

# The atherogenic index of plasma and its impact on recanalization of chronic total occlusion

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## Abstract

**Background:** *The plasma-derived atherogenic index (AIP) is associated with an increasing risk for cardiovascular diseases. Whether an increased AIP may predict the complexity of percutaneous coronary intervention (PCI) of chronic total occlusion (CTO), according to available research, has never been investigated before.*

**Methods:** *Three hundred seventeen patients were included prospectively and treated with PCI for at least one CTO between 2012 and 2017. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) plasma levels were measured 24 h before PCI. All patients were stratified into tertiles of AIP (defined as 0.11, 0.11–0.21, > 0.21) based on their TG/HDL-C (AIP) levels.*

**Results:** *Mean AIP of all patients undergoing CTO-PCI was  $0.53 \pm 0.29$ . The majority of patients were male (82.6%), and mean age was  $61 \pm 10.4$  years. Increased AIP > 0.21 was associated with longer occlusion length (statistical trend  $p = 0.082$ ) and stent routes ( $p = 0.022$ ) and with a higher number of implanted stents ( $n > 4$ ) (statistical trend  $p = 0.072$ ). Success rates were similar in all AIP categories ( $p = 0.461$ ). In-hospital PCI-related complications were rare and not statistically different ( $p = 0.852$ ).*

**Conclusions:** *This study demonstrates for the first time that an increased AIP may predict the complexity of CTO-PCI and additionally may help to improve planning and quality of CTO-PCI. (Cardiol J 2020; 27, 6: 756–761)*

**Key words:** atherogenic index, chronic total occlusion, coronary artery disease, percutaneous coronary intervention

## Introduction

Recanalization of chronic total occlusion (CTO) still remains a challenging procedure in interventional cardiology. A CTO of a coronary artery can be identified in up to 18% among

patients with a clinical indication for coronary angiography. With the advent of novel recanalization techniques and emerging devices, percutaneous coronary intervention (PCI) has become promising leading treatment option for these patients [1–5].

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The atherogenic index of plasma (AIP), the logarithm of molar ratio of triglyceridemia (TG) to high-density lipoprotein cholesterol (HDL-C) has been established as one marker to predict plasma atherogenicity and coronary artery disease (CAD) [6, 7]. Although some lipid variables were associated with the extent of CAD, the specific ratio of TG to HDL-C ratio showed the strongest association respectively. Variation of TG/HDL-C ratio may also be more associated with substantial alterations in metabolic indices predictive for increasing risk of ischemic heart disease compared to variation of low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio [6, 7]. It has been shown recently that AIP may reveal highest sensitivity for predicting acute coronary events [8].

Within this context, this study assessed the association between AIP, as a major risk factor of CAD, and CTO and CTO-PCI, as a complex coronary intervention.

## Methods

Between 2012 and 2017, a total of 317 patients undergoing CTO-PCI in a German high volume CTO center. All patients had a clinical indication for CTO-PCI and/or positive functional ischemia test assessed by magnetic resonance imaging (MRI) or stress-echocardiography in the territory of the occluded coronary artery.

All procedures were performed via femoral access using 7-french guiding catheters; in the majority of patients contralateral injections of contrast were performed to determine the length of the lesion and the existence and extent of collateral connections. Decisions to treat patients either by antegrade or retrograde CTO-PCI techniques was based on operator discretion. To prevent thrombotic complications heparin was administered intravenously during CTO-PCI, guided by activated clotting time (> 300 s).

The J-CTO score, combining several parameters of CTO including the degree of calcification of lesion, bending > 45° in CTO segment, blunt proximal cap, length of occluded segment (> 20 mm) and a previously failed recanalization attempt, was calculated for all patients [9].

After PCI a dual antiplatelet therapy consisting of 100 mg of acetylsalicylic acid once daily indefinitely and 75 mg of clopidogrel once daily for at least 6 months was continued. Procedural success was defined as successful recanalization of CTO with a residual stenosis < 30% and res-

toration of Thrombolysis in Myocardial Infarction (TIMI)-flow grade 3.

A composite safety endpoint summarizing severe complications such as all-cause mortality, vessel perforation, myocardial infarction (MI) and thrombotic events was evaluated for all patients.

Triglycerides and HDL-C levels were measured after taking venous blood samples in EDTA tubes 24 h before the procedure. Analysis of plasma or serum total cholesterol (TC) and HDL was measured directly in serum while TG were measured enzymatically in serum or plasma [10]. TG/HDL-C was calculated as TG (mmol/L) divided by HDL-C (mmol/L). The patients were separately grouped into tertiles based on TG/HDL-C levels. It has been demonstrated before that an AIP value of under 0.11 is associated with low risk of cardiovascular disease (CVD); the values between 0.11 to 0.21 and upper than 0.21 are associated with intermediate and increased risks, respectively [6, 7].

