Article type: Original Research Article

Running head: Modelling Lifetime Outcomes in Type 1 Diabetes

Simulating Lifetime Outcomes Associated with Complications for People with Type 1 Diabetes

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Acknowledgments: This report is independent research commissioned by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number 08/67/03). The views expressed in this publication are those of the authors and not necessarily those of the UK NHS, the NIHR or the Department of Health (UK). In regard to other funding, P.M.C. was funded from an Australian National Health and Medical Research Council (NHMRC) Career Development Award

(571122). T.W.C.L. was partially funded from a NHMRC Capacity Building Grant (571372) and an NHMRC project grant (1028335). A.J.H. was supported by an NHMRC Capacity Building Grant (571372). A.F. receives support from the NIHR Oxford Biomedical Research Centre.

Contributions: The authors would like to thank Andrew Palmer and Bill Herman for their comments on previous versions to the manuscript. All authors conceived and planned the work that led to the manuscript. T.W.C.L. was responsible for the analysis and development of the model, whilst P.M.C., A.J.H., R.J.S. and A.F. made substantive suggestions for revision and approved the final submitted version.

Conflicts of Interest: The authors have no competing interests that are directly relevant to the content of this article.

Abstract

Objectives: The aim of this study was to develop a discrete-time simulation model for people with type 1 diabetes mellitus, to estimate and compare mean life expectancy and quality-adjusted life-years (QALYs) over a lifetime between intensive and conventional blood glucose treatment groups.

Methods: We synthesized evidence on type 1 diabetes patients using several published sources. The simulation model was based on 13 equations to estimate risks of events and mortality. Cardiovascular disease (CVD) risk was obtained from results of the DCCT (Diabetes Control and Complications Trial). Mortality post-CVD event was based on a study using linked administrative data on people with diabetes from Western Australia. Information on incidence of renal disease and the progression to CVD was obtained from studies in Finland and Italy. Lower-extremity amputation (LEA) risk was based on the type 1 diabetes Swedish inpatient registry, and the risk of blindness was obtained from results of a German-based study. Where diabetes-specific data were unavailable, information from other populations was used. We examine the degree and source of parameter uncertainty and illustrate an application of the model in estimating lifetime outcomes of using intensive and conventional treatments for blood glucose control.

Results: From 15 years of age, male and female patients had an estimated life expectancy of 47.2 (95 % CI 35.2–59.2) and 52.7 (95 % CI 41.7–63.6) years in the intensive treatment group. The model produced estimates of the lifetime benefits of intensive treatment for blood glucose from the DCCT of 4.0 (95 % CI 1.2–6.8) QALYs for women and 4.6 (95 % CI 2.7–6.9) QALYs for men. Absolute risk per 1,000 person-years for fatal CVD events was simulated to be 1.37 and 2.51 in intensive and conventional treatment groups, respectively.

Conclusions: The model incorporates diabetic complications risk data from a type 1 diabetes population and synthesizes other type 1-specific data to estimate long-term outcomes of CVD, end-

stage renal disease, LEA and risk of blindness, along with life expectancy and QALYs. External validation was carried out using life expectancy and absolute risk for fatal CVD events. Because of the flexible and transparent nature of the model, it has many potential future applications.

Key Points for Decision Makers

- A specific simulation model for type 1 diabetes is required as the disease progression is different to that of type 2 diabetes patients. Risk of diabetes complications has been estimated using a type 1 diabetes-specific population, a novel approach in type 1 diabetes modelling
- Our model provides estimates of the substantial increase in life expectancy and quality-adjusted life-years, and reduction in absolute risk of cardiovascular events over a lifetime arising from intensive blood glucose control when compared with conventional blood glucose control

1 Introduction

Type 1 diabetes mellitus (insulin-dependent diabetes mellitus, or juvenile diabetes) results from autoimmune destruction of insulin-producing beta cells of the pancreas and accounts for 5–15 % of all people with diabetes (1). The incidence of type 1 diabetes has been increasing worldwide over the past 50 years (2-4), and patients are at high risk of cardiovascular disease (CVD), lower-extremity amputation (LEA), blindness and end-stage renal disease (ESRD). Given the long-term nature of the disease, most economic evaluations require simulation modelling to extrapolate the effect of interventions such as intensive blood glucose control over a lifetime horizon.

