A Computer Simulation Model of Diabetes Progression, Quality of Life, and Cost

HONGHONG ZHOU, PHD[1]
DEANNA J.M. ISAMAN, PHD[1]
SHARI MESSINGER, PHD[1]
MORTON B. BROWN, PHD[1]
RONALD KLEIN, MD, MPH[2]
MICHAEL BRANDLE, MD, MS[3,4]
WILLIAM H. HERMAN, MD, MPH[3,4]

OBJECTIVE — To develop and validate a comprehensive computer simulation model to assess the impact of screening, prevention, and treatment strategies on type 2 diabetes and its complications, comorbidities, quality of life, and cost.

RESEARCH DESIGN AND METHODS — The incidence of type 2 diabetes and its complications and comorbidities were derived from population-based epidemiologic studies and randomized, controlled clinical trials. Health utility scores were derived for patients with type 2 diabetes using the Quality of Well Being–Self-Administered. Direct medical costs were derived for managed care patients with type 2 diabetes using paid insurance claims. Monte Carlo techniques were used to implement a semi-Markov model. Performance of the model was assessed using baseline and 4- and 10-year follow-up data from the older-onset diabetic population studied in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).

RESULTS — Applying the model to the baseline WESDR population with type 2 diabetes, we predicted mortality to be 51% at 10 years. The prevalences of stroke and myocardial infarction were predicted to be 18 and 19% at 10 years. The prevalences of nonproliferative diabetic retinopathy, proliferative retinopathy, and macular edema were predicted to be 45, 16, and 18%, respectively; the prevalences of microalbuminuria, proteinuria, and end-stage renal disease were predicted to be 19, 39, and 3%, respectively; and the prevalences of clinical neuropathy and amputation were predicted to be 52 and 5%, respectively, at 10 years. Over 10 years, average undiscounted total direct medical costs were estimated to be $53,000 per person. Among survivors, the average utility score was estimated to be 0.56 at 10 years.

CONCLUSIONS — Our computer simulation model accurately predicted survival and the cardiovascular, microvascular, and neuropathic complications observed in the WESDR cohort with type 2 diabetes over 10 years. The model can be used to predict the progression of diabetes and its complications, comorbidities, quality of life, and cost and to assess the relative effectiveness, cost-effectiveness, and cost-utility of alternative strategies for the prevention and treatment of type 2 diabetes.

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Type 2 diabetes is associated with long-term complications that ultimately cause more cases of adult blindness, renal failure, and amputation than any other disease in the U.S. (1). In addition, people with type 2 diabetes are at increased risk for stroke and myocardial infarction, and mortality rates for people with type 2 diabetes are about twice those for people without diabetes (2). Because of the high morbidity, mortality, and cost associated with type 2 diabetes, there has been great interest in identifying strategies for the prevention and treatment of type 2 diabetes and in assessing the impact of those strategies on survival, disease progression, complications, comorbidities, quality of life, and cost.

To address these issues, we have developed a comprehensive model that synthesizes information on the major complications and comorbidities of type 2 diabetes. Our model differs from previously published models (3–7) in that it predicts the onset and progression of type 2 diabetes; incorporates features to assess the impact of medical screening, diagnosis, and treatment compliance on outcomes; and integrates new data on health utilities and direct medical costs.

RESEARCH DESIGN AND METHODS

Model structure

The model is based on the assumption that the natural history of type 2 diabetes and its complications and comorbidities can be described by a series of discrete health states that represent the progression of glucose tolerance (normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes), the microvascular and neuropathic complications of type 2 diabetes (retinopathy, nephropathy, and neuropathy), and the two major comorbidities (stroke and coronary heart disease [CHD]). Monte Carlo techniques are used to model disease progression. At each step, a uniform random number between zero and one is generated and is compared with the transition probability for progression from the current health state to the subsequent health state. If the random number is less than or equal to the transition probability, the transition occurs and is irreversible.

The probabilities of transition between health states depend on background variables, the actual health state, and treatment. The actual health state is the individual's true state of glucose tolerance, complications, and comorbidities. The diagnosed state is the level at

From the [1]Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; the [2]Department of Ophthalmology, University of Wisconsin, Madison, Wisconsin; the [3]Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; and the [4]Department of Epidemiology, University of Michigan, Ann Arbor, Michigan.

