Title

Astronaut Cardiovascular Health and Risk Modification (Astro-CHARM) Coronary Calcium Atherosclerotic Cardiovascular Disease Risk Calculator.

Journal

Circulation, 138(17)

ISSN

0009-7322

Authors

Khera, Amit
Budoff, Matthew J
O'Donnell, Christopher J
et al.

Publication Date

2018-10-01

DOI

10.1161/circulationaha.118.033505

Peer reviewed

Circulation

ORIGINAL RESEARCH ARTICLE

Astronaut Cardiovascular Health and Risk Modification (Astro-CHARM) Coronary Calcium Atherosclerotic Cardiovascular Disease Risk Calculator

Amit Khera, MD, MSc
Matthew J. Budoff, MD
Christopher J. O'Donnell, MD, MPH
Colby A. Ayers, MS
James Locke, MD
James A. de Lemos, MD
Joseph M. Massaro, PhD
Robyn L. McClelland, PhD
Allen Taylor, MD
Benjamin D. Levine, MD

BACKGROUND: Coronary artery calcium (CAC) is a powerful novel risk indicator for atherosclerotic cardiovascular disease (ASCVD). Currently, there is no available ASCVD risk prediction tool that integrates traditional risk factors and CAC.

METHODS: To develop a CAC ASCVD risk tool for younger individuals in the general population, subjects aged 40 to 65 without prior cardiovascular disease from 3 population-based cohorts were included. Cox proportional hazards models were developed incorporating age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, smoking, diabetes mellitus, hypertension treatment, family history of myocardial infarction, high-sensitivity C-reactive protein, and CAC scores (Astro-CHARM model [Astronaut Cardiovascular Health and Risk Modification]) as dependent variables and ASCVD (nonfatal/fatal myocardial infarction or stroke) as the outcome. Model performance was assessed internally, and validated externally in a fourth cohort.

RESULTS: The derivation study comprised 7382 individuals with a mean age 51 years, 45% women, and 55% nonwhite. The median CAC was 0 (25th, 75th [0,9]), and 304 ASCVD events occurred in a median 10.9 years of follow-up. The c-statistic was 0.784 for the risk factor model, and 0.817 for Astro-CHARM (P<0.0001). In comparison with the risk factor model, the Astro-CHARM model resulted in integrated discrimination improvement (0.0252), and net reclassification improvement (0.121; P<0.0001), as well. The Astro-CHARM model demonstrated good discrimination (c=0.78) and calibration (Nam-D'Agostino χ^2, 13.2; P=0.16) in the validation cohort (n=2057; 55 events). A mobile application and web-based tool were developed to facilitate clinical application of this tool (www.AstroCHARM.org).

CONCLUSION: The Astro-CHARM tool is the first integrated ASCVD risk calculator to incorporate risk factors, including high-sensitivity C-reactive protein and family history, and CAC data. It improves risk prediction in comparison with traditional risk factor equations and could be useful in risk-based decision making for cardiovascular disease prevention in the middle-aged general population.

Key Words: calcification of joints and arteries ■ coronary vessels ■ risk assessment

Sources of Funding, see page 1825

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Coronary artery calcium is among the most powerful novel cardiovascular risk assessment tests, but there previously was no available tool to combine coronary artery calcium and traditional risk factor information.
- The Astro-CHARM tool (Astronaut Cardiovascular Health and Risk Modification) is the first integrated atherosclerotic cardiovascular disease risk calculator to incorporate risk factors and coronary artery calcium data.
- It was developed using 3 population-based cohorts and was validated in a fourth cohort.

What Are the Clinical Implications?

- The Astro-CHARM tool significantly improves atherosclerotic cardiovascular disease risk prediction in comparison with traditional risk factors.
- It could be useful in risk-based decision making for cardiovascular disease prevention in the middle-aged general population.

Coronary artery calcium (CAC) scanning is one of the most powerful novel tests to improve cardiovascular (CV) risk assessment. Numerous prospective studies have demonstrated significant improvement in discrimination of CV events and enhanced clinical risk reclassification when CAC testing is added to traditional risk factors for CV disease.[1–3] CAC scanning may also improve the efficiency and appropriateness of statins and aspirin allocation for primary prevention.[4,5] A cornerstone of the new 2013 American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Guidelines is the primacy of informed decision making regarding statin use through the physician-patient discussion.[6] Although CAC scanning holds significant promise for assessing CV risk and informing individual patient decisions, the optimal method of integrating CAC data with other risk factor data are unclear.