While there are several existing simulation models for type 1 diabetes (5, 6), these were constructed without access to recently published studies reporting the risk of CVD specifically for people with type 1 diabetes. Instead these models have used risks from the UKPDS (United Kingdom Prospective Diabetes Study) (7) and Framingham study (8), and therefore are based on data from type 2 diabetes or non-diabetic populations. This is a clear limitation, especially as a recent study that attempted to validate CVD risk prediction in type 1 diabetes using the general population Framingham study (8) was shown to “poorly predict events in type 1 diabetes” (9). Therefore, further work is required to develop a simulation model that accurately predicts CVD risk in the type 1 diabetes population.

In recent years, several studies have reported risk information derived specifically from patients with type 1 diabetes (10-12). The aim of this study was to use information from these new studies to develop a simulation model for type 1 diabetes patients that would more accurately reflect their risk of major diabetes complications. We use the model to derive estimates of mean life expectancy and compare these with estimates obtained from other sources. We then illustrate how the model can be used to estimate the long-term outcomes from the intensive and conventional blood glucose treatment arms in the DCCT (Diabetes Control and Complications Trial) (13). Finally, we explicitly incorporate parameter uncertainty and examine the degree to which uncertainty in different elements of the model contributes to uncertainty in aggregate outcomes such as life expectancy.

2 Methods

2.1 Overview of the Simulation Model

The aim of this discrete-time simulation model was to predict the first occurrence of a CVD event (with or without ESRD, LEA or blindness) and mortality in order to estimate lifetime outcomes and quality-adjusted life expectancy. Using multiple data sources, we developed a patient-level simulation model that integrates parametric equations describing risk of events, mortality and utilities associated with events.

Fig. 1 illustrates the sequence of events of the simulation model within annual cycles of the model. As our population cohort consists only of type 1 diabetes patients, they enter the model at a pre-determined early age and we assume they have no past history of complications. Patients can progress to microalbuminuria or macroalbuminuria, at which point they are at elevated risk of progressing to ESRD or experiencing a CVD event. We define a CVD event as either a stroke or a myocardial infarction (MI), and our model only captures the first occurrence of such an event over a lifetime. Each patient can have only one complication of each type in a lifetime, but can have multiple complications of different types. To determine occurrence of events or death at a patient level, the probability of death or of experiencing one of the aforementioned events is calculated and compared against a random number, ranging from 0 to 1, which is drawn from a uniform distribution. Whilst CVD, LEA and ESRD are potentially fatal, blindness is not considered to increase mortality. Patients may experience multiple events in any cycle of the model which impacts on risk of future events and/or mortality.

2.2 Data Sources Used in Model Construction and Parametric Equations

The progression of albumin creatinine ratio (ACR) from normoalbuminuria to microalbuminuria was modelled on data from the Oxford Regional Prospective Study of type 1 diabetes, using a random effects model for log ACR in type 1 diabetes patients, allowing for an average upward trend in ACR over time and variation between individuals in both initial ACR and rate of change (14). The parameter estimates for trends, variability of ACR and details of the model are reported in Appendix S1 in the supplementary online resource.

Table 1 shows a summary of the other data sources used in the model to estimate transition probabilities to different health states, the risk predictors in the equations governing those transitions and quality of life scores associated with health states. Table 2 reports the coefficients for each equation used in the simulation model.

