Preprints.org

Article

Not peer-reviewed version

Serial Coronary Artery Calcium Progression and Risk of Major Adverse Cardiovascular Events in an Asian Cohort

Jin-Man He , Yu-Chen Wang * , Kuan-Cheng Chang *

Posted Date: 12 May 2026

doi: 10.20944/preprints202605.0805.v1

Keywords: coronary artery calcium; calcium score progression; major adverse cardiovascular events; statin therapy; residual risk; inverse probability weighting; personalized medicine

Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC, OpenAlex.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Article

Serial Coronary Artery Calcium Progression and Risk of Major Adverse Cardiovascular Events in an Asian Cohort

Jin-Man He [1], Yu-Chen Wang [2,3,4,5,*] and Kuan-Cheng Chang [4,5,6,*]

[1] Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan
[2] Division of Cardiology, Department of Internal Medicine, Asia University Hospital, Taichung, Taiwan
[3] Department of Medical Laboratory Science and Biotechnology, Asia University, Taichung, Taiwan
[4] Division of Cardiovascular Medicine, Department of Medicine, China Medical University Hospital, Taichung, Taiwan
[5] School of Medicine, China Medical University, Taichung, Taiwan
[6] Division of Cardiovascular Medicine, Department of Medicine, Taichung Municipal Geriatric Rehabilitation General Hospital - Managed by China Medical University, Taichung, Taiwan
* Correspondence: richard925068@gmail.com (Y.-C.W.); kuancheng.chang@gmail.com (K.-C.C.)

Abstract

Background: The prognostic value of serial coronary artery calcium (CAC) progression remains uncertain in Asian populations, particularly among patients receiving statin therapy. We evaluated whether CAC progression predicts major adverse cardiovascular events (MACE) in a Taiwanese cohort and whether this association differs by statin use. **Methods:** We retrospectively studied 1,942 individuals who underwent two cardiac computed tomography scans for CAC scoring at a tertiary medical center in Taiwan between 2006 and 2021. CAC progression was defined as an annualized Agatston score increase of ≥20 units/year. The primary outcome was MACE, defined as acute myocardial infarction, stroke, or cardiovascular death. Predictors of CAC progression were assessed using logistic regression. Associations between CAC progression and MACE were evaluated using Cox models with propensity score–based inverse probability weighting; 1,621 participants with complete covariate data were included in weighted analyses. **Results:** CAC progression occurred in 397 participants (20.4%). Independent predictors included male sex, hypertension, fasting glucose, lipid parameters, and baseline CAC score. CAC progression was associated with a higher risk of MACE, with increasing event rates across higher categories of annualized CAC change (p for trend < 0.0001). This association was consistent across clinical subgroups and was observed in both statin and non-statin users, without a significant CAC progression × statin interaction ($p = 0.163$). **Conclusions:** In this Asian serial CAC cohort, CAC progression was strongly associated with future MACE and may serve as a marker of residual cardiovascular risk, including among statin-treated patients. Serial CAC assessment may support dynamic risk stratification, but prospective studies are needed to determine whether progression-guided management improves outcomes.

Keywords: coronary artery calcium; calcium score progression; major adverse cardiovascular events; statin therapy; residual risk; inverse probability weighting; personalized medicine

---

Introduction

Coronary artery calcium (CAC), quantified by the Agatston scoring method, is a well-validated biomarker of subclinical atherosclerosis and a robust predictor of future cardiovascular events [1,2]. The 2018 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines endorse CAC scoring as a tool for refining risk assessment in individuals at borderline or intermediate 10-year atherosclerotic cardiovascular disease (ASCVD) risk [3]. Accumulating

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

evidence from landmark studies, including the Multi-Ethnic Study of Atherosclerosis (MESA), has established a dose–response relationship between baseline CAC burden and incident coronary heart disease (CHD), with CAC scores exceeding 300 conferring risk equivalent to established ASCVD [4,5].

While baseline CAC provides a snapshot of cumulative atherosclerotic burden, atherosclerosis is inherently a dynamic process. Serial CAC measurement offers the potential to capture disease activity over time. The MESA cohort demonstrated that annualized CAC progression independently predicts incident CHD and all-cause mortality beyond baseline CAC scores [6,7]. In the population-based HNR study, CAC progression was associated with incident coronary and cardiovascular events, but provided only limited incremental prognostic value beyond the most recent CAC score and updated risk factor assessment [8]. However, several important questions remain unresolved.

First, the optimal definition of clinically meaningful CAC progression lacks standardization, with different studies employing various thresholds including absolute change, percentage change, and square-root or log-transformed metrics [6–8]. Second, the interaction between statin therapy and CAC progression introduces a clinical interpretation paradox: meta-analyses demonstrate that statins significantly accelerate Agatston score progression while simultaneously reducing cardiovascular events [9,10]. This apparent contradiction reflects the dual nature of the Agatston score, which conflates plaque volume (a marker of disease burden) with calcification density (a marker of plaque stabilization) [11]. Third, the vast majority of serial CAC data originates from Western populations, with limited representation from East Asian cohorts where baseline CAC prevalence and atherosclerosis kinetics may differ [12,13].

Furthermore, whether CAC progression retains prognostic significance in statin-treated patients remains a critical knowledge gap. If statin therapy inherently promotes plaque calcification as a stabilization mechanism, clinicians need to understand whether observed CAC progression in treated patients represents benign plaque remodeling or ongoing pathological disease activity. This distinction may have implications for residual risk assessment and subsequent optimization of preventive therapy.

To address these gaps, we conducted a retrospective cohort study in a Taiwanese population to evaluate: (1) independent predictors of CAC progression; (2) the association between CAC progression and MACE across clinical subgroups using propensity score–based inverse probability weighting (IPW); and (3) the prognostic value of CAC progression stratified by statin use. We hypothesized that CAC progression independently predicts MACE and that this association persists even among statin-treated individuals, reflecting residual cardiovascular risk.

Methods

Study Design

This was a retrospective, single-center cohort study conducted at China Medical University Hospital (CMUH), a tertiary medical center in Taichung, Taiwan. We identified all individuals who underwent at least two non-contrast cardiac computed tomography (CT) scans for CAC scoring between January 2006 and December 2021. A total of 2,155 individuals were initially identified. The following exclusion criteria were applied: (1) second CT scan performed within 7 days of the first (n = 5); (2) history of coronary stent implantation at CMUH prior to the baseline scan (n = 40); and (3) history of MACE prior to the baseline scan (n = 162). After exclusions, the final study population comprised 1,942 individuals. The study protocol was approved by the Institutional Review Board of CMUH (IRB No. CMUH105-REC2-047), and the requirement for informed consent was waived because of the retrospective nature of the study.

Coronary Artery Calcium Scoring

CAC scoring was performed using electrocardiogram (ECG)-gated non-contrast cardiac CT. Agatston scores were calculated using standard methodology [1]. Baseline CAC was defined as the

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

score from the first qualifying CT scan, and follow-up CAC was defined as the score from the most recent qualifying scan.

Definition of CAC Progression

CAC progression was defined as an annualized change in Agatston score of 20 or more units per year, calculated as: (follow-up CAC score − baseline CAC score) / inter-scan interval in years. This threshold was adapted from prior literature demonstrating its clinical relevance in identifying rapid progressors [14]. Participants were classified into two groups: a CAC progression group (n = 397) and a non-progression group (n = 1,545).

