White paper

Development of Personalised CARDIovascular risk Assessment for Chinese (P-CARDIAC): A prediction model

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1. Executive Summary

- Cardiovascular diseases (CVD) are the third leading cause of death in Hong Kong, and represents a considerable healthcare burden [1]; this is attributable to an increasing prevalence of established CVD risk factors in the population (e.g., hypertension, diabetes mellitus, and hypercholesterolaemia).[2]
- CVD are preventable via timely modification of risk factors.[3,4] Reducing disability and premature death from non-communicable diseases, including CVD, is a key policy of the government in Hong Kong.[5,6]
- Current cardiovascular (CV) prediction models lack discrimination and calibration in the Chinese population of Hong Kong.[7-9]
- The increased use of big data and artificial intelligence (AI) approaches (e.g., machine learning) in various clinical settings,[10-12] enables the development of a risk-prediction model that allows real-time risk assessment and can be incorporated into existing electronic healthcare systems.[11-13]
- P-CARDIAC (Personalised CARDIovascular risk Assessment for Chinese) is a public–private joint venture that was developed by The University of Hong Kong with support from the Innovation and Technology Bureau (HKSAR Government), and Amgen Hong Kong Limited.
- P-CARDIAC represents the first machine learning risk-prediction model developed specifically for a Chinese population[14] and is based on information collected from Hong Kong's Hospital Authority – a statutory body that manages government hospitals and includes data from public-funded primary, secondary, and tertiary care services in Hong Kong.[15]
- P-CARDIAC is a clinically and locally relevant CVD-predictive tool to identify patients in Hong Kong who are at risk of first or subsequent CVD event, regardless of whether they have established CVD or prior use of lipid-lowering therapy.

- Incorporation of P-CARDIAC as part of comprehensive CV risk assessment will enable a paradigm shift to a predict-and-prevent approach in CVD management in Hong Kong. This will contribute to reducing premature CVD-associated mortality by 25%, in accordance with the target set by the Hong Kong government in 2018,[6] and will align with the Hong Kong Hospital Authority's Strategic Plan (2022–2027) of adopting data-driven care for patients.[16]
- Preliminary results of internal and external validation of P-CARDIAC demonstrated good discrimination and calibration performance.[14]
- The use of P-CARDIAC can help improve patient outcomes by accurately predicting the risk of CVD events and supporting clinical decision-making regarding the need for therapeutic intervention, diagnostic testing, or monitoring.
- Incorporation of P-CARDIAC into clinical practice in Hong Kong can ensure provision of personalised risk scores to patients, using a tool that was specifically developed for the local population, and that has the ability to adjust over time to reflect the effect of therapeutic interventions.
- The P-CARDIAC tool can provide considerable benefits to stakeholders over the short, medium, and long term, including serving as a clinical support tool to help stratify patients and select appropriate interventions, providing a means of communicating the risk of CVD to patients, reducing healthcare costs associated with poor CV outcomes, and thereby helping to provide more sustainable CVD care pathways.

2. Introduction

2.1. Burden of cardiovascular diseases in Hong Kong

Cardiovascular diseases (CVDs) are the number one cause of death globally - approximately 50,000 people died from CVDs each day (according to data for 2019), 58% of which occurred in Asia and Australasia.[17] China has the largest absolute burden in terms of CVD deaths, with a total 5.5 million deaths attributed to CVD in 2021,[18] and a 20.9% increase from 1990 to 2017 in age-standardised years lived with disability for cardiovascular (CV) diseases.[19] CVD also represents a considerable economic burden, with a 2018 report forecasting that the annual direct and indirect cost of CVD in China and Hong Kong would exceed USD$21 billion and USD$4.8 billion, respectively.[20] In Hong Kong, CVD is the third leading cause of death after cancer and pneumonia.[1] This may be attributed to an increasing prevalence of established CVD risk factors in the population of Hong Kong; for instance, there was an increased prevalence from 2013 to 2020 in hypertension (9.9% to 12.6%), diabetes mellitus (4.4% to 5.2%), and hypercholesterolaemia (1.9% to 5.1%).[2] Population aging is a further CVD risk factor, with the proportion of elderly persons aged 65 and older expected to nearly double in Hong Kong between 2020 and 2040.[21]

