Model of Complications of NIDDM

I. Model construction and assumptions

RICHARD C. EASTMAN, MD
JONATHAN C. JAVITT, MD
WILLIAM H. HERMAN, MD
ERIK J. DASBACH, PHD
ARTHUR S. ZBROZEK, MBA
FRED DONG
DIANE MANNINEN, PHD
SANFORD A. GARFIELD, PHD
CATHERINE COPLEY-MERRIMAN, MBA
WILLIAM MAIER, PHD
JEFFERY F. EASTMAN, PHD
JAMES KOTSANOS, MD
CATHERINE C. COWIE, PHD
MAUREEN HARRIS, PHD

OBJECTIVE — To develop a model of NIDDM for analyzing prevention strategies for NIDDM.

RESEARCH DESIGN AND METHODS — A Markov type model with Monte Carlo techniques was used. Age, sex, and ethnicity of cohort was based on U.S. data. Incidence rates of complications were also based on community and population studies.

RESULTS — Nonproliferative retinopathy, proliferative retinopathy, and macular edema are predicted in 79, 19, and 52%, respectively, of people with NIDDM; 19% are predicted to develop legal blindness. Microalbuminuria, gross proteinuria, and end-stage renal disease related to diabetes are predicted in 53, 40, and 17%, respectively. Symptomatic sensorimotor neuropathy and lower-extremity amputation are predicted in 31 and 17%, respectively. Cardiovascular disease is predicted in 39%. Higher rates of complications (1.1–3.0×) are predicted in minority populations. Predicted average life expectancy is 17 years after diagnosis.

CONCLUSIONS — A probabilistic model of NIDDM predicts the vascular complications of NIDDM in a cohort representative of the incident cases of diabetes in the U.S. before age 75 years. Predictions of complications and mortality are consistent with the known epidemiology of NIDDM. The model is suitable for evaluating the effect of preventive interventions on the natural history of NIDDM.

To understand the present natural history of NIDDM and its complications and to ultimately determine the effect of preventive strategies on this natural history, it is necessary to develop a chronic disease model that incorporates the known epidemiology of the disease and allows the effects of interventions to be modeled. Alternatively, large-scale long-term clinical trials could be conducted, but these are logistically difficult and expensive and would take years to yield results. In practice, chronic disease models have been used to model screening and photocoagulation for retinopathy, antihypertensive treatment of patients with diabetic nephropathy, and preventive interventions for cardiovascular disease (CVD) (1–4). Although previous models have separately modeled interventions for retinopathy, nephropathy, and CVD, the current model incorporates these processes in an integrated way that allows study of the interaction between treatments. We describe a model that predicts rates of microvascular complications, CVD, and mortality that are consistent with the known epidemiology of NIDDM in the U.S.

From the Division of Diabetes, Endocrinology, and Metabolic Diseases (R.C.E., S.A.G., C.C.C., M.H.), National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland; the Department of Ophthalmology (J.C.J.), Worthen Center for Eye Care Research, Georgetown University, School of Medicine, Washington, D.C.; the Division of Endocrinology and Metabolism (W.H.H.), Department of Internal Medicine, University of Michigan; Epidemiology and Outcomes Research (C.C.-M., W.M.), Parke-Davis Inc., Ann Arbor, Michigan; Merck Inc. (E.J.D.), Bluebell, Pennsylvania; Bayer Inc. (A.S.Z.), West Haven, Connecticut; Battelle Inc. (F.D., D.M.), Seattle, Washington; Windward Solutions (J.F.E.), Redwood City, California; and Eli Lilly Inc. (J.K.), Indianapolis, Indiana.

Address correspondence and reprint requests to Richard C. Eastman, MD, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, Building 31, Room 9A16, 31 Center Dr. MSC 2560, National Institutes of Health, Bethesda, MD 20892-2560.

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BDR, background retinopathy; CVD, cardiovascular disease; ESRD, end-stage renal disease; GPR, gross proteinuria; LEA, lower-extremity amputation; MA, microalbuminuria; ME, macular edema; NHANES, National Health and Nutrition Examination Survey; PDR, proliferative retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

RESEARCH DESIGN AND METHODS

Construction of model

A model was developed using Monte Carlo techniques, using simulation software (@Risk version 3.5b for Windows, Palisades, Inc., Newfield, NJ) and Excel Version 7 (Microsoft, Seattle, WA).

Hypothetical patients are randomly assigned demographic characteristics, weighted to yield the age, sex, and ethnicity of the incident cases of clinically diagnosed NIDDM in the U.S. population aged 25–74 years (5,6), representing 85% of the incident cases of NIDDM in the U.S. Patients with onset of diabetes after age 74 years are not included in the cohort because of the short life expectancy, low rate of complications, and lack of natural history data for patients in this age range. Cohorts of 10,000 people are simulated for the base analysis.

