, or daily dose of oral anti-diabetic drugs. It is also equally possible, however, that providers chose to reduce dosing or to discontinue oral anti-diabetic drugs in the post-index period due to changes in treatment protocols, incident co-morbid conditions, or other unidentifiable reasons, or to simply reduce patient copayments or pill burden.

As mentioned, one important factor to be considered when interpreting the results of the current study is the impact that patient copayments or other financial barriers to accessing pen devices, including prior authorization, may have had [74–76]. Given the evidence that less favorable tier assignment may induce suboptimal adherence [19], and the fact that insulin analogs and pen devices are typically placed on less favorable managed care formulary tiers compared with human insulin and insulin vials, the finding of improved MPR despite a likely increase in cost-sharing after conversion to pen therapy may be particularly noteworthy [76]. Consideration of the level of cost-sharing to the patient (i.e., drug copayment) might also highlight in more detail a variable impact on adherence and the true pharmacy costs to a third-party payer, and may also provide insight to characteristics of optimal health plan benefit designs in terms of facilitating improved adherence and cost containment for patients with diabetes.

Limitations of MPR and Claims Analyses

Limitations inherent to this and other claims data analyses require mentioning. First, although MPR is well established in the literature as an appropriate measure of treatment adherence, the ability to analyze the continuity of treatment usage with this value is limited. Particularly, when calculating MPR, important aspects in evaluating drug intake such as drug sharing or wastage are notable to be included. Although efforts were made

to reduce potential skewing effects in our calculation of MPR, the drugs in the present analysis are dispensed in disparate volumes (i.e., 10-ml vials and a 15-ml box of pens [3 x 5 ml] per prescription), potentially affecting refill gaps.

Second, although MPR provides insight as to whether a patient was adequately or inadequately in possession of the correct amount of drug, it is not possible to confirm with claims data that patients are correctly or accurately administering their drugs. Third, although efforts were made to use appropriate multivariate analyses to adjust for differences in demographic and clinical characteristics, data on race or income were absent, which may have revealed notable effects on clinical and economic outcomes and resource use. Fourth, although the data source used in this analysis contained a study population that was well-dispersed geographically and covered by a variety of private managed care structures, prudence should be taken in generalizing these results across populations receiving health benefits in other countries or within public health insurance systems, as potentially confounding factors regarding treatment paradigms and access to therapy may be unobserved or missed.

Fifth, data were not available regarding over-the-counter drugs, which may have included testing supplies related to diabetes care. However, whether the requirement for or actual adherence to such resource use would differ between the pre-index and post-index drug therapies is unknown. A sixth limitation may be that although the Poisson and generalized linear model multivariate analyses adjusted for occurrence of pre-index hypoglycemic events and log-transformed pre- and post-index treatment duration, it is not possible to exclude the potential for clinicians to have converted to BIAsp 70/30 pen therapy specifically to ameliorate problems with pre-index hypoglycemia, or that any of the reported benefits were sustained over a longer follow-up period than was observed. Also, with all retrospective claims database analyses, the possibility exists for miscoding of events or for missing data, and thus the potential to either inflate or underestimate any outcomes results. Finally, these study findings are those from a retrospective observational approach, evaluating data from a community practice rather than within a randomized controlled setting. Thus, the data allow examination of associations between patient or treatment variables and outcomes, but limit the ability to draw conclusions regarding causality.

Conclusion

Patients with T2D who receive private health care insurance coverage may exhibit an improvement in treatment adherence and be associated with reductions in the resource use and related costs of treating hypoglycemia after insulin therapy conversion from vial and syringe to a premixed biphasic analog pen device. Facilitating optimal levels of adherence among patients with T2D may be significantly associated with reducing not only the likelihood of hypoglycemia, but also health care costs, particularly through reduced emergency department and physician visits.

Future research is warranted and should address the potential effects that disparate health plan benefit designs may have on health and economic outcomes for patients with

diabetes, while further exploring the potential correlation among improved MPR, reduced hypoglycemia, and A1C laboratory values.

References

1. Centers for Disease Control and Prevention. National diabetes fact sheet, United States 2005. Available from http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf. Accessed September 12, 2006.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; **27**:1047–53.
3. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The third national health and nutrition examination survey (NHANES) 1988–1994. Diabetes Care 1998; **21**:518–24.
4. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; **321**:405–12.
5. Brown JB, Pedula KL, Bakst AW. The progressive cost of complications in type 2 diabetes mellitus. Arch Intern Med 1999; **159**:1873–80.
6. Menzin J, Langley-Hawthorne C, Friedman M, Boulanger L, Cavanaugh R. Potential short-term economic benefits of improved glycemic control: a managed care perspective. Diabetes Care 2001; **24**:51–5.
7. Wagner EH, Sandhu N, Newton KM, McCulloch DK, Ramsey SD, Grothaus LC. Effect of improved glycemic control on health care costs and utilization. JAMA 2001; **285**:182–9.
8. United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; **352**:837–53. (Erratum in Lancet 1999;354:602.)
9. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; **329**:977–86.
10. Stephens JM, Botteman MF, Hay JW. Economic impact of antidiabetic medications and glycemic control on managed care organizations: a review of the literature. J Manag Care Pharm 2006; **12**:130–42.
11. Jonsson L, Bolinder B, Lundkvist J. Cost of hypoglycemia in patients with type 2 diabetes in Sweden. Value Health 2006; **9**:193–8.
12. Heaton A, Martin S, Brelje T. The economic effect of hypoglycemia in a health plan. Manag Care Interface 2003; **16**:23–7.
13. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999–2002: the national health and nutrition examination survey. Diabetes Care 2006; **29**:531–7.
14. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2004; **27**(suppl 1):S15–35.

15. Spann SJ, Nutting PA, Galliher JM, et al. Management of type 2 diabetes in the primary care setting: a practice-based research network study. Ann Fam Med 2006; **4**:23-31.
16. Saadinne JB, Cadwell B, Gregg EW, et al. Improvements in diabetes processes of care and intermediate outcomes: United States, 1988–2002. Ann Intern Med 2006; **144**:465–74.
17. Hartz A, Kent S, James P, Xu Y, Kelly M, Daly J. Factors that influence improvement for patients with poorly controlled type 2 diabetes. Diab Res Clin Pract 2006; **74**:227–32.
18. American Diabetes Association. Standards of medical care in diabetes: 2006. Diabetes Care 2006; **29**(suppl 1):S4–42. (Erratum in Diabetes Care 2006; **29**:1192.)
19. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. Manag Care Interface 2006; **19**:31–41.
20. Marre M. Before oral agents fail: the case for starting insulin early. Int J Obes Relat Metab Disord 2002;26(suppl 3):S25–30.
21. Rolla AR, Rakel RE. Practical approaches to insulin therapy for type 2 diabetes mellitus with premixed insulin analogues. Clin Ther 2005; **27**:1113–25.
22. American Association of Clinical Endocrinologists, American College of Endocrinology. Medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management—2002 update. Endocr Pract 2002; **8**(suppl 1):40–82.
23. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes [simultaneous publication]. Diabetologia 2006; **49**:1711–21 and Diabetes Care 2006; **29**:1963–72. (Erratum in Diabetes Care 2006; **49**: 2816–18.)
24. Campbell RK. Update on insulin injection devices. Available from http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/may00insulin.cfm&pub_id=8&article_id=52 0. Accessed September 13, 2006.
25. Korytkowski M, Niskanen L, Asakura T. FlexPen: addressing issues of confidence and convenience in insulin delivery. Clin Ther 2005; **27**(suppl B):S89–100.
26. Coonrod BA. Insulin syringes and pens: finding the best match for your patients' needs. Clin Diabetes 1997; **15**:114–20.
27. Asakura T, Seino H. Assessment of dose selection attributes with audible notification in insulin pen devices. Diabetes Technol Ther 2005; **7**:620–6.
28. Albrecht G, Hoogstraten J. Satisfaction as determination of compliance. Community Dent Oral Epidemiol 1998; **26**:139–46.
29. Hogan P, Dall T, Nikolov P, for the American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. Diabetes Care 2003; **26**:917–32.
30. Anderson RT, Marrero D, Skovlund SE, Cramer J, Schwartz S. Self-reported compliance with insulin injection therapy in subjects with type 1 and 2 diabetes [abstract]. Diabetologia 2003;46(suppl 2):A275.
31. Korytkowski M, Bell D, Jacobsen C, Suwannasari R, for the FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional

vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clin Ther 2003; **25**:2836–48.
32. Niskanen L, Jensen LE, Rastam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. Clin Ther 2004; **26**:531–40.
33. Stockl K, Ory C, Vanderplas A, et al. An evaluation of patient preference for an alternative insulin delivery system compared to standard vial and syringe. Curr Med Res Opin 2007; **23**: 133–46.
34. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther 2004; **26**:1498–505.
35. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version ll) among outpatient pharmacy consumers. Value Health 2005; **8**(suppl 1):S9–24.
36. Clark C, Snyder JW, Meed RL, Stutz LM, Parkin CG. A systematic approach to risk stratification and intervention within a managed care environment improves diabetes outcomes and patient satisfaction. Diabetes Care 2001; **24**:1079–86.
37. Weijman I, Ros WJ, Rutten GE, Schaufeli WB, Schabracq MJ, Winnubst JA. Frequency and perceived burden of diabetes selfmanagement activities in employees with insulin-treated diabetes: relationships with health outcomes. Diabetes Res Clin Pract 2005; **68**:56–64.
38. Anderson RT, Skovlund SE, Marrero D, et al. Development and validation of the insulin treatment satisfaction questionnaire. Clin Ther 2004; **26**:565–78.
39. Graff MR, McClanahan MA. Assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. Clin Ther 1998; **20**:486–96.
40. Sucic M, Galic E, Cabrijan T, et al. Patient acceptance and reliability of new Humulin/Humalog 3.0 mL prefilled insulin pen in ten Croatian diabetes centres. Med Sci Monit 2002; **8**:PI21–6.
41. Kadiri A, Chraibi A, Marouan F, et al. Comparison of NovoPen 3 and syringes/vials in the acceptance of insulin therapy in NIDDM patients with secondary failure to oral hypoglycaemic agents. Diabetes Res Clin Pract 1998; **41**:15–23.
42. Rubin RR, Peyrot M. Quality of life, treatment satisfaction, and treatment preference associated with use of a pen device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. Diabetes Care 2004; **27**:2495–7. (Erratum in Diabetes Care 2004; **27**:3032.)
43. Albano S, for the Orbiter Study Group. Assessment of quality of treatment in insulin-treated patients with diabetes using a pre-filled insulin pen. Acta Biomed Ateneo Parmense 2004; **75**:34–9.
44. Testa M. Improving diabetes therapy: improving satisfaction. Diabetes Voice 2003; **48**:23–5.
45. Raskin P, Allen E, Hollander P, for the INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005; **28**:260–5.
46. Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. Diabet Med 2002; **19**:393–9.

47. Hermansen K, Colombo M, Storgaard H, Ostergaard A, Kolendorf K, Madsbad S. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. Diabetes Care 2002; **25**:883–8.
48. Mortensen H, Kocova M, Teng LY, Keiding J, Bruckner I, Philotheou A. Biphasic insulin aspart vs human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. Pediatr Diabetes 2006; **7**:4–10.
49. Hepke KL, Martus MT, Share DA. Costs and utilization associated with pharmaceutical adherence in a diabetic population. Am J Manag Care 2004; **10**:144–51.
50. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and health care cost. Med Care 2005; **43**:521–30.
51. Bullano MF, Al-Zakwani IS, Fisher MD, Menditto L, Willey VJ. Differences in hypoglycemia event rates and associated cost-consequence in patients initiated on long-acting and intermediate-acting insulin products. Curr Med Res Opin 2005; **21**:291–8.
52. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. Clin Ther 2006; **28**:1712–25.
53. U.S. Department of Health and Human Services, Office for Civil Rights. Health insurance portability and accountability act. Available from http://www.hhs.gov/ocr/hipaa/. Accessed November 14, 2006.
54. Meissner B, Dickson M, Shinogle J, Reeder CE, Belazi D, Senevirante V. Drug and medical cost effects of a drug formulary change with therapeutic interchange for statin drugs in a multistate managed Medicaid organization. J Manag Care Pharm 2006; **12**:331–40.
55. Krasuski RA, Doeppenschmidt D, Henry JS, et al. Conversion to atorvastatin in patients intolerant or refractory to simvastatin therapy: the CAPISH study. Mayo Clin Proc 2005; **80**:1163–8.
56. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid lowering medications: a cross-national study. JAMA 1998; **279**:1458–62.
57. Lawrence M, Guay DRP, Benson SR, Anderson MJ. Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a population analysis. Pharmacotherapy 2000; **20**:470–5.
58. Li J, McCombs JS, Stimmel GL. Cost of treating bipolar disorder in the California Medicaid (Medi-Cal) program. J Affect Disord 2002; **71**:131–9.
59. Moulton BR. Random group effects and the precision of regression estimates. J Econom 1986; **32**:385–97.
60. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. Psychol Bull 1995; **118**:392–404.
61. Long J. Regression models for categorical and limited dependent variables. Thousand Oaks, CA: Sage Publications; 1997.
62. U.S. Department of Labor, Bureau of Labor Statistics. Consumer price index. Available from http://www.bls.gov/cpi/home.htm. Accessed September 14, 2006.
63. Morris AD, Boyle DI, McMahon AD, et al, for the DARTS/MEMO Collaboration (Diabetes Audit and Research in Tayside Scotland Medicines Monitoring Unit).

Adherence to insulin treatment, glycemic control, and ketoacidosis in insulin-dependent diabetes mellitus. Lancet 1997; **350**:1505–10.
64. Gaster B, Hirsch IB. The effects of improved glycemic control on complications in type 2 diabetes. Arch Intern Med 1998; **158**:134–40.
65. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med 1993; **328**:1676–85.
66. Rhee MK, Slocum W, Ziemer DC, et al. Patient adherence improves glycemic control. Diabetes Educ 2005; **31**:240–50.
67. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care 2002; **25**:1015–21.
68. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003; **26**:1902–12.
69. Cryer PE, Childs BP. Negotiating the barrier of hypoglycemia in diabetes. Diabetes Spectrum 2002; **15**:20–7.
70. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR, for the U.K. Prospective Diabetes Study Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. prospective diabetes study (UKPDS 57). Diabetes Care 2002; **25**:330–6. (Erratum in Diabetes Care 2002; **25**:1268.)
71. The Diabetes Control and Complication Trial Research Group. Hypoglycemia in the diabetes control and complications trial. Diabetes 1997; **46**:271-86.
72. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin 2006; **22**:1523–34.
73. Cefalu CA, Cefalu WT. Controlling hypoglycemia in type 2 diabetes: which agent for which patient? J Fam Pract 2005; **54**:855–62.
74. Bishop G. One states's Medicaid managed care formulary operations: A look at Pennsylvania, 2001-2002. March 2005. Kaiser Family Foundation. Available from http://www.kff.org/medicaid/upload/One-State-s-Medicaid-Managed-Care-Formulary-Operations-A-Look-at-Pennsylvania-2001-2002-Report.pdf#search='Gene%20Bishop%2C%20MD.%20One%20State%27s%20Medicaid%20Managed%20Care%20Formulary%20Operations%3A'. Accessed September 17, 2006.
75. Fleming T, ed. Red book: pharmacy's fundamental reference. Montvale, NJ: Thomson PDR, 2005.
76. Goldman DP, Joyce GF, Escarce JJ, et al. Pharmacy benefits and the use of drugs by the chronically ill. JAMA 2004; **291**:2344–50.

Chapter 8

Correlating self-management, perceptions of care, and health economic outcomes

Adapted from: Cobden D, Niessen LW, Rutten FFH, Barr CE, Redekop WK. Relationships among Self-Management, Patient Perceptions of Care, and Health Economic Outcomes for Decision-Making and Clinical Practice in Type 2 Diabetes. *Value in Health*. 2010 Jan/Feb; 13(1): 138-47.

