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ORIGINAL RESEARCH

EMERGING TECHNOLOGIES AND INNOVATIONS

AI-Enabled CT Cardiac Chamber Volumetry Predicts Atrial Fibrillation and Stroke Comparable to MRI

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ABSTRACT

BACKGROUND AI-CAC provides more actionable information than the Agatston coronary artery calcium (CAC) score. We have recently shown in the MESA (Multi-Ethnic Study of Atherosclerosis) that AI-CAC automated left atrial (LA) volumetry enabled prediction of atrial fibrillation (AF) as early as 1 year.

OBJECTIVES In this study, the authors evaluated the performance of AI-CAC LA volumetry versus LA measured by human experts using cardiac magnetic resonance imaging (CMRI) for predicting incident AF and stroke and compared them with Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation (CHARGE-AF) risk score, Agatston score, and N-terminal pro b-type natriuretic peptide (NT-proBNP).

METHODS We used 15-year outcomes data from 3,552 asymptomatic individuals (52.2% women, age 61.7 ± 10.2 years) who underwent both CAC scans and CMRI in the MESA baseline examination. CMRI LA volume was previously measured by human experts. Data on NT-proBNP, CHARGE-AF risk score, and the Agatston score were obtained from MESA. Discrimination was assessed using the time-dependent area under the curve.

RESULTS Over 15 years follow-up, 562 cases of AF and 140 cases of stroke accrued. The area under the curve for AI-CAC versus CMRI volumetry for AF (0.802 vs 0.798) and stroke (0.762 vs 0.751) were not significantly different. AI-CAC LA significantly improved the continuous net reclassification index for prediction of 5-year AF when added to CHARGE-AF risk score (0.23), NT-proBNP (0.37, 0.37), and Agatston score (0.44) (*P* for all <0.0001).

CONCLUSIONS AI-CAC automated LA volumetry and CMRI LA volume measured by human experts similarly predicted incident AF and stroke over 15 years. Further studies to investigate the clinical utility of AI-CAC for AF and stroke prediction are warranted. (JACC Adv. 2024;3:101300) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AI-CAC = AI-enabled cardiac chambers volumetry in CT

ASCVD = atherosclerotic cardiovascular disease

AUC = area under the curve

CAC = coronary artery calcium

CMRI = cardiac magnetic resonance imaging

CT = computed tomography

CVD = cardiovascular disease

EBCT = electron-beam computed tomography

ICD = International Classification of Diseases

LA = left atrial/atrium

LV = left ventricle

LVH = left ventricular hypertrophy

MDCT = multidetector computed tomography scanners

NRI = net reclassification index

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RV = right ventricle

Left atrial (LA) size normalized by the body surface area has been studied extensively as a predictor of incident atrial fibrillation (AF), stroke, and other adverse cardiovascular events.[1,2] However, this valuable biomarker has not been widely introduced to patient care for AF prediction and stroke prevention. Contrast-enhanced cardiac magnetic resonance imaging (CMRI) is the gold standard for measuring LA volume. However, CMRI is more time-consuming, has a higher cost, and is not as widely available as a non-contrast cardiac computed tomography (CT) scan obtained for coronary artery calcium (CAC) scoring.[3] Robustly measuring LA volume in a CAC scan without additional radiation exposure to patients or using any contrast-enhanced agent would be of significant clinical value. Such an add-on measurement can offer valuable insights into a patient's cardiovascular risk beyond the Agatston CAC score, which is the strongest predictor of atherosclerotic cardiovascular disease (ASCVD) in asymptomatic individuals today.

We have developed an artificial intelligence-enabled tool that automatically and reliably estimates cardiac chambers volume in non-contrast cardiac CT scans obtained for CAC score AI enabled cardiac chambers volumetry in cardiac CT (AI-CAC). This tool is very rapid (averaging 21 seconds per scan in this cohort) compared to CMRI measurements (averaging 30-45 minutes)[3] and reports the volume of all 4 cardiac chambers as well as left ventricular mass. We have recently applied AI-CAC to CAC scans obtained in the baseline examination (years 2000-2002) of the MESA (Multi-Ethnic Study of Atherosclerosis) and demonstrated its ability to predict AF in as early as 1 year.[4] We additionally compared AI-CAC LA volume to the Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation (CHARGE-AF) risk score and N-terminal pro-B-type natriuretic peptide (NT-proBNP). CHARGE-AF is a widely recognized risk model used to predict the 5-year risk of AF in asymptomatic populations.[5] NT-proBNP is a blood biomarker associated with enlarged cardiac chambers, and recent studies have linked it to the incidence of AF.[6]

This study evaluates the performance of AI-CAC automated LA volumetry versus LA volume measured by human experts using CMRI for predicting AF and stroke. Furthermore, we compared their predictive value with that of known predictors that are associated with incident AF and stroke: the CHARGE-AF risk score, Agatston CAC score, and NT-proBNP (**Central Illustration**).