Address correspondence and reprint requests to William H. Herman, MD, MPH, University of Michigan Health System, 3920 Taubman Center, 1500 East Medical Center Dr., Ann Arbor, MI 48109-0354. E-mail: wherman@umich.edu.

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Abbreviations: CHD, coronary heart disease; ESRD, end-stage renal disease; QWB-SA, Quality of Well Being–Self-Administered; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

which the individual is diagnosed. This may be less than or equal to the actual health state depending on whether the individual is examined while in the actual health state. The treatment state is the level of treatment that the individual is receiving. Treatment depends on the probability that a subject is examined and diagnosed as being in a health state and the probability that the subject complies with the treatment prescribed for the health state. The treatment state may be less than or equal to the level appropriate for the diagnosed state depending on patient compliance. In the model, we assumed that if examined, an individual is properly diagnosed. However, in the absence of examination, the diagnosed state remains unchanged. If diagnosed, we assume that appropriate treatment is prescribed even though the individual may decline it at some specified level of probability.

Figure 1 shows the structure of the simulation model. Background variables for each subject are age, age at diagnosis of diabetes, length of time in the current health state, sex, race, HbA_{1c} (A1C), BMI, systolic and diastolic blood pressure, hypertension, serum total cholesterol level, and smoking status. For each subject, the model initializes the values of the background variables and then advances the subject through a specified number of years or until death. Each year, the model first updates the background variables and then loops through the glucose tolerance, complications, and comorbidities incidence matrices. The glucose tolerance state is updated first using an algorithm that depends on A1C level and current status. If a subject does not have diabetes in the current year, the model does not allow progression of microvascular or neuropathic complications but does allow progression to stroke and CHD. For each complication and comorbidity, the current state is first updated, which depends on current level of background variables, the actual and treatment states from the previous year, and disease progression. Then, examination (thus diagnosis) and compliance to recommended treatment are determined, both of which depend on background variables and both the actual and diagnosed states. At the end of the year, health utilities and costs are computed and survival is assessed. The model accumulates statistics on background variables, health states, health utility scores, and direct medical costs. At the end of the simulation, statistics on health states, utilities, and costs are summarized, and the results can be used to compare alternative prevention and treatment strategies. The model was implemented in SAS version 6.12 (SAS Institute, Cary, NC). In this analysis, baseline characteristics of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) cohort with type 2 diabetes were used to initialize the simulation and to evaluate the performance of the model (8–10).

Disease model

Transition probabilities for the disease model were developed by performing reviews of the epidemiology of type 2 diabetes, diabetic retinopathy, nephropathy, neuropathy, stroke, and CHD and by developing data to describe the incidence and prevalence of these complications and comorbidities (Fig. 2 and online appendix [available at http://care.diabetesjournals.org]) (11–32). Blindness was defined by severe visual impairment (best corrected visual acuity of 20/200 or worse).

Health utility model

The health utility model provides health utility scores that account for demographic factors, treatments, complications, and comorbidities. The health utility score ranges from zero to one, where zero represents death and one represents perfect health. The progression of disease results in a decrease in the health utility scores. Utility scores for type 2 diabetic subjects were obtained by relating utility scores derived from the Quality of Well Being–Self-Administered (QWB-SA), a validated multiattribute utility model derived from community-based preference assessments, to self-reported health status. Specifically, QWB-SA–derived health utility scores were fit by a multiple linear regression model to demographic and disease state variables for type 2 diabetes. Variables with multiple categories were represented by indicator variables. In the fitting process, all variables were initially entered into the regression model. We computed the estimates of the variables, and we noted those variables with adjacent levels that were not in order of increasing severity. Adjacent inconsistently ordered levels of one variable were then combined, and the model was run again. The process was repeated in a stepwise fashion until the ordering of all variable coefficients increased in severity (33). Blindness was defined by patient self-report.

Table 1 presents utility scores and penalty functions employed in the model. On average, the health utility score for a nonobese, diet-controlled, type 2 diabetic man without complications or comorbidities is 0.69. The utility score for a nonobese, diet-controlled woman with type 2 diabetes and no microvascular, neuropathic, or cardiovascular complications is 0.65. Blindness, dialysis, symptomatic neuropathy, foot ulcers, amputation, debilitating stroke, and congestive heart failure result in substantial decrements in utility scores. For example, our model suggests that the health utility score for a white woman with insulin-treated type 2 diabetes, treated high blood pressure, and end-stage renal disease (ESRD) is 0.53 ($0.689 - 0.038 - 0.034 - 0.011 - 0.078 = 0.53$).

