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REVIEW

# The Association of Coronary Artery Calcium Score with Heart Failure – a Literature Review

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**ABSTRACT**

One of the main principles of cardiovascular disease prevention is early intervention. Heart failure represents an end stage of most cardiovascular diseases and is a consequence of persistent damage caused by conditions such as coronary artery disease, hypertension, or valvular heart disease. Since its introduction, the coronary artery calcium (CAC) score has proven to be a comprehensive, reproducible, and accessible measure to quantify atherosclerotic burden. This review aimed to assess the prognostic value of the CAC score in patients with heart failure and its association with heart failure-related mortality. We searched the PubMed, Web of Science, and Google Scholar databases for studies examining the relationship between the CAC score and heart failure. After an initial selection of 32 articles, 23 were deemed eligible for inclusion. Based on the findings of these studies, the CAC score can be considered a useful tool for assessing heart failure risk, either alone or in combination with other parameters, across diverse populations, thereby supporting earlier initiation of pharmacological therapy.

**Keywords:** coronary artery calcium score, heart failure, computed tomography, atherosclerosis

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## INTRODUCTION

Atrial fibrillation (AF) is associated with a significant burden on healthcare systems and poses considerable risk-Heart failure (HF) is a clinical syndrome in which the heart's ability to fill or eject blood efficiently is impaired by functional or structural abnormalities, resulting in an insufficient cardiac output to meet the body's metabolic needs. To maintain proper circulation, it may need compensatory neurohormonal responses and elevated ventricular filling pressures. Although the incidence of heart failure has shown a modest decline over time, its overall prevalence continues to rise. This increase is largely caused by advances in HF management and the extended life expectancy of the general population. In Europe, the median HF incidence is estimated at 3.2 cases per 1,000 person-years, whereas the median prevalence is around 17.2 cases per 1,000 individuals.[1]

One of the leading causes of HF is ischemic heart disease, characterized by the loss of functional myocardial

tissue, which leads to a decline in contractile strength. In coronary artery disease (CAD), restricted oxygen supply to the myocardium results in a reduction in both systolic and diastolic function. For this reason, current cardiologic research and practice are primarily centered on the coronary atheromatous plaque, more specifically, its origin, preventive strategies, diagnostic assessment, and therapeutic approaches.[2] Cardiac computed tomography angiography (CCTA) has become a reliable, efficient, and cost-effective imaging technique for assessing CAD. Among the parameters obtained from non-contrast CCTA (NC-CCTA), the coronary artery calcium (CAC) score has proven increasingly valuable. This measurement quantifies the extent of calcified deposits within the coronary arteries and serves as an index of atherosclerotic plaque burden, while also being a good predictor of future cardiovascular risk.[3]

Since the development of the CAC score as a reliable, widely available parameter, the association between this measurement and HF has been the subject of several studies. One of the main advantages of this association is that it links coronary atherosclerosis to myocardial dysfunction. CAC scoring measures the burden of vascular injury, inflammation, and calcification that leads to myocardial remodeling and reduction of ventricular function. The study of this relationship may help improve risk stratification and promote early therapeutic intervention in HF. This review aims to summarize current evidence linking CAC score to the incidence and progression of HF, highlight pathophysiological mechanisms, integrate results from major cohort and observational studies, and explore differences among HF subtypes.

## METHODS

We performed a detailed search to identify all available studies investigating the relationship between the CAC score and HF. Electronic searches were conducted in PubMed, Web of Science, and Google Scholar. Boolean operators were used to create the following search string: (coronary artery calcium OR coronary calcium OR coronary artery calcium score OR CAC OR CACS OR Agatston) AND (heart failure OR heart-failure OR HFpEF OR HFrEF OR congestive heart failure OR cardiac failure). The search was limited to English-language publications. Case reports, clinical trials, animal studies, review articles, and editorials were excluded.

## RESULTS

### RESULTS OF THE LITERATURE SEARCH

The initial screening was based on article titles and abstracts, from which 32 studies were selected. After removing duplicates and excluding articles that did not meet the main inclusion criteria of the review, 23 studies were included. Of these, 12 investigated the association between CAC and the risk of HF or HF-related mortality. Eight studies examined the relationship between CAC and cardiovascular disease (CVD), cardiovascular disease events (CVDE), or major adverse cardiovascular events (MACE), which included HF. The remaining three studies assessed the prognostic value of the CAC score in patients with HF.

### GENERAL CHARACTERISTICS OF INCLUDED STUDIES

Of the 23 studies included in the review, 19 were cohort studies and 4 were cross-sectional. The mean age of the participants ranged from 40 to 74 years, and sample sizes ranged from 157 to 66,636. The studies were conducted in various regions; most in the United States, involving large cohorts (e.g., MESA and CARDIA), and in Europe (e.g., the Heinz Nixdorf Recall cohort study in Germany and the Rotterdam Study in the Netherlands). Other study locations included Canada, Japan, South Korea, Thailand, and Saudi Arabia (Table 1).

Four of the included studies used the Multi-Ethnic Study of Atherosclerosis (MESA) cohort as their study population. MESA was designed as a prospective, observational epidemiological cohort study aimed at characterizing the development and progression of subclinical cardiovascular disease in a large population without known cardiovascular disease. Between 2000 and 2002, the study enrolled 6,814 participants aged 45–84 years from four different ethnic groups across six regions in the United States. Participants with pacemakers or defibrillators, previous coronary bypass surgery, heart valve replacement, percutaneous revascularization, or other cardiac surgery were excluded.[4]

The included studies used different approaches to evaluate the relationship between the CAC score and HF. Some studies assessed the direct association between CAC and the risk of developing HF, whereas others analyzed outcomes separately for HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). Risk stratification for HF-related mortality was investigated in studies such as those from the Coronary Artery Consortium, while other studies focused on the

association between higher CAC scores and the risk of HF development.

