DEVELOPMENT AND VALIDATION OF A COST-UTILITY MODEL FOR TYPE 1 DIABETES MELLITUS

Running Head:

Cost-Utility Model for Type 1 Diabetes

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Novelty Statement:

- A simple cost-utility model was developed to evaluate new interventions for Type 1 diabetes mellitus by assessing the association between the interventions' effects on mean glycated haemoglobin and long-term complications and the risk of hypoglycaemic events.
- High-quality, recently reported data specific to people with Type 1 diabetes mellitus were identified by a systematic review.
- Model validation included review by clinical and economic experts, verification of input data and formulae, and comparison of model predictions with observations from studies used to build the model and other published data.

ABSTRACT

Aims: To develop a health economic model to evaluate the cost-effectiveness of new interventions for Type 1 diabetes mellitus (Type 1 DM) by their effects on long-term complications (measured through mean glycated haemoglobin) while capturing the impact of treatment on hypoglycaemic events.

Methods: Through a systematic review, we identified complications associated with Type 1 DM and data describing the long-term incidence of these complications. An individual patient simulation model was developed and included the following complications: cardiovascular disease, peripheral neuropathy, microalbuminuria, end-stage renal disease, proliferative retinopathy, ketoacidosis, cataract, and adverse birth outcomes. Risk equations were developed from published cumulative incidence data and hazard ratios for the effect of glycated haemoglobin, age, and duration of diabetes. We validated the model by comparing model predictions with observed outcomes from studies used to build the model (internal validation) and from other published data (external validation). We performed illustrative analyses for typical patient cohorts and a hypothetical intervention.

Results: Model predictions were within 2% of expected values in the internal validation and within 8% of observed values in the external validation (percentages represent absolute differences in the cumulative incidence).

Conclusions: The model utilised high-quality, recent data specific to people with Type 1 DM. In the model validation, results deviated less than 8% from expected values.

Key words: diabetes mellitus, type 1; models, economic, economics, medical; costs and cost analysis

INTRODUCTION

Since the Diabetes Control and Complications Trial (DCCT) established that intensive therapy slows the progression of Type 1 diabetes mellitus (Type 1 DM) complications [1], a number of new blood glucose management interventions have been developed. Evaluation of the value for money associated with new interventions is needed to assist decision makers in the efficient allocation of health care resources. Because the costs and quality-of-life impairments resulting from Type 1 DM complications develop over several decades, an economic model is needed. Until recently, economic models providing analyses for Type 1 DM had been designed primarily for Type 2 DM and did not include recent, systematically identified data specific to Type 1 DM [2].

Our objective was to develop a transparent cost-utility model in line with good practice guidelines [3] specifically for new Type 1 DM interventions. This article presents the model design and validation and the example results for a hypothetical intervention. The model structure and input data were based on a systematic review [4] and guided by a clinical expert.

PATIENTS AND METHODS

The model simulated costs and outcomes over the lifetimes of a hypothetical cohort of people in the United Kingdom (UK) with Type 1 DM (as defined by the World Health Organization; see Supporting Information). The population characteristics (Table S1) and all model parameters and sources are presented in the Supporting Information.

The base-case analysis was conducted from the perspective of the UK's National Health Service and Personal Social Services and included costs associated with hospital care, primary care, and social care. Total government and societal perspectives also could be evaluated.

Treatments and Treatment Effects

To compare an intervention of interest versus a control intervention, treatment effects are entered into the model as differences in glycated haemoglobin (HbA1c) and rates of hypoglycaemia (as measured in trials). HbA1c levels are used in the model to predict the incidence of Type 1 DM complications over peoples' lifetimes. Annual treatment costs also are entered into the model; people were assumed to continue on the assigned treatment for the entire model timeframe.

Model Structure

An individual patient simulation model with 1-year cycle was programmed in Microsoft Excel (Fig. 1). At the start of the model, the characteristics of individual patients were sampled from the population characteristics (Table S1). During each model year, people could develop complications or could die of a complication or other causes. Trends in HbA1c over time were not included because HbA1c levels are relatively stable in Type 1 DM [5] (see Supporting

Information). Total costs, life-years, and QALYs accrued over the analysis timeframe were calculated and discounted at a rate of 3.5% per annum [6].

Complications of Type 1 DM were identified by a systematic review [4]. Complications were included in the model where there was evidence for a statistical association between Type 1 DM, HbA1c, and an impact on mortality, costs, and/or health-related quality of life (Table S2). The following complications were selected: cardiovascular disease, peripheral neuropathy, renal disease, retinopathy, cataract, hypoglycaemia, and ketoacidosis. The risk of stillbirth, perinatal mortality, and infant congenital malformation are substantially increased with Type 1 DM [7]. Therefore, the model included an optional analysis of life-years and quality-adjusted life-years (QALYs) lost due to infant death or congenital malformation.

Prediction of Disease Progression and Death

Data describing the development of complications over time were identified by the systematic review; 281 publications reporting 72 unique studies were identified. Because the model performs analyses over people's lifetimes, data from long-term follow-up studies describing the development of complications over several decades were preferred. However, long-term studies are unlikely to accurately represent outcomes in current clinical practice because of improvements in Type 1 DM management. The DCCT and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study provide more than 20 years of follow-up in a cohort who received intensive HbA1c control (e.g., [1]). These studies were used, where possible, to estimate the underlying risk of complications. Other studies were used for validation, and the effects of HbA1c were summarised from all studies so that alternative values could be explored.

With the exception of hypoglycaemia and pregnancy outcomes, development of complications was governed in the model by time-dependent probabilities derived from parametric functions (shown as ellipses in Fig. 1) fitted to published cumulative incidence curves. Data from published curves were estimated electronically (Digitize Software; DigitizeIt 1.5, Köln, Germany). Parametric functions were fitted using the Solver function in Excel and individually selected for each complication based on minimising the sum squared of residuals, visual goodness of fit, and clinical plausibility of long-term predictions. Each function was adjusted for the effects of HbA1c and other risk factors, using published hazard ratios, (Table 1). Risk factors were limited to age and duration of diabetes, due to the limitations of available data. The development of subsequent complications (e.g., death from cardiovascular disease, conditional upon a first event) was governed by fixed probabilities.

A summary of the remaining model parameters is presented in Table S3. An overview of the modelling approach for each complication is provided in the following subsections.

[FIG. 1 HERE]

Cardiovascular Disease

Probabilities of a first cardiovascular event were derived from a Weibull function fitted to data from the DCCT and EDIC studies (Table 1 [1]). The type of first event was specified (death, non-fatal acute myocardial infarction, silent myocardial infarction, revascularisation, confirmed angina, or non-fatal cerebrovascular event), using conditional probabilities based on the type of first event observed. The probabilities of subsequent events also were based on the DCCT and EDIC studies, with the exception of stroke (where no subsequent events were observed). The risk of death from cardiovascular complications was not available for people with Type 1 DM; probabilities were based on data for general cardiovascular patients.

Cataract and Cataract Surgery

Probabilities of cataract surgery were calculated from a Weibull function (Table 1 [8]). People were assumed to have clinically significant visual impairment for 1 year prior to cataract surgery [9]. Up to two cataract surgeries were modelled.

Peripheral Neuropathy (Foot Ulcer and Lower Extremity Amputation)

Probabilities of peripheral neuropathy were derived from a Weibull function fitted to data from the DCCT and EDIC studies (Table 1 [10]).

Neuropathy-related conditions, such as erectile dysfunction, urinary incontinence, and urinary tract infections, were excluded from the model because there was insufficient evidence that effective diabetes management reduced their risk.

Probabilities of diabetic foot ulcer, amputation (conditional upon having peripheral neuropathy), gangrene and infection for people with a foot ulcer, and the probabilities of peri-operative death for people with lower-extremity amputation are presented in Table S3. Up to two lower-extremity amputations per patient were modelled.

People with peripheral neuropathy were at higher risk for hypoglycaemia. The rate of hypoglycaemia was adjusted using the hazard ratio for hypoglycaemia for peripheral neuropathy versus no peripheral neuropathy [11]. Thus, patient populations with more advanced disease (and a higher prevalence of peripheral neuropathy) were at a higher risk for hypoglycaemia.

Microalbuminuria and End-Stage Renal Disease

Probabilities of microalbuminuria were derived from a Weibull function fitted to data from the DCCT and EDIC studies (Table 1 [12]). Conditional probabilities for end-stage renal disease in people with microalbuminuria [13] and for death in people with end-stage renal disease were based on published literature.

Proliferative Diabetic Retinopathy and Blindness

Probabilities of proliferative diabetic retinopathy were derived from a Weibull function fitted to data from the DCCT and EDIC studies [5]. The annual probability of blindness (defined as severe vision loss, < 5/200) in people with proliferative diabetic retinopathy was estimated from the Early Treatment Diabetic Retinopathy Study trial.

Diabetic Ketoacidosis

The rate per patient-year was estimated from a linear function describing the change in the rate of diabetic ketoacidosis with age, fitted to data from the DCCT and EDIC studies [5]. Although poor glycaemic control and compliance have been reported to increase the risk of hospital admission for recurrent diabetic ketoacidosis [14], no hazard ratio estimates were identified for the association between ketoacidosis and HbA1c. The model allowed the user to enter a hazard ratio for HbA1c in order to explore the impact of a possible association. The probability of death from diabetic ketoacidosis was based on a published study.

Pregnancy Outcomes

The number of pregnancies during the model time horizon was estimated from UK general population birth rates. Probabilities of stillbirth, perinatal mortality, and congenital malformation were applied to estimate the number of cases of infant death and congenital malformation. Probabilities were adjusted for HbA1c using a published hazard ratio [15].

Infant deaths, life-years, and QALYs lost were estimated from the average life expectancy at birth for the UK population and an average lifetime utility weight. For infants with congenital malformation, life-years and QALYs lost were estimated using the difference in life expectancy and utility between infants with congenital malformation and infants in the general population.

[TABLE 1 HERE]

Hypoglycaemia

Hypoglycaemia was modelled as four separate events—non-severe day, non-severe nocturnal, severe day, and severe nocturnal—and were driven by user-entered data (e.g., observations from pivotal trials). No adjustment to the risk of hypoglycaemia was made for differences in HbA1c because any differences between interventions in the incidence of hypoglycaemia are expected to be observed during the trial (and the trial data would reflect any impact of differences in HbA1c levels between the two groups on the incidence of hypoglycaemia).

No data were identified for the probability of death from individual severe hypoglycaemia events. The probabilities were calibrated so that the model result for the proportion of all deaths that were due to hypoglycaemia was consistent with published data [18].

Death From Other Causes

Death from other causes was modelled using standard age- and sex-specific mortality rates for the UK general population.

Valuation of Health Effects

Default utility weights were based on the CORE diabetes model (Table S4). For people with multiple complications, the lowest utility weight of all chronic complications was applied to that year. Utility decrements for acute events were subtracted from the QALYs accrued during the year.

Resource Utilisation and Costs

Direct costs to the health care provider included interventions (drug acquisition, needles, and other costs) and management of Type 1 DM complications (based on published data; see Table S4). No estimates of indirect costs were available. The cost-year for the analysis was 2010.

Sensitivity Analysis

To account for uncertainty, the model was programmed to allow for univariate and probabilistic sensitivity analyses for all parameters. Distributions for the probabilistic sensitivity analyses were individually selected as appropriate for the underlying distribution of the data [19]. All variables were assumed to vary independently of one another.

Validation

Model validation was performed in alignment with best practice guidelines [20] and other diabetes models (e.g., [21]).

Face validity (first-order validation in the diabetes modelling literature [20]) was ensured by clinical and economics experts' (MD and AB) review of the model structure, data inputs, assumptions, and results. Internal validity was ensured by verification of all input parameters with original sources, checking of model formulae by an independent health economist, scenario testing, and verification of model results against independent calculations.

Dependent external validation (second-order validation in the diabetes literature) was performed by comparing model predictions with outcomes observed in the studies used to build the model (the intensive-treatment groups from the DCCT and EDIC studies). Comparison with the conventional-treatment groups also was performed after adjustment of the population characteristics (HbA1c, age, duration of diabetes) and a further adjustment for the residual effect of treatment observed in the studies after adjusting for HbA1c.

Independent external validation (third-order validation in the diabetes modelling literature) was conducted by comparing model predictions with outcomes observed in studies that were not used to build the model. Studies identified by the systematic review were selected in which long-term cumulative incidence for a complication using similar endpoint definitions to the DCCT and EDIC studies were reported for a large cohort of people with T1DM and where sufficient baseline characteristics were reported to allow predictions for that population to be estimated within the model.

RESULTS

Model Validation

Model predictions were within 2% of expected values in the dependent external (second order) validation and within 8% of values reported from other studies in the independent external (third-order) validation (Table 2 and Table 3, Fig. 2, Fig. 3) (percentages represent absolute differences in the cumulative incidence).

[TABLE 2, TABLE 3 [22-29 NEW], FIG. 2, FIG. 3 HERE]

Model Predictions for Example Patient Cohorts

Table 4 presents model predictions for the general Type 1 DM population in the UK and for subpopulations of men, women (including and excluding adverse pregnancy outcomes), and people with specific ages and durations of diabetes.

