Recalibration of risk prediction equations for cardiovascular diseases in the Taiwanese population with type 2 diabetes

Kah-Suan Chong, Chun-Ting Yang, Chi-Chuan Wang, Huang-Tz Ou, Tsen-Chieh Yen, Shihchen Kuo

Presenter: Kah Suan Chong, MS

Affiliation: Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Conflict of interest

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Outline

1. Background
2. Methods and results
   - Data source, study population, variables and outcomes
   - External validation and results
   - Recalibration **across study institutions** by overall baseline risks and results
   - Recalibration **across study institutions** by decile groups and results
   - Brief summary of results
3. Conclusions and future insights

Background

Risk equations for diabetes complications

Input risk predictors
Baseline characteristics (e.g., age, sex, blood pressure), medication use, past medical histories

↓

Apply to risk equations for events
(i.e., myocardial infarction, stroke, and heart failure)

↓

Predict the events risks
(e.g., a 5-year stroke)

↓

Projection into economically relevant outcomes
(e.g., life years)

- Clinical prediction models
- Simulation models for economic evaluation

Existing simulation models

- **International** (e.g., IQVIA CORE model[1], UKPDS-OM2 model[2], RECODe model[3], CHIME model[4])
- **Taiwan**
  - Type 2 diabetes mellitus Holistic Care model[5]

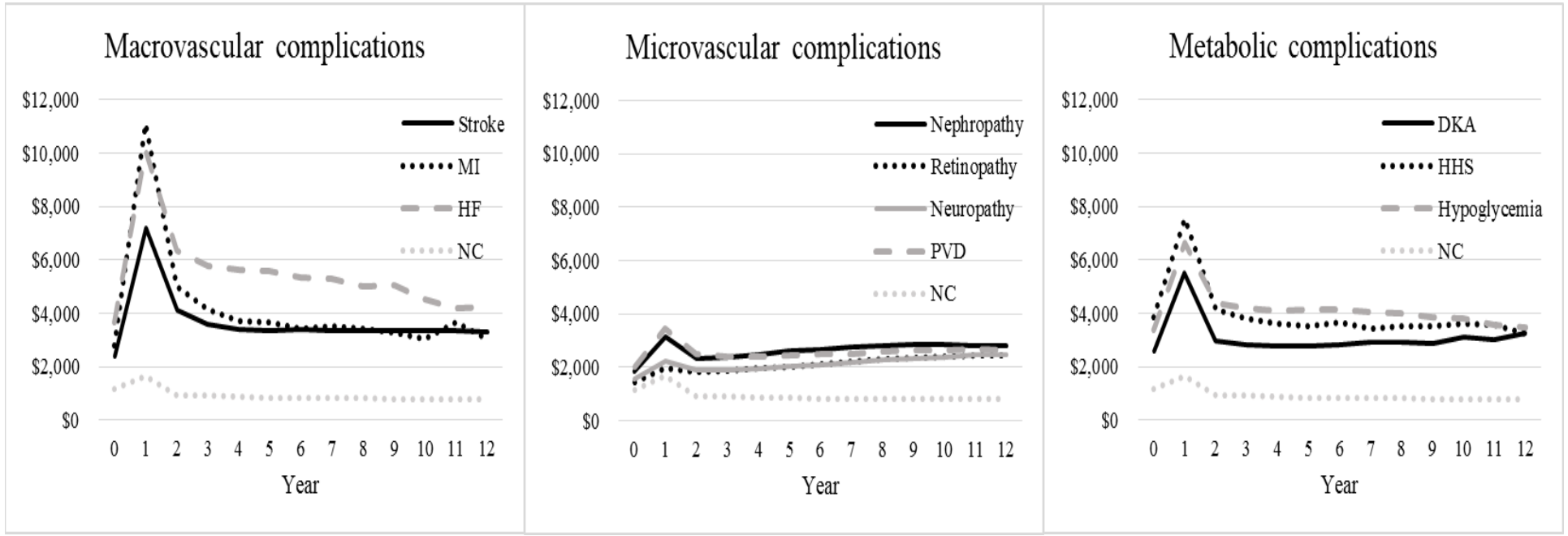
UKPDS-OM 2, the United Kingdom Prospective Diabetes Study Outcomes Model 2; RECODe, Risk Equations for Complications Of type 2 Diabetes; CHIME, Chinese Hong Kong Integrated Modeling and Evaluation

Consideration
Public accessibility

Refs. [1] IQVia. United States, 2002. Web Archive. https://www.loc.gov/item/lcwaN0016975/. [2] *Diabetologia,* 2013. 56(9): p. 1925-33.
[3] *Lancet Diabetes Endocrinol,* 2017. 5(10): p. 788-798. [4] *PLoS Med.* 2021 Jun 24;18(6):e1003692. [5] *Information,* 2021. 12(8): p. 326.

