Coronary artery disease progression is associated with C-reactive protein and conventional risk factors but not soluble CD40 ligand

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BACKGROUND: Coronary artery disease (CAD) is a major cause of death worldwide. Epidemiological studies have documented conventional risk factors; however, no studies to date have addressed the roles of soluble CD40 ligand (sCD40L) and monocyte chemoattractant protein-1 (MCP-1), and there have been few reports on other novel risk factors in CAD progression. The aim of the present study was to explore the roles of novel and conventional risk factors in CAD progression.

METHODS: Patients with stable angina pectoris who underwent repeat coronary angiograms and had serum samples at the time of their first catheterization between March 1999 and January 2004 were enrolled. Those who had progression of coronary atherosclerosis were classified into the progression group (n=66). Those who did not have CAD progression were classified into the nonprogression group (n=124).

RESULTS: There were more cases of diabetes mellitus (36% versus 20%; $P=0.024$) and more men (92% versus 81%; $P=0.040$) in the CAD progression group than in the nonprogression group, respectively. The progression group also had poorer lipid profiles than the nonprogression group, including higher total cholesterol (188 ± 42 mg/dL versus 173 ± 39 mg/dL, respectively; $P=0.014$) and low density lipoprotein cholesterol (122 ± 38 mg/dL versus 112 ± 36 mg/dL, respectively; $P=0.025$). In terms of inflammatory markers, progression patients had higher baseline high-sensitivity C-reactive protein (hs-CRP) concentrations ($P=0.018$), which was also related to the subsequent angiographic severity score changes; however, sCD40L (6182 ± 4352 pg/mL versus 6244 ± 4602 pg/mL; $P=0.961$), MCP-1 (427 ± 540 pg/mL versus 341 ± 128 pg/mL; $P=0.580$) and adhesion molecules concentrations were indifferent between the progression group and the nonprogression group, respectively. Using a multivariate logistical regression model, the ORs for predicting progression were 2.19 for diabetes mellitus, 2.04 for hypercholesterolemia and 1.52 for hs-CRP ($P<0.05$).

CONCLUSION: In the present study, only conventional risk factors, and particularly hs-CRP, were markers for predicting CAD progression. Novel risk factors, such as concentrations of sCD40L, MCP-1 and adhesion molecules, did not play significant roles.

Key Words: Adhesion molecules; CAD progression; CD40 ligand; CRP; Inflammatory markers; MCP-1

La progression de la coronaropathie s'associe à la protéine C réactive et aux facteurs de risque classiques, mais pas au ligand CD40 soluble

HISTORIQUE : La coronaropathie est une cause importante de décès de par le monde. Les études épidémiologiques ont documenté les facteurs de risque classiques. Cependant, aucune étude n'a encore porté sur les rôles du ligand CD40 soluble (lCD40s) et de la protéine chimioattractante monocytaire 1 (MCP-1), et peu de comptes rendus traitent d'autres nouveaux facteurs de risque de progression de la coronaropathie. La présente étude visait à explorer le rôle des facteurs de risque nouveaux et classiques dans la progression de la coronaropathie.

MÉTHODOLOGIE : Les patients atteints d'un angor stable qui ont subi des angiogrammes coronaires et des échantillons sériques au moment de leur premier cathétérisme entre mars 1999 et janvier 2004 ont participé à l'étude. Ceux dont l'athérosclérose coronarienne progressait étaient classés dans le groupe de progression (n=66). Ceux dont la coronaropathie ne progressait pas étaient classés dans le groupe sans progression (n=124).