METHODS

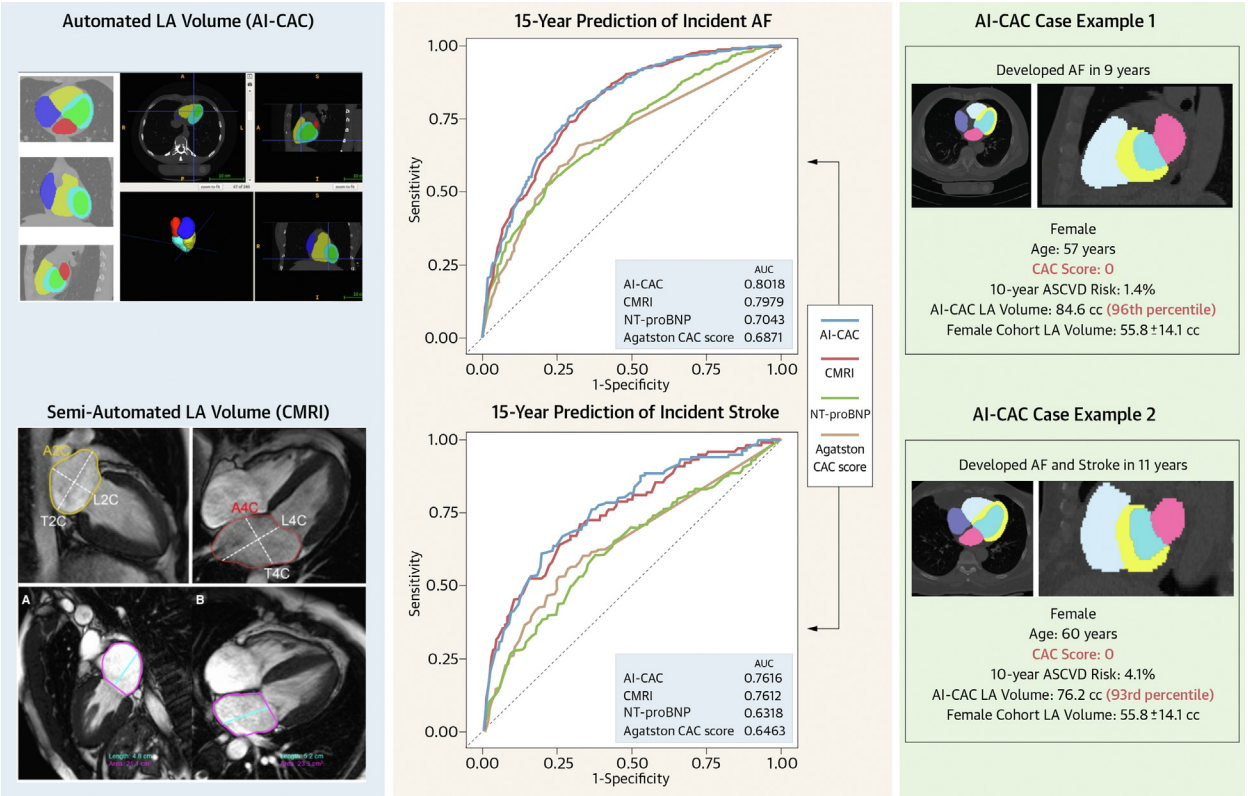
STUDY POPULATION. The MESA is a prospective, population-based, observational cohort study of 6,814 men and women without clinical cardiovascular disease (CVD) at the time of recruitment. Six field centers in the United States participated in the study: Baltimore, Maryland; Los Angeles, California; Chicago, Illinois; Forsyth County, North Carolina; New York City, New York; and St. Paul, Minnesota. As part of the initial evaluation (2000-2002), participants received a comprehensive medical history, clinic examination, and laboratory tests. Demographic information, medical history, and medication use at baseline were obtained by self-report. An electrocardiogram (ECG)-gated non-contrast CT was performed at the baseline examination to measure CAC. Non-CT scan covariates included NT-proBNP and covariates used in the CHARGE-AF score: age, sex, ethnicity, height, weight, systolic blood pressure, diastolic blood pressure, current smoking, hypertension medication, and diabetes, which were obtained in MESA baseline exam 1 previously described.[7]

AF AND STROKE EVENTS. Participants were contacted by telephone every 9 to 12 months during follow-up and asked to report all new cardiovascular diagnoses. International Classification of Diseases (ICD) codes were obtained. Incident AF was identified by ICD codes 427.3x (version 9) or I48.x (version 10) from inpatient stays and, for participants enrolled in fee-for-service Medicare, from Medicare claims for outpatient and provider services. Incident stroke was classified as hemorrhagic or ischemic. Stroke was identified as present or absent and consisted of rapid onset of a documented focal neurologic deficit lasting 24 hours or until death, or if <24 hours, there was a clinically relevant lesion on brain imaging. Patients with focal neurologic deficits secondary to brain trauma, tumor, infection, or other nonvascular causes were excluded. Transient ischemic attack was not included in this definition. A more detailed protocol of AF and stroke event adjudication is available at www.mesa-nhlbi.org and was published previously.[7]

A detailed description of manuscript exclusion criteria is shown in **Figure 1**.

THE AI-CAC TOOL FOR AUTOMATED CARDIAC CHAMBERS VOLUMETRY. The automated cardiac chambers volumetry component of AI-CAC used in this study is called AutoChamber (HeartLung.AI), a deep learning model that used TotalSegmentator[8] to

CENTRAL ILLUSTRATION **In MESA, AI-Enabled Automated Left Atrial Volumetry in Noncontrast CT Obtained for CAC Scoring (AI-CAC) Predicts Incident Atrial Fibrillation and Stroke Over 15 Years Comparably to Cardiac MRI and Outperforms NT-proBNP and Agatston CAC Score**



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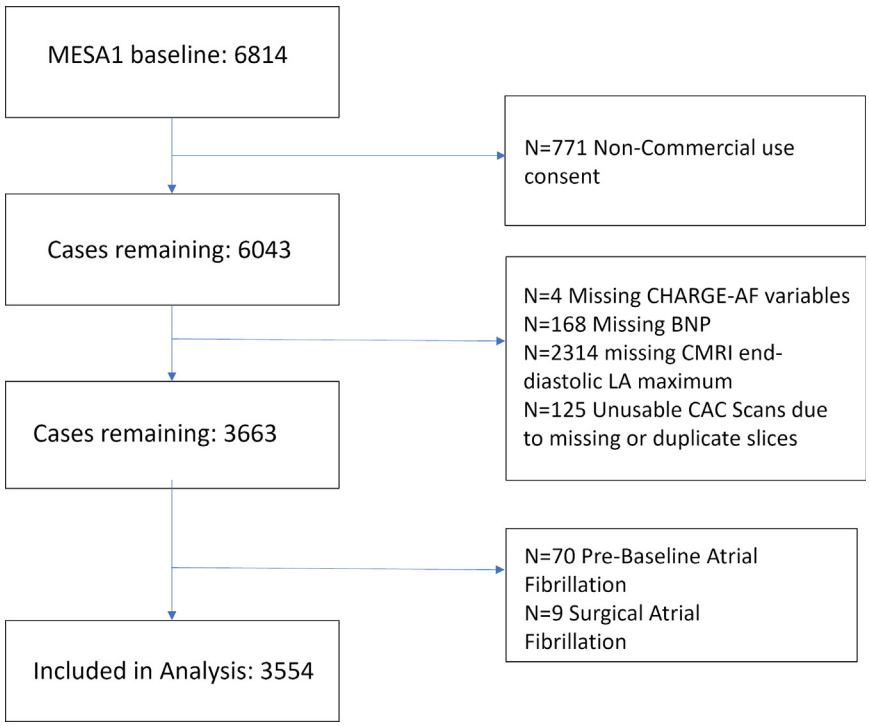
Furthermore, AI-CAC volumetry (LA, LV, RV volumes, and LV mass) outperformed NT-proBNP and Agatston CAC score for incident AF and stroke prediction over 2–5-year follow-up. CT = computed tomography; other abbreviations as in Figures 1 and 2.

segment the 4 cardiac chambers: left atrium (LA), left ventricle (LV), right atrium, right ventricle (RV), and several other components which are not presented here. The cardiac chambers component of AI-CAC is adapted from TotalSegmentator which is a widely used anatomical model published and validated by investigators independent from our group. The base architecture of the TotalSegmentator model was trained using nnU-Net and validated on 1,139 whole-body CT examinations cases with 447 cases of coronary CT angiography randomly sampled from the University Hospital Basel.[8] The initial input training data were matched non-contrast and contrast-enhanced ECG-gated cardiac CT scans with 1.5 mm slice thickness. Because the images were taken from the same patients in the same session, registration was done with good alignment.

