The Michigan Model for Diabetes User Manual

Version 3.2
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Produced by the University of Michigan
Michigan Diabetes Modeling Group
https://michigandiabetesmodelinggroup.github.io/

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List of Abbreviations

HbA1c	Glycated hemoglobin
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
MI	Myocardial infarction
CHD	Coronary heart disease
CHF	Congestive heart failure
DR	Diabetic retinopathy
MMD	Michigan Model for Diabetes
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ACR	Albumin/creatinine ratio (for urine albumin test)
PTCA	Percutaneous transluminal coronary angioplasty
CABG	Coronary artery bypass graft
ACE-I	Angiotensin converting enzyme-inhibitor
ARB	Angiotensin receptor blocker
QALE	Quality-adjusted life expectancy
QALYs	Quality-adjusted life years
IEST	Indirect Estimation and Simulation Tool
AIS	Acute Ischemic Stroke

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1. Introduction and Background

The Michigan Model for Diabetes (MMD) is a computerized disease model that enables the users to simulate the progression of diabetes over time, its complications (retinopathy, neuropathy and nephropathy), and its major comorbidities (cardiovascular and cerebrovascular disease), and death. Transition probabilities can be a function of individual characteristics, current disease states or treatment status. The model also estimates the medical costs of diabetes and its comorbidities, as well as the quality of life related to the current health state of the subject.

In contrast to other proposed models, the transition probabilities implemented in the MMD were obtained by synthesizing the published literature. Specifically, transition probabilities in the newly updated coronary heart disease sub-model that reflects the direct effects of medical therapies on outcomes were derived from the literature and calibrated to recently published population-based epidemiologic studies and randomized controlled clinical trials. 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 by incorporating data from new studies as they become available.

In addition, different from other proposed models, our model allows a user to control risk factor changes by defining treatment thresholds and compliance rates for hyperglycemia, dyslipidemia, and hypertension, and compliance to quitting smoking and taking aspirin. Given the fact that modern medicines have largely decreased the complication rate in type 2 diabetes through management of these risk factors, it is important to explicitly model these management strategies and allow users to modify them to match the specific scenarios that they are simulating.

Some of the risk equations adapted in the coronary heart disease sub-model and cerebrovascular disease sub-model are from the UKPDS Outcomes Model I (Clarke et al., 2004), which was based on a population of newly diagnosed diabetics between 25 and 65 years of age that were followed for 14 years. These equations model race with only two categories, Caucasians and Blacks. In light of this, and recognizing that the other data sources for our model are studies that were conducted in the United States and Western Europe, and considering the difference in medical practice across countries, caution should be applied when model results are extrapolated to populations that differ significantly from the model target population: relatively young (25-79 years of age) Caucasians or Black populations with type 2 diabetes in the United States and Western Europe. Despite this, the R Shiny Web App which houses our model, allows users to adjust parameters to better suit their own situations. In addition, we share the R code with users who need to make additional changes. 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.

2. MMD versions

2.1. Changes from Version 1.0 to Version 2.0

The MMD 2.0 had been substantially revised from its original publication in 2005 (Zhou et al., 2005) and is implemented by using the IEST (Barhak et al., 2010) software that models chronic diseases.

New features of the MMD 2.0 compared to MMD 1.0 include:

(1) Modeling disease progression through evolution of multiple biomarkers and risk factors
(2) An updated coronary heart disease sub-model that incorporates the possibility of recurrence of myocardial infarction (MI), congestive heart failure, and cardiac procedures either before or after MI
(3) Modeling modern diabetes treatment regimens and management for hyperglycemia, dyslipidemia, and hypertension
(4) Modeling direct benefits of medications and compliance.
(5) Updated transition probability tables for end stage renal disease
(6) Updated competing death table
(7) Updated cost and utility models

2.2. Changes from Version 2.0 to Version 3.0

MMD 3.0 is now implemented in an R Shiny App that can be run remotely online.
New feature of the MMD 3.0 include:

(1) An updated cerebrovascular sub-model that incorporates both ischemic and hemorrhagic stroke. To better model complications after AIS, the new model allows patients to transit to two different survival states in a year after AIS: 1) history of AIS with minor disability due to temporary (no neurologic sequelae) or mild ischemic stroke; 2) history of AIS with major disability due to moderate or severe ischemic stroke.
(2) An updated other death equation using a Weibull survival model developed using NHANES mortality data.
(3) Updated treatment module according to new American Diabetes Association, American Heart Association guidelines

2.3. Changes from Version 3.0 to Version 3.2

MMD 3.2 is now implemented in an R Shiny App that can be run remotely online.
New feature of the MMD 3.0 include:

(1) Further updated cerebrovascular sub-model to reflect the newest development in AIS treatment
(2) Updated weight change module using parameters derived based on ACCORD trial data

3. About the RShiny Web App

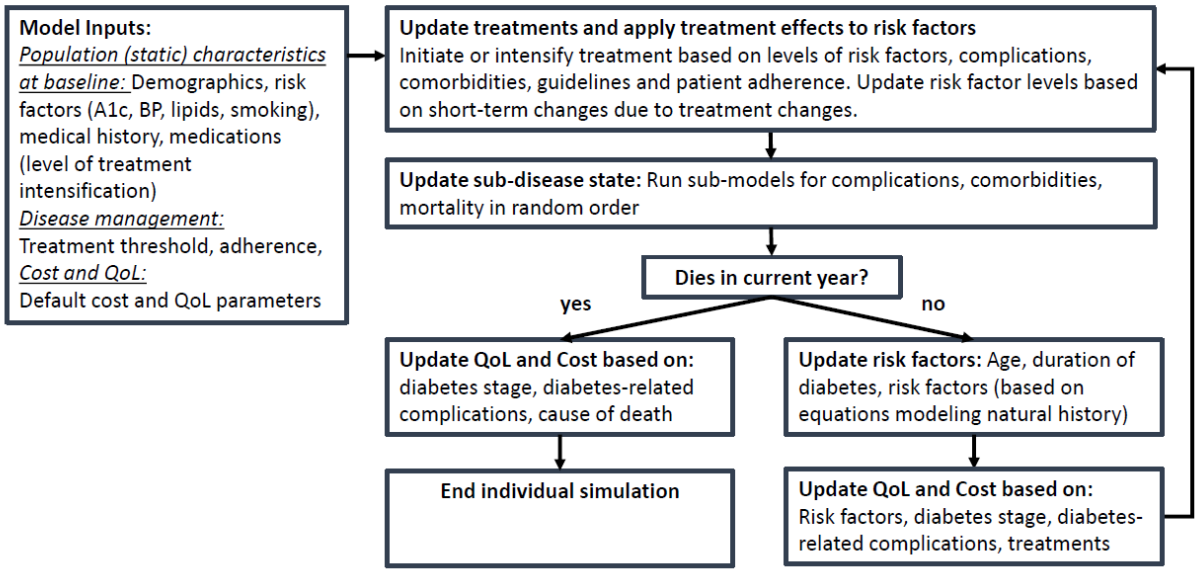
We use an RShiny Web App to host and distribute the MMD 3.0. This Web App provides a self-explanatory user interface and allow use to input study population, define simulation length, number of iterations, modify cost, quality of life related parameters, and treatment related parameters with ease. It also provides summary statistics in both figure and table formats.
It also provides raw simulated data for all simulated individuals, e.g. risk factors, complications status, yearly medical cost and utility score for each simulated year. Using the raw results, users can also write their own programs to summarize other quantities of their own interest.
This RShiny Web App will also evolve over time to allow more functions, such as one-way sensitivity analysis, probability sensitivity analysis, handling missing data in the individual-level baseline population data.

4. MMD Modules and Its implementation

4.1. MMD Modules and Simulation Flow

For each subject, the model software reads in or simulates the subject's baseline characteristics (See **Section 5.1** for details) and then advances the subject through a specific number of years or until death. Each year, the model updates in the four stages as indicated by blue blocks in the following figure 1, including:

Figure 1. MMD Simulation flow chart and algorithm



1) Update treatments based on patient's risk factor levels and medical history, treatment guidelines, and patient's adherence parameters. The program then calculated the short-term changes in risk factors changes due to treatment changes. See **Section 5.4** for details. This step is skip for the first simulation cycle.
2) Update disease states and complications based on transition probabilities which can be functions of individual characteristics, current disease states or treatment status. See **Section 5.2** for details of model specification. Hypoglycemia events are also simulated based on parameters defined in **Section 5.3.**
3) Update risk factors (i.e. weight/BMI, HbA1c, fasting glucose, systolic blood pressure (SBP)/diastolic blood pressure (DBP), lipids) according natural history of changes or medication modified natural history changes from beginning of the year to the end of the year. See **Section 5.5** for details.
4) Calculate cost and utility values for the specific year according to risk factors, medications, and history of complications and comorbidities. See **Section 5.6 and 5.7** for details.

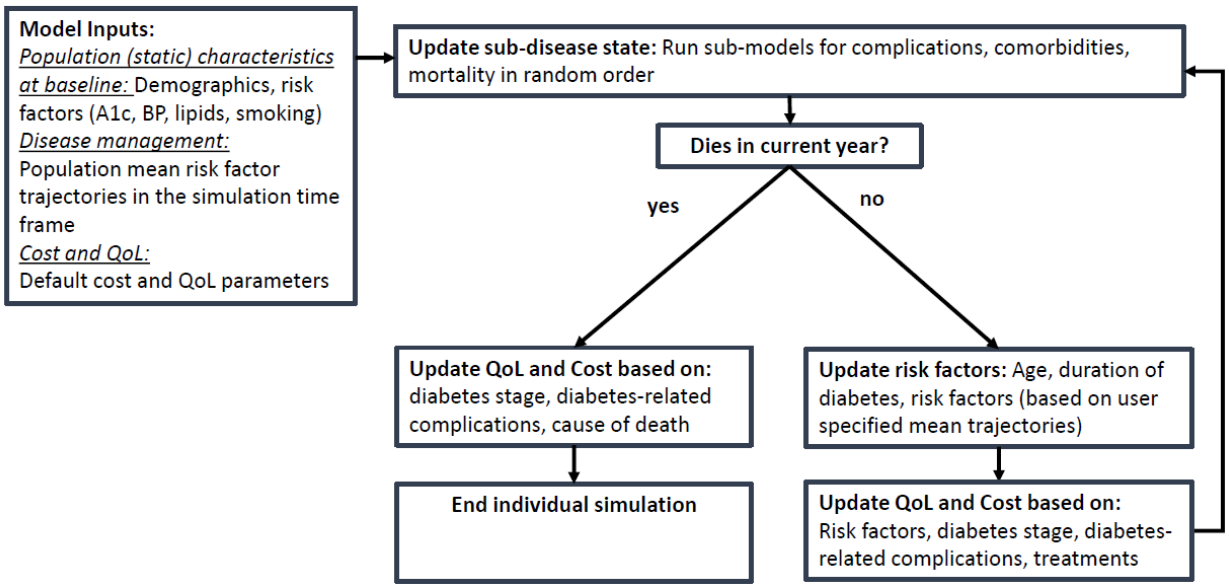
4.2. Full MMD 3.0 and Simplified MMD 3.0

The treatment module and risk factor progression module in MMD 3.0 are very helpful for evaluating treatment management strategies. However, it is not needed for all simulation cost-effectiveness analysis. Some users prefer specifying the population average trajectory of risk factors for the simulation.

For meet this need, we also implemented a simplified version of MMD 3.0. In this version, treatment module and risk factors module have been removed. Instead of defining treatment thresholds and adherence rate to adjust risk factor changes over time, user can directly define pre-specified population means over time for each risk factor. Figure 2 shows the flow chart for the simplified version.