The majority of CVD cases are preventable. Timely modification of risk factors is critical to lowering the associated morbidity and mortality, consequently reducing the healthcare burden.[3,4] The government in Hong Kong published an action plan in 2018 aimed at reducing disability and premature death from non-communicable diseases by 2025. A key requirement for CVD prevention and treatment is an effective and sustainable health system that provides comprehensive primary care for prevention, early detection, and management of CVD.[5,6]

Assessment of CVD risk is a pivotal step in CVD prevention to inform the introduction, or adjustment of, risk-reducing strategies.[22] Clinical guidelines recommend the use of risk prediction models to stratify patients according to their risk of disease, so that high-risk patients receive the necessary interventions to reduce their risk while low-risk patients do not get overtreated.[23] In current clinical practice, prediction models that are frequently used to determine CV risk include QRISK3,[24] Framingham Risk Score,[25] and the Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention (TRS-2ºP).[26,27] However, these prediction models have several limitations:

- They are based on a static set of limited variables and do not include information on the use of therapies demonstrated to modify CV risk (**Table 1**).
- The models are based on Western populations and may be less sensitive and applicable to Chinese populations.[7-9] For example, the Framingham Risk Score, which is recommended by the Hong Kong Department of Health, was shown to overestimate 10-year CVD events by approximately 1.2-fold in both sexes when tested in older patients in Hong Kong. Recalibration of the model with local data from an elderly Chinese cohort from Hong Kong did not improve the sensitivity of the score.[9] Indeed, it is preferred that country-specific risk scores are used for CV risk stratification.[28]
- Current models are typically unable to capture changes in CVD risk in individual patients.[11]

There is, therefore, a need for more clinically relevant CVD risk prediction models that can more accurately predict CV risk in Hong Kong by including broader and longitudinal data and by considering the impact of lipid-lowering therapies. Development of such a model may be facilitated by advances in artificial intelligence (AI), including the use of machine learning techniques to interrogate big data.

2.2. Big data and healthcare

With the increasing ageing population in Hong Kong,[21] a more sustainable healthcare system with cost-effective primary care interventions focused on preventive health is needed. In response to this, the Hong Kong Hospital Authority's Strategic Plan 2022–2027 set out a vision for smarter healthcare with an increasing leverage of big data and the adoption of digital health solutions.[16,29] Globally, the digitisation of medical records has facilitated a greater role for big data and machine learning in aspects of patient care, including providing opportunities to develop and refine risk prediction algorithms using the clinical patient information captured in electronic health records (EHRs).[10-12] The benefits of EHR-based risk-prediction models, whereby large patient datasets are analysed using machine-learning algorithms to identify a set of variables to be used for personalised risk prediction,[12] include:

- The generalisability of the data, because EHR-based models are generally based on large sample population sizes,[11]
- The ability to analyse multiple outcomes using the same dataset, as EHRs are not disease-specific,[11]
- The availability of a large data size enables the creation of validation sets,[11]
- The ability to identify relevant covariates, because of the inclusion of a large number of variables, including both static (e.g., demographics) and dynamic (e.g., laboratory test results, disease diagnoses) information,[11,12]
- Better predictive capabilities over time with the availability of longitudinal data;[12] this facilitates learning about factors involved in disease progression,[13]
- Results that better reflect real-world clinical practice than cohort studies, and[11]
- The ability to incorporate risk prediction models into existing electronic systems.[11]

2.2.1 Clinical use of EHR-based risk prediction models

In clinical settings, the benefits of applying big data and machine learning are being realised, with promising results from EHR-based risk-prediction models reported in various clinical situations. Examples include:

- A proof-of-concept study conducted in the Unites States used multimodal images (acquired from patients with a neurologist-confirmed clinical diagnosis of Alzheimer's disease and from cognitively healthy controls) to train, validate, and test a convolutional neural network that predicted the probability of Alzheimer's disease.[30]

