CAC PREVENTABLE

STUDY PROTOCOL

Coronary **A**rtery **C**alcium

in **PR**agmatic **EV**aluation of ev**ENT**s **A**nd **B**enefits of **L**ipid-lowering in old**E**r adults

(**CAC PREVENTABLE**)

Protocol Amendment 1

Version Date: 09 December 2022

Protocol Amendment 2

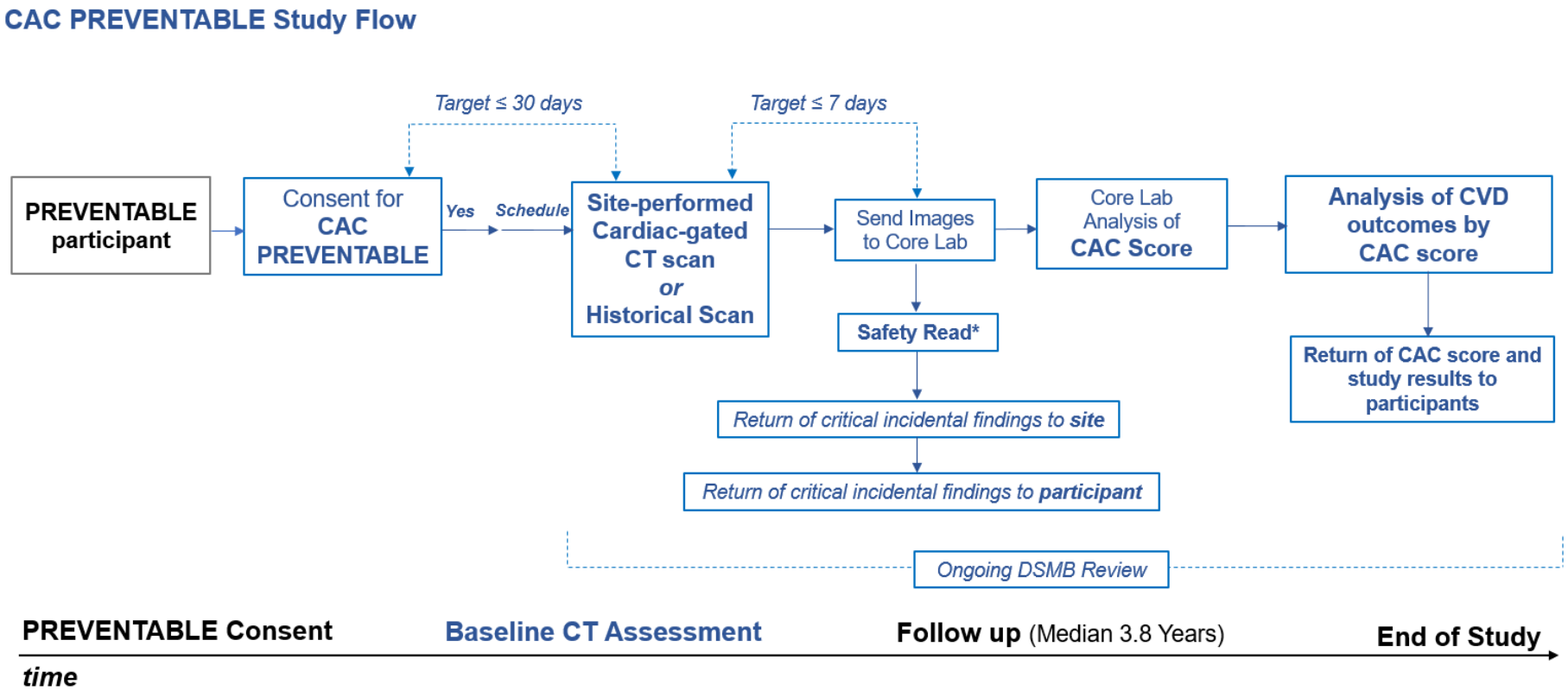
Version Date: 13Sep2024

STUDY SUMMARY:

Title	**C**oronary **A**rtery **C**alcium in **PR**agmatic **EV**aluation of ev**ENT**s **A**nd **B**enefits of **L**ipid-lowering in old**E**r adults (**CAC PREVENTABLE**)
Primary Objective	To determine the value of a biomarker-guided precision medicine approach for assessing subclinical atherosclerotic cardiovascular disease (ASCVD) as reflected by coronary artery calcium (CAC) score to inform individual benefit of statin therapy in an older primary prevention population.
Secondary Objective	Develop a comprehensive ASCVD risk classification model for calculating estimated benefit of statin therapy in the age ≥75 years primary prevention population using traditional risk factors, CAC, and accounting for non-CVD competing risks.
Study Hypothesis	Older adults with high CAC scores gain greater absolute benefit in lowering ASCVD events with statin therapy, while those with zero or low CAC do not benefit.
Study Design	CAC PREVENTABLE is a substudy of the multi-center PREVENTABLE trial, in which participants are randomized 1:1 to atorvastatin 40mg or placebo.
Population	PREVENTABLE participants, all of whom are age ≥75 years without dementia, disability or clinically evident cardiovascular disease.
Study Location	Approximately 60 sites
Inclusion Criteria	Enrolled in PREVENTABLE
Exclusion Criteria	None