[TABLE 4 HERE]

Cost-Utility Analysis Results for a Hypothetical Intervention

An analysis was performed for a hypothetical intervention with an annual drug cost of £700 (vs. £600 for the control drug). The mean change in HbA1c from baseline was 12 mmol/mol (1.1%) for the intervention and 11 mmol/mol (1.0%) for the control. The analysis was conducted over a timeframe of 50 years for a Type 1 DM population in the UK with the following characteristics: mean age, 39 years; mean disease duration, 11 years; mean HbA1c, 72 mmol/mol (8.7%); and 43% women (adverse pregnancy outcomes were excluded). The number of first-order simulations required for this analysis was investigated at intervals between 1,000 and 100,000 simulations (Table S5). In simulation models, a standard error of less than 5%

of the mean is typically considered acceptable [30]. This was achieved with 50,000 first-order simulations.

Fig. 4 presents the cumulative incidence of complications for the intervention and control cohorts. As expected, the cumulative incidence of events was slightly lower for the intervention cohort (solid lines) than for with the control cohort (dotted lines). Table 5 presents the results for a hypothetical intervention. Cost-offsets due to reduced complications outweighed the increased drug costs, resulting in lower overall costs for the cohort receiving the intervention of interest. The intervention therefore was dominant. An analysis was performed to estimate the maximum value-based price for the intervention at a willingness-to-pay threshold of £20,000 per QALY. The maximum annual cost of the intervention was £460 higher than that of the control drug. The results of a probabilistic sensitivity analysis for 1,000 second-order and 50,000 first-order simulations are presented in Fig. S1 and Fig. S2, respectively.

[TABLE 5 HERE; FIG. 4 HERE]

DISCUSSION

To our knowledge, this is the first cost-effectiveness model developed specifically for Type 1 DM using up-to-date, systematically identified evidence. Only complications for which improved glycaemic control has been demonstrated to reduce the risk were modelled. A comprehensive model validation process was undertaken; in the dependent and independent external validation, model predictions were within 2% and 8% of expected values, respectively. This compares well with validation results from other diabetes models [21]. In analyses of the example patient cohorts, model predictions were consistent with expected results.

Several simplifying assumptions were made due to limitations in the available data and to meet the objective to develop a simple and accessible model. Assumptions included simplifying the interactions between complications and applying the lowest utility weight of all complications in people with more than one complication. The latter approach is consistent with other diabetes models (e.g., the CORE model [21]); however, this approach may underestimate QALY losses if the presence of multiple complications results in greater impairment than does the worst of the complications alone. It is possible that simplification of interactions between complications may result in a wider distribution of complications among the population. For simplicity and due to paucity of available data, the risk of complications worsening or recurring was not adjusted for the HbA1c level. For example, the risk of a first cardiovascular event was adjusted for HbA1c, but the risk of subsequent events was not.

A number of Type 1 DM complications (e.g., anxiety, depression, autoimmune thyroiditis, and limited joint mobility) were excluded from the model (Table S2). It is possible that these complications are influenced by HbA1c levels, but research demonstrating such an

association has been insufficient. If improved glycaemic control does reduce the incidence of these complications, the model may underestimate the benefit of improved control and therefore may be conservative when considering the benefit of interventions associated with improved glycaemic control.

A limitation of the model is that reduction in HbA1c levels may not reflect the full benefit of more effective glycaemic control. In the DCCT, HbA1c accounted for approximately 90% of the treatment effect, but there was a residual treatment effect that was not explained by HbA1c [1]. In addition, the model does not explicitly incorporate the costs and effects of treatments that are used to prevent cardiovascular complications (e.g., statins and antihypertensive agents).

The prediction of long-term outcomes and the effect of HbA1c, age, and disease duration is subject to uncertainty. The risk of death from hypoglycaemia was difficult to estimate. This is likely to be an important driver of cost-effectiveness estimates when the incidence of severe hypoglycaemia differs among treatments.

In our model, the treatment effects can be user defined. Therefore, it is not possible to provide firm guidelines regarding the number of individual people that should be simulated in order to achieve reproducible results. This should be determined by the user for individual analyses, as demonstrated in the example analysis for a hypothetical intervention. Run times for the probabilistic sensitivity analysis will vary from less than an hour to many hours, depending on the number of first-order (individual patient) simulations and second-order (probabilistic) simulations required and the speed of the computer processor. Whilst Excel is not the optimum software with respect to speed, it was selected in order to provide the required transparency and accessibility for multiple users.

In conclusion, we have developed a simple, probabilistic individual patient-simulation model based on recent data specific to Type 1 DM (where available) that included only those complications for which improved glycaemic control has been demonstrated to reduce the risk. In external validations, model predictions varied by less than 8% from expected values.

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CONFLICTS OF INTEREST

The systematic review and model development were performed by RTI Health Solutions. The authors were responsible for the content and development of the manuscript. Mr Barrie Chubb and Dr Jens Gundgaard are employed by Novo Nordisk. Dr Sorrel Wolowacz, Dr Isobel Pearson, Mr Paul Shannon, Professor Andrew Briggs, and Professor Melanie Davies have received consultancy fees from Novo Nordisk.

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REFERENCES

1. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005 Dec 22; 353(25): 2643-53.

2. Mount Hood 4 Modeling Group. Computer modeling of diabetes and its complications: a report on the Fourth Mount Hood Challenge Meeting. Diabetes Care 2007 Jun; 30(6): 1638-46.

3. Caro JJ, Briggs AH, Siebert U, Kuntz KM; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices—overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Value Health 2012 Sep; 15(6): 796-803.

4. Pearson I, Wolowacz S, Irving A, Brockbank J, Chubb B, Gundgaard J, et al. A systematic review of recent data describing the risk of complications in type 1 diabetes mellitus patients. 15th Annual European Congress of the International Society For Pharmacoeconomics and Outcomes Research; November 3-7, 2012. Berlin, Germany.

5. Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and

Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. 2009; 169(14): 1307-16.

6. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal. 2013. Available at http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf Last accessed 20 November 2013.

7. Jensen DM, Damm P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004 Dec; 27(12): 2819-23.

8. Grauslund J, Green A, Sjølie AK. Cataract surgery in a population-based cohort of patients with type 1 diabetes: long-term incidence and risk factors. Acta Ophthalmol 2011 Feb; 89(1): 25-9.

9. Healthcare Improvement Scotland. Technologies Scoping Report. Number 9. August 2012. Available at http://www.healthcareimprovementscotland.org/his/idoc.ashx?docid=28523742-34ec-486a-9cb4-6ef2566ffeb3&version=-1 Last accessed 22 July 2013.

10. Albers JW, Herman WH, Pop-Busui R, Feldman EL, Martin CL, Cleary PA, et al. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care 2010; 33(5): 1090-6.

11. Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Rasmussen AK, Jørgensen HV, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev 2004 Nov-Dec; 20(6): 479-86.

12. de Boer IH, Rue TC, Cleary PA, Lachin JM, Molitch ME, Steffes MW, et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 2011; 171(5): 412-20.

13. Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. JAMA 2005; 294(14): 1782-7.

14. Wright J, Ruck K, Rabbitts R, Charlton M, De P, Barrett T, et al. Diabetic ketoacidosis (DKA) in Birmingham, UK, 2000-2009: an evaluation of risk factors for recurrence and mortality. Br J Diabetes Vasc Dis 2009; 9(6): 278-82.

15. Nielsen GL, Møller M, Sørensen HT. HbA1c in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. Diabetes Care 2006 Dec; 29(12): 2612-6.

16. Gordin D, Waden J, Forsblom C, Thorn L, Rosengard-Barlund M, Tolonen N, et al. Pulse pressure predicts incident cardiovascular disease but not diabetic nephropathy in patients with type 1 diabetes (The FinnDiane Study). Diabetes Care 2011; 34(4): 886-91.

17. 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(7): 1649-55.

18. Heller S. Sudden death and hypoglycemia. Diabet Hypoglycem 2008 Sep; 1(2): 2-7.

19. Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. Value Health 2005; 8(1): 1-2.

20. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB; ISPOR SMDM Modeling Good Research Practices Task Force. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Value Health 2012 Sep-Oct; 15(6): 843-50.

21. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE diabetes model against epidemiological and clinical studies. Curr Med Res Opin 2004 Aug; 20(suppl 1): S27-40.

22. Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, et al.; DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care 2006 Feb; 29(2): 340-4.

23. Soedamah-Muthu SS, Chaturvedi N, Toeller M, Ferriss B, Reboldi P, Michel G, et al.; EURODIAB Prospective Complications Study Group. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. Diabetes Care 2004 Feb; 27(2): 530-7.

24. Conway B, Costacou T, Orchard T. Is glycaemia or insulin dose the stronger risk factor for coronary artery disease in type 1 diabetes? Diab Vasc Dis Res 2009; 6(4): 223-30.

25. Bragd J, Adamson U, Bäcklund LB, Lins PE, Moberg E, Oskarsson P. Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? Diabetes Metab 2008 Dec; 34(6 Pt 1): 612-6.

26. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005; 352(4): 341-50.

27. Tesfaye S, Selvarajah D. The EURODIAB study: what has this taught us about diabetic peripheral neuropathy? Curr Diab Rep 2009; 9(6): 432-4.

28. Giordano C, Amato MC, Ciresi A, Citarrella R, Mantione L, Accidenti M, et al. Predictors of microvascular complications in type 1 diabetic patients at onset: the role of metabolic memory. Eur J Intern Med 2011; 22(3): 266-74.

29. Hietala K, Harjutsalo V, Forsblom C, Summanen P, Groop PH. Age at onset and the risk of proliferative retinopathy in type 1 diabetes. Diabetes Care 2010; 33(6): 1315-9.

30. Stevenson MD, Oakley JE, Chilcott JB. Gaussian process modeling in conjunction with individual patient simulation modeling: a case study describing the calculation of cost-effectiveness ratios for the treatment of established osteoporosis. Med Decis Making 2004; 24: 89-100.

TABLES

Table 1. Risk Functions for Type 1 DM Complications

	Source	Function	γ	α	Hazard Ratio: HbA1c	Hazard Ratio: Age	Hazard Ratio: Duration of Diabetes
CVD[a]	DCCT/EDIC Nathan et al. [1]	Weibull	0.4574	4.3074	1.25 (1.10-1.43)	1.06 (1.04-1.08)[b]	NA[a]
Cataract surgery	Grauslund et al. [8]	Weibull	0.9648	3.6095	1.22 (0.91-1.64)	None[c]	1.16 (0.88-1.53)
Peripheral neuropathy[d]	DCCT/EDIC Albers et al. [10]	Weibull	0.7123	3.3370	1.53 (0.99-2.37)	NA[d]	1.06 (1.01-1.11)
Micro-albuminuria[e]	DCCT/EDIC de Boer et al. [12]	Partitioned (Weibull + log-logistic)[e]	Weibull: 0.4238 Log-logistic:	Weibull: 2.6727 Log-logistic:	1.80 (1.54-2.10)	1.03 (1.00-1.07)	None[g]

	Source	Function	γ	α	Hazard Ratio: HbA1c	Hazard Ratio: Age	Hazard Ratio: Duration of Diabetes
			0.0048[f]	0.9919[f]			
Proliferative diabetic retinopathy[h]	DCCT/EDIC Nathan et al. [5]	Weibull	0.3184	3.8612	1.38 (1.31-1.46)	None[h]	None[g]

CVD = cardiovascular disease; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications study; FinnDiane = Finnish Diabetic Nephropathy study; HbA1c = glycated haemoglobin; NA = not applicable; Type 1 DM = Type 1 diabetes mellitus.

[a] The function described the cumulative incidence of CVD with time and was adjusted for HbA1c and age. Statistical models did not include duration of diabetes due to colinearity with age (e.g., [16]). Adjustment for diabetes duration was performed by selecting the appropriate start point on a curve based on the baseline diabetes duration of the model population.

[b] Gordin et al. [16] (FinnDiane) (not available from DCCT or EDIC).

[c] Adjustment of the function for age was not appropriate because the function described the cumulative incidence with age.

[d] The function described the cumulative incidence of peripheral neuropathy with time and was adjusted for HbA1c and diabetes duration. Statistical models did not include age due to colinearity with diabetes duration. Adjustment for age was performed by selecting the appropriate start point on curve based on the baseline age of the model population.

[e] The function described the cumulative incidence of microalbuminuria with increasing disease duration and was adjusted for HbA1c and age. A partitioned function was used in which the risk of a proportion of was described by a Weibull function and the risk to the remaining patients was described by a log-logistic function. The proportion of patients governed by the log-logistic function (86%) was estimated as a parameter during the fitting of the partitioned function.

[f] Log-logistic location parameter.

[g] Adjustment for duration was not appropriate because the function described the cumulative incidence with duration of diabetes.

[h] The function described the cumulative incidence of proliferative diabetic retinopathy with duration of diabetes and was adjusted for HbA1c. The function was not adjusted for age because many studies found no independent association between age and retinopathy after adjustment for duration of diabetes (e.g., De Block et al. [17]).

Table 2. Internal Validation Results

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence	Difference/ Comments
CVD	DCCT and EDIC Nathan et al. [1] (Fig. 1, intensive-treatment group)	2.9%	2.6%	–0.3%
Microalbumin-uria	DCCT and EDIC de Boer et al. [12] (Fig. 1, intensive-treatment group)[a]	21.0%	20.6%	–0.4%
Proliferative diabetic retinopathy	DCCT and EDIC Nathan et al. [5] (Fig. 2A, intensive-treatment group)[b]	7.8%	6.3%	–1.5%

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence	Difference/ Comments
Cataract surgery	Grauslund et al. [8] (Fig. 2, Type 1 diabetes mellitus group)[c]	0.0%	0.0%	0.0%
Peripheral neuropathy	EDIC Martin et al. [22] (Fig. 1, intensive-treatment group)[d]	33.9%	33.2%	–0.7%

CVD = cardiovascular disease; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications study.

