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TECHNICAL REPORT FOR ADOLESCENT-YOUNG ADULT COHORT MODEL ("Youth Model")

Accompanying the Manuscript
Morbidity and Mortality in Adolescents and Young Adults Diagnosed with Type 2 Diabetes Mellitus
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Adapted from Technical Report May 2004
A Markov Model of Disease Progression and Cost-Effectiveness for Type 2 Diabetes ("RTI Model") Model Version 5.6
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This technical report describes basic aspects of the RTI Model of disease progression for type 2 diabetes and how it was adapted for adolescents and young adults diagnosed with type 2 diabetes between ages of 15 and 24 years.

Diabetes Progression Module

The Diabetes Progression module of the RTI Model models how type 2 diabetes progresses along five disease complication paths. It can include four types of treatment interventions: intensive glycemic control, blood pressure control, cholesterol reduction, and smoking cessation. The RTI Model calculates outcomes, measured in remaining life expectancy and quality-adjusted life years (QALYs), associated with each intervention. The RTI Model can incorporate costs of treatments although costs of treatments were not evaluated in the Youth Model.

The RTI Model builds on previous diabetes models constructed by Eastman et al. (1, 2) Dong, Orians, and Manninen (3) and the CDC Diabetes Cost-Effectiveness Study Group (4). It incorporates much of the structure and many of the parameters from these models. However, the RTI Model differs in several ways. First, it employs a Markov model structure to simulate disease progression for patient cohorts; the other models employ Monte Carlo simulation of individual patients. Second, it extends the previous models to put more emphasis on cardiovascular disease (CVD) and CVD interventions such as hypertension control, cholesterol reduction, and smoking cessation. Third, the Markov structure allows the introduction of interdependencies between different diabetes progression paths that provide a richer description of disease progression. For example, in this version of the RTI Model adapted for the Youth Model, persons with microalbuminuria develop hypertension.

In the RTI Model, most of the key transition probabilities and intervention effects are based on data from patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) that were not available when the earlier models described above were created. These earlier models instead used data on type 1 patients from the Diabetes Control and Complications Trial (DCCT). Although glycemic control is expected to slow development of complications for both type 1 and type 2 diabetes, the magnitude of effect may differ across types. Therefore, for the model of disease progression for type 2 patients, the UKPDS data are preferable. The UKPDS also provides information on hypertension control. As described below, for the Youth Model adaptation, for each individual complication path, age specific transition probabilities for the 15-24 year-olds were substituted, whenever available.

For the Youth Model, age- specific data were identified through the following sources:

1) A systematic literature review was conducted in 3/2007 to identify studies examining glycemic control and microvascular and macrovascular outcomes in adolescents/young adults with type 2 diabetes diagnosed before age 25 years. Databases searched included PubMed, EMBASE, CINAHL, and ProQuest Dissertation and Theses and electronic searchable abstracts from annual proceedings of the American Diabetes Association, Lawson Wilkins Pediatric Endocrine Society, and The Endocrine Society. A total of 817 relevant studies were identified of which 110 articles and dissertations/theses and 12 abstracts were reviewed. Targeted searches of the published literature through 12/2009 were performed to identify relevant new information.

2) An expert panel convened in 3/2008 informed key estimates for which there remained ongoing uncertainty and limited or no available data. Expert Panel members included Sonia Caprio MD (Yale University School of Medicine), Robert Lustig MD (University of California, San Francisco), Thomas Songer PhD (University of

Pittsburgh Graduate School of Public Health), Marc Weigensberg MD (University of Southern California), and Ruth Weinstock MD PhD (State University of New York Upstate).

1.MODEL STRUCTURE AND PARAMETERS

In the Markov model, a series of cohorts progress through the model. For the Youth Model, the cohorts had the following characteristics:

- Age, 15-24 years
- Sex (male/female),
- Race/Ethnicity (non-Hispanic White, African-American, Hispanic, Native-American, Asian),
- Hypertension (normal/above normal),
- Cholesterol (normal/above normal), and
- Current Smoking (no/yes).

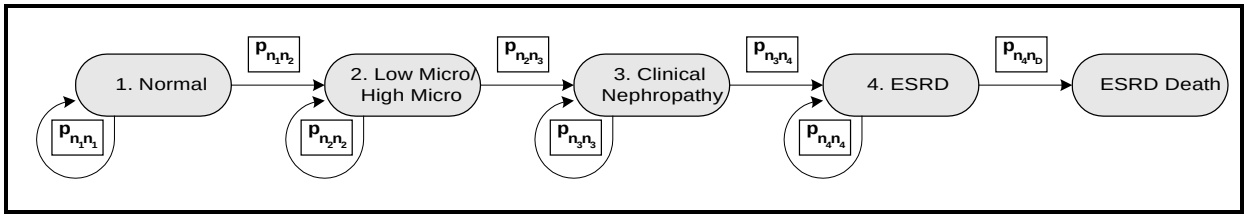
This produces a total of 80 subgroups (1 age group × 2 sexes × 5 race/ethnicity groups × 2 hypertension groups × 2 cholesterol groups × 2 smoking groups).

The time from onset of diabetes to diagnosis is set to 0 years (see SECTION 2). All patients entering the model are assumed to have been newly diagnosed with diabetes. Cohorts are followed along the disease paths until they turn 95 years old, when they are assumed to die.

Cohort members progress simultaneously on five different disease paths. Disease paths and disease states in each path are as follows:

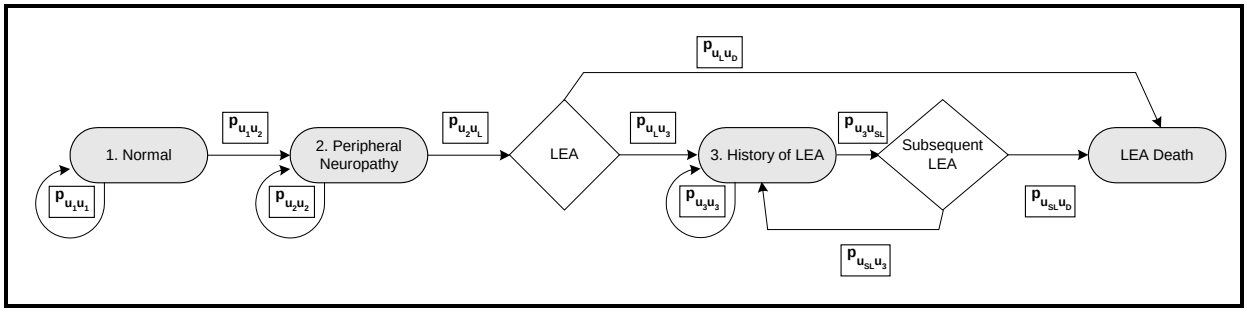
- Nephropathy (shown in eFigure 1)
  - Normal (n_1)
  - Low microalbuminuria/high microalbuminuria (n_2)
  - Clinical nephropathy (n_3)
  - End stage renal disease (ESRD) (n_4)
  - ESRD death (n_D)

eFigure 1. States and Transition Probabilities: Nephropathy



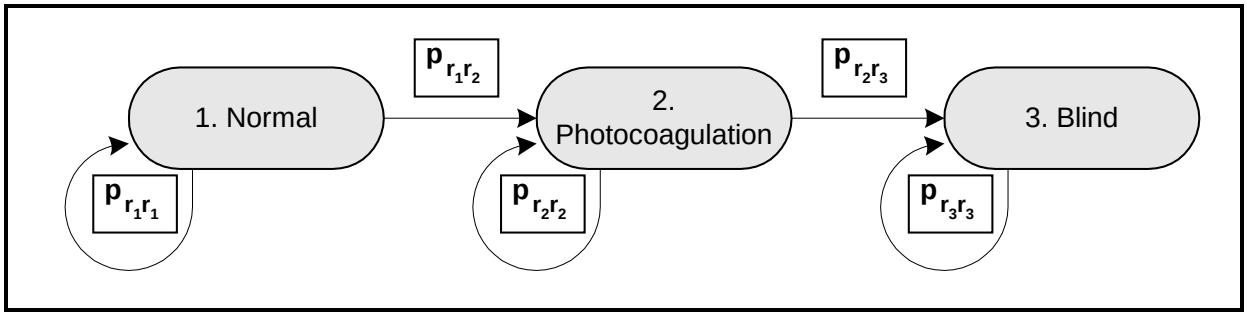
- Neuropathy (shown in eFigure 2)
  - Normal
  - Peripheral neuropathy (u_2)
  - History of LEA (u_3)
  - LEA death (u_D)

eFigure 2. States and Transition Probabilities: Neuropathy



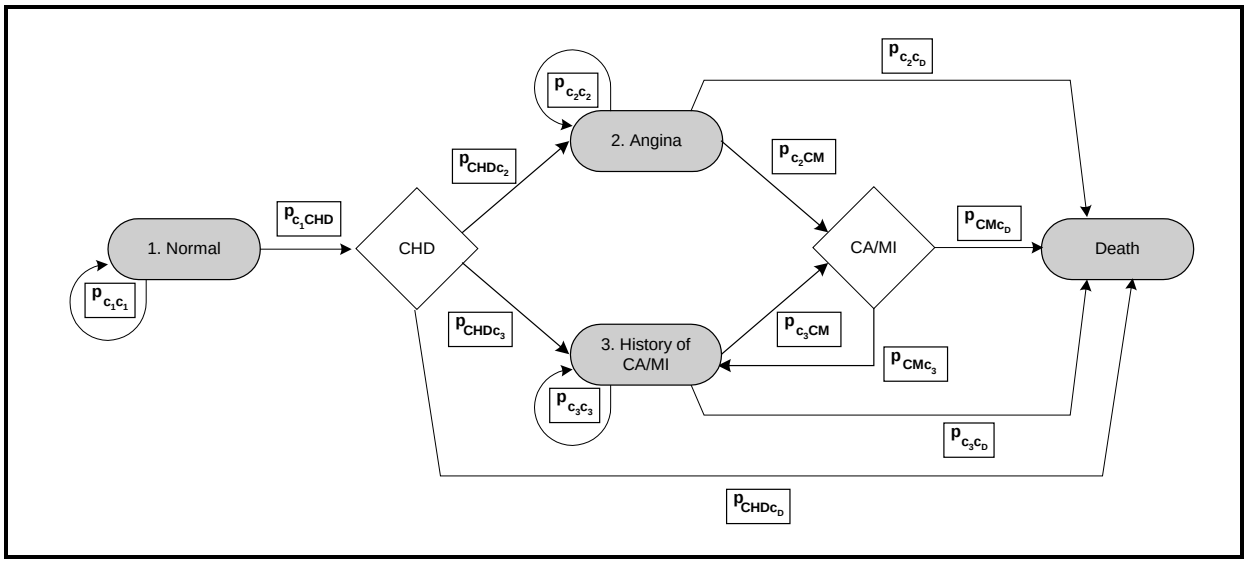
- Retinopathy (shown in eFigure 3)
  - Normal (r_1)
  - Photocoagulation (r_2)
  - Blind (r_3)

eFigure 3. States and Transition Probabilities: Retinopathy



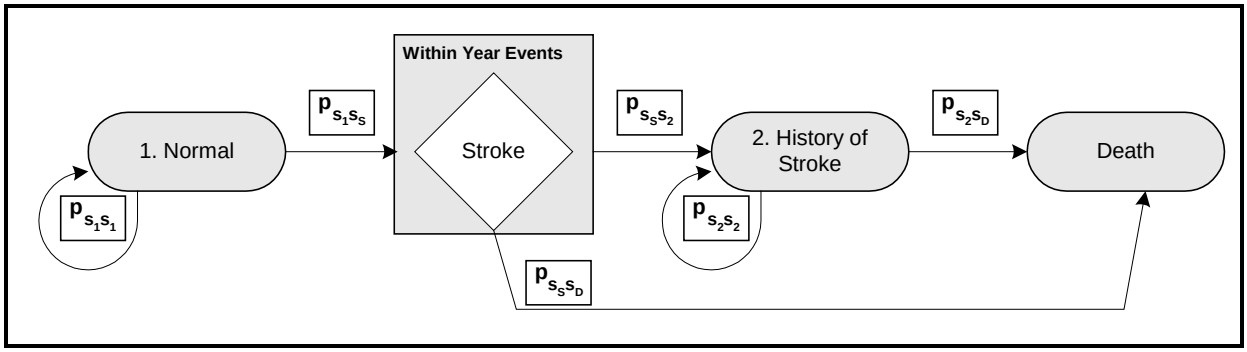
- Coronary Heart Disease (CHD) (an abbreviated version is shown in eFigure 4 and described in detail in Section 1.2.1)
  - Normal (c_1)
  - Angina (c_2)
  - History of Cardiac Arrest (CA)/Myocardial Infarction (MI) (c_3)
  - CHD death (c_d)

eFigure 4. States and Transition Probabilities: Coronary Heart Disease



- Stroke (shown in eFigure 5)
  - Normal (s_1)
  - History of Stroke (s_2)
  - Stroke death (s_D)

eFigure 5. States and Transition Probabilities: Stroke



At the end of any period, the cohort occupies one state on each of the disease paths. For the simulation, transitions between states take place at discrete time intervals 1 year apart. Thus, at the end of each 1-year period, portions of the cohort can move from one disease state to another or stay in the same disease state. The simulation program determines what proportion of the cohort will move from one state to another based on the transition probability.