## OVERALL ASSOCIATION AND RISK ASSESSMENT OF CAC WITH HF

All included studies reported an association between CAC and HF, although results varied after adjustment for traditional risk factors. In the Rotterdam Study, a prospective, population-based cohort study initiated in 1990 that included subjects older than 55 years, 1,897 asymptomatic individuals underwent CAC scoring and were followed for a median of 6.8 years. The primary outcome was HF or coronary heart disease (CHD). After adjustment for other cardiovascular risk factors, higher CAC scores were associated with an increased risk of HF, with a hazard ratio (HR) of 4.1 for CAC scores > 400 compared with scores < 10.[5]

Another study by Ahmed Fathala *et al.* evaluated 204 patients with new-onset HF who underwent CCTA in the preceding 3 months, of whom 35 had obstructive CAD. In multivariable logistic regression analysis, the CAC score was the independent predictor of HF attributable to CAD. Notably, 63% of patients had a CAC score of 0, which correlated with normal CCTA findings and yielded a 100% negative predictive value.[6]

Regarding the different results after adjustment for traditional risk factors, a study including participants from the Heinz Nixdorf Recall Study reported attenuation of the association between CAC score and the presence of congestive heart failure (CHF). The Heinz Nixdorf Recall Study is a prospective epidemiological cohort study conducted in Germany that enrolled 4,814 participants, aiming to improve cardiovascular risk prediction using imaging and non-imaging variables.[7] In the study by Kälsch *et al.*, 4,230 participants without known CAD but with a diagnosis of CHF were included. CHF was identified in 105 participants (2.5%), and CAC extent was significantly higher in subjects with CHF (median CAC score 64.7) than in those without CHF (median CAC score 11.6). To assess the association between CAC and CHF, a logarithmically transformed CAC burden was used. In univariate analysis, the CAC score was associated with CHF (odds ratio (OR) 1.16). However, in the fully adjusted multivariate model, which included age, sex, Framingham risk factors, and cardiovascular medication, the association became statistically non-significant (OR 1.07). The authors concluded that the observed association between CAC and CHF is partly explained by risk factors that are common in the pathophysiology of both CAC and CHF.[8]

In contrast, the study with the largest sample size among the included studies, conducted by Mhaimeed *et al.*, demonstrated a strong correlation between CAC score and HF-related mortality. The study included 66,636 participants from the CAC Consortium, a multicenter, retrospective, observational real-world cohort study of patients older than 18 years who underwent CAC scoring.[9] The primary outcome was HF-related mortality, with a median follow-up of 12.5 years. A total of 260 HF-related deaths were recorded, of which 75.3% occurred in patients with a CAC score ≥ 100, and more than half (53.1%) occurred in participants with a CAC score ≥ 400. Participants were categorized into four groups based on CAC score: 0 (reference), 1–99, 100–399, and ≥ 400. After multivariable adjustment for demographic factors, traditional cardiovascular risk factors, and competing risks of non-cardiovascular death, subdistribution hazard ratios (SHR) for HF-related mortality compared with the reference group were 2.27 for CAC 1–99, 3.68 for CAC 100–399, and 7.05 for CAC ≥ 400. Overall, the study demonstrated that higher CAC scores are strongly associated with an increased risk of HF-related mortality.[10]

Although most studies demonstrate an association between CAC score and HF, the degree of independent predictive value after adjustment for traditional risk factors remains inconsistent. This is mainly attributable to differences in study design, patient populations, and definitions of HF. One important methodological factor is the nature of the analysis (cross-sectional or prospective). For example, the Heinz Nixdorf Recall Study assessed the prevalence of self-reported CHF, whereas the Rotterdam Study evaluated the incidence of HF, and the CAC consortium focused on HF-related mortality. Additional variation arises from differences in the age and health status of the studied populations. The mean age in the Heinz Nixdorf Recall Study was 59 years, compared with 69.9 years in the Rotterdam Study and 54.4 years in the CAC Consortium cohort.

## CAC AND HFPEF/HFREF

Some studies stratified HF outcomes into HFpEF and HFrEF. Three of these used data from the MESA cohort and demonstrated the predictive value of CAC for HF risk assessment using different methodological approaches. De la Rosa *et al.* used log-transformed CAC together with other CCTA biomarkers, such as left ventricular size index, aortic valve, mitral annulus, and thoracic aorta measurements, to predict new-onset HF among 6,667 patients from the MESA cohort. During a median follow-up of 17.7

