Supplementary Data

MMD CHD submodel structure

Model parameters

Given different calibration studies often overlapped with one another in terms of the transitions they described, multiple studies can be involved in obtained parameters for calibrating the same transition as shown in Supplementary Tables S1 and S2.

The age and gender modifier in the *P*(CHF) equations in Supplementary Table S2 are shown in Supplementary Table S3.

Prediction model for the risk of CHF in T2DM based on the CHS

Data source. The CHS was a study of risk factors for the development and progression of CHD and stroke in people 65 years of age and older. The 2,962 women and 2,239 men were recruited and examined yearly from 1989 through 1999. The added minority cohort of 256 men and 431 women was examined from 1992 to 1999. Examination components included medical history questionnaires, echocardiograms, ambulatory electrocardiograms, cerebral magnetic resonance imaging, abdominal and carotid ultrasound studies, measurement of ankle-brachial index, spirometry, and retinal photographs. CHS has undertaken extensive follow-up for ascertainment of cardiovascular events including MI, CHF, stroke, claudication, and death.

Our goal was to develop a long-term prediction model for CHF in T2DM conditional on the subject's history of angina and MI. In the original CHS cohort, 862 subjects had diabetes at the baseline visit without history of CHF, including 416 who had newly diagnosed diabetes (incident cohort) and 446 who had previously diagnosed diabetes (prevalent cohort). Duration of diabetes of the prevalent cohort is unknown. During the median follow-up 10 years, 308 subjects in the prevalent cohort and 134 subjects in the incident cohort developed CHF.

Predictors. Selection of potential predictors was informed by characteristics included in the UKPDS Outcome Models (I and II)[S2,S12] and risk equations for first and second cardiovascular events from Swedish register data.[S13] Initially, 15 risk factors were selected as candidate predictors for the regression model, including history of angina, history of MI, history of angioplasty, history of bypass surgery, atrial fibrillation, most recent value of fasting glucose, low-density lipoprotein, lipid ratio (total cholesterol/high-density lipoprotein), systolic blood pressure, diastolic blood pressure, body mass index (BMI), sex, race, smoking status, and age at CHS study baseline visit. Of these 15 risk factors, sex, race, smoking status, and age at baseline are time-independent covariates; the other nine risk factors are time-dependent covariates.

Data analysis and model selection. Given that duration of diabetes is a very important risk factor for CHF,[S13] one would typically use the incident cohort only to derive the CHF prediction model. However, the smaller number of events in the incidence cohort limited the statistical power for model development. At least 10–20 events per candidate predictor have been proposed in previous guidelines for the development of prediction models.[S14]

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 types (i.e., prevalent cohort and incident cohort). This model allowed us to derive a nonparametric estimation of baseline hazard function for each of the two cohorts separately, while using data from both cohorts to select predictors and estimate corresponding risk coefficients. By including data from both cohorts, we had a total of 442 CHF events, which provided approximately 29 events per candidate predictor. This was more powerful than <10 events per candidate predictor that the incident cohort alone would have provided. This model also allowed us to accommodate both time-independent and time-dependent 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 Weibull model assumes a baseline hazard given by the following function:

$$h_0(t) = \rho t^{\rho - 1} \exp(\lambda)$$

and the hazards model for the i^{th} subject at time t is

$$h(t|x_i(t)) = h_o(t) \exp(\beta x_i(t)) = \rho t^{\rho - 1} \exp(\lambda + \beta x_i(t))$$

where $x_i(t)$ is a vector of the risk factors for subject i at time t.

This two-step strategy allowed us to derive a Weibull proportional hazard model with time-dependent and time-independent predictors. Ideally, a one-step analysis to fit a Weibull proportional hazard model is preferred. However, such a model requires modeling the multiple longitudinal factors simultaneously, and no existing software is available. Supplementary Figure S3 compares the nonparametric cumulative baseline hazard from the Cox proportional hazard model and the fitted Weibull function. The Weibull function fits the nonparametric function very well.

Before any modeling was performed, the distributions of all potential predictors were carefully examined for extreme values. Biologically implausible values were set to missing values, and the remaining extreme values were truncated by shifting the values below 1 centile and above 99 centile to ''truncated points.'' Such truncation may prevent distortion of the relationship between predictor and outcome due to high leverage of the extreme values.

