# Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eTable 1. Net gains in quality adjusted life expectancy, by age, starting A1c, and treatment disutility

### 15% reduction in CHD events per 1 point reduction in A1c; no effect of albuminuria on CHD risk

| Disutility | | | | |
|---|---|---|---|---|
| | 0.001 | 0.01 | 0.025 | 0.05 |
| Age | A1c 7.5 to 6.5% | | | |
| 45 | 0.766 | 0.471 | -0.015 | -0.818 |
| 55 | 0.450 | 0.223 | -0.152 | -0.771 |
| 65 | 0.219 | 0.057 | -0.210 | -0.652 |
| 75 | 0.084 | -0.019 | -0.189 | -0.471 |
| | | | | |
| | A1c 8.5 to 7.5% | | | |
| Age | | | | |
| 45 | 0.906 | 0.616 | 0.136 | -0.653 |
| 55 | 0.544 | 0.320 | -0.052 | -0.665 |
| 65 | 0.269 | 0.108 | -0.158 | -0.599 |
| 75 | 0.104 | 0.001 | -0.169 | -0.450 |

## eTable 2. Net gains in quality adjusted life expectancy, by age, starting A1c, and treatment disutility

### 15% reduction in CHD events per 1 point reduction in A1c; direct effect of albuminuria on CHD risk

| | Disutility | | | |
|---|---|---|---|---|
| | 0.001 | 0.01 | 0.025 | 0.05 |
| Age | A1c 7.5 to 6.5% | | | |
| 45 | 0.962 | 0.677 | 0.206 | -0.569 |
| 55 | 0.606 | 0.385 | 0.019 | -0.583 |
| 65 | 0.319 | 0.160 | -0.102 | -0.537 |
| 75 | 0.129 | 0.028 | -0.141 | -0.421 |
| | | | | |
| | A1c 8.5 to 7.5% | | | |
| Age | | | | |
| 45 | 1.110 | 0.831 | 0.372 | -0.383 |
| 55 | 0.718 | 0.501 | 0.141 | -0.450 |
| 65 | 0.389 | 0.231 | -0.029 | -0.459 |
| 75 | 0.161 | 0.060 | -0.108 | -0.387 |

# eAppendix. Technical Appendix: The effects of patients' risks and preferences on health gains with glucose lowering in type 2 diabetes

## Background

Type 2 diabetes has staggering health and economic effects. There are an estimated 18 million people with diabetes in the United States and, given the aging of the population, changes in ethnic makeup, and the dramatic increase in obesity and sedentary lifestyles in the United States, the prevalence of diabetes is increasing at an epidemic rate.[1,2] It has recently been estimated that if current trends continue, 1 in 3 Americans born in 2004 will develop diabetes.[3] The complications of diabetes are a cause of frequent morbidity and mortality. Microvascular diabetes complications, such as retinopathy, nephropathy, and neuropathy, are the leading causes of blindness, end-stage renal disease, and non-traumatic amputation, respectively, in the United States.[4] Even more important is macrovascular disease (including coronary artery disease, stroke, and peripheral vascular disease). Patients with diabetes have two to four times the risk of macrovascular disease and mortality compared to age and sex-matched controls; as a result, over 70 percent of patients with diabetes die from these complications.[5-9] The total economic burden of diabetes and its complications was estimated at over $132 billion in 2002.[10]

There is emerging evidence that there are differences in control of risk factors for diabetes complications in a variety of settings. Differences in control of risk factors is particularly concerning because effective treatments exist that can improve these factors and modify the risk of disease outcomes. Indeed, randomized trials have convincingly

demonstrated that the risk of macrovascular diabetes complications can be reduced through control of blood pressure and serum lipid levels (primarily though the use of HMG CoA reductase inhibitors, or "statins").[11,12] Microvascular diabetes complications can be reduced through control of blood pressure and blood glucose.[13,14] The poor control of these risk factors in some populations is thus an almost certain source of disparities in health outcomes. However, disparities in long-term health outcomes have only been examined in a limited fashion; instead, most studies have focused on process measures or intermediate outcomes, such as the risk factors we described above, in part because these represent an "actionable" point – modifying these factors is currently the best strategy to prevent long-term outcomes. However, the long-term goal of quality improvement interventions is to modify patient-centered and symptomatic disease outcomes; thus a clearer understanding of the impact of quality improvement measures on quality-adjusted life years (QALYs) is critical. In particular, the use of QALYs as a measure of quality of care has not been explored. QALYs have potential advantages and disadvantages as a quality of care measure. Most obviously, QALYs are a measure of something that actually matters to patients, rather than typically asymptomatic intermediate outcomes such as blood glucose or blood pressure levels. QALYs also have the advantage of considering multiple endpoints and risk factors simultaneously; they can be compared across disease processes; and they naturally provide a weighting scheme, assigning more value to factors that have more benefit. The major drawback of using QALYs is that it requires a relatively intensive effort to compile and model the effects of the comparatively easy to measure intermediate outcomes.