**TABLE 1.** Summary of analyzed studies

| Author | Year | Sample size | Mean age (years) | Study design | Imaging | Statistical analysis | Main findings |
|---|---|---|---|---|---|---|---|
| Naghavi *et al.*[26] | 2024 | 5,830 | 62 ± 10 | Prospective cohort study (MESA) | Non-contrast CAC scans enhanced by AI-enabled automated cardiac chamber volumetry and calcified plaque characterization | • Survival analysis using Cox proportional hazards regression<br>• Discrimination was assessed using time-dependent ROC area under the curve (AUC) and Uno's C-statistic<br>• AUC difference calculated using inverse probability of censoring weighting (IPCW) estimator | The AI-CAC model significantly improved the prediction of all CVD events (including HF, AF, and stroke) compared to the Agatston score alone. |
| Sakuragi *et al.*[28] | 2016 | 487 | 69 ± 11 | Prospective cohort study | MDCT | • One-way ANOVA and the Kruskal–Wallis test (for continuous variables)<br>• Chi-squared test (for categorical variables)<br>• Kaplan–Meier analysis with the log-rank test<br>• Cox proportional hazards regression | Severe CAC is an independent determinant of high N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and a predictor of admission for HF in patients without a history of CAD or HF. |
| Ota *et al.*[25] | 2022 | 550 | 72.5 ± 13.5 | Retrospective cohort study | Non-ECG-gated MDCT<br>Invasive coronary angiography | • Mann–Whitney U test (for continuous variables)<br>• Chi-squared test (for categorical variables)<br>• Kaplan–Meier analysis with the log-rank test<br>• Cox proportional hazards regression | Higher CAC score detected via non-contrast chest CT is significantly associated with all-cause mortality among patients with CHF. |
| Carr *et al.*[21] | 2017 | 3,043 | 40.3 ± 3.6 | Prospective cohort study (CARDIA) | Non-contrast CT | • Cox proportional hazards regression adjusted for covariates<br>• Poisson regression<br>• Linear regression | In younger adults, a CAC score > 0 was associated with incident all CHD and all-cause death. |
| Kälsch *et al.*[8] | 2010 | 4,230 | 59 ± 8 | Prospective cohort study (Heinz Nixdorf Recall Study) | EBCT | • Mann–Whitney U test (for continuous variables)<br>• Chi-squared test or Fisher's exact test (for categorical variables)<br>• Multivariable analysis using logistic regression | CAC is associated with the presence of CHF. This association is partially diminished after adjusting for traditional risk factors. |
| Haddad *et al.*[17] | 2022 | 2,082 | 50.6 ± 17.0 | Prospective cohort study | Non-contrast CT | • Multidimensional analysis using maximal information coefficient (MIC) to weight edges<br>• Multivariable regression analysis<br>• Stepwise linear regression | CAC score was independently associated with LV diastolic function. |
| de la Rosa *et al.*[11] | 2025 | 6,667 | 62 ± 10 | Prospective cohort study (MESA) | Non-contrast CT<br>EBCT | • Cox proportional hazards models and time-dependent ROC analysis | CAC score was a significant predictor of new-onset HFrEF. |
| Nitta *et al.*[18] | 2019 | 157 | 71 ± 8 years for patients with CAC<br>66 ±13 years for patients without CAC | Retrospective cohort study | Non-contrast CT<br>Gated SPECT for myocardial perfusion<br>TTE | • Chi-squared test (for categorical variables)<br>• Mann–Whitney U test (for continuous variables)<br>• Pearson's correlation<br>• Linear regression analysis (univariate and multivariate) | Log-transformed CAC score was significantly and independently associated with indices of impaired LV diastolic function (PFR and 1/3MFR). |

| Author | Year | Sample size | Mean age (years) | Study design | Imaging | Statistical analysis | Main findings |
|---|---|---|---|---|---|---|---|
| Mhaimeed *et al.*[10] | 2025 | 66,636 | 54.4 ± 10.6 | Retrospective cohort study | Non-contrast CT<br>EBCT | • Student's t test and Wilcoxon signed-rank test<br>• Chi-squared test<br>• Subdistribution hazard ratios (SHRs) | A higher CAC score was associated with an increasing incidence of HF-related mortality in primary prevention patients. |
| Kitjanukit *et al.*[29] | 2024 | 442 | 62.5 ± 10.4 | Retrospective cohort study | Non-contrast CT | • Extended Wilcoxon rank-sum test by Cuzick (for trending variables)<br>• Cox regression (to estimate HR)<br>• Weighted Cohen's Kappa (to measure disagreement | Increasing CAC score categories were associated with a significantly increased HR for MACE. |
| Leening *et al.*[5] | 2012 | 1,897 | 69.9 ± 6.5 | Prospective population-based cohort study (The Rotterdam Study) | EBCT | • Cox proportional hazards models (implied by use of HR, C-statistic, and reclassification metrics) Measures included c-statistic, integrated discrimination index (IDI), and continuous net reclassification index (NRI). | CAC has a clear and graded association with the risk of developing HF in the elderly population, independent of traditional cardiovascular risk factors and incident overt CHD |
| Fathala *et al.*[6] | 2019 | 204 | 48 ± 13 | Retrospective cohort study | Contrast CT<br>ICA | • Descriptive statistics<br>• Pearson's Chi-squared test<br>• Independent samples t-test or ANOVA<br>• Multivariate logistic regression | The mean CAC score was significantly higher in the CAD HF group compared to the non-CAD HF group. |
| Choi *et al.*[19] | 2025 | 15,193 | 55.8 ± 8.6 | Longitudinal cohort study | Non-contrast CT<br>Echocardiography | • Linear regression models<br>• Log-binomial regression<br>• Linear mixed models | CAC ≥ 100 significantly affects the progression of DD independently of other clinical factors. |
| Singh *et al.*[30] | 2024 | 1,988 | DM cohort: 63.4 ± 8.9<br>Non-DM cohort: 60.3 ± 9.6 | Prospective cohort study | Contrast CT | • t-tests and p-tests (for categorical variables)<br>• Survival analysis metrics including c-index and hazard ratio (HR)<br>• Cox proportional hazard models with elastic net regularization<br>• 5-fold cross-validation with bootstrap iterations<br>• Kaplan–Meier curves | Models leveraging radiomic features of calcium-omics and epicardial adipose tissue (fat-omics) extracted via deep learning from CTCS scans showed competitive or superior performance in predicting incident HF compared to traditional models. |
| Wakaki *et al.*[22] | 2025 | 353 | 68.6 ± 12.7 | Retrospective cohort study | Non-ECG-gated CT<br>ICA | • One-way ANOVA Kruskal–Wallis test<br>• Chi-squared test<br>• Log-rank test<br>• Kaplan–Meier method<br>• Univariable and multivariable analysis | The CAC score significantly predicted cardiovascular events (including CHF). |
| Hashimoto *et al.*[23] | 2021 | 108 | 74 ± 13 | Retrospective observational study | Non-contrast CT<br>I-BMIPP SPECT | • Chi-squared test<br>• Kaplan–Meier method<br>• Univariable and multivariable analysis | Increased CAC scores were associated with all-cause mortality in patients with CHF. |
| Tian et al.27 | 2025 | 1,310 | 56.5 ± 11.8 | Prospective cohort study (Chronic Renal Insufficiency Cohort) | | • t test and chi-squared test<br>• Multiple imputation<br>• Comparison of models using Akaike's information criterion<br>• Schoenfeld residuals to confirm proportional hazard assumptions<br>• Survival analysis using methods appropriate for competing risks | Progression of CAC is associated with a higher risk of atherosclerotic CVD and all-cause mortality, but not with CHF. |

