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The paper:

PREDICTING CORONARY ARTERY DISEASE IN PRIMARY CARE: DEVELOPMENT AND VALIDATION OF A DIAGNOSTIC RISK SCORE FOR MAJOR ETHNIC GROUPS IN SOUTHEAST ASIA

Why was this study conducted?

Coronary artery disease (CAD) is the most common type of heart disease that caused by plaque build-up in the wall of the arteries that supply blood to the heart[1]. CAD risk prediction tools are useful decision supports to aid physicians in objectively evaluating the probability of CAD among patients presenting with chest pain. The decision support is particularly useful in the primary healthcare setting where the prevalence of actual disease is low. The pre-test probability (PTP) of CAD reflects a continuum of risk and has been recommended to use for selecting at-risk patients for further cardiac investigations. Patients with low pre-test risk do not benefit from routine additional testing, while those with intermediate pre-test risk are most likely to benefit from an initial non-invasive test. There are several established prediction models for CAD diagnosis such as The Duke Clinical Score (DCS), CAD Consortium Score (CCS), and Marburg Heart Score (MHS). However, these existing models have been found to overestimate CAD risk and to date, the clinical implications of using these models have not been compared in a primary care setting. It is also unknown which tool is best calibrated for use in an Asian population. Hence, the present study was primarily conducted to develop and validate a new diagnostic prediction model for CAD in Southeast Asians using clinical parameters readily available in primary care, and to compare the performance and clinical utility of three existing prediction tools (DCS, CCS, and MHS) against the new model.

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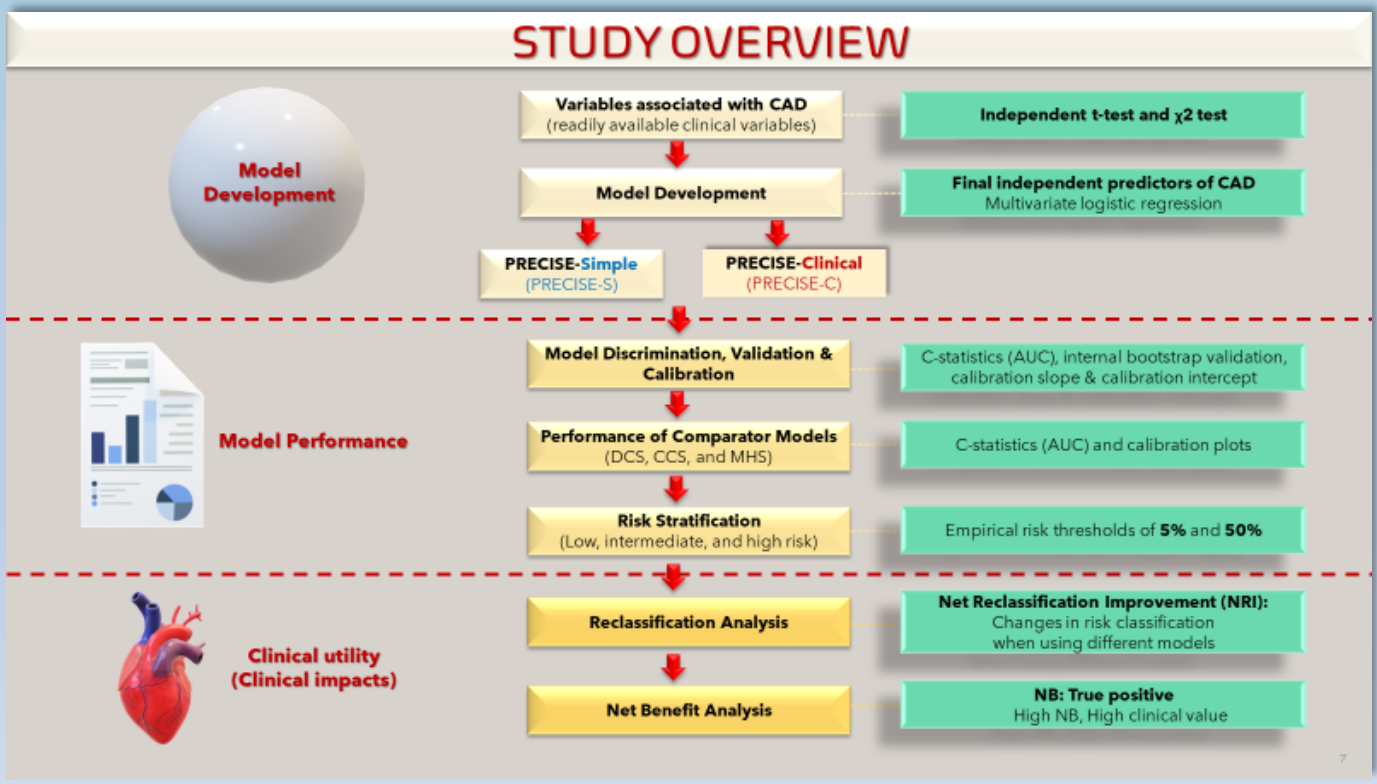
How was it done?