## Basic Model Structure

The model is a non-stationary Markov model that estimates the likelihood of progressing from uncomplicated to complicated diabetes. The basic model states include diabetes without complication; photocoagulation; visual loss; microalbuminuria; overt proteinuria; end-stage renal disease; neuropathy; amputation; coronary artery disease; stroke; and death, along with all possible interactions between these states (e.g., photocoagulation and coronary artery disease).

A schematic of the basic model is shown in figure 1. The figure describes the basic progression path through each of the types of diabetes complications. However, for parsimony, we do not display model states that represent combinations of states; for example, people who have had a stroke may also have nephropathy and visual loss. The basic model structure is based upon previously published models, and are updated to consider simultaneous endpoints and simultaneous combinations of risk factors, something that most previously published models of diabetes lack.[15-19]

## Baseline model states

We assumed that the baseline model states (e.g., degree of microvascular disease at diagnosis) were distributed as they were at diagnosis in the UKPDS 33.[14]

## Transition Probabilities: general approach

Transition probabilities were largely derived from randomized, controlled trials, or from re-analysis of data presented in randomized trials. In order to tie the transition probabilities directly to risk factors, we focused the derivation of probabilities on trials that directly assessed rates of progression with and without modification of the various risk factors. Using the randomized trials avoids problems with confounding in observational studies; the drawback is that the trial population tends to be less generalizable than that of many observational studies.

We examined two approaches to develop estimates that are based on a continuous mapping of the risk factors to the probabilities of disease progression. In the first, we followed the CDC diabetes model to derive these probabilities from randomized trials.[19] In this case, we developed coefficients that relate the degree of change in risk factors to the degree of change in risks of outcomes. These coefficients are analogous to the coefficients of a regression model. The basic function for calculating a rate at a particular risk factor level is:

$$\text{Rate}_{[\text{RF Level 2}]} = \text{Rate}_{[\text{RF level 1}]} * (\text{RF level 2}/\text{RF level 1})^{\beta}$$

Where the RF levels are the levels of the risk factors (e.g., LDL levels of 100 and 120). Solving for β using the observed rates and risk factor levels in the randomized trials allows us to extrapolate this relationship to other levels of risk factors. This assumes a continuous function that is curvilinear in nature; this type of relationship has been consistently found in re-analyses of randomized trials and in observational studies, and is

the generally accepted functional form for the relationship between each of our studied risk factors and the risk of events. However, the degree of curve (e.g., non-linearity of effect) is dependent on the efficacy of the intervention; the higher the β, the greater the curve, but also the greater the effectiveness of the intervention at any point.

In a second approach, we assumed a log-linear function to the relationship between risk factor levels and risks of outcomes. This assumes, that for any absolute change in a risk factor (e.g., a change in A1c of 1.0%, or a change in blood pressure of 10mm Hg), that there is a constant relative increase in the transition rate. This has been consistently observed in analyses of complication risks in diabetes. For example, with A1c, we assumed that there was a 29% change in risk of progression to photocoagulation per 0.9% change in A1c, as was seen in the UKPDS.[14] As an example, in the control arm of the UKPDS, at an A1c of 7.9%, the annual probability of photocoagulation is about 1%. For each 0.9% increase in A1c, this risk would increase by 29%, so that an A1c of 8.8% would translate to a risk of 1.29%.

While both approaches provide similar overall rates when used in the model, we found that the relative risk approach fit the UKPDS glucose outcomes better, so we opted for this as our primary approach for the A1c analyses.

Of note, all calculated rates were converted to probabilities prior to use in the model, using the standard formula:

$$\text{Probability} = 1\text{-}e^{(\text{-rate}*\text{time})}$$

eTable 3 displays our calculations of the transition probabilities for the model, and the estimation of the beta coefficient that maps risk factor level to risk. Note that this table does not include other transition probabilities (e.g., mortality rates) that are discussed below.

