Research Square

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Atherogenic index of plasma is associated with major adverse cardiovascular events in patients with type 2 diabetes mellitus

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Research Article

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Abstract

Background

Previous studies have reported the prognostic value of the atherogenic index of plasma (AIP) in the course of atherosclerosis and other cardiovascular diseases (CVDs). However, the utility of the AIP for prediction is unknown among patients with type 2 diabetes mellitus (T2DM).

Methods

This was a secondary analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study which randomized 10,251 patients with long-lasting T2DM. ROC curve analysis was used to determine an optimal threshold for AIP and the study population was divided into high and low AIP groups. Univariate and multivariate Cox proportional hazards regression analyses were used to find the association between AIP and primary (MACEs) and second outcomes (all-cause mortality). Stratified analyses were performed to control the confounding factors.

Results

AIP was an independent risk factor for the prognosis of T2DM (HR = 1.309; 95% CI, 1.084–1.581; *P* = 0.005). The threshold for AIP was determined to be 0.34 among the study population. After adjustments for confounding factors, multivariate analysis showed that AIP was associated with the risk of MACEs (Model 1: HR = 1.333, 95%CI: 1.205–1.474, *P*□0.001; Model 2: HR = 1.171, 95%CI: 1.030–1.333, *P* = 0.016; Model 3: HR = 1.194, 95%CI: 1.049–1.360, *P* = 0.007) and all-cause mortality (Model 1: HR = 1.184, 95%CI: 1.077–1.303, *P*□0.001), especially cardiovascular deaths (Model 1: HR = 1.422, 95%CI: 1.201–1.683, *P*□0.001; Model 3: HR = 1.264, 95%CI: 1.015–1.573, *P* = 0.036) and nonfatal myocardial infarction (Model 1: HR = 1.447, 95%CI: 1.255–1.669, *P*□0.001; Model 2: HR = 1.252, 95%CI: 1.045–1.499, *P* = 0.015; Model 3: HR = 1.284, 95%CI: 1.071–1.539, *P* = 0.007). Subgroup stratified analyses showed that AIP might interact with gender, a classical risk factor of cardiovascular events.

Conclusions

Our study showed that AIP might be a strong biomarker that could be used to predict the risk of cardiovascular events in patients with T2DM.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) refers to a condition that involves cholesterol buildup in the arteries, often presenting as coronary heart disease, cerebrovascular disease, and peripheral arterial disease of atherosclerotic origin in patients. ASCVD is the leading cause of morbidity and mortality among individuals with diabetes in the world, resulting in an estimated annual cost of $37.3 billion[1]. Type 2

diabetes mellitus (T2DM) has been associated with the early onset of ASCVDs[1]. Specifically, diabetic patients typically develop cardiovascular abnormality with greater severity 14.6 years in advance compared to individual without diabetes mellitus (DM)[2, 3]. Established risk factors for ASCVDs include conditions such as hypertension and dyslipidemia, which are common in patients with T2DM[1]. Studies showed that patients pre-conditioned with dyslipidemia had dysregulated lipid and glucose metabolism (insulin resistance), resulting in poorer prognosis of ASCVDs[4]. Although the incidences of T2DM complications have reduced over the years due to advances in medicine, more than 382 million people in the world are currently suffering from diabetes, making them more vulnerable to ASCVD-related disability and deaths[5]. Therefore, there is an urgent need for ASCVD prevention in diabetic individuals. To achieve this goal, it is necessary to first develop effective ways to predict and diagnose T2DM-related ASCVDs more accurately at early stages.

Various indices have been used for the diagnosis and prognosis of cardiovascular diseases (CVDs) alone[6]. For instance, atherogenic index of plasma (AIP), a logarithmically transformed ratio of triglyceride (TG) to high-density lipoprotein-cholesterol (HDL-C) in molar concentration, was reported to be a sensitive marker of lipoprotein profiles[7]. Specifically, AIP could predict the size of lipoprotein particles, subsequently showing a positive correlation with the risk of CVDs[8, 9]. Furthermore, AIP can also provide information on the severity of insulin resistance[10], which is associated with impaired glucose metabolism. Recently, AIP was reported as a novel independent prognostic biomarker of coronary artery disease[11–15] and arterial stiffness[16] beyond traditional risk factors.

Studies on T2DM showed AIP was involved in major adverse cardiovascular events of T2DM, which high AIP value might be indicative of a more severe form of T2DM[17–19]. In fact, a recent meta-analysis with a total sample size of 4010 suggested AIP might be used as a simple, easy-to-calculate parameter in the prognosis of T2DM[20]. Moreover, diabetic patients with high AIP were reported to be at significantly higher risks for arterial stiffness and atherosclerosis[17]. Another study enrolled 2356 patients with T2DM showed that AIP mainly affected the prognosis of T2DM after percutaneous coronary intervention, a procedure used to open up blood vessels after the development of atherosclerosis[7]. Therefore, AIP might be a good indicator used to predict the progression of T2DM in patients, especially after they were treated for blood vessel narrowing. However, it is still not known if AIP could be used as an even earlier prognostic marker for predict the onset of atherosclerosis or other CVDs along with diabetes in individuals.

