Accepted Manuscript

Ranking of stroke and cardiovascular risk factors for an optimal risk calculator design: Logistic regression approach

Elisa Cuadrado-Godia, Ankush D. Jamthikar, Deep Gupta, Narendra N. Khanna, Tadashi Araki, Md Maniruzzaman, Luca Saba, Andrew Nicolaides, Aditya Sharma, Tomaz Omerzu, Harman S. Suri, Ajay Gupta, Sophie Mavrogeni, Monika Turk, John R. Laird, Athanasios Protogerou, Petros Sfikakis, George D. Kitas, Vijay Viswanathan, Jasjit S. Suri

PII: S0010-4825(19)30099-X

DOI: https://doi.org/10.1016/j.compbiomed.2019.03.020

Reference: CBM 3248

To appear in: *Computers in Biology and Medicine*

Received Date: 23 January 2019

Revised Date: 21 March 2019

Accepted Date: 21 March 2019

Please cite this article as: E. Cuadrado-Godia, A.D. Jamthikar, D. Gupta, N.N. Khanna, T. Araki, M. Maniruzzaman, L. Saba, A. Nicolaides, A. Sharma, T. Omerzu, H.S. Suri, A. Gupta, S. Mavrogeni, M. Turk, J.R. Laird, A. Protogerou, P. Sfikakis, G.D. Kitas, V. Viswanathan, J.S. Suri, Ranking of stroke and cardiovascular risk factors for an optimal risk calculator design: Logistic regression approach, *Computers in Biology and Medicine* (2019), doi: https://doi.org/10.1016/j.compbiomed.2019.03.020.

Ranking of Stroke and Cardiovascular Risk Factors for an Optimal Risk Calculator Design: Logistic Regression Approach

Elisa Cuadrado-Godia, MD,[a] **Ankush D. Jamthikar,** MTech,[b] **Deep Gupta,** PhD,[b] **Narendra N. Khanna,** MD, DM, FACC,[c] **Tadashi Araki**, MD,[d] **Md. Maniruzzaman,** M.Sc,[e] **Luca Saba,** MD,[f] **Andrew Nicolaides,** MS, PhD, FRCS,[g] **Aditya Sharma,** MD,[h] **Tomaz Omerzu,** MD,[i] **Harman S. Suri**,[j] **Ajay Gupta,** MD, MS,[k] **Sophie Mavrogeni,** MD PhD FESC,[l] **Monika Turk,** MD, PhD,[m] **John R. Laird,** MD, FACC, FACP,[n] **Athanasios Protogerou,** MD, PhD,[o] **Petros Sfikakis,** MD,[p] **George D. Kitas,** MD, PhD, FRCP,[q] **Vijay Viswanathan**, MD, PhD,[r] **Jasjit S. Suri,** MS, PhD, MBA, Fellow AIMBE,[s]

[a]Department of Neurology, IMIM - Hospital del Mar, Barcelona, SPAIN
[b]Department of ECE, VNIT, Nagpur, Maharashtra, INDIA
[c]Department of Cardiology, Indraprastha APOLLO Hospitals, New Delhi, INDIA
[d]Division of Cardiovascular Medicine, Toho University, Tokyo, JAPAN
[e]Statistics Discipline, Khulna University, Khulna, BANGLADESH
[f]Department of Radiology, University of Cagliari, ITALY
[g]Vascular Screening and Diagnostic Centre, University of Cyprus, Nicosia, CYPRUS
[h]Cardiovascular Medicine, University of Virginia, VA, USA
[i]Department of Neurology, University Medical Centre Maribor, SLOVENIA
[j]Brown University, Rhode Island, USA
[k]Department of Radiology, Cornell Medical Center, NY, USA
[l]Cardiology Clinic, Onassis Cardiac Surgery Center, Athens, GREECE
[m]Department of Neurology, University Medical Centre Maribor, Maribor, SLOVENIA
[n]Heart and Vascular Institute, Adventist Health St. Helena, St Helena, CA, USA
[o]Department of Cardiovascular Prevention & Research Unit Clinic & Laboratory of Pathophysiology, National and Kapodistrian Univ. of Athens, GREECE
[p]Rheumatology Unit, National Kapodistrian University of Athens, GREECE
[q]Research & Development-Academic Affairs, Dudley Group NHS Foundation Trust, Dudley, UNITED KINGDOM
[r]MV Hospital for Diabetes and Professor M Viswanathan Diabetes Research Centre, Chennai, INDIA
[s]Stroke Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA

Running Title: Ranking of Stroke and Cardiovascular Risk Factors

Address for correspondence:
Dr. Jasjit S. Suri, PhD., MBA, Fellow AIMBE
AtheroPoint™, Roseville,
Roseville, CA 95661, USA
Phone: (916)-749-5628
FAX: 916 797 4942
Email: jasjit.suri@atheropoint.com

Ranking of Stroke and Cardiovascular Risk Factors for an Optimal Risk Calculator Design: Logistic Regression Approach

Abstract

Purpose: Conventional cardiovascular risk factors (CCVRFs) and carotid ultrasound image-based phenotypes (CUSIP) are independently associated with long-term risk of cardiovascular (CV) disease. In this study, 26 cardiovascular risk (CVR) factors which consisted of a combination of CCVRFs and CUSIP together were ranked. Further, an optimal risk calculator using AtheroEdge composite risk score (AECRS1.0) was designed and benchmarked against seven conventional CV risk (CVR) calculators.

Methods: Two types of ranking were performed: (i) ranking of 26 CVR factors and (ii) ranking of eight types of 10-year risk calculators. In the first case, multivariate logistic regression was used to compute the odds ratio (OR) and in the second, receiver operating characteristic curves were used to evaluate the performance of eight types of CVR calculators using SPSS23.0 and MEDCALC12.0 with validation against STATA15.0.

***Results*:** The left and right common carotid arteries (CCA) of 202 Japanese patients were examined to obtain 404 ultrasound scans. CUSIP ranked in the top 50% of the 26 covariates. Intima-media thickness variability (IMTV) and $IMTV_{10yr}$ were the most influential carotid phenotypes for left CCA (OR=250, P<0.0001 and OR=207, P<0.0001 respectively) and right CCA (OR=1614, P<0.0001 and OR=626, P<0.0001 respectively). However, for the mean CCA, AECRS1.0 and $AECRS1.0_{10yr}$ reported the most highly significant OR among all the CVR factors (OR=1.073, P<0.0001 and OR=1.104, P<0.0001). $AECRS1.0_{10yr}$ also reported highest area-under-the-curve (AUC=0.904, P<0.0001) compared to seven types of conventional calculators. Age and glycated haemoglobin reported highest OR (1.96, P<0.0001 and 1.05, P=0.012) among all other CCVRFs.

Conclusion: $AECRS1.0_{10yr}$ demonstrated the best performance due to presence of CUSIP and ranked at the first place with highest AUC.

Key Words: Cardiovascular risk calculator, conventional cardiovascular risk factors, covariates, image-based phenotypes, logistic regression, ranking, odds ratio, p-value, AUC, performance.

Introduction

In 2016, the World Health Organisation reported mortality of 17.9 million people due to cardiovascular diseases (CVD) out of which 85% were due to stroke and heart attack [1]. The trend of these diseases is comparable in developed and developing countries of the world [2]. In general, 90% of cardiovascular deaths are attributed to conventional cardiovascular risk factors (CCVRFs) such as age, gender, ethnicity, dyslipidaemia, diabetes, smoking, obesity, physical inactivity, and hypertension [3, 4]. However, CCVRFs do not explain morphological changes in blood vessels. Hence, it is essential to investigate the role of other advanced risk factors along with CCVRFs to accurately assess the long-term risk of CVD.

Advancements in imaging techniques [5], especially the carotid ultrasound (CUS), have provided a non-invasive and cost-effective means of investigating sub-clinical atherosclerosis using carotid ultrasound image-based phenotypes (CUSIP) such as carotid intima-media thickness (cIMT) and total carotid plaque [6]. Both of these phenotypes are associated with an increased risk of cardiovascular (CV) events [6]. Combining both CCVRFs and CUSIP improves the risk stratification of patients. CCVRFs have been ranked previously to assess the risk of coronary heart disease [7]. Ranking of both CCVRFs and psychosocial risk factors has also been performed for CVD risk assessment [8]. But an analysis of the joint impact of CCVRFs on current CUSIP ($CUSIP_{curr}$) and the resulting predicted 10-year CUSIP ($CUSIP_{10yr}$ i.e., fusion-based phenotypes) has never been published. Nor has the modelling of the 10-year composite risk score ($AECRS1.0_{10yr}$) from these combined parameters.

Typically, all the conventional cardiovascular risk calculators (CCVRCs) are ethnicity-specific and include a unique set of CCVRFs in their computational model [9-15]. In order to provide accurate risk assessment, it is important to identify the risk factors that contribute most

to the development of CVD/stroke. Ranking of the conventional risk factors using the odds ratio (OR) aids in identification of risk factors which are more influential towards the progression of atherosclerotic disease. These factors can then be potential targets for the management of CVD/stroke.

AECRS1.0$_{10yr}$ is a novel integrated risk calculator that combines both CCVRFs and the CUSIP$_{curr}$. Since this contains two diverse (conventional vs. image-based) sets of CV risk factors, it is imperative to rank all the risk factors, and identify those that contribute most to CVD/stroke risk. This is the first and fundamental challenge. The second goal of this study is to benchmark the new calculator AECRS1.0$_{10yr}$ against the existing CV risk calculators to determine whether it outperforms these for the Japanese diabetic cohort.

To accomplish these two objectives, *i.e.*, (i) the identification of the order of the risk factors and (ii) benchmarking the integrated risk calculator, AECRS1.0$_{10yr}$, we adapted multivariate logistic regression (MLR) as our framework. Since our study had a total of 26 risk factors consisting of 13 CCVRFs and 13 CUSIP (both CUSIP$_{curr}$ and CUSIP$_{10yr}$), we determined the odds ratio (OR) and used this to rank the covariates in decreasing order. A similar approach was followed to measure the risk of all CCVRCs and then rank them in decreasing order based on the AUC as a metric.

