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ORIGINAL ARTICLE

The Michigan Model for Coronary Heart Disease in Type 2 Diabetes: Development and Validation

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Abstract

Objectives: The aim of this study was to develop and validate a computer simulation model for coronary heart disease (CHD) in type 2 diabetes mellitus (T2DM) that reflects current medical and surgical treatments.
Research Design and Methods: We modified the structure of the CHD submodel in the Michigan Model for Diabetes to allow for revascularization procedures before and after first myocardial infarction, for repeat myocardial infarctions and repeat revascularization procedures, and for congestive heart failure. Transition probabilities that reflect the direct effects of medical and surgical therapies on outcomes were derived from the literature and calibrated to recently published population-based epidemiologic studies and randomized controlled clinical trials. Monte Carlo techniques were used to implement a discrete-state and discrete-time multistate microsimulation model. Performance of the model was assessed using internal and external validation. Simple regression analysis (simulated outcome $= b_0 + b_1 \times$ published outcome) was used to evaluate the validation results.
Results: For the 21 outcomes in the six studies used for internal validation, R^2 was 0.99, and the slope of the regression line was 0.98. For the 16 outcomes in the five studies used for external validation, R^2 was 0.81, and the slope was 0.84.
Conclusions: Our new computer simulation model predicted the progression of CHD in patients with T2DM and will be incorporated into the Michigan Model for Diabetes to assess the cost-effectiveness of alternative strategies to prevent and treat T2DM.

Introduction

In the past few decades, the medical management of type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia, as well as the medical and surgical management of cardiovascular disease (CVD), has changed dramatically. For the general population, uptake of and adherence to secondary prevention measures (aspirin, β-blockers, statins, and angiotensin converting enzyme [ACE] inhibitors) increased in patients hospitalized for coronary heart disease (CHD).[1] Rates of revascularization (coronary artery bypass grafting and percutaneous coronary intervention) have also increased in both the United States and Europe.[2–5] As a consequence, rates of many diabetes-related cardiovascular events have declined substantially in the past two decades.[6] In addition, mortality among diabetes patients experiencing myocardial infarction (MI) has fallen,[7] probably because of both the availability and use of tests to diagnose less severe and hence less life-threatening disease and the increased use of medical and surgical therapies. In addition, it is now recognized that medications, including ACE inhibitors,[8,9] β-blockers,[10–12] and statins,[13] have health benefits beyond their effects on biomarkers such as systolic blood pressure and low-density lipoprotein cholesterol.

Despite improvements in the management of T2DM, the prevalence of diabetes continues to increase globally. In 2012, 371 million people, or approximately 8.3% of the world's adult population, were estimated to have diabetes.[14] Diabetes also has enormous economic consequences. In 2012, 471 billion U.S. dollars were spent for healthcare for people with diabetes around the world.[15] Because of the high morbidity, mortality, and cost associated with T2DM, there is a need to develop models to simulate the long-term outcomes and costs of T2DM beyond the time horizon of clinical trials. Because CVD is the leading cause of morbidity and mortality in people with T2DM,[16,17] it is important that any computer

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model for T2DM incorporate a valid submodel for CHD. Unless that model simulates medication effects and surgical practices explicitly, it will not accurately predict the CVD outcomes observed in clinical studies. In addition, because each study enrolls a unique population, some older and some sicker, it is critical that simulation models account for patient heterogeneity.

The Michigan Model for Diabetes (MMD) is a discrete-state discrete-time microsimulation model designed to predict the progression of T2DM and its complications, comorbidities, quality of life, and cost and to assess the relative effectiveness and cost-utility of alternative strategies for the prevention and treatment of T2DM. The cycle length used in the MMD is 1 year (i.e., the status of subjects is updated yearly). The original model was composed of six submodels that simulated the progression of glucose tolerance (normal glucose tolerance, impaired glucose tolerance, and T2DM), three microvascular or neuropathic complications (retinopathy, nephropathy, and peripheral neuropathy), and two major macrovascular comorbidities (stroke and CHD).[18] The previously validated CHD submodel had a simple structure with five states including no CHD, angina, MI, survive MI, and CHD death. It did not include revascularization procedures or congestive heart failure (CHF). Although the transition between no CHD and MI was governed by the risk engine developed by the United Kingdom Prospective Diabetes Study (UKPDS) Research Group,[19] the other transition probabilities were not related to the levels of cardiovascular risk factors. In addition, the parameter estimates in the MMD were based on data abstracted from studies conducted in the 1980s and 1990s. As a result, the previous MMD CHD submodel no longer captures current clinical practices and does not accurately predict the outcomes of more recent clinical trials.

