

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Coronary artery disease risk prediction using machine learning with clinical variables and medical image-derived patient-specific insights: protocol for the retrospective GeoCAD cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054881
Article Type:	Protocol
Date Submitted by the Author:	26-Jun-2021
Complete List of Authors:	Adikari, Dona; University of New South Wales; Prince of Wales Hospital and Community Health Services, Cardiology Gharleggi, Ramtin; University of New South Wales Moses, Daniel; University of New South Wales; Prince of Wales Hospital and Community Health Services, Cardiology Ooi, Sze-Yuan; University of New South Wales; Prince of Wales Hospital and Community Health Services, Cardiology Department Beier, Susann; University of New South Wales
Keywords:	Coronary heart disease < CARDIOLOGY, Computed tomography < RADIOLOGY & IMAGING, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

TITLE PAGE

Title: Coronary artery disease risk prediction using machine learning with clinical variables and medical image-derived patient-specific insights: protocol for the retrospective GeoCAD cohort study

First author: Dona Adikari MBBS^{ab}

Second author: Ramtin Gharleghi BSc^a

Third author: Daniel Moses BSc MBBS MEngSc PhD^{ab}

Fourth author: Sze-Yuan Ooi MBBS MD^{ab}

Fifth author: Susann Beier BE ME PhD^a

^a The University of New South Wales, Sydney, Australia

^b Cardiology Department, The Prince of Wales Hospital, Sydney, Australia

Corresponding author:

Dr Dona Adikari

Eastern Heart Clinic, The Prince of Wales Hospital

Barker Street, Randwick NSW 2031

Email: z5283805@ad.unsw.edu.au

Word count: 4,088

Dates of the study: 09/06/2021 to 21/09/2022

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide. More than a quarter of cardiovascular events are unexplained by current absolute cardiovascular disease risk calculators and individuals without clinical risk factors have been shown to have worse outcomes. The 'anatomy of risk' hypothesis recognizes that adverse anatomical features of coronary arteries enhance atherogenic haemodynamics which in turn mediate the localisation and progression of plaques. We propose a novel approach predicated on advanced computed tomography coronary angiography (CTCA) data and state-of-the-art machine learning methods to address the gap in our understanding of anatomical risk for CAD. The early implementation of personalised preventive therapies in susceptible individuals may be the key to addressing the growing burden of CAD.

Methods and analysis

GeoCAD is a retrospective cohort study in 5,000 adult patients who have undergone CTCA for investigation of suspected CAD. It is a proof-of-concept study to test the hypothesis that advanced image-derived patient-specific data can accurately predict long-term cardiovascular events. The objectives are to profile CTCA images with respect to variations in anatomical shape and associated haemodynamic risk comprising an individual's anatomical risk, develop a machine-learning algorithm for the rapid assessment of anatomical risk directly from unprocessed CTCA images and build a novel CAD risk model combining traditional risk factors with novel anatomical biomarkers to improve the accuracy of CAD risk prediction.

Ethics and dissemination

The study protocol has been approved by the St Vincent's Hospital Human Research Ethics Committee, Sydney. The project outcomes will be published in peer-reviewed and biomedical journals, scientific conferences and as a higher degree research thesis.

For peer review only

ARTICLE SUMMARY

Strengths and limitations of this study

- GeoCAD is a retrospective cohort study to assess anatomical risk in 5,000 adult patients who have undergone computed tomography coronary angiography (CTCA) for suspected coronary artery disease (CAD).
- We propose a novel approach predicated on our current understanding of clinical and additional demographic risk factors, coronary artery calcium scoring and machine learning methods to non-invasively determine the relationship between shape features, wall shear stress and the risk of clinical endpoints in a large population.
- This provides an unprecedented opportunity to translate advanced imaging analyses to clinical practice, using novel anatomical biomarkers to develop improved risk models for CAD.
- This is a single centre cohort study which limits the external validity of the findings.

1
2
3 **KEYWORDS**
4

5 Cardiovascular events
6

7
8 Coronary artery disease
9

10 Computed tomography coronary angiography
11

12 Machine learning
13

14 Risk factors
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

INTRODUCTION

The landmark Framingham Heart Study, which was commenced in 1948, established the principle of coronary risk profiling using a simple equation with clinical risk factors independently predictive of coronary artery disease (CAD) and remains commonly used today.[1] However, CAD is still the leading cause of death worldwide despite the later implementation of statin therapy and the movement towards aggressive low-density lipoprotein (LDL) cholesterol lowering.[2-4] In fact, more than a quarter of cardiovascular events are unexplained by clinical risk equations from which it has been inferred that there are other risk factors for atherosclerosis that have not been identified.[5-6] Even more concerning, ST-segment elevation myocardial infarct (STEMI) patients without standard modifiable risk factors (SMuRFs) have been shown to have significantly worse in-hospital outcomes compared to those with one or more risk factor.[7] Contemporary scoring algorithms such as PREDICT in New Zealand and QRISK3 in the United Kingdom proved promising in improving the accuracy of cardiovascular risk estimation in vulnerable high-risk subpopulations by incorporating additional demographic predictors such as socioeconomic deprivation and ethnicity.[8, 9] Thus, there is a tremendous opportunity to shift the paradigm from intervention to a greater focus on a comprehensive approach to primary prevention of cardiovascular disease with demonstrated potential for improved risk prediction using additional risk factors for atherosclerosis.

Anatomical biomarkers and the haemodynamic risk which they encompass explain, at least partially, some of the variance in susceptibility to cardiovascular disease among individuals and may help to

1
2
3 improve cardiovascular risk identification and stratification.[6, 10, 11] Specifically, atherosclerosis is the
4
5
6 manifestation of the complex interplay between the triad of systemic risk factors, haemodynamic factors
7
8
9 and the biological response of the arterial wall.[11] Systemic risk factors have been compounded to
10
11
12 create current probabilistic risk scores.[1] However, it has been observed that atherosclerotic plaques
13
14
15 form and progress preferentially at geometrically predisposed locations, such as arterial bifurcations,
16
17
18 despite the fact that the entire arterial tree is exposed to systemic risk factors.[11] These distinct regions
19
20
21 are characterised by low wall shear stress (WSS), which enhances atherogenic molecular, cellular and
22
23
24 vascular responses.[12] A low shear-dependent mass transfer mechanism for atherogenesis was first
25
26
27 proposed by Caro et al. in 1971.[13, 14] It was observed that early atherosclerotic lesions developed
28
29
30 preferentially in regions which experienced low WSS along the outer wall of arterial bifurcations in a
31
32
33 series of cadaver human arteries. This led to the conclusion that cholesterol accumulated in low WSS
34
35
36 regions in arteries because its diffusional efflux from the arterial wall to intraluminal blood was inhibited
37
38
39 by the reduced concentration gradient.

40
41 This formed the understanding that WSS directly modulates the haemodynamic environment of the
42
43
44 arterial wall and can enhance the predilection for atherosclerosis in localized regions.[15] Subsequent
45
46
47 studies validated this proposal whereby low WSS (<0.5 Pa) was found to stimulate an atherogenic
48
49
50 endothelial phenotype, which is characterised by greater endothelial proliferation under the influence of
51
52
53 vasoconstrictors and mitogenic substances such as endothelin I, angiotensin II and platelet-derived
54
55
56 growth factor B, apoptogenic stimuli such as oxidised LDL and tumour necrosis factor α , inflammatory
57
58
59 mediators such as monocyte chemotactic peptide 1 and adhesion molecules such as vascular cell
60

1
2
3 adhesion molecule 1.[16, 17] In addition to low WSS, time-averaged WSS (TAWSS) (<0.5 Pa) was also
4
5
6 identified as a key regulator in the vascular pathophysiology of atherosclerosis.[18]
7

8
9 Recognising that WSS and the endothelial response is in turn mediated by the coronary anatomy
10
11 measured through its geometric variables led to the so-called 'anatomy of risk' hypothesis.[11, 12] In
12
13 essence, anatomy has direct effects on vascular fluid mechanics and the resulting local haemodynamic
14
15 factors influence endothelial structure and function.[15] As such, it is increasingly accepted that
16
17 haemodynamic factors may enable more accurate cardiovascular risk prediction beyond clinical risk
18
19 scores. This concept of geometric risk factors was first proposed by Friedman et al. in a study of pulsatile
20
21 flow through casts of human aortic bifurcations in 1983.[6] They identified four geometric features of
22
23 arterial bifurcations with sufficient variability among individuals to cause significant variability in WSS
24
25 distribution. These were a flow divider which was offset from the aortic axis, an inward curvature in the
26
27 aorta as the flow divider was approached, a markedly angulating daughter branch and an asymmetrical
28
29 T-shaped bifurcation. The data suggested that the localisation and progression of plaques in susceptible
30
31 arterial segments with atherogenic haemodynamics is mediated by corresponding adverse geometric
32
33 features. Furthermore, they proposed that these geometrical risk factors may contribute to the variance
34
35 in disease susceptibility to atherosclerosis among individuals which is unexplained by systemic risk
36
37 factors.
38
39
40
41
42
43
44
45
46
47
48
49
50

51
52 Recent computational studies have built on Friedman's early work, leading to the discovery of several
53
54 geometric features which can significantly influence WSS (Table 1).[19-26] Despite the progress in
55
56 recent years, there are areas in which further work is needed to provide important new information. In
57
58
59
60

1
2
3 particular, investigating the link between haemodynamics and clinical outcomes is critical to our
4
5
6 understanding of anatomical risk and will be relevant to identifying individuals without SMuRFs at risk
7
8
9 of developing CAD. Such work has previously been limited by the lack of advanced imaging data,
10
11
12 computational resources and large-scale population studies. The evolution of computed tomography
13
14
15 coronary angiography (CTCA) technology with improved spatial and temporal resolution has enabled a
16
17
18 wide range of new applications in the field of preventive cardiology. One of these is the integration of
19
20
21 coronary artery calcium score (CACS) with clinical risk equations, which has been shown to have
22
23
24 incremental predictive value for CAD.[27, 28] In addition, the use of machine learning approaches has
25
26
27 now made it feasible to investigate the relationship between shape features, haemodynamic
28
29
30 parameters and clinical outcomes, enabling a fast and practical system for risk assessment.[29] This
31
32
33 provides a powerful framework to translate advanced imaging analyses to clinical practice, using novel
34
35
36 anatomical biomarkers to develop improved risk models for CAD.

37
38 We propose a novel approach predicated on our current understanding of clinical and additional
39
40
41 demographic risk factors, CACS and machine learning methods to non-invasively determine the
42
43
44 relationship between shape features, WSS and the risk of clinical endpoints in a large population. To
45
46
47 the best of our knowledge, it is the first time that a machine learning approach has been applied to
48
49
50 establish the link between cardiovascular outcomes and haemodynamics, predicted by detailed image-
51
52
53 derived analysis. The use of advanced CTCA technology will overcome a key weakness of previous
54
55
56 scoring algorithms which have been limited by the lack of additional patient-specific data and now offers
57
58
59 an unprecedented opportunity to study detailed anatomical biomarkers for CAD other than CACS in
60

1
2
3 normal populations without manifest atherosclerosis. State-of-the-art machine learning methods can
4
5
6 then be applied to develop a practical system to generate new insights into previously unexplained
7
8
9 susceptibility in a large number of individuals without SMuRFs.

10
11
12 Our expert team is well positioned to build a sophisticated risk model to predict CAD using machine
13
14
15 learning algorithms. We previously constructed the Coronary Atlas, the World's first and largest three-
16
17
18 dimensional CT computational atlas describing the detailed statistical anatomy of the coronary tree.[10,
19
20
21 30, 31, 32] This led to the introduction of a new coronary shape parameter – the inflow angle, defined
22
23
24 as the angle with which the proximal vessel enters the bifurcation plane, as well as the first classification
25
26
27 of coronary shape features.[10, 31] The Coronary Atlas provides a systematic and comprehensive
28
29
30 framework to integrate large-scale datasets from multiple individuals and to generate new insights into
31
32
33 the relationship between coronary anatomy and WSS patterns, which we then successfully predicted
34
35
36 directly using machine learning.[22, 33] This has directly contributed to our understanding of CAD and
37
38
39 underpins the current proposal to address the gap in our understanding of anatomical risk for CAD. The
40
41
42 identification of susceptible individuals and the early implementation of targeted therapies based on
43
44
45 patient-specific data may take us one step closer to the Holy Grail of preventive cardiology.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

METHODS AND ANALYSIS

Patient and public involvement

Patients/the public were not directly involved in the research. However, the concept of the study was designed to address the gap in our understanding of susceptibility to CAD in the one quarter of individuals without standard clinical risk factors who suffer from unexplained cardiovascular events. The study outcomes will be disseminated in peer-reviewed journals, scientific conferences and as a higher degree research thesis which will provide a powerful framework to translate the findings to clinical practice in order to improve coronary risk profiling in the general population.

Objectives

The primary objective of the GeoCAD study is:

1. To identify novel anatomical biomarkers to improve the accuracy of CAD risk prediction.

The secondary objectives of the GeoCAD study are (Figure 1):

1. To profile CTCA images of a large population with respect to variations in anatomical shape and associated haemodynamic risk, comprising an individual's anatomical risk.
2. To develop a machine-learning algorithm for the rapid assessment of anatomical risk directly from unprocessed CTCA images.
3. To develop a novel CAD risk model combining traditional risk factors with anatomical risk.

Study type

GeoCAD is a retrospective cohort study (Figure 2). It is a proof-of-concept study to test the hypothesis that advanced image-derived patient-specific information can accurately predict long-term cardiovascular events.

Study population

5000 adult patients referred for CTCA for investigation of suspected CAD from 2010 onwards will be identified from the CTCA database at Spectrum Medical Imaging (SMI), Sydney. We will use the oldest records available to allow for a longer follow-up period. The first 6,000 consecutive patients from 2010 onwards will be recruited and screened to account for patients with exclusion criteria. The first 5,000 patients to meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study.

