The Impact of IGF-I Gene Polymorphisms on Coronary Artery Disease Susceptibility

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Background: Coronary artery disease (CAD) was the second leading cause of death for the past 3 years in Taiwan. The insulin-like growth factor (IGF) system is considered a new risk factor of CAD because investigations show that the levels and bioactivity of IGF-I and IGFBP-3 (where IGFBP is insulin-like growth factor-binding protein) may be involved in elevating the risk of CAD. This study investigated the relationships among *IGF-I* +1770, *IGF-I* +6093, and *IGFBP-3* -202 genetic polymorphisms and CAD in the Taiwanese population. **Methods:** A total of 581 subjects, including 390 non-CAD controls and 191 patients with CAD, were recruited and the isolated DNA was subjected to real-time polymerase chain to evaluate the effects of these three polymorphic variants on CAD. **Results:** Our results showed a significant association between the *IGF-I*

+1770 gene polymorphism and increased risk of CAD. Furthermore, CAD patients with a minimum of one mutant C allele, T/C or C/C, in *IGF-I* +1770 gene polymorphism had significantly high blood pressure including systolic blood pressure (SBP; $P = 0.025$) and diastolic blood pressure (DBP; $P = 0.004$), compared to CAD patients with T/T homozygotes. Moreover, CAD patients with a minimum of one mutant A allele, G/A or A/A, in the *IGF-I* +6093 gene polymorphism had a 1.695-fold elevated risk of congestive heart failure (CHF), compared to CAD patients with the G/G homozygote. **Conclusions:** Polymorphism of *IGF-I* +1770 was associated with increased CAD risk. In CAD patients, the contributions of *IGF-I* +1770 and +6093 could be through the effect on blood pressure in CAD patients. *J. Clin. Lab. Anal.* 27:162–169, 2013. © 2013 Wiley Periodicals, Inc.

Key words: IGF-I; IGFBP-3; single nucleotide polymorphism; coronary artery disease

INTRODUCTION

Insulin-like growth factor-I (IGF-I), which is encoded on chromosome 12, is a single-chain polypeptide consisting of 70 amino acids (1, 2). IGF-I, a peptide hormone predominantly synthesized by the liver, is a significant mediator of growth hormone activities (3). IGF-I is involved in cellular development, proliferation, differentiation, and cell survival, and thus, is related to tissue remodeling and homeostasis (4–6). Moreover, IGF-I has been reported to be involved in energy metabolism, such as glucose and

lipid metabolism (1, 7). Because of the biological mechanisms of IGF-I, it has been suggested to have a potential

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role in the pathogenesis of numerous diseases, such as tumorigenesis (8–10), rheumatic disease (11), osteoporosis (11), obstructive sleep apnea (11), and cardiovascular diseases (CVDs) (1, 12, 13). A widely investigated topic is the association between IGF-I and cancer or CVD.

Previous studies have shown that elevated circulating IGF-I levels may contribute to increased cancer risk. For example, high circulating IGF-I is positively associated with an increased incidence of prostate cancer (14–16), premenopausal breast cancer (17–20), and colon cancer (21). In the past decade, many researchers have attempted to explain the relationship between IGF-I levels and CVD because patients suffering from hypopituitarism had an elevated prevalence of atheromatous plaques (22) and a higher proportion of cardiovascular mortality (27, 28). This finding implies that decreased circulating IGF-I concentrations may be involved in increasing the risk for CVD. Previous research has shown that low circulating IGF-I concentrations are associated with an increased risk of developing ischemic heart disease (IHD; 23–26), Left ventricular (LV) dysfunction (27), heart failure (27), coronary artery disease (CAD), ischemic stroke (28), and myocardial infarctions (MI; 25, 29, 30).

In blood circulation, IGF-I is circulated by a group of specific IGF-binding proteins (IGFBPs), in which IGFBP-3 is the primary IGF-I carrier (>80%; 31). IGFBP-3, which is encoded on chromosome 7p12, is primarily expressed in the liver. IGFBP-3 is thought to regulate IGF-I distribution and biological activity in IGF-I by binding their specific cell surface receptors. Many researchers have recently investigated the relationship between IGFBP-3 and CVD. For example, high IGFBP-3 is thought to have a positive association with an elevated risk of developing IHD (32), coronary arteriosclerosis in men (33), and ischemic strokes (28).