The fundamental requirement for evaluation of a model's performance in the MLR framework is to establish the endpoint which will be used to evaluate the objectives. These endpoints are either cerebrovascular/cardiovascular events, or an event-equivalent endpoint (EEE). Patients reach event-equivalent endpoints when they are identified to have very high risk of a life-threatening event if not treated aggressively. The hard core endpoints are always driven by the nature of trials, prospective or longitudinal. Under the longitudinal paradigm, patients are

followed-up over a course of time, and this has its own challenges both in terms of economics and the sheer complexity of the patient management. EEEs are prospective events where morphological changes in the atherosclerotic disease reach a risk threshold point through a combination of factors such as (a) plaque formation above the focal thickening region [16], (b) the severity of diabetes mellitus (DM) [17, 18], (c) plaque score, as defined by the number and thickness of plaques [19, 20], and (d) severity of elevation of blood pressure, hypertension, which is associated with stroke or myocardial infarction (MI) [21, 22]. Using these parameters, we have developed an EEE (so-called composite response variable), which includes the unbiased measurements of glycated Haemoglobin (HbA1c), hypertension (HT), plaque score (PS), and maximum intima-media thickness (IMT_{max}). These four risk factors were selected from the combination of CCVRFs and $CUSIP_{curr}$. The rationale for the response variable has been provided in the "Discussion" section of this manuscript.

In summary, the study has the following hypotheses: (i) CUSIP are highly influential compared to CCVRFs to assess the 10-year risk in Japanese cohort; and (ii) the proposed integrated $AECRS1.0_{10yr}$ provides better risk stratification of patients compared to conventional cardiovascular risk (CCVR) calculators. In this manuscript, the suffix 'curr' and '10yr' will be used to indicate current and 10-year measurements, respectively. For ease of reference, all abbreviations used in this study are listed in the Appendix (Table 1 to Table 3). The proposed study has the following novel aspects:

(i) Measurement of composite risk score (CRS) which includes automated measurement of five image-based phenotypes
(ii) Design of the integrated calculator $AECRS1.0_{10yr}$ which can measure the 10-year risk of CVD and stroke using 10-year image-based phenotypes

(iii) A ranking algorithm that compares AECRS1.0$_{10yr}$ with seven well-established 10-year conventional risk calculators

(iv) Ranking of 26 cardiovascular risk factors (predictors or covariates) using odds ratio, that includes both conventional and image-based risk factors

(v) Determining the predictive power of image-based phenotypes compared to the conventional risk calculators

(vi) Validation of Multiple Logistic Regressions (MLR) against a machine learning algorithm

(vii) Bias estimation method and analysis in MLR and ML frameworks

(viii) The system is in clinical use and was developed in the C++ programming language.

Materials and Methods

Study Population

With institutional review board (Toho University Japan) approval, a cohort of 202 patients was recruited for this study. Informed consent was received from all participants. This study includes a unique analysis compared to previous studies published using this same Japanese cohort [23, 24]. Ultrasound examination was conducted between July 2009 and December 2010 and a total of 404 B-mode ultrasound scans was collected from both the left and right common carotid artery (CCA). The scans were retrospectively analysed by two operators (novice and experienced) as well as an expert with 15 years of experience in the field of radiology. The baseline characteristics of this cohort are presented in the results section.

Ultrasound Image Acquisition

An ultrasound scanner (Aplio XG, Xario, Aplio XV, Toshiba Inc., Tokyo, Japan) supplied with 7.5 MHz linear array transducer was used to perform the carotid artery examination. All the CUS were acquired by a skilled sonographer with 15 years of experience, as previously described [24]. The average calibration factor over all the B-mode scans was 0.0529 mm/pixel. The

guidelines of American Society of Echocardiography Carotid Intima-Media Task Force 16 were adopted in this study [25].

Carotid Image-based Phenotype Measurements Using AtheroEdge

Five types of $CUSIP_{curr}$ – average intima-media thickness (IMT_{ave}), maximum IMT (IMT_{max}), minimum IMT (IMT_{min}), variability in IMT (IMTV), and morphological total plaque area (mTPA) – were automatically measured from all the 404 ultrasound scans using an automated system (AtheroEdge from AtheroPoint™, Roseville, CA, USA) [26-28]. The mTPA (also referred to as TPA) includes the focal thickening region [29, 30] which is above the 1-mm average baseline distance between the lumen-intima (LI) and media-adventitia (MA) interfaces of the far wall of the carotid artery. A detailed protocol for computation of the five types of phenotypes using AtheroEdge system has been discussed in our previous studies [26-28]. In this study, all the automated $CUSIP_{curr}$ were validated against the gold standard (in this case an expert) and computed tomography [31, 32].

It has been reported that the progression of cIMT and carotid plaque has a strong association with CCVRF [33-36]. In other words, CCVRFs influence the annual progression of carotid plaque burden that is measurable using ultrasound scans. Thus, in our recent study [37], we integrated eight types of CCVRFs with the current five types of $CUSIP_{curr}$ (IMT_{ave}, IMT_{max}, IMT_{min}, IMTV, and TPA) to predict the $CUSIP_{10yr}$ ($IMT_{ave10yr}$, $IMT_{max10yr}$, $IMT_{min10yr}$, IMV_{10yr}, and TPA_{10yr}) using a nonlinear model. Both $CUSIP_{curr}$ and $CUSIP_{10yr}$ have been used to risk stratify the patients into three bins (Figure 1): (i) low-risk, (ii) moderate-risk, and (ii) high-risk.

10-year Cardiovascular Risk Calculators

In this study, we developed a 10-year CUSIP risk calculator, referred to as "$AECRS1.0_{10yr}$" which produces an automated measurement of the 10-year CV risk using five types of 10-year

predicted measurements ($IMT_{ave10yr}$, $IMT_{max10yr}$, $IMT_{min10yr}$, IMV_{10yr}, and TPA_{10yr}). $AECRS1.0_{10yr}$ measurement is a two-step process, as shown in Supplementary Material (Section A, Figure 1).

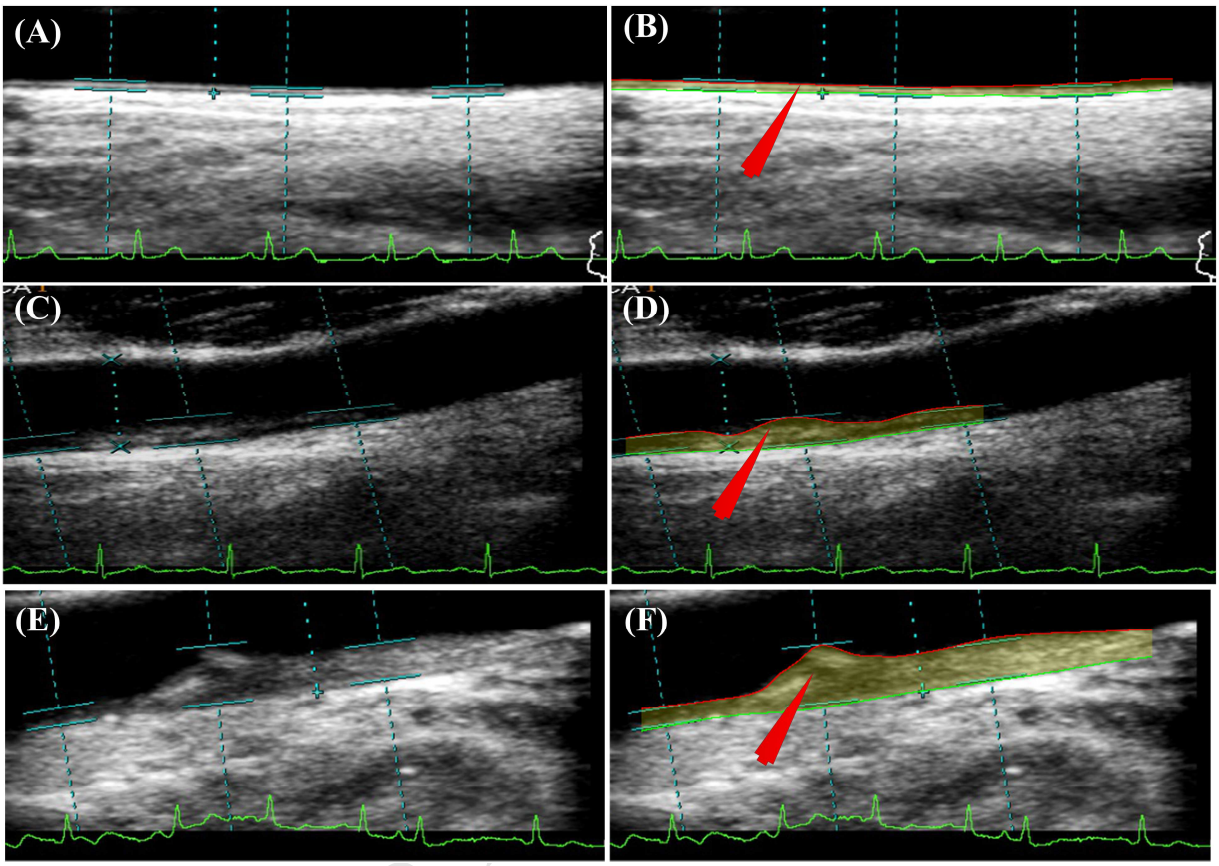

Figure 1 Risk stratification based on automated $CUSIP_{curr}$ and $CUSIP_{10yr}$.

Row 1 - Patient 192L **(low-risk)**: (**A**) Original Image; (**B**) Processed image using AtheroEdge™ 2.0; $CUSIP_{curr}$: IMTave=0.56 mm, IMTmax=0.73 mm, IMTmin=0.49 mm, IMTV=0.05 mm, TPA=18.22 mm^2, and $ARCRS1.0_{curr}$=37.71%; $CUSIP_{10yr}$: $IMTave_{10yr}$=0.79 mm, $IMTmax_{10yr}$=0.96 mm, $IMTmin_{10yr}$=0.72 mm, $IMTV_{10yr}$=0.096 mm, TPA_{10yr}=18.45 mm^2, and $AECRS1.0_{10yr}$=53.09%; PS=10.

