Atherosclerosis

Combined Framingham Risk Score and Coronary Artery Calcium Score Predict Subclinical Coronary Plaque Assessed by Coronary Computed Tomography Angiogram in Asymptomatic Taiwanese Population

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Background: We sought to determine the predictive value of the combined traditional Framingham risk score (FRS) and coronary artery calcium score (CACS) for subclinical coronary plaque detected by computed tomography coronary angiogram (CTCA) in asymptomatic subjects.

Method: We evaluated 167 asymptomatic Taiwanese subjects (mean age, 57 ± 11.2 years), who underwent CTCA as part of a health evaluation. We examined the associations between FRS, CACS, serum biomarkers, and coronary plaque assessed by CTCA.

Results: Out of 167 subjects in the study, 95 had coronary artery atheroma. Of those possible predictors for coronary atherosclerosis, both FRS and CACS were independent predictors for the presence of coronary plaque [relative risk (RR): 1.29, 95% confidence interval (CI): 1.07-1.54, p = 0.006 and RR: 1.42, 95% CI: 1.16-1.75, p = 0.001, respectively]. Receiver operating characteristics curve analysis revealed that CACS and FRS were indicators of the presence of coronary plaque. The area under the curve for FRS and CACS was 0.729 and 0.889, respectively (p < 0.001). Furthermore, the area under the curve for combination of FRS and CACS was 0.936 (95% CI: 0.887-0.969, p < 0.001), and this combination provided a better diagnostic advantage than either FRS or CACS alone (p < 0.001 and p = 0.012 by C-statistic, respectively).

Conclusions: In asymptomatic Taiwanese subjects with low to intermediate cardiovascular risk, both FRS and CACS were independently related to subclinical atherosclerosis. A combined FRS and CACS evaluation improved the efficacy of prediction for atherosclerotic plaque burden.

Key Words: Atherosclerosis ● Computed coronary tomography angiogram ● Coronary artery calcium score ● Framingham risk score ● Subclinical coronary plaque

INTRODUCTION

Atherosclerosis is a pathophysiological process that progresses from childhood. Subclinical vulnerable plaque often leads to acute cardiovascular events. Therefore, effective and noninvasive means of precisely detecting early subclinical coronary artery disease may aid in providing a more targeted preventive therapy.

Several biomarkers have been reported as predictors of cardiovascular events and subclinical atheroscle-

rosis.[1,2] Among these, high sensitivity C-reactive protein (hsCRP) is most commonly used for cardiovascular risk stratification in this specific patient population.[3,4] Furthermore, 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 for detecting subclinical coronary atherosclerosis, especially in asymptomatic adults with intermediate cardiovascular risk.[10] However, in addition to calcium deposits, atherosclerotic plaque may contain several other components, including a necrotic fatty core or fibrotic tissue. Thus, the use of CAC alone as a signal of coronary atherosclerosis may mean that some non-calcified coronary artery plaques have been missed; furthermore, a low coronary calcium score (CACS) is less reliable for predicting plaque burden due to its association with high overall non-calcified coronary artery plaque. Previous studies using a 64-slice CT coronary artery angiography (CTCA) revealed that up to 15% of patients with a low CACS had coronary plaque with stenosis.[11,12] The prognostic predictive potential of coronary plaque detection by CTCA has also been demonstrated in patients with suspected or known coronary artery disease.[13] Thus, a more effective and systemic stratification tool for the prediction of subclinical coronary plaque in asymptomatic subjects is warranted. Therefore, we examined the role of a conventional risk stratification module based on the CACS, the Framingham risk score (FRS) equation, and hsCRP for predicting the presence of subclinical coronary atherosclerotic plaque with CTCA in subjects with low to intermediate cardiovascular risk.

MATERIALS AND METHODS

Patient enrollment

Between January 2010 and November 2010, 250 consecutive asymptomatic Taiwanese adults underwent health screening during which patient CACS was determined, and was followed immediately by a 64-slice CTCA at Taipei Medical University Hospital. At the time of imaging, the patient's detailed medical history (coronary artery disease, diabetes, hypertension, and hyper-

cholesterolemia) and medication usage were recorded. Serum was collected at the time of the initial screening evaluation and stored at -70 °C (for 0-13 months).

In order to focus our study on the low to intermediate cardiovascular risk population, we excluded patients with a history of coronary artery disease and diabetes, which is a coronary heart disease equivalent.[14] In total, 167 subjects were recruited for the study. All screened individuals provided their informed consent to undergo a 64-slice CTCA and data collection, and our study received approval from the Human Investigations Committee.