Epidemiological studies of IGF-I and IGFBP-3 have shown that genetic or environmental factors may contribute to a person's susceptibility to CVD or cancer by affecting the protein concentrations of IGF-I and IGFBP-3 (34, 35). Two single nucleotide polymorphism (SNP) located at positions +1770 (C > T, rs7965399) and +6093 (G > A, rs7978742) of *IGF-I* 5'-untranslated regions have influenced IGF-I levels by increasing the expression of IGF-I mRNA (36). In addition, an SNP located at position -202 (A > C, rs2854744) of *IGFBP-3* has been suggested to reduce the expression products of circulating IGFBP-3 (37–39).

Currently, IHD including CAD is ranked first among the top ten leading causes of death by the World Health Organization (WHO). In addition, heart disease is ranked second among the top 10 leading causes of death in the last 3 years in Taiwan. Well-known risk factors associated with CAD include smoking, alcohol use, hypertension,

hyperlipidemia, diabetes mellitus (DM), and obesity (40). The IGF system is a new risk factor in CAD because numerous studies have shown that the levels and bioactivity of IGF-I and IGFBP-3 may be involved in elevating the risk of CVD, such as CAD. However, no reports have focused on the association of the IGF-I or IGFBP-3 polymorphisms with the development of CAD. Therefore, we investigated the relationship between the three SNPs, *IGF-I* +1770, *IGF-I* +6093, *IGFBP-3* -202, and CAD in the Taiwanese population.

MATERIALS AND METHODS

Population

Between the years 2005 and 2009, a total of 581 Taiwanese patients (Han population) were recruited and analyzed in this study. The demographic and clinical characteristics of patients such as age, gender, family history, smoking habit, and blood pressure were documented. Of these, 390 patients (287 male and 103 female; mean age 65.71 ± 11.20 years) were diagnosed as CAD. Non-CAD subjects consisted of 191 cases (130 male and 61 female; mean age 65.95 ± 12.44 years) randomly selected from the same geographic area. All subjects received an echocardiographic examination (Philips Healthcare, SONOS 7500) during their clinic visit. CAD group was diagnosed as $\geq$ Left ventricular 50% narrowing of the lumina of at least one major coronary artery by coronary angiography. Non-CAD group were enrolled from the echocardiographic examination from the same hospitals. In addition, subjects with malignant diseases were excluded. All the patients were given informed consent, and were made aware of the study protocol. The study was approved by the hospital ethnic committee. Blood samples were collected via venipuncture, and were analyzed by the central research laboratory. The patients also received echocardiographic examination during the study period.

Genomic DNA Extraction

Venous blood from each subject was drawn into vacutainer tubes containing Ethylenediaminetetraacetic Acid (EDTA) and stored at 4°C. Genomic DNA was extracted by QIAamp DNA blood mini kits (Qiagen, Valencia, CA) according to the manufacturer's instructions. DNA was dissolved in Tris-EDTA (TE) buffer [10 mM Tris (pH 7.8), 1 mM EDTA] and then quantitated by a measurement of OD260. Final preparation was stored at -20°C and used as templates for polymerase chain reaction (PCR).

Real-Time PCR

Allelic discrimination of the *IGF-I* +1770, *IGF-I* +6093, and *IGFBP-3* -202 genetic polymorphisms was

assessed with the ABI StepOne™ Real-Time PCR System (Applied Biosystems, Foster City, CA) and analyzed using SDS vers. 3.0 software (Applied Biosystems) with the TaqMan assay (34). The final volume for each reaction was 5 μ l, containing 2.5 μ l TaqMan Genotyping Master Mix, 0.125 μ l TaqMan probe mix, and 10 ng genomic DNA. The real-time PCR included an initial denaturation step at 95°C for 10 min, followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min.