The incidence of CVD events (equations 1 and 2) was estimated using information from the DCCT. The DCCT was a clinical study conducted from 1983 to 1993 to compare the effects of standard blood glucose control versus intensive control on the complications of diabetes (10). Intensive control consisted of three or more daily injections of insulin or treatment with an external insulin pump, with the goal of maintaining glycosylated haemoglobin (HbA_{1c}) levels as close as possible to a normal level of 6 % (42 mmol/mol) or less (13). A follow-up study known as the EDIC (Epidemiology of Diabetes Interventions and Complications), with over 90 % of patients from the DCCT, was conducted and assessed the incidence and predictors of CVD and diabetic complications (15).

To predict CVD risk we derived parametric proportional hazards regression models from cumulative incidence curves of the first occurrence of nonfatal MI, stroke or death from CVD reported in the

DCCT and EDIC studies (10). This involved using a program called Dagra (16) to turn the graphical curves of cumulative incidence into survival times for each reported event in both the conventional and intensive treatment groups. By importing the graph into Dagra, the cumulative incidence curve was traced using Bezier curves (16) and then exported as time-to-event data to a tab delimited text file (17). Using Stata 11 (StataCorp LP, College Station, TX, USA), the cumulative incidence curve was recreated, separate Weibull proportional hazards regression models estimated and absolute risk calculated in both intensive and conventional treatment groups. Time at risk in the equation was measured by age, and the coefficients used in equations 1 and 2 were microalbuminuria and albuminuria, as reported by Nathan et al. (10), and age and sex coefficients estimated from the UKPDS 68 (7) as there was no type 1 diabetes-specific information on those risks. Based on the average number of CVD events from two large diabetes trials (7, 18), CVD events were assumed to be 70 % MIs and 30 % strokes.

Mortality following the occurrence of CVD events, ESRD and LEA was based on equations 3–5, which were derived from a recent study involving linked administrative data on people with type 1 and type 2 diabetes over the age of 35 years from Western Australia (19). The study included 630 patients with type 1 diabetes identified through diagnostic codes indicating insulin-dependent diabetes on one or more hospital admissions and no evidence of oral anti-diabetic medication use. We estimated mortality within the first month post-event for MI, stroke and ESRD (equations 3–5, respectively) using the study-reported logistic regressions (19) with appropriate coefficients for type 1 diabetes. We used sex-specific Gompertz proportional hazards models (equations 6 and 7) reported in the same study (19) to estimate mortality of a CVD event beyond 1 month. Coefficients of age and macroalbuminuria (20) were used in both equations, whilst a coefficient for patients with LEA was used in equation 6 only.

Patients were at risk of progressing to the ESRD state in the model (equations 8 and 9) only if they had microalbuminuria or macroalbuminuria. To estimate the incidence of ESRD in our model, we used data from a cohort study of 20,005 type 1 diabetes patients in Finland followed from 1965 to 1999 (11). All patients were diagnosed at younger than 30 years of age and were identified from the Finnish Diabetes Register, with a maximum follow-up of 37 years (median 16.7 years). Cumulative incidence estimates of ESRD among male and female patients with type 1 diabetes were obtained according to age at diagnosis of diabetes. Age- and sex-specific cumulative incidence of type 1 patients progressing to ESRD were reported (11), and we used Dagra (16) to estimate a Gompertz proportional hazards model to determine incidence of patients progressing to ESRD.

Equations 10 and 11 estimate the transitions from ESRD to CVD events and all-cause mortality from a cohort study of patients with ESRD with 53 months of follow-up (21). The study cohort included 228 haemodialysis patients, 15 % of whom were listed as diabetes patients. Kaplan-Meier survival curves for CVD events and all-cause death were reported in the study. Using the same technique used to estimate CVD and ESRD incidence, Gompertz proportional hazards models were estimated for type 1 diabetes patients with ESRD for progression to either a CVD event or death. Coefficients of age and diabetes were included in both equations, whilst a male-specific coefficient was included in equation 10.