To our knowledge, none of the published, diabetes disease-state simulation models,[20–33] including the recently published UKPDS Outcomes Model 2,[34] takes into account currently available medical and surgical treatments. For the general population, various CHD policy models exist.[35] However, these CHD models do not reflect the current complexity of CHD management. The aim of this study was to develop a new CHD submodel that reflects contemporary CHD management in patients with T2DM and to validate the model against recently published trial results that were not used to develop the model.

Research Design and Methods

We have modified the structure of our CHD submodel for T2DM to accommodate revascularization procedures before and after a first MI, to allow for repeat MIs and repeat revascularization procedures, and to model CHF before and after MI. To account for heterogeneity among diabetes patients, we have incorporated risk equations from the UKPDS Outcomes Model[19] for the events of ischemic heart disease (defined as coronary artery disease without MI), MI, and death after MI. We have also developed a prediction equation for CHF based on data from the Cardiovascular Health Study (CHS),[36] which we then incorporated into our new CHD submodel (see Supplementary Data [available online at www.liebertonline.com/dia]).

We modified these equations to adjust for the direct benefits of aspirin,[37] ACE inhibitors,[8,9] β-blockers,[10–12] and statins[13] independent of their effects on biomarkers. We calibrated all the model parameters (including the baseline hazard parameters in the UKPDS Outcomes Model equations and the CHF risk equation) to recently published prospective observational studies and clinical trials.

Model structure

In keeping with the structure of the MMD, we developed the new CHD submodel as a discrete-state and discrete-time microsimulation model, in which the status of a subject is updated yearly. (Supplementary Figures S1 and S2 show the structure of the CHD submodel.) The model was implemented in the Indirect Estimation and Simulation Tool (IEST) using Python (version 0.85.0.0; February 27, 2012).[38]

There are two types of states in the model: annual states and event states (Supplementary Figs S1 and S2). Patients may stay in an annual state for one or more simulation cycles. Patients progress through event states, such as CHD procedures and MI, instantaneously and transit to other annual states.

A study based on the Global Registry of Acute Coronary Events reported that approximately 75% of diabetes patients who have nonfatal MIs have revascularization procedures performed in the first year following the MI.[39] Jensen et al.[40] showed that after revascularization, 17% of patients experience re-infarction in the first year following the index MI. In order to capture these events, we modeled both MI and repeat MI as modules that included multiple events that could occur within 1 year of the index MI. The MI and repeat MI modules share the same structure (Supplementary Fig. S2), although the transition probabilities for the two modules may differ (details described later in this section and in Supplementary Tables S2 and S3). In these modules, reaching the state of short-term survival after MI is equivalent to having had a nonfatal MI. The definitions used in the model are presented in Table 1.

Subject characteristics considered in the model include age, sex, race, age at diagnosis of T2DM, duration of diabetes, body mass index, systolic blood pressure, diastolic blood pressure, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, smoking status, and use of medications including aspirin, ACE inhibitors, β-blockers, statins, and antihyperglycemic treatments (e.g., intensive lifestyle therapy, monotherapy with an oral agent, dual oral therapy, basal insulin, and basal–bolus intensive insulin therapy).

For each subject, the model assigns the value of each baseline characteristic by simulating the values from distributions based on summary statistics for the variable in the population. It then advances the subject through a specified number of 1-year cycles or until death. In each cycle, the model first updates the values of the risk factors and then the state of CHD. Transition probabilities for updating the state of CHD are calculated based on the updated risk factors and the current state. At the end of each cycle, the model updates lifestyle risk factors (i.e., intensive life style intervention, smoking) and drug treatments (i.e., antihyperglycemic medications, aspirin, ACE inhibitors, β-blockers, and statins) according to levels of risk factors and the cardiovascular events that have occurred in the subject.

