

# Association between Atherogenic Index of Plasma and Coronary Artery Calcification Progression in Korean Adults

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## Original investigation

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# Abstract

## Background

Dyslipidemia is a well-known risk factor for cardiovascular disease (CVD). Recently, atherogenic index of plasma (AIP) has been proposed as a novel predictive marker for CVD, and there are few cross sectional studies that demonstrated a relationship between AIP and coronary artery disease. We investigated the association between AIP and the progression of coronary artery calcification (CAC) in Korean adults without CVD.

## Methods

A total of 1,124 participants who had undergone CAC measurement at least twice by multi-detector CT in a health care center were enrolled. Anthropometric profiles and multiple cardiovascular risk factors were assessed. The AIP was defined as the base 10 logarithm of the ratio of the concentration of TG to HDL-C. The CAC progression was defined as either incident CAC in a CAC-free population at baseline or an increase of  $\geq 2.5$  units between the square roots of the baseline and follow-up coronary artery calcium scores (CACS) among subjects with detectable CAC at baseline

## Results

CAC progression was observed in 290 subjects (25.8%) during the mean 4.2 years of follow-up. All subjects were stratified into three groups according to AIP. There were significant differences in cardiovascular parameters among the groups at baseline. The follow-up CAC and the incidence of CAC progression increased gradually with the rising AIP tertiles. In the logistic regression analysis, the odds ratio for CAC progression was 2.27 when comparing the highest to the lowest tertile of the AIP (95% CI: 1.61-3.19; P for trend  $<0.01$ ). However, this association was attenuated after adjustment for multiple risk factors (P for trend = 0.67).

## Conclusions

There is a significant correlation between AIP and CAC and its progression in subjects without CVD, but AIP is not an independent predictor of CAC progression.

## Background

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality throughout the world. Coronary artery calcification (CAC), as determined by multi-detector computed tomography (CT), is a sensitive measure to detect the existence of early coronary atherosclerosis. Moreover, CAC is considered an important risk factor for cardiovascular events[1–3].

Dyslipidemia is one of the most important contributing factors to CVD. The association between CVD and the traditional lipid measures, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C),

triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and Lipoprotein (a) has been well demonstrated [4].

Recently, the atherogenic index of plasma (AIP), a logarithmically transformed ratio of molar concentrations of TG to HDL-C, has been suggested as a novel marker for atherosclerosis and CVD[5–7]. Some studies have reported its superiority in predicting atherosclerosis compared with traditional lipid parameters[7, 8].

Most of the prior studies compared AIP between patients with overt coronary artery disease (CAD) and controls, and they showed inconsistent results, and some assessed correlations between AIP and traditional CVD risk factors including Framingham risk score[9–11]. Currently, there is no study that investigated the relationship between the AIP and the early coronary atherosclerosis in relatively low risk subjects without CVD. Furthermore, while CAC progression has been suggested to be a stronger predictor of CVD mortality compared with baseline coronary artery calcification score (CACS) or traditional cardiovascular risk factors[12], there is a lack of data on the relationship between AIP and CAC progression.

Therefore, the present study was designed to investigate the relationship between AIP and CACS and CAC progression in Korean adults without CVD.

## Methods

### Study population

The present study is a retrospective longitudinal study. The study subjects were comprised of 9,581 Korean adults who, as a part of self-referred checkup program, underwent cardiac CT examination at Gangnam Severance Hospital Health Promotion Center, Seoul, Korea, between July 2006 and April 2018. Initially, 1,329 individuals who had undergone at least two cardiac CT scans were enrolled. Then, subjects with any malignancy, renal disease, acute inflammatory disease, missing data or a history of previous cerebrovascular event, myocardial infarction, or angina were excluded. Patients taking lipid-lowering medication were also excluded. Finally, 1,124 subjects were analyzed. This study was approved by the Institutional Review Board of Yonsei University College of Medicine.

### Anthropometric measurement and laboratory assessment

Subjects were examined after 12 hours of fasting. They wore light clothing without shoes during body weight measurements. Body mass index (BMI) was determined using the formula, body weight, in kg divided by the square of person's height in meters. Measurements of systolic and diastolic blood pressure were taken by trained nurses with an automatic blood pressure monitor (HEM-7080IC; Omron Healthcare, Lake Forest, IL, USA).