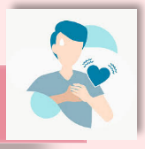
METHODOLOGY

PROSPECTIVE COHORT STUDY

PARTICIPANTS

Inclusion Criteria

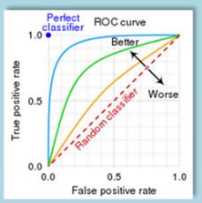
- **Consecutive patients** who attended all SHP branch clinics for **chest pain**.
- **Stable clinically**.
- Subsequently referred for **cardiac evaluation** at NHCS between **July 2013** and **December 2016**.



Exclusion Criteria

- **Existing or prior history of CAD**.
- **Acute coronary syndromes** (Unstable angina and evolving acute myocardial infarction).
- **Age below 30 years**.

MAIN MEASURES



Model Performance

Discrimination

Calibration

Clinical Utility

Net reclassification improvement (NRI)

Net benefit (NB)

STUDY PROCEDURE

Patients: interviewer-administered questionnaire and resting electrocardiogram (ECG).

Electronic medical records (EMR)- To determine clinical history and laboratory test results.

Patients without investigations in the preceding year had fasting blood tests taken upon enrolment to determine their lipid and glucose levels.

The patient and his attending doctors (primary care physician and cardiologist) were blinded to the CAD pre-test probability (PTP) results, computed using the various models tested.

All subsequent cardiac investigations at NHCS were determined at the clinical discretion of the reviewing cardiologist.

OUTCOMES MEASURES

Primary Outcome:

Diagnosis of significant CAD:

a. ≥ 70% luminal stenosis of at least one major coronary artery or ≥ 50% left main stenosis (based on either catheter-based or CT coronary angiography), or
b. Clinical diagnosis of CAD in patients without coronary angiography.