Summary

Type 2 diabetes (T2D) treatment involves complex interactions between biological, psychological and behavioral factors of care, requiring multifaceted efforts in clinical practice and disease management to reduce health and economic burdens. We aimed to quantify correlations amongst these factors and characterize their level of inclusion in economic analyses that are part of informed medical decision-making. A comprehensive, stepwise systematic literature review was performed on published articles dated 1993-2008 using medical subject heading and keyword searches in electronic reference libraries. Data were collected using standardized techniques and were analyzed descriptively.

A total of 97 manuscripts fulfilling all inclusion criteria were reviewed, including 16 on economic models (17% of articles). Most studies were retrospective (41/97; 42%) and from managed care perspectives (66%). Oral anti-diabetic drugs were a central focus, appearing in 83% of studies. Behavioral factors, particularly medication adherence and persistence, are well-researched (n=65) and may influence diabetes outcomes, cardiovascular risk, mortality rates, and treatment-specific resource use (eg, hospitalizations) and costs (≤ $3400 annually per patient). However, they are absent from current economic models.

Strong correlations exist between patient behaviors, perspectives of care, health outcomes and costs in T2D. Their inclusion in pharmacoeconomic modeling, notably the influence on clinical effectiveness of variation in self-management between treatments, should ultimately lead to more accurate estimates of comparative cost-effectiveness, and thereby improve value-based resource allocation and patient access to appropriate therapy.

Introduction

The health and economic burden of Type 2 diabetes (T2D) is rapidly growing in rural, urban, developing and industrialized nations alike. Costs doubled in India from 1998 to 2005 [1], rose 395% in the U.S. over the last decade [2,3] and are projected to exceed $550 billion in China by 2015 [4]. Lifestyles, dietary choices and ageing populations have contributed to a 400% increase in number of diagnoses among adolescents to the elderly [5,6,7,8]. This trend will likely continue: U.S. prevalence is estimated to triple by 2050 (to 50 million patients) [5], and prevalence and costs in the U.K. are projected to increase 20-30% and 40-50%, respectively, in the near future [6].

Payers and policymakers have aggressively responded to this crisis through disease management and reimbursement reform [9], where pharmacy benefits are a common focal point for cost containment [10]. Although adjusting formularies and increasing copayments can lead to short-term cost savings [11], this may jeopardize patient acceptance of prescribed therapy, resulting in poor clinical outcomes and higher costs over the long-term [10,12-14]. The difficulty of minimizing costs while maximizing clinical effectiveness has broadened the definition of value in healthcare and led to

mainstream use of economic models, particularly in evaluating diabetes and other chronic diseases [15,16].

Diabetes economic models traditionally employ data from large clinical trials and epidemiological studies to calculate disease progression and future costs. These have historically been driven by: (1) biological/clinical parameters (eg, HbA_{1c} change, complication risks) [17] and (2) treatment- and demographic-specific effects (to estimate the cost-effectiveness of competing therapies in defined populations) [18]. However, biological/clinical mechanisms alone may explain as little as 6-8% of variation in resource use and costs among T2D patients, leaving potential for large margins of uncertainty to exist in current economic evaluations [19,20,21]. Despite increased use of models to inform disease management, most patients are still not achieving target HbA_{1c}, indicating the need to conduct economic evaluations that more accurately predict what will actually happen in real-world clinical practice [5,22].

One worthwhile focus to achieving this goal can be found in psychological and behavioral patient factors, namely self-management and perceptions of care. These factors have been defined in terms of (1) medication adherence and persistence, and (2) satisfaction, preferences, psychological wellbeing, and related patient-reported outcomes (PROs) [23,24]. Various studies have observed that these factors can affect metabolic control, hypoglycemia, diabetes-related resource use and healthcare costs [25-28].

The primary aim of this study was to review the literature regarding the clinical and economic impact of correlations between psychological and behavioral factors of care among T2D patients. Furthermore, we examined the extent to which these factors have been included in T2D economic models to date.

Methods

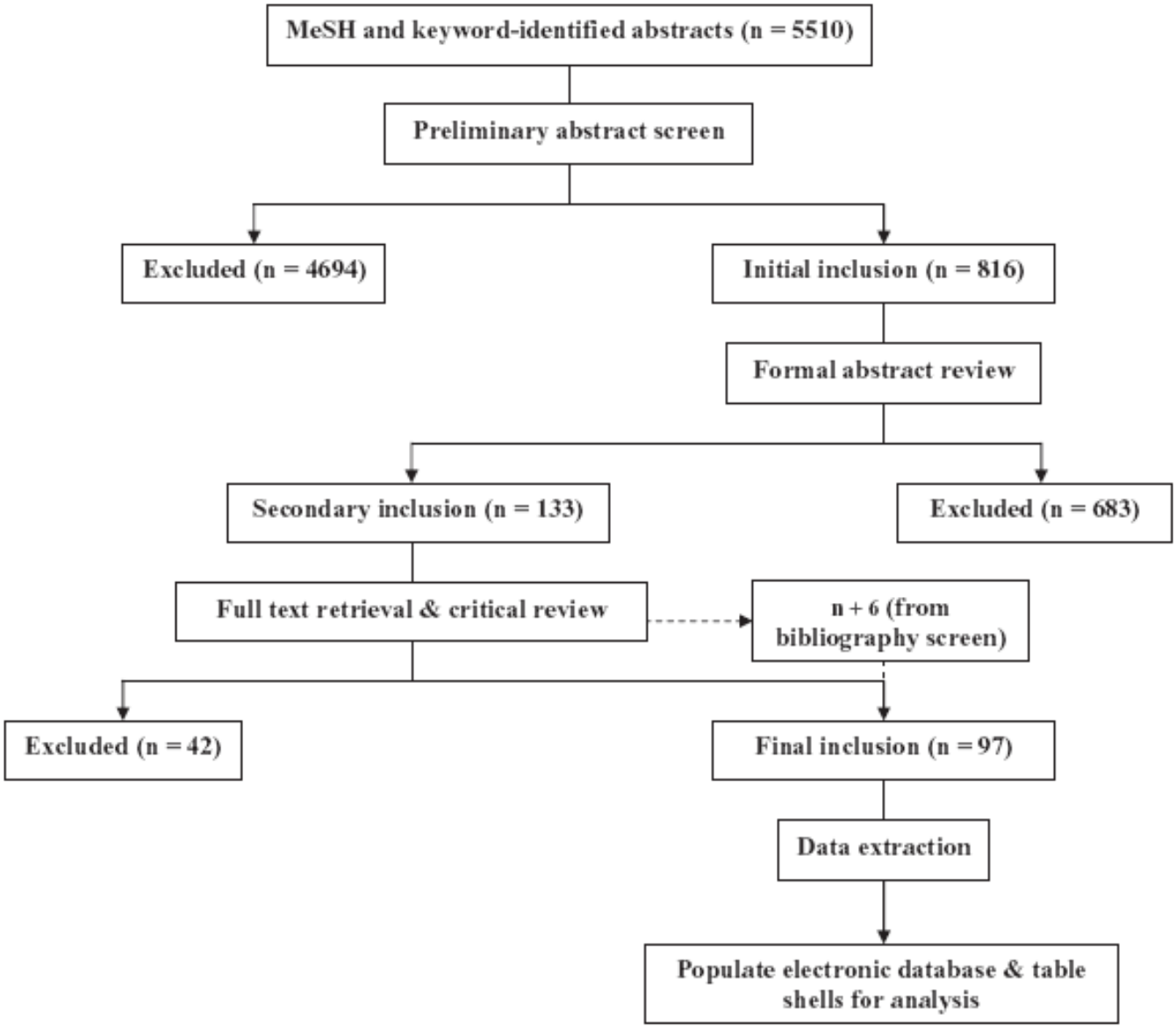
Data Sources

We performed a comprehensive systematic literature review based on standard methodology [29] among published, peer-reviewed articles in electronic reference libraries (EMBASE, MEDLINE (PubMed) and CENTRAL). Article bibliographies were searched for references that were undetected electronically.

Search Strategy

A four-step approach was taken (see Figure 1): (1) preliminary screening of articles, (2) formal abstract review, (3) full-text retrieval with bibliography screen and (4) manuscript critique with population of table shells in electronic databases. Each paper was evaluated independently by a trained researcher.

Figure 1. Stepwise literature search strategy



We examined the impact of the following psychological and behavioral factors on clinical and economic outcomes:

- self-management
- patient perceptions of care
- direct and indirect correlations of these factors

Rigid inclusion criteria on study populations, content matter and formatting were applied (see Table 1). Studies were required to satisfy all criteria.

Table 1. Article selection criteria

Subject matter
Population: must have sole or predominant focus on type 2 diabetes (T2D) patients
First objective: must analyze ≥2 measures of the following: self-management, clinical outcomes, resource use, economics, satisfaction, preferences, and psychological well-being
Patient-reported outcomes: must be captured by self- or proxy-administered questionnaire
Second objective: must fully detail the structure, input variables, and application of economic modeling in T2D patients
Study designs: randomized controlled or noncontrolled observational; must include comparative assessment (crossover or parallel) of T2D treatment or other health-care intervention (vs. competing regimen, other intervention, and/or placebo)
Formatting features
For economic models: only primary publications included (for those with multiple published applications)
Articles published between January 1993 and April 2008
Limited to predefined MeSH and keyword terms
Peer-reviewed, indexed journal articles only (exclusion of gray literature, book chapters)
Applied analysis required (exclusion of methods-only and review-only articles)
English language only

Applied MeSH terms were: “Type 2 diabetes mellitus” combined with “patient compliance” or “economics” or “treatment costs” or “decision modeling” or “patient acceptance of healthcare” or “aversion therapy” or “treatment failures” or “medication self” or “patient satisfaction” or “patient preference” or “quality of life” or “self management”.

Free text keyword combinations were: “Type 2 diabetes” combined with “therapy conversion” or “adherence” or “persistence” or “compliance” or “MPR” or “patient-reported outcomes” or “treatment satisfaction” or “wellbeing” or “economic model” or “therapy switch” or “treatment substitution” or “therapy conversion” or “treatment alteration” or “therapy burden” or “treatment addition” or “therapy replacement” or “treatment modification”.

Data Extraction & Critical Appraisal

Electronic data tables captured relevant information. Pre-defined metrics were populated concurrently alongside critique of individual articles (see Table 2).

Table 2. Metrics of data collection

All studies
Publication date
Research design
Study setting
Data source
Population source
Therapeutic intervention(s)
Follow-up length
Primary and secondary outcome measure(s)
Summary of economic impact of primary or secondary outcome measure(s)
Summary of main results and conclusions
Economic models
Model type (structure/design)
Base-case time horizon
Presence of treatment modification as input variable(s) (*yes/no*)
Incorporation of patient perceptions as input variable(s) (*yes/no*)
Application of self-management variable(s) (*yes/no*)

Data Analysis

Descriptive statistics were calculated to aggregate and report main attributes of reviewed articles. The substantial heterogeneity of research designs, populations and outcome measures found in collected articles precluded formal meta-analysis.

Results

Initial searches generated over 5500 candidate abstracts. After eliminating duplicates and screening for general subject matter, 816 studies were entered into a master reference database. Formal abstract review applying all content and formatting criteria resulted in the selection of 133 full articles. A search of references within these 133 articles yielded 6 additional references, raising the total to 139 manuscripts. A second critique (formal review of 139 manuscripts) yielded 97 articles satisfying all criteria. Most excluded studies were disqualified by lacking correlations of multiple (≥ 2) measures of interest or because therapeutic interventions were not explicit.

Table 3. Breakdown of characteristics for full-text articles (n = 97)

Parameter	n	% of articles
Study type		
Prospective clinical	19	19.6
Retrospective outcomes	41	42.3
Cross-sectional	21	21.6
Modeling analysis	16	16.5
Main population source		
Clinical trial	19	19.6
Managed/community care	64	66.0
Academic medical center	11	11.3
Multinational	3	3.1
Data source*		
Medical charts/clinical forms	30	30.1
Administrative claims	25	25.8
Patient questionnaire	47	48.5
Therapeutic intervention*		
Insulin (vial/syringe)	72	74.2
Insulin (device)	13	13.4
Oral antidiabetic drugs	80	82.5
Oral + insulin combination	70	72.2
Follow-up period†		
<6 months	9	9.3
6–12 months	35	36.1
>12 months	16	26.7
Outcome variables analyzed*		
Adherence/Persistence	65	67.0
Resource use	41	42.3
Costs	35	36.1
Health event rates	35	36.1
Clinical lab values	50	51.6
Satisfaction/Preference/Well-being	31	32.0
Treatment burden/intensity	35	36.1
Publication date		
1993–1997	2	2.1
1998–2002	19	19.6
>2002	76	78.4

*Not mutually exclusive per article.
†Cross-sectional and economic modeling studies excluded.

Psycho-behavioral factors of T2D

We evaluated psychological and behavioral factors as follows:

- self-management: *medication adherence; treatment persistence*
- patient perceptions of care: *treatment satisfaction; psychological wellbeing; preferences*

Medication adherence or persistence was analyzed in 67% of articles (n=65) across treatment groups, primarily in observational/uncontrolled settings and defined by medication possession ratio (MPR; for adherence) and treatment duration/continuation (for persistence).

Patient perceptions of care were addressed in 31 articles (32%), usually captured with validated PRO instruments. Correlations involving treatment modification and economic or clinical outcomes occurred in 36% of articles (n=35), and correlations among 3 or more psychological and behavioral factors were analyzed in 27 papers (28%).

Medication Adherence

Thirteen articles measuring self-management correlated adherence with costs or resource use, nearly all retrospectively using medical records or administrative claims data. Although adherence was measured in numerous ways, including prospectively and cross-sectionally via questionnaire and electronic monitoring, calculating MPR (describing the proportion of days in possession of prescribed medication) was most common. Cutoff levels > 80% were frequently used to define optimal adherence.

Twenty articles demonstrated statistically significant, inverse correlations between adherence and glycemic or cardiovascular outcomes. Poor adherence has been associated with up to a 3.4% rise in HbA_{1c}. Conversely, optimal adherence promotes a greater likelihood of achieving target HbA_{1c}; patients achieving an $HbA_{1c} \leq 7\%$ on oral anti-diabetic drugs (OADs) have averaged 15% greater adherence (vs. patients > 7% HbA_{1c}) [30,31], and may achieve 0.1% absolute HbA_{1c} reductions for every 10% relative increase in adherence [24]. Amongst patients whose initial HbA_{1c} is above target, up to 8% more patients who maintain good adherence (vs. poor) may reach $HbA_{1c} \leq 7\%$ within 6 months [32]. Additionally, increased adherence to diabetes medications over 2 years may contribute to LDL cholesterol reductions (-12.4 mg/dl) and likelihood of improved hypertension (by 56-60%) [33,34], although it remains unclear the extent to which increased adherence to OADs and insulin may individually have on cardiovascular outcomes.

Additional studies where patients were stratified into levels of adherence found that those with optimal adherence show a greater reduction in HbA_{1c} (by up to 1.4%) than patients with poor adherence [35]. Incrementally, 10-25% relative increases in drug adherence over 1 year may decrease HbA_{1c} by 0.05-0.2% among indigent, minority and caucasian

populations alike [36-38]. The ability to achieve glycemic control through treatment intensification/positive clinical inertia may depend on – or at least be predicted by – the degree of adherence to previous medication [39]. Insulin users with an MPR > 80% had a 0.7% lower mean HbA_{1c} (6.6% vs. 7.3%) than insulin users with an MPR < 80%. In addition, insulin users with an optimal MPR also showed 30% greater adherence to cardiovascular medication [40,41]. Among highly uncontrolled patients, adherent patients may reduce HbA_{1c} by 2.1% more (11.2% to 8.3%; $p<0.01$) than non-adherent (11.4% to 10.6%; p=*NS*) after 1 year; 84% of those who reduced HbA_{1c} > 2% were in the adherent group [42].

Other studies correlated MPR for T2D medications with major hypoglycemia and cardiovascular outcomes (comprehensive BP, CHF and LDL cholesterol) [25,26,43]. Two studies, one a prospective clinical trial, also examined the relationship between risk of mortality and adherence among T2D patients. The chance of death was 81% higher amongst patients with poor adherence [43], and patients with physician-rated "very bad" adherence had 2.7 times higher risk of mortality than patients with "rather good" or "very good" adherence [44].