If you are only interested in using the simplified version, you can skip Sections 5.4 and 5.5.

Figure 2. Simplified MMD Simulation flow chart and algorithm



5. MMD Structures and Parameters

5.1. Population Input Module

Populations can either be inputted as data (to be used in a simulation), or set by specifying a distribution (to be used in Estimation or for randomly generating population sets). It is the responsibility of the users of MMD to ensure that only valid values are entered as the software applies a few data entry checks.

5.1.1. Individual level data

If you wish to use individual-level data, the variables needed for each subject are listed in the following table.

Table 1. Variable specificiations for individual-level data input

Varaible Name	Definition	Legal Range	Notes
Demographics Characteristics			
Age	Current age in years	[1,100]	
Duration_Of_Diabetes	Duration in years since diagnosis of diabetes	<=Age	
Male	Gender Variable	1=Male, 0=Female	
Race	Race	Non-Hispanic White Non-Hispanic Native American Non-Hispanic Black/African American Non-Hispanic Asian Hispanic	
Weight	Weight in kilograms[1.0kg = 2.2 pounds]	[30, 400]	
Height	Height in meters [1.0meter=39 inches]	[0, 2.5]	
Current Risk Factors			
SBP	Systolic blood pressure(mmHg)	[60, 280]	
DBP	Diastolic blood pressure(mmHg)	[20, 140]	
Smoke	Smoking Status	0 = Non-smoker, 1=Smoker	
HDLCholesterol	High-density lipoprotein cholesterol in mmol/L [1mmol/L = 38.6mg/dl]	[0.3, 5]	

LDLCholesterol	Low-density lipoprotein cholesterol in mmol/L [1mmol/L = 38.6mg/dl]	[0.3, 11]	
Triglycerides	Triglycerides in mmol/L [1mmol/L = 88.5mg/dl]	[0, 20]	
A1c	Hemoglobin A1c(%)	[0, 20]	
Afib	Atrial fibrillation	1=Yes, 0=No	
Disease Status (Within each sub-model defined below, one and only one variable should be set to 1)			
Cerebrovascular disease sub-model			At most, only one of them can be set to 1.
No_Cerebrovascular_Disease	No cerebrovascular disease	1=Yes, 0=No	
Hx_Is_MinorDisability	History of Ischemic Stroke with minor/no disability	1=Yes, 0=No	
Hx_Is_MajorDisability	History of Ischemic Stroke with major disability	1=Yes, 0=No	
Hx_Hs	History of Hemorrhagic Stroke	1=Yes, 0=No	
Coronary heart disease sub-model			
No_CVD	No history of coronary heart disease	1=Yes, 0=No	One and only one of these categories should be set to 1.
CADwoMI	Coronary artery disease without history of MI or heart failure	1=Yes, 0=No	
CHFwoMI	History of heart failure but not MI	1=Yes, 0=No	
CADwProc	History of revascularization procedure with no history of MI	1=Yes, 0=No	
Survive_MI	History of MI(can be more than once) with no history of heart failure	1=Yes, 0=No	
CHF_after_MI	History of heart failure and history of MI	1=Yes, 0=No	
Nephropathy sub-model			
No_Nephropathy	No nephropathy	1=Yes, 0=No	One and only one of these categories should be set to 1.
Micro_Albuminuria	Microalbuminuria is defined as 30mg/g <=ACR < 300mg/g	1=Yes, 0=No	
Proteinuria	ACR >= 300mg/g	1=Yes, 0=No	
ESRD_Dialysis	End stage renal disease with need of dialysis but no history of transplant	1=Yes, 0=No	
ESRD_Transplant	End stage renal disease with history of transplant	1=Yes, 0=No	
Neuropathy sub-model			
No_Neuropathy	No neuropathy	1=Yes, 0=No	

Clinical_Neuropathy	Distal symmetric(sensory) neuropathy	1=Yes, 0=No	One and only one of these categories should be set to 1.
Left-Eye retinopathy sub-model			
No_Proliferative_Retinopathy_left	Normal left eye	1=Yes, 0=No	One and only one of these categories should be set to 1.
Nonproliferative_left	Left eye has non-proliferative retinopathy	1=Yes, 0=No	
Proliferative_left	Left eye has proliferative retinopathy	1=Yes, 0=No	
Blind_Eye_left	Left eye is blind	1=Yes, 0=No	
Right-Eye retinopathy sub-model			
No_Proliferative_Retinopathy_right	Normal right eye	1=Yes, 0=No	One and only one of these categories should be set to 1.
Nonproliferative_right	Right eye has non-proliferative retinopathy	1=Yes, 0=No	
Proliferative_right	Right eye has proliferative retinopathy	1=Yes, 0=No	
Blind_Eye_right	Right eye is blind	1=Yes, 0=No	
Left-Eye retinopathy sub-model (If left eye is blind, both variables below should be set to 0)			
No_Macular_edema_left	Left eye does not have macular edema	1=Yes, 0=No	One and only one of these categories should be set to 1.
Macular_edema_left	Left eye has macular edema	1=Yes, 0=No	
Right-Eye retinopathy sub-model (If right eye is blind, both variables below should be set to 0)			
No_Macular_edema_right	Right eye does not have macular edema	1=Yes, 0=No	One and only one of these categories should be set to 1.
Macular_edema_right	Right eye has macular edema	1=Yes, 0=No	
Medication			
IntensiveLifeStyle	Diet and exercise	1=Yes, 0=No	There are five stages for anti-hyperglycemia treatment in MMD. These five stages are mutually exclusive of each other. At most, only one of them can be set to 1. [a]
Metformin	Metformin	1=Yes, 0=No	
OtherOralMedication	Two or more oral/non-insulin medication (e.g., metformin+sulfonylureas)	1=Yes, 0=No	
BasalInsulin	Basal Insulin	1=Yes, 0=No	
Insulin	Intensive bolus insulin	1=Yes, 0=No	
Beta_Blocker*	Whether a subject is taking beta-blocker	1=Yes, 0=No	
ACE_ARB*	Whether a subject is taking ACE/ARB	1=Yes, 0=No	

Number_of_BPMeds	Number of hypertension drug(exclude beta-blocker) the subject is taking	[0, 100]	
Statin*	Whether a subject is taking any medication for dyslipidemia	1=Yes, 0=No	
Aspirin/Clopidogrel*	Whether a subject is taking aspirin	1=Yes, 0=No	
Warfarin*	Whether a subject is taking warfarin	1=Yes, 0=No	
NOAC*	Whether a subject is taking noval oral anti-coagulants	1=Yes, 0=No	
Sampling weights			
Sampling_Weight	Sampling weights assigned to each subject		If there is no sampling weights, enter 1 for each subject.

[a]Additional instructions to set up five variables of medications for anti-hyperglycemia treatment: 1) If a subject is on insulin therapy in which only basal insulin or only premixed insulin is used, s/he should be considered at the 4th stage treatment for hyperglycemia, and therefore only the variable BasalInsulin is set to be 1. 2) If a subject is on insulin therapy in which any of rapid-acting insulin, short-acting insulin, or intermediate-acting insulin is used, s/he should be considered at the 5th stage treatment for hyperglycemia, and therefore only the variable Insulin is set to be 1.*Not needed for the simplified version

5.1.2. Specify a distribution

An alternative to inputting a data set with individual information is to simulate a baseline population using population level summary statistics. The RShiny Web App provides an input template that can be modified.

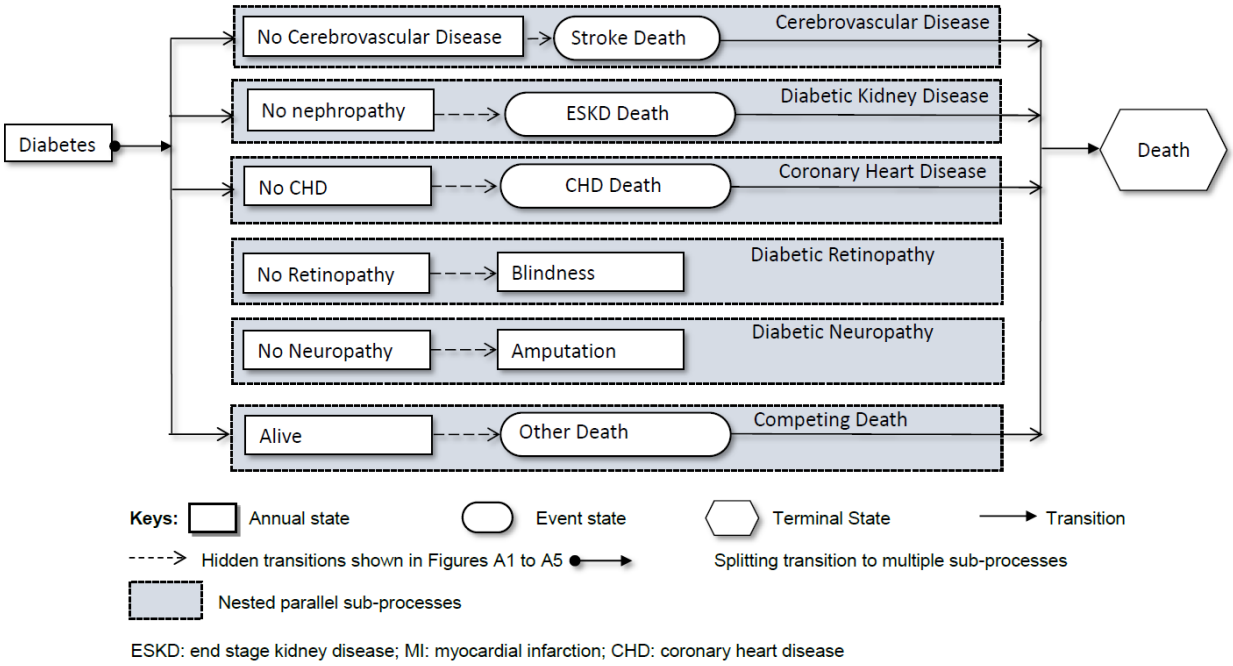
5.2. Disease Progression Module

5.2.1 Disease Progression Model Overall Structure

Michigan Model for Diabetes (MMD) is a discrete-state, discrete-time micro-simulation model in which the health status of each simulated subject is updated yearly. There are two types of states in the model: annual states and event states. Patients may stay in an annual state for one or more simulation cycles. Patients progress through event states, such as stroke and MI, instantaneously and transit to other annual states.

Figure 3 shows the overall structure of MMD model, which includes six parallel sub-models (cardiovascular disease [CVD], diabetic kidney disease, coronary heart disease [CHD] (Ye et al., 2015), diabetic retinopathy, diabetic neuropathy, and competing death).