RÉSULTATS : Il y avait plus de cas de diabète (36 % par rapport à 20 %; $P=0,024$) et plus d'hommes (92 % par rapport à 81 %; $P=0,040$) dans le groupe de progression de la coronaropathie que dans le groupe sans progression. Le groupe de progression présentait un profil lipidique moins reluisant que le groupe sans progression, y compris une élévation du cholestérol total (188 ± 42 mg/dL par rapport à 173 ± 39 mg/dL, respectivement; $P=0,014$) et du cholestérol à lipoprotéines de basse densité (122 ± 38 mg/dL par rapport à 112 ± 36 mg/dL, respectivement; $P=0,025$). Pour ce qui est des marqueurs inflammatoires, les patients en progression avaient de plus fortes concentrations de protéine C réactive de haute sensibilité (PCR-hs) en début d'étude ($P=0,018$), lesquelles étaient également reliées aux modifications subséquentes aux indices de gravité angiographique. Cependant les concentrations de lCD40s (6182 ± 4352 pg/mL par rapport à 6244 ± 4602 pg/mL; $P=0,961$), de MCP-1 (427 ± 540 pg/mL par rapport à 341 ± 128 pg/mL; $P=0,580$) et de molécules d'adhésion étaient semblables entre le groupe de progression et le groupe sans progression, respectivement. Au moyen d'un modèle de régression logistique multivarié, les RR pour prédire la progression étaient de 2,19 pour le diabète, de 2,04 pour l'hypercholestérolémie et de 1,52 pour le PCR-hs ($P<0,05$).

CONCLUSION : Dans la présente étude, seuls les facteurs de risque classiques, notamment la PCR-hs, étaient des marqueurs prédictifs de progression de la coronaropathie. De nouveaux facteurs de risque, comme les concentrations de lCD40s, de MCP-1 et de molécules d'adhésion, ne jouaient pas de rôle significatif.

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Coronary artery disease (CAD) is one of the leading causes of death and imposes a great burden on health care worldwide. Atherosclerosis is a disease that is initiated by disorder of lipid metabolism and deposition, leading to endothelial dysfunction; it is perpetrated by infiltration of inflammatory cells and migration of vascular smooth muscle cells (1,2). The well-documented conventional atherosclerotic risk factors are diabetes mellitus (DM), hypertension, elevated low density lipoprotein cholesterol (LDL-C), decreased high density lipoprotein cholesterol, obesity and cigarette smoking (3-5). In recent years, inflammatory markers, cytokines and adhesion molecules such as high-sensitivity C-reactive protein (hs-CRP), soluble CD40 ligand (sCD40L), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM-1) and platelet-selectin (P-selectin) have all been recognized to participate in processes of atherosclerosis development (6-10). Blood-circulating monocytes and lymphocytes adhere to vascular endothelial cells through VCAM-1, ICAM-1 and/or P-selectin, expressed at the surface of endothelium in the proatherogenic milieu. Monocytes become entrapped in the subendothelial space and transformed into tissue macrophages, releasing MCP-1 to attract more monocytes.

Clinical studies have shown increased release of MCP-1 in acute coronary syndrome and the subgroup with highest expression of MCP-1 has the worst prognosis (11). In addition, Cipollone et al (12) reported that increased expression of MCP-1 was associated with restenosis after angioplasty. Recently, studies have disclosed an important receptor, CD40, and its counterpart, CD40L, in atherosclerosis development and plaque destabilization, mediated by production of reactive oxygen species, enhanced MCP-1, adhesion molecule, tissue factor and metalloproteinase expression (9,13). Increased sCD40L was observed in patients with hypercholesterolemia, diabetes and acute coronary syndrome (9,14,15). Studies found that elevated sCD40L in acute coronary syndrome is associated with increased risk of death or recurrent infarction (10,16). In addition, Mezzetti et al (17) reported that the preprocedural level of sCD40L is predictive of enhanced immune response and restenosis after angioplasty.

However, no studies to date have addressed the roles of sCD40L and MCP-1, and there have been few reports on novel risk factors in CAD progression, especially in an Asian population. Herein, we conducted a study to investigate these questions.