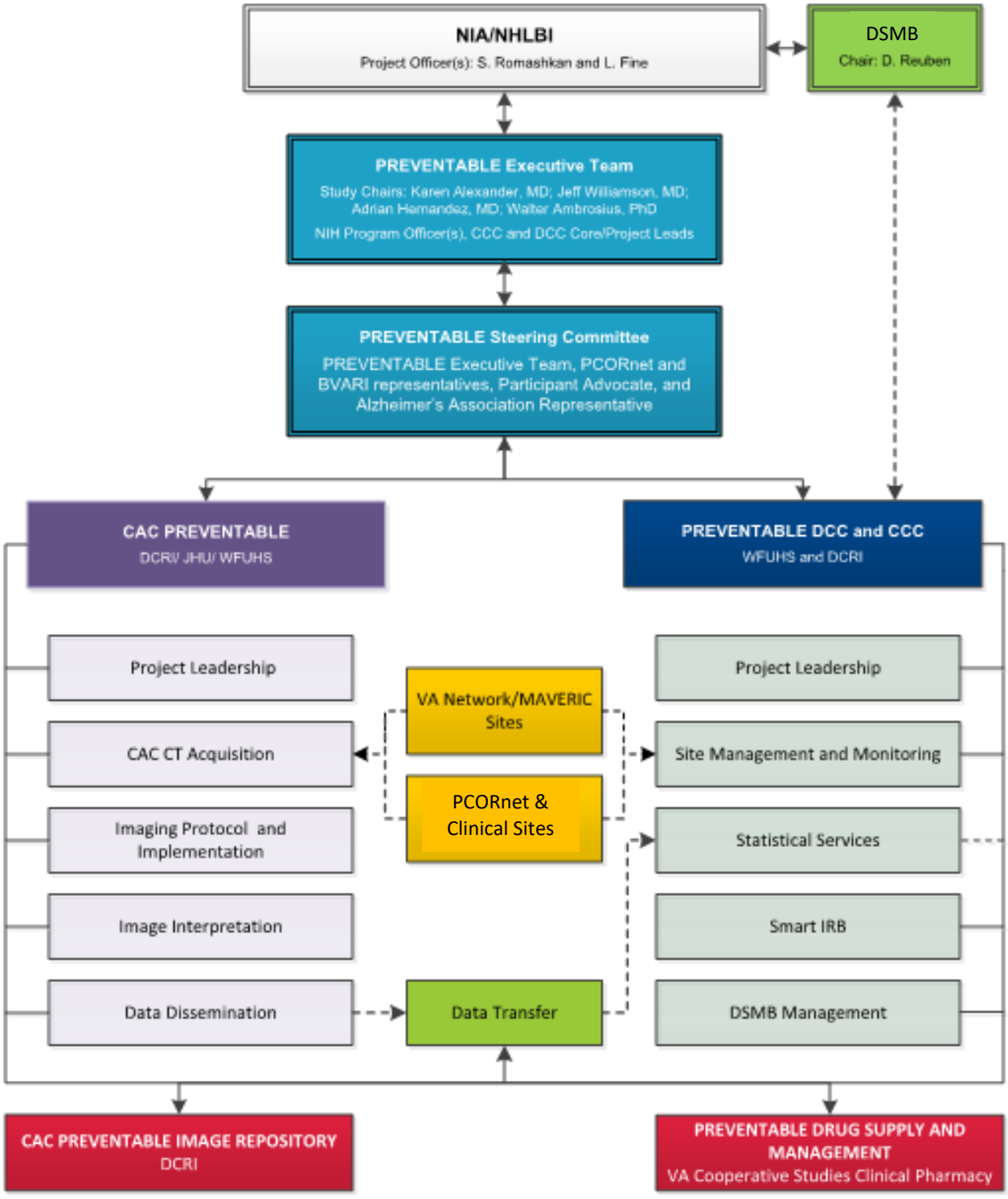
Primary Endpoint	ASCVD composite outcome of cardiovascular death, hospitalization for myocardial infarction (MI)/unstable angina, heart failure, stroke, or revascularization.
Secondary Endpoint(s)	Incidence of ASCVD composite as a function of CAC
Exploratory Endpoint(s)	• Individual components of the primary endpoint • Composite of incident mild cognitive impairment, probable dementia, or persistent disability, and all-cause mortality • All-cause mortality
Data Sources	Electronic health record, Medicare claims, National Death Index, telephone/electronic contact, and in-person assessment
Study Length	Recruitment over approximately 3 years; median follow-up 3.8 years.
Statistical Considerations	A sample size of approximately 10,000 participants is expected to provide >85% power to evaluate heterogeneity for the effects of statin therapy on ASCVD outcomes stratified by CAC

STUDY DESIGN:



CAC PREVENTABLE flow in blue; PREVENTABLE flow in black. CAC = coronary artery calcium; CT = computed tomography; CVD = Cardiovascular Disease; DSMB = Data Safety and Monitoring Board; PREVENTABLE = PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults
**Safety reads will not be done on historical scans because a prior clinical interpretation has already been performed.*

OPERATIONAL STRUCTURE:



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CHAPTER 1: BACKGROUND AND RATIONALE

1.1 Cardiovascular Risk Assessment in Older Adults

Clinical practice guidelines recommend risk assessment as the first step in medical decision-making for primary prevention of atherosclerotic cardiovascular disease (ASCVD), with the dual goal of *limiting overtreatment* and *maximizing benefit* of those who are treated.[1-7] For example, the 2019 ACC/AHA Primary Prevention Guidelines recommend using the Pooled Cohort Equations (PCE) to estimate 10-year risk of ASCVD in adults age 40-75 without diabetes, providing a Class I recommendation for moderate to high intensity statin therapy (Class I) in those with >7.5% risk.[2] However, while current guidelines outline recommendations for patients age 40-75, they provide little guidance for risk assessment in adults ≥75 years of age.[1, 2] This is predominantly due to lack of proven risk prediction tools and the increased complexity of decision making in this population.

Traditional risk factors, such as hypertension and hyperlipidemia, are highly prevalent with aging and isolated measurements of blood pressure or low density lipoprotein cholesterol (LDL-C) show reduced capacity for risk discrimination in older as compared to younger adults.[8, 9] More importantly, current guideline-approved risk prediction models are heavily weighted by age, indiscriminately assigning high risk status and therefore recommending treatment for nearly all older adults even before the age of 75.[10-12] This raises concerns about overmedication, drug-drug interactions, lack of personalization, and misallocation of limited healthcare resources in an aging population which often requires multiple pharmacotherapies.

Competing risks (e.g., cancer, chronic kidney disease, and dementia) are another critical issue in this population, requiring a fine balance between accurate ASCVD risk prediction and prevention vs. focusing management on other comorbidities.[13, 14] Currently, accurate person-centered risk prediction at older ages remains unachievable using traditional risk factor models as these approaches do not capture lifetime cumulative exposure or account for individual resiliency to disease.

1.2 Coronary Artery Calcium

Coronary artery calcium (CAC) scoring, obtained from a computed tomography (CT) scan of the heart, is a direct measure of atherosclerotic burden and is an established and robust tool that quantifies a composite of: 1) Lifelong cumulative risk factor exposure; and 2) Individual resilience or vulnerability to risk factors.[15-17] Indeed, CAC is the strongest single risk factor for ASCVD.[18-22] In addition, zero and low CAC are strong “negative risk factors”, useful for “de-risking” individuals who may be less suitable for preventive therapy despite presence of traditional risk factors.[23-29] Moreover, by integrating the cumulative lifetime exposure to risk factors, both measurable (traditional risk factors) and unmeasurable (environmental exposure, genetics), while also accounting for individual susceptibility and resilience, CAC appears to be an even more comprehensive risk factor indicative of many outcomes important to older adults. Obtaining historical non-gated, non-contrast chest CTs will provide important insights about the analytic and predictive potential of routinely acquired chest CT obtained for other clinical indications, which has already shown significant promise in selected populations (patients with a history of Hodgkins lymphoma, breast cancer, and individuals undergoing lung cancer screening). The COVID-19 pandemic increased the clinical indication for non-contrast chest CTs, making it likely that more PREVENTABLE participants will have an eligible scan that can be transmitted for a pragmatic analysis of CAC.

