BMJ Open

Cohort profile: AI driven national Platform for CCTA for clinicaL and industriaL applicatiOns (APOLLO)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-089047
Article Type:	Cohort profile
Date Submitted by the Author:	21-May-2024
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Keywords:	Coronary heart disease < CARDIOLOGY, Computed tomography < RADIOLOGY & IMAGING, Artificial Intelligence

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Cohort profile: AI driven national Platform for CCTA for clinicaL and industriaL applicatiOns (APOLLO)

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ABSTRACT

Purpose: Coronary computed tomography angiography (CCTA) is well-established in the diagnostic evaluation and prognostication of coronary artery disease (CAD). The growing burden of CAD in Asia and the emergence of novel CT-based risk markers necessitate an automated platform to integrate patient data with CCTA findings, providing tailored, accurate cardiovascular risk assessments. This study aims to build an AI-driven platform for CAD assessment using CCTA in the context of the multi-ethnic population of Singapore. We will conduct a hybrid retrospective-prospective review of patients who underwent CCTA as part of the diagnostic work-up for CAD, along with a prospective follow-up for clinical endpoints. CCTA images will be analyzed locally and by a core lab for coronary stenosis grading, Agatston scoring, epicardial adipose tissue, and plaque analysis. Images and analyses will also be uploaded to an AI platform for deidentification, integration, and automated reporting to create precision AI toolkits for each of these parameters.

Participants: CCTA images and baseline characteristics have been collected and verified for 4,196 recruited patients. Preliminary demographic data indicated that the study population consisted of 76% Chinese, 6% Malay, 9% Indian, and 9% from other ethnic groups. Among the participants, 44% were female, with a mean age of 55±11 years. Additionally, 43% had hypertension, 52% had dyslipidemia, 16% had diabetes, and 21% had a history of smoking.

Findings to date: The cohort data has been used to develop four AI modules for training, testing, and validation. During the development of each AI module, the data preprocessing standardized the format, resolution, and other relevant attributes of the images.

Future plans: We will conduct prospective follow-up on the cohort to track clinical endpoints, such as cardiovascular events, hospitalizations, and mortality. Additionally, we will monitor the long-term impact of the AI-driven platform on patient outcomes and healthcare delivery.

Trial registration: ClinicalTrials.gov (Identifier: NCT05509010).

Keywords: Computed Tomography Angiography; Coronary Artery Disease; Artificial Intelligence

Strengths and limitations of this study

- APOLLO is a first-in-Asia, AI-driven national platform for CCTA for clinical, and industrial applications in Singapore.
- APOLLO is a hybrid, retrospective-prospective, open-label, observational, multi-centre study. It will involve a retrospective review of patients who underwent CCTA as part of diagnostic work-up for CAD, as well as prospective follow-up for several clinical endpoints.
- The AI-based toolkit will automatize de-identification, identification of coronary stenoses, plaque characterization, as well as quantification of epicardial adipose tissue and coronary artery calcium score.
- This study only included patients from an Asian population. Therefore, additional Western-inclusive population studies are warranted to further validate the findings.

INTRODUCTION

As in the rest of the world, coronary artery disease (CAD) is a leading cause of death in Asia, and its increasing prevalence portends a significant healthcare and economic burden.[1 2] Coronary computed tomography angiography (CCTA) is now firmly established as an essential modality in the early detection, clinical evaluation, and risk stratification of patients with CAD. This is reflected in guidelines from the National Institute of Clinical Excellence (NICE),[3] as well as European Society of Cardiology (ESC)[4] and American Heart Association (AHA).[5] These recommendations are built on a body of evidence demonstrating that upstream use of CCTA for the diagnosis of CAD improves event-free survival through earlier initiation of guidelines-directed medical therapy,[6] reduces rates of needless cardiac catheterization[7] and facilitates earlier discharge of patients presenting with possible acute coronary syndrome to Accident and Emergency.[8]

CCTA is not only the modality-of-choice for anatomical assessment of the coronary vasculature, but also an essential tool for disease characterization and risk stratification. CT-generated parameters including Agatston score,[9] epicardial adipose tissue (EAT),[10] and plaque characteristics[11] are each of incremental value in this regard. However, uptake of these measurements in routine clinical practice is hampered by the laborious and time-consuming nature of manual quantification. Furthermore, manual determination of these parameters suffers from significant inter-observer variability, reportedly up to 20% even between expert readers.[12] Therefore, there is an unmet need for accurate automatization and streamlining of these parameters to better harness the diagnostic and prognostic utility of CCTA for patients with CAD.

Moreover, whilst several models have been studied and reported, they have been found to be poor predictors of cardiovascular risk in Asian populations. For example, The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry

(CONFIRM) revealed that Asian sites had a three-fold lower-than-expected prevalence of CAD. Similarly, in an observational study Villadsen et al. found ethnic differences in the composition of coronary atherosclerotic plaque between Caucasian and South Asian patients, reporting a significantly lower proportion of non-calcified plaque in the former.[13] Our group has previously studied the performance of the CAD Consortium (CAD2) model in a mixed Asian population in Singapore and found suboptimal discriminative power, though it improved significantly with local calibration.[14] More recently, we evaluated the prognostic utility of both pooled cohort equations (PCEs) and Agatston score in a symptomatic, mixed Asian population. We found that PCE alone provided no discriminative value over random chance, and furthermore, this was not significantly improved after the addition of Agatston scores.[15] Therefore, an automated model must consider these differences for accurate prediction of cardiovascular risk in the mixed Asian population of Singapore. To develop this, a contemporary study of CAD prevalence in Asia is needed.

COHORT DESCRIPTION

Patient and public involvement

Patients and/or the public were not directly involved in the design, or conduct, or reporting, or dissemination plans of this research. The study outcomes will be disseminated through publication in peer-reviewed biomedical, cardiac imaging, and clinical journals, as well as presentations at scientific conferences. This will pave the way for a range of clinical, population health, research, and commercial applications.

Cohort objectives

We aim to build a first-in-Asia, AI-driven national platform for CCTA for clinical, and industrial applications (APOLLO), to create a mixed-ethnic phenotypic registry of CAD in Singapore (**Graphical abstract**). APOLLO will serve a range of clinical, research and industrial purposes. First, as a large, registry, APOLLO stands to offer valuable insights into patient demographics and disease patterns within a highly characterized multi-ethnic Asian population. Second, the development of precision AI toolkits may enable automation of anonymization, reporting, Agatston scoring, EAT and plaque quantification, facilitating integration of these tasks into routine clinical practice. Third, as a de-identified and sharable database, APOLLO will facilitate the calibration and development of Asian-based prediction models whilst expediting the advent of novel medical and device therapies in the Asian context (**Figure 1**).

Study type

APOLLO is a hybrid, retrospective-prospective, open-label, observational, multi-centre study. It will involve a retrospective medical record review of patients who underwent CCTA as part of

diagnostic work-up for CAD, as well as prospective follow-up for several clinical endpoints. Details of the study design are also available on ClinicalTrials.gov (Identifier: NCT05509010).

Study population

There are three hospital sites participating in the creation of APOLLO: National Heart Centre Singapore (NHCS), National University Health System (NUHS) and Tan Tock Seng Hospital (TTSH). These represent the three largest cardiac healthcare systems in the country. Patients who underwent CCTA after 1 January 2007 will be included, with recruitment to be continue until 31 December 2025. The inclusion and exclusion criteria are listed in **Table 1**. Patients aged 21 and above were included. Exclusion criteria include acute coronary syndrome, a body mass index exceeding 40 kg/m^2, and a history of percutaneous or surgical intervention for CAD. Baseline demographic and clinical characteristics will be obtained from the electronic medical records and case notes, including but not limited to: (1) age, gender, race, socioeconomic status, marital status, (2) comorbidities, (3) laboratory tests, (4) radiological tests, (5) cardiac investigations, (6) cardiac procedures, (7) medication use, (8) chest pain characteristics.

CCTA protocol

CCTA acquisition will be conducted using 6 state-of-the-art CT scanners (Canon, Siemens, GE, Philips) with ≥256-detector rows, following image acquisition protocols outlined in the Society of Cardiovascular Computed Tomography (SCCT) guidelines.[16] Medication, as per guidelines, can be administered to moderate heart rate in patients with a heart rate higher than 60 bpm. Sublingual glyceryl trinitrate is administered prior to scanning. The CCTA scans employ a prospective ECG-triggered scanning mode. A tri-phasic injection protocol is applied, involving contrast injections

of approximately 50ml at 5ml/s and 20ml at 3.5ml/s sequentially, followed by a third injection of 30ml saline at 3ml/s.

CCTA analysis

The CCTA images will be analyzed and interpreted both at the clinical site level and at the core laboratory. At the clinical site read, CCTA interpretation will be done in accordance with the 2016 SCCT guidelines.[16] Core lab analysis will be performed at the CardioVascular Systems Imaging and Artificial Intelligence (CVS.AI) research core of NHCS, blinded to the clinical site interpretation. Core lab analyses will include:

(1) **Coronary stenosis grading**: The assessment focuses on the severity of stenosis and precise localization within the coronary circulation. A crucial aspect involves visually estimating luminal narrowing caused by plaque. Following the SCCT guideline,[16] stenosis is graded across a spectrum, ranging from minimal to total occlusion. Additionally, distinctions between obstructive and non-obstructive categories are made, with the SCCT model guiding the accurate determination of stenosis location.

(2) **Agatston scoring analysis**: Calcified plaque is evaluated using Agatston scoring programs, aligned with SCCT clinical practical guidelines.[16] Pixels exceeding 130 Hounsfield Units (HU) are identified as indicative of calcium on non-contrast studies.[17] Lesions within each vessel distribution are discerned, and the scoring program generates a comprehensive summed score for each vessel based on area-density (Agatston score) measurements. The total coronary Agatston score aggregates all calcified lesions throughout coronary beds.

(3) **EAT analysis**: This analysis focuses on the total volume and anatomical locations of EAT and pericardial adipose tissue (PAT), metabolically active fats associated with heightened

cardiovascular disease risk.[18] Quantification on non-contrast CT scans involves meticulous annotation by manually drawing the pericardium. EAT is identified using adipose tissue attenuation references between -190 and -30 HU.[19] Given potential variations in HU values due to CT scan noise and attenuation changes, the final EAT region is verified by an experienced radiologist or cardiologist.