METHODS

Study population

A Windows 2000 (Microsoft Corp, USA)-based cardiac catheterization report databank has recently been established at Taichung Veterans General Hospital (Taichung, Taiwan), using the hospital information system data stored in the mainframe and containing all of the angiographic report data for the past 12 years. In addition, a serum databank consisting of data from all of the patients who underwent different types of cardiac catheterization and were willing to donate their blood samples for academic use was established in March 1999. The present study was part of the projects using these two databanks to investigate unresolved and challenging cardiovascular issues. During the study period from March 1999 to January 2004, there were 11,200 coronary angiogram procedures undertaken at the

catheterization laboratories. Among them, 1566 patients underwent more than one procedure for various reasons. Patients with a diagnosis of unstable angina or acute myocardial infarction at their first (index) admission were precluded, as were those who received coronary angiographic studies for cardiogenic shock or cardiomyopathy with heart failure. Patients who had acute infection or systemic inflammation disorders such as connective tissue disease were also excluded from the study. Those who had a history of coronary revascularization before the first (index) coronary angiogram in the study period were excluded. Patients who had severe heart failure, surgery, advanced renal insufficiency or cerebrovascular events in the two months before the index coronary angiograms were also excluded. Patients who already had significant triple-vessel disease at baseline were also precluded because of difficulty in defining further disease progression. Those who progressed only within the original diseased vessel were excluded to avoid confusion with in-segment restenosis of the precedent interventions. A total of 233 patients with angiographic studies for noncomplicated, stable angina recruited from the angiographic databank were then queried in the serum databank for the availability of serum samples at the first (index) coronary angiographic study. Finally, 190 patients met these inclusion criteria and were recruited into the present study.

Angiographic definition

The complete coronary angiogram was reviewed and angiographic measurements were made on a dedicated workstation with software for quantitative analysis of angiograms (Philips Inturis Suite, R2.2, Philips Medical Systems, USA). Patients with coronary angiograms showing normal or less than 50% diameter stenoses were classified as normal. Patients with more than 50% diameter stenoses in one of the three major coronary arteries and their major branches were classified as having significant CAD. A modified Gensini score was used for evaluating the coronary severity on the baseline and follow-up angiograms (18,19). To summarize this scoring system, five points were given for left main lesion; 2.5 points for proximal left anterior descending artery (LAD) or left circumflex (LCX); 1.5 points for mid-segment LAD; one point for distal segment of LAD, first diagonal branch, LCX obtuse marginal branch or right coronary artery, and 0.5 points for second diagonal branch or LCX posterolateral branch. The severity score at follow-up angiogram added up the original score at index angiogram plus the newly increased score. The numbers of diseased vessels at the follow-up was also calculated according to this algorithm. Patients who progressed from normal angiogram to CAD or from documented baseline CAD to new lesion(s) in a different vessel within this five-year period were classified into the progression group. Those who had normal angiograms or similar CAD lesions at the first and following admissions were classified into the nonprogression group.

Definition of conventional risk factors for atherosclerosis

Hypertension was defined as systole pressure more than 140 mmHg or diastole pressure more than 90 mmHg after multiple measurements in a sitting position at rest, or patients already on antihypertensive medication. DM was defined as fasting blood sugar more than 126 mg/dL on two occasions, or as patients already on oral hypoglycemic agents or insulin shots. Hypercholesterolemia was defined as total cholesterol more than 200 mg/dL or LDL-C more than 130 mg/dL, or as patients already on statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) treatment.