Row 2 - Patient 28R **(moderate-risk)**: (**C**) Original Image; (**D**) Processed image using AtheroEdge™ 2.0; $CUSIP_{curr}$: IMTave=0.87 mm, IMTmax=1.04 mm, IMTmin=0.65 mm,

IMTV=0.09 mm, TPA=28.54 mm^2, and $ARCRS1.0_{curr}$=56.05%; $CUSIP_{10yr}$: $IMTave_{10yr}$=1.13 mm, $IMTmax_{10yr}$=1.29 mm, $IMTmin_{10yr}$=0.9 mm, $IMTV_{10yr}$=0.205 mm, TPA_{10yr}=28.74 mm^2, and $AECRS1.0_{10yr}$=72.35%; PS=9.

Row 3 - Patient 10L **(high-risk)**: (**E**) Original Image; (**F**) Processed image using AtheroEdge™ 2.0; $CUSIP_{curr}$: IMTave=3.04 mm, IMTmax=4.22 mm, IMTmin=1.57 mm, IMTV=0.62 mm, TPA=94.56 mm^2, and $ARCRS1.0_{curr}$=93.32%; $CUSIP_{10yr}$: $IMTave_{10yr}$=3.26 mm, $IMTmax_{10yr}$=4.44 mm, $IMTmin_{10yr}$=1.79 mm, $IMTV_{10yr}$=0.73 mm, TPA_{10yr}=94.73 mm^2, and $AECRS1.0_{10yr}$=95.13%; PS=10.

To validate the performance of the $AECRS1.0_{10yr}$, we have also computed the 10-year CV risk for all the 202 patients (404 scans) using seven other types of CCVRCs: (i) Framingham risk score (FRS), (ii) the United Kingdom Prospective Diabetes Study (UKPDS) 56 (UKPDS56), (iii) UKPDS60, (iv) NIPPON, (v) Reynolds's Risk Score (RRS), (vi) the Pooled Cohort Risk Score (PCRS also called as Atherosclerosis CVD or ASCVD score), and (vii) QRISK3, using well established mathematical expressions [9-15].

Statistical Analysis

Statistical analysis was performed using SPSS23.0 and MEDCALC12.0 and validated against STATA15.0. In order to show the recruited sample size of 404 was enough to perform the statistical tests, we performed a power analysis with 95% confidence interval and a margin of error of 5%. Our calculations showed that a sample size of 334 was sufficient, thus our sample size of 404 was 21% more than the minimum required for the study.

In the baseline characteristics table (Table 1), continuous variables are expressed as mean±standard deviation and categorical variables are expressed in percentages. The non-parametric Wilcoxon signed rank test was used with an alpha level of 0.05. The Wilcoxon signed

rank test does not require the data to be normally distributed, thus it was feasible to test the significance of the all the baseline risk factors using this test. MLR and receiver operating characteristic (ROC) analysis were performed using a response variable that included a composite of HbA1c, fasting blood sugar (FBS), PS, and IMT_{max} as a gold standard dependent variable. The patients were risk-stratified into low-risk or high-risk bins by using a slightly different composite response variable composed of the combination of HbA1c, PS, HT, PS, and $IMT_{max,}$ while adapting the MLR and ROC analysis. The rationale behind the selection of the response variable is further discussed in detail in the "Discussion" section.

Ranking of (a) 26 Risk Covariates and (b) 8 Conventional CV Risk Calculators

Two types of ranking were performed:

(a) Ranking of 26 risk covariates using OR, evaluated using MLR. These 26 covariates consisted of 13 CUSIP: Six types of $CUSIP_{curr}$ (IMTave, IMTmax, IMTmin, IMTV, TPA, $AECRS1.0_{curr}$), six types of $CUSIP_{10yr}$ ($IMTave_{10yr}$, $IMTmax_{10yr}$, $IMTmin_{10yr}$, $IMTV_{10yr}$, TPA_{10yr}, $AECRS1.0_{10yr}$), and a plaque score; and 13 CCVRFs: age, gender, smoking, FBS, HbA1c, HT, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), family history (FH), and TC/HDL-C ratio.

(b) Ranking of eight types of risk calculators (FRS, UKPDS56, UKPDS60, NIPPON, RRS, PCRS, QRISK3, and $AECRS1.0_{10yr}$) based on the area-under-the-curve (AUC) while using MLR.

These two types of crucial information allow us to evaluate the high-risk covariates and further help us to identify best performing risk calculator.

Results

Baseline Characteristics

In this cohort, 156 (77.23%) patients were males and 46 (22.77%) were females. The average age of the cohort was 68.97±10.96 years (ranging from 29 to 88 years). Out of 202 patients, 147 (72.72%) had hypertension, 49 (24.25%) were diabetic, 81 (40.09%) were current smokers, and 24 (11.88%) had a family history of MI in first degree relatives. The criteria for hypertension were SBP ≥ 130 mm/Hg and DBP ≥ 80 mm/Hg, or treatment with anti-hypertensive medication. The criteria for dyslipidaemia were LDL-C > 130 mg/dl or treatment with lipid-lowering drugs. The blood biomarkers had the following average values: LDL-C: 101±31.5 mg/dl, HDL-C: 50.5±15 mg/dl, TC: 174±36.7 mg/dl, TC/HDL-C ratio: 3.65±0.01, FBS: 131±34.8 mg/dl, and HbA1c: 6.28±1.11%. A response variable which was a combination of four covariates: HbA1c, HT, PS, and IMT_{max} was used to stratify the patients into low-risk, and high-risk class (a detailed discussion on response variable is provided in the "Discussion" section). It was observed from Table 1 that FBS, HbA1c, HT, SBP, and DBP are the significant confounding risk factors, and thus they are used for OR adjustments.

Ranking of 26 Cardiovascular Covariates

The OR for automated CUSIP was significantly higher compared to the OR of CCVRFs (Table 2). IMTV and $IMTV_{10yr}$ consistently had significantly high OR in both left CCA (OR=207; P<0.0001 and OR=250; P<0.0001 respectively) and right CCA (OR=1614; P<0.0001 and OR=626; P<0.0001 respectively). $CUSIP_{10yr}$ in all three CCAs were ranked in the top 50% of total covariates. HbA1c, TC/HDL-C ratio, and age were the predictors with highest ranked OR among all the CCVRFs (Table 2).

Ranking of 10-year Risk Calculators

Performance of AECRS1.0$_{10yr}$ was ranked against seven other types of CCVRCs using ROC analysis (Table 3). As shown in Table 3, the ROC and MLR analysis were performed on the left CCA (row R1 to row R8), right CCA (row R9 to row R16), and mean CCA (row R17 to row R24). AECRS1.0$_{10yr}$ reported the highest AUC and OR compared to seven other types of CCVRC in each of the three segments: (i) left CCA (row R1, AUC=0.904; OR=1.197; P<0.0001), (ii) right CCA (row R9, AUC=0.933; OR=1.261; P=0.001), and (iii) mean CCA (row R17, AUC=0.944; OR=1.503; P<0.0001). AECRS1.0$_{10yr}$, QRISK3, and NIPPON were the top three calculators among all the eight CCVRCs in left CCA (row R1 to R3), right CCA (row R9 to R11), and mean CCA (row R17 to R19).

Discussion

This study mainly focused on two types of ranking: (a) ranking of 26 cardiovascular risk covariates and (b) ranking of eight types of cardiovascular risk calculators. The 26 covariates were taken from a combination of 7 demographics-based, 6 blood biomarker-based, and 13 CUSIP. The five types of 10-year image-based phenotypes (out of 13) were measured by integrating eight CCVRF with five types of current carotid image-based phenotypes [37]. In the second objective, we ranked the eight cardiovascular risk calculators including the proposed AECRS1.0$_{10yr}$.

The main findings of our study of the 26 CV covariates were: (i) CUSIP provided higher OR compared to the CCVRFs and (ii) age, FH, and TC/HDL-C ratio reported the highest OR among CCVRFs. The more significant OR for CUSIP compared to CCVRFs indicated a strong association between CUSIP and subclinical atherosclerotic disease. This is also the reason for higher OR for the CUSIP$_{10yr}$. Carotid atherosclerotic plaque formation progresses with aging and

thus elevates the risk of CVD [38]. In our study, higher OR for age and HbA1c among other CCVRFs is consistent with earlier published studies [39, 40]. The IMTV biomarker [28] is also high in covariate ranking, in accordance with previous studies in risk stratification [41].

Regarding the ranking of eight risk calculators, AECRS1.0$_{10yr}$ ranked the first having highest OR and AUC among other the CCVRCs enabling its use as a reliable and accurate clinical tool for CVD/stroke risk stratification of patients. This is because of the integration of CCVRFs with CUSIP$_{curr}$ for 10-year risk prediction. The 10-year risk computed using CCVR calculators was based only on the traditional risk factors, resulting in underperformance compared to the integrated approach taken by AECRS1.0$_{10yr}$.

Benchmarking

Table 4 benchmarks the proposed study for ranking of covariates using OR in the MLR framework. Limited studies were available in the literature that ranked all the types of covariates included in ours. However, it is worth noting that most of the studies have evaluated the association of CCVRFs with CVD risk using OR. It is also worth noting that in the analysis nearly all the studies (Table 4: rows R1 to R9) showed CCVRFs such as age, HbA1c, smoking, and gender as significant risk factors (column C7). There are a handful of studies that examined the role of CUSIP$_{curr}$ while computing OR in MLR framework. Cuadrado-Godia et al. [24] recently presented a study in which six CUSIP$_{curr}$ were ranked using OR in MLR framework. This was very similar to Touboul et al.[42], who ranked the CUSIP$_{curr}$ and FRS, showing the superior OR value for image-based phenotypes (OR=2.73; P<0.0001).