In several cases, an individual can experience a complication event that the patient either dies from or survives during the period. On the neuropathy path, a patient with neuropathy can undergo an LEA and either die or survive. Similarly, a person with a history of LEA may undergo an additional LEA and either die or survive. On the CHD path, patients can experience a CHD event (angina, CA/MI, or recurrent CA/MI). Finally, on the stroke path, patients can either survive or die from a stroke suffered within a period.

Such events are incorporated within the overall Markov model by bridge models (5). Each bridge model covers the incidence and probabilities of death and survival from the event within one period. These values are incorporated into the transition probabilities between model states. The events themselves are not model states, though they are closely related. To see the distinction, consider a patient who is in the peripheral neuropathy state on the neuropathy path at time t. During the next period, the patient may experience an LEA. If the patient survives the LEA, he or she progresses to the state History of LEA at time t+1. Alternatively, if the patient dies from the LEA, he or she progresses to the Death state at t+1. The Markov model keeps track of the number of patients who are in each state in each period. It also keeps track of the cumulative incidence of patients who have undergone complication events such as LEA, angina, CA/MI, and stroke. In the diagrams, events within the bridge models are represented by diamonds, and the states are numbered and represented by ovals.

The initial distribution of the cohort among disease states within each stage for the Youth Model is shown in eTables 1 through 5 along with the RTI Model parameters for comparison. These have been adapted for the 15-24 year-old age group based on available data (identified as discussed below) and/or Expert Panel consensus. For example, the Youth model assumes that 16 percent of 15-24 year olds have microalbuminuria when they are diagnosed with diabetes based on the SEARCH for Diabetes in Youth Study (6).

eTable 1a. Initial Youth Model Distribution of Cohort in Nephropathy for 15-24 year olds

Disease State	Initial Distribution (%)
Normal	84.0
Microalbuminuria	16.0
Nephropathy	0.0
End Stage Renal Disease	0.0

Source: Maahs et al. 2007 (6); Reviewed and approved by Expert Panel.

eTable 1b. Initial Distribution of Cohort in Nephropathy for Adults in RTI Model

Disease State	Initial Distribution (%)
Normal	89.5
Microalbuminuria	10.5
Nephropathy	0.0
End Stage Renal Disease	0.0

Source: Eastman et al. (2) who calculate the value from data in Klein et al.(7)

eTable 2a. Initial Youth Model Distribution of Cohort in Neuropathy for 15-24 year olds

Disease State	Initial Distribution (%)
Normal	100.0
Peripheral Neuropathy	0.0
Lower Extremity Amputation	0.0
Subsequent Lower Extremity Amputation(s)	0.0

Source: Assumption; Reviewed and approved by Expert Panel.

eTable 2b. Initial Distribution of Cohort in Neuropathy for Adults in RTI Model

Disease State	Initial Distribution (%)
Normal	96.5
Peripheral Neuropathy	3.5
Lower Extremity Amputation	0.0
Subsequent Lower Extremity Amputation(s)	0.0

Source: Eastman et al.(2) citing Eastman(8)

eTable 3a. Initial Youth Model Distribution of Cohort in Retinopathy for 15-24 year olds

Disease State	Initial Distribution (%)
Normal	100.0
Photocoagulation	0.0
Blind	0.0

Source: Assumption; Reviewed and approved by Expert Panel.

eTable 3b. Initial Distribution of Cohort in Retinopathy for Adults in RTI Model

Disease State	Initial Distribution (%)
Normal	100.0
Photocoagulation	0.0
Blind	0.0

Source: Assumption.

eTable 4a. Initial Youth Model Distribution of Cohort in Coronary Heart Disease for 15-24 year olds

Disease State	Initial Distribution (%)
Normal	100.0
History of Cardiac Arrest/Myocardial Infarction	0.0
History of Angina	0.0

Source: Assumption.

eTable 4b. Initial Distribution of Cohort in Coronary Heart Disease for Adults in RTI Model

Disease State	Initial Distribution (%)
Normal	100.0
History of Cardiac Arrest/Myocardial Infarction	0.0
History of Angina	0.0

Source: Assumption.

eTable 5a. Initial Youth Model Distribution of Cohort In Stroke for 15-24 year olds

Disease State	Initial Distribution (%)
Normal	100.0
History of Stroke	0.0

Source: Assumption.

eTable 5b. Initial Distribution of Cohort In Stroke for adults in RTI Model

Disease State	Initial Distribution (%)
Normal	100.0
History of Stroke	0.0

Source: Assumption.

We specify the mathematical model based on the Markov model using transition probabilities. The transition probability $p_{i,j}(t)$ is the probability that the patient in state i at time t will be in state j at time t+1. The hazard rates and hence the transition probabilities are dependent on a variety of variables including the following:

- time since diagnosis of diabetes,
- time between onset of diabetes and diagnosis,
- age,
- sex,
- race/ethnicity,
- glycemic levels,
- smoking,
- cholesterol levels, and
- hypertension.

In the Youth model, age, sex, smoking, and cholesterol level affect only the transition probabilities associated with CHD and stroke. The time between onset of diabetes and diagnosis affects only the glycemic level at the time of diagnosis. Glycemic level affects all of the transition probabilities. Glycemic level has a multiplicative effect on the hazard rates, which in turn determine the transition probabilities used in the model. Race/ethnicity affects glycemic levels and death probabilities. The influence of time since diagnosis and hypertension are evaluated in sensitivity analyses.

In this report, we distinguish between the related terms "hazard rates" and "transition probabilities." Hazard rate shows the rate at which individuals change from one state to the next; this rate can take values between 0 and ∞. Transition probability is the probability that an individual patient makes the transition between states during one period. The transition probability has a range between 0 and 1. The relationship between the hazard rate (r) and the transition probability (p) for time period t is given by

$$p = 1 - e^{-rt} . \quad (1)$$

Although p and r are fairly close when r is near zero (as is the case for most of the hazard rates in the tables), they are not equal.

1.1. Parameters for Nephropathy, Neuropathy, and Retinopathy

We show the hazard rates for nephropathy, neuropathy, and retinopathy in eTables 6 through 8.

1.1.1. Nephropathy

eTable 6a shows the hazard rates for nephropathy for the 15 to 24 year olds in the Youth Model and eTable 6b shows the hazard rate for adults used in the RTI Model for comparison. The hazard rate for transition from Normal to Microalbuminuria for the adolescent/young adult cohort was derived from the weighted average of two studies with data from the United States (Ettinger 2005 (9); Farah 2006 (10)) adjusted for the prevalence of microalbuminuria at diagnosis in the United States (from Maahs 2007 (6) using the population with duration <12 months) derived from the SEARCH study. Two other studies were considered (11, 12), but not included in the base case hazard rate for the Youth Model because the prevalence of microalbuminuria was lower than the prevalence at diagnosis observed in the SEARCH study (6). However, for sensitivity analysis, we calculated a hazard rate based on the weighted average of these 4 studies (assuming 0% prevalence of microalbuminuria at diagnosis) and the data from Maahs 2007 (6) on patients with type 2 diabetes of duration

between 12 months and <60 months adjusted for baseline prevalence in the US as observed in that study (6). As there were no longitudinal data to differentiate transition from normal to microalbuminuria for hypertensive vs. non-hypertensive adolescent/young adult patients, we used the same hazard rate for both groups. The RTI Model used this approach as well based on data from UKPDS 38 (13). The impact of this assumption was evaluated in sensitivity analyses. Other studies relating to progression to microalbuminuria in youth onset type 2 diabetes from populations around the world were also identified in our literature search (14-21) but were not included in the hazard rate estimation because the populations were felt to be less representative of the US sample. However, the derived hazard rates from these studies were used to inform ranges for sensitivity analysis. Hazard rate for transition to clinical nephropathy rates and ESRD rates were retained from the RTI Model as there were limited data available for the adolescent/young adult age group except in specific ethnic populations that were not felt to be generalizable (e.g., Pima Indians (22, 23)). This decision was approved by our Expert Panel (March 2008).

The clinical nephropathy rates used in the RTI Model were derived from the transition probabilities reported in Figure 1 in UKPDS 64 (24).

eTable 6a. Youth Model Hazard Rates: Nephropathy for 15-24 year-olds

Years Since Diagnosis	Normal to Microalbuminuria (No Hypertension)	Normal to Microalbuminuria (Hypertension)	Microalbuminuria to Clinical Nephropathy (No Hypertension)	Microalbuminuria to Clinical Nephropathy (Hypertension)	Clinical Nephropathy to ESRD
All Years	0.1455	0.1455	0.0284	0.0284	0.02327

Source: See text.

eTable 6b. RTI Model Hazard Rates: Nephropathy for adults

Years Since Diagnosis	Normal to Microalbuminuria (No Hypertension)	Normal to Microalbuminuria (Hypertension)	Microalbuminuria to Clinical Nephropathy (No Hypertension)	Microalbuminuria to Clinical Nephropathy (Hypertension)	Clinical Nephropathy to ESRD
All Years	0.0202	0.0202	0.0284	0.0284	0.02327

Source: UKPDS 64 (24) and UKPDS 38 (13)

They were converted to hazard rates using Equation (1). Calculation of the clinical nephropathy rates in the RTI Model was more complicated, because the hazard rates are conditional on having had microalbuminuria. The number of patients who had progressed to microalbuminuria at each year was initially

simulated. The clinical nephropathy transition probability necessary to yield the number of patients who had progressed to nephropathy by the end of the study period was then calculated and converted into a hazard rate.

The hazard rates for ESRD were estimated in the RTI Model by Eastman et al. using data reported in Humphrey et al.(25) Based on examination of data from UKPDS 38 (13), the same rates are applied to both nonhypertensive and hypertensive patients.

1.1.2. Neuropathy

The neuropathy path includes the four states and two intermediate events that are shown in eFigure 2. An individual who begins in the Normal state may progress to peripheral neuropathy with probability P_{u1u2} or may remain in the Normal state with probability P_{u1u1}. An individual with peripheral neuropathy may experience an LEA with probability P_{u2uL}. At this point, the individual enters the bridge model and—within the time period—either dies and moves to LEA Death with probability P_{uLuD} or survives and moves to the History of LEA state with probability P_{uLu3}. Once an individual reaches the History of LEA state, she will remain there (P_{u3u3}) unless she experiences a subsequent LEA event. The individual will enter the subsequent LEA bridge model with probability P_{u3uSL}. At this point, the individual either dies and moves to LEA Death with probability P_{uSLuD} or survives and returns to the History of LEA with probability P_{uSLu3}.

eTable 7a shows the hazard rates for neuropathy for the 15 to 24 year olds in the Youth Model and eTable 7b shows the hazard rate for adults used in the RTI Model for comparison. The hazard rate for peripheral neuropathy for 15 to 24 year olds was derived from the weighted average of the hazard rate in 3 studies with data from the United States and the United Kingdom (Davis 2006 (26); Karabouta 2008 (27); Neufeld 1998 (28)). Other studies identified that were used to inform the range for sensitivity analysis were Eppens et al. (14) and McGrath et al. (20). The remaining estimates were retained from the RTI Model. The probability for a subsequent LEA and the mortality rate for LEA come from Tables 18.8 and 18.10, respectively, in Reiber et al.(29). As separate hazard rates for persons with hypertension are not available from the UKPDS hypertension study, the Youth model applies the same rates to persons with and without hypertension as in the RTI Model.

eTable 7a. Youth Model Hazard Rates: Neuropathy for 15 to 24 year olds

Years Since Diagnosis	Normal to Peripheral Neuropathy	Peripheral Neuropathy to LEA	History of LEA to Subsequent LEA(s) (Transition Probability)	Death from LEA (Transition Probability)	Probability of Foot Ulcers (States of Neuropathy and History of LEA)
All Years	0.0085	0.00672	0.11	0.105	0.04

See text.

eTable 7b. RTI Model Hazard Rates: Neuropathy for Adults

Years Since Diagnosis	Normal to Peripheral Neuropathy	Peripheral Neuropathy to LEA	History of LEA to Subsequent LEA(s) (Transition Probability)	Death from LEA (Transition Probability)	Probability of Foot Ulcers (States of Neuropathy and History of LEA)
All Years	0.02250	0.00672	0.11	0.105	0.04

See text.

Individuals in the neuropathy and History of LEA states are also assumed to face a 4 percent annual incidence of diabetic foot ulcers. This incidence rate is assumed to be independent of past history of foot ulcers. Estimates of the incidence of diabetic foot ulcers for the entire type 2 population include 2.6 percent for 1 year (Moss et al. (30)) and 5.8 percent cumulative incidence for 3 years (Ramsey et al. (31)). Most (78 percent) foot ulcers occur among persons with neuropathy (Reiber et al. (29)). Assuming that the annual incidence rate for all persons with type 2 diabetes is 2 percent, persons with neuropathy account for 80 percent of foot ulcers, and about 40 percent of persons with type 2 diabetes have neuropathy yields an estimated annual incidence of 4 percent for persons with neuropathy.

