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## Atherogenic index of plasma is related to arterial stiffness but not to blood pressure in normotensive and never-treated hypertensive subjects

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### ABSTRACT

**Background and aims:** Atherogenic index of plasma (AIP), defined as the logarithm of triglycerides to high-density lipoprotein cholesterol (HDL-C) ratio, is a strong predictor of future cardiovascular disease. Our aim was to examine the association of AIP with haemodynamic variables in normotensive and never-treated hypertensive subjects in a cross-sectional study.

**Methods:** Supine haemodynamics in 615 subjects without antihypertensive and lipid-lowering medications were examined using whole-body impedance cardiography and radial pulse wave analysis. Linear regression analysis was applied to investigate the association of AIP with haemodynamic variables and age, sex, body mass index (BMI), smoking status, alcohol consumption, plasma C-reactive protein, electrolytes, uric acid, low density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate, and quantitative insulin sensitivity check index.

**Results:** The demographics and laboratory values of the study population were (mean  $\pm$  95% confidence interval): age  $44.9 \pm 1.0$  years, BMI  $26.8 \pm 0.4$  kg/m<sup>2</sup>, office blood pressure  $140.6 \pm 1.6$ /  $89.4 \pm 1.0$  mmHg, total cholesterol  $5.2 \pm 0.08$ , LDL-C  $3.1 \pm 0.08$ , triglycerides  $1.2 \pm 0.08$ , HDL-C  $1.6 \pm 0.04$  mmol/l, and AIP  $-0.15 \pm 0.02$ . Age (standardized coefficient Beta 0.508,  $p < .001$ ) and aortic systolic blood pressure (Beta 0.239,  $p < .001$ ) presented with the strongest associations with pulse wave velocity. However, AIP was also associated with pulse wave velocity (Beta 0.145,  $p < .001$ ). AIP was not related with aortic or radial blood pressure, cardiac output, systemic vascular resistance, or augmentation index.

**Conclusions:** AIP is directly and independently associated with arterial stiffness, a variable strongly related to cardiovascular risk. This supports more widespread use of AIP in standard clinical cardiovascular disease risk evaluation.

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## Introduction

Cardiovascular diseases due to atherosclerosis and its complications, such as myocardial infarction and stroke, are the leading cause of mortality worldwide representing 31% of all deaths [1]. Among 82.6 million U.S. adults, the prevalence of cardiovascular diseases due to high blood pressure (BP), coronary heart disease, and stroke is estimated to exceed 33%, with the majority of the cases found in subjects older than 60 years of age [2].

Dyslipidaemia is a major risk factor for cardiovascular disease, and the primary focus has been on the dominant role of low density lipoprotein cholesterol (LDL-C) in atherosclerosis. The benefits of LDL-C lowering in cardiovascular disease are well recognized

[3,4]. In clinical practice, the influence of LDL-C has overridden the significance of high density lipoprotein cholesterol (HDL-C) and triglycerides [3,4]. Previous studies have reported that not only low, but also extremely high, levels of HDL-C increase the risk of cardiovascular disease and mortality [5–7]. Elevated serum triglycerides level is also a risk factor for cardiovascular disease [8,9]. A meta-analysis of 17 population-based prospective studies with 46,413 men and 10,864 women reported that plasma triglyceride level, independent of HDL-C, was a risk factor for cardiovascular disease [10].

Increased pulse wave velocity (PWV) that designates arterial stiffness is a strong predictor of cardiovascular disease and mortality, independent of the level

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of BP [11]. The role of unfavourable lipid profile in atherosclerosis is well recognized, but the associations of plasma lipids with arterial stiffness are not straightforward. In spite of the dominant role of LDL-C in atherosclerosis, the relationship of LDL-C with PWV is rather weak [12]. Recently, we found that LDL-C was not associated with PWV when the level of BP was taken into account [13], and this finding is concordant with the majority of published papers [12]. High triglycerides concentration in 11,640 and 1,447 subjects, and low HDL-C levels in 15,302 subjects, were associated with increased PWV [14–16]. However, Wang et al. found that HDL-C was inversely associated with PWV in 2,375 Chinese subjects, while total cholesterol or triglycerides were not associated with PWV [17].

The atherogenic index of plasma (AIP) is defined as the logarithm of plasma triglycerides to HDL-C ratio [18–22]. In contrast to plasma triglycerides concentration, AIP shows normal distribution [23], and is therefore well suited for the mathematical modelling of cardiovascular variables. AIP is particularly useful in predicting plasma atherogenicity [18,20–22]. AIP is also a strong marker for the future risk of atherosclerosis and cardiovascular disease [18–21,24–27], and the routine calculation of AIP in clinical cardiovascular disease risk evaluation would seem warranted.

To our knowledge, the association of AIP with haemodynamic variables has not been previously examined. Due to the weak association of LDL-C with arterial stiffness in our previous report [13], our objective in this cross-sectional study was to examine the associations of AIP with functional haemodynamic variables, and especially to test the hypothesis whether AIP is related to arterial stiffness.