Table 1. Definitions of Health States

Health state	*Definition*
CAD without procedure	Angina or CAD (ischemic heart disease) confirmed by electrocardiogram, stress test, echocardiogram, cardiac catheterization, coronary calcium score, or magnetic resonance angiography
CHD procedures	Either coronary artery bypass grafting or percutaneous coronary intervention with coronary angioplasty with or without stenting
MI	Nonfatal MI (ICD-9 code 410), fatal vascular cardiac event (ICD-9 codes 410–414.9 or 428–428.9), or sudden death (ICD-9 codes 798–798.9)
CHF	CHF is defined by a constellation of symptoms (such as shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea) and physical signs (such as tachycardia, a gallop rhythm, a displaced point of maximal impulse, rales, and peripheral edema) that occur in a patient whose cardiac output cannot match metabolic need despite adequate filling pressures. CHF may be related to either systolic or diastolic cardiac dysfunction.
Repeat MI	MI more than 1 year after a first MI. The CHD model also allows repeat MI within the first year after the index MI as shown in Supplementary Figure S2.
Short-term survival following MI	An event state that patients who have survived 30 days after the index MI (nonfatal MI) pass through instantaneously and either enter the state of history of MI (no further CHD event during that year), revascularization procedure after MI, or CHF
CHD death	Cardiac death, including sudden cardiac death. Cardiac death is defined as death within 1 h to 30 days after a documented or probable MI, death from intractable CHF or cardiogenic shock, or other documented cardiac cause. Sudden cardiac death was defined as death occurring instantaneously or within 60 min of the onset of cardiac symptoms.

CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; ICD-9, International Classification of Disease, Ninth Revision; MI, myocardial infarction.

The full model accumulates summary statistics on risk factors, health states, utilities, and costs (available at www.med.umich.edu/mdrtc/cores/DiseaseModel/model.htm).

Model data sources and transition probabilities

Transition probabilities for the CHD submodel were developed using PubMed searches to identify prospective observational studies and clinical trials[39–47] that described various stages of CHD in patients with T2DM. Transition probabilities and references are reported in Supplementary Tables S1 and S2. Although there are large numbers of published studies of CHD in T2DM, direct information on individual transition probabilities is rare because of the complexity of the natural history and treatment of this disease (as shown in Supplementary Figs. S1 and S2). We selected our information sources based on three criteria: (1) whether an article presents sufficient information on baseline characteristics of the subjects and on the transition probabilities included in the model; (2) whether the treatment protocols reflect current standards of care; and (3) whether the results of the study are generalizable to the U.S. population with T2DM according to the opinions of the clinical experts on our team.

When computer models are used for comparative effectiveness research, study populations of interest often represent samples with specific demographic and clinical characteristics. For example, the baseline demographic characteristics of the population (age, duration of diabetes), risk factors (e.g., hemoglobin A1c, blood pressure, lipids, smoking status, etc.), baseline treatments, and baseline disease status (presence or absence of known CVD) may vary widely. Unfortunately, studies often do not provide estimates of how these factors affect the outcomes of interest. Similarly, only limited information can be obtained from incidence counts stratified by categorical variables such as age or sex. In many studies, the sample sizes are not large enough to obtain these estimates. In the previous version of the MMD CHD submodel, we used parameters with the single best estimate for each transition probability except for the transition from No CHD to MI. However, because of heterogeneity among subjects within studies and between studies in which subjects were selected with different inclusion and exclusion criteria and because of changes in medical practice over time, simulation models using parameters with only one estimate for each transition probability often have relatively poor predictive power and generalizability.

The UKPDS Outcomes Model[19] provides risk equations for several cardiovascular outcomes in T2DM patients (e.g., ischemic heart disease, MI, and CHF). However, there are drawbacks in applying these equations directly in a diabetes simulation model. More than three decades have passed since the UKPDS was initiated. Medical practice in the UKPDS reflected the standard of care in the United Kingdom in the 1980s, but diabetes management and the treatment of hypertension, dyslipidemia, and cardiovascular disease have changed substantially since then.[6] For example, the proportion of diabetes patients taking antihypertensive medications (ACE inhibitors, β-blockers, etc.) and statins has greatly increased. As a result, applying the UKPDS equations directly in a simulation model has poor or moderate discrimination and overestimates CHD risk for populations with T2DM under current medical treatment.[48,49]