The blood sampling was done for biochemical assessments including triglyceride (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) using Hitachi

7600 – 120 automated chemistry analyzer (Hitachi, Tokyo, Japan). Calculation of low-density lipoprotein cholesterol (LDL-C) was done using the Friedewald formula. The AIP is defined as the base 10 logarithm of the ratio of the concentration of TG to HDL-C, where each concentration is expressed in mmol/L[7].

Data on lifestyle habits, personal medical information, and medication history were collected with a questionnaire. A subject was considered current smoker, if he/she smoked regularly in the last 6 months. A subject who had alcoholic drinks more than three times a week was considered current drinker. Exercise with a moderate intensity for more than half an hour, at least three times a week, was defined as a regular exercise. A subject was considered diabetic on the basis of previous history of diabetes, current use of antidiabetic medications, or American Diabetes Association diagnostic criteria. A systolic blood pressure (SBP) or diastolic blood pressure (DBP)  $\geq$  140/90 mmHg and/ or antihypertensive medication usage was considered as criteria for hypertension.

## **CAC assessment**

A multi-detector CT scanner (Phillips Brilliance 64; Philips Medical System, Best, The Netherlands) was used to measure CAC. A prospective electrocardiogram-gating protocol with a step-and-shoot technique was used[13]. All subjects were in the supine position and held their breath during the imaging process. One of the three trained radiologists, who were all blinded to the laboratory and clinical information, performed the analysis of coronary CT images. The CACS was quantified automatically with dedicated software, and the severity was assessed with the Agatston score (Aquarius Workstation, TeraRecon, Inc., San Mateo, CA). A CACS above zero, was defined as coronary artery calcification. CAC progression was defined as either (A) incident CAC, indicating a baseline Agatston score of zero but detectable CAC at follow-up examination in a population free from CAC at baseline[14], or (B) an increase of  $\geq$  2.5 units between baseline and final square root of CACS in participants with detectable CAC at baseline[15].

## **Statistical analysis**

Continuous variables are shown as mean  $\pm$  SD. Chi square tests were done to compare categorical variables, expressed as percentages. Analysis of variance was used to for between-group analyses. The association between CAC progression and the AIP was assessed by logistic regression, following adjustment for any potential confounders. In the multivariate model, the following covariates were chosen because of their clinical importance and statistical significance in the univariate analysis: age, sex, BMI, SBP, LDL-C, exercise, alcohol, smoking, presence of diabetes or hypertension, and baseline  $\text{Ln}(\text{CACS} + 1)$ . Statistical analyses were done using SPSS 25.0 (SPSS, Inc, Chicago, IL, USA), and  $p < 0.05$  was considered statistically significant.

## **Results**

### **Baseline characteristics**

A total 1,124 subjects were analyzed in this study. Table 1 shows the clinical and biochemical characteristics of the enrolled subjects. The subjects were stratified into three groups based on their AIP

level. Significant differences were observed in metabolic parameters among the groups. SBP, DBP, BMI and serum FPG, TC, TG and LDL-C levels increased and HDL-C level decreased in the order of increasing AIP tertile. In addition, the highest AIP group had the greatest number of subjects with hypertension, diabetes, and current smoking. Alcohol intake and exercise habits were not significantly different among the groups. Baseline CACS gradually increased with the increasing order of AIP tertile.