## Methods

### Participants

All subjects were from an ongoing study with the primary aim to examine haemodynamics in primary and secondary hypertension versus normotensive controls (DYNAMIC study; ClinicalTrials.gov identifier NCT01742702). The participant recruitment was recently published in the form of a study flow-chart [13], and altogether 615 from 1349 subjects were included. The exclusion criteria for the study were volunteers taking (1) statin or other lipid-lowering or BP-lowering medication, or with a history of (2) coronary artery disease, (3) stroke, (4) heart failure, (5) valvular heart disease, (6) diabetes, (7) chronic kidney disease, (8) secondary hypertension, (9) alcohol or substance abuse, (10) psychiatric illness other than

mild depression or anxiety, or (11) abnormal heart rhythm other than sinus.

Physical examination and office BP measurements were performed by a medical doctor, and routine laboratory analyses for elevated BP according to the guidelines of the European Society of Hypertension were performed to all enrolled subjects [28]. Beside the medical history, lifestyle habits and use of dietary supplements, medicines, and other substances not registered as drugs were also documented along with information about smoking and alcohol consumption as standard drinks (~12 grams of absolute alcohol) per week.

The study included 314 men and 301 women, altogether 615 normotensive and never-treated subjects with primary hypertension, aged 19–72 years. Based on the office BP measurements on a single occasion, 249 (40.5%) of the participants were normotensive and 366 (59.5%) were hypertensive. The subjects were divided into age- and sex-adjusted AIP tertiles (Tertile 1,  $n = 202$ ; Tertile 2,  $n = 208$ ; Tertile 3,  $n = 205$ ). The study complies with the declaration of Helsinki, and was approved by the ethics committee of the Tampere University Hospital (study code R06086M) and the Finnish Medicines Agency (EudraCT registration number 2006-002065-39). Signed informed consent was obtained from all participants.

Altogether 230 (37.4%) of the 615 persons used some medications. Full description about medicine consumption has been described in our previous study [13].

### Laboratory analyses

Blood and urine sampling was performed after ~12 hours of fasting. Plasma total, HDL-C, LDL-C, triglycerides, C-reactive protein (CRP), sodium, potassium, glucose, cystatin-C, and creatinine concentrations were determined using Cobas Integra 700/800 (F. Hoffmann-Laroche Ltd, Basel; Switzerland) or Cobas6000, module c501 (Roche Diagnostics, Basel, Switzerland), insulin using electrochemiluminescence immunoassay (Cobas e411, Roche Diagnostics), and blood cell count by ADVIA 120 or 2120 (Bayer Health Care, Tarrytown, NY, USA). To exclude patients with renal disease, urine dipstick analysis was made by an automated refractometer test (Siemens Clinitec Atlas or Advantus, Siemens Healthcare GmbH, Erlangen, Germany). AIP was defined as  $\text{Lg}_{10}(\text{plasma triglycerides}/\text{plasma HDL-C})$  [18–21]. Quantitative insulin sensitivity check index (QUICKI) was calculated for evaluation of insulin sensitivity [29], and glomerular filtration rate (eGFR) was estimated using the CKD-EPI cystatin C formula [30].

### Pulse wave analysis

Continuous pulse wave and radial BP were recorded using a tonometric sensor (Colin BP-508T, Colin Medical Instruments Corp., USA) that was attached on the left radial artery pulsation pulse with a wrist band. The radial BP signal was calibrated twice during each 5 minute-period by right brachial BP measurements. Aortic BP was derived with the SphygmoCor system (SphygmoCor PWMx<sup>®</sup>, AtCor medical, Australia) [31], and augmentation index (AIx, augmented pressure/pulse pressure\*100), and AIx adjusted to heart rate 75/min (AIx@75) were determined [32].

### Whole-body impedance cardiography

Beat-to-beat heart rate, stroke volume, cardiac output, and PWV were recorded using whole-body impedance cardiography (CircMon<sup>®</sup>, JR Medical Ltd., Tallinn, Estonia). This method detects changes in body electrical impedance during cardiac cycles, and the electrode configuration has been previously reported [33]. Systemic vascular resistance was calculated from the tonometric BP and cardiac index measured by CircMon<sup>®</sup> so that normal central venous pressure (4 mmHg) was subtracted from mean arterial pressure and the value was divided by cardiac output. Systemic vascular resistance and cardiac output were related to body surface area and presented as indexes (cardiac index, and systemic vascular resistance index (SVRI), respectively). The stroke volume values measured using CircMon<sup>®</sup> correlate well with 3 dimensional ultrasound [34]. The supine cardiac output values measured with CircMon<sup>®</sup> correlate well with the values measured using thermodilution [33].

To measure the PWV, the CircMon<sup>®</sup> software records the time difference between the onset of the decrease in the impedance of the whole-body signal and the signal from the popliteal artery region, and PWV is then determined from the time difference and the distance between the electrodes [35]. Thus, the values measured using this method reflect cardio-popliteal PWV. The whole-body impedance cardiography tends to overestimate PWV, and a validated equation was utilized to calculate values correspond to the ultrasound method ( $PWV = PWV_{impedance} * 0.696 + 0.864$ ) [35]. By the use of this equation, the PWV values recorded using CircMon<sup>®</sup> show very good correlations with values measured using either the tonometric SphygmoCor<sup>®</sup> method ( $r = 0.82$ , bias 0.02 m/s, 95% confidence interval  $-0.21$  to  $0.25$ ) [32] or ultrasound ( $r = 0.91$ ) [35].

