BMJ Open

Evaluating atherosclerosis prevalence via coronary calcium in executives with normal LDL levels in the US: a cohort study–the clear protocol

Basem M Ratrout,[1] Basant E Katamesh ,[2] Ann Vincent,[3] Ryan T Hurt,[1] Sara Bonnes,[1] Jayanth Adusumalli,[2] Donna K Lawson,[1] Darrell Schroeder,[1] Christina D VerNess,[1] Ivana Croghan[2]

To cite: Ratrout BM, Katamesh BE, Vincent A, *et al* . Evaluating atherosclerosis prevalence via coronary calcium in executives with normal LDL levels in the US: a cohort study–the clear protocol. *BMJ Open* 2025;**15**:e094899. doi:10.1136/bmjopen-2024-094899

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-094899).

Received 10 October 2024
Accepted 01 May 2025

[1]Mayo Clinic, Rochester, Minnesota, USA
[2]General Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA
[3]Division of General Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to
Dr Basem M Ratrout; Ratrout.Basem@Mayo.edu

ABSTRACT

Introduction The coronary artery calcium (CAC) scan serves as a crucial tool in assessing the risk of coronary atherosclerosis in patients with hyperlipidaemia, particularly when there is ambiguity surrounding pharmacotherapy decisions. In addition to CAC, advanced glycation end products (AGEs), glycated proteins and lipids involved in ageing are emerging as markers for atherosclerosis. However, the relationship between AGEs score and CAC scores has not been evaluated to date. Our primary objective is to evaluate abnormal CAC scores in patients with low and borderline ASCVD risk and normal low-density lipoprotein cholesterol (LDL-C) levels ≤100 mg/dL. The secondary objective is to explore potential associations between CAC and AGEs scores.

Methods and analysis We will retrospectively review health records of adult patients seen at the General Internal Medicine Executive Health Program (Mayo Clinic; Rochester, Minnesota) between 1 September 2023 and 31 March 2024, where all patients were offered the option of a baseline CAC scan. For our primary aim, we will determine the percentage of patients with low and borderline 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk, not receiving pharmacotherapy for hyperlipidaemia, who have LDL-C levels ≤100 mg/dL and have an abnormal CAC score. For our secondary aim, we will examine potential associations between CAC and AGEs scores.

Ethics and dissemination This study was determined to be exempt from institutional review board approval (ID 24–0 03 921; 45 CFR 46.104d, category/subcategory 4(iii)) at the Mayo Clinic, Rochester. The findings of this study will be published in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study benefits from comprehensive data collection using multiple data sources, including CAC scores, AGEs scores, lipid levels and cardiac imaging results, providing a multidimensional view of cardiovascular risk.
⇒ This study will ensure the collection of accurate and reliable data by training data collectors, adapting prevalidated research tools and conducting regular quality checks.
⇒ This single-centre study is limited by its reliance on the type of patients that present to unique practice, and thus results cannot be generalised to the general population.
⇒ The study is limited by its reliance on patient records, which restricts reviewers to the availability and quality of documented information.

BACKGROUND

Coronary artery disease (CAD) poses a significant global health challenge, contributing substantially to morbidity and mortality worldwide.[1 2] CAD manifests through the gradual formation of atherosclerotic plaques within the coronary arteries, necessitating effective risk assessment and management strategies.[3] The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommend using 10-year ASCVD risk calculators to estimate cardiovascular risk, categorising it into four groups: low risk (< 5%), borderline (5% to <7.5%), intermediate risk (≥ 7.5% to <20%) and high risk (≥20% or greater).[4 5] Coronary artery calcium (CAC) scans are recommended for patients in the intermediate risk category when treatment decisions are unclear.[4 5] The CAC scan, a non-invasive CT procedure, quantifies the amount of calcified plaque present in the coronary arteries, aiding in the prediction of future cardiovascular events and guiding clinical decision-making.[4–6] A positive CAC scan indicates the presence of atherosclerosis. While international guidelines differ on the threshold for starting statin therapy, most agree on initiating it when the CAC score exceeds 100.[5] Notably, CAC scores over 300 are associated with a risk of adverse cardiac events comparable with that of patients with established CAD.[7]