1.1.3. Retinopathy

eTable 8a shows the hazard rates for retinopathy for the 15 to 24 year olds in the Youth Model and eTable 8b shows the hazard rate for adults used in the RTI Model for comparison. The hazard rate for photocoagulation for the 15 to 24 year olds was derived from the weighted average of the hazard rate in 3 studies with data from the United States and the United Kingdom (Davis 2006 (26); Shield 2009 (12); Farah 2006 (10)). As the severity of the retinopathy in these studies was not always clearly identified, this hazard rate may over or underestimate this rate of progression. Further, no data were available to distinguish the rate of progression for hypertensives vs. non-hypertensives adolescent/young adult patients so the same rate was assumed for both groups. The impact of these assumptions was evaluated in sensitivity analyses. (See

additional discussion on page 48, eTable 26) Other studies relating to progression to retinopathy in youth onset type 2 diabetes from populations around the world were also identified in our literature search (14, 15, 17, 18, 20, 23, 32) but were not included in the hazard rate estimation because the populations were felt to be less representative of the US sample. However, the derived hazard rates from these studies were used to inform ranges for sensitivity analysis.

eTable 8a. Youth Model Hazard Rates: Retinopathy for 15 to 24 year olds

Years Since Diagnosis	Normal to Photocoagulation (No Hypertension)	Normal to Photocoagulation (Hypertension)	Photocoagulation to Blindness
All years	0.006	0.006	0.10650

See Text.

eTable 8b. RTI Model Hazard Rates: Retinopathy for Adults

Years Since Diagnosis	Normal to Photocoagulation (No Hypertension)	Normal to Photocoagulation (Hypertension)	Photocoagulation to Blindness
All years	0.01100	0.01660	0.10650

See text.

We assumed the same rate of progression from photocoagulation to blindness for adolescents/young adults in the Youth Model as in the RTI Model. This hazard rate was originally derived from data from Figure 5 in UKPDS 38 (13). Data from persons with intensive glycemic control and conventional glycemic control were combined in the calculation, under the assumption that the hazard rate for blindness—conditional on photocoagulation—is the same for both groups. The rate was assumed to be the same for persons with and without hypertension. The number of patients who had progressed to photocoagulation at each year was simulated. The blindness transition probability necessary to yield the number of patients who had progressed to blindness by the end of the study period was calculated and into a hazard rate.

1.2. Cardiovascular Disease

Cardiovascular diseases, including CHD and stroke, are leading causes of mortality for persons with diabetes. In the RTI Model, CHD and stroke are treated as separate disease components using either probabilities generated from Anderson et al.(33) and Weinstein et al.(5) or the UKPDS risk engine, presented in UKPDS 56 (34) and UKPDS 60 (35), as well as other data sources. The disease path for the stroke arm was developed for the RTI Model through a

literature review of the disease and its progression. In the interest of simplicity and manageability, only clearly defined disease states are included. What follows is a description of the treatment of cardiovascular disease in the RTI Model and adaptations made for the Youth Model.

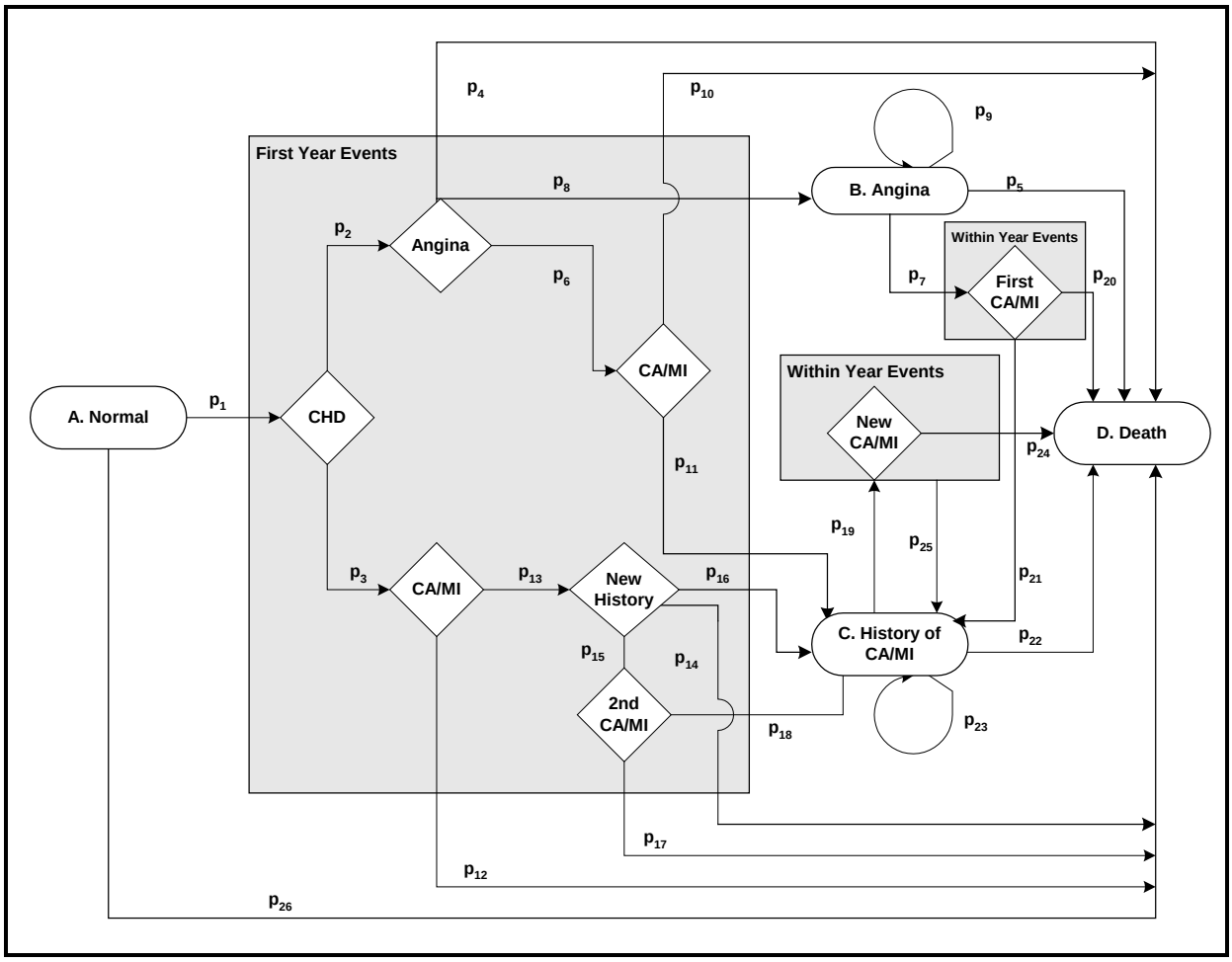
1.2.1. Coronary Heart Disease

The CHD component of the RTI Model is an abbreviated version of the Coronary Heart Disease Policy Model developed at Harvard University by Weinstein et al. (5). The complete version of the Coronary Heart Disease Policy Model has 12 CHD states. The RTI Model has been simplified by eliminating the states associated with coronary artery bypass graft surgery and by combining the CA and MI states into a single state. As a result, the RTI Model includes four CHD states: Normal, Angina, History of CA or MI, and Death. Due to the very low survival rates associated with CA, the transition probabilities given a history of CA/MI are those given a history of MI; however, mortality rates associated with CA are incorporated as appropriate. Most of the probabilities are derived from the probabilities outlined by Weinstein et al. (5) and its updated version in Hunink et al. (36).

The basic structure for the CHD component is shown in eFigure 6. The states labeled A (Normal), B (Angina), C (History of CA/MI), and D (Death) represent the states where individuals end up at the end of each year; these are the actual states that are programmed in the model. The remaining diamonds and arrows show what happens to the individual within the course of each year as they move between states (hence the shading for “First Year Events” and “Within Year Events”). These events are incorporated within the model’s transition probabilities, as described below.

Consider an individual beginning at A in the Normal state. With probability P_1, the individual may experience a CHD event. Otherwise, the individual either dies from a non-CHD event or remains in the Normal state. This part of the model corresponds to the Demographic–Epidemiologic model component of the Coronary Heart Disease Policy Model, so named because P_1 depends on demographic and epidemiologic factors such as age, sex, blood pressure, and cholesterol levels. Unlike the Coronary Heart Disease Policy Model, the P_1 in the RTI Model includes a variable for the presence of diabetes.

eFigure 6. States and Transition Probabilities: Coronary Heart Disease, Detailed



Following the Coronary Heart Disease Policy Model, we carefully model what happens to an individual in the first 30 days following their first CHD event. This corresponds to the bridge model component of the Coronary Heart Disease Policy Model. If an individual experiences a first CHD event, the event may be either angina with probability P_2 or CA/MI with combined probability P_3. If the first event is angina, there is a cost associated with the immediate treatment of angina but no immediate other events. If the first event is CA or MI, the individual may either die within 30 days with probability P_{12} or survive to move to the new History of CA/MI box with probability P_{13}.

The Coronary Heart Disease Policy Model allows surviving individuals to incur a second CHD event during the remainder of the year (11 months) following the first 30 days of the first CHD event (this is part of the model's Disease History model component), and we have also incorporated this possibility within our

model. Thus, an individual whose first event is angina may either die from angina-related causes (with probability P_4), experience a CA/MI (P_6), or continue on with angina (P_8) during the remainder of the year following the first CHD event. If they experience a CA/MI, they may either die within 30 days (P_{10}) or survive (P_{11}). An individual who survives an initial CA/MI may experience a second CA/MI (P_{15}), die from chronic conditions related to MI (P_{14}), or continue on with no further events (P_{16}). An individual who experiences a second CA/MI will either die within 30 days (P_{17}) or survive (P_{18}).

Thus, at the end of the first year, patients either remain at the Normal state, have angina, have a history of CA/MI, or are dead. The process repeats itself for patients in the Normal state. Patients in the Angina and History of CA/MI states can experience one additional CHD event in the following period. Angina patients can experience a first CA/MI event (P_7), with subsequent probabilities of death (P_{20}) or survival (P_{21}). Alternatively, they may die from angina-related causes (P_5) or continue with angina (P_9). Patients with a history of CA/MI can experience a new CA/MI event (P_{19}), with subsequent probabilities of death (P_{24}) or survival (P_{25}). Alternatively, they may die from chronic conditions related to MI (P_{22}) or survive with no additional CHD event (P_{23}). Naturally, patients in the death state experience no new events.

Below, the derivation and source for each of the probabilities shown in eFigure 6 for the RTI Model is described. The RTI Model assigned relevant probabilities and relative risks for those aged 35 years and older. In most cases, for the Youth Model, we assumed the same probabilities or relative risks for those aged 15-24 years and 25-34 years as those aged 35 to 44 years. We assessed the impact of these assumptions in sensitivity analyses as described below.

The user has two options for calculating P_1, the probability of moving from the Normal state to CHD; P_2, the probability that the CHD event is angina; and P_3, the probability that the CHD event is a CA/MI. The two options are the Framingham Equation or the UKPDS Risk Engine.

Framingham Equation.

Calculating the value of P_1. From Anderson et al.,(33) the probability of a new case of CHD at period t is given by

$$CHD(t) = [F(t) - F(t-1)] / [1 - F(t-1)]$$

where

$$F(t) = 1 - \exp(-\exp\{[\ln(t) - \mu(t)] / \sigma(t)\})$$

(the Weibull function)

μ = $15.5305 + 28.4441 \times \text{female} - 1.4792 \times \ln[\text{age}(t)] - 14.4588 \times \ln[\text{age}(t)] \times \text{female} + 1.8515 \times \ln[\text{age}(t)]2 \times \text{female} - 0.9119 \times \ln[\text{sbp}(t)] - 0.2767 \times \text{smoker}(t) - 0.7181 \times \ln[\text{totalc}(t) / \text{HDL}(t)] - 0.1759 \times \text{diagnosed diabetic} - 0.1999 \times \text{diabetic} \times \text{female} - 0.5865 \times \text{LVH}(t, \text{gender})$

sbp = systolic blood pressure

totalc = total cholesterol level

HDL = high density lipoprotein cholesterol level

LVH = left ventricular hypertrophy

$\ln\sigma$ = $0.9145 - 0.2784 \times \mu$

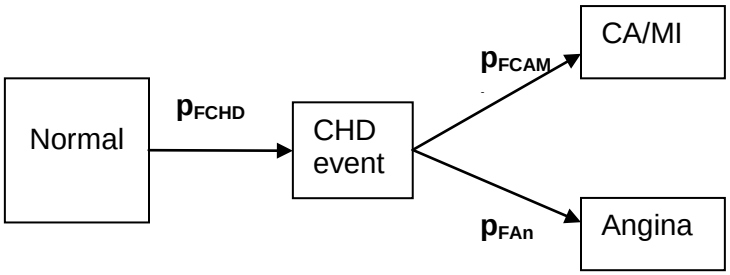
Note: In the RTI and Youth model, t was set equal to 8, to estimate an average annual mortality based on the valid range of follow-up (4 to 12 years).

UKPDS Risk Engine.

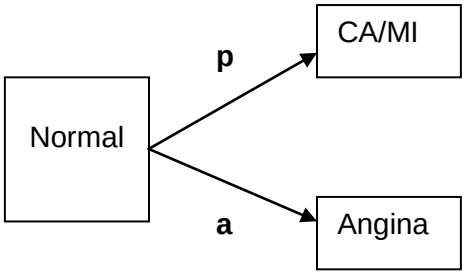
The UKPDS Risk Engine can be applied to calculate the risk of a myocardial infarction or the risk of having a stroke event. The Risk Engine calculations are based on individuals with type 2 diabetes participating in the UKPDS study. For the Youth Model, we chose to use the UKPDS Risk Engine in the base case analysis. Although neither the Framingham Equation nor the UKPDS Risk Engine account for body mass index, which was felt to be an important risk factor by our Expert Panel, the UKPDS Risk Engine accounts for both duration of diabetes and age at diagnosis, which are key features of the Youth Model. Based on this and further research suggesting that the UKPDS risk engine may be preferable to the Framingham risk equation in younger adult populations with type 2 diabetes (37), this was chosen for our base case in the Youth Model.