(4) **Plaque analysis**: This facet involves analysis of plaque volume, burden, type, and anatomical locations. Coronary segmentation and analysis are performed for segments with a diameter ≥ 1.5 mm, with the SCCT model[16] aiding in precise plaque localization. For each plaque, detailed assessments, including start and end points, area, volume, and plaque burden, and type (non-calcified, calcified, or mixed),[20] are conducted. Additionally, non-calcified plaque is further subclassified into low attenuation plaque (LAP), with HU <30 signifying LAP and >30 signifying non-LAP.

Patient outcomes

Patients whose CCTA data will be utilized for the purpose of this study will also be prospectively followed up till 31 December 2025 for several outcome measures. This will enable prognostic validation of AI-derived measurements. The patient outcomes to be monitored for are as follows:

(1) **Mortality (all-cause and cardiovascular):** Over the course of one to five years from the baseline, the study will examine mortality rates, including both all-cause mortality and mortality specifically attributable to cardiovascular events.

(2) **Major Adverse Cardiovascular Events (MACE):** Besides mortality, the study will assess MACE, including, but not limited to, myocardial infarction, stroke, heart failure, percutaneous/surgical revascularization, and arrhythmias.

(3) **Re-hospitalization:** Another critical aspect of the outcome measures involves evaluating the incidence of re-hospitalization within the one to five-year period from the baseline. This parameter serves as a valuable indicator of the long-term impact of AI interventions on the need for repeated hospital admissions, shedding light on the potential benefits in terms of sustained health outcomes and healthcare resource utilization.

These data will be recorded from hospital medical records as well as national registries in accordance to institution, ministry and national-level regulations. At the institutional level, tracking and extraction of outcomes will be performed by the respective IT teams under PI/study team supervision. The respective institution's Clinical Research Coordinator (CRC) will also track and match outcomes via electronic medical records (EMR). At the national level, matching and tracking of outcome data from national registries (National Registry of Diseases Office; NRDO) will be delegated to NRDO staff. One of the registries to be analysed via NRDO is Singapore Myocardial Infarction Registry (SMIR) for aggregate data.

Data sharing

Data sharing will be through the National University Health System (NUHS)'s DISCOVERY AI platform, a production system that houses centralized anonymization, equitable data access and differential data linkage capabilities.[21] DISCOVERY AI platform processes are summarized in **Figure 2**. Oversight rests with the custodian of a particular database. DISCOVERY AI incorporates centralized anonymization and data handling measures that are in accordance with the Singapore Personal Data Protection Act (PDPA) 2012,56 Human Biomedical Research Act 2015,57 and Human Biomedical Research Regulations 2017.58 In keeping with PDPA guidelines, all data on board DISCOVERY AI are anonymized by removing protected health identifiers (PHI)

such as name, address and identification number. DISCOVERY AI also features proprietary security features, such as data obfuscation and ledger-based access logs.

Ethics and dissemination

The study protocol has been approved by the SingHealth Centralised Institutional Review Board. The project outcomes will be disseminated through publication in peer-reviewed biomedical, cardiac imaging, and clinical journals, as well as presentations at scientific conferences. Patient confidentiality will be maintained by not including any individually identifying information in the publications.

FINDINGS TO DATE

CCTA images and baseline characteristics have been collected and verified for 4,196 recruited patients. Preliminary demographic data (n = 1844) indicated that the study population consisted of 76% Chinese, 6% Malay, 9% Indian, and 9% from other ethnic groups. Among the participants, 44% were female, with a mean age of 55 ± 11 years. Additionally, 43% had hypertension, 52% had dyslipidemia, 16% had diabetes, and 21% had a history of smoking (**Table 2**). All data collected has been anonymized and stored in DISCOVERY AI. Furthermore, the four AI modules are in development using 2,983 CT imaging studies for training, testing and validation. During the development of each AI module, the data pre-processing standardized the format, resolution, and other relevant attributes of the images.

DISCUSSION

The APOLLO study targets a cohort reflective of the current real-world Asian population undergoing assessment for CAD. Given the growing clinical burden of CAD, a national AI platform to facilitate CCTA analysis is desirable for several reasons. First, as the largest CCTA registry of patients with suspected CAD, APOLLO will provide much needed and highly representative insight into current and emerging states of clinical diagnostic testing in the region. Second, APOLLO aims to enhance the efficiency of CCTA reporting, including analysis of otherwise manually laborious parameters such as plaque characterization and EAT quantification. Third, through robust validation against patient outcomes, APOLLO may enable cardiovascular risk prediction, thus facilitating triage and clinical workflow. Last, but not least, this large, de-identified, and well-characterized patient registry will have a myriad of clinical, research and industrial applications. Recruitment is progressing ahead of schedule, indicating comprehensive and efficient cooperation across Singapore's largest cardiac healthcare institutions.

In a forecast analysis based on 2007 to 2018 data from the Singapore myocardial infarct registry[22] 2025 to 2050, the incidence of acute myocardial infarction (AMI) in Singapore is predicted to rise by 194.4% from 482 to 1418 per 100,000 population.[23] The largest percentage increase in metabolic risk factors within the population with AMI is projected to be overweight/obesity (880.0% increase), followed by hypertension (248.7% increase), diabetes (215.7% increase), hyperlipidemia (205.0% increase), and active/previous smoking (164.8% increase).[22] The number of AMI-related deaths is expected to increase by 294.7% in individuals with overweight/obesity, while mortality is predicted to decrease by 11.7% in hyperlipidemia, 29.9% in hypertension, 32.7% in diabetes and 49.6% in active/previous smokers, from 2025 to 2050.

Similar trends are expected in Asia as the ethnic distribution in Singapore of Chinese, Malay and Indian broadly represent the ethnic distribution of large parts of Asia.[24] The baseline characteristics of the study population recruited suggests notable differences in the prevalence of cardiovascular risk factors from existing study cohorts. For example, as compared to the Danish population studied by Winther et al, our study population appears to have a higher prevalence of both dyslipidemia and diabetes mellitus (52% vs 30% and 16% vs 7%, respectively).[25] Similarly, over one-half of all participants in the SCOT-HEART (Scottish Computed Tomography of the Heart) study were current or former smokers, in contrast to one in five as seen in our local population.[6] Given that most of our study population is of Chinese ethnicity, the prevalence of cardiovascular risk factors is most similar to that noted in the Chinese populations studied by Zhou et al.[26] and Tay et al.,[27] albeit with a markedly higher prevalence of dyslipidemia in the overall cohort. This difference may not be entirely due to a higher prevalence of dyslipidemia in the Indian and Malay patient sub-groups, as prior dyslipidemia studies in Singapore found no significant differences between ethnic sub-groups.[28 29] Instead, it is possible that the higher prevalence of dyslipidemia is a reflection of local dietary and lifestyle factors. Similarly, in comparison to an analysis of CAC incidence and progression in 698 (majority Indian) subjects from the MASALA (Mediators of Atherosclerosis in South Asians Living in America) study, our current study population has half the prevalence of diabetes mellitus.[30] These differences in baseline characteristics from other existing cohorts emphasizes the need for a tailored approach in the creation of an AI-platform for cardiovascular risk prediction.

Furthermore, APOLLO will be the largest study of CCTA-based risk prediction in Asia. The largest studies to date have been from China, most notably that by Zhou et al., comprising 4207 subjects, which demonstrated that a combination of CAC and clinical risk factors offers the

greatest utility in identifying the lowest risk group among patients with stable chest pain.[26] Other cohort studies in the Chinese population are generally 2000 patients or fewer.[31-38] Moreover, these studies are limited to identification of functional significant coronary lesions rather than global assessment of CT-based risk markers, as in the APOLLO study design. Similarly, Shiono et al. have previously studied and reported on the 1829 subjects from Japan in the ADVANCE (Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care) registry,[39] whilst in Korea, Yang et al studied 1100 lesions in 643 patients to delineate CCTA markers of functionally obstructive CAD as well as poor vessel-oriented outcomes.[40 41] Therefore, the APOLLO study may not only supersede existing CCTA studies in Asia in terms of sample size, but also in terms of the wealth of CCTA-based information utilized in the risk stratification model.

Data sharing is a common challenge for all healthcare entities with data privacy, consent, ethical use and scalability concerns being the common barriers. Platform solutions to address these at scale include deidentification, anonymization, secured data instances, common data models and federated analysis have been trialed at multiple institutions in Singapore. Examples of this include DISCOVERY AI[21] and Odyssey[42] in two Singapore healthcare clusters which federate data under a common governance mechanism and permits users to share and use data securely. These instances have successfully demonstrated that on-premise cloud instances can support multiple clinical and research groups with inherent safety, scalability and economies of scale. It also permits large scale AI model training using on-premise supercomputing resources that affords the lowest cost per GPU utilization, if adequately utilized across multiple research groups.

To scale on this successful infrastructure, the Ministry of Health in Singapore and developed a national platform called TRUST,[43] which permits national level data sharing in a secured commercial cloud instance. Issues of cross institution data sharing and access are mediated

by a multi stakeholder data access committee. It ensures fair access to specific datasets generated by public entities. The commercial cloud also affords multi-party remote access, larger range of online tools, and on a pay-per use basis which further enhances effective data use.

In summary, APOLLO is the first-of-its-kind, robust, national AI platform for the diagnosis, collection, analysis, interpretation, and automatization of CAD using CCTA. The development of the one-stop AI toolkit may transform the contemporary use of CCTA for the detection of CAD, integrating a range of patient demographics and CT-based risk markers to produce an efficient, accurate and individualized estimation of cardiovascular risk that will be longitudinally validated in a multi-ethnic Asian population. APOLLO also allows for scalability, with the use of a secure, data sharing platform. This may further pave the way for translational impact on the population health, clinical, research and commercial domains in Singapore.

Acknowledgement

The authors would like to thank Malay Singh, Arvind Srinivasa, and Tan Ruphing for their contribution on APOLLO software development.