Findings from two landmark studies indicate that traditional ASCVD risk models may fail to identify some patients with atherosclerosis, an issue of particular importance especially for those at high risk.[7 8] The COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) study, which assessed 4511 patients without prior ASCVD, reported that 703 healthy individuals had a score of >300, signifying a high risk for future ASCVD.[7] These patients would have been missed if CAC scans were not part of their clinical evaluation.[7] Similarly, in the MESA study, 480 out of 2174 patients were categorised as low-ASCVD risk and 356 out of 772 patients with borderline ASCVD risk had a positive CAC score, with a CAC ≥400 in 20 and 32 patients in these groups, respectively.[8] Therefore, adding CAC scoring to traditional risk assessment measures could be a method to identify higher-risk patients who might otherwise be overlooked.[9]

In clinical practice, ASCVD risk calculation is often initiated on observing elevated low-density lipoprotein cholesterol (LDL-C) levels, one of the variables inputted into the 10-year ASCVD risk calculation.[10] The 2018 AHA/ACC practice guidelines categorised LDL-C into optimal (below 100 mg/dL), near optimal/above optimal (100–129 mg/dL), borderline high (130–159 mg/dL), high (160–189 mg/dL), and very high (190 mg/dL and above). According to these guidelines, statins are typically recommended for high and very high LDL-C categories regardless of ASCVD risk.[10] The relationship between LDL-C levels and CAC scores is not yet well understood. At least one study has demonstrated evidence that even normal LDL-C levels are associated with subclinical atherosclerosis in the absence of other cardiovascular risk factors.[11] In this study, 4% of patients with LDL-C between 90 and 100 mg/dL and 7% of patients with LDL-C ranging 80–90 mg/dL, considered optimal LDL-C levels, showed subclinical atherosclerosis.[11] This suggests that some patients with optimal LDL-C may have subclinical atherosclerosis and could benefit from further diagnostic studies such as a CAC.[11] However, there is currently no data to guide clinical scenarios such as these.

In addition to 10-year ASCVD risk and LDL-C levels, other biomarkers, such as advanced glycation end products (AGEs), glycated proteins and lipids, are currently being investigated as potential supplementary biomarkers of ageing and atherosclerosis.[12–14] AGEs influence atherosclerosis by making LDL-C more atherogenic, promoting oxidative stress and inflammation, and raising blood pressure through vascular stiffness and endothelial dysfunction. A review by Sharifi-Zahabi *et al* reported that higher AGEs were significantly associated with increased all-cause and mortality.[15] Assessing the feasibility of incorporating AGEs into routine cardiovascular evaluations could be worthwhile, but this necessitates further study.[16 17]The objective of our study is to determine the percentage of patients with low and borderline ASCVD risk, particularly those with normal LDL-C levels who have a positive CAC score. Additionally, we aim to explore potential associations between CAC scores and AGEs scores.

METHODS

Study design and setting

We will retrospectively review the medical records of adult patients who received medical care and completed a CAC study at the Mayo Clinic Executive Health Programme (MCEHP) in Rochester, Minnesota, between 1 September 2023 and 31 March 2024. The project is scheduled to commence in the third-quarter of 2024, with anticipated completion by 31 December 31.

Objectives

For all included patients, we will assess and categorise 10-year ASCVD risk, CAC scores, LDL-C levels, and AGEs.