Cost model

The cost model provides year 2000 patient-level direct medical costs that account for demographic factors, treatments, complications, and comorbidities. Subjects represent the employed, elderly, poor, and disabled type 2 diabetic population of southeastern Michigan (34). Empiric health states were assessed using patient interviews and medical record review, and costs were assessed from paid health insurance claims at the patient level. Medical encounter and/or claims data were obtained from a health maintenance organization to describe inpatient, outpatient, laboratory, and pharmacy utilization for each subject over the year immediately preceding the subjects' interview. Costs reflect the health maintenance organization's contracted payment or reimbursement rates and represent direct medical costs from the perspective of a large health system (34).

Table 1 summarizes the cost model. The disease state–related cost function is multiplicative. The median annual direct medical cost for a diet-controlled white man with type 2 diabetes, BMI 30 kg/m^2, and without microvascular, neuropathic, or cardiovascular risk factors or complications is $1,684. The cost for a diet-controlled white woman with type 2 diabetes, BMI 30 kg/m^2, and without complications or comorbidities is $2,105. Insulin treatment, presence of proteinuria, history of stroke, history of CHD, and ESRD result in substantial increments in cost. The costs for acute events are additive to the costs associated with disease states. The median, total, 1-year direct

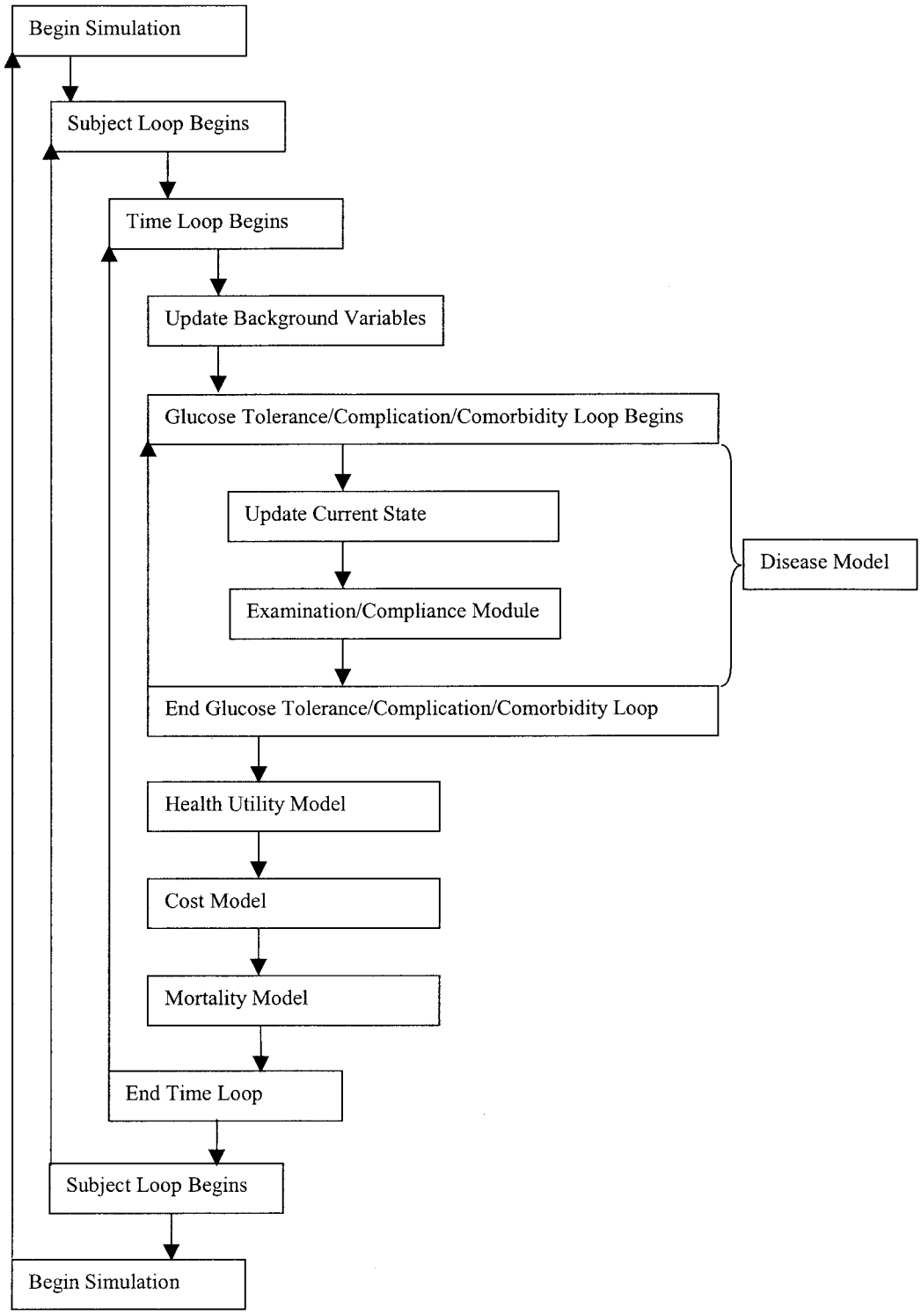

Figure 1—*Structure of the simulation model.*

medical costs for incident stroke, myocardial infarction, and amputation are $27,000, $25,000, and $38,000, respectively (34).

Mortality model

The mortality model assumes that an individual can die from one of four causes: ESRD, stroke, CHD, and nonrenal noncardiovascular causes. The first three causes are related to paths associated with diabetes progression and are implemented in the disease model. Death due to nonrenal, nonstroke, and non-CHD causes is implemented in the mortality module.

To model causes of death, renal, stroke, CHD, and nonrenal, noncardiovascular mortality risks are calculated for each patient for each year of life. Age-, sex-, and race-specific diabetic ESRD mortality risks are obtained from the U.S. Renal Data System (23). Estimates of stroke and CHD mortality risk are those developed by the U.K. Prospective Diabetes Study (12). Estimates of nonrenal, nonstroke, and non-CHD mortality are taken