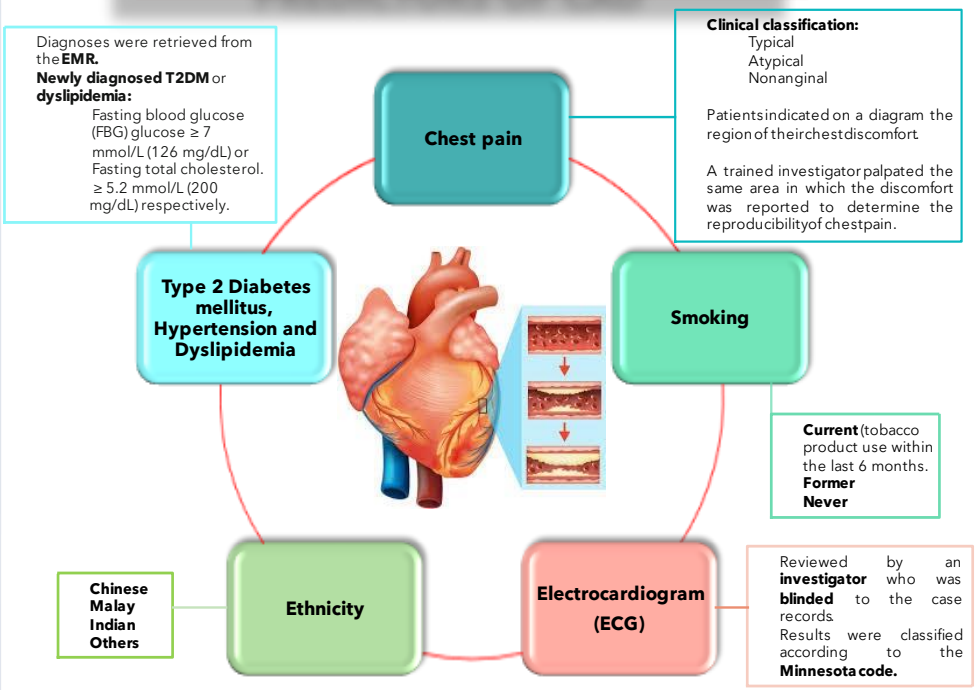
All clinical diagnoses were independently adjudicated by an investigator who was blinded to the diagnosis of the attending cardiologist. Discrepancies in diagnoses were arbitrated independently by another cardiologist in the study team.

1 year of follow-up: Matching was done at the respective national registries for mortality and major adverse cardiovascular events (MACE). MACE includes:

- Non-fatal myocardial infarction (MI)
- Non-fatal stroke
- Coronary revascularization (coronary artery bypass grafting and/or percutaneous coronary intervention).

Data on revascularization was obtained from EMR and phone interviews were conducted using standardized scripts.

PREDICTORS OF CAD

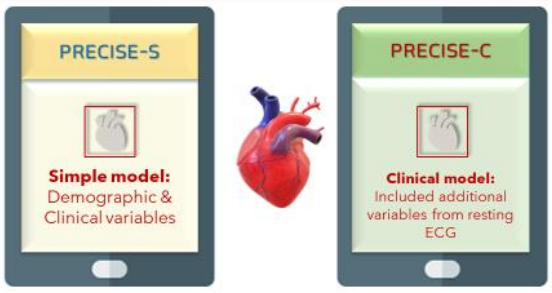


1 MODEL DEVELOPMENT

Predictive Risk score for CAD In Southeast Asians with chEst pain (PRECISE)

- **Independent t-test and χ2 test**: To determine **variables associated with CAD**.
- **Clinician input and p< 0.05**: To determine the **variable retention in the final regression model**.
- **Odds ratios (OR)** and **95% CI** were calculated.
- **Univariate and multivariate logistic regression analyses** were performed: To determine the **final independent predictors of CAD.**
- **Complete-case analysis**: To handle **missing data for predictors and outcome**.
- Values predicted by the **PRECISE score** represent the **probability of CAD** - **Range: 0 to 1**
- Two **independent risk calculators**: **PRECISE-S** and **PRECISE-C.**

Predictive Risk score for CAD In Southeast Asians with chEst pain (PRECISE)



2 MODEL DISCRIMINATION, VALIDATION AND CALIBRATION

DISCRIMINATION

Discrimination

- **The ability to differentiate between those with and without the disease.**
- Measured by AUC and its 95% CI.

Area under the curve (AUC)
- **< 0.5 –** Very poor
- **0.5 –** No better than predicting an outcome than random chance
- **>0.7 –** Good model
- **>0.8 –** Strong model

VALIDATION

Internal validation

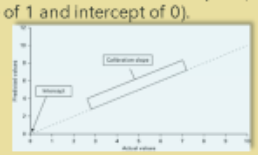
Internal Validation: To correct for over-optimism within the data.

- **829** (50%) new data sets were used by randomly sampling selected subjects from the main data set, with replacement.
- Next **stepwise multivariable logistic regression analysis** was performed on each of these data sets (significant **univariable p<0.01).**
- **Internal bootstrap validation** (829 bootstrap samples) was used to provide optimism-corrected estimates.
- The optimism is **the decrease in model performance between the bootstrap and the original samples** (can adjust the developed model for overfitting).
- The corrected calibration slope was used as a shrinkage factor for the regression coefficients and AUC with 95% CI corrected for over-optimism was estimated.