*Myocardial Infarction***.** The UKPDS Risk Engine calculates the probability of a myocardial infarction, whereas the Framingham equation computes the probability of angina or CA/MI (eFigure 7). Because the UKPDS Risk Engine also incorporates angina as a state of CHD, it calculates the probability of moving from normal to CA/MI or angina in one step.

eFigure 7. Progression to initial CHD event using the Framingham Equation and the UKPDS Risk Engine



Framingham equation



UKPDS risk engine

*Calculating the value of **p** using the UKPDS Risk Engine.* From UKPDS 56,(34) the probability of a first myocardial infarction at period t is given by

$$MI(t) = 1 - \exp(-qd^{t-1})$$

where

$$Q = q_0\beta_1^{AGE-55}\beta_2^{SEX}\beta_3^{AC}\beta_4^{SMOK}\beta_5^{h-6.72}\beta_6^{(SBP-135.7)/10}\beta_7^{ln(LR)-1.59}$$

and

q_0 = Intercept = 0.0112
β_1 = Risk ratio for one year of age at diagnosis of diabetes = 1.059
β_2 = Risk ratio for female sex = 0.525
β_3 = Risk ratio for Afro-Caribbean ethnicity = 0.390
β_4 = Risk ratio for smoking = 1.350
β_5 = Risk ratio for 1% increase in HbA1c = 1.183
β_6 = Risk ratio for 10 mmHg increase in systolic BP = 1.088
β_7 = Risk ratio for unit increase in logarithm of lipid ratio = 3.845
d = Risk ratio for each year increase in duration of diagnosed diabetes = 1.078

and

AGE = Age (yrs) at diagnosis of diabetes

SEX = Individual's sex
1 = female, 0 = male

AC = Indicator of Afro-Caribbean race
1 = Afro-Caribbean,
0 = Caucasian or Asian-Indian
(By default, set to represent African-American)

SMOK = Indicator of smoking status
1 = current smoker at diagnosis of diabetes,
0 = non-smoker at diagnosis of diabetes

H = HbA1c (%), mean of values at years 1 and 2

SBP = Systolic BP, mean of values at years 1 and 2

LR = Total cholesterol/HDL cholesterol ratio, mean of values at years 1 and 2

T = Years since diagnosis

Notes: Regression dilution adjustments were not made, therefore assuming that HbA1c is the mean of 2 values, systolic blood pressure is the mean of 6 values (two groups of three values), and total and HDL cholesterol are each the mean of 2 values. By default, the Afro-Caribbean risk factor in the UKPDS risk engine will be applied to African American cohorts. User may turn off this assumption; However, we kept this application in the Youth Model.

*Calculating the value of **a** using the Framingham Equation.*

Let p_{FCHD} = Framingham probability of CHD event,
p_{FCAMI} = P(CA/MI | CHD)
p_{FAng} = P(Angina | CHD)
p = UKPDS risk engine probability of MI
m = P(CA/MI| Normal)
a = P(Angina| Normal)

Then $p_{FCAMI} + p_{FAng} = 1$
$m = p_{FCHD} * p_{FCAMI}$
$a = p_{FCHD} * p_{Fang}$
$a = m * p_{FAng} / p_{FCAMI}$, when using either risk engine/equation, based on keeping the rate of angina relative to CA/MI the same
m = p (ignoring the CA-MI distinction)

So, $a = p * p_{FAng} / p_{FCAMI}$,

if $p_{FCAMI} > 0$ and $p * p_{FAng} / p_{FCAMI} <= 1 - p$

$a = 1 - p$, if $p_{FCAMI} = 0$ or $p * p_{FAng} / p_{FCAMI} > 1 - p$

We use one of these two equations to compute the probability of moving from the normal state to the angina state when using the UKPDS risk model. We expect $p_{FCAMI} > 0$ generally, so the second equation will usually be used only when the first equation gives a value that makes the sum (p + a) larger than 1.

Using this calculation strategy, P_1 is never explicitly defined. We assume, though, that $P_1 * P_2 = a$ and $P_1 * P_3 = m$.

Calculating the value of P_2.

P_2 = P(Angina | CHD) = 1 – P(CA/MI | CHD) = 1 – P3.

See P_3 below.

Source: Hunink et al.(36)

Calculating the value of P_3.

P_3 = P(CA/MI | CHD) = P(CA | CHD) + P(MI | CHD)

Source: Hunink et al.(36)

See eTable 9. For the 15-24 and 25-34 year olds in the Youth Model, we assumed the same probabilities as the 35 to 44 year olds in the RTI Model. In sensitivity analyses, we fit a polynomial equation to the data available for males and females to impute plausible values for the 15-24 and 25-34 year old age groups.

eTable 9. Probability that Initial Coronary Heart Disease Event is Cardiac Arrest or Myocardial Infarction

Age (years)	Probability (CA | CHD)		Probability (MI | CHD)	
	Male	Female	Male	Female
15-24	0.1024	0.0803	0.6171	0.5864
25-34	0.1024	0.0803	0.6171	0.5864
35–44	0.1024	0.0803	0.6171	0.5864
45–54	0.1070	0.0917	0.5440	0.4942
55–64	0.1085	0.0852	0.4739	0.4199
65–74	0.1297	0.0998	0.4929	0.4916
75+	0.1527	0.1793	0.5101	0.4983

Source: Hunink et al.(36) For 15-24, 24-34- Assumption; Reviewed by Expert Panel.

P_4 = P(Death | History of Angina) * (11/12)

Source: Weinstein et al.(5)

See eTable 10. For the 15-24 and 25-34 year olds in the Youth Model, we assumed the same probabilities as the 35 to 44 year olds in the RTI Model. In sensitivity analyses, we fit a polynomial equation to the data available for males and females to impute plausible values for the 15-24 and 25-34 year old age groups.

eTable 10. Probability of Death Given a History of Angina

Age (years)	Probability (Death | History of Angina)	
	Male	Female
15-24	0.00460	0.00249
25-34	0.00460	0.00249
35–44	0.00460	0.00249
45–54	0.01070	0.00618
55–64	0.01841	0.01196
65–74	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al.(5) For 15-24, 24-34- Assumption;

- P_5 = P(Death | History of Angina)

  See eTable 10.

  Source: Weinstein et al.(5)

- P_6 = P(CA/MI | Angina) * (11/12) * AgeRisk1

  The age-relative risk of CA or MI given a History of Angina was assumed to be equal to AgeRisk1, the age-relative risk of CA or MI given a History of CHD (eTable 11).

  Source: Hunink et al.(36)

  For the 15-24 and 25-34 year olds in the Youth Model, we assumed the same probabilities as the 35 to 44 year olds in the RTI Model. In sensitivity analyses, we fit a line through the data available for males and females to impute plausible values for the 15-24 and 25-34 year old age groups.

eTable 11. Relative Risk of Cardiac Arrest or Myocardial Infarction Given a History of Angina (AgeRisk1)

Age (years)	Relative Risk
15-24	0.261
25-34	0.261
35–44	0.261
45–54	0.630
55–64	1.000
65–74	1.371
75+	1.826

Source: Hunink et al.(36)

- P_7 = P(CA/MI | Angina) * AgeRisk1

  P(CA/MI | Angina) = 0.0303 for males, 0.0120 for females

- $P_8 = 1 - P_6 - P_4$
- $P_9 = 1 - P_5 - P_7$
- P_{10} = P(Death | 1st CA/MI)

  = P(Death | CA) * P(CA | CA/MI) +

  P(Death | 1st MI) * P(MI | CA/MI)

  P(CA | CA/MI) = 0.2

  P(MI | CA/MI) = 0.8

  P(Death | CA) = 1 – [P(Survival to Admission) * P(Survival to Discharge)]

  See eTable 12.

  For the 15-24 and 25-34 year olds in the Youth Model, we assumed the same probabilities as the 35 to 44 year olds in the RTI Model. In sensitivity analyses, we fit a polynomial equation to the data available for males and females for survival to discharge and a line to the data for survival to hospital admission to impute plausible values for the 15-24 and 25-34 year old age groups.

eTable 12. Probability of Death Given Cardiac Arrest

Age (years)	Probability		
	Survival to Hospital Admission	Survival to Discharge	Death Given CA
15-24	0.3885	0.6446	0.7496
25-34	0.3885	0.6446	0.7496
35–44	0.3885	0.6446	0.7496
45–54	0.3316	0.5837	0.8064
55–64	0.2747	0.4974	0.8634
65–74	0.2178	0.3661	0.9203
75+	0.1609	0.1419	0.9772

P(Death | 1st MI) = eTable 13

For the 15-24 and 25-34 year olds in the Youth Model, we assumed the same probabilities as the 35 to 44 year olds in the RTI Model. In sensitivity analyses, we fit an exponential equation to the data available for males and females to impute plausible values for the 15-24 and 25-34 year old age groups.

eTable 13. Probability of Death Given the First Myocardial Infarction

Age (years)	Probability (Death | 1st MI)	
	Male	Female
15-24	0.0154	0.0154
25-34	0.0154	0.0154
35–44	0.0154	0.0154
45–54	0.0336	0.0336
55–64	0.0730	0.0730
65–74	0.1587	0.1587
75+	0.2953	0.2953

Source: Hunink et al.(36)

- $P_{11} = 1 - P_{10}$
- $P_{12} = P_{10}$
- $P_{13} = 1 - P_{12}$
- P_{14} = P(MI Chronic Death) * (11/12)

  See eTable 14.

  Assumptions and sensitivity analyses for 15-24 and 25-34 year olds in the Youth Model are the same as eTable 10.

- P_{15} = P(Recurrent CA/MI in year of first MI | 1st MI)

  = [P(CA | History of CA/MI) + P(MI | History of CA/MI)] * (11/12) * AgeRisk1

  P(CA | History of CA/MI) = 0.01432 for males, 0.01132 for females

eTable 14. Probability of Death from Chronic Myocardial Infarction

Age (years)	Probability (MI Chronic Death)	
	Male	Female
15-24	0.00460	0.00249
25-34	0.00460	0.00249
35–44	0.00460	0.00249
45–54	0.01070	0.00618
55–64	0.01841	0.01196
65–74	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al.(5)

P(MI | History of CA/MI) = 0.0573 for males, 0.0453 for females

Source: Hunink et al.(36)

The age-relative risk of MI given a History of CA/MI is assumed to be equal to AgeRisk1, the age-relative risk of CA or MI given a History of CHD (eTable 11).

- P_{16} = $1 - P_{14} - P_{15}$
- P_{17} = P(CA | CA/MI) * P(Death | CA) +

  P(MI | CA/MI) * P(Death | Recurrent MI)

  P(CA | CA/MI) = 0.2

  P(MI | CA/MI) = 0.8

  P(Death | CA) = 1 – [P(Survival to Admission) * P(Survival to Discharge)]

  See eTable 12.

  See eTable 15 for probability of death given recurrent MI.

  For the 15-24 and 25-34 year olds in the Youth Model, we assumed the same probabilities as the 35 to 44 year olds in the RTI Model. In sensitivity analyses, we fit an exponential equation to the data available for males and females to impute plausible values for the 15-24 and 25-34 year old age groups.

eTable 15. Death Rates After Recurrent Myocardial Infarction

Age (years)	Probability (Death | Recurrent MI)	
	Male	Female
15–24	0.0867	0.0867
25–34	0.0867	0.0867
35–44	0.0867	0.0867
45–54	0.1120	0.1120
55–64	0.1446	0.1446
65–74	0.1867	0.1867
75+	0.2953	0.2953

See eTable 13 for probability of death given the first MI.

- P_{18} = 1 – P17
- P_{19} = P(CA/MI | History of CA/MI) * AgeRisk1 = [P(CA | History of CA/MI) + P(MI | History of CA/MI)] * AgeRisk1

  P(CA | History of CA/MI) = 0.01432 for males, 0.01132 for females

  P(MI | History of CA/MI) = 0.0573 for males, 0.0453 for females

  Source: Hunink et al.(36)

The age-relative risk given a History of CA/MI was set equal to AgeRisk1, relative risk of MI or CA given a History of CHD (eTable 11).

See eTable 13 for probability of death given the first MI.

- $P_{20} = P_{10}$
- $P_{21} = 1 - P_{20}$
- P_{22} = P(MI Chronic Death)

  See eTable 14.

  Source: Weinstein et al.(5)
- $P_{23} = 1 - P_{19} - P_{22}$
- $P_{24} = P_{17}$
- $P_{25} = 1 - P_{17}$

Finally, there is the chance of death from all other causes, represented by P_{26}, the transition probability from Normal to Death. This probability is incorporated into the overall model as a separate calculation done after all other transitions have taken place for the year.

These transition probabilities are based on the general population rather than on people with diabetes. In order to account for the increased risk of CHD among people with diabetes, transition probabilities are multiplied by the relative risk of CHD in a person with diabetes versus a healthy person. Relative risks are shown in eTable 16. The relative risk of incurring an initial CHD event is already incorporated into P_1 in the form of the coefficients for diabetes.