Inclusion criteria:

- Patients who were referred for CTCA for investigation of suspected CAD from 2010 onwards at SMI
- Age: 18 years or older

Exclusion criteria:

- Patients who have had a prior myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)

Data Collection

Imaging data will be collected from SMI and will include the following:

- CTCA digital imaging and communication in medicine (DICOM) files
- Dominance
- Presence or absence of the ramus intermediate artery
- CACS
- Location, severity and plaque composition of all lesions according to the 16-segment AHA classification.[34]

Clinical data will be collected from SMI and the Centre for Health Record Linkage (CHeReL) datasets

(Admitted Patient Data Collection, the Registry of Births, Deaths and Marriages and the Australian

Coordinating Registry Cause of Death Unit Record File). Data obtained from the CHeReL datasets

will be coded based on the International Classification of Diseases, 10th Revision (ICD-10). Clinical

data will include the following:

- Demographic data (age, sex).
- Standard modifiable risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking).
- Past medical history (e.g. prior MI, PCI or CABG).
- Medication history
- Clinical outcomes (all-cause death, cardiovascular death, coronary angiography, hospitalisation for heart failure, non-fatal MI, non-fatal stroke, revascularisation and unstable angina requiring

1
2
3 hospitalisation). Major adverse cardiovascular events (MACE) will be defined as cardiovascular
4
5
6 death, non-fatal MI and non-fatal stroke.
7
8
9

10 11 12 **Data governance** 13

14
15 Data management practices will follow the principles of the Australian Code for the Responsible
16
17 Conduct of Research. A research data management plan for the project will be established and
18
19 managed using the University of New South Wales (UNSW) ResData platform. All research data will
20
21 be classified according to UNSW Classification Standards and handled in accordance to UNSW data
22
23 handling guidelines.
24
25
26
27

28
29 There is a central repository of CTCA images at SMI. We have clear guidelines on the cases that we
30
31 will require as per the inclusion and exclusion criteria. Once we have a list of accession numbers we
32
33 will download the DICOM files and reports to a local server inside the SMI firewall. We can then
34
35 anonymise the cases within the SMI firewall and then copy the relevant parts of the anonymised
36
37 cases to a password protected drive on a secure UNSW server for storage and analysis. We have
38
39 written a MATLAB script to do this. UNSW Data Archive will be used for back-up.
40
41
42
43
44
45

46
47 The imaging data will be securely linked with the CHeReL datasets as follows:
48

- 49
50 1. Splitting, data integration and disclosure: Identifying information such as name, address and date
51
52 of birth is separated from content information such as imaging data. All participants will be
53
54 assigned an arbitrary Person Number which replaces identifying information. A research Project-
55
56
57
58
59
60

1
2
3 specific Person Number (PPN) will be made for each participant using an encrypted version of the
4
5
6 arbitrary Person Number. All records for a participant will have the same PPN.
7
8

- 9
10 2. Creating a research dataset: Using the PPN, the research team can combine records for a
11
12 participant without accessing identifying information. The data is made available to the research
13
14
15 team in a non-identifiable format.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Data analysis plan

Shape Features

Virtual models of the coronary anatomy will be reconstructed for each patient based on CTCA imaging. The left main (LM) bifurcation will be extracted and the relevant geometric features quantified using in-house python scripts. The extracted models will be smoothed using Taubin's algorithm to better represent the smoothness of arteries and remove artefacts. Vessel centrelines will be extracted using the Vascular Modelling Toolkit (VMTK).[35] Angles between vessels will be calculated based on the average centreline direction. For each vessel, the median diameter will be used for analysis. Tortuosity is measured for each vessel, defined as the length of the vessel divided by straight distance between the vessel end points. The curvature of vessel centerline will be measured according to the Frenet-Serret formulas with the average curvature used for analysis.[36]

Haemodynamic Indicators

Computational Fluid Dynamic (CFD) simulations will be carried out to establish blood flow patterns in the LM bifurcation for each patient. Transient simulations will be used to investigate flow conditions throughout the cardiac cycle with data from important time steps used for analysis. Non-newtonian behaviour of blood will be accounted for using the Carreau-Yasuda viscosity model.[37] An automated workflow has been developed to handle setting up, solving and post-processing of CFD simulations, taking approximately 25 central processing unit hours for each patient. VMTK will be used to generate tetrahedral meshes with prismatic boundary layers and ANSYS CFX used for solving the

1
2
3 simulations. Settings used for CFD simulations are based on the expert recommendations as
4
5
6 described in.[38]
7

8 9 *Machine Learning*

10
11
12 We have previously developed machine learning models to generate haemodynamic risk indicators
13
14 based on the vessel geometry, avoiding the need for high computation cost associated with CFD.[33]
15
16
17 Additional features such as demographic information and medical history will be incorporated into the
18
19
20 model to improve the prediction accuracy. The performance of the machine learning model in
21
22
23 predicting disease risk will be evaluated and compared with other risk models using 10-fold cross
24
25
26 validation.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Statistical analysis plan

Continuous variables will be presented as mean (\pm standard deviation) and categorical variables as proportions (%). Comparisons between groups will be performed using independent student *t*-tests with Bonferroni correction for continuous variables and χ^2 or Fisher's exact tests for continuous variables. Univariate and multivariate analyses will be performed using Mantel-Haenszel logistic regression. Univariate variables with $p < 0.10$ will be included in the multivariate analysis. The discriminative performance of the multivariable model will be assessed using Harrell's c-statistic. Comparisons between the multivariable models will be assessed using net reclassification index. A two-tailed *p* value < 0.05 with Bonferroni correction will be considered significant.

We estimate that will need a sample size of 445 patients to show that a c-statistic of 0.80 is significantly different from the null hypothesis (assuming a c-statistic of 0.71 for the Framingham risk score), taking into account a *p* value of 0.05, power of 80% and event rate of 20%.

Ethics and dissemination

The study protocol has been approved by the St Vincent's Hospital Human Research Ethics Committee, Sydney – 2020/ETH02127. The committee granted a waiver of the usual requirement of consent.

The project outcomes will be published in peer-reviewed and biomedical journals, scientific conferences and as a higher degree research thesis. Patient confidentiality will be maintained by not including any individually identifying information in publications. Statistical shape analyses and

1
2
3 haemodynamic simulations will be shared with other researchers on the Coronary Atlas website,
4
5
6 GitHub and/or the Amazon Web Services (AWS) Public Dataset Program. We will not share any raw
7
8
9 imaging data or unit record data with other researchers.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

DISCUSSION

Several studies have suggested that bifurcation angle (Figure 3), defined as the angle between the daughter vessels after branching, is a geometric risk factor for atherosclerosis.[19-21] Two computational studies have found consistent observations between wider LM bifurcation angles and atherogenic haemodynamics.[19, 20] The first, showed that wider bifurcation angles (75° to 120°) correlated with lower WSS and the second, showed that wider-angled models (70° to 110°) strongly altered WSS distribution.[19, 20] Interestingly, a study investigating the high incidence of left anterior descending (LAD) artery disease in young MI patients, found that the LAD-left circumflex (LCx) angle was not significantly different in patients with stenotic LAD arteries compared to patients with normal arteries, whilst the LM-LAD angle was significantly wider in the stenotic group.[22]

The current state of evidence suggests that in stented populations with LM disease, there is a complex interaction between wider bifurcation angles as well as mechanical factors such as stent underexpansion and multiple layers of stent that confers an increased risk of adverse cardiovascular events.[39, 40] To the best of our knowledge, there are no studies evaluating the relationship between bifurcation angles and clinical outcomes in non-stented populations, which is critical to understanding the true biologic effect of the bifurcation angle and addressing the gap in our understanding of anatomical risk for CAD.

While much attention has been paid to the bifurcation angle and its relationship with WSS, several studies have shown that bifurcation angle alone has minimal haemodynamic impact.[22-24] One such study performed CFD in 101 models derived from CTCAs of asymptomatic subjects.[22] Other shape

1
2
3 characteristics (inflow angle, diameter and tortuosity) had stronger adverse effects on WSS distribution
4
5
6 compared to bifurcation angle. A similar study found a strong correlation between tortuosity of the LM-
7
8
9 LAD segment and low WSS in the proximal LAD as well as a weak correlation between tortuosity of the
10
11
12 LM-LCx segment and low WSS in the proximal LCx.[23] There was no significant correlation between
13
14
15 bifurcation angles and low WSS although this may have been due to the fact that all patients had similar
16
17
18 bifurcation angles. Yet another study showed that cardiac curvature led to higher exposure to low WSS
19
20
21 while bifurcation angle had a minor effect.[24]

22
23
24 Pinho et al. assessed several geometric parameters of the coronary arteries and their influence on
25
26
27 WSS-based haemodynamic descriptors in the first statistical study of its kind using fluid-structure
28
29
30 interaction simulations based on CTCA images.[25, 26] Higher cross-sectional areas of LM, LAD and
31
32
33 LCx and higher tortuosity between LM-LCx were strongly correlated with low TAWSS in the LAD, as
34
35
36 were higher angles between LM-LAD, LAD-LCx and LAD-septum to a lesser extent. In contrast, higher
37
38
39 angles between LM-LCx negatively correlated with low TAWSS in the LAD.[25] In the right coronary
40
41
42 artery (RCA), lower tortuosity and smaller cross-sectional areas of the right ventricular (RV) branch and
43
44
45 a higher angle between the RCA and RV branch had the strongest correlation with low WSS.[26]

46
47 Smaller cross-sectional areas of the RCA ostium also promoted lower WSS more propitious to
48
49
50 atherosclerosis formation.

51
52
53 Inconsistent observations of geometric parameters in the literature suggest that anatomical risk factors
54
55
56 remain little understood, possibly due to their complex three-dimensional structure with interdependent
57
58
59 haemodynamic impact of several shape characteristics (Table 1).[22]

60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Table 1: Candidate anatomical biomarkers and haemodynamic variables for coronary artery disease.

Geometric biomarkers
<ul style="list-style-type: none"> • Flow divider which is offset from the aortic axis • Inward curvature in the aorta as the flow divider is approached • Markedly angulating daughter branch • Asymmetrical T-shaped bifurcation • Bifurcation angle • Cardiac curvature • Diameter • Inflow angle • Tortuosity
Haemodynamic parameters
WSS
Time-averaged WSS

WSS = wall shear stress

Current absolute cardiovascular disease risk calculators in Australia are based on the Framingham risk equation.[1] The model was developed to estimate an individual's five- and 10-year risk of cardiovascular disease using a point-score algorithm including clinical risk factors (age, female sex,

1
2
3 systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes and
4
5
6 electrocardiographic left ventricular hypertrophy). A recent meta-analysis of validation studies
7
8
9 evaluating the discriminative performance of the 10-year Framingham risk model found a pooled c-
10
11
12 statistic of 0.68 (95% CI 0.66 to 0.69) to 0.71 (95% CI 0.66 to 0.76).[5] From this modest discriminative
13
14
15 power, we can infer that more than a quarter of cardiovascular events are unexplained by the
16
17
18 Framingham risk model and that there are other risk factors for atherosclerosis which have not yet been
19
20
21 identified. Indeed, a recent study using two large multicentre Australian registries, showed that a
22
23
24 substantial and increasing proportion of STEMI patients were individuals without SMuRFs.[7] 19% of
25
26
27 patients were SMuRF-less, and this proportion increased from 14% to 23% during the study period.
28
29
30 Concerningly, SMuRF-less patients had a higher in-hospital mortality rate than patients with one or
31
32
33 more SMuRF (6% versus 4%, $p=0.032$). Advanced image-derived patient-specific information may
34
35
36 account for some of the unexplained susceptibility to atherosclerosis in SMuRF-less individuals.
37
38
39 CTCA technology already has a well-established role in the field of preventive cardiology. The Scottish
40
41
42 Computed Tomography of the Heart (SCOT-HEART) and Prospective Multicentre Imaging Study for
43
44
45 Evaluation of Chest Pain (PROMISE) trials were landmark studies which showed that a CTCA-guided
46
47
48 strategy improves clinical outcomes in symptomatic patients with stable angina by increasing the
49
50
51 diagnostic certainty and frequency of CAD and the subsequent implementation of appropriate
52
53
54 secondary prevention and revascularisation.[41-43]
55
56
57 The role of CTCA in asymptomatic patients with CAD remains uncertain. The Factor-64 trial has been
58
59
60 the only randomised clinical trial to date to assess the prognostic value of routine screening for CAD

1
2
3 using CTCA in this population.[44] Nine-hundred high-risk diabetic patients were randomized to CTCA
4
5
6 or standard national guidelines-based optimal medical care. At four years, there was no difference in
7
8
9 the primary outcome of death, non-fatal MI or unstable angina requiring hospitalisation. However, the
10
11
12 trial was not adequately powered due to a lower than anticipated event rate. A meta-analysis evaluating
13
14
15 the prognostic value of CTCA in 6,225 diabetic patients, 4,145 of whom were asymptomatic, observed
16
17
18 a higher hazard ratio for obstructive CAD in the studies that included revascularisation in the endpoints
19
20
21 compared with those that did not, suggesting that CTCA in this population could have prognostic
22
23
24 implications by identifying patients who may be appropriate for revascularisation.[45] Registry studies
25
26
27 in broader asymptomatic populations have also suggested that CTCA findings (location, severity and
28
29
30 plaque composition) have incremental prognostic utility beyond traditional risk factors alone.[46]

31
32 Several studies have demonstrated the incremental predictive value of the CACS, in addition to
33
34
35 traditional risk factors for CAD.[27, 28] The South Bay Heart Watch Study found that a CACS >300
36
37
38 combined with the Framingham risk score significantly improved the discriminative ability of the
39
40
41 Framingham risk score (c-statistic 0.68 vs 0.63, $p < 0.001$).[27] Similarly, the St. Francis Heart Study
42
43
44 showed that CACS was superior to the Framingham risk index for the prediction of atherosclerotic
45
46
47 cardiovascular disease events (c-statistic 0.79 vs 0.69, $p = 0.0006$).[28] Furthermore, the distribution of
48
49
50 calcium has been shown to be incremental to its presence and extent in predicting cardiovascular
51
52
53 events.[47, 48] An analysis of 1,268 participants from the Offspring and Third Generation cohorts of the
54
55
56 Framingham Heart Study showed that the number of coronary arteries with calcium, and especially the
57
58
59 presence of calcium in the proximal dominant coronary artery, as detected by CTCA, independently
60

1
2
3 predicted coronary heart disease after adjustment for the Framingham risk score and CACS.[48] The
4
5
6 addition of calcium distribution improved the discriminatory capacity of the multivariable model with
7
8
9 Framingham risk score and CACS for coronary heart disease events (c-statistic 0.79 to 0.80 vs 0.77,
10
11
12 relative integrated discriminatory index 0.14). This study confirmed the observations of an earlier
13
14
15 analysis of 3,262 participants in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, which showed
16
17
18 that diffusely distributed calcium, as assessed by the number of coronary arteries with calcified plaque,
19
20
21 significantly improved the capacity to predict cardiovascular events beyond the CACS (c-statistic 0.67
22
23
24 vs 0.64, $p=0.0001$).[47]

25
26 There is a tremendous opportunity to improve the accuracy of CAD risk prediction by integrating
27
28
29 additional patient-specific anatomical risk with traditional risk models. Geometry shapes flow; adverse
30
31
32 geometric features of coronary artery bifurcations enhance atherogenic WSS patterns which govern the
33
34
35 localisation and progression of plaques.[11] The distribution of atherosclerosis, in turn, has been
36
37
38 demonstrated to predict cardiovascular events independently of systemic risk factors.[47, 48] The use
39
40
41 of anatomical surrogate markers for plaque distribution, such as bifurcation angle, rather than CACS or
42
43
44 the number of coronary arteries with calcified plaques will enable us to extend the application of CTCA-
45
46
47 guided risk prediction from diseased individuals to normal populations without atherosclerosis. This
48
49
50 unprecedented opportunity has been underpinned by advanced imaging analysis, sophisticated
51
52
53 computational technology and state-of-the-art machine learning algorithms which offer a fast and
54
55
56 practical approach to risk assessment in large-scale population studies. More than a quarter of
57
58
59 cardiovascular events remain unexplained by systemic risk factors, and individuals without SMuRFs
60

1
2
3 have been shown to have poor outcomes.[5, 7] Understanding the mechanism of personal susceptibility
4
5
6 to atherosclerosis and the early implementation of targeted therapies in susceptible individuals may be
7
8
9 the key to addressing the growing burden of CAD.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

REFERENCES

1. Anderson KM, Wilson PW, Odell PM et al. An updated coronary risk profile. A statement for health professionals. *Circulation*. 1991;83(1):356-62.
2. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2019.
3. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-9.
4. Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372(25):2387-97.
5. Damen JA, Pajouheshnia R, Heus P et al. Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. *BMC Med*. 2019;17(1):109.
6. Friedman MH, Deters OJ, Mark FF et al. Arterial geometry affects hemodynamics. A potential risk factor for atherosclerosis. *Atherosclerosis*. 1983;46(2):225-31.
7. Vernon ST, Coffey S, D'Souza M et al. ST-Segment-Elevation Myocardial Infarction (STEMI) Patients Without Standard Modifiable Cardiovascular Risk Factors-How Common Are They, and What Are Their Outcomes? *J Am Heart Assoc*. 2019;8(21):e013296.