- A machine-learning model has been developed based on data from over 1 million patients in the Chinese Stroke Center Alliance, to predict stroke-associated pneumonia in patients who have an acute intracranial haemorrhage. In a clinical setting, the new risk score (ICH-LR2S2) demonstrated superior performance in predicting stroke-associated pneumonia compared with previous risk scores, and good utility in identifying high-risk patients in the early stages of disease.[31]
- An algorithm called Artificial Intelligence Sepsis Expert (AISE), which allows real-time prediction of sepsis onset, was developed using EHR data in combination with high-resolution time series dynamics of blood pressure and heart rate. Results of a preliminary observational cohort study in the United States indicate that AISE could predict the onset of sepsis in patients in the intensive care unit 4–12 hours prior to clinical recognition.[33]

2.3. Rationale for a Hong Kong-specific CVD prediction model

The burden associated with CVD and the trend for increasing CV risk factors among the Hong Kong population indicate a heightened need to identify and treat individuals at high risk of CVD.[2,20] Given the limitation of current CVD risk prediction models, there remains an unmet need for a sensitive, clinically relevant, personalised CVD risk prediction model for Chinese populations.[7-9,11] Previous studies have shown that with a sufficiently large population of training data, accurate CV risk prediction can be achieved from EHR and machine-learning methods.[34]

3. The P-CARDIAC risk prediction model

P-CARDIAC (Personalised CARDIovascular risk Assessment for Chinese) is the first machine learning CVD risk prediction model developed specifically for a Chinese population.

It is a public–private joint venture that was developed by the School of Nursing, the School of Public Health, the Department of Pharmacology and Pharmacy, the School of Clinical Medicine, and the Department of Computer Science (Faculty of Engineering) at The University of Hong Kong, with support from the Innovation and Technology Bureau (HKSAR Government), and Amgen Hong Kong Limited. Key features of the P-CARDIAC model are as follows:

- The model is based on information collected from Hong Kong's Hospital Authority, a statutory body that manages government hospitals and includes data from public-funded primary, secondary, and tertiary care services in Hong Kong.[15]
- The model utilises machine learning to process large volumes of heterogeneous EHR data to form a robust representation of health status, risk, and treatment efficacy in chronic diseases.[35,36]
- The model adopts a web-based interface that estimates CVD-free survival probability and years with and without the influence of medical treatment (**Figure 1**).

3.1 Purpose of the P-CARDIAC prediction model

The aims of the P-CARDIAC risk prediction model are as follows:

- Establish a clinically and locally relevant CVD predictive tool to identify patients who are at risk of first or subsequent CV event, regardless of whether they have established CVD or prior use of lipid-lowering therapy.
- Enable a predict-and-prevent approach to CVD management in Hong Kong.
- Contribute to reducing premature CVD-associated mortality by 25%, in accordance with the target set by the Hong Kong government in 2018,[6] thereby reducing the CVD-related public healthcare burden.
- Align with the Hong Kong Hospital Authority's Strategic Plan (2022–2027) by adopting data-driven care to predict or verify the health risk for patients so that personalised treatment can be provided.[16]

3.2 P-CARDIAC validation

Development and validation of the P-CARDIAC risk prediction model is described in detail by Chui et al., 2022[14] [Please note that this is a placeholder ref for the full publication] and is based on data from patients with established CVD events from Hong Kong. Patients were assigned a geographical tag representing the region that patients most frequently visited for healthcare utilization; these regions were the Hong Kong West Cluster, Kowloon, and New Territories.[14] Ethics approval was obtained from the Hospital Authority Institutional Review Board of the University of Hong Kong.

Internal validation was performed on the patients from the Hong Kong West Cluster ('derivation cohort', whereby 30% of this cohort were used for validation purposes and 70% were used to develop the model). These data were extracted from the Hospital Authority database and were based on the EHRs of eligible patients aged ≥18 years who received an initial lipid test at any Hospital Authority service outlet within the Hong Kong West Cluster between 1 January 2004 and 31 March 2014 (N=145,875).[37] Seventy percent of the dataset was used for the development of the training model, which acted as a benchmark for comparison. The remaining 30% of the dataset was validated against the training model. Final (external) validation was performed against two 'validation cohorts' which were from different geographic regions of Hong Kong (i.e., the Kowloon region with 119,672 participants and the New Territories region with 140,533 participants). These Hospital Authority-derived datasets were based on the EHRs of patients who used services provided by the Hospital Authority between 1 January 2005 and 31 December 2019. The performance of P-CARDIAC was compared with existing risk scores (TRS-2ºP and SMART2) in internal and external validation.