**Sources of transition probabilities**

We assumed, based on the best available randomized trials, that the transition probabilities for macrovascular disease were related to LDL-cholesterol level and to blood pressure level.[11,12] The transition probabilities for microvascular disease were related to blood pressure level and blood glucose level.[13,14] For microvascular disease, these risk factors were primarily related to the development of early and intermediate complications of diabetes – e.g., photocoagulation, microalbuminuria and nephropathy, and neuropathy.[13,14] In this section, we detail the sources of estimates for the relationships between risk factors and the development of diabetes complications. In the following section, we detail the sources of estimates for progression beyond these states.

As noted in the main manuscript, we estimated baseline rates of CHD events using Framingham risk equations. We populated these equations using risk factor distributions for patients with diabetes derived from the 2009-2010 iteration of the NHANES survey. Modification of these baseline risks was driven by the assumptions outlined below.

1. LDL-cholesterol level and macrovascular disease

There are many lipid-lowering studies that include small subgroups with patients with diabetes, and a recent meta-analysis showed that the effects were relatively consistent (and when combined, statistically significant).[11] However, only two studies have had a primary focus on diabetes: the Collaborative Atorvastatin Diabetes Study (CARDS) and the Heart Protection Study. In each of these studies, there were significant reductions in cardiovascular events and mortality associated with the use of HMG-CoA reductase inhibitors ("statins") in patients with diabetes.[20,21]

In each study, there was a 35-40 mg/dl lowering of LDL cholesterol with moderate doses of statin agents, resulting in a 26% relative risk reduction in cardiovascular events in the HPS and a 37% relative risk reduction in CARDS.

2. Blood pressure and macrovascular disease

   The relationship between blood pressure and risk of macrovascular disease in diabetes is well documented. Many of the original trials focused on specific agents vs. placebo rather than targeting of specific blood pressure levels; because we are most interested in mapping the effects of blood pressure (rather than of specific drugs) to risks, we chose to use trials that focus on specific blood pressure targets. There are two large scale trials that have published adequate detail to map this relationship: the UK Prospective Diabetes Study (UKPDS) and the Hypertension Optimal Treatment Study (HOT).[13,22]

To ensure consistency across studies, we mapped the effects on blood pressure using mean arterial pressure (MAP) rather than isolating systolic or diastolic blood pressure. The mean arterial pressure is a direct calculation from systolic and diastolic blood pressures and thus reflects the fact that in both studies, systolic and diastolic blood pressures were significantly lowered (even though the HOT study targeted primarily diastolic blood pressure).

3. Blood pressure and early microvascular disease

   Only one study, the UKPDS, has mapped the effects of blood pressure on microvascular diabetes outcomes. This study found substantial differences in the risks of microvascular outcomes, particularly photocoagulation and early progression of diabetic nephropathy. However, they found no effect on end-stage renal disease (presumably due to infrequent events) or neuropathy.[13]

   One result that was not detailed in the UKPDS results was the rate of progression from microalbuminuria to nephropathy. Instead, they presented separate results for progression from normal to microalbuminuria, and from normal to nephropathy. Other investigators have used simulation methods to estimate the progression rates from microalbuminuria to nephropathy.[19] We have used these rates in our model as well. We tested the rates and found that they accurately reproduce the overall rates of nephropathy in the original UKPDS report.

4. Blood glucose level and early microvascular disease

The UKPDS is the only long-term study that has examine the effects of blood glucose control on complications in patients with type 2 diabetes.[14] The UKPDS compared "conventional" control, manifested as a mean HbA1c of 7.9%, with intensive control, with a mean HbA1c of 7.0%. The study found a reduction in the risk of intermediate microvascular endpoints (e.g. early stages of nephropathy, neuropathy, retinopathy), and a reduction in the risk of retinal photocoagulation. There were no significant differences in risks of macrovascular complications or mortality. We mapped the 0.9% difference in HbA1c onto the risk of complications noted in the trial. For retinopathy, we focused on risk of progression to photocoagulation, while for nephropathy and neuropathy, we focused on risks of intermediate outcomes (i.e., microalbuminuria, nephropathy, neuropathy).