## Statistical analysis

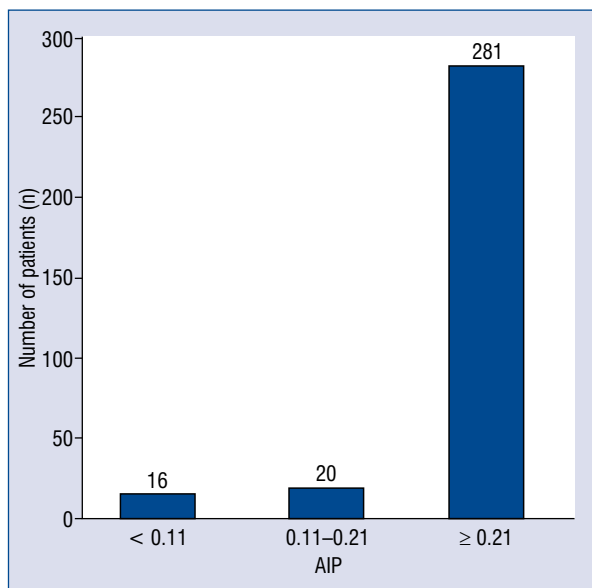
The distribution of continuous variables is characterized by mean  $\pm$  standard deviation, or median and minimum–maximum, the distribution of categorical variables by absolute and relative frequencies.

The Shapiro-Wilk test was used to test for normality of data. The differences of distributions of continuous variables between three AIP categories were tested with the Kruskal–Wallis test (rejected normality) or F test. Differences in distributions of categorical variables were tested using the Fisher exact test.

According to the exploratory character of analysis all p values were interpreted as descriptive measures rather than as definitive inferential measures.

## Results

The overall procedural success rate was 86% which is in accordance with actual trials. The majority of the patients were male (82.6%), and the mean age was  $61 \pm 10.4$  years. The mean AIP of all patients was  $0.53 \pm 0.29$ ; male patients were younger than women ( $60.3 \pm 10.2$  years vs.  $64.6 \pm 10.7$  years;  $p < 0.005$ ). 92% of patients were already under medication with cholesterol synthesis enzyme (CSE) inhibitors. No differences were found between patients with CSE inhibitor to those without CSE in this study population.



**Figure 1.** Distribution of atherogenic index of plasma (AIP) categories.

Figure 1 shows a disproportionate distribution of AIP categories in the present cohort. Only 5% of patients (n = 16) had a normal AIP level of

< 0.11. Table 1 presents baseline characteristics of the patients studied, and are classified by AIP categories.

Patients with an AIP > 0.21 were more frequent male (p = 0.075) and had a higher body mass index (BMI) (p = 0.023). They also had a higher LDL-C (p = 0.043) and suffered more frequently from arterial hypertension (p = 0.084). There was an increase of frequency of diabetes mellitus (DM), BMI, smoking and family history of CAD alongside an increase in AIP. In summary, these cardiovascular risk factors were associated with a high AIP.

This increase was also seen for some periprocedural characteristics as shown in Table 2.

A high AIP > 0.21 was associated with longest occlusions (statistical trend p = 0.082), the longest stent routes (p = 0.022; Table 1) and highest number of the implanted stents (n > 4) after successful recanalization (statistical trend p = 0.072) (Table 2). Although the J-CTO score — representing the complexity of the CTO lesion — was related to a high AIP (p = 0.015; Fig. 2), procedural variables such as amount of contrast medium, examination time and fluoroscopy time were independent of the extent of AIP.

**Table 1.** Baseline and periprocedural characteristics of the study patients, classified by atherogenic index of plasma (AIP) categories.