Table 5 shows the ranking of risk calculators proposed over the past decade that used either standalone CCVRFs or the integration of CCVRFs with CUSIP$_{curr}$. There were no studies which used the fusion-based approach except our study. Further, to our knowledge, there was no study

that computed $CUSIP_{10yr}$ taking into account CCVRFs. This is one of the shortfalls of previous risk prediction models.

A Special Note on the Ranking of Covariates and Risk Calculators

HbA1c has also been ranked at first place followed by age with the highest significant OR when ranking the 26 covariates (Table 2). Patient demographics mainly determine the OR ranking of the risk predictors. In our study, we have ranked and compared eight types of 10-year CV risk calculators. While $AECRS1.0_{10yr}$ consistently ranked first place among all the other risk calculators, QRISK3 consistently ranked at second place. One plausible reason is the integration of 23 types of conventional and demographics-based risk factors in this model, which is a much larger number of covariates compared to other CCVRCs. Compared to $AECRS1.0_{10yr,}$ QRISK3 does not offer the benefit of inclusion of carotid atherosclerotic phenotypes, which may result in its slightly lower performance. UKPDS60 was one of the lowest rank calculators in our study (AUC=0.75; P<0.0001). The reason for its underperformance may be an exclusion of HbA1c in its risk prediction model (see Table 4: row R2, column C5). HbA1c is an influential confounding CCVRF (P<0.0001). This is quite the opposite in another CCVR calculator, where HbA1c has been included, which can be seen in Table 4 (column C5). The performance of the calculators was based on AUC and discussed previously in the result subsection: for RRS (0.76), UKPDS56 (0.78), FRS (0.786), PCRS (0.797), NIPPON (0.80), and QRISK3 (0.86) and $AECRS1.0_{10yr}$ (0.904), respectively. This improvement in the AUC is consistent in all three scenarios: left CCA (LCCA), right CCA (RCCA), and mean CCA (MCCA).

Role of Event Equivalent Endpoints as Response Variables in Ranking Risk Calculators

The choice of the dependent variable (response variable) plays an important role in MLR analysis during the ranking of CCVRFs (covariates) and CV risk calculators. Large magnitudes

of the OR were observed for all the predictors which were part of the dependent variable. The composite response variable was modified during risk stratification of patients into either low- or high-risk bins from inclusion of FBS to HT, along with HbA1c, PS and IMTmax which remained consistent. The main motivation for modifying the response variable thus was to ensure that we did not introduce bias, while maintaining the balance of risk identification. Further, this avoided producing larger unstable values of ORs during MLR analysis. Thus, our analysis using the composite response variable can be considered as an effective factor equivalent to having a cerebrovascular or cardiovascular event.

We believe the selection of risk factors was appropriate because the baseline characteristics already took into account corrections for FBS due to its strongly significant contribution ($P<0.0001$). As per the baseline evaluation (Table 1), six CCVRFs such as HbA1c, FBS, HT, SBP, DBP, and PS were significant ($P<0.05$). However, since HbA1c, HT, and PS were already part of a process by which dependent variables were derived, these three CCVRFs were not used for adjusting the OR. This further justifies the usage of the combination set for the response variable. Note that the use of an event equivalent response variable is applicable to both prospective and longitudinal trial designs. This is further justified by the rationale that atherosclerotic constriction of blood vessels leads to MI or stroke, and PS and IMT_{max} are measures of plaque burden causing this constriction. Thus, this composite response variable is a powerful predictor of cardiovascular events.

A Note on Sample Size

The database consisted of 404 ultrasound scans collected from 202 patients. In should be noted that, even though the two artery types have similar genetic makeup and physiology, they work independently along two different pathways. Furthermore, deposition of atherosclerotic plaque is

independent in these two artery types. Thus, each of the 404 ultrasound scans extracted from left and right CCAs of 202 patients can be treated as coming from different patients. Taking this fact into consideration, a power analysis was performed in this study. The power analysis computations showed that 404 samples are enough to perform the entire statistical test (as shown in the statistical analysis section) and further to perform the risk analysis by ranking the risk predictors. Thus our approach on the population size justifies the ranking analysis for calculators and covariates. Further, we want to share that all our phenotype measures involved automated morphological capture of far wall LI and MA interfaces which were sampled with 100 normalised points, unlike the conventional method of collecting the measurements at only a few locations along the artery [43-45]. Thus, our system automatically generated approximately 80,000 samples (200 samples at LI and MA in 404 arteries). Our measurements therefore have data points which are several-fold over the required sample size, representing a very large dataset. This methodology for large sample sizes has been described in our previously published papers [43-45]. This is the key observation in statistical analysis and comprehensive MLR analysis enabling higher AUC contributions.

Sensitivity Analysis for Seven Types of Risk Calculator Coefficients

In our study, the performance of AECRS1.0$_{10yr}$ was evaluated using AUC and was compared against seven other CCVRCs such as FRS [9], UKPDS56 [10], UKPDS60 [11], RRS [13], PCRS [14], NIPPON [12], and QRISK3 [15]. Each of the seven CCVRCs used a set of predetermined coefficients which were obtained from Cox regression analysis in their risk prediction model. In this study, we have used these risk prediction models in their original form without altering the predetermined coefficients. However, we have performed a sensitivity analysis in which each of the coefficients was varied from 0.1% to 2%. It was observed that the net effect due to variation

in the coefficients resulted in a small variation of less than 5% on the 10-year risk. Due to very low sensitivity, we decided to use the original settings in the Cox coefficients for CCVRCs.

Justification of the Higher OR

The response variable plays an important role in statistical analysis and understanding the higher OR values for IMTV and IMTV10yr. There are two kinds of predictors which can be taken into consideration for response variable (RV) design. These predictors can be chosen from the conventional pool of risk factors or image-based pool of risk factors. We considered two factors from the conventional pool and two factors from the image-based pool, ensuring a balance. Since HT and HbA1c were shown to be significant risk factors during analysis of non-normal distribution using Wilcoxon signed rank test, we selected these two from the conventional group. Since Plaque Score (PS) and IMTmax were the image-based risk factors which best reflected the atherosclerotic vulnerability, we selected these two risk factors from pool two. Because PS was supplied as the gold standard by the cardiologist and is a direct measure of image-based phenotypes, it was one of our choices. Thus, our OR analysis was based on the combination of these four selected risk factors.

To further understand the effect of response variable on OR analysis, we used a different combination while selecting these four risk factors as shown in Table 6. These combinations of RV are reflected as SN1, SN2, SN3 and SN4. The corresponding OR values are shown in column 5. As seen from the Table 6, the OR value increases as we keep adding the image-based risk factors. Even though we took choice #4 (HT+HbA1c+IMTmax+PS), one can choose different combinations (as shown in the SN1, SN2 or SN3). This choice would depend upon the clinical dataset and its baseline characteristics. Since we had a mild or moderate risk in our cohort, we took SN4 as the combination HT+HbA1c+IMTmax+PS, however one has a choice to

have lower strength of the response variable. Modifying the factors included in the composite response variable can vary the OR, for example HT+HbA1c, HT+HbA1c+PS, or HT+HbA1c+IMTmax, gives OR for IMTV/$IMTV_{10yr}$ in the range of <5, less than 13, and less than 250, respectively. Certainly, in order to avoid any bias due to too many of either type of risk factors (conventional or image-based), it is reasonable to take a balanced four variable combination such as HT+HbA1c + IMTmax+PS when considering the RV.

Our observation for RCCA and MCCA showed similar OR results when using the same response variable. The corresponding results (Table A and Table B) have been added in Section C of the supplementary material as a reference.

Validation Using Machine Learning

One of the key contributions of our study is that the current image-based phenotypes (or risk factors) and the 10-year integrated image-based phenotypes (or risk factors) provided a better estimate of the CVD/stroke risk as compared to conventional cardiovascular risk factors. This was evaluated using the MLR analysis by ranking all the risk factors using OR. The ranking of the risk factors was based on the significance level indicated by the p-values. It has been observed that both the current and 10-year image-based phenotypes indicated more highly significant p-values compared to that of conventional CV risk factors.

In order to confirm this finding, we went one step further, and used a computational intelligence-based tool called machine learning (ML) to investigate the effect of including image-based phenotypes compared to the stand-alone conventional CV risk factors for CVD risk stratification. We used a supervised random forest (RF) approach to risk-stratify the patients using two types of models. In the first type, called AtheroRisk-Conventional, a total of 13 conventional cardiovascular risk factors were used as feature set. In the second type, called

AtheroRisk-Integrated, the combined 26 risk factors (13 CCVRF and 13 CUSIP) were used to perform the CVD risk stratification. Given the response variable labels and the feature set, the RF algorithm trains the ML system using the training data set, which is then used to transform the feature set on the test data set to predict the risk classes. We hypothesised that inclusion of direct measurements of severity of vascular disease based on imaging of the carotid arteries, integrated with the conventional system, would lead to a higher accuracy or AUC compared to the conventional system.

Using the ML architecture with the RF-based classification model, our results indicated a higher risk stratification accuracy and AUC for the AtheroRisk-Integrated ML-based system (Accuracy=97.08%, AUC=0.87, P<0.001) compared to that of the AtheroRisk-Conventional system (Accuracy=85.25%, AUC=0.63, P<0.001). The objective in performing this ML-based analysis was to validate the better performance of the integrated phenotypes compared to conventional CV risk factors, using a second method. The ML-based analysis clearly supports our hypothesis tested by MLR analysis.

Study Limitations, Strengths, and Future Objectives

Though we did not observe any major limitations, the study could be improved in the following areas: (i) although power analysis indicated that the sample size for this study was sufficient, we intend to have a larger and more diversified cohort over time for evaluation of the risk calculators; (ii) though we had a strong set of covariates leading to comprehensive data analysis to test the hypothesis, in the future we intend to add missing covariates including estimated glomerular filtration rate, uric acid, high sensitivity C-reactive protein, and erythrocyte sedimentation rate to our analysis; and (iii) while we strongly believe that our event equivalent response variable was appropriate for this pilot study, endpoints such as actual cerebrovascular

or cardiovascular events were not included due to the long term time commitment of such data collection [46]. Despite these challenges, this is the first study of its kind that that showed reliable and accurate results with following key features: (i) it included 26 predictors of CVD/stroke and their ranking; (ii) 10-year carotid image-based phenotypes ($CUSIP_{10yr}$) were computed by integrating CCVRFs with the current image-based phenotypes[46]; (iii) design of $AECRS1.0_{10yr}$, benchmarked against seven other CCVRCs and its ranking by computing odds ratio and AUC. Though these results are preliminary, this is a strong contribution in the area of preventive cardiology, allowing optimisation of the dependent variable(s) using MLR and their application to a longitudinal trial with a larger cohort having specific endpoints.