Authors' contributions

LB, MC, LZ contributed to the study design. LB, LT, MSY, and MC contributed in data acquisition. RV contributed to statistical planning. WMH, HKL, ZKL, XHW, EWPT, NZYC contributed to AI development. KYN contributed to data anonymization and storage. LB, SL and UD drafted the manuscript. LT, MSY, CHS, NWSC, WMH, HKL, RV, KYN, ZKL, XHW, EWPT, NZYC, SYT, MC, and LZ contributed to revising the manuscript. All authors read and approved the final manuscript.

Funding

This study received funding support from the Industry Alignment Fund – Pre-positioning Programme (H20c6a0035). Lohendran Baskaran was supported by the National Medical Research Council (NMRC) of Singapore Centre Grant [Program for Transforming and Evaluating Outcomes in Cardiometabolic disease (PROTECT), Grant number: CG21APR1006] and the National Medical Research Council (NMRC) of Singapore Transitional Award Grant (Improving Obstructive Coronary Artery Disease and Cardiovascular Risk Prediction Using Deep Learning Analysis on Coronary Artery Calcium Imaging, Grant number: TA21nov-0001.

Competing interests: none

Collaboration: The APOLLO team invites researchers to contact the corresponding author to request collaboration of any kind.

Table 1. Inclusion and exclusion criteria for prospective patient recruitment.

Inclusion criteria
• Age ≥21 years old
• Clinically indicated for evaluation by CCTA
Exclusion criteria
• Known complex congenital heart disease
• Planned invasive angiography for reasons other than coronary artery disease
• Non-cardiac illness with life expectancy <2 years
• Pregnancy
• Concomitant participation in another clinical trial in which subject is subject to investigational drug or device
• Cardiac event and/or coronary revascularization (percutaneous coronary intervention and/or coronary artery bypass grafting and/or valvular repair/replacement prior to CCTA
• Glomerular filtration rate ≤30mL/min
• Known allergy to iodinated contrast agent
• Contraindications to beta blockers or nitroglycerin or adenosine

CCTA, coronary computed tomography angiography.

Table 2. Baseline characteristics.

	All (*n* = 1844)	**Retrospective (*n* = 698)**	**Prospective (*n* = 1146)**
Age, years	55±11	55±11	56±11
Gender, Male/Female	1033/811	412/286	621/525
Height, cm	165±9	164±10	165±9
Weight, kg	70±15	70±15	71±16
Body mass index, kg/m²	26±5	26±5	26±5
Race			
Chinese, n (%)	1401 (76)	523 (75)	878 (77)
Malay, n (%)	105 (6)	34 (5)	71 (6)
Indian, n (%)	172 (9)	65 (9)	107 (9)
Others, n (%)	166 (9)	76 (11)	90 (8)
Cardiac risk factors			
Hypertension, n (%)	792 (43)	325 (47)	467 (41)
Diabetes, n (%)	300 (16)	102 (15)	198 (17)
Dyslipidemia, n (%)	962 (52)	382 (55)	580 (51)
Family history, n (%)	485 (26)	149 (21)	336 (29)
Smoking, n (%)	390 (21)	117 (17)	273 (24)
Peripheral artery disease, n (%)	5 (0.3)	4 (1)	1 (0.1)
Medication			
Aspirin, n (%)	236 (13)	131 (19)	105 (9)
Thienopyridine, n (%)	63 (3)	42 (6)	21 (2)
Ticagrelor, n (%)	3 (0.2)	1 (0.1)	2 (0.2)
Statin, n (%)	727 (39)	296 (42)	431 (38)
Beta blocker, n (%)	269 (15)	142 (20)	127 (11)
Calcium channel blocker, n (%)	323 (18)	114 (16)	209 (18)
ACE-inhibitor, n (%)	107 (6)	50 (7)	57 (5)
Angiotensin II antagonist, n (%)	241 (13)	86 (12)	155 (14)
Mineralocorticoid antagonist, n (%)	17 (1)	10 (1)	7 (1)
Oral hypoglycemics, n (%)	198 (11)	66 (9)	132 (12)
Insulin, n (%)	32 (2)	13 (2)	19 (2)
Blood test			
Glomerular filtration rate, mL/min	96 (86, 103)	96 (86, 104)	95 (86, 103)
Total cholesterol, mmol/L	4.9 (4.2, 5.7)	5.1 (4.3, 5.7)	4.9 (4.2, 5.6)
High-density cholesterol, mmol/L	1.3 (1.1, 1.6)	1.3 (1.1, 1.5)	1.4 (1.1, 1.6)
Triglycerides, mmol/L	1.3 (1.0, 1.8)	1.3 (0.9, 1.7)	1.3 (1.0, 1.8)
Low-density cholesterol, mmol/L	2.9 (2.2, 3.6)	3.1 (2.4, 3.8)	2.8 (2.2, 3.5)
Hemoglobin, g/dL	14 (13, 15)	14 (13, 15)	14 (13, 15)
Hemoglobin A1c, %	5.9 (5.5, 6.6)	5.8 (5.4, 6.3)	6.0 (5.6, 6.8)

Figure legends

Figure 1. Workflow of the APOLLO platform. CT images are first anonymized and uploaded into APOLLO's database. The images are then processed using AI engines and results uploaded into the database again. A summary report will be generated and presented to the end user. CAD: coronary artery disease; AI: artificial intelligence; EAT: epicardial adipose tissue; CVD: cardiovascular disease.

Figure 2. DISCOVERY AI tribrid platform processes. Clinical and research data processed by various production AI modules to make predicted clinical warnings on the electronic health record system. AI: artificial intelligence; ICU: intensive care unit; EPIC: an American private held healthcare software company; I2B2: informatics for integrating biology & the bedside; SDSD: surgical data systems directorate dataset; SPH: School of Public Health.

Graphical abstract. APOLLO Study Design. Integration of risk markers derived from coronary CT angiography together with patient demographics, cardiovascular risk factors, medications, laboratory findings and survival data. Coronary CT angiography parameters will include characterization of coronary artery lesion, epicardial adipose tissue and coronary artery calcium score. To generate a sharable database for clinical, research and industrial purposes. AI: artificial intelligence; CAD: coronary artery disease; CT: computed tomography.

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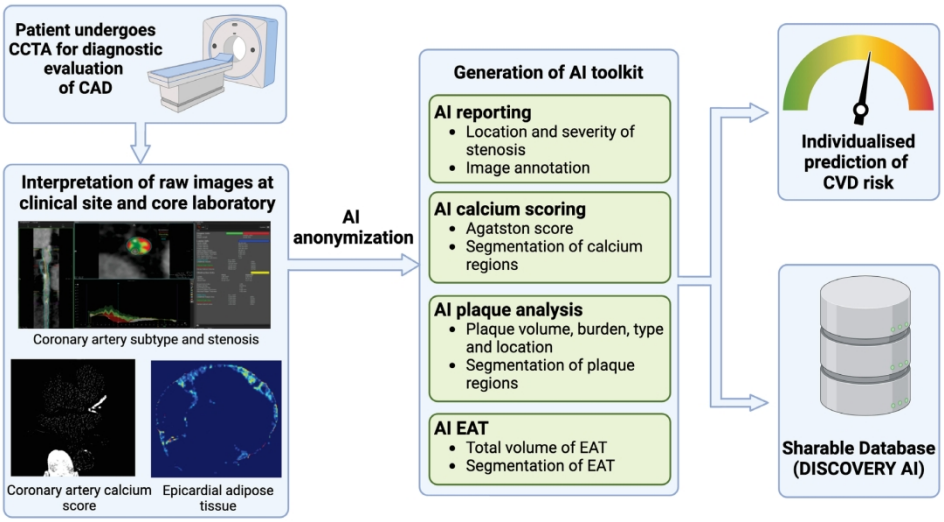

Figure 1. Workflow of the APOLLO platform. CT images are first anonymized and uploaded into APOLLO's database. The images are then processed using AI engines and results uploaded into the database again. A summary report will be generated and presented to the end user. CAD: coronary artery disease; AI: artificial intelligence; EAT: epicardial adipose tissue; CVD: cardiovascular disease.

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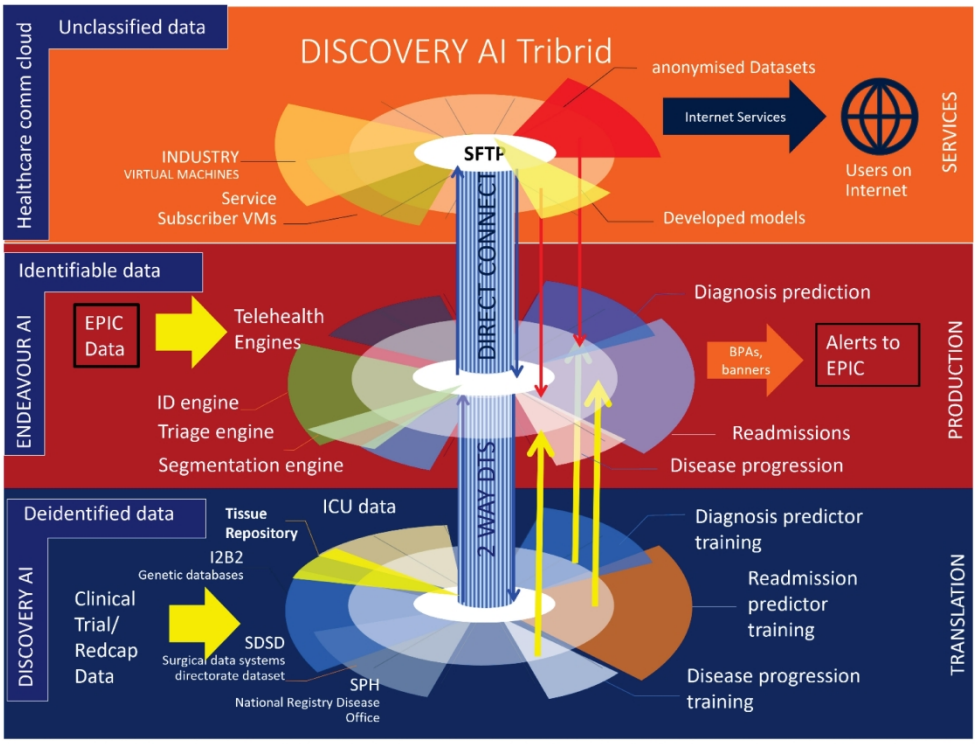

Figure 2. DISCOVERY AI tribrid platform processes. Clinical and research data processed by various production AI modules to make predicted clinical warnings on the electronic health record system. AI: artificial intelligence; ICU: intensive care unit; EPIC: an American private held healthcare software company; I2B2: informatics for integrating biology & the bedside; SDSD: surgical data systems directorate dataset; SPH: School of Public Health.