CALIBRATION

Calibration

- **The agreement between predicted and observed outcomes.**
- **Observed risks (y-axis)** against **predicted risks (x-axis).**
- The calibration slope and calibration intercept were calculated.
- **Calibration slope**: Evaluates the spread of the estimated risks (Target value: 1)
- **Calibration intercept**: Assessment of calibration-in-the-large (Target value: 0)
- Perfect calibration: Predictions lying on the 45° line of the calibration plot (i.e., a slope of 1 and intercept of 0).



3 PERFORMANCE OF COMPARATOR MODELS

- The **predictive performance** of **DCS, CCS (basic & clinical models),** and **MHS** was quantified using the original equations.
- The respective **AUC** and **calibration plots** were presented.

4 RISK STRATIFICATION

- **Cohort stratification:**
- **Low, intermediate**, and **high** CAD risk groups (empirical risk thresholds of **5%** and **50%**).
  - **Low risk**: Manage expectantly.
  - **Intermediate risk**: Should be referred for further cardiac investigations.
  - **High risk**: Receive invasive diagnostic tests (e.g. cardiac angiography).

5 RECLASSIFICATION ANALYSIS

- Cross-tabulate **the probability classification** of patients - **PRECISE-C** vs other risk models.
- **Correct reclassification**: If the predicted probability using PRECISE-C was **closer** to the observed CAD probability than DCS or CCS-Clinical.
- **Net reclassification improvement (NRI)**: Quantifies changes in risk classification when using different models.
- **NRI = NRIcase + NRInon−case**
- NRI reports differences in proportions of patients moving "up" and "down" for cases and non-cases.
  - ***Up**: Moving to a **higher-risk category***
  - ***Down**: Moving to a **lower-risk category***
  - ***Case**: Patient with CAD*
  - ***Non-case**: Patient without CAD*
- NRI values were applied to compare the reclassification capacities of the various models across the pre-determined risk thresholds.

To offer insights into the use of each predictive model in clinical practice.

6 NET BENEFIT ANALYSIS

- **Threshold probability of 5%:** Cutoff between **low**-and **intermediate-risk** groups.
- **Net benefit:** The **trade-off** between **benefits** (of detecting CAD among "true positive") VS **harm** (of unnecessary cardiac tests among "false positives")
- Unit of NB: **"True positive"**
- NB was calculated and compared for each risk model.
- The model with the **highest NB** demonstrates the **highest clinical value.**

RESULTS

KEY RESULTS

OUTCOME	PRECISE
CAD Prevalence	**9.5%** (158 of 1658 patients)
Predictors of CAD	**Age, gender, T2DM, hypertension, smoking, chest pain type, neck radiation, Q waves, and ST-T changes**
Reclassification analysis	**100% reclassification as compared to DCS and CCS-clinical.**

OUTCOME	PRECISE-S	PRECISE-C	DCS	CCS-basic	CCS-clinical	MHS
C-statistic	**0.808** (95% CI 0.776-0.840)	**0.815** (95% CI 0.782-0.847)	**0.795** (95% CI 0.759-0.831)	**0.756** (95% CI 0.717-0.794)	**0.787** (95% CI 0.752-0.823)	**0.661** (95% CI 0.621-0.701)
Net benefit (at 5% threshold probability)	**0.061**	**0.063**	**0.056**	**0.060**	**0.065**	

PARTICIPANTS WITH CAD (n=158)

- **Mean age: 61.1 ± 9.3 years**
- **Males: 127 (80.4%)**
- **Chinese:126 (79.7%)**
- **Diabetes mellitus: 48 (30.4%)**
- **Hypertension: 99 (62.7%)**
- **Hyperlipidemia: 124 (78.5%)**