1.3 CAC in ASCVD Risk Assessment and Statin Treatment

Despite a wealth of high quality observational epidemiological evidence on the prognostic value of CAC for ASCVD risk assessment,[15-35] and the recent US and European class IIa guideline recommendation for further risk assessment in borderline/intermediate risk individuals,[1-3] the persistent barrier to more widespread use and reimbursement of CAC in routine patient care is the lack of a large RCT enabling pre-specified analysis by baseline CAC.[36, 37] In the last few years, several studies have been published supporting the hypothesis that CAC identifies subgroups more likely to derive relative and absolute benefit from statins.[38-41] Secondary analyses of the small underpowered 1,005 participant St. Francis Heart RCT, the only primary prevention statin trial with baseline CAC measurement, demonstrated little benefit of atorvastatin 20 mg in patients with low CAC scores, yet a hypothesis-generating 42% relative risk reduction (RRR) and 6.3% absolute risk reduction (ARR, number needed to treat =13) in those with CAC >400.[38] In a real-world analysis of clinical data from Walter Reed Medical Center which used sophisticated statistical tools to allow matching of statin users vs. non-users, over 12 year follow-up there was no observed benefit of statin therapy in those with CAC=0 (hazard ratio [HR] 0.99), yet 44% RRR in those with CAC >400.[39] In secondary analysis of the WOSCOPS RCT, pravastatin was shown to decrease hs-Tn concentration, with absolute reduction in CHD outcomes proportion to the decrease in troponin.[41] Results from these preliminary studies, if confirmed in a large RCT such as CAC PREVENTABLE, would guide statin treatment among older adults that have been understudied in clinical trials and for whom clinical guidelines are currently silent.

1.4 Atherosclerosis Imaging and Serum Biomarker-Based Precision Medicine to Guide Preventive Therapy

The promise of precision medicine is the ability to individualize prevention and focus treatment on those most likely to derive benefit.[42] Currently, asymptomatic individuals taking statins for primary ASCVD prevention represent a mix of those who may benefit and those who will not. Similarly, a large number of individuals likely to benefit from preventive statin therapy are not being treated due to inadequate risk assessment. By directly visualizing atherosclerotic plaque (the substrate against which statins modify risk) with CAC, we believe our proposed approach in CAC PREVENTABLE is the most promising for informing person-centered care in older adults. CAC PREVENTABLE will fundamentally change the approach to preventive therapy, potentially limiting overtreatment and focusing statin therapy on those most likely to benefit.

CHAPTER 2: HYPOTHESIS AND OBJECTIVES

2.1 Evaluate the hypothesis that older adults with high CAC scores gain greater absolute benefit in lowering ASCVD events with randomization to statin therapy, while those with zero or low CAC do not benefit from statins.

2.2 Develop a comprehensive ASCVD risk classification model and online tool for calculating estimated benefit of statin therapy in the age ≥75 primary prevention population using traditional risk factors and CAC with detailed accounting for non-CVD competing risks.

CHAPTER 3: STUDY DESIGN AND ENDPOINTS

3.1 Study Design

CAC PREVENTABLE will enroll 10,000 PREVENTABLE participants willing and able to undergo cardiac-gated non-contrast chest CT and/or a pre-existing chest CT for CAC assessment at baseline. For participants that are unable to attend an in-person visit for the study CT, but have an eligible pre-existing chest CT prior to or while in PREVENTABLE, this historical scan will be submitted and analyzed for CAC (if multiple, then the CT closest to PREVENTABLE enrollment date). All PREVENTABLE participants can be enrolled in CAC PREVENTABLE. CAC scans should be performed within 30 days of consent for CAC PREVENTABLE. After the CAC scan, participants will be notified by the site of potential clinically significant incidental findings on the CAC scans via safety reads performed centrally at the DCRI Imaging Core Laboratory. Historical chest CTs will not have a safety read performed because a prior clinical interpretation has occurred.

The CAC scores will remain blinded to participants and site investigators until after database lock. At study conclusion, all participants undergoing a dedicated CAC scan will receive a detailed report with their individualized CAC score and information about statin effect on risk reduction for their given CAC score. Follow-up of outcomes will be conducted as per the PREVENTABLE protocol through 2027, targeting a median follow-up of 3.8 years in CAC PREVENTABLE. The primary and secondary CAC-PREVENTABLE study outcomes will be analyzed and presented after primary database lock for the PREVENTABLE trial.

3.2 Endpoints

CAC PREVENTABLE will determine the benefit of statin therapy in the age ≥75 primary prevention population for reduction of ASCVD events based on CAC with detailed accounting for traditional risk factors and non-CVD competing risks.

3.2.1 Primary Endpoint

ASCVD composite outcome of cardiovascular death, hospitalization for myocardial infarction (MI)/unstable angina, heart failure, stroke, or revascularization

3.2.2 Secondary Endpoint

Incidence of ASCVD composite as a function of CAC

3.2.3 Exploratory Endpoints

- Individual components of the primary endpoint
- Composite of incident mild cognitive impairment, probable dementia, or persistent disability; and all-cause mortality
- All-cause mortality

CHAPTER 4: CAC PREVENTABLE POPULATION

4.1 Cohort identification.

CAC PREVENTABLE will recruit 10,000 participants ≥75 years of age from participating PREVENTABLE sites across the United States. All participants must be enrolled in PREVENTABLE to be included in CAC PREVENTABLE.

4.2 Inclusion Criteria

- Enrolled in PREVENTABLE

4.3 Exclusion Criteria

- None

CHAPTER 5: RECRUITMENT STRATEGY

CAC PREVENTABLE will enroll a subgroup of PREVENTABLE participants, which allows for strategies to enrich for racial/ethnic diversity, including targeted recruitment via community engagement and potentially capped enrollment of overrepresented groups. The target is to oversample minority populations among older adults. We will also be monitoring enrollment by sex, education, and geographic socioeconomic indicators (Area Deprivation Index)[43] to ensure equity and balanced representation in the CAC PREVENTABLE population.

CHAPTER 6: SCHEDULE OF EVENTS

TABLE 1	After PREVENTABLE Enrollment	CAC PREVENTABLE Consent to 30 Days	7 Days from CAC Scan	21 Days from CAC Scan Receipt	End of PREVENTABLE Study
Informed Consent	X[1]				
Historical CT scan*	X				
CAC scan		X[2]			
CAC scan transmission			X[3]		
Historical chest CT scan transmission		X			
Safety Report				X[4]	
CAC Report					X[5]

[1]Any participants enrolled in PREVENTABLE may be consented for CAC PREVENTABLE.
[2]Sites will be responsible for: 1.scheduling the CAC scan for participants within a target of 30 days of consenting for CAC PREVENTABLE; and 2. entering the CAC scan appointment into the PREVENTABLE website.
[3]Sites will be required to transmit CAC scan via AGMednet to the imaging core laboratory within approximately 7 business days of CAC scan being performed.
[4]Safety report for potentially clinically significant incidental findings will be sent to sites +/- 21 business days from a query-free CAC scan received by the imaging core laboratory; site to distribute to participant & notify site PI of positive results. No safety read on historical scans.
[5]At PREVENTABLE study end, participants will receive, from the data coordinating center, a detailed report with their personal CAC score. Information about statin effect on risk reduction for their given CAC score will also be provided in the report.
*Pre-existing clinical CT scans used in lieu of, or in addition to a CAC scan, can be submitted utilizing the waiver of consent in PREVENTABLE

Schedule of Events:
After site activation, all PREVENTABLE participants will be approached about consent for CAC PREVENTABLE during their enrollment visit (Table 1) and medical records will be reviewed for eligible pre-existing clinical scans. In addition, those participants previously randomized to PREVENTABLE may also be contacted for participation in CAC PREVENTABLE and medical records will be reviewed for eligible pre-existing clinical scans. Sites will be responsible for scheduling the CAC scan at their site or local diagnostic imaging center to be performed within approximately 30 days of consent for CAC PREVENTABLE. The site coordinator will enter the

appointment for the CAC scan into the PREVENTABLE website to facilitate a patient reminder text or email. No clinical interpretation of the CAC scan is required to be performed at the site; all interpretation and analysis will be performed in the imaging core laboratory. Sites are required to deidentify and transmit the CAC scans via AGMednet to the imaging core laboratory within approximately 7 business days of scan acquisition.