Annual crude healthcare costs on diabetes complications in Taiwan

In 2017 USD



Abbreviations: MI: myocardial infarction, HF: heart failure, PVD: peripheral vascular disease, DKA: diabetic ketoacidosis, HHS: hyperosmolar hyperglycemic syndrome, NC: no complications; CVD, cardiovascular disease

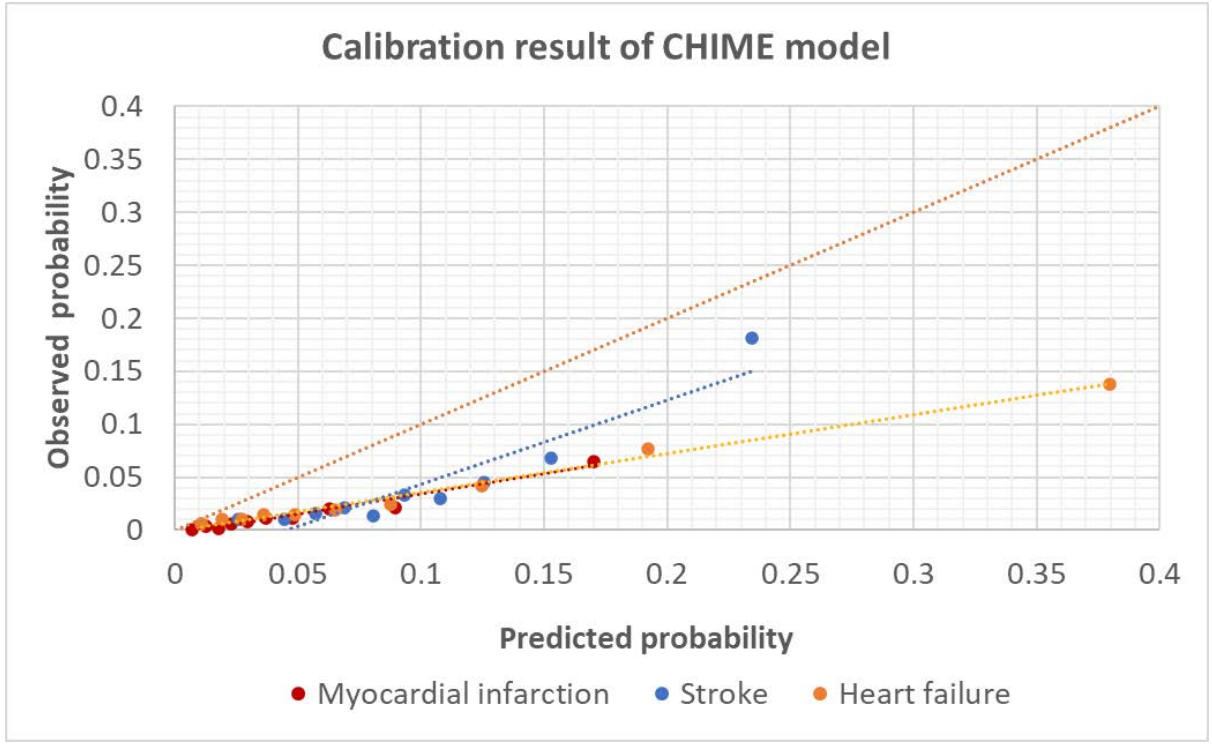
Higher costs in macrovascular complications (MI, stroke, HF), especially in the year when the event occurred.

Ref. [1] *Diabetes Care,* 2020. 43(8): p. 1732-1740.

Validation of risk equations of cardiovascular diseases among Taiwanese type 2 diabetes population

Existing simulation models

- **International** (e.g., UKPDS-OM2 model[1], RECODe model[2], CHIME model[3])
  - ➢ **CHIME model**: satisfactory discrimination (AUROC≥ 0.7) but poor calibration in our previous unpublished work



Predicted risks tend to be overestimated.

Note: the calibration results were obtained using individual data from National Taiwan University hospital.

UKPDS-OM 2, the United Kingdom Prospective Diabetes Study Outcomes Model 2; RECODe, Risk Equations for Complications Of type 2 Diabetes; CHIME, Chinese Hong Kong Integrated Modeling and Evaluation; AUROC, area under the receiver operating characteristic

Refs. [1] *Diabetologia,* 2013. 56(9): p. 1925-33. [2] *Lancet Diabetes Endocrinol,* 2017. 5(10): p. 788-798. [3] *PLoS Med.* 2021 Jun 24;18(6):e1003692.

Recalibration

Purpose

- To adjust formulas to improve the risk equations' performance in Taiwanese population

Challenge we faced

- Unable to utilize and pool out patient-level data across different institutions
  - ➢ Adopt institution multipliers in this study according to a published study titled "Addressing Regional Differences in Diabetes Progression: Global Calibration for Diabetes Simulation Model"[1]

$$\mathrm{Ln}\left(\frac{Observed_i}{predicted_i}\right) = \beta_0 + \gamma_{EU}EU_i + \gamma_{US}(US_i - 1) + \gamma_{Asia}Asia_i + \gamma_{others}others_i + \varepsilon_t$$

β_0: systematic bias of the original baseline hazard of the original model; EU, Europe; US, United States; γ: region multiplier; Ɛ: error term

$$\ln\frac{\mathrm{Observed}_i}{\mathrm{Predicted}_i} = \beta_0 + \gamma_{\boldsymbol{Institution\ A}} \times \boldsymbol{Institution\ A}_i + \gamma_{Institution\ B} \times \boldsymbol{Institution\ B}_i + \varepsilon_t$$

Ref. [1] *Value Health.* 2019 Dec;22(12):1402-1409.