Three studies highlighted the importance of optimal T2D medication adherence in comparison to other chronic diseases. Diabetes adherence may significantly influence annual healthcare costs and risk for hospitalization (by 2.5 fold), whereas adherence to cardiovascular medication for hypertension, dyslipidemia and heart failure may not [45,46]. Furthermore, a 10% decline in adherence to OADs may increase HbA_{1c} (by 0.14%) and LDL cholesterol (by 4.9 mg/dl), whereas adherence to ACE-inhibitors may not significantly affect clinical outcomes [47].

Numerous studies have examined the possible impact of adherence on resource use and costs (see Table 4). One reported that after 1 year, patients were more adherent to OADs versus insulin, requiring fewer physician visits and incurring 35% lower hospitalization costs, 18% lower total healthcare costs and 25% lower T2D-related costs [48]. Another study stratified patients according to MPR and also found that higher MPR levels were associated with lower costs: patients with an MPR < 75% incurred the highest annual patient costs ($5706), patients with an MPR of 75-95% incurred $5314, and patients with an MPR > 95% incurred the lowest costs ($4835) [49]. It was reported that each 20% increase in adherence may contribute to an approximate $1500 reduction in costs [45]. Similarly, 8.6% to 28.9% decreases in annual costs were found for every 10% MPR increase for OAD-treated patients [50], although studies in minority populations suggest only a 2% reduction in healthcare costs for the same degree of MPR improvement [36,51].

This correlation between MPR and costs appears true for insulin regimens as well. An 8% increase in MPR during conversion to pen devices from a vial/syringe may be associated with $1400 and $1800 annual reductions in T2D-related and overall healthcare costs, respectively. These cost differences were primarily attributed to 56% and 61% drops in emergency room and physician visits, respectively, and patients having an MPR

> 80% experienced fewer hypoglycemic events (by 67%) and incurred lower total costs (by 45%) [25,26].

Table 4. The economic impact of between-treatment differences in diabetes medication adherence

	Annual adherence difference range (%)	Annual cost ($) impact range	References
One or more OAD(s)	5–13	200–3263	[49–56]
Insulin with/without OAD(s)	6–20	721–3421	[25,26,47,96,99]

OAD, oral antidiabetic drug.

Treatment Persistence

Ten articles (10.3% of total) analyzed persistence to therapy, defined as treatment duration without modification, or rate of discontinuation.

Treatment attributes were found to influence persistence. Based on 352,955 patient days of follow-up, higher dosing of anti-diabetic medications predicted early discontinuation by up to 2 fold, and patients initiating therapy through self-injection (insulin monotherapy) versus an OAD were 33% less persistent over 1 year, and up to 3 times more likely to be non-persistent (OR 3.00 [95% CI: 2.30-3.91]) [52]. In contrast, treatment by an endocrinologist may predict greater persistency, and patients may exhibit an 8-9% increase in OAD persistence with use of extended-release tablets and/or once-daily dosing versus twice-daily administration [53,54]. Regardless of treatment, however, OAD persistence decreases consistently after 1 year (by about 50%) and varies widely, ranging from 31% to 65% [52,55]. Similarly, low rates of persistency have been reported for insulin use, at 32% over a 12 month period [52].

Several studies illustrated the economic impact of persistence. One analyzed a U.S. Medicaid population to reveal that 10% greater persistence in OAD patients may reduce annual healthcare costs by 16% [56]. Long-term assessment of these patients revealed that a 4% increase in persistency may reduce annual costs by up to 20% [57]. Another demonstrated that improved persistency may improve HbA_{1c}, and reduce sick days and costs by $1200-1800 per patient [58]. However, persistency and costs are not always inversely related; short-term cost reductions can occur in non-persistent patients inasmuch as they do not use/seek treatment [59].

Additional research links persistency to psychological wellbeing; 23% of depressed T2D patients discontinue, switch or augment therapy, 7% higher than non-depressed [60].

Furthermore, a 6% decrease in OAD persistence was reported to predict onset of depression, and depressed patients (vs. non-depressed) are 72% more likely to modify therapy and 89% more likely to augment OADs, increasing pharmacy costs.

Patient Perceptions of Care

We focused on three primary areas of patient perceptions: treatment satisfaction, psychological wellbeing and preferences. Of the 31 articles that evaluated these outcomes, 23% (n=7) analyzed interrelations of ≥ 3 psychological or behavioral factors.

Treatment Satisfaction

Strong associations were discovered between clinical outcomes and level of satisfaction with treatment attributes and treatment-related health events [24,61,62].

Among 50 patients new to insulin, improved satisfaction correlated with improved HbA_{1c} (-1.43%), lipid profile and frequency of hypoglycemia over 7 months, even as BMI increased (+1.1 kg/m^2) [63]. Extensive analysis of 233 patients in a multi-country randomized controlled trial comparing device and syringe-based insulin revealed that domain-specific and overall treatment satisfaction was highly associated with: (1) reduced HbA_{1c} (-0.4%), (2) achieving target $HbA_{1c} \leq 7\%$, (3) neuropathy, (4) retinopathy, (5) frequency, timing and severity of hypoglycemia, (6) age and (7) weight change (BMI reductions ≥ 2.57 kg/m^2) [23]. Pearson coefficients revealed a statistically significant association between HbA_{1c} and 3 different satisfaction domains, including treatment attributes (device subscale). Additional evidence reaffirms this correlation across diverse geographical locations and populations [64].

Similar to adherence, the correlation between treatment satisfaction and clinical outcomes may partly drive changes in resource utilization. Improved satisfaction has been associated with reduced utilization of emergency room and preventive services by up to 63% [65]. Related analyses demonstrate that increased satisfaction may improve persistence and thereby lower HbA_{1c} [66,67].

Psychological Wellbeing

Of 11 articles focusing on relationships between psychological wellbeing and health economic outcomes, 9 (82%) studied the extent to which depressive symptoms and mental distress were correlated with measures of self-management.

Cross-sectional analysis of 5104 patients and 3827 care providers revealed that poor psychological wellbeing was correlated with suboptimal adherence to preventive treatments [68]. Two studies that together examined over 1000 patients reported similar results: up to 67% of T2D patients may be depressed, and these patients show a 130% increased frequency of missed medication doses per week [69,70]. Furthermore, the prevalence of severe/major depression in T2D patients may range from 19-33%, and may

have a particularly strong impact on medication adherence in male and minority populations [71,72].

Two studies demonstrate that increasing severity of depressive symptoms incrementally affects adherence to both preventive and later-stage therapies [73,74]. These studies also found that elevated depression may reduce adherence by 8%, increase the use of emergency department and specialty care services, and increase primary care, ambulatory and total healthcare costs by 51%, 75% and 86%, respectively.

Depressive symptoms may also affect T2D progression through inadequate glucose control and increased BMI due to an inability or unwillingness to maintain adherence [75,76]. Interestingly, psychological distress may even account for greater variation in long-term and transient glycemic control than biological mechanisms [77]. For patients with substantially elevated HbA_{1c}, restoration of glycemic control may actually improve psychological wellbeing [78].

Patient Preference

The impact of choice and acceptance of treatments, which varies considerably in T2D [79], was reviewed in 4 studies.

A randomized, crossover clinical trial evaluating insulin devices showed that differences in patient preference and stated desire to continue treatment were important factors in reducing HbA_{1c} [80]. Observational analysis of 445 T2D patients revealed that medication side effects may significantly reduce patient preference for treatment and result in non-adherence [81]. An additional study utilized willingness-to-pay methodology to correlate T2D preferences to economic outcomes, illustrating that preference was a strong indicator of likely future adherence and pharmacy costs [82]. Another found massive preference among elderly patients for an insulin injection device versus vial/syringe (82% vs. 18%), which was associated with a reduced need for nursing/caregiver assistance and an average daily cost savings of approximately $80 [83].

Current T2D Economic Models

Sixteen articles described the structure of T2D-related economic models (Table 5). Most modeling approaches are recent (70% developed after 2002) and have been used to evaluate the cost-effectiveness of OADs. Considerable diversity exists, but there is a fairly even distribution between model types: 6 models (38%) primarily involve simulations with regression-weight risk equations validated against randomized controlled trials or large epidemiological studies, 3 employ linear-state transitions (eg, decision-analysis), and the remaining 7 are open-state transition models (e.g., recurrent and/or inter-linked Markov states).

Table 5. Characteristics of type 2 diabetes economic modeling assessments (n = 16)

Parameter	n	% of models
Central model design		
Equation-based simulation (algorithmic)	6	37.5
Linear state transition (decision analytic)	3	18.8
Open state transition	7	43.8
Time horizon (base case as default)		
Lifetime	6	37.5
Variable	4	25.0
Short term (≤10 years)	3	18.8
Long term (>10 years)	3	18.8
Primary model drivers/variable components		
Patient demographics	11	68.8
Clinical lab values	16	100.0
Treatment changes	4	25.0
Patient perceptions of care	0	0.0
Self-management (adherence, persistence)	0	0.0
Publication date		
1993–1997	1	6.3
1998–2002	4	25.0
>2002	11	68.8

The time horizons examined in base-case scenarios also varied, although most (38%; n=6) simulated entire patient lifetimes, projecting outcomes until death. Three models (19%) had short-term (≤ 10 years) or long-term (> 10 years) horizons, and the rest (n=10) had no implicit default or intended scenario.

Primary Model Drivers

Input variables were arranged into five categories: (1) patient demographics, (2) baseline and continuous clinical lab values, (3) changes in treatment regimens (modification), (4) patient perceptions of care, and (5) measures of self-management (adherence or persistence).

Most models incorporated demographic factors when projecting outcomes. Clinical lab values, as either intermediate predictive outcomes or absorbing states (ie, achieving target=end simulation), influenced risk adjustment in all models. The majority focused on HbA_{1c}, however, post-meal and fasting blood glucose also appeared as clinical drivers, such as in accounting for patients' ability to reach intermediate dual control (HbA_{1c}+post-meal) [84].

Twenty-five percent (n=4) of models allowed some level of treatment modification, as observed in one short-term (3 year) decision analysis where estimation of outcomes for 1st-line OAD strategies permitted transition to OAD or insulin combinations based on

achieving glycemic control [85]. Other models utilize similar factors such as time-to-impaired glucose tolerance under specified treatments [86,87], or stratifying regimens based on treatment patterns [88]. However, most models apply single, fixed treatments, often over lifetimes.

Patient perceptions of care and measures of self-management were absent as input variables in identified models.

Interventions and Study Types

Sizeable emphasis was placed on OADs, appearing in >80% of modeled applications, at times in combination with insulin (Table 6). For example, the Centers for Disease Control model of T2D progression employs epidemiological risk data to allow choice of simulating insulin or sulfonylurea [86].

Table 6. Identified economic models by therapeutic intervention and study type (n = 16)

	Oral only* n (%)	Oral + insulin* n (%)	Insulin only* n (%)
Cost-effectiveness (life expectancy)*	8 (50.0)	5 (31.3)	5 (31.3)
Cost-effectiveness (clinical outcomes)*	13 (81.3)	10 (62.5)	9 (56.3)
Cost utility*	7 (43.8)	6 (37.5)	5 (31.3)
Cost minimization	2 (12.5)	0 (0)	0 (0)
Cost benefit	0 (0)	0 (0)	0 (0)

*Modeled outcomes and therapeutic applications not always discrete or mutually exclusive.

Overall, cost-effectiveness evaluations were most prevalent (≥80% depending on therapy). Only 2 cost-minimization analyses and zero cost-benefit approaches were identified.

Discussion

We reviewed 97 articles to (1) investigate the clinical and economic impact of correlations between psychological and behavioral factors of care in T2D, and (2) characterize their application in current economic evaluations used to inform medical decision-making. Our results indicate that medication adherence, persistence, treatment satisfaction, patient preferences and psychological wellbeing are interrelated, well-studied and directly or indirectly affect clinical outcomes, health events, resource use and costs. These results suggest that psychological and behavioral factors can play a critical

role in determining the value of healthcare interventions, beyond the impact of biological mechanisms alone.

Relationships between psycho-behavioral factors, and health economic outcomes are multifaceted throughout stages of treatment and disease progression, and studies have often analyzed them in triplets, with one factor mediating relationships between the other two. For example, patient willingness to self-manage may be explained by satisfaction with or preference for treatment, which is influenced collectively by that treatment's attributes and biological response. These attributes may include actual and perceived efficacy (e.g., HbA_{1c}, BMI), side effects (e.g., hypoglycemia, neuropathy, weight gain), device usability, route and frequency of administration, and dosage.

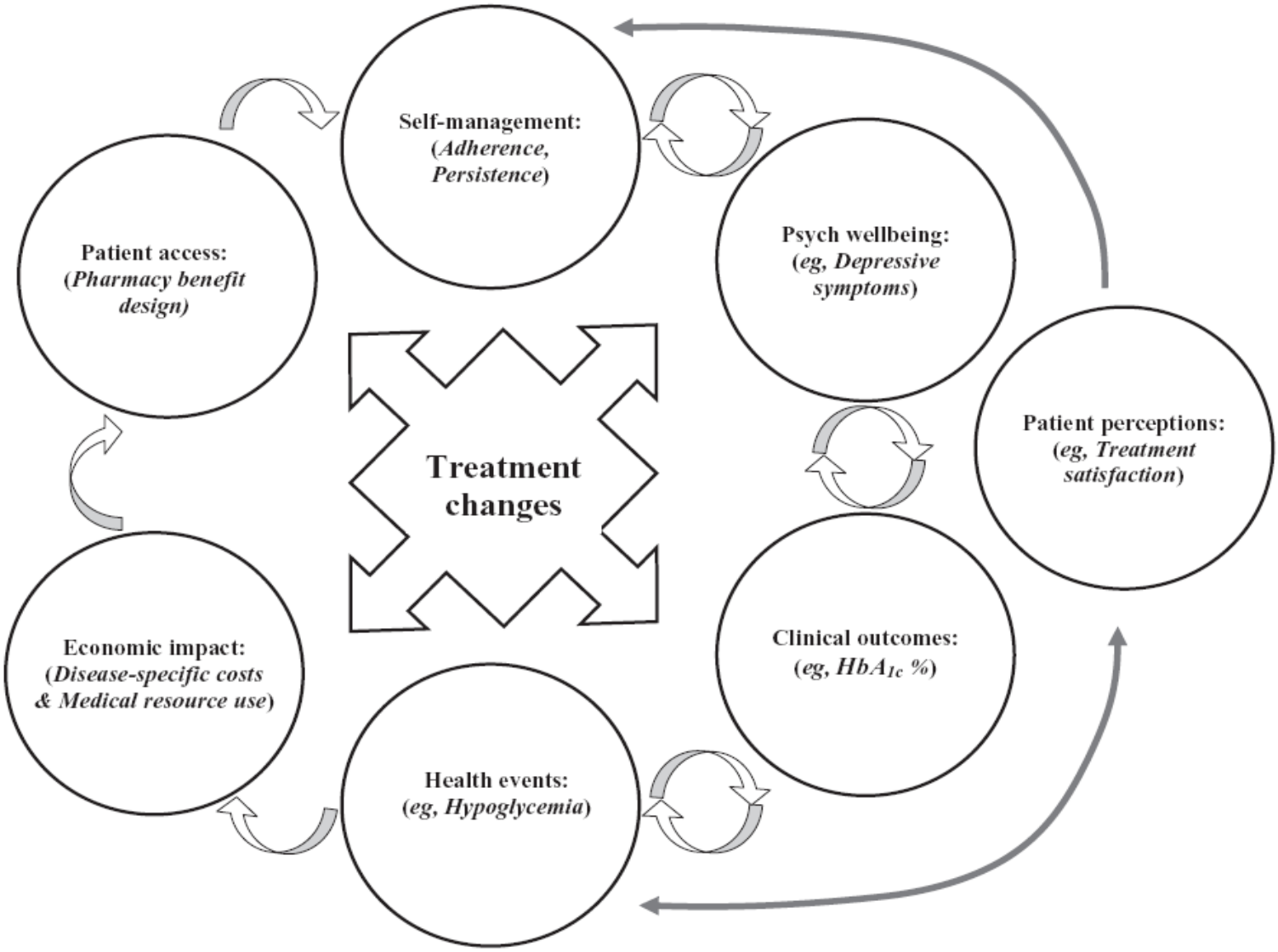
Similarly, psychological wellbeing may influence self-management, treatment satisfaction and clinical outcomes; satisfied patients are less likely to become depressed, and may therefore be more likely to exhibit better adherence, persistence and, subsequently, health status and costs [62,90-94]. Furthermore, self-management can mediate the relationship between psychological wellbeing and glucose control. Depressed patients are more likely to be unable or unwilling to properly self-manage and thereby experience poor HbA_{1c} control. Conversely, poor HbA_{1c} control can reduce psychological wellbeing and decrease the likelihood of adherence. Additionally, treatments which increase satisfaction and decrease depression may help patients achieve glycemic control and reduce resource use and costs [95-98].