Statistical Analysis

The average age are presented as the mean $\pm$ SE. A Mann–Whitney *U* test and a Fisher's exact test were used to compare the differences of age as well as demographic characteristics distributions between non-CAD and patients with CAD, since the small sample size was present in some categorical variables. Hardy–Weinberg equilibrium was assessed using a goodness-of-fit χ^2 test for biallelic markers. The odds ratios (ORs) with their 95% confidence intervals (CIs) of the association between genotype frequencies and CAD susceptibility as well as clinical characteristics were estimated by multiple logistic regression models. A *P*-value < 0.05 was considered significant. The data were analyzed on SAS statistical software (Version 9.1, 2005; SAS Institute, Inc., Cary, NC).

RESULTS

Table 1 shows the demographic and clinical characteristics of our study groups, comprising non-CAD and CAD patients. The CAD group and non-CAD group have significant differences in atrial fibrillation (AF), aspirin use in the past 7 days, recent (<24 hr) severe angina, cardiac marker (cardiac troponin I) elevation (*P* < 0.001), and congestive heart failure (CHF; *P* = 0.001). Second, there are also statistical differences in hypertension (*P* = 0.011) and increased CAD risk (more than three; *P* = 0.014).

Table 2 shows the OR and 95% CI of CAD patients associated with genotypic frequencies of *IGF-I* and *IGFBP-3* in the Taiwanese population. In our recruited control group, the frequencies of *IGF-I* +1770 T/C (*P* = 0.182, χ^2 value: 1.780), *IGF-I* +6093 G/A (*P* = 0.886, χ^2 value: 0.021), and *IGFBP-3* –202 A/C (*P* = 0.232, χ^2 value: 1.429) were in Hardy–Weinberg equilibrium, respectively. For the *IGF-I* +1770 genetic polymorphism, C/C homozygote participants had a 1.776-fold (95% CI = 1.044–3.020) significant elevated risk of CAD compared to T/T homozygote participants. Neither the *IGF-I* +6093 genetic polymorphism nor the *IGFBP-3* –202 genetic polymorphism has a significant association with CAD risk.

Table 3 shows the comparison of demographics and pathological features between two genotypes of *IGF-I* and *IGFBP-3* for the CAD patients group. For the *IGF-I*

TABLE 1. Demographics and Clinical Pathological Features of Subjects in non-CAD and CAD Patients (N = 581)

	Non-CAD (n = 191)	CAD (n = 390)	<i>P</i> -value
Gender			
Male ^a	130 (68.1%)	287 (73.6%)	0.164
Age (years) ^b	65.95 $\pm$ 12.44	65.71 $\pm$ 11.20	0.813
Height (cm)	161.59 $\pm$ 8.49	161.75 $\pm$ 8.48	0.824
Weight (kg)	66.21 $\pm$ 12.73	66.94 $\pm$ 12.59	0.514
BMI (kg/m ²)	25.05 $\pm$ 3.75	25.56 $\pm$ 4.40	0.418
AF positive (%)	49 (25.7%)	39 (10.0%)	<0.001
CAD risk $\geq$ 3 (%)	92 (48.2%)	230 (59.0%)	0.014
Age > 65 year (%)	109 (57.1%)	210 (53.8%)	0.463
Family history (%)	44 (23.0%)	81 (20.8%)	0.532
Hypertension (%) ^c	121 (63.4%)	287 (73.6%)	0.011
Diabetes mellitus (%) ^d	68 (35.6%)	166 (42.6%)	0.108
Active smoker (%) ^e	75 (39.3%)	170 (43.6%)	0.322
Cholesterol > 200 (%)	72 (38.3%)	158 (40.7%)	0.578
Aspirin use in the past 7 days (%)	50 (26.3%)	154 (41.4%)	<0.001
Recent (<24 hr) severe angina (%)	111 (58.1%)	284 (73.2%)	<0.001
Cardiac markers elevation (%) ^f	76 (39.8%)	223 (57.2%)	<0.001
Stroke	24 (13.4%)	41 (11.0%)	0.416
CHF	66 (35.9%)	86 (22.8%)	0.001
SBP (mmHg)	131.92 $\pm$ 19.79	132.32 $\pm$ 21.30	0.831
DBP (mmHg)	78.74 $\pm$ 14.75	79.09 $\pm$ 15.31	0.797

^aData were presented as a number (percentage) with χ^2 test/Fisher exact test.

^bMean $\pm$ SD with independent two-sample *t*-test.