After CAC images have been transmitted to the central imaging core laboratory, images will be reviewed for critical incidental findings within approximately 21 business days of query-free receipt of scan. Safety reports will be generated by physician readers in the central imaging core laboratory for the presence or absence of six potentially clinically significant incidental findings in the cardiac field of view (see section 8.2). Safety reports indicating the absence or presence of incidental findings will be generated by the imaging core laboratory and returned to the sites for distribution to participants. The site PI and site coordinator will receive an alert and email notifying them of any positive incidental findings. Clinical follow-up should be arranged as per standard of care at each site. Historical chest CTs will not have a safety read performed because a prior clinical interpretation has occurred.

For participants that are unable to attend an in-person visit for the study CT, but have an eligible pre-existing chest CT prior to or while in PREVENTABLE, this scan will be submitted and analyzed for CAC (if multiple, then the CT closest to PREVENTABLE enrollment date). Sites will transmit the most recently available pre-existing chest CT scans via AGMednet to the imaging core laboratory for CAC analysis. Historical chest CTs will not have a safety read performed because a prior clinical interpretation has occurred. Additionally, participants who have dedicated study CT and an eligible pre-existing chest CT, both will be submitted for CAC analysis. This will be important for internal control and validation between gated and non-gated chest CT.

CAC scores will remain blinded to participants, clinicians and site investigators. Participant's individual CAC score reports generated from dedicated CAC scans will be returned at the conclusion of the trial by the data coordinating center. This detailed report will include participant's personal CAC score from the dedicated CAC scan done for this research study. Information about statin effect on risk reduction for their given CAC score will also be provided in the report.

CHAPTER 7: SITE RESPONSIBILITIES AND MANAGEMENT

Any willing participant who has consented to PREVENTABLE is eligible to participate in CAC PREVENTABLE. Only one additional visit for the CAC scan is required for those able to attend an in-person visit for the study CT. The CAC scan should be performed within approximately 30 days of consent for CAC PREVENTABLE. Individualized reporting on incidental findings in the short-term safety report will help to keep participants informed and engaged. No additional visits are required for those who cannot attend an in-person visit and for whom only a historical non-gated, non-contrast chest CT will be submitted and analyzed.

Specific Site Responsibilities:

1. Consent participants for CAC PREVENTABLE (any participant enrolled in PREVENTABLE is eligible).
2. Schedule CAC scan at site or local diagnostic imaging center (can occur prior to randomization).

3. Enter CAC scan appointment into PREVENTABLE website to facilitate reminder text or email to participant.
4. Review EMR for potentially qualifying pre-existing (historical) chest CT.
5. Deidentify and transmit CAC scan via AGMednet to imaging core laboratory in 7 business days.
6. Deidentify and transmit historical chest CT via AGMednet to imaging core laboratory.
7. Distribute safety reports generated by imaging core laboratory to participants undergoing the study related CAC scan. Site team (site coordinator and site PI) will be notified by alert and email of any positive incidental findings. Clinical follow-up should be arranged as per standard of care at each site.

Participant compensation for time and travel expenses incurred for CAC scan will be distributed centrally by the clinical coordinating center. Participants who are not having an in-person CAC scan performed will not receive compensation.

The data coordinating center will be responsible for sending the final individualized CAC report to participants, as well as a copy to site investigators/coordinators, at the end of the study.

CHAPTER 8: CHEST CT AND CORONARY ARTERY CALCIUM (CAC) ANALYSIS

8.1 Coronary Artery Calcium Analysis

Cardiac-gated non-contrast chest CT scans will be obtained using 16-slice multi-detector CT (MDCT) scanner (or greater) with cardiac-gating software capabilities at each participating site or at local diagnostic imaging facility. Scan acquisition will be consistent with that used for routine clinical CAC scoring, which requires a brief (10 second) breath hold and arm raise for optimal imaging. Scan acquisition will incorporate the "as low as reasonably achievable" (ALARA) ionizing radiation principle by using axial scanning mode with prospective ECG gating, 75% R-R interval, 2.5-3 mm slice increment, 120 kVp, and the minimal tube current (mAs) necessary to maintain diagnostic noise-to-image ratio. Scans will be reconstructed in a narrow (cardiac) field of view and transferred to the imaging core lab for analysis. Total CT scanner room time will be approximately 10-15 minutes per participant; time required to acquire the CT scan is less than 1 minute. Consistent with data from the Multi-Ethnic Study of Atherosclerosis (MESA), radiation dose will be expected to average 1 mSv per participant, which is equivalent to the exposure received with 10 chest x-rays or 1/3 annual background radiation.[44] Quality control measures, including extraction of scanner header metadata for assessment of imaging technique, radiation dose, and protocol deviations, will follow a protocol similar to that used other National Heart, Lung, and Blood Institute (NHLBI)-funded studies including MESA and the Atherosclerosis Risk in communities (ARIC). Images are deidentified within in AGMednet prior to transmission to the imaging core laboratory.

The CT scan analysis and CAC scoring will be performed in the Imaging Core Laboratory at the Duke Clinical Research Institute (DCRI). Following secure transmission of deidentified, uncompressed image files to DCRI through dedicated software (AGMednet), images will undergo quality control (QC) using JUDI software within AGMednet.[45] CAC scans will be interpreted by highly experienced blinded readers, and interpretations will be performed in the cardiac field of view using procedures consistent with MESA and ARIC. Core lab reader training will be

conducted prior to and throughout the course of the trial to 'harmonize eyes' and reduce the interpretation variability. Intra- and inter-reader reproducibility will be assessed, and repeat training will occur as needed to maintain an intraclass correlation coefficient >0.80 for continuous variables and a kappa statistic >0.90 for categorical variables. CT image interpretation and CAC score analysis will be conducted using dedicated software (Terarecon).[46] Both the Agatston score and the volume score, which is density independent, will be calculated for each scan.[47, 48] CAC burden and score will remain masked until the end of study at which time CAC scores will be placed into context with the overall PREVENTABLE results, and CAC score reports will be returned to participants at the conclusion of the trial.

8.2 Chest CT and Critical Incidental Findings

Non-coronary chest structures visualized in the cardiac field of view of the chest CT will be interpreted in the central imaging core laboratory at DCRI. Incidental findings with potential or established clinical significance that may warrant further clinical evaluation or intervention (Table 2) will be reported in a safety report sent to the sites for distribution to participants. The safety findings listed in Table 2 are consistent with other NHLBI cohort studies (ARIC and MESA) with similar demographics conducting CAC in asymptomatic individuals. Incidental findings for which there is uncertainty regarding the clinical significance will not be reported, thus limiting unnecessary anxiety and excessive downstream testing in this older population.