To calculate the transition probabilities between the lettered states (A-D in eFigure 6), the probabilities of movement between each state must be multiplied together along every possible path between any two lettered states. The transition probability is then the sum of these products (eTable 17).

eTable 16. Relative Risk of Coronary Heart Disease Events Among People with Diabetes

Event	Relative Risk		Probabilities Affected
	Male	Female	
Death within 30 days after CA/MI	1.58[a]	2.60[a]	P_{10}, P_{12}, P_{17}, P_{20}, P_{24}
Death within 1 year after CA/MI	1.97[a]	4.17[a]	P_{14}, P_{22}
Second CA/MI	2.00[b]	2.00[b]	P_{15}, P_{19}

[a]Table 3 in Miettinen et al.(38) [b]Table 19.8 in Wingard and Barrett-Connor(39)

eTable 17. Transition Probabilities Between Coronary Heart Disease States

	A	B	C	D
A	$1 - P_1$	$P_1 * P_2 * P_8$	$P_1 * P_2 * P_6 * P_{11} + P_1 * P_3 * P_{13} * P_{16} + P_1 * P_3 * P_{13} * P_{15} * P_{18}$	$P_1 * P_2 * P_4 + P_1 * P_2 * P_6 * P_{10} + P_1 * P_3 * P_{12} + P_1 * P_3 * P_{13} * P_{14} + P_1 * P_3 * P_{13} * P_{15} * P_{17}$
B	0	P_9	$P_7 * P_{21}$	$P_7 * P_{20} + P_5$
C	0	0	$P_{23} + P_{19} * P_{25}$	$P_{19} * P_{24} + P_{22}$
D	0	0	0	1

1.2.2. Stroke

The stroke component of the RTI Model has three states: Normal, History of Stroke, and Death (see eFigure 5). All individuals begin in the Normal state. The probability of experiencing a stroke is P_{S_S}. The probability of dying from the stroke within the period is given by $P_{S_S S_D}$. If the individual survives the stroke, she progresses to History of Stroke. Thus, at the end of 1 year, individuals may be in the Normal, History of Stroke, or Death states. Once an individual reaches the History of Stroke state, she may remain there ($P_{S_2 S_2}$) or may die ($P_{S_2 S_D}$).

The user has two options for calculating the transition probability from Normal to Stroke: the Framingham equation (Anderson et al.(33)) and the UKPDS Risk Engine (Kothari et al.(35)); The other transition probabilities come from the literature (eTable 18). For the Youth Model, the same probabilities are applied to the 15-24 year old cohort as those used in the RTI Model.

Table e18. Transition Probabilities: Stroke

Transition	Probability	Source	Notes
Normal to Stroke	P(S)	Anderson et al.(33) Kothari et al.(35)	See eTable 1. Diabetes is included as a risk factor in the Anderson et al. model. See text.
Stroke to Death History of Stroke to Death	Immediate (0–6 months): 0.1420 One-year: 0.0915	Sacco et al.(40)	Sacco et al. include the 1-month, 1-year, and 5-year transition probabilities. Those were converted to hazard rates from which 6-month and 1-year transition probabilities were calculated. Since this study found that history of diabetes was not a significant predictor of stroke recurrence, the transition probabilities for the entire cohort were used.

Letting s_1 = Normal, s_2 = History of Stroke, and s_D = Death, the equations for the transition probabilities from Normal to History of Stroke and Normal to Death follow:

Starting with the individuals in s_1

- the proportion who experience a stroke and die immediately (within 6 months)

  = P(s) * P(Stroke to Death, immediate) (2)

- the proportion who experience a stroke but do not die immediately

  = P(s) * [1 – P(Stroke to Death, immediate)]

- all others remain in the Normal state.

For individuals with a history of stroke (s_2)

- the percentage who die

  = P(History of Stroke to Death; 1 year)

- all others remain in the History of Stroke state.

Death is an absorbing state. The total number of individuals who have had a stroke are those who pass into state s_2 plus those who transition to death due to stroke with Equation (2).

If the Framingham equation is applied, the probability of a new case of stroke at period t is given by

$$Prob(S[t]) = [F(t) – F(t ! 1)] / [1 – F(t ! 1)]$$

where

$F(t) = 1 - \exp(-\exp\{[\ln(t) - \mu(t)] / \sigma(t)\})$ (the Weibull function)

μ = $26.5116 + 0.2019 \times \text{female} - 2.3741 \times \ln[\text{age}(t)] - 2.4643 \times \ln[\text{sbp}(t)] - 0.3914\ \text{smoker}(t) - 0.0229 \times \ln[\text{totalc}(t) / \text{HDL}(t)] - 0.3087 \times \text{diagnosed diabetic} - 0.2627 \times \text{diabetic} \times \text{female} - 0.2355 \times \text{LVH}$

$\ln\sigma$ = –0.4312

This is the equation used for P(s) above.

Note: In the RTI and Youth models, t was set equal to 8, to estimate an average annual mortality based on the valid range of follow-up (4 to 12 years).

UKPDS Risk Engine uses the method outlined in UKPDS 60(35) to calculate the probability of a first stroke (P(s)) during period t. This calculation involves the same equation used to calculate the risk of CHD, except that the value of q is calculated using a slightly different formula and different coefficients.

$\text{Stroke}(t) = 1 - \exp(-qd^{t-1})$

where

$q=q_0\beta_1^{\text{AGE-55}}\beta_2^{\text{SEX}}\beta_4^{\text{SMOK}}\beta_5^{\text{h-6.72}}\beta_6^{(\text{SBP-135.5})/10}\beta_7^{\text{LR-5.11}}\beta_8^{\text{AF}}$

and

q_0 = Intercept = 0.00186

β_1 = Risk ratio for one year of age at diagnosis of diabetes = 1.092

β_2 = Risk ratio for female sex = 0.700

β_4 = Risk ratio for smoking = 1.547

β_6 = Risk ratio for 10 mmHg increase in systolic BP = 1.122

β_7 = Risk ratio for unit increase in lipid ratio = 1.138

β_8 = Risk ratio for atrial fibrillation = 8.554

d = Risk ratio for each year increase in duration of diagnosed diabetes = 1.145

and

AF Atrial fibrillation at diagnosis of diabetes, 1 = yes, 2 = no

The definitions for AGE, SEX, SMOK, SBP, LR and T are defined as above in the Risk Engine calculations for myocardial infarction. For the Youth Model, the UKPDS Risk Engine is used in the base case analysis.

1.3. Death

In the Youth model the patient can die from five different causes:

- ESRD,
- LEA,
- CHD,
- stroke, and
- other causes.

The first four causes of death are all related to disease paths specific to patients with diabetes. The final mode of death is the general, nonspecific population death rate from other causes. For the Youth Model, we used the RTI Model parameters as described below.

Patients who have ESRD face a higher mortality risk than patients without ESRD. Patients who require LEA have a risk of dying from the surgical procedure. Patients with CHD can die from CA, MI, or sudden death. Once a patient has experienced a CHD event, they face a higher mortality risk than patients who have not had one. Patients experiencing stroke can die immediately; if they survive, they face higher mortality rates in subsequent periods.

Mortality rates from ESRD are a function of the cohort's age, sex, and race/ethnicity as shown in eTable 19. We assume that a person does not die during the period in which he or she develops ESRD.

eTable 19. Mortality Rate for End Stage Renal Disease

	Male (%)					Female (%)				
Age	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian
0	6.06	8.40	6.06	8.40	6.06	6.49	10.42	6.49	10.42	6.49
5	6.06	8.40	6.06	8.40	6.06	6.49	10.42	6.49	10.42	6.49
10	6.06	8.40	6.06	8.40	6.06	6.49	10.42	6.49	10.42	6.49
15	4.85	8.40	4.85	8.40	4.85	7.30	10.42	7.30	10.42	7.30
20	7.15	4.57	7.15	4.57	7.15	3.22	6.35	3.22	6.35	3.22
25	9.89	8.08	9.89	8.08	9.89	6.45	7.60	6.45	7.60	6.45
30	12.44	10.30	12.44	10.30	12.44	8.95	9.61	8.95	9.61	8.95
35	13.19	12.65	13.19	12.65	13.19	10.94	8.89	10.94	8.89	10.94
40	15.70	11.76	15.70	11.76	15.70	10.93	9.71	10.93	9.71	10.93
45	16.76	12.80	16.76	12.80	16.76	12.99	10.69	12.99	10.69	12.99
50	19.37	14.76	19.37	14.76	19.37	14.64	11.32	14.64	11.32	14.64
55	23.58	16.32	23.58	16.32	23.58	14.60	14.28	14.60	14.28	14.60
60	26.23	20.27	26.23	20.27	26.23	18.22	15.92	18.22	15.92	18.22
65	29.55	24.41	29.55	24.41	29.55	20.04	18.95	20.04	18.95	20.04
70	33.80	29.54	33.80	29.54	33.80	23.58	22.99	23.58	22.99	23.58
75	39.58	33.98	39.58	33.98	39.58	26.03	25.31	26.03	25.31	26.03
80	45.24	38.31	45.24	38.31	45.24	30.51	29.74	30.51	29.74	30.51
85	50.00	40.00	50.00	40.00	50.00	35.39	32.45	35.39	32.45	35.39
90	50.00	40.00	50.00	40.00	50.00	35.39	32.45	35.39	32.45	35.39
95	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Source: Dong et al.(3)

The mortality rate from LEA in the United States was found in Table 18.10 in Reiber et al.(29) and is not dependent on any other variables. The 1-year probability of death from LEA is

$$P(LEA\_M) = 10.5 \text{ percent}$$

The portion of individuals in U_2 who

- have an LEA and then die immediately from the LEA

$$= P(LEA) * P(LEA\_M) \quad (3)$$

- have an LEA and survive the initial operation

$$= P(LEA) * [1 – P(LEA\_M)]$$

- all others remain in the peripheral neuropathy state.

The probability of having a subsequent amputation in the United States comes from Table 18.8 in Reiber et al.(29) Estimates from studies conducted in the United States were averaged to calculate the estimate. The probability of a subsequent amputation is

$$P(\text{Subsequent LEA}) = 11 \text{ percent}$$

The proportion of individuals in u_3 who

- have a subsequent LEA and die immediately from the LEA

$$= P(\text{Subsequent LEA}) * P(LEA\_M)$$

- have a subsequent LEA and survive

$$= P(\text{Subsequent LEA}) * [1 – P(LEA\_M)]$$

- remain in u_3

$$= 1 – P(\text{Subsequent LEA})$$

The probability of death after a subsequent LEA is assumed to be equal to the probability of death after the initial amputation. No distinction is made between the second, third, fourth, etc. amputations in terms of probabilities. The total number of individuals who have had an LEA are those who are in state u_3 at the end of the simulation plus those individuals who have transitioned to death from LEA or subsequent LEA.

CHD mortality is calculated as described in Section 1.2.1, and stroke mortality is calculated from eTable 18. The mortality rate from other causes is shown in eTable 20.

eTable 20. Mortality Rate for Other Causes

	Male (%)					Female (%)				
Age	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.04	0.08	0.04	0.04	0.03	0.03	0.07	0.03	0.03	0.02
2	0.04	0.08	0.04	0.04	0.03	0.03	0.07	0.03	0.03	0.02
3	0.04	0.08	0.04	0.04	0.03	0.03	0.07	0.03	0.03	0.02
4	0.04	0.08	0.04	0.04	0.03	0.03	0.07	0.03	0.03	0.02
5	0.02	0.04	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.01
6	0.02	0.04	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.01
7	0.02	0.04	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.01
8	0.02	0.04	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.01
9	0.02	0.04	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.01
10	0.03	0.04	0.03	0.03	0.02	0.02	0.03	0.02	0.02	0.01
11	0.03	0.04	0.03	0.03	0.02	0.02	0.03	0.02	0.02	0.01
12	0.03	0.04	0.03	0.03	0.02	0.02	0.03	0.02	0.02	0.01
13	0.03	0.04	0.03	0.03	0.02	0.02	0.03	0.02	0.02	0.01
14	0.03	0.04	0.03	0.03	0.02	0.02	0.03	0.02	0.02	0.01
15	0.11	0.22	0.11	0.11	0.07	0.04	0.05	0.04	0.04	0.03
16	0.11	0.22	0.11	0.11	0.07	0.04	0.05	0.04	0.04	0.03
17	0.11	0.22	0.11	0.11	0.07	0.04	0.05	0.04	0.04	0.03
18	0.11	0.22	0.11	0.11	0.07	0.04	0.05	0.04	0.04	0.03
19	0.11	0.22	0.11	0.11	0.07	0.04	0.05	0.04	0.04	0.03
20	0.14	0.32	0.14	0.14	0.08	0.04	0.08	0.04	0.04	0.03
21	0.14	0.32	0.14	0.14	0.08	0.04	0.08	0.04	0.04	0.03
22	0.14	0.32	0.14	0.14	0.08	0.04	0.08	0.04	0.04	0.03
23	0.14	0.32	0.14	0.14	0.08	0.04	0.08	0.04	0.04	0.03
24	0.14	0.32	0.14	0.14	0.08	0.04	0.08	0.04	0.04	0.03
25	0.15	0.36	0.15	0.10	0.08	0.05	0.13	0.05	0.80	0.03

(continued)

eTable 20. Mortality Rate for Other Causes (continued)