[a] Incidence for a duration of diabetes of 21 years (6 years at model entry + 15 years in model). Estimate was approximate as it was taken from a Kaplan-Meier curve with large steps at this point.

[b] Incidence for a duration of diabetes of 21 years (6 years at model entry + 15 years in model).

[c] Age at 15 years = 42; incidence of cataract surgery before age 50 = 0 [8].

[d] Approximate data. The incidence in the DCCT and the EDIC study at baseline was 7%; at 13.5 years, incidence was 25% [10]. The derived Weibull function for the intensive-treatment group predicted a cumulative incidence of 26.9% at 15 years (incidence at baseline = 0). Estimated incidence at 15 years therefore was 26.9% + 7% = 33.9%.

Table 3. External Validation Results

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence		Difference/ Comments
Cardiovascular disease	Cumulative incidence, hazard ratio, HbA1c: DCCT and EDIC, Nathan et al. [1] Cardiovascular disease included myocardial infarction,[a] stroke, angina,[b] revascularisation,[c] and cardiovascular death Hazard ratio, age and duration: EURODIAB, Soedamah-Muthu et al.	EDC, Conway et al. [24] Coronary artery disease included myocardial infarction,[d] revascularisation,[e] stenosis,[f] and fatal coronary artery disease Patients diagnosed 1950-1980; enrolled in EDC 1986-1988	26% at 20 years of follow-up[g]	Risk equation: 21% at 20 years of follow-up	Model adjusted for difference in HbA1c between population underpinning model data (DCCT intensive treatment) and EDC, but other effects of contemporary management may account for the higher incidence in EDC

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence		Difference/ Comments
	[23] Coronary heart disease included clinical myocardial infarction, angina, coronary artery bypass graft surgery, electrocardiogram abnormality				
Cataract surgery	Confidence interval: Grauslund et al. [8]	None	Not applicable	Not applicable	External validation was not possible because no studies were identified that reported cumulative incidence of cataract surgery in patients with

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence		Difference/ Comments
					Type 1 DM other than Grauslund et al. [8]
Peripheral neuropathy	Confidence interval: DCCT and EDIC, Albers et al. [10] Confirmed clinical neuropathy based on neurologist's examination[h] Hazard ratio, HbA1c: Nordic registry, Bragd et al. [25] Sensory neuropathy, as indicated by pathological thresholds revealed by	EURODIAB, Tesfaye et al. [26,27] Abnormalities in at least 2 of 4 assessments[i] Baseline examinations were conducted between 1989 and 1991 Patients with no peripheral neuropathy at baseline were followed up Mean duration of diabetes: 14.7 ± 9.3 years	23.5% at 7.3 years of follow-up	Risk equation: 22.2% at 7.3 years of follow-up	Model estimate was close to and lower than observed in EURODIAB The EURODIAB studied patients who were diagnosed relatively recently

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence		Difference/ Comments
	neurometry and/or a vibration test with tuning fork and monofilament testing				
Microalbumin-uria	DCCT and EDIC, de Boer et al. [12] Persistent microalbuminuria, albumin excretion rate of at least 30 mg per 24 hours at 2 consecutive study visits	Giordano et al. [28] Microalbuminuria, albumin levels of 30-300 mg in a 24-hour urine collection	23.0% at 10 years from diagnosis[j]	28.5% at 10 years from diagnosis	Giordano cohort consisted of 336 of 1,118 treatment-naïve Sicilian patients hospitalised for Type 1 DM in 1991-2005 Definition of microalbuminuria in Giordano study was less stringent (albumin excretion rate e 30 mg in 1

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence		Difference/ Comments
					sample rather than 2 consecutive samples)
Proliferative diabetic retinopathy	DCCT and EDIC, Nathan et al. [5] Proliferative diabetic retinopathy or worse, ETDRS grading scale, and DCCT methods	FinnDiane, Hietala et al. [29] ETDRS grading scale	23.0% at 20 years and 46.0% at 30 years from diagnosis[k]	16.5% at 20 years and 47.7% at 30 years from diagnosis	Model estimate was lower at 20 years and higher at 30 years
All-cause mortality	Multiple data sources used for death from individual Type 1 DM complications and other causes	Finne et al. [13] 20,005 patients younger than 30 years diagnosed with Type 1 DM in Finland between 1965 and 1999, identified from the Finnish	15%	18.9%	Model estimate was higher than that observed by Finne et al. [13] Assumptions about baseline characteristics (as these were not

Complication	Study	Study Estimate for Cumulative Incidence or Validation Study Details	Validation Estimate for Cumulative Incidence or Model Estimate for Cumulative Incidence	Difference/ Comments
		Diabetes Register Baseline characteristics were not fully reported, so assumptions were applied during the validation		reported by Finne et al. [13]) may have introduced error

DCCT = Diabetes Control and Complications Trial; EDC = Epidemiology of Diabetes Complications study; EDIC = Epidemiology of Diabetes Interventions and Complications study; ETDRS = Early Treatment Diabetic Retinopathy Study; EURODIAB = Epidemiology and Prevention of Diabetes in Europe study; FinnDiane = Finnish Diabetic Nephropathy study; HbA1c = glycated haemoglobin; Type 1 DM = Type 1 diabetes mellitus.

[a] Clinical and subclinical (silent) myocardial infarction (identified on the annual electrocardiograms).

[b] Confirmed by ischaemic changes on exercise tolerance testing or by clinically significant obstruction on coronary angiography.

[c] With angioplasty or coronary artery bypass graft.

[d] Confirmed on medical records or Q-waves (Minnesota code 1.1 or 1.2).

[e] Including coronary artery bypass graft, angioplasty, and coronary endarterectomy.

[f] Coronary artery stenosis e 50% without revascularisation.

[g] Estimated from Conway et al. [24], Fig. 1 (top left).

[h] Required at least 2 positive responses among symptoms, sensory signs, or reflex changes consistent with a distal symmetrical polyneuropathy (e.g., symptoms or signs showing a length-dependent gradient in a stocking or stocking-glove distribution) and nerve conduction study abnormalities involving 2 or more nerves among the median, peroneal, and sural nerves.

[i] The assessment of neuropathy included (1) evaluation of neuropathic symptoms, (2) scored clinical examination, (3) measurement of vibration perception threshold, and (4) autonomic function tests by measuring 2 cardiovascular reflex responses. The criterion for the presence of diabetic peripheral neuropathy was if abnormalities were found in 2 or more of these 4 assessments.

[j] Estimated from Giordano et al. [28], Fig. 3A.

[k] Estimated from Hietala et al. [29], Fig. 1.

Table 4. Model Predictions for Example Population Cohorts (Mean Total Expected Lifetime Values; 50,000 Iterations; Costs and Outcomes Discounted at 3.5%)

Population	Total Cost	Total LYs	Total QALYs
UK Type 1 DM Population[a]	£148,600	17.62	5.77
Males	£147,808	17.64	5.79
Females (including pregnancy outcomes)	£148,547	17.41	5.20
Females (excluding pregnancy outcomes)	£148,547	17.70	5.81
Aged 25 years[b]	£170,151	20.90	6.96
Aged 30 years[b]	£164,997	20.11	6.68
Aged 35 years[b]	£156,828	18.86	6.24
Diabetes duration of 5.5 years[c]	£128,167	18.46	6.80
Diabetes duration of 15 years[c]	£162,367	17.13	5.13
Diabetes duration of 20 years[c]	£180,580	16.55	4.31

HbA1c = glycated haemoglobin; LY = life-year; QALY = quality-adjusted life-year; Type 1 DM = Type 1 diabetes mellitus; UK = United Kingdom.

[a] Age = 39 years; duration of diabetes = 11 years; HbA1c level = 72 mmol/mol (8.7%); gender (% female) = 43%; angina = 4%; prior myocardial infarction = 1.5%; prior revascularisation = 0.0%; disabled from stroke = 1.0%; cataract, partially sighted = 1.0%; peripheral neuropathy = 6.8%; active foot ulcer = 0.0%; amputee = 0.5%; microalbuminuria = 1.0%; end-stage renal disease = 1.5%; proliferative diabetic retinopathy = 3.5%; proliferative diabetic retinopathy blind = 1.0%. Adverse pregnancy outcomes not included.

[b] Diabetes duration set at default: 11 years.

[c] Age set at default: 39 years.

Table 5. Cost-Utility Analysis Results for a Hypothetical Intervention (Costs and Outcomes Discounted at 3.5%)

Model Set-Up	**Intervention**	**Control**	
Annual drug cost	£700	£600	
Annual other treatment cost	£100	£100	
Mean change in HbA1c	–12 mmol/mol [1.1%]	–11 mmol/mol [1.0%]	
(standard error)	(1 mmol/mol [0.1%])	(1 mmol/mol [0.1%])	
Severity	**Rate Ratio Hypoglycaemia[a] (Standard Error)**		
Non-severe (day)	1.00 (0.05)		
Non-severe (nocturnal)	0.90 (0.05)		
Severe (day and nocturnal)	0.95 (0.05)		
Results	**Intervention**	**Control**	**Incremental Cost**
Drug	£10,674	£8,872	£1,801
Other treatment cost	£1,779	£1,774	£5
Complications	£133,191	£136,759	–£3,568
Total cost (95% CI)	£145,644 (116,468, 326,076)	£147,406 (117,151, 178,109)	–£1,762 (–13,451, 8,629)
Life-years (95% CI)	17.70 (16.72, 18.50)	17.64 (16.71, 18.42)	0.05 (–0.11, 0.19)
QALYs (95% CI)	6.02 (3.82, 7.57)	5.79 (3.72, 7.33)	0.23 (–0.30, 0.73)
Incremental cost per QALY	Intervention dominant; probability of cost-effectiveness: 0.72[b]		

CI = confidence interval; HbA1c = glycated haemoglobin; QALY = quality-adjusted life-year.

[a] Rate ratio for intervention versus control.

[b] Probability of cost-effectiveness at a willingness-to-pay threshold of £20,000 per QALY.

FIGURE LEGENDS

Figure 1. Diagrammatic Representation of the Individual Patient-Simulation Model

AMP = amputation; CS = cataract surgery; CVD = cardiovascular disease; DKA = diabetic ketoacidosis; ESRD = end-stage renal disease; FU = foot ulcer; HbA1c = glycated haemoglobin; hypo = hypoglycaemia; ICM = infant congenial malformation; ID = infant death; MA = microalbuminuria; MI = myocardial infarction; PDR = proliferative diabetic retinopathy; PN = peripheral neuropathy; REVASC = revascularisation; Type 1 DM = Type 1 diabetes mellitus.

Note: All-cause mortality was included in the model; people with any complications or none could die of other causes.

[a] The data used to estimate the parametric function for CVD represented the time to the first of any predefined CVD event (non-fatal acute MI, silent MI, stroke, death from CVD, confirmed angina, or the need for coronary artery revascularisation). Patients with silent MI were assumed to have no CVD.

[b] Separate costs and utilities were applied for the first year (in which the event occurred) and for subsequent years. Patients can become permanently disabled or can recover. For patients without permanent disability, no cost or utility impact were applied after recovery.

[c] Patients are assumed to have substantially impaired vision due to cataract for the year before the cataract surgery. The probability of a second surgery was assumed independent of previous cataract surgery.

[d] FUs can become infected and patients could develop gangrene.

[e] Patients can have up to 2 amputations.

[f] Hypoglycaemic events were modelled separately as follows: non-severe day, non-severe nocturnal, severe day, and severe nocturnal. Specific mortality was for severe events only.

[g] Data from this outcome can be included or excluded from the results of individual analyses. Fixed probabilities were adjusted using the hazard ratio for HbA1c.

Figure 2. Dependent External (Second-Order) Validation: Comparison With the DCCT and EDIC Conventional-Treatment Group (IA Through IVA) and Independent External (Third-Order) Validation: (IB Through IVB)

CT = conventional treatment; DCCT = Diabetes Control and Complications Trial; EDC = Epidemiology of Diabetes Complications study; EDIC = Epidemiology of Diabetes Interventions and Complications study; EURODIAB = Epidemiology and Prevention of Diabetes in Europe study; FinnDiane = Finnish Diabetic Nephropathy study; IT = intensive treatment.

Sources: Fig. IB, the EDC Study, Conway et al. [24]; Fig. IIB, the EURODIAB Study, Tresfaye et al. [26]; Fig. IIIB, Giordano et al. [28]; Fig. IVB, the FinnDiane Study, Hietala et al. [29].

Figure 3. Graphical Presentation of the Results of the Dependent External (Second-Order) and Independent External (Third-Order) Validation of the Model

CT = conventional treatment; DCCT = Diabetes Control and Complications Trial; IT = intensive treatment.

Note: Model estimates are plotted against data reported in the external validation studies (original data). The straight line represents equivalence between the model estimates and the original data.

Figure 4. Cumulative Incidence of Complications for a Hypothetical Intervention and Control

CVD = cardiovascular disease; MA = microalbuminuria; PDR = proliferative diabetic retinopathy; PN = peripheral neuropathy.