To define appropriate transformation of continuous variables, we used p-spline[S15] functions to explore the potential nonlinear effect of potential continuous predictors. The only continuous predictor that has a nonlinear function form is BMI. Based on visual inspection, we assumed no BMI effect until the centered BMI (centered at 28.2) was approximately equal to 5, and a linear effect for centered BMI >5. Therefore we used linear splines with one knot at BMI = 33 (centered BMI = 4.2) to model the BMI effect. The χ^2 test showed that

this transformed BMI variable provided a significantly better fit ($P = 0.012$).

To select the best prediction model, we used a stepwise selection procedure with higher than standard P value. We used Akaike's Information Criterion, which implies a P value <0.157 for selection of predictions with 1 degree of freedom.

Results. The stepwise selection approach selected a model with 10 predictors. Estimated regression confidents are reported in Supplementary Table S4. The C-index for this model varies from 0.678 to 0.699 at 1 to 10 years, indicating acceptable discrimination. Using nonlinear regression analysis we fitted a Weibull baseline cumulative function to the estimated nonparametric baseline function of the incidence cohort strata (Supplementary Fig. S3). The estimated Weibull function parameters (ρ and λ) are also shown in Supplementary Table S4.

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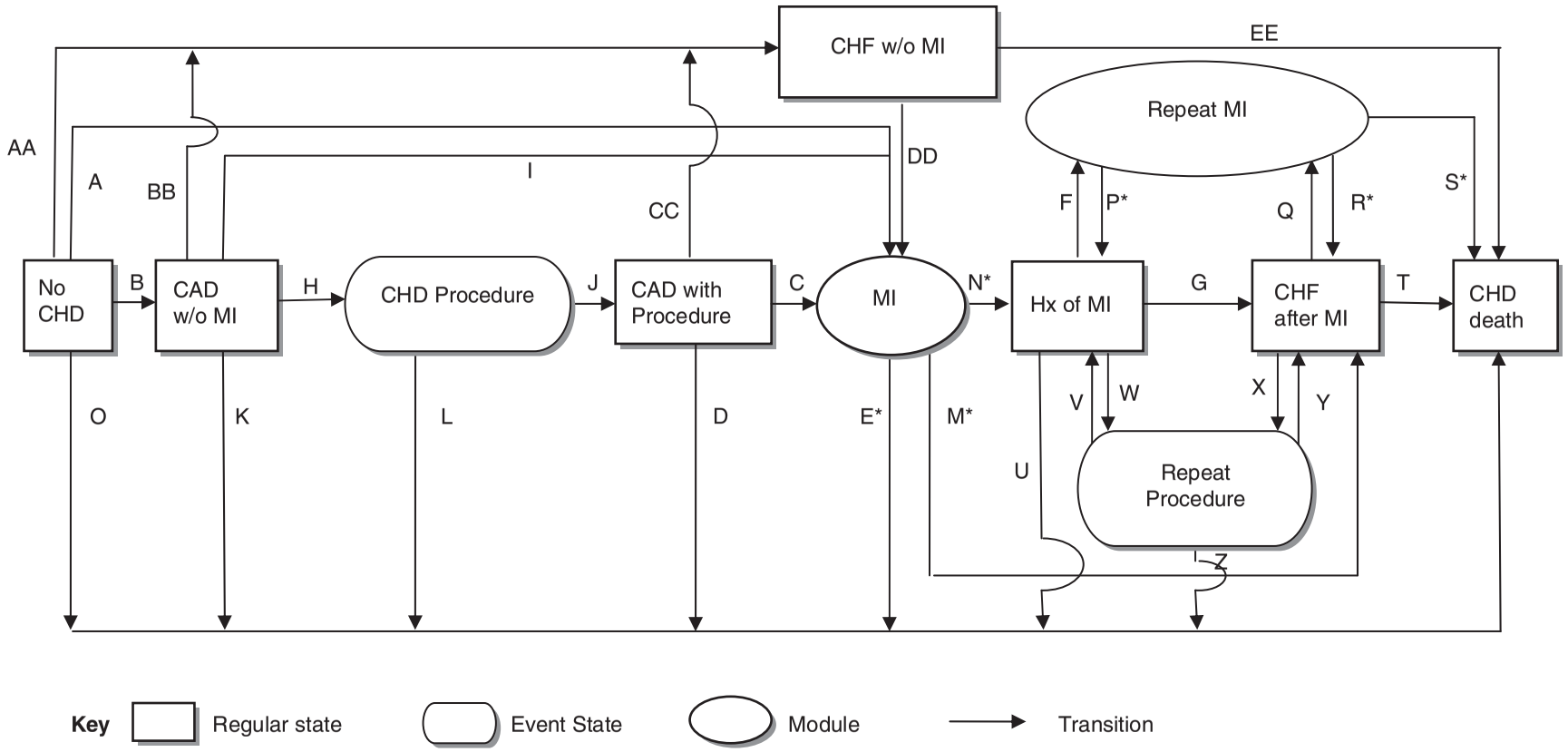
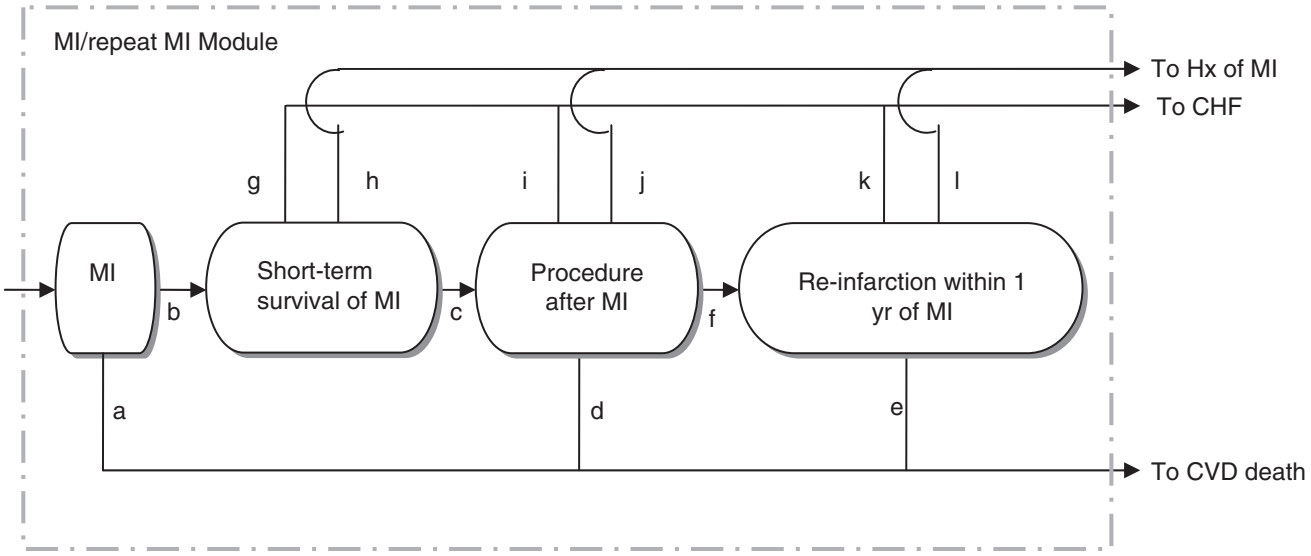
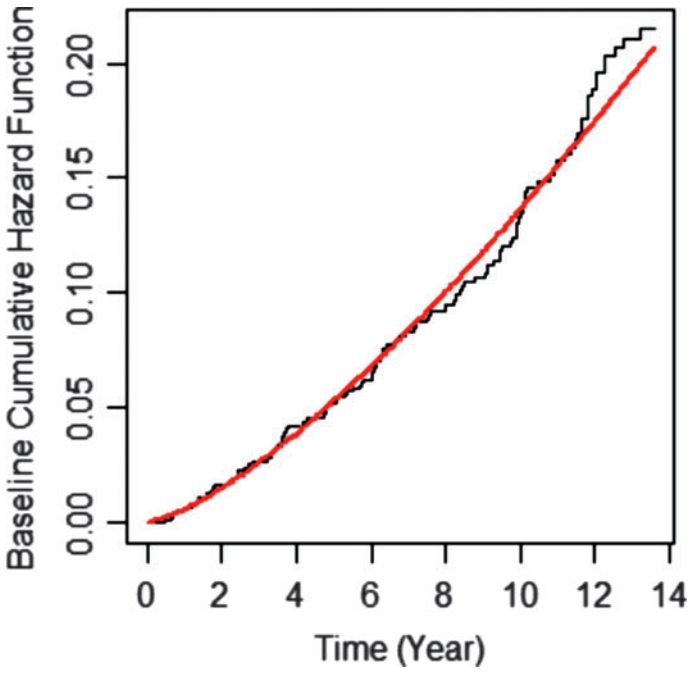


SUPPLEMENTARY FIG. S1. CHD states and progression. CAD w/o MI, CAD without MI; CHD Procedure, revascularization procedure; CHF, CHF after experience of MI; CHF w/o MI, CHF without MI; Hx, history.



SUPPLEMENTARY FIG. S2. MI module. Rectangles indicate regular states, and ovals indicate instant state.