^cHypertension was defined as systolic and/or diastolic blood pressure above 140/90 mmHg.

^dDiabetes mellitus was defined as a fasting plasma glucose level of 126 mg/dl or more, or a 2-hr postload plasma glucose level of 200 mg/dl or more.

^eActive smoker was defined as a person who currently smoked at least one cigarette/day.

^fCardiac marker: cardiac troponin I.

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

+1770 genetic polymorphism, participants with a minimum of one mutant C allele, T/C or C/C, had significantly high blood pressure, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), compared to T/T homozygote participants. For the *IGF-I* +6093 genetic polymorphism, participants with a minimum of one mutant A allele, G/A or A/A, had significantly high blood pressure, including SBP and DBP, compared to G/G homozygote participants. For the *IGFBP-3* –202 genetic polymorphism, no significant association between the *IGFBP-3* –202 genetic polymorphism and the demographics and pathological features of CAD patients was found.

Table 4 shows the comparison of clinical features between two genotypes of the *IGF-I* +1770 genetic

TABLE 2. Odds Ratio (OR) and 95% Confidence Interval (CI) of CAD Patients Associated with Genotypic Frequencies of IGF-I and IGFBP-3

Variable	Non-CAD (<i>n</i> = 191) (%)	CAD (<i>n</i> = 390) (%)	OR (95% CI)	<i>P</i> -value
IGF-I +1770				
TT	63 (33.0%)	113 (29.0%)	1.00	
TC	101 (52.9%)	191 (49.0%)	1.054 (0.713–1.559)	<i>P</i> = 0.791
CC	27 (14.1%)	86 (22.1%)	1.776 (1.044–3.020)	<i>P</i> = 0.033*
TT	63 (33.0%)	113 (29.0%)	1.00	
TC + CC	128 (67.0%)	277 (70.0%)	1.207 (0.831–1.751)	<i>P</i> = 0.323
T	227 (59.4%)	345 (53.5%)	1.00	
C	155 (40.6%)	439 (46.5%)	1.275 (0.995–1.634)	<i>P</i> = 0.055
IGF-I +6093				
GG	138 (72.3%)	274 (70.3%)	1.00	
GA	49 (25.7%)	109 (27.9%)	1.120 (0.755–1.662)	<i>P</i> = 0.572
AA	4 (2.1%)	7 (1.8%)	0.881 (0.254–3.062)	<i>P</i> = 0.842
GG	138 (72.3%)	274 (70.3%)	1.00	
GA + AA	53 (27.7%)	116 (29.7%)	1.102 (0.751–1.618)	<i>P</i> = 0.619
G	325 (85.1%)	657 (84.2%)	1.00	
A	57 (14.9%)	123 (15.8%)	1.067 (0.759–1.501)	<i>P</i> = 0.708
IGFBP-3 –202				
AA	108 (56.5%)	221 (56.7%)	1.00	
AC	67 (35.1%)	149 (38.2%)	1.087 (0.752–1.572)	<i>P</i> = 0.658
CC	16 (8.4%)	20 (5.1%)	0.611 (0.304–1.226)	<i>P</i> = 0.162
AA	108 (56.5%)	221 (56.7%)	1.00	
AC + CC	83 (43.5%)	169 (43.3%)	0.995 (0.702–1.411)	<i>P</i> = 0.995
A	283 (74.1%)	591 (75.8%)	1.00	
C	99 (25.9%)	189 (24.2%)	0.914 (0.690–1.211)	<i>P</i> = 0.532

The odds ratio (OR) with their 95% confidence intervals were estimated by logistic regression. **P* value < 0.05

polymorphism for the CAD patient group. There was no significant association between the *IGF-I* +1770 genetic polymorphism and clinical features in the CAD patient group. However, in *IGF-I* +6093 genetic polymorphism, participants with a minimum of one mutant A allele, G/A or A/A, had a 1.695-fold (95%, CI = 1.026–2.802) elevated risk of CHF, compared to G/G homozygote patients. In addition, patients with a minimum of one mutant A allele, G/A or A/A, were less likely to be male, compared to G/G homozygote patients (*P* = 0.019) (Table 5).