Framingham global coronary risk scores and high sensitivity C-reactive protein

Framingham sex-specific risk equations were used to predict the risk of developing severe coronary disease events, such as myocardial infarction or cardiovascular death, in the next 10 years as previously described.[15] These traditional risk assessment scores were estimated based on the subject's description of their reported lipid profile, smoking habits, age, current blood pressure, and whether they were receiving antihypertensive therapy. Measurement of the hsCRP level was performed with a particle-enhanced immunoturbidimetric latex agglutination assay.[16] Testing was performed in random order by a technician who was blinded to all clinical and serologic data. The samples were run in duplicate on consecutive days, and an average of the results was calculated.

A 64-slice CT technique

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 using a prospectively gated low-dose sequential CT scan of the heart.[17] A contrast-enhanced, retrospectively gated spiral CT scan covering the distance from the tracheal bifurcation to the diaphragm during which a single inspiratory breath hold (6-10 seconds) was performed. We used a timing bolus sequence to detect the arrival of contrast material in the coronary artery. A bolus of contrast agent (Optiray 350, 350 mg/ml, Montreal, Quebec, Canada) was injected into an antecubital vein with a flow rate of 4 ml/s followed by a saline chaser bolus. Patients with heart rates over 70 beats per minute

before the CT scan received oral beta-blocker therapy (10-50 mg propranolol) 30 minutes prior to the CT scan if no contraindications were present. The images were retrospectively reconstructed from the mid- to the end-diastolic phase, according to ECG gating. Other reconstruction parameters for slice thickness, field of view, and convolution kernel were as previously described.[18-21] The CACS was then determined, and atheromas on the vessel walls were analyzed.

Imaging analysis of the CACS

We used the SmartScore software package (Advantage Workstation 4.3, GE Healthcare, Milwaukee, WI, USA) to determine the CACS, which is based on the scoring algorithm of Agaston et al.[22] By this measure, the total calcium burden in the coronary arteries was quantified. Coronary calcifications were defined as any lesion with an area > 1 mm^2 and a peak intensity > 130 Hounsfield units (HU). The CACS was determined for the 4 main coronary arteries in all slices and was summed up to generate the total score.[23]

Plaque analysis on a 64-slice CT scan

All scans were analyzed independently using a 3D workstation (Brilliance; Philips Medical Systems, Best, The Netherlands) by 2 experienced radiologists who were blinded to the clinical information. After making independent evaluations, a consensus interpretation was arrived at to obtain a final CCTA diagnosis. For plaque differentiation, an optimal image display setting was chosen at a window between 600 and 900 HU and at a level between 40 and 250 HU.[24] Plaque analyses were performed on longitudinal sections of straight multi-planar reconstructions (along the vessel center line) and 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, WI, USA). Coronary plaques were defined as structures ≥ 1 mm^2 (visible in at least 1 of the cross-sections) on the vessel wall that could be clearly distinguished from the vessel lumen and the surrounding tissue.[25] The degree of stenosis of the coronary artery was recorded as < 50% and > 50%.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) if normally distributed, or otherwise as the median (range). Mean levels of continuous variables were compared using analysis of variance (ANOVA) and the mean levels of categorical variables by χ^2 tests. Numerical variables and frequency between the groups were compared by Student's t test, χ^2-test, and/or by 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 coronary plaque, we used receiver operating characteristic (ROC) curve analysis. Two models were built for the ROC analysis (model 1: FRS only; model 2: FRS with CACS). The C-statistic was used to indicate the statistical difference between these 2 curves;[26] p < 0.05 was considered statistically significant. All computations were performed with SPSS version 15.1 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 167 asymptomatic subjects without coronary artery disease or myocardial infarction were recruited (mean age, 57 ± 11.2 years). Coronary atherosclerotic plaque was detected in 95 subjects using a 64-slice CCTA. Out of these 95 subjects, 17 had non-calcified plaques and the others had mixed-type coronary plaques. Table 1 shows the comparative demographic data of the subjects with and without coronary atherosclerotic plaque. In general, subjects with coronary atherosclerotic plaque were older. They also had higher systolic blood pressure, and higher total cholesterol, total triglyceride, and high sensitivity C-reactive protein levels. Notably, the FRS and CACS were also higher in these subjects. We also performed a multivariate logistic regression of possible predictors of coronary atherosclerosis. As Table 2 shows, CACS and FRS were independent predictors of the presence of coronary atherosclerotic plaque [relative risk (RR): 1.29, 95% confidence interval (CI): 1.07-1.54, p = 0.006 and RR: 1.42, 95% CI: 1.16-1.75, p = 0.001, respectively].