Table 1  
Baseline characteristics of participants according to AIP tertiles

	T1	T2	T3	P value
N	376	373	375	
Age (years)	51.4 ± 8.0	52.0 ± 7.4	51.3 ± 7.7	0.43
Sex (M/F)	182/194	281/92	331/44	
SBP (mmHg)	120.5 ± 16.6	123.4 ± 15.6	126.6 ± 14.5	< 0.01
DBP (mmHg)	74.8 ± 10.5	77.6 ± 9.6	80.1 ± 8.7	< 0.01
BMI (kg/m <sup>2</sup> )	22.9 ± 2.8	24.1 ± 2.7	25.4 ± 2.8	< 0.01
FPG (mmol/L)	5.08 ± 0.80	5.40 ± 0.80	5.67 ± 1.11	< 0.01
TC (mmol/L)	5.00 ± 0.83	5.09 ± 0.92	5.25 ± 0.99	< 0.01
TG (mmol/L)	0.75 ± 0.18	1.21 ± 0.26	2.17 ± 0.67	< 0.01
HDL-C (mmol/L)	1.60 ± 0.29	1.28 ± 0.22	1.06 ± 0.2	< 0.01
LDL-C (mmol/L)	3.04 ± 0.76	3.3 ± 0.82	3.37 ± 0.89	< 0.01
AIP	-0.34 ± 0.13	-0.28 ± 0.08	0.30 ± 0.14	< 0.01
HTN (%)	68(18.1)	102(27.3)	114(30.5)	< 0.01
DM (%)	17(4.5)	27(7.2)	37(12.6)	< 0.01
Alcohol (%)	46(12.2)	62(16.6)	64(17.1)	0.12
Smoking (%)	19(5.1)	44(11.8)	59(15.8)	< 0.01
Exercise (%)	63(16.8)	73(19.6)	52(13.9)	0.12
Baseline CACS	13.3 ± 46.9	23.8 ± 79.1	25.8 ± 90.3	< 0.05
Categorical CACS				< 0.01
0	289(76.9)	265 (71.0)	260 (69.3)	
0 < and ≤ 10	23 (6.1)	29 (7.8)	26 (6.9)	
> 10	64(17.0)	79(21.2)	89 (23.8)	
Baseline Ln (CACS + 1)	0.75 ± 1.53	1.02 ± 1.78	1.03 ± 1.77	0.03

Data are mean ± SD, number (percentage).

SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; AIP, atherogenic index of plasma; HTN, hypertension; DM, diabetes mellitus; Alcohol, moderate drinking; Smoking, current smoker; Exercise, regular exercise of moderate intensity; CACS, coronary artery calcium score

	T1	T2	T3	P value
CAC > 0 (%)	87 (23.1)	108 (29.0)	117 (31.2)	< 0.05
Data are mean ± SD, number (percentage).				
SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; AIP, atherogenic index of plasma; HTN, hypertension; DM, diabetes mellitus; Alcohol, moderate drinking; Smoking, current smoker; Exercise, regular exercise of moderate intensity; CACS, coronary artery calcium score				

## Follow-up CACS

Table 2 shows the follow-up CACS and related parameters according to baseline AIP. The average follow-up period was  $4.2 \pm 2.2$  years, and it was not significantly different among the groups. Follow-up CACS and the incidence of CAC progression significantly increased in the order of increasing AIP tertile.

Table 2  
Follow-up CAC-related parameters according to baseline AIP tertiles.

	T1	T2	T3	P value
N	376	373	375	
Follow-up CACS	$27.8 \pm 83.5$	$53.3 \pm 162.7$	$64.0 \pm 191.6$	< 0.01
Categorical CACS				< 0.01
0	271 (72.1)	223 (59.8)	208 (55.5)	
< 0 and ≤ 10	14 (3.7)	27 (7.2)	29 (7.7)	
> 10	91 (24.2)	123 (33.0)	138 (36.8)	
Follow-up Ln (CACS + 1)	$1.07 \pm 1.88$	$1.54 \pm 2.12$	$1.77 \pm 2.19$	< 0.01
Observation time (years)	$4.1 \pm 2.2$	$4.2 \pm 2.3$	$4.3 \pm 2.2$	0.32
CAC progression (%)	66 (17.6)	102 (27.3)	122 (32.5)	< 0.01
Data are mean ± SD, number (percentage).				
CACS, coronary artery calcium score				
AIP, atherogenic index of plasma				

Figure 1 demonstrates that both the  $\Delta \sqrt{\text{transformed CACS}}$  (T1,  $0.90 \pm 2.40$ ; T2,  $1.47 \pm 3.42$ ; T3,  $2.01 \pm 3.61$ ;  $p < 0.01$ ) and annualized  $\Delta \sqrt{\text{transformed CACS}}$  (T1,  $0.20 \pm 0.70$ ; T2,  $0.36 \pm 1.31$ ; T3,  $0.45 \pm 0.81$ ;  $p < 0.01$ ) values increase across the tertiles of AIP at baseline. The group with the higher baseline AIP had the greater  $\Delta \sqrt{\text{transformed CACS}}$  and also the annualized  $\Delta \sqrt{\text{transformed CACS}}$  values.

