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ORIGINAL ARTICLE

The Role of High Sensitivity C-Reactive Protein and Coronary Artery Calcium as Predictors of the Long-term Prognosis in Men with Coronary Artery Disease

Zhong-Xuan Ye [1,4*], Po-Hsun Huang [2,4], Hsin-Bang Leu [3,4], Tao-Cheng Wu [2,4], Shing-Jong Lin [4,5], Jaw-Wen Chen [4,5]

[1] Division of Cardiovascular Medicine, School of Medicine, Taipei Medical University, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[2] Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[3] Division of Health Management, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[4] Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan
[5] Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan

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Purpose: Measurements of coronary artery calcium (CAC) and of high sensitivity *C*-reactive protein (hsCRP) are used to predict the risk of cardiovascular events in patients with coronary artery disease (CAD). The aim of our study was to investigate the hypothesis that combining the hsCRP level and CAC score can increase the predictive value of these parameters for future cardiovascular events in male patients with suspected CAD.

Methods: We included 90 male patients with stable angina. We measured their serum hsCRP and CAC scores by using electron-beam computerized tomography. These baseline parameters were correlated to the clinical cardiovascular events within the follow-up period.

Results: During the follow-up period of up to 50 months (median 27 months), 13 major cardiovascular events were recorded. In multivariate regression analysis, after being adjusted for conventional risk factors, hsCRP and CAC score, hsCRP level was the only independent predictor of cardiovascular events. Further analysis was performed among the four groups classified by CAC score (CAC score $\geq$100 or $<$ 100) and hsCRP (hsCRP $\geq$ 1 or $<$ 1 mg/l). The relative risk for the hsCRP $\geq$ 1 mg/l and CAC score $\geq$ 100 group, when compared with that for the hsCRP $<$ 1 mg/l and CAC score $<$ 100 group, showed a marked increase to 7.50 (95% confidence interval: 1.42–39.61, $p = 0.018$) for the cardiovascular events.

Conclusion: We concluded that risk stratification on the basis of both hsCRP level and CAC score might be of benefit to male patients with suspected CAD, as the combined use of these two markers allowed significantly more accurate prediction of cardiovascular events.

1. Introduction

Despite the availability of effective preventive measures and strategies, coronary artery disease (CAD) remains the leading cause of morbidity and mortality in most developed countries. Epidemiological study of CAD shows that its presentation and prognosis differ in men and women,[1] and the condition is more prevalent among the male population that it is in the female population. Current studies have shown that inflammation and coronary artery calcium deposits might contribute to the process of coronary artery atherosclerosis. High sensitivity C-reactive protein (hsCRP), an inflammation marker, has been shown to be a predictor of cardiovascular events in people with CAD.[2,3] Furthermore, the measurement of an individual's coronary artery calcium (CAC) score by computed tomography (CT) is a noninvasive means of assessing advanced atherosclerosis before the occurrence of clinical events.[4] However, the combination of these predictive markers, especially in men, in whom CAD is more prevalent that it is in women, needs more clarification. Therefore, we examined the hypothesis that the combined use of both the inflammation marker hsCRP and the CAC score might have better predictive value for future cardiovascular events in male patients than either parameter alone.

2. Methods

2.1. Study population

The study population comprised 90 consecutive male patients, with the symptoms of typical stable angina, who attended an

* Corresponding author. Division of Cardiology, Department of Medicine, Taipei Medical University-Wan Fang Hospital, No. 111, Section 3, Hsin-Long Road, Taipei, Taiwan.
E-mail: Z.-X. Ye <yvesyeh@gmail.com>

