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ORIGINAL ARTICLE

# Diagnostic Value of Coronary Artery Plaque Detected on Computed Tomography Coronary Angiography in Healthy Adults with Zero to Low Coronary Calcium Scores

Jong-Shiuan Yeh [1,2,3], Feng-Yen Lin [2,4], Yung-Ta Kao [4], Nai-Wen Tsao [5], Ming-Hsiung Hsieh [1,2], Hsiao Wen-Tien [6], Kuo-Gi Shyu [7,8], Jaw-Wen Chen [9], Nen-Chung Chang [2,4], Chun-Ming Shih [2,4**], Chun-Yao Huang [2,4*]

[1] Division of Cardiology, Taipei Medical University-Wan Fang Medical Center, Taipei, Taiwan
[2] Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3] Skirball Center for Cardiovascular Research, Cardiovascular Research Foundation, Orangeburg, NY, USA
[4] Division of Cardiology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan
[5] Division of Cardiovascular Surgery, Department of Surgery, Taipei Medical University Hospital, Taipei, Taiwan
[6] Department of Diagnostic Radiology, Taipei Medical University Hospital, Taipei, Taiwan
[7] Division of Cardiology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[8] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[9] Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan

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**Background:** We evaluated the predictive value of traditional Framingham Risk Score (FRS) for subclinical coronary plaque detected by computed tomography coronary angiogram (CTCA) in asymptomatic patients with zero to low coronary artery calcium (CAC) scores.
**Methods:** We assessed 167 asymptomatic Taiwanese patients (mean age, 57 ± 11.2 years) who underwent CTCA as part of a health check-up evaluation, and examined the association between FRS, serum biomarkers, and coronary plaque assessed by CTCA.
**Results:** Of 127 patients with CAC scores between <100 and zero, 55 (43%) had coronary artery atheroma. Among the possible predictors of coronary atherosclerosis, FRS was an independent predictor (relative risk 1.25, 95% confidence interval 1.05–1.50, $p < 0.05$). A receiver-operating-characteristic curve analysis revealed that FRS is a good indicator of the presence of coronary plaque. The area under the FRS curve was 0.70 ($p < 0.001$), with 62% sensitivity and 63% specificity. Furthermore, adding high-sensitivity C-reactive protein with FRS provides limited advantages for predicting the presence of coronary plaque over FRS alone.
**Conclusion:** FRS could be helpful for physicians in assessing coronary artery disease risk for more targeted therapy among patients with zero to low CAC scores.
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## 1. Introduction

Atherosclerosis is a progressive pathophysiological process that starts in childhood. Subclinical vulnerable plaque often leads to acute cardiovascular events. Several biomarkers have been established as predictors of cardiovascular events and subclinical atherosclerosis.[1,2] Among these biomarkers, high-sensitivity C-reactive protein (hsCRP) is most commonly used for cardiovascular risk stratification in a specific patient population.[3,4] As an anatomic marker of atherosclerosis, coronary artery calcification (CAC) detected by computed tomography (CT) has been correlated with the presence and extent of coronary atherosclerosis as well as with the risk of future cardiovascular events.[5–9] CAC has been applied extensively to detect subclinical coronary atherosclerosis, especially in asymptomatic adults with intermediate risk.[10] Besides calcium deposits, atherosclerotic plaque may contain several other components including a necrotic fatty core or fibrotic tissue. Thus, CAC used as a signal marker of coronary atherosclerosis may misdetect noncalcified coronary artery plaque. Furthermore, a low CAC score is less reliable in predicting plaque burden due to its

* Corresponding author. Chun-Yao Huang, Division of Cardiology, Department of Internal Medicine, Taipei Medical University Hospital, 110, No 250 Wu-Hsing St. Taipei, Taiwan.
** Corresponding author. Chun-Ming Shih, Division of Cardiology, Department of Internal Medicine, Taipei Medical University Hospital, 110, No 250 Wu-Hsing St. Taipei, Taiwan.
E-mails: (C.-M. Shih) <cmshih@tmu.edu.tw>, (C.-Y. Huang) <cyhuang@tmu.edu.tw>.

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association with high overall noncalcified coronary artery plaque. Previous studies using 64-slice CT coronary artery angiography (CTCA) revealed that up to 15% of patients with a zero CAC score have coronary plaque with stenosis.[11,12] Only age and sex are associated with the presence of coronary plaque in patients with a zero CAC score.[11,12] We need a more effective and systemic stratification tool for the prediction of subclinical coronary plaque in patients with zero or low CAC scores. Thus, in this study, we intended to examine the ability of a conventional risk stratification module, based on the Framingham Risk Score (FRS) equation and hsCRP, in predicting the presence of subclinical coronary atherosclerotic plaque detected on CTCA in low- to intermediate-cardiovascular-risk patients with zero to low CAC scores.