Baseline Clinical Variables

Demographic and clinical data were extracted from electronic medical records at the time of the baseline CT scan. Variables included age, sex, body mass index (BMI), history of diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease. Laboratory parameters included systolic and diastolic blood pressure, high-sensitivity C-reactive protein (hs-CRP), homocysteine, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (GFR), fasting glucose (AC), glycated hemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and uric acid. Medication data, including statin use, antihypertensive agents, antithrombotic agents, and antidiabetic medications, were recorded.

Outcome Definition

The primary outcome was the occurrence of MACE, defined as a composite of acute myocardial infarction (AMI), stroke, or cardiovascular death. Only the first MACE event during follow-up was counted. Events were ascertained from CMUH electronic medical records, including discharge diagnoses (ICD-10 coded), cardiac catheterization reports, brain imaging studies, and death records. Stroke was defined as a new ischemic or hemorrhagic stroke confirmed by imaging; transient ischemic attacks were not included. Cardiovascular death was defined as death attributed to ischemic heart disease, heart failure, fatal arrhythmia, or stroke based on death certificates and inpatient records. Patients with prior MACE before the baseline CAC scan were excluded (n = 162) to avoid overlap with prevalent disease. Person-years were calculated from the date of the baseline CAC examination until the date of the first MACE, death, or December 31, 2022, whichever occurred first.

Statistical Analysis

Baseline characteristics were summarized according to CAC progression status and compared using chi-square tests for categorical variables and independent-samples t tests for continuous variables. Predictors of CAC progression were assessed using univariable and multivariable logistic regression models, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). Incidence rates of MACE were calculated per 1,000 person-years from the baseline CAC examination to the first MACE event, death, or December 31, 2022, whichever occurred first. The association between CAC progression and MACE was evaluated using Cox proportional hazards models. To reduce measured baseline differences between participants with and without CAC progression, propensity score–based inverse probability weighting (IPW) was applied; propensity scores were estimated using stepwise logistic regression including sex, hypertension, homocysteine, LDL-cholesterol, baseline CAC score, and fasting glucose. Standardized IPW weights were then applied to the Cox models, and 1,621 participants with complete data for all propensity model covariates were included in the weighted analyses. To assess the relationship between the magnitude of CAC change and MACE, participants were categorized by annualized CAC change as 0, 0.1–20, 21–49, and ≥50 units/year, and a trend test for proportions was performed. Subgroup analyses were conducted according to sex, age, diabetes, hypertension, cardiovascular disease history, and statin use, with interaction terms tested for each subgroup. The joint association of CAC progression and statin use

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

with MACE was evaluated using four groups defined by statin use and CAC progression status, with the non-statin/non-progression group as the reference; pairwise comparisons were performed using IPW-adjusted Cox models. Receiver operating characteristic curve analysis was used to assess the ability of CAC progression to predict 10-year MACE according to statin use. All analyses were performed using SAS version 9.4, and a two-tailed p value <0.05 was considered statistically significant.

Results

Study Cohort and Group Categorization

A total of 2,155 individuals who underwent serial cardiac computed tomography between 2006 and 2021 were initially identified. After excluding participants with a second scan within 7 days (n = 5), prior coronary stent implantation (n = 40), and a history of MACE before baseline (n = 162), a final cohort of 1,942 individuals was included in the analysis. Participants were subsequently categorized according to the annualized change in CAC score: 397 individuals were classified into the CAC progression group, while 1,545 were assigned to the non-progression group.

Baseline Characteristics

Baseline demographic and clinical characteristics stratified by CAC progression are presented in Table 1. Compared with the non-progression group, individuals with CAC progression were older (58.5 ± 9.52 vs. 53.0 ± 9.25 years, $p < 0.0001$) and exhibited a higher baseline cardiovascular risk profile. Specifically, the progression group demonstrated a higher body mass index (BMI; 26.8 ± 3.99 vs. 25.1 ± 3.50 kg/m^2, $p < 0.0001$), as well as a greater prevalence of diabetes mellitus (18.4% vs. 7.64%, $p < 0.0001$), hypertension (36.0% vs. 18.9%, $p < 0.0001$), hyperlipidemia (31.5% vs. 20.4%, $p < 0.0001$), and cardiovascular disease (19.7% vs. 11.2%, $p < 0.0001$). In addition, baseline CAC scores were markedly higher in the progression group than in the non-progression group (338.5 ± 455.8 vs. 44.1 ± 223.3, $p < 0.0001$). Among laboratory parameters, HDL-C levels were lower in the progression group (42.1 ± 10.4 vs. 45.9 ± 12.7 mg/dL, $p < 0.0001$), whereas no significant difference was observed in LDL-C levels between the two groups (124.5 ± 39.0 vs. 124.8 ± 33.3 mg/dL, $p = 0.92$). Overall, these findings indicate that participants with CAC progression had a higher burden of baseline cardiometabolic risk factors and greater initial coronary calcification.

Table 1. Baseline Demographic and Clinical Characteristics According to Coronary Artery Calcium Score Progression.

Variable	Progression (n=397)	Non-Progression (n=1,545)	p-value
Age, years, mean (SD)	58.5 (9.52)	53.0 (9.25)	<0.0001
Male sex, n (%)	357 (89.9)	1,079 (69.8)	<0.0001
BMI, kg/m², mean (SD)	26.8 (3.99)	25.1 (3.50)	<0.0001
Diabetes mellitus, n (%)	73 (18.4)	118 (7.64)	<0.0001
Hypertension, n (%)	143 (36.0)	292 (18.9)	<0.0001
Hyperlipidemia, n (%)	125 (31.5)	315 (20.4)	<0.0001
Cardiovascular disease, n (%)	78 (19.7)	173 (11.2)	<0.0001
SBP, mmHg, mean (SD)	133.4 (18.7)	126.3 (18.1)	<0.0001

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

DBP, mmHg, mean (SD)	80.9 (11.7)	77.9 (12.0)	0.002
hs-CRP, mg/L, mean (SD)	0.18 (0.23)	0.27 (0.74)	0.003
Homocysteine, μmol/L, mean (SD)	11.0 (3.45)	9.88 (3.23)	<0.0001
BUN, mg/dL, mean (SD)	13.3 (6.95)	11.7 (4.40)	0.0002
Creatinine, mg/dL, mean (SD)	1.00 (0.75)	0.88 (0.37)	0.002
GFR, mL/min/1.73m², mean (SD)	85.4 (15.6)	92.3 (14.6)	<0.0001
Fasting glucose (AC), mg/dL, mean (SD)	112.7 (29.7)	100.0 (24.6)	<0.0001
HbA1c, %, mean (SD)	6.44 (1.18)	5.10 (0.78)	<0.0001
Total cholesterol, mg/dL, mean (SD)	201.1 (43.5)	203.2 (38.4)	0.411
Triglycerides, mg/dL, mean (SD)	169.3 (114.6)	150.0 (118.6)	0.006
HDL-C, mg/dL, mean (SD)	42.1 (10.4)	45.9 (12.7)	<0.0001
LDL-C, mg/dL, mean (SD)	124.5 (39.0)	124.8 (33.3)	0.92
Uric acid, mg/dL, mean (SD)	6.64 (1.59)	6.19 (1.43)	<0.0001
Baseline CAC score, mean (SD)	338.5 (455.8)	44.1 (223.3)	<0.0001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAC, coronary artery calcium.