Conclusion

Ranking of CV risk factors allowed us to determine the influential risk predictors that can be included in risk prediction models for reliable and accurate CV risk stratification. Multivariate logistic regression indicated the highest impact of current and 10-year carotid ultrasound image phenotypes in CV risk stratification. Among the 26 covariates analysed, IMTV and IMT_{10yr} reported the most highly significant OR. HbA1c, age, and TC/HDL-C ratio reported highest OR among all CCVRFs. The proposed novel design of $AECRS1.0_{10yr}$ risk calculator showed the most reliable, accurate performance compared with seven other CCVRCs.

Acknowledgements: None

Financial Support/Grants: None

Disclosure: Dr. Jasjit Suri is affiliated with AtheroPoint™, focussed on the area of stroke and cardiovascular imaging

Conflicts of interest: None

References

[1] W.H. Organization, Cardiovascular diseases (CVDs): Key facts by WHO May 2016, 2017.

[2] D. Prabhakaran, P. Jeemon, A. Roy, Cardiovascular diseases in India, Circulation, 133 (2016) 1605-1620.

[3] A. Rosengren, S. Hawken, S. Ôunpuu, K. Sliwa, M. Zubaid, W.A. Almahmeed, K.N. Blackett, C. Sitthi-amorn, H. Sato, S. Yusuf, Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study, The Lancet, 364 (2004) 953-962.

[4] M.J. O'Donnell, D. Xavier, L. Liu, H. Zhang, S.L. Chin, P. Rao-Melacini, S. Rangarajan, S. Islam, P. Pais, M.J. McQueen, Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study, The Lancet, 376 (2010) 112-123.

[5] J.M. Tarkin, M.R. Dweck, N.R. Evans, R.A. Takx, A.J. Brown, A. Tawakol, Z.A. Fayad, J.H. Rudd, Imaging atherosclerosis, Circulation research, 118 (2016) 750-769.

[6] T.Z. Naqvi, M.-S. Lee, Carotid intima-media thickness and plaque in cardiovascular risk assessment, JACC: Cardiovascular Imaging, 7 (2014) 1025-1038.

[7] P. Schnohr, J.S. Jensen, H. Scharling, B. Nordestgaard, Coronary heart disease risk factors ranked by importance for the individual and community. A 21 year follow-up of 12000 men and women from The Copenhagen City Heart Study, European heart journal, 23 (2002) 620-626.

[8] P. Schnohr, J.L. Marott, T.S. Kristensen, F. Gyntelberg, M. Grønbæk, P. Lange, M.T. Jensen, G.B. Jensen, E. Prescott, Ranking of psychosocial and traditional risk factors by

importance for coronary heart disease: the Copenhagen City Heart Study, European heart journal, 36 (2015) 1385-1393.

[9] R.B. D'agostino, R.S. Vasan, M.J. Pencina, P.A. Wolf, M. Cobain, J.M. Massaro, W.B. Kannel, General cardiovascular risk profile for use in primary care: the Framingham Heart Study, Circulation, 117 (2008) 743-753.

[10] R.J. Stevens, V. Kothari, A.I. Adler, I.M. Stratton, R.R. Holman, The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56), Clinical science, 101 (2001) 671-679.

[11] V. Kothari, R.J. Stevens, A.I. Adler, I.M. Stratton, S.E. Manley, H.A. Neil, R.R. Holman, UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine, Stroke, 33 (2002) 1776-1781.

[12] N.D.R. Group, Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population, Circulation Journal, 70 (2006) 1249-1255.

[13] P.M. Ridker, J.E. Buring, N. Rifai, N.R. Cook, Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score, Jama, 297 (2007) 611-619.

[14] D.C. Goff, D.M. Lloyd-Jones, G. Bennett, S. Coady, R.B. D'agostino, R. Gibbons, P. Greenland, D.T. Lackland, D. Levy, C.J. O'donnell, 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Journal of the American College of Cardiology, 63 (2014) 2935-2959.

[15] J. Hippisley-Cox, C. Coupland, P. Brindle, Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study, BMJ, 357 (2017).

[16] J.F. Polak, M.J. Pencina, K.M. Pencina, C.J. O'Donnell, P.A. Wolf, R.B. D'Agostino, Sr., Carotid-wall intima-media thickness and cardiovascular events, The New England journal of medicine, 365 (2011) 213-221.

[17] P.K. Myint, S. Sinha, N.J. Wareham, S.A. Bingham, R.N. Luben, A.A. Welch, K.-T. Khaw, Glycated hemoglobin and risk of stroke in people without known diabetes in the European Prospective Investigation into Cancer (EPIC)–Norfolk prospective population study: a threshold relationship?, Stroke, 38 (2007) 271-275.

[18] I. Cavero-Redondo, B. Peleteiro, C. Álvarez-Bueno, F. Rodriguez-Artalejo, V. Martínez-Vizcaíno, Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis, BMJ open, 7 (2017) e015949.

[19] T. Hirata, Y. Arai, M. Takayama, Y. Abe, K. Ohkuma, T. Takebayashi, Carotid Plaque Score and Risk of Cardiovascular Mortality in the Oldest Old: Results from the TOOTH Study, Journal of atherosclerosis and thrombosis, 25 (2018) 55-64.

[20] N. Ikeda, L. Saba, F. Molinari, M. Piga, K. Meiburger, K. Sugi, M. Porcu, L. Bocchiddi, U.R. Acharya, M. Nakamura, M. Nakano, A. Nicolaides, J.S. Suri, Automated carotid intima-media thickness and its link for prediction of SYNTAX score in Japanese coronary artery disease patients, Int Angiol, 32 (2013) 339-348.

[21] J.A. Staessen, T. Kuznetsova, K. Stolarz, Hypertension prevalence and stroke mortality across populations, Jama, 289 (2003) 2420-2422.

[22] M.H. Mehlum, K. Liestøl, S.E. Kjeldsen, S. Julius, T.A. Hua, P.M. Rothwell, G. Mancia, G. Parati, M.A. Weber, E. Berge, Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks, European Heart Journal, 39 (2018) 2243-2251.

[23] M. Biswas, V. Kuppili, T. Araki, D.R. Edla, E.C. Godia, L. Saba, H.S. Suri, T. Omerzu, J.R. Laird, N.N. Khanna, A. Nicolaides, J.S. Suri, Deep learning strategy for accurate carotid intima-media thickness measurement: An ultrasound study on Japanese diabetic cohort, Computers in biology and medicine, 98 (2018) 100-117.

[24] E. Cuadrado-Godia, M. Maniruzzaman, T. Araki, A. Puvvula, M.J. Rahman, L. Saba, H.S. Suri, A. Gupta, S.K. Banchhor, J.S. Teji, Morphologic TPA (mTPA) and composite risk score for moderate carotid atherosclerotic plaque is strongly associated with HbA1c in diabetes cohort, Computers in biology and medicine, 101 (2018) 128-145.

[25] J.H. Stein, C.E. Korcarz, R.T. Hurst, E. Lonn, C.B. Kendall, E.R. Mohler, S.S. Najjar, C.M. Rembold, W.S. Post, Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force endorsed by the Society for Vascular Medicine, Journal of the American Society of Echocardiography, 21 (2008) 93-111.

[26] L. Saba, F. Molinari, K. Meiburger, M. Piga, G. Zeng, U.A. Rajendra, A. Nicolaides, J. Suri, What is the correct distance measurement metric when measuring carotid ultrasound intima-media thickness automatically?, International angiology: a journal of the International Union of Angiology, 31 (2012) 483-489.

[27] F. Molinari, G. Zeng, J.S. Suri, A state of the art review on intima–media thickness (IMT) measurement and wall segmentation techniques for carotid ultrasound, Computer methods and programs in biomedicine, 100 (2010) 201-221.

[28] L. Saba, G. Mallarini, R. Sanfilippo, G. Zeng, R. Montisci, J. Suri, Intima Media Thickness Variability (IMTV) and its association with cerebrovascular events: a novel marker of carotid therosclerosis?, Cardiovascular diagnosis and therapy, 2 (2012) 10.

[29] J.D. Spence, K. Solo, Resistant atherosclerosis: The need for monitoring of plaque burden, Stroke, 48 (2017) 1624-1629.

[30] T. Rundek, J.D. Spence, Ultrasonographic Measure of Carotid Plaque Burden, JACC: Cardiovascular Imaging, 6 (2013) 129.

[31] L. Saba, R. Montisci, F. Molinari, N. Tallapally, G. Zeng, G. Mallarini, J.S. Suri, Comparison between manual and automated analysis for the quantification of carotid wall by using sonography. A validation study with CT, European journal of radiology, 81 (2012) 911-918.

[32] F. Molinari, K.M. Meiburger, L. Saba, U.R. Acharya, L. Famiglietti, N. Georgiou, A. Nicolaides, R.S. Mamidi, H. Kuper, J.S. Suri, Automated Carotid IMT Measurement and Its Validation in Low Contrast Ultrasound Database of 885 Patient Indian Population Epidemiological Study: Results of AtheroEdge® Software, Multi-Modality Atherosclerosis Imaging and Diagnosis, Springer2014, pp. 209-219.

[33] M. Herder, S.H. Johnsen, K.A. Arntzen, E.B. Mathiesen, Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromso Study, Stroke, 43 (2012) 1818-1823.

[34] I.M. van der Meer, A. Iglesias del Sol, A.E. Hak, M.L. Bots, A. Hofman, J.C. Witteman, Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam Study, Stroke, 34 (2003) 2374-2379.