	Male (%)					Female (%)				
Age	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian
26	0.15	0.36	0.15	0.10	0.08	0.05	0.13	0.05	0.80	0.03
27	0.15	0.36	0.15	0.10	0.08	0.05	0.13	0.05	0.80	0.03
28	0.15	0.36	0.15	0.10	0.08	0.05	0.13	0.05	0.80	0.03
29	0.15	0.36	0.15	0.10	0.08	0.05	0.13	0.05	0.80	0.03
30	0.20	0.46	0.20	0.10	0.08	0.07	0.19	0.07	0.80	0.04
31	0.20	0.46	0.20	0.10	0.08	0.07	0.19	0.07	0.80	0.04
32	0.20	0.46	0.20	0.10	0.08	0.07	0.19	0.07	0.80	0.04
33	0.20	0.46	0.20	0.10	0.08	0.07	0.19	0.07	0.80	0.04
34	0.20	0.46	0.20	0.10	0.08	0.07	0.19	0.07	0.80	0.04
35	0.25	0.61	0.25	0.50	0.10	0.10	0.27	0.10	1.30	0.06
36	0.25	0.61	0.25	0.50	0.10	0.10	0.27	0.10	1.30	0.06
37	0.25	0.61	0.25	0.50	0.10	0.10	0.27	0.10	1.30	0.06
38	0.25	0.61	0.25	0.50	0.10	0.10	0.27	0.10	1.30	0.06
39	0.25	0.61	0.25	0.50	0.10	0.10	0.27	0.10	1.30	0.06
40	0.31	0.80	0.31	0.50	0.14	0.14	0.37	0.14	1.30	0.09
41	0.31	0.80	0.31	0.50	0.14	0.14	0.37	0.14	1.30	0.09
42	0.31	0.80	0.31	0.50	0.14	0.14	0.37	0.14	1.30	0.09
43	0.31	0.80	0.31	0.50	0.14	0.14	0.37	0.14	1.30	0.09
44	0.31	0.80	0.31	0.50	0.14	0.14	0.37	0.14	1.30	0.09
45	0.43	1.07	0.43	0.50	0.22	0.23	0.51	0.23	1.50	0.15
46	0.43	1.07	0.43	0.50	0.22	0.23	0.51	0.23	1.50	0.15
47	0.43	1.07	0.43	0.50	0.22	0.23	0.51	0.23	1.50	0.15
48	0.43	1.07	0.43	0.50	0.22	0.23	0.51	0.23	1.50	0.15
49	0.43	1.07	0.43	0.50	0.22	0.23	0.51	0.23	1.50	0.15
50	0.66	1.42	0.66	0.50	0.37	0.38	0.76	0.38	1.50	0.23
51	0.66	1.42	0.66	0.50	0.37	0.38	0.76	0.38	1.50	0.23

(continued)

eTable 20. Mortality Rate for Other Causes (continued)

	Male (%)					Female (%)				
Age	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian
52	0.66	1.42	0.66	0.50	0.37	0.38	0.76	0.38	1.50	0.23
53	0.66	1.42	0.66	0.50	0.37	0.38	0.76	0.38	1.50	0.23
54	0.66	1.42	0.66	0.50	0.37	0.38	0.76	0.38	1.50	0.23
55	1.07	2.10	1.07	1.50	0.62	0.61	1.17	0.61	1.80	0.40
56	1.07	2.10	1.07	1.50	0.62	0.61	1.17	0.61	1.80	0.40
57	1.07	2.10	1.07	1.50	0.62	0.61	1.17	0.61	1.80	0.40
58	1.07	2.10	1.07	1.50	0.62	0.61	1.17	0.61	1.80	0.40
59	1.07	2.10	1.07	1.50	0.62	0.61	1.17	0.61	1.80	0.40
60	1.73	2.92	1.73	1.50	0.95	0.98	1.66	0.98	1.80	0.56
61	1.73	2.92	1.73	1.50	0.95	0.98	1.66	0.98	1.80	0.56
62	1.73	2.92	1.73	1.50	0.95	0.98	1.66	0.98	1.80	0.56
63	1.73	2.92	1.73	1.50	0.95	0.98	1.66	0.98	1.80	0.56
64	1.73	2.92	1.73	1.50	0.95	0.98	1.66	0.98	1.80	0.56
65	2.69	4.03	2.69	2.50	1.58	1.51	2.38	1.51	2.50	0.90
66	2.69	4.03	2.69	2.50	1.58	1.51	2.38	1.51	2.50	0.90
67	2.69	4.03	2.69	2.50	1.58	1.51	2.38	1.51	2.50	0.90
68	2.69	4.03	2.69	2.50	1.58	1.51	2.38	1.51	2.50	0.90
69	2.69	4.03	2.69	2.50	1.58	1.51	2.38	1.51	2.50	0.90
70	4.01	5.72	4.01	2.50	2.49	2.36	3.32	2.36	2.50	1.38
71	4.01	5.72	4.01	2.50	2.49	2.36	3.32	2.36	2.50	1.38
72	4.01	5.72	4.01	2.50	2.49	2.36	3.32	2.36	2.50	1.38
73	4.01	5.72	4.01	2.50	2.49	2.36	3.32	2.36	2.50	1.38
74	4.01	5.72	4.01	2.50	2.49	2.36	3.32	2.36	2.50	1.38
75	6.15	7.05	6.15	6.50	3.88	3.67	4.48	3.67	10.00	2.29
76	6.15	7.05	6.15	6.50	3.88	3.67	4.48	3.67	10.00	2.29
77	6.15	7.05	6.15	6.50	3.88	3.67	4.48	3.67	10.00	2.29

(continued)

eTable 20. Mortality Rate for Other Causes (continued)

	Male (%)					Female (%)				
Age	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian	Non-Hispanic White	African-American	Hispanic	Native-American (Pima)	Asian
78	6.15	7.05	6.15	6.50	3.88	3.67	4.48	3.67	10.00	2.29
79	6.15	7.05	6.15	6.50	3.88	3.67	4.48	3.67	10.00	2.29
80	9.70	10.97	9.70	6.50	6.46	6.15	7.07	6.15	10.00	4.00
81	9.70	10.97	9.70	6.50	6.46	6.15	7.07	6.15	10.00	4.00
82	9.70	10.97	9.70	6.50	6.46	6.15	7.07	6.15	10.00	4.00
83	9.70	10.97	9.70	6.50	6.46	6.15	7.07	6.15	10.00	4.00
84	9.70	10.97	9.70	6.50	6.46	6.15	7.07	6.15	10.00	4.00
85	17.96	16.72	17.96	6.50	12.63	14.02	13.26	14.02	10.00	9.56
86	17.96	16.72	17.96	6.50	12.63	14.02	13.26	14.02	10.00	9.56
87	17.96	16.72	17.96	6.50	12.63	14.02	13.26	14.02	10.00	9.56
88	17.96	16.72	17.96	6.50	12.63	14.02	13.26	14.02	10.00	9.56
89	17.96	16.72	17.96	6.50	12.63	14.02	13.26	14.02	10.00	9.56
95	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Source: Dong et al.(3)

2. INTERVENTIONS

The RTI Model considers a series of interventions including intensive glycemic control and interventions for each CVD risk factor (hypertension, high cholesterol, and smoking). Adaptation and application to the Youth Model is described below.

2.1. Glycemic Control

Intensive glycemic control is incorporated by adjusting the hazard rate using the ratio between HbA_{1c} under intensive control and HbA_{1c} under conventional treatment raised to an exponent that varies across progression steps. The adjusted hazard rates are given by

$$h^*_{i,\,j}(t) = h_{i,\,j}(t) \times [g(t)/G(t)]^{\beta_{i,j}}$$

where

- $h^*_{i,j}(t)$ = the adjusted hazard rate for going from state i to state j at time t,
- $h_{i,j}(t)$ = the baseline hazard rate for going from state i to state j at time t,
- $g(t)$ = the glycemic level under intensive glycemic control,
- $G(t)$ = the glycemic level under conventional glycemic control, and
- $\beta_{i,j}$ = a positive exponent associated with the transition from i to j.

The Diabetes Control and Complications Research Group (41) showed that progression rates for type 1 diabetes depend on glycemic levels using a similar equation, with the exponents varying between progression steps. Following Eastman et al.(1) the RTI Model assumed that this general functional form also holds for type 2 diabetes. This form allows analysis of the effects of alternative interventions that have smaller or larger effects on glycemic control. The glycemic levels under intensive and conventional glycemic control are approximated by

$$g(t) = \min(mx,\ ini + rcbf*on - imp + rcaf*t)$$

$$G(t) = \min(mx,\ ini + rcbf*on - imp + rcaf*t)$$

where

- mx = maximum level
- ini = initial HbA_{1c} at onset
- rcbf = rate of change for HbA_{1c} before treatment
- on = time between onset of disease and diagnosis (assumed to be the same for each cohort)

imp = treatment impact

rcaf = rate of change after treatment

t = time since diagnosis

The values for these variables in the Youth Model are shown in eTable 21a and for the RTI Model in Table 21b for comparison. Updates in the Youth model were derived from review of the pediatric literature (42-46). The minimum HbA1c assumed in both the RTI and Youth models is 6.0%. Treatment effects are based on UKPDS 33 (47). The initial (one-time) effect of treatment was based on the difference in HbA1c between the start of the run-in period for newly diagnosed patients and just after the actual treatments began (47).

eTable 21a. Rate of Change of Glycemic Levels for Youth Model

	Conventional Glycemic Control G(t)	Intensive Glycemic Control g(t)	Source
Initial HbA_{1c} at Onset	7.4	7.4	White et al.(45)
Annual Rate of Change for HbA_{1c} Before Treatment	0.24	0.24	Pettiti et al.(46)
Years Between Onset and Diagnosis	0	0	Assumption supported by (42-44)
One-time Initial Treatment Effect	–2.0	–2.9	UKPDS 33(47)
Rate of Change After Treatment	0.24	0.24	Pettiti et al.(46)
Max Level Without Treatment	12.0	12.0	Dong et al.(3)
Max Level With Treatment	11.0	9.0	Dong et al.(3)

eTable 21b. Rate of Change of Glycemic Levels for RTI Model

	Conventional Glycemic Control G(t)	Intensive Glycemic Control g(t)	Source
Initial HbA_{1c} at Onset	6.8	6.8	Dong et al.(3)
Annual Rate of Change for HbA_{1c} Before Treatment	0.2	0.2	Dong et al.(3)
Years Between Onset and Diagnosis	10	10	Assumption
One-time Initial Treatment Effect	–2.0	–2.9	UKPDS 33(47)
Rate of Change After Treatment	0.2	0.2	UKPDS 33(47)
Max Level Without Treatment	12.0	12.0	Dong et al.(3)
Max Level With Treatment	11.0	9.0	Dong et al.(3)

Information about the rate of HbA1c change over time in youth with type 2 diabetes beyond the first year after diagnosis is limited. To estimate this annual rate of change for the Youth Model, we used cross-sectional data from the SEARCH for Diabetes in Youth Study (46). In this sample, youth with type 2 diabetes of duration between 24 and 47 months had an HbA1c that was 0.72 %

higher (95%CI 0.08, 1.36) than those with duration <12 months. Assuming an average duration of 36 months, we estimated a rate of change of 0.24% per year and tested a range of 0.18%/year to 0.72%/year in sensitivity analyses. This estimate was consistent with the annual HbA1c rate of change in a retrospective review performed in June 2005 of longitudinal data on type 2 diabetes patients at Children's Hospital Boston who were <26 years old as of 1/31/2005 and had at least one visit in the Diabetes/Endocrine or Obesity Programs at Children's Hospital Boston between 7/1/2003 and 1/31/2005. We analyzed rate of HbA1c change in a subsample of these patients who had at least two visits with an HbA1c at least 6 months after diabetes diagnosis (48). A study from Children's Hospital of Philadelphia has also demonstrated that the nadir of HbA1c occurs 6 to 12 months after diagnosis and then HbA1c begins to rise after 1.5 years (49). However, the subsequent rate of change over time is not constant and so could not be incorporated into the Youth model but may inform future modeling efforts.

For the Youth model, assumed onset of diabetes was less than 1 year from diagnosis, and therefore, at diagnosis for the purpose of modeling. Very low rates of screening-detected diabetes in youth (43, 44) support this assumption. Weiss et al. showed that 24.2% of obese youth with impaired glucose tolerance screened with OGTT at 18 to 24 month intervals progressed to type 2 diabetes over an average follow up of 20.4±10.3 months (42). Therefore, 0 to 2 years from onset to diagnosis was used as the range for sensitivity analysis.

Intensive glycemic control has significant effects on the progression rates for microalbuminuria, nephropathy, peripheral neuropathy, and photocoagulation.(47) eTable 22 shows the differences between conventional and intensive control for each progression step. The relative risk reduction associated with intensive glycemic control is given by the ratio of the hazard rate for intensive control to the hazard rate for conventional control. For comparison, the hazard rate for conventional glycemic control in the Youth Model is also shown in the table. However, we utilized the derived $\beta_{i,j}$ from the RTI Model in the Youth model in the absence of data for hazard rates under intensive glycemic control for the 15-24 year old age group. The average glycemic level for patients with intensive control in the UKPDS is 7.0%, and the corresponding level for patients with conventional control is 7.9% (47).

eTable 22. Hazard Rates for Conventional and Intensive Glycemic Control

Health State	Conventional Glycemic Control *Youth Model*	Conventional Glycemic Control *RTI Model*	Intensive Glycemic Control *RTI Model*	Beta *RTI and Youth Models*
Microalbuminuria	0.1455	0.01734	0.01034	4.28
Proteinuria	0.0284	0.03356	0.02532	2.33
Peripheral Neuropathy	0.0085	0.02250	0.01552	3.07
Photocoagulation	0.006	0.01100	0.00790	2.74

Source: UKPDS 33(47) See Text for conventional glycemic control.