TABLE 1
Baseline demographic data of progression and nonprogression groups

	Progression (n=66)	Nonprogression (n=124)	P
Sex, n (men/women)	61/5	100/24	0.040
Age, years (mean $\pm$ SD)	65 $\pm$ 12	67 $\pm$ 10	0.554
Diabetes mellitus, n (%)	24 (36)	25 (20)	0.024
Hypertension, n (%)	49 (74)	86 (69)	0.507
Smoking, n (%)	28 (42)	37 (30)	0.123
Months between CAG (mean $\pm$ SD)	20 $\pm$ 13	20 $\pm$ 13	0.971
Use of statin therapy, n (%)	22 (33)	40 (32)	0.873
Use of ACEI therapy, n (%)	25 (38)	42 (34)	0.634
Use of acetylsalicylic acid, n (%)	55 (83)	100 (81)	0.702

ACEI Angiotensin-converting enzyme inhibitor; CAG Coronary angiogram

sCD40L, MCP-1, hs-CRP and adhesion molecule measurements

All serum samples were stored at -70°C until use. These blood samples were drawn from the antecubital vein from 07:00 to 08:00 after overnight fasting and before angiographic procedures. The adequately sized aliquots of serum samples of all enrolled patients were thawed and analyzed in a single batch for circulating sCD40L, MCP-1, hs-CRP, ICAM-1, VCAM-1 and P-selectin levels. Serum triglyceride and cholesterol concentrations were assayed by an enzymatic method using commercial kits (WAKO, Japan). The high density lipoprotein cholesterol level was determined in the supernatant of plasma after magnesium chloride-phosphotungstic precipitation of apolipoprotein B-containing lipoproteins. The LDL-C concentration was estimated by the formula of Friedewald et al (20). The serum hs-CRP level was determined by particle-enhanced immunoturbidimetry (latex microparticles sensitized with Duck anti-CRP IgY kit, Good Biotech Corp, Taiwan). Serum sCD40L, MCP-1, ICAM-1, VCAM-1 and P-selectin concentrations were all measured by ELISA (R&D Systems Inc, USA).

Statistical analysis

Continuous variables are expressed as means $\pm$ SDs and categorical data are expressed as percentages. Differences in continuous variables between progression and nonprogression groups were assessed by independent Student's *t* tests or Mann-Whitney U tests as appropriate. Categorical variables were compared using χ^2 test with Yate's correction or Fisher's exact test. hs-CRP values were analyzed in tertiles using χ^2 tests. The upper boundary of the lowest tertile was 0.084 mg/L, and the lower boundary of the highest tertile was 0.317 mg/L. The independent predictors of CAD progression were further assessed by binary logistic regression model in which significant risk factors identified in univariate analysis were entered. A two-tailed $P < 0.05$ was considered statistically significant. The SPSS 12.1 statistical software package (SPSS Inc, USA) was used for all calculations.

RESULTS

Baseline demographic data

The baseline demographic data are listed in Table 1. The patient age (65 $\pm$ 12 and 67 $\pm$ 10 years; $P = 0.554$) and follow-up intervals between angiograms were similar between the progression and the nonprogression groups, respectively. Among the conventional risk factors, there was no difference in hypertension between the progression and the nonprogression

TABLE 2
Coronary angiographic findings in progression and nonprogression groups

	Progression (n=66)	Nonprogression (n=124)	P
Baseline			
Normal, n (%)	15 (23)	41 (33)	0.187
Coronary artery disease, n (%)	51 (77)	83 (67)	0.187
Single-vessel disease, n (%)	35 (53)	69 (56)	0.848
Left anterior descending artery, n (%)	14 (21)	51 (41)	
Left circumflex artery, n (%)	9 (14)	13 (10)	
Right coronary artery, n (%)	12 (18)	5 (4)	
Double-vessel disease, n (%)	14 (21)	14 (11)	0.105
Left main coronary disease, n (%)	3 (4.5)	0 (0)	0.041
Severity score (mean $\pm$ SD)	2.0 $\pm$ 1.3	1.6 $\pm$ 0.7	0.171
Follow-up			
Normal, n (%)	0 (0)	41 (33)	<0.001
Coronary artery disease, n (%)	66 (100)	83 (67)	<0.001
Single-vessel disease, n (%)	15 (23)	69 (56)	<0.001
Double-vessel disease, n (%)	35 (53)	14 (11)	<0.001
Triple-vessel disease, n (%)	16 (24)	0 (0)	<0.001
Left main coronary disease, n (%)	10 (15)	0 (0)	<0.001
Severity score (mean $\pm$ SD)	3.6 $\pm$ 2.2	1.6 $\pm$ 0.7	<0.001

groups, whereas DM prevalence (36% versus 20%; $P = 0.024$) and male sex (92% versus 81%; $P = 0.040$) were significantly higher in the progression group than in the nonprogression group, respectively. There was no difference in medication use, including acetylsalicylic acid, statins and angiotensin-converting enzyme inhibitors, during the follow-up period between the angiograms in the two groups.