[35] L.E. Chambless, A.R. Folsom, V. Davis, R. Sharrett, G. Heiss, P. Sorlie, M. Szklo, G. Howard, G.W. Evans, Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987-1998, American journal of epidemiology, 155 (2002) 38-47.

[36] L.A.V. Baroncini, L. de Castro Sylvestre, R.P. Filho, Carotid intima-media thickness and carotid plaque represent different adaptive responses to traditional cardiovascular risk factors, International journal of cardiology. Heart & vasculature, 9 (2015) 48-51.

[37] N.N. Khanna, A.D. Jamthikar, T. Araki, D. Gupta, M. Piga, L. Saba, C. Carcassi, A. Nicolaides, J.R. Laird, H.S. Suri, A. Gupta, S. Mavrogeni, G.D. Kitas, J.S. Suri, Nonlinear model for the carotid artery disease 10-year risk prediction by fusing conventional cardiovascular factors to carotid ultrasound image phenotypes: A Japanese diabetes cohort study, Echocardiography (Mount Kisco, N.Y.), (2019).

[38] O. van Oostrom, E. Velema, A.H. Schoneveld, J.P.P. de Vries, P. de Bruin, C.A. Seldenrijk, D.P. de Kleijn, E. Busser, F.L. Moll, J.H. Verheijen, Age-related changes in plaque composition: a study in patients suffering from carotid artery stenosis, Cardiovascular Pathology, 14 (2005) 126-134.

[39] Y. Shimizu, M. Nakazato, S. Sato, J. Koyamatsu, H. Yamanashi, M. Nagayoshi, K. Kadota, N. Hayashida, H. Yamasaki, Y. Kusano, Association between hemoglobin A1c and carotid atherosclerosis in rural community-dwelling elderly Japanese men, Journal of physiological anthropology, 34 (2015) 16.

[40] B. Coll, A. Betriu, S.B. Feinstein, J.M. Valdivielso, J.L. Zamorano, E. Fernández, The role of carotid ultrasound in assessing carotid atherosclerosis in individuals at low-to-intermediate cardiovascular risk, Revista Española de Cardiología (English Edition), 66 (2013) 929-934.

[41] P. Lucatelli, E. Raz, L. Saba, G.M. Argiolas, R. Montisci, M. Wintermark, K.S. King, F. Molinari, N. Ikeda, P. Siotto, Relationship between leukoaraiosis, carotid intima-media thickness and intima-media thickness variability: Preliminary results, European radiology, 26 (2016) 4423-4431.

[42] P.-J. Touboul, J. Labreuche, E. Vicaut, P. Amarenco, Carotid intima-media thickness, plaques, and Framingham risk score as independent determinants of stroke risk, Stroke, 36 (2005) 1741-1745.

[43] L. Saba, S.K. Banchhor, N.D. Londhe, T. Araki, J.R. Laird, A. Gupta, A. Nicolaides, J.S. Suri, Web-based accurate measurements of carotid lumen diameter and stenosis severity: An ultrasound-based clinical tool for stroke risk assessment during multicenter clinical trials, Computers in biology and medicine, 91 (2017) 306-317.

[44] T. Araki, N. Ikeda, D. Shukla, P.K. Jain, N.D. Londhe, V.K. Shrivastava, S.K. Banchhor, L. Saba, A. Nicolaides, S. Shafique, PCA-based polling strategy in machine learning framework for coronary artery disease risk assessment in intravascular ultrasound: A link between carotid and coronary grayscale plaque morphology, Computer methods and programs in biomedicine, 128 (2016) 137-158.

[45] F. Molinari, G. Zeng, J.S. Suri, Intima-media thickness: setting a standard for a completely automated method of ultrasound measurement, IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 57 (2010) 1112-1124.

[46] N. Khanna, A. Jamthikar, T. Araki, D. Gupta, M. Piga, L. Saba, C. Carcassi, A. Nicolaides, J. Laird, H. Suri, A. Gupta, S. Mavrogeni, G. Kitas, J. Suri, Nonlinear model for the carotid artery disease 10-year risk prediction by fusing conventional cardiovascular factors to carotid ultrasound image phenotypes: a Japanese diabetes cohort study, Echocadiography, Accepted Article (In Production) (2018).

[47] R.J. Stevens, R.L. Coleman, A.I. Adler, I.M. Stratton, D.R. Matthews, R.R. Holman, Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66, Diabetes Care, 27 (2004) 201-207.

[48] J.-F. Boyer, P.-A. Gourraud, A. Cantagrel, J.-L. Davignon, A. Constantin, Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis, Joint Bone Spine, 78 (2011) 179-183.

[49] B. Ismail, M. Anil, Regression methods for analyzing the risk factors for a life style disease among the young population of India, indian heart journal, 66 (2014) 587-592.

[50] L. Ren, J. Cai, J. Liang, W. Li, Z. Sun, Impact of cardiovascular risk factors on carotid intima-media thickness and degree of severity: a cross-sectional study, PLoS One, 10 (2015) e0144182.

[51] U. Waje-Andreassen, H. Naess, L. Thomassen, T.H. Maroy, K.Y. Mazengia, G.E. Eide, C.A. Vedeler, Biomarkers related to carotid intima-media thickness and plaques in long-term survivors of ischemic stroke, Translational stroke research, 6 (2015) 276-283.

[52] D.-G. Lee, J.-H. Han, K.-Y. Kwon, J.-H. Kim, K.-H. Han, E.-J. Lee, Association of 10-year atherosclerotic cardiovascular disease risk score with carotid intima-media thickness and plaque, Korean journal of family medicine, 36 (2015) 310-315.

[53] M.J. O'Donnell, S.L. Chin, S. Rangarajan, D. Xavier, L. Liu, H. Zhang, P. Rao-Melacini, X. Zhang, P. Pais, S. Agapay, Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study, The Lancet, 388 (2016) 761-775.

[54] P.M. Ridker, N.P. Paynter, N. Rifai, J.M. Gaziano, N.R. Cook, C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men, Circulation, 118 (2008) 2243-2251.

[55] J. Hippisley-Cox, C. Coupland, Y. Vinogradova, J. Robson, R. Minhas, A. Sheikh, P. Brindle, Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2, Bmj, 336 (2008) 1475-1482.

Tables

Table 1 Baseline characteristics of the patients divided into low-risk and high-risk classes.

SN	C1	C2	C3	C4	C5
R1	Parameters	Overall	High-Risk	Low-Risk	P-value
R2	Total (n)	202	18	184	-
R3	Male, n (%)	156 (77.23%)	13 (8.33%)	143 (91.67%)	0.597
R4	Age (years)	68.97±10.96	69.33±8.87	68.93±11.16	0.918
R5	HbA1c (%)	6.28±1.11	7.59±1.03	6.15±1.03	< 0.001
R6	FBS (mg/dl)	121.21±34.81	137.78±38.80	119.59±34.08	< 0.050
R7	LDL-C (mg/dl)	100.75±31.48	101.17±33.16	100.71±31.41	0.978
R8	HDL-C (mg/dl)	50.49±14.97	49.67±14.04	50.57±15.09	0.869
R9	TC (mg/dl)	174.33±36.73	175.44±33.52	174.22±37.11	0.879
R10	TC/HDL-C	3.65±1.01	3.77 ±1.18	3.64±1.00	0.735
R11	HT, n (%)	147 (72.77%)	18 (12.24%)	129 (87.76%)	< 0.001
R12	SBP (mm Hg)	134.55±8.92	140.00±0.00	134.02±9.18	< 0.001
R13	DBP (mm Hg)	87.28±4.46	90.00±0.00	87.01±4.59	< 0.001
R14	Smoking, n (%)	81 (40.10%)	8 (9.88%)	73 (90.12%)	0.694
R15	FH, n (%)	24 (11.88%)	2 (8.33%)	22 (91.67%)	0.916
R16	PS	9.09±5.31	11.72±4.04	8.84±5.36	< 0.050

Table 2. Ranking of covariates corresponding to LCCA, RCCA and MCCA.

Artery Type	Ranking*	Covariate	OR	P-Val	AUC	95% CI	
						Lower	Upper
LCCA	1	IMTV	250.046	0.000	0.889	0.835	0.944
	2	$IMTV_{10yr}$	207.638	0.000	0.894	0.84	0.947
	3	$IMT_{max10yr}$	3.954	0.000	0.911	0.864	0.958
	4	IMT_{max}	3.93	0.000	0.91	0.863	0.957
	5	HbA1c	3.808	0.000	0.958	0.931	0.984
	6	$AECRS1.0_{10yr}$	1.197	0.000	0.904	0.852	0.955
	7	AECRS1.0	1.137	0.000	0.913	0.869	0.957
	8	TPA_{10yr}	1.067	0.000	0.882	0.821	0.943
	9	TPA	1.066	0.000	0.882	0.821	0.943
	10	$IMT_{ave10yr}$	6.296	0.001	0.874	0.807	0.94
	11	IMT_{ave}	6.243	0.001	0.868	0.8	0.936
	12	IMT_{min}	8.753	0.019	0.804	0.716	0.891
	13	$IMT_{min10yr}$	8.354	0.021	0.806	0.719	0.894
	14	PS	1.102	0.041	0.809	0.743	0.875
	15	TC/HDL-C	1.242	0.382	0.745	0.64	0.851
	16	Gender	0.72	0.571	0.768	0.689	0.847
	17	HDL-C	0.991	0.631	0.764	0.673	0.855
	18	TC	1.002	0.787	0.749	0.65	0.848
	19	Age	0.993	0.792	0.751	0.654	0.847
	20	LDL-C	1.002	0.816	0.747	0.647	0.847
	21	FH	0.873	0.865	0.765	0.679	0.851
	22	Smoking	1.005	0.993	0.757	0.665	0.849
	23	SBP	2.612	0.997	0.757	0.666	0.849
RCCA	1	IMTV	1614.489	0.000	0.946	0.906	0.987
	2	$IMTV_{10yr}$	626.21	0.000	0.947	0.907	0.987
	3	$IMT_{ave10yr}$	45.337	0.000	0.951	0.917	0.985
	4	IMT_{ave}	39.194	0.000	0.945	0.907	0.984
	5	$IMT_{max10yr}$	7.225	0.000	0.942	0.904	0.981
	6	IMT_{max}	7.212	0.000	0.94	0.9	0.98
	7	AECRS1.0	1.166	0.000	0.948	0.913	0.984
	8	$AECRS1.0_{10yr}$	1.261	0.001	0.933	0.889	0.977
	9	TPA	1.105	0.001	0.913	0.85	0.975
	10	TPA_{10yr}	1.105	0.001	0.913	0.85	0.975
	11	PS	1.21	0.004	0.862	0.775	0.95
	12	HbA1c	1.958	0.012	0.91	0.863	0.957
	13	$IMT_{min10yr}$	19.947	0.06	0.822	0.697	0.947