A common method of incorporating CAC results is to use fixed values or thresholds, such as a CAC score of 0 or >300, to downgrade or upgrade CV risk, respectively.[7] Although this is a clinically simple approach, it ignores the spectrum of risk along gradations of both CAC scores and risk factor levels. In fact, even among those with CAC=0, CV risk varies widely depending on the severity of risk factors.[5] An alternate approach is to integrate actual CAC scores and risk factor data into a combined risk calculator to provide a more accurate actuarial assessment of CV risk. Recently, the MESA investigators (Multi-Ethnic Study of Atherosclerosis) developed the first such integrated CAC calculator to predict coronary heart disease (CHD) risk, which was validated in 2 external cohorts.[8] This calculator, which was derived in a predominantly older cohort (45–85 years; mean, 65 years), offers much clinical utility and is already being applied to enhance the clinician-patient risk discussion. High-resolution risk assessment can also be critical in younger populations of individuals, in particular, those in high-risk occupations. Indeed, this study was stimulated by the National Aeronautics and Space Administration to enhance CV risk prediction for the astronaut population who are predominantly middle-aged men and women. The MESA CHD calculator also did not assess the broader ASCVD end point, which includes stroke and which is the focus of the 2013 ACC/AHA Cholesterol and Risk Guidelines.[6,7]There is currently no such integrated CAC and risk factor calculator available to determine the risk of ASCVD.

Thus, using data from 3 large, population-based cohorts with risk factor, CAC, and event information, we sought to develop an integrated risk factor and CAC calculator for younger individuals in the general population (40–65 years) to estimate the risk of ASCVD. The tool, termed the Astronaut Cardiovascular Health and Risk Modification (Astro-CHARM) calculator, was assessed for validity in a fourth cohort, the FHS (Framingham Heart Study).

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure; however, the MESA and FHS study data are publicly accessible, and we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Study Populations

Data were pooled from study participants from examination 1 of MESA, phase 1 of the Dallas Heart Study (DHS), and the PACC study (Prospective Army Coronary Calcium Project) for the derivation cohort. The model validation cohort derived from the FHS Offspring and Third Generation cohorts. The development of the Astro-CHARM model was supported by the National Space Biomedical Research Institute to create an ASCVD risk assessment tool for astronauts, who undergo routine CAC screening, and a tool that can be used for the general population, as well. As such, these studies were selected because they comprised US population–based cohorts that included CAC scanning and ASCVD outcomes data, and that spanned middle-aged individuals (ie, 40–65 years). The study designs for MESA,[9] the DHS,[10] PACC,[11,12] and the FHS cohorts[1,13] have been previously described, and a detailed description of cohort methods and included participants are provided in the online-only Data Supplement and Figure I in the online-only Data Supplement. Each separate study was approved by the respective local institutional review boards, and all participants gave written informed consent for participation in those studies as described in the online-only Data Supplement. The overall Astro-CHARM study protocol was

approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

Data Collection and Variable Definitions

Race/ethnicity, history of CVD, and smoking status were self-reported in all studies. Diabetes mellitus was defined using the following definitions across studies: MESA, fasting plasma glucose level >140 mg/dL or a history of medical treatment for diabetes mellitus; DHS, medical treatment for diabetes mellitus, a fasting blood glucose of ≥126 mg/dL, or a nonfasting blood glucose level of ≥200 mg/dL; PACC, self-report of medical history of diabetes mellitus or use of hypoglycemic medications; FHS, fasting glucose 126 mg/dL at a Framingham examination or treatment with either insulin or a hypoglycemic agent. Definitions for family history of myocardial infarction (MI) included first-degree relative with MI at any age for MESA and DHS; premature family history of MI was not available in the MESA baseline examination for sensitivity analyses. Family history definition varied slightly for the other studies and included a history of sudden death, MI, or coronary revascularization in a first- or second-degree relative for PACC, and family history of coronary death, MI, stable or unstable angina pectoris for first-degree relatives in FHS, with both studies requiring the events before the age of 55 (men) or 65 (women) years. High-sensitivity C-reactive protein (hs-CRP) levels were measured by using the following assays (Table I in the online-only Data Supplement): MESA, BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc); DHS, Roche/Hitachi 912 System, Tina-quant assay (Roche Diagnostics), a latex-enhanced immunoturbidimetric method; PACC, particle-enhanced immunoturbidimetric latex agglutination assay; FHS, enhanced immune turbidimetric high-sensitivity assay (Roche Diagnostics). In the PACC study, hs-CRP measures were not performed in 907 subjects; these values were imputed as described in the online-only Data Supplement.

CAC Assessment

For all studies, CAC scores were quantified by using standard Agatston unit methodology.[14] Detailed methods for CAC scanning in each study are provided in the online-only Data Supplement and Table I in the online-only Data Supplement. In brief, CAC was measured by electron-beam computed tomography in 3 MESA sites, in DHS, and in PACC, and by multidector computed tomography in 3 other MESA sites and in the FHS.