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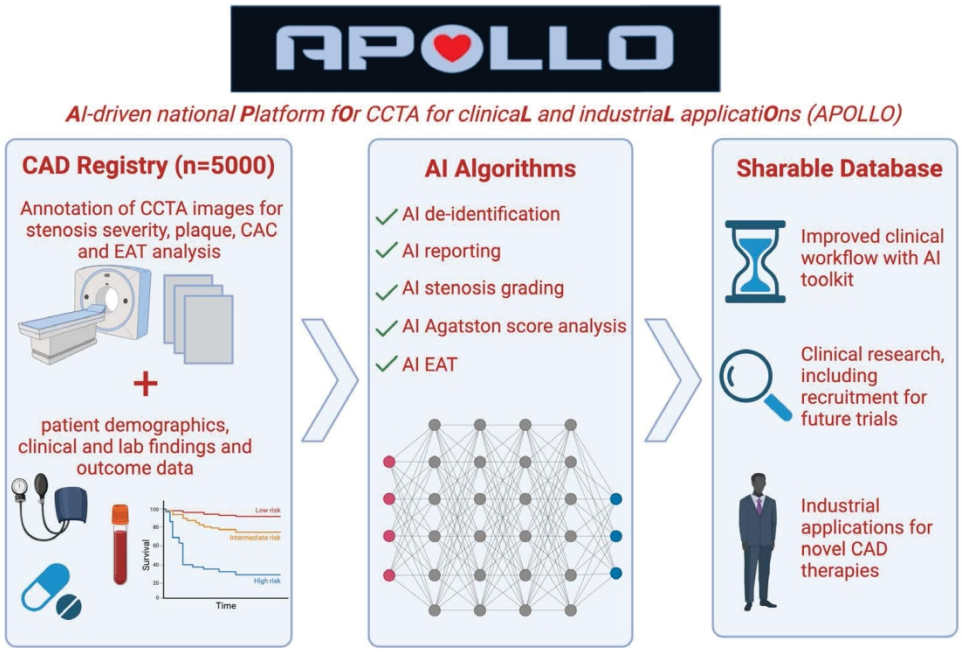

Graphical abstract. APOLLO Study Design. Integration of risk markers derived from coronary CT angiography together with patient demographics, cardiovascular risk factors, medications, laboratory findings and survival data. Coronary CT angiography parameters will include characterization of coronary artery lesion, epicardial adipose tissue and coronary artery calcium score. To generate a sharable database for clinical, research and industrial purposes. AI: artificial intelligence; CAD: coronary artery disease; CT: computed tomography.

269x190mm (300 x 300 DPI)

BMJ Open

Cohort profile: AI driven national Platform for CCTA for clinicaL and industriaL applicatiOns (APOLLO)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-089047.R1
Article Type:	Cohort profile
Date Submitted by the Author:	25-Oct-2024
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Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Research methods, Cardiovascular medicine

Keywords:	Coronary heart disease < CARDIOLOGY, Computed tomography < RADIOLOGY & IMAGING, Artificial Intelligence

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Cohort profile: AI driven national Platform for CCTA for clinicaL and industriaL applicatiOns (APOLLO)

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ABSTRACT

Purpose: Coronary computed tomography angiography (CCTA) is well-established for the diagnostic evaluation and prognostication of coronary artery disease (CAD). The growing burden of CAD in Asia and the emergence of novel computed tomography-based risk markers highlight the need for an automated platform that integrates patient data with CCTA findings to provide tailored, accurate cardiovascular risk assessments. This study aims to develop an artificial intelligence (AI)-driven platform for CAD assessment using CCTA in Singapore's multi-ethnic population. We will conduct a hybrid retrospective-prospective recruitment of patients who have undergone CCTA as part of the diagnostic work-up for CAD, along with prospective follow-up for clinical endpoints. CCTA images will be analyzed locally and by a core lab for coronary stenosis grading, Agatston scoring, epicardial adipose tissue evaluation, and plaque analysis. The images and analyses will also be uploaded to an AI platform for de-identification, integration, and automated reporting, generating precision AI toolkits for each parameter.

Participants: CCTA images and baseline characteristics have been collected and verified for 4,196 recruited patients, comprising 75% Chinese, 6% Malay, 10% Indian, and 9% from other ethnic groups. Among the participants, 41% are female, with a mean age of 55±11 years. Additionally, 41% have hypertension, 51% have dyslipidemia, 15% have diabetes, and 22% have a history of smoking.

Findings to date: The cohort data have been used to develop four AI modules for training, testing, and validation. During the development process, data preprocessing standardized the format, resolution, and other relevant attributes of the images.

Future plans: We will conduct prospective follow-up on the cohort to track clinical endpoints, including cardiovascular events, hospitalizations, and mortality. Additionally, we will monitor the long-term impact of the AI-driven platform on patient outcomes and healthcare delivery.

Trial registration: ClinicalTrials.gov (Identifier: NCT05509010).

Keywords: Coronary Computed Tomography Angiography; Coronary Artery Disease; Artificial Intelligence

Strengths and limitations of this study

- The study utilizes a large, multi-ethnic Asian cohort, allowing for diverse population sampling.
- A hybrid retrospective-prospective design allows for comprehensive clinical follow-up and outcome validation.
- A standardized CCTA protocol ensures consistency across multiple healthcare centers.
- The use of advanced AI models facilitates automated analysis of calcium score, epicardial adipose tissue, and plaque characteristics.
- The study population is exclusively Asian, limiting the generalizability of the findings to other ethnic groups.

INTRODUCTION

As in the rest of the world, coronary artery disease (CAD) is a leading cause of death in Asia, and its increasing prevalence signals a significant healthcare and economic burden.[1 2] Coronary computed tomography angiography (CCTA) has become firmly established as an essential modality for the early detection, clinical evaluation, and risk stratification of CAD. This is reflected in guidelines from the National Institute for Health and Care Excellence (NICE),[3] the European Society of Cardiology (ESC),[4] and the American Heart Association (AHA).[5] These recommendations are based on robust evidence demonstrating that early use of CCTA improves event-free survival by facilitating the timely initiation of guideline-directed medical therapy,[6] reduces unnecessary cardiac catheterization,[7] and enables faster discharge of patients presenting with possible acute coronary syndrome in emergency settings.[8]

CCTA is not only the preferred modality for anatomical assessment of the coronary vasculature but also an indispensable tool for disease characterization and risk stratification. Computed tomography (CT)-derived parameters, including the Agatston score,[9] epicardial adipose tissue (EAT),[10] and plaque characteristics,[11] offer incremental value in these assessments. However, the routine clinical adoption of these measurements is limited by the laborious and time-intensive nature of manual quantification. Additionally, manual assessment introduces significant inter-observer variability—reportedly as high as 20%, even among expert readers.[12] Thus, there is an unmet need for automated solutions to streamline these processes and fully harness the diagnostic and prognostic potential of CCTA in CAD management.

Moreover, existing cardiovascular risk prediction models have shown limited accuracy in Asian populations. For example, the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM) revealed that Asian sites reported a three-fold

lower-than-expected CAD prevalence.[13] Similarly, an observational study by Villadsen et al. identified ethnic differences in coronary plaque composition, with South Asian patients exhibiting a higher proportion of non-calcified plaque compared to Caucasians.[14] Our group previously assessed the performance of the CAD Consortium (CAD2) model in a mixed Asian population in Singapore and found suboptimal predictive accuracy, though it improved significantly after local calibration.[15] More recently, we evaluated the prognostic utility of pooled cohort equations (PCEs) and Agatston scores in a symptomatic, mixed Asian cohort. PCEs alone showed no discriminative value beyond random chance, and the addition of Agatston scores did not provide meaningful improvement.[16] These findings highlight the need for automated models that account for ethnic variations to accurately predict cardiovascular risk in Singapore's multi-ethnic population. To achieve this, a contemporary study of CAD prevalence and characteristics in Asia is essential.

COHORT DESCRIPTION

Patient and public involvement

Patients and/or the public were not directly involved in the design, or conduct, or reporting, or dissemination plans of this research. The study outcomes will be disseminated through publication in peer-reviewed biomedical, cardiac imaging, and clinical journals, as well as presentations at scientific conferences. This will pave the way for a range of clinical, population health, research, and commercial applications.

Cohort objectives

We aim to build a first-in-Asia, AI-driven national platform for CCTA for clinical, and industrial applications (APOLLO), creating a mixed-ethnic phenotypic registry of CAD in Singapore (**Graphical abstract**). APOLLO will serve a range of clinical, research, and industrial purposes. First, as a large registry, APOLLO will offer valuable insights into patient demographics and disease patterns within a highly characterized multi-ethnic Asian population. Second, the development of precision AI toolkits will enable the automation of anonymization, reporting, Agatston scoring, EAT, and plaque quantification, facilitating the integration of these tasks into routine clinical practice. Third, as a de-identified and sharable database, APOLLO will support the calibration and development of Asian-based prediction models and accelerate the introduction of novel medical and device therapies in the Asian context (**Figure 1**).

Study type

APOLLO is a hybrid, retrospective-prospective, open-label, observational, multi-centre study. It includes retrospective recruitment of patients who underwent CCTA as part of the diagnostic

work-up for CAD, along with prospective follow-up to monitor several clinical endpoints. Additionally, prospective patient recruitment will involve identifying and enrolling eligible patients from multiple participating centres. These patients will undergo CCTA as part of their clinical care and will be followed over time to track key outcomes, including cardiovascular events, hospitalizations, and mortality. Details of the study design are also available on ClinicalTrials.gov (Identifier: NCT05509010).