The distribution of baseline CAC categories also differed markedly between the two groups (Table 2, $p < 0.0001$). In the progression group, 65.5% had baseline CAC > 100, 32.5% had CAC between 0.1 and 100, and only 2.02% had CAC = 0. In contrast, the non-progression group was predominantly composed of individuals with CAC = 0 (61.1%), with 31.7% having CAC 0.1–100 and only 7.25% having CAC > 100. These data indicate that CAC progression was overwhelmingly observed in individuals with established baseline calcification.

Table 2. Distribution of Baseline CAC Categories in the Progression and Non-Progression Groups.

Baseline CAC category	Progression (n=397) n (%)	Non-Progression (n=1,545) n (%)	p-value
CAC > 100	260 (65.5)	112 (7.25)	<0.0001
0.1 ≤ CAC ≤ 100	129 (32.5)	489 (31.7)	
CAC = 0	8 (2.02)	944 (61.1)	

Abbreviations: CAC, coronary artery calcium.

Independent Predictors of CAC Progression

Univariable and multivariable logistic regression analyses identifying predictors of CAC progression are presented in Table 3. In the univariable analysis, several factors were significantly associated with CAC progression, including age, male sex, BMI, diabetes mellitus, hypertension,

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

hyperlipidemia, cardiovascular disease, systolic blood pressure, homocysteine, BUN, GFR, fasting glucose (AC), triglycerides, HDL-C, uric acid, and baseline CAC score (all $p < 0.05$).

Table 3. Independent Predictors of Coronary Artery Calcium Score Progression Using Univariable and Multivariable Logistic Regression.

Variable	Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age	1.06	1.05–1.08	<0.0001	1.05	0.99–1.10	0.066
Male vs. female	3.86	2.73–5.44	<0.0001	7.40	2.20–24.9	0.001
BMI	1.13	1.08–1.18	<0.0001	1.00	0.89–1.12	0.981
Diabetes	2.73	1.99–3.74	<0.0001	1.29	0.42–3.99	0.661
Hypertension	2.42	1.90–3.08	<0.0001	2.80	1.05–7.48	0.040
Hyperlipidemia	1.79	1.40–2.29	<0.0001	0.47	0.16–1.38	0.171
Cardiovascular disease	1.94	1.45–2.60	<0.0001	1.88	0.49–7.28	0.360
SBP	1.22	1.13–1.33	<0.0001	1.12	0.92–1.37	0.262
hs-CRP	0.67	0.42–1.06	0.088	0.32	0.05–2.15	0.239
Homocysteine	1.10	1.05–1.14	<0.0001	1.03	0.92–1.16	0.590
BUN	1.06	1.03–1.09	<0.0001	0.98	0.91–1.06	0.656
GFR	0.97	0.96–0.98	<0.0001	0.98	0.79–1.03	0.819
Fasting glucose (AC)	1.02	1.01–1.02	<0.0001	1.02	1.01–1.04	<0.001
Total cholesterol	1.00	0.99–1.00	0.376	0.96	0.93–0.99	0.035
Triglycerides	1.00	1.00–1.00	0.009	1.01	1.00–1.02	0.008
HDL-C	0.76	0.68–0.85	<0.0001	2.07	1.28–3.35	0.003
LDL-C	1.00	0.96–1.03	0.913	1.70	1.16–2.49	0.007
Uric acid	1.23	1.13–1.34	<0.0001	1.12	1.08–1.16	0.240
Baseline CAC score	1.04	1.04–1.05	<0.0001	1.12	1.08–1.16	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAC, coronary artery calcium. Note: For clinical interpretability, SBP, HDL-C, LDL-C, and baseline CAC score were modeled per 10-unit increase, whereas other continuous variables were modeled per 1-unit increase.

After multivariable adjustment, male sex remained the strongest independent predictor of CAC progression (adjusted OR: 7.40; 95% CI: 2.20–24.9; $p = 0.001$), and hypertension was also independently associated with an increased likelihood of progression (adjusted OR: 2.80; 95% CI: 1.05–7.48; $p = 0.040$). Among metabolic parameters, fasting glucose was independently associated with CAC progression (adjusted OR: 1.02 per 1 mg/dL increase; 95% CI: 1.01–1.04; $p < 0.001$). Lipid-

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

related variables demonstrated mixed associations after simultaneous adjustment. Triglyceride levels were positively associated with CAC progression (adjusted OR: 1.01 per 1 mg/dL increase; 95% CI: 1.00–1.02; p = 0.008), and LDL-C was also independently associated with progression when modeled per 10 mg/dL increase (adjusted OR: 1.70; 95% CI: 1.16–2.49; p = 0.007). HDL-C showed an unexpected positive association after multivariable adjustment when modeled per 10 mg/dL increase (adjusted OR: 2.07; 95% CI: 1.28–3.35; p = 0.003), whereas total cholesterol exhibited a modest inverse association (adjusted OR: 0.96; 95% CI: 0.93–0.99; p = 0.035). Baseline CAC score remained an independent predictor of CAC progression when modeled per 10 Agatston-unit increase (adjusted OR: 1.12; 95% CI: 1.08–1.16; p < 0.001). Other variables, including age, BMI, diabetes mellitus, hyperlipidemia, cardiovascular disease, systolic blood pressure, inflammatory markers, renal function indices, and uric acid, were not significantly associated with CAC progression after adjustment.

CAC Progression and Risk of MACE

Of the 1,942 participants, 1,621 had complete data on all covariates required for the propensity score model and were included in the IPW-adjusted Cox analyses. To evaluate the potential impact of complete-case inclusion on the weighted analyses, baseline characteristics were compared between participants included in and excluded from the IPW-adjusted Cox models (Table S1). Although several baseline characteristics differed between the two groups, including diabetes, hyperlipidemia, cardiovascular disease history, selected laboratory parameters, and medication use, the distributions of CAC progression status and MACE events were not significantly different. These findings suggest that exclusion due to missing propensity model covariates was unlikely to materially alter the primary association between CAC progression and MACE, although residual selection bias cannot be completely excluded. As shown in Figure 1A, CAC progression was associated with a significantly higher risk of MACE compared with non-progression after IPW adjustment (HR: 11.8; 95% CI: 10.1–13.7). In analyses according to the magnitude of annualized CAC change, the risk of MACE was also elevated in participants with CAC increases of 21–49 units/year (HR: 10.4; 95% CI: 8.67–12.6) and ≥50 units/year (HR: 14.6; 95% CI: 11.7–18.2), suggesting a graded association between CAC progression severity and subsequent cardiovascular risk.