Clinical End Point Ascertainment and Definition

The primary end point for the study included a composite of nonfatal MI, nonfatal stroke, or death from CHD or stroke. The components of this end point were available for MESA, DHS, and FHS, but only nonfatal MI and CVD death were available for PACC. Few nonfatal stroke events would have been anticipated in this younger, generally healthy cohort with a low prevalence of hypertension, and fatal stroke is included in the CVD death end point. Data acquisition methods, end point adjudication, and primary end point components for each individual study are described in the online-only Data Supplement and Table I in the online-only Data Supplement.

Statistical Methods

Individual participant level data from MESA, DHS, and PACC were combined for model derivation. Associations of risk factors with study outcomes were assessed by using Cox proportional hazards models. The baseline risk factor model comprised those variables included in the ACC/AHA Pooled Cohorts Equation (PCE)[7]: age, sex, race/ethnicity (white, black, Hispanic, other), total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, hypertension medication use, current smoking, and diabetes mellitus. β-Coefficients for these variables were fit to the derivation set and were not those from the original PCE, and all components of the PCE were intentionally retained in the model regardless of statistical significance. The Astro-CHARM model was constructed by then adding CAC scores as ln (CAC+1) given the skewed distribution. Next, family history of MI, hs-CRP, statin use, and fasting glucose levels were added based on a priori determination of their potential to improve the model.[3,8,15] Only family history of MI and hs-CRP were independently associated with ASCVD events and were included in the full Astro-CHARM model. Nonlinear relationships were explored by assessing exponential terms for age, and interactions were also assessed between CAC and age, sex, or race (no statistically significant interactions found). Assumptions for the Cox proportional hazards models were verified by Schoenfeld residuals. Weibull models were also evaluated, but β-coefficients were similar to those determined using Cox models.

Discrimination was assessed using the Harrell c-statistic, with 95% CIs determined by a jackknife resampling method. Improvement in the c-statistic was determined by using bootstrap resampling. Integrated discrimination improvement, reflecting the difference in discrimination slopes between models with and without the markers, was determined using the failure probabilities from the Cox proportional hazards models. Categorical net reclassification improvement (NRI) was performed according to methods of Pencina et al[16] by cross-tabulating the risk factor model with the Astro-CHARM model, using predicted risk categories of <5%, 5 to <7.5%, and ≥7.5% 10-year ASCVD risk. Separate analyses were performed for events and nonevents, and 95% CIs were calculated using bootstrapping. Calibration of the Astro-CHARM model was assessed by the Nam D'Agostino χ^2 test for time-to-event data.

Bootstrapping was used in determining the β-coefficients for the Astro-CHARM model.[17] Bootstrapping has the advantage that the entire data set is used for model development, as opposed to cross-validation techniques. In particular, 1000 model fits were created, and the average β-coefficient was determined across all these iterations. The β-coefficients were optimized by calculating the optimism in the β-coefficients and averaging the optimism estimates to arrive at the overall β-coefficient optimism values. The bootstrap-corrected β-coefficients were calculated; this is an honest estimate of internal validity of the β-coefficients. The coefficients were then applied to the FHS cohort where model discrimination was assessed using the Harrell c-statistic. Calibration plots were constructed and calibration was assessed using the Nam D'Agostino χ^2 test. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc), and all *P* values are 2-sided with an α of 0.05.

RESULTS

The baseline characteristics of the derivation and validation study cohorts are provided in Table 1. The mean age of the pooled derivation overall cohort was 51.0 years (SD ±7.5), 55% were men, and 30% were black with some heterogeneity among individual study cohorts. Among the pooled derivation cohort, the median CAC score was 0 (25th, 75th percentiles [0, 9]). The proportions of individuals with CAC scores of 0, 1 to 99, 100 to 399, and ≥400 were 63%, 27%, 7%, and 3%, respectively.

Over a median of 10.9 years, 304 hard ASCVD events occurred. When added to the baseline risk factor model including all PCE components, CAC, family history of MI, and hs-CRP all remained significantly associated with incident ASCVD and comprised the full Astro-CHARM model, whereas fasting glucose and statin use were not associated (Table 2). The c-statistics for the risk factor model, CAC model, risk factor model+CAC, and full Astro-CHARM model were 0.784, 0.720, 0.813 (P=0.0002), and 0.817 (P≤0.0001 versus risk factor model), respectively (Figure 1). The Astro-CHARM model was superior for prediction of MI (c-statistic risk factor model without recalibration=0.743, Astro-CHARM=0.827) versus stroke (risk factor model without recalibration=0.778, Astro-CHARM=0.781), although the model β-coefficients were optimized for the composite ASCVD end points rather than fit for each end point separately.