Figure 3. Overall Structure of MMD



5.2.2 Structure and transition probabilities CHD sub-model

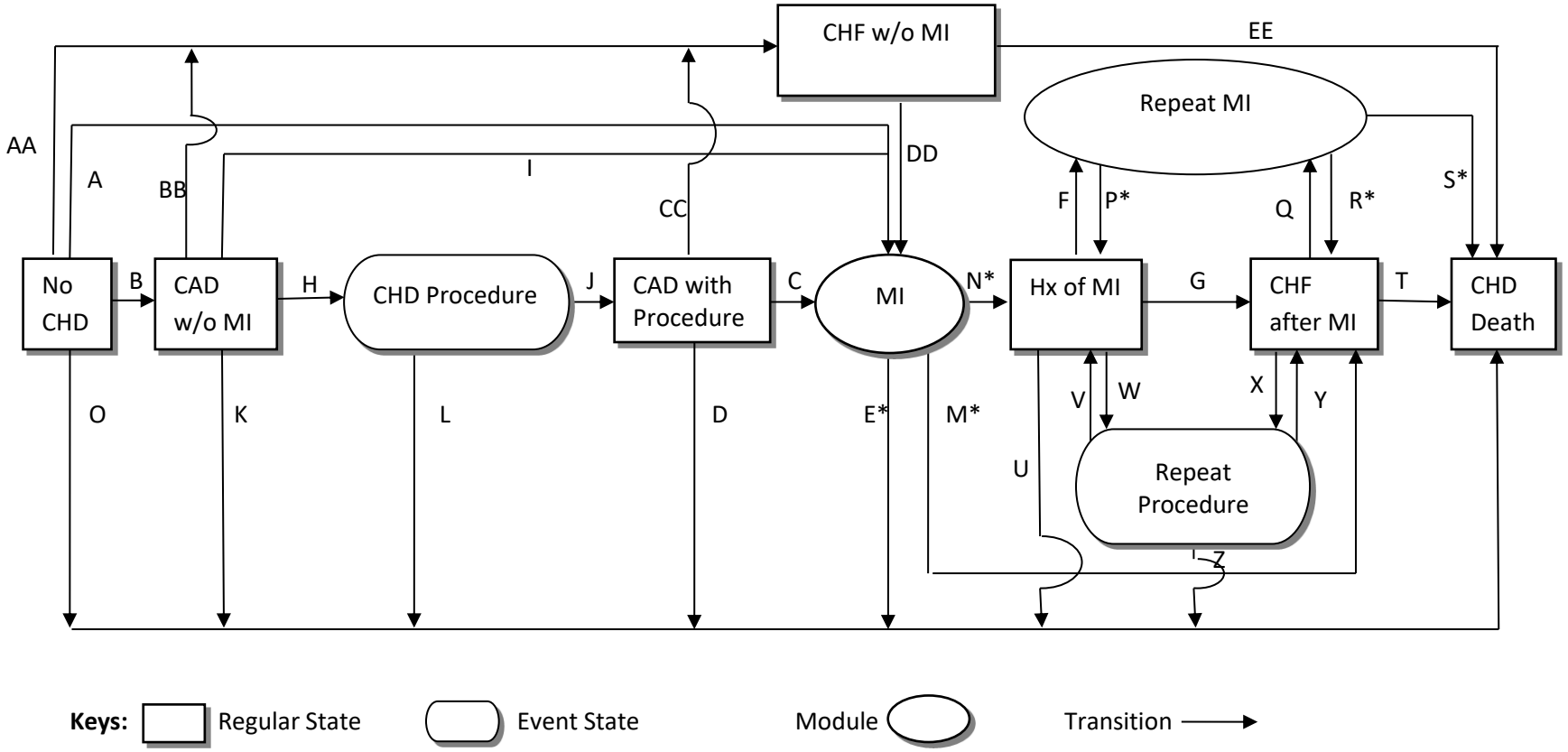


Figure 4. Coronary heart disease states and progression. CHD=coronary heart disease, CAD=coronary artery disease, CHF w/o MI=congestive heart failure without MI, MI=myocardial Infarction, CHF after MI=congestive heart failure after experience of MI, Hx=history, w/o=without, CHD procedure=revascularization procedure.

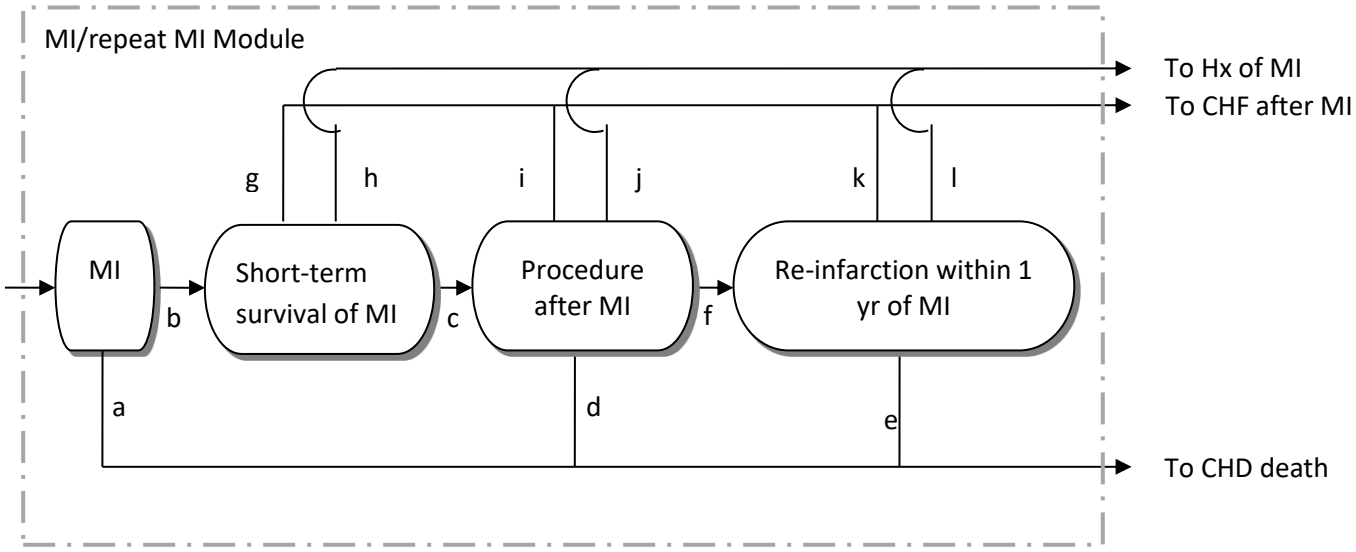


Figure 5. Myocardial infarction module. Ovals indicate instant states.

Table 2. Calibration and references for transition probabilities in the main CHD sub-model (Figure 4).

Transition	Transition Probability	Calibration	Risk factors	Reference
A (No CHD → MI	UKPDS MI equation (IHD=0, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.7.	Calibrated to Avogaro et al (2007) men and women separately	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Avogaro et al (2007)
B (No CHD → CAD w/o MI)	UKPDS IHD equation adjusted for medication benefit and by additionally adjusting the hazard function by a factor of 3.			
O (No CHD → CHD death)	UKPDS MI equation (IHD=0, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.091.			
AA (No CHD → CHF w/o MI)	CHS risk equation (Section C in this document; Angina=0, MI=0) adjusted for medication benefit	None	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI,	Fried LP et al. (1991)

			history of angina, history of MI, AF, and medications[§].	
K (CAD w/o MI → CHD death)	The UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.668.	Calibrated to Colhoun et al. (2004) placebo groups	Age, sex, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Colhoun et al. (2004)
I (CAD w/o MI → MI)	The UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 1.68.			
H (CAD w/o MI → CHD procedure)[#]	The UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 7.62.			
BB (CAD w/o MI → CHF w/o MI)	CHS risk equation (Section C in this document; Angina=1, MI=0) adjusted for medication benefit	None	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Fried LP el al. (1991)
L (Immediate death after CHD procedure)	5%	None	None	Cole (2002)
J (Survive CHD procedure)	95%			
C (CAD with procedure → MI)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 1.387.	Calibrated to the prompt group in Chaitman et al. (2009)	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Chaitman et al. (2009)
D (CAD with procedure → CHD death)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 0.37 based on calibration.			
CC (CAD with procedure → CHF w/o MI	CHS risk equation (Section C in this document; Angina=1, MI=0) adjusted for medication benefit		Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Fried LP el al. (1991)
DD (CHF w/o MI → MI)	UKPDS MI equation (IHD=1 if subjects had history of angina, CHF=1) adjusted for medication benefit and by	Calibrated to	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI,	Clarke et al.(2004);

	additionally adjusting the hazard function by a factor 0.07.	Deedwania (2011) and Mellbin et al (2011)	history of angina, history of MI, AF, and medications[§].	Deedwania (2011); Mellbin et al (2011)
EE (CHF w/o MI → CHD death)	UKPDS MI equation (IHD=1 if subjects had history of angina, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 0.43.	Calibrated to Deedwania (2011) and Mellbin et al (2011)	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Clarke et al.(2004); Deedwania (2011); Mellbin et al (2011)
E* (MI → CHD death)	See details in the MI/repeat MI module (Table A2)	See Table 3	See Table 3	See Table 3
M*(MI → CHF after MI)	See details in the MI/repeat MI module (Table A2)			
N* (MI → Hx of MI)	See details in the MI/repeat MI module (Table A2)			
U (Hx of MI → CHD death)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 0.232.	Calibrated to Jensen et al. (2012) and Mellbin et (2011)	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Mellbin et al. (2011); Jensen et al. (2012)
F (Hx of MI → Repeat MI)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor by 1.247.			
W (Hx of MI→ Repeat procedure)[#]	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor by 3.074.			
G (Hx of MI → CHF after MI)	CHS risk equation (Section C in this document; Angina=1, MI=1) adjusted for medication benefit	None	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Fried LP el al. (1991)
P* (Repeat MI → Hx of MI)	See details in the MI/repeat MI module (Table A2)	See Table 3	See Table 3	See Table 3
R* (Repeat MI → CHF after MI)	See details in the MI/repeat MI module (Table A2)			

S* (Repeat MI → CHD death)	See details in the MI/repeat MI module (Table A2)			
Q (CHF after MI→ Repeat MI)	The UKPDS MI equation (IHD=1, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard by a factor 1.088.	Calibrated to Deedwania (2011) and Mellbin et al (2011)	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Deedwania et al. (2011) Mellbin et al. (2011)
T (CHF after MI→ CHD death)	The UKPDS MI equation (IHD=1, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.489.			
X (CHF after MI→ Repeat procedure) [#]	The UKPDS MI equation (IHD=1, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard by a factor 6.201			
V (Repeat procedure → Hx of MI)	95% if subject does not have CHF 0% if subject have CHF	None	None	Cole et al. (2002)
Y (Repeat procedure → CHF)	95% if subject have CHF 0% if subject does not have CHF	None	None	
Z (Repeat procedure → CHD death)	5%	None	None	

[#]According to the statements in 2 JACC papers, about one third of patients undergoing PCI in the US have diabetes (see page e83 in the attached File 1) and about 35% of CABG patients have diabetes (see page e167 in the attached File 2). Also, according to a recent Circulation paper, it was estimated that in 2010, in the US, 492,000 patients underwent PCI while 219,000 underwent CABG (see page e275 in the attached File 3). With calculations using these data, what we could have is: The estimated number of diabetic patients treated with PCI in 2010 in the US would be 164,000 (=492,000*1/3), while that treated with CABG would be 76,650 (=219,000*0.35). Thus, based on these 2 calculated numbers, we could get that about 68% of diabetic patients who need the coronary revascularization procedures may use PCI, while 32% of them may get CABG.

[§]Medications in this table refer to aspirin, lipid drug, ACE-I, and beta-blocker**.** See Table 16 for details.