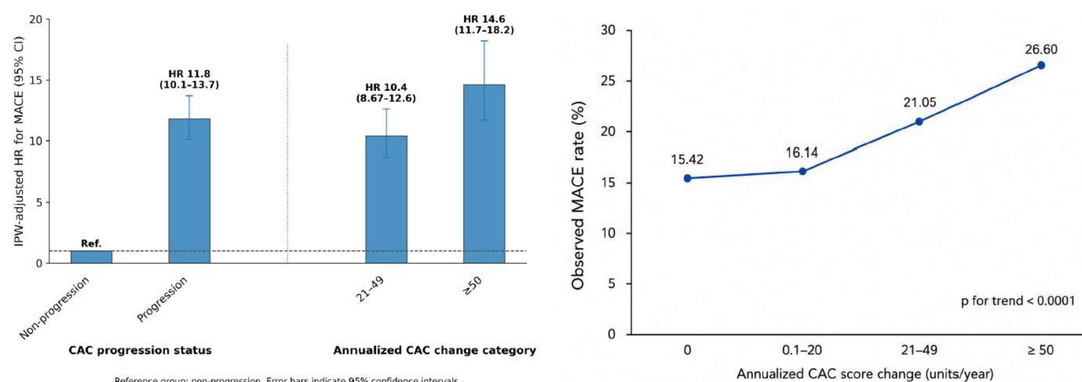

Figure 1. Association Between CAC Progression and Risk of MACE. (A) IPW-adjusted hazard ratios for MACE according to CAC progression status and annualized CAC score change categories. CAC progression was defined as an annualized CAC increase ≥20 units/year. Error bars indicate 95% confidence intervals. (B) Observed MACE rates across annualized CAC score change categories. MACE rates increased progressively with greater CAC change (P for trend < 0.0001).

Further descriptive analysis demonstrated a stepwise increase in the observed MACE rate across categories of annualized CAC change. As shown in Figure 1B, MACE rates increased from 15.42% in participants with no CAC increase to 16.14%, 21.05%, and 26.60% in those with annualized CAC

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

increases of 0.1–20, 21–49, and ≥50 units/year, respectively (p for trend < 0.0001). These findings suggest that a greater magnitude of CAC progression was associated with a higher observed event rate.

Joint Effects of CAC Progression and Statin Use

The joint effects of CAC progression and statin use on the risk of MACE are presented in Figure 2. Within both statin strata, CAC progression was associated with a significantly higher risk of MACE compared with non-progression. Among participants not receiving statin therapy, CAC progression was associated with increased MACE risk (HR: 10.38; 95% CI: 8.74–12.3; p < 0.0001). A similar association was observed among statin users, although with a numerically lower point estimate (HR: 6.68; 95% CI: 3.88–11.5; p < 0.0001). The CAC progression × statin interaction was not statistically significant (p for interaction = 0.163), indicating no clear evidence that the association between CAC progression and MACE differed by statin use.

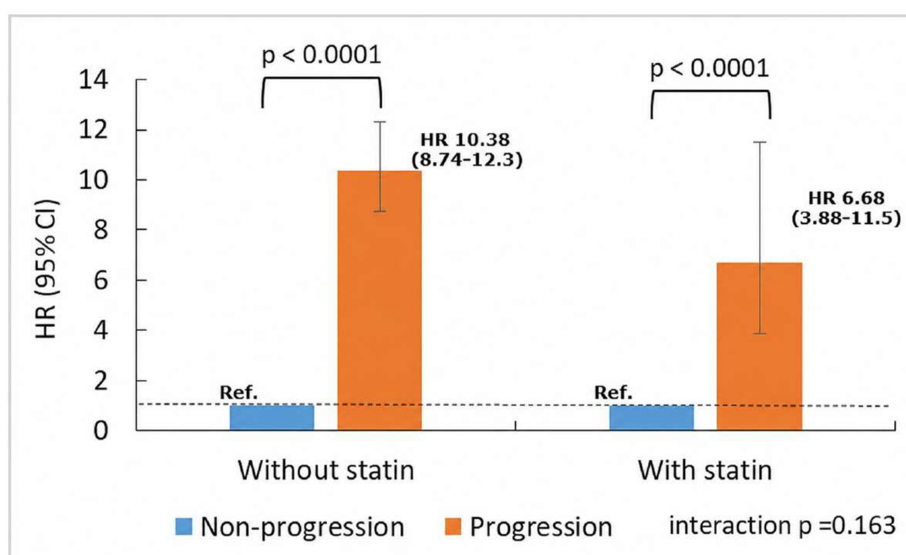

Figure 2. Adjusted Hazard Ratios for MACE According to Joint Stratification by CAC Progression and Statin Use. IPW-adjusted hazard ratios for MACE in four groups defined by combinations of statin use status and CAC progression status. Within each statin stratum, the non-progression group served as the reference. CAC progression was significantly associated with increased MACE risk in both statin and non-statin strata (both P < 0.0001). Although the HR appeared numerically higher in non-statin progressors than in statin progressors, the formal interaction between CAC progression and statin use was not statistically significant (P for interaction = 0.163). Full pairwise comparisons among all four groups are provided in Supplementary Figure 1.

Full pairwise comparisons among the four statin/progression groups are shown in Supplementary Figure 1. In this analysis, statin-treated participants with CAC progression showed the highest relative risk compared with the non-statin/non-progression reference group. However, because statin users had a substantially higher baseline cardiovascular risk profile and greater atherosclerotic burden, this finding should be interpreted cautiously and may reflect confounding by indication rather than a harmful effect of statin therapy.

Among the 1,942 participants, 158 (8.1%) were receiving statin therapy. Statin users were older, had a higher prevalence of comorbidities, and had higher baseline CAC scores compared with non-statin users (Table 4). Medication use according to CAC progression status is summarized in Table S2. Compared with non-progressors, participants with CAC progression were more frequently treated with cardiac drugs, diuretics, calcium-channel blockers, renin–angiotensin system inhibitors, antithrombotic agents, antidiabetic medications, and statins, reflecting a higher baseline

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026
doi:10.20944/preprints202605.0805.v1

cardiovascular risk profile and greater treatment burden. In the medication-based regression analysis, statin use was associated with CAC progression in univariable analysis but was attenuated and no longer statistically significant after multivariable adjustment (Table S3), consistent with confounding by indication.

Table 4. Baseline Characteristics of Patients With and Without Statin Therapy.

Variable	Non-statin (n=1,784)	Statin (n=158)	p-value
Age, years, mean (SD)	53.8 (9.51)	58.5 (8.97)	<0.0001
Male sex, n (%)	1,323 (74.2)	113 (71.5)	0.469
BMI, kg/m², mean (SD)	25.4 (3.69)	26.1 (3.39)	0.136
Diabetes mellitus, n (%)	135 (7.57)	56 (35.4)	<0.0001
Hypertension, n (%)	329 (18.4)	106 (67.1)	<0.0001
Hyperlipidemia, n (%)	298 (16.7)	142 (89.9)	<0.0001
Cardiovascular disease, n (%)	172 (9.64)	79 (50.0)	<0.0001
SBP, mmHg, mean (SD)	127.4 (18.2)	132.0 (20.5)	0.021
RDW, mean (SD)	13.3 (1.01)	13.2 (0.85)	0.703
hs-CRP, mg/L, mean (SD)	0.25 (0.68)	0.26 (0.61)	0.915
Homocysteine, µmol/L, mean (SD)	10.1 (3.30)	10.4 (3.39)	0.401
BUN, mg/dL, mean (SD)	11.9 (4.39)	13.6 (8.36)	0.041
GFR, mL/min/1.73m², mean (SD)	91.2 (14.6)	87.7 (16.0)	0.005
Fasting glucose (AC), mg/dL, mean (SD)	101.4 (25.6)	113.8 (30.3)	<0.0001
Total cholesterol, mg/dL, mean (SD)	204.7 (38.6)	183.9 (43.6)	<0.0001
Triglycerides, mg/dL, mean (SD)	155.4 (120.9)	140.3 (84.0)	0.043
HDL-C, mg/dL, mean (SD)	45.0 (12.3)	45.6 (12.8)	0.588
LDL-C, mg/dL, mean (SD)	126.5 (33.7)	107.3 (37.8)	<0.0001
Uric acid, mg/dL, mean (SD)	6.28 (1.47)	6.31 (1.52)	0.801
Baseline CAC score, mean (SD)	95.9 (299)	199 (404)	0.002
Antihypertensive, n (%)	16 (0.9)	3 (1.9)	0.197
Cardiac drug, n (%)	81 (4.54)	52 (32.9)	<0.0001
Diuretics, n (%)	25 (1.4)	21 (13.3)	<0.0001
Beta-blocker, n (%)	38 (2.13)	12 (7.59)	0.0004