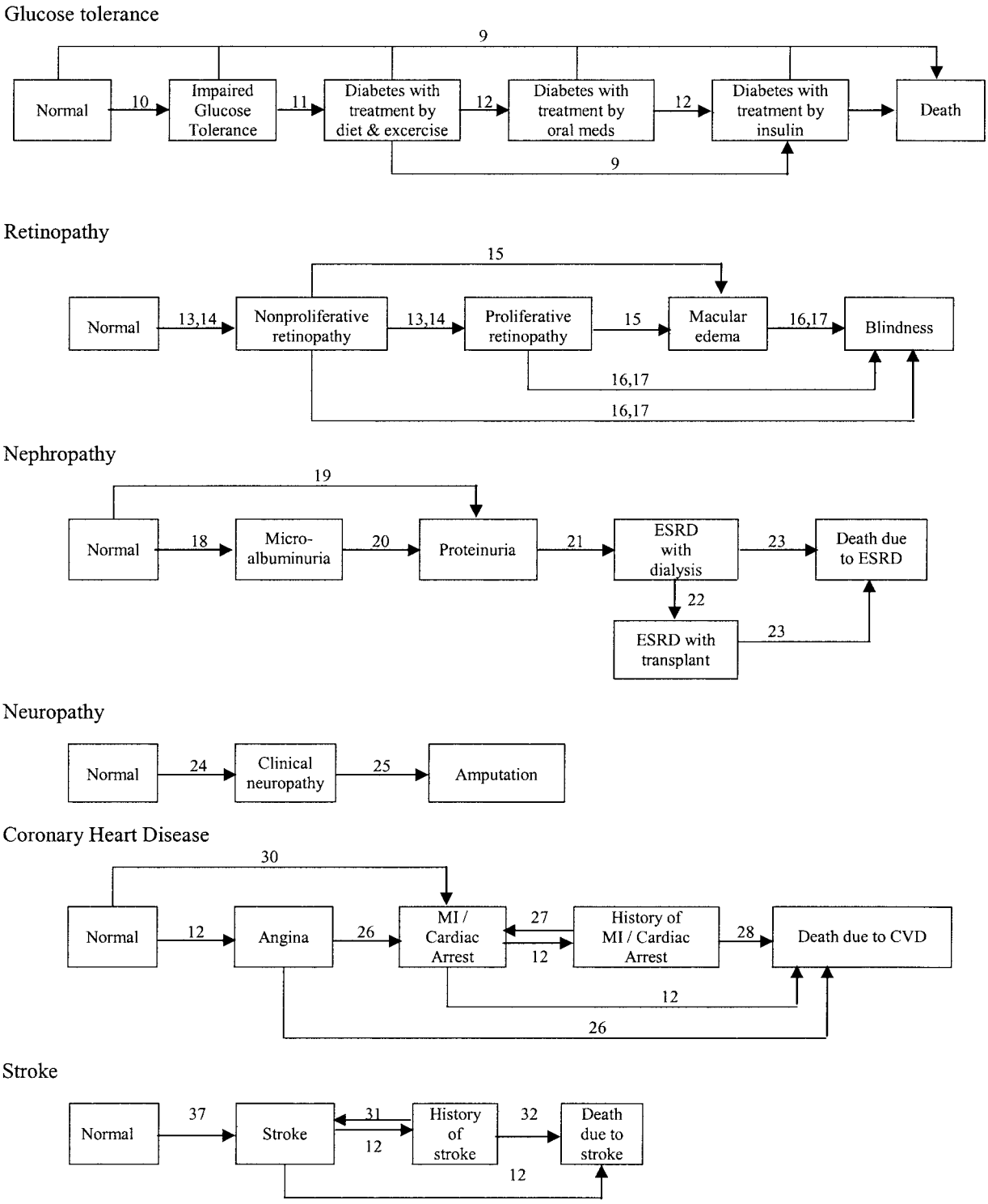

Figure 2—*Disease states and progression. MI, myocardial infarction.*

from the age-, sex-, and race-specific mortality for the U.S. population (9).

Since we modeled mortality on four different disease paths simultaneously, we took precautions to avoid overestimating total mortality. An individual was assumed to be at risk to die from the complication with the highest mortality risk for the current state. For example, a patient may have ESRD and may have experienced a myocardial infarction. If his or her mortality risk from CHD is higher than that from ESRD and other causes, then mortality will depend only on the risk associated with CHD. In this way, the model avoids overestimating total mortality and is intentionally conservative.

RESULTS — To test the validity of the computer simulation model, we applied it

Table 1—*Health utility scores and direct medical costs associated with demographic characteristics, treatment, diabetes complications, and comorbidities*

	Health utility score 0.689	Cost $1,684	
Baseline	Penalty ± SE	Increment ± SE (log_{10})	Multiplier for cost
Sex			
Female	−0.038 ± 0.007	0.095 ± 0.025	1.25
Race			
African American	NA	−0.088 ± 0.036	0.82
BMI (kg/m^2)			
Obese	−0.021 ± 0.007		
Every unit over 30 kg/m^2		0.004 ± 0.002	1.01
Diabetes intervention			
None or diet only	NA	NA	NA
Oral antidiabetic agents	−0.023 ± 0.013	0.040 ± 0.056	1.10
Insulin	−0.034 ± 0.013	0.200 ± 0.058	1.59
Retinopathy			
Blind in one eye only	−0.043 ± 0.011	*	*
Blind in two eyes	−0.170 ± 0.011	*	*
Nephropathy			
Microalbuminuria	−0.011 ± 0.009	0.067 ± 0.048	1.17