After the person's age, race, and sex status are assigned, each year of life is simulated until death occurs. Fourteen health states are modeled (Table 1), reflecting the natural history of the vascular and neuropathic complications of diabetes. We have not included results of modeling peripheral vascular disease because of the difficulty in separating the natural history of vascular disease and neuropathy leading to amputation; thus, the analysis underestimates the total number of amputations and is intentionally conservative.

Progression to a health state (e.g., from microalbuminuria [MA] to gross proteinuria [GPR]) within an organ system is dependent on the current health state, as shown in Fig. 1. An almost infinite number of compound health states occur in the modeling process if one takes into account

Table 1—*Clinical definitions of the health states modeled*

Health state	Clinical definition
Retinopathy (R1)	No retinopathy
Retinopathy (R2)	Nonproliferative retinopathy (1)
Retinopathy (R3)	PDR (1)
Retinopathy (R4)	Significant ME (1)
Retinopathy (R5)	Visual acuity <20/100 in better eye (1)
Nephropathy (N1)	No nephropathy
Nephropathy (N2)	MA 0.03–0.3 g/l (14) American Indians 30–299 mg/g creatinine (16)
Nephropathy (N3)	Proteinuria ≥0.4 g/l (17)
Nephropathy (N4)	ESRD (18)
Neuropathy (Nu1)	No neuropathy
Neuropathy (Nu2)	Symptomatic neuropathy (20)
Neuropathy (Nu3)	First LEA (22)
CVD (C1)	No CVD
CVD (C2)	CVD morbidity and mortality (26)

the potential occurrence of multiple events and the temporal sequence. For example, a patient may first become blind and subsequently develop renal failure, have an amputation, and die of CVD. Alternatively, the amputation may occur first; there is no set sequence of events. However, we do not accumulate statistics on compound health states because of computer memory constraints. At the end of each year, it is determined whether death has occurred. If the person is alive, progression through the health states occurs in the subsequent year.

Probabilistic (Monte Carlo) techniques are used to progress people through the model. At each step, a random number is drawn. Transition to the next health state occurs and is irreversible if the random number is less than or equal to the transition probability for progression from the current health state to the subsequent health state. This approach allows many health states to be modeled simultaneously and has been used in other established models (1,4).

Retinopathy model

Twenty percent of patients are assumed to have background retinopathy (BDR) at the time of clinical diagnosis of diabetes (7,8). Hazard rates are the averages of the rates for patients taking insulin and those not taking insulin in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (1,9). Minorities are assigned higher rates (10,11) (Table 2). Because data on Asian-Americans are limited, they are assumed to have the same risk as non-Hispanic whites. Patients with macular edema (ME) or proliferative retinopathy (PDR) are treated with appropriate photocoagulation that reduces the risk of blindness (Table 2) (1,13).

Nephropathy model

Development of MA is based on the WESDR, where the prevalence of MA was 23.3% after 5–9 years and 43.5% after 25 years (14). A baseline prevalence of MA of 11.5% is assumed, which is consistent with back-projection of the WESDR data. The hazard rates are adjusted for ethnicity (Table 2) (10,15). We use incidence rates of MA in Pima Indians (16).

A hazard rate of 0.0131/year for nephropathy was calculated from data from the Rochester Epidemiology Project, where GPR occurred in 28% after 25 years (17) (see APPENDIX A, Eq. 1). This predicts GPR in the population but does not predict progression from MA to GPR. A conditional transition probability was derived from the hazard rates for MA and proteinuria (see APPENDIX A) and is ~12 times the risk for developing GPR. We use different risks for MA to reflect the effect of ethnicity and assume that the same rates apply to all ethnic groups for progression from MA to GPR and from GPR to renal failure. Either approach or a combined approach could be used, and we know of no data that favors one approach over the other.

ESRD occurred in Rochester in those without proteinuria at the time of diagnosis of diabetes in ~0.3, 3.2, 6.7, and 9.4% after 11, 20, 25, and 30 years of diabetes (18). Hazard rates were calculated for each interval (0.0003, 0.0033, and 0.0061/year for 0–11, 12–20, and 21–25 years, respectively). Conditional transition probabilities were ~15 times the nonconditional rates for years 0–11, and ~12 times the nonconditional rates for subsequent years. The same probabilities are used for all races. We do not model ESRD in patients who present with proteinuria, since this is a small