- 1
2
3
4 8. Pylypchuk R, Wells S, Kerr A et al. Cardiovascular disease risk prediction equations
5
6
7 in 400 000 primary care patients in New Zealand: a derivation and validation study. *Lancet*.
8
9
10 2018;391(10133):1897-907.
11
- 12
13 9. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk
14
15
16 prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort
17
18
19 study. *BMJ*. 2017;357:j2099.
20
- 21
22 10. Medrano-Gracia P, Ormiston J, Webster M et al. A computational atlas of normal
23
24
25 coronary artery anatomy. *EuroIntervention*. 2016;12(7):845-54.
26
27
- 28
29 11. Morbiducci U, Kok AM, Kwak BR et al. Atherosclerosis at arterial bifurcations:
30
31
32 evidence for the role of haemodynamics and geometry. *Thromb Haemost*. 2016;115(3):484-
33
34
35 92.
36
37
- 38
39 12. Antoniadis AP, Mortier P, Kassab G et al. Biomechanical Modeling to Improve
40
41
42 Coronary Artery Bifurcation Stenting: Expert Review Document on Techniques and Clinical
43
44
45 Implementation. *JACC Cardiovasc Interv*. 2015;8(10):1281-96.
46
47
- 48
49 13. Caro CG, Fitz-Gerald JM, Schroter RC. Atheroma and arterial wall shear.
50
51
52 Observation, correlation and proposal of a shear dependent mass transfer mechanism for
53
54
55 atherogenesis. *Proc R Soc Lond B Biol Sci*. 1971;177(1046):109-59.
56
57
58
59
60

- 1
2
3 14. Caro CG. Discovery of the role of wall shear in atherosclerosis. *Arterioscler Thromb*
4
5
6
7 *Vasc Biol.* 2009;29(2):158-61.
8
9
- 10 15. Nerem RM. Vascular fluid mechanics, the arterial wall, and atherosclerosis. *J*
11
12
13 *Biomech Eng.* 1992;114(3):274-82.
14
15
- 16 16. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in
17
18
19 atherosclerosis. *JAMA.* 1999;282(21):2035-42.
20
21
- 22 17. Friedman MH, Hutchins GM, Barger CB et al. Correlation between intimal
23
24
25 thickness and fluid shear in human arteries. *Atherosclerosis.* 1981;39(3):425-36.
26
27
- 28 18. Dolan JM, Kolega J, Meng H. High wall shear stress and spatial gradients in vascular
29
30
31 pathology: a review. *Ann Biomed Eng.* 2013;41(7):1411-27.
32
33
- 34 19. Chaichana T, Sun Z, Jewkes J. Computation of hemodynamics in the left coronary
35
36
37 artery with variable angulations. *J Biomech.* 2011;44(10):1869-78.
38
39
- 40 20. Dong J, Sun Z, Inthavong K et al. Fluid-structure interaction analysis of the left
41
42
43 coronary artery with variable angulation. *Comput Methods Biomech Biomed Engin.*
44
45
46
47
48 2015;18(14):1500-8.
49
- 50 21. Ikeda U, Kuroki M, Ejiri T et al. Stenotic lesions and the bifurcation angle of coronary
51
52
53
54 arteries in the young. *Jpn Heart J.* 1991;32(5):627-33.
55
56
57
58
59
60

- 1
2
3
4 22. Beier S, Ormiston J, Webster M et al. Impact of bifurcation angle and other
5
6 anatomical characteristics on blood flow - A computational study of non-stented and stented
7
8 coronary arteries. *J Biomech.* 2016;49(9):1570-82.
9
10
11
12
13 23. Malvè M, Gharib AM, Yazdani SK et al. Tortuosity of coronary bifurcation as a
14
15 potential local risk factor for atherosclerosis: CFD steady state study based on in vivo
16
17 dynamic CT measurements. *Ann Biomed Eng.* 2015;43(1):82-93.
18
19
20
21
22
23 24. Chiastra C, Gallo D, Tasso P et al. Healthy and diseased coronary bifurcation
24
25 geometries influence near-wall and intravascular flow: A computational exploration of the
26
27 hemodynamic risk. *J Biomech.* 2017;58:79-88.
28
29
30
31
32 25. Pinho N, Castro CF, António CC et al. Correlation between geometric parameters of
33
34 the left coronary artery and hemodynamic descriptors of atherosclerosis: FSI and statistical
35
36 study. *Med Biol Eng Comput.* 2019;57(3):715-29.
37
38
39
40
41
42 26. Pinho N, Sousa LC, Castro CF et al. The Impact of the Right Coronary Artery
43
44 Geometric Parameters on Hemodynamic Performance. *Cardiovasc Eng Technol.*
45
46 2019;10(2):257-70.time
47
48
49
50
51 27. Greenland P, LaBree L, Azen SP et al. Coronary artery calcium score combined with
52
53 Framingham score for risk prediction in asymptomatic individuals. *JAMA.* 2004;291(2):210-5.
54
55
56
57
58
59
60

- 1
2
3
4 28. Arad Y, Newstein D, Roth M et al. Rationale and design of the St. Francis Heart
5
6
7 Study: a randomized clinical trial of atorvastatin plus antioxidants in asymptomatic persons
8
9
10 with elevated coronary calcification. *Control Clin Trials*. 2001;22(5):553-72.
11
12
13 29. Liang L, Liu M, Martin C et al. A machine learning approach to investigate the
14
15
16 relationship between shape features and numerically predicted risk of ascending aortic
17
18
19 aneurysm. *Biomech Model Mechanobiol*. 2017;16(5):1519-33.
20
21
22 30. Beier S. The Coronary Atlas 2020 [Available from: <https://www.coronaryatlas.org/>.
23
24
25 31. Medrano-Gracia P, Ormiston J, Webster M et al. A Study of Coronary Bifurcation
26
27
28 Shape in a Normal Population. *J Cardiovasc Transl Res*. 2017;10(1):82-90.
29
30
31 32. Medrano-Gracia P, Ormiston J, Webster M et al. Construction of a coronary artery
32
33
34 atlas from CT angiography. *Med Image Comput Comput Assist Interv*. 2014;17(Pt 2):513-20.
35
36
37 33. Gharleghi R, Samarasinghe G, Sowmya A et al. Deep Learning for Time Averaged
38
39
40 Wall Shear Stress Prediction in Left Main Coronary Bifurcations. 2020 IEEE 17th
41
42
43 International Symposium on Biomedical Imaging (ISBI); 2020: IEEE.
44
45
46 34. Austen WG, Edwards JE, Frye RL et al. A reporting system on patients evaluated for
47
48
49 coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery
50
51
52 Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*.
53
54
55 1975;51(4 Suppl):5-40.
56
57
58
59
60

- 1
2
3
4 35. Antiga L, Steinman DA, Itomi. Robust and objective decomposition and mapping of
5
6 bifurcating vessels. 2004;23(6):704-13.
7
8
9
10 36. Crenshaw HC, Edelstein-Keshet L, Bomb. Orientation by helical motion—II.
11
12 Changing the direction of the axis of motion. 1993;55(1):213-30.
13
14
15
16 37. Razavi A, Shirani E, Sadeghi M, Job. Numerical simulation of blood pulsatile flow in a
17
18 stenosed carotid artery using different rheological models. 2011;44(11):2021-30.
19
20
21
22 38. Gijzen F, Katagiri Y, Barlis P et al. Expert recommendations on the assessment of
23
24 wall shear stress in human coronary arteries: existing methodologies, technical
25
26 considerations, and clinical applications. 2019;40(41):3421-33.
27
28
29
30
31
32 39. Girasis C, Serruys PW, Onuma Y et al. 3-Dimensional bifurcation angle analysis in
33
34 patients with left main disease: a substudy of the SYNTAX trial (SYnergy Between
35
36 Percutaneous Coronary Intervention with TAXus and Cardiac Surgery). JACC Cardiovasc
37
38 Interv. 2010;3(1):41-8.
39
40
41
42
43
44 40. Chen S, Zhang J, Ye F et al. Final kissing balloon inflation by classic crush stenting
45
46 did not improve the clinical outcomes for the treatment of unprotected left main bifurcation
47
48 lesions: the importance of double-kissing crush technique. Catheter Cardiovasc Interv.
49
50
51
52 2008;71(2):166-72.
53
54
55
56
57
58
59
60

- 1
2
3
4 41. investigators S-H. CT coronary angiography in patients with suspected angina due to
5
6
7 coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial.
8
9
10 Lancet. 2015;385(9985):2383-91.
11
12
13 42. Newby DE, Adamson PD, Berry C et al. Coronary CT Angiography and 5-Year Risk
14
15
16 of Myocardial Infarction. N Engl J Med. 2018;379(10):924-33.
17
18
19 43. Douglas PS, Hoffmann U, Patel MR et al. Outcomes of anatomical versus functional
20
21
22 testing for coronary artery disease. N Engl J Med. 2015;372(14):1291-300.
23
24
25
26 44. Muhlestein JB, Lappé DL, Lima JA et al. Effect of screening for coronary artery
27
28
29 disease using CT angiography on mortality and cardiac events in high-risk patients with
30
31
32 diabetes: the FACTOR-64 randomized clinical trial. JAMA. 2014;312(21):2234-43.
33
34
35
36 45. Celeng C, Maurovich-Horvat P, Ghoshhajra BB et al. Prognostic Value of Coronary
37
38
39 Computed Tomography Angiography in Patients With Diabetes: A Meta-analysis. Diabetes
40
41
42 Care. 2016;39(7):1274-80.
43
44
45 46. Cho I, Al'Aref SJ, Berger A et al. Prognostic value of coronary computed tomographic
46
47
48 angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective
49
50
51 multicentre international CONFIRM study. Eur Heart J. 2018;39(11):934-41.
52
53
54
55
56
57
58
59
60

1
2
3 47. Blaha MJ, Budoff MJ, Tota-Maharaj R et al. Improving the CAC Score by Addition of

4
5
6 Regional Measures of Calcium Distribution: Multi-Ethnic Study of Atherosclerosis. JACC

7
8
9 Cardiovasc Imaging. 2016;9(12):1407-16.

10
11
12 48. Ferencik M, Pencina KM, Liu T et al. Coronary Artery Calcium Distribution Is an

13
14
15 Independent Predictor of Incident Major Coronary Heart Disease Events: Results From the

16
17
18 Framingham Heart Study. Circ Cardiovasc Imaging. 2017;10(10).
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

AUTHORS' CONTRIBUTIONS

DA contributed to the study design, drafting the manuscript and revising it critically for important intellectual content. RG and DM contributed to revising the manuscript. SB and SO are joint first authors. They contributed equally to the study design and conception, revising the manuscript critically for important intellectual content and final approval of the version to be published.

ACKNOWLEDGEMENTS

Nil

FUNDING

DA is supported by an Australian Government research training program scholarship. Award/grant number not applicable.