| Author | Year | Sample size | Mean age (years) | Study design | Imaging | Statistical analysis | Main findings |
|---|---|---|---|---|---|---|---|
| Ahmad *et al.*[15] | 2025 | 6,592 | 62 ± 10 | Prospective cohort study (MESA) | Non-contrast CT EBCT | Chi-squared test ANOVA Kruskal–Wallis test Kaplan–Meier plot and log-rank test Multivariable Cox proportional hazard models Proportional hazards assumption evaluated using Schoenfeld residuals and formal testing Benjamin–Hochberg (BH) adjusted p value. | The combination of elevated IL-6 and CAC > 0 was associated with a higher risk of HFrEF, showing significant additive and multiplicative interactions. There was an antagonistic interaction for HFpEF. |
| Wada *et al.*[20] | 2023 | 982 | 64.7 ± 6.6 | Prospective cohort study (NADESICO) | Non-contrast CT | Univariable and multivariable analysis Cox proportional hazard models C-statistic analysis | Adding the CAC score to the conventional cardiovascular risk factors (Suita score) significantly improved the predictive ability for future MACE in Japanese patients. |
| Elnagar *et al.*[31] | 2024 | 435 | 48.04 ± 7.19 (Group I: CAC <400) and 49.77 ± 7.15 (Group II: CAC >400). | Retrospective cohort study | Contrast CT | Independent sample t-test Chi-squared test Multivariate logistic regression analysis | CAC scores ≥ 400 predict MACE. |
| Sharma *et al.*[12] | 2017 | 5,282 | 62 ± 10 | Prospective cohort study (MESA) | Non-contrast CT EBCT | Cox proportional hazard models Proportional hazard assumption Test for trend | The CAC score was positively associated with incident HFpEF risk in women, but not in men. |
| Abunassar *et al.*[32] | 2011 | 4,394 | No prior HF/LV dysfunction: 51.7 ± 10.3 HF and abnormal EF: 58.8 ± 11.7 High-risk CAD: 62.1 ± 9.7 | Retrospective cohort study | Contrast CT | Wilcoxon rank-sum test Fisher's exact test | CAC = 0 excludes ischemic cardiomyopathy in patients presenting with HF. |
| Lehmann *et al.*[33] | 2018 | 3,281 | 58.7 ± 7.5 | Prospective cohort study (Heinz Nixdorf Recall study) | EBCT | Chi-squared test Mann–Whitney U test Univariate and multivariable logistic regression Multivariable Cox proportional hazards regression Net reclassification index Integrated discrimination index | The CAC score is associated with CHF in persons without clinically overt CAD, but in longitudinal progression analysis, the predictive value of CAC progression has reduced risk prediction for CVDE when compared to the most recent CAC value. |

EBCT, electron-beam computed tomography; ICA, invasive coronary angiography; MDCT, multidetector computed tomography; TTE, transthoracic echocardiography

years, new-onset HF was diagnosed in 426 patients: 173 (40.6%) with HFrEF, 193 (45.3%) with HFpEF, and 60 (14.1%) without a recorded ejection fraction (EF). Cox regression analysis showed that log-transformed CAC was an independent predictor of both new-onset HFrEF (HR 1.15) and new-onset HFpEF (HR 1.09).[11]

In contrast, Sharma *et al*. examined the predictive value of CAC specifically for HFpEF and reported sex-specific differences. A total of 6,809 participants underwent CAC scoring and were followed for a median time of 11.2 years, during which 127 incident HFpEF hospitalizations were recorded. The overall incidence rate of HFpEF was 1.82 per 1,000 person-years, with a slightly higher rate in men than women (2.00 vs. 1.66 events per 1,000 person-years). Across CAC categories, HFpEF incidence increased progressively, from 0.99 events per 1,000 person-years in participants with a CAC score of 0 to 1.48 for CAC 1–100, 2.95 for CAC 101–300, and 5.39 for CAC > 300. In adjusted analyses, a CAC score of >300 was associated with an increased risk of HFpEF (HR 1.68); however, this association was significant only in women (HR 2.82) and not in men (HR 0.91). The authors concluded that, beyond traditional risk factors, CAC may be useful in HFpEF risk stratification in women but not in men, highlighting the need for further research to clarify sex-specific pathophysiological mechanisms in HFpEF.[12]