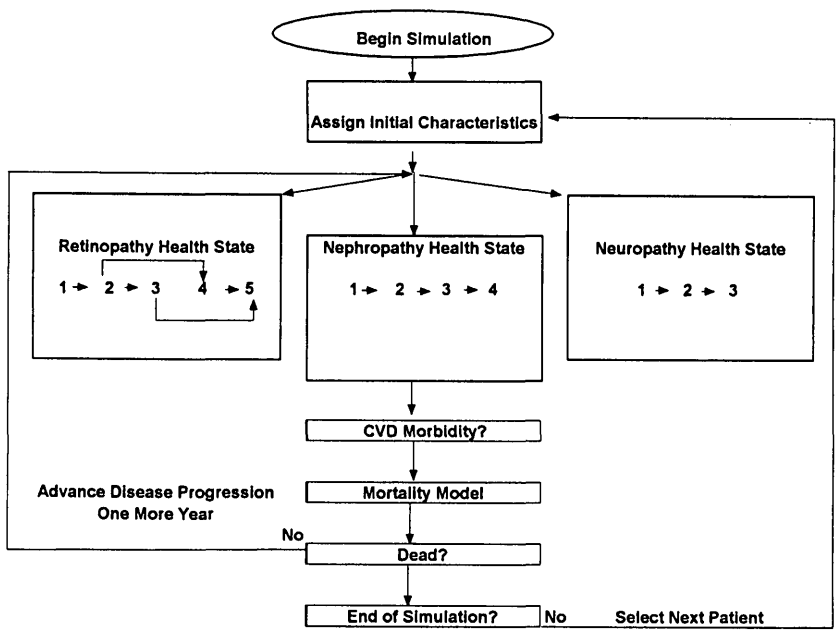

Figure 1—*Flow diagram of the simulation model of NIDDM complications and mortality.*

Table 2—*Demographics of the populations modeled, transition probabilities for the health states, and assumptions used in the analysis*

Characteristics	Description		
Baseline			
	Proportion of cohort (%)		*Reference*
Age			3
25–44	30.5		
45–54	21.7		
55–64	17.7		
65–74	30		
Sex	Males = Females		6
Ethnicity			6
Non-Hispanic white	70		
African-American	20		
Hispanic American	5		
Asian American	2.5		
American Indian/other	2.5		
Diabetes	Model entry at clinical diagnosis of NIDDM in U.S. at mean age of 51 years, African-Americans 49 years, Hispanic Americans and American Indians 46 years		6
Retinopathy module			
	Duration of diabetes (years)	*Hazard rate (per year)*	
BDR risk present in 20% at diagnosis-of diabetes	1–4	0.073	1,7
	5–9	0.129	
	10–14	0.116	
	15+	0.113	
ME risk	1–4	0.047	1
	5–9	0.095	
	10–14	0.092	
	15+	0.08	
PDR risk	1–4	0.0025	1
	5–9	0.009	
	10–14	0.0095	
	15+	0.026	
Ethnicity adjustment		Rates for BDR, ME, and PDR multiplied by 2.11 in African-Americans and American Indians, and 2.68 in Hispanic Americans	10,11
	Condition	*Hazard rate (per year)*	
Dilated eye exam	ME/PDR not detected	0.5	12
	ME/PDR detected	1.0	
Progression of PDR to severe vision loss	Untreated	0.088	1
	Treated	0.0148	
Progression of ME to blindness	Untreated	0.05	1
	Treated	0.033	
Treatment	ME and/or PDR is present, and patient has an eye examination	—	1
Disease progresses symmetrically in both eyes		—	1
Outcome of treatment is the same in both eyes		—	
Loss of central acuity from ME is independent of vision loss from PDR		—	1
Relative benefit of treatment is permanent		—	1

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Table 2 *(continued from page 727)*

Characteristics	Description		
Nephropathy module			
	Duration of diabetes (years)	*Hazard rate (per year)*	*Reference*
Progression to MA: present in 10.5% at diagnosis of diabetes (see METHODS)	All durations	0.0267	14
American Indians	1–4	0.0379	16
	5–8	0.0552	
	9–13	0.1265	
	14	0.1622	
Ethnicity adjustment		MA rate from (14) is multiplied by 4.55 in African-Americans and 6.44 in Hispanic Americans	15
Progression to GPR	All durations	0.1572	17
Progression to ESRD			18
	1–11	0.0042	
	12–20	0.0385	
	21+	0.074	
Neuropathy module			
Progression to diabetic neuropathy: present in 3.5% at diagnosis of diabetes (see METHODS)	All durations	0.0144	20
Ethnicity adjustment		Neuropathy rates are multiplied by 3 in African- and Hispanic Americans and American Indians	
Progression to LEA			22
	1–8	0.028	
	9–13	0.0350	
	14–19	0.0467	
	20+	0.14	
		Second LEA subsequent to first LEA 0.1386/year, based on U.S. studies	23

fraction of the cases in the Rochester Study (8.2%), and the patients were older and more likely to be men with hypertension and CVD.

Neuropathy model

The prevalence of significant diabetic neuropathy at the time of clinical diagnosis of diabetes was ~3.5% in National Health and Nutrition Examination Survey (NHANES) II (16). Symptomatic neuropathy occurred in 13% of individuals after median follow-up of 8.1 years in Rochester (20). A hazard rate of 0.0144/year yielded a predicted cumulative incidence of 13% 8 years after diagnosis of diabetes, which is similar to the rate in IDDM (21). Neuropathy rates are increased threefold in minorities (10,11,15).