Table 2. Critical incidental findings being evaluated in CAC PREVENTABLE

Finding	Threshold for Reporting	Prevalence in ARIC
Aortic Diameter	5.0 cm or greater	<2.2%
Lung mass	3.0 cm or greater	0.3%
Lobar pneumonia	Present	0.3%
Pneumothorax	Present	0.2%
Pericardial effusion	2.0 cm or greater	0.3%
Large pleural effusion	Present	2.2%

CHAPTER 9: STATISTICAL CONSIDERATIONS

CAC PREVENTABLE was designed to:

- Ensure adequate sample size to provide robust estimates of treatment effects for the primary and secondary endpoints
- Ensure the use of state-of-the-art statistical methodology for analyses
- Conduct analyses that help inform clinical decision-making
- Address analytic complexities of high relevance to older adults, including competing risks and the incorporation of patient-centered outcomes.

9.1 Primary Statistical Analyses

9.1.1 Analysis of CAC

We will approach our analyses both from the perspective of relative benefit (effect modification) as well as absolute benefit (risk magnification), maximizing both power and clinical relevance. The primary outcome for CAC PREVENTABLE is survival free of the ASCVD composite of cardiovascular death, hospitalization for myocardial infarction (MI)/unstable angina, heart failure, stroke, or revascularization. We will model the effect of atorvastatin 40 mg vs. placebo as a function of baseline CAC based on stratified extensions of the Fine and Gray subdistribution hazard model to account for the competing risk of non-CVD death, stratified by clinic site and adjusting for age and sex.[49, 50] For modeling both the effect of age and CAC, we will use natural

cubic splines, formally testing for heterogeneity in the effect of atorvastatin as a function of CAC using likelihood ratio tests.[51] We will conduct complementary analyses using an innovative absolute benefit model estimating the restricted mean survival time (RMST) to test for clinically meaningful absolute benefit from atorvastatin as a function of baseline CAC score.[52, 53] Statistically, the RMST has the advantage of being robust to deviations from the typical proportional hazards assumption, and published methods extend its estimation to the context of competing risks. Modeling the effect of atorvastatin 40 mg vs. placebo as a function of baseline CAC will be based on stratified extensions of the Fine and Gray subdistribution hazard model to account for the competing risk of non-CVD death, stratified by clinic site and adjusting for age and sex.[49, 50] For modeling both the effect of age and CAC, we will use natural cubic splines, formally testing for heterogeneity in the effect of atorvastatin as a function of CAC using likelihood ratio tests.[51] All comparisons will be based on the intent to treat principle.[54]

9.1.2 Analyses of cognitive impairment, persisting disability, and all-cause mortality. These analyses will largely rely up an analogous statistical framework, modeling the effect of atorvastatin 40 mg vs. placebo as a function of baseline CAC using stratified extensions of the Fine and Gray subdistribution hazard model, stratified by clinic site and adjusting for age and sex. We will similarly use natural cubic splines for modeling both the effect of age and CAC, formally testing for heterogeneity in the effect of atorvastatin as a function of CAC using likelihood ratio tests. For analyses that consider mortality as part of the outcome (vs as a competing risk), we will utilize Cox proportional hazards regression with the baseline hazard stratified by clinic site, adjusting for age and sex.

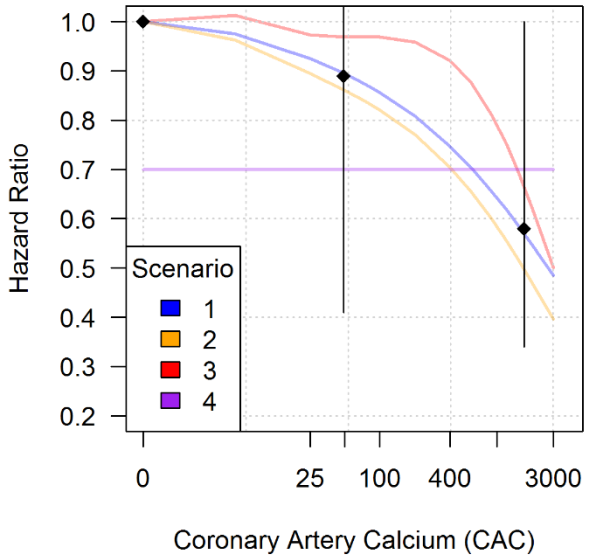
9.1.3 Develop a comprehensive ASCVD risk classification model and online tool for calculating estimated benefit of statin therapy in the age ≥75 primary prevention population. We will utilize sex-specific competing risk models, considering traditional risk factors as a base model (age, race/ethnicity, smoking status, blood pressure, diabetes, and cholesterol). We will quantify the degree to which CAC improves prediction of ASCVD. In addition to traditional calibration (modified Hosmer-Lemeshow χ^2 statistic) and discrimination (Harrell's c-statistic) parameters, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) will be assessed.[55, 56] A method taking into account censoring will be used for both NRI and IDI.[57] As risk thresholds, we will primarily use 3.8-year risk of 2.85% and 7.6% (corresponding to 10-y risk of 7.5% and 20%, respectively) but also test higher thresholds (e.g., 5.7% and 11.4% in 3.8-year corresponding to 15% and 30% in 10 years) to increase specificity.

9.2 Sample Size

We estimated power to detect heterogeneity in the effect of statins as function of baseline CAC based on simulation.[58] The simulations primarily focused on scenarios reflecting *effect modification,* that is heterogeneity in the relative risk reduction (RRR) associated with atorvastatin 40 mg (vs placebo) as a function of CAC (Table 2). Primarily, our hypothesized interest is in scenarios where patients with low baseline CAC levels gain little from statin treatment, whereas those with elevated CAC levels experience reductions in the incidence of CVD. The simulations assume a 2-year recruitment period, a total study length of 5 years, and a loss to follow-up rate of 3% per year. Given that our primary analytic approach proposes adjusting for age and sex, we assumed our recruited population will be 52% female, and that the age distribution mimics participants from the Systolic Blood Pressure Intervention Trial (SPRINT) who are ≥75 years (without a history of CVD and not on a statin at baseline, mean age = 79.7 years, 15% ≥85 years).[59] Conditional on age and sex, we assumed a population distribution of CAC scores based on the Coronary Artery Consortium, MESA, and ARIC, reflecting higher CAC levels in men compared to women.[31, 60, 61] ASCVD event rates in the placebo group were based on data from SPRINT,[59, 62] ASPREE,[63, 64] and MESA**,** which agree on estimated ASCVD event rates between 30-35 per 1000 participant-years in this population. Risk increases associated with increasing

CAC were drawn from MESA and meta-analyses.[61, 65]

Mean estimated risk reductions (hazard ratios) with atorvastatin 40mg were derived from the Cholesterol Treatment Trialists collaboration. Meta-analyses indicate a ~22% reduction in the risk of major ASCVD events per 1 mmol/L reduction in LDL-C.[66, 67] With our estimated baseline LDL-C of 119 mg/dL (based on SPRINT and MESA), and 50% LDL-C reduction with atorvastatin 40mg,[1] a conservative mean estimate of overall RRR is 30%. We created scenarios for CAC by statin interaction based on the St. Francis Heart Study randomized trial and the Walter Reed clinical experience.[38, 39] For example, in the Walter Reed clinical experience, the adjusted hazard ratio with statin treatment was null in patients with CAC=0, 0.83 in patients with CAC 1-100, 0.32 in patients with CAC >100 to 400, and 0.56 in patients with CAC>400.[39]



The adjacent figure depicts several scenarios we considered for patterns of RRR across the spectrum of CAC scores, overlaid with the estimated HRs for CAC 100-400 and >400 from the St. Francis Heart Study, with additional consideration of no treatment interaction. As shown in the table below the first three scenarios use an overall ~20-35% RRR, indicating that we will have 80-95% power in scenarios where there is limited effect of atorvastatin for participants with baseline CAC<100, contrasted with increasingly stronger effects in participants with higher CAC. Note that scenario 4 represents a fixed treatment effect (i.e. no heterogeneity in RRR by CAC).