Study population

There are three hospital sites participating in the creation of APOLLO: National Heart Centre Singapore (NHCS), National University Hospital (NUH), and Tan Tock Seng Hospital (TTSH). These institutions represent the three largest cardiac healthcare systems in the country. The study utilizes a hybrid recruitment approach, both retrospective and prospective, targeting a total of 5,000 CAD patients. For the retrospective arm, patients who underwent CT scans between 2007 and 2017 will be screened and included if they meet the inclusion criteria. Outcomes will be obtained through a review of medical records and national registries, with follow-up continuing until December 31, 2025. For the prospective arm, patient recruitment occurred from October 2021 to July 2024. Clinical events and outcomes will be tracked for a period of five years following enrollment, with data collected from hospital medical records and national databases. The inclusion and exclusion criteria are listed in **Table 1**. Patients aged 21 and above were included. Exclusion criteria include acute coronary syndrome, a body mass index exceeding 40 kg/m^2, and a history of percutaneous or surgical intervention for CAD. Baseline demographic and clinical characteristics will be obtained from the electronic medical records and case notes, including but not limited to: (1) age, gender, race, socioeconomic status, marital status, (2) comorbidities, (3)

laboratory tests, (4) radiological tests, (5) cardiac investigations, (6) cardiac procedures, (7) medication use, (8) chest pain characteristics.

CCTA protocol

CCTA acquisition will be performed using six state-of-the-art CT scanners (Canon, Siemens, GE, Philips) with ≥256-detector rows, following image acquisition protocols outlined in the Society of Cardiovascular Computed Tomography (SCCT) guidelines.[17] Medication, as per guidelines, may be administered to control heart rate in patients with a heart rate above 60 bpm. Sublingual glyceryl trinitrate will be administered prior to scanning. The CCTA scans will use a prospective ECG-triggered scanning mode. A tri-phasic injection protocol will be applied, consisting of contrast injections of approximately 50 ml at 5 ml/s and 20 ml at 3.5 ml/s sequentially, followed by a third injection of 30 ml saline at 3 ml/s.

Cardiac CT analysis

The CT images will be analyzed and interpreted both at the clinical site level and at the core laboratory. At the clinical site, CT interpretation will follow the SCCT guidelines.[17] Core lab analysis will be performed at the CardioVascular Systems Imaging and Artificial Intelligence (CVS.AI) research core of NHCS, blinded to the clinical site interpretation. Core lab analyses will include:

(1) **Coronary stenosis grading**: This assessment focuses on the severity and precise localization of stenosis within the coronary circulation. A key aspect involves visually estimating luminal narrowing caused by plaque. Following the SCCT guidelines,[17] stenosis is graded across a spectrum from minimal narrowing to total occlusion. Additionally, distinctions are made

between obstructive and non-obstructive stenosis, with the SCCT model guiding accurate localization.

(2) **Agatston scoring analysis**: Calcified plaque is evaluated using Agatston scoring programs, aligned with SCCT clinical guidelines.[17] Pixels exceeding 130 Hounsfield Units (HU) are identified as indicative of calcium on non-contrast studies.[18] Lesions within each coronary vessel distribution are identified, and the scoring program generates a summed score for each vessel based on area-density (Agatston score) measurements. The total coronary Agatston score aggregates all calcified lesions across the coronary tree.

(3) **EAT analysis**: This analysis quantifies the total volume of EAT and pericardial adipose tissue (PAT), both metabolically active fats associated with increased cardiovascular disease risk.[19] Quantification on non-contrast CT scans requires manual annotation of the pericardium. EAT is identified using adipose tissue attenuation values between -190 and -30 HU.[20] Due to potential variations in HU values from scan noise or attenuation changes, the final EAT region is verified by an experienced radiologist or cardiologist.

(4) **Plaque analysis**: This analysis focuses on plaque volume, burden, type, and anatomical locations. Coronary segmentation is performed for segments with a diameter ≥1.5 mm, with the SCCT model[17] aiding in precise plaque localization. For each plaque, detailed assessments are conducted, including start and end points, area, volume, burden, and type (non-calcified, calcified, or mixed).[21] Non-calcified plaque is further subclassified as low attenuation plaque (LAP) if HU <30, or non-LAP if HU >30.

Patient outcomes

Patients whose CCTA data are utilized for this study will be followed for several outcome measures. This follow-up will enable the prognostic validation of AI-derived measurements. The patient outcomes to be monitored are as follows:

(1) **Mortality (all-cause and cardiovascular):** Throughout the follow-up period, the study will track mortality rates, including both all-cause mortality and deaths specifically attributable to cardiovascular events.

(2) **Major Adverse Cardiovascular Events (MACE):** In addition to mortality, the study will assess MACE, which includes acute myocardial infarction, stroke, heart failure, and percutaneous or surgical revascularization.

(3) **Re-hospitalization:** A key aspect of the outcome measures will involve evaluating the incidence of re-hospitalization. This parameter serves as a valuable indicator of the long-term impact of AI interventions on the need for repeated hospital admissions, providing insights into sustained health outcomes and healthcare resource utilization.

These data will be collected from hospital medical records and national registries in accordance with institutional, ministry, and national-level regulations. At the institutional level, tracking and extraction of outcomes will be performed by the respective IT teams under the supervision of the principal investigator/study team. The clinical research coordinator at each institution will also track and match outcomes using electronic medical records. At the national level, the matching and tracking of outcome data from national registries will be handled by staff from the National Registry of Diseases Office (NRDO). One of the registries analyzed through the NRDO will be the Singapore Myocardial Infarction Registry (SMIR) for aggregate data.

AI-based parameters

The images, data, and analyses will be uploaded to an AI platform for de-identification, analysis, integration, and automated reporting. A container will encapsulate all AI solutions developed during the study, allowing for seamless deployment across third-party environments, including laptops, cloud platforms, and both Windows and Linux operating systems. The toolkits can also be integrated with commercial third-party software platforms.

(1) **AI anonymization:** The anonymization of pixel data follows a pipeline consisting of the following steps:

- Extracting personal data from the DICOM metadata that may be present in the pixel image. This information defines a set of words the pipeline searches for within the image.
- Preprocessing the image to enhance contrast and reduce noise.
- Deploying a convolutional neural network (CNN) for alphabet recognition, which identifies characters within the image.
- Matching and removing personal data by cross-referencing identified words with those found in the DICOM metadata.

(2) **AI stenosis grading:**

- Coronary artery tree detection: Error-tolerant graph neural network technology[22] is integrated into the platform. Building on prior work by Huang et al.,[23] we use an enhanced 3D U-Net model to identify coronary arteries. A graph U-Net model further filters these candidates based on topological, positional, and image features (**Supplementary Figure 1**). Non-coronary segments and discontinuous arteries are either removed or reconnected

as necessary. The result is a coronary artery tree that is easily mapped due to its graph structure.

- Joint stenosis grading and plaque quantification on 3D images: Stenosis grading and plaque quantification are performed simultaneously by an algorithm combining a 3D U-Net model and a 3D image classifier (**Supplementary Figure 2**). The U-Net generates segmentation masks for the lumen, calcified plaque, and non-calcified plaque. These are then used as inputs for the image classifier, which outputs stenosis grades and plaque types.

(3) **AI Agatston score analysis:** AI-based Agatston scoring begins with the segmentation of calcified plaque on non-contrast CT scans (**Supplementary Figure 3**), leveraging CNNs.[24 25] A novel approach in our platform involves combining non-contrast and contrast CT scans, aligned through multimodal image registration. A deep learning multitask network analyzes both plaque and calcification. This interpretable multitask learning algorithm provides more accurate analysis.

(4) **AI EAT:** AI-based EAT quantification uses 2D axial slices (**Supplementary Figure 4**), with segmentation achieved through fully convolutional networks (e.g., U-Net) or fully annotated CTs.

(5) **AI reporting:** The AI-generated reports include Agatston scoring and stenosis grading. Automated tasks include:

- CCTA image quality evaluation
- Heart segmentation
- EAT segmentation and analysis
- Aorta segmentation
- Detection and registration of the coronary artery tree

- Agatston scoring and stenosis grading

Data sharing

Data sharing will be facilitated through the National University Health System (NUHS)'s DISCOVERY AI platform, a production system that provides centralized anonymization, equitable data access, and differential data linkage capabilities.[26] The processes of the DISCOVERY AI platform are summarized in **Figure 2**, with oversight resting with the custodian of each database. DISCOVERY AI incorporates centralized anonymization and data handling measures in compliance with the Singapore Personal Data Protection Act (PDPA) 2012, the Human Biomedical Research Act 2015, and the Human Biomedical Research Regulations 2017. In accordance with PDPA guidelines, all data managed within DISCOVERY AI are anonymized by removing protected health identifiers, such as names, addresses, and identification numbers. The platform also features proprietary security measures, including data obfuscation and ledger-based access logs.

Sample size calculation

Conventional sample size calculations rely on a predefined margin of error; however, in AI, estimating the required sample size prior to experimentation is not always feasible because this margin of error cannot be established until the deep learning model development process has begun. Instead, during deep learning analysis, we will use cross-validation techniques, such as k-fold cross-validation and hold-out test sets, to ensure robust statistical confidence in our model. These methods allow us to derive confidence intervals and assess model performance iteratively.

To further ensure statistical rigor, we will also perform a post-hoc power analysis to evaluate the actual power achieved by the analysis and report these findings. Additionally, previous studies provide support for the adequacy of our dataset size. For example, a coronary artery calcium deep learning project using 377 subjects achieved over 90% accuracy.[27] Similarly, Commandeur et al. demonstrated improved predictive performance using AI on cardiac CT in 1912 asymptomatic subjects, achieving a higher AUC (0.82 vs. 0.77, $P<0.05$) compared to conventional methods like coronary artery calcium scoring.[28] These results suggest that the dataset collected in our current study should be sufficient to train the deep learning models effectively and achieve high performance for each specific aim.