To update the CHD submodel, we incorporated hazard equations from the UKPDS Outcomes Model[28] and calibrated

them to recent clinical studies to provide summary counts or cumulative risks to derive transition probabilities for our model. For ease of exposition, we refer to the studies that provide summary counts or cumulative risks as calibration studies. For each calibration, we first sampled baseline risk factors from probability distributions based on tables describing the demographic and clinical characteristics of the study population. We then ran the model and compared the outcomes from the simulation model with those reported in the study. While keeping the relative risk estimates for risk factors in the UKPDS Outcome Models unchanged, we adjusted the baseline hazard in the hazard equation to match the cumulative counts reported in the calibration study. These steps were repeated until a parameter estimate for the baseline hazard was found to provide model results as close to the calibration study results as possible.

Calibration studies usually involved more than one disease state and multiple transitions among states. In addition, different calibration studies overlapped with one another in terms of the transitions they described. Therefore, tuning a parameter for one study could change the simulation results for a study that was previously used for calibration. To simplify the procedure, we began calibration with the studies that reported outcomes that involved the fewest transitions and performed calibration iteratively among all calibration studies until calibration results became stable. For each calibration, a simulated population of 10,000 subjects was used. In addition, in order to incorporate risk factor effects into more transitions than those explicitly modeled in the UKPDS Outcomes Model, we applied the UKPDS equations to transitions that were not previously modeled. For example, for the transition from ''coronary artery disease without MI'' to ''CHD Procedure'' (path J in Supplementary Fig. S1), we also used the UKPDS MI hazard function. Our rationale was that subjects at higher risk for experiencing a future MI are more likely to undergo a revascularization procedure.

Both angina and MI increase the risk of CHF.[50,51] However, in the UKPDS risk equation, history of angina and MI are not included as risk factors for CHF. To obtain a better risk equation for CHF that quantifies the impact of angina and MI on CHF, we analyzed individual-level data from the CHS to develop a prediction model for CHF.[36] In the original CHS cohort, 862 subjects with diabetes had no history of CHF at the baseline visit, including 416 who had newly diagnosed diabetes (incident cohort) and 446 who had previously diagnosed diabetes (prevalent cohort). Duration of diabetes was not reported for the prevalent cohort.

In order to overcome the problem caused by missing duration of diabetes in the prevalent cohort and to make use of the information provided by this cohort, we used the following analysis strategy. First, we used a Cox proportional hazard regression model stratified by cohort type (i.e., prevalent cohort and incident cohort). This model allowed us to derive a nonparametric estimation of the baseline hazard function for each of the two cohorts separately, while using data from both cohorts to select predictors and estimate corresponding risk coefficients. A stepwise selection procedure with Akaike's Information Criterion was then used to select the best prediction model with nine predictors (from the original list of 13 candidate predictors). Second, in order to use the model for long-term prediction, we used a nonlinear regression model to fit a Weibull cumulative hazard function to the estimated nonparametric cumulative baseline hazard function of the incident cohort derived from the Cox proportional hazard model. The 10-year C-index[52] of the model is 0.699, which indicates acceptable discrimination. (See Supplementary Data for more details about this CHF prediction model.)

We also applied a multiplicative modifier to the transition probabilities to adjust for direct medication benefits (beyond risk factor modification) for UKPDS-derived risk equations used in the new CHD submodel, where the Medication Benefit Modifier for MI was set at the minimum of

1. If taking aspirin[37]: 0.8 for males (the risk for females was not changed)
2. If taking an ACE inhibitor or angiotensin receptor blocker[8]: 0.8
3. If taking a β-blocker[9,10]: 0.8 for subjects who are 70 years of age or older or African American, and 0.7 otherwise
4. If taking a statin[10]: 0.66.

In the CHF risk equation, the Medication Benefit Modifier was set at the minimum of

1. If taking an ACE inhibitor or angiotensin receptor blocker[9]: 0.75
2. If taking a β-blocker[12]: 0.8.

We assumed that the combined effect of multiple medications was equal to the maximum of the individual medication effects.