Table 2 Scenario	Overall Relative Risk Reduction	Power CAC x Statin Interaction
1	30%	0.80
2	35%	0.95
3	20%	0.88
4	30%	N/A

CHAPTER 10: ASSESSMENT OF SAFETY

10.1 Risks and Benefits

Risks: The main risk to participation in CAC PREVENTABLE exposure to ionizing radiation from CT heart imaging for CAC evaluation. However, the radiation dose is very low (≤10 chest X-rays or 1/3 of annual background environmental radiation),[68, 69] which is considered to be broadly

acceptable, particularly at older ages where there is less latency time for the development of cancer. To further mitigate risk, radiation dose will be monitored for each patient, as well as at the site level. Any sites consistently performing CT heart imaging above the anticipated average radiation dose will be required to undergo training by the DCRI imaging core laboratory.

Benefits: There is no direct benefit to the participant apart from generating evidence to support healthy life years in individuals of advanced age. Participants will receive a safety report regarding any potentially significant incidental findings after the CT heart scan. Additionally, participants will be sent a CAC report with their individual CAC score placed into the context of study results at the conclusion of the trial. The knowledge gained from CAC PREVENTABLE will be a benefit to others in the future, particularly in regards to cardiovascular prevention among those ≥ 75 years of age.

10.2 Data and Safety Monitoring Board

The independent Data and Safety Monitoring Board (DSMB) overseeing PREVENTABLE will also monitor the CAC PREVENTABLE study. The DSMB will be provided with scheduled study updates including, but not limited to, study enrollment, aggregate safety events and endpoints, as defined by PREVENTABLE, and events by blinded CAC scores provided in closed session when available. After each meeting, the DSMB will make recommendations to the NHLBI and study leadership about the continuation of the study. A summary of the DSMB report and recommendations will be forwarded to investigators for submission to the IRB/Ethics Committees, as applicable. DSMB reports will be the primary mechanism for reporting safety concerns to NHLBI and IRBs.

CHAPTER 11: ETHICAL STANDARDS

The investigators will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

11.1 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to central IRB(s) for review and approval, and this approval must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB(s) before being implemented in the study. All changes to the consent form will also be IRB-approved and a determination will be made regarding whether previously consented participants need to be re-consented. The SMART IRB Master Common Reciprocal Institutional Review Board Authorization Agreement (SMART IRB Agreement) will support single IRB review [in compliance with NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research]. Duke University Medical Center IRB has agreed to serve as the Reviewing IRB, and Relying Institutions have agreed to cede review. The sites have agreed that IRB review, regulatory oversight, and roles and responsibilities of the parties will be governed by the SMART IRB Agreement and the SMART IRB Standard Operating Procedures throughout the life of the project. In accordance with the SMART IRB Agreement and SOPs, (1) The Clinical Coordinating Center at Duke Clinical Research Institute (DCRI) will serve as the primary contact and will distribute the results of IRB reviews and manage ongoing communications across non-VA site study teams; (2) The POC for the Reviewing IRB (Duke) will ensure

appropriate communication with Relying Institution POCs. The Boston VA Coordinating Center will serve as the central IRB, primary contact, and distribute the results of IRB reviews and manage ongoing communications across the VA sites.

11.2 Informed Consent Process

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and documentation of informed consent is required prior to starting study procedures. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. This may include a video consent process to facilitate review of information about the study. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator (or their delegate) will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. There is a waiver of consent for PREVENTABLE participants enrolled with pre-existing scans.

11.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical and private information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study participant's contact information will be securely stored in the clinical study database. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Wake Forest School of Medicine (WFSM). The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

CHAPTER 12: DATA HANDLING AND RECORD KEEPING

12.1 Data Collection and Management Responsibilities

Site entered data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The site investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of site entered data, only. All study data will be entered into DEACON, a data capture system provided by the WFSM DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Data in the EHR or as entered

in the study website are source documents and should be maintained. Data reported in the study website derived from source documents should be consistent with source documents or discrepancies should be explained in the official study record.

12.2 Study Records Retention

Study documents should be retained for a minimum of six years after the study has ended. However, if required by local regulations, these documents should be retained for a longer period. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 Protocol Deviations

A protocol deviation is defined as non-compliance with the clinical study protocol or GCP requirements. The non-compliance may be on the part of the participant, site investigator, or the site staff. In the event a protocol deviation occurs, corrective actions by the site should be implemented promptly. These practices are consistent with ICH E6 as detailed in their document for Compliance with section related to the Protocol (4.5.1, 4.5.2, and 4.5.3), Quality Assurance and Quality Control (5.1.1), and Non-compliance (5.20.1, and 5.20.2). It is the responsibility of the study team to use continuous vigilance to identify and report deviations within five working days of identification, or within five working days of the scheduled protocol-required activity. Protocol deviations must be sent to the study IRB and local IRB per their guidelines, recorded in source documents, and reported to the coordinating center. The site investigator and site staff is responsible for knowing and adhering to their human participant protection, institutional requirements, and SMART IRB Master Reliance agreement. Further details about the handling of protocol deviations will be included in the MOP.

12.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the results of NIH-funded research. It requires that scientists submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive, PubMed Central, upon acceptance for publication. Methods of data sharing for PREVENTABLE will include 1) archiving de-identified data in a data repository and 2) sharing of limited datasets under a Data Use Agreement (DUA) and IRB approval. Data will be made available to qualified investigators by archiving a fully de-identified dataset in the NIH Biobank. Both repositories allow users to search, view study information, and then submit an application to receive data. Prior to archiving study data, the DCC will produce a final dataset that will be stripped of all personal health information (PHI), including full date elements, in compliance with the Health Insurance Portability and Accountability Act (HIPAA) privacy rule. The relative timing of an event will be retained in the dataset converting to study days instead of dates.

We plan to return study results, including some participant specific results, to enhance value from participation. We plan to disseminate study results to the public and the medical community through presentations at scientific meetings and publishing manuscripts in high impact peer-reviewed journals. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical studies registration policy as a condition for publication. The ICMJE defines a clinical study as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study

the cause-and-effect relationship between a medical intervention and a health outcome. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical studies be registered in a public registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. In accordance with these policies, the PREVENTABLE trial will be registered on https://clinicaltrials.gov. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the study in an acceptable registry, so the research results may be considered for publication in ICMJE member journals.