In comparison with the risk factor model, the full Astro-CHARM model resulted in a significant categorical NRI of 0.121, P<0.0001 (Figure 2), and integrated discrimination improvement of 0.0252 (0.0157–0.0346). The overall significant NRI result was driven by a 12% appropriate upclassification of risk, with no statistical difference in appropriate downclassification. In sensitivity analyses expanding the intermediate risk group to 5% to 15% 10-year risk, the performance of the Astro-CHARM model was enhanced with a categorical NRI of 0.141, P<0.0001 (Figure II in the online-only Data Supplement), and a 15% appropriate upclassification of risk. The Astro-CHARM model was well-calibrated internally (Figure 3) (Nam D'Agostino χ^2=9.58, P=0.39). In sensitivity analysis, the predicted 10-year ASCVD risks of the Astro-CHARM model including all 3 cohorts, or a model using just MESA and DHS, were highly correlated (rho=0.999, P≤0.0001) (Figure III in the online-only Data Supplement).

A modified Astro-CHARM model without hs-CRP was also constructed that demonstrated good discrimination (c-statistic, 0.826) and calibration, and a significant categorical NRI and integrated discrimination improvement (Tables II and III in the online-only Data Supplement, Figure IV in the online-only Data Supplement), as well.

Table 1. Baseline Characteristics of Study Cohorts

Parameter	Overall (n=7382)	Multi-Ethnic Study of Atherosclerosis (n=4029)	Dallas Heart Study (n=1491)	Prospective Army Coronary Calcium Project (n=1862)	Framingham Heart Study (n=2057)
Age, y	51.0 (7.5)	55.1 (6.1)	49.8 (6.7)	43.0 (2.6)	49.8 (6.7)
Men, %	55	47	44	82	48.5
Race, %					
Black	30	27	48	20	
White	45	37	37	69	100
Hispanic	17	24	13	6	
Total cholesterol, mg/dL*	195 (38)	195 (36)	186 (40)	203 (36)	198 (35)
High-density lipoprotein cholesterol, mg/dL*	51 (15)	50 (15)	51 (15)	53 (15)	54 (17)
Statin drug treatment, %	9	11	7	5	11.6
Systolic blood pressure, mm Hg*	123 (18)	121 (19)	129 (17)	123 (13)	121 (15)
Hypertension medication, %	22	28	25	6	16
Diabetes mellitus, %	8	10	11	1	4.8
Smoking, %	16	17	28	7	14
Family history myocardial infarction, %	37	47	37	19	15
High-sensitivity C-reactive protein, mg/L*	1.6 [0.5, 4.3]	1.9 [0.9, 4.4]	2.9 [1.3, 6.6]	0.5 [0.1, 3.6]	1.4 [0.6, 3.3]
Coronary artery calcium, AU*	0 [0, 9]	0 [0, 16]	1.0 [0, 14]	0 [0, 0]	0 [0, 29]
Median follow-up, y	10.9	12.4	10.1	5.6	9.5
Atherosclerotic cardiovascular disease end points	304	206	90	8	55
Event rate (per 1000 person-years)	4.27	4.45	6.20	0.77	2.95

*Data presented as mean values (SD) or median values [25th, 75th].

Table 2. Astro-CHARM Multivariable Predictors of Atherosclerotic Cardiovascular Disease

Parameter	β Coefficient	χ^2	*P* Value	Hazard Ratio	95% CIs	
					Lower	Upper
Age	0.019227	3.7	0.06	1.2*	1.00	1.34
Male sex	0.514818	14.8	<0.001	1.7	1.3	2.2
Race						
Black	0.289896	3.4	0.06	1.3	0.98	1.8
Hispanic	0.319984	2.6	0.10	1.4	0.94	2.0
Other	–0.03008	0.01	0.91	0.97	0.55	1.7
Total cholesterol	0.000405	0.09	0.8	1.01*	0.92	1.12
High-density lipoprotein cholesterol	–0.00407	0.66	0.4	0.94*	0.81	1.1
Systolic blood pressure	0.019908	40.1	<0.001	1.4*	1.3	1.6
Hypertension medication	0.073609	0.3	0.6	1.1	0.8	1.4
Smoking	0.797946	35.0	<0.0001	2.2	1.7	2.9
Diabetes mellitus	0.866738	28.4	<0.001	2.4	1.7	3.3
Family history myocardial infarction	0.46861	11.1	<0.001	1.6	1.2	2.1
High-sensitivity C-reactive protein	0.022105	6.9	0.009	1.1*	1.0	1.2
Coronary artery calcium score, natural log	0.026688	63.4	<0.001	1.5*	1.4	1.7

*Hazard ratio per 1 SD unit of continuous predictor variable; SD for age=7.5; total cholesterol=37.5; high-density lipoprotein cholesterol=14.7; systolic blood pressure=17.5; high-sensitivity C-reactive protein=4.8; and coronary artery calcium score, natural log=1.95.