In previous studies, the 5-year rate of the primary endpoint in the CTA group was reported as 2.3% in one study,[6] while another study observed a primary endpoint event in 164 out of 4,996 patients (3.3%) over a median follow-up of 25 months.[29] Based on these findings, we predict the event rate in our current study to be approximately 3% over the 5-year follow-up period. With a predicted event rate of 3%, we aim to capture at least 100 events to ensure robust model estimation. Following the general rule of 10 events per predictor variable,[30] we anticipate including 10 predictors in our models, resulting in a required sample size of approximately 3333 patients.

Clinical risk model development

This study aims to build a clinical risk model that incorporates parameters derived from AI calcium score, AI EAT, AI stenosis, and AI plaque characteristics to predict patient outcomes or progression of atherosclerosis. In addition to the AI-derived features, traditional clinical and demographic data will also be included. The risk model will be developed using logistic regression, Cox proportional hazards models, or machine learning algorithms. By combining the AI-derived

features with traditional risk factors, patients will be categorized into risk groups (e.g., low, intermediate, high risk) based on output probabilities or risk scores. After model construction, a post-hoc power analysis will be conducted to ensure that the sample size used is sufficient to detect meaningful associations and that the model possesses adequate statistical power.

Ethics and dissemination

The study protocol has been approved by the SingHealth Centralised Institutional Review Board (approval numbers 2021/2363 for the prospective study and 2021/2288 for the retrospective study). Project outcomes will be disseminated through publications in peer-reviewed biomedical, cardiac imaging, and clinical journals, as well as presentations at scientific conferences. Patient confidentiality will be maintained by ensuring that no individually identifiable information is included in publications.

FINDINGS TO DATE

CCTA images and baseline characteristics have been collected and verified for 4,196 recruited patients. Demographic data indicate that the study population consists of 75% Chinese, 6% Malay, 10% Indian, and 9% from other ethnic groups. Among the participants, 41% are female, with a mean age of 55±11 years. Additionally, 41% have hypertension, 51% have dyslipidemia, 15% have diabetes, and 22% have a history of smoking (**Table 2**). All collected data have been anonymized and stored in the DISCOVERY AI platform. Furthermore, four AI modules are in development using 2,983 CT imaging studies for training, testing, and validation. During the development of each AI module, data preprocessing standardized the format, resolution, and other relevant attributes of the images.

DISCUSSION

The APOLLO study targets a cohort that reflects the current real-world Asian population undergoing CAD assessment. Given the growing clinical burden of CAD, a national AI platform to facilitate CCTA analysis is desirable for several reasons. First, as the largest CCTA registry of patients with suspected CAD, APOLLO will provide much-needed, highly representative insights into the current and emerging states of diagnostic testing in the region. Second, APOLLO aims to enhance the efficiency of CCTA reporting, including the analysis of labor-intensive parameters such as plaque characterization and EAT quantification. Third, through robust validation against patient outcomes, APOLLO may enable cardiovascular risk prediction, thus improving triage and clinical workflows. Finally, this large, de-identified, and well-characterized patient registry will have extensive clinical, research, and industrial applications. Recruitment is progressing ahead of schedule, reflecting comprehensive and efficient collaboration across Singapore's largest cardiac healthcare institutions.

A forecast analysis based on data from the Singapore Myocardial Infarction Registry[31] (2007-2018) predicts that from 2025 to 2050, the incidence of acute myocardial infarction (AMI) in Singapore will rise by 194.4%, from 482 to 1,418 cases per 100,000 population.[32] The largest projected increases in metabolic risk factors among AMI patients include overweight/obesity (880.0% increase), followed by hypertension (248.7%), diabetes (215.7%), hyperlipidemia (205.0%), and active/previous smoking (164.8%).[32] The number of AMI-related deaths is expected to increase by 294.7% among individuals with overweight/obesity, while mortality is predicted to decline by 11.7% for hyperlipidemia, 29.9% for hypertension, 32.7% for diabetes, and 49.6% for smoking from 2025 to 2050.

Similar trends are expected across Asia, as the ethnic distribution in Singapore (comprising Chinese, Malay, and Indian populations) broadly reflects that of many Asian regions.[33] The baseline characteristics of the APOLLO cohort suggest notable differences in cardiovascular risk factors compared to other study populations. For example, compared to the Danish cohort studied by Winther et al., APOLLO participants exhibit a higher prevalence of dyslipidemia (51% vs. 30%) and diabetes mellitus (15% vs. 7%).[34] Likewise, while over half of the participants in the SCOT-HEART study were current or former smokers,[6] only one in five participants in the APOLLO cohort reported smoking. Given the predominantly Chinese composition of APOLLO's cohort, the prevalence of cardiovascular risk factors aligns most closely with that observed in Chinese populations studied by Zhou et al.[35] and Tay et al.,[36] albeit with a notably higher prevalence of dyslipidemia in the overall cohort. This discrepancy may reflect dietary and lifestyle differences rather than ethnic variations, as previous studies in Singapore found no significant differences in dyslipidemia prevalence across ethnic subgroups.[37 38] Additionally, compared to the MASALA study,[39] which analyzed coronary artery calcium progression among South Asians in the U.S., the APOLLO cohort shows half the prevalence of diabetes mellitus. These variations in baseline characteristics underscore the need for a tailored approach to developing an AI platform for cardiovascular risk prediction in Asia.

APOLLO will be the largest CCTA-based risk prediction study in Asia. The most comparable study to date, conducted by Zhou et al. in China, involved 4,207 participants and demonstrated that combining coronary artery calcium with clinical risk factors effectively identified the lowest-risk patients with stable chest pain.[35] Other Chinese cohort studies[40-47] have generally included fewer than 2,000 participants and have focused on functionally significant coronary lesions rather than comprehensive CT-based risk markers, as APOLLO does. In Japan,

the ADVANCE registry by Shiono et al. studied 1,829 subjects,[48] while Yang et al. in Korea examined 1,100 lesions across 643 patients, focusing on CCTA markers for functionally obstructive CAD and poor vessel outcomes.[49 50] APOLLO not only exceeds these studies in sample size but also offers a more comprehensive evaluation of CCTA-based information for risk stratification.

Data sharing presents challenges for all healthcare institutions, with concerns surrounding privacy, consent, ethics, and scalability. Platform solutions, such as de-identification, anonymization, secure data instances, common data models, and federated analysis, have been implemented across multiple institutions in Singapore. Notable examples include the DISCOVERY AI[26] and Odyssey[51] platforms, which federate data under a shared governance framework to allow secure data usage. These platforms demonstrate that on-premise cloud infrastructure can support multiple clinical and research teams while providing safety, scalability, and cost-effective supercomputing resources.

Building on these successes, Singapore's Ministry of Health has developed a national platform called TRUST,[52] which enables secure, cloud-based data sharing at a national level. TRUST facilitates cross-institution data sharing through a multi-stakeholder access committee, ensuring equitable access to datasets generated by public entities. The platform also offers remote access, a wider range of online tools, and pay-per-use pricing, enhancing data-sharing efficiency.

This study has limitations. First, although APOLLO utilizes a national, multi-centre platform, there may still be inherent limitations regarding the completeness and consistency of data across different centres—an issue commonly encountered in multi-centre studies. Second, challenges may arise with the scalability of data sharing and the federated use of data across various healthcare entities. Third, the study focuses exclusively on a multi-ethnic Asian

population, which may limit the generalizability of the findings to Western populations. Differences in genetic, environmental, and lifestyle factors indicate that further validation studies are needed to ensure the broader applicability of the developed AI models.

A planned sub-study could focus on comparing CAD characteristics across different Asian ethnic groups within the APOLLO study cohort. The aim would be to investigate potential ethnic-specific variations in CAD presentation, severity, and plaque characteristics. This sub-study would leverage CCTA combined with AI-driven analyses to: (1) assess the distribution and extent of coronary artery plaques across various ethnic groups (e.g., Chinese, Malay, Indian); (2) examine differences in plaque composition (e.g., calcified, non-calcified, or mixed plaques) and their association with cardiovascular risk factors (e.g., hypertension, diabetes); and (3) explore how genetic, environmental, and lifestyle factors contribute to CAD risk and progression among different ethnicities, potentially revealing unique risk profiles or protective factors in specific groups.

In summary, APOLLO is a first-of-its-kind national AI platform for the diagnosis, collection, analysis, and interpretation of CAD using CCTA. The development of an integrated AI toolkit may revolutionize the use of CCTA for CAD detection by incorporating a diverse range of patient demographics and CT-based risk markers to produce accurate, individualized cardiovascular risk estimates. This platform will undergo longitudinal validation in a multi-ethnic Asian population, with the potential for scalability and secure data-sharing capabilities. APOLLO is poised to deliver transformative impact across clinical, research, public health, and commercial domains in Singapore.

Acknowledgement

The authors would like to thank Malay Singh, Arvind Srinivasa, and Tan Ruphing from the Bioinformatics Institute, Agency for Science, Technology and Research, Singapore, for their contributions to the development of the APOLLO software. Special thanks also to Xiaomeng Wang from Duke-NUS Medical School, Singapore, for his assistance with manuscript editing.

Authors' contributions

LB, MC, LZ contributed to the study design. LB, LT, MSY, and MC contributed in data acquisition. RV contributed to statistical planning. WMH, HKL, ZKL, XHW, EWPT, NZYC contributed to AI development. KYN contributed to data anonymization and storage. LB, SL and UD drafted the manuscript. LT, MSY, CHS, NWSC, WMH, HKL, RV, KYN, ZKL, XHW, EWPT, NZYC, SYT, MC, and LZ contributed to revising the manuscript. LZ was the guarantor. All authors read and approved the final manuscript.

Funding

This study received funding support from the Industry Alignment Fund – Pre-positioning Programme (H20c6a0035). Lohendran Baskaran was supported by the National Medical Research Council (NMRC) of Singapore Centre Grant [Program for Transforming and Evaluating Outcomes in Cardiometabolic disease (PROTECT), Grant number: CG21APR1006] and the National Medical Research Council (NMRC) of Singapore Transitional Award Grant (Improving Obstructive Coronary Artery Disease and Cardiovascular Risk Prediction Using Deep Learning Analysis on Coronary Artery Calcium Imaging, Grant number: TA21nov-0001.