Angiographic findings at baseline and follow-up in the progression and nonprogression groups

The proportions of patients with normal angiograms or CAD at baseline were not different between the progression and nonprogression groups (baseline CAD 77% versus 67%, respectively; $P = 0.187$) (Table 2). Furthermore, among the patients with CAD at baseline, the angiographic findings were similar between the two groups in terms of the percentages of patients with single- or double-vessel diseases as well as the modified Gensini severity score (2.0 $\pm$ 1.3 in the progressive group versus 1.6 $\pm$ 0.7 in the nonprogressive group; $P = 0.171$). However, there were more cases of left main disease in the progression group (Table 2). A total of 45 (68%) and 75 (60%) patients in the progressive group and the nonprogressive group, respectively, received percutaneous coronary intervention at the index coronary procedures. The angiographic findings at follow-up are also presented in Table 2. The mean increase in severity score is 2.1 $\pm$ 1.6 between the two angiograms in the progression group, in contrast to no increase in the nonprogression group ($P < 0.001$).

sCD40L, MCP-1, hs-CRP and adhesion molecule levels in the progression and nonprogression groups

The progression group had poorer lipid profiles than the nonprogression group including higher total cholesterol (188 $\pm$ 42 mg/dL versus 173 $\pm$ 39 mg/dL, respectively; $P = 0.014$), LDL-C (122 $\pm$ 38 mg/dL versus 112 $\pm$ 36 mg/dL, respectively; $P = 0.025$) and triglyceride concentrations (170 $\pm$ 118 mg/dL

TABLE 3
Comparisons of serum biochemistry profiles, inflammatory cytokines and adhesion molecules between coronary artery disease progression and nonprogression groups

	Progression group (n=66)	Nonprogression group (n=124)	P
Fasting glucose, mg/dL (mean ± SD)	132±65	108±39	0.022
Triglyceride, mg/dL (mean ± SD)	170±118	139±84	0.016
HDL cholesterol, mg/dL (mean ± SD)	32±8	34±9	0.295
Cholesterol, mg/dL (mean ± SD)	188±42	173±39	0.014
LDL cholesterol, mg/dL (mean ± SD)	122±38	112±36	0.025
sCD40L, pg/mL (mean ± SD)	6182±4352	6244±4602	0.961
MCP-1, pg/mL (mean ± SD)	427±540	341±128	0.580
ICAM-1, ng/mL (mean ± SD)	247±119	222±73	0.282
VCAM-1, ng/mL (mean ± SD)	1165±593	1137±533	0.912
P-selectin, ng/mL (mean ± SD)	85±6	82±39	0.528

HDL High density lipoprotein; ICAM Intercellular adhesion molecule; LDL Low density lipoprotein; MCP-1 Monocyte chemoattractant protein-1; P-selectin Platelet-selectin; sCD40L Soluble CD40 ligand; VCAM Vascular cell adhesion molecule