We developed a post processing pipeline to flag cases with poor quality segmentations where the region of interest was missing. This affected a significant number of cases in some way (64%). This automatic quality control step consisted of a signal processing algorithm based on 3-dimensional connected components that retain the largest component and disregards the small, fragmented segmentations. This phenomenon mostly occurs at the bottom of the heart where the heart overlaps with the diaphragm and is well-known as the area with maximum noise. Nonetheless, this study did not involve the development of a new AI model.

Expert rules built in the AI-model excluded 125 cases due to missing slices in image reconstruction created by some of the electron beam CT scanners used in MESA baseline. These cases were random,

FIGURE 1 Flow Chart Depicting Manuscript Inclusion and Exclusion Criteria



Overlapping missing variables account for higher cases included in analysis. CAC = coronary artery calcium; CMRI = cardiac magnetic resonance imaging; LA = left atrial/atrium; MESA = Multi-Ethnic Study of Atherosclerosis.

and our investigations did not reveal any association with dependent or independent variables in our study.

CMRI MEASUREMENT. In MESA, CMRI quantified volume and dimensions of all 4 cardiac chambers during systole and diastole. For incident AF prediction, the focus was end-diastolic LA maximum volume. Multimodality Tissue Tracking software (MTT, version 5.0) was used to quantify LA volume from baseline 4- and 2-chamber cine CMR images. A detailed protocol used for CMRI measurements in MESA has been previously described.[9,10]

CHARGE-AF RISK SCORE. The CHARGE-AF risk score was developed to predict risk of 5-year incident AF in 3 American cohorts, and it was validated in 2 European cohorts. The linear predictor from the CHARGE-AF risk score is calculated based on known risk factors.[5] Due to the asymptomatic cohort, presence of heart failure (HF) was not included in the equation.

NT-proBNP MEASUREMENT. Details on BNP assays used in MESA have been reported.[11] Intra-assay and inter-assay coefficients of variation at various concentrations of NT-proBNP have been previously reported.[12,13] The analytical measurement range for NT-proBNP in exam 1 was 4.9 to 1,1699 pg/ml, thus cases below 4.99 were treated as 4.99 pg/mL. Clinically, values are not reported below 4.99 pg/mL because the analytical accuracy is poor (ie, typically a coefficient of variation of >20% between repeat measures).

AGATSTON CAC SCORE MEASUREMENT. Out of 6 study sites, 3 used cardiac-gated electron-beam CT scans, whereas the other 3 sites used multidetector CT scans. Each participant was scanned twice at baseline examination, with mean Agatston score used for analysis.[14] All scans were phantom adjusted and read by 2 trained CT image analysts at a central MESA CT reading center, with high reproducibility and comparability between electron beam CT and multidetector CT scanning.[15,16] Detailed information on CT scan methods and interpretation has been given previously.[15]

STATISTICAL ANALYSIS. We used SAS (SAS Institute Inc) and Python software for statistical analyses. All tests of significance were 2-tailed, and significance was defined at the $P < 0.05$ level.

Cumulative incidence for AF and stroke was calculated using 1 minus the Kaplan-Meier survival estimate. Group differences were determined using the log-rank test. The time-dependent receiver operator curve area under the curve (AUC) was calculated using estimated survival probabilities with the inverse probability of censoring weighting estimator. For each follow-up time, the *P* value for the comparison between predictors was calculated using the variance of the difference of the iid-representation of the AUC estimators.

NT-proBNP and Agatston CAC score were natural logarithm-transformed (ln-transformed) to avoid undue influence of large values. The AI-CAC model as presented in this manuscript incorporates LA volume for AF prediction, and LA, LV, RV volumes, and LV mass for stroke prediction. CMRI measurements were incorporated similarly for AF and stroke. All predictors displayed a linear relationship with outcomes and were modeled continuously.

Category-free (continuous) net reclassification index (NRI) was calculated using the sum of the differences between the proportions of upward reclassifications and downward reclassifications for AF and stroke events and nonevents, respectively. NRI was developed as a statistical measure to evaluate the improvement in risk prediction models when additional variables are incorporated into a base model.[17] We have analyzed data for AF and stroke prediction over 15 years of follow-up.

ETHICAL APPROVAL. As a longitudinal population-based study sponsored by the National Institute of Health (NIH), MESA has received proper ethical oversight. The MESA protocol was approved by the Institutional Review Board of the 6 field medical centers (Columbia University, Johns Hopkins Medicine, Northwestern University, University of California-Los Angeles, University of Minnesota, Wake Forest) and the National Heart, Lung, and Blood Institute. Data from participants who did not consent to commercial use were removed from our study (**Figure 1**).

RESULTS

BASELINE CHARACTERISTICS. 28.1% of participants were aged 45 to 54 years, 27.3% aged 55 to 64 years, 29.8% aged 65 to 74 years, and 14.8% aged 75 to 84 years. 52.2% of participants were female, 39.7% were White, 26.1% Black, 22% Hispanic, and 12.1% Chinese. **Table 1** shows the baseline characteristics of MESA participants who were diagnosed with incident AF and stroke versus those who were not over the period of 15 years of follow up. The incident AF cases for AI-CAC had higher cardiac chamber volumes for LA, LV, right atrium, LV wall, and CMRI had higher cardiac chamber volumes for LA, LV, and LV wall. CHARGE-AF risk scores, Agatston CAC score, and NT-proBNP levels were elevated in incident AF and stroke cases versus those without incident AF and stroke (all comparisons $P < 0.001$) (**Table 1**).

SHORT-TERM PREDICTION OF INCIDENT AF AND STROKE. AI-CAC LA volume significantly outperformed CHARGE-AF, NT-proBNP, and Agatston CAC score for short-term AF prediction (**Table 2**). The AUC at 1-year follow-up for AI-CAC LA (0.83) was significantly higher than CHARGE-AF (0.74), NT-proBNP (0.74), and Agatston CAC score (0.68) (**Figure 2A**). Additionally, AI-CAC LA volume outperformed CHARGE AF over 2 to 3 years for incident AF ($P < 0.02$), but the difference was not statistically significant for year 4 ($P = 0.11$) and year 5 ($P = 0.08$). The AUC for AI-CAC LA volume was significantly higher than NT-proBNP over 1 to 5 years of follow-up. AI-CAC volumetry was investigated for short-term stroke prediction vs NT-proBNP and Agatston CAC score (**Table 3**). The AUC for AI-CAC volumetry (LA, LV, RV volumes, and LV mass) was not significantly higher than NT-proBNP or Agatston CAC score for 1-year stroke prediction (**Figure 2b**) due to small number of events but was significantly higher than both for 2- to 5-year follow-up.