### Experimental protocol

Haemodynamics were recorded by research nurses in a quiet, temperature-controlled laboratory. Smoking, caffeine containing products or heavy meals were to be avoided for  $\geq 4$  hours, and alcohol consumption for  $> 24$  hours prior to the participation in the studies. The subjects rested supine, the left arm with the tonometric sensor abducted to 90 degrees in an arm support. After getting accustomed to the laboratory for about 10 minutes, supine haemodynamics were recorded for five minutes. For the statistical analyses the mean values of each 1-minute period of recording were calculated. The good repeatability and reproducibility of the measurement protocol has been demonstrated [36].

### Statistics

Continuous variables were expressed as the mean, standard deviation (SD) or 95% confidence interval (CI) of the mean. Baseline characteristics were depicted as age- and sex-adjusted tertiles of AIP (Table 1). The demographic and laboratory data was analysed using analysis of variance (ANOVA), and the Bonferroni correction was applied in the post-hoc analyses. For the illustrations, the haemodynamic differences between the tertiles were examined using one-way ANOVA with the Bonferroni correction in the post-hoc analyses. The homogeneity of variances was tested with the Levene's test.

Spearman's correlations ( $r_s$ ) were calculated, and the variables that correlated with the variable of interest with  $p < .1$  were included in the regression analyses, as appropriate. The skewed distributions of CRP and PWV were corrected by  $Lg_{10}$ -transformation for these analyses, while alcohol intake was treated as a series of discrete variables that were assigned a score of either 0 or 1; cut-points for women 0, 1–7, 8–14, and above 15 doses per week; for men 0, 1–14, 15–24, and above 25 doses per week, according to the Finnish Guidelines [37]. Multiple regression analysis with stepwise elimination was applied to evaluate the associations between age, sex, body mass index (BMI), smoking status, alcohol consumption, insulin sensitivity evaluated by QUICKI [29], plasma CRP, sodium, uric acid, LDL-C, AIP, and cystatin C based eGFR [30] (independent variables), and radial systolic and diastolic BP, heart rate, and PWV (dependent variables). In the case of PWV, heart rate was also included as an independent variable. The above variables comprised the model 1. The variables in the model 2 were model 1 + PWV (independent

**Table 1.** Age and sex adjusted characteristics of the study population in tertiles of atherogenic index of plasma.

	Overall	Tertile 1	Tertile 2	Tertile 3
Male / female (n/n)	314 / 301	104 / 98	106 / 102	104 / 101
Age (years)	44.9 (11.9)	44.7 (12.3)	44.1 (11.9)	44.9 (11.6)
BMI (kg/m <sup>2</sup> )	26.8 (4.4)	25.1 (3.7)	26.4 (4.0)*	28.9 (4.7)*†
Alcohol (standard doses/week)	4.5 (5.7)	3.9 (5.4)	4.2 (5.3)	5.2 (6.4)
Smokers (number / percentage)	76 / 12.4%	19 / 9.4%	27 / 13%	30 / 14.6%
Office blood pressure (mmHg)				
Systolic	140.6 (20.6)	135.7 (19.8)	140.2 (20.3)	145.7 (20.7)*†
Diastolic	89.5 (12.3)	86.1 (12.1)	89.5 (12.7)*	93.0 (11.4)*†
eGFR (ml/min per 1.73 m <sup>2</sup> )	98.8 (18.1)	102.6 (16.8)	97.9 (18.2)*	95.1 (18.7)*
QUICKI	0.360 (0.042)	0.375 (0.048)	0.360 (0.037)*	0.341 (0.040)*†
Creatinine (μmol/l)	74.0 (13.5)	72.4 (13.2)	75.0 (13.0)	73.8 (14.3)
Cystatin C (mg/l)	0.85 (0.15)	0.81 (0.14)	0.85 (0.14)*	0.87 (0.15)*
Sodium (mmol/l)	140.4 (2.0)	141.0 (2.0)	140.3 (1.8)	140.3 (2.1)
Potassium (mmol/l)	3.81 (0.28)	3.80 (0.29)	3.78 (0.27)	3.83 (0.28)
Uric acid (μmol/l)	303 (76)	280 (71)	300 (70)*	327 (81)*†
CRP (mg/l)	1.7 (2.9)	1.3 (2.3)	1.4 (1.7)	2.4 (4.0)*†
Total cholesterol (mmol/l)	5.2 (1.0)	4.83 (1.0)	5.17 (1.0)*	5.44 (1.0)*†
Triglycerides (mmol/l)	1.23 (0.77)	0.70 (0.21)	1.09 (0.33)*	1.92 (0.92)*†
HDL-C (mmol/l)	1.58 (0.44)	1.90 (0.40)	1.58 (0.37)*	1.30 (0.34)*†
LDL-C (mmol/l)	3.1 (1.0)	2.70 (0.90)	3.12 (0.90)*	3.40 (1.0)*†
Atherogenic index	−0.15 (0.31)	−0.44 (0.17)	−0.17 (0.16)*	0.15 (0.23)*†
Insulin (mU/L)	8.89 (17.0)	8.1 (28.4)	7.6 (4.7)	10.9 (7.10)
Glucose (mmol/l)	5.44 (0.59)	5.33 (0.62)	5.40 (0.52)	5.60 (0.58)*†

Mean (standard deviation), \* $p < .05$  vs Tertile 1; † $p < .05$  vs Tertile 2.