Table 6 shows the comparison of clinical features between two genotypes of the *IGFBP-3* –202 genetic polymorphism for the CAD group. Our results found that patients with a minimum of one mutant C allele, A/C or C/C, had a 0.459-fold (95%, CI = 0.222 to 0.947) significantly decreased risk of stroke, compared to A/A homozygote patients.

DISCUSSION

Numerous current investigations indicate that decreased circulating IGF-I levels may contribute to many cardiovascular risk factors, such as oxidized Low-density lipoprotein (LDL), smoking, diabetes, obesity, and re-

duced coronary flow (41–44). Thus, IGF-I reduces the risk of CVD by reducing risk factors, such as atherogenesis (45–47), stabilizing plaque (47), antiplatelet activity (48, 49), and exerting endothelial survival (50, 51). Effectors that circulate concentrations of IGF-I and IGFBP-3 include both genetic (52, 53) and environmental factors, such as aging (54), diet (55, 56), sex (54), and other personal and lifestyle factors (19, 57).

Currently, GC repeating in the *IGF-I* promoter region is a frequently investigated polymorphism that may have a suppressive effect on IGF-I expression. Noncarriers of the 192 nt (wild type) allele were suggested to have an elevated risk of type 2 diabetes (58), MI, and heart failure (59) by affecting the circulating IGF-I levels (60). We show higher polymorphic frequency of the *IGF-I* +1770 C/C homozygote in CAD patients compared to the non-CAD group with 22.1% and 14.1% (OR = 1.776, *P* = 0.033), respectively. The polymorphism of *IGF-I* +1770, which was first described by Cheng et al., may be associated with prostate cancer risks in five racial or ethnic groups: African Americans, Native Hawaiians, Japanese, Latinos, and Caucasians (36, 61). Furthermore, Zaharani et al. showed that the C allele of *IGF-I* +1770 expressed higher IGF-I plasma levels, compared to the A allele in breast cancer patients (62). In Table 2, our data show that the CC homozygote of *IGF-I* +1770 gene

TABLE 3. Comparison of Demographics and Pathological Features Between Two Genotypes of IGF-I and IGFBP-3 for CAD Patients Group

	IGF-I +1770 TT (<i>n</i> = 113)	IGF-I +1770 TC + CC (<i>n</i> = 277)	<i>P</i> -value
Age (years)	65.19 ± 11.53	65.92 ± 11.07	0.562
Height (cm)	162.55 ± 7.37	161.43 ± 8.89	0.237
Weight (kg)	68.06 ± 12.92	66.48 ± 12.44	0.260
BMI (kg/m ²)	25.66 ± 4.04	25.51 ± 4.55	0.760
SBP(mmHg)	128.54 ± 19.20	133.90 ± 21.96	0.025*
DBP(mmHg)	75.65 ± 13.61	80.52 ± 15.77	0.004*
	IGF-I +6093 GG (<i>n</i> = 274)	IGF-I +6093 GA+AA (<i>n</i> = 116)	
Age (years)	65.60 ± 10.86	65.97 ± 12.00	0.762
Height (cm)	162.21 ± 8.73	160.68 ± 7.77	0.104
Weight (kg)	67.75 ± 12.94	65.01 ± 11.53	0.051
BMI (kg/m ²)	25.73 ± 4.63	25.13 ± 3.82	0.213
SBP(mmHg)	130.70 ± 20.46	136.09 ± 22.80	0.023*
DBP(mmHg)	77.70 ± 14.55	82.33 ± 16.58	0.006*
	IGFBP-3 AA (<i>n</i> = 221)	IGFBP-3 AC+CC (<i>n</i> = 169)	
Age (years)	65.59 ± 11.21	65.86 ± 11.22	0.813
Height (cm)	161.80 ± 7.87	161.70 ± 9.23	0.913
Weight (kg)	66.81 ± 13.15	67.11 ± 11.84	0.817
BMI (kg/m ²)	25.43 ± 4.17	25.71 ± 4.70	0.536
SBP(mmHg)	133.06 ± 21.32	131.34 ± 21.30	0.432
DBP(mmHg)	79.85 ± 15.55	78.09 ± 14.99	0.264

Data were presented as mean ± SD with independent two-sample *t*-test.