FIFTEEN-YEAR PREDICTION OF INCIDENT AF AND STROKE. The cumulative incidence of AF over 15 years for AI-estimated LA volume, CMRI estimated LA volume, CHARGE-AF risk score, NT-proBNP, and CAC were not significantly different (**Figures 3A to 3E**). The incidence of AF in the 99th percentile of AI-LA volume, CMRI LA volume, Agatston CAC score, CHARGE-AF risk score, and BNP were 78.6%, 81%, 67.4%, 73.4%, and 58%, respectively. The incidence of AF in the 95th percentile of AI-LA volume, CMRI LA volume, Agatston CAC score, CHARGE-AF risk score, and BNP were 45.2%, 37.9%, 46.4%, 49.8%, and 45.5%, respectively.

The AUC for 15-year AF prediction by AI-estimated LA volume (0.801) was comparable to CMRI LA volume (0.797) and significantly higher than Agatston CAC score (0.687) and NT-proBNP (0.704), (**Figure 4A**). Similarly, the AUC for 15-year stroke prediction for AI-CAC volumetry (0.761) was comparable to CMRI volumetry (0.751) and significantly higher than NT-proBNP (0.631) and Agatston CAC score (0.646) (**Figure 4B**).

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TABLE 1 Baseline Characteristics of the MESA Participants Including Cases With and Without Incident AF and Stroke at 15 Years

	Overall (N = 3,552)	AF (n = 562)	Stroke (n = 140)
Age (per 10 y)			
Age 45-54	28.1%	8.7%	11.1%
Age 55-64	27.3%	23.6%	23.8%
Age 65-74	29.8%	41.9%	34.5%
Age 75-84	14.8%	25.7%	30.7%
Female	52.2%	47.9%	48.7%
Body surface area	1.90 ± 0.24	1.92 ± 0.25	1.90 ± 0.23
Race/ethnicity (%)			
White	39.5%	39.4%	36.8%
Chinese	12.4%	12.2%	6.5%
Black	25.8%	26.3%	28.0%
Hispanic	22.3%	22%	28.7%
AI-CAC volumes (cc)			
LV volume	102.23 ± 24.96	108.0 ± 31.1	104.9 + 24.1
LA volume	60.94 ± 15.10	73.5 ± 24.5	67.8 + 20.0
RV volume	134.30 ± 34.43	136.0 ± 37.7	131.7 + 31.4
RA volume	76.76 ± 18.75	83.3 ± 26.0	71.7 + 18.7
LV mass (g)	107.53 ± 26.08	114.2 ± 30.6	109.5 + 25.2
Total heart (cc)	481.76 ± 108.69	514.9 ± 134.9	485.7 + 103.2
CMRI volumes[a] (cc)			
LA maximum volume	56.0 ± 20.4	64.1 ± 26.3	59.8 + 24.6
LV volume	127.2 ± 30.7	128.9 ± 35.4	122.9 + 28.8
RV volume	125.1 ± 30.8	124.2 ± 31.7	120.2 + 27.4
LV mass (g)	144.7 ± 38.7	154.3 ± 43.9	155.3 + 40.9
CHARGE-AF score	11.7 ± 1.2	12.8 ± 0.9	12.5 + 1.0
NT-proBNP (pg/mL)	51.41 (23.19-104.4)	115.8 (62.42-236)	72.5 (35.8-171.4)
NT-proBNP (mean)	82.1 ± 95.0	175.7 ± 159.6	124.8 + 136.6
CAC	0 (0-80.84)	59.5 (3.1-257.6)	50.4 (0-255.7)
CAC (mean)	133.7 ± 379.0	333.3 ± 686.8	257.2 + 485.6
Risk factors			
Diabetes	12.1%	15.7%	22.2%
Hypertension	43.8%	62.7%	67.0%
Smoking (current vs former/never)	12.8%	10.6%	11.9%
Alcohol (current use)	69.3%	63.5%	62.2%
Family history of coronary heart disease	42.6	45.5%	48.2%
Blood pressure lowering Rx	36.0%	54.9%	53.1%
Lipid lowering Rx	16.4%	16.6%	20.2%
LDL cholesterol (mg/dL)	117.2 ± 31	115.4 ± 33.4	118.3 + 30.1
HDL cholesterol (mg/dL)	50.9 ± 15	50.0 ± 13.9	48.8 + 14.3
Total cholesterol (mg/dL)	194.4 ± 35.3	192.2 ± 38.0	194.8 + 35.1

Values are %, mean ± SD, or median (IQR). [a]Right atrial (RA) end-diastolic volumes were unavailable for analysis.

AI-CAC = AI enabled cardiac chambers volumetry in cardiac CT; CAC = coronary artery calcium; CHARGE-AF = Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation; CMRI = cardiac magnetic resonance imaging; HDL = high-density lipoprotein; LA = left atrial; LDL = low-density lipoprotein; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RV = right ventricle.

RISK RECLASSIFICATION. A significant number of low-risk participants with CAC 0 have enlarged cardiac chambers (**Figure 5**). Examples of 3 high-risk patients with enlarged LA and LV volume with CAC score 0 and CAC below 50th percentile, who are currently categorized as low risk have been provided.

The continuous NRI for prediction of AF when AI-estimated LA volume and CMRI LA volume was added to CAC score as the only predictor in the base model was substantial (0.69, 0.41, respectively, $P < 0.0001$). Similarly, the NRI for AI-LA volume and CMRI LA volume when added to base model with CHARGE-AF risk score (0.28, 0.31) and BNP (0.43, 0.32), respectively, was significant for incident AF prediction ($P < 0.0001$). AI-CAC volumetry improved the predictive value of NT-proBNP with category-free NRI of 0.50 at year 1 to 0.36 at year 5 for stroke.

A total of 699 (17.6%) participants classified as low-risk (<2.5%) for 5-year incident AF by CHARGE-AF were flagged by AI-CAC for enlarged LA volume (top quartile). Of these 699 participants, 30 (4.3%) experienced incident AF within 5 years. Similarly, 476 (18%) participants in the lowest risk quartile (4.9-23.6 pg/mL) of NT-proBNP had enlarged LA. Sixty-five (13.7%) participants out of the 476 participants experienced incident AF within 5 years. 468 (17.7%) of participants with CAC score of 0 had an enlarged LA (**Figures 6A to 6C**).

DISCUSSION

Our study demonstrated that automated LA volumetry using AI-CAC has comparable predictive value to that of the gold standard (CMRI). Despite the marginal differences between AI-CAC and CMRI in AUC for AF and stroke discrimination, these differences were not found to be statistically significant. Furthermore, both AI-CAC and CMRI provided for a sizable NRI when added to CHARGE-AF risk score and NT-proBNP which are current contenders for AF prediction.[18,19] To our knowledge, this is the first report comparing the predictive value of LA volume measured by an artificial intelligence (AI) tool in non-contrast cardiac CT scans versus measured by human experts using cardiac MRI for the prediction of incident AF and stroke in a multiethnic asymptomatic population.