Competing interests: none

Collaboration: The APOLLO team invites researchers to contact the corresponding author to request collaboration of any kind.

Table 1. Inclusion and exclusion criteria for prospective patient recruitment.

Inclusion criteria
• Age ≥21 years old
• Clinically indicated for evaluation by CCTA
Exclusion criteria
• Known complex congenital heart disease
• Planned invasive angiography for reasons other than coronary artery disease
• Non-cardiac illness with life expectancy <2 years
• Pregnancy
• Concomitant participation in another clinical trial in which subject is subject to investigational drug or device
• Cardiac event and/or coronary revascularization (percutaneous coronary intervention and/or coronary artery bypass grafting) and/or valvular repair/replacement prior to CCTA
• Glomerular filtration rate ≤30mL/min
• Known allergy to iodinated contrast agent
• Contraindications to beta blockers or nitroglycerin or adenosine

CCTA, coronary computed tomography angiography.

Table 2. Baseline characteristics.

	All (*n* = 4196)	**Retrospective (*n* = 1929)**	**Prospective (*n* = 2267)**
Age, years	55±11	54±11	55±11
Gender, Male/Female	2487/1709	1177/752	1310/957
Height, cm	165±9	165±9	166±9
Weight, kg	71±15	71±15	71±15
Body mass index, kg/m²	26±5	26±5	26±5
Race			
Chinese, n (%)	3143 (75)	1381 (72)	1762 (78)
Malay, n (%)	253 (6)	122 (6)	131 (6)
Indian, n (%)	407 (10)	197 (10)	210 (9)
Others, n (%)	393 (9)	229 (12)	164 (7)
Cardiac risk factors			
Hypertension, n (%)	1731 (41)	864 (45)	867 (38)
Diabetes, n (%)	638 (15)	295 (15)	343 (15)
Dyslipidemia, n (%)	2153 (51)	1013 (53)	1140 (50)
Family history, n (%)	1115 (27)	412 (21)	703 (31)
Smoking, n (%)	921 (22)	373 (19)	548 (24)
Peripheral artery disease, n (%)	7 (0.2)	5/ (0.3)	2 (0.1)
Medication			
Aspirin, n (%)	511 (12)	307 (16)	204 (9)
Thienopyridine, n (%)	156 (4)	111 (6)	45 (2)
Ticagrelor, n (%)	8 (0.2)	5 (0.3)	3 (0.1)
Statin, n (%)	1531 (36)	746 (39)	785 (35)
Beta blocker, n (%)	610 (15)	376 (19)	234 (10)
Calcium channel blocker, n (%)	708 (17)	321 (17)	387 (17)
ACE-inhibitor, n (%)	224 (5)	130 (7)	94 (4)
Angiotensin II antagonist, n (%)	527 (13)	249 (13)	278 (12)
Mineralocorticoid antagonist, n (%)	28 (1)	19 (1)	9 (0.4)
Oral hypoglycemics, n (%)	413 (10)	193 (10)	220 (10)
Insulin, n (%)	55 (1)	27 (1)	28 (1)
Blood test			
Glomerular filtration rate, mL/min	96 (86, 104)	96 (86, 105)	95 (86, 103)
Total cholesterol, mmol/L	5.0 (4.3, 5.7)	5.0 (4.3, 5.7)	5.0 (4.3, 5.8)
High-density cholesterol, mmol/L	1.3 (1.1, 1.6)	1.3 (1.0, 1.5)	1.4 (1.1, 1.6)
Triglycerides, mmol/L	1.3 (1.0, 1.9)	1.3 (1.0, 1.9)	1.3 (1.0, 1.9)
Low-density cholesterol, mmol/L	3.0 (2.3, 3.7)	3.1 (2.4, 3.7)	2.9 (2.3, 3.6)
Hemoglobin, g/dL	14 (13, 15)	14 (13, 15)	14 (13, 15)
Hemoglobin A1c, %	5.8 (5.5, 6.5)	5.8 (5.4, 6.4)	5.8 (5.5, 6.6)

Figure legends

Figure 1. Workflow of the APOLLO platform. CT images are anonymized and uploaded into the APOLLO database. The images are then processed using AI engines, and the results are re-uploaded into the database. A summary report is generated and presented to the end user. CAD: coronary artery disease; AI: artificial intelligence; EAT: epicardial adipose tissue; CVD: cardiovascular disease.

Figure 2. DISCOVERY AI tribrid platform processes. Clinical and research data are processed by various production AI modules to generate predictive clinical warnings within the electronic health record system. AI: artificial intelligence; ICU: intensive care unit; EPIC: an American privately held healthcare software company; I2B2: Informatics for Integrating Biology & the Bedside; SDSD: Surgical Data Systems Directorate dataset; SPH: School of Public Health.

Graphical abstract. APOLLO Study Design. The study integrates risk markers derived from coronary CT angiography with patient demographics, cardiovascular risk factors, medications, laboratory findings, and survival data. Coronary CT angiography parameters will include coronary artery lesion characterization, epicardial adipose tissue measurement, and coronary artery calcium scoring, aimed at creating a sharable database for clinical, research, and industrial purposes. AI: artificial intelligence; CAD: coronary artery disease; CT: computed tomography.

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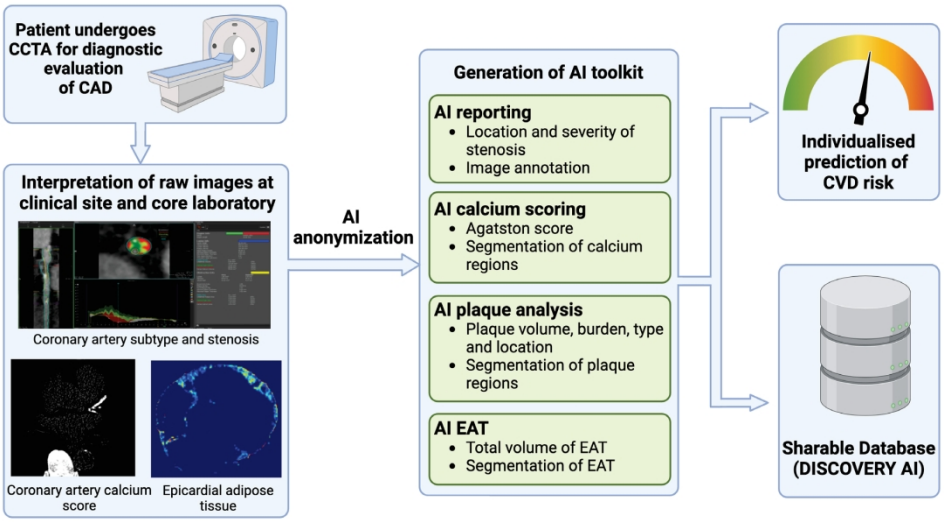

Figure 1. Workflow of the APOLLO platform. CT images are anonymized and uploaded into the APOLLO database. The images are then processed using AI engines, and the results are re-uploaded into the database. A summary report is generated and presented to the end user. CAD: coronary artery disease; AI: artificial intelligence; EAT: epicardial adipose tissue; CVD: cardiovascular disease.

338x190mm (600 x 600 DPI)

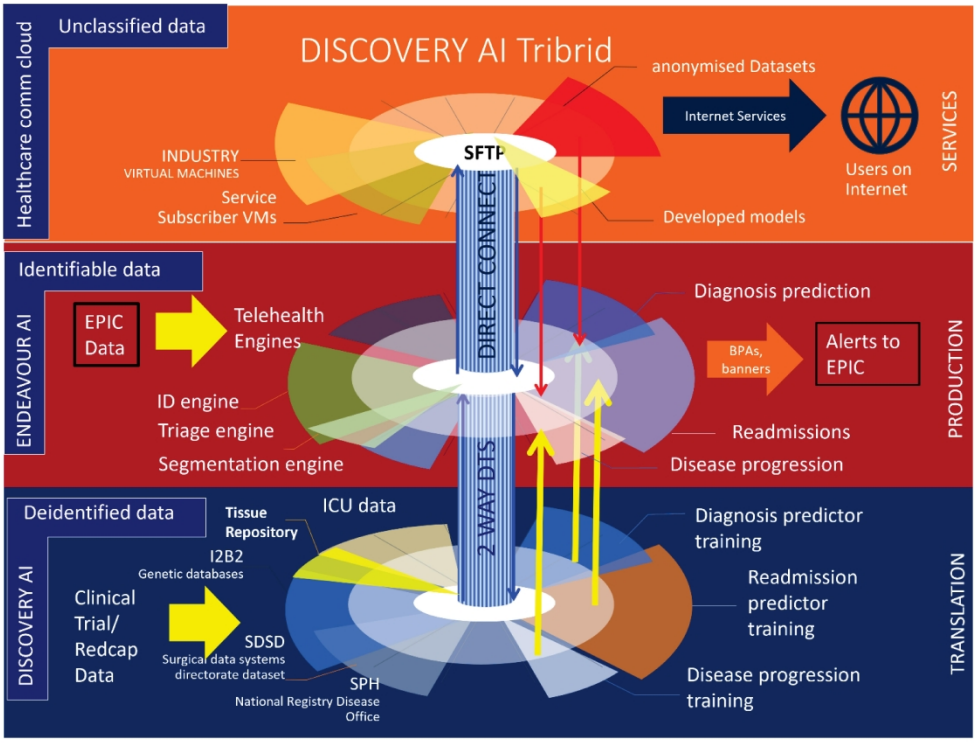

Figure 2. DISCOVERY AI tribrid platform processes. Clinical and research data are processed by various production AI modules to generate predictive clinical warnings within the electronic health record system. AI: artificial intelligence; ICU: intensive care unit; EPIC: an American privately held healthcare software company; I2B2: Informatics for Integrating Biology & the Bedside; SDSD: Surgical Data Systems Directorate dataset; SPH: School of Public Health.