From these observations, we developed a conceptual, cyclical framework describing the nature of relationships between psycho-behavioral factors and health economic outcomes in T2D (see Figure 2). Adherence and persistence with treatment, which may be explained by a patient's psychological wellbeing on that treatment, may readily influence clinical outcomes (namely HbA_{1c}). Glycemic control is a primary determinant of short and long-term health events and subsequent resource use and costs. Changes in resource use and costs may in turn affect decisions on healthcare benefits, influencing copayment levels, patient access and ultimately, self-management (since higher copayments may further reduce adherence/persistence). Patient satisfaction and preferences, which are sensitive to treatment attributes, clinical response and health events at various stages of treatment and disease progression, may affect self-management, psychological wellbeing and costs, and thereby impact all elements of the loop.

There are several areas where further research and innovation in diabetes economic modeling are warranted. Firstly, models to date have assumed that changes in HbA_{1c} and health outcomes are determined solely by changes in clinical risk and biological mechanisms. Although ample studies exist, no models yet address the potential impact of patient self-management, satisfaction or preferences on glycemic control, health outcomes or costs.

Secondly, although we found studies demonstrating considerable variation in adherence and persistence for T2D treatments, even over short-term (1-2 year) periods, these are

Figure 2. Conceptual framework for psycho-behavioral factors and health economic outcomes in type 2 diabetes.



either absent as a modifiable factor, or assumed to be perfect (100%) and constant, in current models, often over patient lifetimes. Our review illustrates that this does not reflect reality, and that there is sufficient evidence to incorporate additional heterogeneity in self-management when evaluating cost-effectiveness across numerous treatments and populations.

Thirdly, treatment changes were only allowed in 25% of the models we reviewed; 12 out of 16 assumed all patients remain on baseline treatment for the entire duration of

simulations. However, we found substantial data demonstrating that (1) T2D treatment modification occurs frequently, even over short-term periods, and (2) costs related to these changes may be strongly determined by factors such as adherence, persistence, satisfaction and psychological wellbeing.

Fourthly, models assumed constant dosing, although in reality, dosing can widely vary according to numerous factors, including clinical response and patient behavior. By applying fixed dose and treatment type (with fixed levels of adherence and persistence), variation in health event rates is not fully captured, and effects on pharmacy costs become fixed, misrepresenting true budgetary impact and misinforming what should be expected in real-world scenarios.

Although detailed proposals for methodological innovation fall outside the scope of our analysis, it is worthwhile to note that current mechanisms exist whereby psycho-behavioral parameters could potentially be incorporated into modeling. These may be employed directly or indirectly to address interrelations depicted in our conceptual framework, particularly between medication adherence and: (1) clinical effectiveness (e.g., HbA_{1c}); (2) mortality rates; (3) resource use; and (4) subsequent healthcare costs.

For example, where adequate evidence exists, equation-based modeling could incorporate regression functions to predict future HbA_{1c} levels, where medication adherence (as an independent and user-identified input variable alongside other modifiable factors such as age, gender, etc.) would adjust HbA_{1c} (the dependent variable) and subsequent health economic outcomes, such as hospitalization rate, over time. With this approach, improved adherence could be programmed to more accurately predict glycemic response for a target population (ie, better controlled HbA_{1c}), thereby reducing complications, lowering costs and generating improved cost-effectiveness ratios. Furthermore, structural models (those with temporal linear or open-state transitions, as in Markov or discrete event modeling), could utilize added transient states to adjust outcomes based on grouped or cutoff levels of adherence (e.g., 80-100%, 60-79%, etc.).

It is also worthwhile to note the importance of sensitivity analysis when incorporating psycho-behavioral parameters into modeling. Univariate or multivariate analysis of uncertainty around these factors would increase the robustness and validity of modeled results. For example, one could use documented levels of mean adherence as a baseline default input, and subsequently perform sensitivity analysis around these levels and their relative impact on outcomes (including incremental effectiveness, resource use, costs, and comparative cost-effectiveness). This could be accomplished through standard error techniques or by utilizing upper- and lower-bound limits (derived from literature or expert opinion) within probabilistic / 2^{nd} order Monte-Carlo simulation. Conducting sensitivity analysis would be especially important when the underlying mechanisms linking psycho-behavioral parameters to health economic outcomes are less clear or unknown (e.g., in utilizing medication adherence to adjust mortality rates / modeled survival and quality-adjusted life year (QALY) estimates).

Many forthcoming T2D medications will be differentiated by attributes that largely influence psychological and behavioral factors (e.g., route of administration, dosing frequency, device convenience). This further underscores the importance of developing techniques to better understand how to determine the value of interventions based on the economic impact of these factors.

It is important to note several limitations to our review:

- we were only able to identify, retrieve and analyze data in the public domain
- we included only peer-reviewed articles
- we utilized a pre-defined list of (1) terms, (2) publication dates and (3) data sources

The potential impact of these limitations include: (1) overlooking important data in grey literature, textbooks and scientific conferences, which might limit the completeness of our review; (2) reporting and publication bias, where certain types of results are more likely to be reported or published than others.

Additionally, since many of the studies in our review were performed retrospectively using observational data, some of their findings may simply reflect statistical associations and not cause-effect relationships (e.g., for persistence and costs). However, we also reviewed prospective, controlled studies that demonstrate causality elsewhere (e.g., for adherence and glycemic control). All in all, we believe that psychological and behavioral factors have at least a plausible direct relationship with clinical and economic outcomes as depicted in our conceptual framework.

Conclusions

In summary, we found clinical outcomes, resource use, and costs to be strongly associated with psychological and behavioral factors of care among T2D patients. Better-informed decision-making in T2D will require future research on integrating the complexity of these relationships in economic evaluations to reduce uncertainty in modelled results and more accurately reflect real-world treatment. Successful efforts to this end are likely to improve clinical practice and patient health through cost-effective allocation of healthcare resources.

References

1. Ramachandran A, Ramachandran S, Snehalatha C, Augustine C, Murugesan N, Viswanathan V et al. Increasing expenditure on health care incurred by diabetic subjects in a developing country: a study from India. Diabetes Care 2007; **30**(2): 252-256.
2. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. Diabetes Care 2002; **26**(3): 917-932.

3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. Diabetes Care 2008; **31**(3): 596-615.
4. World Health Organization. The Economic Burden of Diabetes. Available from http://www.who.int/mediacentre/factsheets/fs312/en/, accessed 27 August 2007.
5. Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. Diabetes Care 2006; **29**(9): 2114-2116
6. Bagust A, Hopkinson PK, Maslove L, Currie CJ. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060. Diabet Med 2002; **19** Suppl 4: 1-5.
7. Liese AD, D'Agostino RB Jr, Hamman RF, Kilgo PD, Lawrence JM, Liu LL et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics 2006; **118**(4): 1510-1518.
8. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. Diabetes Care 2006; **29**(11): 2415-2419.
9. Sidorov J, Shull R, Tomcavage J, Girolami S, Lawton N, Harris R. Does diabetes disease management save money and improve outcomes? A report of simultaneous short-term savings and quality improvement associated with a health maintenance organization-sponsored disease management program among patients fulfilling health employer data and information set criteria. Diabetes Care 2002; **25**(4): 684-689.
10. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. JAMA 2007; **298**(1): 61-69.
11. Sidorov J, Gabbay R, Harris R, Shull RD, Girolami S, Tomcavage J et al. Disease management for diabetes mellitus: impact on hemoglobin A1c. Am J Manag Care 2000; **6**(11): 1217-1226.
12. Roblin DW, Platt R, Goodman MJ, Hsu J, Nelson WW, Smith DH et al. Effect of increased cost-sharing on oral hypoglycemic use in five managed care organizations: how much is too much? Med Care 2005; **43**(10): 951-959.
13. Nair KV, Ganther JM, Valuck RJ, McCollum MM, Lewis SJ. Impact of multi-tiered pharmacy benefits on attitudes of plan members with chronic disease states. J Manag Care Pharm 2002; **8**(6): 477-491.
14. Ganther-Urmie JM, Nair KV, Valuck R, McCollum M, Lewis SJ, Turpin RS. Consumer attitudes and factors related to prescription switching decisions in multitier copayment drug benefit plans. Am J Manag Care 2004; **10**(3): 201-208.
15. Buxton MJ. Economic evaluation and decision making in the UK. Pharmacoeconomics 2006; **24**(11): 1133-1142.
16. Watkins JB, Minshall ME, Sullivan SD. Application of economic analyses in U.S. managed care formulary decisions: a private payer's experience. J Manag Care Pharm 2006; **12**(9): 726-735.
17. Valentine WJ, Palmer AJ, Nicklasson L, Cobden D, Roze S. Improving life expectancy and decreasing the incidence of complications associated with type 2 diabetes: a modelling study of HbA1c targets. Int J Clin Pract 2006; **60**(9): 1138-1145.
18. Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH. Adv Ther 2006; **23**(2): 191-207.
19. Nichol MB, Knight TK, Epstein J, Honda DH, Tretiak R. Opinions regarding the Academy of Managed Care Pharmacy dossier submission guidelines: results of a small

survey of managed care organizations and pharmaceutical manufacturers. J Manag Care Pharm 2007; **13**(4): 360-371.
20. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics 2006; **24**(4): 355-371.
21. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999-2002: the National Health and Nutrition Examination Survey. Diabetes Care 2006; **29**(3): 531-537.
22. Joish VN, Malone DC, Wendel C, Draugalis JR, Mohler MJ. Development and validation of a diabetes mellitus severity index: a risk-adjustment tool for predicting health care resource use and costs. Pharmacotherapy 2005; **25**(5): 676-684.
23. Brod M, Cobden D, Lammert M, Bushnell D, Raskin P. Examining correlates of treatment satisfaction for injectable insulin in type 2 diabetes: lessons learned from a clinical trial comparing biphasic and basal analogues. Health Qual Life Outcomes 2007; **7**: 5-8.
24. Rozenfeld Y, Hunt JS, Plauschinat C, Wong KS. Oral antidiabetic medication adherence and glycemic control in managed care. Am J Manag Care 2008; **14**(2): 71-75.
25. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. Clin Ther 2006; **28**(10): 1712-1725.
26. Cobden D, Lee WC, Balu S, Joshi AV, Pashos CL. Health outcomes and economic impact of therapy conversion to a biphasic insulin analog pen among privately insured patients with type 2 diabetes mellitus. Pharmacotherapy 2007; **27**(7): 948-962.
27. Walker EA, Molitch M, Kramer MK, Kahn S, Ma Y, Edelstein S et al. Adherence to preventive medications: predictors and outcomes in the Diabetes Prevention Program. Diabetes Care 2006; **29**(9): 1997-2002.
28. Fischer JS, McLaughlin T, Loza L, Beauchamp R, Schwartz S, Kipnes M. The impact of insulin glargine on clinical and humanistic outcomes in patients uncontrolled on other insulin and oral agents: an office-based naturalistic study. Curr Med Res Opin 2004; **20**(11): 1703-1710.
29. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6. Available from http://www.cochrane.org/resources/handbook/hbook.htm, accessed 27 March 2007.
30. Kadmon PM, Gruppuso PA. Glycemic control with metformin or insulin therapy in adolescents with type 2 diabetes mellitus. J Pediatr Endocrinol Metab 2004; **17**(9): 1185-1193.
31. Lawrence DB, Ragucci KR, Long LB, Parris BS, Helfer LA. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. J Manag Care Pharm 2006; **12**(6): 466-471.
32. Karter AJ, Moffet HH, Liu J, Parker MM, Ahmed AT, Go AS et al. Glycemic response to newly initiated diabetes therapies. Am J Manag Care 2007; **13**(11): 598-606.

33. Elis A, Rosenmann L, Chodick G, Heymann AD, Kokia E, Shalev V. The association between glycemic, lipids and blood pressure control among Israeli diabetic patients. QJM 2007; **101**(4): 275-280.
34. Morisky DE, Kominski GF, Afifi AA, Kotlerman JB. The Effects of a Disease Management Program on Self-Reported Health Behaviors and Health Outcomes: Evidence From the "Florida: A Healthy State (FAHS)" Medicaid Program. Health Educ Behav 2008; [Epub ahead of print].
35. Guillausseau PJ. Influence of oral antidiabetic agents in type 2 diabetes: A survey in general practice. Diabetes Metab 2003; **29**: 79-82.
36. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care 2002; **25**(6): 1015-1021.
37. Hill-Briggs F, Gary TL, Bone LR, Hill MN, Levine DM, Brancati FL. Medication adherence and diabetes control in urban African Americans with type 2 diabetes. Health Psychol 2005; **24**(4): 349-357.
38. Adams AS, Trinacty CM, Zhang F, Kleinman K, Grant RW, Meigs JB et al. Medication Adherence and Racial Differences in HbA1c Control. Diabetes Care 2008; [Epub ahead of print].
39. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB et al. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. Diabetes Care 2007; **30**(4): 807-812.
40. Kindmalm L, Melander A, Nilsson JL. Refill adherence of antihyperglycaemic drugs related to glucose control (HbA1c) in patients with type 2 diabetes. Acta Diabetol 2007; **44**(4): 209-213.
41. Donnelly LA, Morris AD, Evans JM; DARTS/MEMO collaboration. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes. QJM 2007; **100**(6): 345-350.
42. Singh R, Press M. Can we predict future improvement in glycaemic control? Diabet Med 2008; **25**(2): 170-173.
43. Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med 2006; **166**(17): 1836-1841.
44. Rothenbacher D, Rüter G, Brenner H. Prognostic value of physicians' assessment of compliance regarding all-cause mortality in patients with type 2 diabetes: primary care follow-up study. BMC Fam Pract 2006; **7**: 42.
45. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care 2005; **43**(6): 521-530.
46. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. Diabetes Care 2004; **27**(9): 2149-2153.
47. Pladevall M, Williams LK, Potts LA, Divine G, Xi H, Lafata JE. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. Diabetes Care 2004; **27**: 2800-2805.
48. Kalsekar I, Iyer S, Mody R, Rajagopalan R, Kavookjian J. Utilization and costs for compliant patients initiating therapy with pioglitazone or rosiglitazone versus insulin in a Medicaid fee-for-service population. J Manag Care Pharm 2006; **12**(2): 121-129.