FIGURES

Figure 1. Diagrammatic Representation of the Individual Patient-Simulation Model

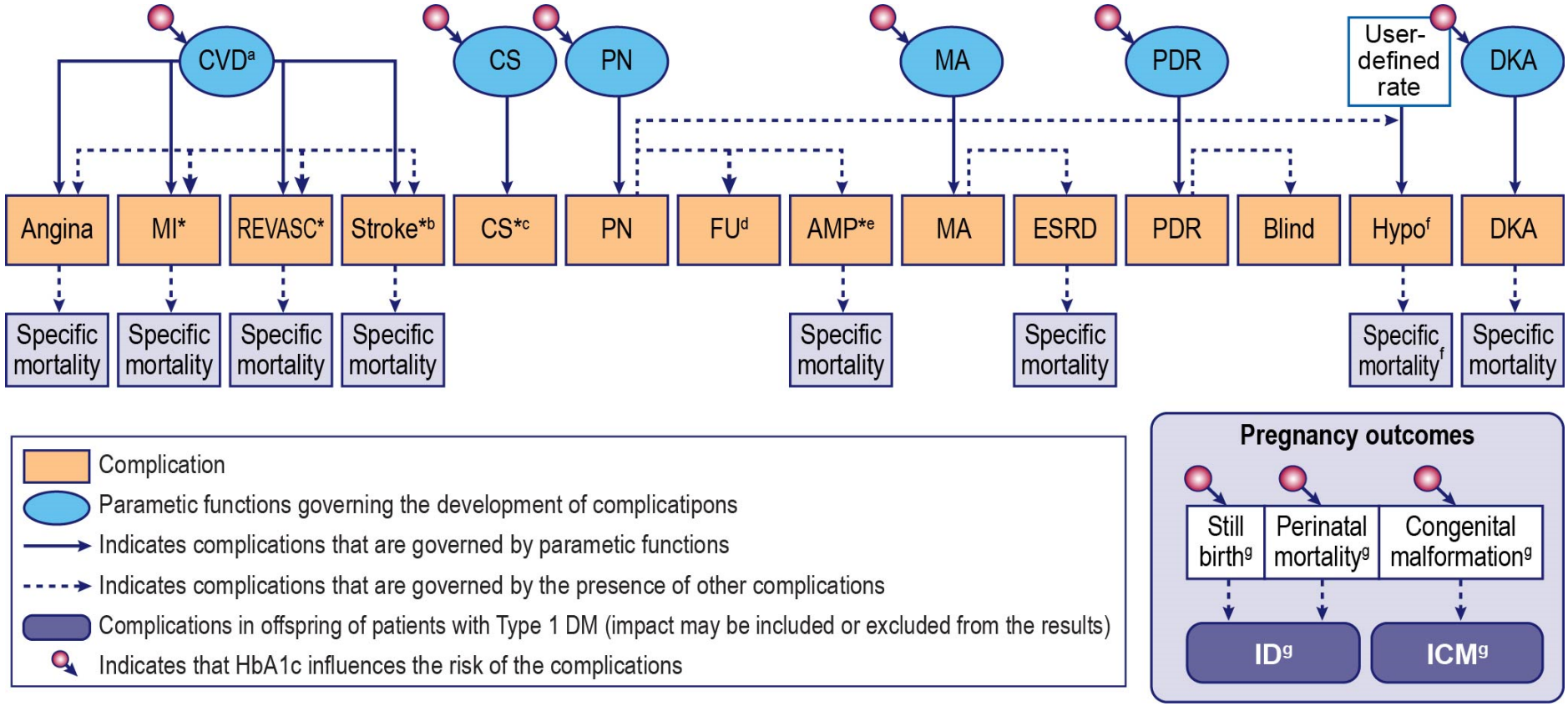

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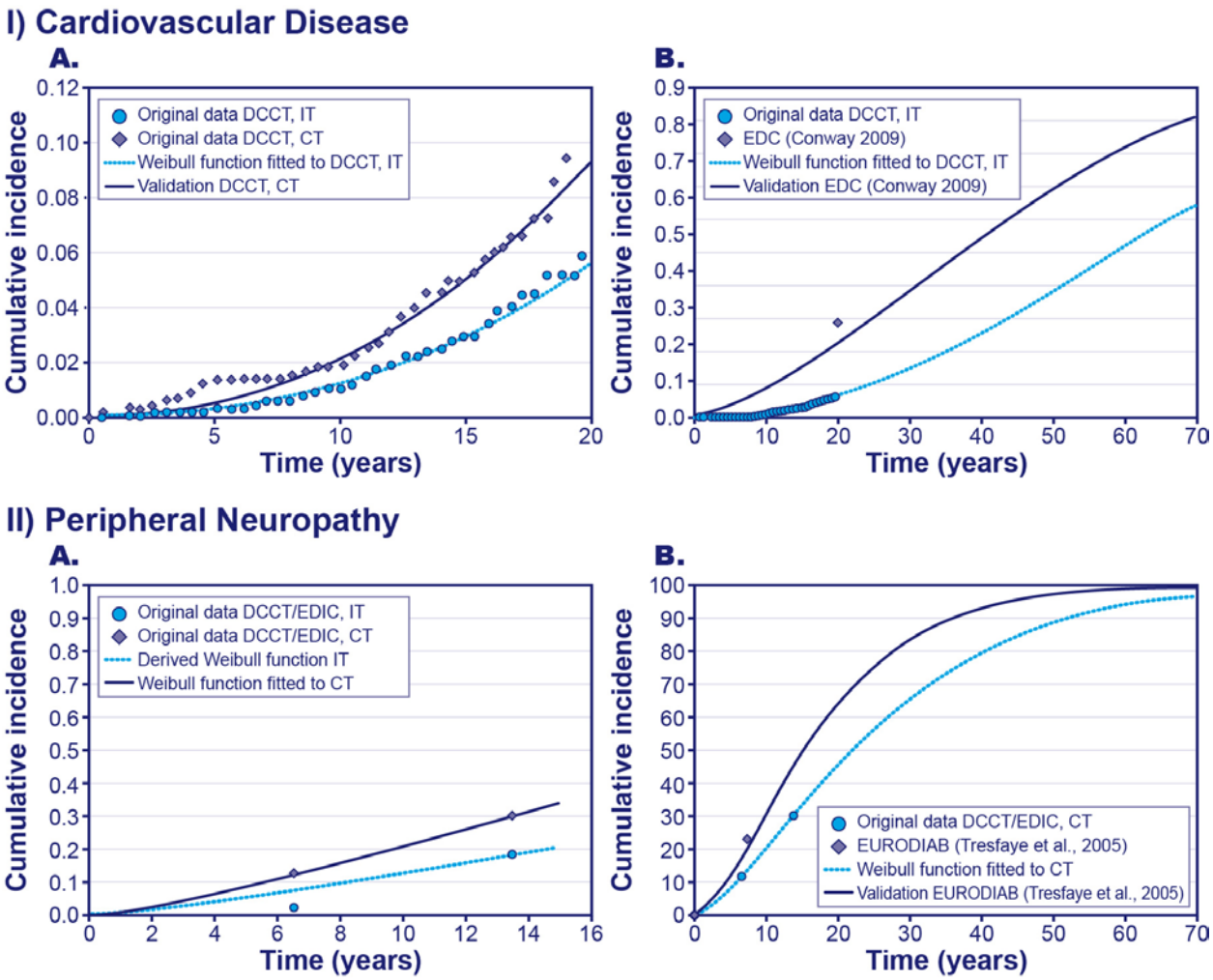
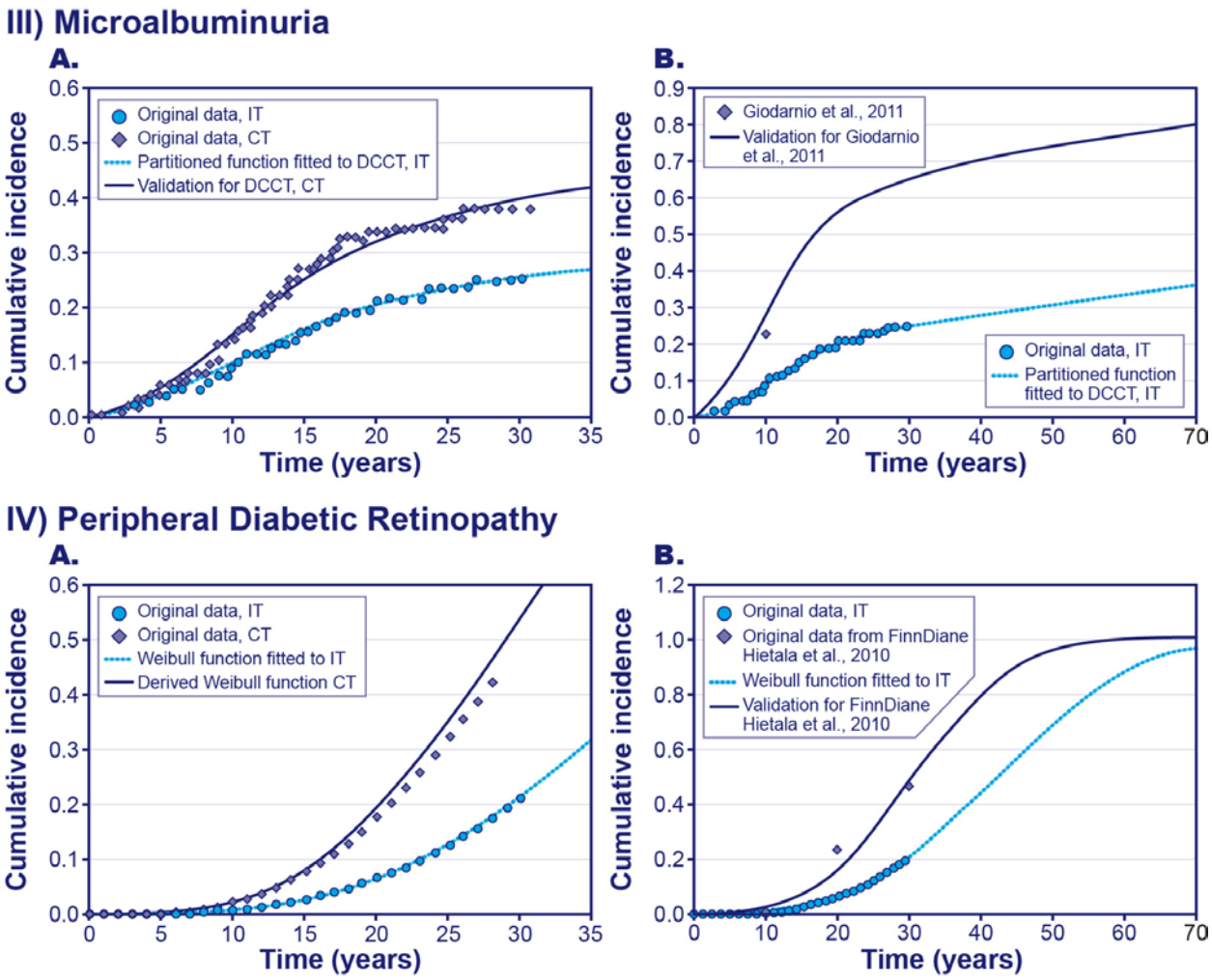
Figure 2. Dependent External (Second-Order) Validation: Comparison With the DCCT and EDIC Conventional-Treatment Group (IA Through IVA) and Independent External (Third-Order) Validation: (IB Through IVB)





CT = conventional treatment; DCCT = Diabetes Control and Complications Trial; EDC = Epidemiology of Diabetes Complications study; EDIC = Epidemiology of Diabetes Interventions and Complications study; EURODIAB = Epidemiology and Prevention of Diabetes in Europe study; FinnDiane = Finnish Diabetic Nephropathy study; IT = intensive treatment.

Sources: Fig. IB, the EDC Study, Conway et al. [24]; Fig. IIB, the EURODIAB Study, Tresfaye et al. [26]; Fig. IIIB, Giordano et al. [28]; Fig. IVB, the FinnDiane Study, Hietala et al. [29].