## 2. Methods

### 2.1. Patient enrollment

Between January 2010 and November 2010, 250 consecutive asymptomatic adults received physical check-up, including an estimation of the CAC scores followed immediately by 64-slice CTCA at Taipei Medical University Hospital, Taipei, Taiwan. At the time of imaging, a detailed medical history (coronary artery disease, diabetes, hypertension, and hypercholesterolemia) and medication records were gathered. Patients' peripheral blood samples were collected at the time of the initial screening evaluation and stored at −70°C (0–13 months).

We excluded patients with a history of coronary artery disease and diabetes, which is equivalent to coronary heart disease.[13] We recruited 167 patients who provided informed consent to undergo 64-slice CTCA and data collection, and our study was approved by the joint institutional review board of Taipei Medical University.

### 2.2. Framingham global coronary risk scores and hsCRP

We used Framingham sex-specific risk equations to predict the risk of developing severe coronary disease events (myocardial infarction or cardiovascular death) over the next 10 years, as described previously.[14] These traditional risk assessment scores were estimated based on the patients' description of their lipid profile, smoking habit, age, and current blood pressure and whether they were receiving any antihypertensive therapy. We measured the hsCRP level with a particle-enhanced immunoturbidometric latex agglutination assay.[15] Testing was performed randomly by a technician who was blinded to all clinical and serologic data. The samples were run in duplicate on consecutive days, and the results were averaged.

### 2.3. CT technique (64-slice CTCA)

CTCA was performed using an electrocardiographic-gated 64-slice CT scanner (GE LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). We detected CAC and quantified the amount with a prospectively gated low-dose sequential CT scan of the heart.[16] We also performed a contrast-enhanced, retrospectively gated spiral CT scan covering the distance from the tracheal bifurcation to the diaphragm during a single inspiratory breath hold (6–10 seconds). We used a timing bolus sequence to detect the arrival of contrast material in the coronary artery. A 70 mL bolus of contrast agent (Optiray 350, 350 mg/mL, Mallinckrodt Pharmaceuticals, Montreal, QC, Canada) was injected into an antecubital vein at a flow rate of 4 mL/s, followed by a saline chaser bolus. Patients who had heart rates over 70 beats per minute prior to the CT scan received oral beta-blocker therapy (propranolol 10–50 mg) 30 minutes prior to the CT scan, if not contraindicated. Images were reconstructed retrospectively from the mid- to the end-diastolic phase according to electrocardiography gating. Other reconstruction parameters for slice thickness, field of view, and convolution kernel were described previously.[17–20] The CAC scores and atheromas on the vessel wall were then analyzed.

### 2.4. Image analysis of CAC scores

We used the SmartScore software package (Advantage Workstation 4.3, GE Healthcare, Milwaukee, USA) to determine the CAC score, which is based on the scoring algorithm of Agatston et al.[21] The total calcium burden in the coronary arteries was quantified (Figure 1). Coronary calcification was defined as any lesion with an area greater than 1 $mm^2$ and a peak intensity of greater than 130 Hounsfield units (HU). We determined CAC scores for the four main coronary arteries in all slices and summed them up to obtain the total score based on a previously published method.[22]