The third study examining HFpEF and HFrEF included, in addition to the CAC score, the pro-inflammatory cytokine interleukin-6 (IL-6). The rationale for including IL-6 was that chronic inflammation is a key contributor to both clinical and subclinical atherosclerosis and HF.[13,14] Ahmad *et al*. the association between HF and combined IL-6 and CAC burden in 6,592 participants from the MESA cohort. Participants were categorized into four groups: low CAC/low IL-6, low CAC/high IL-6, high CAC/low IL-6, and high CAC/high IL-6. A total of 422 HF events were reported, with incidence rates increasing across categories: 1.58 per 1,000 person-years in the low IL-6/low CAC group, 3.63 in the low IL-6/high CAC group, 5.04 in the high IL-6/low CAC group, and 9.14 in the high IL-6/high CAC group. In adjusted analyses, high IL-6 alone (HR 1.61) and high CAC score alone (HR 1.56) were each associated with increased HF risk compared with the reference group. For HFrEF, neither high IL-6 nor high CAC alone showed a statistically significant association after multivariable adjustment; however, their combination was associated with a higher risk of HFrEF (HR 2.34). In contrast, for HFpEF, both high IL-6 alone (HR 2.43) and high CAC score alone (HR 2.12) were associated with increased risk, whereas the combination of high IL-6 and high CAC did not confer additional risk.[15]

Similar to studies examining the overall association between CAC and HF, some analyses reported conflicting results, largely due to differences in methodology and variable definitions. For example, de la Rosa *et al*.[11] primarily used log-transformed CAC as a continuous variable, whereas Ahmad *et al*.[15] categorized CAC into two groups, and Sharma *et al*.[12] used both categorical CAC and log-transformed CAC. Another important difference concerned the left ventricular ejection fraction (LVEF) thresholds used to define HF subtypes. In the study by de la Rosa *et al*.,[11] HFrEF was defined as EF < 45% and HFpEF as EF ≥ 45%, while Ahmad *et al*.[15] defined HFrEF as EF ≤ 40% and HFpEF as EF ≥ 50%.

## CAC SCORE AND DIASTOLIC DYSFUNCTION

Diastolic dysfunction (DD) refers to a range of alterations in cardiac function, including increased myocardial stiffness, abnormal relaxation, and increased end-diastolic pressure, and represents a major contributor to HFpEF.[16] Of the 23 included studies, three investigated the association between CAC score and DD. Although all three demonstrated an independent association between CAC and DD, they differed in study population, methodology, and endpoints. For example, Haddad *et al*. studied 2,082 participants from the Project Baseline Health Study who underwent CAC scoring and echocardiography. After multivariable adjustment, subclinical coronary atherosclerotic burden assessed by CAC score was independently associated with DD. Two continuous diastolic parameters, e' velocity and the E/e' ratio, showed an independent association with increasing CAC score categories.[17]

In contrast to the other studies, Nitta *et al*. assessed diastolic function using gated single-photon emission computed tomography (SPECT). The study tested the hypothesis that CAC extent is associated with left ventricle (LV) diastolic parameters in patients without evidence of myocardial ischemia, with peak filling rate (PFR) as a key parameter. The results showed that patients with CAC had lower PFR than those without CAC. After multivariate linear regression adjusting for sex, hypertension, LV end-diastolic volume (LVEDV), and LV mass index, ln(CAC score + 1) was identified as an independent predictor of LV diastolic parameters. The authors suggested that microvascular damage secondary to arterial stiffness and endothelial dysfunction caused by CAC may represent a pathophysiological mechanism underlying DD.[18]

While the studies by Haddad *et al*. and Nitta *et al*. were cross-sectional, the third study, by Choi *et al*., performed a retrospective longitudinal analysis examining the rela-

tionship between CAC score and the progression of DD in a cohort of 15,193 adults in Korea. The CAC scores were categorized into three groups: CAC 0, CAC 1–99, and CAC ≥ 100. DD was defined using echocardiographic parameters, including septal e', septal E/e', left atrial volume index (LAVI), and tricuspid regurgitation velocity. Definite DD was defined as ≥ 3 of 4 abnormal parameters, whereas definite or probable DD was defined as ≥ 2 of 4 abnormal DD parameters. The adjusted prevalence ratio for definite DD in patients with CAC ≥ 100 was 1.72 compared with those with CAC = 0, while the prevalence ratio for definite or probable DD was 1.83. Regarding mortality and the combined effect of CAC and DD, patients with CAC ≥ 100 and definite DD had the highest mortality risk with an HR for all-cause mortality of 3.91 compared with to the reference group (CAC < 100 without definite DD). In addition, CAC ≥ 100 was independently associated with progression to definite DD over time, with an adjusted HR of 1.95 compared with CAC = 0. Overall, the study demonstrated a strong association between CAC score and the prevalence of DD, an increased mortality risk when both CAC and DD were present, and an independent effect of significant CAC burden (≥ 100) on DD progression over time.[19]

## ASSOCIATION BETWEEN CAC SCORE AND HF-RELATED CVDE OR MACE

Most studies included in this review focused specifically on the association between CAC and HF; however, some also evaluated HF as part of broader cardiovascular outcomes such as stroke, aortic disease, unstable angina, myocardial infarction, and coronary artery revascularization procedures. All studies demonstrated a strong predictive value of CAC for CVDE or MACE, although results varied owing to differences in study populations and methodologies. For example, Wada *et al*. focused on a Japanese population and identified sex-specific CAC thresholds for MACE prediction,[20] whereas a study based on the CARDIA cohort examined young adults and found that any CAC score above zero was associated with an increased risk for CVD.[21] In contrast, Wakaki *et al*. demonstrated that high CAC scores predict CVDE using non-ECG-gated CT imaging.[22]