Figure 3. Graphical Presentation of the Results of the Dependent External (Second-Order) and Independent External (Third-Order) Validation of the Model

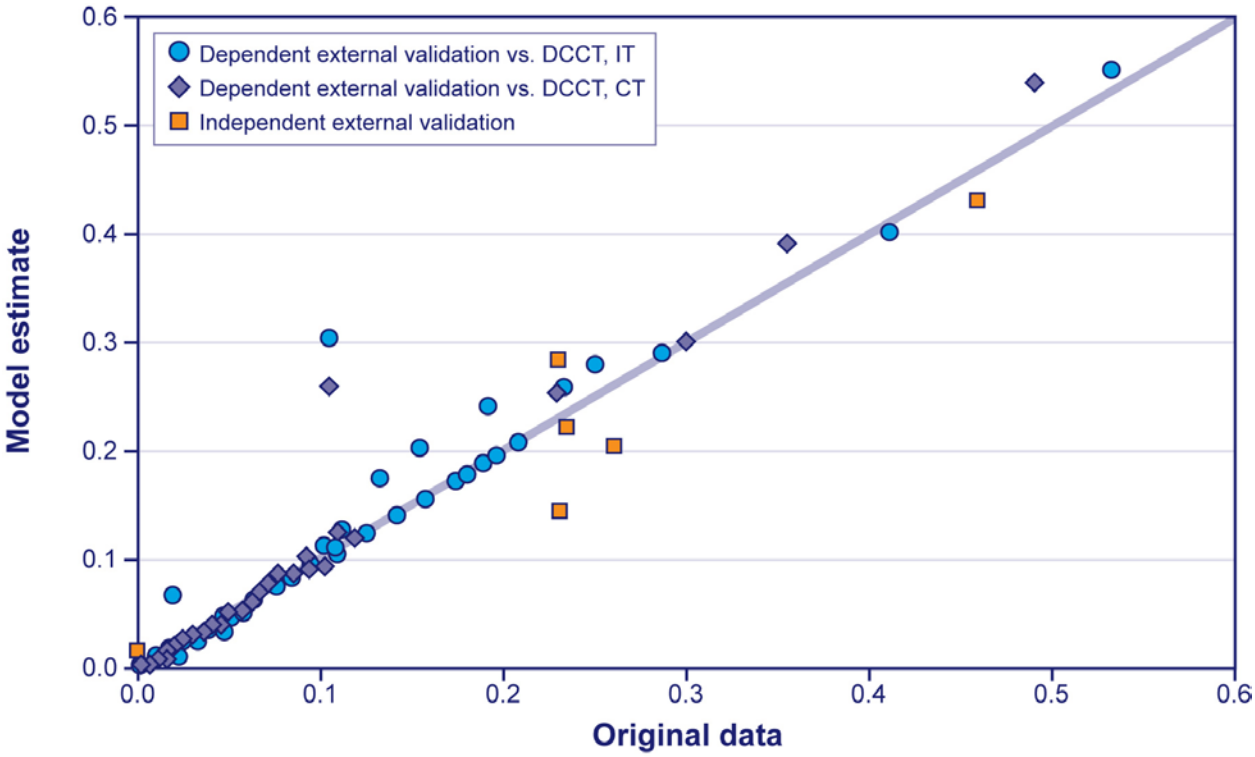


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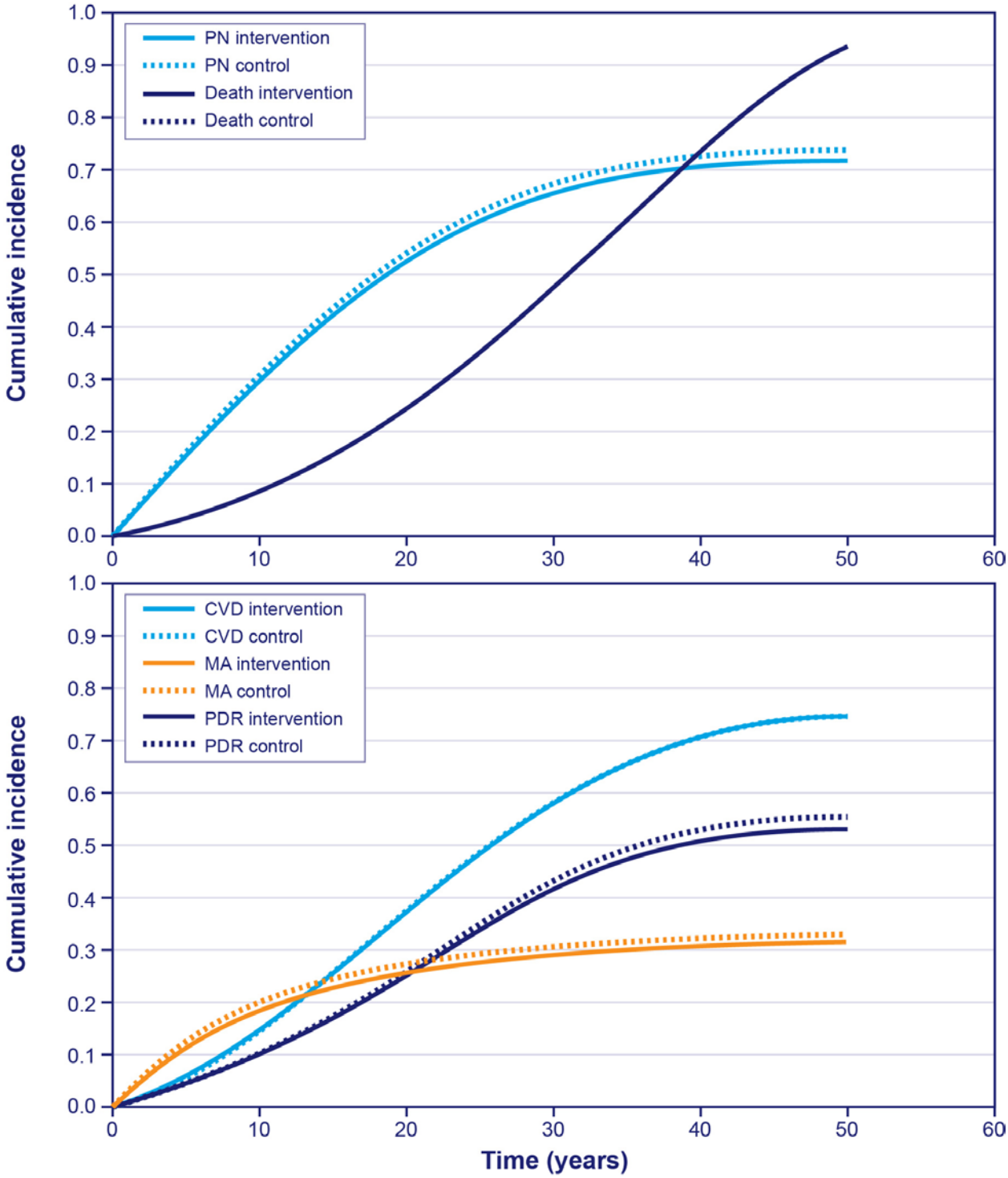
Figure 4. Cumulative Incidence of Complications for a Hypothetical Intervention and Control



CVD = cardiovascular disease; MA = microalbuminuria; PDR = proliferative diabetic retinopathy; PN = peripheral neuropathy.

SUPPORTING INFORMATION

DEVELOPMENT AND VALIDATION OF A COST-UTILITY MODEL FOR TYPE 1 DIABETES MELLITUS

S. Wolowacz, I. Pearson, P. Shannon, B. Chubb, J. Gundgaard, M. Davies and A. Briggs

Definition of Type 1 Diabetes Mellitus

The World Health Organization defines Type 1 diabetes mellitus (DM) as a condition of deficiency of insulin secretion from the pancreas, usually due to auto-immune damage of the insulin-producing cells. However, the clinical condition generally is recognised on the basis of diabetes (high blood glucose levels) occurring in mainly younger and thinner people in the absence of other precipitating causes (WHO, 1999).

Published Diabetes Models

- Mueller E, Maxion-Bergemann S, Gultyaev D, Walzer S, Freemantle N, Mathieu C, et al. Development and validation of the Economic Assessment of Glycemic Control and Long-Term Effects of diabetes (EAGLE) model. Diabetes Technol Ther 2006; 8: 219-36.
- Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, 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(suppl 1): S5-26.
- Eddy DM, Schlessinger L. Archimedes: a trial-validated model of diabetes. Diabetes Care 2003; 26: 3093-1.
- Mount Hood 4 Modeling Group. Computer modeling of diabetes and its complications, a report on the Fourth Mount Hood Challenge Meeting. Diabetes Care 2007; 30: 1638-46.

Table S1. Default Model Population Characteristics at Entry

Characteristic[a]	Value	Source
Mean age, in years	39	Lauterbach et al., 2010
Mean duration of diabetes, in years	11	Lauterbach et al., 2010
Mean HbA_{1c}, in mmol/mol (%)	72 (8.7)	Lauterbach et al., 2010
Sex (% female)	43	Lauterbach et al., 2010
Angina (%)	4.0	United Kingdom National Diabetes Audit, 2010[b]
Prior myocardial infarction (%)	1.5	United Kingdom National Diabetes Audit, 2010[b]
Prior revascularisation (%)	0.0	Assumption
Disabled from stroke (%)	1.0	United Kingdom National Diabetes Audit, 2010
Cataract, partially sighted (%)	1.0	Assumption
Peripheral neuropathy (%)	6.8	Lauterbach et al., 2010
Active foot ulcer (%)	0.0	Assumption
Amputee (%)	0.5	United Kingdom National Diabetes Audit, 2010
Microalbuminuria (%)	1.0	Färnkvist and Lundman, 2003
End-stage renal disease (%)	1.5	United Kingdom National Diabetes Audit, 2010
Proliferative diabetic retinopathy (%)	3.5	United Kingdom National Diabetes Audit, 2010
Proliferative diabetic retinopathy, blind (%)	1.0	Assumption

HbA_{1c} = glycosylated haemoglobin.

[a] The model adjusted the probabilities of complications for patients' age, duration of diabetes, and HbA_{1c}; probabilities of death were dependent on age and sex. Probabilities of hypoglycaemia were adjusted for the presence of peripheral neuropathy.

[b] Data for Type 1 diabetes mellitus estimated from the United Kingdom National Diabetes Audit, 2010, Figure 14, page 19.

Table S2. Selection of Type 1 Diabetes Mellitus Complications for Incorporation in the Economic Model

Complication	Associated With Type 1 Diabetes Mellitus	Associated with Glycaemic Control and/or HbA_{1c}	Selected (Yes/No)	Reason for Exclusion
Anxiety and depression	Unclear; conflicting evidence, possibly confounded by comorbidities	Unclear; association demonstrated but causality is questionable	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Autoimmune thyroiditis	Yes; approximately 10% of patients require treatment; screening programmes are in place in some countries (Kordonouri et al., 2005; Mantovani et al., 2007)	Unclear; not investigated	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus; minor impact on costs and health-related quality of life
Cardio-vascular disease	Yes; angina, hypertension, myocardial infarction, and stroke (Klein et al., 2004)	Yes; the decrease in HbA_{1c} values during DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease (Nathan et al., 2005)	Yes	Not applicable
Carpel tunnel syndrome	Yes; predicted lifetime risk was approximately 85% after 54 years of Type 1 diabetes mellitus (Singh et al., 2005)	No; there was no demonstrable effect of glycaemic control on the incidence of carpel tunnel syndrome (Singh et al., 2005)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus; relatively minor impact on health-related quality of life

Complication	Associated With Type 1 Diabetes Mellitus	Associated with Glycaemic Control and/or HbA_{1c}	Selected (Yes/No)	Reason for Exclusion
Cataract	Yes; 25-year crude incidence of cataract surgery was approximately 20% (Grauslund et al., 2011)	Yes; the hazard ratio for risk of cataract surgery was 1.22 (95% confidence interval: 0.91-1.64) [reported value inverted to give the hazard ratio for an 11-mmol/mol (1.0%) increase in HbA_{1c}] (Grauslund et al., 2011)	Yes	Not applicable
Cognitive dysfunction	Unclear; conflicting evidence	Unclear; association demonstrated but cause and effect not established	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Cutaneous manifestations	Yes; there was a higher prevalence in patients with Type 1 diabetes mellitus than in control subjects (Pavlovic et al., 2007)	No; there was no evidence to relate diabetic hand to metabolic control (Pavlovic et al., 2007)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Female sexual dysfunction	Unclear; conflicting evidence	Unclear; conflicting evidence	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Male sexual dysfunction	Unclear; only 1 study identified (Enzlin et al., 2003)	Unclear; only 1 study identified (Enzlin et al., 2003)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Fracture	Unclear; conflicting evidence	Unclear; no evaluation of the impact of HbA_{1c} levels on fracture risk identified	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Hypogly-caemia	Yes; reported severe hypoglycaemia (coma or seizure) rates ranged from	Yes; HbA_{1c} was inversely related with rate of severe hypoglycaemia with an effect	Yes	Not applicable

Complication	Associated With Type 1 Diabetes Mellitus	Associated with Glycaemic Control and/or HbA_{1c}	Selected (Yes/No)	Reason for Exclusion
	5.4% to 19.0% per 100 patient-years in the EDIC, DCCT, and EDC Type 1 diabetes mellitus populations (Nathan et al., 2009)	corresponding to a relative risk of 1.4% in the lowest HbA_{1c} quartile, compared with the upper quartile (Pedersen-Bjergaard et al., 2004)		
Ketoacidosis	Yes; rate of ketoacidosis events reported in DCCT, EDIC, and EDC ranged from 0% to 3.1% per 100 patient-years (Nathan et al., 2009)	Yes; HbA_{1c} was a significant predictor of ketoacidosis (P = 0.001) (Craig et al., 2007)	Yes	Not applicable
Limited joint mobility	Unclear; limited evidence, only 1 study identified (Lindsay et al., 2005)	Unclear; limited evidence, only 1 study identified (Lindsay et al., 2005)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Myopia	Unclear; limited evidence, only 1 study identified (Jacobsen et al., 2008)	Unclear; limited evidence, only 1 study identified (Jacobsen et al., 2008)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Non-alcoholic fatty liver disease	Unclear; limited evidence, only 1 study identified (Targher et al., 2010)	Unclear; limited evidence, only 1 study identified (Targher et al., 2010)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Peripheral neuropathy, foot ulcer, and amputation	Yes; incidence rate for lower-extremity amputation was 3.2% (95% confidence interval: 1.2-9.4) per 1,000 patients with Type 1 diabetes mellitus (McAlpine et al., 2005)	Yes; higher HbA_{1c} (per 11-mmol/mol (1.0%) odds ratio: 1.40; 95% confidence interval: 1.24-1.58) was independently associated with the incidence of lower-extremity amputation (Sahakyan et al., 2011)	Yes	Not applicable
Pregnancy, birth outcomes	Yes; the congenital malformation rates was 5.0%	Yes; for HbA_{1c} levels > 53 mmol/mol (7.0%), there	Yes	Not applicable

