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Coronary Artery Disease

Dyslipidemia, Not Inflammatory Markers or Adipokines, Contributes Significantly to a Higher SYNTAX Score in Stable Coronary Artery Disease (from the Taichung CAD Study)

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Background: The SYNTAX score is an index of coronary severity used to determine the revascularization strategy of a patient. Our previous study confirmed that the SYNTAX score is helpful in predicting major adverse cardiac events in patients with stable coronary artery disease (CAD). However, few studies have comprehensively investigated the predictors for SYNTAX scores in patients with stable CAD, including conventional risk factors, lipid parameters, inflammatory markers and adipokines.

Methods: The coronary severities of 181 revascularization-naïve CAD patients who had received coronary angiograms were coded using SYNTAX scores. Conventional risk factors, inflammatory markers, and adipokines were investigated in order to determine the independent predictors for SYNTAX severity in the patients with stable CAD.

Results: The SYNTAX severity score was divided according to the generally accepted criterion (low: ≤ 22, intermediate-high: ≥ 23). In univariate comparisons, the intermediate-high SYNTAX group had a significantly higher low-density lipoprotein cholesterol (LDL-C) level compared to the low SYNTAX score group ($p = 0.046$). In binary logistic regression, LDL-C, total cholesterol, ratio of total cholesterol/high-density lipoprotein cholesterol (HDL-C) and pre-admission statin use were significant predictors for a higher SYNTAX severity score in the patients with stable CAD. In contrast, circulating adipokines, high-sensitivity C-reactive protein and HDL-C alone were not.

Conclusions: In revascularization-naïve CAD patients, dyslipidemia, including elevated LDL-C, total cholesterol, total cholesterol/HDL-C ratio and pre-index admission statin use, were associated with an intermediate-high SYNTAX severity score.

Key Words: Adiponectin • Cholesterol • Coronary artery disease • High-sensitivity C-reactive protein • Low-density lipoprotein cholesterol • SYNTAX score

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INTRODUCTION

Coronary severity scores have been designed to quantify lesion complexities, estimate the myocardium at risk and also guide the revascularization strategy.[1-4] The SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery (SYNTAX) score is a comprehensive angiographic scoring system that is derived from coronary anatomy and lesion characteristics. It was first applied in the SYNTAX trial to compare the revascularization strategy of percutaneous coronary

intervention (PCI) or coronary-artery bypass grafting.[2,5] It is typically categorized as being a low score (≤ 22), an intermediate score (23 to 32), or a high score (≥ 33).[2] The SYNTAX scoring system has been proven to be able to predict major adverse cardiovascular events (MACEs) after PCI in multi-vessels[2,6] or left main coronary artery disease (CAD).[7,8] Our previous study showed that the SYNTAX score predicted MACEs in an Asian stable de novo CAD cohort.[9]

Conventional atherosclerotic risk factors include diabetes mellitus (DM), hypertension, elevated low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), obesity, and cigarette smoking.[10-12] High-sensitivity C-reactive protein (hs-CRP) is a well-documented inflammatory marker for predicting coronary atherosclerosis.[13,14] Our previous study showed that baseline hs-CRP level could be a useful biomarker for predicting coronary angiographic severity progression,[15] while also forecasting MACEs in patients with stable de novo CAD.[9] In CAD patients, the circulating adiponectin level has been shown to be inversely related to angiographic severity,[16] CAD progression,[17] and future risk of myocardial infarction.[18] An elevated serum leptin level has also been shown to be an independent risk factor for the development of atherosclerotic cardiovascular disease and metabolic syndrome.[19]

Some studies have investigated the factors that determine a higher SYNTAX score in patients with CAD. One study showed that both LDL-C and apolipoprotein B were significant predictors of a higher SYNTAX score in stable CAD patients.[20] Another study revealed that the presence of DM, along with lower values of HDL-C, left ventricular ejection fraction, and estimated glomerular filtration rate were independent predictors of a higher SYNTAX score.[21] Regarding inflammatory markers and the SYNTAX score, Karadeniz et al.[22] reported that the strongest predictor of a higher SYNTAX score in acute coronary syndrome patients was increased serum hs-CRP levels. However, no previous studies have addressed correlations between circulating adipokines and the SYNTAX coronary severity score.

Therefore, the aim of the present study was to investigate predictors including conventional atherosclerotic risk factors, inflammatory markers and adipokines of a higher SYNTAX score in revascularization-naïve CAD patients.

METHODS

Study population

The retrospective enrollment protocol of revascularization-naïve CAD subjects who had a SYNTAX score > 0 and did not have any past history of surgical or percutaneous coronary revascularizations prior to the index admission has been thoroughly described in our previous publication.[9] We retrospectively reviewed all patients' angiographic images, catheterization reports, and medical chart records. The study protocol was approved by the Human Research Review Committee.