Proteinuria	−0.011 ± 0.009	0.113 ± 0.036	1.30
ESRD with dialysis	−0.078 ± 0.026	1.023 ± 0.183	10.53
Neuropathy			
Tingling and burning	−0.060 ± 0.010	NA	NA
Neuropathy	−0.065 ± 0.008	*	*
Sores	−0.099 ± 0.013	NA	NA
History of amputation	−0.105 ± 0.020	*	*
Stroke			
Transient ischemic attack or stroke	−0.044 ± 0.012	0.113 ± 0.035	1.30
Stroke with residual	−0.072 ± 0.016	NA	NA
Cardiovascular disease			
Congestive heart failure	−0.052 ± 0.011	NA	NA
Angina	NA	0.239 ± 0.061	1.73
History of myocardial infarction	NA	0.278 ± 0.029	1.90
Peripheral vascular disease	NA	0.116 ± 0.028	1.31
High blood pressure, high blood pressure with meds (combined)	−0.011 ± 0.007	0.092 ± 0.028	1.24

*Variables did not enter the model. NA, variables were not applicable.

to the baseline characteristics of the WESDR population with type 2 diabetes (8–10). The WESDR is a population-based study of individuals with diabetes in southern Wisconsin. At baseline, 1,370 people with type 2 diabetes were examined, 1,223 of whom provided demographic data and information on their complications and comorbidities. Nine hundred eighty-seven were examined in the 4-year follow-up and 533 in the 10-year follow-up. The main reason for nonparticipation over the 10-year course of the study was death. We used the model to predict survival and diabetes progression for the 1,223 patients examined at baseline over 10 years and compared the results with the observed outcomes from follow-up examinations at 4 and 10 years. At baseline, the average age of these patients was 66.4 years and the average duration of diabetes was 12.5 years.