*Significance *P*-value < 0.05.

polymorphism may increase the risk of CAD. However, previous research has shown that low circulating IGF-I concentrations are associated with an increased risk of developing IHD (23–26). The reason for those discrepancies is not well known, the different diseases and racial/ethnic difference are a potential reason.

We show that CAD patients with a minimum of one mutant C allele, A/C or C/C, of the polymorphism of *IGFBP-3* –202 have less incidence of stroke, compared to A/A homozygote patients. Deal et al. showed that

the C allele of *IGFBP-3* –202 expressed products with 50% lower activity, compared to the A allele in vitro (36). Moreover, the C allele of *IGFBP-3* –202 was involved in decreased IGFBP-3 levels in serum (*P* < 0.01; 63), including in African Americans, Native Hawaiians, Japanese Americans, Latinos, and Caucasians (64). Mong et al. indicated that the C allele of *IGFBP-3* –202 contributed to reduced IGFBP-3 levels (*P* = 1.21×10^{-13}) and decreased LDL-C (*P* = 0.020; (65)). Li et al. showed that the A/A genotype of *IGFBP-3* –202 significantly reduced cancer

TABLE 4. Comparison of Clinical Feature Between Two Genotypes of IGF-I +1770 Gene Polymorphism for CAD Patients Group

	IGF-I +1770 TT (<i>n</i> = 113)	IGF-I +1770 TC + CC (<i>n</i> = 277)	OR (95% CI)	<i>P</i> -value
Male	87 (77.0%)	200 (72.2%)	0.776 (0.466–1.294)	0.330
AF positive (%)	7 (6.2%)	32 (11.6%)	1.978 (0.846–4.623)	0.110
CAD risk ≥ 3 (%)	61 (54.0%)	169 (61.0%)	1.334 (0.858–2.075)	0.201
Age >65 year (%)	58 (51.3%)	152 (54.9%)	1.153 (0.744–1.787)	0.524
Family history (%)	20 (17.7%)	61 (22.0%)	1.313 (0.750–2.300)	0.340
Hypertension (%)	77 (68.1%)	210 (75.8%)	1.465 (0.905–2.373)	0.119
Diabetes mellitus (%)	43 (38.1%)	123 (44.4%)	1.300 (0.831–2.034)	0.250
Active smoker (%)	51 (45.1%)	119 (43.0%)	0.916 (0.590–1.422)	0.695
Cholesterol > 200 (%)	45 (39.8%)	113 (41.1%)	1.054 (0.674–1.648)	0.817
Aspirin use in the past 7 days (%)	44 (41.9%)	110 (41.2%)	0.971 (0.614–1.535)	0.901
Recent (<24 hr) severe angina (%)	83 (74.1%)	201 (72.8%)	0.936 (0.568–1.542)	0.796
Cardiac markers elevation (%)	67 (59.3%)	156 (56.3%)	0.885 (0.568–1.380)	0.590
Stroke	13 (12.4%)	28 (10.5%)	0.829 (0.412–1.670)	0.600
CHF	17 (16.2%)	69 (25.4%)	1.759 (0.979–3.164)	0.057

TABLE 5. Comparison of Clinical Features Between Two Genotypes of IGF-I +6093 Gene Polymorphism for CAD Patients Group

	IGF-I +6093 GG (<i>n</i> = 274)	IGF-I +6093 GA + AA (<i>n</i> = 116)	OR (95% CI)	<i>P</i> -value
Male	211 (77.0%)	76 (65.5%)	0.567 (0.353–0.912)	0.019
AF positive (%)	23 (8.4%)	16 (13.8%)	1.746 (0.886–3.443)	0.104
CAD risk $\geq$ 3 (%)	163 (59.5%)	67 (57.8%)	0.931 (0.559–1.446)	0.751
Age >65 year (%)	148 (54.0%)	62 (53.4%)	0.977 (0.632–1.511)	0.918
Family history (%)	59 (21.5%)	22 (19.0%)	0.853 (0.494–1.473)	0.568
Hypertension (%)	198 (72.3%)	89 (76.7%)	1.265 (0.763–2.097)	0.361
Diabetes mellitus (%)	114 (41.6%)	52 (44.8%)	1.140 (0.736–1.767)	0.556
Active smoker (%)	123 (44.9%)	47 (40.5%)	0.836 (0.538–1.299)	0.426
Cholesterol > 200 (%)	110 (40.4%)	48 (41.4%)	1.040 (0.668–1.617)	0.863
Aspirin use in the past 7 days (%)	109 (41.9%)	45 (40.2%)	0.930 (0.593–1.461)	0.754
Recent (<24 hr) sever angina (%)	200 (73.5%)	84 (72.4%)	0.945 (0.580–1.540)	0.820
Cardiac markers elevation (%)	159 (58.0%)	64 (55.2%)	0.890 (0.575–1.379)	0.602
Stroke	27 (10.3%)	14 (12.6%)	1.251 (0.629–2.488)	0.523
CHF	52 (19.8%)	34 (29.6%)	1.695 (1.026–2.802)	0.038*