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outpatient department between January 2004 and August 2005. Coronary artery disease was suspected in these patients on the basis of evidence of myocardial ischemia, obtained by a noninvasive examination (a treadmill exercise test or myocardial perfusion scan). Patients were excluded if they had a history of previous cardiac intervention (including percutaneous coronary intervention, coronary artery bypass grafting, valve replacement surgery), myocardial infarction, hospitalization for heart failure, congenital heart disease, valvular heart disease, malignant hypertension, significant endocrine disease, hepatic disease (total bilirubin $>$ 1.6 mg/dl) or renal disease (serum creatinine $>$ 2.0 mg/dl), or if regular follow-up would not be possible. Before the study, a detailed review of each patient's chart and an interview were conducted to gather data on symptoms, medications, coronary risk factors, previous cardiac events, smoking status, exercise habits, and family history of CAD and other systemic diseases. Blood biochemistry was analyzed for lipid profiles, fasting sugar, uric acid and creatinine. All patients provided written informed consent. We recruited patients who agreed to undergo coronary artery calcification measurement and blood sampling.

2.2. Serum levels of hsCRP

For determination hsCRP levels we used a latex-enhanced immunophelometric assay (Dade Behring, Marburg, Germany). Each standard and each plasma sample was analyzed twice, and the mean values were used for all subsequent analysis.

2.3. Coronary artery calcium analysis

Coronary artery calcification was measured using an electron-beam CT scanner (Imatron C-150 LXP; Imatron Inc., South San Francisco, CA, USA) that was calibrated daily with air and water phantoms and twice monthly with contrast and resolution phantoms. Images were obtained using a 40–50-slice (3 mm thickness) protocol with image acquisition triggered to 60% to 80% of the electrocardiographic RR interval while respirations were held. Scans were interpreted in a blinded manner by an experienced radiologist using the Agatston scoring method.[5] A focus of coronary calcium was defined as the presence of four or more contiguous pixels with $>$ 130 Hounsfield units. Total CAC score was determined as the sum of individual scores from four major epicardial coronary arteries.[6]

Table 1 The comparison of baseline characteristics in male patients with or without later cardiovascular events

Variables	Male patients ($N = 90$)		
	Without events ($n = 77$)	With events ($n = 13$)	p
Age (y)	69.7 ± 12.00	72.5 ± 10.31	0.424
Body mass index	24.7 ± 3.17	23.6 ± 1.95	0.213
Hypertension	40 (52%)	10 (79%)	0.133
Diabetes mellitus	17 (22%)	3 (5%)	1.000
Smoker	15 (19%)	4 (31%)	0.356
Triglyceride (mg/dl)	129.3 ± 68.82	163.2 ± 141.21	0.412
Total cholesterol (mg/dl)	188.7 ± 35.36	185.5 ± 25.35	0.706
Low-density lipoprotein (mg/dl)	118.3 ± 34.66	101.0 ± 25.87	0.104
High-density lipoprotein (mg/dl)	44.7 ± 5.69	47.8 ± 28.18	0.597
Fasting blood glucose (mg/dl)	106.3 ± 27.57	104.3 ± 23.49	0.812
High sensitivity C-reactive protein (mg/l)	1.88 ± 0.26	3.75 ± 0.37	0.030
Coronary artery calcium score	358.9 ± 705.42	690.0 ± 819.76	0.131
Flow-mediated dilatation (%)	4.8 ± 2.70	3.5 ± 1.94	0.104
Nitrate-mediated dilatation (%)	14.2 ± 6.30	12.7 ± 6.07	0.428
Drug at enrollment			
Aspirin	41 (92.3%)	9 (100%)	0.757
Nitrate	25 (17.9%)	7 (63.2%)	0.356
Calcium-channel blockers	27 (46.2%)	9 (57.9%)	0.071
Beta-blockers	33 (46.2%)	6 (36.8%)	1.000
Angiotensin converting enzyme inhibitor	11 (69.2%)	4 (42.1%)	0.252
Statin	15 (43.6%)	3 (15.8%)	1.000

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

Table 2 Cardiovascular events during follow-up in 90 male patients with symptoms of typical angina at presentation