BMI: body mass index; eGFR: cystatin C based CDK-EPI formula for estimated glomerular filtration rate [30]; QUICKI: quantitative insulin sensitivity check index [29]; CRP: C-reactive protein; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol.

variables) for radial systolic and diastolic BP and heart rate (dependent variables), and model 1 + aortic systolic BP (independent variables) for PWV (dependent variable). The coefficient B, standardized coefficient Beta, and R squared values were presented in the Table 2, and  $p < .05$  was considered statistically significant. SPSS version 25.0 (IBM SPSS Statistics, Armonk, NY, USA) was used for the statistics.

## Results

### Study population and laboratory values

Altogether, 314 (51%) male and 301 (49%) female subjects were included in the analyses (Table 1). The age range was 19–72 years. The demographics and laboratory values of the study population were (mean  $\pm$  SD): age  $45 \pm 12$  years, BMI  $27 \pm 4$  kg/m<sup>2</sup>, office systolic/diastolic BP  $141 \pm 21/90 \pm 12$  mmHg, eGFR  $98.8 \pm 18.1$  ml/min/1.73 m<sup>2</sup>, total cholesterol  $5.2 \pm 1.0$ , LDL-C  $3.1 \pm 0.6$ , triglycerides  $1.2 \pm 0.8$ , HDL-C  $1.6 \pm 0.4$  mmol/l, and AIP  $-0.15 \pm 0.3$  (Table 1). In the morning urine sample, none of the study participants had glucosuria or proteinuria. The fasting plasma glucose was in the range of 7.1–10.3 mmol/l in 6 (1%) subjects, while impaired fasting plasma glucose (6.1–7.0 mmol/l) was detected in 80 (13%) of the subjects.

The participants were divided into age- and sex-adjusted AIP tertiles. The average AIP in the tertiles

ranged from  $-0.44 \pm 0.17$  (Tertile 1) to  $0.15 \pm 0.23$  (Tertile 3) (Table 1). The age and sex adjusted AIP tertiles presented with differences in BMI, office systolic and diastolic BP, eGFR, QUICKI, and plasma cystatin C, uric acid, CRP, total cholesterol, triglycerides, HDL-C, LDL-C and glucose concentrations. Age, alcohol intake, smoking status, and plasma creatinine, sodium, potassium, and insulin concentrations were not different between the tertiles (Table 1).

### Haemodynamic variables in the tertiles of AIP adjusted for age and sex

Radial and aortic systolic and diastolic BP and heart rate were higher in the highest than in the lowest AIP tertile, while radial systolic BP and heart rate were also higher in the highest versus the middle AIP tertile (Figures 1(A–D), Figure 2(A)). Cardiac index, SVRI and AIx@75 (Figures 2(B,C), Figure 3(A)) were not different between the tertiles. PWV was higher in the highest and the middle tertile than in the lowest AIP tertile (Figure 3(B)).

### AIP and haemodynamic variables in stepwise linear regression analyses

To examine the relationships of AIP with BP, heart rate and PWV, we performed linear regression analyses with two applied models (see methods) (Table 2). The regression analyses were not performed for