Evaluation of angiographic coronary atherosclerosis severity with SYNTAX scores

In the SYNTAX scoring system,[2,5] for example, in right dominance, each segment is given a weighted score as follows: left main 5, left anterior descending (LAD)-proximal 3.5, LAD middle 1.5, LAD apical 1, diagonal branch 1, left circumflex (LCX) proximal 1.5, distal LCX 1, obtuse marginal 1, right coronary artery (RCA) proximal 1, RCA distal 1, and posterior descending artery 1. The SYNTAX score also includes obstruction factors: total obstruction ×5, and significant stenosis (50%-99%) ×2. In addition, some special anatomical factors are also given scores, including, aortic ostial lesion +1, heavy calcification +2, thrombus +1, bifurcation type A, B, C +1, D, E, F, G +2, length > 20 mm +1, and severe tortuosity +2, among others.[5] According to the SYNTAX trial, scores ≤ 22 are considered to be low and scores ≥ 23 are considered to be intermediate-high.[2,23]

Definition of conventional risk factors for atherosclerosis

Hypertension was defined as systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg, after multiple measurements were taken with the patient in a sitting position at rest. Subjects with hypertension included those already on anti-hypertensive medication. DM was defined as fasting blood sugar over 126 mg/dl on two occasions. Subjects with DM included those already on oral anti-diabetic agents or those receiving insulin injections.

Lipid profiles, hs-CRP, and adipokines

Serum hs-CRP was determined using particle-en-

hanced immunoturbidimetry (Latex microparticles sensitized with a duck anti-CRP IgY kit, provided by Good Biotech Corp., Taichung, Taiwan).[24,25] The intra- and inter-assay coefficients of variance were 0.75% and 1.89%, respectively. Serum triglyceride and cholesterol concentrations were assayed using an enzymatic method with commercial kits (WAKO, Tokyo, Japan). The HDL-C level was determined in the supernatant of plasma after the magnesium chloride-phosphotungstic precipitation of apolipoprotein B-containing lipoproteins. The LDL-C concentration was estimated using the formula devised by Friedewald et al.[26] Serum adiponectin and leptin levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (R & D Systems, Inc., Minneapolis, MN, USA). The intra- and inter-assay coefficients of variation for adiponectin were 3.53% and 6.50%, respectively, with a minimum detectable concentration of 0.079-0.891 ng/mL. The intra- and inter-assay coefficients of variation for leptin were 3.17% and 4.37%, respectively, with a minimum detectable concentration of less than 7.8 pg/mL.[27]

Statistical analysis

Categorical data were expressed as percentages and compared using the chi-square test with Yate's correction. Continuous variables were expressed as mean ± standard deviation and were compared between the low and intermediate-high SYNTAX score groups using independent t tests or the Mann-Whitney U test, as appropriate. Multivariate binary logistic regression analysis was used to test independent predictors for an intermediate-high SYNTAX score in the revascularization-naive CAD patients. SPSS (version 12.1) statistical software package (SPSS, Inc., Chicago, IL, USA) was used for all calculations. A two-tailed p value of less than 0.05 was considered to be statistically significant.

RESULTS

Demographic data and lipid profiles

Age and gender were similar between the low and intermediate-high SYNTAX score CAD groups. The proportions of patients with DM or hypertension were also similar. The subjects with an intermediate-high SYNTAX score had a significantly higher LDL-C level (p = 0.046) and a borderline higher total cholesterol (p = 0.086) level compared to those in the low SYNTAX score group (Table 1).

Table 1. Demographic data in subjects with revascularization-naive coronary artery disease (N = 181), who had received coronary angiograms with SYNTAX scoring for severity

	All cases (N = 181)	Low score (< 23) (N = 128)	Intermediate-high score (≥ 23) (N=53)	p value
Gender (M/F)	141/40	100/28	41/12	1.000
Age (years)	67 ± 12	67 ± 12	68 ± 13	0.439
Hypertension (N) (%)	144 (80%)	98 (77%)	46 (87%)	0.177
DM (N) (%)	92 (51%)	64 (50%)	28 (53%)	0.855
Current cigarette smoker (N) (%)	25 (14%)	18 (14%)	7 (13%)	1.000
BMI (kg/m^2)	26.6 ± 4.0	26.7 ± 4.1	26.5 ± 3.7	0.777
Cholesterol (mg/dl)	174 ± 41	171 ± 38	182 ± 46	0.086
HDL-C (mg/dl)	45 ± 12	45 ± 11	45 ± 13	0.847
Cholesterol/HDL-C ratio	4.0 ± 1.1	3.9 ± 1.2	4.2 ± 1.1	0.130
LDL-C (mg/dl)	99 ± 37	96 ± 34	108 ± 42	0.046
Triglyceride (mg/dl)	147 ± 86	147 ± 92	146 ± 72	0.960
Medication use before index admission				
Use of statin (N) (%)	36 (20%)	22 (17%)	14 (26%)	0.226
Use of ACEI or ARB (N) (%)	60 (33%)	43 (34%)	17 (32%)	0.981

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index: body weight (kg)/height (m)^2; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M/F, male/female; Statins, HMG-CoA reductase inhibitors; SYNTAX score: score derived from the trial, "The SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery".
Continuous data are expressed as mean ± standard deviation.
Categorical data are expressed as percentages.
p value: comparisons between patients with low vs. intermediate-high SYNTAX scores.