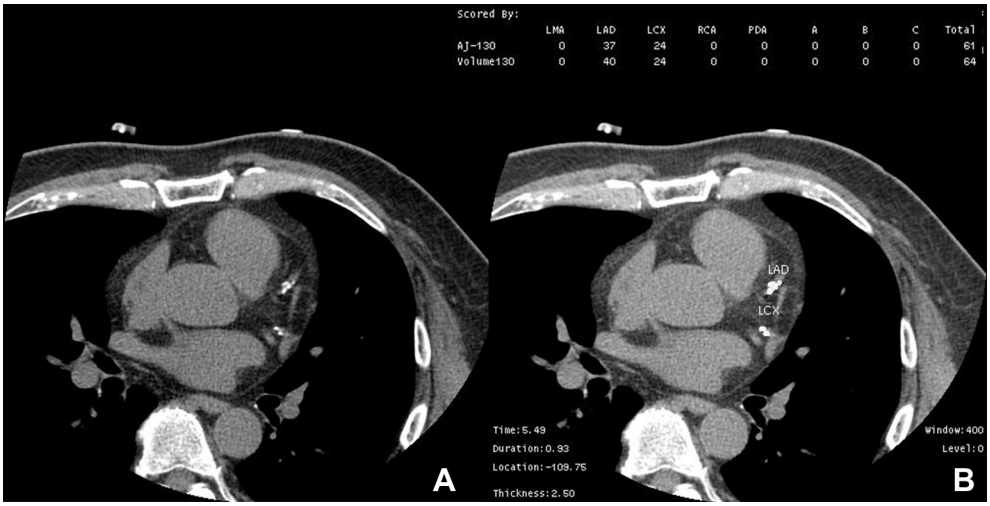


**Figure 1** (A) Axial view of the heart and coronary arteries. (B) Coronary calcifications were detected by computer automatically when the peak intensity is greater than 130 HU. In addition, based on the scoring algorithm of Agatston, the CAC scores were generated. CAC = coronary artery calcium; HU = Hounsfield unit.

### 2.5. Plaque analysis on a 64-slice CT scan

Two experienced radiologists who were blinded to the clinical information analyzed all scans independently using a 3D workstation (Brilliance; Philips Medical Systems, Best, The Netherlands). After making independent evaluations, a consensus interpretation was reached regarding a final CCTA diagnosis. For plaque differentiation, an optimal image display setting was chosen at a window between 600 HU and 900 HU and at a level between 40 HU and 250 HU. Plaque analyses were performed on longitudinal sections of straight multiplanar reconstructions (along the vessel center-line) and on their axial cross-sections (perpendicular to the vessel center-line) with a thickness of 1 mm using the Coronary Vessel Analysis protocol software on an Advantage Workstation 4.3 (GE Healthcare, Milwaukee, USA).[23] Coronary plaques were defined as structures of greater than or equal to 1 $mm^2$ in size (visible in at least one of the cross-sections) present on the vessel wall, which can clearly be distinguished from the vessel lumen and the surrounding tissue.

### 2.6. Statistical analysis

Data were expressed as mean ± standard deviation (SD) if normally distributed or as median (range) if otherwise. The mean levels of the variables were compared by an analysis of variance or continuous variables and by a $\chi^2$ test for categorical variables. Numerical variables and frequencies between the groups were compared using Student $t$ test, $\chi^2$ test, and/or Mann–Whitney $U$ test, as appropriate. Binary logistic regression analysis was used to determine the independent predictors of the end point in each group. To determine the predictive value of the FRS for the coronary plaque, we used receiver-operating-characteristic (ROC) curve analysis. Two models were built for the ROC analysis: FRS only and FRS with hsCRP. C-statistic was used to demonstrate the statistical difference between these two curves.[24,25] Differences between groups were considered significant for $p < 0.05$. All computations were performed using SPSS, version 15.1 (SPSS Inc., Chicago, IL, USA).

## 3. Results

Figure 1A presents the axial view of the heart and coronary arteries and Figure 1B demonstrates automatic detection of coronary calcifications using computer. Figure 2 shows the ROC curves of hsCRP, FRS, and FRS with hsCRP for predicting coronary atherosclerotic plaque detected on CTCA. Table 1 lists the baseline characteristics of individuals with low CAC deposit. Table 2 compares the characteristics of individuals (with CAC scores between 0 and <100) with or without coronary artery plaque. Table 3 shows the multivariable logistic regression analysis of possible predictors of coronary plaque in patients with low CAC scores. Table 4 presents the ROC curve analysis results of different models and comparison of each model.

## 4. Discussion

Our current study demonstrated the correlation between FRS and the existence of coronary atherosclerotic plaque among asymptomatic adults with CAC scores ranging from zero to low values. FRS is also an independent predictor of coronary atheroma among patients with zero or low CAC scores. Among the various imaging modalities designed to assist in the investigation of subclinical atherosclerosis, detection of CAC scores by CT scanning has, undoubtedly, gained the most attention. Previous studies using intracoronary ultrasound have demonstrated the correlation between CAC and the existence of atherosclerotic plaque. CAC has been shown to be an independent predictor of coronary artery stenosis.[26] However, CAC detection by CT scanning still has limitations with respect to the discovery of atherosclerotic plaque. Using CTCA, Cheng et al[11] found that the prevalence of detectable noncalcified coronary artery plaque is 6.5% in patients with a CAC score of zero and 65.2% in those with CAC scores <100. Our study also suggested that 43% of patients (Table 1) with zero to low CAC scores have coronary plaques, either calcified or noncalcified, as found on CTCA. This current work and our previous study suggest that CAC might be less reliable in predicting coronary plaque in those with zero to low CAC scores. Although patients with zero to low CAC scores are viewed as a group at low risk for cardiovascular events, those with existing coronary plaque still require aggressive lifestyle modification or medical intervention to prevent the progression of atherosclerosis and future coronary events.