REFERENCES:

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS and Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082-e1143.
2. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Munoz D, Smith SC, Jr., Virani SS, Williams KA, Sr., Yeboah J and Ziaeian B. 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-e646.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O and Group ESCSD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European heart journal*. 2020;41:111-188.
4. Piepoli MF, Abreu A, Albus C, Ambrosetti M, Brotons C, Catapano AL, Corra U, Cosyns B, Deaton C, Graham I, Hoes A, Lochen ML, Matrone B, Redon J, Sattar N, Smulders Y and Tiberi M. Update on cardiovascular prevention in clinical practice: A position paper of the European Association of Preventive Cardiology of the European Society of Cardiology. *European journal of preventive cardiology*. 2020;27:181-205.
5. Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J, Jr., Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GB, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G and Ward R. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol*. 2016;32:1263-1282.
6. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD and Wright JT, Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2018;71:e127-e248.
7. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I and Group ESCSD. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal*. 2018;39:3021-3104.
8. Prospective Studies C, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R and Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370:1829-39.
9. Orkaby AR. The Highs and Lows of Cholesterol: A Paradox of Healthy Aging? *Journal of the American Geriatrics Society*. 2020;68:236-237.

10. Karmali KN, Goff DC, Jr., Ning H and Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. *Journal of the American College of Cardiology*. 2014;64:959-68.
11. Ridker PM and Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet*. 2013;382:1762-5.
12. Han BH, Weinberger Y and Sutin D. Statinopause. *Journal of general internal medicine*. 2014;29:1702-6.
13. Prevention. CfDCa. 10 Leading Causes of Death by Age Group, United States. *Available online at: https://wwwcdcgov/injury/wisqars/LeadingCauseshtml* 2017.
14. Berry SD, Ngo L, Samelson EJ and Kiel DP. Competing risk of death: an important consideration in studies of older adults. *Journal of the American Geriatrics Society*. 2010;58:783-7.
15. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF and Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation*. 1995;92:2157-62.
16. Greenland P, Blaha MJ, Budoff MJ, Erbel R and Watson KE. Coronary Calcium Score and Cardiovascular Risk. *Journal of the American College of Cardiology*. 2018;72:434-447.
17. Erbel R and Budoff M. Improvement of cardiovascular risk prediction using coronary imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure. *European heart journal*. 2012;33:1201-13.
18. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND and Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *The New England journal of medicine*. 2008;358:1336-45.
19. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P and Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA : the journal of the American Medical Association*. 2012;308:788-95.
20. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, Blaha MJ, Miedema MD, Sibley CT, Carr JJ, Burke GL, Goff DC, Jr., Psaty BM, Greenland P and Herrington DM. Utility of Nontraditional Risk Markers in Atherosclerotic Cardiovascular Disease Risk Assessment. *Journal of the American College of Cardiology*. 2016;67:139-147.
21. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ and Krumholz HM. Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *Journal of the American College of Cardiology*. 2015;66:1657-68.
22. Peters SA, den Ruijter HM, Bots ML and Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart*. 2012;98:177-84.
23. Mortensen MB, Fuster V, Muntendam P, Mehran R, Baber U, Sartori S and Falk E. Negative Risk Markers for Cardiovascular Events in the Elderly. *Journal of the American College of Cardiology*. 2019;74:1-11.
24. Blaha MJ, Blumenthal RS, Budoff MJ and Nasir K. Understanding the utility of zero coronary calcium as a prognostic test: a Bayesian approach. *Circulation Cardiovascular quality and outcomes*. 2011;4:253-6.
25. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, Dardari Z, Sibley CT, Burke GL, Kronmal RA, Szklo M, Blumenthal RS and Nasir K. Role of Coronary Artery Calcium Score of Zero and Other Negative Risk Markers for Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2016;133:849-58.

26. Budoff MJ, McClelland RL, Nasir K, Greenland P, Kronmal RA, Kondos GT, Shea S, Lima JA and Blumenthal RS. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *American heart journal*. 2009;158:554-61.
27. Le VT, Knight S, Min DB, McCubrey RO, Horne BD, Jensen KR, Meredith KG, Mason SM, Lappe DL, Anderson JL, Muhlestein JB and Knowlton KU. Absence of Coronary Artery Calcium During Positron Emission Tomography Stress Testing in Patients Without Known Coronary Artery Disease Identifies Individuals With Very Low Risk of Cardiac Events. *Circulation Cardiovascular imaging*. 2020;13:e009907.
28. Blaha MJ, Cainzos-Achirica M, Dardari Z, Blankstein R, Shaw LJ, Rozanski A, Rumberger JA, Dzaye O, Michos ED, Berman DS, Budoff MJ, Miedema MD, Blumenthal RS and Nasir K. All-cause and cause-specific mortality in individuals with zero and minimal coronary artery calcium: A long-term, competing risk analysis in the Coronary Artery Calcium Consortium. *Atherosclerosis*. 2020;294:72-79.
29. Nasir K. Message for 2018 Cholesterol Management Guidelines Update: Time to Accept the Power of Zero. *Journal of the American College of Cardiology*. 2018;72:3243-3245.
30. Miedema MD, Dardari ZA, Nasir K, Blankstein R, Knickelbine T, Oberembt S, Shaw L, Rumberger J, Michos ED, Rozanski A, Berman DS, Budoff MJ and Blaha MJ. Association of Coronary Artery Calcium With Long-term, Cause-Specific Mortality Among Young Adults. *JAMA Netw Open*. 2019;2:e197440.
31. Tota-Maharaj R, Blaha MJ, McEvoy JW, Blumenthal RS, Muse ED, Budoff MJ, Shaw LJ, Berman DS, Rana JS, Rumberger J, Callister T, Rivera J, Agatston A and Nasir K. Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. *European heart journal*. 2012;33:2955-62.
32. McClelland RL, Nasir K, Budoff M, Blumenthal RS and Kronmal RA. Arterial age as a function of coronary artery calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *The American journal of cardiology*. 2009;103:59-63.
33. Handy CE, Desai CS, Dardari ZA, Al-Mallah MH, Miedema MD, Ouyang P, Budoff MJ, Blumenthal RS, Nasir K and Blaha MJ. The Association of Coronary Artery Calcium With Noncardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis. *JACC Cardiovascular imaging*. 2016;9:568-576.
34. Kuller LH, Lopez OL, Mackey RH, Rosano C, Edmundowicz D, Becker JT and Newman AB. Subclinical Cardiovascular Disease and Death, Dementia, and Coronary Heart Disease in Patients 80+ Years. *Journal of the American College of Cardiology*. 2016;67:1013-1022.
35. Mortensen MB, Gaur S, Frimmer A, Botker HE, Sorensen HT, Kragholm KH, Niels Peter SR, Steffensen FH, Jensen RV, Maeng M, Kanstrup H, Blaha MJ, Shaw LJ, Dzaye O, Leipsic J, Norgaard BL and Jensen JM. Association of Age With the Diagnostic Value of Coronary Artery Calcium Score for Ruling Out Coronary Stenosis in Symptomatic Patients. *JAMA Cardiol*. 2021.
36. Sandoval Y, Bielinski SJ, Daniels LB, Blaha MJ, Michos ED, DeFilippis AP, Szklo M, deFilippi C, Larson NB, Decker PA and Jaffe AS. Atherosclerotic Cardiovascular Disease Risk Stratification Based on Measurements of Troponin and Coronary Artery Calcium. *Journal of the American College of Cardiology*. 2020;76:357-370.
37. Cainzos-Achirica M, Anugula D, Mszar R, Grandhi G, Patel KV, Bittencourt MS, Blankstein R, Blaha MJ, Blumenthal RS, Ray KK, Bhatt DL and Nasir K. Rationale and pathways forward in the implementation of coronary artery calcium-based enrichment of randomized trials. *American heart journal*. 2021;243:54-65.
38. Blaha MJ, Nasir K, Budoff MJ, Dardari ZA, Blumenthal RS, Pollack S, Reichek N and Guerci AD. Impact of C-Reactive Protein and Coronary Artery Calcium on Benefit Observed With Atorvastatin. *Journal of the American College of Cardiology*. 2018;71:2487-2488.
39. Mitchell JD, Fergestrom N, Gage BF, Paisley R, Moon P, Novak E, Cheezum M, Shaw LJ and Villines TC. Impact of Statins on Cardiovascular Outcomes Following Coronary Artery Calcium Scoring. *Journal of the American College of Cardiology*. 2018;72:3233-3242.