The total numbers of deaths over 4 and 10 years were predicted to be 285 ± 4 and 621 ± 6, respectively, compared with 289 and 678 observed in the WESDR over these periods of follow-up (Table 2). The model predicted 23 and 51% mortality at 4 and 10 years, respectively, similar to that observed in the WESDR (24 and 55%, respectively). Of 285 deaths predicted to occur over 4 years, 59% were due to CHD, 6% to stroke, and 1% to renal disease. For 621 subjects who were predicted to die in 10 years, 57% were due to CHD, 7% to stroke, and 2% to renal disease. The model-predicted mortality due to CHD was higher and that due to stroke was lower than was observed in the WESDR (Table 2).

Table 3 illustrates the observed and predicted diabetes treatments and rates of microvascular, neuropathic, and cardiovascular complications at 4 and 10 years follow-up. The prevalence of treatment with oral antidiabetic medications and insulin were 23 and 69% at 10 years. The predicted prevalence of nonproliferative diabetic retinopathy and proliferative diabetic retinopathy were 45 and 16% at 10 years, respectively. In addition, 18% of the cohort was predicted to have macular edema at 10 years. Microalbuminuria, proteinuria, and ESRD rates were predicted to be 19, 39, and 3% at 10 years. At 10 years, 52% of the cohort had clinical neuropathy and 5% had amputations. At 10 years, 18% were predicted to have histories of stroke, 8% to have angina, and 19% histories of myocardial infarction or cardiac arrest.

Over 10 years, the average undis-

Table 2—*Observed and predicted mortality in the WESDR cohort with type 2 diabetes*

	Over 4 years		Over 10 years	
	WESDR	Model prediction	WESDR	Model prediction
Cause of Death				
Renal disease	5	2.8 ± 0.4	10	13.6 ± 1.5
Stroke	26	18.4 ± 2.3	64	44.0 ± 2.8
CHD	145	168.6 ± 5.0	296	354.4 ± 4.5
Diabetes	27	—	75	—
Other	84	95.2 ± 1.8	219	209.2 ± 6.8
Not coded	2	—	14	—
Overall	289 (24%)	285.0 ± 4.4 (23%)	678 (55%)	621.2 ± 6.2 (51%)

Data are means ± SE, unless otherwise indicated. —, no information

Table 3—*Observed and predicted percent prevalence of complications in the WESDR cohort with type 2 diabetes*

	Baseline	End of 4 years		End of 10 years	
	WESDR	WESDR	Model prediction	WESDR	Model prediction
Diabetes status					
Diabetes treated with diet and exercise	17.6	11.8*	13.5	11.6*	7.7
Diabetes treated with oral antidiabetic medication(s)	33.5	32.7*	27.0	27.3*	23.1
Diabetes treated with insulin	48.9	55.5*	59.5	61.2*	69.2
Diabetic retinopathy					
None	42.6	34.0*	30.9	21.9*	18.3
Nonproliferative retinopathy	42.0	47.0*	45.7	48.0*	44.7
Proliferative retinopathy	3.8	6.6*	8.8	8.8*	15.6
Macular edema	9.6	9.3*	12.5	17.9*	18.1
Blindness	2.0	3.0*	2.1	3.4*	3.3
Nephropathy					
None	78.8	58.3*	60.2	58.0*	39.0
Microalbuminuria	—	20.0*	12.0	16.6*	19.0
Proteinuria/macroalbuminuria	20.9	20.0*	26.6	24.2*	38.7
ESRD with dialysis	0.3	1.2*	1.1	0.8*	3.1
ESRD with kidney transplant	0	0.5*	0.1	0.4*	0.2
Neuropathy					
None	73.5	73.7	59.4	60.0	42.8
Clinical neuropathy	26.5	26.3	39.3	40.0	52.1
Neuropathy with amputation	—	—	1.4	—	5.1
Stroke					
Not present	90.2	86.4*	86.8	83.3*	81.6
Stroke occured	9.8	13.4*	13.2	16.7*	18.4
CHD					
Not present	77.9	74.9*	76.1	68.1*	72.9
Angina	5.7	10.0*	6.6	13.5*	7.7
History of cardiac arrest or myocardial infarction	16.4	15.2*	17.3	18.4*	19.4