We used information from 12 published studies to derive our model parameters. Among these publications, we relied on two older studies, UKPDS and CHS, to define the structure of the prediction equations. The remaining 10 publications, all of which began enrollment after 1998, were used for calibration. To reflect the current rates of disease progression, we calibrated the transition probabilities from the UKPDS and CHS to these more recent epidemiologic studies and randomized controlled clinical trials. As a result, our new CHD submodel better reflects the development and progression of CHD in patients with T2DM receiving contemporary medical and surgical treatments.

Validation procedures

We validated the CHD submodel according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research Task Force.[53] We first tested and debugged the new CHD submodel. To assess the validity of the model, we performed both internal and external validation by comparing the model-simulated outcomes with the outcomes from published observational studies and clinical trials.

Internal validation was performed using the studies we used for model calibration. We used 21 outcomes and complications from six published cohort studies and randomized trials[40–42,44–46] using the new, stand-alone, CHD submodel. No other submodels from the MMD were implemented during the internal validation. In the first step, we used the baseline characteristics reported in the study to generate a simulation population of 20,000 subjects. For all subjects, risk factors, biomarkers, and medications were programmed to match the mean levels reported in the

Table 2. Internal Validation Results

Study (year)	Population studied	Demographic/ treatment group	Study length (years)	Outcome (cumulative incidence rate)	Results (per 1,000 PY)	
					Study	Model
Avogaro et al.[41] (2007)	A cohort of 6,032 women and 5,612 men sampled from a nationwide (Italian) network of hospital-based diabetes clinics was followed up for 4 years, 1998–2003.	Men	4	Non-AMI CAD	21.7	13.9
				MI	5.8	6.0
				Other CHD death	0.9	1.2
		Women	4	Non-AMI CAD	17.8	19.3
				MI	11.9	11.2
				Other CHD death	2.7	2.3
BARI 2D (Chaitman et al.[42]) (2009)	2,368 patients with angiographically defined CAD, randomized to receive early versus only if necessary revascularization strategies, 2001–2008	Prompt revascularization	5	MI	23.0	23.2
				Total cardiac death	11.8	9.0
Colhoun et al.[44] (2004)	Ages 45–75 years in the United Kingdom and Ireland with type 2 diabetes and one CVD risk factor but no history of CVD. Randomized cholesterol control trial, 1997–2002	Placebo	5	MI	11.5	7.4
				Other acute CHD death	0.8	1.4
				Procedures	3.4	4.8
EPHESUS (Deedwania et al.[45]) (2011)	Patients with history of diabetes in a multicenter, international (37 countries), randomized placebo-controlled trial that randomized 6,632 patients with AMI complicated with symptoms of heart failure, 1999–2004	Patients with history of diabetes mellitus	3	MI death	18.0	22.1
				MI	64.0	61.6
				Cardiovascular death	80.0	67.5
Jensen et al.[40] (2012)	Ages 56–72 years from Denmark with type 2 diabetes and ST-segment elevation MI treated with primary percutaneous coronary intervention, 2002–2008		1	MI	87.0	86.0
				Cardiac death	139.0	141.0
			3	MI	47.0	49.5
				Procedures	96.0	97.1
				Cardiac death	79.0	71.6
Mellbin et al.[46] (2011)	DIGAMI 2 trial: type 2 diabetes and suspected AMI randomized to three different management strategies, 1998–2006	All three treatment groups combined	4	Non-stroke cardiovascular death	59.6	58.4
				Death from re-infarction	32.5	30.7

AMI, acute myocardial infarction; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; DIGAMI, Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction; MI, myocardial infarction; PY, person-year.

