A population-based macro-simulation model for policy evaluation in diabetes prevention and treatment: the MICADO model

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ABSTRACT

Objectives: Simulation models can assist in diabetes policy by giving projections of future health care use and costs, evaluating policy scenarios for prevention and treatment and extrapolating trial results over time. Most existing models concentrate on known diabetes patients. The MICADO model aims to estimate long-term effects of preventive interventions in persons with and without diabetes.

Methods: MICADO includes micro- and macrovascular diseases in relation to their risk factors. Strengths of the model are its population scope and the possibility to assess parameter uncertainty by ways of probabilistic sensitivity analyses. Outcomes are incidence and prevalence of complications, quality of life, costs and cost-effectiveness. We externally validated MICADO’s estimates of micro- and macrovascular complications, comparing these to empirical data.

Results: MICADO’s estimate was 592 (95% Inter-quantile Range (IR): 291 to 842) for the annual number of amputees, which compared well to the registered number of diabetes related amputees in the Netherlands (728). MICADO’s incidence of end-stage renal disease (ESRD) was 247 (95% IR: 120 to 363), similar to the registered incidence of ESRD in the Netherlands (277). MICADO performed well in the validation of macrovascular outcomes of population-based cohorts, while it had more difficulty to reflect a highly selected trial population.

Conclusions: Validation by comparison with independent empirical data showed that the MICADO model simulates the natural course of diabetes and its micro- and macrovascular complications well. As a population bases model, it can be applied for projections as well as scenario analyses and to evaluate the long-term (cost-) effectiveness of diabetes-related and cardio-vascular interventions.
INTRODUCTION

Medical or lifestyle interventions can reduce the risk of diabetes-related complications.\(^1\) However, benefits of interventions might occur only several years after initiation.\(^3\) Because monitoring long-term results of such interventions can be very time-consuming and expensive, simulation models can be used to evaluate interventions by extrapolating trial outcomes to long-term effects and costs.\(^4\)

Several models exist to assess the long-term cost-effectiveness of diabetes-related interventions.\(^4-13\) One of these models is the Chronic Diseases Model (CDM) in which incidence, prevalence and mortality of macrovascular diseases are extensively modelled based on data from large countrywide GP registries.\(^9\) The CDM has been used for disease projections and the evaluation of policy scenarios regarding long-term effects on morbidity, mortality, quality of life and costs.\(^9,14,15\) Until now, microvascular complications were not included in this model. While relatively low mortality risks are associated with microvascular complications,\(^16\) they add a substantial part to the burden of diabetes, and are an important target for interventions next to cardiovascular risks. For these reasons, the CDM was extended with modules on the development of microvascular complications (diabetic foot, nephropathy and retinopathy) enabling a complete assessment of diabetes interventions and was called the MICADO (Modelling Integrated Care for Diabetes based on Observational data) model.

Strength of the CDM and MICADO model is the combination of a similar model for persons with and without diabetes, which allows comparing the long-term effects of interventions targeting at persons with and without diabetes.\(^17\) MICADO also includes uncertainty for a wide range of parameters. Therefore probabilistic sensitivity analysis can be performed, varying model parameters based on distributions that reflect the uncertainty introduced when estimating these input parameters from data. The MICADO model structure is best described as a dynamic population model following overlapping cohorts of patients as they age over time. This differs considerably from most other diabetes models that use patient level Markov modelling and risk equations to simulate individual patient disease histories.\(^,\) The different structure offers considerable savings in computation time. Moreover, MICADO’s incidence and prevalence of complications as well as mortality risks were estimated from representative national registries and systematic literature reviews, resulting in a model that reflects the Dutch population and effects of care as usual treatment in daily practice. This makes the model specifically fit for policy support since the results will reflect a typical diabetes population, rather than the highly selected trial populations.