RESULTS

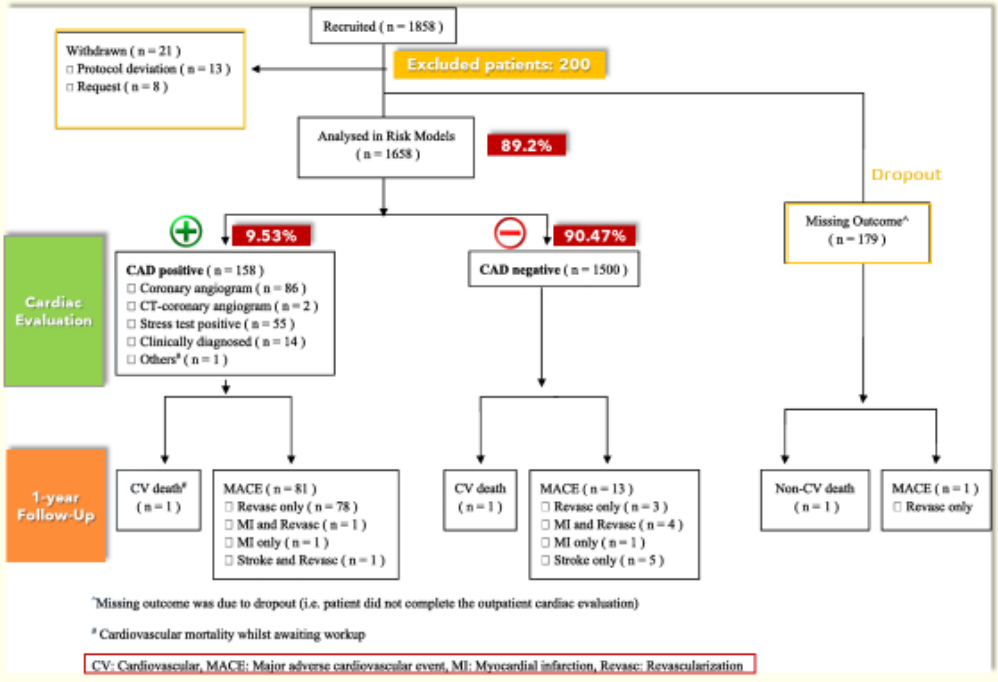
- Total recruited patients: 1858
- Total completed outcome data: 1658
- Excluded patients:
  - Dropped out: 179
  - Withdrawn: 21
- Prevalence of CAD: n= 158 (9.5%)
- Evidence of stenosis on catheter-based angiography: n= 86 (54.4%)
- CT evidence of stenosis: n= 2 (1.3%)
- Positive stress test: n=55 (34.8%)
- Clinically diagnosis of CAD by a cardiologist: n= 14 (8.9%)

1-Year Follow-up

Outcome	CAD +VE	CAD -VE	Missing Outcome
	n (%)		
Died of CV cause	1 (0.6)	1 (0.1)	1 (0.6)
MACE	81 (51.3)	13 (0.9)	1 (0.6)

PARTICIPANTS

Figure 1: Flow diagram of patients from recruitment until 1-year follow-up.



PREDICTORS OF CORONARY ARTERY DISEASE

Multivariate logistic regression analyses

- **Older age** OR 1.03 (1.02-1.05)
- **Male** OR 5.75 (3.63 -9.11)
- **Diabetes mellitus** OR 1.82 (1.20-2.76), p =0.005
- **Hypertension** OR 1.64 (1.12-2.42), p =0.012
- **Smoker** OR 2.08 (1.30 - 3.34), p=0.002
- **Typical chest pain** OR 3.95 (2.40 - 6.50), p<0.001)
- **Chest pain radiating to neck** OR 3.18 (1.50-6.74), p =0.003
- **Q waves on ECG** OR 2.77 (1.54 - 5.01), p =0.001
- **ST-T changes on ECG** OR 1.74 (1.07-2.83), p = 0.027