One method of studying the predictive value of the CAC score has been to assess whether adding it to traditional risk scores improves risk stratification. In this regard, Wada *et al*. conducted a multicenter, prospective cohort study in Japan that enrolled 982 patients to evaluate the contribution of CAC to the prediction of MACE. CAC scores were categorized as no CAC (0), mild (0 < score < 100), moderate (100 ≤ score < 300), and severe (above 300). MACE included hospitalization for unstable angina, HF, aortic disease, cardiovascular death, myocardial infarction, revascularization, and stroke. A key finding of the study was the presence of sex differences in CAC burden: CAC was detected in 77.5% of male participants compared with 55.3% of female participants, and severe CAC was detected in 25.5% of men but only 7.5% of women. The primary objective was to determine whether adding CAC to the Suita risk score improved the C-statistic for predicting MACE.[20] The Suita score, developed for the Japanese population, estimates cardiovascular risk based on age, sex, smoking, diabetes, blood pressure, low-density lipoprotein, high-density lipoprotein, and chronic kidney disease.[23] In this cohort, the C-statistic for the Suita score alone was 0.650. Adding CAC improved the C-statistic when thresholds of ≥ 100, ≥ 200, ≥ 300, or ≥ 400 were applied, with the greatest improvement observed at the ≥ 300 threshold, yielding a continuous net reclassification index (NRI) of 0.652. In men, the C-statistic improved with CAC thresholds of ≥100 and ≥200, with an NRI of 0.630 at the ≥ 200 threshold. In women, improvement was observed only when a CAC threshold of ≥400 was added, with an NRI of 0.698. Overall, the study demonstrated that the CAC score has a significant predictive value for MACE, with sex-specific differences in its impact on risk stratification.[20]

One demographic that is often underrepresented in cardiovascular risk assessment studies is young adults. Carr *et al*. addressed this gap by evaluating the association between CAC, CHD, CVD (including HF), and all-cause mortality in adults aged 32–46 years. A total of 3,043 participants from the CARDIA study were included and followed for 12.5 years. The presence of CAC was associated with a higher risk of CVD events (HR 3.0) and an increased rate of CHD events (HR 5.0). The study also demonstrated that even low CAC scores (1–19) significantly increased the risk of CHD in young adults, suggesting that early screening should be considered.[21]

In a retrospective cohort study, Wakaki *et al*. examined the relationship between CAC score and future CVD and non-CVD events in patients with established CVD. Participants were categorized into three groups based on CAC score: low (median 0), intermediate (median 200), and high (median 1,601). The primary endpoint was CVD events, including cardiac death, nonfatal myocardial infarction, hospitalization for CHF, stroke, and unplanned cardiac surgery. Kaplan–Meier analysis confirmed that patients with a high CAC score had a higher risk of CVD events than those with a low score. In multivariable Cox analysis, CAC score, smoking, and dialysis were independently associated with CVD events.[22]

### CAC AS A PROGNOSTIC FACTOR FOR PATIENTS WITH HF

An additional application of the CAC score has been explored in studies evaluating its prognostic value in patients already diagnosed with HF. Both Ota *et al.* and Hashimoto *et al.* reported that higher CAC scores are associated with worse clinical outcomes.[23,25] Ota *et al.* investigated the prognostic value of CAC for all-cause mortality in patients with CHF. A total of 550 patients were enrolled and stratified into three groups based on CAC score: 0, 1–999, and ≥ 1,000. After adjustment for traditional risk factors, brain natriuretic peptide (BNP) and LVEF, patients with CAC ≥ 1,000 had a significantly higher risk of all-cause mortality (HR 1.564) compared with those with CAC 0.[25]

Hashimoto *et al.* evaluated the role of CAC in predicting MACE in patients with non-ischemic HFpEF (NIHFpEF), comparing its prognostic value with that of the I-beta-methyl-piodophenyl-pentadecanoic acid (I-BMIPP) defect score (BDS). The study included 108 patients with NIFHpEF who underwent non-contrast chest CT and I-BMIPP SPECT. Multivariable Cox regression analysis demonstrated that both CAC score >0 and high BDS (≥4) were independent predictors of MACE. When combined, CAC score and BDS provided improved prognostic stratification, with a 75% MACE rate in patients with CAC >0 and high BDS compared with 3% in those with CAC = 0 and low BDS.[24]

## DISCUSSION

In this review, we aimed to investigate the role of the CAC score, a measure of subclinical coronary atherosclerosis, as a tool for assessing the risk of HF and HF-related mortality. The main consensus of the 23 included studies was that the CAC score is an accessible, reproducible, and reliable marker for HF risk. There were some differences in the findings and conclusions of the studies, primarily due to the research methodologies. Several studies focused on sex-specific differences in the predictive value of CAC for HF or MACE. For example, Sharma *et al.* showed that CAC stratified the risk of HFpEF in women beyond the traditional cardiovascular risk factors,[12] whereas Wada *et al.* reported a higher risk of MACE in men, even at lower CAC levels.[20] Other studies reported different findings for HFpEF versus HFrEF. For instance, Ahmad *et al.*, using data from the MESA cohort, demonstrated that in HFpEF, high CAC score and elevated IL-6 each had independent predictive value but not when combined, whereas the opposite pattern was observed for HFrEF.[15]

One tool that has been increasingly integrated into scientific research in recent years is artificial intelligence (AI). Medical imaging, as one of the medical fields showing particularly promising results with AI implementation, has seen significant advances applied to the well-established CAC score. Some of the studies included in this review incorporated AI in different ways, such as image analysis, risk prediction, or editorial assistance. Naghavi *et al.* used AI algorithms to extract additional data from NC-CCTA scans, improving CVDE risk assessment. Beyond standard CAC scoring, AI algorithms enabled automated quantification of cardiac chambers volumes indexed to body surface area and provided more detailed characterization of atherosclerotic plaques, including their number, location, density, and the number of affected vessels. Compared with CAC score alone, these AI-based models demonstrated improved predictive performance for CVDE.[26]