¹Data were presented as mean $\pm$ SD with independent two-sample *t*-test.

*Significance *P*-value < 0.05.

risk in breast cancer and prostate cancer, compared to the CC genotype (66). Safarinejad showed that the A allele of *IGFBP-3* –202 significantly reduced cancer risk of clear cell renal cell carcinoma (OR = 4.75, 95% CI = 3.64–7.64, *P* = 0.001; (67)). Our study shows that the polymorphism of *IGFBP-3* –202 may have an association with decreased risk in stroke and CAD patients. Therefore, the C allele, A/C or C/C, of the polymorphism of *IGFBP-3* –202 may exert a protective function from stroke in CAD patients.

In conclusion, our results show that the polymorphism of *IGF-I* +1770 is associated with increased CAD risk. Furthermore, in CAD patients, the polymorphisms of *IGF-I* +1770 and +6093 may have an influence on blood pressure during the pathogenesis of CAD. The polymorphism of *IGF-I* +6093 may have an association

with increased CHF risk in CAD patients; however, the polymorphism of *IGFBP-3* –202 may have an association with decreased stroke risk in CAD patients. With further investigation of the mechanism in which IGF-I and IGFBP-3 is involved, IGF-I and IGFBP-3 might be potential candidates for the therapy and diagnosis of CAD.

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TABLE 6. Comparison of Clinical Features Between Two Genotypes of IGFBP-3 -202 Gene Polymorphism for CAD Patients Group

	IGFBP-3 AA (<i>n</i> = 221)	IGFBP-3 AC + CC (<i>n</i> = 169)	OR (95% CI)	<i>P</i> -value
Male	161 (72.9%)	126 (74.6%)	1.092 (0.692–1.722)	0.705
AF positive (%)	23 (10.4%)	16 (9.5%)	0.900 (0.460–1.263)	0.759
CAD risk $\geq$ 3 (%)	133 (60.2%)	97 (57.4%)	0.891 (0.593–1.339)	0.580
Age >65 year (%)	115 (52.0%)	95 (56.2%)	1.183 (0.791–1.770)	0.412
Family history (%)	44 (19.9%)	37 (21.9%)	1.128 (0.689–1.844)	0.632
Hypertension (%)	169 (76.5%)	118 (69.8%)	0.712 (0.453–1.119)	0.140
Diabetes mellitus (%)	100 (45.2%)	66 (39.1%)	0.775 (0.516–1.165)	0.220
Active smoker (%)	103 (46.6%)	67 (39.6%)	0.753 (0.501–1.129)	0.169
Cholesterol > 200 (%)	83 (37.7%)	75 (44.6%)	1.331 (0.885–2.003)	0.170
ASA use in the past 7 days (%)	88 (42.1%)	66 (40.5%)	0.936 (0.617–1.418)	0.754
Recent (<24 hr) sever angina (%)	167 (75.9%)	117 (69.6%)	0.728 (0.464–1.143)	0.167
Cardiac markers elevation (%)	133 (60.2%)	90 (53.3%)	0.754 (0.503–1.130)	0.171
Stroke	30 (14.0%)	11 (7.0%)	0.459 (0.222–0.947)	0.032*
CHF	52 (24.0%)	34 (21.3%)	0.856 (0.524–1.398)	0.535

¹Data were presented as mean $\pm$ SD with independent two-sample *t*-test.

*Significance *P*-value < 0.05.

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