Table 3. Calibration and references for transition probabilities in MI/repeat MI module (Figure 5)			
Transition	Transition Probability	Calibration	Reference
a (MI → CHD death: fatal MI)	MI: Modified the UKDPS fatality equation by add gender effect. The new odds of death is -3.251+2.772*Ln(Age/52.59)+(HbA1c-7.09)*0.114+2.640+Female*Ln(3.5) We then calculate the probability of death using the odds and adjusted by a factor 0.18, disregard whether a patient has CHF or not.	Calibrated to10% fatal MI for men and 15% fatal MI among all first MI events in Colhoun et al. (2004) study. These fatality rate is based on information in Roffi et al.(2013)	Clarke et al.(2004); Colhoun et al. (2004); Roffi et al. (2013)
	Repeat MI: For subjects with CHF: Using the probability from the modified odds as described above. For subjects without CHF: Using the probability from the modified odds further adjusted by a factor 0.53	Calibrated to Jensen et al. (2012)	Clarke et al.(2004); Jensen et al. (2012)
b (MI → Short-term survival of MI)	1-transition probability in a		Clarke et al.(2004); Colhoun et al. (2004); Roffi et al. (2013)
c (Short-term survival of MI → Procedure after MI)	MI: 75%	Jensen et al. (2012)	Franklin et al. (2004); Jensen et al. (2012) Deedwania (2011)
	Repeat MI: 63%	Jensen et al. (2012); Deedwania (2011)	
g (Short-term survival of MI → CHF after MI)	MI: For subject who has CHF before MI: 25% For subject who does not have CHF before MI: 25%×P(CHF)[†]	Jensen et al. (2012)	
	Repeat MI: For subject who has CHF before MI: 37% For subject who does not have CHF before MI: 37%×P(CHF)[†]	Jensen et al. (2012); Deedwania (2011)	
h (Short-term survival of MI → Hx of MI)	MI: For subject who has CHF before MI: 0% For subject who does not have CHF before MI: 25%×(1-P(CHF))[†]	Jensen et al. (2012)	
	Repeat MI: For subject who has CHF before MI: 0%	Jensen et al. (2012); Deedwania (2011)	

	For subject who does not have CHF before MI: 37%×(1-P(CHF))†		
d (Procedure after MI → CHD death)	MI: 12.5%	Jensen et al. (2012)	
	Repeat MI: 10%	Jensen et al. (2012); Deedwania (2011)	
f (Procedure after MI →Re-infarction within a year of MI)	MI: 8.75%	Jensen et al. (2012)	
	Repeat MI: 9%	Jensen et al. (2012); Deedwania (2011)	
i (Procedure after MI → CHF after MI)	MI: For subject has CHF before MI: 78.75% For subject has no CHF before MI: 78.75%×P(CHF)†	Jensen et al. (2012)	
	Repeat MI: For subject has CHF before repeat MI:81%×P(CHF)† For subject has no CHF before repeat MI: 81%%×P(CHF)†	Jensen et al. (2012); Deedwania (2011)	
j (Procedure after MI → Hx of MI)	MI: For subject has CHF before MI: 0 For subject has no CHF before MI: 78.75%×(1-P(CHF))†	Jensen et al. (2012)	Franklin et al. (2004); Jensen et al. (2012)
	Repeat MI For subject has CHF before repeat MI: 0 For subject has no CHF before repeat MI: 78.75%×(1-P(CHF))†	Jensen et al. (2012); Deedwania (2011)	
e (Re-infarction within a year of MI → CHD death	17%	Jensen et al. (2012)	
k (Re-infarction within a year of MI → CHF after MI)	83%×P(CHF)		
l (Re-infarction within a year of MI → Hx of MI)	83%×(1-P(CHF))†		
†P(CHF)=0.13*Age_Modifier*Gender_Modifier*0.45*Medication_Modifier for MI module; P(CHF)=0.13*Age_Modifier*Gender_Modifier Medication_Modifier for repeat MI module. The age and gender modifier in the P(CHF) equations are shown in Table 4.			

Table 4. Age and Gender Modifier in Table 3 (Franklin et al., 2004)		
Factor	Category	Modifier
Age	<55	0.53
	55-64	0.87
	65-74	1.09
	>=75	1.51
Gender	Male	0.86
	Female	1.14
For example, for a 60 years old male subject not on beta-blocker or ACE-I, P(CHF) for the MI module = 0.13*0.87*0.86*0.45 Medication_Modifier is as Table 16.		

Prediction model for the risk of congestive heart failure (CHF) in type 2 diabetes (T2DM) based on the Cardiovascular Health Study (Fried LP et al, 1991)

Table 5. Parameters in the prediction model for risk of congestive heart failure in T2DM				
Parameter		Parameter Estimate	P-Value	Hazard Ratio (95% CI)
λ		-5.136		
ρ		1.364		
MI		0.665	<0.0001	1.95 (1.44, 2.62)
Angina		0.409	0.0039	1.51 (1.14, 1.99)
Ln TC/HDL (centered at 4.62)		0.782	0.00026	2.19 (1.44, 3.32)
SBP (centered at 136.9)		0.019	<0.0001	1.020 (1.013, 1.026)
DBP (centered at 69.4)		-0.017	0.0068	0.984 (0.972. 0.995)
BMI*	BMI (centered at 28.2)	0.004	0.81	1.00 (0.97, 1.04)
	BMI Plus function $(BMI-33)_+$	0.162	0.0057	1.18 (1.05, 1.32)
Gender: Male vs. Female		0.331	0.010	1.39 (1.08, 1.79)
AF: Yes vs. No		0.897	<0.0001	2.45 (1.56, 3.85)
Age at diabetes onset (centered at 65)		0.045	0.00037	1.05 (1.02, 1.07)
C index at 10 year		0.699		

*$(BMI-33)_+$ = BMI-33 when BMI-33>0, otherwise 0.

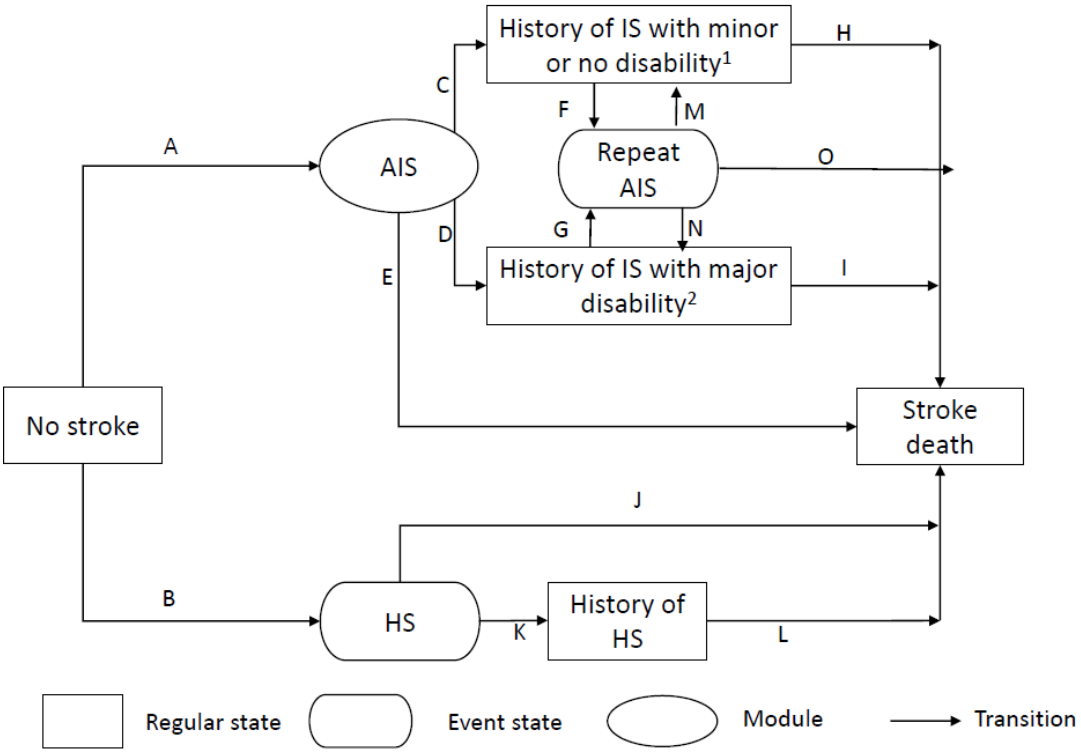
5.2.3 Structure and transition probabilities for stroke sub-model

Same as the structure of other sub-models in MMD, the stroke sub-model is a discrete-state and discrete-time micro-simulation model (Figure 5), in which the status of a subject is updated yearly. There are two types of states in the model: annual/regular states and event states. Patients may stay in an annual/regular state for one or more simulation cycles. Patients may progress through event states, such as ischemic stroke, instantaneously and transit to other annual/regular states.

The structure of the stroke sub-model accommodates both ischemic and hemorrhagic stroke. In addition, to model complications after AIS, this model allows patients to transit to two different survival states in a year after AIS: 1) history of AIS with minor disability due to temporary (no neurologic sequelae) or mild ischemic stroke; 2) history of AIS with major disability due to moderate or severe ischemic stroke. Repeat AIS event enabled from both states with history of AIS.

Parameters for deriving transition probabilities to recurrent AIS and mortality after minor/major disability were estimated from a secondary data analysis of the Brain Attack Surveillance in Corpus Christi (BASIC) Project, an ongoing population-based stroke surveillance study in Nueces County, Texas. Methods of the BASIC Project have been described previously (Piriyawat et al, 2002, Smith et al., 2004). In 2016, the county population was 361,350, with 63% being MA, the vast majority of whom are 2nd or 3rd-generation US-born citizens. Briefly, ischemic stroke cases were identified between April 2006 and June 2012 by trained abstractors through active and passive surveillance methods and validated by stroke fellowship trained physicians. Those with age <45 years, traumatic stroke, residence outside of Nueces County, and with a race-ethnicity other than MA or NHW were excluded. Post-stroke FO is measured at ~90 days from an outcome interview using an average score (range 1-4) of self-reported levels of difficulty with 22 ADL/IADL tasks (Spector et al., 1998) Patients with an average score of 3-5 were considered as having major disability. Among the 569 AIS patient who had outcome interviews at 90 day, 257 of them had a history of known diabetes. The transition probabilities derived from this analysis is included in Table 1.

Figure 6. Structure of Cerebrovascular Sub-model

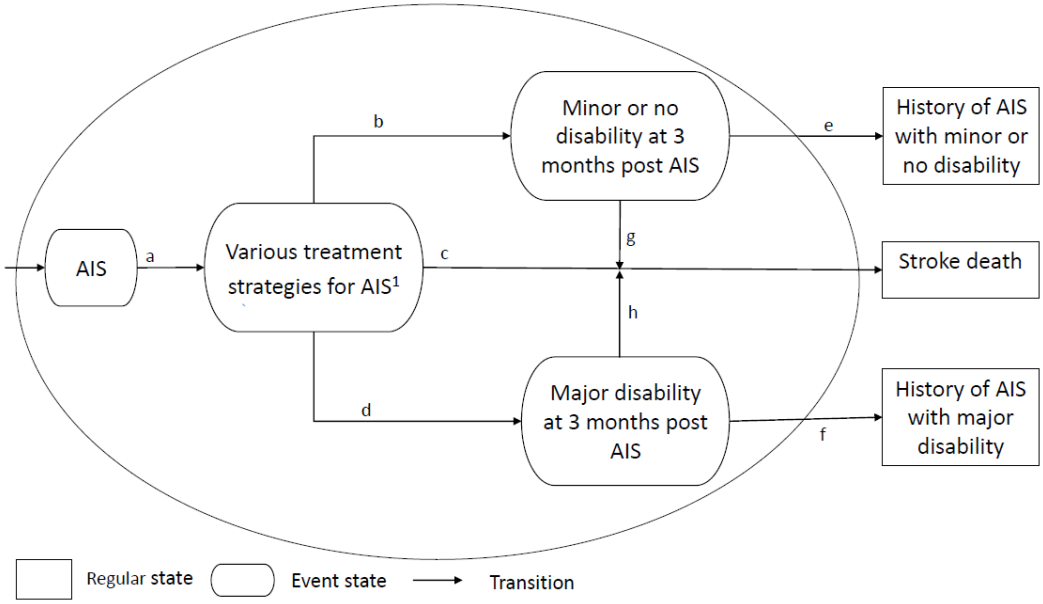


Abbreviations: IAS, ischemic acute stroke; HS, hemorrhagic stroke.
[1]Minor disability was due to temporary (no neurologic sequelae) or mild ischemic stroke.
[2]Major disability was due to moderate or severe ischemic stroke.