*Calculated based on observed data. —, no information.

counted direct medical costs per person-year were predicted to be $7,100. The average utility score among survivors decreased from 0.58 at baseline to 0.56 at 10 years.

CONCLUSIONS — Our objective was to develop a model to predict the progression of diabetes and its complications and comorbidities and its quality of life and costs in order to permit the evaluation of the cost-utility of diabetes prevention and treatments strategies. This report describes the basic assumptions and structure of the model. We show that the model is internally valid in that the model-predicted outcomes for the WESDR cohort with type 2 diabetes are consistent with the observed WESDR outcomes over 10 years.

The model predicted the total number of deaths occurring in the WESDR cohort with type 2 diabetes at 4 and 10 years of follow-up with only minor differences from the observed numbers. The predictions of causes of death were not as close. The model assumed that a subject could only die from ESRD, stroke, CHD, and nonrenal, nonstroke, and non-CHD causes, whereas the WESDR classified deaths as occurring due to diabetes itself. In addition, since each subject had multiple risk factors for mortality, including all of the probabilities would have greatly overestimated the probability of death. Our approach, which assumed that an individual was at risk to die from the complication with the highest mortality risk, did not overestimate the probability of death but attributed more deaths to the causes with the highest probabilities. This may account for some of the observed differences in cause of death.

The model predicted that intensification of therapy with oral antidiabetic medications and insulin would be more aggressive than was observed in the WESDR cohort. At both 4 and 10 years, more type 2 diabetic patients were predicted to be treated with insulin than was observed in the WESDR. This discrepancy likely arose from the fact that in the model, intensification of therapy was based on the progressive rise in A1C observed in the U.K. Prospectives in Diabetes Study and on American Diabetes Association recommendations for intensification of therapy according to A1C levels (35). It is likely that the model's predictions are a better reflection of current standards of care than was observed in Wisconsin in the 1980s.

In general, the model's predictions of the development and progression of retinopathy were similar to that observed in the WESDR, although the model-predicted prevalence of proliferative retinopathy at 10 years was higher than the observed prevalence. The higher predicted prevalence of proliferative retinopathy may reflect the fact that the model predicted a higher prevalence of insulin treatment at 10 years, and insulin treatment, often begun as a result of the development of severe diabetes complications,

is associated with a higher incidence of proliferative retinopathy (14,15). It may also reflect the fact that retinopathy and nephropathy were modeled separately, and ESRD (but not retinopathy) was associated with an increased risk of mortality. Validation of the nephropathy model was limited by the fact that microalbuminuria was not measured at baseline in the WESDR cohort. In general, the model predicted a higher prevalence of proteinuria and ESRD with dialysis than was observed in the WESDR cohort. Predictions of the prevalence of clinical neuropathy also tended to be higher in the model. This may reflect the fact that the definitions of clinical neuropathy used in the WESDR (history only) and in the model (history and physical exam) were quite different. The model predictions of the prevalence of stroke and cardiovascular disease were quite similar to those observed in the WESDR cohort.

Like all simulation models, our model has limitations (36). Models and their results are not statements of scientific fact but aids to decision making. Models are used to integrate data from diverse sources of varying quality to make inferences about future economic, quality of life, and health outcomes and to provide data for decision making. We have validated our model on the basis of its ability to predict outcomes when tested under hypothetical conditions in which the results should be obvious and by its ability to predict outcomes as defined by a long-term epidemiologic study. Further studies are under way to evaluate the ability of the model to predict the outcomes of additional epidemiologic studies and clinical trials and outcomes obtained by other independently developed and programmed models.

In summary, we have developed and validated a model to predict the progression of diabetes and its complications and comorbidities and its quality of life and costs. In this report, the predicted rates are consistent with the observed WESDR data, and the model appears to be a valid representation of progression of type 2 diabetes and its complications and comorbidities.

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