SUPPLEMENTARY FIG. S3. Weibull baseline cumulative hazard functions.

SUPPLEMENTARY TABLE S1. CALIBRATION AND REFERENCES FOR TRANSITION PROBABILITIES IN THE MAIN CHD MODEL (FIG. S1)

Transition	*Transition probability*	*Calibration*	*Risk factors*[a]	*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 of 0.7.	Calibrated to Avogaro et al.[S1] with men and women separately	Age, gender, race, smoking, A1c, SBP, lipid ratio, and medications	Avogaro et al.,[S1] Clarke et al.[S2]
B (No CHD → CAD without MI)	UKPDS IHD equation adjusted for medication benefit and by additionally adjusting the hazard function by a factor of 3			
O (No CHD → CVD death)	UKPDS MI equation (IHD = 0, CHF = 0) adjusted for medication benefit and by additionally adjusting the hazard by a factor of 0.091			
AA (No CHD → CHF without MI)	CHS risk equation (Prediction model section in Supplementary Data; Angina = 0, 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 et al.[S3]
K (CAD without MI → CVD death)	The UKPDS MI equation (IHD = 1, CHF = 0) adjusted for medication benefit and by additionally adjusting the hazard by a factor of 0.668	Calibrated to placebo groups of Colhoun et al.[S4]	Age, sex, race, smoking, A1c, SBP, lipid ratio, and medications	Clarke et al.,[S2] Colhoun et al.[S4]
I (CAD without MI → MI)	The UKPDS MI equation (IHD = 1, CHF = 0) adjusted for medication benefit and by additionally adjusting the hazard by a factor of 1.68			
H (CAD witout MI → 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 (Prediction model section in Supplementary Data; 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 et al.[S3]
L (immediate death after procedure)	5%	None	None	Cole et al.[S5]
J (survive 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 of 1.387	Calibrated to the prompt group in Chaitman et al.[S6]	Age, gender, race, smoking, A1c, SBP, lipid ratio, and medications	Clarke et al.[S2] Chaitman et al.[S6]
D (CAD with procedure → CVD death)	UKPDS MI equation (IHD = 1, CHF = 0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor of 0.37 based on calibration			
CC (CAD with procedure → CHF without MI)	CHS risk equation (Prediction model section in Supplementary Data; 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 et al.[S3]

(*continued*)

SUPPLEMENTARY TABLE S1. (CONTINUED)

Transition	*Transition probability*	*Calibration*	*Risk factors*[a]	*Reference*
E* (MI → CHD death)	See details in the MI/repeat MI module (Table S2)	See Table S2		
M* (MI → CHF)	See details in the MI/repeat MI module (Table S2)	See Table S2		
N* (MI → Hx of MI)	See details in the MI/repeat MI module (Table S2)	See Table S2		
U (Hx of MI → CVD death)	UKPDS MI equation (IHD = 1, CHF = 0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor of 0.232	Calibrated to Jensen et al.[S7] and Mellbin et al.[S8]	Age, gender, race, smoking, A1c, SBP, lipid ratio, and medications	Clarke et al.,[S2] Jensen et al.,[S7] Mellbin et al.[S8]
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 of 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 of 3.074			
G (Hx of MI → CHF)	CHS risk equation (Prediction model section in Supplementary Data; 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 et al.[S3]
P* (repeat MI → Hx of MI)	See details in the MI/repeat MI module (Table S2)	See Table S2		
R* (repeat MI → CHF)	See details in the MI/repeat MI module (Table S2)	See Table S2		
S* (repeat MI → CVD death)	See details in the MI/repeat MI module (Table S2)	See Table S2		
Q (CHF → repeat MI)	The UKPDS MI equation (IHD = 1, CHF = 1) adjusted for medication benefit and by additionally adjusting the hazard by a factor of 1.088	Calibrated to Deedwania et al.[S9] and Mellbin et al.[S8]	Age, gender, race, smoking, A1c, SBP, lipid ratio, and medications	Clarke et al.,[S2] Mellbin et al.,[S8] Deedwania et al.[S9]
T (CHF → CVD death)	The UKPDS MI equation (IHD = 1, CHF = 1) adjusted for medication benefit and by additionally adjusting the hazard by a factor of 0.489			
X (CHF → repeat procedure)	The UKPDS MI equation (IHD = 1, CHF = 1) adjusted for medication benefit and by additionally adjusting the hazard by a factor of 6.201			
V (repeat procedure → history of MI)	95% if subject does not have CHF 0% if subject has CHF	None	None	Cole et al.[S5]
Y (repeat procedure → CHF)	95% if subject has CHF 0% if subject does not have CHF	None	None	
Z (repeat procedure → CVD death)	5%	None	None	

[a]Medications in this table refer to aspirin, lipid drug, ACE inhibitor, and β-blocker.
A1c, hemoglobin A1c; AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; Hx, history; IHD, ischemic heart disease; SBP, systolic blood pressure.