Table 6. Transition probabilities in cerebrovascular disease sub-model (Figure 6)		
Transition	Transition probability	Reference and additional information
A: No stroke to AIS	UKPDS I x 92.6%	Clarke et al., 2004; Eriksson et al., 2008
B: No stroke to HS	UKPDS I x 7.4%	
C: AIS to history of IS with minor or no disability	22.5%	Piriyawat et al, 2002; Smith et al., 2004; del Zoppo et al., 2009; Spector et al., 1998; Reeves et al., 2010
D: AIS to history of IS with major disability	47.1%	
E: AIS to stroke death	30.4%	
F: Hx of AIS and minor or no disability to AIS (repeat stroke)	3.0%	Derived from data collected from BASIC study (Skolarus et al., 2013); details not included.
G: Hx of AIS and major disability to AIS (repeat stroke)	3.0%	
H: Hx of AIS and minor or no disability to stroke death	4.1%*0.30 for first AIS 7.5%*0.30 for repeat AIS	
I: Hx of AIS and major disability to stroke death	7.1%*0.30 for first AIS 13.0% *0.30 for repeat AIS	
J: HS to stroke death	53%	Arbois et al, 2000
K: HS to Hx of HS	47%	
L: Hx of HS to stroke death	5.4%	Claessens et al., 2017
M: Repeat AIS to history of IS with minor or no disability	13.2% if a subject had minor or no disability before repeat AIS; 0% if a subject had major disability before repeat AIS	Derived from data collected from BASIC4 study (Skolarus et al., 2013) and Hardie et al. (2004).
N: Repeat AIS to history of IS with major disability	28.0% if a subject had minor or no disability before repeat AIS; 39.2% if a subject had major disability before repeat AIS	
O: Repeat AIS to death	58.8% if a subject had minor or no disability before repeat AIS; 60.8% if a subject had major disability before repeat AIS	

The structure of the stroke sub-model accommodates both ischemic and hemorrhagic stroke. In addition, to model complications after AIS, this model allows patients to transit to two different survival states in a year after AIS: 1) history of AIS with minor disability due to temporary (no neurologic sequelae) or mild ischemic stroke (mRS 0-1); 2) history of AIS with major disability due to moderate or severe ischemic stroke (mRS 2-5). Repeat AIS event enabled from both states with history of AIS.

Figure 7. Within-year events in acute ischemic stroke (AIS) module

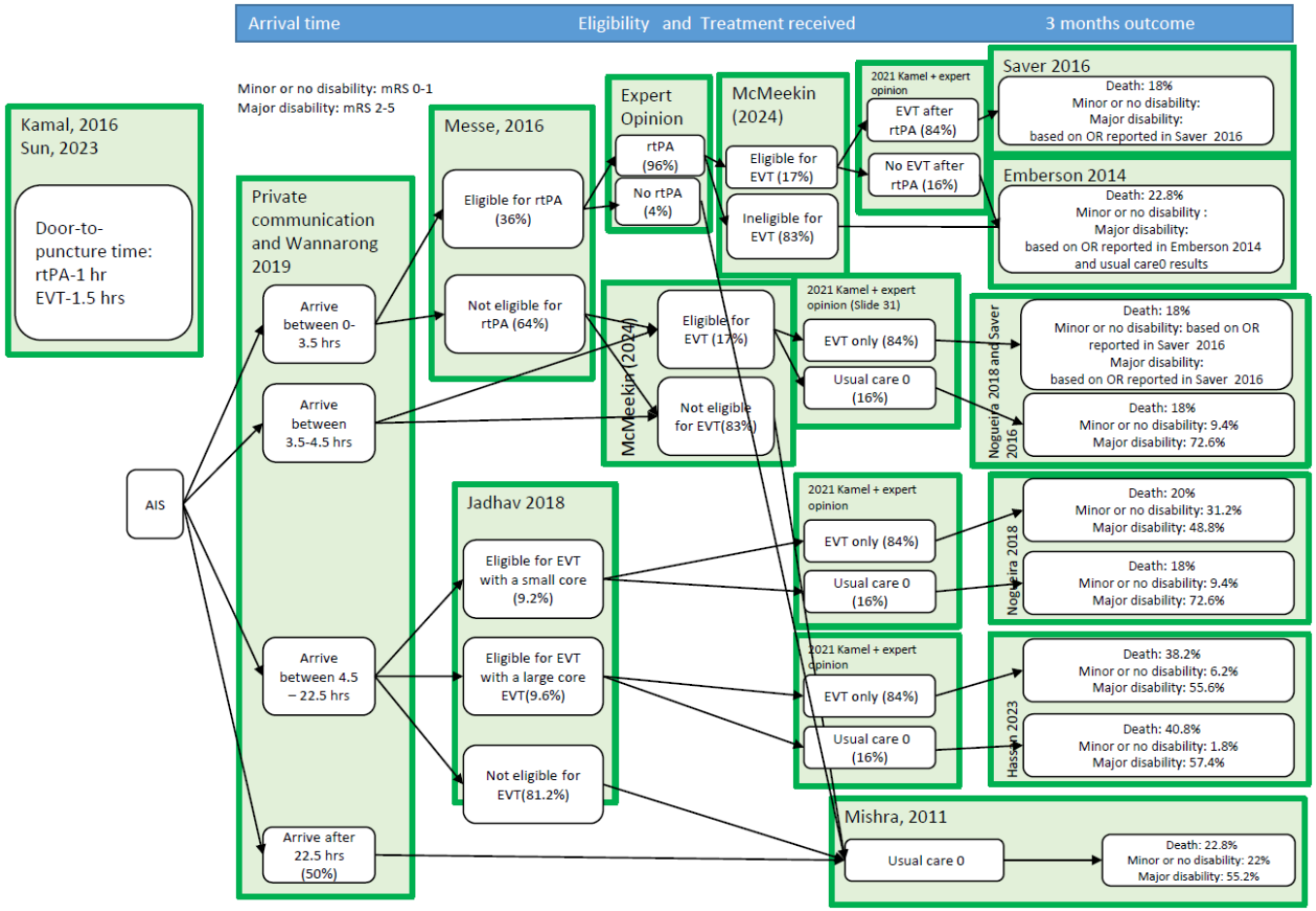


[1]Treatment may include 1) general supportive care and treatment of acute complications, 2) intravenous fibrinolysis (e.g., rtPA), 3) endovascular intervention (e.g., intra-arterial fibrinolysis, mechanical thrombectomy (clot disruption/extraction).

Table 7. Transition probability for within-year events in acute ischemic stroke module			
Transition	Transition probability	Reference	Notes
a: AIS to Various treatment strategies for AIS	See details in Stroke management and outcome after AIS (Figure 8)		
b: Various treatment strategies for AIS to minor or no disability at 3 months post AIS			
c: Various treatment strategies for AIS to major disability at 3 months post AIS			
d: Various treatment strategies for AIS to stroke death at 3 months post AIS			
e: Minor or no disability at 3 months post AIS to History of AIS with minor or no disability	100%	Based on analysis using BASIC4 Study data	Assume no change of disability status from 3 months to 1 year post AIS
f: Major disability at 3 months post AIS to history of AIS with major disability	86%	Based on analysis using BASIC4 Study data	Assume no change of disability status from 3 months to 1 year post AIS
g: Minor or no disability at 3 months post AIS to death at one year post AIS	0%	Based on analysis using BASIC4 Study data	Assume no change of disability status from 3 months to 1 year post AIS
h: Major disability at 3 months post AIS to death at one year post AIS	14%	Based on analysis using BASIC4 Study data	Assume no change of disability status from 3 months to 1 year post AIS

In order to better predict outcomes of early management of AIS events, we model AIS as module which include multiple events that could occur within one year of the index ischemic stroke. The AIS module has a structure as shown in Figure 7. The post AIS treatment state was further expanded to model hospital arrival and treatment received by AIS patients, as shown in Figure 8. In Figure 8, usual care refers to general supportive care and treatment of acute complications, rtPA refers to intravenous recombinant tissue plasminogen activator, endovascular intervention intra-arterial fibrinolysis, mechanical thrombectomy (clot disruption/extraction), and acute angioplasty and stenting (intracranial or extracranial carotid or vertebral arteries).

Figure 8. Stroke management and outcomes after first AIS



5.2.4 Structure and transition probabilities for nephropathy sub-model

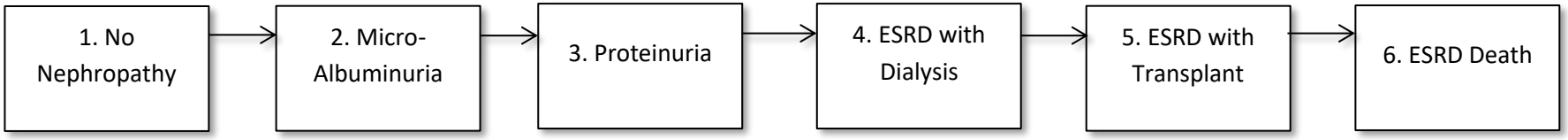


Figure 7. Structure of nephropathy sub-model

Table 7. Transition probabilities in nephropathy sub-model (Figure 7)		
Transition	Transition probability	Comments
1 to 2	0.0509	Gall et al. (1997) - number for 5 year progression in key messages p.787 is 0.23. Adjusted for 1 year from 5 years. ~ 1-(1-0.23)**(1/5)
2 to 3	0.1032	Ravid et al. (1993) (the risk for developing this degree of proteinuria within 5 years of follow-up was 19/45 (42%) in the placebo group. Number adjusted for 1 year from 5 years: 0.1032 ~ 1-(1-0.42)**(1/5)
3 to 4	0.0082	Humphrey et al. (1989): page 791, page 791, after 5 year, 7.0%, 8.4% developed it by 10 years and 11.6% by 15 years, the 15 year number was selected. Number adjusted for 1 year from 15 years: 0.0082 ~ 1-(1-0.116)**(1/15)
4 to 5	0.006 to 0.084 depends on age, gender, and race,	https://adr.usrds.org/2020/chronic-kidney-disease/6-healthcare-expenditures-for-persons-with-ckd This data of the renal transplant rates in dialysis patients in year 2013 was provided by KECC at the University of Michigan. The data was processed using the following criteria: 1) only the data for diabetes as ESRD cause was selected; 2) the data depended on age, gender, and race; 3) the data for White and Black was selected; 4) the data was divided by 100 to represent the yearly transition probability; and 5) the case counts for 0-21 age groups were probably too low to report the rates appropriately, and thus the transplant rates in 22-44 age groups were used for 0-21 age groups.
4 to 6	0.0625 to 0.5344 depends on gender, age, race, hypertension (adjusted by other death causes)	https://usrds.org/media/1708/esrd_ref_h_mortality_2018.xlsx Table H.2_adj The data from the USRDS table was processed using the following criteria: 1) only the data for diabetes was selected; 2) the data depended on age, gender, and race; 3) the data was

		divided by 1,000 to represent the yearly transition probability; 4) based on average between 2011- 2016.
5 to 6	0.0083 to 0.2487 depends on gender, age, race, hypertension (adjusted by other death causes)	https://usrds.org/media/1708/esrd_ref_h_mortality_2018.xlsx Table H.10_adj The data from the USRDS table was processed using the following criteria: 1) only the data for diabetes was selected; 2) the data depended on age, gender, and race; 3) the data was divided by 1,000 to represent the yearly transition probability; 4) based on average between 2011- 2016.