Objective

To recalibrate CHIME risk equations of cardiovascular diseases for Taiwanese type 2 diabetes (T2D) patients

CHIME, Chinese Hong Kong Integrated Modeling and Evaluation; MI, myocardial infarction; HF, heart failure

Methods and Results

Data source, study population, variables and outcomes

Data source (study period of 2014-2019)

1. National Taiwan University Hospital (NTUH), a medical center
2. National Cheng Kung University Hospital (NCKUH), a medical center

Study population

- T2D patients aged above 18 years (index date: the date of first T2D diagnosis record)

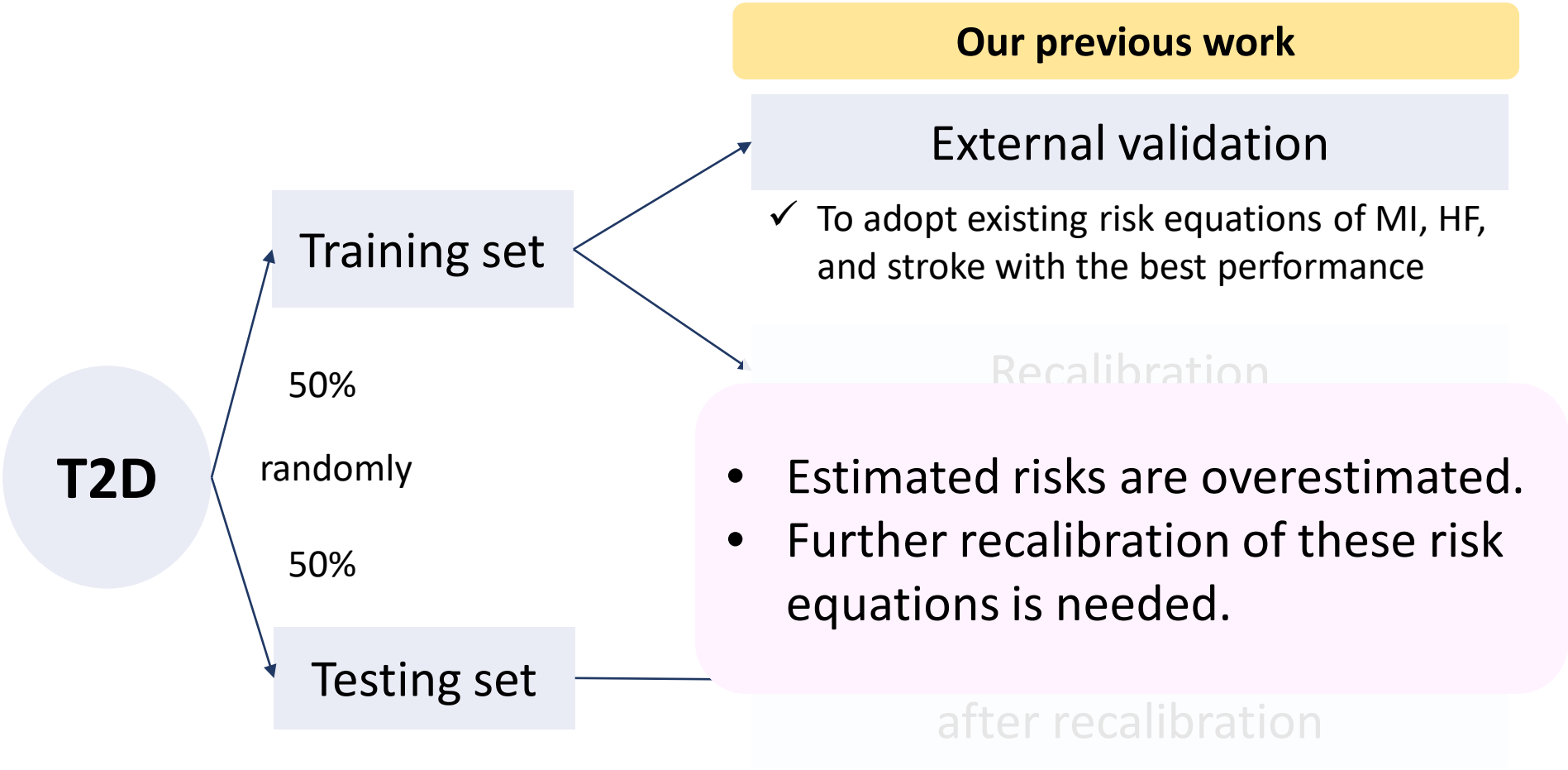
Variables

- Demographic, disease history, medication:
  - ✓ within 1 year before and at the index date
- Laboratory data, body mass index:
  - ✓ average value within 1 year before and at the index date

