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The Prime Diabetes Model: Novel Methods for Estimating Long-Term Clinical and Cost Outcomes in Type 1 Diabetes Mellitus

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ABSTRACT

Background: Recent publications describing long-term follow-up from landmark trials and diabetes registries represent an opportunity to revisit modeling options in type 1 diabetes mellitus (T1DM). **Objectives:** To develop a new product-independent model capable of predicting long-term clinical and cost outcomes. **Methods:** After a systematic literature review to identify clinical trial and registry data, a model was developed (the PRIME Diabetes Model) to simulate T1DM progression and complication onset. The model runs as a patient-level simulation, making use of covariance matrices for cohort generation and risk factor progression, and simulating myocardial infarction, stroke, angina, heart failure, nephropathy, retinopathy, macular edema, neuropathy, amputation, hypoglycemia, ketoacidosis, mortality, and risk factor evolution. Several approaches novel to T1DM modeling were used, including patient characteristics and risk factor covariance, a glycated hemoglobin progression model derived from patient-level data, and model averaging approaches to evaluate complication risk. **Results:** Validation analyses comparing modeled outcomes with published studies demonstrated that the PRIME Diabetes Model projects long-term patient outcomes consistent with those reported for a number of long-term studies. Macrovascular end points were reliably reproduced across five different populations and microvascular complication risk was accurately predicted on the basis of comparisons with landmark studies and published registry data. **Conclusions:** The PRIME Diabetes Model is product-independent, available online, and has been developed in line with good practice guidelines. Validation has indicated that outcomes from long-term studies can be reliably reproduced. The model offers new approaches to long-standing challenges in diabetes modeling and may become a valuable tool for informing health care policy.

Keywords: cost-effectiveness, model, risk prediction, type 1 diabetes mellitus.

Introduction

Type 1 diabetes mellitus (T1DM) is a serious, chronic condition that is associated with significant morbidity and mortality, and its incidence is increasing annually [1–3]. Daily management of the condition is demanding, placing a burden on patients, their caregivers, and health care providers, requiring attention to insulin administration, blood glucose monitoring, meal planning, and screening for comorbid conditions and diabetes-related complications [1]. Landmark studies such as the Diabetes Control and Complications Trial (DCCT), its follow-up study—the Epidemiology of Diabetes and Its Complications (EDIC) trial, and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) have provided evidence that optimizing therapy, particularly in terms of glycemic control, is key to minimizing the risk of long-term microvascular and macrovascular complications [4,5]. There have been several advances in insulin therapy in the last 20 years responding to this need. The first insulin analog, designed to overcome the problems of poor stability and erratic absorption profile of human insulin formulations, was launched in 1996 (insulin lispro) and has been followed by several other short-acting and long-acting insulin analogs designed for prandial and bolus administration in recent years [6].

As new therapies for T1DM become available, tools to evaluate their impact on clinical outcomes and costs are needed to assist decision makers in the efficient allocation of health care resources. Economic evaluation can, however, be challenging in T1DM because it is a chronic condition and it is common for complications to take several decades to develop. Health economic models can play an important role in addressing this challenge, provided they are accepted by health care authorities, which requires them to be transparent, on the basis of robust clinical data, and externally validated in line with published guidelines [7,8].

Although advances have been made with new models and validation studies in type 2 diabetes mellitus (T2DM), progress has been less notable in the T1DM modeling space [9]. Historically, health economic models of T1DM have been adapted from their T2DM counterparts and have relied on data from mixed