The final equation for the simple model (PRECISE-S):

y = −6:632 + (0.035*Age) + (1.694*Male) + (0.613*Diabetes) + (0.542*Hypertension) + (0.791*Smoker) + (0.063*ExSmoker) + (1.395*Typical Pain) + (0.877*Atypical Pain) + (1.143*Pain Radiating to Neck)

The final equation for the clinical model (PRECISE-C) with resting ECG parameters:

y =−6:714 + (0.033*Age) + (1.75*Male) + (0.597*Diabetes) + (0:497*Hypertension) + (0.733*Smoker) + (0.07*ExSmoker) + (1.374*Typical Pain) + (0.875*Atypical Pain) + (1.157*Pain Radiating to Neck) + (1.020*Q waves present) + (0.552*ST−T changes present).

PERFORMANCE OF RISK SCORES

DISCRIMINATION AND VALIDATION

OUTCOME	PRECISE-S	PRECISE-C
AUC	**0.808** (95% CI: 0.776-0.840)	**0.815** (95% CI:0.782-0.847)
AUC Bootstrap Validation Cohort	**0.825** (95% CI: 0.782-0.868)	**0.841** (95% CI: 0.799-0.883)

OUTCOME	DCS	CCS-basic	CCS-clinical	MHS
AUC	**0.795** (95% CI 0.759-0.831)	**0.756** (95% CI 0.717-0.794)	**0.787** (95% CI 0.752-0.823)	**0.661** (95% CI 0.621-0.701)

CALIBRATION

OUTCOME	PRECISE-S	PRECISE-C	DCS	CCS-basic	CCS-clinical
Calibration intercept	**0.025**	-0.044	-0.037	0.014	0.013
Calibration slope	**0.503**	2.00	0.313	0.400	0.382

PRE-TEST PROBABILITY (PTP) SCORES

MODEL	RISK OF CAD	
	LOW	INTERMEDIATE
DCS	-	60.9%
CCS-basic	-	76.5%
CCS-clinical	-	70.2%
PRECISE-S	47.8%	51.0%
PRECISE-C	49.8%	48.8%

PTP Score	PRECISE-S	PRECISE-C
Range	0 - 67%	0 - 78%

RECLASSIFICATION ANALYSIS

PRECISE-C vs DCS

- **73.1%** of patients were classified into a different risk category when PRECISE-C was used instead of DCS.

PRECISE-C vs CCS-clinical

- **32.3%** of patients were classified into a different risk category when PRECISE-C was used instead of CCS-clinical.

NET BENEFIT ANALYSIS

OUTCOME	PRECISE-S	PRECISE-C	DCS	CCS-basic	CCS-clinical
Net benefit (at 5% pre-determined threshold probability)	0.061	0.063	0.056	0.060	0.065

Taking PRECISE-C as an example for illustration:

- The primary care physician is willing to refer 20 "at-risk" patients for tertiary evaluation in order to find 1 patient with CAD (i.e.,5% threshold probability).
- He decides to use PRECISE-C as a clinical decision support tool to identify patients with ≥ 5% PTP of CAD for referral.
- With the aid of PRECISE-C, he refers a total of 1000 patients for tertiary evaluation, out of which a net of 63 patients are "true positive" for CAD (i.e., a net of 1 "true positive" out of every 16 patients referred) → 1000/63 = 15.87
- In comparison, NB for DCS, CCS-basic, and CCS-clinical was 0.056, 0.060, and 0.065 respectively.

How much can we take out from this research/paper?

In the present study, the authors developed a diagnostic tool, named as the Predictive Risk scorE for CAD In Southeast Asians with chEst pain (PRECISE) in order to predict the development of coronary artery disease (CAD) among Southeast Asians. The PRECISE was then validated by comparing it against three existing tools, namely the Duke Clinical Score (DCS), CAD Consortium Score (CCS), and Marburg Heart Score (MHS). The Marburg Heart Score (MHS) is worth comparing and not the other tools from the perspectives of study population and setting.