AF is the most common sustained cardiac arrhythmia with an increased risk of CVD outcomes including a 5-fold higher risk of stroke.[20] However, it often goes undiagnosed in approximately 30% of cases due to its paroxysmal nature and minimal or even absent symptoms.[21] In the United States alone, it is estimated that around 1 million cases of AF are asymptomatic or undiagnosed.[22] Consequently, while

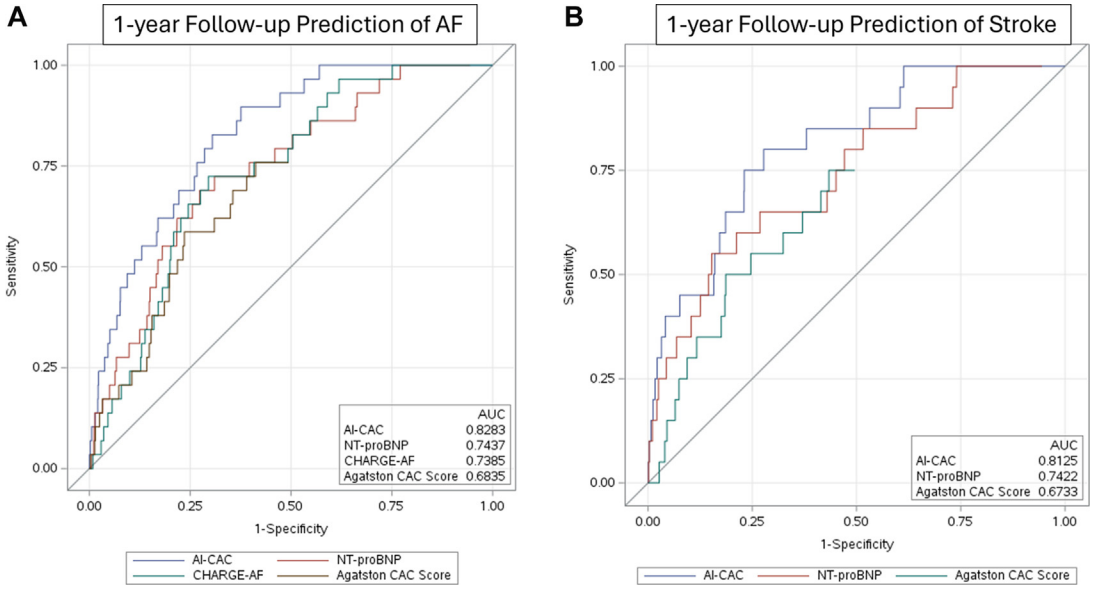
TABLE 2 Time-Dependent AUC for AF Prediction Between AI-CAC LA Volume, CHARGE-AF Score, and NT-proBNP Over 1 to 5 Years in the MESA

	1 Year		2 Years		3 Years		4 Years		5 Years	
AF events	36		77		123		182		236	
Predictors	**AUC**	***P* Value**	**AUC**	***P* Value**	**AUC**	***P* Value**	**AUC**	***P* Value**	**AUC**	***P* Value**
AI-CAC LA volume[a]	0.83	-	0.84	-	0.81	-	0.78	-	0.77	-
CHARGE-AF	0.74	0.010	0.80	0.003	0.78	0.022	0.76	0.110	0.76	0.080
NT-proBNP	0.74	0.003	0.77	0.005	0.75	0.001	0.73	0.001	0.73	0.001
Agatston CAC score	0.68	<0.0001	0.71	<0.0001	0.71	<0.0001	0.67	<0.0001	0.67	<0.0001
CHARGE-AF + NT-proBNP	0.77	0.070	0.83	0.660	0.81	0.990	0.79	0.500	0.79	0.410
CHARGE-AF + AI-CAC LA volume	0.80	0.076	0.82	0.020	0.79	0.059	0.77	0.309	0.77	0.513
Category-Free Net Reclassification Index (NRI) Adding AI-LA	**NRI**	***P* Value**	**NRI**	***P* Value**	**NRI**	***P* Value**	**NRI**	***P* Value**	**NRI**	***P* Value**
To base model CHARGE-AF	0.60	<0.0001	0.28	<0.0001	0.33	<0.0001	0.19	<0.0001	0.23	<0.0001
To base model NT-proBNP	0.68	<0.0001	0.44	<0.0001	0.42	<0.0001	0.30	<0.0001	0.37	<0.0001
To base model Agatston CAC score	0.73	<0.0001	0.49	<0.0001	0.53	<0.0001	0.39	<0.0001	0.44	<0.0001

[a]Adjusted for age and body surface area (BSA).
Abbreviations as in Table 1.

the risk of stroke in patients with AF can be reduced by two-thirds with oral anticoagulation therapy, more than 10% of patients experience their first manifestation of undiagnosed AF as a stroke. A reasonable intervention following the detection of individuals at high risk of AF would be recommending a wearable ECG monitor to watch for episodes of asymptomatic AF. More importantly than detection of asymptomatic AF is prediction of high-risk cases who will develop AF in the near future.

FIGURE 2 Time-Dependent ROC AUC for 1-Year Atrial Fibrillation and Stroke Prediction



(A) AI-CAC showed nonsignificantly greater AUC for prediction of 1-year incident AF Vs the CHARGE-AF risk score, Agatston CAC score and NT-proBNP. (B) AI-CAC showed nonsignificantly greater AUC for prediction of 1-year incident stroke Vs Agatston CAC score and NT-proBNP. AF = atrial fibrillation; AI-CAC = AI enabled cardiac chambers volumetry in cardiac CT; CHARGE-AF = Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation; NT-proBNP = N-terminal pro b-type natriuretic peptide; other abbreviation as in Figure 1.

TABLE 3 Time-Dependent AUC for Stroke Prediction for AI-CAC Volumetry vs NT-proBNP, and Agatston CAC Score Over 1 to 5 Years in the MESA

	1 Year		2 Years		3 Years		4 Years		5 Years	
Stroke events	20		38		48		62		75	
Predictors	**AUC**	***P* Value**	**AUC**	***P* Value**	**AUC**	***P* Value**	**AUC**	***P* Value**	**AUC**	***P* Value**
AI-CAC volumetry[a]	0.81	-	0.80	-	0.77	-	0.77	-	0.77	-
NT-proBNP	0.74	0.1393	0.71	0.0076	0.68	0.0044	0.69	0.0107	0.68	0.0025
Agatston CAC score	0.67	0.0574	0.69	0.0252	0.69	0.0958	0.68	0.0113	0.67	0.0061
Category-Free NRI Adding AI-CAC Volumetry	**NRI**	***P* Value**	**NRI**	***P* Value**	**NRI**	***P* Value**	**NRI**	***P* Value**	**NRI**	***P* Value**
To base model NT-proBNP	0.50	0.0245	0.39	0.0155	0.28	0.0494	0.29	0.0246	0.36	0.0019
To base model CAC	0.48	0.0291	0.37	0.0163	0.31	0.0218	0.39	0.0011	0.41	0.0002

[a]AI-CAC volumetry: LA volume, LV volume + LV mass sum, RV adjusted for age and body surface area (BSA).
NRI = net reclassification index; other abbreviation as in Table 1.