**Progression beyond early/intermediate diabetes complications**

For microvascular disease, we assumed that progression beyond the intermediate stages (i.e., nephropathy to end-stage renal disease; neuropathy to amputation; and photocoagulation to visual loss) was not related to levels of risk factor control. The UKPDS did not find significant relationships (possibly in part because of the rarity of advanced complications), and cohort studies have also not identified a clear link between risk factors and progression from intermediate to end-stage outcomes. The rates of risks of progression from the intermediate to end-stages of the various microvascular outcomes were taken from a variety of sources.

For progression from photocoagulation to visual loss, we used data from the Early Treatment of Diabetic Retinopathy Study, which was a randomized trial comparing the effects of various photocoagulation strategies on risks of visual loss.[16,23,24] These rates are widely published and have been used in previous models of diabetic eye disease, including one published by our group.[16,25]

For progression from nephropathy to end-stage renal disease, we used data from randomized trials comparing the effects of drug therapy for nephropathy on risk of end-stage renal disease.[26-28] We also considered using cohort data, which have been used in other models, but the best cohort data have very limited minority populations, in contrast to the randomized trial data.[29,30]

For progression from neuropathy to amputation, we used data from cohort and population-based studies, as there are no long-term randomized trials from which to draw estimates. These summary rates were published in the textbook "Diabetes in America" in tabular form, and were converted to transition probabilities using the standard formula.[4]

For macrovascular disease, the rates of recurrent events and of mortality were taken from observational data that report the relative risk of new events once a baseline event has occurred.[31,32] We assume that the relative risk of recurrent events is similarly related to the various risk factors as it is for primary events; this is supported by clinical trial data. For example, in a meta-analysis of lipid-lowering therapy in diabetes conducted by one of our investigators, we found that the relative risk reduction for secondary prevention was

essentially identical to that of primary prevention (24 vs. 22% risk reduction); this confers a greater absolute risk reduction, as baseline event rates are increased.[11]

In addition, we modeled a link between the presence of nephropathy and the risk of cardiovascular disease. It is well established that patients with diabetes and early stages of renal disease (microalbuminuria, nephropathy) have substantial elevations in cardiovascular risk and mortality. This relationship is felt to be causal by most experts.[33-35] Thus, this increased risk was factored into the model. Prevention of these renal disease states therefore not only confers benefits by reducing risk of end-stage renal disease, but also by reducing risk of cardiovascular events. Specific values are shown in eTable 4. We did not separately model CV events in patients with ESRD; because mortality rates are so substantial, we used overall ESRD mortality rates from the US renal data systems.

Age-based mortality hazard rates were obtained from year 2000 U.S. life tables. Mortality rates for cardiovascular events were derived from the randomized trials used to derive risks of these events. Mortality rates for end-stage renal disease were taken from data published by the US Renal Data Systems.[36] A proportional hazards model was applied to remove cardiovascular disease and diabetes mortality from baseline age-based hazards, as these are calculated separately in our model.[37]

**Quality-Adjusted Life Years (QALYs)**

Utilities for various disease states were taken from a variety of published data sources.[19,38-42] Where available, we use utilities from a general population;[42] however, for

some utilities, such as MI, there are limited data and we use data from individuals who have experienced the event.[38] Key utility values are listed in eTable 5. We note that these utilities are in accord with those used in many other models in order to minimize debate over values.[17-19] Although a goal of this project is to use individual risk and benefit of treatment to better inform profiling, we also note that we do not have (and it is not really possible) to collect individual utilities for all of the patients who are run through the simulation model.

Although there are studies that suggest that the baseline utility values for patients with diabetes may be as low as 0.88, we did not use these values because these take into account all patients with diabetes, regardless of health status, and we track the individual outcomes that contribute to declines in utility in the model. Further, the baseline utility will not have any effect on the primary focus of the project, which is the calculation of incremental QALYs.

All QALYs were discounted at 3%. We assumed that utilities were multiplicative for patients with multiple disease states; e.g., those who had a stroke and visual loss would have a utility of 0.69 * 0.64.

**Model validation simulations**

We validated model predictions using two main approaches, although "true" model validation is difficult given the lack of data on the effect of risk factors on long-term

population risks, particularly for microvascular endpoints (ESRD, visual loss, amputation).