Preliminary results of internal and external validation of P-CARDIAC for recurrent CVD demonstrated good discrimination and calibration performance, as described by Chui et al, 2022.[14] [Please note that this is a placeholder ref for the full publication.] Two versions of the

P-CARDIAC model were developed – a basic model, with mandatory covariates that were identified based on multivariate statistical testing of the Hospital Authority data, and a full model, which incorporated additional covariates. The full model had better performance than the basic model, because it accurately accounted for non-linear effects and the effects from supplementary risk factors. Compared with the P-CARDIAC model, TRS-2ºP and SMART2 both underperformed in the two Hong Kong cohorts representing Chinese populations. Following successful validation, user acceptance testing will be conducted to allow optimisation of the tool prior to release.

3.3 Application of P-CARDIAC

Given that P-CARDIAC is being developed under a government–private partnership and all parties were involved from the start of this initiative, the incorporation of P-CARDIAC into existing electronic healthcare systems has been well planned, and P-CARDIAC may serve as a frontline tool to predict CVD risks in the general public. Patient data can be directly extracted from clinical management systems into P-CARDIAC to generate a CVD risk score. Based on the risk score, healthcare professionals can:

- Predict patients' 1- to 10-year risk of a CVD event,
- Stratify patients according to their risk of disease,
- Discuss the impact of different interventions on CV risk, and
- Involve patients in decisions relating to CV risk management using representations of CVD-free survival probability with and without interventions.

3.4 Key strengths/benefits of P-CARDIAC

The performance of an algorithm is dependent on the dataset it is trained on.[38] The P-CARDIAC model, which represents the first machine learning CVD risk score developed specifically for a Chinese population, has been trained and validated based on local data. It is also the first machine-learning model to predict the risk of CVD in Hong Kong. The potential benefits of P-CARDIAC are manifold (illustrated in the proposed Hong Kong setting in **Figure 2**):

1. **Integration into healthcare management systems.** P-CARDIAC is a clinical support tool that can be easily integrated into electronic healthcare systems and uses clinical data that is available in patients' EHR.
2. **Personalised and accurate risk prediction.** By considering multiple modifiable factors (e.g., biochemical indications) and non-modifiable factors (e.g., age, sex, or family disease history), P-CARDIAC can accurately predict the risk of CVD events (as it is based on 120+ covariates from the EHR), prompting intervention, diagnostic testing, or monitoring to improve patient outcomes.
3. **Dynamic data**. P-CARDIAC can provide personalised CVD prediction throughout the patient journey. This can facilitate timely intervention, as well as provide a real-time estimate of how CVD risk changes with interventions, which may indirectly motivate greater patient engagement and increase adherence to treatment.
4. **Utility as a clinical support tool to aid treatment decision-making.** P-CARDIAC adopts an interactive, web-based interface that facilitates visualisation of the impact of different interventions (e.g., statins, antihypertensive drugs, antidiabetic drugs, non-statin lipid-lowering drugs, and antiplatelets) on an individual's CVD risk.
    - The risks associated with starting, stopping, and continuing medication may be measured and visualised. While the current model only includes pharmacological interventions (with an assumption of 100% treatment adherence), the impact of lifestyle changes may be included in future iterations of the model.
    - This will enable healthcare professionals to adopt a more comprehensive assessment and personalised treatment approach in prescribing preventative treatments for CVD.