Astro-CHARM indicates Astronaut Cardiovascular Health and Risk Modification.

Model Validation

The mean age of the FHS cohort (n=2052) was 49.6 years (±6.7), with 49% men and 100% white individuals (Table 1). The median follow-up for the cohort was 9.5 years, and a total of 55 hard ASCVD events occurred during this interval. The full Astro-CHARM model demonstrated good discrimination in this validation cohort (c-statistic =0.78 [0.72–0.84]) as did the model excluding CRP (c-statistic=0.79 [0.73–0.85]). Both Astro-CHARM models were well-calibrated in the FHS cohort (Nam-D'Agostino χ^2 *P*>0.1 each) (Figure 4 and Figure V in the online-only Data Supplement).

Mobile Application and Web-Based Tool

To facilitate clinical application of the Astro-CHARM CAC risk calculator, a mobile application (Figure VI in the online-only Data Supplement) was developed, and a web-based tool (www.Astro-CHARM.org) (Figure VII in the online-only Data Supplement). Both instruments provide an estimated 10-year risk of ASCVD based on Astro-CHARM parameters including those from the PCE risk score, and the CAC score and family history of MI, with or without hs-CRP measures, as well.

DISCUSSION

In the present study, we provide the first integrated CAC and risk factor calculator that estimates the 10-year risk of ASCVD events. The Astro-CHARM calculator was developed using 3 large, population-based cohorts, 2 of which involved multiethnic populations, enhancing generalizability. We validated the Astro-CHARM tool in a fourth population-based cohort where it demonstrated very good discrimination and calibration. The Astro-CHARM can be a valuable tool for ASCVD risk assessment in younger individuals in the general population.

In clinical medicine, risk assessment is at the center of CV disease prevention strategies. Determining an individual's absolute risk allows calculation of the absolute risk reduction and number needed to treat for any preventive strategy, thus providing quantitative measures of potential benefits. Current recommendations for aspirin and statin use are based on 10-year ASCVD thresholds (>10% and >7.5%, respectively), weighing the potential benefits against potential harms of each therapy.[6,18] Indeed, there is increased interest in not only providing more accurate risk estimates, but also in enhanced communication of risk to patients to better inform their involvement in treatment strategies.[19] These objectives are core components of the National Institute of Health Precision Medicine Initiative All of Us Research Program that seeks to identify prevention and treatment strategies that take individual variability into account, to individualize medical treatments and decision making to the patient.[20]

Of all the emerging risk indicators, CAC scanning has demonstrated the most substantial impact on enhancing CV risk estimates and the most robust evidence base to support its use.[1–3] Nevertheless, there remains hetero-

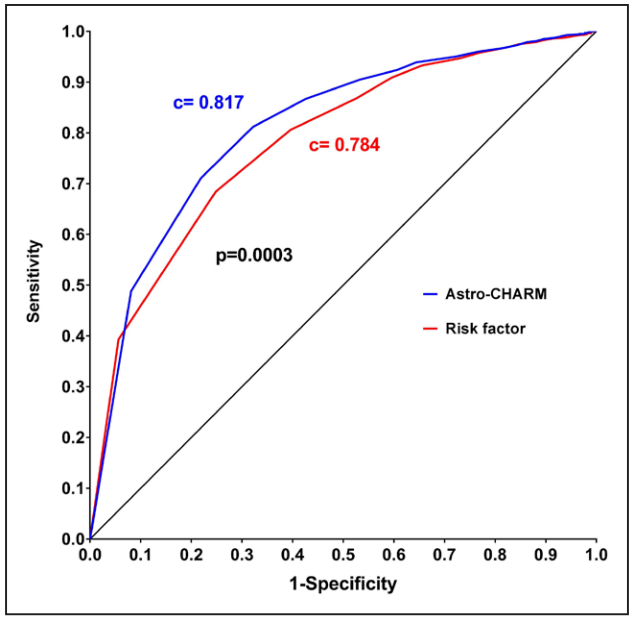

Figure 1. Discrimination of Astro-CHARM versus risk factor model for ASCVD.
The areas under the receiver operating curves for prediction of atherosclerotic cardiovascular disease (ASCVD) events are presented for the Astro-CHARM and risk factor–only models, with significant improvement using Astro-CHARM (*P*=0.0003).