First lower-extremity amputation (LEA) was estimated from the Rochester Study (22). Hazard rates were calculated from the cumulative incidence for first LEA (22) and made conditional on neuropathy in the model. The conditional probabilities are ~14 times the nonconditional rates. Patients experiencing a first LEA are at risk for a second amputation (23) (Table 2).

Cardiovascular disease

Each person is assigned CVD risk factors by sampling probability distributions for these risk factors (see APPENDIX B). Smoking status (yes or no) is based on age-, sex-, and race-specific prevalence of smoking (see APPENDIX B) (24,25). A multivariate model was used to calculate the incidence of CVD, using the coefficients for age, sex, systolic blood pressure, cigarette smoking (yes or no), total/HDL cholesterol, and diabetes, but not left ventricular hypertrophy (26). Model-predicted CVD closely approximates the data from the Framingham 26-year follow-up study (27). For patients with ESRD, we assume that 50% have CVD, since CVD (excluding pericarditis and valvular heart disease) accounts for 50% of the deaths in patients with diabetes-related ESRD (28).

Mortality model

A 1.6–3.2-fold increase in mortality risk persists in patients with NIDDM after adjusting for multiple risk factors, including age, BMI, smoking, cholesterol, blood pressure, race, income, physical activity, stress score, marital status, occupation, and family history of myocardial infarction (29). To reflect this risk, non–cardiovascular disease (non-CVD) mortality risk and CVD mortality risk are calculated for each patient for each year of life. CVD mortality risk is calculated using the person's CVD risk factors (see above) in the multivariate model

(26). For patients predicted to develop ESRD, the CVD mortality risk is 50% of the ESRD mortality risk (28).

Non-CVD mortality is the age-, sex-, and race-specific mortality risk in people without diabetes in the U.S. (30) (Pima Indian data are used in lieu of census data [31]) minus the calculated multivariate CVD risk for nondiabetic subjects described previously. Relative mortality risk in people with diabetes is 2.75 in the model (non-CVD risk for a person with diabetes equals non-CVD risk for a nondiabetic person × 2.75). Non-CVD mortality risk reflects sepsis, metabolic catastrophes, influenza, etc. Pima Indian relative mortality risk for non-CVD deaths is used for American Indians (1.1 for men and 1.25 for women [31]). The predicted life expectancy using the coefficient of 2.75 is ~10 years less than for a middle-aged person without diabetes, which is consistent with life expectancy in patients with NIDDM in the U.S. (29). The sensitivity to this assumption is evaluated.

When ESRD develops, we use the age-, sex-, and race-specific mortality risks for patients in the ESRD program with diabetes-related kidney failure (28).

We emphasize that this model of the vascular complications of diabetes makes no assumption about the level of glycemic control in the populations modeled. In an accompanying manuscript, however, we will discuss and evaluate assumptions about the prevailing level of glycemia in the population.

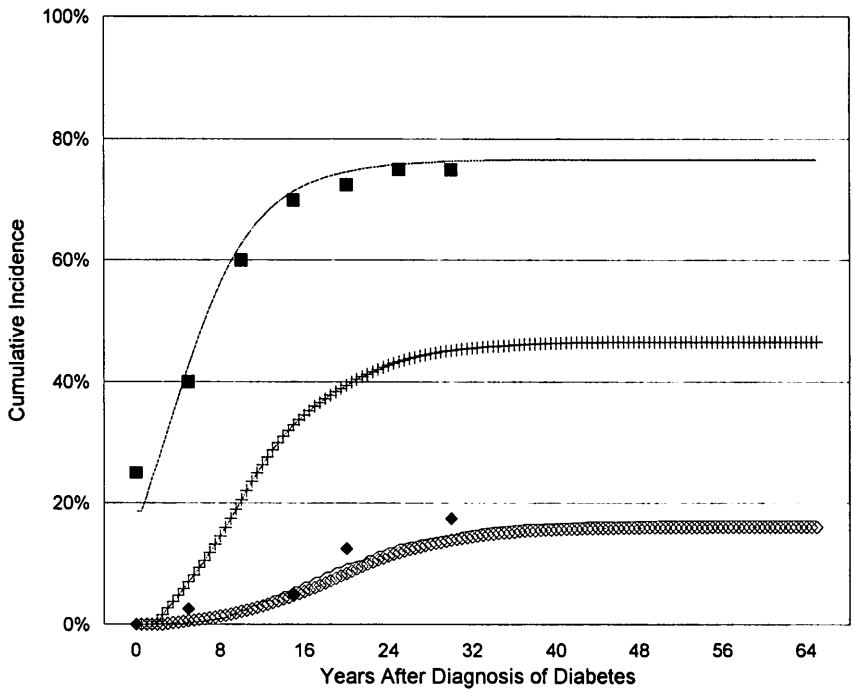

Figure 2—*Comparison of model-predicted cumulative incidence of retinopathy health states with data from WESDR. Cumulative incidence of BDR (■), ME (+), PDR (◇), and blindness (—) in non-Hispanic whites. The lines are model predictions of cumulative incidence. Point estimates for BDR and PDR (◆) are taken from Klein and Klein (8). The 4-year incidence of ME in WESDR was 5.2%; however, detailed incidence data by duration of diabetes are not published (8).*