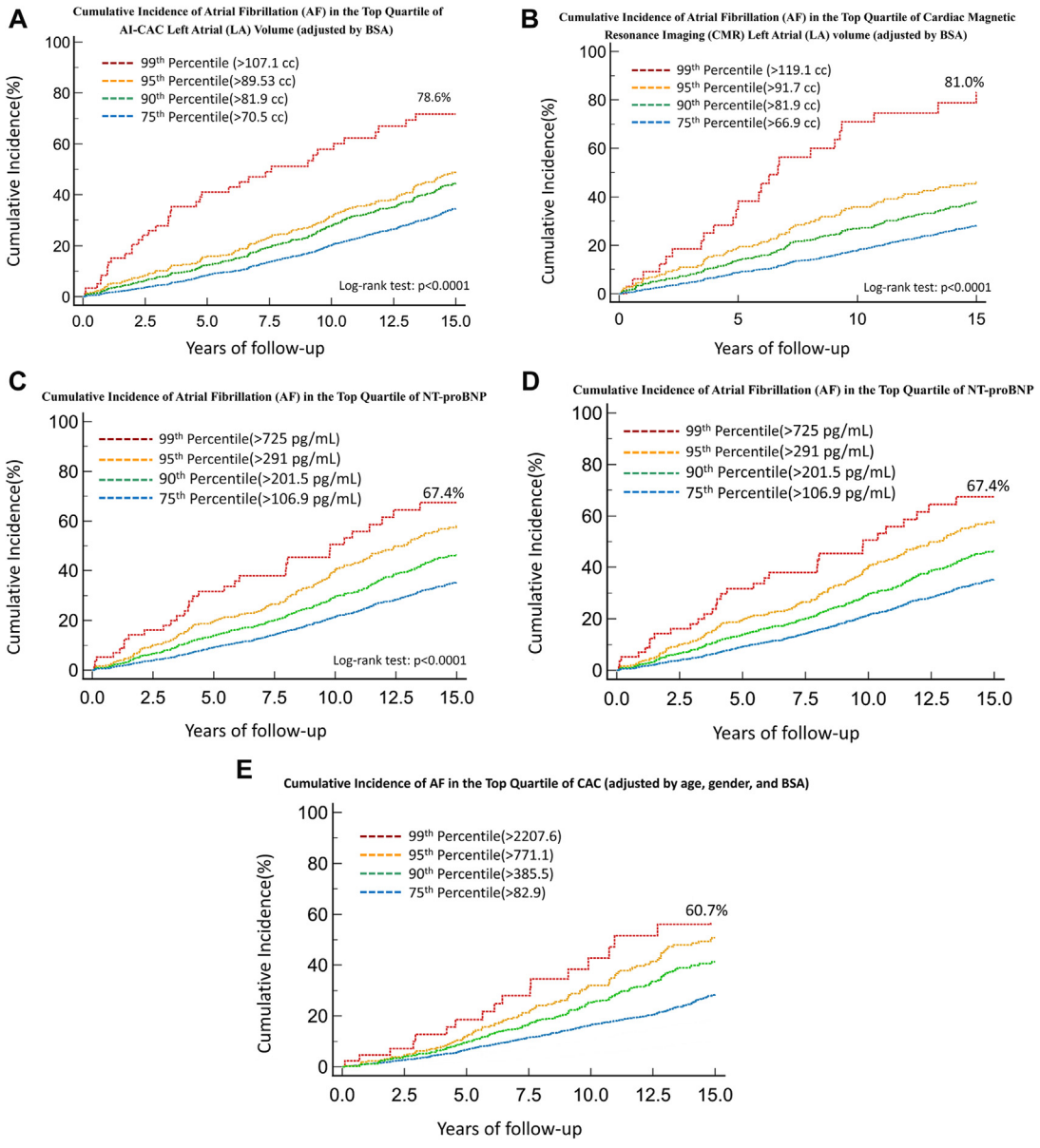
While traditional risk prediction models such as ASCVD pooled cohort equations and the predicting risk of cardiovascular disease EVENTs risk score include stroke prediction as part of overall ASCVD risk assessment, they do not report stroke risk separately. The revised Framingham stroke risk score is specific to stroke; however, it is limited to White population and does not apply to multiethnic populations. To our knowledge, this is the first study applying AI-enabled cardiac chambers volumetry for prediction of incident AF and stroke.

USING AI TO MAXIMIZE THE VALUE OF CAC SCANS. Since 1990 when Agatston and Janowitz[19] introduced their CAC scoring technique, there has been minimal advancement in the scoring and utility of CAC scans. Despite significant advancements in cardiac CT imaging and the transition from electron beam CT to multi-detector CT, CAC scoring reports given to patients remain limited to providing the Agatston score based on measurements from 4 coronary arteries and its interpretation in relation to ASCVD risk. In the meantime, numerous research studies have shown the value of noncoronary findings in CAC scans.[1,2,23,24] Our study brings to light the practical use of noncoronary findings in CAC scans and corroborates recommendations by Heinz Nixdorf Recall Study investigators for a comprehensive CVD risk assessment in CAC scans beyond the CAC score and coronary heart disease.[1,2,23,25] It is noteworthy that the application of AI-enabled cardiac chambers volumetry is not limited to CAC scans. In fact, it can be replicated in non-gated lung cancer screening scans. We have recently demonstrated in 169 patients with ECG-gated cardiac and non-gated lung CT scans in the same patients (paired scans done same day) that cardiac chambers volume measure in the 2 scans were strongly correlated (R = 0.92-0.97 for different chambers, all $P < 0.001$).[26]

AI-CAC VS CMRI. Although cardiac MRI is considered the gold standard for assessment of cardiac structure and function assessment, it is not practical for use as an add-on screening tool. Moreover, screening with CMRI would be cost and resource prohibitive. Volumetry screening with echocardiography is prone to excessive variability and operator dependency. Non-contrast chest CT scans including CAC scans and lung cancer screening CT scans provide opportunities for more wide-spread detection of patients with enlarged cardiac chambers and left ventricular hypertrophy (LVH) using AI-CAC. We have recently compared the diagnostic performance of AI-CAC for detection of LVH versus NT-proBNP against CMRI.[27] In our study, AI-CAC showed an AUC of 0.871 for LVH in males and 0.854 in females. Our findings, while requiring further validation, point toward the clinical utility AI-enabled cardiac chambers volumetry for automatic screening among 10+ million CT scans done each year in the United States alone.[28] Such an AI tool can run in the background of radiology picture archiving and communication systems and flag cases with enlarged LA and other cardiac chambers. Today many of such high-risk patients are undetected, therefore untreated. Early detection of those at risk may lead to earlier opportunities to treat those at increased risk of AF and stroke.