Study sample and sampling techniques

Study entry criteria will include being an empaneled patient aged 40–75 years old in the MCEHP, having provided authorisation for research, completed a CAC scan (done in all patients aged 45 and above in our practice), had low or borderline 10 year ASCVD risk and completed a lipid profile, figure 1. We anticipate that a total of approximately 1000 patients will meet the inclusion criteria. Based on a preliminary review of our practice, we anticipate that approximately 250 of the 1000 patients will have normal LDL-C, no established CAD and will not be taking pharmacotherapy. We hypothesise that 5%–10% of individuals with normal LDL-C levels will have abnormal CAC scores. With a denominator of 250 and an expected calcium scan abnormality rate of 10% or less, the margin of error for a 95% CI is expected to be approximately 3.5%, such that any observed calcium abnormality rate (CAR) of 10% or less would yield a CI of CAR+/-3.5%. This is based on using nQuery Advisor 7.0 (CI for a proportion using the normal approximation).

Definition

Abnormal coronary calcium will be defined as a CAC score above 0. The coronary artery calcification scoring protocol in our institution involves performing an ECG-gated CT scan of the heart. The patient's calcium score is calculated using the Agatston–Janowitz scale, with a threshold of 130 Hounsfield units (HU) to differentiate calcified plaque from other tissues. We define normal LDL-C as ≤100 mg/dL. The calculation of LDL-C in our institution uses the Sampson NIH equation. The 10-year ASCVD will be estimated using the ASCVD risk estimator offered by the ACC. [18]The AGEs reader, a non-invasive and clinically validated device, will be used to estimate glycated proteins by measuring autofluorescence in human skin tissue.[16]

Team composition and training

A comprehensive training reference guide will be created before data extraction. This guide will serve as a vital resource, outlining the project's specific objectives. Any