In our first approach, to validate the effect of A1c on life expectancy, we compared our predicted results with actuarial analyses of the UKPDS.[43] We set the baseline population characteristics to that of the UKPDS (e.g., age, initial distribution of complications, risk factor levels), and then predicted life expectancy, assuming either no relationship between A1c and CHD risk or a 15% change in CHD risk per 1% change in A1c. Because our model is not gender specific, we weighted the results from the UKPDS by gender to provide a closer comparison.

In our second set of validations, we compared the model's predictions of reduction in various diabetes endpoints with that seen in the Steno-2 study.[44] The Steno-2 study evaluated the effect of multifactorial risk factor treatment (e.g., blood pressure, lipids, A1c) on risk of diabetes complications, particularly CHD events. Again, to conduct these simulations, we set initial model parameters to those reported in the study, and ran the simulation over the 8-year follow-up period of the study.

Our model predictions of life expectancy were similar to those predicted from the UKPDS (eTable 4). While the UKPDS was used to provide some estimates in our model, these were only for early microvascular complications; cardiovascular risk, which is the dominant factor in life expectancy determination, was derived from Framingham risk so

that this provides a reasonably independent estimate of life expectancy. The relative comparability of the two estimates suggests there is some convergent validity between the two models.

The results of comparisons to the Steno-2 results are shown in eTable 7. Note that to make reasonable comparisons with the model, the RR for the trial are estimated based on the percentage of patients reaching an endpoint (e.g., 16/80 developed nephropathy in the intensive arm, compared to 31/80 in the conventional arm, for a RR of 0.52). The simulations generally track the trial well. In addition to relative risks with therapy, the absolute risks of events were highly comparable. For example, in the conventional arm of the trial, 21.3% of patients had an MI; the model predicts 20.2%. In the intensive arm, 6.3% had an MI, compared to model predictions of 7.9%. In the conventional arm of the trial, 38.8% developed nephropathy and 17.5% had amputations, while the Markov model predicts 36.4% and 14.6%, respectively.

**Sensitivity analysis**

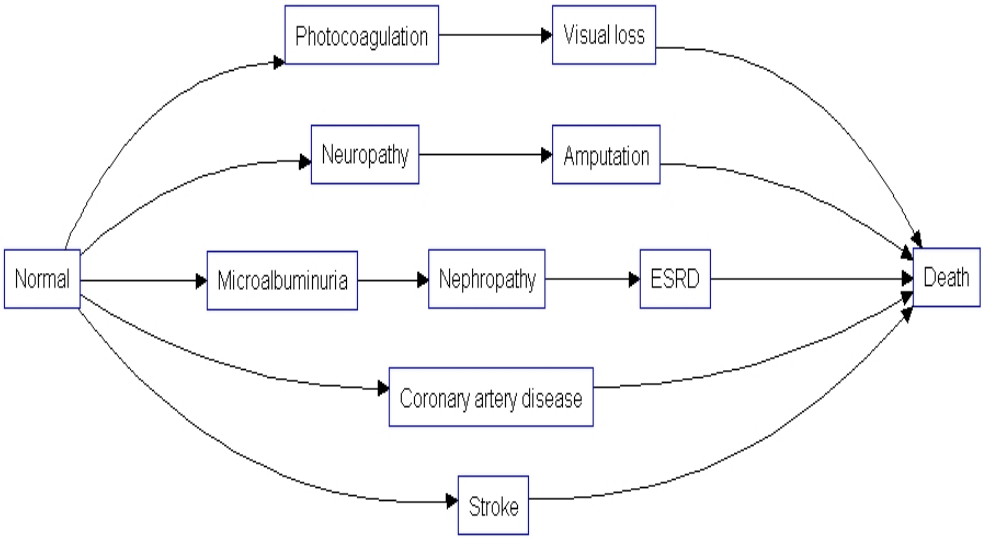
Our main sensitivity analyses are on the 4 primary factors outlined in the main paper (age, A1c level, treatment disutility, and the effect of A1c lowering on CHD risk). We conducted one-way sensitivity analyses on all model variables, fixing the above 4 variables at age 65; A1c 7.5%; treatment disutility 0.001; and assuming a 15% CHD effect).

For individual estimates of risk reduction (e.g., the effect of A1c on risk of complication risks), we conducted our sensitivity analyses across the 95% confidence intervals reported in the UKPDS (for microvascular risks) and meta-analyses (for cardiovascular risks). The range of relative risks did not have large impact on outcomes.