The objective of this paper is to describe the MICADO model and to externally validate its performance regarding prediction of micro- and macrovascular complications. We
compared model outcomes to independent empirical estimates for the incidence of end-stage microvascular complications in the Netherlands. For the macrovascular complications, independently provided datasets for a Swedish, US HMO and trial population were fed into the model and then used to predict events over a 5 year time horizon, being blinded from the actual event rates. These were then compared to actual event rates from the empirical datasets that were provided later.

**METHODS**

**Model design**
The CDM is a Markov-type, multistate transition model with one-year cycle length, which describes the general population as well as type 1 and type 2 diabetes patients’ progression through risk factor classes and (complications of) diabetes. It describes changes risk factors (smoking status, BMI, physical activity level, blood pressure, total cholesterol, and HbA1c) and prevalence of diabetes and 4 macrovascular complications (coronary heart disease, stroke, chronic heart failure, myocardial infarction). Also, the effects of antihypertensive and lipid lowering drug use on cardiovascular risks are included. Macrovascular diseases and diabetes were linked to risk factors and to each other using relative risks derived from systematic literature reviews. Relative risks for complications were carefully disentangled to correct for double counting, with risk factors being a risk for intermediate risk factors like diabetes. This is illustrated in figure 1.

![Figure 1. Dependency relations between risk factors, diabetes and macrovascular complications of diabetes](image)

Incidence and prevalence as well as mortality were estimated from representative national registries. All transition rates between risk factor classes and stages of complications are age- and sex specific. More detailed descriptions of model structure and its input data regarding risk factors and macrovascular complications have been published previously. In the MICADO model 3 types of microvascular complications in diabetes patients were added, that is, the diabetic foot, nephropathy and retinopathy. For each complication, transition rates were estimated for each one-year time step for
The MICADO model

each of the severity stages distinguished from literature and empirical data (Appendix C). For all microvascular complications, HbA1c was chosen as a summary factor of disease control. In several stages of the complications, transition to a more severe stage was made dependent on the level of HbA1c using an adapted version of the formula used by Eastman et al (Appendix A, supplementary material).21, 22 The increased risk for complications due to higher levels of HbA1c apply to type 1 and type 2 diabetes patients.2, 23 HbA1c was divided into 8 categories increasing from an HbA1c level lower than 6.5% to an HbA1c higher than 9.5%, with a range of 0.5% per category. Given the implementation of interventions aiming at a decrease of HbA1c,1, 2 current practice annual mean increase in HbA1c in the Netherlands is probably lower than the 0.2% observed in the UKPDS, published 15 years ago.2 Therefore, MICADO assumed an annual increase in HbA1c of 0.1%. The model was constructed using Mathematica software package version 6.1 (Wolfram Research) for Windows.

Mortality
Disease-specific mortality rates were estimated from age- and sex-specific disease incidence and prevalence rates available from registries in general practice in combination with cause specific mortality rates form statistics Netherlands. This has been described in detail previously.9 MICADO models mortality specific from diabetes, coronary heart disease, myocardial infarction, chronic heart failure, stroke or other causes unrelated to diabetes, taking account of competing risks. Mortality rates were age and sex-specific.

Diabetic foot
Complications of the foot were modelled distinguishing 4 stages, based on the classification systems described by Ortegon et al (Figure 2A)24. Because most patients who develop an ulcer are healed after 6 months according to empirical data,25 these transient stage was incorporated in the stage “healed”. The transition from the stage in which the diabetes patient is uncomplicated regarding the lower extremity to the stage with neuropathy, an early stage of the diabetic foot, depends on the level of HbA1c.21, 22 The remaining transition rates were estimated from prospective cohort studies.24

Nephropathy
Progression of nephropathy was modelled through the stages microalbuminuria (0.03-0.3 g/l), gross proteinuria (>0.3 g/l) and end-stage renal disease (ESRD) (Figure 2B). Transition rates based on the DCCT study21 were combined with transition rates based on the UKPDS study.26 Progression to microalbuminuria and macroalbuminuria was dependent of the level of HbA1c.22
Retinopathy
MICADO distinguishes 4 stages of retinopathy (Figure 2C). The first stage was background retinopathy. From this stage patients could progress to the stage proliferative diabetic retinopathy or to macular oedema. The transition rate to background retinopathy, proliferative retinopathy and macular edema increased with a higher level of HbA1c. The transition rate from proliferative diabetic retinopathy or macular edema to blindness was dependent of treatment with photocoagulation.