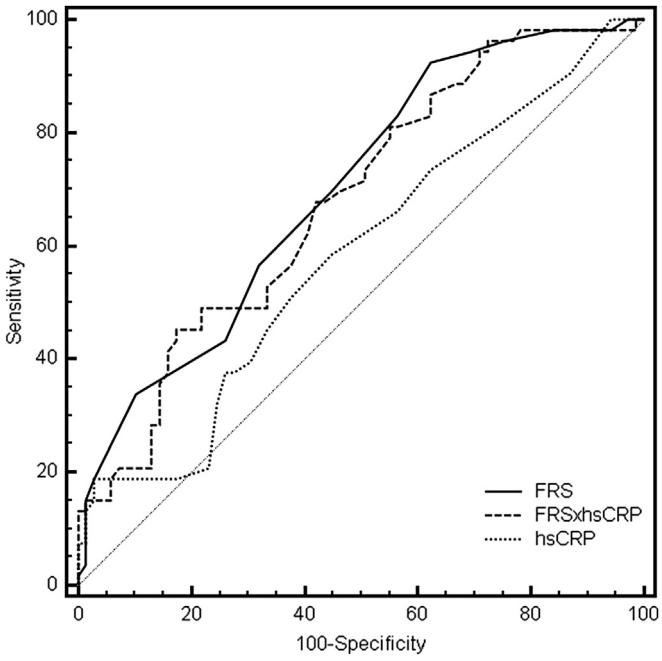


**Figure 2** Receiver-operating-characteristic curve of hsCRP, FRS, and FRS with hsCRP for the prediction of coronary atherosclerotic plaque at computed tomographic coronary angiogram. FRS = Framingham Risk Score; hsCRP = high-sensitivity C-reactive protein.

**Table 1** Baseline characteristics of individuals with low coronary artery calcium deposit

| Variables | Coronary artery calcium score <100 ($n$ = 127) |
|---|---|
| Age (y) | 54.3 ± 9.8 |
| Male/female | 76/51 |
| Hypertension | 31 (24) |
| Smoking | 16 (12.6) |
| Body mass index ($kg/m^2$) | 24.6 ± 3.5 |
| Systolic blood pressure (mmHg) | 122.9 ± 12.8 |
| Diastolic blood pressure (mmHg) | 71.8 ± 10.7 |
| Fasting blood glucose (mg/dL) | 81.3 ± 15.8 |
| Total cholesterol (mg/dL) | 219.2 ± 34.9 |
| Total triglyceride (mg/dL) | 152.3 ± 89.8 |
| Low-density lipoprotein cholesterol (mg/dL) | 146.9 ± 34.5 |
| High-density lipoprotein cholesterol (mg/dL) | 42.9 ± 13.9 |
| Creatinine (mg/dL) | 1.1 ± 0.2 |
| Framingham Risk Score | 5.6 ± 3.5 |
| High-sensitivity C-reactive protein (mg/dL) | 0.13 ± 0.28 |
| Patients without coronary artery calcium deposit | 84 (66) |
| Coronary artery calcium score | 8.50 ± 17.45 |
| Presence of coronary artery plaque | 55 (43) |

Data are expressed as mean ± SD or $n$ (%).

**Table 2** Comparison of the characteristics of individuals (with coronary artery calcium scores between 0 and <100) with or without coronary artery plaque