**Table 2.** Explanatory factors for haemodynamic variables in linear regression analyses with stepwise elimination.

Radial systolic BP: model 1 (R squared 0.278)				Radial systolic BP: model 2 (R squared 0.338)			
	B	Beta	p		B	Beta	p
(Constant)	5.667		.915	(Constant)	-54.968		.281
eGFR	-0.265	-0.251	<.001	PWV	81.530	0.396	<.001
BMI	0.613	0.142	.001	QUICKI	-53.779	-0.120	.001
Male sex	5.257	0.137	<.001	eGFR	-0.207	-0.196	<.001
LDL-C	3.242	0.162	<.001	Male sex	3.270	0.086	.021
Sodium	1.000	0.102	.006	Sodium	1.089	0.111	.002
QUICKI	-45.295	-0.101	.010	LDL-C	2.220	0.111	.006
Present smoker	-4.690	-0.081	.025	Age	-0.209	-0.130	.011
Radial diastolic BP: model 1 (R squared 0.274)				Radial diastolic BP: model 2 (R squared 0.333)			
	B	Beta	p		B	Beta	p
(Constant)	21.741		.540	(Constant)	-37.667		.254
eGFR	-0.199	-0.282	<.001	PWV	54.136	0.393	<.001
LDL-C	2.227	0.166	<.001	eGFR	-0.157	-0.222	<.001
QUICKI	-31.547	-0.105	.008	QUICKI	-33.656	-0.112	.002
Male sex	2.851	0.112	.003	LDL-C	1.622	0.121	.003
High alcohol intake	8.612	0.096	.008	Sodium	0.661	0.101	.004
Present smoker	-3.173	-0.082	.024	Age	-0.150	-0.140	.006
BMI	0.276	0.096	.024	High alcohol intake	6.602	0.074	.033
Sodium	0.495	0.076	.042				
Heart rate: model 1 (R squared 0.108)				Heart rate: model 2 (R squared 0.171)			
	B	Beta	p		B	Beta	p
(Constant)	80.017		<.001	(Constant)	51.106		<.001
QUICKI	-38.761	-0.172	<.001	PWV	43.525	0.421	<.001
CRP	2.310	0.096	.023	QUICKI	-42.282	-0.188	<.001
Male sex	-3.532	-0.184	<.001	Male sex	-4.161	-0.217	<.001
Atherogenic index	4.485	0.143	.003	Age	-0.215	-0.266	<.001
Moderate alcohol intake	3.798	0.111	.006	Moderate alcohol intake	4.584	0.134	.001
				Previous smoker	-1.709	-0.082	.037
Pulse wave velocity: model 1 (R squared 0.582)				Pulse wave velocity: model 2 (R squared 0.616)			
	B	Beta	p		B	Beta	p
(Constant)	0.482		<.001	(Constant)	0.444		<.001
Age	0.004	0.567	<.001	Age	0.004	0.508	<.001
Atherogenic index	0.030	0.100	.007	Aortic systolic BP	0.001	0.239	<.001
Heart rate	0.002	0.197	<.001	Atherogenic index	0.044	0.145	<.001
Uric acid	0.0002	0.129	.001	Heart rate	0.002	0.174	<.001
Present smoker	-0.024	-0.086	.002	Uric acid	0.0002	0.161	<.001
LDL-C	0.007	0.076	.021	Present smoker	-0.021	-0.076	.004
BMI	0.002	0.079	.020				
Male sex	0.015	0.080	.023				

Variables in model 1: age, sex, BMI, smoking status, categorised alcohol consumption, QUICKI,  $\text{Lg}_{10}$  of plasma CRP, sodium, uric acid, LDL-C, atherogenic index, and eGFR [30], and for PWV also heart rate. Model 2: model 1 + PWV; for PWV model 2: model 1 + aortic systolic BP.

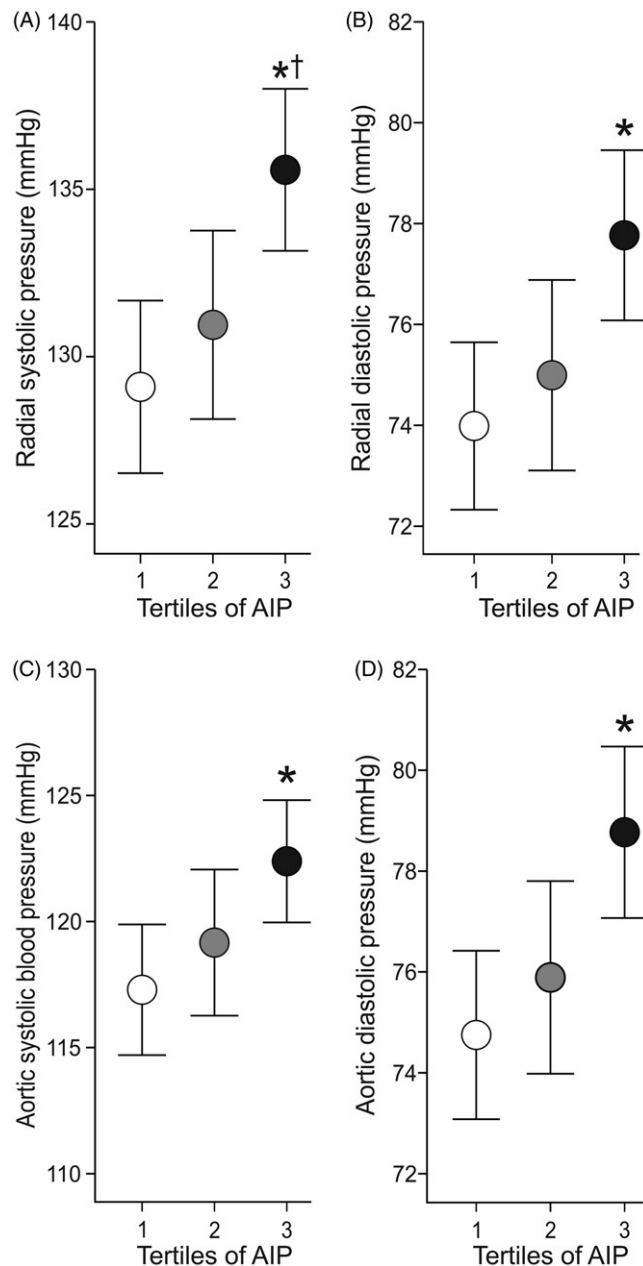
Blood pressure (BP), coefficient of regression (B), standardized coefficient of regression (Beta), cystatin C based CDK-EPI formula for estimated glomerular filtration rate (eGFR) [30], body mass index (BMI), low density lipoprotein cholesterol (LDL-C), quantitative insulin sensitivity check index (QUICKI) [29]; the skewed distributions of C-reactive protein (CRP) and pulse wave velocity (PWV) were  $\text{Lg}_{10}$  transformed.

cardiac index and SVRI, as these variables were not different between the AIP tertiles (Figures 2(B,C)). The univariate correlations (rS) between AIP and radial systolic and diastolic BP, heart rate, and PWV were 0.296, 0.252, 0.169, and 0.401 ( $p < .001$  for all), respectively.