	Group 1 ($n = 25$)	Group 2 ($n = 20$)	Group 3 ($n = 21$)	Group 4 ($n = 24$)
Cardiac death	0 (0%)	0 (0%)	1 (5%)	1 (4%)
Myocardial infarction	0 (0%)	1 (5%)	0 (0%)	1 (4%)
Coronary revascularization	2 (8%)	1 (5%)	0 (0%)	6 (26%)
Cardiovascular events	2 (8%)	2 (10%)	1 (5%)	8 (35%)*

Data are presented as n (%); * $p < 0.05$ by χ^2 test; Group 1: CAC score $<$ 100, hsCRP $<$ 1 mg/l; Group 2: CAC score $<$ 100, hsCRP $\geq$ 1 mg/l; Group 3: CAC score $\geq$ 100, hsCRP $<$ 1 mg/l; Group 4: CAC score $\geq$ 100, hsCRP $\geq$1 mg/l.
CAC = coronary artery calcium; hsCRP = high sensitivity C-reactive protein.

2.4. Clinical follow-up for adverse cardiovascular events

The primary clinical end-point of this study was the occurrence of a major cardiovascular event. We contacted all participants by telephone periodically and also followed up their medical records regularly. For each patient, the occurrences of major cardiovascular events, including myocardial infarction, unscheduled percutaneous coronary intervention, emergency coronary artery bypass grafting, ischemic stroke, and peripheral artery revascularization, were recorded. Myocardial infarction was confirmed if ischemic symptoms were presented with elevated plasma cardiac enzyme levels or characteristic electrocardiograph changes, or both. The unscheduled coronary revascularization procedures (percutaneous coronary intervention or coronary artery bypass surgery) were confirmed by medical record review. Stroke was defined if there was a new neurologic deficit lasting for at least 24 h with definite image evidence of cerebrovascular accident by magnetic resonance imaging or CT scan.

2.5. Statistical analysis

Data were expressed as mean ± standard deviation (SD) for numeric variables and as number (percent) for categorical variables. The numerical variables and frequencies were compared by the Student t test and the χ^2 or Mann–Whitney U test, or both, as appropriate. Binary logistic regression and Cox regression analyses were performed to determine independent predictors of adverse cardiovascular events. The data were analyzed using SPSS software (version 12, SPSS Inc., Chicago, IL, USA). A p value of < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Patients' characteristics

The mean age of the 90 male participants was 70.1 ± 11.7 years. Fifty-five percent of participants had hypertension and 22% had diabetes mellitus. All of the patients were followed up, for up to 50

Table 3 Relative risk of cardiovascular events

Variable	Relative risk	95% confidence interval	p
CAC score $<$100, hsCRP $<$ 1 mg/l	1	–	–
CAC score $<$100, hsCRP $\geq$ 1 mg/l	2.52	1.14–7.97	0.052
CAC score $\geq$100, hsCRP $<$ 1 mg/l	1.99	0.56–7.12	0.288
CAC score $\geq$100, hsCRP $\geq$ 1 mg/l	7.5	1.42–39.60	0.018

CAC = coronary artery calcium; hsCRP = high sensitivity C-reactive protein.