	14	IMT_{min}	15.27	0.08	0.815	0.689	0.941
	15	Age	1.047	0.244	0.773	0.659	0.888
	16	FH	2.115	0.383	0.773	0.649	0.898
	17	Gender	0.651	0.563	0.764	0.645	0.884
	18	TC	1.005	0.589	0.772	0.656	0.888
	20	Smoking	0.761	0.693	0.761	0.634	0.889
	21	HDL	0.994	0.794	0.776	0.66	0.891
	22	LDL-C	1.001	0.911	0.771	0.657	0.884
	23	SBP	2.524	0.997	0.774	0.66	0.888
MCCA	1	IMTV	23040.30	0.001	0.866	0.798	0.933
	2	$IMTV_{10yr}$	8796.01	0.001	0.873	0.811	0.936
	3	HbA1c	2.78	0.001	0.947	0.916	0.977
	4	AECRS1.0	1.073	0.001	0.914	0.868	0.96
	5	$AECRS1.0_{10yr}$	1.104	0.004	0.897	0.844	0.951
	6	$IMT_{min10yr}$	125.01	0.005	0.874	0.8	0.949
	7	$IMT_{ave10yr}$	9.387	0.008	0.891	0.837	0.945
	8	IMT_{min}	85.38	0.009	0.87	0.795	0.946
	9	$IMT_{max10yr}$	3.389	0.01	0.883	0.823	0.944
	10	PS	1.145	0.011	0.875	0.816	0.934
	11	TPA_{10yr}	1.063	0.011	0.887	0.825	0.949
	12	IMT_{max}	3.265	0.012	0.88	0.818	0.942
	13	TPA	1.063	0.012	0.887	0.825	0.949
	14	IMT_{ave}	8.22	0.013	0.885	0.827	0.943
	15	Age	1.034	0.265	0.848	0.777	0.918
	16	TC/HDL-C	1.333	0.276	0.844	0.767	0.921
	17	TC	1.008	0.306	0.847	0.77	0.925
	18	FH	1.896	0.376	0.843	0.762	0.923
	19	LDL-C	1.006	0.492	0.837	0.756	0.917
	20	Smoking	1.201	0.736	0.849	0.774	0.924
	21	HDL-C	0.999	0.944	0.845	0.769	0.921
	22	Gender	1.008	0.991	0.847	0.771	0.922
	23	SBP	2.616	0.997	0.846	0.771	0.922

*All the Covariates were ranked as per the increasing order of P-Val
(Covariate with smallest P-Val has the first rank and covariate with largest P-Val has the last rank).

Table 3. Ranking of eight 10-year cardiovascular risk calculators based on AUC.

C1	C2	C3	C4	C5	C6	C7	C8	
Artery Type	Row#	Ranking	Calculator	OR	P-Val	AUC	95% CI for AUC	
							Lower	Upper
LCCA	R1	1	AECRS1.0$_{10yr}$	1.197	0.000	0.904	0.852	0.955
	R2	2	QRISK3	1.047	0.004	0.863	0.797	0.929
	R3	3	NIPPON	1.035	0.206	0.799	0.715	0.883
	R4	4	PCRS	1.061	0.057	0.797	0.699	0.895
	R5	5	FRS	1.023	0.079	0.786	0.688	0.883
	R6	6	UKPDS56	1.174	0.306	0.774	0.692	0.856
	R7	7	RRS	1.007	0.696	0.764	0.674	0.854
	R8	8	UKPDS60	0.996	0.733	0.75	0.652	0.848
RCCA	R9	1	AECRS1.0$_{10yr}$	1.261	0.001	0.933	0.889	0.977
	R10	2	QRISK3	1.068	0.001	0.911	0.854	0.969
	R11	3	NIPPON	1.11	0.026	0.853	0.753	0.954
	R12	4	PCRS	1.077	0.047	0.832	0.747	0.918
	R13	5	RRS	1.037	0.071	0.814	0.721	0.906
	R14	6	FRS	1.027	0.104	0.806	0.705	0.907
	R15	7	UKPDS56	1.344	0.133	0.784	0.684	0.885
	R16	8	UKPDS60	1.02	0.204	0.783	0.68	0.887
MCCA	R17	1	AECRS1.0$_{10yr}$	1.503	0.000	0.944	0.894	0.995
	R18	2	QRISK3	1.059	0.002	0.919	0.87	0.968
	R19	3	NIPPON	1.119	0.008	0.911	0.841	0.98
	R20	4	UKPDS56	1.513	0.029	0.876	0.805	0.946
	R21	5	PCRS	1.062	0.094	0.858	0.77	0.945
	R22	6	UKPDS60	1.026	0.085	0.85	0.764	0.937
	R23	7	RRS	1.022	0.275	0.85	0.76	0.939
	R24	8	FRS	1.016	0.306	0.848	0.756	0.941

Table 4. Benchmarking table for ranking of the cardiovascular risk factors.

C1	C2	C3	C4	C5	C6	C7	C8
SN	Author/Year	N	Phenotype Ranking	CCVRF Ranking	Conventional Risk Factors	Significant Risk Factors	Technique used
R1	Van der Meer et al.[34] (2003)	7983	×	✓	Age, Gender, Smoking, BMI, WHR, TC, HDL-C, SBP, DBP, DM	Smoking, Age, and BMI	LR & OR
R2	Stevens et al.[47] (2004)	5102	×	✓	Age, HbA1c, SBP, Urinary Albumin, Gender, WBC count, Subsequent Stroke	Subsequent stroke versus the first stroke, Gender, Urinary albumin	OR
R3	Touboul et al.[42] (2005)	510	✓	×	CCA-IMT, FSRS, Carotid Plaque	Carotid Plaque	LR & OR
R4	Boyer et al.[48] (2010)	6669	×	×	Smoking, HT, DM, LDL-C, HDL-C	Smoking, DM	OR
R5	Ismail et al.[49] (2014)	498	×	✓	Obesity, Smoking, LDL-C, BMI, Tobacco Consumption, and Age	Smoking, BMI, LDL-C	LR & OR
R6	Ren et al.[50] (2015)	4394	×	✓	Age, HT, Dyslipidaemia, DM	Age	Chi-Square test
R7	Andreassen et al.[51] (2015)	232	×	✓	Age, Male Gender, Arterial events, BP, TC, SR, Triglycerides, Creatinine, HbA1c and Receptor polymorphism	HbA1, Gender, Age, and Fc gamma receptor polymorphism	LR & OR
R8	Lee et al.[52] (2015)	201	×	✓	10-year ASCVD score, BMI, Waist circumference, DBP, LLT, Glucose, Triglyceride, LDL-C	10-year ASCVD score	LR & OR
R9	O'Donnell et al.[53] (2016)	26919	×	×	HT, Physical Activity, Apolipoprotein (Apo) B/ApoA1 ratio, Diet, WHR, Psychosocial Factors, Smoking, Alcohol Consumption, DM, Age, Gender	HT, Smoking, DM, and Apolipoproteins	LR & OR
R10	Proposed (2018)	202	✓	✓	Age, Gender, HbA1c, FBS, LDL-C, HDL-C, TC, SBP, DBP, FH, PS, IMTave, IMTmax, IMTmin, IMTV, TPA, AECRS1.0, IMTave10, IMTmax10, IMTmin10, IMTV10, TPA10, $AECRS1.0_{10yr}$	All 13 carotid phenotypes, Age, Smoking	LR & OR

N: Number of patients; LR: Logistic Regression; BMI: Body mass Index; WHR: Waist-to-hip ratio; DM: Diabetes Mellitus; WBC: White Blood Cells; ASCVD: Atherosclerosis CVD;

Table 5. Benchmarking of AECRS1.0$_{10yr}$ against the ten different risk calculators.

C1	C2	C3	C4	C5	C6	C7	C8	C9
SN	Author/Year	Risk Calculator	N	CCVRF	Image Phenotypes	CCVRF -based Calculator	Fusion -based Calculator	AUC
R1	Stevens et al.[10] (2001)	UKPDS56	4540	Age, Gender, Ethnicity, Smoking, HbA1c, SBP, Lipid Ratio	×	✓	×	×
R2	Kothari et al.[11] (2002)	UKPDS60	4549	Age, Gender, Ethnicity, Smoking, BMI, SBP, TC/HDL-C, AF [No HbA1c]	×	✓	×	×
R4	Ueshima et al.[12] (2006)	NIPPON	9638	Age, SBP, Smoking, TC, and Glucose levels	×	✓	×	×
R5	Ridker et al.[13] (2007)	RRS	24558	Age, SBP, HbA1c, Smoking, TC, HDL-C, hs-CRP, FH	×	✓	×	×
R6	Agostino et al.[9] (2008)	FRS	-	Age, TC, HDL-C, SBP, BP Treatment, Smoking, Diabetes	×	✓	×	×
R7	Ridker et al.[54] (2008)	RRS	10724	Age, BP, Smoking, TC, HDL-C, hs-CRP, and Parental History	×	✓	×	×
R8	Cox et al.[55] (2008)	QRISK2	2.3 Million	Ethnicity, Age, Gender, Smoking, SBP, LR, BMI, FH, Deprivation Score, HT, Diabetes, Renal Disease, AF, and RA	×	✓	×	×
R9	Yang et al. (2010)	UKPDS56	372	HbA1C, Age, FH, Spot Urine Albumin-to-Creatinine Ratio	×	×	×	×
R10	Goff et al.[14] (2013)	PCRS	-	Age, Gender, TC, HDL-C, SBP, BP Treatment, Diabetes, Smoking	×	✓	×	×
R11	Proposed (2018)	AECRS1.0$_{10yr}$	202	Ethnicity, Gender, Artery, Age, HbA1c, LDL-C, Hypertension (SBP), Smoking	IMT$_{ave}$, IMT$_{max}$, IMT$_{min}$, IMTV, TPA, IMT$_{ave10}$, IMT$_{max10}$,	✓	✓	✓

					IMT_{min10}, IMTV10, TPA10			
N: Number of patients; BMI: Body Mass Index; WHR: Waist-to-Hip Ratio; DM: Diabetes Mellitus; WBC: White Blood Cells; ASCVD: Atherosclerosis CVD; AF: Atrial Fibrillation; hs-CRP: High Sensitivity C-Reactive Protein; RA: Rheumatoid Arthritis								

Table 6. Response Variable Design vs. OR values of IMTV/IMTV10yr.