COMPETING INTERESTS

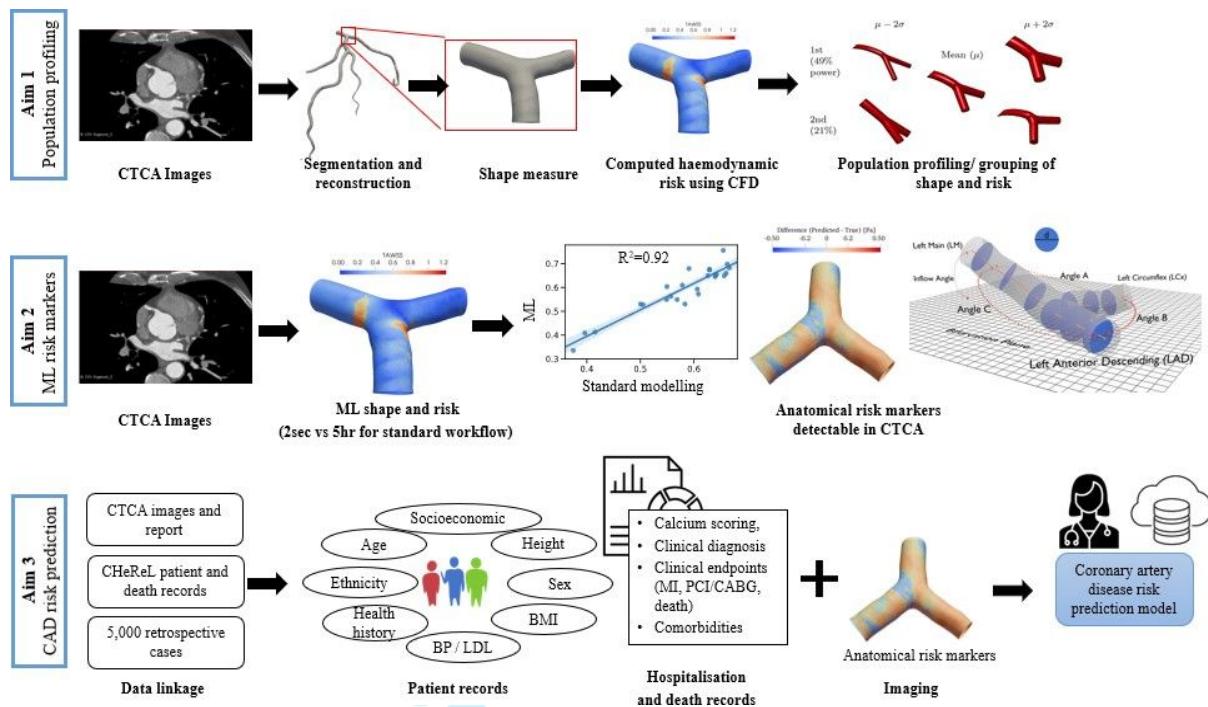
None declared

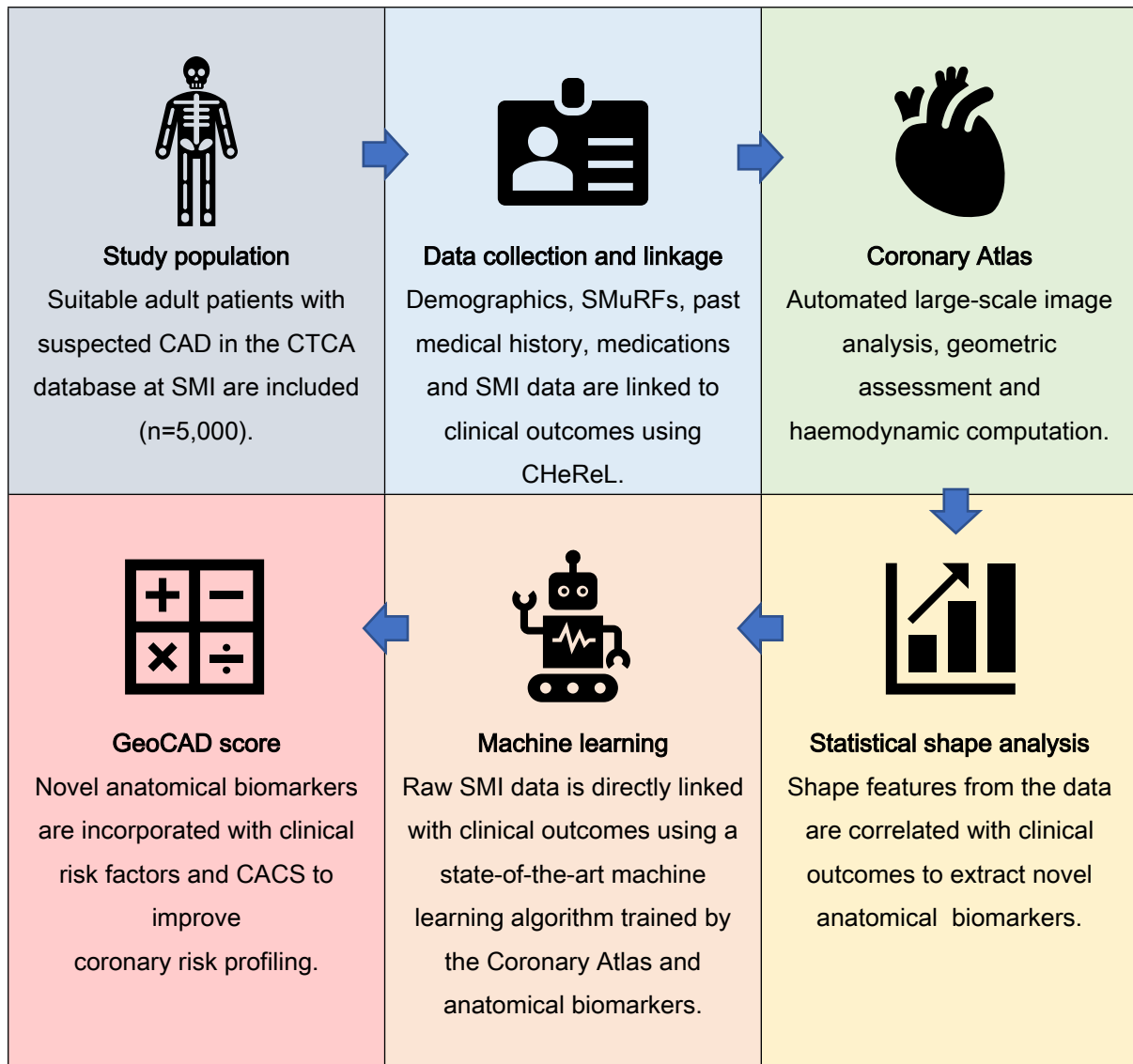
FIGURE LEGENDS

Figure 1: Secondary objectives of the GeoCAD study. CTCA = computed tomography coronary angiography, CFD = computational flow dynamics, ML = machine learning, CHeReL = Centre for Health Record Linkage, BP = blood pressure, LDL = low density lipoprotein, BMI = body mass index, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting

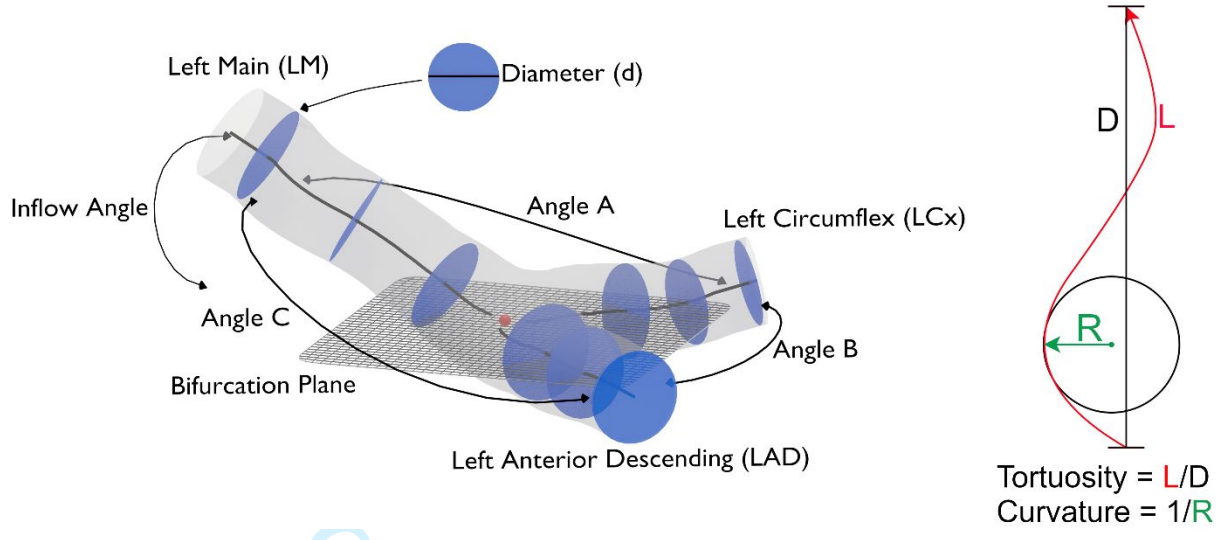
Figure 2: GeoCAD study flowchart – clockwise from top left to bottom left. CAD = coronary artery disease, CTCA = computed tomography coronary angiography, SMI = spectrum medical imaging, SMuRF = standard modifiable risk factor, CHeReL = Centre for Health Record Linkage, CACS = coronary artery calcium score

Figure 3: Three-dimensional representation of candidate anatomical biomarkers: 1) bifurcation angle (Angle B), defined as the angle between the daughter vessels after branching, 2) inflow angle, defined as the angle with which the proximal vessel enters the bifurcation plane, 3) diameter, 4) curvature (1/radius) and 5) tortuosity (length/diameter)





1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



or peer review only

Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPOD reporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

	Reporting Item	Page Number
Title		
	#1 Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1

Abstract

1			
2	#2	Provide a summary of objectives, study design, setting,	2
3			
4		participants, sample size, predictors, outcome, statistical	
5			
6		analysis, results, and conclusions.	
7			
8			
9	Introduction		
10			
11			
12	#3a	Explain the medical context (including whether diagnostic or	5
13			
14		prognostic) and rationale for developing or validating the	
15			
16		multivariable prediction model, including references to	
17			
18		existing models.	
19			
20			
21			
22	#3b	Specify the objectives, including whether the study describes	9
23			
24		the development or validation of the model or both.	
25			
26			
27	Methods		
28			
29			
30	Source of data	#4a Describe the study design or source of data (e.g.,	9
31			
32		randomized trial, cohort, or registry data), separately for the	
33			
34		development and validation data sets, if applicable.	
35			
36			
37			
38	Source of data	#4b Specify the key study dates, including start of accrual; end of	1
39			
40		accrual; and, if applicable, end of follow-up.	
41			
42			
43	Participants	#5a Specify key elements of the study setting (e.g., primary care,	9
44			
45		secondary care, general population) including number and	
46			
47		location of centres.	
48			
49			
50			
51	Participants	#5b Describe eligibility criteria for participants.	10
52			
53			
54	Participants	#5c Give details of treatments received, if relevant	n/a
55			
56			
57			
58			
59			
60			

1	Outcome	#6a	Clearly define the outcome that is predicted by the prediction	11
2			model, including how and when assessed.	
3				
4				
5				
6	Outcome	#6b	Report any actions to blind assessment of the outcome to be	11
7			predicted.	
8				
9				
10				
11				
12	Predictors	#7a	Clearly define all predictors used in developing or validating	10
13			the multivariable prediction model, including how and when	
14			they were measured	
15				
16				
17				
18				
19	Predictors	#7b	Report any actions to blind assessment of predictors for the	11
20			outcome and other predictors.	
21				
22				
23				
24				
25	Sample size	#8	Explain how the study size was arrived at.	9, 10, 13
26				
27				
28	Missing data	#9	Describe how missing data were handled (e.g., complete-	n/a
29			case analysis, single imputation, multiple imputation) with	
30			details of any imputation method.	
31				
32				
33				
34				
35	Statistical	#10a	If you are developing a prediction model describe how	12, 13
36			predictors were handled in the analyses.	
37	analysis methods			
38				
39				
40				
41	Statistical	#10b	If you are developing a prediction model, specify type of	12, 13
42			model, all model-building procedures (including any	
43	analysis methods		predictor selection), and method for internal validation.	
44				
45				
46				
47				
48	Statistical	#10c	If you are validating a prediction model, describe how the	n/a
49			predictions were calculated.	
50	analysis methods			
51				
52				
53				
54	Statistical	#10d	Specify all measures used to assess model performance	12, 13
55			and, if relevant, to compare multiple models.	
56	analysis methods			
57				
58				
59				
60				

1	Statistical	#10e	If you are validating a prediction model, describe any model	n/a
2				
3	analysis methods		updating (e.g., recalibration) arising from the validation, if	
4			done	
5				
6				
7				
8				
9	Risk groups	#11	Provide details on how risk groups were created, if done.	n/a
10				
11				
12	Development vs.	#12	For validation, identify any differences from the development	n/a
13	validation		data in setting, eligibility criteria, outcome, and predictors.	
14				
15				
16				
17	Results			
18				
19				
20	Participants	#13a	Describe the flow of participants through the study, including	Figure 2
21			the number of participants with and without the outcome	
22			and, if applicable, a summary of the follow-up time. A	
23			diagram may be helpful.	
24				
25				
26				
27				
28				
29				
30	Participants	#13b	Describe the characteristics of the participants (basic	9, 10
31			demographics, clinical features, available predictors),	
32			including the number of participants with missing data for	
33			predictors and outcome.	
34				
35				
36				
37				
38				
39				
40	Participants	#13c	For validation, show a comparison with the development	n/a
41			data of the distribution of important variables (demographics,	
42			predictors and outcome).	
43				
44				
45				
46				
47				
48	Model	#14a	If developing a model, specify the number of participants	n/a
49			and outcome events in each analysis.	
50	development			
51				
52				
53	Model	#14b	If developing a model, report the unadjusted association, if	n/a
54			calculated between each candidate predictor and outcome.	
55	development			
56				
57				
58				
59				
60				

1	Model	#15a	If developing a model, present the full prediction model to	n/a
2				
3	specification		allow predictions for individuals (i.e., all regression	
4				
5			coefficients, and model intercept or baseline survival at a	
6				
7			given time point).	
8				
9				
10				
11	Model	#15b	If developing a prediction model, explain how to the use it.	n/a
12				
13	specification			
14				
15				
16	Model	#16	Report performance measures (with CIs) for the prediction	n/a
17				
18	performance		model.	
19				
20				
21				
22	Model-updating	#17	If validating a model, report the results from any model	n/a
23				
24			updating, if done (i.e., model specification, model	
25				
26			performance).	
27				
28				
29	Discussion			
30				
31				
32	Limitations	#18	Discuss any limitations of the study (such as	3
33				
34			nonrepresentative sample, few events per predictor, missing	
35				
36			data).	
37				
38				
39				
40	Interpretation	#19a	For validation, discuss the results with reference to	n/a
41				
42			performance in the development data, and any other	
43				
44			validation data	
45				
46				
47	Interpretation	#19b	Give an overall interpretation of the results, considering	n/a
48				
49			objectives, limitations, results from similar studies, and other	
50				
51			relevant evidence.	
52				
53				
54				
55	Implications	#20	Discuss the potential clinical use of the model and	3
56				
57			implications for future research	
58				
59				
60				

1 **Other information**

2

3

4 Supplementary [#21](#) Provide information about the availability of supplementary n/a

5 information resources, such as study protocol, Web calculator, and data

6 sets.

7

8

9

10

11

12 Funding [#22](#) Give the source of funding and the role of the funders for the 25

13 present study.

14

15

16

17 The TRIPOD checklist is distributed under the terms of the Creative Commons Attribution License

18 CC-BY. This checklist was completed on 23. June 2021 using <https://www.goodreports.org/>, a tool

19

20 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

BMJ Open

A new and automated risk prediction of coronary artery disease using clinical endpoints and medical imaging-derived patient-specific insights: protocol for the retrospective GeoCAD cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054881.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Apr-2022
Complete List of Authors:	Adikari, Dona; University of New South Wales; Prince of Wales Hospital and Community Health Services, Cardiology Gharleggi, Ramtin; University of New South Wales Zhang, Shisheng; University of New South Wales Jorm, Louisa; University of New South Wales Centre for Big Data Research in Health Sowmya, Arcot; University of New South Wales Moses, Daniel; University of New South Wales; Prince of Wales Hospital and Community Health Services, Cardiology Ooi, Sze-Yuan; University of New South Wales; Prince of Wales Hospital and Community Health Services, Cardiology Department Beier, Susann; University of New South Wales
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Coronary heart disease < CARDIOLOGY, Computed tomography < RADIOLOGY & IMAGING, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

1
2
3 1 **TITLE PAGE**
4
5

6 2 Title: A new and automated risk prediction of coronary artery disease using clinical endpoints and
7
8
9 3 medical imaging-derived patient-specific insights: protocol for the retrospective GeoCAD cohort study
10
11

12 4
13
14
15 5 First author: Dona Adikari MBBS^{ab}
16

17
18 6 Second author: Ramtin Gharleghi BSc^a
19

20
21 7 Third author: Shisheng Zhang BSc MPE^a
22

23
24 8 Fourth author: Louisa Jorm BVSc MSc PhD^c
25

26
27 9 Fifth author: Daniel Moses BSc MBBS MEngSc PhD^{ab}
28

29
30 10 Sixth author: Arcot Sowmya BSc MSc MTech PhD^d
31

32
33 11 Seventh author: Sze-Yuan Ooi MBBS MD^{ab}
34

35
36 12 Eighth author: Susann Beier BE ME PhD^a
37

38
39 13 ^a The University of New South Wales, Sydney, Australia
40

41
42 14 ^b Cardiology Department, The Prince of Wales Hospital, Sydney, Australia
43

44
45 15 ^c Centre for Big Data Research in Health, Faculty of Medicine, The University of New South Wales,
46
47 16 Sydney, Australia

48
49 17 ^d School of Computer Science and Engineering, The University of New South Wales, Sydney,
50
51 18 Australia

52
53 19
54

55
56 20
57

58
59 21
60

1
2
3 1 Corresponding author:
4
5

6 2 Dr Dona Adikari
7
8

9 3 Eastern Heart Clinic, The Prince of Wales Hospital
10
11

12 4 Barker Street, Randwick NSW 2031
13
14

15 5 Email: dona.adikari@unsw.edu.au
16
17

18 6
19
20

21 7 Word count: 4354
22
23

24 8
25
26

27 9 Dates of the study: 17/03/2022 to 16/03/2027
28
29

30 10 ABSTRACT
31

32 11 **Introduction**
33

34 12 Coronary artery disease (CAD) is the leading cause of death worldwide. More than a quarter of
35
36
37 13 cardiovascular events are unexplained by current absolute cardiovascular disease risk calculators,
38
39
40 14 and individuals without clinical risk factors have been shown to have worse outcomes. The ‘anatomy
41
42
43 15 of risk’ hypothesis recognises that adverse anatomical features of coronary arteries enhance
44
45
46 16 atherogenic haemodynamics, which in turn mediate the localisation and progression of plaques. We
47
48
49 17 propose a new risk prediction method predicated on computed tomography coronary angiography
50
51
52 18 (CTCA) data and state-of-the-art machine learning methods based on a better understanding of
53
54
55 19 anatomical risk for CAD. This may open new pathways in the early implementation of personalised
56
57
58
59
60

1
2
3 1 preventive therapies in susceptible individuals as a potential key in addressing the growing burden of
4
5
6 2 CAD.