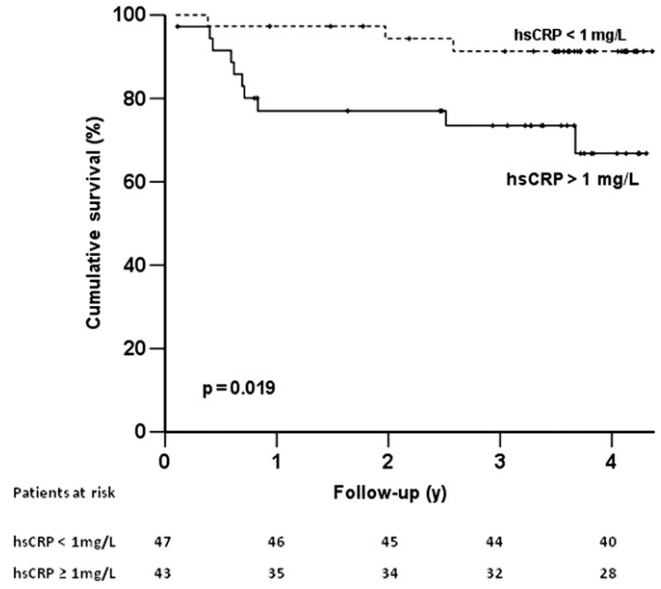

Figure 1 Kaplan–Meier curves of event-free survival for major cardiovascular events in male patients according to baseline hsCRP level. The cumulative survival rate was significantly reduced in individuals with baseline serum hsCRP level <1 mg/l ($p = 0.019$ by log-rank test).

months (median, 27 months). In total during follow-up there were 13 adverse cardiovascular events, including two cardiac deaths (2.5% of all patients), two nonfatal myocardial infarctions (2.5% of all patients) and nine ischemia-driven revascularizations (11.1% of all patients). No patients died from noncardiac causes. We divided our study participants into two groups according to their development of cardiovascular events. Table 1 shows a comparison of baseline characteristics, CAC score, and hsCRP values between patients with and without cardiovascular events. The patients who experienced cardiovascular events had higher triglyceride levels, more nitrate usage and less statin usage, although these differences were not statistically significant. They also had significantly higher hsCRP levels (3.75 ± 0.37 mg/dl versus 1.88 ± 0.26 mg/dl, $p = 0.03$, respectively). Additionally, we noted higher CAC scores in the study group with cardiovascular events, although the difference was not significant. We performed a multivariate Cox analysis to determine the prognostic value of conventional risk factors, hsCRP and CAC score. The baseline hsCRP level was the only predictive marker for future cardiovascular events in our group of male patients ($p = 0.015$).

3.2. Combined use of hsCRP and CAC score

To clarify the benefit of the combined use of hsCRP value and CAC score for predicting cardiovascular events, we stratified our study subjects into four groups for further analysis on the basis of their CAC score and hsCRP level (Group 1: hsCRP $<$ 1 mg/l, CAC score $<$ 100; Group 2: hsCRP $\geq$ 1 mg/l, CAC $<$100; Group 3: hsCRP $<$ 1 mg/l, CAC score $\geq$ 100; Group 4: hsCRP $\geq$1 mg/l, CAC score $\geq$ 100). As Table 2 shows, patients from Group 4 with hsCRP $\geq$1 mg/l and CAC score $\geq$ 100 had more cardiovascular events then those in other groups ($p < 0.05$). Furthermore, we compared the relative risk of cardiovascular events for these four groups; Table 3 shows that compared with hsCRP $<$ 1 mg/l and CAC score $<$ 100, the subjects with hsCRP $\geq$1 mg/l and CAC score $\geq$ 100 had the highest relative risk for cardiovascular events (relative risk 7.5, 95% confidence interval 1.4–39.6, $p = 0.018$).

To demonstrate the relationship between survival free of cardiovascular events and both the serum hsCRP level and CAC score, Kaplan–Meier analysis was performed for our study population. As shown in Figure 1, hsCRP $\geq$ 1 mg/l was an independent predictor for cardiovascular events ($p = 0.019$, by log-rank test). Furthermore, Figure 2 shows the patients with hsCRP $\geq$1 mg/l and CAC score $\geq$ 100 (Group 4) had significantly more cardiovascular events than those with hsCRP $<$ 1 mg/l and CAC score $<$ 100 (Group 1) ($p = 0.032$). No significant difference in cardiovascular event development was noted between patients in Group 2 and Group 3.