TABLE 4
The relationship between high-sensitivity C-reactive protein (hs-CRP) tertiles and coronary artery disease progression and changes in severity scores

	hs-CRP tertiles (mg/L)			P
	<0.084	0.084–0.317	>0.317	
Coronary change, n (%)				
Progression (n=66)	17 (26)	18 (27)	31 (47)	0.018
Nonprogression (n=124)	47 (38)	44 (35)	33 (27)	
Increases in severity score, n (%)				
0 (n=124)	47 (38)	44 (35)	33 (27)	0.041
>0 to 1 (n=36)	8 (22)	9 (25)	19 (53)	
>1 to 2 (n=8)	2 (25)	4 (50)	2 (25)	
>2 to 5 (n=19)	7 (37)	5 (26)	7 (37)	
>5 (n=3)	0 (0)	0 (0)	3 (100)	

versus 139±84 mg/dL, respectively; $P=0.016$) (Table 3). Regarding inflammatory markers, the progression group had more patients in the upper hs-CRP tertiles ($P=0.018$) (Table 4). The mean (0.69 mg/L) and median (0.22 mg/L) hs-CRP values in the progression group were significantly higher than the mean (0.49 mg/L) and median (0.13 mg/L) hs-CRP values in the nonprogression group ($P=0.044$). Moreover, the baseline hs-CRP level was significantly associated with the increase in severity score at follow-up (Table 4). The subgroup of patients with increases in severity score of more than five fell in the upper hs-CRP tertile. However, there were no differences in the sCD40L (6182±4352 pg/mL versus 6244±4602 pg/mL; $P=0.961$), MCP-1 (427±540 pg/mL versus 341±128 pg/mL; $P=0.580$), ICAM-1 (247±119 ng/mL versus 222±73 ng/mL; $P=0.282$), VCAM-1 (1165±593 ng/mL versus 1137±533 ng/mL; $P=0.912$) and P-selectin (85±6 ng/mL versus 82±39 ng/mL; $P=0.528$) concentration between the progression group and the nonprogression group, respectively (Table 3).

Multivariate analysis of conventional and novel risk factors

The binary logistic regression model was used to analyze the impact of conventional and novel risk factors on the coronary atherosclerosis progression (Table 5). DM was an important predictor for coronary atherosclerosis progression ($OR=2.19$; $P=0.029$). Patients with an hs-CRP measurement in the highest

TABLE 5
Multivariate analysis of conventional and nonconventional risk factors for coronary artery disease progression

Risk factors	OR (95% CI)	Adjusted P
Sex (men/women)	3.51 (1.22 to 10.01)	0.020
High-sensitivity C-reactive protein (in tertiles)	1.52 (1.03 to 2.24)	0.036
Diabetes mellitus	2.19 (1.08 to 4.42)	0.029
Hypercholesterolemia	2.04 (1.07 to 3.91)	0.031

tertile were more at risk for CAD progression than the patients in the lowest tertile ($OR=1.52$; $P=0.036$). Hypercholesterolemia and male sex were also predictive of CAD progression.

DISCUSSION

In summary, we conducted a retrospective study to analyze different atherosclerotic risk factors in predicting progression of coronary atherosclerosis. Our results showed that sCD40L, MCP-1 and adhesion molecules did not play significant roles in predicting CAD progression in the general population. On the other hand, conventional risk factors as disclosed in the Framingham study (4,5), such as total cholesterol, LDL-C, DM and male sex, were predictive of CAD progression. In terms of the inflammatory markers, hs-CRP was significantly higher in the progression group and related to subsequent increases in CAD severity. To the best of our knowledge, this is the first study to investigate sCD40L and MCP-1 in CAD progression, and is also the only report on conventional and novel risk factors in CAD progression in an Asian population with complete long-term coronary angiographic follow-ups.