3 **Methods and analysis**

4 GeoCAD is a retrospective cohort study in 1,000 adult patients who have undergone CTCA for
5
6 investigation of suspected CAD. It is a proof-of-concept study to test the hypothesis that advanced
7
8 image-derived patient-specific data can accurately predict long-term cardiovascular events. The
9
10 objectives are to 1) profile CTCA images with respect to variations in anatomical shape and
11
12 associated haemodynamic risk expressing, at least in part, an individual's CAD risk, 2) develop a
13
14 machine-learning algorithm for the rapid assessment of anatomical risk directly from unprocessed
15
16 CTCA images, and 3) to build a novel CAD risk model combining traditional risk factors with these
17
18 novel anatomical biomarkers to provide a higher accuracy CAD risk prediction tool.

12 **Ethics and dissemination**

13 The study protocol has been approved by the St Vincent's Hospital Human Research Ethics
14
15 Committee, Sydney – 2020/ETH02127 and the NSW Population and Health Service Research Ethics
16
17 Committee – 2021/ETH00990. The project outcomes will be published in peer-reviewed and
18
19 biomedical journals, scientific conferences and as a higher degree research thesis.

1 ARTICLE SUMMARY

2 Strengths and limitations of this study

- 3 • GeoCAD is a retrospective cohort study to assess anatomical risk in 1,000 adult patients who
4 have undergone computed tomography coronary angiography (CTCA) for suspected coronary
5 artery disease (CAD).
- 6 • We propose a novel approach predicated on our current understanding of clinical and additional
7 demographic risk factors, coronary artery calcium scoring and machine learning methods to non-
8 invasively determine the relationship between shape features, wall shear stress and the risk of
9 clinical endpoints in a large population.
- 10 • This provides an unprecedented opportunity to translate advanced imaging analyses to clinical
11 practice, using novel anatomical biomarkers to develop improved risk models for CAD.
- 12 • This is a single centre study which potentially limits the patient cohort considered and the findings
13 may thus be limited to such cohort.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **KEYWORDS**

2 Cardiovascular events

3 Coronary artery disease

4 Computed tomography coronary angiography

5 Machine learning

6 Risk factors

7

For peer review only

1 INTRODUCTION

2 The landmark Framingham Heart Study, which was commenced in 1948, established the principle of
3 coronary risk profiling using a simple equation with clinical risk factors independently predictive of
4 coronary artery disease (CAD) and remains commonly used today.[1] However, CAD is still the leading
5 cause of death worldwide despite the implementation of statin therapy and a movement towards
6 aggressive low-density lipoprotein (LDL) cholesterol lowering.[2-4] In fact, more than a quarter of
7 cardiovascular events are unexplained by clinical risk equations, surmising that there are other risk
8 factors for atherosclerosis that have not been identified.[5, 6] Even more concerning, ST-segment
9 elevation myocardial infarct (STEMI) patients without standard modifiable risk factors (SMuRFs) have
10 significantly worse in-hospital outcomes compared to those with one or more risk factors.[7]
11 Contemporary scoring algorithm studies such as PREDICT in New Zealand and QRISK3 in the United
12 Kingdom showed promising improvements in the accuracy of cardiovascular risk estimation in
13 vulnerable high-risk sub-populations by incorporating additional demographic predictors such as
14 socioeconomic indicators and ethnicity.[8, 9] Inevitably, there is a tremendous opportunity for improved
15 CAD risk prediction by identifying the remaining risk indicators which may yield a paradigm shift from
16 intervention to a greater focus on primary prevention.

17

18 Anatomical biomarkers encompass haemodynamic risk which explain , at least in part, some of the
19 variance in susceptibility to cardiovascular disease among individuals and thus can help to improve
20 cardiovascular risk identification and stratification.[6, 10, 11] Specifically, atherosclerosis is the

1
2
3 1 manifestation of the complex interplay between the triad of systemic risk factors, haemodynamic factors
4
5
6 2 and the physiological response of the arterial wall.[10] Systemic risk factors have been compounded to
7
8
9 3 create current probabilistic risk scores,[1] yet the latter two, haemodynamic factors and the physiological
10
11
12 4 response, remain ignored in clinical risk assessments. However, it has been observed that
13
14
15 5 atherosclerotic plaques form and progress preferentially at geometrically predisposed locations such
16
17
18 6 as arterial bifurcations, despite the fact that the entire arterial tree is exposed to systemic risk
19
20
21 7 factors.[10] These distinct regions are characterised by low wall shear stress (WSS), which is known to
22
23
24 8 enhance atherogenic molecular, cellular, and vascular responses.[12] A low shear-dependent mass
25
26
27 9 transfer mechanism for atherogenesis was first proposed by Caro et al. in 1971,[13, 14] and it was later
28
29
30 10 demonstrated that cholesterol accumulates in low WSS arterial regions because of the inhabitation of
31
32
33 11 diffusional efflux from the arterial wall to the intra-luminal blood due to the reduced concentration
34
35
36 12 gradient.[13] This formed the understanding that WSS directly modulates the haemodynamic
37
38
39 13 environment of the arterial wall and can enhance the predilection for atherosclerosis in localised
40
41
42 14 regions.[15] Subsequent studies validated this hypothesis, whereby low WSS (<0.5 Pa) was found to
43
44
45 15 stimulate an atherogenic endothelial phenotype, characterised by greater endothelial proliferation under
46
47
48 16 the influence of vasoconstrictors and mitogenic substances such as endothelin I, angiotensin II and
49
50
51 17 platelet-derived growth factor B, apoptogenic stimuli such as oxidised LDL and tumour necrosis factor
52
53
54 18 α , inflammatory mediators such as monocyte chemotactic peptide 1 and adhesion molecules such as
55
56
57 19 vascular cell adhesion molecule 1.[16, 17] Later, in addition to instantaneous low WSS, cardiac cycle
58
59
60 20 time-averaged low WSS was also identified as a key regulator in the vascular pathophysiology of

1 atherosclerosis.[18] As such, it is increasingly recognised that haemodynamic factors can form a
2 valuable indicator for higher accuracy cardiovascular risk prediction beyond commonly used clinical risk
3 scores.

4 It is important to notice that coronary anatomy governs the localised development of WSS within the
5 arterial tree and thus mediates the endothelial response,[15] formulating the 'Anatomy of Risk'
6 hypothesis.[10, 12] While haemodynamic factors are difficult to assess in-vivo, coronary anatomical
7 characteristics are apparent in standard medical images and may offer a pathway into future integration
8 into standard clinical CAD risk assessments.

9 The concept of arterial geometric risk was first proposed by Friedman et al. in a study of pulsatile flow
10 through casts of human aortic bifurcations in 1983,[6] which identified geometric bifurcations features
11 causing significant variability in WSS distribution. Recent computational studies have built on
12 Friedman's early work, leading to the discovery of several anatomical features which can significantly
13 influence WSS (Table 1).[19-26] Despite the progress in recent years, investigating the link between
14 coronary haemodynamics and clinical outcomes remains critical to our understanding of anatomical risk
15 and is likely directly relevant to identifying individuals without SMuRFs at risk of developing CAD.

16 Meaningful progress towards such understanding has been hindered by the lack of advanced imaging
17 technology and computational resources, prohibiting large-scale population studies until recently. The
18 evolution of computed tomography coronary angiography (CTCA) technology with improved spatial and
19 temporal resolution has enabled a wide range of new applications in the field of preventive cardiology,
20 such as the integration of coronary artery calcium scoring with clinical risk equations, with incremental

1
2
3 1 predictive value for CAD risk.[27, 28] Combined with the increase in processing power and storage
4
5
6 2 facilitating high-fidelity (mainly medical images-based) big data efforts coupled with the rise of machine
7
8
9 3 learning approaches, fast and practical automated systems for better CAD risk assessment are now
10
11
12 4 not a distant vision but a near future opportunity.[29] Traditional machine learning methods (logistic
13
14
15 5 regression, k-nearest neighbours, support vector machines, tree-based algorithms) have previously
16
17
18 6 been used for risk stratification.[30-32] More recent methods, including deep neural networks, now
19
20
21 7 outperform these earlier attempts.[33-36] These latest developments in the field are thus a powerful
22
23
24 8 framework for the translation of advanced imaging analyses into clinical CAD risk assessment practice.
25
26
27 9 Still, cardiac CT requires unfavourable radiation exposure and some studies attempted to leverage non-
28
29
30 10 cardiac imaging to investigate CAD risk factors.[37-39] Deep learning models have shown promising
31
32
33 11 results in using low dose CT imaging for lung cancer screening,[37] and risk factors such as blood
34
35
36 12 pressure, smoking history, and diabetes, have been successfully identified in retinal vasculature from
37
38
39 13 retinal images only,[38] showing correlation with CAD risk and all-cause mortality.[39] This showcases
40
41
42 14 the potential for general investigation of the anatomy of risk and patient-specific image-derived
43
44
45 15 biomarkers, as these may not just be linked to cardiac CT but can also be deployed to a range of
46
47
48 16 available imaging modalities.

49
50 17 Other noteworthy approaches in better CAD risk prediction includes machine learning systems including
51
52
53 18 systemic lifestyle factors combined with data from wearable devices together with traditional risk
54
55
56 19 factors,[40] and a similar deep learning system, aimed at including localised markers by automatically
57
58
59 20 predicting coronary artery calcium scores.[41] These works showcase the potential of such efforts,
60

1
2
3 1 which may be especially relevant when considering better risk assessments for specific sub-groups
4
5
6 2 including more vulnerable populations.[8, 9]
7
8

9 3 Here, we propose a novel approach to build upon this previous knowledge and to non-invasively
10
11
12 4 determine the relationship between shape features, WSS and the risk of clinical endpoints in a large
13
14
15 5 population, with the aim to generate a superior CAD risk prediction model. To the best of our knowledge,
16
17
18 6 vessel geometry and its haemodynamic impact has not been accounted for in CAD risk models to date,
19
20
21 7 and our approach thus offers an unprecedented opportunity to study detailed anatomical biomarkers
22
23
24 8 driving haemodynamic processes linked to CAD in addition to calcium scoring and standard risk
25
26
27 9 assessment. State-of-the-art machine learning methods will be applied to develop a practical system to
28
29
30 10 generate new insights into previously unexplained susceptibility in many individuals without SMuRFs.
31
32
33 11 Our expert team is well positioned to build such a sophisticated CAD risk model using machine learning
34
35
36 12 algorithms. Specifically, SB and team previously developed the Coronary Atlas, the world's first and
37
38
39 13 largest three-dimensional CT computational atlas describing the detailed statistical anatomy of the
40
41
42 14 coronary tree.[11, 42-44] This led to the introduction of a new coronary shape parameter – the inflow
43
44
45 15 angle, defined as the angle with which the proximal vessel enters the bifurcation plane, as well as the
46
47
48 16 first classification of coronary shape features.[11, 43] The Coronary Atlas provides a systematic and
49
50
51 17 comprehensive framework to integrate large-scale datasets from multiple individuals and to generate
52
53
54 18 new insights into the relationship between coronary anatomy and WSS patterns, which we then
55
56
57 19 successfully predict directly using machine learning.[22, 45] This has elucidated the understanding of
58
59
60 20 WSS in individuals with direct implications for individual CAD susceptibility and underpins the current

1
2
3 1 proposal to address the gap in our understanding of anatomical risk for CAD. The identification of
4
5
6 2 susceptible individuals and the early implementation of targeted therapies based on patient-specific
7
8
9 3 data may take us one step closer to the Holy Grail of preventive cardiology.
10
11
12 4

13
14
15 5 **Table 1:** Candidate anatomical biomarkers and haemodynamic variables for coronary artery disease.
16
17

Geometric biomarkers
<ul style="list-style-type: none"> • Flow divider which is offset from the aortic axis • Inward curvature • Marked angulating daughter branches • Asymmetrical T-shaped bifurcation • Bifurcation angle • Cardiac curvature • Vessel diameter • Inflow angle • Tortuosity
Haemodynamic parameters
Wall Shear Stress (WSS)
Time-averaged WSS

18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56 6

57
58
59 7
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1

For peer review only

1 METHODS AND ANALYSIS

2

3 **Patient and public involvement**

4 Patients/the public were not directly involved in the research. However, the concept of the study was
5 designed to address the gap in our understanding of susceptibility to CAD in the one quarter of
6 individuals without standard clinical risk factors who suffer from unexplained cardiovascular events.
7 The study outcomes will be disseminated in peer-reviewed journals, scientific conferences and as a
8 higher degree research thesis, which will provide a powerful framework to translate the findings into
9 clinical practice to improve coronary risk profiling in the general population.

10

11 **Objectives**

12 *The primary objective of the GeoCAD study is:*

- 13 1. To identify novel anatomical biomarkers to improve the accuracy of CAD risk prediction.

14 *The secondary objectives of the GeoCAD study are (Figure 1):*

- 15 1. To profile CTCA images of a large population with respect to variations in anatomical shape and
16 associated haemodynamic risk, comprising an individual's anatomical risk.
- 17 2. To develop a machine-learning algorithm for the rapid assessment of anatomical risk directly from
18 unprocessed CTCA images.
- 19 3. To develop a novel CAD risk model combining traditional risk factors with anatomical risk.

20

21 **Study type**

1
2
3 1 GeoCAD is a retrospective cohort study (Figure 1). It is a proof-of-concept study to test the hypothesis
4
5
6 2 that advanced image-derived patient-specific information can accurately predict long-term
7
8
9 3 cardiovascular events.

14 5 **Study population**

16
17 6 Retrospectively, 1,000 adult patients referred for CTCA due to suspected CAD will be identified from
18
19
20 7 the CTCA database at Spectrum Medical Imaging, Sydney, Australia. We will identify patients who
21
22
23 8 have undergone at least two CTCA scans from 2010 onwards (due to available CTCA image
24
25
26 9 resolution) to allow comparison of geometry and plaque features over time. We will use the oldest
27
28
29 10 records available to allow for a longer follow-up period. The patients will be selected and screened
30
31
32 11 and patients who meet all of the inclusion criteria and none of the exclusion criteria will be selected for
33
34
35 12 the study.