49. White TJ, Vanderplas A, Chang E, Dezii CM, Abrams GD. The costs of nonadherence to oral antihyperglycemic medication in individuals with diabetes mellitus and concomitant diabetes mellitus and cardiovascular disease in a managed care environment. Disease Management and Health Outcomes 2004; **12**: 181-188.
50. Balkrishnan R, Rajagopalan R, Camacho FT, Huston SA, Murray FT, Anderson RT. Predictors of medication adherence and associated health care costs in an older population with type 2 diabetes mellitus: a longitudinal cohort study. Clin Ther 2003; **25**(11): 2958-2971.
51. Shenolikar RA, Balkrishnan R, Camacho FT, Whitmire JT, Anderson RT (2006) Comparison of medication adherence and associated health care costs after introduction of pioglitazone treatment in African Americans versus all other races in patients with type 2 diabetes mellitus: a retrospective data analysis. Clin Ther 2006; 28(**8**): 1199-1207.
52. Hertz RP, Unger AN, Lustik MB. Adherence with pharmacotherapy for type 2 diabetes: a retrospective cohort study of adults with employer-sponsored health insurance. Clin Ther 2005; 27(**7**): 1064-1073.
53. Catalan VS, Couture JA, LeLorier J. Predictors of persistence of use of the novel antidiabetic agent acarbose. Arch Intern Med 2001; 161(**8**): 1106-1112.
54. Dezii CM, Kawabata H, Tran M. Effects of once-daily and twice-daily dosing on adherence with prescribed glipizide oral therapy for type 2 diabetes. South Med J 2002; 95(**1**): 68-71.
55. Boccuzzi SJ, Wogen J, Fox J, Sung JC, Shah AB, Kim J. Utilization of oral hypoglycemic agents in a drug-insured U.S. population. Diabetes Care 2001; 24(**8**): 1411-1415.
56. Balkrishnan R, Rajagopalan R, Shenolikar RA, Camacho FT, Whitmire JT, Anderson RT. Healthcare costs and prescription adherence with introduction of thiazolidinedione therapy in Medicaid type 2 diabetic patients: a retrospective data analysis. Curr Med Res Opin 2004; 20(**10**): 1633-1640.
57. Balkrishnan R, Rajagopalan R, Shenolikar RA, Camacho FT, Anderson RT. Outcomes associated with introduction of thiazolidinedione therapy in Medicaid enrolled patients with type 2 diabetes: an updated and expanded retrospective analysis. Curr Med Res Opin 2006; 22(**3**): 551-559.
58. Cranor CW, Bunting BA, Christensen DB. The Asheville Project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. J Am Pharm Assoc (Wash) 2003; 43(**2**): 173-184.
59. Brown JB, Nichols GA, Glauber HS, Bakst A. Ten-year follow-up of antidiabetic drug use, nonadherence, and mortality in a defined population with type-2 diabetes mellitus. Clin Ther 1999; **21**: 1045-1057.
60. Kalsekar ID, Madhavan SS, Amonkar MM, Douglas SM, Makela E, Elswick BL et al. Impact of depression on utilization patterns of oral hypoglycemic agents in patients newly diagnosed with type 2 diabetes mellitus: a retrospective cohort analysis. Clin Ther 2006; 28(**2**): 306-318.
61. Weaver M, Patrick DL, Markson LE, Martin D, Frederic I, Berger M. Issues in the measurement of satisfaction with treatment. Am J Manag Care 1997; 3(**4**): 579-594.
62. Anderson RT, Skovlund SE, Marrero D, Levine DW, Meadows K, Brod M et al. Development and validation of the insulin treatment satisfaction questionnaire. Clin Ther 2004; 26(**4**): 565-578.

63. Wilson M, Moore MP, Lunt H. Treatment satisfaction after commencement of insulin in Type 2 diabetes. Diabetes Res Clin Pract 2004; 66(**3**): 263-267.
64. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GE, Wolffenbuttel BH, Niessen LW. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care 2002; 25(**3**): 458-463.
65. Gary TL, Maiese EM, Batts-Turner M, Wang NY, Brancati FL. Patient satisfaction, preventive services, and emergency room use among African-Americans with type 2 diabetes. Dis Manag 2005; 8(**6**): 361-371.
66. Alazri MH, Neal RD. The association between satisfaction with services provided in primary care and outcomes in Type 2 diabetes mellitus. Diabet Med 2003; 20(**6**): 486-490.
67. Gross R, Tabenkin H, Porath A, Heymann A, Greenstein M, Porter B. The relationship between primary care physicians' adherence to guidelines for the treatment of diabetes and patient satisfaction: findings from a pilot study. Fam Pract 2003; 20(**5**): 563-569.
68. Peyrot M, Rubin RR, Lauritzen T, Snoek FJ, Matthews DR, Skovlund SE. Psychosocial problems and barriers to improved diabetes management: results of the Cross-National Diabetes Attitudes, Wishes and Needs (DAWN) Study. Diabet Med 2005; 22(**10**): 1379-1385.
69. Park H, Hong Y, Lee H, Ha E, Sung Y. Individuals with type 2 diabetes and depressive symptoms exhibited lower adherence with self-care. J Clin Epidemiol 2004; 57(**9**): 978-984.
70. Gonzalez JS, Safren SA, Cagliero E, Wexler DJ, Delahanty L, Wittenberg E et al. Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. Diabetes Care 2007; 30(**9**): 2222-2227.
71. Gilmer TP, Walker C, Johnson ED, Philis-Tsimikas A, Unützer J. Improving Treatment of Depression Among Latinos with Diabetes Using Project Dulce and IMPACT. Diabetes Care 2008 [Epub ahead of print].
72. Nau DP, Aikens JE, Pacholski AM. Effects of gender and depression on oral medication adherence in persons with type 2 diabetes mellitus. Gend Med 2007; 4(**3**):205-213.
73. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch Intern Med 2000; 160(**21**): 3278-3285.
74. Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. Am J Med 2005; 118 Suppl **5A**: 27S-34S.
75. McKellar JD, Humphreys K, Piette JD. Depression increases diabetes symptoms by complicating patients' self-care adherence. Diabetes Educ 2004; 30(**3**):485-492.
76. Sacco WP, Wells KJ, Vaughan CA, Friedman A, Perez S, Matthew R. Depression in adults with type 2 diabetes: the role of adherence, body mass index, and self-efficacy. Health Psychol 2005; 24(**6**):630-634.
77. Peyrot M, McMurry JF Jr, Kruger DF. A biopsychosocial model of glycemic control in diabetes: stress, coping and regimen adherence. J Health Soc Behav 1999; 40(**2**): 141-158.
78. Pibernik-Okanović M, Szabo S, Metelko Z. Quality of life following a change in therapy for diabetes mellitus. Pharmacoeconomics 1998; 14(**2**): 201-207.

79. MacKeigan LD, O'Brien BJ, Oh PI. Holistic versus composite preferences for lifetime treatment sequences for type 2 diabetes. Med Decis Making 1999; 19(**2**): 113-121.
80. Stockl K, Ory C, Vanderplas A, Nicklasson L, Lyness W, Cobden D et al. An Evaluation of Patient Preference for an Alternative Insulin Delivery System compared to Standard Vial and Syringe. Curr Med Res & Opin 2007; 23(**1**): 133-146.
81. Chao J, Nau DP, Aikens JE. Patient-reported perceptions of side effects of antihyperglycemic medication and adherence to medication regimens in persons with diabetes mellitus. Clin Ther 2007; 29(**1**): 177-180.
82. Aristides M, Weston AR, FitzGerald P, Le Reun C, Maniadakis N. Patient preference and willingness-to-pay for Humalog Mix25 relative to Humulin 30/70: a multicountry application of a discrete choice experiment. Value Health 2004; 7(**4**): 442-454.
83. Shelmet J, Schwartz S, Cappleman J, Peterson G, Skovlund S, Lytzen L et al. Preference and resource utilization in elderly patients: InnoLet versus vial/syringe. Diabetes Res Clin Pract 2004; 63(**1**): 27-35.
84. Caro JJ, Salas M, O'Brien JA, Ishak K, Sung J, Raggio G. Modeling the efficiency of reaching a target intermediate end point: a case study in type 2 diabetes in the United States. Value Health 2004; 7(**1**): 13-21.
85. Ramsdell JW, Braunstein SN, Stephens JM, Bell CF, Botteman MF, Devine ST. Economic model of first-line drug strategies to achieve recommended glycaemic control in newly diagnosed type 2 diabetes mellitus. Pharmacoeconomics 2003; 21(**11**): 819-837.
86. Shearer AT, Bagust A, Ampudia-Blasco FJ, Martínez-Lage Alvarez B, Pérez Escolano I, París G. Lifetime health consequences and cost-effectiveness of rosiglitazone in combination with metformin for the treatment of type 2 diabetes in Spain. Pharmacoeconomics 2006; 24 Suppl **1**: 49-59.
87. Caro JJ, Getsios D, Caro I, Klittich WS, O'Brien JA. Economic evaluation of therapeutic interventions to prevent Type 2 diabetes in Canada. Diabet Med 2004; 21(**11**): 1229-1236.
88. CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA. 2002; 287(**19**): 2542-2551.
89. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther 2004; 26(**9**): 1498-1505.
90. Chao J, Nau DP, Aikens JE, Taylor SD. The mediating role of health beliefs in the relationship between depressive symptoms and medication adherence in persons with diabetes. Res Social Adm Pharm 2005; 1(**4**): 508-525.
91. Oglesby AK, Secnik K, Barron J, Al-Zakwani I, Lage MJ. The association between diabetes related medical costs and glycemic control: A retrospective analysis. Cost Eff Resour Alloc 2006; 16(**4**): 1.
92. Shetty S, Secnik K, Oglesby AK. Relationship of glycemic control to total diabetes-related costs for managed care health plan members with type 2 diabetes. J Manag Care Pharm 2005; 11(**7**):559-564.
93. Menzin J, Langley-Hawthorne C, Friedman M, Boulanger L, Cavanaugh R. Potential short-term economic benefits of improved glycemic control: a managed care perspective. Diabetes Care 2001; 24(**1**): 51-55.

94. Loke SC, Jong M. Metabolic control in type 2 diabetes correlates weakly with patient adherence to oral hypoglycaemic treatment. Ann Acad Med Singapore 2008; 37(**1**): 15-16.
95. Hepke KL, Martus MT, Share DA. Costs and utilization associated with pharmaceutical adherence in a diabetic population. Am J Manag Care 2004; 10(**2**): 144-151.
96. Rosenblum MS, Kane MP. Analysis of cost and utilization of health care services before and after initiation of insulin therapy in patients with type 2 diabetes mellitus. J Manag Care Pharm 2003; 9(**4**): 309-316.
97. Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycemic control. Diabetes Care 1997; 20(**12**): 1847-1853.
98. Surwit RS, van Tilburg MA, Parekh PI, Lane JD, Feinglos MN. Treatment regimen determines the relationship between depression and glycemic control. Diabetes Res Clin Pract 2005; 69(**1**): 78-80.
99. Pawaskar M, Camacho FT, Anderson RT, Cobden D, Joshi AV, Balkrishnan R Health Care Costs and Medication Adherence Associated with Initiation of Insulin Pen Therapy in Medicaid-Enrolled Patients with Type 2 Diabetes: A Retrospective Database Analysis. Clin Ther 2007; **29**:1294-1305.

Chapter 9

Modeling the economics of medication adherence in Type 2 diabetes

Adapted from: Cobden D, Niessen LW, Rutten FFH, Redekop WK. Modeling the Economic Impact of Medication Adherence in Type 2 Diabetes: a Theoretical Approach. *Patient Preference & Adherence*. 2010 August; (4): 283-90.

Summary

While *s*trong correlations exist between medication adherence and health economic outcomes in Type 2 diabetes (T2D), current economic analyses do not adequately consider them. We propose a new approach to incorporate adherence in cost-effectiveness analysis. Our study describes a theoretical approach to incorporating the effect of adherence when estimating the long-term costs and effectiveness of an anti-diabetic 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.

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 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. Incorporating medication adherence into economic analyses can meaningfully influence the estimated cost-effectiveness of T2D treatments, and should therefore be considered in healthcare decision-making. Future work on the impact of adherence on health economic outcomes, and validation of different approaches to modeling adherence, is warranted.

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 U.S. 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 HbA1c 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 diabetes treatment on clinical outcomes, health events, quality-of-life, 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, healthcare 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 "non-clinical" 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 anti-T2D medications (OAD), since needle phobia, multiple daily injections, and varied dosing schedules (e.g., 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.

Methods

We developed a novel approach to modeling medication adherence among T2D patients using conventional health economic techniques and software (*MS Excel* and *TreeAge Pro 2009*). To test our approach, two 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 healthcare 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.

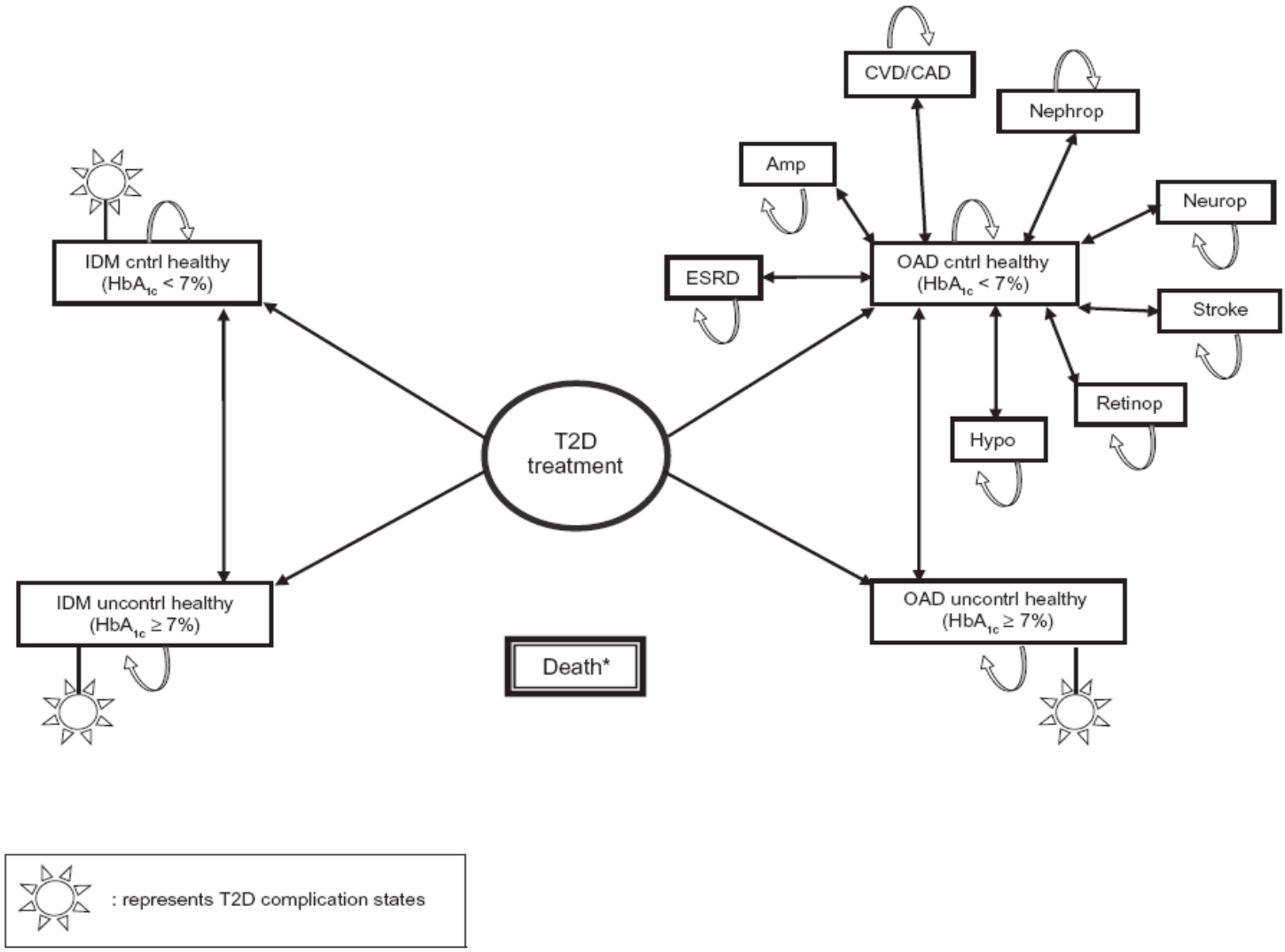
In this model, patients receive either IDM (insulin in our example) or OADs, chosen as mutually-exclusive comparators because of the inherent differences between them which readily impact adherence. Patients on both therapies begin at a baseline HbA1c that is either < 7% or ≥ 7%, and through subsequent annual iterations, may (1) remain in a 'healthy' state with controlled (< 7%) or uncontrolled (≥ 7%) HbA1c, (2) progress between T2D complication states (with controlled or uncontrolled HbA1c), or (3) die. Probabilities for patients to move from one complication state to another are based on HbA1c over time, since patients with controlled HbA1c are much less likely to develop complications [10,14]. Treatment effects (mean of -1.2% HbA1c and -0.8% HbA1c for IDM and OAD, respectively, to reflect greater potency of insulin use) were applied to assumed baseline HbA1c means of 8.1% and 6.8% for patients modeled to HbA1c ≥ 7% and < 7%, respectively [14,15]. An annual increase in HbA1c – 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 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 HbA1c < 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), U.S. 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 U.S. T2D populations, including the percentage of patients receiving specific OADs and IDM, the percentage of patients with baseline HbA1c<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 (e.g., smokers:

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.