The variables with the largest impact on outcomes were related to the risks of microalbuminuria; in particular, the relative risk of cardiovascular events (stroke and MI), and the baseline risk of developing microalbuminuria. In part this was because we lack direct knowledge of the whether albuminuria is causally related to higher rates of CV events; thus our range in the analysis was wide. We assumed in the base case that there was no additional effect of albuminuria beyond that captured by the assumption that a reduction in A1c leads to a 15% reduction in CHD event rates. A more detailed set of results around the key assumptions (risks of developing albuminuria and the relative risks of MI and CVA with microalbuminuria) are shown in eTable 8.

The other parameters that had moderate effects on the absolute predictions of QALYs included the case fatality rates for CVA and MI. However, as we assumed no relationship between A1c and these rates, they had no bearing on the marginal effects of lowering A1c. Of the factors that do vary with A1c (e.g., risks of photocoagulation, neuropathy) did not substantially alter the marginal effects of A1c lowering within the range of our sensitivity analyses.

eFigure 1. Schematic representation of model



## eTable 3. Transition probabilities and risk factor modifications for the model

| Outcome | Group | Risk | Time | Annual Probability | RF level | Beta | RR |
|---|---|---|---|---|---|---|---|
| **Lipid studies** | | | | | | | |
| | | | | | | | |
| ***CARDS*** | | | | | | | |
| Stroke | Control | 0.0280 | 3.9 | 0.0071 | 120.65 | | |
| | Intervention | 0.0150 | 3.9 | 0.0038 | 81.6 | 1.5960 | 1.87 |
| | | | | | | | |
| MI | Control | 0.0550 | 3.9 | 0.0137 | 120.65 | | |
| | Intervention | 0.0360 | 3.9 | 0.0091 | 81.6 | 1.0837 | 1.53 |
| | | | | | | | |
| ***HPS*** | | | | | | | |
| Stroke | Control | 0.0650 | 5 | 0.0126 | 123.7 | | |
| | Intervention | 0.0500 | 5 | 0.0098 | 88.9 | 0.7942 | 1.30 |
| | | | | | | | |
| MI | Control | 0.1260 | 5 | 0.0237 | 123.7 | | |
| | Intervention | 0.0940 | 5 | 0.0179 | 88.9 | 0.8869 | 1.34 |
| **BP Studies** | | | | | | | |
| | | | | | | | |
| ***UKPDS*** | | | | | | | |
| Stroke | Control | 0.0872 | 8.4 | 0.0099 | 109.33 | | |
| | Intervention | 0.0501 | 8.4 | 0.0058 | 102.67 | 8.8036 | 1.74 |
| | | | | | | | |
| MI | Control | 0.1769 | 8.4 | 0.0193 | 109.33 | | |
| | Intervention | 0.1412 | 8.4 | 0.0157 | 102.67 | 3.5929 | 1.25 |
| | | | | | | | |
| Photocoagulation | Control | 0.1205 | 8.4 | 0.0135 | 109.33 | | |
| | Intervention | 0.0805 | 8.4 | 0.0092 | 102.67 | 6.4249 | 1.50 |
| | | | | | | | |
| Microalbuminuria | Control | 0.2850 | 6 | 0.0413 | 109.33 | | |
| | Intervention | 0.2030 | 6 | 0.0306 | 102.67 | 5.3982 | 1.40 |
| | | | | | | | |
| Nephropathy* | Control | 0.1505 | 1 | 0.1397 | 109.33 | | |
| | Intervention | 0.1281 | 1 | 0.1202 | 102.67 | 2.5640 | 1.17 |
| | | | | | | | |
| ***HOT*** | | | | | | | |
| Stroke | Control | 0.0339 | 3.8 | 0.00878 | 104.7 | | |
| | Intervention | 0.0240 | 3.8 | 0.006253 | 100.63 | 8.6839 | 1.41 |
| | | | | | | | |
| MI | Control | 0.0359 | 3.8 | 0.009287 | 104.7 | | |
| | Intervention | 0.0301 | 3.8 | 0.007793 | 100.63 | 4.4975 | 1.19 |
| | | | | | | | |

*rates calculated to match the cumulative risk of nephropathy observed in the trial