Figure 2. Transitions between stages of nephropathy, the diabetic foot and retinopathy. Arrows between the stages of complications represent the disease progression in one year. In each stage of complication there is a probability of death which is not shown in the figure. In the diabetic foot module, most diabetes patients who develop an ulcer, recover within one year which is symbolized by the dashed circle and the possibility to progress from uncomplicated to healed within one cycle year.

ESRD=End Stage Renal Disease

Baseline characteristics of the modelled population
The simulation cohort entered into the MICADO model reflected the total Dutch population in 2003, as regards age, sex and the prevalence of diabetes and cardiovascular diseases. It was a closed cohort existing of persons with and without diabetes. Transition rates for risk factors, cardiovascular diseases and mortality rates applied to the Dutch (diabetes) population. The number of diabetes patients in each category of HbA1c at baseline was estimated from a prospective population-based study in the Netherlands. Detailed representative data on the prevalence of microvascular complications in the diabetes population in 2003 was unavailable. Therefore, uncomplicated diabetes patients entered into the model and disease progression was simulated. Baseline prevalence for all stages of the three microvascular complications was then estimated from prevalence after a simulation period of 10 years (burn-in period), which is the mean diabetes duration of the Dutch diabetes population. Resulting baseline prevalence of the microvascular complications is shown in the table and was used in the final version of the model.
The MICADO model

Probabilistic sensitivity analysis and validation of the model
To account for uncertainty in model parameters, probabilistic sensitivity analysis was performed with the MICADO model. For each transition rate, random values were drawn from independent probability distributions based on the data used to estimate these transitions (Appendix A, supplementary material). Applying Monte Carlo Simulation, the model was run 300 times using a new set of randomly sampled transition rates in each run. After all runs, the expected incidence of diseases was estimated after the preset simulation period, including a calculation of the 95% inter-quantile ranges (IR) using the 0.975 quantile and the 0.025 quantile obtained after ranking the estimated incidence or prevalence of the outcome of interest in each run in numeric order. Increasing the number of runs above 300 did not substantially change (<5%) the limits of the 95% inter-quantile ranges.

To externally validate the MICADO model, we compared model-based estimates to empirical estimates of end-stage microvascular complications in the Netherlands. We checked whether the inter-quantile limits of our estimated incidence included the empirical incidence of the microvascular endpoints.

External validation of the microvascular complications
Hospital discharge records from the Dutch Medical Register (LMR) were used to obtain information on the total amount of amputations performed in 2003. The LMR contains all hospital admissions in the Netherlands including performed medical procedures and discharge diagnosis, coded according to the International Classification of Diseases, ninth revision clinical modification. Validity of the discharge data and diagnosis registered in the LMR was shown to be adequate. A number of 1055 amputations (minor and major amputations in the lower extremity) had been performed in patients with diabetes as primary diagnosis. Because the stage ‘amputation’ of the diabetic foot in the MICADO model is an absorbing state, we had to adjust for double counting patients that had multiple amputations. The proportion of number of amputees to total amputations was 0.69 which was stable from 1991 till 2000. We multiplied the number of amputations registered in the Netherlands by 0.69 to adjust for double counting, resulting in 728 amputees in 2003.

The number of diabetes patients starting dialysis in 2003 was obtained from the countrywide renal replacement registry which contains information about every patient treated with a form of renal replacement in the Netherlands. The number of new dialysis patients who had a diagnosis of diabetes was 277 in 2003 and varied between 252 and 296 during the period 2000 to 2005.