# Association between CAC progression and AIP

The relationship between the AIP and the progression of CAC was explored by categorizing the baseline AIP into tertiles taking the first tertile as the reference (Table 3). An unadjusted multivariate logistic regression analysis revealed that, with T1 as the reference, the AIP levels for T2 and T3 increased the ORs for CAC progression. This relationship remained statistically significant after adjustment for sex and age. However, this association was attenuated after additional adjustments for BMI, SBP, FPG, LDL-C, exercise, alcohol, smoking, presence of diabetes and hypertension, and baseline Ln(CACS + 1).

Table 3  
Odds ratios and 95% confidence intervals for CAC progression according to AIP tertiles

	OR (95% CI)			P for trend
	T1	T2	T3	
AIP				
Model 1	1.00	1.77 (1.25–2.51)	2.27 (1.61–3.19)	< 0.01
Model 2	1.00	1.37 (0.94–1.99)	1.65 (1.14–2.39)	0.03
Model 3	1.00	1.13 (0.75–1.70)	1.21 (0.80–1.85)	0.67
Model 1: Unadjusted				
Model 2: Adjusted for age and sex				
Model 3: Model 2 + BMI, SBP, FPG, LDL-C, exercise, alcohol, smoking, presence of diabetes and hypertension, and baseline Ln(CACS + 1)				

## Discussion

In this study, we observed a significant relationship between AIP and CAC as well as the progression of CAC over 4-year period in Korean adults without CVD. These findings are consistent with previous studies that showed strong associations between AIP and cardiovascular risk factors and CVD. Furthermore, to the best of our knowledge, this study is the first study to reveal a longitudinal association between AIP and CAC progression.

When we categorized the subjects into tertiles according to AIP, those at the highest tertile had the highest BP, BMI, CACS, and adverse lipid profiles. Also, the incidences of diabetes, hypertension, alcohol drinking, and smoking were highest in this group. In line with our results, prior studies demonstrated that AIP is an independent predictor of CAD among Chinese subjects, Chinese postmenopausal women, and very young adults[9, 10, 16]. Another recent study revealed that AIP predicts a plaque burden in intermediate CVD risk patients presented with chest pain[17]. In addition, AIP was associated with various metabolic disorders including fatty liver disease, hypertension, diabetes, and diabetic complications[18, 19]. While most of

these studies were conducted on subjects with overt CAD or chest pain, or those diagnosed with diabetes, which is considered CAD equivalent, our study excluded people with CAD or cerebrovascular disease as well those on lipid lowering therapy. Despite the relatively low cardiovascular risk of our study population, the higher AIP was still associated with the higher CACS.

Furthermore, the higher AIP was associated with the progression of CAC. While 17.6% of subjects in the lowest AIP tertile showed the CAC progression, 32.5% of subjects in the highest tertile showed the progression. Moreover, the  $\Delta \sqrt{\text{transformed CACS}}$  and the annual  $\Delta \sqrt{\text{transformed CACS}}$  increased gradually across the tertile, indicating that the baseline AIP predicts the progression of CAD and possibly future coronary events.

However, after adjusting for various conventional cardiovascular risk factors such as blood pressure, glucose, LDL-C, exercise, alcohol, smoking, BMI, and the presence of hypertension and diabetes, the predictive value of AIP on CAC progression lost the significance. There are several possible reasons for this. First, a near normal, narrow range of lipid parameters of our study subjects may have attributed. Even the subjects in the highest tertile AIP had the mean TG level of 2.17 mmol/L and mean HDL-C level of 1.06 mmol/L. Previous studies show that a high TG and low HDL-C are closely related with CAC, even more than LDL-C[20, 21]. If the range of AIP in our study was wider with more extreme values, it may have resulted in a significant relationship. Also, while AIP is an independent risk factor for CAD in a cross section setting[9, 10], other factors may be more critical to the CAD progression. For example, insulin resistance is an important risk factor for atherosclerosis[22], and our previous study also demonstrated that triglyceride-glucose (TyG) index, which is a surrogate marker of insulin resistance, is an independent predictor of CAC progression[23].