AI-CAC VS NT-proBNP. NT-proBNP has been studied extensively in various CVDs, particularly heart failure.[29] However, numerous studies have linked NT-proBNP with incident AF and stroke.[30,31] For example, Asselberg et al[32] found that in the general

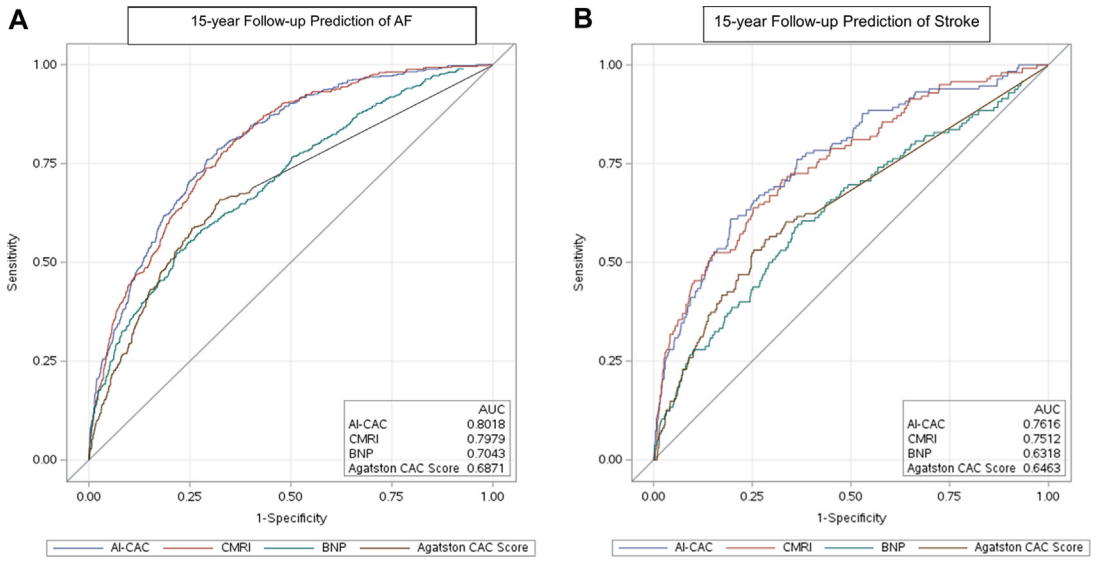
FIGURE 3 Cumulative Incidence of AF



(A) Cumulative incidence of af in the top quartile of AI-CAC left atrial (LA) volume, (B) cardiac magnetic resonance imaging (CMR) LA volume, (C) NT-proBNP (BNP), (D) CHARGE-AF risk score, and (E) Agatston CAC score over 15 years of follow-up. BSA = body surface area; other abbreviations as in Figures 1 and 2.

population, elevated BNP levels at baseline predicted the development of AF when reassessed at 4 years. The baseline median level was 62.2 pg/ml in those who eventually developed AF compared to 35.7 pg/mL in those who did not ($P = 0.001$). In our studies, LA volume measured by AI-CAC and CMRI both outperformed NT-proBNP for prediction of AF and stroke. Additionally, we have shown that AI-CAC improved the predictive value of NT-proBNP by category-free NRI of 0.69 at year 1 to 0.38 at year 5 for AF, and

FIGURE 4 Time-Dependent ROC AUC for 15-Year Atrial Fibrillation and Stroke Prediction

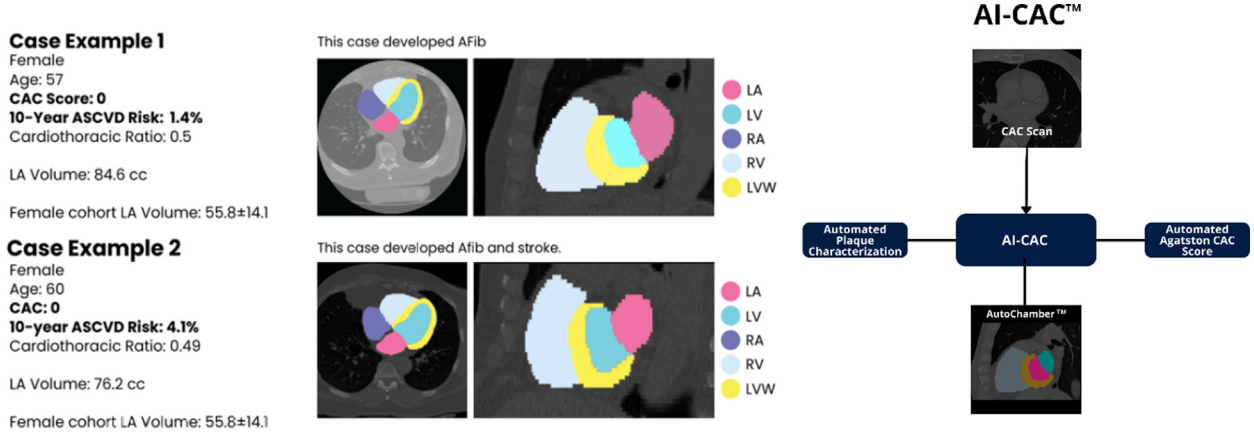


(A) AI-CAC and CMRI LA demonstrated nonsignificant difference for prediction of 15-year AF. AI-CAC LA showed significantly greater discrimination for 15-year AF than Agatston CAC score and NT-proBNP. (B) AI-CAC and CMRI volumetry demonstrated nonsignificant difference for prediction of 15-year stroke. AI-CAC volumetry showed significantly greater discrimination for 15-year stroke than Agatston CAC score and NT-proBNP Abbreviations as in Figures 1 and 2.

0.50 at year 1 to 0.36 at year 5 for stroke. Unlike an enlarged LA, elevated NT-proBNP may not be specific to LA or LV volume and can be influenced by other factors.