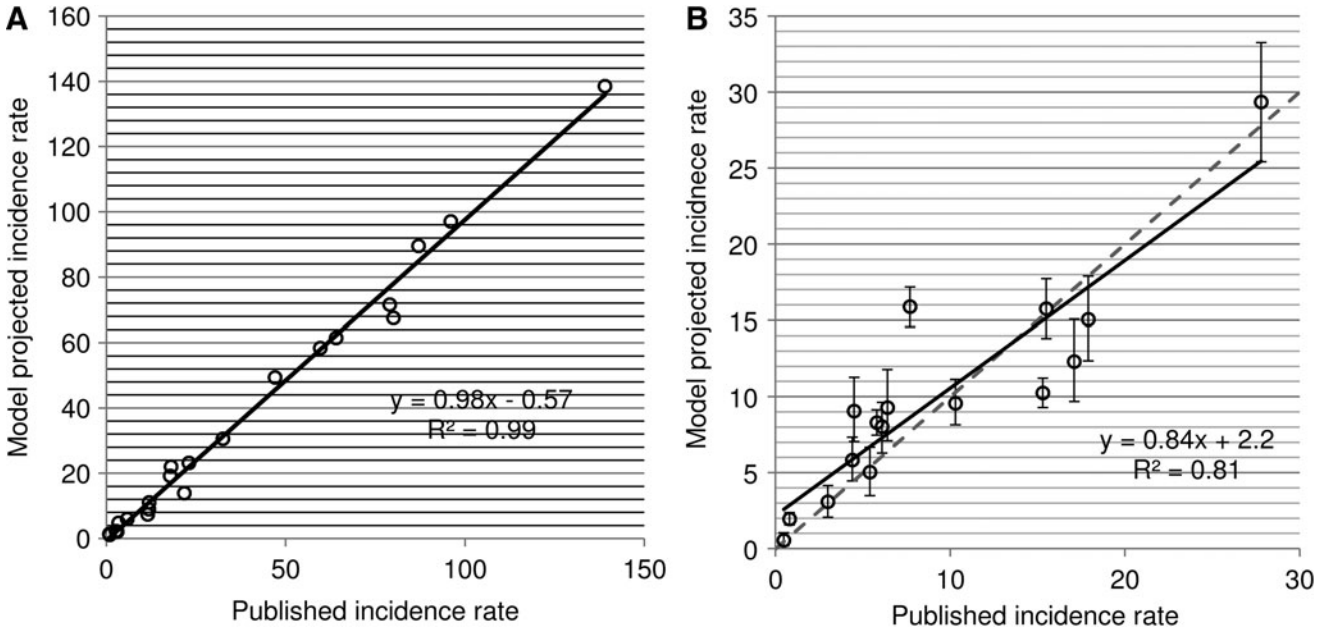

FIG. 1. **(A)** Internal and **(B)** external validation: complication events per 1,000 person-years. The solid line is the linear regression line; the dashed line is the line with intercept = 0 and slope = 1. **(A)** Circles indicate the results from a single simulation based on 20,000 subjects. **(B)** Circles indicate the mean of the results from 500 simulation iterations. Side bars on each data point indicate the 95% confidence intervals of results from the 500 simulation iterations.

study. We then ran the simulation for the median or mean length of follow-up reported in the study.

For the external validation, we examined the studies used to validate the CDC-RTI Diabetes Cost-Effectiveness Model and included three of the studies that were conducted after 2000 and were not used to develop our model or calibrate its parameters. We identified two additional trials conducted since 2000. We performed external validation using 16 outcomes from the standard therapy groups in the five randomized trials that we had identified: Veterans Administration Diabetes Trial (VADT),[54] Action to Control Cardiovascular Risk in Diabetes (ACCORD),[55] A Diabetes Outcome Progression Trial (ADOPT),[56] Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),[57] and the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION).[58] To conduct the external validation, we first integrated the calibrated and internally validated CHD submodel into the MMD and then performed the external validation using the updated MMD.

The first step in all of the external validations was similar to the first step in the internal validations. In the second step, treatment schemes and intensity of treatment were adjusted according to the results published in the external validation study. Adherence to treatment was adjusted to allow medication adherence, risk factor levels, and biomarker levels to match those reported in the study. In the calibration procedure, we had modify the risk equation to match the simulated outcome to the reported results; therefore for internal validation we performed a single simulation run with a large sample size (20,000) for each study. In the external validation, we performed each simulation with the number of subjects reported in each trial with 500 repetitions. Because sample size affects the uncertainty of the observed results in the actual trial, we used this strategy to allow us to evaluate how closely the simulated results matched the observed results based on calculated 95% confidence intervals of the simulated results.

Mean and standard deviation of the results across 500 iterations were calculated. Given that ACCORD, ADVANCE, and VADT showed no beneficial effects of intensive glucose control on the primary cardiovascular end points in T2DM,[59] we only validated our model against the routine treatment groups in these trials. Because the routine care and intensive treatment groups in ADDITION also showed very similar CVD outcomes, we only validated our model against the routine care group in ADDITION. We calculated incidence rates per 1,000 person-years for all of the outcomes based on the best available information provided in each study and used these incidence rates as the outcomes for both the internal and external validation exercises.