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026

doi:10.20944/preprints202605.0805.v1

CCB, n (%)	98 (5.46)	58 (36.7)	<0.0001
RAS inhibitor, n (%)	62 (3.48)	48 (30.4)	<0.0001
Antithrombotic, n (%)	92 (5.16)	86 (54.4)	<0.0001
Antidiabetic, n (%)	36 (2.02)	25 (15.8)	<0.0001

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CAC, coronary artery calcium; CCB, calcium channel blocker; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; RAS, renin–angiotensin system; RDW, red cell distribution width; SBP, systolic blood pressure; SD, standard deviation.

Subgroup Analyses

Subgroup analyses examining the association between CAC progression and the risk of MACE are presented in Table 5. Overall, CAC progression was consistently associated with a significantly increased risk of MACE across all examined subgroups, with higher incidence rates observed in the progression group compared with the non-progression group within each stratum.

Table 5. Incidence Rates and IPW-Adjusted Hazard Ratios for MACE According to CAC Progression Across Clinical Subgroups.

Subgroup	Non-Prog N	Events	IR	Prog N	Events	IR	Adj HR (95% CI)	p-value	Interaction p
Sex									<0.001
Women	466	84	20.31	40	15	48.15	2.70 (1.92–3.79)	<0.001	
Men	1,079	159	15.32	357	79	24.42	11.0 (9.19–13.2)	<0.001	
Age									<0.001
<65 years	1,379	199	15.14	303	59	21.30	12.0 (9.64–14.9)	<0.001	
≥65 years	166	44	32.05	94	35	45.02	9.84 (6.65–14.5)	<0.001	
Diabetes									<0.001
No	1,427	219	16.26	324	69	23.45	22.0 (16.0–30.2)	<0.001	
Yes	118	24	22.96	73	25	41.35	2.30 (1.64–3.22)	<0.001	
Hypertension									<0.001
No	1,253	188	15.82	254	47	19.86	13.9 (9.33–20.8)	<0.001	
Yes	292	55	20.90	143	47	39.79	3.12 (2.53–3.84)	<0.001	
CVD history									<0.001
No	1,372	210	16.13	319	69	23.87	9.51 (6.81–13.3)	<0.001	
Yes	173	33	22.09	78	25	38.13	3.47 (2.66–4.51)	<0.001	

Abbreviations: IR, incidence rate per 1,000 person-years; Adj HR, IPW-adjusted hazard ratio; Int. p, interaction p-value; Prog, progression; Non-Prog, non-progression; CVD, cardiovascular disease. Reference group: non-progression within each subgroup. Adjusted for standardized IPW weights.

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

Among subgroups, however, the magnitude of the relative risk varied significantly. The association was stronger in men (HR 11.0, 95% CI 9.19–13.2) than in women (HR 2.70, 95% CI 1.92–3.79; p for interaction < 0.001). A more pronounced effect was observed in younger individuals (<65 years: HR 12.0, 95% CI 9.64–14.9) compared with older individuals (≥65 years: HR 9.84, 95% CI 6.65–14.5; p for interaction < 0.001). Notably, the relative impact of CAC progression on MACE risk was substantially greater in individuals without diabetes than in those with diabetes (HR 22.0 vs. 2.30; p for interaction < 0.001), and in those without hypertension compared with those with hypertension (HR 13.9 vs. 3.12; p for interaction < 0.001). A similar pattern was observed for cardiovascular disease, with a stronger relative association in individuals without prior cardiovascular disease than in those with established disease (HR 9.51 vs. 3.47; p for interaction < 0.001). These findings suggest that, while CAC progression is universally informative, the relative risk increment is more pronounced in subgroups with otherwise lower baseline event rates.

Although the relative associations were attenuated in several higher-risk subgroups, absolute incidence rates remained higher among CAC progressors. For example, women with CAC progression had an incidence rate of 48.15 versus 20.31 per 1,000 person-years in non-progressors, and patients with diabetes had rates of 41.35 versus 22.96 per 1,000 person-years, respectively.

ROC Curve Analysis Stratified by Statin Use

ROC curve analyses evaluating the performance of CAC progression for predicting 10-year MACE according to statin use are presented in Figure 3. Among statin users (Figure 3A), CAC progression demonstrated modest discriminative ability for predicting MACE (AUC = 0.637; sensitivity 67.8%; specificity 69.4%; optimal cutoff 0.109). The ROC curve showed deviation above the reference line, indicating modest predictive performance in this subgroup. In contrast, among non-statin users (Figure 3B), CAC progression showed poor discriminative ability that approached the chance level (AUC = 0.522; sensitivity 47.9%; specificity 56.6%; optimal cutoff 0.002). The ROC curve in this group closely approximated the diagonal reference line, indicating minimal predictive value. Overall, CAC progression demonstrated modest discrimination for 10-year MACE among statin users, while discrimination among non-statin users was poor and approached the chance level.

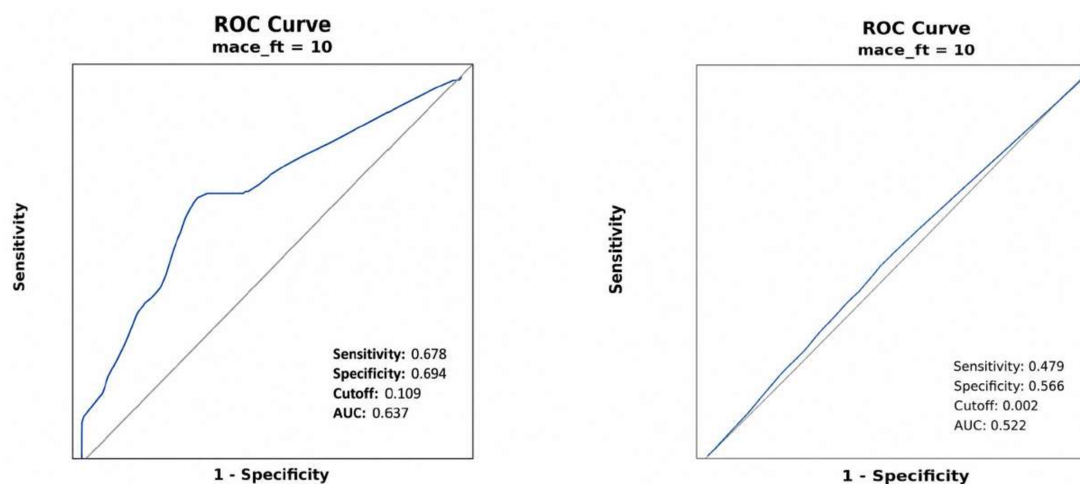

Figure 3. Receiver Operating Characteristic Curve Analysis of CAC Progression for Predicting 10-Year MACE According to Statin Use. (A) ROC curve for CAC progression predicting 10-year MACE among statin users, with an AUC of 0.637, sensitivity of 67.8%, specificity of 69.4%, and optimal cutoff of 0.109. (B) ROC curve for CAC progression predicting 10-year MACE among non-statin users, with an AUC of 0.522, sensitivity of 47.9%, specificity of 56.6%, and optimal cutoff of 0.002. CAC progression showed modest discriminative ability among statin users, whereas its discriminative performance among non-statin users was limited.