4. Discussion

In this small-cohort observational study, we demonstrated that in male patients with suspected myocardial ischemia, the combined

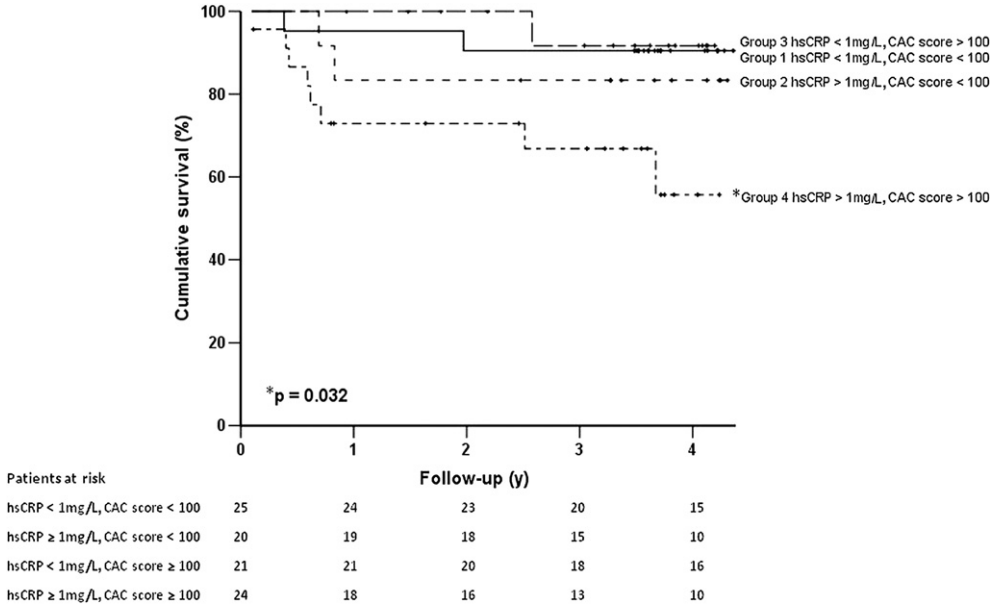

Figure 2 Kaplan–Meier curves of cumulative survival for major cardiovascular events in male patients according to hsCRP level and CAC score. The event-free survival rate was significantly lower in those with hsCRP $\geq$ 1 mg/l and CAC score $\geq$ 100 ($p = 0.032$ by log-rank test).

use of serum hsCRP level and CAC score can increase the ability to predict future cardiovascular events.

Numerous publications have demonstrated that both hsCRP, as a measure of inflammation, and CAC, as a measure of coronary plaque burden, can improve the assessment of cardiovascular event risk.[7,8] Blaha et al showed that CAC seems to further stratify risk in patients with hsCRP $\geq$ 2 mg/dl.[9] Möhlenkamp et al presented an improvement in coronary risk prediction and discrimination that was predominantly driven by CAC, although hsCRP appears to have a role, especially in individuals with a very low CAC score.[10] Our study could not prove a direct association between hsCRP and CAC, suggesting that systemic inflammation and subclinical coronary calcification may have different roles in the progression of coronary atherosclerosis.[11,12] This implies that CAC and hsCRP may be complementary markers for use in the prediction of cardiovascular risk. The study results suggested that enhanced vascular inflammation and increased CAC have a synergistic effect on coronary atherosclerosis. The combined use of serum hsCRP level and CAC score showed additional predictive ability for cardiovascular events in male patients with suspected CAD. In addition, we noted a trend toward higher serum total triglyceride level, more nitrate usage and less statin usage among those individuals who experienced cardiovascular events during follow up compared with those who did not. This suggests that that these factors may contribute to the cardiovascular events, although the differences were not statistically significant. After correcting for these factors with multivariate analysis, we still demonstrated the predictive value of hsCRP level and CAC score.

5. Conclusions

In the male population, the hsCRP level is an independent predictor of future cardiovascular events. The results of this study demonstrate that obtaining both an hsCRP level and a coronary artery calcification score permits more accurate identification of men at high risk of cardiovascular events than is possible using either parameter alone. More patients need to be recruited, and more pathophysiology studies conducted, to clarify the mechanism underlying the combined effect of coronary artery calcification and vascular inflammation in coronary atherosclerosis; in the meantime, more aggressive treatment strategies should be applied to those patients identified as being at high risk of cardiovascular events.

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