| Variables | Without coronary plaque ($n = 72$) | With coronary plaque ($n = 55$) |
|---|---|---|
| Age (y) | 53.1 ± 10.7 | 55.8 ± 8.3 |
| Male/female | 40/32 | 36/19 |
| Hypertension | 15 (21) | 16 (29) |
| Smoking | 6 (8.3) | 10 (18.2) |
| Body mass index (kg/m$^2$) | 24.3 ± 3.6 | 24.9 ± 3.3 |
| Systolic blood pressure (mmHg) | 121.2 ± 14.9 | 124.8 ± 9.6 |
| Diastolic blood pressure (mmHg) | 70.6 ± 11.3 | 73.1 ± 9.8 |
| Fasting blood glucose (mg/dL) | 80.8 ± 15.6 | 81.8 ± 16.3 |
| Total cholesterol (mg/dL) | 209.4 ± 27.6 | 229.1 ± 38.8* |
| Total triglyceride (mg/dL) | 132.9 ± 78.6 | 170.9 ± 96.4* |
| Low-density lipoprotein cholesterol (mg/dL) | 139.3 ± 29.6 | 154.2 ± 37.5* |
| High-density lipoprotein cholesterol (mg/dL) | 44.9 ± 14.3 | 41.0 ± 13.2 |
| Creatinine (mg/dL) | 1.1 ± 0.2 | 1.1 ± 0.2 |
| Framingham Risk Score | 4.5 ± 3.6 | 7.1 ± 3.1** |
| High-sensitivity C-reactive protein (mg/dL) | 0.09 ± 0.09 | 0.19 ± 0.41* |

Data are expressed as mean ± SD or *n* (%).
*$p < 0.05$.
**$p < 0.01$.

Although currently CTCA is accessible as a way to detect either calcified or noncalcified coronary plaque, it is invasive, and high-dose radiation and contrast medium exposure are unavoidable.[27] Currently, it is not recommend as a routine screening tool in intermediate cardiovascular risk population either.[10] Thus, we sought to determine whether the traditional coronary risk stratification protocols are usable for coronary plaque prediction in patients with zero to low CAC scores. Previous studies showed that only gender and age might be correlated with subclinical coronary plaque presentation in patients with zero or low CAC scores.[28] In our study, we showed that although hsCRP is higher in patients with zero to low CAC scores (Table 4) and coronary artery plaque, this association is not independent of other traditional cardiovascular risk factors, as revealed by multivariate analysis. However, hsCRP level has been proved to be associated with cardiovascular events in patients with intermediate to high cardiovascular risk.[29] Some controversy remains regarding the relationship between inflammation markers, especially hsCRP, and subclinical atherosclerotic plaque in low-cardiovascular-risk asymptomatic population.[30] The possible rational might be that hsCRP presents the inflammation and stability of atherosclerotic plaque in high-cardiovascular-risk patients. In those with low cardiovascular risk, atherosclerotic plaques are more stable and have less inflammation, so hsCRP might not correlated with the formation of these plaques. Our study demonstrated that traditional FRS may have the potential to predict coronary plaque in asymptomatic patients with zero to low CAC scores. In addition, in our study population, combined FRS and hsCRP may not be advantageous for predicting coronary plaque when compared to FRS alone.

**Table 3** Multivariable logistic regression analysis of possible predictors of coronary plaque in individuals with low coronary calcium scores

| Variable | Relative risk | 95% confidence interval |
|---|---|---|
| Framingham Risk Score | 1.252 | 1.048–1.496* |
| Body mass index | 1.050 | 0.887–1.242 |
| Fasting glucose | 1.008 | 0.979–1.039 |
| Total triglyceride | 1.004 | 0.997–1.011 |
| Total cholesterol | 1.023 | 1.000–1.047 |
| Serum creatinine | 4.375 | 0.462–41.417 |
| High-sensitivity C-reactive protein | 3.135 | 0.308–31.872 |

*$p < 0.05$.

**Table 4** Receiver-operating-characteristic curve analysis results of different models and comparison of these models

| Variable | Area under the curve | Standard error | 95% confidence interval |
|---|---|---|---|
| FRS* | 0.70 | 0.046 | 0.612–0.778 |
| hsCRP | 0.58 | 0.051 | 0.489–0.666 |
| FRS/hsCRP* | 0.68 | 0.053 | 0.588–0.757 |

*$p < 0.05$.
FRS = Framingham Risk Score; hsCRP = high-sensitivity C-reactive protein.

There are some limitations to this study. The study population is relatively small in size, and the results are therefore applicable only to a specific population with low to intermediate cardiovascular risk. In addition, this study is cross-sectional in design, and the relationship between FRS, the existence of plaque in low and zero CAC patients, as well as in long-term cardiovascular prognosis deserves further investigation.

In conclusion, although zero and low CAC scores are viewed as signs of low risk for future cardiovascular events, this condition can by no means exclude the possibility of the existence of plaque and further cardiovascular events. FRS may be helpful for physicians in the assessment of coronary artery disease risk among patients with zero and low CAC scores for more targeted therapy.

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