Recent studies have disclosed the significance of CD40, an important receptor in the tumour necrosis factor receptor family, and its counterpart CD40L in atherosclerosis development and plaque destabilization (9,13). When CD40L engages CD40 on atheroma-associated cells, the signalling results in upregulation of cellular adhesion molecules and MCP-1, promoting leukocyte recruitment. Activated macrophage releases matrix metalloproteinase and tissue factors, which promote plaque rupture and thrombogenicity. The activated platelets secondarily generate more sCD40L, reinforcing the inflammatory reaction (9,13). Endothelial dysfunction and the changes subsequent to the CD40L/CD40 pathway foster environments conducive to plaque progression and instability. The balance between the synthesis and breakdown of collagen, the predominant structural component of the fibrous cap, is shifted toward degradation by CD40 ligation. Studies have found that elevated sCD40L in acute coronary syndrome is associated with increased risk of death or recurrent infarction (10,16). One prospective study (21) showed that apparently healthy women with elevation of baseline sCD40L will have higher future cardiovascular event rate. However, de Lemos et al (22) reported sCD40L was not associated with subclinical atherosclerosis, as evaluated by the coronary calcium score of the electron beam computed tomography examination in a population-based study. Moreover, Verma et al (23) reported poor correlation between sCD40L and the calculated Framingham CAD risk score in a healthy, middle-aged male cohort. The aim of our study was to analyze the role of sCD40L in CAD progression. Our study was based on the retrospective coronary angiographic databank

to assess quantitative and chronological atherosclerosis progression. However, the result revealed no such significant association.

MCP-1 promotes transmigration of circulating monocytes into tissues and stimulates superoxide anion induction, cytokine production and adhesion molecule expression. Elevation of MCP-1 expression has been found in patients with acute coronary syndrome and heart failure (11,24). Patients who have increased MCP-1 expression also are prone to have restenosis after angioplasty (12). However, no studies to date have addressed the effect of MCP-1 on CAD progression. To the best of our knowledge, our study is the first to show that there is no significant association between CAD progression and serum circulating MCP-1 levels in the general population.

CRP, a classic acute-phase reactant and innate immune response protein, has several direct effects on vascular disease progression. CRP has the ability to bind and activate complement, induce expression of cell adhesion molecules and tissue factor, mediate LDL uptake by subendothelial macrophages, induce monocyte recruitment into the arterial wall and enhance production of MCP-1 (2). More than one dozen large-scale studies have demonstrated that baseline CRP levels predict future cardiovascular events (25-27). hs-CRP is a well-documented marker for predicting future coronary events in CAD patients or even healthy persons (25,26,28). Reports (27) have shown that it is a marker for development of coronary atherosclerosis. In our study with complete angiographic follow-up data to define coronary atherosclerosis progression, we showed that hs-CRP is a useful predictor for coronary lesion progression and that baseline hs-CRP level may be a useful marker for predicting the severity of angiographic progression, as measured by the increases in the modified Gensini severity score. In terms of adhesion molecules, several large studies (28-30) have shown that baseline ICAM-1 is a marker for

predicting future cardiovascular events in healthy people and that VCAM-1 is a predictor for the prognosis of CAD patients. ICAM-1, VCAM-1 and P-selectin were all reported to be elevated in acute coronary syndrome cases (31). Some studies (30-32) did report elevated cellular adhesion molecule levels in CAD and peripheral artery disease. However, our findings failed to show a significant association between adhesion molecule levels and CAD progression, at least in our study population. This negative finding is difficult to interpret. Our result may argue for the hypothesis that elevated adhesion molecule levels may be responsible for precipitation of acute presentation or clinical events that lead to clinical diagnosis and study enrollment, whereas adhesion molecules may not play a critical role in the underlying CAD progression. This needs to be investigated in future studies.

Many studies have tried to link the inflammatory markers, adhesion molecules or cytokines with coronary atherosclerosis progression (7,8). However, the results have been inconclusive (10,33). Our study results may provide useful information that these novel risk factors, except hs-CRP, may not be of significant value in assessing CAD progression or may not be the target of interventions to halt such progression. On the other hand, simply measuring hs-CRP, conventional risk factors and lipid profiles is needed to guide our clinical practices.

CONCLUSION

Our study found that novel biomarkers sCD40L, MCP-1 and adhesion molecules did not play significant roles in predicting CAD progression. However, conventional risk factors, and particularly hs-CRP, remained useful for predicting progression.

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