Independent data on the incidence of blindness in diabetes patients in the Netherlands was not available and hence model outcomes for this complication could not be compared to external empirical data.
External validation of the macrovascular complications
Datasets used to validate the macrovascular events consisted of the Kaiser Permanente insured diabetes patients (USA) (n=29,247), patients with type 2 diabetes in the Swedish National Diabetes Registry in which started in 1996 (n=29,034), and all patients in the ADVANCE study (Asia, Eastern Europe, and the Established Market Economies (n=11,140)). For all these datasets, information on HbA1c, blood pressure, cholesterol, BMI, number of smokers and prevalence of macro- and microvascular complications were provided for year t0. These variables were used to calibrate the model to the dataset. Then the model was run for 5 years, estimating incidence of macrovascular complications. Finally, the actual empirical event rates of cardiovascular events (being provided on a later point in time) were compared to the model outcomes.

Sensitivity analysis
In addition to the probabilistic sensitivity analyses, univariate sensitivity analyses were performed to test model robustness and the effect of assumptions regarding input data. First, the effect of an increase in HbA1c of 0.2% per year according to the UKPDS was tested.

Because the baseline distribution of the microvascular complications in the simulation cohort could not be estimated directly from empirical data, but was determined indirectly using transition rates, the effects of variation in the baseline distribution were tested in a second sensitivity analysis. This was performed by decreasing and increasing baseline prevalence of all stages of complications with 10% and increasing or decreasing the uncomplicated stage accordingly. Then the 10 and 20 years outcomes were simulated.

Regarding the treatment of retinopathy and macular edema, a sensitivity analysis tested outcomes when appropriate photocoagulation was performed in 95% instead of 100% of patients with proliferative diabetic retinopathy or macular edema. The sensitivity analysis showed how the magnitude of improper treatment with photocoagulation affected the prevalence of blindness.

For the macrovascular events, no univariate sensitivity analyses were performed.

All results were shown for a time horizon of 10 and 20 years. For the present manuscript, focus was on incidence and prevalence of complications and discounting was irrelevant.

RESULTS

The estimated prevalence of the stages of microvascular complications at baseline and 10 and 20 years after baseline were presented (Table). After 10 years, the model predicted that 61% of the initial diabetes population had died; the prevalence of amputees was
0.7%, 0.4% of the patients had ESRD and 1.1% of the population was blind. The estimated number of ulcers and abscesses during twenty years was 52,600. Twenty years after baseline another 2,720 patients had developed proliferative diabetic retinopathy and 53,500 patients had developed macular edema. All these patients (11% of the baseline cohort) were assumed to receive appropriate treatment with photocoagulation.