In the UKPDS, intensive glycemic control was associated with a 16 percent relative risk reduction in MI, and this reduction just missed significance at the 5 percent level (p = 0.052). While the 10 year follow up UKPDS study has demonstrated risk reductions in CHD associated with intensive treatment (50), there has been inconsistency in the results of large RCTs evaluating the impact of intensive treatment for diabetes on CHD outcomes (51-53). In our base case analysis for the Youth Model, therefore, we assumed that intensive glycemic control has no effect on the probability of CHD. In sensitivity analyses, we allowed intensive glycemic control to reduce the probability of CHD by 16 percent. The association between intensive glycemic control and stroke did not approach significance in the UKPDS (p = 0.52); therefore, we do not include glycemic control effects on stroke in the model.

Two methods can be used to determine the time that tight glycemic control starts – time since diabetes onset and HbA1c level. We assume that individuals receive their assigned intervention at the time of diagnosis.

2.2. Hypertension

In the Youth model, hypertension control intervention affects the probabilities of CHD and stroke. This intervention is only applied to cohorts who have hypertension.

In the RTI Model, for those aged 25 years and older, the percentage of persons with diabetes who have hypertension comes from Appendix 7.19 on p. 149-50 of *Diabetes in America* (54) where hypertension is defined as systolic blood pressure greater than or equal to 160 mm Hg *or* diastolic blood pressure greater than or equal to 95 mm Hg *or* person taking anti-hypertensive medications. Average blood pressure levels by age group are shown in eTable 23. For adults

over 25, these estimates were derived from NHANES III data. Levels for adults over 25 with hypertension are based on measurements for individuals with diabetes who have hypertension and are not receiving anti-hypertensive medications.

In the Youth model, for the 15 to 24 year old cohort, we identified the percentage of persons with diabetes who have hypertension from the SEARCH for Diabetes in Youth study, in which the definition of hypertension was based on systolic and/or diastolic blood pressure at or above the 95th percentile for age, sex and height (55-59). Estimates of normal and abnormal blood pressure for 15 to 24 year olds were derived from the Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents from the National Heart, Lung and Blood Institute (60). Normal systolic blood pressure (SBP) was defined as the average of the 50th percentile SBP for 17 year-old males and females at the 50th percentile for height. Normal diastolic blood pressure (DBP) was defined as the average of the 50th percentile DBP for 17 year-old males and females at the 50th percentile for height. Abnormal SBP was defined as the average of the 95th percentile SBP for 17 year-old males and females at the 50th percentile for height. Abnormal DBP was defined as the average of the 95th percentile DBP for 17 year-old males and females at the 50th percentile for height. These were added to eTable 23 as the 15-24 year old age group.

2.2.1. Risk Reduction

The effects of the blood pressure interventions are modeled as a reduction in the risk of a CHD event. The efficacy of the hypertension interventions comes from the United Kingdom Prospective Diabetes Study (13). Because the results of the UKPDS showed that an ACE inhibitor and a beta blocker were equally effective in reducing the likelihood of CHD, the results are for a ”hypertension intervention” rather than results for individual hypertension drugs. These risk reductions are presented in eTable 24.

eTable 23. Blood Pressure Levels, by Age

Age Group	No Hypertension		Hypertension	
	Normal Systolic	Normal Diastolic	Above Normal Systolic	Above Normal Diastolic
15-24	115	67	133	86
25–34	118	73	160	99
35–44	115	74	160	99
45–54	122	76	168	93
55–64	128	74	164	92
65–74	134	71	168	81
75–84	135	70	174	73
85–94	142	72	172	78

Sources: See Text

eTable 24. Risk Reduction in Likelihood of Coronary Heart Disease

Treatment	Risk Reduction	Relative to	Source
Moderate	13% (relative to no treatment)	No treatment	Inferred from UKPDS 38(13)
Intensive	21%	Moderate treatment	UKPDS 38(13)

The risk reduction associated with moderate control relative to no treatment was not calculated in the UKPDS. Based on the UKPDS, the RTI Model (and carried over into the Youth Model as a standard of care (61)) assumed that all persons with hypertension receive at least moderate control. Therefore, the model's default setting used for the base case is moderate control.

According to the UKPDS results, the risk reduction associated with intensive control relative to moderate control is 21 percent. However, this risk reduction was not significant (p=0.13). The impact of intensive hypertension control was evaluated in sensitivity analyses.

The implied risk reduction for the probability of progressing from Normal to CHD under moderate control was calculated in the RTI Model using the Framingham equation and the UKPDS data as follows: The UKPDS population characteristics were entered into the Framingham equation to determine the probability of CHD without treatment. The probabilities of CHD for the moderate control treatment group and for the intensive control group were then calculated. It was determined that 5/12 of the total reduction in risk of CHD is

achieved between no control and moderate control and 7/12 of the total reduction is achieved between moderate control and intensive control. As the UKPDS results indicate that the reduction in risk from intensive control reduced the probability of progressing from Normal to CHD by 21 percent relative to moderate control (for this calculation, we use the UKPDS point estimate, rather than a zero effect), the new absolute level of risk under intensive control

= (1 – 0.21)(1 – x), where x is the risk reduction associated with moderate control

The total change in risk

= 1 – x + [x – (1 ! 0.21)(1 – x)]

= 1 – (1 – 0.21)(1 – x) =1 – 0.79(1 – x) = 0.21 + 0.79x

Since the reduction in risk between no control and moderate control is 5/12 of the total reduction in risk,

x = 5/12(0.21 + 0.79x)

x = 0.3292 + 0.0875x

x = 0.1304

Therefore, the reduction in risk due to moderate control is 13.0 percent. Thus, P_1(moderate) = P_1(1 – 0.13) and P_1(intensive) = P_1(1 – 0.13)(1 – 0.21).

The reduction in the risk of stroke from a hypertension intervention was determined in a similar fashion calculating an implied risk reduction for the probability of progressing from Normal to Stroke under moderate control using the Framingham equation and the UKPDS data. All persons with hypertension are assumed to receive at least moderate control. The probability of progressing from Normal to nonfatal or fatal Stroke with moderate control is reduced by 17 percent. Thus, $P_{S_1S_2}$(moderate) = $P_{S_1S_2}$(1 – 0.17).

The reduction in risk of fatal or nonfatal stroke associated with intensive hypertension control in the UKPDS was 44 percent (13). Thus, $P_{S_1S_2}$(intensive) = $P_{S_1S_2}$(1 – 0.17)(1 – 0.44). These risk reductions are presented in eTable 25.

eTable 25. Risk Reduction in Likelihood of Stroke

Treatment	Risk Reduction	Source
Moderate	17% (relative to no treatment)	Inferred from UKPDS 38(13)
Intensive (Atenolol or Captopril)	44% (relative to moderate treatment [diuretic])	UKPDS 38(13)

Hypertension control for patients with a History of CHD or Stroke (i.e., secondary prevention) has long been accepted practice. The Youth model assumes that all patients with a history of CHD or stroke receive hypertension treatment. The effects of this treatment are assumed to be incorporated within the corresponding transition probabilities.

In the RTI Model, based on the UKPDS 38 hypertension study (13), persons with hypertension had higher hazard rates for photocoagulation than persons without hypertension, and intensive hypertension control intervention reduced the hazard rate for this complication (eTable 26). As comparable data for 15-24 year olds were not available to inform difference in the hazard rate for photocoagulation in those with and without hypertension or to determine the impact of intensive hypertension control on this hazard rate, the same hazard rate was assumed for photocoagulation for both persons with and without hypertension (Table e8a) and with conventional (i.e., moderate) and intensive hypertension control in the Youth Model. However, the impact of these assumptions was evaluated in sensitivity analyses. Consistent with the UKPDS 38, hypertension status was assumed to have no effect on the nephropathy or neuropathy hazard rates in the model (13).

eTable 26. Photocoagulation Hazard Rates for Conventional and Intensive Hypertension Control (RTI Model)

Transition	Conventional Hypertension Control	Intensive Hypertension Control
Photocoagulation	0.01660	0.01020

Source: UKPDS 38(13)

2.3. Cholesterol

In the Youth model, interventions that reduce cholesterol lower the probability of CHD and stroke. Cholesterol reduction interventions are only applied to cohorts with high cholesterol, defined by a total cholesterol≥200 mg/dl.

In order to identify cohorts with high cholesterol we must define normal and above normal cholesterol levels. In the RTI Model, for cohorts with age 25 years and older, normal total cholesterol was defined as less than 200 mg/dL and above normal total cholesterol as greater than or equal to 200 mg/dL. These definitions came from the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (62). Estimates for cholesterol level by age combined the borderline-high blood cholesterol together with the high-blood cholesterol to provide a conservative estimate for above normal cholesterol. This information was used in the Framingham and UKPDS calculations to determine the risk for MI and stroke. The equations also require an HDL estimate. For adults 25 and older, the average HDL level for persons in the normal and above normal total cholesterol groups in the NHANES III data were used for this estimate.

In the Youth Model, for the 15 to 24 year old cohort, we estimated the proportion of the newly diagnosed type 2 diabetes population with abnormal cholesterol defined by total cholesterol >200 mg/dl from the SEARCH for Diabetes in Youth study (63). The estimates for normal and abnormal cholesterol levels for 15-24 year olds were derived from the NHANES III, 1988-1994 data (64). Abnormal total cholesterol was estimated as the weighted average of the male and female estimates for the 90^{th} - 95^{th} percentile for total cholesterol in 16 to 19 year-olds (64). Normal total cholesterol was estimated as the weighted average of the mean total cholesterol for males and females in 16 to 19 year-olds. Abnormal HDL cholesterol was estimated as the weighted average of the male and female estimates for the 5^{th} - 10^{th} percentile for HDL cholesterol in 16 to 19 year-olds (64). Normal HDL cholesterol was estimated as the weighted average of the mean HDL cholesterol for males and females in 16 to 19 year-olds.

Average cholesterol levels by age are shown in eTable 27.

2.3.1 Primary Prevention

The estimates of risk reduction achieved with cholesterol reduction were not changed for the Youth morel. As in the RTI Model, risk reduction estimates come from two studies, the West of Scotland Coronary Prevention Study (pravastatin) (65) and the Helsinki Heart Study (gemfibrozil) (66). Both of

these were randomized, controlled clinical trials although they were not specifically in a diabetic population.

eTable 27. Cholesterol Levels, by Age

Age Group	Normal Total Cholesterol	Normal HDL	Above Normal Total Cholesterol	Abnormal HDL
15-24	165	49	218	34
25–34	168	49	228	49
35–44	172	51	233	48
45–54	174	49	238	49
55–64	175	47	243	52
65–74	174	49	241	52
75–84	175	48	244	53
85–94	175	48	244	53

Sources: See Text

The risk reductions in major CHD attained in the trials were very similar. Pravastatin and gemfibrozil produced risk reductions of 31 percent and 34 percent, respectively. Because these reductions come from primary prevention trials, they will affect the probability of CHD (P_1). No specific data applicable to the 15 to 24 year old age group were identified and therefore the same risk reductions were assumed. As the statin class of lipid lowering medications are typically the first choice in the adolescent type 2 diabetes population following lifestyle modification (67), Pravastatin was used in the base case analysis in the Youth Model. Use of Gemfibrozil as an alternative was considered in sensitivity analyses.

2.3.2 Secondary Prevention

The cholesterol risk reduction estimates come from two studies, the Cholesterol and Recurrent Events Trial (CARE) (pravastatin) (68) and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention (VA Hit) (gemfibrozil) (69). Both of these studies were randomized, controlled clinical trials with significant numbers of diabetic enrollees. The CARE study published a subgroup analysis of diabetics, which contains the diabetes-specific risk reductions that we present here. The VA Hit study included some specific information about the 627 people with diabetes who were enrolled in the study.

The risk reductions in major CHD achieved by each of the interventions were similar. Gemfibrozil and pravastatin reduced major CHD by 24 percent and 25 percent, respectively. Because both of these studies tested secondary interventions, they will affect transition probabilities that follow CHD. These risk reductions will be applied to the following transition probabilities: P_4, P_5, P_6, P_7, P_{14}, P_{15}, P_{19}, P_{22}, and P_{24} (eTable 28).

eTable 28. Risk Reduction in Coronary Heart Disease with Cholesterol Treatment

Transition Probability	Fibrate (Gemfibrozil)	Statin (Pravastatin)
Primary (P_1)	34%	31%
Secondary (P_4, P_5, P_6, P_7, P_{14}, P_{15}, P_{19}, P_{22}, P_{24})	24%	25%

2.3.3 Cholesterol and Stroke

We do not model an effect from cholesterol treatment on the likelihood of stroke.