Equations derived from a Swedish diabetes register (equations 12 and 13) were used to predict the incidence of LEA (12). The cohort study consisted of 31,354 patients with type 1 diabetes, followed for mean duration of 12.5 years. Kaplan-Meier cumulative probability of non-traumatic LEA (by sex) was reported in this study, from which we were able to estimate sex-specific Weibull proportional

hazards models for progression to the first incidence of non-traumatic LEA. The progression to blindness was estimated from a study that reported age- and sex-specific standardized incidence rates (22), which we then incorporated as a ‘look-up table’ into our model.

Finally, in order to develop a realistic lifetime simulation model, the transition to death from non-CVD causes was important to consider as a competing risk. Because of the lack of information from a type 1 diabetes population, we derived these from age- and sex-specific mortality rates from a US cause elimination life table for the general population (23). Non-CVD mortality was calculated by differencing the all-cause mortality from the reported CVD-cause-specific mortality for 5-year age intervals. This transition takes into account the competing risk of any mortality unrelated to cardiovascular mortality.

2.3 Simulating Outcomes

The model is based on an integrated system of parametric equations for estimating absolute risk of the diabetes complications of CVD, LEA, blindness and ESRD on the basis of patient characteristics (e.g. age and sex), and time varying risk factors such as levels of renal function. Monte Carlo discrete-time simulation (24) with annual cycles was used to estimate outcomes for patients with type 1 diabetes. Patients start with a given health status (i.e. no complications) and progress to experience complications and/or die in any model cycle.

While the model can estimate the risk over time of each complication and death, it primarily uses life expectancy and quality-adjusted life-years (QALYs) to quantify health outcomes. The QALY, which adjusts life-expectancy by the degree of morbidity, is usually determined using a ‘utility weight’ in which 0 represents death and 1 represents full health in each year of life. We used utility estimates from a recent meta-analysis (25). Patients with no CVD were estimated to have a utility of 0.81, whilst patients with a history of an MI or stroke had a health utility of 0.75 and 0.59, respectively. LEA and blindness were assigned health utilities of 0.56 and 0.53, respectively. Finally, ESRD patients had an estimated utility of 0.48 (25). If a patient experienced more than one type of event, their utility value was estimated as the lower of the health utilities (e.g. a patient who experienced both CVD and ESRD would have an estimated utility of 0.48).

2.4 Modelling Uncertainty

It is important to recognize that estimates from a simulation model are subject to uncertainty surrounding health outcomes. Two forms of uncertainty were addressed within the modelling exercise: (a) first order or Monte Carlo uncertainty (due to probabilistic determination of whether events occur at the patient level) and (b) second order or parameter uncertainty. In regard to the former, the random variation between simulations was minimized by taking 100,000 Monte Carlo replications until the expectation of the outcome of interest was stable. We captured parameter uncertainty by taking 1,000 draws from normal distributions for the major parameters of the model. When accounting for uncertainty in our model, we assumed independence between (i) variables in the same risk equation and (ii) different risk equations.

To examine which elements of the model contributed most to uncertainty, identical model simulations were repeatedly run with an increasing number of equations subject to parametric uncertainty. We determined life expectancy estimates and 95 % confidence intervals (CIs) for both conventional and intensive treatment arms using (i) point estimates only—no parameter uncertainty; (ii) parameter

uncertainty of CVD incidence parameters; (iii) parameter uncertainty of all CVD and ESRD incidence equations; and (iv) parameter uncertainty of all model equations.

2.5 Model Validation

Internal validation of the model was carried out for the risk equations that were estimated using Dagra (equations 1–2 and 8–13). This was done by comparing the simulated curves to the published curves and observing their goodness of fit and fulfilment of proportional hazards assumptions. These are shown in Appendix S2 in the supplementary online resource.

We carried out an external validation exercise by comparing our simulated estimates of mortality in type 1 diabetes against the results of a study that estimated all-cause mortality rates in type 1 diabetes patients compared with a general non-diabetic population from the UK General Practice Research Database (GPRD) (26). A total of 7,713 type 1 diabetes patients were selected and compared with 38,518 non-diabetic patients from January 1992 to 1999. The study estimated increased mortality rates in patients with type 1 diabetes compared with the non-diabetic population, with a hazard ratio of 3.3 for men and 4.5 for women, respectively (26). By using the UK life tables for 2007–2009 (27), we multiplied the age-specific mortality rates of the general population by the appropriate hazard ratios of the external study (26) at 5 yearly intervals and determined that life expectancy at birth was 63.8 years for males and 65.6 years for females.