RESULTS — BDR, proliferative retinopathy (PDR), and ME are predicted in 76, 16, and 47%, respectively, of non-Hispanic whites, similar to the rates in WESDR (Fig. 2) (8). Blindness is predominantly from ME and is predicted in 17% of subjects, with only 2–3% of blindness from PDR. In the mixed ethnicity cohort, BDR, PDR, ME, and blindness are predicted in 79, 19, 52, and 25%, respectively (Table 3). The relative risk of blindness varied from 1.3–2.3 in minorities (Table 3).

Forty-four percent of non-Hispanic whites develop MA, which is comparable to WESDR data (44% after 25 years of diabetes) (Table 3, Fig. 3) (14). The cumulative incidence is 80% in American Indians, which is comparable to the rate in Pima Indians after 15 years of diabetes (16). Thirty-three percent of non-Hispanic whites develop GPR, which is comparable to the cumulative incidence of 30–40% in the Rochester Study 25–30 years after diagnosis of diabetes (Fig. 3) (17). In WESDR, the cumulative incidence was 34% after 10 years of diabetes (32). ESRD is predicted in 14% of non-Hispanic whites, which is comparable to the rate in Rochester in patients without baseline proteinuria (Fig. 3) (18). MA, GPR, and ESRD are predicted in 53, 40, and 17% of the mixed ethnicity cohort, respectively (Table 3). The relative risk of ESRD varies from 1.3–3.0 in minorities (Table 3).

The predicted cumulative incidence of symptomatic distal sensorimotor neuropathy is 24% in non-Hispanic whites (Fig. 4) (20), and first LEA occurs in 13% (22). The rates are 31 and 17% in the mixed ethnicity cohort. A second amputation is predicted in 61% of those experiencing a first amputation. The relative risk of LEA varied from 1.6–2.9 in minorities (Table 3) (10,11,15). Cardiovascular events are predicted in 39% of the mixed ethnicity cohort, including those with ESRD. The relative risk compared with non-Hispanic whites with diabetes varies from 0.7 in African-Americans to 1.1 in Asian-Americans. The higher rates predicted in American Indians reflect the higher smoking rates in men of all ages and women 18–43 years old, and lower HDL cholesterol in women (see APPENDIX B).

Predicted life expectancy is inversely proportional to the relative risk for non-CVD death. If a coefficient of 1 is used (diabetic equals nondiabetic non-CVD risk), the predicted life expectancy is 23 years after diagnosis of diabetes at age 51 years. This is ~5 years less than the life expectancy (~28 years) for a nondiabetic person of the same age (29). Using the coefficient of 1, higher rates of blindness, ESRD, and LEA are predicted than are observed in the reference populations. In contrast, simulations using a coefficient of 2.75 predicted life expectancy of 17 years, which is ~10 years less than life expectancy in middle-aged people in the U.S. without diabetes (29). This is the lower limit of life expectancy seen in observational studies of NIDDM (29).

Patients developing diabetes earlier in life are predicted to experience more complications (Table 4). However, predicted age at death increases with age at diagnosis of diabetes and is 12 years longer for 65-year-old people than for 35-year-old people. Predicted CVD peaks at age 45 (40–50) and then declines, reflecting lower CVD rates in those surviving beyond age 55 years.

CONCLUSIONS — Our goal was to

Table 3—*Model predictions of complications in non-Hispanic whites and the mixed ethnicity cohort*

	Mixed cohort	Non-Hispanic whites	African-Americans	Hispanic Americans	Asian-Americans	American Indians
Average age at diagnosis of diabetes	51	52	49	46	52	46
Predicted average life expectancy after diagnosis (years)	17	17.3	14.8	19.0	20.5	22.5
	Cumulative incidence %			*Relative risk to non-Hispanic whites*		
BDR (R2)	79	76	1.1	1.2	1.1	1.2
PDR (R3)	19	16	1.6	2.6	1.3	2.7
ME (R4)	52	47	1.4	1.7	1.2	1.7
Blind (R5)	19	17	1.3	2.1	1.3	2.3
MA (N2)	53	44	1.8	2.1	1.1	1.9
GPR (N3)	40	33	1.7	2.2	1.2	2.0
ESRD (N4)	17	14	1.7	2.7	1.3	3.0
Diabetic distal sensorimotor neuropathy (Nu2)	31	24	1.9	2.2	1.2	2.4
LEA (Nu3)	16	13	1.6	2.3	1.2	2.9
CVD (C2)	39	41	0.7	0.9	1.1	1.1

Relative risk of complications in populations with different ethnicity is shown. Predicted complications are in the mixed-ethnicity cohort and in non-Hispanic whites. The relative risk of complications is in comparison with non-Hispanic whites.

develop a model of NIDDM that incorporates most of the complications of the disease, to be used for analyzing the effects of preventive strategies and cost-effectiveness of treatment. This article is the first in a series of studies and describes the basic assumptions and working of the model. We show that the model is internally valid and predicts complication rates that are consistent with the observed rates in the reference populations. We extrapolate these rates to the U.S. population, recognizing that it is much more difficult to prove external validity without data on the entire U.S. population. Many assumptions were required because population-based incidence rates are not available for all ethnic groups or for all health states modeled. However, the model is intentionally conservative and is unlikely to overestimate the impact of complications.