Outcomes

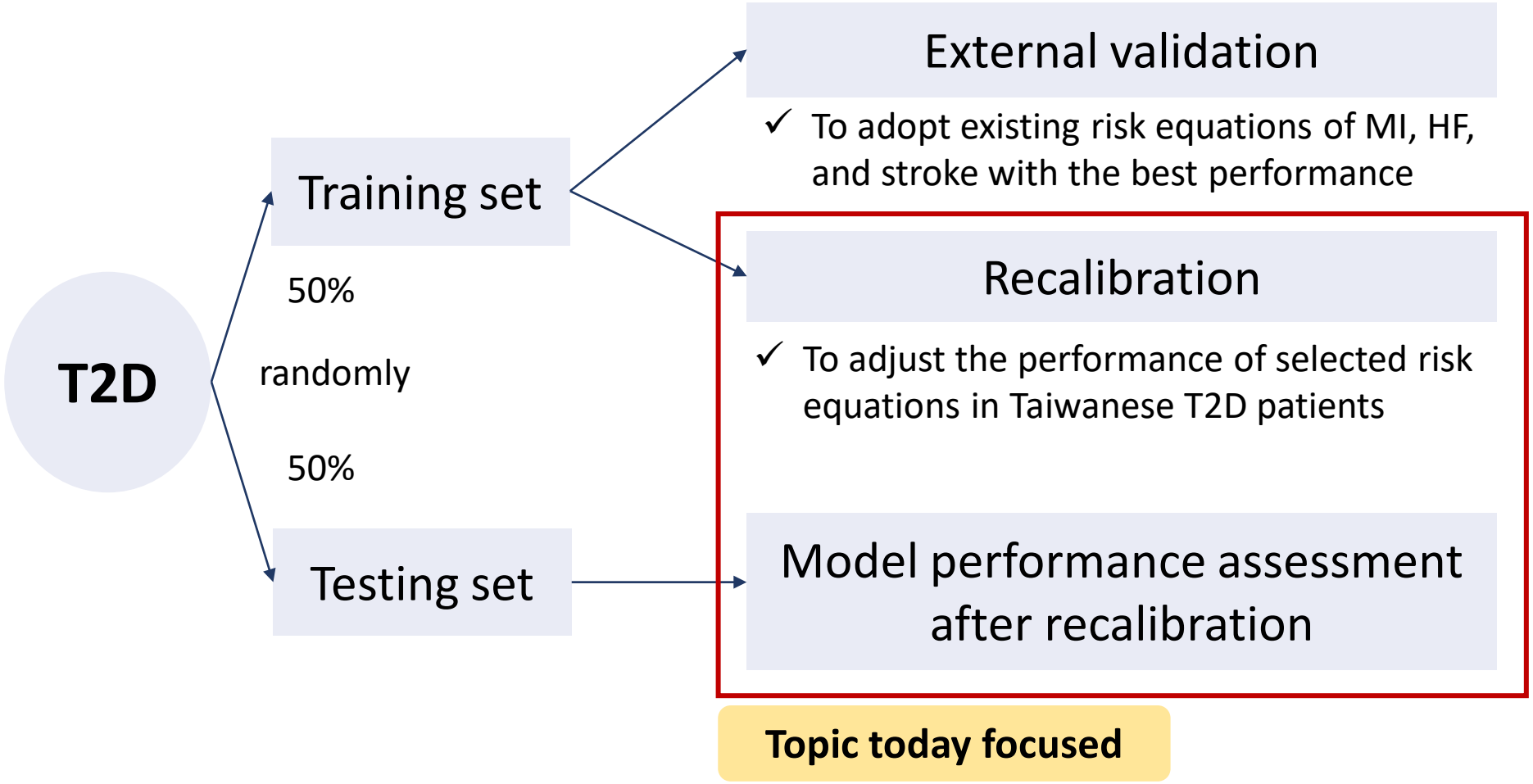
- Myocardial infarction, stroke, and heart failure
- A 5-year follow-up period

Before external validation and recalibration



MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes

Before external validation and recalibration



MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes

Baseline characteristics and event rates in T2D patients

	NTUH		NCKUH	
Baseline characteristic	**Train set**	**Test set**	**Train set**	**Test set**
Age (years), mean (SD)	65 (12)	65 (12)	63 (12)	63 (12)
Sex (female), %	47.2	46.9	45.6	45.8
Laboratory value				
Haemoglobin A1c, % (SD)	7.23 (1.35)	7.21 (1.36)	7.70 (1.66)	7.72 (1.61)
Past history				
Myocardial infarction, %	2.4	2.3	3.0	3.1
Stroke, %	3.6	3.7	8.7	9.4
Heart failure, %	3.5	3.4	5.5	5.4
5-year outcomes (/100 PY)	**Observed (train set)**	**Observed (test set)**	**Observed (train set)**	**Observed (test set)**
Myocardial infarction	0.35	0.36	0.55	0.52
Stroke	1.02	0.97	1.54	1.60
Heart failure	0.84	0.83	2.02	2.02