Further external validation of the model was carried out by comparing the absolute risk per 1,000 person-years for fatal CVD events in our model with the reported absolute risk from two large type 1 diabetes cohorts (28, 29).

2.6 Application

In order to model the long-term outcomes of the DCCT trial, we use a hypothetical group of 10,000 patients, 52 % female, with a mean age at entry into the model of 15 years. They were randomized to intensive and conventional treatment groups, in accordance with the DCCT trial (10) and were simulated until death. Life expectancy, quality-adjusted life expectancy and incidence of diabetes complications were calculated and compared by treatment group.

3 Results

3.1 Modelling Uncertainty

Fig. 2 shows the uncertainty in life expectancy estimates in the form of 95 % CIs when parameter distributions were assigned incrementally to model parameters. It demonstrates that uncertainty in the measurement of CVD risk contributes most to uncertainty in the life expectancy estimates in the current version of the model.

3.2 Application

Simulated mean life expectancy by sex and treatment group is shown in Fig. 3. Compared with men, women have a higher life expectancy in both different treatment groups, which is similar to the general population (27).

At 15 years, males and females across both treatments were simulated to have a remaining life expectancy of 44.3 (95 % CI 32.4–56.1) and 49.9 (95 % CI 38.8–61.2) years, respectively, which compares with a mean life expectancy of 48.3 years at 15 years in the general population of the UK (2007–2009) (27). This suggests a loss of approximately 18 years of life attributable to type 1 diabetes. Table 3 reports the simulated life expectancy and quality-adjusted life expectancy from 15 years of age for males and females in intensive and conventional treatment groups. The quality-adjusted life expectancy for the conventional group was 31.8 (95 % CI 23.0–40.5) and 35.9 (95 % CI 27.6–50.5) QALYs for males and females, respectively, and in the intensive treatment group was 36.4 (95 % CI 26.8–45.9) and 39.9 (95 % CI 31.5–48.4). The increase in quality-adjusted life expectancy attributable to treatment was 4.6 (95 % CI 2.7–6.9) and 4.0 (95 % CI 1.2–6.8) QALYs for males and females, respectively.

Fig. 4 shows the cumulative incidence curves for CVD events in our simulation model for both intensive and conventional treatment arms. In the intensive treatment arm, approximately 37 % of patients were predicted to have a CVD event, compared with the conventional arm where approximately 60 % of all patients are simulated to have a CVD event. This translates to an absolute risk per 1,000 person-years of 1.37 and 2.51 for fatal CVD events over a lifetime for intensive and conventional treatment arms, respectively. The absolute risk per 1,000 person-years of patients progressing to ESRD, LEA and blindness was 0.52, 0.77 and 0.15 across both treatment groups, respectively.

Our simulated reduction in the absolute risk of any CVD event over a lifetime through intensive treatment was approximately 23 %, which is lower than the EDIC study findings, which showed that intensive blood glucose control reduces risk of any CVD event by 42 % (30).

3.3 Validation results

Our simulated results of life expectancy lie within 1 standard deviation of life expectancy estimates from the external study (26). Reported absolute risk estimates per 1,000 person-years for fatal CVD events of 2.8 and 2.6 (28, 29) in two large diabetes cohorts shows our conventional group estimates to lie within 1 standard deviation of the reported results.

4 Discussion

We have constructed a simulation model to assimilate evidence from several type 1 diabetes studies, in particular, the use of risk data for most major complications specific to type 1 diabetes (10). We quantify the lifetime impact of cardiovascular and renal complications on patients with type 1 diabetes and the long-term benefits of intensive blood glucose control when compared with conventional blood glucose control. Mean and quality-adjusted life expectancy was also estimated over a lifetime, and our model showed that type 1 diabetes patients are likely to suffer increased mortality and lower life expectancy when compared with the general population.