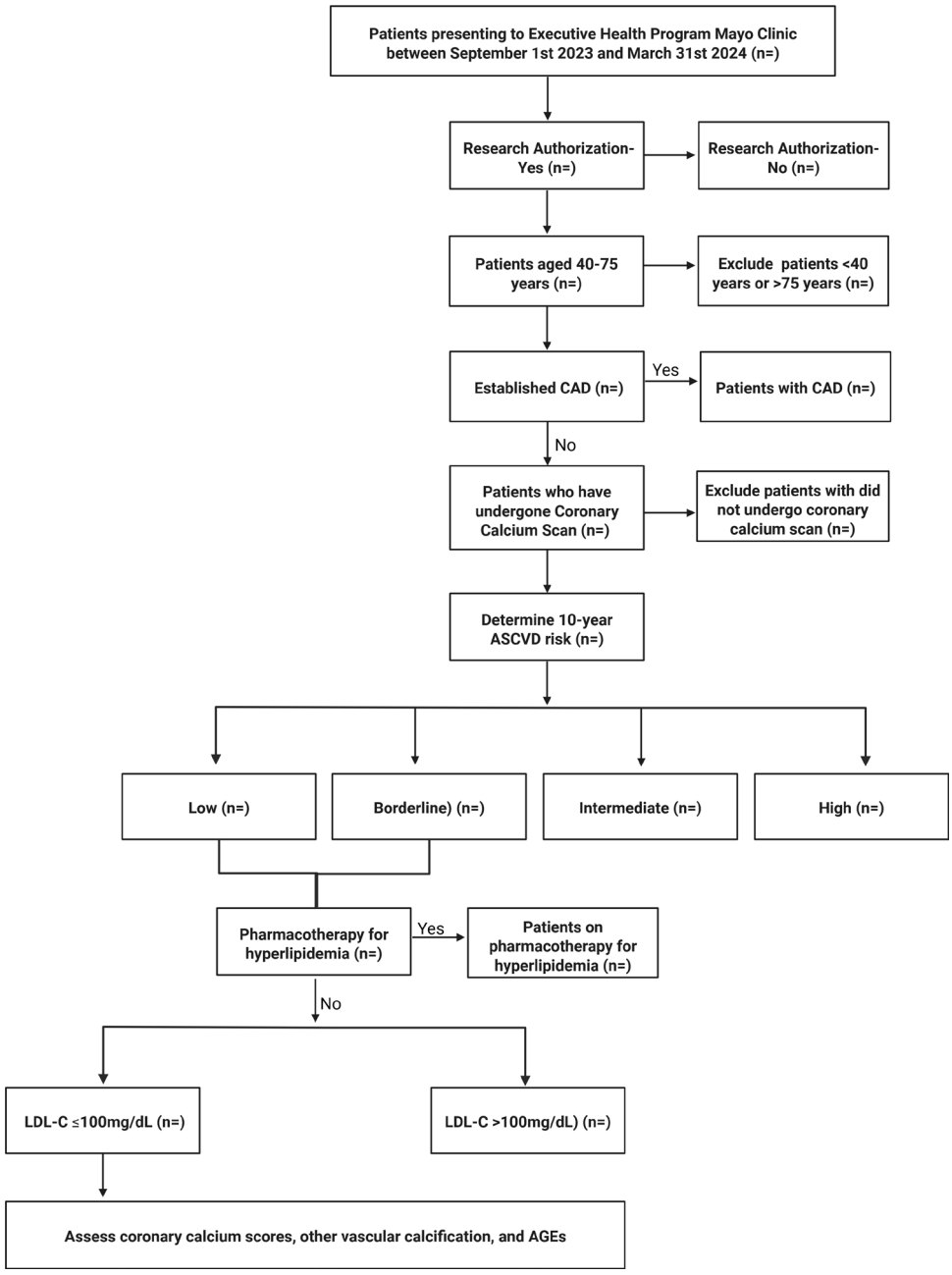

Figure 1 Enrollment and Screening Process Flowchart. AGEs, advanced glycation end products.

updates or changes to the project will be promptly incorporated into this guide and communicated to other members of the team. Training sessions will be conducted whenever a new abstractor joins the team, ensuring that each member is well trained in the extraction process. Prior to chart reviews, all members of the reviewing team will undergo training on the study protocol, key definitions and the use of research tools. They will practise with test cases created by the adjudicators to familiarise themselves with the tools and identify any issues for review.

Record review and data collection approach

Data for this study will be abstracted from the electronic health record (Epic software; Epic Systems Corporation), and data will be subsequently collated through REDCap (Research Electronic Data Capture).[19 20] The data abstraction sheet will be structured into five distinct sections: baseline demographic characteristics, laboratory test results, CAC scan and scoring details, cardiac imaging findings, and AGEs scores and risk categories, online supplemental 1–4. The first section of the data extraction sheet will include baseline demographic characteristics that were already collected at the time of their physical exam as illustrated in online supplemental 1. The second section of the data extraction sheet are laboratory variable results collected closest to their CAC scan, online supplemental 2. The third section of the data extraction sheet will detail variables obtained from CAC scans, online supplemental 3. The fourth section of the data extraction

sheet will consist of imaging variables, including findings from baseline ECG, echocardiography, carotid ultrasonography, stress echocardiography and exercise electrocardiography, online supplemental 4. For the secondary objective of this cohort study, AGEs scores and risk categories will be extracted. All variables closest to the CAC date will be collected and their dates recorded in the abstraction sheet. This will help us determine the effect of temporality, if any, following data abstraction.

Quality assurance

To ensure the accuracy and reliability of the extracted data, we plan to do random spot checks on the REDCap dashboard. Our objective is to maintain a 10% spot-check rate, equating to approximately 10 checks per page, with each page containing 100 patient records. These spot checks will be assigned randomly to avoid bias and will be conducted by reviewers independent of those who initially extracted the data. This dual-review process is crucial for identifying any discrepancies or errors that may have been overlooked during the initial data extraction phase. If mistakes are identified during the spot checks, they will be promptly corrected. In addition to correcting the errors, individuals responsible for the mistakes will undergo retraining to address any gaps in knowledge.