NTUH, National Taiwan University Hospital; NCKUH, National Cheng Kung University; SD: standard deviation; PY, person-year

Recalibration across study institutions by overall baseline risks

Recalibration of existing risk equations for MI, stroke, and HF

Recalibration in **train** set[1]

$$\ln \frac{\text{Observed}_i}{\text{Predicted}_i} = \beta_0 + \gamma_{\mathbf{NTUH}} \times \mathbf{NTUH}_i + \gamma_{\mathbf{NCKUH}} \times \mathbf{NCKUH}_i + \varepsilon_t$$

β_0: systematic bias of the original baseline hazard of the original model; γ: hospital multiplier; ε: error term

After recalibration, model performance was assessed in **test** set

- Discrimination (ideal result)
  - C-statistic (area under the receiver operating characteristic curves, AUROC ≥0.7)
- Calibration (ideal result)
  - Intercept (closer to 0)
  - Slope (closer to 1)
  - Greenwood-Nam-D'Agostino (GND) statistic (*p*-value >0.05)

Ref. [1] *Value Health.* 2019 Dec;22(12):1402-1409.

Take one institution’s results as an example

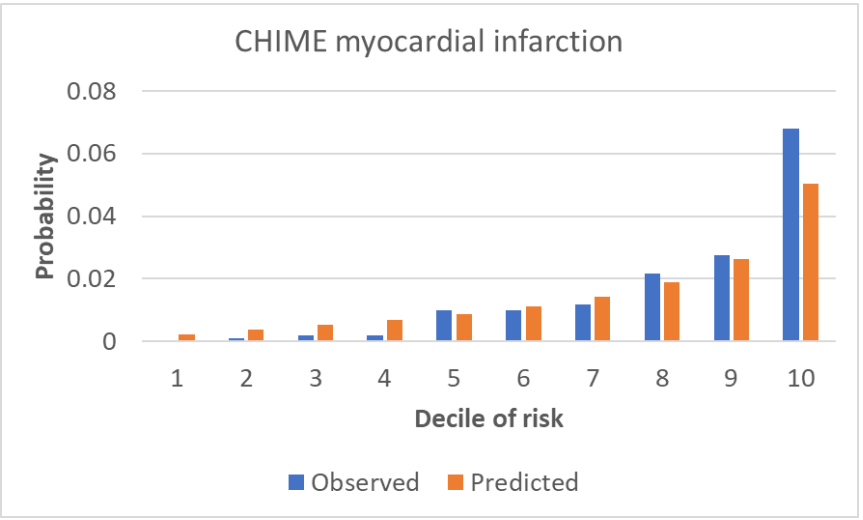
Note: Results from National Taiwan University hospital (NTUH) were shown.