geneity in the recommendations for its clinical use. The ACC/AHA 2013 Cholesterol Guidelines stated that, if there is uncertainty regarding statin use after quantitative risk assessment, a coronary calcium score ≥300 or ≥75th percentile may be used to upgrade risk. Others have advocated for an alternate strategy of using CAC to downgrade risk for scores of 0.[21] Both approaches exchange simplicity for precision and may lead to erroneous risk-based decision making. For example, in the Heinz Nixdorf Recall study, among all individuals with a CAC score >400, observed 5-year CHD events varied markedly based on risk factor clustering, ranging from 3.5% in those at low Framingham Risk Score estimated 10-year CHD risk to 10.6% for those at high estimated Framingham Risk Score risk.[22] Similarly, in the MESA study, subjects with a CAC score of 0 had a 10-year ASCVD event rate of ≈2.7% if they were also in an estimated ASCVD risk category of 7.5% to 9.9% in comparison with ≈12% event rate if they were in an estimated risk category of >20%.[5] Both the Heinz Nixdorf and MESA data suggest that using simplified CAC thresholds may ignore valuable information that can impact risk-based decisions.

Recently, McClelland et al[8] developed an integrated risk factor and CAC calculator using the MESA study cohort. This tool estimates the 10-year risk of CHD, inclusive of coronary revascularization, and was validated in 2 external cohorts. In the current study, we developed a CAC risk calculator from 3 different cohorts to estimate the risk of hard ASCVD (MI, stroke, CHD death, stroke death) in accordance with the 2013 ACC/AHA Cholesterol and Risk Assessment Guidelines.[6,7] This Astro-CHARM tool also focuses on a younger population (40–65 years; mean age, 51 years), in comparison with the MESA CHD calculator derived from an older population (45–85 years; mean age, 65 years). Given the dominance of age in risk assessment, most older individuals are already eligible for statins, and CAC risk calculators may have differing applications for younger populations, especially in those working in high-risk occupations like astronauts. Indeed, the main impact of Astro-CHARM was to appropriately upclassify clinical risk category (ie, statin eligibility), whereas CAC scanning is commonly used to downgrade risk and statin eligibility in older individuals with CAC of zero.[23]

Our findings validate recent observations from both MESA and FHS that CAC measures can enhance risk assessment of ASCVD events.[1,3] In addition, both family history of MI and hs-CRP measures also remained independently predictive of ASCVD beyond CAC values, and were incorporated in the full Astro-CHARM model. Prior studies have demonstrated the additive value of family history of MI and CAC, in particular, in younger populations.[24] Given that hs-CRP is not always obtained in clinical practice, an additional model excluding hs-CRP was provided. It is interesting to note that statin use was not predictive of ASCVD events when added to the Astro-CHARM model. This may signify that CAC

Event

Risk Factor	Astro-CHARM <5%	5-<7.5	>=7.5	Total
<5%	69	21	17	107
5-<7.5	11	12	26	49
>=7.5	8	8	132	148
Total	88	41	175	304

Increased Risk	Decreased Risk	Net Correctly Reclassified	
64	27	0.1217	p<0.0001

No Event

Risk Factor	Astro-CHARM <5%	5-<7.5	>=7.5	Total
<5%	5365	230	109	5704
5-<7.5	258	244	129	631
>=7.5	77	130	536	743
Total	5700	604	774	7078

Increased Risk	Decreased Risk	Net Correctly Reclassified	
468	465	-0.0004	p=0.922

NRI= 0.121, p<0.0001

Figure 2. Net reclassification improvement tables, Astro-CHARM versus risk factor models.
NRI indicates net reclassification improvement.

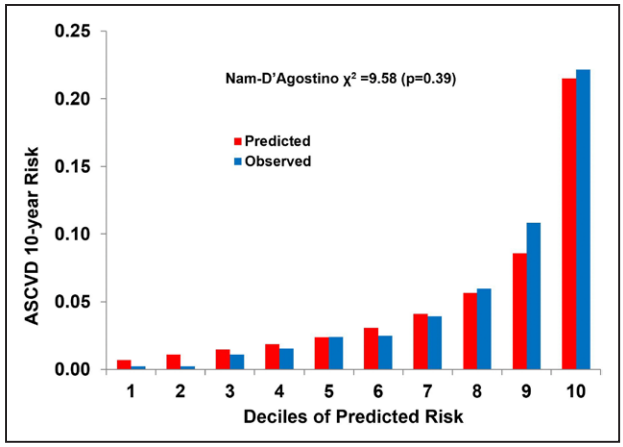

Figure 3. Internal calibration of Astro-CHARM model in the derivation cohort.
Nam-D'Agostino χ^2 *P* value >0.05, indicating adequate calibration. ASCVD indicates atherosclerotic cardiovascular disease.

and lipid values encompass the predictive information provided by statin prescription. In the MESA CHD calculator, lipid-lowering medication use was also not statistically associated with CHD events but was nominally associated with increased risk among those taking these medications. The Astro-CHARM model is best applied to individuals not already on statins for risk-based decisions given the complexity of ascertaining treatment effects in observational data sets, and because such individuals comprise >90% of the Astro-CHARM data set.