Blindness, predominantly due to loss of central visual acuity, is predicted by the model to occur in 17% of non-Hispanic whites. Comparable data for blindness due to central acuity loss are not yet published for the WESDR, but the model rates for ME are based on WESDR data and have been used previously to model retinopathy (1). Blindness predicted by the model is less than the 10-year rate of visual impairment and doubling of the visual angle in the WESDR (30 and 27%, respectively) (8).

Model-predicted outcome rates for minorities are lower than reported in some studies (10,11,15). This may reflect differences in the reference populations among different studies, different susceptibility to complications for similar degrees of glycemic control, differences in glycemic control (24,25), effects of hypertension, or other unknown effects. For example, the relative risk of renal failure in black American populations is 2.6–5.6 (10), while the modeled relative risk is 1.7 (Table 3). This may reflect that we do not model renal failure in patients who have proteinuria at the time of diagnosis of NIDDM, who progress relatively rapidly to ESRD (18). They may have ESRD from other causes because they are older and are more likely to be men with hypertension and CVD (18).

Compared with a non-Hispanic white person with diabetes, the relative risk of CVD in minorities varies from 0.7 to 1.1. The multivariate method may not accurately reflect CVD risk in the populations

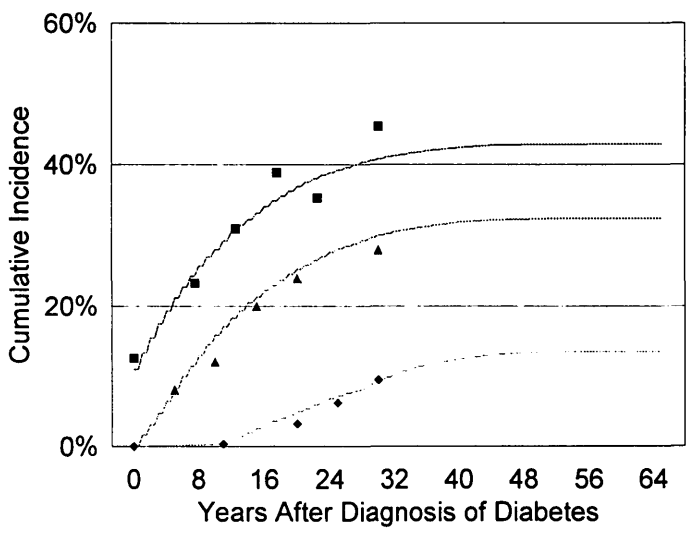

Figure 3—*Comparison of model-predicted nephropathy health states with data from reference populations. Cumulative incidence of MA (■), GPR (▲), and ESRD (◆) in non-Hispanic whites. The lines are model predictions of cumulative incidence. The point prevalence of MA is from Klein et al. (14). The point prevalence for GPR is from Ballard et al. (17) and for ESRD, from Humphrey et al. (18).*

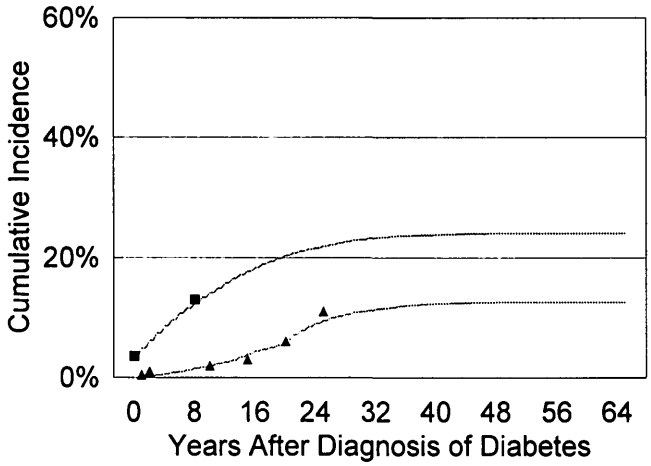

Figure 4—*Comparison of model-predicted neuropathy health states with data from reference populations. Cumulative incidence of symptomatic sensorimotor diabetic neuropathy (■) and LEA (▲) in non-Hispanic whites. The lines are model predictions of cumulative incidence. The point estimates for neuropathy are from NHANES II (baseline prevalence) and the Rochester Diabetes Study (19,20). The point estimates for first LEA are from Humphrey et al. (22).*

modeled (26). However, model predictions are consistent with the high rates of CVD in all populations with NIDDM, regardless of ethnicity.