Complication	Associated With Type 1 Diabetes Mellitus	Associated with Glycaemic Control and/or HbA_{1c}	Selected (Yes/No)	Reason for Exclusion
	in the Type 1 diabetes mellitus population and 2.8% (relative risk: 1.7; 95% confidence interval: 1.3-2.2) in the background population (Jensen et al., 2004)	was an almost linear association between HbA_{1c} and risk of adverse outcome, whereby an 11-mmol/mol (1.0%) increase in HbA_{1c} corresponded to 5.5% (95% confidence interval: 3.8-7.3) increased risk of adverse pregnancy outcome (Nielsen et al., 2006)		
Renal disease	Yes; there was a 5-year incidence of renal replacement therapy of 10.2% in patients with Type 1 diabetes mellitus recruited to the ETDRS trial (Cusick et al., 2004)	Yes; 11-mmol/mol (1.0%) increment in HbA_{1c} level was a significant risk factor of renal replacement therapy ($P \leq 0.01$) (Cusick et al., 2004); the adjusted hazard ratio for microalbuminuria per 11-mmol/mol (1.0%) increase in HbA_{1c} was 1.80 (95% confidence interval: 1.54-2.10) (de Boer et al., 2007)	Yes	Not applicable
Retinopathy	Yes; there was a cumulative incidence of 84.1% for any retinopathy and 50.2% for advanced retinopathy after 40 years of Type 1 diabetes mellitus (Hammes et al., 2011)	Yes; an HbA_{1c} level of > 58 mmol/mol (7.5%) was a significant risk factor for both any retinopathy and advanced retinopathy ($P < 0.0001$) (Hammes et al., 2011); progression of diabetic retinopathy also was more likely after an increase in HbA_{1c} level (Klein et al., 2008)	Yes	Not applicable
Sleep disturbances	Unclear; limited evidence, only 1 study identified (van	Unclear; limited evidence, only 1 study identified (van	No	Insufficient evidence that effective diabetes management

Complication	Associated With Type 1 Diabetes Mellitus	Associated with Glycaemic Control and/or HbA_{1c}	Selected (Yes/No)	Reason for Exclusion
	Dijk et al., 2011)	Dijk et al., 2011)		reduces the risk of Type 1 diabetes mellitus
Urinary incontinence	Unclear; limited evidence, only 1 study identified (Sarma et al., 2009)	Unclear; limited evidence, only 1 study identified (Sarma et al., 2009)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes mellitus
Urinary tract infections or symptoms	No; sexual activity, rather than measures of diabetes control and complications, was the main risk factor for urinary tract infection (Czaja et al., 2009)	No; no association was observed between HbA_{1c} levels at the DCCT baseline or end of study or the year 10 EDIC examination (urological assessment component of the EDIC) (Van Den Eeden et al., 2009)	No	Insufficient evidence that effective diabetes management reduces the risk of Type 1 diabetes

DCCT = Diabetes Control and Complications Trial; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes interventions and Complications study; ETDRS = Early Treatment of Diabetic Retinopathy Study; HbA_{1c} = glycosylated haemoglobin.

Table S3. Probabilities for Type 1 Diabetes Mellitus Complication Events

Event	Probability	Source
Type of first cardiovascular event: conditional upon having a first event		
Death from cardiovascular disease	0.08	Nathan et al., 2005
Non-fatal acute myocardial infarction	0.20	Nathan et al., 2005
Silent myocardial infarction	0.24	Nathan et al., 2005
Revascularisation	0.12	Nathan et al., 2005
Confirmed angina	0.28	Nathan et al., 2005
Non-fatal cerebrovascular event	0.07	Nathan et al., 2005
Subsequent Cardiovascular event annual probability: conditional upon having a first event[a]		
Death from cardiovascular disease	0.0110	Nathan et al., 2005
Non-fatal acute myocardial infarction	0.0132	Nathan et al., 2005
Silent myocardial infarction	0.0176	Nathan et al., 2005
Revascularisation	0.0685	Nathan et al., 2005
Confirmed angina	0.0219	Nathan et al., 2005
Non-fatal cerebrovascular event	0.0825[b]	National Audit Office, 2010
Death from angina and myocardial infarction		
Angina		
Age, in years: male/female		
35-44	0.0046/0.0025	Hunink et al., 1997[c]
45-54	0.0107/0.0062	Hunink et al., 1997[c]
55-64	0.0184/0.0120	Hunink et al., 1997[c]
65-74	0.0327/0.0251	Hunink et al., 1997[c]
75 and over	0.1059/0.0964	Hunink et al., 1997[c]
Myocardial infarction: year 1		
Age, in years: first event/subsequent event		
35-44	0.0154/0.0867	Hunink et al., 1997[c]
45-54	0.0336/0.1120	Hunink et al., 1997[c]
55-64	0.0730/0.1446	Hunink et al., 1997[c]
65-74	0.1587/0.1867	Hunink et al., 1997[c]
75 and over	0.2953/0.2953	Hunink et al., 1997[c]

Event	Probability	Source
Myocardial infarction: year 2+		
Age, in years: male/female		
35-44	0.0046/0.0025	Weinstein et al., 1987[c]
45-54	0.0107/0.0062	Weinstein et al., 1987[c]
55-64	0.0184/0.0120	Weinstein et al., 1987[c]
65-74	0.0327/0.0251	Weinstein et al., 1987[c]
75 and over	0.1059/0.0964	Weinstein et al., 1987[c]
Death from revascularisation and death and disability from stroke		
Death from revascularisation	0.263	Mak and Faxon, 2003[d]
Death from stroke	0.142	Sacco et al., 1994[c,e]
Permanent disability from stroke	0.500	National Audit Office, 2010[c]
Death from disabled from stroke	0.0915	Sacco et al., 1994[c,e]
Foot ulcer, infection, amputation, and death due to amputation		
Foot ulcer for patients with peripheral neuropathy	0.040	RTI-CDC model (Moss et al., 1992; Ramsey et al., 1999; Reiber et al., 1995)[d,f]
Infection for patients with foot ulcer	0.580	Eurodiale Study Group, 2008
Lower-extremity amputation (defined as a non-traumatic lower-extremity amputation above or below the knee) for patients with peripheral neuropathy	0.120	Value calibrated so that the model reproduced the incidence of lower-extremity amputation reported by Jonasson et al., 2008 (11% at age 65 years)[g]
Second lower-extremity amputation for patients with prior lower-extremity amputation	0.110	Reiber et al., 1995 (for Type 1 diabetes mellitus and Type 2 diabetes mellitus)
Peri-operative death for patients undergoing amputation	0.093	Vamos et al., 2010 0.348: 30-day mortality = 9.3% (all individuals admitted to National Health Service hospitals for non-traumatic amputations in 2004-2005 in England; data for 376 patients with Type 1 diabetes mellitus and major lower-extremity amputations)

Event	Probability	Source
End-stage renal disease and death due to end-stage renal disease		
End-stage renal disease for patients with microalbuminuria (annual probability)	0.0180	Calibrated with respect to Finne et al., 2005
Death for patients with end-stage renal disease	0.1640	United Kingdom Renal Registry, 2010, for Type 1 diabetes mellitus and Type 2 diabetes mellitus Diabetic-prevalent patient 1-year survival was 83.6% in 2009 Annual rate = (–Ln (1 – (1 – 0.836)) / 1) Probability = (1 – exp(annual rate))
Annual probability of blindness for patients with proliferative diabetic retinopathy		
Blindness for patients with proliferative diabetic retinopathy	0.0064	Early Treatment Diabetic Retinopathy Study Research Group, 1991 (for Type 1 diabetes mellitus or Type 2 diabetes mellitus) Incidence = 2.6% – 3.7% at 5 years (midpoint = 3.15% assumed) Annual rate = –Ln(1 – 0.0315) / 5 Annual probability = 1 – exp(–annual rate)
Death from severe hypoglycaemia[h] and diabetic ketoacidosis		
Death from severe day hypoglycaemia	0.002	Assumption[i]
Death from severe nocturnal hypoglycaemia	0.004	Assumption[i]
Death from diabetic ketoacidosis	0.05	Powers, 2005
Stillbirth, perinatal mortality, and congenital malformation[j]		
Stillbirth	0.0210	Jensen et al., 2004
Perinatal mortality	0.0310	Jensen et al., 2004
Congenital malformation	0.0500	Jensen et al., 2004

DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes interventions and Complications study; HbA_{1c} = glycosylated haemoglobin; Ln = natural logarithm; RTI-CDC = Research Triangle Institute/Centers for Disease Control and Prevention; UK = United Kingdom.

Note: Death from other causes was modelled using age- and sex-specific mortality rates for the UK general population (Office for National Statistics, 2010).

[a] Calculated as 1 – exp(rate per patient-year). The total patient-years of follow-up for patients with any first cardiovascular event was estimated as 451 years, based on the number at risk and the cumulative incidence of first cardiovascular event, as reported by Nathan et al., 2005.

[b] Probability was derived from data reported by the National Audit Office, 2010, as no subsequent non-fatal cerebrovascular events were observed in the DCCT and EDIC studies (35% of patients had a subsequent stroke over a period of 5 years after the first stroke; annual rate = –((Ln(1 – 0.35)) / 5); probability = (1 – exp(rate)).

[c] Not specific to patients with diabetes.

[d] Patients with Type 2 diabetes mellitus.

[e] Sacco et al., 1994, included 1-month, 1-year, and 5-year transition probabilities. These were converted to hazard rates, from which 6-month and 1-year transition probabilities were calculated.

[f] Estimates of the incidence of diabetic foot ulcers for the entire Type 2 diabetes mellitus population included 2.6% for 1 year (Moss et al., 1992) and 5.8% cumulative incidence for 3 years (Ramsey et al., 1999). Most (78%) foot ulcers occurred among patients with neuropathy (Reiber et al., 1995). Assuming that the annual incidence rate for all patients with Type 2 diabetes mellitus was 2%, patients with neuropathy account for 80% of foot ulcers and that about 40% of patients with Type 2 diabetes mellitus have neuropathy, the calculation yields an estimated annual incidence of 4% for patients with neuropathy.

[g] The cumulative probability of having a non-traumatic lower-extremity amputation by age 65 years was 11.0% for women with Type 1 diabetes mellitus and 20.7% for men with Type 1 diabetes mellitus (Jonasson et al., 2008, based on 31,354 patients with Type 1 diabetes mellitus in the Swedish Inpatient Register between 1975 and 2004). Probability calibrated to give a model estimate at default settings (timeframe to yield mean age of 65 years) of 11% (the lower end of the reported range was selected because the Swedish Registry data included patients from 1975 and incidence was expected to decrease with more modern diabetes management).

[h] The model was set to a mean age of 33 years, disease duration of 15 years, HbA_{1c} of 72 mmol/mol (8.7%), and 49% female. The rate of severe hypoglycaemia per patient-year was based on the DCCT and EDIC studies (omitting the conventional treatment group of the DCCT study on the basis that that group represented out-of-date treatment). Severe hypoglycaemia (day and nocturnal combined) = 11.5 per 100 patient-years (Nathan et al., 2009, reported a range of 6.7-16.4). The proportion of all severe hypoglycaemic events that are nocturnal = 55% (The Diabetes Control and Complications Trial Research Group, 1993). The model was run to age 40 (7 years), and probability was adjusted to reproduce the proportion of all early deaths (age < 40 years) due to hypoglycaemia equal to 12%. The probability of death from a nocturnal hypoglycaemic event was assumed to be approximately double that for such an event during the day. Standard error was assumed to be 66% of the mean, based on the percentage difference in the reported range (66% = (12 – 4) / 12).

[i] It is well recognised that the risk of death from hypoglycaemia is very difficult to estimate; the cause of death (particularly in cases of “dead in the bed”) is often unclear (Heller, 2008). No data were identified from which the probability of death from severe hypoglycaemia could be estimated. However, estimates of the proportion of all early deaths that were due to hypoglycaemia have been reported. In a review by Heller (2008), estimates of 4%, 7%, and 27% were reported. Patterson et al. (2007) reported an estimate of 9% (of 134 deaths, 5 were due to hypoglycaemia and 7 were dead in the bed; 12/134 = 9%). The average of these reported values was 12%. Default values for the probability of death from severe hypoglycaemic events were estimated using these data as follows: The probability of death from a severe day event was assumed to be approximately half that of a severe nocturnal event. These probabilities then were adjusted so that the proportion of all deaths that were due to hypoglycaemia was equal to 12% of all early deaths (age < 40 years).

[j] The number of expected pregnancies during the model’s time horizon was estimated from UK general population birth rates, by age (Office for National Statistics, 2009).