Our model has advantages over previous type 1 diabetes simulation models (5, 6) in that we synthesized data primarily from type 1 diabetes populations on macrovascular events. A total of 6 out of the 13 equations are based exclusively on data from type 1 diabetes patients; 5 mortality equations are based on data that included both type 1 and type 2 patients, but we used coefficients to capture the differential risk of type 1 diabetes where they were statistically significant. Currently, it is difficult to compare results produced by this simulation model with previous models as working versions of these

models are not in the public domain. However, there is now an established forum to compare diabetes simulation models in the form of the Mt Hood Challenges (31), and so this can be undertaken in the future. Further, to test the external validity of our model, we have compared the absolute risk of fatal CVD events per 1,000 person-years with those of two large type 1 diabetes cohorts (28, 29) and shown these to be similar.

An important finding of our simulation model is the estimated benefits of intensive blood glucose control in type 1 diabetes obtained by extrapolating the DCCT/EDIC results over remaining lifetimes. The large reduction in relative risks of CVD (30) observed in the DCCT due to intensive blood glucose control results in over 5 life-years (4 QALYs) gained for both men and women over remaining lifetimes. Such incremental benefits are much greater than those estimated for type 2 diabetes of between 0.27 and 0.88 QALYs (32). This only underlines the importance of a type 1-specific simulation model to inform cost-effectiveness analyses of interventions for this population.

There are a number of limitations that require acknowledgment in our model. Multiple CVD events are not included in the model as the source equation from the DCCT only reports the first occurrence of a CVD event. This model can be enhanced as information on second events for people with type 1 diabetes becomes available in future. Secondly, while the DCCT/EDIC has comparatively long follow-up of around 17 years, this is a relatively short period when compared with a patient's overall lifetime; hence, there is considerable uncertainty surrounding the lifetime extrapolation relating to the data. This is reflected in the reported uncertainty surrounding the life expectancy estimates when allowing for parameter uncertainty.

There are some new type 1-specific studies that can potentially be incorporated into our model in the future (9, 33, 34). The flexible and transparent structure of the model facilitates the addition of other complications, such as heart failure, which can potentially be linked with the existing mortality equations (19). New information on CVD risk will enhance understanding of whether variations in risk exist between different type 1 diabetes populations and reduce uncertainty surrounding these estimates.

We have not assumed a treatment effect for outcomes other than CVD as there currently is no evidence that intensive treatment under DCCT guidelines reduces the risk of these complications. Legacy effects have been captured in our model as the intensive treatment arm from the DCCT (equation 1) reflects differing glycaemic control in the conventional treatment arm (equation 2). Any legacy effect will be captured when comparing the intensive (equation 1) treatment versus the conventional (equation 2) treatment as these two equations reflect the different risk of alternative treatment regimens. However, this can be revisited again and updated in the model at a later date. Currently, this model uses risk equations based on the two trial arms of the DCCT to predict macrovascular complications over a lifetime. We used risk factors where published and available, but a limitation of this is the lack of clinical risk factors reported in the literature that could be incorporated into the model (HbA_{1c} levels, cholesterol levels, etc.). It should be noted that this represents a first step to building a more comprehensive type 1 diabetes model, which would involve incorporating other types of complications such as diabetic retinopathy and clinical risk factors where possible. As type 1 diabetes patient-level data become available, new risk equations can be developed and replace old ones, as a result of the flexible and transparent structure of the model.

The model has many potential future applications. Where complication-specific costs are available (35, 36), these could be used to estimate lifetime costs for people with type 1 diabetes. This could be

useful from a planning perspective, especially as the incidence of type 1 diabetes is rising and past costs are not a guide for future resource needs. When patient-level data is incorporated, this model can become a more generalized type 1 diabetes model, which can then inform future economic evaluations of interventions for populations with type 1 diabetes such as screening for renal disease.