Data analysis plan

Patients will be initially categorised into established CAD or no established CAD, figure 1. Patients with established CAD will be excluded. Patients without established CAD and those who have completed a coronary calcium study will be categorised according to 10-year ASCVD risk. Patients with low or borderline 10-year ASCVD risk who are not on pharmacotherapy for hyperlipidaemia will be categorised based on LDL-C levels into two groups: ≤100 mg/dL (group 1) and >100 mg/dL (group 2). Data on CAC scores, other vascular calcifications and AGEs in this group will be summarised. Following this, we will compare baseline characteristics of group one with the other groups: patients with established CAD (group 3), patients with high 10-year ASCVD (group 4), patients with intermediate 10-year ASCVD (group 5), patients with low and borderline 10-year ASCVD on pharmacotherapy (group 6), and patients with low and borderline 10 year ASCVD and LDL >100 (group 2), figure 1.

Group 1 will be categorised based on the presence or absence of detectable coronary calcium, and two group comparisons will be done. Data will be summarised using median (25^{th}, 75^{th} percentile) for continuous variables and n (%) for categorical variables. Following this, unadjusted, age-adjusted and sex-adjusted analyses will be performed using logistic regression for group 1. Analysis will be conducted using the SAS V. 9.4 (SAS Institute Inc, Cary NC).[21] For the secondary aim of this investigation, correlation analyses and general linear models will be used to assess the association of AGEs, indicative of cumulative metabolic stress, with CAC scores and lipid profiles. For these analyses, distributional assumptions will be assessed with variable transformations (eg, log transformation) used as appropriate. Several other variables, such as echocardiogram, carotid ultrasound, cardiac perfusion stress test, and incidental CT findings, online supplemental 3 and 4, are being collected as part of the chart review and will be used at a later date in the preparation of additional manuscripts.

Patient and public involvement and ethics

Patient or public involvement was not incorporated in the design, conduct, reporting or dissemination plans of this research.

DISCUSSION

The rationale for this study stems from the limitations of traditional ASCVD risk models in identifying all patients with atherosclerosis, particularly those with normal LDL-C levels.[22] Asymptomatic individuals with normal or borderline 10-year ASCVD risk and normal LDL-C levels may still have subclinical atherosclerosis, detectable through CAC scanning. Clinical observations, along with results from the MESA and CONFIRM studies, demonstrate that atherosclerosis can occur in patients with low cardiovascular risk.[7 8] Additionally, Fernández-Friera *et al* have observed abnormal CAC scores in patients with normal LDL-C levels, suggesting that relying solely on risk models or LDL-C levels may be insufficient for detecting potentially at-risk patients with atherosclerosis.[11] This supports the rationale for our study. These patients are often seen in primary care settings that do not routinely use CAC scans and could benefit from such scans, enabling timely interventions. By investigating the prevalence of abnormal CAC scores in this cohort, we aim to contribute to the existing literature on the potential benefits of CAC scans for these patients.

The rationale for this study arises from the limitations of traditional ASCVD risk models in identifying all patients with atherosclerosis, especially those with normal LDL-C levels. Asymptomatic individuals with normal or borderline 10-year ASCVD risk and normal LDL-C levels may still have subclinical atherosclerosis, detectable through CAC scanning.[22] Clinical observations, results from the MESA and CONFIRM studies that demonstrate atherosclerosis in patients with low cardiovascular risk and observations of abnormal CAC scores in patients with normal LDL-C levels by Fernández-Friera *et al* suggest that relying solely on risk models or LDL-C levels may be inadequate for detecting potentially at-risk patients with atherosclerosis and support the rationale for this study.[7 9 11] These patients are often seen in primary care settings that do not routinely use CAC scans and could benefit from such scans enabling timely interventions. By investigating the prevalence of abnormal CAC scores in this cohort, we aim to contribute to the existing literature on the potential benefits of CAC scans for these patients.

Building on this, evidence suggests a pathophysiological link between AGEs and atherosclerosis, cardiovascular

disease and mortality[12–14] . It is plausible that AGEs may correlate with coronary calcium, a marker for detecting coronary atherosclerosis.[15 23–28] However, no studies have explored possible associations between AGEs and CAC, which will be unique to this retrospective cohort study. By investigating this potential association, we aim to determine whether AGEs could serve as a predictive biomarker for CAD, even in patients with normal LDL-C levels. This could provide valuable insights into the underlying mechanisms of cardiovascular disease and help identify individuals at higher risk, thereby improving prevention and treatment strategies.