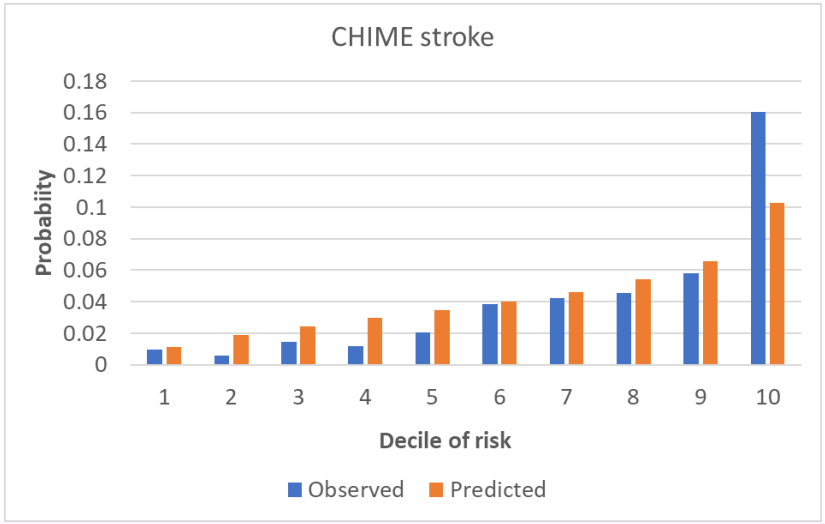
Brief summary of results

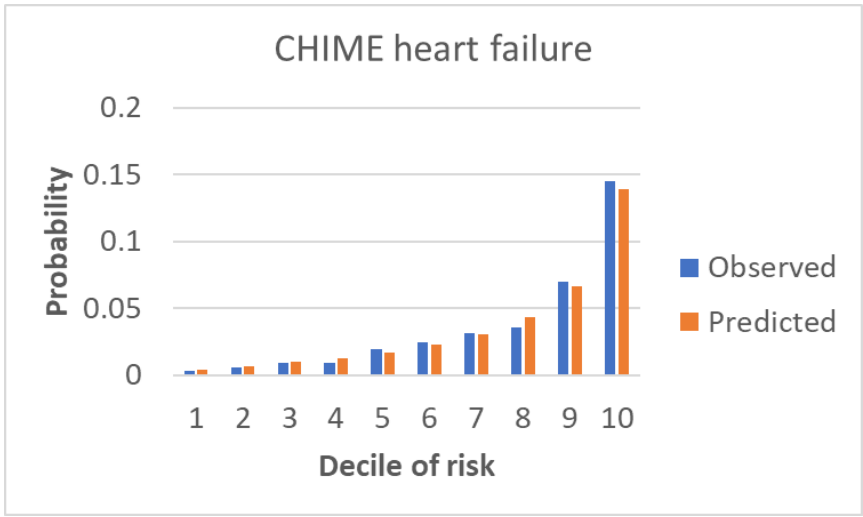
Ideal condition: slope closer to 1, Greenwood-Nam-D'Agostino (GND) test with *p*-value >0.05

$$\ln \frac{\text{Observed MI}_i}{\text{Predicted MI risk}_i} = \gamma_{\mathbf{NTUH}} \times \mathbf{NTUH}_i$$

Outcome (slope/GND test)	Before recalibration	$\gamma_{\mathbf{NTUH}}$ (Institution multiplier)	After recalibration
Myocardial infarction	0.38/<0.001	−1.1936	1.41/<0.001
Stroke	0.80/<0.001	−0.8404	1.62/<0.001
Heart failure	0.37/<0.001	−1.0227	1.05/>0.1



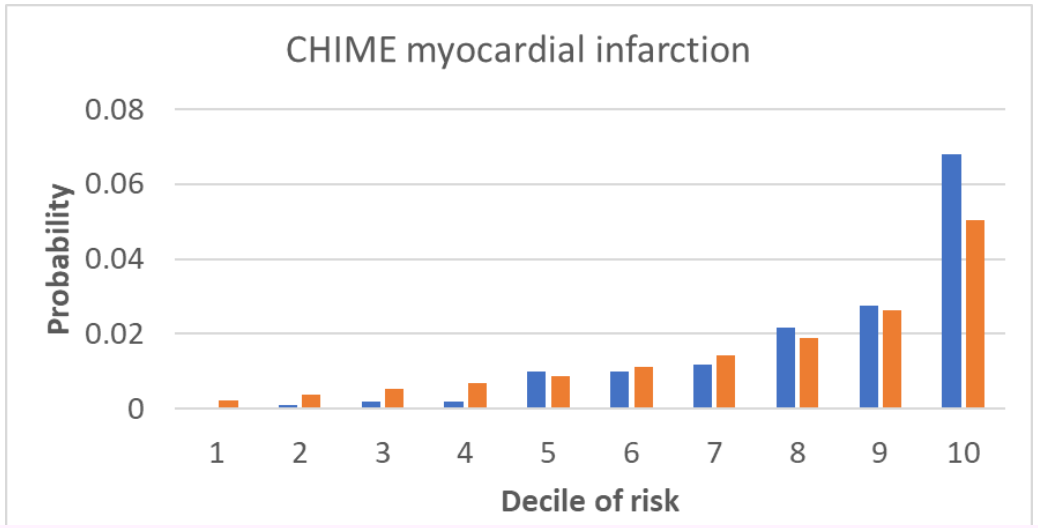


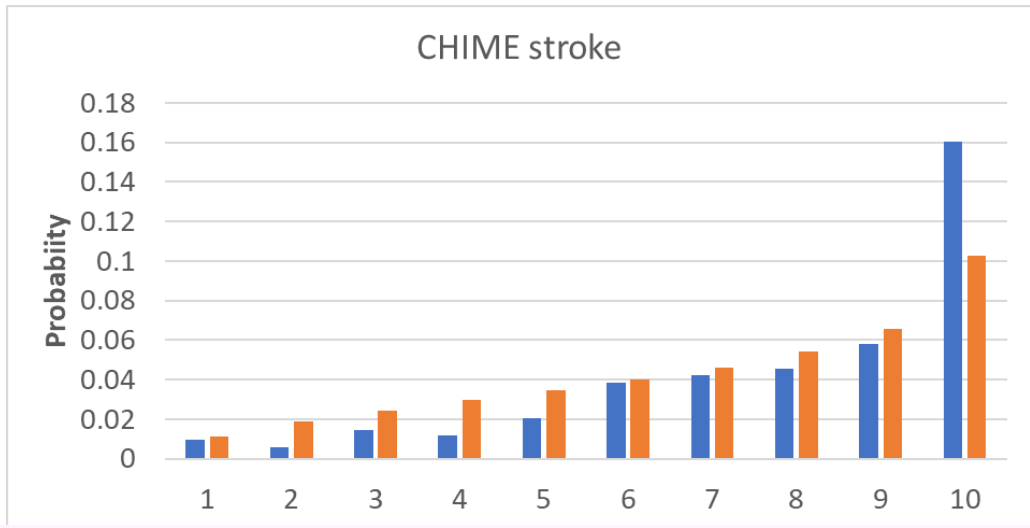


Only calibration result for heart failure achieved a satisfactory level.