The model has used a variety of data sources, including the USA, Australia and several European populations, to estimate risks. It may be worth exploring in future whether there are any significant differences across these populations (or across time) in these transition rates, as well as examining the applicability to other populations. For example, it is known that Asian populations with type 2 diabetes have higher rates of stroke and renal disease (37), but it is less clear whether this also applies to type 1 patients.

Finally, we note that this simulation model has been reported in sufficient detail so that others can replicate the model. We have also externally validated our estimates of life expectancies with data from another published study using a large UK type 1 diabetes database (26). Monte Carlo and statistical variability has been explicitly accounted for and limitations of the model have been highlighted. In all of these respects, we have attempted to meet important aspects of the American Diabetes Association guidelines on computer simulation modelling of diabetes and its complications (38).

5 Conclusions

We have described in detail how we developed a simulation model to address life expectancy and the incidence of cardiovascular events in a lifetime for type 1 diabetes patients. This is the first comprehensive type 1 diabetes model that uses primarily type 1 diabetes data to populate the model. We have aimed to provide as much detail of the model as possible to ensure transparency. The model has produced estimates of the lifetime benefits of intensive treatment for blood glucose from the DCCT of 4.0 (95 % CI 1.2–6.8) QALYs for women and 4.6 (95 % CI 2.7–6.9) QALYs for men. The model results of life expectancies and absolute risk estimates of CVD have been validated against external studies (26, 28, 29). The flexible structure of the model allows current equations to be updated or additional features to be added in the future when further data are made available in the literature. This model could potentially be used for future lifetime cost assessments and cost-effectiveness analysis of interventions for type 1 diabetes.

6 Figure Captions

Fig. 1 Diagram depicting the structure and relationship between equations used in the simulation model. *CVD* cardiovascular disease, *ESRD* end-stage renal disease, *LEA* lower-extremity amputation, *QALYs* quality-adjusted life-years

Fig. 2 Life expectancy (95 % confidence interval) when different equations in the model are assigned normal distributions around their point estimates. *Point* point estimates for all equations, *CVD* cardiovascular disease equations only, *CVD+ESRD* cardiovascular disease and end-stage renal disease equations only, *All* all equations

Fig. 3 Life expectancy of patients in the intensive and conventional treatment arms of the DCCT and a large type 1 diabetes study (Soedamah-Muthu et al. (26)) (from the age of 15 years), by sex

Fig. 4 Incidence curves for cardiovascular disease (CVD) events in the simulation model of intensive and conventional treatment arms over a lifetime

7 Tables

Table 1 Summary of equations and data sources used in the simulation model

Publication	Data source	Transitions of model	Equation no.	No. of patients
Nathan et al. (10)	DCCT	Progression to CVD event	1, 2	1,441 type 1 diabetes patients
UKPDS 68 (7)	UKPDS	Progression to CVD event	1, 2	3,642 type 2 diabetes patients
Hayes et al. (19)	Western Australia	Mortality post CVD (MI, stroke) event	3, 4, 5	12,162 type 2 diabetes patients; 603 type 1 diabetes patients
		History of CVD event (sex specific)	6, 7	
Finne et al. (11)	Finnish Diabetes Register	Progression to ESRD (sex specific)	8, 9	20,005 type 1 diabetes patients
Zoccali et al. (21)	Italian hospital data	ESRD patients progression to CVD mortality or all cause death	10, 11	202 ESRD patients (30 type 1)
Kelly et al. (20)	Swedish Diabetes Registry	History of CVD event	6, 7	22,751 type 2 diabetes patients
Miao et al. (12)	Swedish Inpatient Register	Incidence of LEA	12, 13	31,354 type 1 diabetes patients
Lung et al. (25)	Meta-analysis	Utility values	N/A	Type 1 and type 2 diabetes patients