To determine the accuracy of the model and to assess goodness of fit, simulated outcomes were plotted against the observed outcomes from the published studies. We ran two sets of simple linear regressions to evaluate how well our model was able to predict the observed outcomes: one for the internal validation and the other for the external validation.

Results

Table 2 summarizes the information from the internal validation studies and compares the simulated outcomes with the observed outcomes. The results from the new CHD submodel agreed closely with the results of the internal validation studies. Figure 1A shows a scatter plot of the simulated and observed outcomes from the internal validation studies. For the 21 outcomes reported by the six studies included in the internal validation exercise, the R^2 was 0.99, and the slope of the regression line was 0.98. Almost all of the values fell close to or

Table 3. External Validation Results

Study	Population studied	Demographic/ treatment group	Study length (years)	Outcome	Results (per 1,000 PY)	
					Model	Study
ADOPT[56]	Ages 30–75 years from the United States, Canada, and Europe with type 2 diabetes and no pharmacological treatment. Double-blinded randomized trial of three monotherapies, 2000–2006	Metformin	4	Fatal MI	0.55	0.47
				MI	5.0	5.4
				CHF	9.1	4.5
ADVANCE[57]	Ages 55 years or older with type 2 diabetes, from 20 countries beginning in 2001	Standard therapy	5	Major coronary event (death due to CHD and nonfatal MI)	15.8	15.5
				CVD death	9.6	10.3
VADT[54]	Open label study targeting patients with poorly controlled type 2 diabetes to compare the effects of intensive and standard glucose control on cardiovascular events, 2000–2008	Standard therapy	6	CVD death	9.3	6.4
				MI	12.3	17.1
				CHF	15.1	17.9
				Procedures	29.4	27.8
ACCORD[55]	Ages 40–79 years with type 2 diabetes, hemoglobin A1c over 7.5%, and CVD, or ages 55–79 years with atherosclerosis, albuminuria, left ventricular hypertrophy, or two additional CVD risk factors, 2001–2008	Standard therapy	4	MI	10.3	15.3
				Fatal MI	2.0	0.8
				CVD death	8.3	5.8
				CHF	15.9	7.7
ADDITION[58]	A pragmatic, cluster-randomized, parallel-group trial. Between April 2001 and December 2006, 343 general practices in Denmark, The Netherlands, and the United Kingdom were randomly assigned screening of registered patients 40–69 years of age without known diabetes followed by routine care of diabetes or screening followed by intensive treatment of multiple risk factors.	Standard therapy	5	MI	5.8	4.4
				Procedures	8.0	6.1
				CVD death	3.1	3.0

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; ADOPT, A Diabetes Outcome Progression Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular death; MI, myocardial infarction; PY, person-year; VADT, Veterans Administration Diabetes Trial.

on the 45° line, indicating an almost perfect match between the model results and the published results.

The simulated and observed outcomes from the five external validation studies are summarized in Table 3 and Figure 1B. The R^2 value was 0.81, and the slope of the regression line was 0.84. For eight of the 16 outcomes, the observed outcomes fell within the 95% confidence interval of the simulated outcomes. For the ACCORD trial, the simulated MI incidence rate was approximately 28% lower than the observed rate, and the simulated CHF rate was more than twice the observed rate.

Discussion

According to the International Society for Pharmacoeconomics and Outcomes Research disease modeling guidelines,[53] ''models…should be repeatedly updated, and sometimes abandoned and replaced, as new evidence becomes available to inform their structure or input values.'' Hence, we updated the MMD CHD submodel to reflect changes in medical and surgical practice over the past decade. The new model accounts for the impact of medical treatments on CVD outcomes independent of their effects on biomarkers. It also accommodates revascularization procedures before and after first MI, allows for repeat MIs and revascularization procedures, and describes CHF.