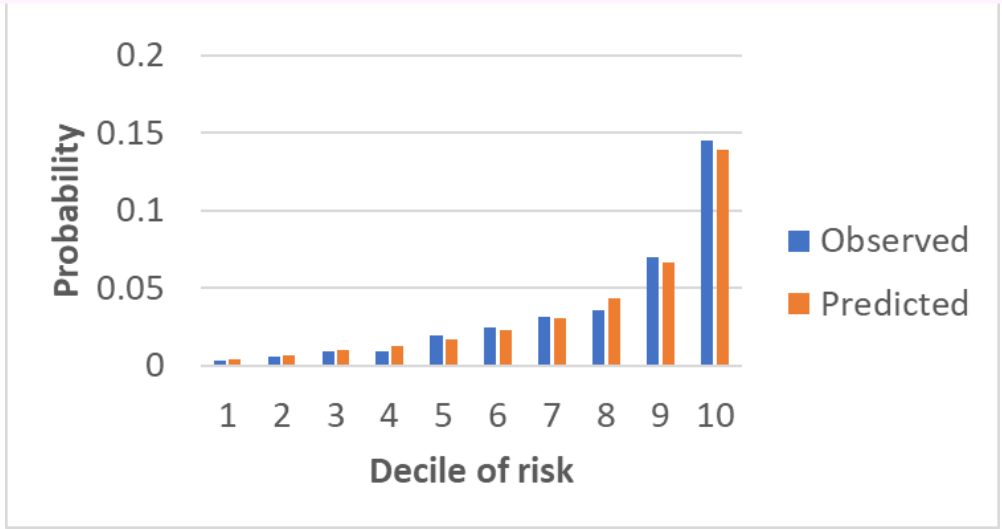
Recalibration across study institutions by decile groups

Observed vs. predicted risks after recalibration by overall baseline risk





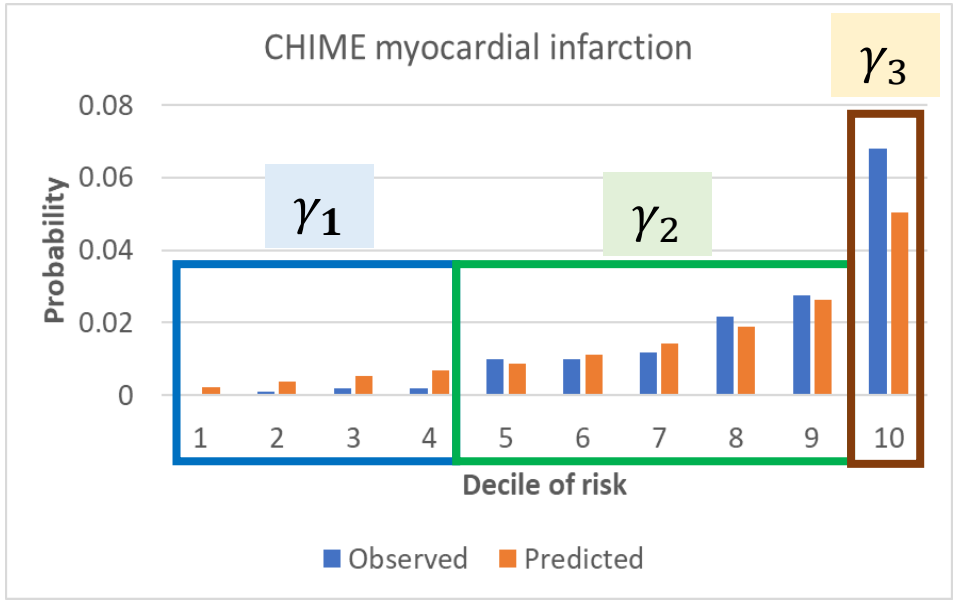
Different tendency of over-/underestimated across decile groups was observed in MI and stroke outcomes after recalibration by overall baseline risk