The findings of our study could pave the way for future research to evaluate the use of CAC scans in cardiovascular risk stratification, potentially enhancing clinical guidelines and practices, and integrating CAC scoring into risk prediction models.

Ethics and dissemination

This study underwent expedited review procedures and was determined to be exempt from institutional review board approval (ID 24–003921; 45 CFR 46.104d, category/subcategory 4(iii)). Ethical principles have and will continue to be carefully considered and adhered to, and only patients who previously consented to the use of their data for research purposes will be included in this cohort. Unique identifiers will be created to document all findings, ensuring the anonymity of the patients whose records are being reviewed. Data will be securely stored on encrypted, institution-approved cloud services, with access limited to the investigating team. Any modifications to the study design will be promptly submitted to the ethics review committee for review.

The results of this study will be disseminated through publication in a peer-reviewed journal and presentations at both national and international academic conferences. Additionally, we aim to promote our findings via social media platforms.

X Ivana Croghan @IvanaCroghanPhD

Contributors All persons listed as contributors met the International Committee of Medical Journal Editors (ICMJE) authorship criteria. Each author has made significant contributions to the writing and revisions to the study and has provided complete assent for publication. BMR, BEK, AV, RTH, SB, JA, CDV and IC were responsible for the conceptualisation of the study. AV, RTH, SB, DKL and IC were responsible for supervising all activities. All authors contributed to designing the methodology. BMR, BEK, AV and DS were responsible for calculating the sample size and formulating the data analysis plan. Each author is responsible for the content and has read and approved the final manuscript. BMR is the guarantor of this work and accepts full responsibility for the integrity of the data, the accuracy of the analysis and the decision to submit for publication.

Funding This research will be supported by internal division funds, Division of General Internal Medicine, Department of Medicine, Mayo Clinic. Statistical support for this project will be provided by the Mayo Clinic Department of Medicine Research Hub. REDCap will be the data entry system for this study. The REDCap data entry system was supported in part by the Center for Clinical and Translational Science Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but This study was determined to be exempt from institutional review board approval (ID 24-003921; 45 CFR 46.104d, category/subcategory 4[iii]) at Mayo Clinic, Rochester. The findings of this study will be published in a peer-reviewed journal. exempted this study Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD

Basant E Katamesh http://orcid.org/0000-0001-9992-2387

REFERENCES

1 Vaduganathan M, Mensah GA, Turco JV, *et al*. The Global Burden of Cardiovascular Diseases and Risk: A Compass for Future Health. *J Am Coll Cardiol* 2022;80:2361–71.
2 WHO. Cardiovascular diseases (cvds). 2021. Available: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
3 Mitsis A, Khattab E, Christodoulou E, *et al*. From Cells to Plaques: The Molecular Pathways of Coronary Artery Calcification and Disease. *J Clin Med* 2024;13:6352.
4 Arnett DK, Blumenthal RS, Albert MA, *et al*. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596–646.
5 Golub IS, Termeie OG, Kristo S, *et al*. Major Global Coronary Artery Calcium Guidelines. *JACC Cardiovasc Imaging* 2023;16:98–117.
6 Lo-Kioeng-Shioe MS, Vavere AL, Arbab-Zadeh A, *et al*. Coronary Calcium Characteristics as Predictors of Major Adverse Cardiac Events in Symptomatic Patients: Insights From the CORE 320 Multinational Study. *J Am Heart Assoc* 2019;8:e007201.
7 Budoff MJ, Kinninger A, Gransar H, *et al*. When Does a Calcium Score Equate to Secondary Prevention?: Insights From the Multinational CONFIRM Registry. *JACC Cardiovasc Imaging* 2023;16:1181–9.
8 Dzaye O, Razavi AC, Michos ED, *et al*. Coronary artery calcium scores indicating secondary prevention level risk: Findings from the CAC consortium and FOURIER trial. *Atherosclerosis* 2022;347:70–6.
9 Greenland P, Blaha MJ, Budoff MJ, *et al*. Coronary Calcium Score and Cardiovascular Risk. *J Am Coll Cardiol* 2018;72:434–47.
10 Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. *J Am Coll Cardiol* 2019;73:e285–350.
11 Fernández-Friera L, Fuster V, López-Melgar B, *et al*. Normal LDL-Cholesterol Levels Are Associated With Subclinical Atherosclerosis in the Absence of Risk Factors. *J Am Coll Cardiol* 2017;70:2979–91.
12 Hegab Z, Gibbons S, Neyses L, *et al*. Role of advanced glycation end products in cardiovascular disease. *World J Cardiol* 2012;4:90–102.
13 Hodgkinson CP, Laxton RC, Patel K, *et al*. Advanced glycation end-product of low density lipoprotein activates the toll-like 4 receptor pathway implications for diabetic atherosclerosis. *Arterioscler Thromb Vasc Biol* 2008;28:2275–81.