Given the rapid changes in treatment, no single longitudinal study can completely describe the impact of current medical and surgical treatments on the natural history of a chronic disease like T2DM. One strategy for developing disease simulation models involves analyzing individual-level data from a single study over a long period of time as was done to develop the UKPDS Outcomes Models.[28,34] An alternative strategy that we used involved synthesizing the published literature. This method not only allowed us to build a model without access to individual-level data from a long-term prospective study, but allowed us to update the model to reflect current practice.

Most of the risk equations incorporated in the new CHD submodel were derived from the UKPDS Outcomes Model, which is based on a white or black population with newly diagnosed T2DM between 25 and 65 years of age. In light of this, recognizing that we calibrated our CHD submodel using studies that were conducted for the most part in the United States and Western Europe and considering the differences in medical practice across countries, our new CHD submodel should be applied to relatively young (25–79 years of age) white or black populations with T2DM in the United States and Western Europe. The IEST software that houses our model allows users to adjust parameters to better suit their own situations. For example, when applying the model to a population in a country with less access to revascularization procedures, users can adjust the transition probabilities to match the revascularization procedure rates in their countries.

The external validation shows that the CHD submodel predicts the outcomes of five recent clinical trials reasonably well. However, eight of the observed incidence rates were outside the simulated 95% confidence intervals provided by the simulation model.

Because the sample size used in a study affects the Monte Carlo error, we performed each simulation with the number of patients reported in the trial with 500 repetitions. The resulting 95% confidence intervals are likely to be too narrow because they did not take into account the uncertainty in model parameters and unmeasured or unreported characteristics of the study population. One potential reason for the differences between the simulated and the observed outcomes may be related to important differences between the actual and simulated study populations that were not reported by the study or captured by the simulation. The CVD death rate in the VADT trial was lower than the simulation model results (6.4% vs. 9.3%). This may be explained in part by the stringent exclusion criteria used in VADT (e.g., exclusion of subjects who had a cardiovascular event in the previous 6 months or who had severe angina, advanced CHF, or a life expectancy of less than 7 years). This would not, however, explain the higher MI rate observed in VADT.

Another potential reason relates to differences between the definitions of outcomes reported in the published studies and by our simulation model. For example, in ACCORD, fatal MI was defined as death within 7 days of the onset of MI. In our CHD submodel, fatal MI was defined as death within 30 days of the onset of MI. When validating against the ACCORD study, the simulated MI incidence rate was 28% lower than the observed rate, and the simulated fatal MI rate was three times higher than observed, reflecting at least in part the different definitions of fatal MI used in the ACCORD study and our simulation model.

McMurray et al.[60] reported that CHF occurs much more frequently than MI and stroke in cohort studies. In contrast, in recent trials of glucose-lowering therapies, CHF occurred at a frequency similar to that of stroke and MI. Most of those trials excluded patients with more than mild CHF. Given these facts, it is not surprising that our CHD submodel predicted a higher CHF incidence in the ADOPT and ACCORD cohorts in which subjects with CHF were excluded.

Because the relationship between control of hyperglycemia and cardiovascular risk remains largely controversial,[59] as shown in the trials we used for external validation, we chose not to validate against the intensive treatment arms. Future work on the influence of patient characteristics on the effect of control of hyperglycemia on cardiovascular risk is needed. We are currently updating the other complication and comorbidity submodels (retinopathy, nephropathy, neuropathy, and cerebrovascular disease), as well as the cost and health utility modules in the MMD. Considering the rapid changes in diabetes management, this will be an ongoing process. More information about the current version of MMD can be found at www.med.umich.edu/mdrtc/cores/DiseaseModel/

In conclusion, our CHD submodel predicts the development and progression of CHD in T2DM. When incorporated into the MMD, it should improve the model's ability to assess the effectiveness and cost-effectiveness of alternative strategies for the prevention and treatment of T2DM.

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Author Disclosure Statement

No competing financial interests exist.

W.Y. contributed to the study design, built the CHD submodel, conducted literature searches and data analysis, interpreted the data, calibrated and validated the model, and wrote the manuscript. M.B. contributed to the study design, conducted literature searches, and wrote the manuscript. M.B.B. contributed to the study design, provided technical support, interpreted data, and wrote the manuscript. W.H.H. contributed to the study design, interpreted data, obtained funding, wrote the manuscript, and supervised the study. All authors reviewed, edited, and approved the final manuscript.

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