2.4 Smoking

There are five possible smoking interventions in the RTI Model: (1) a nicotine patch and individual intensive counseling; (2) nicotine gum and individual intensive counseling; (3) individual intensive counseling; (4) full counseling; and (5) brief counseling. The marginal quit rate (over and above the no-intervention quit rate) associated with each of these programs varied, ranging from 16.64 percent to 1.86 percent, as shown in eTable 29. In addition, the number of quitters was reduced by 45 percent to account for post-follow-up relapse (70).

The effect of quitting smoking is modeled by reducing the likelihood of CHD and stroke in persons who have not yet experienced these complications. No effect is modeled for persons who have already experienced CHD or stroke. The reduction in risk is realized in the quitter over time. One year after the individual quits smoking, his risk is halved. Fifteen years after the individual quits smoking, his risk is equal to that of a person who has never smoked (71). The model assumes that the risk will decline in a linear fashion until reaching the risk of a never-smoker at year 15.

For the Youth Model, the Brief Counseling intervention is applied in the base case analysis. We assumed that the data for adults were applicable to the 15 to

24 year old cohort and chose the minimum standard of care for clinical practice (61) for the base case.

eTable 29. Smoking Interventions

Intervention	Description of Intervention	Marginal Quit Rate (%)	Post-Follow-Up Relapse Rate (%)	Source
Nicotine Patch and Intensive Counseling	Intensive counseling consists of 5 30-minute counseling sessions with a smoking cessation expert.	16.64	45	Cromwell et al.(70)
Nicotine Gum and Intensive Counseling	Intensive counseling consists of 5 30-minute counseling sessions with a smoking cessation expert.	11.50	45	Cromwell et al.(70)
Intensive Counseling	Intensive counseling consists of 5 30-minute counseling sessions with a smoking cessation expert.	6.62	45	Cromwell et al.(70)
Full Counseling	15 minutes of physician time during initial visit with 2 10-minute follow-up visits.	6.20	45	Cromwell et al.(70)
Brief Counseling	7 minutes of physician time during initial visit with 1 10-minute follow-up visit	1.86	45	Cromwell et al.(70)

3. DISTRIBUTION OF DIABETIC POPULATION

In order to run the Youth model for a national cohort of newly diagnosed diabetic patients in the 15 to 24 year old age group, it was necessary to determine the distribution of the population among the different population subgroups as defined by age, sex, race/ethnicity, hypertension status, cholesterol status, and smoking status.

Using data available from several sources, a population distribution was calculated (eTable 30). Based on these data, the incidence of type 2 diabetes and the probability of smoking and hypertension in this population varied by race/ethnicity. The prevalence of high cholesterol was 33% (63). The size of this cohort based on the sources in eTable 30 was approximately 3,500 individuals.

eTable 30. Sources for the Distribution of Diabetics for 15-24 Year-old Cohort

Characteristic	Source
Population in Each Age, Race/Ethnicity, and Sex Group, 2006	U.S. Bureau of the Census (July, 2006)(72, 73)
Incidence Rate	SEARCH for Diabetes in Youth Study(55-59)
P (smoking)	SEARCH for Diabetes in Youth Study;(56, 58, 59, 74)
P (hypertensive)	SEARCH for Diabetes in Youth Study(55-59)
P (high cholesterol)	SEARCH for Diabetes in Youth Study(63)

4. RACE/ETHNICITY ADJUSTMENTS

Race/ethnicity has three effects in the Youth model. First, race/ethnicity differences in the prevalence of high cholesterol, hypertension, and smoking are reflected in the initial distribution.

Second, mean race/ethnicity differences in glycemic levels are incorporated in patients' glycemic levels and consequently affect the hazard rates for neuropathy, nephropathy, and retinopathy. Following Eastman et al.(75) the effect of these differences in glycemic levels is described in the equation

$$h^*_{i,j}(t) = h_{i,j}(t) \times [g(t)/G(t)]^{\beta_{i,j}} \times [RGL]^{\beta_{i,j}}$$

where RGL is the relative glycemic level for the race/ethnicity group, and the other variables are as in the equation in Section 2.1. As in the RTI Model, the hazard rates are assumed to be based on the average for all Americans. The average glycemic level for non-Hispanic Whites is 98 percent of the American average. Average glycemic levels for other race/ethnicity groups, relative to levels for non-Hispanic Whites, are shown in eTable 31.

Third, race/ethnicity affects mortality rates from ESRD and other causes (see Section 1.3).

eTable 31. Race/Ethnicity Differences in Glycemic Levels, Relative to Non-Hispanic Whites

	Males	Females	Source
Non-Hispanic White	1.00	1.00	Harris et al.(76)
African-American[a]	1.04	1.09	Harris et al.(76)
Hispanic	1.09	1.04	Harris et al.(76)
Native-American	1.19	1.19	Eastman et al.(75)
Asian	0.95	0.95	Eastman et al.(75)

[a]Non-Hispanic.

5. HEALTHY UTILITY AND QUALITY OF LIFE ADJUSTMENTS

Health utility values between 0 and 1 are used to calculate quality-adjusted life years (QALYs) for patients who are alive. The minimum combination method was used such that an individual experiencing multiple complications at the same time was assigned the lowest quality-of-life value.

For the Youth Model, quality of life adjustments were derived from a study conducted at Children's Hospital Boston and Joslin Diabetes Center (Boston) between 2006 and 2008 (77, 78). A total of 70 adolescents with or at risk of type 2 diabetes were enrolled in a study to evaluate preferences for health states related to type 2 diabetes or its treatments using in person, standard gamble interviews. We applied the mean utilities obtained in this study for the available health states in the Youth model (eTable 32), which included ESRD, LEA, blindness, and angina (78) (median utilities were similar (77)) . We assigned the same utility to history of CA/MI and stroke as that for angina. All other live health states were set to 1. We assumed intensive treatment for youth with type 2 diabetes included insulin (79, 80). For the base case, utility of insulin treatment was set at 1.0, reflecting no disutility, i.e., loss in health-related quality of life. In sensitivity analyses, the disutility of intensive treatment (with insulin) relative to conventional treatment with diet therapy was assessed. The disutility was the difference in the mean utility for each treatment.

Quality of life adjustments are shown in eTable 32 for comparison with the RTI Model. In the RTI Model, health utility values for diabetes complications were taken from Dong et al.(3). Quality adjustments were 0.69 for blindness, 0.61 for ESRD, and 0.8 for LEA (81). Stroke utilities were reported in terms of minor and major stroke (82). In order to calculate one utility for all stroke, the RTI Model used a weighted average from Wolf et al.(83) to estimate the health utility for stroke. The resulting utility for stroke was 0.5. Health utility for an individual who experienced CA/MI and survived was 0.88 (84). The health utility estimate for an individual with angina was 0.947. This was the weighted average of two severity groups in Tables 1 and 3 from Nease et al.(85). All other live health states were set to 1.

eTable 32. Quality of Life Adjustments

Health State	Adolescent Valuations for Youth Model	Adult Valuations for RTI Model
Blindness	0.547	0.69
ESRD	0.511	0.61
LEA	0.557	0.80
Angina	0.587	0.947
History of CA/MI	0.587	0.88
Stroke	0.587	0.50
	Disutility of Treatment	**Disutility of Treatment**
Intensive Treatment with Insulin vs. Diet Rx	-0.063	N/A

Source; Rhodes et al. (77, 78) *N=66 valid respondents

6. MODEL COMPUTATIONS

The global state transition matrix ($S_{nurcs + death}$) is computed from the transition matrices for each of the five disease paths. Each of the five indices on the S matrix indicates a specific disease state in each of the five disease paths (nephropathy, neuropathy, retinopathy, CHD, and stroke). In this manner, S_{42321} represents the state where individuals have ESRD (n_4), peripheral neuropathy (u_2), blindness (r_3), history of CHD (c_2), and no history of stroke (s_1). The single "death" state is a global death state and encompasses all of the individual deaths from each disease path as well as deaths from other causes. The matrix is large with 217 states ($4 \times 3 \times 3 \times 3 \times 2 + 1$).

We use a global state transition matrix instead of the matrices for the five individual disease paths separately due to the

- interaction between the CHD and nephropathy disease paths,
- ability to include other dependency relationships in the future,
- different causes of death and the appropriate accounting techniques necessary to avoid double counting deaths, and
- computational issues.

Presently, the Youth Model contains one major interdependency between disease paths. Once patients reach microalbuminuria on the nephropathy disease path, they are assumed to have high blood pressure. Because hypertensives have higher risk of CHD and stroke, this assumption leads to faster progression on each of these paths.

To compute the transition probability for going from S_{nurcs} to $S_{n'u'r'c's'}$, the computer program looks up the transition probability of going from n to n', the transition probability of going from u to u', the transition probability of going from r to r', the transition probability of going from c to c', and the transition probability of going from s to s', and multiplies all of the probabilities to obtain the global transition probability. The multiplicative approach is appropriate because the transition probabilities are independent across disease states, conditional on hypertension status. The patient's hypertension status is updated once microalbuminuria is reached.

Deaths caused by disease progression in one of the five disease paths are incorporated into the model formulation. To account for deaths from other causes, a few additional calculations are necessary. We assume deaths from other causes are equally likely to occur to individuals in any state. Let the age-specific probability of death = p_d. Once the global state transition matrix has been calculated and implemented for the specific time period, we multiply all of

the alive states in the resulting state vector by $(1 - p_d)$. In this manner, $newS_{nurcs} = S_{nurcs}*(1 - p_d)$. We then add $newS_{death} = S_{nurcs}*(p_d)$ individuals from each state to the death state.

To avoid double counting deaths from the different diabetic disease paths, there is only one death state. Recall that a cohort is simultaneously in a nephropathy, neuropathy, retinopathy, CHD, and stroke state. The probability of being in a given state is the product of the probability of transitioning to each state in the individual disease paths. The probability of transitioning to the global death state equals 1 minus the sum of the probabilities of transitioning to all the other possible states. The death rates from the individual disease paths are used to calculate the transition probability of remaining in a disease state within the individual disease path. For example, the probability of staying in ESRD is 1 minus the probability of dying due to ESRD. At the end of each 1-year time interval, the entire cohort is diminished by the death from other causes, each state being equally affected.

6.1. Summary of Youth Model Hazard Rate Assumptions

eTable 33. Hazard Rates and Ranges for Sensitivity Analyses in Youth Model

Parameter Hazard Rates[#]	Intensive	Conventional	Beta Exponent (see eTable 22)	Ranges for Sensitivity Analysis
Normal to Microalbuminuria (6, 9, 10)	Calculated[††]	0.1455	4.28	Faster nephropathy progression, HR 0.42 (17); Slower progression to microalbuminuria, HR=0.042 (6, 9-12)[**]
Normal to Retinopathy requiring Photocoagulation (10, 12, 26)	Calculated[††]	0.006	2.74	Faster retinopathy progression, HR 0.04 (20); Slower progression to retinopathy, HR=0.001[‡‡]
Normal to Peripheral Neuropathy (26-28)	Calculated[††]	0.0085	3.07	Faster neuropathy progression, HR 0.4702 (27); Slower progression to neuropathy, HR=0.0019 (26)

Numbers in brackets are references [#] Appendix eTables 6a-8a [**]Weighted average of five studies as described in section 1.1.1. [††] Hazard rate (HR) for intensive treatment is derived in the model by the impact of the beta exponent on the conventional treatment HR. [‡‡] Assumption supported by (12). HR= Hazard rate.

eTable 34. Multi-Way Sensitivity Analyses in Youth Model

Model Description	Parameters
Faster progression of all microvascular complications and significant microvascular disease at diagnosis	Faster progression refers to the following hazard rates: normal to retinopathy (photocoagulation) HR=0.04; normal to microalbuminuria HR=0.42; normal to neuropathy HR=0.4702; all other HR represent a 20% increase from base case. Significant microvascular disease at diagnosis: Microalbuminuria 40% Retinopathy (photocoagulation) 10% Neuropathy 10%
Poor glycemic control at diagnosis and faster deterioration in glycemic control	HbA1c 10.9% at diagnosis Faster deterioration in glycemic control: HbA1c change 0.72%/yr Max HbA1c 13% conventional and 11% Intensive
Higher estimate for abnormal blood pressure and adult microvascular progression after 10 years	Abnormal blood pressure 145/90 Adult microvascular progression: see eTables 6b, 7b, 8b
Intermediate glycemic control at diagnosis and adult microvascular progression after 10 years	Intermediate glycemic control: HbA1c 8.5% Adult microvascular progression: see eTables 6b, 7b, 8b
Good glycemic control at diagnosis and slower deterioration of glycemic control	HbA1c at diagnosis 6.8% Slower deterioration of glycemic control: HbA1c change 0.18%/yr, 11% conventional and 9% Intensive
Intermediate glycemic control at diagnosis, adult microvascular progression after 10 years; Hypertensives progress faster; intensive hypertension control	HbA1c at diagnosis 8.5% Adult microvascular progression: see eTables 6b, 7b, 8b Hypertensives progress faster leads to faster progression from normal to retinopathy Intensive hypertension control leads to reduced risk of CHD, stroke and retinopathy (after 10 years at adult rate).
Slower progression of all microvascular complications and no microvascular disease at diagnosis	Slower progression of all microvascular complications refers to the following rates: Normal to retinopathy (photocoagulation) HR=0.001; normal to microalbuminuria HR=0.042; normal to neuropathy HR=0.019; all other HR represent a 20% decrease from base case No microvascular disease at diagnosis leads to prevalence of microalbuminuria, neuropathy, and retinopathy (photocoagulation) at baseline equal to 0%

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