    - The model may facilitate greater involvement of patients in shared decision-making, as patients may feel better informed of the outcomes with different interventions.
5. **Improves resource management.** The ease of use of P-CARDIAC may allow healthcare professionals other than cardiologists to access, review, and discuss CVD risk with patients.
    - For instance, P-CARDIAC may be used by community healthcare professionals, and pilot studies of P-CARDIAC are ongoing in a community pharmacy setting.
    - Additionally, P-CARDIAC data may support decision-making regarding the need for specialist care, thereby offering the potential to reduce specialist referrals.
    - With optimised stratification and triage, P-CARDIAC may help improve care pathways and address long waiting times for specialist cardiology services.
6. **Adaptability to different patient populations**. The model may be recalibrated to incorporate additional data from alternative sources, thereby enabling the model to be adapted for different patient populations.

3.5 Potential impact of P-CARDIAC

Incorporation of the P-CARDIAC CVD risk prediction model into routine clinical practice can offer considerable benefits to multiple stakeholders, including patients, carers, healthcare providers, and payors. The potential impact over the short, medium, and long term are outlined below.

Short term (1–3 years)

- The P-CARDIAC risk prediction model can serve as a clinical support tool to help stratify patients into different risk categories and to inform the intensity of risk factor management in both public and private healthcare sectors; this may facilitate better resourcing and help alleviate pressure on public specialist care. There may also be the potential for expanding care provision to patients via an increase in clinical public–private partnership.

- Identification of individuals at high risk of CVD will facilitate greater patient access to CVD preventive medicine, thereby improving outcomes for patients.
- The incorporation of P-CARDIAC in clinical practice may help the government to achieve the target of reducing premature CVD-associated mortality by 25% in Hong Kong.[6]

Medium term (4–10 years)

- Patient recognition of CVD risk factors is important in the prevention of CV events. Use of P-CARDIAC in routine clinical practice over the medium-to-long term in Hong Kong may help to raise awareness of CVD and the measures that patients can take to reduce their CV risk. Increasing awareness of CVD risk factors may also be facilitated by the use of P-CARDIAC in the community healthcare setting.
- Use of the P-CARDIAC CVD risk prediction model will prompt earlier intervention, which may result in an increased demand for preventive care services over the medium term; however, this may be negated by reduced use of the Framingham Risk Score, which is associated with overestimation of risk among older Hong Kong Chinese adults.[9]

Long term (10 years)

- Use of the P-CARDIAC CVD risk prediction model in the longer term will facilitate a paradigm shift in CVD management in Hong Kong from treatment of CV events to a predict-and-prevent approach.

- By reducing the occurrence and recurrence of heart attacks, the P-CARDIAC model will help to alleviate a major public healthcare burden, including the burden on patient carers.
- The P-CARDIAC CVD risk prediction model may have a favourable impact on healthcare costs because unnecessary costs due to overestimation of risk by the Framingham Risk Score will be reduced. Furthermore, use of the new score, which has been trained and validated based on local data, will identify those who are truly in need of preventative measures. This will reduce the morbidity and mortality, as well as the healthcare burden, that are associated with CV events (e.g., reduced need for emergency surgery following a heart attack or fewer coronary artery bypass grafts).

3.6 Future directions with P-CARDIAC

To ensure the outcomes of P-CARDIAC are representative of, and validated across, the broader mainland Chinese population, a collaborative data network approach using databases from across China may be desirable; this is because results of a recent nationwide, population-based screening project reported a clustering of risk factors for CVD in different regions of China.[39]

A potential approach would be to collaborate with and collate EHR data from hospitals across mainland China. Such an approach would require data to be cleaned and standardised, because language, International Statistical Classification of Diseases and Related Health Problems (ICD) code, drug codes, and drug names typically vary between sites. A risk prediction model to determine coronary heart disease risk in patients with hypertension has been developed using EHR from the Shenzhen Health Information platform, which comprise 83 local public hospitals and over 600 community health service centers.[34]

Several large data networks such as the Observational Health Data Sciences and Informatics (OHDSI) and Health Data Research UK are currently in development internationally and may provide other opportunities for collaboration. The OHDSI data network consists of standardised data from 331 data sources (284 electronic health record and 28 administrative claims databases) from across 34 countries with 810 million unique patient records, equating to approximately 10% of the world's population.[40] The Health Data Research Innovation Gateway gives researchers access to health-related datasets from across the UK.[41]

With increasing interest in incorporating wearable technology in the healthcare setting, there is the potential for future integration of P-CARDIAC with wearable devices, to enable remote collection of data to help improve the performance of the algorithm in a positive-feedback manner. Further research is required to identify potential future opportunities and collaborations to validate and further develop the P-CARDIAC CVD risk prediction model.