In some cases, the CAC score was not found to be statistically associated with HF or HF-related mortality. A study based on the Heinz Nixdork Recall Study population demonstrated reduced association between CAC score and CHF after adjustment for multiple variables, including cardiovascular risk factors; the most likely explanation was that CAC and CHF share common pathophysiological mechanisms.[8] In another study involving patients with chronic kidney disease, progression of CAC was associated with an increased risk of atherosclerotic CVD and all-cause mortality, but not with CHF.[27]

## CONCLUSIONS

The majority of available evidence supports the CAC score as a useful tool for risk stratification in HF and cardiovascular mortality. This applicability extends beyond populations traditionally considered at high risk of CVD. Incorporating CAC scoring into primary prevention strategies and expanding its use through AI-based algorithms may help identify individuals at increased risk of HF. Furthermore, this risk identification may allow earlier implementation of targeted treatment aimed at modifying factors involved in the pathophysiological progression of HF and CVD.

## CONFLICT OF INTEREST

Nothing to declare.

## AUTHORS CONTRIBUTIONS

D.S. conceptualized the study and prepared the original draft. G.T. conducted the investigation. R.O.C. curated the data. L.M. reviewed and edited the manuscript. C.F. supervised the study and managed the project administration.

K.B. and B.S. performed the formal analysis and validation. All authors have read and agreed to the published version of the manuscript.

## REFERENCES


1. Beghini A, Sammartino AM, Papp Z, et al. 2024 update in heart failure. ESC Heart Fail. 2025 Feb;12(1):8-42. doi: 10.1002/ehf2.14857
2. Severino P, D'Amato A, Pucci M, et al. Ischemic Heart Disease and Heart Failure: Role of Coronary Ion Channels. Int J Mol Sci. 2020 Apr 30;21(9):3167. doi: 10.3390/ijms21093167
3. Mattesi G, Savo MT, De Amicis M, et al. Coronary artery calcium score: we know where we are but not where we may be. Monaldi Arch Chest Dis [Internet]. 2023 Sept 6 [cited 2025 Oct 25]; Available from: https://www.monaldi-archives.org/index.php/macd/article/view/2720. doi: 10.4081/monaldi.2023.2720
4. Qureshi WT, Nasir K, Hacioglu Y, et al. Determination and distribution of left ventricular size as measured by noncontrast CT in the Multi-Ethnic Study of Atherosclerosis. J Cardiovasc Comput Tomogr. 2015 Mar;9(2):113-119. doi: 10.1016/j.jcct.2015.01.001
5. Leening MJG, Elias-Smale SE, Kavousi M, et al. Coronary Calcification and the Risk of Heart Failure in the Elderly. JACC Cardiovasc Imaging. 2012 Sept;5(9):874-880. doi: 10.1016/j.jcmg.2012.03.016
6. Fathala A, Shwaihi D, Shoukri M, Alrujaib M. Diagnostic accuracy of computed tomography coronary angiography in patients presenting with heart failure of unknown etiology in the middle east. Heart Views. 2019;20(3):77. doi: 10.4103/HEARTVIEWS.HEARTVIEWS_50_18
7. Erbel R, Eisele L, Moebus S, et al. Die Heinz Nixdorf Recall Studie. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2012 June;55(6-7):809-815. doi: 10.1007/s00103-012-1490-7
8. Kälsch H, Lehmann N, Möhlenkamp S, et al. Association of coronary artery calcium and congestive heart failure in the general population: results of the Heinz Nixdorf Recall Study. Clin Res Cardiol. 2010 Mar;99(3):175-182. doi: 10.1007/s00392-009-0104-3
9. Blaha MJ, Whelton SP, Al Rifai M, et al. Rationale and design of the coronary artery calcium consortium: A multicenter cohort study. J Cardiovasc Comput Tomogr. 2017 Jan;11(1):54-61. doi: 10.1016/j.jcct.2016.11.004
10. Mhaimeed O, Dardari ZA, Khorsandi M, et al. Coronary Artery Calcium for Risk Stratification of Heart Failure Mortality: The Coronary Artery Calcium Consortium. J Card Fail. 2025 July;31(7):1005-1015. doi: 10.1016/j.cardfail.2024.10.437
11. De La Rosa AL, Mehta A, Hansen S, et al. Cardiac computed tomography imaging biomarkers for prediction of new-onset heart failure: Multi-ethnic study of atherosclerosis. J Cardiovasc Comput Tomogr. 2025 May;19(3):316-321. doi: 10.1016/j.jcct.2025.03.013
12. Sharma K, Al Rifai M, Ahmed HM, et al. Usefulness of Coronary Artery Calcium to Predict Heart Failure With Preserved Ejection Fraction in Men Versus Women (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol. 2017 Nov;120(10):1847-1853. doi: 10.1016/j.amjcard.2017.07.089
13. Hamid A, Yimer WK, Oshunbade AA, et al. Trajectory of C-Reactive Protein and Incident Heart Failure in Black Adults: The Jackson Heart Study. Circ Heart Fail [Internet]. 2024 Aug [cited 2025 Nov 3];17(8). Available from: https://www.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.123.011199. doi: 10.1161/CIRCHEARTFAILURE.123.011199
14. Ridker PM, Lei L, Louie MJ, et al. Inflammation and Cholesterol as Predictors of Cardiovascular Events Among 13 970 Contemporary High-Risk Patients With Statin Intolerance. Circulation. 2024 Jan 2;149(1):28-35. doi: 10.1161/CIRCULATIONAHA.123.066213
15. Ahmad MI, Chevli PA, Mirzai S, et al. Relationship between interleukin-6, coronary artery calcium and risk of heart failure: Insights from MESA. Am J Prev Cardiol. 2025 Dec;24:101310. doi: 10.1016/j.ajpc.2025.101310
16. Ladeiras-Lopes R, Araújo M, Sampaio F, Leite-Moreira A, Fontes-Carvalho R. The impact of diastolic dysfunction as a predictor of cardiovascular events: A systematic review and meta-analysis. Rev Port Cardiol. 2019 Nov;38(11):789-804. doi: 10.1016/j.repc.2019.03.007
17. Haddad F, Cauwenberghs N, Daubert MA, et al. Association of left ventricular diastolic function with coronary artery calcium score: A Project Baseline Health Study. J Cardiovasc Comput Tomogr. 2022 Nov;16(6):498-508. doi: 10.1016/j.jcct.2022.06.003
18. Nitta K, Kurisu S, Nakamoto Y, et al. Coronary Artery Calcium Is Associated with Left Ventricular Diastolic Function Independent of Myocardial Ischemia: Assessment by Myocardial Perfusion Single-Photon Emission Computed Tomography. Int Heart J. 2019 May 30;60(3):554-559. doi: 10.1536/ihj.18-355
19. Choi KH, Kang D, Lee SH, et al. Impact of coronary artery calcium on progression of diastolic dysfunction: a cohort study. BMC Med. 2025 Feb 28;23(1):130. doi: 10.1186/s12916-025-03956-9
20. Wada S, Iwanaga Y, Nakai M, Nakao YM, Miyamoto Y, Noguchi T. Significance of coronary artery calcification for predicting major adverse cardiovascular events: results from the NADESICO study in Japan. J Cardiol. 2023 Sept;82(3):172-178. doi: 10.1016/j.jjcc.2023.04.006
21. Carr JJ, Jacobs DR, Terry JG, et al. Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death. JAMA Cardiol. 2017 Apr 1;2(4):391. doi: 10.1001/jamacardio.2016.5493
22. Wakaki T, Takagi Y, Ono Y, Kato R, Abe K, Watanabe H. Prognostic value of coronary calcification detected via non-electrocardiogram-gated computed tomography in patients with cardiovascular disease: A retrospective cohort study. IJC Heart Vasc. 2025 Feb;56:101560. doi: 10.1016/j.ijcha.2024.101560
23. Onishi S, Fukuda A, Matsui M, et al. Association between the Suita Score and Body Composition in Japanese Adults: A Large Cross-Sectional Study. Nutrients. 2023 Nov 17;15(22):4816. doi: 10.3390/nu15224816
24. Hashimoto H, Nakanishi R, Mizumura S, et al. Prognostic values of coronary artery calcium score and 123I-BMIPP SPECT in patients with non-ischemic heart failure with preserved ejection fraction. Int J Cardiovasc Imaging. 2021 Dec;37(12):3573-3581. doi: 10.1007/s10554-021-02332-x
25. Ota K, Nakanishi R, Hashimoto H, et al. Association between coronary artery calcium score on non-contrast chest computed