Variable	AIP			P
	< 0.11	0.11-0.21	> 0.21	
Number	16	20	281	
Age [years]*	62 (37-86)	61 (39-81)	61 (33-87)	0.870
Male gender	68.8% (11)	70.0% (14)	84.3% (237)	0.075
BMI [kg/m <sup>2</sup> ]*	26.0 (21-39)	27.0 (19-35)	27.4 (17-45)	0.023
Diabetes mellitus	18.8% (3)	30.0% (6)	24.6% (69)	0.742
Smoking	25.0% (4)	30.0% (6)	46.6% (131)	0.101
COPD	6.3% (1)	15.0% (3)	7.1% (20)	0.377
LDL-C > 100 mg/dL	18.8% (3)	50.0% (10)	50.5% (142)	0.043
Hypertension	56.3% (9)	75.0% (15)	79.4% (223)	0.084
Family history of CAD	12.5% (2)	25.0% (5)	27.4% (77)	0.446
Prior MI	6.3% (1)	30.0% (6)	28.8% (81)	0.139
Prior CABG	12.5% (2)	0.0% (0)	13.2% (37)	0.245
Prior CTO-PCI attempt	37.5% (6)	35.0% (7)	49.8% (140)	0.325
Prior PCI	37.5% (6)	30.0% (6)	40.2% (113)	0.706
LVEF ≥ 40%	93.8% (15)	100% (20)	97.5% (274)	0.403
Amount of contrast medium [mL]*	220.9 (90-500)	226.8 (90-600)	228.2 (70-600)	0.736
Examination time [min]*	108.4 (45-180)	95.3 (30-220)	110.9 (15-300)	0.110
Fluoroscopy time [min]*	37.4 (11-76)	34.9 (4-94)	37.6 (7-104)	0.476
Length of occlusion [mm]*	32.8 (15-70)	29.5 (15-70)	37.6 (10-100)	0.082
Stent diameter [mm]*	3.0 (2.5-3.5)	2.9 (2.5-3.5)	3.1 (2.25-4.0)	0.122
Length of stent [mm]	61.0 (23-119)	52.2 (18-104)	69.1 (12-157)	0.022

\*Median (min-max); BMI — body mass index; CABG — coronary artery bypass graft surgery; CAD — coronary artery disease; COPD — chronic obstructive pulmonary disease; CTO — chronic total occlusion; LDL-C — low density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; MI — myocardial infarction; PCI — percutaneous coronary intervention

**Table 2.** Angiographic characteristics and procedural outcome, classified by median atherogenic index of plasma (AIP).

Variable	N	Mean AIP	P
CTO in:			0.862
LAD	87	0.511	
LCX	32	0.564	
RCA	197	0.528	
Coronary vessel disease:			0.535
1	93	0.522	
2	123	0.513	
3	102	0.556	
Blunt stump/no stump	215	0.536	0.483
Tortuosity > 90°	226	0.538	0.315
Severe calcification	248	0.538	0.208
J-CTO score:			0.015
0	9	0.358	
1	28	0.366	
2	56	0.587	
3	77	0.539	
4	108	0.558	
5	39	0.502	
Retrograde approach	80	0.596	0.015
Drug eluting stents	270	0.525	0.662
Number of stents:			0.072
0	36	0.545	
1	53	0.424	
2	117	0.553	
3	25	0.531	
≥ 4			
Success	272	0.524	0.461
Complications	20	0.531	0.852

CTO — chronic total occlusion; J-CTO — Japanese chronic total occlusion; LAD — left anterior descending; LCX — left circumflex; RCA — right coronary artery

A majority of patients suffered from a multi-vessel coronary disease; 38.8% had coronary 2-vessel disease and 32.2% coronary 3-vessel disease.

No differences in procedural success rates in different AIP categories was shown ( $p = 0.461$ ). In-hospital, acute procedural complications were rare and showed no statistically significant difference ( $p = 0.852$ ). They included mostly vascular complications such as a local hematoma at puncture site ( $n = 19$ ) and one cardiac tamponade which could be treated with a pericardiocentesis without further

consequences. No severe complications such as peri-procedural death or ST-segment elevation myocardial infarction occurred.

## Discussion

Dyslipidemia is an established risk factor for CVD in the general population.

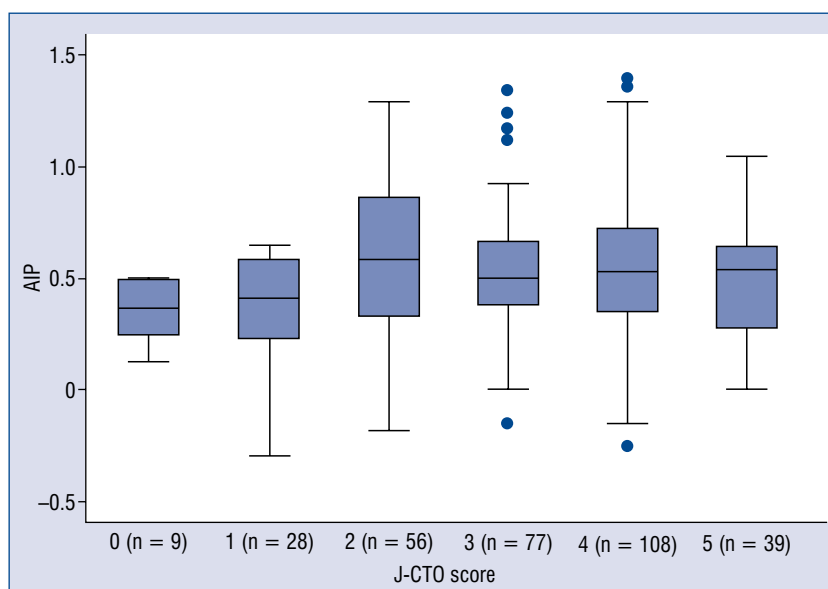
The AIP, which was first described by Dobiášová and Frohlich in 2001 [11], is a comprehensive lipid index, and a strong marker for predicting risk of CAD [8]. In this retrospective study, we examined the association between AIP and patients with CTO and CTO recanalization, respectively. According to available research, no data are available in the current literature about this issue.