4. Summary

CVD is a growing health concern in Hong Kong, due to an increasingly elderly population and other CV risk factors, such as increasing prevalence of hypertension.[2,21,42] This largely preventable disease is associated with considerable morbidity and mortality, and it represents a large burden on the public healthcare sector and on the economy.[3,4] The P-CARDIAC CVD risk prediction model represents a first in terms of a public–private partnership for the application of big data to healthcare in Hong Kong, and in terms of a machine-learning model to predict CVD risk specifically for the Chinese population in Hong Kong. P-CARDIAC can accurately predict the risk of CVD events and support clinical decision-making regarding the need for therapeutic intervention, diagnostic testing, or monitoring, to improve patient outcomes.

Key features of the P-CARDIAC CVD risk prediction model include:

- **Personalised risk score.** P-CARDIAC provides a personalised risk score based on an individual patient's health profile.
- **Relevance.** P-CARDIAC offers greater relevance compared with existing CVD prediction models for the Hong Kong Chinese population, as it was developed and validated based on the EHRs of this population.
- **Accuracy and precision**. P-CARDIAC offers greater accuracy and precision than SMART2 and TRS-2ºP scores for the Hong Kong Chinese population because it is based on 120+ covariates from Hospital Authority data.
- **Dynamic results.** P-CARDIAC provides a dynamic result because the risk-prediction result will adjust over time to reflect the effect of an intervention.

Incorporation of the P-CARDIAC CVD risk prediction model into clinical practice as part of comprehensive cardiovascular risk assessment will facilitate a paradigm shift in CVD management in Hong Kong, from treatment of CV events to a predict-and-prevent approach. P-CARDIAC will provide a valuable support tool for clinicians and has the potential to improve the patient care pathway, thus reducing unnecessary specialist referrals and improving treatment access. The incorporation of P-CARDIAC in clinical practice offers the potential to improve patient outcomes and to help achieve the target of reducing premature CVD-associated mortality by 25% in Hong Kong.[6]

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6. Figures and Tables

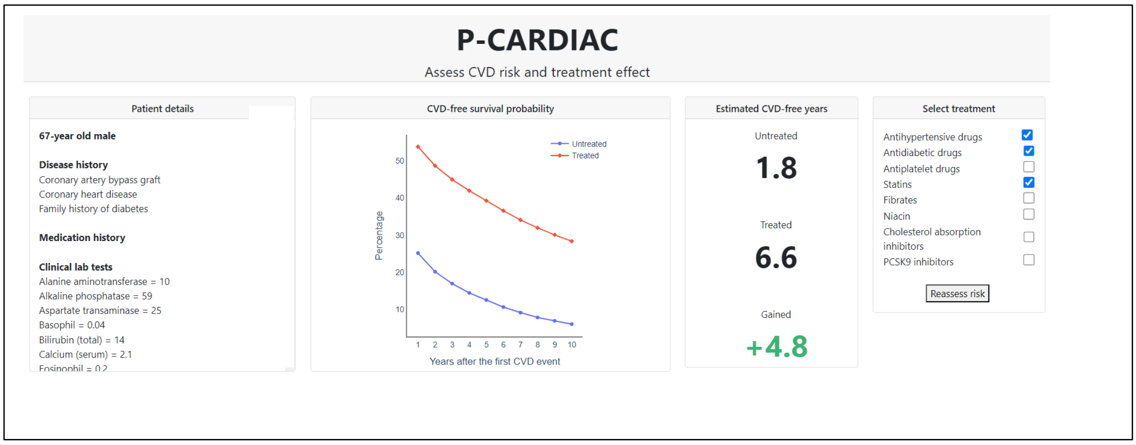
Table 1. Examples of risk prediction models for CVD