The present study has several strengths including derivation and validation using 4 large study cohorts. However, several limitations should be acknowledged. First, the PACC study had shorter follow-up and few ASCVD end points, and CRP values were imputed for ≈50% of this study cohort. However, the risk estimates derived after excluding the PACC cohort were nearly indistinguishable and the Astro-CHARM model without CRP was also well-calibrated. In addition, the Framingham validation cohort had a modest number of ASCVD events. Unfortunately, there are few US population–based studies with CAC and fatal/nonfatal end point data to contribute to validation beyond the 3 cohorts used in model derivation. Nevertheless, the Astro-CHARM demonstrated good discrimination and calibration in this cohort, and the number of events is comparable to validation cohorts for other contemporary widely applied risk scores.[25]

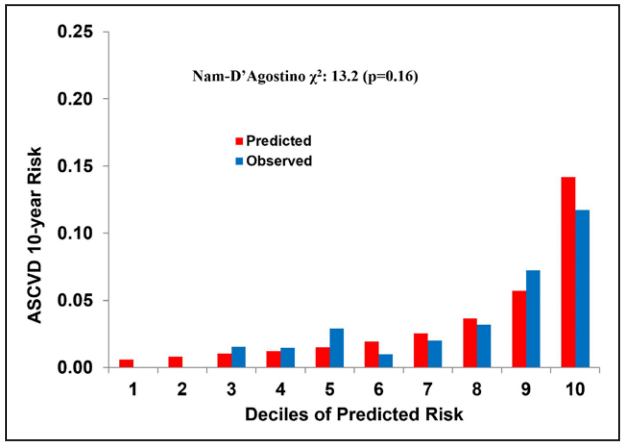

Figure 4. External calibration of the Astro-CHARM model in the Framingham Heart Study validation cohorts.
Nam-D'Agostino χ^2 *P* value >0.05, indicating adequate calibration. ASCVD indicates atherosclerotic cardiovascular disease.

Conclusions

The Astro-CHARM is the first integrated CAC and risk factor calculator for the prediction of ASCVD. It has improved discrimination and net clinical reclassification in comparison with the pooled cohort equations risk factors, and is well calibrated for 10-year ASCVD event estimation. Its development and validation involving 4 population-based cohorts enhances its generalizability for clinical practice. It may be a valuable tool for risk assessment and in risk-based decision making for CV disease prevention in the general middle-aged population.

ARTICLE INFORMATION

Received January 2, 2018; accepted May 31, 2018.
Guest Editor for this article was Pamela S. Douglas, MD.
Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.
The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.118.033505.

Correspondence

Amit Khera, MD, MSc, Division of Cardiology, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390. Email amit.khera@utsouthwestern.edu

Affiliations

Department of Internal Medicine (A.K., J.A.d.L., B.D.L.), Division of Cardiology (A.K., J.A.d.L., B.D.L.), Department of Clinical Sciences (C.A.A.) at the University of Texas Southwestern Medical Center, Dallas, TX. Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, CA (M.J.B.). The National Heart, Lung, and Blood Institute's the Framingham Heart Study, Framingham, Massachusetts; Cardiology Section, Department of Medicine, Boston Veteran's Administration Healthcare (C.J.O.). National Aeronautics and Space Agency, Johnson Space Center, Houston, TX (J.L.). Department of Mathematics, Boston University, MA (J.M.M.). Department of Biostatistics, University of Washington, Seattle (R.L.M.). Divison of Cardiology, Georgetown University; and MedStar Georgetown University Hospital and MedStar Health Research Institute, Washington, DC (A.T.). Institute for Exercise and Environmental Medicine, Presbyterian Hospital, Dallas, TX (B.D.L.).

Sources of Funding

The Astro-CHARM calculator was developed with support from the National Space Biomedical Research Institute through NCC 9-58. The Dallas Heart Study was funded by the Donald W. Reynolds Foundation (Las Vegas, Nevada) and was partially supported by US Public Health Service General Clinical Research Center grant M01-RR00633 from the National Institutes of Health/National Center for Research Resources-Continuing Review. The Framingham Heart Study was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (contract no. N01-HC-25195, HL076784, AG028321, HL070100, HL060040, HL080124, HL071039, HL077447, and HL107385). The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or

approval of the manuscript. The MESA study was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from National Center for Advancing Translational Science. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. The PACC study was Supported by the Congressionally directed, Peer Reviewed Medical Research Program, grant ERMS 00239017-00216. The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Disclosures

C.A. Ayers and Drs Khera, Levine, Lock, McClelland, O'Donnell, and Taylor report no conflicts. Dr Budoff reported grant support from General Electric. Dr de Lemos reported grant support from Roche Diagnostics and Abbott Diagnostics, Consulting from Ortho Clinical Diagnostics, Roche Diagnostics, Abbott Diagnostics, End point Committee for Siemen's Health Care Diagnostics and Radiometer, and Steering Committee from Amgen.