SUPPLEMENTARY TABLE S2. TRANSITION PROBABILITIES IN MYOCARDIAL INFARCTION/ REPEAT MYOCARDIAL INFARCTION MODULE (FIG. S2)

Transition	*Transition probability*	*Calibration*	*Reference*
a (MI → CVD death: fatal MI)	MI: Modified the UKDPS fatality equation by adding gender effect. The new odds of death is −3.251 + 2.772*Ln(Age/52.59) + (A1c-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 of 0.18, disregarding whether a patient has CHF or not.	Calibrated to10% fatal MI for men and 15% fatal MI among all first MI events in the study of Colhoun et al.[S4] These fatality rates are based on information in Roffi et al.[S10]	Clarke et al.,[S2] Colhoun et al.,[S4] Roffi et al.[S10]
	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 of 0.53	Calibrated to Jensen et al.[S7]	Clarke et al.,[S2] Jensen et al.[S7]
b (MI → Short-term survival of MI)	One-transition probability in Transition a		Clarke et al.,[S2] Colhoun et al.,[S4] Roffi et al.[S10]
c (Short-term survival of MI → Procedure after MI)	MI: 75% Repeat MI: 63%	Jensen et al.[S7] Jensen et al.,[S7] Deedwania et al.[S9]	Jensen et al.,[S7] Deedwania et al.,[S9] Franklin et al.[S11]
g (Short-term survival of MI → CHF)	MI: 25% × *P*(CHF)[a] Repeat MI: 37% × P(CHF)[a]	Jensen et al.[S7] Jensen et al.,[S7] Deedwania et al.[S9]	
h (Short-term survival of MI → Hx of MI)	25% × [1 − *P*(CHF)][a] Repeat MI: 37% × [1 − *P*(CHF)][a]	Jensen et al.[S7] Jensen et al.,[S7] Deedwania et al.[S9]	
d (Procedure after MI → CVD death)	MI: 12.5% Repeat MI: 10%	Jensen et al.[S7] Jensen et al.,[S7] Deedwania et al.[S9]	
f (Procedure after MI → Re-infarction within 1 year of MI)	MI: 8.75% Repeat MI: 9%	Jensen et al.[S7] Jensen et al.,[S7] Deedwania et al.[S9]	
i (Procedure after MI → CHF)	MI: for subject who has CHF before MI, 78.75%; for subject who has no CHF before MI, 78.75% × *P*(CHF)[a] Repeat MI: for subject who has CHF before repeat MI, 81% × *P*(CHF)[a]; for subject who has no CHF before repeat MI, 81% × *P*(CHF)[a]	Jensen et al.[S7] Jensen et al.,[S7] Deedwania et al.[S9]	
j (Procedure after MI → Hx of MI)	MI: for subject who has CHF before MI, 0; for subject who has no CHF before MI, 78.75% × [1 − *P*(CHF)][a] Repeat MI: for subject who has CHF before repeat MI, 0; for subject who has no CHF before repeat MI, 78.75% × [1 − *P*(CHF)][a]	Jensen et al.[S7] Jensen et al.,[S7] Deedwania et al.[S9]	Jensen et al.,[S7] Franklin et al.[S11]
e (Re-infarction within 1 year of MI → CVD death)	17%	Jensen et al.[S7]	
k (Re-infarction within 1 year of MI → CHF)	83% × *P*(CHF)		
l (Re-infarction within 1 year of MI → Hx of MI)	83% × [1 − *P*(CHF)][a]		

[a]*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.

Hx, history.

Supplementary Table S3. Age and Gender Modifier in Table S2 (Franklin et al.[S11])

Factor, category	*Modifier*
Age (years)	
< 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-year-old male subject not on β-blocker or ACE inhibitor, P(CHF) for the MI module = 0.13*0.87*0.86*0.45 Medication_Modifier is as described in the main text.

Supplementary Table S4. Parameters in the Prediction Model for Risk of CHF 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+ 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 years)	0.045	0.00037	1.05 (1.02, 1.07)
C-index at 10 years		0.699	

AF, atrial fibrillation; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC/HDL, total cholesterol/high-density lipoprotein.