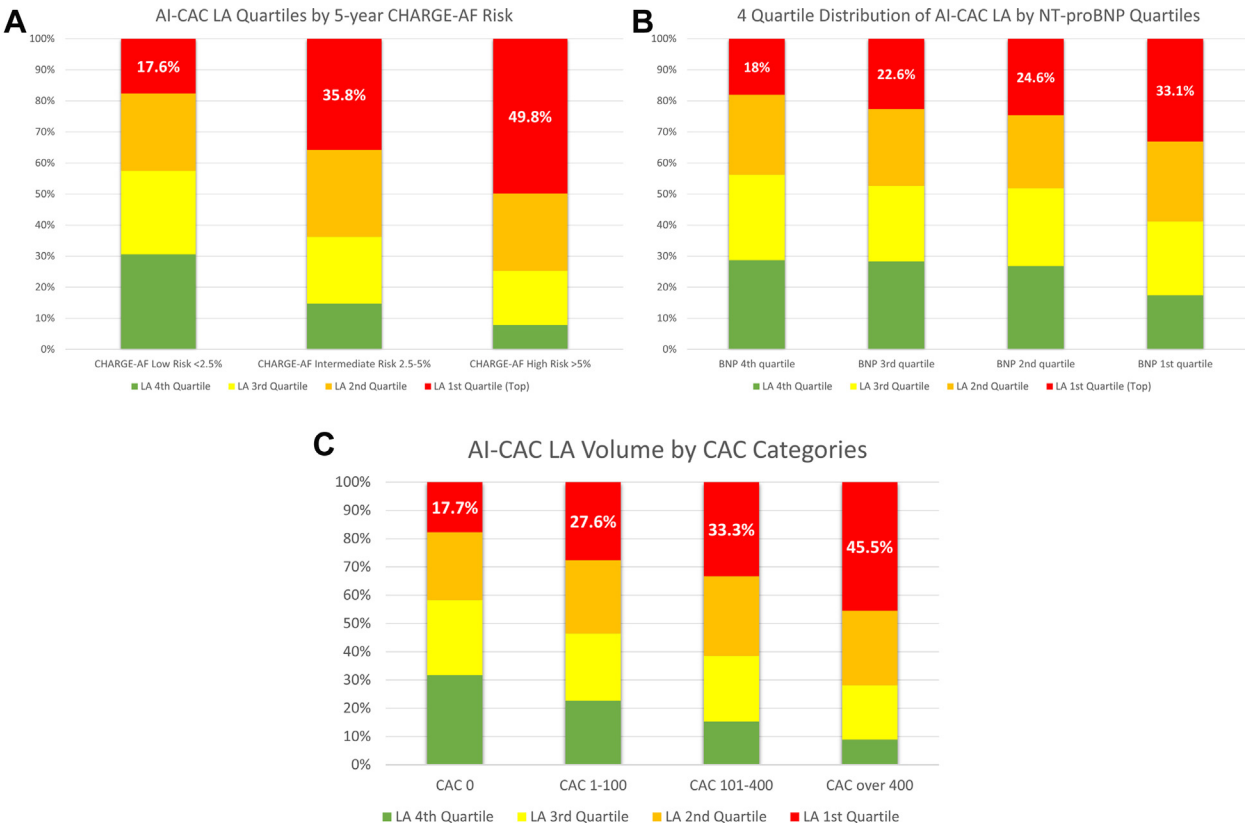
STYDY LIMITATIONS. Our study has some limitations. The MESA Exam 1 baseline CT scans, performed between 2000 and 2002, were predominantly conducted using electron-beam CT (EBCT) and earlier

FIGURE 5 AI-CAC Detection of At-Risk Asymptomatic Patients



Examples of AI-CAC detection of high-risk asymptomatic cardiovascular patients with enlarged left ventricle (LV) in coronary artery calcium (CAC) scans. These patients had Agatston CAC score of zero and were categorized as low risk by ASCVD pooled cohorts equation who experienced adverse Events over 15 years. Afib = atrial fibrillation; AI-CAC = AI enabled cardiac chambers volumetry in cardiac CT; ASCVD = atherosclerotic cardiovascular disease; LA = left atrium; LVW = left ventricular wall; RA = right atrium; RV = right ventricle.

FIGURE 6 **Distribution of AI-CAC LA Volume by CAC Categories, NT-proBNP Quartiles, and CHARGE-AF Risk Score Quartiles**



(A) Quartiles of AI-CAC LA volume by 5-year CHARGE-AF risk categories. (B) Quartiles of AI-CAC LA volume by NT-proBNP quartiles. (C) Quartiles of AI-CAC LA volume by Agatston CAC score categories. Abbreviation as in Figure 2.

generation of multidetector CT scanners (MDCT). However, limited spatial resolution and high noise to signal ratio in older EBCT scans could attenuate the predictive value of AI-CAC applied to MESA CAC scans (possibly making our results conservative), thus using AI-CAC on modern CT scanners should provide similar or better performance. Additionally, the timing difference in MDCT (50% R-R) vs EBCT (80% R-R) results in significant differences in LA volume (65.44 vs 57.41, respectively) measured by CT scans. However, we have conducted analysis and found the relationship between AF risk and LA volume did not significantly differ between MDCT and EBCT scanners in this population. Likewise, techniques used for CMR measurements acquired using FGRE pulse sequence at MESA baseline (2000-2002) are no longer commonly used today. Therefore, newer CT and CMRI imaging technologies could possibly provide a stronger predictive value for stroke.

The CHARGE-AF risk score includes prior HF and MI, but since MESA is asymptomatic, all patients are absent of HF and MI. Because MESA used the ICD codes to identify a history of AF at baseline and newly diagnosed AF, and it is known that ICD-based diagnosis can be inaccurate (PPV 70%-96%, median sensitivity 79%)[33] it is likely that MESA missed some cases of AF. The ICD-10 code of AF does not include AF that was diagnosed and not yet been coded, but most importantly, does not include AF that has not yet been diagnosed. It is possible that a significant number of individuals with paroxysmal AF were missed. Nonetheless, such issues are not expected to affect AI-CAC and CMRI or other predictors differently, therefore

unlikely to have a material impact on the results of our study.

CONCLUSIONS

AI-CAC automated LA volumetry predicted AF as strongly as LA volume measured by human experts in CMRI. Both AI-CAC and CMRI outperformed CHARGE-AF, NT-proBNP, and the Agatston score for AF prediction. The clinical utility of AI-enabled automated cardiac chambers volumetry as an added value to CAC scans is significant and warrants further investigations.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: AI-enabled opportunistic screening of CAC scans as well as lung cancer screening scans for detection of asymptomatic patients with enlarged cardiac chambers can flag patients who are at risk of AF and stroke.

TRANSLATIONAL OUTLOOK 1: Currently without the AI, radiologists and cardiologists are unable to detect enlarged cardiac chambers in non-contrast cardiac and lung CT scans and these patients go undetected hence untreated resulting in future AF, HF, and stroke.

TRANSLATIONAL OUTLOOK 2: By applying AI to new or existing CT scans care providers can flag patients with enlarged cardiac chambers and direct them for necessary follow-up including echocardiography to investigate the underlying cause of the enlarged chambers. Such an AI tool can provide opportunistic value without imposing patients to radiation.

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