The mortality model may influence the development of complications, since patients who live longer have longer exposure to hyperglycemia. To determine the effect of the mortality assumptions, we tested various approaches to modeling mortality risk that have in common the age-, sex-, and race-specific mortality rates for the general population. A method based on retinopathy status resulted in unusually long survival times for patients with ESRD (1). A method based on nephropathy status, with diabetes-attributable risk distributed across the nephropathy health states (37, 68, and 100% for no MA, MA, and GPR, respectively), yielded similar survival predictions but did not specifically model cause of death. Because we wanted to model CVD as a cause of death, the method used in the present model was developed. We used CVD risk and mortality risk from the U.S. Renal Data System for those with diabetes-related kidney failure, since CVD and renal disease are the major causes of death in NIDDM. This method predicts an average twofold overall increase in mortality risk, resulting in a 10-year decrease in life expectancy. These are the features of mortality risk in middle-aged people with NIDDM in the U.S. (29).

This analysis suggests that reducing mortality risk in people with diabetes may increase the prevalence of microvascular complications due to longer exposure to hyperglycemia. This is consistent with the increasing prominence of diabetes in the ESRD program in the U.S., in an era when CVD mortality is decreasing.

The incidence rates for complications are derived from data from reference populations, where available, and the cumulative incidence curves closely follow the observed rates of complications in these populations. Caution is urged in using the model to predict rates of complications in other populations, where the hazard rates may vary, or in individuals, where individual susceptibility, comorbidity, and other risk factors, such as hypertension, may significantly alter the risks. In addition, we have used an exponential model to derive constant hazard rates that fit the reference population data. The model may incorrectly predict complications if other hazard rates apply and, particularly, if hazard rates change with time as a function of other risk factors, such as hypertension.

In summary, a probabilistic model was developed that predicts vascular complications in patients with newly diagnosed NIDDM. The model provides reasonable estimates of the burden of vascular disease and is suitable for analyzing the impact of preventive treatments of NIDDM on disease outcomes in cohorts with a different age, sex, and ethnic mix.

APPENDIX A — Incidence rates (hazard rates, λ) are calculated from cumulative incidence data using an exponential model:

$$\lambda = \mathrm{Ln}\,(1/(1 - E_{obs}))/T_{obs} \qquad (1)$$

where λ is the exponential hazard rate, Ln is the natural logarithm, E_{obs} is the proportion of events in the population at risk, and T_{obs} is the period of observation over which E_{obs} develops. This relationship is used to estimate transitional probabilities between health states in the following manner.

If the sequential development of a complication is State 1 (no complication) → State 2 (intermediate stage) → State 3 (end-stage) and E_{obs2} is the cumulative incidence of State 2 at time T_{obs2}, the exponential rate for State 2, using Eq. 1, is

$$\lambda_2 = \mathrm{Ln}\,(1/(1 - E_{obs2}))/T_{obs2}. \qquad (2)$$

In the same population, if E_{obs3} is the cumulative incidence of State 3 at time T_{obs3}, the exponential rate for State 3 in the

Table 4—*Effect of the age at the time of clinical diagnosis of diabetes on model-predicted outcomes*

Age of cohort (years) [mean (range)]	Cumulative incidence (%) (average person-years with complication predicted)			Predicted cumulative incidence of CVD	Predicted average life expectancy	Predicted average death age
	Blindness	ESRD	LEA			
25 (20–30)	45 (7.1)	47 (1.5)	36 (5.7)	40	33	58
35 (30–40)	35 (4.6)	33 (0.8)	29 (3.7)	43	27	62
45 (40–50)	24 (2.5)	19 (0.4)	19 (1.9)	44	21	67
55 (50–60)	14 (1)	9 (0.13)	11 (0.8)	40	14	69
65 (60–70)	6 (0.4)	3 (0.04)	4 (0.3)	35	9	74
75 (70–80)	2 (0.11)	0.01 (0.004)	2 (0.1)	25	5	80

Cohorts were modeled with diagnosis of diabetes at average ages of 25, 35, 45, 55, 65, and 75 years. Blindness, vision loss equating to legal blindness; ESRD, end-stage renal disease requiring renal replacement therapy; LEA, first lower-extremity amputation.

population is

$$\lambda_3 = \text{Ln}\,(1/(1 - E_{obs3}))/T_{obs3}. \quad (3)$$

λ_3 is the hazard rate for the entire population at risk, but will underestimate the risk in those with Health State 2. The conditional hazard rate for progression from State 2 to State 3 is approximated by combining equations 2 and 3, as follows:

$$\lambda_{2\rightarrow3} = \text{Ln}\,(1/(1 - E_{obs3}/E_{obs2}))/(T_{obs3} - T_{obs2}), \quad (4)$$

where E_{obs3}/E_{obs2} is the proportion of those in State 2 who have progressed to State 3, and $T_{obs3} - T_{obs2}$ is the difference in median time to State 2 and State 3.