Table S4. Utility Weights and Costs Associated With Type 1 Diabetes Mellitus Complications (Consistent With the CORE Model; Palmer et al., 2004)

	Utility Weight			Cost (£)		
Complication[a]	**Value**	**Comment**	**Source**	**Value**	**Comment**	**Source**
No complications	0.814	Utility applied annually	Clarke et al., 2002	Not applicable	Not applicable	Not applicable
Angina	0.682	Utility applied annually	Clarke et al., 2002	Not applicable	Not applicable	Not applicable
Angina, year 1	As above for angina	—	—	2,623	Annual costs due to an angina event in the first year of angina	Dyer et al., 2008
Angina, years 2+	As above for angina	—	—	2,196	Annual costs in subsequent years	Cameron and Bennett, 2009
Myocardial infarction, year of event	–0.129	Utility decrement applied annually	Clarke et al., 2002	5,093	Annual costs due to an myocardial infarction event in the year of a first or recurrent event	National Institute for Health and Clinical Excellence, 2007
Myocardial infarction, years 2+ post-event	0.736	Utility applied annually	Clarke et al., 2002	573	Annual costs in subsequent years after an event	National Institute for Health and Clinical Excellence, 2007

	Utility Weight			Cost (£)		
Complication[a]	**Value**	**Comment**	**Source**	**Value**	**Comment**	**Source**
Revascularisation, year of event	–0.129	Utility decrement applied annually	Assumption	5,000	Annual costs due to a revascular-isation event in the year of a first or recurrent event	Assumption
Revascularisation, years 2+ post-event	0.736	Utility applied annually	Assumption	1,500	Annual costs in subsequent years after an event	Assumption
Stroke, year of event	–0.181	Utility decrement applied annually	Clarke et al., 2002	9,401	Annual costs due to a stroke event in the year of a first or recurrent event	National Institute for Health and Clinical Excellence, 2006
Stroke, years 2+	As above for stroke, year of event	—	—	2,527	Annual costs in subsequent years after an event	National Institute for Health and Clinical Excellence, 2006
Stroke, permanently disabled, years 2+ post-event	0.545	Utility applied annually	Clarke et al., 2002	Not applicable	Not applicable	Not applicable

	Utility Weight			Cost (£)		
Complication[a]	**Value**	**Comment**	**Source**	**Value**	**Comment**	**Source**
Stroke, death	0.000	—	—	8,242	Annual costs in the year of death due to stroke	Youman et al., 2003
Cataract, partially sighted (year before surgery)	0.794	Utility applied annually	Palmer et al., 2004	0	—	Assumption
Cataract, year of surgery	–0.010	Utility decrement applied annually	Assumption	833	Annual costs in the year of cataract surgery	National Health Service, 2010
Cataract, years 2+ (after operation)	0.000	—	Assumption	383	Annual costs in subsequent years	Clarke et al., 2003
Neuropathy, year 1	0.624	Utility applied annually	Palmer et al., 2004	399	Annual costs in the year of developing neuropathy	National Health Service, 2010
Neuropathy, years 2+	0.624	Utility applied annually	Palmer et al., 2004	399	Annual costs in subsequent years	National Health Service, 2010
Foot ulcer	0.600	Utility applied annually	Palmer et al., 2004	Infected: 25,858 Uninfected: 25,351	Cost per episode	Ghatnekar et al., 2002
Amputation (year of event)	–0.109	Utility decrement applied annually	Clarke et al., 2002	4,437	Annual costs in the year of having an amputation	National Health Service, 2010

	Utility Weight			Cost (£)		
Complication[a]	**Value**	**Comment**	**Source**	**Value**	**Comment**	**Source**
Amputation prosthesis (per event)	Not applicable	Not applicable	Not applicable	2,234	Costs per prosthesis and fitting	Ghatnekar et al., 2002
Post-amputation (years 2+ post-event)	0.680	Utility applied annually	Clarke et al., 2002	0	Annual cost in years after amputation	Palmer et al., 2004
Gangrene treatment (per event)	Not applicable	Not applicable	Not applicable	45,100	Cost per episode	Ghatnekar et al., 2002
Microalbuminuria	0.814	Utility applied annually	Clarke et al., 2002	Not applicable	Not applicable	Not applicable
End-stage renal disease[b]						
Haemodialysis, year 1	0.490	Utility applied annually	Tengs and Wallace, 2000	37,882	Annual costs in the first year of haemodialysis	National Institute for Health and Clinical Excellence, 2008
Haemodialysis, years 2+	0.490	Utility applied annually	Tengs and Wallace, 2000	37,882	Annual costs in subsequent years	National Institute for Health and Clinical Excellence, 2008
Peritoneal dialysis, year 1	0.560	Utility applied annually	Tengs and Wallace, 2000	20,832	Annual costs in the first year of peritoneal dialysis	National Institute for Health and Clinical Excellence, 2008

	Utility Weight			Cost (£)		
Complication[a]	**Value**	**Comment**	**Source**	**Value**	**Comment**	**Source**
Peritoneal dialysis, years 2+	0.560	Utility applied annually	Tengs and Wallace, 2000	20,832	Annual costs in subsequent years	National Institute for Health and Clinical Excellence, 2008
Renal transplant, year 1	0.762	Utility applied annually	Tengs and Wallace, 2000	22,385	Annual costs in the year of renal transplant	National Institute for Health and Clinical Excellence, 2008
Renal transplant, years 2+	0.762	Utility applied annually	Tengs and Wallace, 2000	7,275	Annual costs in subsequent years	National Institute for Health and Clinical Excellence, 2008
Proliferative diabetic retinopathy, year 1 (laser treatment)	0.794	Utility applied annually	Palmer et al., 2004	290	Annual costs in the year of development of proliferative diabetic retinopathy	National Health Service, 2010
Proliferative diabetic retinopathy, years 2+ (after laser treatment)	0.794	Utility applied annually	Palmer et al., 2004	100	Annual costs in subsequent years	Assumption
Blindness, year of onset	0.700	Utility applied annually	Assumption	4,406	Annual costs in the first year of blindness	Meads and Hyde, 2003

	Utility Weight			Cost (£)		
Complication[a]	**Value**	**Comment**	**Source**	**Value**	**Comment**	**Source**
Blindness, following years	0.700	Utility applied annually	Assumption	4,406	Annual costs in subsequent years of blindness	Meads and Hyde, 2003
Non-severe hypoglycaemic event, day	–0.005	Utility decrement per event, applied annually	Assumption	0	Cost per event	Assumption
Non-severe hypoglycaemic event, nocturnal	–0.005	Utility decrement per event, applied annually	Assumption	0	Cost per event	Assumption
Severe hypoglycaemic event, day	–0.012	Utility decrement per event, applied annually	Assumption	354	Cost per event	National Institute for Health and Clinical Excellence, 2009
Severe hypoglycaemic event, nocturnal	–0.012	Utility decrement per event, applied annually	Assumption	354	Cost per event	National Institute for Health and Clinical Excellence, 2009
Diabetic ketoacidosis event	0.000	Utility decrement per event, applied annually	Assumption	995	Cost per event	Ray et al., 2007

	Utility Weight			Cost (£)		
Complication[a]	**Value**	**Comment**	**Source**	**Value**	**Comment**	**Source**
Average lifetime utility for infant with congenital malformation	0.700	Utility applied annually	Assumption	Not applicable	Not applicable	Not applicable
Average lifetime utility for general infant	0.820	Utility applied annually	Assumption	Not applicable	Not applicable	Not applicable

[a] No data describing the uncertainty in cost and utility estimates were available. In the probabilistic sensitivity analysis, the user could select from a range of alternative distributional forms and enter estimates of the uncertainty.

[b] Of all patients with end-stage renal disease, 44% were assumed to have haemodialysis; 8%, peritoneal dialysis; and 48%, renal transplantation (United Kingdom Renal Registry, 2010).

Table S5. Mean Net Monetary Benefit and Standard Error as a Function of the Number of Individual Patient (First-Order) Simulations

	Net Monetary Benefit (at £20,000 per QALY)		
Number of First-Order Simulations	Mean[a]	Standard Error[a]	Standard Error (% of Mean)[a]
1,000	£5,079	£2,191	43.1%
2.000	£7,464	£2,237	30.0%
5,000	£6,754	£926	13.7%
10,000	£6,425	£854	13.3%
20,000	£7,249	£679	9.4%
50,000	£6,254	£288	4.6%
100,000	£6,647	£179	2.7%

QALY = quality-adjusted life-year.

Note: The individual patient (first-order) simulation was run 5 times for each of the intervals. The mean net monetary benefit and standard error were calculated for each simulation; the standard error was expressed as a percentage of the mean.

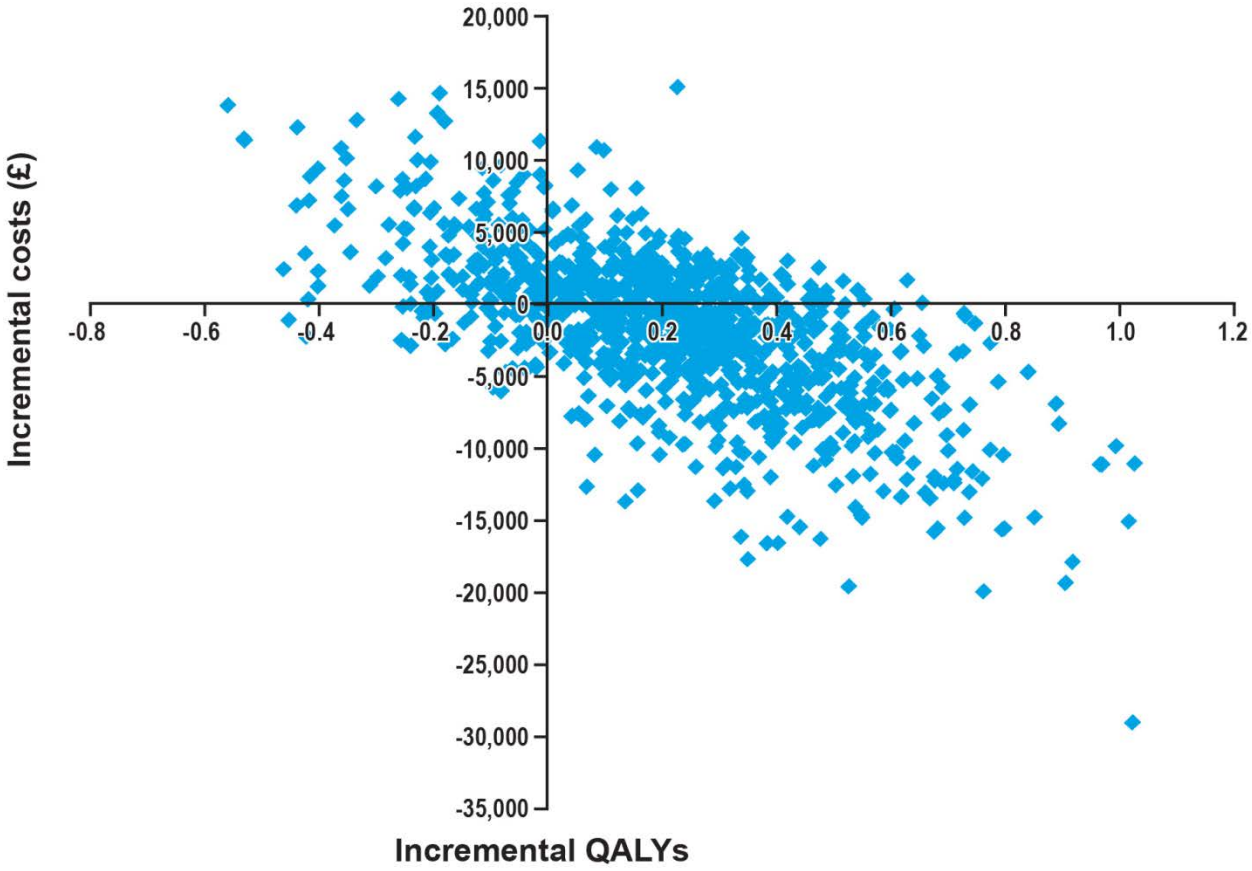
[a] Mean and standard error of successive first-order simulation results.

Progression of HbA1c in Patients With Type 1 Diabetes Mellitus

There is no apparent trend over time in glycated haemoglobin (HbA1c) levels in patients with Type 1 diabetes mellitus. Nathan et al. (2009) investigated the distribution of HbA1c levels over time in patients participating in the Diabetes Control and Complications Trial, the Epidemiology of Diabetes Interventions and Complications study, and the Epidemiology of Diabetes Complications study. HbA1c levels were relatively stable over the 18 years of follow-up observed in the Diabetes Control and Complications Trial, the Epidemiology of Diabetes Interventions and Complications study, and the Epidemiology of Diabetes Complications study.