In the regressions analyses AIP was not an explanatory factor for radial systolic and diastolic BP in either model, in contrast to PWV, QUICKI, eGFR, age, sex, BMI, present smoker, high alcohol consumption, and plasma sodium and LDL-C concentrations (Table 2). AIP was a moderate explanatory factor for heart rate in model 1, in addition to

QUICKI, CRP, sex, and moderate alcohol consumption, however when PWV was included in the model, AIP was no longer an explanatory factor for heart rate (Table 2).

In both of the applied models, AIP was a significant independent explanatory factor for PWV (Table 2). The other significant explanatory factors for PWV were age, aortic systolic BP, heart rate, plasma uric acid and present smoking (Table 2, model 2). If aortic systolic BP was replaced by aortic mean BP or aortic diastolic BP in the model 2, AIP still remained as an independent explanatory factor for PWV (data not shown).



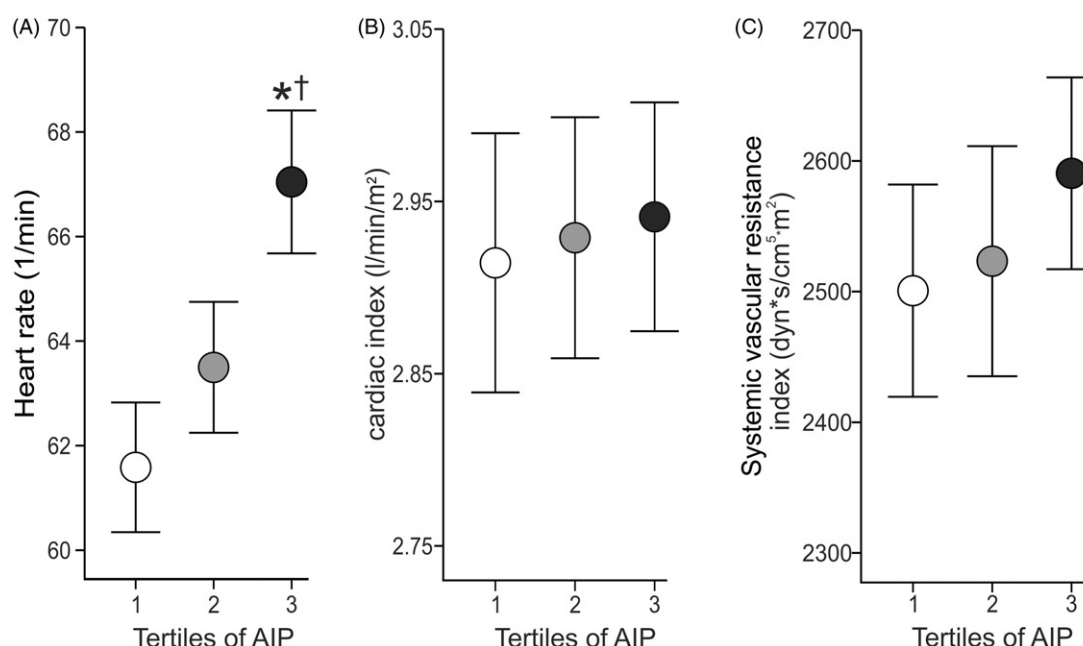
**Figure 1.** Averages of radial systolic (A) and diastolic (B) blood pressure, and aortic systolic (C) and diastolic (D) blood pressure in age- and sex-adjusted tertiles of atherogenic index of plasma (AIP) during 5-minute recordings in the supine position. Tertile 1 ( $n = 202$ ), Tertile 2 ( $n = 208$ ), and Tertile 3 ( $n = 205$ ); mean and 95% confidence interval; \* $p < .05$  vs Tertile 1; † $p < .05$  vs Tertile 2, one-way ANOVA.

## Discussion

There is paucity of studies on the associations of AIP with haemodynamic variables. Although some reports have associated triglycerides and HDL-C with arterial stiffness [14–16], all studies do not support this finding [38–40]. Moreover, the association of LDL-C with arterial stiffness has been surprisingly weak in the published literature [12,13]. Therefore, our goal was to assess the association between AIP and functional cardiovascular variables using non-invasive recordings of haemodynamics. The present results showed that

AIP was independently associated with arterial stiffness, while it was not related to aortic or radial BP, cardiac output, systemic vascular resistance, or AIx.