## eTable 3 (continued). Transition probabilities and risk factor modifications for the model

| | Group | Risk | Time | Annual Probability | RF level | Beta | RR |
|---|---|---|---|---|---|---|---|
| **Glucose control study** | | | | | | | |
| | | | | | | | |
| ***UKPDS*** | | | | | | | |
| Retinopathy | Control | 0.1028 | 10 | 0.0098 | 7.9 | | |
| (photocoag) | Intervention | 0.0759 | 10 | 0.0073 | 7 | 2.5144 | 1.29 |
| | | | | | | | |
| Microalb. | Control | 0.2538 | 9 | 0.0249 | 7.9 | | |
| | Intervention | 0.1922 | 9 | 0.0194 | 7 | 2.3009 | 1.33 |
| | | | | | | | |
| Proteinuria | Control | 0.0750 | 1 | 0.0722 | 7.9 | | |
| | Intervention | 0.0656 | 1 | 0.0635 | 7 | 1.1025 | 1.14 |
| | | | | | | | |
| Neuropathy | Control | 0.2768 | 9 | 0.0269 | 7.9 | | |
| | Intervention | 0.2327 | 9 | 0.0231 | 7 | 1.4325 | 1.19 |
| | | | | | | | |

## eTable 4. Risks of CV events by nephropathy status

| Nephropathy status | Relative risk: MI (sensitivity analysis range) | Relative risk: CVA (sensitivity analysis range) |
|---|---|---|
| Microalbuminuria | 1.96 (1.00 – 3.00) | 2.20 (1.00 – 3.40) |
| Proteinuria | 2.73 (1.00 – 4.40) | 2.33 (1.00 – 3.60) |

**eTable 5. Utilities**

| Health State | Utility (range) |
|---|---|
| Diabetes | 1.0 (-) |
| Myocardial infarction | 0.88 (0.7-0.99) |
| Stroke | 0.64 (0.5-0.99) |
| End-stage renal disease | 0.61 (0.5-0.99) |
| Visual loss | 0.69 (0.5-0.99) |
| Amputation | 0.60 (0.5-0.99) |

**eTable 6. Life expectancy predictions: UKPDS actuarial estimates vs. simulation model at an A1c of 6.0%**

| Age | UKPDS | Model: 15% CHD risk reduction* | Model: No CHD risk reduction* |
|---|---|---|---|
| 55 | 20.7 years | 20.6 years | 20.2 years |
| 65 | 14.9 years | 15.1 years | 14.8 years |
| 75 | 9.9 years | 10.0 years | 9.9 years |

*The presence or absence of a 15% reduction in risk of CHD events with a 1 point reduction in A1c

**eTable 7. Relative risk of outcomes with intensive therapy: Steno-2 Trial vs. Markov Model**

| | Macrovascular | Nephropathy | Retinopathy |
|---|---|---|---|
| Trial | 0.47 | 0.52 | 0.75 |
| Model | 0.43 | 0.69 | 0.71 |

## eTable 8. Marginal QALY gains with additional parameters identified in sensitivity analysis

### A. Annual risk of microalbuminuria

| | Baseline annual risk of microalbuminuria | | |
|---|---|---|---|
| | | | |
| Age | 0.018 | 0.028 | 0.038 |
| | A1c 7.5 to 6.5% | | |
| 45 | 0.612 | 0.721 | 0.798 |
| 55 | 0.374 | 0.442 | 0.494 |
| 65 | 0.195 | 0.230 | 0.260 |
| 75 | 0.078 | 0.092 | 0.104 |
| | A1c 8.5% to 7.5% | | |
| Age | | | |
| 45 | 0.729 | 0.840 | 0.906 |
| 55 | 0.453 | 0.527 | 0.579 |
| 65 | 0.239 | 0.281 | 0.313 |
| 75 | 0.093 | 0.113 | 0.128 |

### B. Relative risk of CVA with microalbuminuria

| | Relative risk of CVA | | |
|---|---|---|---|
| | | | |
| Age | 1 | 2.2 | 3.4 |
| | A1c 7.5 to 6.5% | | |
| 45 | 0.688 | 0.721 | 0.752 |
| 55 | 0.409 | 0.442 | 0.471 |
| 65 | 0.204 | 0.230 | 0.254 |
| 75 | 0.078 | 0.092 | 0.104 |
| | A1c 8.5% to 7.5% | | |
| Age | | | |
| 45 | 0.813 | 0.840 | 0.866 |
| 55 | 0.496 | 0.527 | 0.556 |
| 65 | 0.252 | 0.281 | 0.306 |
| 75 | 0.097 | 0.113 | 0.128 |

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