To test the prediction potential of FRS, CACS, and hsCRP for subclinical coronary atheroma in our study population, we used ROC curve analysis to test whether CACS, FRS, hsCRP, or FRS combined with CACS were indi-

Table 1. Comparison of individuals with or without coronary artery atherosclerotic plaque deposit

Variables	Without coronary artery atheroma (n = 72)	With coronary artery atheroma (n = 95)	p value
Age (years)	53.1 ± 10.7	59.2 ± 11.0	0.001
Male/female	40/32	68/27	0.04
Hypertension (%)	15 (21%)	31 (33%)	0.12
Hyperlipidemia (%)	21 (29%)	35 (37%)	0.32
Current smoking (%)	6 (9%)	17 (22%)	0.06
Body mass index (kg/m^2)	24.3 ± 3.6	25.0 ± 3.0	0.23
Systolic blood pressure (mmHg)	121.2 ± 14.9	129.1 ± 13.1	0.001
Diastolic blood pressure (mmHg)	70.6 ± 11.4	72.3 ± 9.7	0.32
Pulse rate (beats/min)	67.8 ± 10.8	66.3 ± 9.6	0.38
Fasting blood glucose (mg/dl)	80.8 ± 15.6	82.1 ± 19.5	0.70
Total cholesterol (mg/dl)	209.4 ± 27.6	222.1 ± 38.7	0.02
Total triglyceride (mg/dl)	132.9 ± 78.6	172.0 ± 101.7	0.02
Low-density lipoprotein cholesterol (mg/dl)	139.3 ± 29.6	146.2 ± 39.8	0.28
High-density lipoprotein cholesterol (mg/dl)	44.9 ± 14.3	41.4 ± 12.8	0.13
Creatinine (mg/dl)	1.1 ± 0.2	1.1 ± 0.2	0.42
High sensitive C-reactive protein (mg/dl)	0.09 ± 0.09	0.19 ± 0.39	0.01
Framingham risk score	4.5 ± 3.5	7.5 ± 3.2	< 0.001
Coronary artery calcium score	0.3 ± 1.4	187.2 ± 345.7	< 0.001

Values are means ± SDs or numbers of patients (percentages).

Table 2. Multivariable logistic regression analysis of possible predictors of coronary plaque

Variable	Relative risk	95% confidence interval	p value
Framingham risk score	1.29	1.07-1.54	0.006
Coronary calcium score	1.42	1.16-1.75	0.001
Body mass index	1.15	0.89-1.48	0.264
Fasting blood glucose	0.99	0.95-1.03	0.603
Total triglyceride	1.00	0.99-1.01	0.592
High sensitive C-reactive protein	1.34	0.14-124.50	0.884

cators of the presence of coronary atherosclerotic plaque. Figure 1 and Table 3 indicate that CACS, FRS, and FRS plus CACS are good indicators of the presence of coronary atherosclerotic plaque. The area under the FRS curve was 0.73 (95% CI: 0.65-0.79, p < 0.001) and that under the CACS curve was 0.89 (95% CI: 0.84-0.94, p < 0.001). In addition, the area under the curve for FRS combined with CACS was 0.93 (95% CI: 0.88-0.96, p < 0.001) and this provided a diagnostic improvement over either FRS or CACS alone according to the C-statistic[26] (p < 0.001 and p = 0.012).
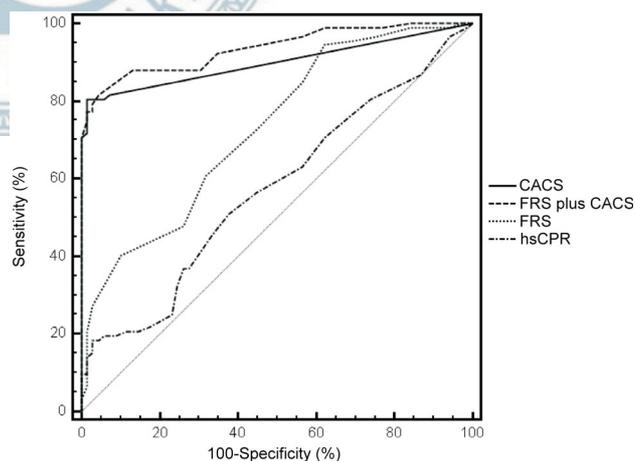