tomography and all-cause mortality among patients with congestive heart failure. Heart Vessels. 2022 Feb;37(2):262-272. doi: 10.1007/s00380-021-01906-y
26. Naghavi M, Reeves A, Atlas K, et al. AI-enabled Cardiac Chambers Volumetry and Calcified Plaque Characterization in Coronary Artery Calcium (CAC) Scans (AI-CAC) Significantly Improves on Agatston CAC Score for Predicting All Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis [Internet]. In Review; 2024 [cited 2025 Oct 29]. Available from: https://www.researchsquare.com/article/rs-4433105/v1. doi: 10.21203/rs.3.rs-4433105/v1
27. Tian L, Jaeger BC, Scialla JJ, et al. Progression of Coronary Artery Calcification and Risk of Clinical Events in CKD: The Chronic Renal Insufficiency Cohort Study. Am J Kidney Dis. 2025 Jan;85(1):67-77.e1. doi: 10.1053/j.ajkd.2024.06.018
28. Sakuragi S, Ichikawa K, Yamada K, et al. An increase in the coronary calcification score is associated with an increased risk of heart failure in patients without a history of coronary artery disease. J Cardiol. 2016 Apr;67(4):358-364. doi: 10.1016/j.jjcc.2015.06.014
29. Kitjanukit S, Kuanprasert S, Suwannasom P, Phrommintikul A, Wongyikul P, Phinyo P. Coronary artery calcium (CAC) score for cardiovascular risk stratification in a Thai clinical cohort: A comparison of absolute scores and age-sex-specific percentiles. Heliyon. 2024 Jan;10(1):e23901. doi: 10.1016/j.heliyon.2023.e23901
30. Singh P, Hoori A, Freeze J, et al. Leveraging calcium score CT radiomics for heart failure risk prediction. Sci Rep. 2024 Nov 6;14(1):26898. doi: 10.1038/s41598-024-77269-x
31. Elnagar B, Habib M, Elnagar R, Khalfallah M. The value of coronary calcium score in predicting clinical outcomes in patients with chronic coronary syndrome. BMC Cardiovasc Disord. 2024 Oct 17;24(1):567. doi: 10.1186/s12872-024-04157-7
32. Abunassar JG, Yam Y, Chen L, D'Mello N, Chow BJW. Usefulness of the Agatston Score = 0 to Exclude Ischemic Cardiomyopathy in Patients With Heart Failure. Am J Cardiol. 2011 Feb;107(3):428-432. doi: 10.1016/j.amjcard.2010.09.040
33. Lehmann N, Erbel R, Mahabadi AA, 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 Feb 13;137(7):665-679. doi: 10.1161/CIRCULATIONAHA.116.027034