The present data emphasizes several important aspects. First, we did show that AIP may predict complexity of a CTO, evaluated by J-CTO score, including severe calcification, tortuosity, stump morphology and lesion length. Second, it could be demonstrated that AIP is associated with peri-procedural characteristics such as number and length of stents after a successful recanalization. Third, it was confirmed that AIP is closely related to several cardiovascular risk factors including male gender.

These findings are in accordance with previous trials, showing a strong association between AIP, cardiovascular risk factors and severity of CAD [7, 12]. Therefore Niroumand et al. [12] has suggested that AIP could be used as a regular monitoring index of CAD in every day practice, while Wan et al. [13] proved that an elevated AIP is a powerful independent predictor of all-cause mortality and for subsequent CVD after coronary revascularization [13]. Lee et al. [14] confirmed prognostic relevance of AIP within a nationwide prospective cohort including more than 1,000 patients with a terminal renal failure. Furthermore Shimizu et al. [15] found a significant positive correlation between DM and AIP and as well as with carotid intima-media thickness, progression and arterial stiffness.

An explanation may be the association of AIP with LDL-C particle size, insulin resistance and metabolic syndrome [11, 16–18]. Hermans et al. [19] demonstrated a relationship between AIP and vascular damage and an association with residual vascular risk, beta-cell function loss and microangiopathy in diabetic patients.

The present study observes that patients with a higher BMI revealed an increased AIP ( $p = 0.023$ ). These findings are in agreement



**Figure 2.** Atherogenic index of plasma (AIP) in Japanese chronic total occlusion (J-CTO) score categories.

with previous data that proved close association between abnormalities of blood lipoproteins and habits of people, such as life style and eating habits [12, 20, 21].

Higher AIP correlates with a higher J-CTO Score, but failed to shown as a predictor for procedural success in CTO recanalization. Lemieux et al. [6] proved that in predicting CAD the AIP is superior to other indices like TC/HDL-C ratio and LDL-C/HDL-C ratio [6]. Furthermore Yildiz et al. [22] suggested that AIP might be a method which can be used for both diagnosis of subclinical atherosclerosis and in deceleration processes of its progression.

The fact that the AIP is associated with male gender in this study ( $p = 0.075$ ) is in accordance with a large chinese cohort with over 430 patients which showed increased AIP being independently associated with coronary heart disease in Chinese males [23].

The AIP may be helpful to estimate the complexity of the procedure in advance and to make a decision on this basis. It is also easy to calculate and may be included in daily clinical practice. Unfortunately it could not demonstrated that this index can predict possible complications related to the complex coronary intervention of CTO-PCI. Gritzenko et al. [24] pointed out that AIP may be necessary to risk assessment before PCI and CABG. In a trial of 186 patients it was shown that

this index can significantly predict re-stenosis after CABG and PCI.

### Limitations of the study

The present study is a retrospective analysis and all data are collected from a single-center. The results of this study may have been influenced by selection criteria, operator experience, and varying techniques used by operators. Furthermore, there was no data about the impact of long term follow-up of AIP in CTO patients. Another limitation may be that the matched and un-matched data used in this study were already collected. Thus, the analysis represents an observational character only.

### Conclusions

The TG/HDL-C ratio may be an independent predictor for complexity of a CTO. Prospective evaluation of AIP as a determinant of the lesion may add adjunctive information for procedural planning of intervention.

**Conflict of interest:** Dr. Kambis Mashayekhi received consulting/speaker honoraria from Abbott Vascular, Asahi Intecc, Biotronik, Boston Scientific, Daiichi Sankyo, Nitiloop, Vascular Solution, Termuo. Other authors declare no conflict of interest.

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