For example, in the WESDR, the median time to MA is ~4 years after diagnosis of diabetes, when ~20% have MA. Using Eq. 1,

$$\lambda_{MA} = \text{Ln}\,(1/(1 - 0.2))/4 = 0.055. \quad (5)$$

In addition, the median time to development of GPR is ~15 years, at which time ~15.5% have proteinuria. Using Eq. 1,

$$\lambda_{Prot} = \text{Ln}\,(1/(1 - 0.155))/15 = 0.0112. \quad (6)$$

The transitional probability for progression from MA to proteinuria is approximated by using Eq. 4,

$$\lambda_{MA\rightarrow Prot} = \text{Ln}\,(1 - 0.155/0.20))/(15 - 4) = 0.1356.$$

Note that $(\lambda_{MA\rightarrow Prot})/\lambda_{Prot} = 0.1356/0.0112 = 12.1$. The conditional transition probability for progression from MA to proteinuria is ~12 times the nonconditional rate because the population at risk for proteinuria is limited to those with MA.

APPENDIX C: GLOSSARY OF TERMS AND PHRASES

Monte Carlo

Term used to describe a modeling technique that uses a probabilistic approach, usually depending on random numbers, to control transitions between health states. For example, an event (renal failure) occurs if a random number between 0 and 1 is less than the incidence of renal failure in those with proteinuria (for example, 10%/year). Used interchangeably with "probabilistic".

Hazard rate

The risk of an event occurring in time t in

APPENDIX B: CVD RISK FACTORS

Prevalence of smoking: U.S. people with diabetes (24,25)

Age (years)	Men	Women
18–43	41	25
44–64	27	22
65+	13	12

Data are %.

Relative smoking rates by race and ethnic origin (derived from smoking prevalence) (24,25)

	Non-Hispanic white	African-American	Hispanic American	Asian-American	American Indian
Men					
Age (years)					
18–43	0.95	1.09	1.12	0.95	1.2
44–64	0.83	1.68	1.03	0.83	1.03
65+	0.94	1.13	1.97	0.94	1.97
Women					
Age (years)					
18–43	1.06	0.98	1.38	1.06	1.38
44–64	1.05	0.97	0.6	1.05	0.6
65+	1.09	0.57	0.93	1.09	0.93

Smoking risk equals prevalence by sex and age × relative risk by sex, age, and ethnicity.

Mean systolic blood pressure (mmHg) in people with diabetes

Age (years)	Non-Hispanic white	African-American	Hispanic American	Asian-American*	American Indian†
20–44	115	122	118	115	118
45–64	128	130	129	140	130
65–74	146	138	133	146	133

*Same as non-Hispanic whites, except values for ages 45–64 (25). †Same as Hispanic Americans, except values for ages 45–64 (11). Men add 1 mmHg, women subtract 1 mmHg (24,25).

Mean total serum cholesterol (mg/dl) in people with diabetes

Age (years)	Non-Hispanic white	African-American	Hispanic American	Asian-American*	American Indian†
20–44	204	204	201	204	201
45–64	207	198	191	228	194
65–74	232	216	224	232	224

*Same as non-Hispanic whites, except values for ages 45–64 (25). †Same as Hispanic Americans, except values for ages 45–64 (11). Men subtract 4 mg/dl, women add 3 mg/dl (24,25).

Mean HDL cholesterol (mg/dl) in people with diabetes

	Non-Hispanic white	African-American	Hispanic American	Asian-American	American Indian
Female	50	53	42	61	44
Male	40	50	38	45	40

Data are from NHANES II and HHANES (Hispanic Health and Nutrition Examination Survey) (24,25). Distributions for Mexican-Americans are used to represent risk factors in all Hispanic populations.

an exponential model is $1 - e^{(-\lambda t)}$. The "hazard rate" is the value for λ.

Transition probability

This term is used to describe the incidence of progressing to the next higher health state (e.g., from MA to gross proteinuria or from no retinopathy to background retinopathy).

Sampling probability distributions

This refers to the process by which the simulation software samples a probability distribution using Latin Hypercube sampling (stratified sampling without replacement) (@Risk, Palisades). For example, the age distribution of the cohort in the model (Table 2) is specified using an @Risk command for Excel as follows:

=RiskHistogrm (25, 75, {0.1606, 0.1663, 0.2135, 0.1868, 0.2727})

Each time the spreadsheet model is calculated, an age is drawn from the range of 25–75, with 0.1606 falling in the range of 25–35, 0.1663 falling in the range of 35–45, etc. After sufficient numbers of ages are sampled (drawn from the distribution), the average will be 51.4 years, the average of the cohort simulated by the model. Similar histogram functions are used to describe the frequency distributions for race, cholesterol, systolic blood pressure, and high-density cholesterol in the model, and are "sampled" to define the demographics and risk factors as each patient's life is "created" in the model and simulated.

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