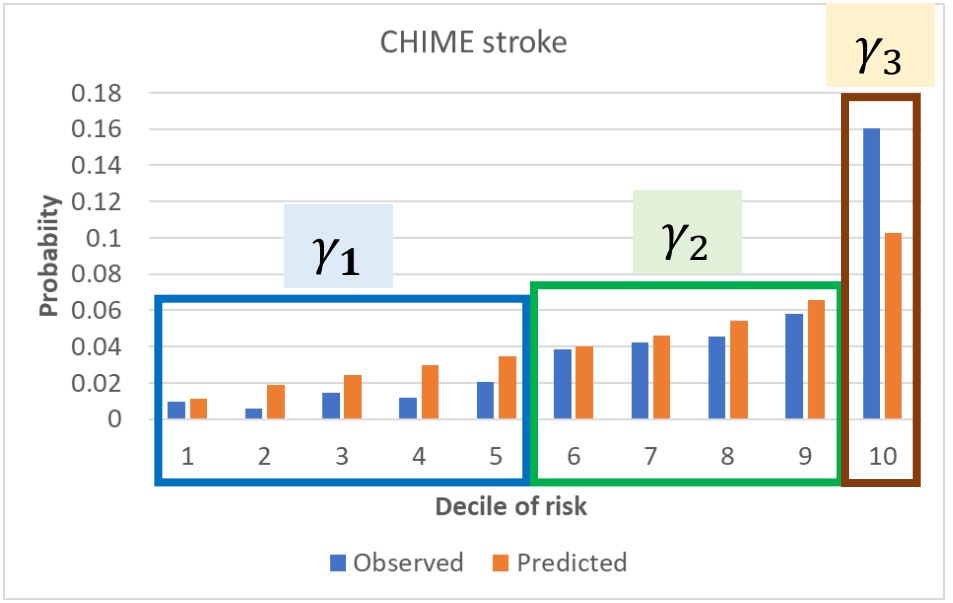


Recalibration by decile groups

$$\ln \frac{\text{Observed}_i}{\text{Predicted}_i} = \beta_0 + \gamma_{\text{1NTUH (low risk)}} \times \text{NTUH}_i + \gamma_{\text{2NTUH (mod. risk)}} \times \text{NTUH}_i + \gamma_{\text{3NTUH (high risk)}} \times \text{NTUH}_i + \varepsilon_t$$

β_0: systematic bias of the original baseline hazard of the original model; γ: hospital multiplier; Ɛ: error term





- Cut-points of low/moderate/high risk: maximum risk score (e.g., 10%) of the aggregate decile groups

Brief summary of calibration results in two institutions

Ideal condition: slope closer to 1, Greenwood-Nam-D'Agostino (GND) test with *p*-value >0.05

NTUH

Outcome (slope/GND test)	Before recalibration	After recalibration by overall baseline risk	Recalibration by decile groups
Myocardial infarction	0.38/<0.001	1.41/<0.001	1.11/>0.05
Stroke	0.80/<0.001	1.62/<0.001	0.87/>0.1
Heart failure	0.37/<0.001	1.05/>0.1	NA

NCKUH

Outcome (slope/GND test)	Before recalibration	After recalibration by overall baseline risk	Recalibration by decile groups
Myocardial infarction	0.47/<0.001	0.98/>0.1	NA
Stroke	0.74/<0.001	1.21/<0.05	1.1/>0.05
Heart failure	0.78/0.05	1.05/>0.1	NA

NTUH, National Taiwan University Hospital; NCKUH, National Cheng Kung University; NA, not applicable

Equations of new predicted risk after recalibration

NTUH, National Taiwan University Hospital; NCKUH, National Cheng Kung University

Myocardial infarction (MI)

Risk **recalibrated_MI**= exp(**institution multiplier**+ ln[Risk **CHIME_MI**])

Risk groups ($Risk_{CHIME}$)	Multiplier for NTUH	Multiplier for NCKUH
Low risk (≤ 2.5%)	-1.55	-0.80
Moderate risk (2.5-10%)	1.30	
High risk (≥ 10%)	-0.96	

Stroke

Risk **recalibrated_stroke**= exp(**institution multiplier** + ln [Risk **CHIME_stroke**])

Risk groups ($Risk_{CHIME}$)	Multiplier for NTUH
Low risk (≤ 8.5%)	-1.37
Moderate risk (8.5-17%)	-1.00
High risk (≥ 17%)	-0.26

Risk groups ($Risk_{CHIME}$)	Multiplier for NCKUH
Low risk (≤ 8%)	-0.54
Moderate risk (8-11%)	-0.73
High risk (≥ 11%)	-0.46

Heart failure (HF)

Risk **recalibrated_HF**= exp(**institution multiplier** + ln [Risk **CHIME_HF**])

Multiplier for NTUH	Multiplier for NCKUH
-1.02	-0.20

Conclusions and Future Insights

Conclusions

Recalibrated CHIME risk equations performed better among Taiwanese T2D patients for predicting CVDs than original risk equations.

1. Adoption of institution multiplier
   - Address the heterogeneity across different institutions
   - Increase generalizability especially when the individual data could not be integrated for analysis

2. Recalibration method by overall baseline risk or by decile groups
   - Does not have same tendency or similar magnitude of over-/underestimation of estimated risk across different decile groups.
     - ➢ Step 1: adjusted by overall baseline risk
     - ➢ Step 2 (if not ideal): recalibrated according to different CVD risks of patients

CVD, cardiovascular diseases

Future insights

1 Feasibility of recalibration method (i.e., by decile groups)

- Validation in other institutions
- Further investigation or discussion on the number of decile groups
- Challenges: no similar magnitude or tendency for decile grouping

2 Advanced recalibration method (e.g., adjusted coefficients of predictors)

- Different impact of predictors on outcome of interest across countries/regions

Thanks for your attention

Contact information
Kah-Suan Chong, email: kahsuan102@gmail.com
Huang-Tz Ou, email: huangtz@mail.ncku.edu.tw