37 13 *Inclusion criteria:*

- 39
40 14 • Patients who were referred for at least two CTCA scans for investigation of suspected CAD from
41
42
43 15 2010 onwards at Spectrum Medical Imaging

- 44
45
46 16 • Age: 18 years or older

48 49 17 *Exclusion criteria:*

- 50
51
52 18 • Patients who have had a prior myocardial infarction (MI), percutaneous coronary intervention
53
54
55 19 (PCI) or coronary artery bypass grafting (CABG)

56
57
58 20

1 Data Collection

2 Imaging and associated data will be collected from Spectrum Medical Imaging and will include the
3 following:

- 4 • CTCA digital imaging and communication in medicine (DICOM) files,
- 5 • Coronary dominance,
- 6 • Presence or absence of the ramus intermediate artery,
- 7 • Coronary artery calcium score, and
- 8 • Location, severity and plaque composition of all lesions according to the 16-segment American
9 Heart Association classification.[46]

10
11 Clinical data will be collected from Spectrum Medical Imaging and from administrative datasets linked
12 by the NSW Centre for Health Record Linkage (CHeReL) (Admitted Patient Data Collection (APDC),
13 the Registry of Births, Deaths and Marriages, and the Australian Coordinating Registry Cause of
14 Death Unit Record File). APDC records include contain diagnoses coded according to the
15 International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM) and
16 procedures coded according to the Australian Classification of Health Interventions. Clinical data will
17 include the following:

- 18 Demographic data (age, sex),
- 19 • Standard modifiable risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking),
- 20 • Past medical history (e.g. prior MI, PCI or CABG),

- 1
- 2
- 3
- 4 1 • Medication history,
- 5
- 6 2 • Clinical outcomes (all-cause death, cardiovascular death, coronary angiography, hospitalisation
- 7
- 8
- 9 3 for heart failure, non-fatal MI, non-fatal stroke, revascularisation and unstable angina requiring
- 10
- 11
- 12 4 hospitalisation), and
- 13
- 14
- 15 5 • Major adverse cardiovascular events (MACE) will be defined as cardiovascular death, non-fatal
- 16
- 17
- 18 6 MI and non-fatal stroke.
- 19
- 20
- 21
- 22
- 23

24 8 **Data governance**

25

26 9 Data management practices will follow the principles of the Australian Code for the Responsible

27

28

29 10 Conduct of Research. A research data management plan for the project has been established and

30

31

32 11 managed using the University of New South Wales (UNSW) ResToolkit platform. All research data will

33

34

35 12 be classified according to UNSW Classification Standards and handled in accordance to UNSW data

36

37

38 13 handling guidelines.

39

40

41 14 Appropriate cases matching the inclusion and exclusion criteria will be selected and their accession

42

43

44 15 numbers noted. DICOM files and reports for cases will be downloaded from a central repository at

45

46

47 16 Spectrum Medical Imaging to a local server inside the firewall. DM will semi-automatically anonymise

48

49

50 17 and copy the data to secure password protected storage on UNSW servers through an encrypted

51

52

53 18 channel. DM will not be involved in the analysis of linked data. The researchers analysing the data

54

55

56 19 will have only access to the anonymised data. The provided data will be transferred to the Data

57

58

59 20 Archive provisioned for this project (RDMP ID: D0240165), rated as appropriate for sensitive data,

60

1
2
3 1 using the Data Archive web application. Data on UNSW Data Archive is encrypted and access to
4
5
6 2 UNSW Data Archive is password protected and requires connection to UNSW's VPN with a valid
7
8
9 3 university account.
10

11 4
12
13
14 5 The imaging data will be securely linked with the CHeReL datasets as follows:
15

- 16
17 6 1. Splitting, data integration and disclosure: Identifying information such as name, address and date
18
19
20 7 of birth is separated from content information such as imaging data. All participants will be
21
22
23 8 assigned an arbitrary Person Number which replaces identifying information. A research Project-
24
25
26 9 specific Person Number (PPN) will be made for each participant using an encrypted version of the
27
28
29 10 arbitrary Person Number. All records for a participant will have the same PPN.
30
31
32 11 2. Creating a research dataset: Using the PPN, the research team can combine records for a
33
34
35 12 participant without accessing identifying information. The data is made available to the analysing
36
37
38 13 research team in a non-identifiable format.
39

40 14 **Data analysis plan**

41 42 43 15 *Shape Features*

44
45
46 16 It is important to note that the analysis of the vessel geometry and its haemodynamics in the same
47
48
49 17 patient years apart will provide critical and unprecedented insights into the development of stable
50
51
52 18 CAD, allowing for the comparison of arterial geometry and plaque changes over time to elucidate the
53
54
55 19 role of haemodynamics. Deep learning methods have gained significant popularity in image
56
57
58 20 segmentation and analysis, particularly due to the success of U-Net in segmenting medical
59
60

1 images.[47] Virtual models of the coronary anatomy will be reconstructed from the CTCA image using
2 deep convolutional neural networks based on nnU-Net architecture,[48] as this method has been
3 shown to work well in automated coronary artery segmentation.[49] After Taubin's algorithm
4 smoothing and vessel centrelines extraction with Vascular Modelling Toolkit (VMTK),[50] relevant
5 geometric arterial tree features will be quantified using in-house python scripts. This includes the
6 median branch diameters, tortuosities, curvature (Frenet-Serret formulas with the average curvature
7 used for analysis).[51, 52] The processing time for each case is approximately two minutes on a
8 single core 2.9GHz Xeon ES-2670.

9 *Haemodynamic Indicators*

10 Haemodynamics will be computed using validated machine learning models,[45] taking less than one
11 minute per case on a single core 2.9GHz Xeon ES-2670. This allows the generation of
12 haemodynamic risk indicators based on vessel geometry, avoiding the need for high computation cost
13 associated with standard computational modelling. Transient simulations will be used to investigate
14 pulsatile flow conditions throughout the cardiac cycle. Non-Newtonian behaviour of blood will be
15 accounted for using the Carreau-Yasuda viscosity model.[53] The haemodynamic modelling follows
16 experts' recommendations for coronary modelling.[54]

17 *Machine Learning*

18 Building on our previous machine learning haemodynamics predictions from reconstructed
19 models,[45] additional features such as demographic information and medical history will be
20 incorporated into the model to improve the prediction accuracy. Locally connected layers,[55] will be

1
2
3 1 used to build 2D feature maps from the global shape, clinical and demographics information,
4
5
6 2 generating feature maps that can appropriately model the effect of this information in different regions
7
8
9 3 of the bifurcation. Convolutional neural network layers are used to predict haemodynamic metrics,
10
11
12 4 vessel response and expected disease development over the surface of the coronary vessels. The
13
14
15 5 deep learning model will be used to generate pixelwise predictions, which can be correlated against
16
17
18 6 the follow-up imaging to investigate localised plaque growth and progression based on
19
20
21 7 haemodynamic descriptors, as well as overall risk metrics which will be evaluated versus the all-cause
22
23
24 8 mortality. Additionally, random forest models [56] will be trained on the same data to investigate
25
26
27 9 performance of traditional machine learning methods versus deep learning, and potentially provide a
28
29
30 10 more interpretable risk model. The performance of the trained models will be evaluated and compared
31
32
33 11 using 10-fold cross validation. The Area Under Receiver Operating Characteristics Curve (AUC)[57]
34
35
36 12 metric will be used to compare predictions of the machine learning models to existing literature on
37
38
39 13 machine learning risk models [41] as well as traditional models.. This allows for easy comparisons
40
41
42 14 against other models as it is commonly reported and simple to interpret.
43
44
45

16 **Statistical analysis plan**

17 Additional statistical analysis will explore the relationships between our developed non-traditional
18 potential risk factors and clinical endpoint data. Continuous variables will be presented as mean (\pm
19 standard deviation) and categorical variables as proportions (%). Comparisons between groups will
20 be performed using independent student *t*-tests with Bonferroni correction for continuous variables

1 and χ^2 or Fisher's exact tests for continuous variables. Univariate and multivariate analyses will be
2 performed using Mantel-Haenszel logistic regression. Univariate variables with $p < 0.10$ will be included
3 in the multivariate analysis. The discriminative performance of the multivariable model will be
4 assessed using Harrell's c-statistic. Comparisons between the multivariable models will be assessed
5 using net reclassification index. A two-tailed p value < 0.05 with Bonferroni correction will be
6 considered significant. Our sample size of 1,000 will be sufficient because we estimated that we will
7 need a sample size of at least 445 patients to show that a c-statistic of 0.80 is significantly different
8 from the null hypothesis (assuming a c-statistic of 0.71 for the Framingham risk score), considering a
9 p-value of 0.05, power of 80% and event rate of 20%.

10

11 **Ethics and dissemination**

12 **The study protocol has been approved by the St Vincent's Hospital Human Research Ethics**
13 **Committee, Sydney – 2020/ETH02127 and the NSW Population and Health Service Research Ethics**
14 **Committee – 2021/ETH00990. The committee granted a waiver of the usual requirement of consent.**
15 **The project outcomes will be published in peer-reviewed and biomedical journals, scientific conferences**
16 **and as a higher degree research thesis. Patient confidentiality will be maintained by not including any**
17 **individually identifying information in publications. Non-identifiable data (statistical shape analyses and**
18 **haemodynamic simulations) will be shared with other researchers on the Coronary Atlas website. We**
19 **will not share any raw imaging data or unit record data with other researchers. DISCUSSION**

20

1
2
3 1 The role of adverse anatomical features in CAD risk remains unclear. Several studies have suggested
4
5
6 2 that bifurcation angle (Figure 2), defined as the angle between the daughter vessels after branching, is
7
8
9 3 a geometric risk factor for atherosclerosis.[19-21] However several later studies have shown that
10
11
12 4 bifurcation angle alone has minimal haemodynamic impact,[22-24] and that in fact the combination with
13
14
15 5 other shape characteristics (inflow angle, diameter and tortuosity) determine either a stronger or
16
17
18 6 mitigating effects on WSS. Others showed that vessel tortuosity,[23, 58] curvature,[24] and cross-
19
20
21 7 sectional area,[25, 26] may also play a role in local WSS development.[59] Overall, inconsistent
22
23
24 8 observations of geometric parameters in the literature suggest that anatomical risk factors remain little
25
26
27 9 understood, possibly due to their complex three-dimensional structure with interdependent
28
29
30 10 haemodynamic impact of several shape characteristics.[22]

31
32 11 Current absolute cardiovascular disease risk calculators in Australia are based on the Framingham risk
33
34
35 12 equation. [1] The model was developed to estimate an individual's five- and ten-year risk of
36
37
38 13 cardiovascular disease using a point-score algorithm including clinical risk factors (age, female sex,
39
40
41 14 systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes, and
42
43
44 15 electrocardiographic left ventricular hypertrophy). A recent meta-analysis of validation studies
45
46
47 16 evaluating the discriminative performance of the ten-year Framingham risk model found a pooled c-
48
49
50 17 statistic of 0.68 (95% CI 0.66 to 0.69) to 0.71 (95% CI 0.66 to 0.76).[5] From this modest discriminative
51
52
53 18 power, it becomes clear that the adverse cardiovascular events in one-of-four patients remain
54
55
56 19 unexplainable by the Framingham risk model, and that there is an urgent need to identify the remaining
57
58
59 20 risk factors for atherosclerosis. Indeed, a recent study using two large multi-centre Australian registries
60

1 showed that a substantial and increasing proportion of STEMI patients were individuals without
2 SMuRFs.[7] Moreover, 19% of patients were SMuRF-less, and this proportion increased from 14% to
3 23% during the study period. Concerningly, SMuRF-less patients had a higher in-hospital mortality rate
4 than patients with one or more SMuRF (6% versus 4%, $p=0.032$). It is likely that advanced image-
5 derived patient-specific information can account for some of these unexplained susceptibilities to
6 atherosclerosis in SMuRF-less individuals, and even be detected through imaging analysis.

7 CTCA technology already has a well-established role in the field of preventive cardiology. The Scottish
8 Computed Tomography of the Heart (SCOT-HEART) and Prospective Multicentre Imaging Study for
9 Evaluation of Chest Pain (PROMISE) trials were landmark studies, showing that CTCA-guided strategy
10 improves clinical outcomes in symptomatic patients with stable angina, increasing the diagnostic
11 certainty and frequency of CAD and the subsequent implementation of appropriate secondary
12 prevention and revascularisation.[60-62]

13 Still, the role of CTCA in asymptomatic patients with CAD remains somewhat uncertain. The Factor-64
14 trial has been the only randomised clinical trial to date to assess the prognostic value of routine CTCA
15 screening for CAD in this population.[63] More than 900 high-risk diabetic patients were randomised for
16 either CTCA or standard national guidelines-based optimal medical care, whereby, at four years follow-
17 up, there was no difference in the primary outcome of death, non-fatal MI or unstable angina requiring
18 hospitalisation. However, the trial was not adequately powered due to a lower than anticipated event
19 rate. Similarly, a meta-analysis evaluating the prognostic value of CTCA in more than 6,000 diabetic
20 patients, whereby two-thirds were asymptomatic, observed a higher hazard-ratio for obstructive CAD if

1
2
3 1 revascularisation was included as an endpoint - meaning that CTCA in some of this population could
4
5
6 2 have important prognostic implications.[64] Still, registry studies in broader asymptomatic populations
7
8
9 3 have also suggested that CTCA findings (location, severity and plaque composition) have incremental
10
11
12 4 prognostic utility beyond traditional risk factors alone.[65]
13
14
15 5 Several studies have demonstrated the predictive value of the coronary artery calcium score in addition
16
17
18 6 to traditional risk factors for CAD.[27, 28] The South Bay Heart Watch Study found that a calcium score
19
20
21 7 higher than 300 combined with the Framingham risk score significantly improved the discriminative
22
23
24 8 ability (c-statistic 0.68 vs 0.63, $p < 0.001$).[27] Similarly, the St. Francis Heart Study showed that coronary
25
26
27 9 artery calcium score was superior to the Framingham risk index for the prediction of atherosclerotic
28
29
30 10 cardiovascular disease events (c-statistic 0.79 vs 0.69, $p = 0.0006$).[28] It should also be noted that the
31
32
33 11 distribution of calcium was found to be more significant in predicting cardiovascular events than the
34
35
36 12 calcium score alone.[66, 67] Specifically, in more than 1,200 participants from the Offspring and Third
37
38
39 13 Generation cohorts of the Framingham Heart Study, it was shown that the number of coronary arteries
40
41
42 14 with calcium, and especially the presence of calcium in the proximal dominant coronary artery,
43
44
45 15 independently predicted coronary heart disease after adjustment for the Framingham risk score and
46
47
48 16 coronary artery calcium score.[67] The addition of calcium distribution improved the discriminatory
49
50
51 17 capacity of the multivariable model with the Framingham risk score and calcium score for coronary heart
52
53
54 18 disease events (c-statistic 0.79 to 0.80 vs 0.77, relative integrated discriminatory index 0.14). This study
55
56
57 19 confirmed the observations of an earlier analysis of 3,262 participants in the MESA (Multi-Ethnic Study
58
59
60 20 of Atherosclerosis) cohort, which showed that diffusely distributed calcium, as assessed by the number

1
2
3 1 of coronary arteries with calcified plaque, significantly improved the capacity to predict cardiovascular
4
5
6 2 events beyond the calcium score (c-statistic 0.67 vs 0.64, $p=0.0001$).[66]
7
8
9 3 Beyond calcium scoring, machine learning-based approaches have been the latest focus of the field
10
11
12 4 and enable the effective processing of even very large datasets with promising potential for cloud-based
13
14
15 5 clinical integration. However, key challenges in such an undertaking are the comparability, and
16
17
18 6 reproducibility across different clinical cohorts, imaging specifications and scan protocols, and of course
19
20
21 7 most importantly, the assurances of patient confidentiality and data security.[68]
22
23
24 8 Machine learning methods have been predominantly used in conjunction with medical images and other
25
26
27 9 medical data [69, 70] to train multiple non-linear classifiers (support vector machine, logistic regression,
28
29
30 10 tree-based models, deep neural networks) to predict mortality rates.[71, 72] CTCA applied deep
31
32
33 11 learning applications allowed detection and quantification of calcified plaques,[73-75] as well as
34
35
36 12 correlating calcium score to mortality.[41] Standard blood test results are also often included in machine
37
38
39 13 learning models for risk stratification.[76]
40
41
42 14 Whilst promising, these machine learning methods are not matured enough to replace the traditional
43
44
45 15 Framingham score,[77] and further research and exploration of the field is required. Existing machine
46
47
48 16 learning methods usually rely on generalised adverse features for CAD risk prediction which may lead
49
50
51 17 to low reproducibility.[68] Additionally, current machine learning approaches,[37-41, 71, 72] focus
52
53
54 18 primarily on overall risk factors. This does not consider the observed trends that particular locations
55
56
57 19 within the coronary tree, for example bifurcations,[10] are at significantly higher risk of disease. More
58
59
60 20 advanced comprehensive machine learning risk prediction and intervention recommendation systems