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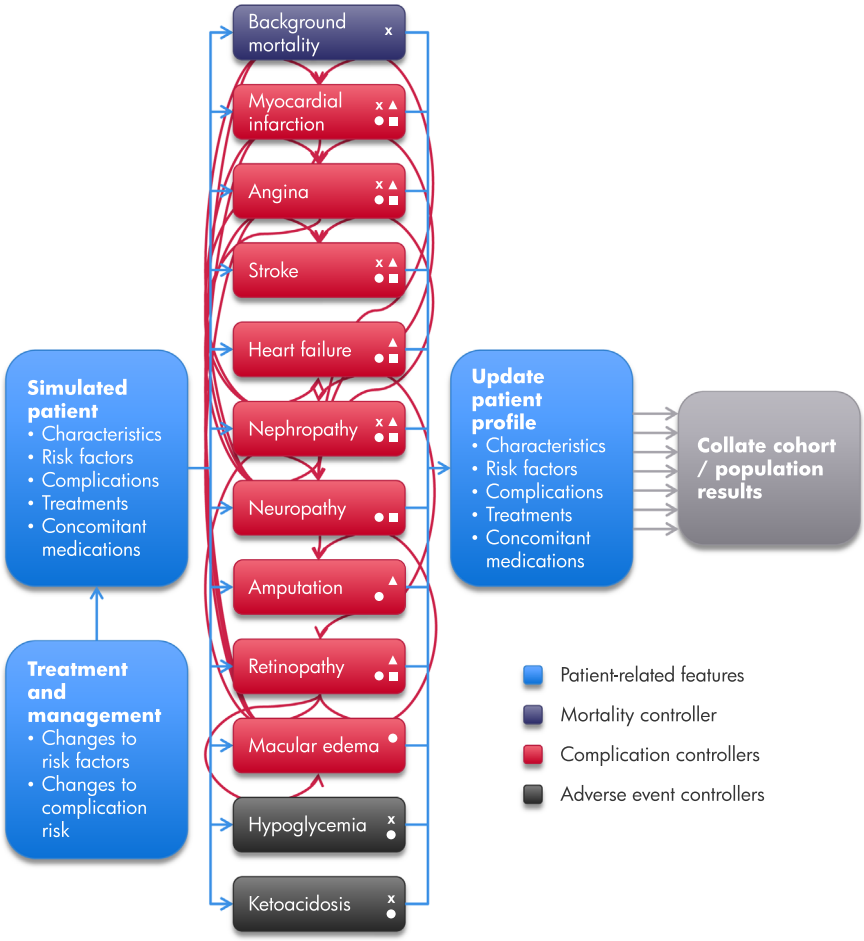

Fig. 1 – Schematic diagram of the PRIME Diabetes Model. Interactions between complication controllers are indicated by red arrows. X, risk of mortality is associated with this complication controller; ▲, SBP is a direct risk factor; ●, HbA_{1c} is a direct risk factor; ■, BMI is a direct risk factor. BMI, body mass index; HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure.

and/or T2DM populations (as well as T1DM studies) to make long-term projections of outcomes [10]. Literature review has revealed numerous publications from landmark trials and registries of T1DM in recent years. These studies represent an opportunity to revisit health economic modeling in T1DM. Our objective was, therefore, to develop a product-independent, computer simulation model of T1DM on the basis of timely data and using new approaches to long-standing challenges in T1DM modeling to provide a resource that can support decision making and inform health care policy for various users and audiences.

Methods

Literature Review

Development of the PRIME Diabetes Model was based on a comprehensive review of relevant literature and expert medical input. To identify published data that could inform diabetes model development, a literature review was conducted to find publications on existing models and clinical results relevant to complications, disease progression, and mortality risk. The search strategy was designed on the basis of high-level Medical Subject Heading terms and keywords to identify trials in diabetes, systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. Searches were limited to publications in English since January 1, 2004, and publications relating to animals were excluded. After the exclusion of duplicates, a total of 12,360 unique hits remained, the titles and abstracts of which were then screened to exclude publications that were not related to T1DM that described studies with duration of follow-up of less than 1 year, or that described studies with fewer than 100 patients (Appendix 1). The review identified a total of 58 publications in T1DM. Manual searches were then performed in January 2014 on the basis of the reference lists from these publications with no time limits applied, and a further 96 articles were identified for review. On the basis of this literature review, availability of patient-level data, and two advisory board meetings with data, clinical, and modeling experts, the model concept was finalized and the model, was developed.

Model Structure and Functionality

The model is programmed in Java Standard Edition 8 (Oracle Corp., Redwood City, CA), relying on the Apache Commons Mathematics Library for random number generation and distribution sampling (The Apache Software Foundation, Forest Hill, MD). It is architected as a patient-level simulation in which a simulated cohort of patients is generated by the model (for each of two simulation arms) on the basis of user-defined parameters and a covariance matrix derived from the DCCT data (Fig. 1). Each