A total of 1858 patients presented to primary care clinics with chest pain between July 2013 and December 2016 were prospectively recruited. This was a good sample size for the CAD event rate. The study samples were not truly representative of Southeast Asians because majority were Chinese. After a year of follow-up, the presence of outcome (CAD) was ascertained. Logistic regression analyses were performed to determine the final independent predictors of CAD. Subsequently, the performance of the PRECISE, DCS, CCS, and MHS models were analysed using discrimination and calibration tests. Finally, Reclassification Analysis and Net Benefit Analysis were performed to compare the clinical benefits between these tools. Reclassification analysis is of questionable relevance, more so when the comparator is not the MHS. Similarly, the net benefit analysis is lacking of convincing explanation, and of its support for the models clinical impact.

It was reported that the PRECISE model consists of nine CAD predictors, including the age, gender, type 2 diabetes mellitus, hypertension, smoking, chest pain type, neck radiation, Q waves, and ST-T changes. These predictors were either selected via multivariable analysis or included to the final model based on experts recommendation. Surprisingly, well established predictors of CAD, such as the family history of CAD, duration of physical activity, and dietary information were not given consideration in this study.

With regards to the diagnosis of CAD, it was mentioned that the diagnosis was made either based on the coronary angiography findings (i.e., objective method) or clinical judgement by the attending cardiologists (i.e., subjective method). Nonetheless, it was unclear of whether these cardiologists abide to a standardised protocol while making the diagnosis of CAD (e.g., the diagnosis of CAD must base on creatine kinase readings, symptomology, ECG findings, etc). We are also unclear to what extend these cardiologists were blinded towards the pre-test probability (PTP) of the study participants. Moreover, the referent (Gold) standard in clinical diagnosis of CAD did not hold up well. A sensitivity analysis with CAD diagnosis based on either catheter-based or CT coronary angiography would be better. Accordingly, the use of clinical diagnosis of CAD is incorrectly taken as the strength of this diagnostic study. Although the authors clearly defined the diagnosis of CAD in the present study as either ≥ 70% luminal stenosis of at least one major coronary artery or ≥ 50% left main stenosis, it seems like such definition of CAD has a discrepancy compared those used in the original DCS and CCS cohorts. As a result, the PRECISE model may not be directly comparable to the DCS and CCS models.

When performing risk stratification, study participants were categorised into low, intermediate, and high CAD risk groups using empirical risk thresholds of 5% and 50%, respectively. However, it was not elaborated on how these risk thresholds (i.e., 5% and 50%) were selected. Were they suggested by existing clinical guidelines? Were they based on clinicians' experience? Another issue requiring further clarification is that why is there such a huge and uneven gaps between the risk groups? Do they have any clinical significance? The models appeared good for low-risk and medium-risk (probability score ≤ 50%) to indicate non-CAD (> 80% accuracy) as compared to the high-risk predicting CAD at just slightly more than 50% accuracy (see supplementary Table 2).

Although the PRECISE-S and PRECISE-C performed better than DCS, CCS and MHS in terms of Reclassification Analysis and Net Benefit Analysis, the difference reported was very subtle and, hence, we are not sure to what extent this difference could result in clinical benefit. It was also puzzling and unexplained of the close similarity in performance of PRECISE-S and PRECISE-C.

Finally, the authors concluded that the PRECISE model performs well and demonstrates utility as a clinical decision support for diagnosing CAD among Southeast Asians. This statement should be interpreted with caution as the study cohort in the PRECISE study was very different from the populations in other Southeast Asian countries, except Malaysia. Future validation of the PRECISE model should therefore be conducted in this region.

References

1. https://www.cdc.gov/heartdisease/facts.htm.
2. Wang ZS, Yap J, Koh YLE, Chia SY, Nivedita N, Ang TWA, Goh SCP et al. (2021). Predicting Coronary Artery Disease in Primary Care: Development and Validation of a Diagnostic Risk Score for Major Ethnic Groups in Southeast Asia. J Gen Intern Med 36(6):1514–24. doi: 10.1007/s11606-021-06701-z.