Additional file 2. Analytical procedures and resources for estimation of transition probabilities among type 2 diabetes patients with and without cardiovascular disease history

Pathway between health states	Estimation for transition probabilities	Reference
T2D patients with CVD history		
(a) Transition from T2D without CVD events to HF	• Number of HF events that occurred in each year (from 2010 to 2018) divided by number of DPP4i users	NHIRD
(b) Transition from T2D without CVD events to MI	• Number of MI events that occurred in each year (from 2010 to 2018) divided by number of DPP4i users	NHIRD
(c) Transition from T2D without CVD events to stroke	• Number of stroke events that occurred in each year (from 2010 to 2018) divided by number of DPP4i users	NHIRD
(d) Transition from T2D without CVD events to all-cause death	• First, a 22-point risk score system that contained risk factors with 0 to 5 points (indicating no to high impact on mortality) was applied. The risk factors and associated points for prediction of 3-, 5-, and 10-year cumulative all-cause mortalities of Taiwanese T2D patients in the base-case analysis of this study were age of 55 years (contributed 3 points), diabetes duration of 8 years (contributed 1 point), use of glucose-lowering agents (1 point), and other risk factors, which were set to average values (i.e., with education ≥ 13 years, without smoking behavior and history of peripheral neuropathy, body mass index in range of 25.0-29.9 kg/m^2, variation of fasting plasma glucose < 22.3%, variation of glycated hemoglobin < 4.5%, variation of diastolic blood pressure < 5.5%, triglycerides < 150 mg/dL) (contributed 0 points). • Second, to fit the yearly model cycle, the risks of 3-, 5-, and 10-year cumulative all-cause mortalities were converted into the mortality for each year using the following equation: cumulative mortality = $1 - e^{(-\text{mortality rate} \times \text{time})}$. The remaining mortalities in the 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 7^{th}, 8^{th}, and 9^{th} years were imputed using the	Liu[1]; Chiang[2]

	interpolation function in TreeAge software. The mortality estimates for patients without CVD history were obtained from these two steps. • Third, to obtain the mortality for each year cycle for patients with CVD history, the mortality estimate for each year for patients without CVD history was multiplied by a factor of 1.24, which reflects the impact of having established CVDs on a patient's mortality.	
(e) Transition from T2D without CVD events to cardiovascular death	• First, a 22-point risk score system that contained risk factors with 0 to 5 points (indicating no to high impact on mortality) was applied. The risk factors and associated points for prediction of 3-, 5-, and 10-year cumulative cardiovascular mortalities of Taiwanese T2D patients in the base-case analysis of this study were age of 55 years (contributed 3 points), diabetes duration of 8 years (contributed 2 point), use of glucose-lowering agents (1 point), and other risk factors, which were set to average values (i.e., with education ≥ 13 years, without smoking behavior and history of peripheral neuropathy, body mass index in range of 25.0-29.9 kg/m^2, variation of fasting plasma glucose < 22.3%, variation of glycated hemoglobin < 4.5%, variation of systolic blood pressure < 9.0%, triglycerides < 150 mg/dL) (contributed 0 points). • Second, to fit the yearly model cycle, the risks of 3-, 5-, and 10-year cumulative cardiovascular mortalities were converted into the mortality for each year using the following equation: cumulative mortality = $1 - e^{(-\text{mortality rate} \times \text{time})}$. The remaining mortalities in the 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 7^{th}, 8^{th}, and 9^{th} years were imputed using the interpolation function in TreeAge software. The mortality estimates for patients without CVD history were obtained from these two steps. • Third, to obtain the mortality for each year cycle for patients with CVD history, the mortality estimate for each year for patients without CVD history was	Liu[1]; Chiang[2]

		multiplied by a factor of 1.24, which reflects the impact of having established CVDs on a patient's mortality.	
(f) Transition from HF to MI	•	Number of subsequent MI events that occurred after HF in each year (from 2010 to 2018) divided by number of patients with HF	NHIRD
(g) Transition from HF to stroke	•	Number of subsequent stroke events that occurred after HF in each year (from 2010 to 2018) divided by number of patients with HF	NHIRD
(h) Transition from MI to HF	•	Number of subsequent HF events that occurred after MI in each year (from 2010 to 2018) divided by number of patients with MI	NHIRD
(i) Transition from stroke to HF	•	Number of subsequent HF events that occurred after stroke in each year (from 2010 to 2018) divided by number of patients with stroke	NHIRD
(j) Transition from HF to death	•	To obtain the mortality for each year after HF occurrence, the transition probability (d) was multiplied by a factor 2.21, which reflects the impact of HF occurrence on mortality	Liu[1]; Chiang[2]
(k) Transition from MI to death	•	To obtain the mortality for each year after MI occurrence, the transition probability (d) was multiplied by a factor 1.24, which reflects the impact of MI occurrence on mortality	Liu[1]; Chiang[2]
(l) Transition from stroke to death	•	To obtain the mortality for each year after stroke occurrence, the transition probability (d) was multiplied by a factor 1.69, which reflects the impact of stroke occurrence on mortality	Liu[1]; Chiang[2]
T2D patients without CVD history			
(a) Transition from T2D without CVD events to HF	•	Number of HF events that occurred in each year (from 2010 to 2018) divided by number of DPP4i users	NHIRD
(b) Transition from T2D without CVD events to MI	•	Number of MI events that occurred in each year (from 2010 to 2018) divided by number of DPP4i users	NHIRD
(c) Transition from T2D without	•	Number of stroke events that occurred in each year (from 2010 to 2018) divided	NHIRD