18.8%), and presence of preexisting complications [10, 14-16].

The magnitude and duration of mean treatment effects remained consistent among IDM and OAD sub-classes, 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].

Quality-of-life (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% non-generic 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 U.S. 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

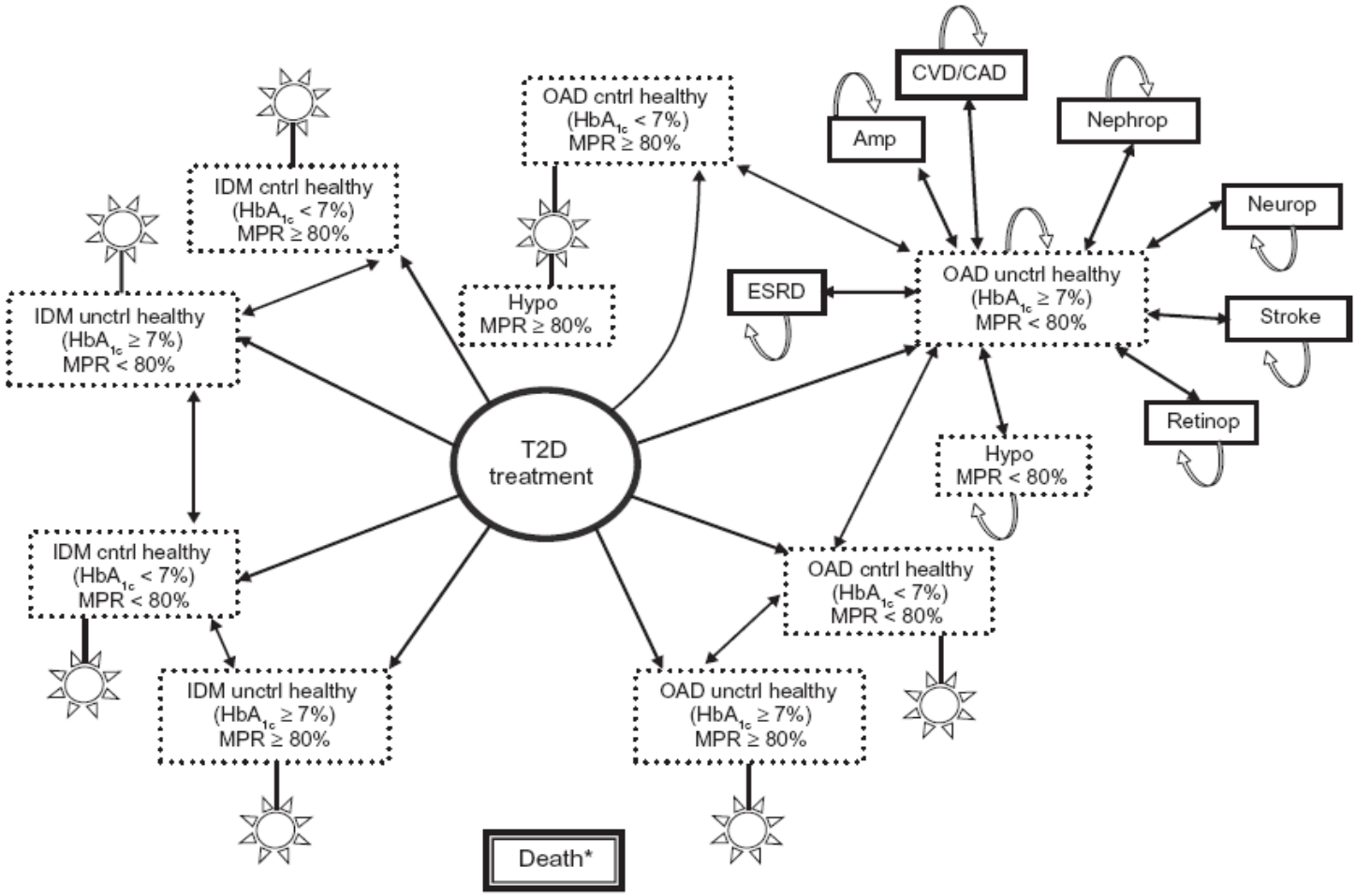
As depicted in Figure 2, adjustments for adherence involved revisions to the degree of modeled glycemic control, risks of subsequent diabetes complications, and costs using current evidence on the impact of real-world medication adherence. Applied rates of adherence were primarily determined using Medication Possession Ratios (MPR)), and were derived from large observational studies [5-7,18-22]. Just as the target of HbA1c < 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 HbA1c control, thereby enabling MPR to directly influence the likelihood of a patient moving to, and remaining in, either of the HbAlc categories (HbA1c < 7% or HbA1c ≥ 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 HbA1c < 7%, have reduced incidence of hypoglycemia and related resource use, and incur lower healthcare 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 HbA1c<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 HbA1c 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 simulation and bootstrapping. The progression of T2D was simulated in a 1000 x 1000 manner (each cohort of 1000 patients was simulated 1000 times), producing individual candidate bootstrap samples. The average costs and health for each cohort

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.

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 incremental cost-effectiveness ratio for IDM versus OAD was $12,097 per QALY gained, using total healthcare costs.

Adherence-adjusted Model: Analysis 2

After adjustment for adherence, IDM still led to a longer LE and QALE than OADs by +0.33 and +0.68 years, respectively, although the differences observed between IDM and OADs were smaller than without adjustment for adherence. 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 incremental cost-effectiveness ratio 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%, 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.

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.

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 (e.g., 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 HbA1c < 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 HbA1c < 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 ≥ 80% than IDM patients, and they therefore experienced less risk of major hypoglycemia (and related QoL disutility) as well as a greater chance of HbA1c < 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 HbA1c-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 HbA1c ≥ 7%, and thus a higher starting HbA1c 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 U.S. 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 disproportionally affects minority sub-populations in the U.S. 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 healthcare from a U.S. societal perspective (up to $297,000/QALY) [23].

Conclusions

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 healthcare decision-making for real-world settings.

References

1. Ramachandran A, Ramachandran S, Snehalatha C, Augustine C, Murugesan N, Viswanathan V et al. Increasing expenditure on health care incurred by diabetic subjects in a developing country: a study from India. Diabetes Care 2007; **30**(2): 252-256.
2. Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. Diabetes Care 2006; **29**(9): 2114-2116
3. Bagust A, Hopkinson PK, Maslove L, Currie CJ. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060. Diabet Med 2002; **19** Suppl 4: 1-5.
4. Cutler DM, Everett W. Thinking Outside the Pillbox — Medication Adherence as a Priority for Health Care Reform. New Engl J Med 2010; Apr 7. [Epub ahead of print].
5. Cobden D, Lee WC, Balu S, Joshi AV, Pashos CL. Health outcomes and economic impact of therapy conversion to a biphasic insulin analog pen among privately insured patients with type 2 diabetes mellitus. Pharmacotherapy 2007; **27**(7): 948-962.

6. Lee WC, Balu S, Cobden D, Joshi AV, Pashos C. Prevalence and Economic Consequences of Medication Adherence in Diabetes: A Systematic Literature Review. Managed Care Interface. 2006; **19**(7): 31-41.
7.Rozenfeld Y, Hunt JS, Plauschinat C, Wong KS. Oral antidiabetic medication adherence and glycemic control in managed care. Am J Manag Care 2008; **14**(2): 71-75.
8. Cobden D, Niessen LW, Rutten FFH, Barr CE, Redekop WK. Relationships among self-management, patient perceptions of care, and health economic outcomes for decision-making and clinical practice in Type 2 diabetes. Value in Health. 2010 Jan/Feb; **13**(1): 138-47.
9. Watkins JB, Minshall ME, Sullivan SD. Application of economic analyses in U.S. managed care formulary decisions: a private payer's experience. J Manag Care Pharm 2006; **12**(9): 726-735.
10. Valentine WJ, Palmer AJ, Nicklasson L, Cobden D, Roze S. Improving life expectancy and decreasing the incidence of complications associated with type 2 diabetes: a modelling study of HbA1c targets. Int J Clin Pract 2006; **60**(9): 1138-1145.
11. Nathan DM. Finding New Treatments for Diabetes — How Many, How Fast . . . How Good? New Engl J Med 2007; **356**(5): 437-440
12.Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Dec Making 1993; **13**: 322–338.
13. Fone D, Hollinghurst S, Temple M, Round A, Lester N, Weightman A, et al. Systematic review of the use and value of computer simulation modelling in population health and health care delivery. J Public Health Med, 2003; **25**(4) 325-335.
14. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-Year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998;**128**:165-175.
15. National Center for Health Statistics, Centers for Disease Control and Prevention. NHANES 2007–2008 Dataset and Diabetes Fact Sheet Survey. http://www.cdc.gov/nchs/fastats/diabetes.htm. Accessed September 22, 2009.
16. Dodd AH, Colby MS, Boye KS, Fahlman C, Kim S, Briefel RR. Treatment approach and HbA1c control among US adults with type 2 diabetes: NHANES 1999-2004. Curr Med Res Opin 2009: **25**(7):1605-13.
17. 2009 Drug Red Book. Medical Economics Co., Inc., Montvale, NJ, USA.
18. Rodin HA, Heaton AH, Wilson AR, Garrett NA, Plocher DW. Plan designs that encourage the use of generic drugs over brand-name drugs: an analysis of a free generic benefit. Am J Manag Care. 2009 Dec;**15**(12): 881-888.
19. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Medication adherence and use of generic drug therapies. Am J Manag Care. 2009 Jul;**15**(7): 450-456.
20. Evans JM, Donnan PT, Morris AD. Adherence to oral hypoglycaemic agents prior to insulin therapy in Type 2 diabetes. Diabet Med 2002; **19**(8): 685-688.
21. Lawrence DB, Ragucci KR, Long LB, Parris BS, Helfer LA. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. J Manag Care Pharm 2006; **12**(6): 466-471.

22. Luna B, Feinglos M. Oral agents in the management of type 2 diabetes mellitus. Am Fam Physician 2001;63:1747-1756.
23. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care. 2008 Apr;**46**(4): 349-356.

Chapter 10

Discussion & Conclusions

Discussion

The primary aim of this thesis has been to improve healthcare decision-making for diabetes patients through development of a novel, enhanced framework for economic evaluation. This new approach at determining the relative cost-effectiveness of diabetes treatments is particularly warranted in a rapidly-evolving clinical environment which increasingly focuses on patient-centered, tailored therapy, and a market environment which increasingly emphasizes product differentiation through non-biological features. Both of these dynamics may influence the successful implementation of prescribed therapy as well as ensuing health outcomes and costs by impacting a patient's perception of care and level of adherence.

Broadly speaking, the steps taken to accomplish our aim have been to (1) establish existing methodologies of diabetes-related economic evaluation upon which to innovate, (2) document and quantify economically important correlations of measures of patient self-management and perceptions of care (which may be impacted by non-biological product features), (3) identify where current modeling techniques inadequately consider these relationships, and (4) propose and test a new approach to economic evaluations which integrate our findings.

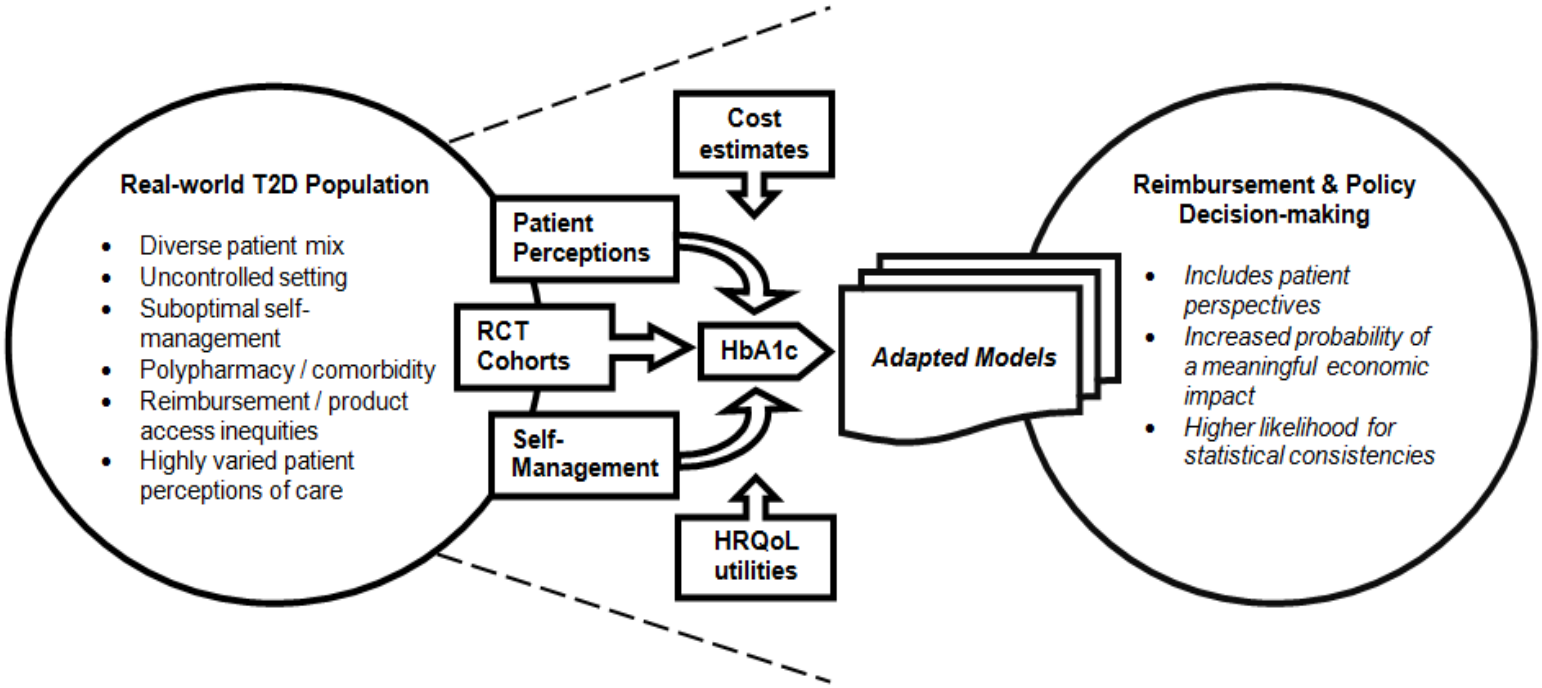
Numerous study designs and data sources contributed to carrying out the plan of research for this thesis. In doing so, the evidence generated to support our new approach is well-rounded and dynamic. The types of studies we conducted fall into 4 main categories: (1) economic modeling analyses, (2) prospective, randomized clinical trials, (3) retrospective, observational studies, and (4) systematic literature reviews. Data sources ranged from publically available research articles, to administrative healthcare claims and self-reported responses using psychometric instruments.

Modeling assessments were the first and last components to this thesis. They served the dual purpose of establishing the initial set of methodologies on which we would base our work, as well as determined the analytic environment in which to test our approach – CEA by way of M/MC simulation. Prospective controlled studies also served several purposes, with particular focus on patient-reported outcomes. First, they were used to differentiate patient perceptions of care (preference and satisfaction) between diabetes treatments with distinct non-biological profiles, namely mode of administration, ergonomics/handling (pen device vs. vial/syringe), and dosing. Secondly, prospectively gathered PROs from one of these trials became a valuable data source for retrospective analysis, correlating treatment satisfaction associated with non-biological product features to clinical parameters (HbA1c and hypoglycemia) used in driving CEA results.