1
2
3 1 are at an early stage of algorithm development, and to our knowledge there is no prior work on a
4
5
6 2 comprehensive machine learning incorporating haemodynamic information within CAD risk models.
7
8

9 3

10
11
12 4 In summary, there is a tremendous opportunity to improve the accuracy of CAD risk prediction by
13
14
15 5 integrating additional patient-specific anatomical risk with traditional risk models. We hope that
16
17
18 6 incorporating haemodynamic metrics, which can provide significantly more granular information beyond
19
20
21 7 the traditionally used models can better predict the expected vessel response and future outcomes.
22

23
24 8 The use of anatomical surrogate markers for CAD will enable us to extend the application of CTCA-
25
26
27 9 guided risk prediction from diseased individuals to normal populations without atherosclerosis, generate
28
29
30 10 new understandings of disease mechanisms and its development in individuals, and open future
31
32
33 11 pathways for application to imaging modalities without or with reduced radiation. This unprecedented
34
35
36 12 opportunity has been underpinned by advanced imaging analysis, sophisticated computational
37
38
39 13 technology, and state-of-the-art machine learning algorithms, which offer a fast and practical approach
40
41
42 14 for CAD risk assessment in large-scale population studies. Understanding the mechanism of personal
43
44
45 15 susceptibility to atherosclerosis opens up the opportunity for early implementation of targeted therapies
46
47
48 16 and may be a key in addressing the growing burden of CAD, especially in individuals without SMuRFs.
49

50 17

51
52
53 18

54
55
56 19

1 REFERENCES

1. Anderson, K.M., et al., *An updated coronary risk profile. A statement for health professionals.* Circulation, 1991. **83**(1): p. 356-62.
2. *World health statistics 2019: monitoring health for the SDGs, sustainable development goals.* 2019, World Health Organization: Geneva.
3. *Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).* Lancet, 1994. **344**(8934): p. 1383-9.
4. Cannon, C.P., et al., *Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes.* N Engl J Med, 2015. **372**(25): p. 2387-97.
5. Damen, J.A., et al., *Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis.* BMC Med, 2019. **17**(1): p. 109.
6. Friedman, M.H., et al., *Arterial geometry affects hemodynamics. A potential risk factor for atherosclerosis.* Atherosclerosis, 1983. **46**(2): p. 225-31.
7. Vernon, S.T., et al., *ST-Segment-Elevation Myocardial Infarction (STEMI) Patients Without Standard Modifiable Cardiovascular Risk Factors-How Common Are They, and What Are Their Outcomes?* J Am Heart Assoc, 2019. **8**(21): p. e013296.
8. Pylypchuk, R., et al., *Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study.* Lancet, 2018. **391**(10133): p. 1897-1907.
9. Hippisley-Cox, J., C. Coupland, and P. Brindle, *Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study.* BMJ, 2017. **357**: p. j2099.
10. Morbiducci, U., et al., *Atherosclerosis at arterial bifurcations: evidence for the role of haemodynamics and geometry.* Thromb Haemost, 2016. **115**(3): p. 484-92.
11. Medrano-Gracia, P., et al., *A computational atlas of normal coronary artery anatomy.* EuroIntervention, 2016. **12**(7): p. 845-54.
12. Antoniadis, A.P., et al., *Biomechanical Modeling to Improve Coronary Artery Bifurcation Stenting: Expert Review Document on Techniques and Clinical Implementation.* JACC Cardiovasc Interv, 2015. **8**(10): p. 1281-96.
13. Caro, C.G., J.M. Fitz-Gerald, and R.C. Schroter, *Atheroma and arterial wall shear. Observation, correlation and proposal of a shear dependent mass transfer mechanism for atherogenesis.* Proc R Soc Lond B Biol Sci, 1971. **177**(1046): p. 109-59.
14. Caro, C.G., *Discovery of the role of wall shear in atherosclerosis.* Arterioscler Thromb Vasc Biol, 2009. **29**(2): p. 158-61.
15. Nerem, R.M., *Vascular fluid mechanics, the arterial wall, and atherosclerosis.* J Biomech Eng, 1992. **114**(3): p. 274-82.
16. Malek, A.M., S.L. Alper, and S. Izumo, *Hemodynamic shear stress and its role in atherosclerosis.* JAMA, 1999. **282**(21): p. 2035-42.
17. Friedman, M.H., et al., *Correlation between intimal thickness and fluid shear in human arteries.* Atherosclerosis, 1981. **39**(3): p. 425-36.
18. Dolan, J.M., J. Kolega, and H. Meng, *High wall shear stress and spatial gradients in vascular pathology: a review.* Ann Biomed Eng, 2013. **41**(7): p. 1411-27.
19. Chaichana, T., Z. Sun, and J. Jewkes, *Computation of hemodynamics in the left coronary artery with variable angulations.* J Biomech, 2011. **44**(10): p. 1869-78.
20. Dong, J., et al., *Fluid-structure interaction analysis of the left coronary artery with variable angulation.* Comput Methods Biomech Biomed Engin, 2015. **18**(14): p. 1500-8.
21. Ikeda, U., et al., *Stenotic lesions and the bifurcation angle of coronary arteries in the young.* Jpn Heart J, 1991. **32**(5): p. 627-33.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1 22. Beier, S., et al., *Impact of bifurcation angle and other anatomical characteristics on blood flow - A computational study of non-stented and stented coronary arteries*. J Biomech, 2016. **49**(9): p. 1570-1582.
- 2 23. Malvè, M., et al., *Tortuosity of coronary bifurcation as a potential local risk factor for atherosclerosis: CFD steady state study based on in vivo dynamic CT measurements*. Ann Biomed Eng, 2015. **43**(1): p. 82-93.
- 3 24. Chiastra, C., et al., *Healthy and diseased coronary bifurcation geometries influence near-wall and intravascular flow: A computational exploration of the hemodynamic risk*. J Biomech, 2017. **58**: p. 79-88.
- 4 25. Pinho, N., et al., *Correlation between geometric parameters of the left coronary artery and hemodynamic descriptors of atherosclerosis: FSI and statistical study*. Med Biol Eng Comput, 2019. **57**(3): p. 715-729.
- 5 26. Pinho, N., et al., *The Impact of the Right Coronary Artery Geometric Parameters on Hemodynamic Performance*. Cardiovasc Eng Technol, 2019. **10**(2): p. 257-270.
- 6 27. Greenland, P., et al., *Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals*. JAMA, 2004. **291**(2): p. 210-5.
- 7 28. Arad, Y., et al., *Rationale and design of the St. Francis Heart Study: a randomized clinical trial of atorvastatin plus antioxidants in asymptomatic persons with elevated coronary calcification*. Control Clin Trials, 2001. **22**(5): p. 553-72.
- 8 29. Liang, L., et al., *A machine learning approach to investigate the relationship between shape features and numerically predicted risk of ascending aortic aneurysm*. Biomech Model Mechanobiol, 2017. **16**(5): p. 1519-1533.
- 9 30. Singh, A. and J.V. Guttag. *A comparison of non-symmetric entropy-based classification trees and support vector machine for cardiovascular risk stratification*. in *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. 2011. IEEE.
- 10 31. Khateeb, N. and M. Usman. *Efficient heart disease prediction system using K-nearest neighbor classification technique*. in *Proceedings of the international conference on big data and internet of thing*. 2017.
- 11 32. Colombet, I., et al. *Models to predict cardiovascular risk: comparison of CART, multilayer perceptron and logistic regression*. in *Proceedings of the AMIA Symposium*. 2000. American Medical Informatics Association.
- 12 33. Krittanawong, C., et al., *Machine learning and deep learning to predict mortality in patients with spontaneous coronary artery dissection*. Scientific reports, 2021. **11**(1): p. 1-10.
- 13 34. Sajeev, S., et al., *Deep Learning to improve heart disease risk prediction*, in *Machine Learning and Medical Engineering for Cardiovascular Health and Intravascular Imaging and Computer Assisted Stenting*. 2019, Springer. p. 96-103.
- 14 35. Bharti, R., et al., *Prediction of heart disease using a combination of machine learning and deep learning*. Computational intelligence and neuroscience, 2021. **2021**.
- 15 36. Tison, G.H., et al., *Cardiovascular risk stratification using off-the-shelf wearables and a multi-task deep learning algorithm*. Circulation, 2017. **136**(suppl_1): p. A21042-A21042.
- 16 37. Chao, H., et al., *Deep learning predicts cardiovascular disease risks from lung cancer screening low dose computed tomography*. Nature communications, 2021. **12**(1): p. 1-10.
- 17 38. Poplin, R., et al., *Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning*. Nature Biomedical Engineering, 2018. **2**(3): p. 158-164.
- 18 39. Cheung, C.Y., et al., *A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre*. Nature biomedical engineering, 2021. **5**(6): p. 498-508.
- 19 40. Huang, W., et al., *Application of ensemble machine learning algorithms on lifestyle factors and wearables for cardiovascular risk prediction*. Scientific Reports, 2022. **12**(1): p. 1-12.
- 20 41. Zeleznik, R., et al., *Deep convolutional neural networks to predict cardiovascular risk from computed tomography*. Nature communications, 2021. **12**(1): p. 1-9.

- 1
2
3 1 42. Beier, S. *The Coronary Atlas*. 2020 [13/09/2020]; Available from:
4 2 <https://www.coronaryatlas.org/>.
5 3 43. Medrano-Gracia, P., et al., *A Study of Coronary Bifurcation Shape in a Normal Population*. J
6 4 Cardiovasc Transl Res, 2017. **10**(1): p. 82-90.
7 5 44. Medrano-Gracia, P., et al., *Construction of a coronary artery atlas from CT angiography*. Med
8 6 Image Comput Comput Assist Interv, 2014. **17**(Pt 2): p. 513-20.
9 7 45. Gharleghi, R., et al. *Deep Learning for Time Averaged Wall Shear Stress Prediction in Left*
10 8 *Main Coronary Bifurcations*. in *2020 IEEE 17th International Symposium on Biomedical*
11 9 *Imaging (ISBI)*. 2020. IEEE.
12 10 46. Austen, W.G., et al., *A reporting system on patients evaluated for coronary artery disease.*
13 11 *Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on*
14 12 *Cardiovascular Surgery, American Heart Association*. Circulation, 1975. **51**(4 Suppl): p. 5-40.
15 13 47. Ronneberger, O., P. Fischer, and T. Brox. *U-net: Convolutional networks for biomedical image*
16 14 *segmentation*. in *International Conference on Medical image computing and computer-*
17 15 *assisted intervention*. 2015. Springer.
18 16 48. Isensee, F., et al., *nnU-Net: a self-configuring method for deep learning-based biomedical*
19 17 *image segmentation*. Nature methods, 2021. **18**(2): p. 203-211.
20 18 49. Gharleghi, R., et al., *Automated Segmentation of Normal and Diseased Coronary Arteries-The*
21 19 *ASOCA Challenge*. Computerized Medical Imaging and Graphics, 2022: p. 102049.
22 20 50. Antiga, L. and D.A.J.I.t.o.m.i. Steinman, *Robust and objective decomposition and mapping of*
23 21 *bifurcating vessels*. 2004. **23**(6): p. 704-713.
24 22 51. Kashyap, V., et al., *Accuracy of vascular tortuosity measures using computational modelling*.
25 23 *Scientific reports*, 2022. **12**(1): p. 1-10.
26 24 52. Crenshaw, H.C. and L.J.B.o.m.b. Edelstein-Keshet, *Orientation by helical motion—II.*
27 25 *Changing the direction of the axis of motion*. 1993. **55**(1): p. 213-230.
28 26 53. Razavi, A., E. Shirani, and M.J.J.o.b. Sadeghi, *Numerical simulation of blood pulsatile flow in a*
29 27 *stenosed carotid artery using different rheological models*. 2011. **44**(11): p. 2021-2030.
30 28 54. Gijssen, F., et al., *Expert recommendations on the assessment of wall shear stress in human*
31 29 *coronary arteries: existing methodologies, technical considerations, and clinical applications*.
32 30 2019. **40**(41): p. 3421-3433.
33 31 55. Chen, Y.-h., et al., *Locally-connected and convolutional neural networks for small footprint*
34 32 *speaker recognition*. 2015.
35 33 56. Boulesteix, A.L., et al., *Overview of random forest methodology and practical guidance with*
36 34 *emphasis on computational biology and bioinformatics*. Wiley Interdisciplinary Reviews: Data
37 35 *Mining and Knowledge Discovery*, 2012. **2**(6): p. 493-507.
38 36 57. Zou, K.H., A.J. O'Malley, and L. Mauri, *Receiver-operating characteristic analysis for*
39 37 *evaluating diagnostic tests and predictive models*. Circulation, 2007. **115**(5): p. 654-657.
40 38 58. Buradi, A. and A. Mahalingam, *Impact of coronary tortuosity on the artery hemodynamics*.
41 39 *Biocybernetics and Biomedical Engineering*, 2020. **40**(1): p. 126-147.
42 40 59. Doutel, E., et al., *Link between deviations from Murray's Law and occurrence of low wall*
43 41 *shear stress regions in the left coronary artery*. Journal of theoretical biology, 2016. **402**: p.
44 42 89-99.
45 43 60. investigators, S.-H., *CT coronary angiography in patients with suspected angina due to*
46 44 *coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial*.
47 45 *Lancet*, 2015. **385**(9985): p. 2383-91.
48 46 61. Newby, D.E., et al., *Coronary CT Angiography and 5-Year Risk of Myocardial Infarction*. N
49 47 *Engl J Med*, 2018. **379**(10): p. 924-933.
50 48 62. Douglas, P.S., et al., *Outcomes of anatomical versus functional testing for coronary artery*
51 49 *disease*. N Engl J Med, 2015. **372**(14): p. 1291-300.
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

63. Muhlestein, J.B., et al., *Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial*. JAMA, 2014. **312**(21): p. 2234-43.
64. Celeng, C., et al., *Prognostic Value of Coronary Computed Tomography Angiography in Patients With Diabetes: A Meta-analysis*. Diabetes Care, 2016. **39**(7): p. 1274-80.
65. Cho, I., et al., *Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study*. Eur Heart J, 2018. **39**(11): p. 934-941.
66. Blaha, M.J., et al., *Improving the CAC Score by Addition of Regional Measures of Calcium Distribution: Multi-Ethnic Study of Atherosclerosis*. JACC Cardiovasc Imaging, 2016. **9**(12): p. 1407-1416.
67. Ferencik, M., et al., *Coronary Artery Calcium Distribution Is an Independent Predictor of Incident Major Coronary Heart Disease Events: Results From the Framingham Heart Study*. Circ Cardiovasc Imaging, 2017. **10**(10).
68. Benjamin, M.M. and M.G. Rabbat, *Machine learning-based advances in coronary computed tomography angiography*. Quantitative Imaging in Medicine and Surgery, 2021. **11**(6): p. 2208.
69. Kadem, M., et al., *Hemodynamic modeling, medical imaging, and machine learning and their applications to cardiovascular interventions*. IEEE Reviews in Biomedical Engineering, 2022.
70. Corrigan, F.E., et al., *Imaging for predicting, detecting, and managing complications after transcatheter aortic valve replacement*. JACC: Cardiovascular Imaging, 2019. **12**(5): p. 904-920.
71. Samad, M.D., et al., *Predicting survival from large echocardiography and electronic health record datasets: optimization with machine learning*. JACC: Cardiovascular Imaging, 2019. **12**(4): p. 681-689.
72. Ulloa Cerna, A.E., et al., *Deep-learning-assisted analysis of echocardiographic videos improves predictions of all-cause mortality*. Nature Biomedical Engineering, 2021. **5**(6): p. 546-554.
73. Kurkure, U., et al., *A supervised classification-based method for coronary calcium detection in non-contrast CT*. The international journal of cardiovascular imaging, 2010. **26**(7): p. 817-828.
74. Lessmann, N., et al., *Automatic calcium scoring in low-dose chest CT using deep neural networks with dilated convolutions*. IEEE transactions on medical imaging, 2017. **37**(2): p. 615-625.
75. Martin, S.S., et al., *Evaluation of a deep learning-based automated CT coronary artery calcium scoring algorithm*. Cardiovascular Imaging, 2020. **13**(2_Part_1): p. 524-526.
76. Li, D., et al., *Machine learning-aided risk stratification system for the prediction of coronary artery disease*. International Journal of Cardiology, 2021. **326**: p. 30-34.
77. Tesche, C. and V. Brandt, *Calling for a New Framingham: Machine Learning in Cardiovascular Risk Assessment—The Key for Improved Outcome Prediction?* 2021, American College of Cardiology Foundation Washington DC. p. 626-628.