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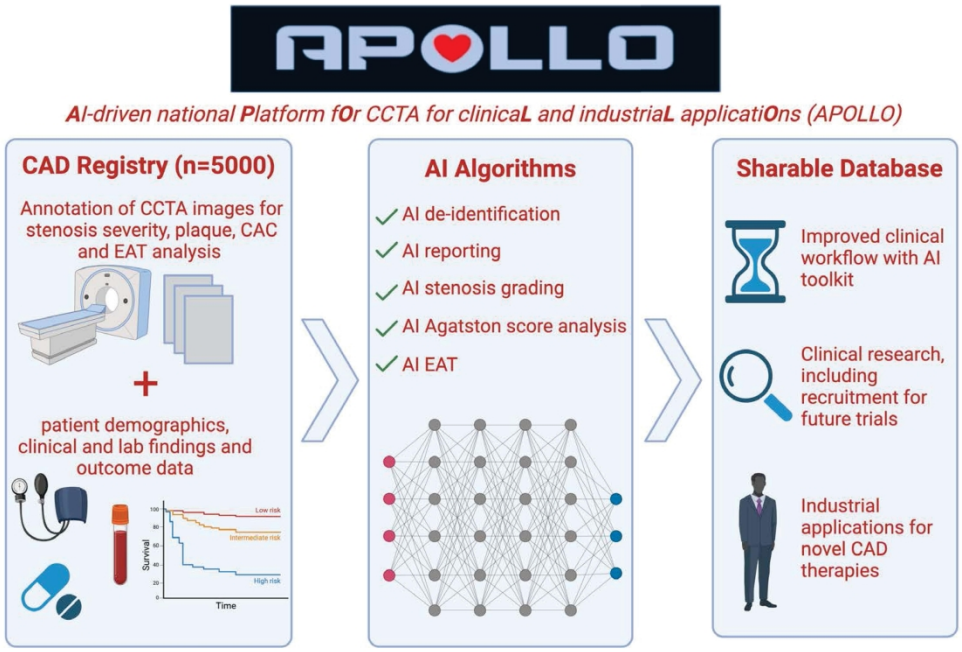
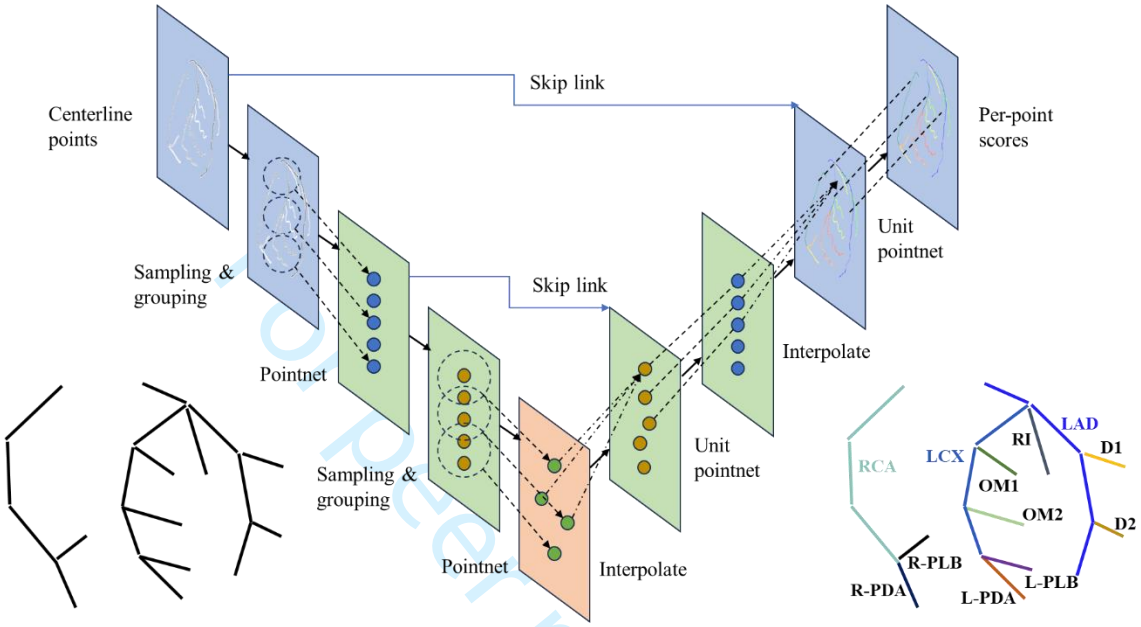


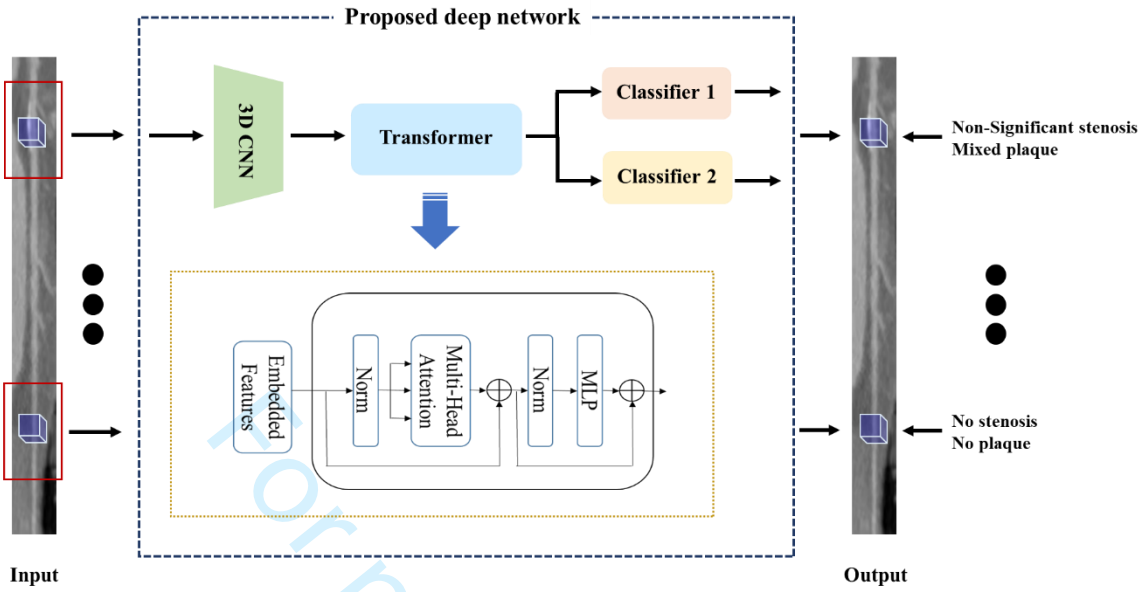
Graphical abstract. APOLLO Study Design. The study integrates risk markers derived from coronary CT angiography with patient demographics, cardiovascular risk factors, medications, laboratory findings, and survival data. Coronary CT angiography parameters will include coronary artery lesion characterization, epicardial adipose tissue measurement, and coronary artery calcium scoring, aimed at creating a sharable database for clinical, research, and industrial purposes. AI: artificial intelligence; CAD: coronary artery disease; CT: computed tomography.

269x190mm (300 x 300 DPI)

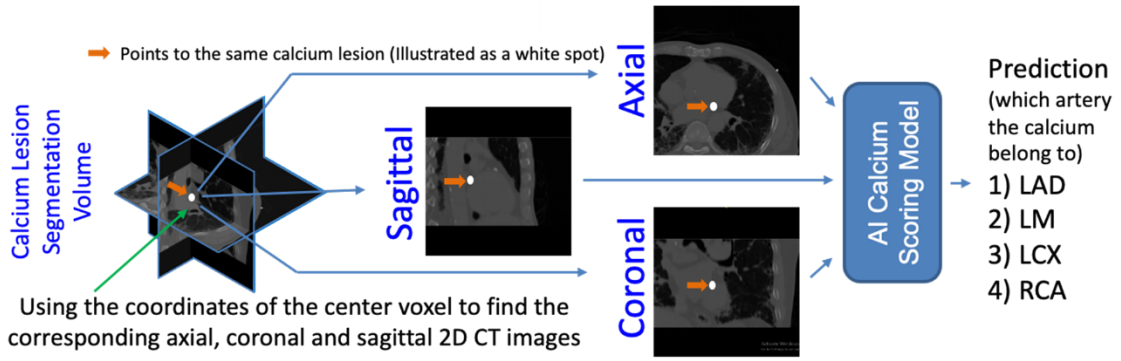
Supplemental Material



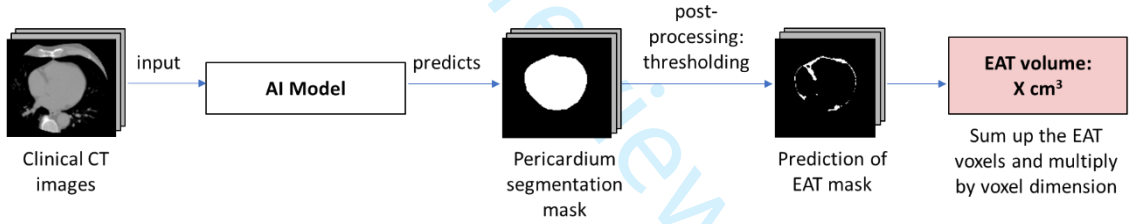
Supplemental Figure 1. Diagram of graph PointNet for coronary artery segment labelling. LAD: left anterior descending; LCX: left circumflex; LM: left main; RCA: right coronary artery; D1: first diagonal artery; D2: second diagonal artery; OM1, OM2: obtuse marginal arteries; RI: ramus intermedius; R-PLB: right posterior lateral branch; R-PDA: right posterior descending artery; L-PLB: left posterior lateral branch; L-PDA: left posterior descending artery.



Supplemental Figure 2. Multiple-target three-dimensional (3D) Transformer on 3D image classifier for joint stenosis grading, plaque quantification and characterization. CNN: convolutional neural networks.



Supplemental Figure 3. Workflow for calcium score quantification using convolutional neural networks (CNN). LM: left main; LAD: left anterior descending; LCX: left circumflex; LM: left main; RCA: right coronary artery.



Supplemental Figure 4. Workflow for AI EAT quantification. AI: artificial intelligence; EAT: epicardial adipose tissue.