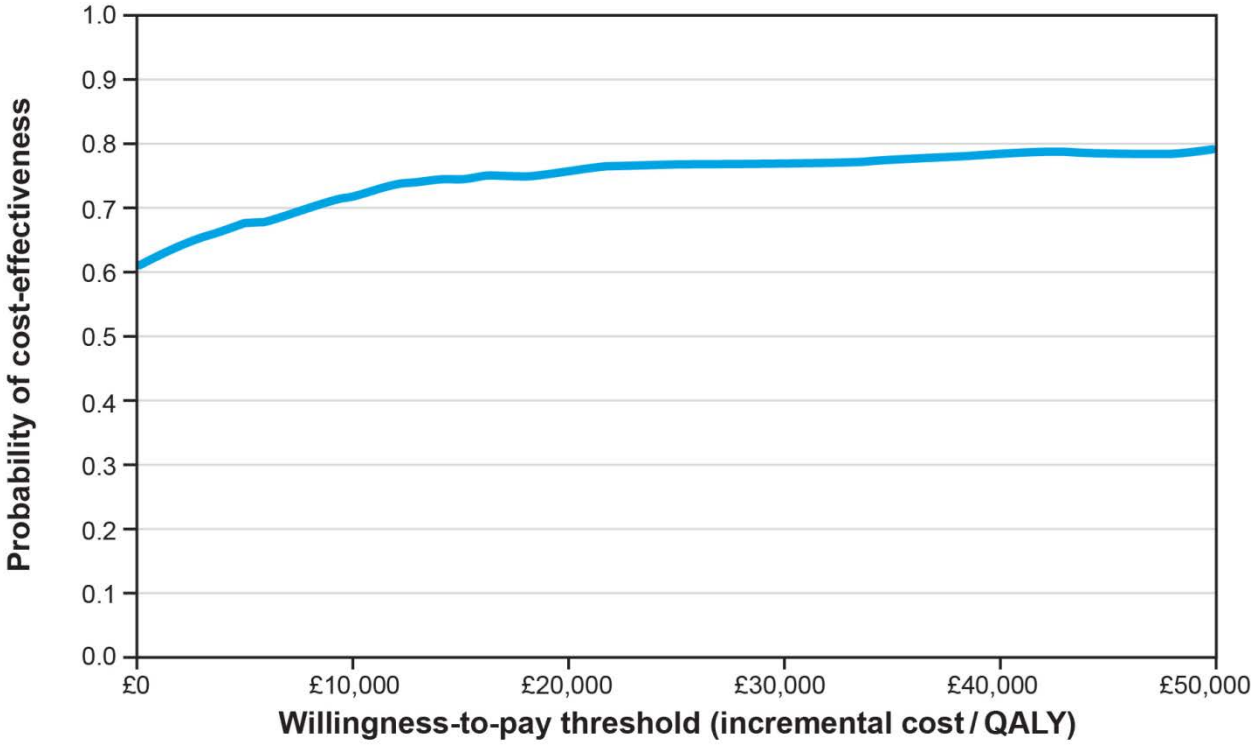
Therefore, trends in HbA1c levels were included in the model. Probabilities of complications were estimated from published cumulative incidence curves and adjusted for differences in HbA1c levels among treatments, using published hazard ratios or relative risks for the association between HbA1c level and each complication.

Figure S1. Cost-effectiveness Plane



QALY = quality-adjusted life-year.

Figure S2. Cost-effectiveness Acceptability Curve



QALY = quality-adjusted life-year.

REFERENCES

Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ 2009 Feb 17; 180(4): 400-7.

Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002; 22: 340-9.

Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No 65). Diabetic Med 2003; 20: 442-50.

Craig ME, Jones TW, Silink M, Ping YJ. Diabetes care, glycemic control, and complications in children with type 1 diabetes from Asia and the Western Pacific Region. J Diabetes Complications 2007; 21(5): 280-7.

Cusick M, Chew EY, Hoogwerf B, Agron E, Wu L, Lindley A, et al. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS): Early Treatment Diabetic Retinopathy Study report No. 26. Kidney Int 2004; 66(3): 1173-9.

Czaja CA, Rutledge BN, Cleary PA, Chan K, Stapleton AE, Stamm WE. Urinary tract infections in women with type 1 diabetes mellitus: survey of female participants in the epidemiology of diabetes interventions and complications study cohort. J Urol 2009; 181(3): 1129-34.

de Boer IH, Sibley SD, Kestenbaum B, Sampson JN, Young B, Cleary PA, et al. Central obesity, incident microalbuminuria, and change in creatinine clearance in the epidemiology of diabetes interventions and complications study. J Am Soc Nephrol 2007 Jan; 18(1): 235-43.

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 Sep 30; 329(14): 977-86.

Dyer MT, Goldsmith KA, Khan SN, Sharples LD, Freeman C, Hardy I, et al. Clinical and cost-effectiveness analysis of an open label, single-centre, randomised trial of spinal cord stimulation (SCS) versus percutaneous myocardial laser revascularisation (PMR) in patients with refractory angina pectoris: the SPiRiT trial. Trials 2008 Jun 30; 9: 40.

Early Treatment Diabetic Retinopathy Study Research Group (ETDRS). ETDRS report number 9. Early photocoagulation for diabetic retinopathy. Ophthalmology 1991 May; 98(suppl 5): 766-85.

Enzlin P, Mathieu C, Van Den Bruel A, Vanderschueren D, Demyttenaere K. Prevalence and predictors of sexual dysfunction in patients with type 1 diabetes. Diabetes Care 2003; 26(2): 409-14.

Eurodiale Study Group. Diabetic Foot Disease in European Perspective; Results From the Eurodiale Study. 2008. Available at http://arno.unimaas.nl/show.cgi?fid=10680#page=33 Last accessed 22 April 2012.

Färnkvist LM, Lundman BM. Outcomes of diabetes care: a population-based study. Int J Qual Health Care 2003 Aug; 15(4): 301-7.

Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. JAMA 2005; 294(14): 1782-7.

Ghatnekar O, Willis M, Persson U. Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. J Wound Care 2002 Feb; 11(2): 70-4.

Grauslund J, Green A, Sjølie AK. Cataract surgery in a population-based cohort of patients with type 1 diabetes: long-term incidence and risk factors. Acta Ophthalmol 2011 Feb; 89(1): 25-9.

Hammes HP, Kerner W, Hofer S, Kordonouri O, Raile K, Holl RW. Diabetic retinopathy in type 1 diabetes-a contemporary analysis of 8,784 patients. Diabetologia 2011; 54(8): 1977-84.

Heller S. Sudden death and hypoglycemia. Diabet Hypoglycem 2008 Sep; 1(2): 2-7.

Hunink MG, Goldman L, Tosteson ANA, Mittleman MA, Goldman PA, Williams LW, et al. The recent decline in mortality from coronary heart disease, 1980-1990. JAMA 1997; 277(7): 535-42.

Jacobsen N, Jensen H, Lund-Andersen H, Goldschmidt E. Is poor glycaemic control in diabetic patients a risk factor of myopia? Acta Ophthalmol 2008; 86(5): 510-4.

Jensen DM, Damm P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004 Dec; 27(12): 2819-23.

Jonasson JM, Ye W, Sparen P, Apelqvist J, Nyren O, Brismar K. Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. Diabetes Care 2008; 31(8): 1536-40.

Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. Arch Intern Med 2004; 164(17): 1917-24.

Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII, the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008 Nov; 115(11): 1859-68.

Kordonouri O, Hartmann R, Deiss D, Wilms M, Gruters-Kieslich A. Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. Arch Dis Child 2005; 90(4): 411-4.

Lauterbach S, Kostev K, Kohlmann T. Prevalence of diabetic foot syndrome and its risk factors in the UK. J Wound Care 2010 Aug; 19(8): 333-7.

Lindsay JR, Kennedy L, Atkinson AB, Bell PM, Carson DJ, McCance DR, et al. Reduced prevalence of limited joint mobility in type 1 diabetes in a U.K. clinic population over a 20-year period. Diabetes Care 2005; 28(3): 658-61.

Mak KH, Faxon DP Clinical studies on coronary revascularization in patients with type 2 diabetes. Eur Heart J 2003; 24: 1087-103.

Mantovani RM, Mantovani LM, Dias VM. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: prevalence and risk factors. J Pediatr Endocrinol Metab 2007; 20(6): 669-75.

McAlpine RR, Morris AD, Emslie-Smith A, James P, Evans JM. The annual incidence of diabetic complications in a population of patients with type 1 and type 2 diabetes. Diabet Med 2005; 22(3): 348-52.

Meads C, Hyde C. What is the cost of blindness? Br J Ophthalmol 2003 Oct; 87(10): 1201-4.

Moss SE, Klein R, Klein B. The prevalence and incidence of lower extremity amputation in a diabetic population. Arch Intern Med 1992; 152: 610-6.

Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005 Dec 22; 353(25): 2643-53.

Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med 2009; 169(14): 1307-16.

National Audit Office. Progress in Improving Stroke Care. 2010. Available at http://www.nao.org.uk/publications/0910/stroke.aspx Last accessed 21 April 2012.

National Health Service, Department of Health. NHS Reference Costs, 2008-2009. 2010. Available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591 Last accessed 26 March 2012.

National Institute for Health and Clinical Excellence. Clinical Guideline 48. MI: Secondary Prevention. 2007. Available at http://guidance.nice.org.uk/CG48 Last accessed 26 March 2012.

National Institute for Health and Clinical Excellence. Clinical Guideline 73. Chronic Kidney Disease. 2008. Available at http://guidance.nice.org.uk/CG73 Last accessed 26 March 2012.

National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 Diabetes—Newer Agents (Partial Update of CG66). 2009. Available at http://guidance.nice.org.uk/CG87 Last accessed 26 March 2012.

National Institute for Health and Clinical Excellence. Technology Appraisal 94. Cardiovascular disease—Statins. 2006. Available at http://guidance.nice.org.uk/TA94 Last accessed 26 March 2012.

Nielsen GL, Møller M, Sørensen HT. HbA1c in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. Diabetes Care 2006 Dec; 29(12): 2612-6.

Office for National Statistics. Birth Statistics 2008, Series FM1 No.37. 2009. Available at http://www.ons.gov.uk/ons/rel/vsob1/birth-statistics--england-and-wales--series-fm1-/no--37--2008/index.html Last accessed 9 February 2012.

Office for National Statistics. Death registrations summary tables, England and Wales. 2010. Available at http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-227638 Last accessed 12 February 2012.

Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, 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(suppl 1): S5-26.

Patterson CC, Dahlquist G, Harjutsalo V, Joner G, Feltbower RG, Svensson J, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia 2007; 50(12): 2439-42.

Pavlovic MD, Milenkovic T, Dinic M, Misovic M, Dakovic D, Todorovic S, et al. The prevalence of cutaneous manifestations in young patients with type 1 diabetes. Diabetes Care 2007; 30(8): 1964-7.

Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Rasmussen AK, Jørgensen HV, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev 2004 Nov-Dec; 20(6): 479-86.

Powers AC. Diabetes mellitus. In: Kasper DL, Braunwald E, Hauser S, Longo D, Jameson JL, Fauci AS. Harrison's Principles of Internal Medicine. 16th Edition. New York: McGraw-Hill, 2005: 2152-80.

Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 1999; 22(3): 382-7.

Ray JA, Boye KS, Yurgin N, Valentine WJ, Roze S, McKendrick J, et al. Exenatide versus insulin glargine in patients with type 2 diabetes in the UK: a model of long-term clinical and cost outcomes. Curr Med Res Opin 2007 Mar; 23(3): 609-22.

Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In: National Diabetes Data Group, editors. Diabetes in America. 2nd Edition. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995:409-28.

Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. Neurology 1994; 44: 626-34.

Sahakyan K, Klein BE, Lee KE, Myers CE, Klein R. The 25-year cumulative incidence of lower extremity amputations in people with type 1 diabetes. Diabetes Care 2011; 34(3): 649-51.

Sarma AV, Kanaya A, Nyberg LM, Kusek JW, Vittinghoff E, Rutledge B, et al. Risk factors for urinary incontinence among women with type 1 diabetes: findings from the epidemiology of diabetes interventions and complications study. Urology 2009; 73(6): 1203-9.

Singh R, Gamble G, Cundy T. Lifetime risk of symptomatic carpal tunnel syndrome in type 1 diabetes. Diabet Med 2005; 22(5): 625-30.

Targher G, Bertolini L, Chonchol M, Rodella S, Zoppini G, Lippi G, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and retinopathy in type 1 diabetic patients. Diabetologia 2010; 53(7): 1341-8.

Tengs TO, Wallace A. One thousand health-related quality-of life estimates. Med Care 2000; 38: 583-637.

United Kingdom National Diabetes Audit. Executive Summary 2009-2010. 2010. Available at http://www.ic.nhs.uk/webfiles/Services/NCASP/Diabetes/200910%20annual%20report%20documents/National_Diabetes_Audit_Executive_Summary_2009_2010.pdf Last accessed 11 February 2012.

United Kingdom Renal Registry, The Renal Association. The Thirteenth Annual Report. December 2010. Available at http://www.renalreg.com/Reports/2010.html Last accessed 21 April 2012.

Vamos EP, Bottle A, Majeed A, Millett C. Trends in lower extremity amputations in people with and without diabetes in England, 1996-2005. Diabetes Res Clin Pract 2010; 87(2): 275-82.

Van Den Eeden SK, Sarma AV, Rutledge BN, Cleary PA, Kusek JW, Nyberg LM, et al. Effect of intensive glycaemic control and diabetes complications on lower urinary tract symptoms in men with type 1 diabetes: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes Care 2009; 32(4): 664-70.

van Dijk M, Donga E, van Dijk JG, Lammers GJ, van Kralingen KW, Dekkers OM, et al. Disturbed subjective sleep characteristics in adult patients with long-standing type 1 diabetes mellitus. Diabetologia 2011; 54(8): 1967-76.

Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. Am J Public Health 1987; 77(11): 1417-26.

World Health Organization. Definition, diagnosis, and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization; 1999.

Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. Pharmacoeconomics 2003; 21(suppl 1): 43-50.