Figure 1. *The receiver operating characteristics (ROC) curve of high sensitivity C-reactive protein (hsCRP), Framingham risk score (FRS), coronary artery calcium score (CACS), and FRS combined with CACS for the prediction of coronary atherosclerotic plaque by computed tomography coronary angiogram.*

DISCUSSION

Our current study revealed a correlation between CACS, FRS, and the presence of coronary atherosclerotic

Table 3. The area under curve of possible coronary plaque predictors

Variables	Area under curve	95% confidence interval	p value
Framingham risk score + Coronary artery calcium score	0.93	0.89 to 0.97	< 0.001
Framingham risk score	0.73	0.65 to 0.80	< 0.001
Coronary artery calcium score	0.89	0.84 to 0.94	< 0.001
High sensitive C-reactive protein	0.57	0.49 to 0.65	0.17

plaque on a 64-slice CCTA among asymptomatic Taiwanese healthy adults. CACS and FRS were independent indicators of atherosclerotic plaque formation in the multivariate logistic regression analysis. When we combined the CACS and FRS scores for further risk stratification, the diagnostic advantage of the combination relative to FRS or CACS alone was demonstrated.

Among the various imaging modalities designed to assist in the investigation of subclinical atherosclerosis, detection of CAC 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 also been shown to be an independent predictor of coronary artery stenosis,[27] and to be correlated with endothelial dysfunction[28] and coronary plaque severity[29] in asymptomatic and symptomatic[30] Taiwanese populations. However, the protocol involved is invasive, and the use of high-dose radiation and exposure to contrast medium are unavoidable.[31] In addition, CAC detection by CT scanning still has limitations with respect to the discovery of atherosclerotic plaque. Using CTCA, Cheng et al. found that a low but detectable CACS is significantly less reliable in predicting the plaque burden due to its association with high overall non-calcified coronary artery plaque prevalence in outpatients with low to intermediate cardiovascular risk.[32] Some studies found that the presence of CAC provided an independent prognostic value for predicting the incidence of cardiovascular events that are incremental to measured coronary risk factors.[33] Hwang et al. discovered that 12% of asymptomatic subjects have non-calcified plaques; in their study, CACS was correlated with significant stenosis, but FRS was effective for predicting coronary artery disease only in symptomatic women.[34] Johnson et al. also reported that the detection of any CAC is highly sensitive and moderately specific for the screening of substantial atherosclerosis in subjects with a low FRS.[35] Our current study demonstrated that both the CACS and the FRS are independent predictors of subclinical coronary atherosclerosis in asymptomatic subjects with low to intermediate cardiovascular risk, and the combination of these 2 risk scoring systems could more precisely predict the presence of coronary atherosclerotic plaque.

In our study, we found that although hsCRP is higher in subjects with coronary artery plaque, this association is not independent from other traditional cardiovascular risk factors when examined by multivariate analysis. Controversy remains regarding the relationship between inflammatory markers, especially hsCRP, and subclinical atherosclerotic plaque.[36] Our study emphasizes the additional role of traditional risk stratification, such as the FRS, in the prediction of coronary plaque presentation alongside imaging. Additional studies should be performed to clarify the role of inflammatory markers in the progression of plaque burden.

Limitations

The study population was relatively small, and the results are only applicable for specific populations with low to intermediate cardiovascular risk. Furthermore, some other cardiovascular risk parameters, like creatinine, may not predict subclinical atherosclerosis plaque due to the small number of cases included in our study. A large-scale survey is required to investigate the predictive roles of other components in addition to FRS and CACS. Finally, this study was cross-sectional, and the relationships among FRS, the presence of plaques in subjects with low to intermediate cardiovascular risk, and long-term cardiovascular prognosis deserve further investigation.

CONCLUSION

In asymptomatic Taiwanese subjects with low to intermediate cardiovascular risk, both CACS and FRS are

correlated with the presence of coronary atherosclerotic plaque. By combining these 2 markers, we can improve our prediction of the presence of coronary plaque on a multi-slice CTCA. Consequently, more precise cardiovascular risk stratification and suitable primary prevention treatments may be applied in this population.

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CONFLICT OF INTEREST

None.

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