1
2
3 **1 AUTHORS' CONTRIBUTIONS**
4
5

6 2 DA contributed to the study design, drafting the manuscript and revising it critically for important
7
8
9 3 intellectual content. RG, SZ and DM contributed to revising the manuscript. LJ, AS and SO
10
11
12 4 contributed to final approval of the version to be published. SB has supervised the process and
13
14
15 5 assisted in the manuscript draft and revisions. All authors contributed to the study design and
16
17
18 6 conception, revising the manuscript critically for important intellectual content and final approval of the
19
20
21 7 version to be published.
22
23
24 8

25
26 **9 ACKNOWLEDGEMENTS**
27
28

29 10 Nil
30
31
32 11

33
34
35 **12 FUNDING**
36
37

38 13 DA is supported by an Australian Government research training program scholarship. Award/grant
39
40
41 14 number not applicable. This research is supported by NHMRC Ideas grant (2012474) and the NSW
42
43
44 15 Cardiovascular Research Capacity Program Early-Mid Career (EMC) Researcher Grant (EMC78).
45
46
47 16

48
49 **17 COMPETING INTERESTS**
50
51

52 18 None declared
53
54
55 19
56
57
58 20
59
60

1
2
3
4 1
5
6 2
7
8
9 3
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

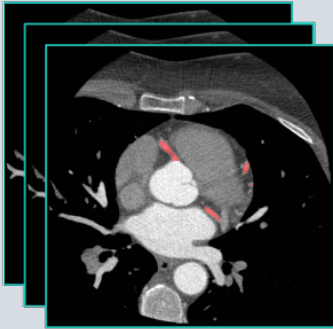
1
2
3 **1 FIGURE LEGENDS**
4
5

6 **2 Figure 1:** GeoCAD study flowchart. BMI = body mass index, BP = blood pressure, CACS = coronary
7
8 artery calcium score, CAD = coronary artery disease, CHeReL = Centre for Health Record Linkage,
9
10
11
12 **4** CTCA = computed tomography coronary angiography, LDL = low-density lipoprotein, SMI = Spectrum
13
14
15 **5** Medical Imaging, SMuRF = standard modifiable risk factor,
16
17

18 **6 Figure 2:** Three-dimensional representation of candidate anatomical biomarkers: 1) bifurcation angle
19
20
21 **7** (Angle B), defined as the angle between the daughter vessels after branching, 2) inflow angle, defined
22
23
24 **8** as the angle with which the proximal vessel enters the bifurcation plane, 3) diameter, 4) curvature
25
26
27 **9** (1/radius) and 5) tortuosity (length/diameter)
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

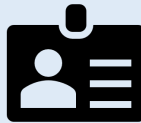
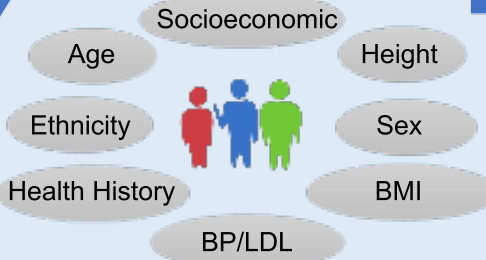
Study Population

Suitable adult patients with suspected CAD in the CTCA database at SMI are included (n=1,000).



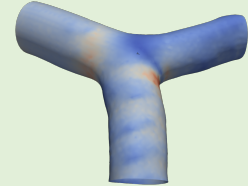
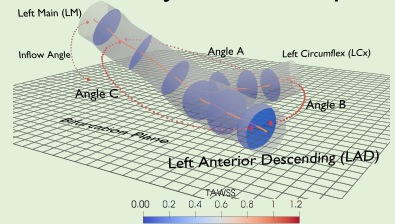
Data Collection And Linkage

Demographics, SMuRFs, past medical history, medications and SMI data are linked to clinical outcomes using CHeReL.



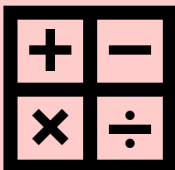
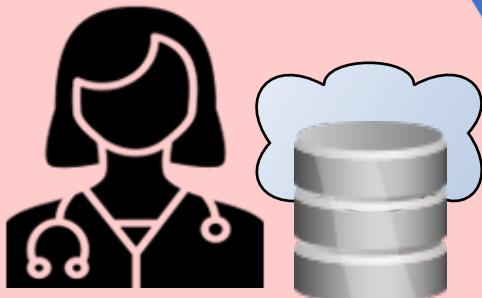
Coronary Atlas

Automated large-scale image analysis, geometric assessment and haemodynamic computation.



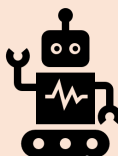
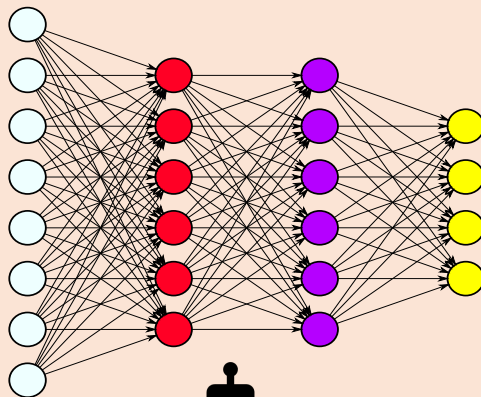
GeoCAD Score

Novel anatomical biomarkers are incorporated with clinical risk factors and CACS to improve coronary risk profiling.



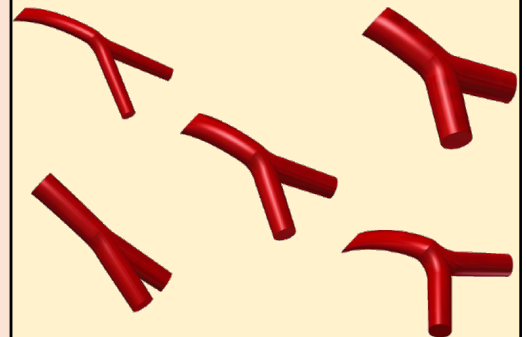
Machine Learning

Raw SMI data is directly linked with clinical outcomes using a state-of-the-art machine learning algorithm trained by the Coronary Atlas and anatomical biomarkers.

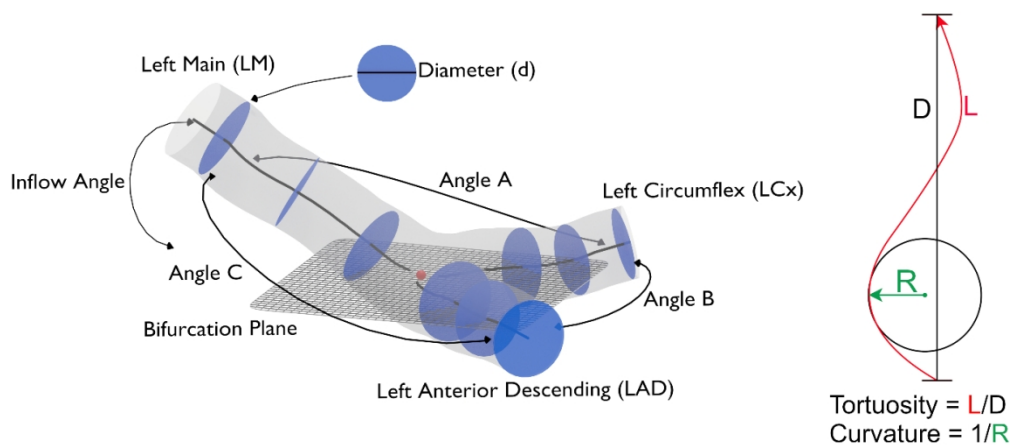


Statistical Shape Analysis

Shape features from the data are correlated with clinical outcomes to extract novel anatomical biomarkers.



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53



Three-dimensional representation of candidate anatomical biomarkers: 1) bifurcation angle (Angle B), defined as the angle between the daughter vessels after branching, 2) inflow angle, defined as the angle with which the proximal vessel enters the bifurcation plane, 3) diameter, 4) curvature (1/radius) and 5) tortuosity (length/diameter)

402x176mm (87 x 87 DPI)

Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPOD reporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

	Reporting Item	Page Number
Title		
	#1 Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1

Abstract

1			
2			
3			
4			
5			
6			
7			
8			
9	Introduction		
10			
11			
12		#2	2
13		Provide a summary of objectives, study design, setting,	
14		participants, sample size, predictors, outcome, statistical	
15		analysis, results, and conclusions.	
16			
17			
18			
19			
20			
21			
22		#3a	5
23		Explain the medical context (including whether diagnostic or	
24		prognostic) and rationale for developing or validating the	
25		multivariable prediction model, including references to	
26		existing models.	
27			
28			
29			
30			
31		#3b	9
32		Specify the objectives, including whether the study describes	
33		the development or validation of the model or both.	
34			
35			
36			
37	Methods		
38			
39			
40			
41			
42			
43			
44	Source of data	#4a	9
45		Describe the study design or source of data (e.g.,	
46		randomized trial, cohort, or registry data), separately for the	
47		development and validation data sets, if applicable.	
48			
49			
50			
51	Source of data	#4b	1
52		Specify the key study dates, including start of accrual; end of	
53		accrual; and, if applicable, end of follow-up.	
54			
55			
56	Participants	#5a	9
57		Specify key elements of the study setting (e.g., primary care,	
58		secondary care, general population) including number and	
59		location of centres.	
60			
	Participants	#5b	10
		Describe eligibility criteria for participants.	
	Participants	#5c	n/a
		Give details of treatments received, if relevant	

1	Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	11
2				
3				
4				
5				
6	Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	11
7				
8				
9				
10				
11				
12	Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	10
13				
14				
15				
16				
17				
18				
19	Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	11
20				
21				
22				
23				
24				
25	Sample size	#8	Explain how the study size was arrived at.	9, 10, 13
26				
27				
28	Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	n/a
29				
30				
31				
32				
33				
34				
35	Statistical	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	12, 13
36	analysis methods			
37				
38				
39				
40				
41	Statistical	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	12, 13
42	analysis methods			
43				
44				
45				
46				
47				
48	Statistical	#10c	If you are validating a prediction model, describe how the predictions were calculated.	n/a
49	analysis methods			
50				
51				
52				
53				
54	Statistical	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	12, 13
55	analysis methods			
56				
57				
58				
59				
60				

1	Statistical	#10e	If you are validating a prediction model, describe any model	n/a
2				
3	analysis methods		updating (e.g., recalibration) arising from the validation, if	
4			done	
5				
6				
7				
8				
9	Risk groups	#11	Provide details on how risk groups were created, if done.	n/a
10				
11				
12	Development vs.	#12	For validation, identify any differences from the development	n/a
13	validation		data in setting, eligibility criteria, outcome, and predictors.	
14				
15				
16				
17	Results			
18				
19				
20	Participants	#13a	Describe the flow of participants through the study, including	Figure 2
21			the number of participants with and without the outcome	
22			and, if applicable, a summary of the follow-up time. A	
23			diagram may be helpful.	
24				
25				
26				
27				
28				
29				
30	Participants	#13b	Describe the characteristics of the participants (basic	9, 10
31			demographics, clinical features, available predictors),	
32			including the number of participants with missing data for	
33			predictors and outcome.	
34				
35				
36				
37				
38				
39				
40	Participants	#13c	For validation, show a comparison with the development	n/a
41			data of the distribution of important variables (demographics,	
42			predictors and outcome).	
43				
44				
45				
46				
47				
48	Model	#14a	If developing a model, specify the number of participants	n/a
49			and outcome events in each analysis.	
50	development			
51				
52				
53	Model	#14b	If developing a model, report the unadjusted association, if	n/a
54			calculated between each candidate predictor and outcome.	
55	development			
56				
57				
58				
59				
60				

1	Model	#15a	If developing a model, present the full prediction model to	n/a
2				
3	specification		allow predictions for individuals (i.e., all regression	
4			coefficients, and model intercept or baseline survival at a	
5			given time point).	
6				
7				
8				
9				
10				
11	Model	#15b	If developing a prediction model, explain how to the use it.	n/a
12				
13	specification			
14				
15				
16	Model	#16	Report performance measures (with CIs) for the prediction	n/a
17			model.	
18	performance			
19				
20				
21				
22	Model-updating	#17	If validating a model, report the results from any model	n/a
23			updating, if done (i.e., model specification, model	
24			performance).	
25				
26				
27				
28				
29	Discussion			
30				
31				
32	Limitations	#18	Discuss any limitations of the study (such as	3
33			nonrepresentative sample, few events per predictor, missing	
34			data).	
35				
36				
37				
38				
39				
40	Interpretation	#19a	For validation, discuss the results with reference to	n/a
41			performance in the development data, and any other	
42			validation data	
43				
44				
45				
46				
47	Interpretation	#19b	Give an overall interpretation of the results, considering	n/a
48			objectives, limitations, results from similar studies, and other	
49			relevant evidence.	
50				
51				
52				
53				
54				
55	Implications	#20	Discuss the potential clinical use of the model and	3
56			implications for future research	
57				
58				
59				
60				

1 **Other information**
2
3

4	Supplementary	#21	Provide information about the availability of supplementary	n/a
5				
6	information		resources, such as study protocol, Web calculator, and data	
7			sets.	
8				
9				
10				
11				
12	Funding	#22	Give the source of funding and the role of the funders for the	25
13				
14			present study.	
15				
16				

17 The TRIPOD checklist is distributed under the terms of the Creative Commons Attribution License
18 CC-BY. This checklist was completed on 23. June 2021 using <https://www.goodreports.org/>, a tool
19
20 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60