The present evaluation of arterial stiffness was performed by the measurement of cardio-popliteal PWV, the pressure wave thus travelling along the thoracic and abdominal aorta, iliac artery, and the femoral artery. The elastic properties of the thoracic and abdominal aorta are higher than those of the more muscular iliac and femoral arteries [41]. According to an expert consensus, PWV is normally 4–5 m/s in the



**Figure 2.** Averages of heart rate (A), cardiac index (B), and systemic vascular resistance index (C) in age- and sex-adjusted atherogenic index of plasma (AIP) during 5-minute recordings in the supine position; mean and 95% confidence interval; \* $p < .05$  vs Tertile 1; † $p < .05$  vs Tertile 2, one-way ANOVA.

ascending aorta, 5–6 m/s in the abdominal aorta, and 8–9 m/s in the iliac and femoral arteries [41,42]. This explains why cardio-popliteal PWV is higher than carotid-femoral PWV. Moreover, PWV in the aorta increases progressively with age due to the loss of elasticity, while PWV in the femoral artery is only moderately increased in the course of aging [43]. On the other hand, both the aorta and the femoro-popliteal arteries are frequently affected by atherosclerosis, making both of these regions relevant in the study of large arterial pathophysiology [44].

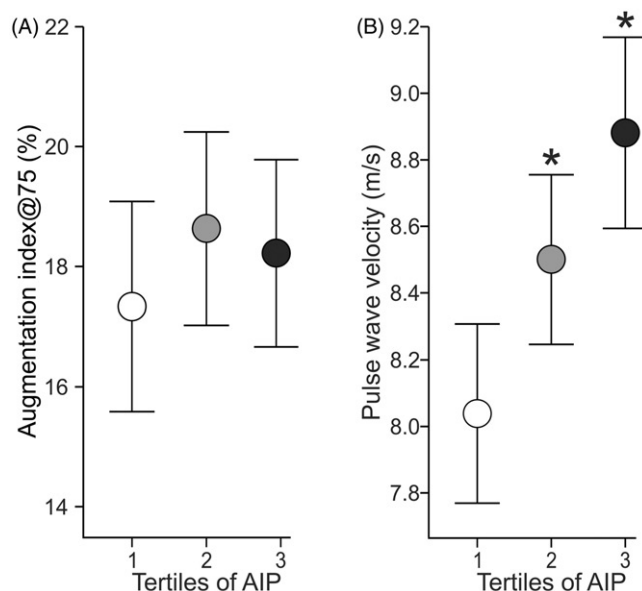
Meta-analyses have demonstrated that statin-induced reduction in LDL-C reduces cardiovascular morbidity and mortality, while several statin trials have also revealed an associated reduction in BP [3,4]. We previously found that LDL-C showed an independent inverse relation with BP and systemic vascular resistance in subjects naive to cardiovascular drugs, but was not associated with arterial stiffness. Thus, LDL-C is not only a major risk factor for atherosclerosis, but it can also be considered as a predisposing factor for elevated BP [13]. However, even when LDL-C is reduced to the recommended levels, some residual cardiovascular risk remains that has been related e.g. to inflammation, and this has encouraged the search for new cardiovascular disease predictors [45,46].

High LDL-C level, smoking, and hypertension have been identified as causes for atherosclerosis that is an intimal disease, while ageing, diabetes, and chronic

kidney disease have been associated with arteriosclerosis, which is a medial disease and especially related to arterial stiffening [47]. Though LDL-C has been the major focus on the link between lipids and cardiovascular disease, the combination of reduced HDL-C and elevated triglycerides has been identified as atherogenic dyslipidaemia [48]. This combination has been associated with more unfavourable cardiovascular risk profile, higher heart rate and systolic BP than hypertriglyceridemia or low HDL-C levels alone [48]. Furthermore, reduced HDL-C together with elevated triglycerides, and also elevated AIP, have been associated with decreased insulin sensitivity [19,48,49]. This view corresponds to the present findings whereby insulin sensitivity, as evaluated by means of QUICKI, was different in every AIP tertile with the lowest values in the highest AIP tertile. In the present regression analyses, insulin sensitivity was also inversely related with BP and heart rate (Table 2).

The ratio of triglycerides to HDL-C is related to the processes involved in LDL size pathophysiology [50]. An increased proportion of small, dense LDL particles is characteristic of patients with diabetes and the metabolic syndrome, and both of these groups have increased risk for cardiovascular disease [51,52]. The mean LDL particle size was also found to be smaller in patients with stroke than in control subjects, despite similar total LDL-C concentrations [53]. When compared with age-matched men with normal





**Figure 3.** Averages of augmentation index adjusted to heart rate of 75 beats per minute (A), and pulse wave velocity (B) in age- and sex-adjusted atherogenic index of plasma (AIP) during 5-minute recordings in the supine position; mean and 95% confidence interval; \* $p < .05$  vs Tertile 1; † $p < .05$  vs Tertile 2, one-way ANOVA.

lipid levels, young men with hypertriglyceridemia presented with small dense LDL particles that were associated increased serum levels of adhesion molecules and impaired flow mediated vasodilation [54]. Some studies have suggested that the definite way to assess potential atherogenicity of LDL particles would be a direct measurement of the LDL particle size [55,56].