Several other retrospective, observational analyses were performed utilizing healthcare claims databases. These facilitated investigation of measures of self-management between diabetes treatments having different non-biological profiles, specifically in terms of resource use and costs. The goal was to detect and quantify improvements in medication adherence and/or persistence for treatments with modern non-biological innovations, and to correlate these with outcomes that could be meaningfully brought into

CEA. Systematic literature reviews also contributed to estimating the health economic impact of medication adherence, specifically among a broader set of diabetes treatments (oral medications). Furthermore, these reviews were a primary means by which we formally identified gaps in current CEA techniques and developed our conceptual framework for relationships between patient perceptions of care, non-biological product features, self-management, clinical parameters, and reimbursement policy. In all, each chapter became an integral part for creating the innovative framework for diabetes cost-effectiveness analysis presented in this thesis. Figure 1 illustrates how the different concepts examined in this thesis are relevant for current decision-making as well as useful in guiding future work. By adapting CEAs to include the impact on outcomes and costs of self-management and patient perceptions (which are influenced by real world factors and non-biological product features), decision-makers may be better equipped when establishing access to new treatments.

Figure 1. Adapted approach of economic evaluation for real-world decision-making in diabetes



A general description and short summary of main conclusions by chapter is provided below to briefly describe each segment's contribution to the overall flow of this thesis.

Chapter 2. The opening chapter establishes a core set of techniques which are suitable for modeling the long-term health and economic outcomes of improvements in HbA1c.

Prior to the inclusion of treatment-specific effects, it was relevant to demonstrate the ability of a defined methodology to generate reasonably-expected ICERs which focus on the main clinical parameter underlying the natural disease progression of diabetes. Based on published examples, and its historically common use in health technology assessment (HTA), cost-effectiveness analysis (more accurately, cost-utility analysis) utilizing a Markov structure of the range of diabetic health states and Monte-Carlo simulation was our chosen methodology.

Hypothetical, step-wise improvements in HbA1c were applied amongst a population of T2D patients exhibiting typical socio-demographic and clinical profiles. Over a long-term time horizon (35 years from diagnosis), three separate scenarios of incremental HbA1c reduction – 9.5 to 8.0%, 7.9 to 6.5%, and 6.4 to 6.0% (all vs. no reduction) – resulted in QALY gains of 0.58, 0.38, and 0.18 years, respectively.

Cumulative incidence of T2D complications, time delay to onset of complications, and related costs were also improved, in parallel. As anticipated, benefit was most pronounced among those experiencing the greatest reduction (i.e., patients with the highest baseline HbA1c), yet notable gains remained present in those able to meet the most stringent goal (6.5%). Sensitivity analyses supported the main results, and we were able to conclude that our baseline approach at modeling diabetes treatments (CEA with HbA1c as the primary clinical parameter) was reliable and appropriate to use.

Chapter 3. Applied within the same general model of diabetic health states as the previous chapter, with transition probabilities modified to fit an adult T1D population (insulin-dependent), our second analysis extended the first by incorporating the treatment-specific efficacy, safety, and costs of 3 separate types of insulin – detemir, glargine, and NPH. Two analyses were conducted – IDet vs. IGlar, and IDet vs. NPH – in order to demonstrate the influence of treatment-specific differences in HbA1c, hypoglycemia, and acquisition costs on ICERs.

The cost-effectiveness of the two competing analog insulins (IDet vs. IGlar) was estimated using trial-reported differences in hypoglycemia (glycemic control was statistically similar). However, when compared to less potent human insulin (NPH), significant reductions in HbA1c favoring IDet were also able to be considered (i.e., along with less hypoglycemia). Pharmacy costs were similar between IDet and IGlar, yet were considerably higher for IDet versus NPH. These 2 scenarios allowed us to test our base modeling approach beyond focus on HbA1c alone by observing: (1) the influence of safety outcomes (major hypoglycemia) in isolation of HbA1c; and (2) the mixed effect of improving HbA1c while reducing hypoglycemia, but at a much higher acquisition cost.

As anticipated, differences in QALYs gained between IDet vs. IGlar, as compared to IDet vs. NPH, were less pronounced due to the added benefit of glycemic control, along with more pronounced reduction in hypoglycemia, which IDet patients received versus NPH. For IDet vs. IGlar, patients gained 0.063 QALYs and incurred approximately $5,000 less in medical costs, attributable predominantly to reduced hypoglycemia, thus producing a dominant base case ICER. Comparing IDet to NPH yielded more considerable gains of

0.698 QALYs, however, at an additional cost of nearly $6,000. Still, an ICER of $14,974/QALY was generated and was shown to have 100% acceptability at a threshold of willingness-to-pay (WTP) equal to approximately $30,000/QALY. These results demonstrate that our modeling approach is sensitive to efficacy and safety outcomes alike, and that it may reasonably accommodate variation in treatment-specific pharmacy costs, whether in isolation or experienced simultaneously.

Chapter 4. Having defined our base modeling approach (to be built upon in later work), focus was placed on investigating differences in patient-reported perceptions of care in the context of therapies which fundamentally differ in a non-biological manner. We began by evaluating patient preferences and treatment satisfaction for adult insulin-dependent diabetes patients (adult T1D and T2D patients included) using two distinct insulin delivery systems – a handheld pen device vs. standard vial/syringe. Non-biological features exhibited by the handheld device include easier dosing (large dose-dial), higher gauge needle (less injection pain), improved ergonomics (handheld fit), and less burdensome administration (single pre-filled device vs. need to manually fill syringe). A randomized, cross-over design was employed using a total of 162 patients (mean age: 59.8 years), and several validated psychometric instruments used to ascertain PRO differences between treatments. Included were the *IDPQ* (Insulin Device Preference Questionnaire) and the *ITSQ* (Insulin Treatment Satisfaction Questionnaire).

Although there were no significant differences in efficacy or safety (bio-equivalent insulin was used for each arm, and there were no per-protocol treatment changes – only device changes), major improvements in preference for and satisfaction with the handheld pen device were seen, attributable to the non-biological features of the pen device. Overall, up to 75% of patients preferred the pen ($p<0.0001$) on various measures, including convenience, ease of use, comfort, less interference with daily activities, and improved social life. Of those who preferred the pen, 4 out of 5 reported a strong or very strong preference (n=92). Treatment satisfaction was similarly improved within each domain, as well as overall satisfaction. Measures of convenience ($p<0.0001$), lifestyle flexibility ($p<0.0006$), perceived glycemic control ($p<0.0001$) and hypoglycemic control ($p<0.0001$), delivery system satisfaction ($p<0.0001$), and overall satisfaction ($p<0.0001$) were significantly improved when the pen device was used.

Chapter 5. After demonstrating improved patient perceptions of care with treatments exhibiting favorable non-biological profiles, it became necessary to further link these improved perceptions with clinical parameters that are a main driver of CEA. In doing so, we would have cause to incorporate the health economic effects associated with patient perceptions into our work on innovating CEAs. This was undertaken through retrospective analysis of PROs captured in a randomized controlled trial comparing two types of insulin (aspart 70/30 vs. IGlar) among T2D patients.

Results from the *ITSQ* were again utilized. However, unlike in Chapter 4, significant improvements in HbA1c and hypoglycemia were found in one of the treatment arms (aspart 70/30). Additionally, patients on aspart 70/30 were administering their insulin with a handheld pen device, while patients on IGlar used vial/syringe. These 2 elements

allowed further insight into the mixed influence on patient perceptions of using a favorable non-biological treatment while concurrently experiencing improved efficacy and safety.

Significantly higher scores in domain-specific as well as overall treatment satisfaction were observed for patients experiencing improved HbA1c and less hypoglycemia, the majority of which were on the pen device. Interestingly, it was also observed that patients using the pen device who had co-morbid retinopathy (low visual acuity), and/or neuropathy, reported improvements in satisfaction. This is very likely due to the non-biological aspects of the pen device, in particular, the large dose-dialer (easier to see and accurately set) and smaller needle (less injection site pain). Combining results from Chapters 4 and 5, it is apparent that favorable non-biological features are associated with improved perceptions of care, and that these improvements are also related to the primary clinical drivers of CEAs.

Chapter 6. Better perceptions of care play an important role in determining a patient's ability to achieve HbA1c control in a safe manner. A logical explanation for this is that improved perceptions of care, associated with favorable non-biological features, may cause patients to adhere better and persist longer to prescribed therapy. Thus, optimal medication adherence is likely to be associated with improved HbA1c, and therefore any health economic impact related to adherence becomes important to consider for CEA.

We performed a systematic literature review to (1) assess levels of adherence with a wide spectrum of injectable and oral treatments among T1D and T2D patients, and (2) document the economic impact of differences in adherence. Medication adherence, measured most frequently by MPRs, was found to have high variation among all treatment types – ranges of 36-87% and 54-81% for orals and injectables, respectively. Cost consequences were also substantial, with an approximate drop of 10-30% in healthcare costs for every 10% increase in adherence (depending on treatment type), stemming mostly from reduced hospitalizations. It became clear from this review that sub-optimal adherence is prevalent among diabetes patients, and that this in turn is associated with higher resource use and a significant economic impact.

Chapter 7. Our next step was to investigate more refined differences in adherence and related cost consequences, focusing on use of a pen device versus vial/syringe, in line with previous chapters examining the same treatments (which have clear non-biological product differences). An intra-patient, pre-post design within a large healthcare claims database was used to assess medication adherence (MPR) before and after use of an insulin pen device among T2D patients.

Patients converting from vial/syringe to a pre-filled pen device (with aspart 70/30 insulin) were identified and observed over a 2 year period (n=486). Measured outcomes included MPR, incidence rates of hypoglycemia, and total, diabetes-related, and hypo-related healthcare costs. Additionally, correlation analyses were employed to detect associations of MPR with hypoglycemia and individual cost groups.

Conversion to the pen device resulted in a 9% absolute gain in medication adherence (pre-MPR: 0.59; post-MPR: 0.68, $p<0.01$) and a 60% reduction in the likelihood of experiencing a hypoglycemic event (OR: 0.4, 95% CI 0.27-0.61, $p<0.05$). This is likely due to more accurate dosing and administration with the pen device (larger dial, better handling, no need to manually fill syringe) and improved convenience. For those with post-MPR $\geq$ 80%, a drop of two-thirds was observed in rate of hypoglycemia. These improvements were associated with 64% and 61% decreases in hypoglycemia-related emergency room and physician visits, respectively, as well as yearly reductions in total, hypoglycemia, and diabetes costs ($1748, $908, $643 per patient, respectively). Furthermore, patients with post-MPR $\geq$ 80% exhibited a reduction of 45% in total annual healthcare costs. These results clearly demonstrate that adherence is significantly associated with the use of a treatment with favorable non-biological features, and that numerous cost benefits may be expected as a result.

Chapter 8. Several gaps remained before we could proceed to developing and testing an innovative approach at CEA. First, we had to assess whether adherence and patient perceptions could be quantified in terms of HbA1c improvements. That is, we had shown in previous chapters that HbA1c is influenced by patient perceptions, but not by how much, and that adherence was related to hypoglycemia, but not HbA1c. This was important because HbA1c is the main clinical driver of our base CEA approach, and we needed to tie our proposed innovations back to this. Also, because our base CEA model includes risk adjustment for non-diabetes factors (CVD), we needed to answer the question, 'does adherence to diabetes treatments impact non-diabetes-specific outcomes?' Secondly, it was necessary to explore the extent to which these relationships are already included in current economic evaluations. This would ensure our contributions to innovating CEA in diabetes would not be redundant.

Medication adherence was found to be significantly associated with HbA1c on several levels: (1) a 15% increase in adherence improves ability to achieve a target HbA1c $\leq$ 7%, and (2) every 10-25% relative increase in MPR may result in a 0.1-0.2% absolute decrease in HbA1c. Additionally, patients with MPR $\geq$ 80% may exhibit up to 0.7% absolute lower HbA1c versus those < 80%. Sustained adherence with diabetes treatments may also improve blood pressure, lower LDL, and reduce mortality. Numerous studies confirmed our findings in Chapters 6 and 7, that improved adherence is associated with significant cost reductions (up to $3,400 per patient per year). Treatment satisfaction and patient preference were also shown to be associated with clinical parameters important for CEA – an absolute HbA1c reduction of 0.4-1.43% may be seen with improved satisfaction, as well as reduced hypoglycemia and better lipid profiles. Cost reductions may also be seen – reduced utilization of emergency room and other services may drop up to 63%, and a daily savings of $80 per patient (due to reduced nursing/caregiver need) may occur with improved perceptions related to use of a pen device.

We were also able to confirm that current approaches at CEA do not adequately consider these economically important relationships. Of 16 economic models we reviewed (up to 82% of which were CEA, depending on treatment type), zero included medication

adherence or patient perceptions (non-HRQoL PROs) as input variables or risk adjusters over time.

Chapter 9. Our conceptual framework in Chapter 8, describing relationships leading to reimbursement decision-making, served as a foundation for developing a new approach at CEA in diabetes. This new approach began where the strongest and most direct link between non-biological product features, HbA1c, and a health economic impact found in previous chapters exist – medication adherence. An entirely new Markov structure of T2D health states and transition probabilities (adapted largely from the CEA model in Chapters 1 and 2, and utilizing the same M/MC methodological approach) was built, and two separate analyses were run – the first which ignored adherence, and the second which incorporated it.

A categorical approach, rather than incremental approach, was taken to incorporate adherence in the second analysis, whereby a cut-off threshold of MPR $\geq$ 80% was used to adjust HbA1c and risk for complications. The categorical approach was chosen because we did not feel there was sufficient evidence to take the incremental approach. As discussed later in more detail, further work is needed in order fully describe how incremental improvements in adherence correlate to HbA1c and cost consequences. Although an incremental approach may facilitate a more realistic reflection of how patients truly act and how costs are incurred in the real-world, this relationship is likely not linear, and the requisite log transformation and regression estimates do not yet exist to adjust modeled outcomes.

The impact of +/- MPR=80% within our second analysis was applied in two main areas – HbA1c level and rates of hypoglycemia, as this is where sufficient data exists (found in our literature reviews and database analysis). Hypothetical oral and injectable treatments were created for our model because non-biological profiles clearly differ, which would logically explain assumed differences in applied adherence rates. Over a long-term horizon, it was found that our adherence-adjusted model (analysis 2) generated an ICER for oral vs. injectable treatment that was 34% higher than when adherence was ignored ($16,421 vs. $12,097/QALY). Although both ICERs may be considered acceptable and 'good value' under most WTP thresholds, the adherence adjustment caused much smaller differences in LE, QALE, and complication rates between treatments. This is due to the fact that evidence from Chapters 5 and 7 suggests that adherence with oral medication is greater than for insulin, thus generating better HbA1c control for oral medication in our adherence-adjusted model, and causing insulin to become less cost-effective.

Summary and Future Work

The overarching conclusions of this thesis are that (1) important relationships exist between non-biological product features, patient perceptions of care, and self-management, particularly in terms of health and economic outcomes, and (2) innovative ways of meaningfully incorporating these relationships into CEAs are possible. Herein, this has been demonstrated among adult patients with diabetes, predominantly T2D, and

may be useful in serving as an example of how economic evaluations for patients with other chronic diseases can be improved upon.

Each chapter leading up to and including development of our conceptual framework and novel approach at CEA illustrates the current need to more robustly consider these relationships within economic evaluations that are frequently a part of informed decision-making. Their inclusion has been shown to meaningfully influence modeled results in CEA, and should therefore be used to generate more accurate estimates of the relative cost-effectiveness of modern therapies.

Further work expanding on our findings is warranted in several areas. The three most crucial, in particular over the short-term (5-10 years), are: (1) expanding the number and richness of data sources; (2) generating more accurate and precise figures on relationships between perceptions of care, self-management, clinical parameters, and cost outcomes; and (3) continuously advancing modeling techniques. It is important that progress be made on all of these fronts as concurrently as possible, as each is complimentary to one another.