	Framingham	QRISK3	TRS-2ºP
Primary or secondary prevention	Primary	Primary	Secondary in patients with atherosclerotic vascular disease
Outcome	Estimates 10-year risk of heart attack	10-year risk of heart attack or stroke	Risk at 3 years of CV death, MI, or ischemic stroke
Age	√	√	√
Sex	√	√	–
Ethnicity	–	√	–
Smoker	√	√	√
Total cholesterol	√	√	–
HDL cholesterol	√	√	–
Systolic blood pressure	√	√	–
Body mass index	–	√	–
Hypertension being treated with medicines	√	√	–
Diabetes/Hypertension/Angina	–	√	√
Congestive heart failure	–	–	√
Prior stroke	–	–	√
Prior coronary artery bypass graft	–	–	√

Peripheral arterial disease	–	–	√
eGFR <60	–	–	√
Chronic kidney diseases	–	√	–
Atrial fibrillation	–	√	–
Rheumatoid arthritis	–	√	–
Migraines	–	√	–
Systemic lupus erythematosus	–	√	–
Severe mental illness	–	√	–
On atypical antipsychotic medication	–	√	–
On regular steroid tablets	–	√	–
Erectile dysfunction	–	√	–

√ included in the model; – not included in the model. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; TRS-2ºP, Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

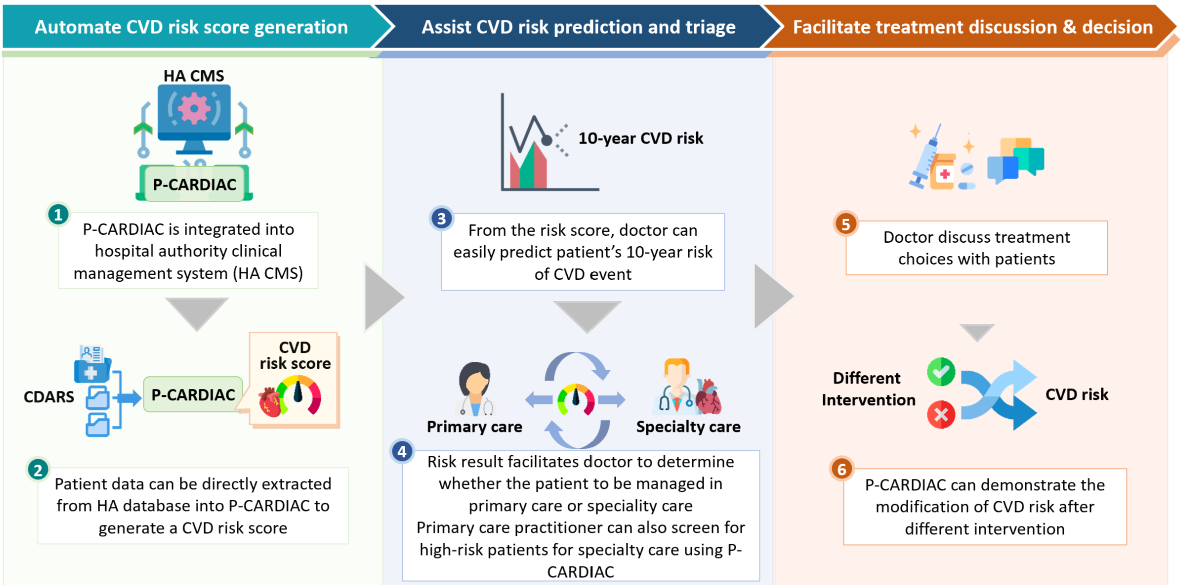
Figure 1. CVD risk prediction with P-CARDIAC over 10 years, showing CVD-free survival probability with/without medical treatment*



*The prediction assumes 100% adherence.

CVD, cardiovascular disease; P-CARDIAC, Personalised CARDIovascular risk Assessment for Chinese.

Figure 2. Potential benefits of implementing the P-CARDIAC CVD risk prediction model



CMS, clinical management system; CVD, cardiovascular disease; HA, Hospital Authority; P-CARDIAC, Personalised CARDIovascular risk Assessment for Chinese.