Table 1: Prevalence of stages of the three microvascular complications in persons with diabetes at baseline and at 10 and 20 years (rounded to thousands). Percentages in brackets reflect proportions of the total population.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Baseline</th>
<th>10 years</th>
<th>20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic foot</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>270,000 (57.7%)</td>
<td>67,000 (31.2%)</td>
<td>8,900 (13.7%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>200,000 (37.3%)</td>
<td>121,000 (56.6%)</td>
<td>43,000 (66%)</td>
</tr>
<tr>
<td>Abscess</td>
<td>900 (0.2%)</td>
<td>700 (0.3%)</td>
<td>300 (0.5%)</td>
</tr>
<tr>
<td>Healed</td>
<td>26,000 (4.6%)</td>
<td>24,000 (11.2%)</td>
<td>12,000 (18.4%)</td>
</tr>
<tr>
<td>Amputation</td>
<td>1,200 (0.2%)</td>
<td>1,500 (0.7%)</td>
<td>900 (1.4%)</td>
</tr>
<tr>
<td><strong>Nephropathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>432,000 (86.6%)</td>
<td>159,000 (74%)</td>
<td>38,000 (58.5%)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>50,000 (10.0%)</td>
<td>35,000 (16.3%)</td>
<td>12,000 (17.8%)</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>16,000 (3.3%)</td>
<td>20,000 (9.3%)</td>
<td>15,000 (22.4%)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>400 (0.1%)</td>
<td>800 (0.4%)</td>
<td>800 (1.3%)</td>
</tr>
<tr>
<td><strong>Retinopathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>425,000 (86.7%)</td>
<td>156,000 (73%)</td>
<td>36,000 (55.2%)</td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>59,000 (11.4%)</td>
<td>34,000 (16%)</td>
<td>13,000 (20%)</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>600 (0.1%)</td>
<td>1000 (0.5%)</td>
<td>900 (1.4%)</td>
</tr>
<tr>
<td>Macular edema</td>
<td>12,500 (1.8%)</td>
<td>20,200 (9.4%)</td>
<td>13,000 (20%)</td>
</tr>
<tr>
<td>Blindness</td>
<td>700 (0.001%)</td>
<td>2,300 (1.1%)</td>
<td>2,200 (3.4%)</td>
</tr>
</tbody>
</table>

External validation of microvascular complications

The number of diabetes patients in which a first amputation was performed over a one-year time horizon as calculated by our model was 592. The 95% inter-quantile range for the estimated incidence ranged from 291 to 842. The incidence projected by our model is hence in line with the number of lower extremity amputees retrieved from the Dutch hospital discharge register (728). The incidence of ESRD estimated by the MICADO model was 247 (95% IR 124 to 373), which compares well to the registered incidence of ESRD by the national register (277).

External validation of macrovascular complications

The MICADO model performed well in estimating the cumulative incidence of macrovascular complications after five years of follow up of the population-based studies from Sweden and the US. The extrapolation of trial results (ADVANCE) and the effect of a slightly lower HbA\textsubscript{1c} and systolic blood pressure was less accurate (Figure 3).
Chapter 5

Figure 3. Proportion of the initial cohort experiencing the event during five years of follow-up. Model-based estimates compared to empirical data of the Kaiser Permanente cohort (A), the Swedish National Database (B) and the ADVANCE study (C). In the ADVANCE study, participants in the intensive treatment arm had a lower level of HbA₁c (-0.75%) and a lower systolic blood pressure (-2.5 mmHg).

Sensitivity analyses

In a first sensitivity analysis, a yearly increase of HbA₁c of 0.2% according to the UKPDS was modelled instead of 0.1%. This did not substantially affect mortality rates after 10 years. The effect of a faster increase in the level of HbA₁c on microvascular endpoints was lowest for the prevalence of amputations, which increased to 1,849 (95% IR: 1,343 to 2,265) and 1,002 (95% IR: 674 to 1,292) after 10 and 20 years respectively and highest for the prevalence of ESRD 1,923 (95% IR: 982 to 2,750) and 1579 (95% IR: 756 to 2,386).

Results of our second sensitivity analyses showed that after both decreasing and increasing the baseline prevalence with 10%, the prevalence of first amputations, ESRD and blindness did not differ significantly after 10 and 20 years compared to the original model estimates (Appendix B, supplementary material).

The prevalence of blindness after 10 and 20 years, assuming appropriate treatment in 95% of the diabetes patients with retinopathy or macular edema instead of 100%, did hardly change: 1.1% (n=2,345 (95% IR 1,370 to 3,330)) compared to 1.1% (n=2,290 (95%
IR 1,280 to 3,310) after 10 years, and 3.5% (n=2,303 (95% IR 1,097 to 3,263) compared to 3.5% (n=2,200 (95% IR: 1,020 to 3,220)) after 20 years.

DISCUSSION

The main purpose of the MICADO model is to enable consistent and integral evaluations of the long-term costs and effects of interventions aiming to reduce micro- and / or macrovascular diabetes complications in existing diabetes patients in comparison with interventions aiming at similar risk factors in the general population. Validation to independent empirical data showed that the model in its current form performed well.