5.2.5 Structure and transition probabilities for neuropathy sub-model

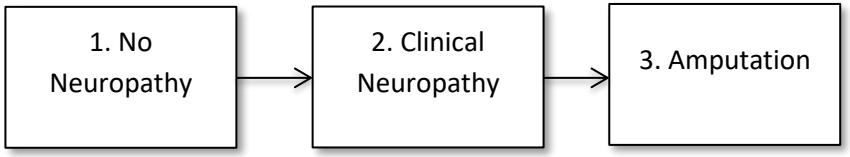


Figure 8. Structure of neuropathy sub-model

Table 8. Transition probabilities in neuropathy sub-model (Figure 8)		
Transition	Transition probability	Comments
1 to 2	0.0518	Sands et al. (1997), Table 1 - first line. Note that in the future it may be possible to use sex or age covariates using the same table data.
2 to 3	0.0113	Adler et al. (1999), Table 4 - last row. Note that the table considers only men, in the future other data may be considered.

5.2.6 Structure and transition probability for retinopathy sub-model

Two eyes are modeled separately and assume to be independent. Retinopathy, macular edema are two parallel sub-sub-processes.

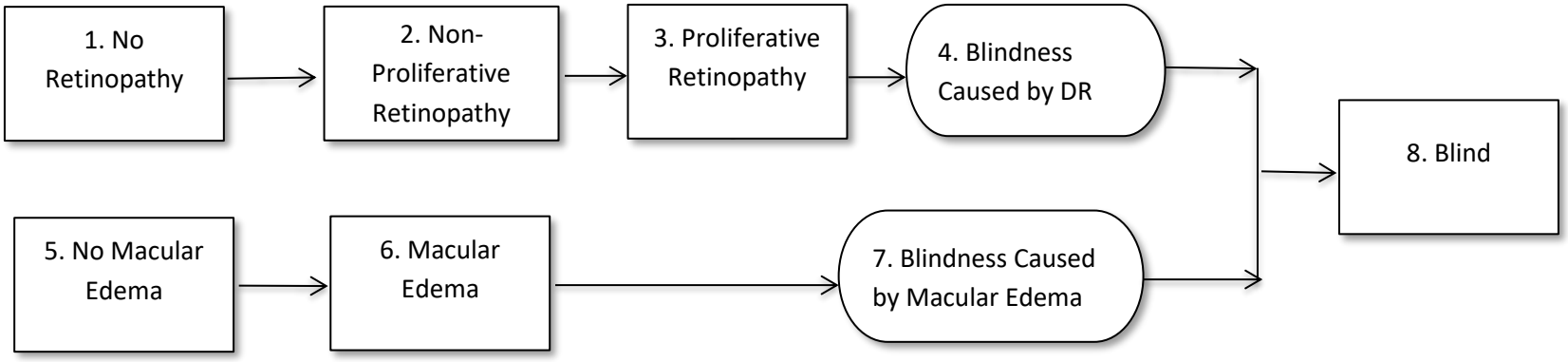


Figure 9. Structure of retinopathy sub-model

Table 9. Transition probabilities in retinopathy sub-model (Figure 9)		
Transition	Transition probability	Comments
1 to 2	0.0653 for diabetics who do not need Insulin treatment 0.1140 for diabetics who need Insulin treatment	Klein (1994), Table 8: 70.2% 10-yr progression rate was used for insulin-taking group and 49.1% 10-yr progression rate was used for non-insulin-taking group. The first row and the progression column for both categories were selected. Numbers were adjusted for 1 year progression 0.1140 ~ 0.114024676 = 1- (1-0.702)**(1/10), 0.0653 ~ 0.065301 = 1- (1-0.491)**(1/10).
2 to 3	0.0390 for diabetics need Insulin treatment 0.0233 for diabetics who do not need Insulin treatment	Klein et al. (1994), Table 8: 70.2% 10-yr progression rate was used for insulin-taking group and 49.1% 10-yr progression rate was used for non-insulin-taking group. The first row and the progression column for both categories were selected. Numbers were adjusted for 1 year progression 0.1140 ~ 0.114024676 = 1- (1-0.702)**(1/10), 0.0653 ~ 0.065301 = 1- (1-0.491)**(1/10).

3 to 4	0.0148 for diabetics need Insulin treatment 0.0166 for diabetics who do not need Insulin treatment	Moss et al. (1994), Table 2: Only older onset numbers were used, the last 4 rows were used (Severity 60-85 - PDR) Incidences were calculated from multiplying % Incidence with Number of risk at each row. Both rounded and not rounded incident counts were close. The rounded calculation was selected. The sum of incidences was divided by the total number at risk to obtain the 10 year probability. The 1 year equivalent transition probabilities were calculated. Since there were no incidences of Blindness for non-taking Insulin at this age group, an assumption is made. The assumption is that the chance of blindness from Proliferative is the same as the probability from Non-Proliferative. These numbers are temporary and require modification
5 to 6	0.0308	Klein et al. (1995), Table 3: Numbers were calculated by summing all the incidents from all rows in the table except the first and last rows. Only older onset numbers were used. Incidences were calculated from multiplying % Incidence with Number of risk at each row. Both rounded and not rounded incident counts were close. The rounded calculation was selected. The sum of incidences was divided by the total number at risk to obtain the 10 year probability. The 1 year equivalent transition probabilities were calculated. See the XL spreadsheet for detailed calculations.
6 to 7	0.0148 for diabetics need Insulin treatment 0.0166 for diabetics who do not need Insulin treatment	It was decided to use progression probabilities similar to the transition from Proliferative to blindness. The reason these were used is that Moss et al. (1994) Table 3 shows Macular Edema has similar loss in the visual angle to Proliferative retinopathy in the taking insulin column (60.7 vs. 52.0, 69.2, 50.0, 81.2). This is an assumption that will be kept until a reference with more information is introduced. Note that for non insulin takers, the number actually originates from the non-proliferative to Blindness transition since the proliferative to Blindness transition inherits this number.
4 to 8	1	
7 to 8	1	

5.2.7 Structure and transition probability for other death sub-model

The "Other Death" sub-model was developed using NHANES mortality data for NHANES wave 2001-2014. Survey weights were included in the analysis to allow the prediction of this model applied to a national representative data.

Table 10. Parameters in the prediction model for risk of other death in one year			
	log(HR) (β)	HR (95% CI)	P-value
H_0(1 year) = 0.00608			
SBP (mmHg)	0.0079	1.0079 (1.0027, 1.013)	0.003
DBP (mmHg)	-0.0074	0.003 (0.986, 0.9998)	0.044
BMI (kg/m^2)	0.0013	1.0013 (0.988, 1.012)	0.86
BMI^2	0.0021	1.0021 (1.0012, 1.003)	<0.001
Log(TotalCholesterol) (mmol/L)	0.157	1.17 (0.75, 1.83)	0.49
(Log(TotalCholesterol))^2	1.40	4.05 (1.96, 8.36)	<0.001
Age (year)	0.071	1.074 (1.059, 1.089)	<0.001
Log(HDLCholesterol) (mmol/L)	-0.603	0.555 (0.368, 0.815)	0.003
Male (Yes vs. No)	0.315	1.37 (1.083, 1.73)	0.009
ESRD Dialysis (Yes vs. No)	1.60	4.95 (2.74, 8.93)	<0.001
History of heart failure (Yes vs. No)	0.781	2.18 (1.66, 2.87)	<0.001
History of stroke (Yes vs. No)	0.294	1.34 (1.013, 1.78)	0.041
SBP centered at 132 BMI centered at 35 Log(Total Cholesterol) centered at 1.5 Log(HDL Cholesterol) centered at 0.2 Age centered at 65.5			

To calculating probability of death in one year, use the following equation:
Probability of death at 1 year= 1- exp(-H_0(1 year)× exp(Xβ))

5.3. Severe hypoglycemia event

MMD 3.0 models rate of severe hypoglycemia eveny by level of anti-hyperglycemia treatment

Table 11. Parameters in the prediction model for risk of other death in one year		
Anti-hyperglycemia treatment	Incidence rate	Comments
Intensive lifestyle (diet and exercise/weight loss)	None	
Metformin (one OAD/non-insulin med)	None	
Metformin + Sulfonylureas (two OADs/non-insulin meds)	0.004 event per person per year	Zoungas et al. (2010)
Add Basal insulin to OAD/non-insulin med	0.02 event per person per year	1. Event per patient per year, median 0; 4 events in 243 patients (1.7%) (Holman et al., 2007) 2. 0 severe event in LANMET study (Yki-Järvinen et al., 2006) 3. 0.03 event per patient per year (Bretzel et al., 2008)
Intensive insulin therapy	0.12 event per person per year	0.02-0.35 event per patient per year (Zammitt and Frier, 2005)

5.4 Treatment Module

Different from other proposed models, MMD 3.0 allows a user to control risk factor changes for the following seven types of treatments and one behavior change:

- Treatment for hyperglycemia
- Treatment for hypertension
- Treatment for dyslipidemia
- Beta-blocker treatment
- Anti-platelet treatment
- Anti-coagulant treatment
- Smoking cessation

Given the fact that modern medicines have largely decreased the complication rate in type 2 diabetes through management of these risk factors, it is important to explicitly model these management strategies and allow users to modify them to match the specific scenarios that they are simulating. For example, MMD explicitly models the treatment regimen for hyperglycemia through five treatment stages. Figure 10 shows a mock trajectory of A1c over time under this treatment regimen using 7% as the treatment threshold.

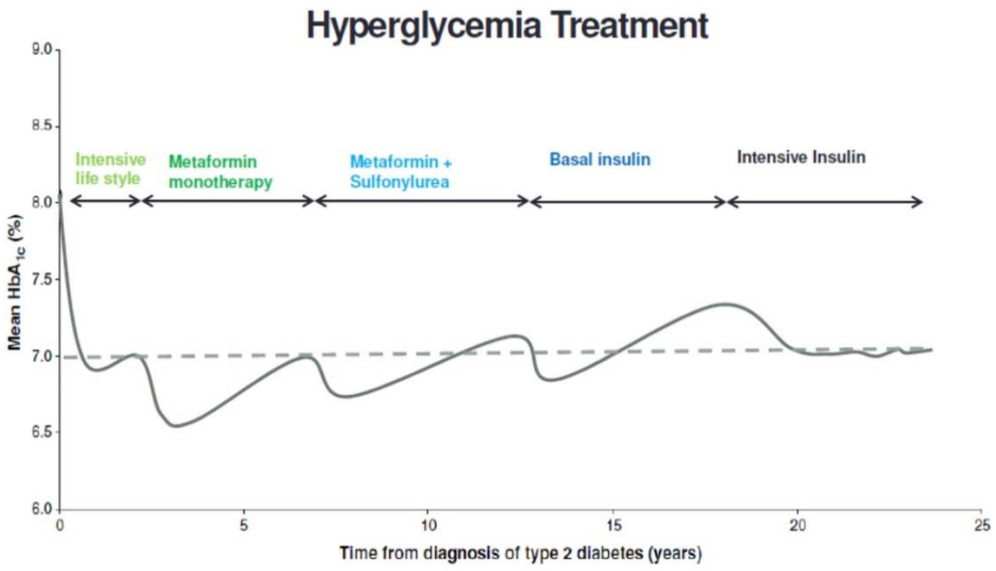


Figure 10. Mock individual trajectory of A1c over time under MMD antiglycemia treatment regimen using 7% as the treatment threshold.