Although AIP did not predict the progression of CAC, it does not imply that it is not a good predictor of CVD. Recently, there has been a controversy over the prognostic value of the repeated measure of CAC in predicting CVD[24]. While earlier studies suggested the additive contribution of changes in CAC in CV risk prediction, other studies showed that CAC change was only the fifth strongest risk marker for CHD, following baseline CAC, gender, SBP, and total cholesterol[25]. Also, MESA demonstrated that CAC change of a greater than  $> 100 \text{ U/y}$  was associated with coronary heart disease independent of risk factors and baseline CAC score[25]. In other words, it may be likely that although AIP was not able to independently predict the progression of AIP, it does not mean that is a good predictive marker of future CVD, and that it may have a synergistic role with the baseline CACS.

There are several limitations in this study. Since it was a retrospective, longitudinal study, not all of the potential confounding factors were controlled. For example, medications such as antiplatelet agent, anti-diabetic, anti-hypertensive drugs that could affect the progression of atherosclerosis as well as diet, exercise, smoking and alcohol consumption patterns were not controlled or monitored during the follow-up period. Also, the follow-up period was variable. Secondly, our study results cannot be generalized. Not only because people with existing CAD were excluded, but those with no CVD risk are unlikely to be included in the study. We only included subjects who voluntarily took repeated coronary CT scans for a

health check-up, and thus there may be a selection bias. Thirdly, we applied the same definition of CAC progression as our previous paper[23], but there is no consensus on the optimal way to quantify CAC change.

In spite of above limitations, this study has significant implications that are clinically relevant, as it is the first to investigate the association between AIP and CAC progression.

## **Conclusion**

Recently, AIP has been suggested as a novel marker for atherosclerosis and CVD, and its prognostic value was shown to be superior to traditional lipid parameters by some studies. Subjects with higher AIP were with an increased risk for cardiovascular disease, a higher CACS, and more prone to CAC progression over a 4-year period in Korean subjects without CAD. Although AIP was not an independent predictor CAC progression, AIP should be considered when estimating the current as well as future CVD risk along with other traditional risk factors.

## **Abbreviations**

CVD: cardiovascular disease; CAC: coronary artery calcification; CT: computed tomography; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; AIP: atherogenic index of plasma; CAD: coronary artery disease; CACS: coronary artery calcium scores; BMI: body mass index; FPG: fasting plasma glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; TyG: triglyceride-glucose.

## **Declarations**

### **Acknowledgement**

Not applicable.

### **Authors' contributions**

JS analyzed the data and wrote the manuscript; MK analyzed the data; KP, SK, and CA contributed to discussion; JP designed the study, edited the manuscript, and contributed to discussion. All authors read and approved the final manuscript.

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## Availability of data and materials

Not applicable.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interest

The authors declare that they have no competing interests.

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## Figures

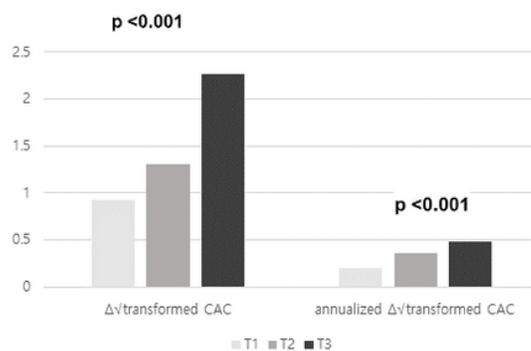


Figure1. Change of CAC according to AIP

## Figure 2

Change of CAC according to AIP  $\Delta\sqrt{\text{transformed CACS}}$  and annualized  $\Delta\sqrt{\text{transformed CACS}}$  values increase across the tertiles of AIP at baseline. (T1: lowest AIP tertile, T2: second AIP tertile, T3: highest AIP

tertile)