Regarding the macrovascular complications, the model performed better in the extrapolation of outcomes of the population-based cohorts compared to trial results and effects of intensified treatment. Reasons for a less precise estimation might be the impossibility to extrapolate a selected high-risk diabetes population using a population-based model such as the MICADO model, designed for projections for public health scenarios.

A number of diabetes models, modelling a microvascular complication,11, 24 or micro-as well as macrovascular complications,5-8,10,12,13 integrate results from several prospective studies. Beyond this, MICADO included parameter uncertainty to reflect the imprecision of the used transition rates.

The effect of several risk factors on the development of macrovascular complications and associated costs and quality of life is extensively modelled in the MICADO model. Most existing diabetes models do not explicitly model the effect of medication use on blood pressure and cholesterol levels.4, 12 Our model distinguished between people using statins or antihypertensive drugs. That is, the direct effect of statins and antihypertensive drugs on cardiovascular outcomes was modelled18-20 and then split into a risk factor related effect and an additional effect. The microvascular complications, dependent of the level of HbA1c, contain stages routinely assessed in diabetes patients, which makes the model easily accessible for the simulation of existing cohorts. Besides neuropathy, a history of ulceration increases the risk of an amputation, which is not included in most models.

Diabetes duration was not modelled as a predictor of the development of microvascular and macrovascular complications. Instead, HbA1c as a more policy-relevant variable indicates the severity of the disease and affects transition rates between stages of complications. Previous studies have shown that HbA1c is an independent predictor of microvascular complications and that the incidence of these complications can be reduced by lowering a patient’s HbA1c level1, 3 Sufficient data on the residual risk of a complication caused by diabetes duration (adjusted for HbA1c level) was not available.
for all stages. For our purpose of developing a model for policy evaluation regarding prevention of diabetes and its complications, HbA1c is a relevant severity indicator.

The incidence of the endpoints of the microvascular complications obtained by projections of the MICADO model was compared with diabetes related incidence according to national registries. The model predicted the annual number of amputees in the lower extremity and the incidence of ESRD quite accurately. We were not able to validate the performance regarding the modelling of retinopathy as specific data on the incidence or prevalence of diabetes related blindness was not available for the Netherlands. Some limitations of the MICADO model should be mentioned. Our MICADO model monitors the marginal distributions of risk factors and comorbidity and thus does not describe the joint probability distribution over all risk factor classes and states for co-morbid diseases. Thus, e.g. the probabilities of having nephropathy as well as having retinopathy are assumed independent, conditional on HbA1c value. However, this assumption maybe justified by the limited amount of empirical data reducing the possibility to reliably estimate the joint distribution. Modelling the joint distribution would mainly increase the uncertainty of the model results without adding much further precision to the outcomes. In addition, the MICADO model is intended to be used for policy evaluations at population level rather than individual prediction.

MICADO has no direct modelling of mortality caused by microvascular complications. However, in most persons with diabetes, mortality is related to macrovascular diseases and a very small percentage of diabetes patients die from (an end stage of) a microvascular complication independently of macrovascular diseases.

All risk factors included in our model were modelled as categorical variables. This means that it was necessary to categorize continuous measures, leading to loss of information. Regarding the variable HbA1c classification into 8 categories implied a very small range of 0.5 units for each category and consequently a limited loss of information.

The current paper concentrated on diabetes outcomes in terms of incidence and prevalence of micro- and macrovascular complications. However, the model also includes costs and utilities related to the microvascular complications of diabetes. To summarize, we have developed and validated a model for the evaluation of long-term complications of diabetes. The MICADO model can be used to evaluate policy scenarios and compare diabetes-related interventions aiming to reduce the risk of vascular diseases.
REFERENCES


PART B

TOWARDS PERSONALIZED CARE