5.4.1. Yearly evaluation and treatment updating rules

The treatment regimens in MMD 3.0 modifies were developed based on guidelines recommendations by the American Diabetes Association (ADA), American Heart Association (AHA), and American Stroke Association (ASA).

At the beginning of reach simulation interval (year), the model algorithm first define whether a patient needs initiation of enhancement of certain treatment based on levels of risk factors, disease history or diagnosis, the maximum level of treatment available, and then make the change according to individual adherence characteristics. The Table 11 describes the treatment updating rules that defines whether an individual needs an update.

Table 12. Treatment updating rules

Treatment/Medication	Updated Rules	References
Anti-diabetes treatment	For age<65, treatment level+1 if A1c>=7 For age>=65, treatment level+1 if A1c>=7.5	American Diabetes Association. Glycemic Target, 2022; Fox et al., 2015; Inzucchi et al, 2015; Ismail-Beigi et al, 2011
Anti-hypertensive treatment	If SBP>=140 OR DBP>=90, treatment level+1	American Diabetes Association. Cardiovascular disease and risk management. 2022; Meschia et al., 2014
ACE-I/ARB	Assume anyone needs additional anti-hypertensive drug is getting ACE-I/ARB.	
Anti-dyslipidemia treatment (Statin)	If ASCVD score>=0.2, high dose statin (trt level=2) If age in [50, 70), high dose statin (trt level=2) Moderate potency for all other cases (trt level=1)	American Diabetes Association. Cardiovascular disease and risk management. 2022;
β-blocker	β-blocker should be used in patients with Heart failure with reduced ejection fraction or after MI in patients with preserved left ventricular function	American Diabetes Association. Cardiovascular disease and risk management. 2022;
Warfarin/NOAC	If has atrial fibrillation/atrial flutter and CHADS 2 Score>=2	Meschia et al., 2014
Aspirin/Clopidogrel	For age<50 or age >=70, aspirin/clopidogrel is not recommended. For 50<=age<70, recommendations for using aspirin as primary prevention include both men and women aged>=50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking or chronic kidney disease/albuminuria) who are not at increased risk of bleeding.	American Diabetes Association. Cardiovascular disease and risk management. 2022;
Non-smoking	Advise all patients not to use cigarettes and other tobacco products or e-cigarettes	American Diabetes Association. Foundations of care, 2022

5.4.2. Adherence

5.4.2.1 Adherence to medication treatment

Not all patients adhere to recommended treatments. One review found that adherence to oral antidiabetic agents ranged from 36 to 93% across studies and that adherence to insulin was ~63% (Cramer, 2004). In MMD 3.0, the user can adjust adherence rate for each treatment (i.e. adherence to treatment for hyperglycemia, treatment for hypertension, treatment for dyslipidemia, beta-blocker treatment, anti-platelet treatment, anti-coagulant treatment) to adjust risk factor changes over time.

For simplicity, we assume adherence to each type of treatment is a fixed characteristic of individual patients and does not change before cardiovascular event happens. For each treatment, user defines a rate of adherence in the simulation population. The program then randomly assign a simulated patient to be adherent or non-adherent based on this population adherence rate.

In addition, we assume when a MI, CHF, or stroke event happens to a patient, he/she might change to adhere to all treatments he/she does not adhere to before the events happen. This adherence parameter is a fixed characteristic of an individual as well.

To implement the above treatment and compliance rules, the simulation program does the following. Before the simulation starts, each patient is assigned a treatment-specific compliance profile that includes seven variables: one for adherence with CVD history and six for treatment-specific adherence rates.

We simulate these adherence variables in a hierarchical structure. For ease of exposition, let's assume 90% of patients comply with all treatments when there is a CVD event, 80%, 70%, 60%, 50%, and 40%, 30% adhere to treatment for hyperglycemia, beta-blocker, dyslipidemia, hypertension, and anti-platelets, and anti-coagulants, respectively. This means 90% of patients will be adherent to all treatments after experiencing a MI, stroke, or CHF event. Among the above 90% of patients, 8 out of 9 (80% of the initial sample) adhere to treatment for hyperglycemia regardless of their CVD complication history; among the 80% of adherent patients with treatment for hyperglycemia, 7 out of 8 (70% of the initial sample) adheres to beta-blocker treatment, etc.; among the total population, 30% adheres to all six treatments regardless of their CVD complication history.

5.4.2.2 Adherence to smoking cessation

All smokers quit smoking each year at a user-specified yearly rate.

5.4.3 Treatment effects on risk factors

At the beginning of each simulation cycle (year), after the algorithm decides treatment changes based on treatment rules and an individual's adherence characteristics, the program calculates the immediate change in weight, HbA1c, lipids and blood pressures, and update these risk factors accordingly.

5.4.3.1 Antiglycemic treatment and weight and HbA1c

MMD 3.0 models six level of antiglycemic treatments

0: No treatment
1: Diet and exercise
2: Oral antidiabetic drug (OAD) /non-insulin medication (metformin)
3: Two oral/non-insulin medications (metformin + sulfonylureas)
4: Basal insulin + OAD
5: Intensive bolus insulin

Change of antiglycemic treatment directly affects weight and HbA1c level in MMD 3.0.

Table 13. Changes of body weight under different anti-hyperglycemia treatment		
Anti-hyperglycemia treatment	Initial effect (first year change)	Comments
No treatment → Intensive lifestyle	Mean change=-3.7kg SD of change=3.5kg	Baseline 80.4kg (SD 15.6 kg) UKPDS 13 (1995)
Intensive lifestyle → one OAD	Mean change=-2kg SD of change=0.3kg	Kahn et al. (2006)
One OAD → two OADs	Mean change=2kg SD of change=1kg	Phung et al. (2010)
two OADs → basal insulin + OAD	Mean change=1.9kg SD of change=4.2kg	Holman et al. (2009)
basal insulin + OAD → Intensive insulin therapy	Mean change=1.2kg SD of change=0.5kg	Rosenstock et al. (2009)

Table 14. Changes of HbA1c under different anti-hyperglycemia treatment scenarios		
Anti-hyperglycemia treatment	Initial effect (first year change)	Comments
No treatment → Intensive lifestyle	Mean change=-1.9%-0.5*(currentHbA1c-9.1%) SD of change=abs(mean change)/3	UKPDS 13 (1995)
Intensive lifestyle → one OAD	Mean change=-1.0%-0.5*(currentHbA1c-8.3%) SD of change=abs(mean change)/3	Sherifali et al. (2010)
One OAD → two OADs	Mean change=-0.8%-0.5*(currentHbA1c-8.3%) SD of change=abs(mean change)/3	Phung et al. (2010)
two OADs → basal insulin + OAD	Mean change=-0.8%-0.5*(currentHbA1c-8.4%) SD of change=abs(mean change)/3	Holman et al. (2007)
basal insulin + OAD → Intensive insulin therapy	Mean change =-0.45-0.5*(currentHbA1c-8.2) SD of change=0.16	Holman et al. (2009)

When a patient newly adapts to intensive lifestyle treatment, the model also applies 6 mmHg and 3 mmHg decrease in SBP and DBP, respectively.

5.4.3.2 Anti-dyslipidemia treatment and lipids level

MMD 3.0 models three level of anti-dyslipidemia treatments

0: No treatment
1: low dose statin Moderate potency statin
2: high dose statin High potency statin

For each of these two levels, the drug-induced change is 25% decrease, 5% increase, and 6% decrease in LDL-C, HDL-C, and triglyceride, respectively.

5.4.3.3 Anti-hypertensive treatment, beta-blocker treatment and blood pressure level

MMD 3.0 models seven level of anti-hypertensive treatments.

1. No treatment
2. One medication with half dose
3. One medication with full dose
4. Two medications, including 1st medication with full dose and 2nd medication with half dose
5. Two medications, including 1st medication with full dose and 2nd medication with full dose
6. Three medications, including 1st medication with full dose, 2nd medication with full dose, and 3rd medication with half dose
7. Three medications, including 1st medication with full dose, 2nd medication with full dose, and 3rd medication with full dose

β-blocker treatment is only triggered by MI, or CHF, but not by blood pressures higher than treatment threshold. Although it does decrease BPs, it is NOT counted for the seven level of anti-hypertensive treatments. We assume ACE-I/ARB is always the first drug to be added regardless of whether a patient is receiving β-blocker or not.

Table 15. Effect of beta-blocker and anti-hypertensive treatment	
Non-β-blocker anti-hypertensive treatment effect	
Anti-hypertensive treatment change	Drug effect
No drug → one drug half standard dose	If patient is not already on β-blocker Median change of SBP in mmHg =-6.9-0.08(SBP-150) Median change of DBP in mmhg =-3.7-0.09(DBP-90) If patient is already on β-blocker Median change of SBP in mmHg =-3.4- 0.04(SBP-150) Median change of DBP in mmHg =-1.8- 0.04(DBP-90)
Already on drug → receive an increase of treatment of n levels (n=1,2)	Median change of SBP in mmHg =-n×3.4- n×0.04(SBP-150) Median change of DBP in mmHg =- n×1.8- n×0.04(DBP-90)
No drug → β-blocker + anti-hypertensive drug (default ACE-I/ARB	Median change of SBP in mmHg =-7.4 -3.4-(0.08+0.04)×(SBP-150) Median change of DBP in mmHg =-5.6-1.8-(0.09+0.04)×(DBP-90)
β-blocker anti-hypertensive effect	
If the patient is not other anti-hypertensive treatment Median change of SBP in mmHg =-7.4 -0.08(SBP-150) Median change of DBP in mmHg =-5.6-0.09(DBP-90) If the patient is already on other anti-hypertensive treatment Median change of SBP in mmHg =-3.4- 0.04(SBP-150) Median change of DBP in mmHg =-1.8- 0.04(DBP-90)	

5.4.4 Treatment direct effect on risk of complications

Table 16. Medication direct effect on risk of complications (not mediated through risk factors)				
Treatment/Medication	Direct risk reduction (hazard ratio)			
	MI event risk	CHF event risk	Ischemic stroke event risk	Hemorrhagic stroke event risk
Statin	0.66 (Freemantle et al., 1999)			
ACE-I/ARB	0.8 (Hope Study Investigators, 2022)	0.75 (Cheng et al., 2014)		
Warfarin			0.32 (Kahwati et al., 2022)	1.94 (Kahwati et al., 2022)
NOAC			0.256 (Kahwati et al., 2022; Patti et al., 2017)	1.82 (Kahwati et al., 2022)
Aspirin/Clopidogrel	0.8 for Male (Pignone et al., 2010)		0.88 (ASCEND Study Collaborative Group, 2018)	
β-blocker	0.8 for subjects who are 70 years of age or older or African American, and 0.7 otherwise (Freemantle et al., 1999; Cheng et al., 2014)	0.8 (Garcia-Egido et al., 2015)		

When multiple medications with direct risk reduction are taken by an individual, the maximum of risk reduction among the medications are used. For example, for an individual who is taking statin and ACE-I/ARB at the same time, 34% risk reduction is used for MI event.

5.5 Risk Factors Progression Module

MMD 3.0 also models diabetes progression through risk factor changes over time.

After simulating complication events, the model will generate changes for each of the risk factor from the start to the end of the simulation year and apply the change to calculate updated risk factor levels.