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

Discussion

In this retrospective cohort study of 1,942 individuals from a Taiwanese tertiary medical center (with 1,621 included in IPW-adjusted survival analyses), we found that CAC progression, defined as an annualized Agatston score increase of ≥20 units/year, was associated with a substantially higher risk of MACE, with a clear dose–response relationship across categories of CAC change. CAC progression was associated with higher MACE risk across all examined subgroups, although the magnitude of the association varied significantly by sex, age, diabetes, hypertension, and cardiovascular disease history. Although the formal interaction between CAC progression and statin use was not statistically significant ($p = 0.163$), the highest absolute MACE risk was observed among statin users with progression, and ROC analysis showed that CAC progression provided modest discrimination of 10-year MACE among statin users but poor discrimination among non-statin users. Together, these findings suggest that CAC progression may serve as a marker of residual cardiovascular risk, including among statin-treated patients, and warrants further investigation as a tool for dynamic risk stratification.

CAC Progression as an Independent Predictor of MACE

Our results are consistent with prior landmark studies demonstrating the prognostic value of serial CAC assessment. The MESA cohort established that annual CAC progression ≥300 AU conferred a hazard ratio of 3.8 for total CHD and 6.3 for hard CHD [6], and that CAC progression ≥15% annualized change predicted a greater than 3-fold increase in all-cause mortality [7]. The Heinz Nixdorf Recall study further confirmed that CAC progression is associated with incident coronary and cardiovascular events, primarily in patients with baseline CAC > 0 [8]. Our study extends these findings to a Taiwanese population and demonstrates positive associations across all examined subgroups, although the magnitude of association differed substantially by baseline clinical characteristics.

The dose–response relationship across categories of annualized CAC change observed in our cohort (Figure 1B; p for trend < 0.0001), with the highest risk observed among participants with annualized progression ≥50 units/year, reinforces the concept that the *rate* of coronary calcium accumulation—rather than baseline CAC alone—captures clinically meaningful disease activity. This graded relationship strengthens the case for serial rather than single time-point CAC assessment in suitably selected patients.

The significant interaction effects observed across demographic and comorbidity subgroups merit discussion. The strikingly high adjusted HR in men (11.0) compared with women (2.70) may reflect the higher baseline prevalence and burden of CAC in men, where progression signals more advanced atherosclerotic disease. Although the relative association was weaker in women than in men, the absolute incidence rate among female progressors was still substantially higher than that among female non-progressors. These findings suggest that CAC progression in women should not be dismissed, as it may identify a subgroup with clinically meaningful excess cardiovascular risk. These sex-specific patterns align with meta-analytic data from Asian populations demonstrating a 2.37-fold higher CAC progression risk in males [12] and suggest the need for sex-specific interpretation thresholds.

The greater relative HRs observed in subgroups without diabetes, hypertension, or prior cardiovascular disease (compared with those with these conditions) likely reflect the underlying baseline event rates: in individuals already at high absolute risk by virtue of comorbidity, CAC progression contributes incrementally rather than dramatically to relative risk, whereas in otherwise lower-risk subgroups, progression identifies a previously underappreciated source of risk and therefore produces a larger relative effect. Importantly, absolute incidence rates remained uniformly higher in progressors across all subgroups, underscoring the universal clinical relevance of CAC progression irrespective of comorbidity profile.

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

Independent Predictors of CAC Progression

The multivariable analysis identified male sex, hypertension, fasting glucose, LDL-C, triglycerides, HDL-C, and baseline CAC score as independent predictors of progression. These findings corroborate a Korean cohort study that identified newly diagnosed hypertension as the strongest predictor of rapid CAC progression (OR 11.3) [14]. Our data similarly highlight hypertension as a key independent driver (adjusted OR 2.8), underscoring the importance of blood pressure control in attenuating atherosclerotic progression.

The unexpected positive association between HDL-C and CAC progression, together with the inverse association observed for total cholesterol, should be interpreted cautiously. Because multiple lipid parameters were included simultaneously in the multivariable model, these findings may reflect collinearity among lipid variables or model instability rather than true biological effects. In addition, HDL-C concentration alone may not adequately capture HDL functionality, which may be more relevant to atheroprotection than HDL-C levels per se.

The finding that baseline CAC score independently predicts future progression is consistent with the concept of "atherosclerotic momentum"—patients with established calcification have a higher substrate for continued plaque development. This aligns with our distributional analysis showing that 65.5% of progressors had baseline CAC > 100, while only 2.02% had CAC = 0. Together with prior evidence from the HNR study showing that repeat CAC assessment provides the greatest risk readjustment in individuals with pre-existing CAC, these findings reinforce the clinical principle that serial monitoring is most informative in patients with established calcification [8].

The Statin Paradox and Residual Risk

Perhaps the most clinically nuanced finding concerns the joint stratification analysis of CAC progression and statin use. Although the interaction between CAC progression and statin therapy did not reach statistical significance (p for interaction = 0.163)—indicating that, in our cohort, CAC progression was a dominant predictor of MACE regardless of statin exposure—two observations warrant attention. First, the highest absolute MACE risk was observed among statin users with CAC progression. Second, ROC analysis showed numerically better discriminative performance of CAC progression among statin users than among non-statin users.

This pattern speaks to the well-recognized "statin paradox," in which statins accelerate Agatston score progression yet reduce cardiovascular events [9,10]. The conventional interpretation posits that statin-induced calcification reflects plaque stabilization through the promotion of dense macrocalcification, which consolidates vulnerable microcalcifications and reduces plaque rupture risk [10,15]. Under this framework, CAC progression in statin users would represent a benign epiphenomenon. Our data, however, do not support a blanket reassurance that all statin-associated progression is benign: statin users with progression had numerically higher MACE risk than statin users without progression, and CAC progression remained a meaningful discriminator of 10-year MACE in the statin-treated subgroup.

Two non-mutually exclusive explanations may account for this finding. First, although statin therapy may increase plaque calcification as part of plaque stabilization, not all increases in CAC among statin-treated patients should be interpreted as benign. In some patients, CAC progression may reflect persistent atherosclerotic activity that exceeds the protective effects of lipid-lowering therapy. Second, because untreated individuals in this cohort generally had a lower baseline atherosclerotic burden, modest CAC changes in this group may have been more susceptible to measurement variability and may have carried a less distinct prognostic signal. In contrast, among statin-treated patients, who typically had higher baseline risk, CAC progression may better identify individuals with treatment-refractory disease and residual cardiovascular risk. Patients exhibiting CAC progression despite statin therapy may therefore represent a high-risk phenotype in whom residual risk—including LDL-C control, lipoprotein(a), inflammation, and other modifiable factors—should be carefully reassessed. Whether treatment intensification (e.g., with ezetimibe, PCSK9

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

inhibitors, bempedoic acid, or anti-inflammatory agents) guided by CAC progression actually improves outcomes requires prospective study.