SN	Response Variable	Risk Factor	P-Val	OR	95% C.I. for OR	
					Lower OR	Upper OR
1	HT+HbA1c	IMTV	0.277	3.99	0.33	48.43
		$IMTV_{10yr}$	0.217	4.19	0.43	40.88
2	HT+HbA1c+ PS	IMTV	0.041	12.87	1.12	148.28
		$IMTV_{10yr}$	0.029	12.22	1.28	116.39
3	HT+HbA1c+IMTmax	IMTV	0.000	250.05	15.30	4087.14
		$IMTV_{10yr}$	0.000	207.64	14.41	2992.05
4	HT+HbA1c+IMTmax+PS	IMTV	0.000	250.046	0.835	0.944
		$IMTV_{10yr}$	0.000	207.638	0.84	0.947

Appendix

Appendix-Table 1. Abbreviation table pertaining to risk calculators and carotid anatomy.

C1	C2	C3
#SN	Abbreviation	Meaning
R1	CCVR	Convectional Cardiovascular Risk
R2	CCVRC	Conventional Cardiovascular Risk Calculator
R3	CCVRCs	Conventional Cardiovascular Risk Calculators
R4	CCVRF	Conventional Cardiovascular Risk Factor
R5	CCVRFs	Conventional Cardiovascular Risk Factors
R6	CUSIP	Carotid ultrasound image-based phenotypes
R7	$CUSIP_{Curr}$	Current carotid ultrasound image-based phenotypes
R8	$CUSIP_{10yr}$	10-year carotid ultrasound image-based phenotypes
R9	RC	Risk Calculator
R10	FRS	Framingham Risk Score
R11	UKPDS	United Kingdom Prospective Diabetes Study
R12	RRS	Reynolds Risk Score
R13	PCRS	Pooled cohort Risk Score
R14	ASCVD	Atherosclerosis Cardiovascular Disease
R15	AECRS	AtheroEdge Composite Risk Score
R16	CVD	Cardiovascular Diseases
R17	CV	Cardiovascular
R18	CCA	Common Carotid Artery
R19	LCCA	Left Common Carotid Artery
R20	RCCA	Right Common Carotid Artery
R21	MCCA	Mean Common Carotid Artery
R22	CUS	Carotid Ultrasound

Appendix-Table 2. Abbreviation table pertaining to cardiovascular risk factors.

C1	C2	C3	C4	C5	C6
#SN	Abbreviation	Description	#SN	Abbreviation	Description
R1	LDL-C	Low Density Lipoprotein Cholesterol	R15	cIMT	Carotid Intima Media Thickness
R2	HDL-C	High Density Lipoprotein Cholesterol	R16	IMTave	Current average value of cIMT
R3	TC	Total Cholesterol	R17	IMTmax	Current maximum value of cIMT
R4	SBP	Systolic Blood Pressure	R18	IMTmin	Current minimum value of cIMT
R5	DBP	Diastolic Blood Pressure	R19	IMTV	Current variability in cIMT
R6	HT	Hypertension	R20	TPA	Current carotid plaque area
R7	DM	Diabetes Mellitus	R21	$IMTave_{10yr}$	10-year average value of cIMT
R8	FH	Family History	R22	$IMTmax_{10yr}$	10-year maximum value of cIMT
R9	HbA1c	Glycated Haemoglobin	R23	$IMTmin_{10yr}$	10-year minimum value of cIMT
R10	TG	Triglyceride	R24	$IMTV_{10yr}$	10-year variability in cIMT
R11	BMI	Body Mass Index	R25	TPA_{10yr}	10-year carotid plaque area
R12	FBS	Fasting Blood Sugar	R26	mTPA	Morphologic Total Plaque Area
R13	PS	Plaque Score	-	-	-
R14	AF	Atrial Fibrillation	-	-	-

Appendix-Table 3. Abbreviation table pertaining to performance metrics.

C1	C2	C3
#SN	Abbreviation	Meaning
R1	OR	Odds Ratio
R2	ROC	Receiver Operating Characteristics
R3	AUC	Area-under-the-curve
R4	MLR	Multivariate Logistic Regression
R5	EEE	Event equivalent endpoint

Biographies

	**Dr. Elisa Cuadrado Godia, Ph. D.,** is with IMIM – Hospital del Mar, Passeig Marítim 25-29, Barcelona, Spain. She works with Neurovascular Research Group and her current research interests are in the field of carotid artery disease and cardio vascular diseases.
	**Ankush D. Jamthikar,** M.Tech. has received MTech in Communication System and currently working as PhD research scholar at Visvesvaraya National Institute of Technology, Nagpur, India.
	**Deep Gupta,** PhD is an Assistant Professor in the Electronics & Communication Engineering Department, VNIT, Nagpur (India). He received his Ph.D. in Medical Image Processing form Indian Institute of Technology Roorkee, India.
	**Narendra N. Khanna**, MD, DM, FACC is Advisor to Apollo Group of Hospitals in India and is working as Senior Consultant in Cardiology & Coordinator of Vascular Services at Indraprastha Apollo Hospital, New Delhi.
	**Tadashi Araki**, MD received the MD degree from Toho University, Japan in 2003. His research topics include coronary intervention, intravascular ultrasound (IVUS) and peripheral intervention.
	**Md. Maniruzzaman**, M.Sc. and is working as a Lecturer, Statistics Discipline, Khulna University, Khulna, Bangladesh. His research interests are machine learning, public Health, and medical imaging.
	**Luca Saba,** MD is with A.O.U. Cagliari, Italy. His research interests are in Multi-Detector-Row Computed Tomography, Magnetic Resonance, Ultrasound, Neuroradiology, and Diagnostic in Vascular Sciences.
	**Andrew Nicolaides,** MS, FRCS, PhD (Hon) is currently the Professor Emeritus at Imperial College, London. He is the co-author of more than 500 original papers and editor of 14 books.
	**Aditya Sharma, MD** is a cardiologist at University of Virginia, where he directs the anticoagulation clinic and the medical optimization clinic, which helps patients with vascular disorders manage their risk factors with medication. His research interests are Peripheral arterial disease, venous thromboembolism, and fibromuscular dysplasia.
	**Tomaz Omerzum, MD** is currently working as at University Medical Centre Maribor, Slovenia. His Research interests are radiology, and cardiovascular medicine.

	**Harman S. Suri** is currently pursuing his BS from Brown University, Providence, RI, USA. He worked in summers of 2015 in the area of telemedicine-based Autism industry at Behavioral Imaging, Boise, Idaho, USA.
	**Ajay Gupta,** MD, MS currently working as associate professor of radiology and neuroscience at Weil Cornell Medical College New York, USA. His research is focused on neuroradiology.
	**Monika Turk,** MD is currently working as Physician at Department of Neurology, University Medical Centre Maribor, Maribor, Slovenia.
	**John R. Laird,** MD, FACC is with St. Helena Hospital, CA, USA. Professor Laird is an internationally renowned interventional cardiologist and his expertise is innovative procedures for carotid artery disease.
	**Sophie Mavrogeni,** MD, PhD currently working at Cardiology Clinic, Onassis, Athens, GREECE. Her research is focused on Non-ischemic Cardiomyopathy, Dystrophinopathies, mayocarditis and rheumatic diseases.
	**Athanasios Protogerou,** MD, PhD currently working at the Department of Cardiovascular Prevention & Research Unit Clinic, National and Kapodistrian Univ. of Athens, GREECE. His research is focused on Cardiovascular prevention.
	**Petros P. Sfikakis**, MD, is the Dean of the School of Medicine at National and Kapodistrian University of Athens, Greece, and a Professor of Internal Medicine and Rheumatology. One of his main research interest focus in the cardiovascular outcomes of patients with immune-mediated diseases.
	**George D. Kitas,** MD, PhD, FRCP is director of Research & Development-Academic Affairs, Dudley Group NHS Foundation Trust, Dudley, UK. He is an Honorary Professor of Rheumatology at the Arthritis Research UK Epidemiology Unit.
	**Vijay Viswanathan** MD, PhD, FRCP is currently working as a chairman and director of MV Hospital for Diabetes and M Viswanathan Diabetes Research Centre, Chennai, India. His Research interests are Endocrinology Diabetes and Metabolism, Diabetes and foot research.
	**Jasjit S. Suri,** PhD, MBA is an innovator, visionary, scientist and an internationally known world leader in the field of biomedical imaging and healthcare management. Dr. Suri is a recipient of President Gold Medal (1980), Fellow of American Institute of Medical and Biological Engineering by National Academy of Sciences, Washington DC (2004) and Marquis Life Time Achievement Award (2018). Dr. Suri is board member with several organizations. Currently, he is chairman of AtheroPoint, USA. Dr. Suri has

	published over 700 papers/patents/books/trademarks with an H-index of 54.