Inflammatory marker and adipokines in low vs. intermediate-high SYNTAX scores

Levels of the circulating inflammatory marker hs-CRP and adipokines including adiponectin and leptin were similar between the low and intermediate-high SYNTAX score CAD subjects (Table 2).

Multivariate binary logistic regression analysis of independent predictors of an intermediate-high SYNTAX coronary severity score in the stable CAD patients

In the revascularization-naive CAD patients, dyslipidemia, including LDL-C, total cholesterol, total cholesterol/HDL-C ratio and pre-index admission statin use were associated with an intermediate-high coronary SYNTAX severity score; however HDL-C alone or DM were not significant predictors (Table 3, Mode 1-3). Neither the inflammatory marker hs-CRP nor adipokines contributed to a higher SYNTAX coronary severity score (Table 3). Hypertension was significantly associated with an intermediate-high SYNTAX score (Table 3).

DISCUSSION

The main finding in this study was that dyslipidemia, including LDL-C, total cholesterol, the total cholesterol/HDL-C ratio and pre-index admission statin use were associated with a higher coronary SYNTAX severity score in revascularization-naive stable CAD patients, while the inflammatory marker hs-CRP and adipokines were not.

Regarding lipid profiles and their correlations with a higher coronary SYNTAX severity score, one study reported that both LDL-C and apolipoprotein B were significant positive predictors, while HDL-C was a negative predictor for higher SYNTAX scores in stable CAD patients.[20] Another study reported that a lower value of HDL-C was an independent predictor of a higher SYNTAX score.[21] Chieng et al.[28] reported that higher LDL-C and elevated lipoprotein (a) levels were significant contributors to a higher SYNTAX coronary severity score. Our study did not consider new or rarely used lipid parameters such as lipoprotein (a) or apolipoprotein B, but rather only investigated clinically used lipid profiles. Our results re-affirmed that routinely used lipid parameters including LDL-C, total cholesterol, and total cholesterol/HDL-C ratio were associated with an intermediate-high SYNTAX severity score in revascularization-naive CAD patients.

In this study, we enrolled newly diagnosed CAD patients without past histories of coronary revascularization. Thus, the statin use rate before the index admission was quite low (20%, Table 1). However, statin use before the index admission, a surrogate of previously confirmed higher cholesterol or LDL-C, remained a significant parameter associated with an intermediate-high SYNTAX score (Table 3).

DM and hypertension are prevalent risk factors for atherosclerosis. Tanaka et al.[29] reported that DM was significantly associated with a higher SYNTAX score in patients with newly diagnosed CAD, while hypertension was not. In contrast, another report showed that hypertension, LDL-C and hs-CRP/albumin ratio were significant predictors of a higher SYNTAX score.[30] Moreover, a report from the Netherlands showed that in a selected cohort of revascularization-naïve patients with CAD undergoing coronary angiography, advanced age, male sex, smoking and renal failure were independently associated with CAD complexity assessed by the SYNTAX score; while DM and hypertension were not significant factors in multivariate analysis.[31] In our study, hypertension, but not DM, was a significant variable for differentiating in-

Table 2. Inflammatory marker and adipokines in subjects with revascularization-naive coronary artery disease (N = 181), who had received coronary angiograms with SYNTAX scoring for severity

	All cases (N = 181)	Low score (< 23) (N = 128)	Intermediate-high score (≥ 23) (N = 53)	p value
hs-CRP (mg/dl)	0.60 ± 1.23	0.52 ± 0.94	0.81 ± 1.73	0.244
Adiponectin (μg/ml)	6.2 ± 6.6	6.7 ± 6.8	5.0 ± 6.0	0.115
Leptin (ng/ml)	10.5 ± 12.7	10.1 ± 13.3	11.5 ± 11.0	0.491
Leptin/adiponectin ratio (×1000)	6.8 ± 39.6	8.1 ± 47.0	3.9 ± 3.9	0.519

hs-CRP, high sensitivity C-reactive protein.