Importantly, the higher absolute MACE risk observed among statin users with CAC progression should not be interpreted as evidence of harm from statin therapy. Statin users in our cohort had substantially higher prevalence of diabetes (35.4% vs. 7.6%), hypertension (67.1% vs. 18.4%), hyperlipidemia (89.9% vs. 16.7%), and prior cardiovascular disease (50% vs. 9.6%), as well as higher baseline CAC scores (199 vs. 96). Their elevated event rates therefore largely reflect confounding by indication and a substantially higher underlying atherosclerotic burden rather than an adverse effect of statin therapy itself. Although the interaction between CAC progression and statin use was not statistically significant, this finding should be interpreted cautiously. The relatively small number of statin-treated participants (n = 158, 8.1%) may have limited the power to detect effect modification. Therefore, the absence of a statistically significant interaction does not exclude the possibility that CAC progression may carry different prognostic implications according to statin treatment status.

Implications for Personalized Cardiovascular Risk Management

Our findings have several implications for personalized medicine approaches. First, they support the role of serial CAC assessment as a tool for dynamic risk monitoring, particularly in patients with established baseline CAC. A recently proposed CAC staging framework—analogous to disease staging in other fields—classifies patients according to CAC burden from Stage 0 (CAC = 0) to Stage 4 (CAC ≥1,000), with progressively more intensive preventive interventions recommended at higher stages [16]. In this context, CAC progression may be viewed as a form of dynamic risk reclassification or potential "stage migration," identifying patients who warrant closer reassessment and more intensive risk-factor optimization. Our data extend this concept by providing empirical evidence from an Asian population that CAC progression carries prognostic significance beyond a single baseline CAC measurement.

Second, the differential predictive value of CAC progression by statin status suggests that serial CAC may be most clinically useful precisely in treated patients, where it identifies residual risk not captured by traditional risk factors or lipid levels. This has implications for guideline development, as current recommendations do not specifically address the interpretation of CAC progression in pharmacologically managed patients.

Third, the 2025 American Heart Association scientific statement supporting opportunistic CAC detection from non-gated chest CTs may substantially expand the population in whom CAC is recognized [17], potentially facilitating broader risk reassessment and, in selected patients, consideration of longitudinal CAC monitoring. Our finding that CAC progression consistently predicts MACE across subgroups supports the clinical utility of incorporating serial CAC data when follow-up imaging is available.

Comparison with Existing Literature

Our study complements and extends the existing evidence base in several ways. While the MESA cohort and Heinz Nixdorf Recall study have established the prognostic value of CAC progression in predominantly Western populations [6–8], our study provides validation in an East Asian cohort. The Asian meta-analysis by Chen et al. confirmed a 5-year warranty period for CAC = 0 in Asian populations and demonstrated sex-specific progression patterns [12], both of which are consistent with our distributional data. The use of propensity score–based inverse probability weighting in our analysis allowed us to reduce measured baseline imbalances between progression and non-progression groups; however, residual and unmeasured confounding cannot be excluded, and our findings should be interpreted as associations rather than causal effects.

The statin–CAC interaction has been examined in prior observational studies [18,19] and meta-analyses [9,10], but few have employed joint stratification with IPW-adjusted Cox models to directly

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

compare MACE risk between statin-using progressors and non-progressors. Our study design thus provides a useful complement to existing literature on this critical clinical question.

Limitations

Several limitations should be acknowledged. First, this was a retrospective, single-center study, which may limit generalizability. However, the sample size (n = 1,942) and the use of IPW strengthen the internal validity of our findings. Second, CAC progression was defined using the Agatston score, which inherently conflates plaque volume with calcification density. We were unable to separately assess volume and density components, and could not distinguish between pathological disease-driven calcification and potentially benign statin-induced calcification. Future studies incorporating dual-metric approaches (volume + density) or serial coronary CT angiography (CCTA) with plaque composition analysis would provide greater mechanistic insight. Third, statin use was classified as a binary variable (present/absent) rather than as a continuous measure of exposure (e.g., annualized statin-days or statin intensity). This approach may obscure the effects of medication adherence, dosage, and duration. Fourth, we lacked data on non-calcified plaque burden, which represents the primary substrate for acute coronary syndromes and may be particularly relevant in patients with low CAC but extensive non-calcified plaque. Fifth, the inter-scan interval varied across patients, which may introduce measurement variability in annualized CAC change calculations. Sixth, although IPW was applied to balance baseline characteristics between progression and non-progression groups, residual imbalance in covariates not included in the propensity model—and confounding by unmeasured variables (e.g., inflammatory biomarkers such as interleukin-6, lipoprotein(a), and genetic risk scores)—cannot be excluded. Seventh, of the 1,942 enrolled participants, 1,621 had complete data on all covariates required for the propensity score model and were included in the IPW-adjusted Cox analyses; the 321 participants excluded from the weighted analyses owing to missing covariate data may introduce selection bias if missingness is not at random. Eighth, because outcomes were ascertained primarily through CMUH medical records, events occurring exclusively at outside hospitals may have been missed. This limitation could have led to outcome underascertainment, particularly among participants who subsequently received care outside the CMUH system. Linkage to the Taiwan National Health Insurance Research Database in future analyses could mitigate this limitation. Ninth, the relatively low prevalence of statin use in our cohort (8.1%) limits the statistical power for statin-stratified analyses, which is particularly relevant to the non-significant CAC progression × statin interaction term. Finally, no randomized controlled trial has demonstrated that serial CAC-guided treatment intensification improves hard cardiovascular endpoints, and our observational data cannot establish such a causal link.

Conclusions

In this Taiwanese cohort undergoing serial cardiac CT, CAC progression was strongly associated with an increased risk of MACE and showed a graded relationship with the magnitude of CAC change. This association was consistent across clinical subgroups and remained clinically relevant among statin-treated patients, suggesting that CAC progression may serve as a marker of residual cardiovascular risk rather than merely reflecting benign plaque calcification. These findings support the potential role of serial CAC assessment for dynamic risk stratification, particularly in patients with established baseline calcification or persistent risk despite preventive therapy. Prospective studies are needed to determine whether CAC progression–guided risk modification can improve clinical outcomes.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Supplementary Table S1. Baseline Characteristics of Participants Included Versus Excluded From the IPW-Adjusted Cox Analysis (n = 1,621 vs. n = 321). Supplementary Table S2. Distribution of Medication Use According to CAC Progression Status. Supplementary Table S3 Univariable and Multivariable

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

Association Between Medication Use and CAC Progression. Supplementary Figure S1. Adjusted Hazard Ratios for MACE Across Joint Categories of CAC Progression and Statin Use.