In many regions globally, the political and market environment continues to emphasize the importance of comparative effectiveness research, health information exchanges, and software technology. Developments in these areas will no doubt lead to opportunities to develop more rich data sources, specifically, in the area of converging real-world, patient-level electronic medical records (EMRs), healthcare claims, and PROs. The contribution of each is critical: EMRs are able to provide clinical parameters such as HbA1c, lipid profiles, blood pressure, daily glucose, and even radiologic imaging; claims data provide diagnostic prevalence, procedural and event rates, drug utilization, and detailed cost information; and PRO scores provide additional patient-centric insight to the role of preferences and satisfaction. Together, these will reveal a much wider spectrum of the healthcare system upon which to perform research. At the moment, each data source exists, however, independently, and at various stages of development.

Expanded data sources will facilitate research producing much more accurate, quantified estimates of correlations between all of the outcomes focused on in this thesis. For example, in theory, we already know that preference and satisfaction are important in determining a patient's success at achieving goals of therapy, likely through a greater willingness to properly self-manage. And we do have some detailed data to support this, as seen throughout several chapters in this thesis – but the surface is just now being scratched. Truly linking patient-level PRO scores with EMRs and claims data, into one data source suitable for research purposes, will create the ability to adequately quantify the interaction of adherence, preferences, and satisfaction, beyond just the conceptual level. The goal should be to generate treatment-specific, non-biological feature-specific, time-dependent, and population-specific regression coefficients and estimates, and calculations for log transformation (or simple linear, where appropriate), which could be used as adjustment factors on HbA1c and other clinical parameters within CEA.

Additionally, as these new data sources are developed and become available across different geographies, there will be greater opportunity to conduct country-specific CEAs to facilitate more localized decision-making. It is important to note that the modeling analyses conducted in this thesis were taken from the perspective of the U.S. healthcare system and payer environment. As such, the results are not necessarily generalizable or representative of what may be seen elsewhere – this is especially true where significant differences exist in (1) types of patient populations (e.g., ethnicities, risk levels, lifestyles) and (2) healthcare system processes and payment structures (e.g., co-payment levels, access to care, finance/reimbursement mechanisms). For example, it is very plausible that healthcare systems with low co-payments, or an infrastructure which improves the doctor-patient relationship over a long time period, will increase a patient's satisfaction with care and result in improved medication adherence, better outcomes, and reduced costs. Such features in healthcare systems are found in several European countries, and therefore, research in these countries on the impact of adherence and other real-world factors is important. Any potential country-specific effects identified in these efforts could be captured for application in a novel framework described in Chapters 8 and 9.

Furthermore, it remains essential to continuously incorporate modern clinical knowledge and practice into modeling. The CEAs found in this thesis utilize HbA1c targets as the primary intermediate clinical outcome driving modeled results. Although optimizing HbA1c has long been suggested as fundamental in determining diabetic outcomes, and remains important as a marker for tracking disease progression, recent evidence puts into question the benefit of strict glucose management on cardiovascular outcomes, and supports the need to counterbalance tight control with a focus on avoiding major hypoglycemia [1,2]. Accordingly, innovative work on modeling methods which properly illustrate the risk-benefit context of the various strategies to treat diabetes are warranted. Of note, as we found in Chapter 7, patients who achieve high levels of adherence experience a significant reduction in risk for major hypoglycemia, even with insulin therapy. It therefore could be possible that when patients use products they prefer and are more adherent with, their risk for serious hypoglycemia can be reduced to some extent. If this is achieved, clinicians may be able to pursue tight glucose control more aggressively than they otherwise would have.

Lastly, modeling techniques must keep pace with product innovation to fit current market conditions and payer needs. This is true at the structural and mathematic level. As the data sources and correlation estimates for various populations and diabetes treatments continue to be developed, models should be modified accordingly. As seen in Chapter 9, additional health states and relationships between adherence, patient perceptions, and clinical parameters may become part of new Markov structures. Simulation techniques, ranges for sensitivity analysis, updated transition probabilities, and related equations which yield more precise findings on these relationships should be developed and applied over time. For example, new techniques may be developed for incremental modeling of adherence, rather than the categorical (+/- MPR 80%) approach that was taken in this thesis. This is important because in the real world, where decisions need to be made, it is very likely that patients moving from 50% to 60% adherence will receive more benefit than those moving from, say, 90% to 100%. Patients with an MPR=79% are likely not

very different from patients with MPR=81%, and this is why relative and absolute changes in adherence, for adjustment purposes in future models, should be taken in context from a patient or population's baseline/starting level of adherence.

As pressure continuously mounts on reimbursement authorities to develop strategies and tactics which curb costs through efficient care, we hope that our approach to improving the quality of CEAs will also improve the quality of decision-making. If this can be achieved, then we can expect to also achieve the ultimate goal of improving the health and well-being of diabetes patients.

References

1. Laakso M. Benefits of Strict Glucose and Blood Pressure Control in Type 2 Diabetes: Lessons from the UK Prospective Diabetes Study. Circulation. 1999. **99**: 461-462.
2. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011. **26**: 343.

Thesis Summary

The incidence and costs of diabetes are rising dramatically across the globe. In response, healthcare decision-makers have attempted to control costs yet maintain appropriate access to care. For this to happen, it's crucial that decision-makers have the most reliable and accurate evidence on which treatments provide the greatest value for the populations that they oversee. Economic evaluations, and in particular cost effective analyses, have become an important part of this evidence.

Type 2 diabetes, which is a metabolic disorder and is commonly diagnosed in adulthood, is the most prevalent form of diabetes. However, there are also many people with Type 1 diabetes, an autoimmune disorder usually diagnosed among children or adolescents. Both types require chronic treatment, and patients may live a full life with effective care. Therefore, adult patients with diabetes, mostly Type 2, represent the greatest health economic burden for this disease and are the focal group of patients in this thesis.

Tailored therapy which emphasizes a patient-centered approach is now an important concept for both clinicians and pharmaceutical manufacturers alike. Treatment guidelines and modern clinical practice highlight the importance of individualized goals given a specific patient's social, demographic, and clinical characteristics. Manufacturers of new diabetes treatments are increasingly enhancing the non-biological features of their products with the goal of making them easier to use and less inconvenient. This patient-centered approach makes it more likely that patients will properly adhere to treatment due to greater preference and satisfaction for certain therapies. Patients who are more adherent with diabetes medication may have more tightly-controlled HbA1c, and thereby experience better outcomes, consume fewer resources, and overall be less costly.

Current economic evaluations in diabetes largely ignore the impact on outcomes and costs that adherence may have. The consequence is that decision-makers who use these evaluations may have incomplete or insufficient evidence when allocating resources and establishing levels of access to care. As non-biological product features, which impact patient perceptions and behavior, become further refined and more prominent in modern treatments, it will be increasingly important to capture their full impact in economic evaluations.

The primary aim of this thesis is to improve the health of diabetes patients by identifying areas in which improvements in economic evaluations are warranted, and proposing a novel framework wherein adaptations addressing these areas can be made. To this end, we have documented associations amongst non-biological product features, patient perceptions, medication adherence, resource use and costs, and have developed a new way of incorporating them into cost effectiveness analysis. This should support better decision-making, and ultimately, help ensure patients receive proper care at the proper time.

Thesis Samenvatting

In de hele wereld zijn de incidentie en kosten van diabetes de laatste jaren dramatisch gestegen. Als reactie hierop hebben beleidsmakers in de gezondheidszorg geprobeerd de kosten te beheersen zonder de toegang naar de noodzakelijke zorg te belemmeren. Om te kunnen bepalen welke behandelingen de meest aantrekkelijke zijn is het van cruciaal belang dat beleidsmakers het meest betrouwbare en nauwkeurige bewijs hebben van de verschillende behandelopties. Economische evaluaties - oftewel kosteneffectiviteitsanalyses - vormen een belangrijk onderdeel van dit bewijs.

Type 2 diabetes is een stofwisselingsziekte die doorgaans bij volwassenen gediagnosticeerd wordt. Alhoewel type 2 diabetes de meest voorkomende vorm van diabetes is, zijn er echter ook veel mensen met type 1 diabetes, een autoimmuunziekte die meestal gediagnosticeerd wordt bij kinderen of adolescenten. Beide typen vereisen chronische behandeling maar met effectieve zorg zijn diabetespatiënten in staat om een normaal leven te leiden. De grootste gezondheids- en economische lasten voor deze ziekte worden veroorzaakt door volwassen diabetespatiënten met vooral type 2 diabetes. Deze patiënten staan centraal in dit proefschrift.

Therapie op maat, een patiëntgeoriënteerde benadering, is inmiddels een belangrijk begrip voor zowel clinici als de farmaceutische industrie. Zowel behandelrichtlijnen als de dagelijkse praktijk wijzen op het belang van het stellen van patiëntspecifieke doelen gebaseerd op sociale, demografische en klinische kenmerken. Fabrikanten van nieuwe diabetes behandelingen besteden steeds meer aandacht aan verbeteringen van de niet-biologische kenmerken van hun producten om zo de patiëntacceptatie en het gebruiksgemak van deze behandeling te vergroten. Deze patiëntgeoriënteerde benadering verhoogt de kans dat patiënten de therapie nauw zullen blijven volgen. Patiënten die trouwer zijn met het gebruik van hun diabetes medicatie kunnen een betere controle hebben over hun HbA1c. Hierdoor ervaren zij een betere gezondheid en maken minder gebruik van de zorg, wat resulteert in minder kosten.

Beleidsmakers maken gebruik van economische evaluaties bij vergoedingsbeslissingen over nieuwe therapieën. In economische evaluaties van diabetesbehandelingen wordt vrijwel geen rekening gehouden met de invloed van therapietrouw op de (kosten)effectiviteit van deze behandelingen. Het gevolg is dat beleidsmakers onvolledige of onvoldoende bewijs hebben van de (kosten)effectiviteit. Als de niet-biologische kenmerken van een therapie nog verder verfijnd worden, zal het steeds belangrijker zijn om de volledige impact goed vast te leggen in economische evaluaties.

Het primaire doel van dit proefschrift is om het beleid van diabetes behandelingen te verbeteren door: a) gebieden te identificeren waarbij economische evaluaties aangepast moeten worden en b) een nieuw kader voor te stellen waarin deze aanpassingen gemaakt kunnen worden. Om dit doel te kunnen bereiken, hebben we de mate van samenhang gedocumenteerd tussen de niet-biologische aspecten van het product, de patiëntpercepties, therapietrouw, het zorggebruik en de zorgkosten. Verder hebben wij een nieuwe methode

ontwikkeld om deze aspecten te integreren in kosteneffectiviteitsanalyses. Dit zou moeten leiden tot het maken van betere vergoedingsbeslissingen waardoor de patiënt verzekerd is van de juiste zorg op het juiste moment.

Publications reprinted in this thesis

Chapter 2 Valentine WJ, Palmer AJ, Nicklasson L, Cobden D, Roze S. Improving Life Expectancy and Decreasing the Incidence of Complications Associated with Type 2 Diabetes: A Modelling Study of HbA1c Targets. *International Journal of Clinical Practice*. 2006;**60**(9):1138-45.

Chapter 3 Valentine WJ, Palmer AJ, Emy-Albrecht KM, Ray JA, Cobden D, Foos V, Lurati FM, Roze S. Cost-Effectiveness of Basal Insulin from a US Health System Perspective: Comparative Analyses of Detemir, Glargine and NPH. *Advances in Therapy*. 2006 Mar-Apr;**23**(2):191-207.

Chapter 4 Stockl K, Ory C, Vanderplas A, Nicklasson L, Lyness W, Cobden D, Chang E. An Evaluation of Patient Preference for an Alternative Insulin Delivery System compared to Standard Vial and Syringe. *Current Medical Research & Opinion*. 2007 Jan;**23**(1):133-46.

Chapter 5 Brod M, Cobden D, Lammert M, Bushnell D, Raskin P. Examining Correlates of Treatment Satisfaction for Injectable Insulin in Type 2 Diabetes: Lessons Learned from a Clinical Trial comparing Biphasic and Basal Analogues. *Health & Quality of Life Outcomes*. 2007. Feb;**7**;5-8.

Chapter 6 Lee WC, Balu S, Cobden D, Joshi AV, Pashos C. Prevalence and Economic Consequences of Medication Adherence in Diabetes: A Systematic Literature Review. *Managed Care Interface*. 2006 Jul;**19**(7):31-41.

Chapter 7 Cobden D, Lee WC, Balu S, Joshi AV, Pashos C. Health Outcomes and Economic Impact of Therapy Conversion to a Biphasic Insulin Analog Pen Among Privately-Insured Patients with Type 2 Diabetes Mellitus. *Pharmacotherapy*. 2007 Jul;**27**(7):948-62.

Chapter 8 Cobden D, Niessen LW, Rutten FFH, Barr CE, Redekop WK. Relationships among Self-Management, Patient Perceptions of Care, and Health Economic Outcomes for Decision-Making and Clinical Practice in Type 2 Diabetes. *Value in Health*. 2010 Jan/Feb; **13**(1):138-47.

Chapter 9 Cobden D, Niessen LW, Rutten FFH, Redekop WK. Modeling the Economic Impact of Medication Adherence in Type 2 Diabetes: a Theoretical Approach. *Patient Preference & Adherence*. 2010 August; **4**:283-90.

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Personal History

David Stanley Cobden is currently a National Clinical Account Director and Health Economist at AstraZeneca Pharmaceuticals LP. Since 2004, he has held numerous roles in health economics, beginning with Novo Nordisk A/S, and then Hoffman-La Roche Ltd. He graduated in 2002 with a Master of Science degree in Biochemistry at Georgetown University, and subsequently earned a Master of Public Health degree in 2004 at Dartmouth Medical School, where he concentrated in health services research and was a Graduate Outcomes Researcher at the Dartmouth Institute for Health Policy and Clinical Practice.

He continued his education at the Erasmus University Rotterdam, institute for Medical Technology Assessment (iMTA), where he wrote his PhD thesis entitled, "*Economic Implications of Patient-related Factors in Diabetes Care*," under the supervision of Prof. Frans F.F.H. Rutten, Prof. Louis W. Niessen, and Dr. W. Ken Redekop. His current research addresses the economics of medication adherence and patient-reported outcomes in diabetes, but he has previously focused on database analysis and cost-effectiveness modeling in numerous therapeutic areas including oncology, dyslipidemia, and autoimmune disorders. He has also been an active member of the International Society for Pharmacoeconomics and Outcomes Research (*ISPOR*), and the International Society for Quality of Life Research (*ISOQOL*), as well as peer-reviewing for several scholarly journals.

Propositions

1. A valid manner to assess future costs and health outcomes for diabetes patients is through economic evalutation performed by Markov/Monte-Carlo (M/MC) methods, utilizing HbA1c as the clinical marker driving modeled disease progression (this thesis)

2. Non-biological product features for diabetes treatments are increasingly prevalent and diverse, and may impact patient perceptions of care as well as ability or willingness to properly self-manage (this thesis)

3. Perceptions of care among diabetes patients, specifically preferences for and satisfaction with treatment, are related to willingness to properly self-manage, and therefore likelihood of attaining HbA1c treatment goals (this thesis)

4. Self-management (medication adherence) is a relevant input parameter for economic evaluations in diabetes due to its relationship with overall, diabetes-related, and adverse-event-related healthcare costs (this thesis)

5. Although methodologic innovations in M/MC modeling which incorporate measures of self-management are possible, many current economic evaluations inadequately capture this impact, and therefore may be providing incomplete information to decision-makers (this thesis)

6. Baseball is 90% mental...the other half is physical (Yogi Berra; N.Y. Yankees)

7. Every system is perfectly designed to achieve the results it yields (W. E. Deming)

8. Many healthcare payers in the U.S. place a primary emphasis on costs in the decision-making process, and often neglect other important factors such as quality of life

9. Any intelligent fool can make things bigger, more complex, and more violent…it takes a touch of genius -- and a lot of courage -- to move in the opposite direction (and) make things as simple as possible, but not simpler (Albert Einstein)

10. Science and religion need not be mortal enemies, for they are connected by human nature and the immortal desire to better understand what seems uncertain

11. Earning a PhD reveals more about one's determination and work ethic than it does raw intelligence

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