Table 3. Multivariate binary logistic regression analysis of independent predictors for an intermediate-high SYNTAX severity score in revascularization-naive coronary artery disease patients (N = 181)

Mode 1

Factors	p value	OR	95% CI	
			Lower limit	Upper limit
Age (years)	0.500	1.011	0.960	1.042
Gender (male vs. female)	0.862	1.076	0.470	2.463
DM (with vs. without)	0.265	1.488	0.740	2.992
Hypetension (with vs. without)	0.049	2.741	1.007	7.466
hs-CRP group (≥ 0.1 vs. < 0.1 mg/dL)	0.526	1.267	0.609	2.635
BMI (kg/m^2)	0.417	0.962	0.875	1.057
Pre-index admission statin use (with vs. without)	0.029	2.591	1.103	6.088
LDL-C (mg/dL)	0.010	1.013	1.003	1.023
Leptin/adiponectin ratio (×1000)	0.560	0.993	0.969	1.017

Mode 2

Factors	p value	OR	95% CI	
			Lower limit	Upper limit
Age (years)	0.473	1.011	0.981	1.043
Gender (male vs. female)	0.716	1.169	0.505	2.705
DM (with vs. without)	0.302	1.441	0.720	2.887
Hypetension (with vs. without)	0.048	2.736	1.008	7.425
hs-CRP group (≥ 0.1 vs. < 0.1 mg/dL)	0.497	1.288	0.621	2.674
BMI (kg/m^2)	0.337	0.954	0.868	1.050
Pre-index admission statin use (with vs. without)	0.030	2.550	1.093	5.550
Total cholesterol (mg/dL)	0.016	1.011	1.002	1.020
Leptin/adiponectin ratio (×1000)	0.574	0.992	0.964	1.020

Mode 3

Factors	p value	OR	95% CI	
			Lower limit	Upper limit
Age (years)	0.468	1.011	0.981	1.042
Gender (male vs. female)	0.810	0.906	0.403	2.035
DM (with vs. without)	0.715	1.134	0.578	2.224
Hypetension (with vs. without)	0.052	2.690	0.990	7.314
hs-CRP group (≥ 0.1 vs. < 0.1 mg/dL)	0.666	1.174	0.567	2.431
BMI (kg/m^2)	0.512	0.969	0.882	1.065
Pre-index admission statin use (with vs. without)	0.037	2.432	1.056	5.600
Total cholesterol/HDL-C ratio	0.045	1.355	1.006	1.825
Leptin/adiponectin ratio (×1000)	0.540	0.992	0.967	1.018

Dependent variable: SYNTAX coronary severity score, intermediate-high (≥ 23) vs. low (< 23).
BMI, body mass index: body weight (kg)/height (m)^2; CI, confidence interval; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; Statins, HMG-CoA reductase inhibitors; SYNTAX score, score derived from the trial, "The SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery".

termediate-high vs. low SYNTAX score in our patients with CAD. It is difficult to interpret the inconsistency amongst studies. We postulate that the different enrollment criteria for the CAD patients and hospital-based selection bias resulted in the inconsistent impacts of hypertension and DM on SYNTAX severity score.

Several studies have investigated the correlation between circulating hs-CRP and SYNTAX severity scores in CAD patients. One study showed that only a plasma fibrinogen level > 300 mg/dL, but not an hs-CRP level > 3 mg/L, predicted a high SYNTAX score > 32 in CAD patients.[32] Another study performed by Liu et al.[33] reported that an hs-CRP level > 10 mg/L was a significant predictor of an intermediate-high SYNTAX score > 22. Karadeniz et al.[22] reported that the strongest predictor of a higher SYNTAX score in acute coronary syndrome patients was increased serum hs-CRP level. In our study, hs-CRP was not associated with an intermediate-high SYNTAX score in the revascularization-native, stable CAD patients. While it is difficult to interpret the discrepancies amongst the studies, we postulate that the different demographics of the CAD subjects, including or excluding acute coronary syndrome or low ejection fraction, along with differences in the variables included in the multivariate analysis resulted in the inconsistent impacts of the inflammatory marker hs-CRP on SYNTAX coronary severity score.

Several studies have investigated circulating adiponectin and CAD, and shown inverse relationship with angiographic severity[16] and CAD progression.[17] However, no previous study has investigated the correlations between circulating adipokines and SYNTAX coronary severity scores. Our results showed that neither circulating adiponectin nor leptin contributed to an intermediate-high SYNTAX score in our stable CAD patients.

There were several limitations to our study. This is a retrospective enrollment study of revascularization-naive CAD subjects who had agreed to donate blood samples for academic research purposes from a catheterization databank of a single medical center. Potential selection bias could not be avoided. We did not investigate novel lipid parameters such as lipoprotein (a) and apolipoprotein B, or comprehensive inflammatory markers such as monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1 in this study.

CONCLUSION

Dyslipidemia, including elevated LDL-C, total cholesterol, total cholesterol/HDL-C ratio and pre-index admission statin use, and hypertension were associated with an intermediate-high SYNTAX severity score in revascularization-naive CAD patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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