AIP reflects the lipoprotein composition in plasma, and it has been postulated as a surrogate marker for small dense LDL particles, and also as a predictor of atherosclerosis, cardiovascular risk, and even effectiveness of therapy [18–21,25,27]. AIP was found to be higher in 2936 patients with coronary artery disease versus 2451 controls [25], while AIP has also been suggested as an independent risk factor for coronary artery disease [24,25]. An AIP value below 0.11 has been associated with low, values from 0.11 to 0.24 with intermediate, and values exceeding 0.24 with high cardiovascular disease risk [20–22,24,57]. Dobiášová et al. examined 1433 subjects with various risks of atherosclerosis and reported that AIP directly correlated with the fractional esterification rate of HDL ( $r = 0.803$ ), and inversely correlated with LDL particle size ( $r = -0.776$ ). The fractional esterification rate of HDL strongly predicted particle size in LDL ( $r = -0.818$ ), and the use of  $\lg_{10}(\text{triglycerides}/\text{HDL-C})$  ratio was considered as a useful predictor of plasma atherogenicity, as it reflected the metabolic interactions within the whole lipoprotein complex [18,20,22].

Plasma triglycerides levels have been previously associated with arterial stiffness [14,16], but

contradictory findings have been published. A study in young type 1 diabetic patients found that an increase in triglycerides level of 48 mg/dl (0.54 mmol/L) resulted in a 1.0% higher PWV during a 4.8-year follow-up, but this increase was no longer significant after adjustment for baseline waist circumference, LDL-C, and HbA1c [39]. In 917 middle-aged French men and women, neither plasma triglycerides nor HDL-C were independently related with carotid-femoral PWV [38]. Although some reports have inversely associated HDL-C with arterial stiffness [15,17], HDL-C was not correlated with brachial-ankle PWV in 12,900 Chinese adults aged 20–79 years [40].

In the present study, the highest tertile with a mean AIP of 0.15 presented with the highest PWV. In the regression analyses, age and the prevailing level of BP showed the strongest associations with PWV, corresponding to previous studies [12,13]. However, AIP was also significantly and independently related with arterial stiffness (Beta values in the two models 0.100–0.145,  $p \leq .007$  for both). As discussed above, controversies remain about the associations of triglycerides and HDL-C with arterial stiffness, while our findings for the first time suggest that AIP is directly and independently associated with PWV, an acknowledged marker of large arterial stiffness that is also strongly related to cardiovascular risk [11]. The present results do not provide an explanation why AIP is better correlated with arterial stiffness than LDL-C. The process leading to increased large arterial stiffness is complex and comprises influences mediated via

mechanical pulsatile stress, inflammatory cells, growth factors, and alterations in endothelial function, enzymes that degrade elastin, changes in smooth muscle cells from the contractile to the synthetic phenotype, and increased extracellular matrix production by fibroblasts [47]. Plasma triglycerides and HDL-C are known to have opposite influences on oxidative stress, inflammation, extracellular matrix formation, and on the change in vascular smooth muscle from the contractile to the synthetic phenotype, and the index AIP summarizes these influences [43].

The current study has limitations and the interpretation of the results should be done cautiously. The present methods have been validated against invasive measurements, 3 dimensional ultrasound, and tonometric recordings of PWV [31–34]. Nevertheless, the non-invasive evaluation of stroke volume and cardiac output is based on mathematical analysis of the bioimpedance signal that simplifies physiology [33]. The present recordings lasted for 5 minutes, which gives a rather narrow window of observation for the examination of haemodynamics. Yet, when compared with single measurements of BP and heart rate, the present analyses were based on recordings collected from more than 300 cardiac cycles. The haemodynamic recordings were performed in subjects who themselves were willing to participate, and this makes a potential source for selection bias. The inclusion of PWV in the regression model 2 resulted in an inverse relationship between age and systolic and diastolic BP in the present population, probably due to the strong interrelationship between PWV and age ( $r_S = 0.67$ ,  $p < .001$ ). A small but significant inverse association between present smoking and PWV was perceived. According to our previous report that was focused on the haemodynamic effects of smoking, and also to a comprehensive review, smoking does not usually influence PWV [12,58]. In our previous study, present smokers had a clear reduction in systemic vascular resistance [58], and such a haemodynamic change may favour reductions in PWV. Finally, the cross-sectional design does not allow conclusions about causality, and the present findings should be confirmed in follow-up studies.

In conclusion, the present results showed that AIP was directly and independently associated with arterial stiffness. AIP is known to inversely correlate with LDL particle size [18,21], and it can be readily calculated from the routine lipid profiles. The link between AIP and large arterial stiffness further supports the

view that calculation of AIP should be included in the normal clinical cardiovascular disease risk evaluation.

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## Disclosure statement

The authors declare no conflicts of interest with respect to this manuscript.

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## Data availability

Analyses and generated datasets that support the current study are not available publicly. The datasets are available from the corresponding author on reasonable request.

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