CVD cardiovascular disease, *ESRD* end-stage renal disease, *LEA* lower-extremity amputation, *MI* myocardial infarction, *N/A* not applicable

Table 2 Functional form, beta coefficients and standard errors (SEs) for equations estimating incidence of a cardiovascular disease (CVD) event, death post event, incidence of end-stage renal disease (ESRD), lower-extremity amputation (LEA), CVD incidence and mortality for ESRD patients

	Eq. 1	Eq. 2	Eq.3	Eq.4	Eq. 5	Eq. 6	Eq. 7	Eq. 8	Eq. 9	Eq. 10	Eq. 11	Eq. 12	Eq. 13
Model section	CVD event	CVD event	CVD death	CVD death	CVD death	History of CVD/ESRD	History of CVD/ESRD	ESRD incidence	ESRD incidence	ESRD + CVD incidence	ESRD-related death	LEA incidence	LEA incidence
Functional form	Weibull	Weibull	Logistic	Logistic	Logistic	Gompertz	Gompertz	Gompertz	Gompertz	Gompertz	Gompertz	Weibull	Weibull
Coefficient (SE)													
γ/ρ (shape parameter of model)	1.73 (0.51)	2.22 (0.38)				0.06 (0.003)	0.05 (0.003)	0.05 (0.01)	0.01 (0.01)	0.06 (0.01)	0.02 (0.01)	6.7 (0.21)	5.5 (0.17)
Constant	-8.87 (1.48)	-9.32 (1.13)	-5.20 (0.23)	-6.62 (0.3)	-7.70 (1.13)	-6.74 (0.22)	-5.57 (0.30)	-6.23 (0.19)	-5.86 (0.19)	-6.67 (0.33)	-5.61 (0.29)	-27.13 (1.07)	-24.94 (1.15)
Microalbuminuria	1.08 (0.24)	1.08 (0.24)											
Macroalbuminuria	0.94 (0.33)	0.948 (0.33)				1.33 (0.02)	1.33 (0.02)						
Age	0.08	0.08	0.03 (0.01)	0.08 (0.01)	0.09 (0.02)			1.21 (0.20)	1.21 (0.20)	1.02 (0.01)	1.04 (0.15)		
Male	0.28	0.28		-0.35 (0.09)				0.12 (0.08)			2.24 (0.23)		
Female	-0.45	-0.45											
Type 1 diabetes			2.53 (0.81)				0.35 (0.10)			1.64 (0.27)	2.24 (0.26)		
Stroke (by age group)													
≤50 years						0.56 (0.26)							
>50 years						0.16 (0.07)							
ESRD (by age group)													
≤50 years						1.71 (0.33)							
51–65 years						1.33 (0.22)	0.59 (0.30)						
66–75 years						0.88 (0.23)	0.69 (0.28)						
>75 years						1.18 (0.30)	1.12 (0.34)						
CVD event						0.58 (0.05)	0.51 (0.06)						
Amputation						0.348 (0.09)							

These estimates were obtained from the UKPDS 68 (7), which did not provide variance around the parameter estimates

Table 3 Predicted life expectancy, quality-adjusted life-years (QALYs) and differences for a cohort of type 1 diabetes patients on conventional and intensive blood glucose regimens, from 15 years of age

	DCCT regimen		Difference
	Conventional group	Intensive group	
Life expectancy [years (95 % CI)]			
Males	41.3 (30.1–52.3)	47.2 (35.2–59.2)	5.9 (3.3–8.5)
Females	47.3 (36.5–58.2)	52.7 (41.7–63.6)	5.4 (3.0–7.8)
Quality-adjusted life expectancy [QALYs (95 % CI)]			
Males	31.8 (23.0–40.5)	36.4 (26.8–45.9)	4.6 (2.7–6.9)
Females	35.9 (27.6–50.5)	39.9 (31.5–48.4)	4.0 (1.2–6.8)

8 References

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*Blindness and other mortality are not equations but look-up tables and are referenced in the text