14 Vekic J, Vujcic S, Bufan B, *et al*. The Role of Advanced Glycation End Products on Dyslipidemia. *Metabolites* 2023;13:77.
15 Sharifi-Zahabi E, Sharafabad FH, Abdollahzad H, *et al*. Circulating Advanced Glycation End Products and Their Soluble Receptors in Relation to All-Cause and Cardiovascular Mortality: A Systematic Review and Meta-analysis of Prospective Observational Studies. *Adv Nutr* 2021;12:2157–71.
16 Diagnoptics. Advanced glycation endproducts readers. n.d. Available: https://www.diagnoptics.com/advanced-glycation-endproducts
17 Perrone A, Giovino A, Benny J, *et al*. Advanced Glycation End Products (AGEs): Biochemistry, Signaling, Analytical Methods, and Epigenetic Effects. *Oxid Med Cell Longev* 2020;2020:3818196.
18 Cardiology ACo. ASCVD risk estimator plus. n.d. Available: https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate
19 Ho JE, Lyass A, Courchesne P, *et al*. Protein Biomarkers of Cardiovascular Disease and Mortality in the Community. *J Am Heart Assoc* 2018;7:e008108.
20 Jensen LJN, Flyvbjerg A, Bjerre M. Soluble Receptor for Advanced Glycation End Product: A Biomarker for Acute Coronary Syndrome. *Biomed Res Int* 2015;2015:815942.
21 Inc. SI. SAS/stat® 15.3 user's guide. Cary, NC SAS Institute Inc. Available: https://documentation.sas.com/api/collections/pgmsascdc/9.4_3.5/docsets/statug/content/sashelp.pdf?locale=en
22 Orringer CE, Blaha MJ, Blankstein R, *et al*. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *J Clin Lipidol* 2021;15:33–60.
23 Ebert H, Lacruz ME, Kluttig A, *et al*. Association between advanced glycation end products, their soluble receptor, and mortality in the general population: Results from the CARLA study. *Exp Gerontol* 2020;131:110815.
24 Raposeiras-Roubín S, Rodiño-Janeiro BK, Grigorian-Shamagian L, *et al*. Relation of soluble receptor for advanced glycation end products to predict mortality in patients with chronic heart failure independently of Seattle Heart Failure Score. *Am J Cardiol* 2011;107:938–44.
25 Schwedler SB, Metzger T, Schinzel R, *et al*. Advanced glycation end products and mortality in hemodialysis patients. *Kidney Int* 2002;62:301–10.
26 Semba RD, Bandinelli S, Sun K, *et al*. Plasma carboxymethyllysine, an advanced glycation end product, and all-cause and cardiovascular disease mortality in older community-dwelling adults. *J Am Geriatr Soc* 2009;57:1874–80.
27 Harris PA, Taylor R, Minor BL, *et al*. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
28 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.