40. Zhou Z, Ong KL, Breslin M, Allison MA, Curtis AJ and Nelson MR. Association of Statin Use With Cardiovascular Outcomes by Coronary Calcium: MESA. *JACC Cardiovascular imaging*. 2020;13:1094-1096.
41. Ford I, Shah AS, Zhang R, McAllister DA, Strachan FE, Caslake M, Newby DE, Packard CJ and Mills NL. High-Sensitivity Cardiac Troponin, Statin Therapy, and Risk of Coronary Heart Disease. *Journal of the American College of Cardiology*. 2016;68:2719-2728.
42. Psaty BM, Dekkers OM and Cooper RS. Comparison of 2 Treatment Models: Precision Medicine and Preventive Medicine. *JAMA : the journal of the American Medical Association*. 2018;320:751-752.
43. Kind AJH and Buckingham WR. Making Neighborhood-Disadvantage Metrics Accessible - The Neighborhood Atlas. *The New England journal of medicine*. 2018;378:2456-2458.
44. Messenger B, Li D, Nasir K, Carr JJ, Blankstein R and Budoff MJ. Coronary calcium scans and radiation exposure in the multi-ethnic study of atherosclerosis. *The international journal of cardiovascular imaging*. 2016;32:525-9.
45. https://agmednet.com/ AAoa.
46. https://www.terarecon.com TAoa.
47. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr. and Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *Journal of the American College of Cardiology*. 1990;15:827-32.
48. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ and Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology*. 1998;208:807-14.
49. Glidden DV and Vittinghoff E. Modelling clustered survival data from multicentre clinical trials. *Stat Med*. 2004;23:369-88.
50. Zhou B, Latouche A, Rocha V and Fine J. Competing risks regression for stratified data. *Biometrics*. 2011;67:661-70.
51. Royston P SW. Two techniques for investigating interactions between treatment and continuous covariates in clinical trials. *Stata J*. 2009;9:230-251.
52. Royston P PM. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol*. 2013;13:152.
53. Kim DH, Uno H and Wei LJ. Restricted Mean Survival Time as a Measure to Interpret Clinical Trial Results. *JAMA Cardiol*. 2017;2:1179-1180.
54. DeMets DL and Cook T. Challenges of Non-Intention-to-Treat Analyses. *JAMA : the journal of the American Medical Association*. 2019;321:145-146.
55. Pencina MJ and D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med*. 2004;23:2109-23.
56. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr. and Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157-72; discussion 207-12.
57. Pencina MJ, D'Agostino RB, Sr. and Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11-21.
58. Bender R, Augustin T and Blettner M. Generating survival times to simulate Cox proportional hazards models. *Stat Med*. 2005;24:1713-23.
59. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT, Jr., Pajewski NM and Group SR. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association*. 2016;315:2673-82.

60. Wang FM, Rozanski A, Arnson Y, Budoff MJ, Miedema MD, Nasir K, Shaw LJ, Rumberger JA, Blumenthal RS, Matsushita K, Blaha MJ and Berman DS. Cardiovascular and All-Cause Mortality Risk by Coronary Artery Calcium Scores and Percentiles Among Older Adult Males and Females. *The American journal of medicine*. 2021;134:341-350 e1.
61. Tota-Maharaj R, Blaha MJ, Blankstein R, Silverman MG, Eng J, Shaw LJ, Blumenthal RS, Budoff MJ and Nasir K. Association of coronary artery calcium and coronary heart disease events in young and elderly participants in the multi-ethnic study of atherosclerosis: a secondary analysis of a prospective, population-based cohort. *Mayo Clin Proc*. 2014;89:1350-9.
62. Group SR, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK and Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *The New England journal of medicine*. 2015;373:2103-16.
63. McNeil JJ, Woods RL, Nelson MR, Reid CM, Kirpach B, Wolfe R, Storey E, Shah RC, Lockery JE, Tonkin AM, Newman AB, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Ryan J, Radziszewska B, Grimm R, Murray AM and Group AI. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. *The New England journal of medicine*. 2018;379:1499-1508.
64. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, Reid CM, Lockery JE, Kirpach B, Storey E, Shah RC, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Johnston CI, Ryan J, Radziszewska B, Jelinek M, Malik M, Eaton CB, Brauer D, Cloud G, Wood EM, Mahady SE, Satterfield S, Grimm R, Murray AM and Group AI. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *The New England journal of medicine*. 2018;379:1509-1518.
65. Yano Y, O'Donnell CJ, Kuller L, Kavousi M, Erbel R, Ning H, D'Agostino R, Newman AB, Nasir K, Hofman A, Lehmann N, Dhana K, Blankstein R, Hoffmann U, Mohlenkamp S, Massaro JM, Mahabadi AA, Lima JAC, Ikram MA, Jockel KH, Franco OH, Liu K, Lloyd-Jones D and Greenland P. Association of Coronary Artery Calcium Score vs Age With Cardiovascular Risk in Older Adults: An Analysis of Pooled Population-Based Studies. *JAMA Cardiol*. 2017;2:986-994.
66. Cholesterol Treatment Trialists C. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393:407-415.
67. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J and Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-81.
68. Wang Y, Osborne MT, Tung B, Li M and Li Y. Imaging Cardiovascular Calcification. *Journal of the American Heart Association*. 2018;7.
69. Kianoush S, Al Rifai M, Cainzos-Achirica M, Umapathi P, Graham G, Blumenthal RS, Nasir K and Blaha MJ. An Update on the Utility of Coronary Artery Calcium Scoring for Coronary Heart Disease and Cardiovascular Disease Risk Prediction. *Curr Atheroscler Rep*. 2016;18:13.