5.5.1. Change in body weight

Table 17. Yearly change of body weight under different anti-hyperglycemia treatment		
Anti-hyperglycemia treatment		**Comments**
No treatment	Mean change=0.8kg/year SD of change=0.3kg/year	
Intensive lifestyle	Mean change=1kg/year SD of change=0.3kg/year	UKPDS 13 (1995)
one OAD	Mean change=-0.3kg/year SD of change=0.3kg/year	Kahn et al. (2006)
two OADs	Mean change=0 kg/year SD of change=0.3 kg/year	Phung et al. (2010)
basal insulin + OAD	See the following paragraph for more details	These equations were derived based on our analysis using ACCORD data
Intensive insulin therapy		

Body weight change among people taking insulin.

1. For a person who just started taking insulin or started taking insulin less than 2 years ago, MMD calculate the yearly change body weight using the following equation

Annual weight change=0.6888-0.0255×Age at insulin treatment initiation -0.0104 × BMI at insulin treatment initiation + 0.3285 × A1c at insulin treatment initiation + 3.454 × ε, where $\varepsilon \sim N(0,1)$

2. For a person who has been on insulin for more than 2 years, MMD calculate the yearly change body weight using the following equation

Annual weight change=0.0595-0.0426×current -0.0492 × current BMI -0.0663 × current A1c + 3.147× ε, where $\varepsilon \sim N(0,1)$

5.5.2. Change in HbA1c

Table 18. Yearly change of HbA1c under different anti-hyperglycemia treatment scenarios		
Anti-hyperglycemia treatment	Changes after one year	Comments
No treatment	Mean change=0.35%/year SD of change=abs(mean change)/3	UKPDS Group (1998) Figure 2 showed 1.5% increase in 6 years. It was arbitrarily increased to reflect faster increase without any treatment. An arbitrary variation was added to allow the change to be between zero and twice the value calculated from the references.
	Mean change=0.2%/year	UKPDS 33 (1998)

Intensive lifestyle	SD of change=0.2/3	
One OAD	Mean change=0.14%/year SD of change=0.14/3	Kahn et al. (2006)
Two OADs	Mean change=0.2%/year SD of change=0.2/3	Charbonnel et al. (2005)
basal insulin + OAD	Mean change=0.2%/year SD of change=0.2/3	Rhoads et al. (2011)
Intensive Insulin	Mean change = 0%/year SD of change=0.1%	Holman et al. (2009)

5.5.3. Change in lipids

Annual changes in lipids are calculated based on three equations derived from secondary analysis using a multivariate model and ARIC, CHS, and CARDIA datasets.

All changes are first calculated for log (e-based) transformed lipid levels based on level of log(HDL), log(LDL), log(triglycerides) at the beginning of the year, change of log (e-base) transformed fasting glucose and change in BMI from the start to the end of the year, age, and sex.

In order for simulate correlated changes in HDL, LDL, and triglycerides, we first simulate three independent standard normal variables, ε_1, ε_2, and ε_3. Then correlated variations in change of the three lipids were added to the calculated mean change levels based on the covariance matrix estimated in the above multivariate model, as shown the following three equations.

Table 19. Equations for calculating change in lipids	
Lipids	Equations
Change in log (HDL)	$0.0340 + Age \times (-.00112) + Age^2 \times 0.0000117 + \log(triglycerides) \times (-.0145) + \log(LDL) \times (-.000961) + \log(HDL) \times (-.0844) +$ change in log(fastingGlucose) $\times (-.0364) +$ change in BMI $\times (-.00414) + Female \times (0.0147) + 0.0648 \times \varepsilon_1$
Change in log (LDL)	$0.0738 + Age \times 0.00412 + Age^2 \times (-.0000463) + \log(triglycerides) \times (0.0114) + \log(LDL) \times (-.138) + \log(HDL) \times (0.00620) +$ change in log(fastingGlucose) $\times$ $0.0821 +$ change in BMI $\times 0.00906 + Female \times 0.00600 + 0.111 \times \varepsilon_1 + 0.00206 \times \varepsilon_2$
Change in log (triglyceride)	$-.157 + Age \times 0.00728 + Age^2 \times (-.0000660) + \log(triglycerides) \times (-.112) +$ $\log(LDL) \times 0.0189 + \log(HDL) \times (-.0496) +$ change in log(fastingGlucose) $\times 0.268 +$ change in BMI $*0.0275 + Female*0.0215 + 0.1359 \times \varepsilon_1 + 0.00734 \times \varepsilon_2 - 0.0189 \times \varepsilon_3$

5.5.4. Change in BPs

Annual changes in SBP and DBP are calculated based on two equations derived from secondary analysis using a multivariate model and ARIC, CHS, and CARDIA datasets.

All changes are first calculated for SBP and DBP levels based on level of SBP and DBP at the beginning of the year, change in BMI from the start to the end of the year, age, and race.

In order for simulate correlated changes in SBP and DBP, we first simulate two independent standard normal variables, ε_4 and ε_5. Then correlated variations in change of the two BP levels were added to the calculated mean change levels based on the covariance matrix estimated in the above multivariate model, as shown in the following two equations.

Table 19. Equations for calculating change in BPs	
Lipids	Equations
Change in DBP	-0.2+Age × 0.28+DBP × 0.031+SBP × 0.031+Age × SBP × (-0.00077)+Age × DBP × (-0.0031) + BMI_Diff × 0.37+Female × (-0.38)+AfricanAmerican × 0.57+2.58 × ε_4
Change in SBP	-34.7+Age×1.02+DBP×0.132+SBP×0.186+Age×SBP× (-0.0059)+Age×DBP× (-0.0027)+BMI_Diff × 1.79 + Female × 0.53 + AfricanAmerican × 0.97 + 7.3 × ε_4+2.5 × ε_5

5.6 Costs Module

Table 20. Costs of complications for Michigan Model for Diabetes			
Event and ongoing costs of complications for Michigan Model for Diabetes	**2014 US dollars[b]**		**Sources**
	Event	**Ongoing**	
Baseline cost[a]		2,315	Brandle et al., 2023
Retinopathy			
Nonproliferative retinopathy	103	103	O'Brian et al., 2000
Macular edema or proliferative retinopathy	1,101	103	
Blindness	2,951	2,951	Ward et al., 2014
Nephropathy			
Microalbuminuria	437	437	Nichole et al., 2011
Proteinuria	748	748	
End-stage renal disease with hemodialysis	99,046	99,046	U.S. Renal Data System, USRDS 2013 Annual Data Report
End-stage renal disease with renal transplant	138,071	44,331	
Neuropathy			
Clinical neuropathy	511	511	O'Brian et al., 2000
Amputation	42,929	1,500	
Coronary heart disease			
Angina	8,282	2,139	O'Brian et al., 2000
Myocardial infarction	41,744	2,307	
Percutaneous transluminal coronary angioplasty[c]	8,282	2,139	
Coronary artery bypass graft[c]	60,685	2,307	
Myocardial infarction with coronary artery bypass graft[c]	60,685	2,307	
Congestive heart failure	34,635	7,620	Liao et al., 2006
Cerebrovascular disease			
Ischemic stroke	55,278		O'Brian et al., 2000
With no/minor disability after ischemic stroke		10,311	O'Brian et al., 2000; O'Brian and Gage, 2005; Freeman et al., 2011; Harrington et al., 2013;
With major disability after ischemic stroke		26,585	
Hemorrhagic stroke	153,633	34,268	

			Nguyen et al., 2016
Hypoglycemia requiring hospitalization	16,991		Ward et al., 2014
Death, by age in years[c]			
74 or younger	74,776	NA	
75-84	60,778	NA	
85 or older	41,156	NA	

[a]The baseline cost is the annual direct medical cost for a white man with type 2 diabetes and BMI of 30 kg/m^2 who is treated with diet and exercise and has no microvascular, neuropathic, or cardiovascular complications.
[b]Costs are expressed in year 2014 US dollars using the general Consumer Price Index to reflect inflation.
[c]These data were from email consultation with Dr. Christopher Hogan on March 19, 2015, who is the president of Direct Research, LLC in Vienna, VA. These costs of death were the incremental per capita medical payments between the diabetes survivors in 2012 (costs in the year of 2012) and the diabetes decedents in 2012 (costs in the last 12 months of life) who were Medicare fee-for-service beneficiaries with Part A and Part B enrollment and with any diagnosis of diabetes on any physician or hospital (inpatient or outpatient) claims in 2011 and 2012.

Table 21. Costs of Medications for Michigan Model for Diabetes (details of deriving these numbers are omitted).

	2014 US dollars[b]	Comments and sources
Medication cost (per year)		
Warfarin	$471.8	Including drug and monitoring costs
NOAC	$5,495	Micromedex 2.0
Aspirin	$4	Micromedex 2.0
Hypertensive treatment		
Level 1: One med with half dose	$22	Micromedex 2.0
Level 2: One med with full dose	$29	
Level 3: Two meds, including 1st med with full dose and 2nd med with half dose	$62	
Level 4: Two meds, including 1st med with full dose and 2nd med with full dose	$44	
Level 5: Three meds, including 1st med and 2nd med with full dose, and 3rd med with half dose (per year)	$77	
Level 6: Three meds, including 1st med, 2nd med, and 3rd med with full dose	$84	
Treatment for hyperglycemia		
Level 1: Intensive lifestyle (IL)	$1,482	Micromedex 2.0
Level 2: One non-insulin medication	$502	
Level 3: Two non-insulin medications	$936	
Level 4: Add basal insulin[1]	$5,504	
Level 5: Intensive insulin therapy (basal/bolus)[2]	$16,488	
Statin		
Moderate potency	$135	Micromedex 2.0
High potency	$135	

5.7 Quality of Life Module

Table 22. Penalty functions for QWB-SA health utility scores			
Disease status/characteristics	Complication Level	QWB-SA Penalty	Sources
	Intercept	0.689	Coffey et al., 2002
Sex	Male	(Ref)	
	Female	-0.038	Coffey et al., 2002
BMI (kg/m^2)	Obese (BMI ≥30)	-0.021	
Diabetes Intervention	None or diet only	(Ref)	
	Oral/non-insulin antidiabetic agents	-0.023	Coffey et al., 2002
	Insulin	-0.034	
Retinopathy	Both eye are not blind	(Ref)	
	Non-proliferative retinopathy	-0.000	Coffey et al., 2002
	Macular edema or proliferative retinopathy	-0.000	
	Blind in one eye	-0.043	
	Blind in two eyes	-0.170	
Nephropathy	No nephropathy	(Ref)	
	Microalbuminuria or proteinuria	-0.011	Coffey et al., 2002
	ESRD dialysis	-0.078	
	ESRD transplant	-0.078	
Neuropathy	No neuropathy	(Ref)	
	Clinical neuropathy	-0.065	Coffey et al., 2002
	Amputation	-0.105	
Cardiovascular disease	No CHD	(Ref)	
	Angina	-0.026[†]	Coffey et al., 2002
	MI/PTCA/CABG	-0.026[†]	Coffey et al., 2002; Zhang et al., 2012
	CHF	-0.052	
Cerebrovascular disease	No history of stroke	(Ref)	
	Ischemic stroke (IS) with no/minor disability after IS	-0.044	Coffey et al., 2002; Rumberger et al., 2010
	Ischemic stroke (IS) with major disability after IS[2]	-0.072	
	History of hemorrhagic stroke (HS)[3]	-0.062	O'Brian and Gage 2005; Freeman et al., 2011; Harrington et al., 2013; Nguyen et al., 2016; Samarasekera et al., 2015
High blood pressure	High BP or on BP medication	-0.011	Coffey et al., 2002
[†]Coffey et al. (2002) did not provide a penalty for having history of Angina or MI/PTCA/CABG. In Zhang et al. (2012), the penalty for other heart disease is approximately half of the penalty for CHF. We therefore imputed the penalty for Angina and MI/PTCA/CABG as half of the penalty for CHF.			

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