CVD events to stroke	by number of DPP4i users	
(d) Transition from T2D without CVD events to all-cause death	• First, a 22-point risk score system that contained risk factors with 0 to 5 points (indicating no to high impact on mortality) was applied. The risk factors and associated points for prediction of 3-, 5-, and 10-year cumulative all-cause mortalities of Taiwanese T2D patients in the base-case analysis of this study were age of 55 years old (contributed 3 points), diabetes duration of 8 years (contributed 1 point), use of glucose-lowering agents (1 point), and other risk factors, which were set to average values (i.e., with education ≥ 13 years, without smoking behavior and history of peripheral neuropathy, body mass index in range of 25.0-29.9 kg/m^2, variation of fasting plasma glucose < 22.3%, variation of glycated hemoglobin < 4.5%, variation of diastolic blood pressure < 5.5%, triglycerides < 150 mg/dL) (contributed 0 points). • Second, to fit the yearly model cycle, the risks of 3-, 5-, and 10-year cumulative all-cause mortalities were converted into the mortality for each year using the following equation: cumulative mortality = $1 - e^{(-\text{mortality rate} \times \text{time})}$. The remaining mortalities in the 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 7^{th}, 8^{th}, and 9^{th} years were imputed using interpolation function in TreeAge software.	Liu[1]
(e) Transition from T2D without CVD events to cardiovascular death	• First, a 22-point risk score system that contained risk factors with 0 to 5 points (indicating no to high impact on mortality) was applied. The risk factors and associated points for prediction of 3-, 5-, and 10-year cumulative cardiovascular mortalities of Taiwanese T2D patients in the base-case analysis of this study were age of 55 years old (contributed 3 points), diabetes duration of 8 years (contributed 2 point), use of glucose-lowering agents (1 point), and other risk factors, which were set to average values (i.e., with education ≥ 13 years, without smoking behavior and history of peripheral neuropathy, body mass index	Liu[1]

	in range of 25.0-29.9 kg/m^2, variation of fasting plasma glucose < 22.3%, variation of glycated hemoglobin < 4.5%, variation of systolic blood pressure < 9.0%, triglycerides < 150 mg/dL) (contributed 0 points). • Second, to fit the yearly model cycle, the risks of 3-, 5-, and 10-year cumulative cardiovascular mortalities were converted into the mortality for each year using the following equation: cumulative mortality = $1 - e^{(-\text{mortality rate} \times \text{time})}$. The remaining mortalities in the 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 7^{th}, 8^{th}, and 9^{th} years were imputed using the interpolation function in TreeAge software. The mortality estimates for patients without CVD history were obtained from these two steps.	
(f) Transition from HF to MI	• Number of subsequent MI events that occurred after HF in each year (from 2010 to 2018) divided by number of patients with HF	NHIRD
(g) Transition from HF to stroke	• Number of subsequent stroke events that occurred after HF in each year (from 2010 to 2018) divided by number of patients with HF	NHIRD
(h) Transition from MI to HF	• Number of subsequent HF events that occurred after MI in each year (from 2010 to 2018) divided by number of patients with MI	NHIRD
(i) Transition from stroke to HF	• Number of subsequent HF events that occurred after stroke in each year (from 2010 to 2018) divided by number of patients with stroke	NHIRD
(j) Transition from HF to death	• To obtain the mortality for each year after HF occurrence, the transition probability (d) was multiplied by a factor 2.21, which reflects the impact of HF occurrence on mortality	Liu[1]; Chiang[2]
(k) Transition from MI to death	• To obtain the mortality for each year after MI occurrence, the transition probability (d) was multiplied by a factor 1.24, which reflects the impact of MI occurrence on mortality	Liu[1]; Chiang[2]
(l) Transition from stroke to death	• To obtain the mortality for each year after stroke occurrence, the transition probability (d) was multiplied by a factor 1.69, which reflects the impact of	Liu[1]; Chiang[2]

stroke occurrence on mortality

Abbreviations: T2D, type 2 diabetes; CVD, cardiovascular disease; HF, heart failure; DPP4i, dipeptidyl peptidase 4 inhibitors; NHIRD, National Health Insurance Research Database; MI, myocardial infarction.

References:

1. Diabetes Obes Metab. 2021;23(2):467-479.
2. PLoS Med. 2020;17(5):e1003094.