REFERENCES

1. Hoffmann U, Massaro JM, D'Agostino RB, Sr., Kathiresan S, Fox CS, O'Donnell CJ. Cardiovascular event prediction and risk reclassification by coronary, aortic, and valvular calcification in the Framingham Heart Study. *J Am Heart Assoc*. 2016;5: e003144. doi: 10.1161/JAHA.115.003144
2. Paixao AR, Ayers CR, El Sabbagh A, Sanghavi M, Berry JD, Rohatgi A, Kumbhani DJ, McGuire DK, Das SR, de Lemos JA, Khera A. Coronary artery calcium improves risk classification in younger populations. *JACC Cardiovasc Imaging*. 2015;8:1285–1293. doi: 10.1016/j.jcmg.2015.06.015
3. 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, Herrington DM. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. *J Am Coll Cardiol*. 2016;67:139–147. doi: 10.1016/j.jacc.2015.10.058
4. Miedema MD, Duprez DA, Misialek JR, Blaha MJ, Nasir K, Silverman MG, Blankstein R, Budoff MJ, Greenland P, Folsom AR. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Qual Outcomes*. 2014;7:453–460. doi: 10.1161/CIRCOUTCOMES.113.000690
5. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Miemdema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ, 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). *J Am Coll Cardiol*. 2015;66:1657–1668. doi: 10.1016/j.jacc.2015.07.066
6. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1–S45. doi: 10.1161/01.cir.0000437738.63853.7a
7. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
8. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, Folsom AR, Khera A, Ayers C, Mahabadi AA, Lehmann N, Jöckel KH, Moebus S, Carr JJ, Erbel R, Burke GL. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). *J Am Coll Cardiol*. 2015;66:1643–1653. doi: 10.1016/j.jacc.2015.08.035
9. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871–881.
10. Victor RG, Haley RW, Willett DL, Peshock RM, Vaeth PC, Leonard D, Basit M, Cooper RS, Iannacchione VG, Visscher WA, Staab JM, Hobbs HH; Dallas Heart Study Investigators. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. *Am J Cardiol*. 2004;93:1473–1480. doi: 10.1016/j.amjcard.2004.02.058
11. O'Malley PG, Taylor AJ, Gibbons RV, Feuerstein IM, Jones DL, Vernalis M, Brazaitis M. Rationale and design of the Prospective Army Coronary Calcium (PACC) Study: utility of electron beam computed tomography as a screening test for coronary artery disease and as an intervention for risk factor modification among young, asymptomatic, active-duty United States Army Personnel. *Am Heart J*. 1999;137:932–941.
12. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol*. 2005;46:807–814. doi: 10.1016/j.jacc.2005.05.049
13. Hoffmann U, Massaro JM, Fox CS, Manders E, O'Donnell CJ. Defining normal distributions of coronary artery calcium in women and men (from the Framingham Heart Study). *Am J Cardiol*. 2008;102:1136–41, 1141.e1. doi: 10.1016/j.amjcard.2008.06.038
14. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827–832.
15. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R Sr, O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. *Circ Cardiovasc Qual Outcomes*. 2008;1:92–97. doi: 10.1161/CIRCOUTCOMES.108.831198
16. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172; discussion 207. doi: 10.1002/sim.2929
17. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387. doi: 10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4
18. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164:836–845. doi: 10.7326/M16-0577
19. Martin SS, Sperling LS, Blaha MJ, Wilson PWF, Gluckman TJ, Blumenthal RS, Stone NJ. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. *J Am Coll Cardiol*. 2015;65:1361–1368. doi: 10.1016/j.jacc.2015.01.043
20. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372:793–795. doi: 10.1056/NEJMp1500523
21. 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, 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;133:849–858. doi: 10.1161/CIRCULATIONAHA.115.018524
22. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Grönemeyer D, Seibel R, Kälsch H, Bröcker-Preuss M, Mann K, Siegrist J, Jöckel KH; Heinz Nixdorf Recall Study Investigative Group. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol*. 2010;56:1397–1406. doi: 10.1016/j.jacc.2010.06.030
23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National

Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.

24. Paixao AR, Berry JD, Neeland IJ, Ayers CR, Rohatgi A, de Lemos JA, Khera A. Coronary artery calcification and family history of myocardial infarction in the Dallas heart study. *JACC Cardiovasc Imaging*. 2014;7:679–686. doi: 10.1016/j.jcmg.2014.04.004

25. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L; DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749. doi: 10.1001/jama.2016.3775