Author Contributions: Conceptualization, Jin-Man He, Yu-Chen Wang and Kuan-Cheng Chang; Methodology, Yu-Chen Wang; Formal analysis, Jin-Man He and Yu-Chen Wang; Investigation, Jin-Man He; Resources, Jin-Man He; Data curation, Jin-Man He; Writing – original draft, Jin-Man He; Writing – review & editing, Yu-Chen Wang and Kuan-Cheng Chang; Supervision, Yu-Chen Wang and Kuan-Cheng Chang; Project administration, Yu-Chen Wang; Funding acquisition, Yu-Chen Wang. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported in part by the Taiwan National Science and Technology Council (NSTC 114-2314-B-039-071, NSTC 112-2314-B-039-031, and MOST 111-2314-B-039- 012), China Medical University Hospital (C1110812016-8 and C1110831002-11) and Asia University Hospital (11251018). None of the funding sources played a role in the study design, data collection, analysis, interpretation, report writing, or decision to submit the manuscript for publication.

Institutional Review Board Statement: This study was conducted in accordance with the ethical standards of the Institutional Review Board of CMUH and with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of CMUH (IRB No. CMUH105-REC2-047).

Informed Consent Statement: Given the retrospective nature of the research and the use of de-identified data, the requirement for written informed consent was waived by the Institutional Review Board.

Data Availability Statement: The authors gratefully acknowledge the Big Data Center of China Medical University Hospital for its continuous support throughout this study.

Acknowledgments: In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Agatston, A.S.; Janowitz, W.R.; Hildner, F.J.; Zusmer, N.R.; Viamonte, M., Jr.; Detrano, R. Quantification of coronary artery calcium using ultrafast computed tomography. J. Am. Coll. Cardiol. 1990, 15, 827–832.
2. Greenland, P.; LaBree, L.; Azen, S.P.; Doherty, T.M.; Detrano, R.C. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004, 291, 210–215.
3. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Circulation 2019, 139, e1082–e1143.
4. Budoff, M.J.; Kinninger, A.; Gransar, H.; Achenbach, S.; Al-Mallah, M.; Bax, J.J.; Berman, D.S.; Cademartiri, F.; Callister, T.Q.; Chang, H.J.; et al. When Does a Calcium Score Equate to Secondary Prevention?: Insights From the Multinational CONFIRM Registry. JACC Cardiovasc. Imaging 2023, 16, 1181–1189.
5. Blaha, M.J.; Cainzos-Achirica, M.; Greenland, P.; McEvoy, J.W.; Blankstein, R.; Budoff, M.J.; Dardari, Z.; Sibley, C.T.; Burke, G.L.; Kronmal, R.A.; et al. 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(9): 849–858.
6. Budoff, M.J.; Young, R.; Lopez, V.A.; Kronmal, R.A.; Nasir, K.; Blumenthal, R.S.; Detrano, R.C.; Bild, D.E.; Guerci, A.D.; Liu, K.; et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis) J. Am. Coll. Cardiol. 2013, 61, 1231–1239.
7. Budoff, M.J.; Hokanson, J.E.; Nasir, K.; Shaw, L.J.; Kinney, G.L.; Chow, D.; Demoss, D.; Nuguri, V.; Nabavi, V.; Ratakonda, R.; Berman, D.S.; Raggi, P. Progression of coronary artery calcium predicts all-cause mortality. JACC Cardiovasc. Imaging 2010; 3(12): 1229–1236.

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 May 2026 doi:10.20944/preprints202605.0805.v1

8. Lehmann, N.; Erbel, R.; Mahabadi, A.A.; Rauwolf, M.; Möhlenkamp, S.; Moebus, S.; Kälsch, H.; Budde, T.; Schmermund, A.; Stang, A.; et al. Value of Progression of Coronary Artery Calcification for Risk Prediction of Coronary and Cardiovascular Events: Result of the HNR Study (Heinz Nixdorf Recall). Circulation 2018;137(7):665–679.
9. Zhang, X.; Miao, D.; Hu, Y.; Jie, X.; Lei, W.; Ji, X. Statins Accelerate Coronary Calcification and Reduce the Risk of Cardiovascular Events. Cardiol. Rev. 2023; 31(6), 293–298.
10. Puri, R.; Nicholls, S.J.; Shao, M.; Kataoka, Y.; Uno, K.; Kapadia, S.R.; Tuzcu, E.M.; Nissen, S.E. Impact of statins on serial coronary calcification during atheroma progression and regression. J. Am. Coll. Cardiol. 2015;65(13): 1273–1282.
11. Meng, Q.; Zhao, L.; Zhao, N.; An, Y.; Lu, B.; Gao, Y. Progression of coronary artery calcium density and major adverse cardiovascular events. Atherosclerosis 2024, 398, 118593.
12. Chen, C.-L.; Wu, Y.-J.; Yang, S.-C.; Wu, F.-Z. New look at the power of zero coronary artery calcium (CAC) in Asian population: a systemic review and meta-analysis. Cardiovasc. Diagn. Ther. 2024;14(3): 377–387.
13. Min, J.K.; Lin, F.Y.; Gidseg, D.S.; Weinsaft, J.W.; Berman, D.S.; Shaw, L.J.; Rozanski, A.; Callister, T.Q. Determinants of Coronary Calcium Conversion Among Patients With a Normal Coronary Calcium Scan: What Is the "Warranty Period" for Remaining Normal? J. Am. Coll. Cardiol. 2010; 55(11):1110–1117.
14. Yoo, J.Y.; Kang, S.R.; Chun, E.J. Progression of Coronary Artery Calcification According to Changes in Risk Factors in Asymptomatic Individuals. J. Pers. Med. 2024;14(7): 757.
15. Lee, S.E.; Chang, H.J.; Sung, J.M.; Park, H.B.; Heo, R.; Rizvi, A.; Lin, F.Y.; Kumar, A.; Hadamitzky, M.; Kim, Y.J.; et al. Effects of Statins on Coronary Atherosclerotic Plaques: The PARADIGM Study. JACC Cardiovasc. Imaging 2018;11(10):1475–1484.
16. Maron, D.J.; Budoff, M.J.; Sky, J.C.; Bommer, W.J.; Epstein, S.D.; Fisher, D.A.; Stock, E.O.; Taylor, A.J.; Wong, N.D.; DeMaria, A.N. Coronary Artery Calcium Staging to Guide Preventive Interventions: A Proposal and Call to Action. JACC Adv. 2024:3(11):101287.
17. Foraker, R.; Sperling, L.; Bratzke, L.; Budoff, M.; Leppert, M.; Razavi, A.C.; Rodriguez, F.; Shapiro, M.D.; Whelton, S.; Wong, N.D.; Yang, E. Opportunistic Detection of Coronary Artery Calcium on Noncardiac Chest Computed Tomography: An Emerging Tool for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. Circulation 2025;152(19): e391–e401.
18. Mitchell, J.D.; Fergestrom, N.; Gage, B.F.; Paisley, R.; Moon, P.; Novak, E.; Cheezum, M.; Shaw, L.J.; Villines, T.C. Impact of Statins on Cardiovascular Outcomes Following Coronary Artery Calcium Scoring. J. Am. Coll. Cardiol. 2018;72(25):3233–3242.
19. Kambalapalli, S.; Bhandari, M.; Punnanithinont, N.; Iskander, B.; Khan, M.A.; Budoff, M. Bridging Prevention and Imaging: The Influence of Statins on CAC and CCTA Findings. Curr. Atheroscler. Rep. 2025;27(1): 50.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

© 2026 by the author(s). Distributed under a Creative Commons CC BY license.