In this study, we speculated that patients with higher AIP might have a higher risk of developing major adverse cardiac events (MACEs) when accompanied by T2DM. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a clinical trial that originally aimed to study the effect of intensive glycemic control, intensive blood pressure control, and multiple lipid management in diabetic patients showing high risk of CVD[21]. The ACCORD Follow-On Study (ACCORDION) was designed and conducted additional follow-up of participants[22]. We performed a secondary analysis on the data collected from ACCORD/ACCORDIN and established three statistical regression models to rule out the confounding factors, so as to assess the relationship between AIP and MACEs in T2DM patients with higher confidence. According to data analysis of the ACCORD study, the current study would be established a model of AIP,

MACEs and T2DM, which would be extremely useful in advancing the early detection and prognosis of cardiovascular events in diabetic patients.

Methods

Study population and patients

We performed a secondary analysis on the published data of the ACCORD/ACCORDIN trial (ClinicalTrials.gov number, NCT00000620)[21]. The rationale and design of the ACCORD trial have been described previously[21, 23, 24]. Briefly, ACCORD was a 2×2 factorial trial aimed to test whether strict control of blood glucose, blood pressure, and lipids could reduce the incidence of CVD in T2DM patients. The ACCORD closeout visits were completed by June 2009. Following approval by the coordinating center (Wake Forest University) and participating in clinical site institutional review board approval and consenting participants were invited for these final trial visits to participate in the post-trial, nontreatment, observation-only ACCORDION study. Follow-up ended on October 31, 2014 (or 60 months post ACCORD), for a total of 5 years of post-trial observation[22]. In this randomized study, all 10,251 T2DM patients were recruited from 77 clinical sites across North America from January 2001 to October 2005. All individuals participated in this study were T2DM patients between 40 and 79 years old who had a glycosylated hemoglobin (HbA1c) concentration of at least 7.5% and a history of CVD indicated by the anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular diseases. Tight control of both blood pressure and lipids also did not reduce the chance of CVD. On the other hand, the intensive glycaemic intervention was terminated after a mean follow-up of 3.7 years owing to increased mortality in the intensive glycaemia control group, and all participants were transitioned to the standard glycaemia control intervention. Follow-up continued for the remaining participants in the ACCORD trial.

Data collection

The data included patients' demographic and clinical characteristics, age, gender, ethnicity, education, smoking history, medical history and previous medications, body measurements, blood content (i.e. plasma triglycerides, cholesterol, LDL-C and HDL-C), etc. was collected.

The primary outcome of the study was major adverse cardiovascular events (MACEs), including nonfatal myocardial infarction (MI), nonfatal stroke, and/or death from cardiovascular causes[25, 26]. Secondary endpoints were all-cause mortality. Participants were followed up every 2–4 months via phone interview or visits at the outpatient clinic. Relevant medical information was collected during each follow-up. The occurrence of MACEs in each patient was determined by a Working Group of the Morbidity and Mortality subcommittee. And major adverse cardiovascular events were also collected with follow-up ended on October 31, 2014, or 60 months after ACCORD, all patients for a total of 5 years of post-trial observation.

Definitions

The atherogenic index of plasma (AIP) is a logarithmically transformed ratio of triglyceride (TG) to high-density lipoprotein-cholesterol (HDL-C) in molar concentration (mmol/L) and it is mathematically derived

from: log (TG/HDL-C)[7]. Receiver operating characteristic (ROC) curve was used to determine the optimal threshold of AIP. More specifically, the threshold was computed as the value that maximized the sum of sensitivity and specificity (y- and x- axes). Subsequently, all patients were divided into a high AIP group and a low AIP group according to threshold of ROC.

Statistical analysis

For categorical variables, baseline characteristics of patients across the quartiles were defined in the form of frequencies and percentages. Chi-square tests were performed to analyze and compare the distributions of categorical variables. For continuous variables, the distribution was assessed by normal Q-Q plots. Depending on whether datasets were normally distributed, either means and standard deviations (SDs) or median and interquartile ranges were used to describe baseline characteristics. Normally distributed continuous variables were compared using one-way ANOVA. Mann–Whitney U-tests were performed otherwise.

The Receiver operating characteristic (ROC) curve was plotted to determine the optimal cut-off value of AIP. The relationship between AIP and our study outcomes (whether MACEs were developed) was evaluated by Cox proportional hazard models. The resulting survival analyses were adjusted for confounding factors including age, gender, race, education, weight, duration of diabetes, hypertension, hyperlipidemia, history of smoking, medication, cardiovascular events and congestive heart failure, fasting plasma glucose, eGFR, HbA1c, plasma triglycerides, total plasma cholesterol, plasma LDL-C and plasma HDL-C. The Kaplan–Meier method provided a visual representation of survival over time, estimating the survival curves based on time-related events among patients. Subsequently, the survival curves were compared with log-rank tests. Stratified analyses were performed to test for interaction and control for confounding in categorical variables including gender, age (<65 or ≥ 65), race, history of cardiovascular disease, treatment, trial involved, blood sugar concentration (HbA1C<8.0% or ≥ 8.0%), as well as the incidence of depression. Stata 15.1 (Stata Corp LLC, Texas, USA) was used to perform above-mentioned statistical analyses. $P < 0.05$ was considered statistically significant for all variables.

Results

Differences in baseline clinical characteristics among the MACE and non-MACE groups of the study population

Demographics and clinical characteristics of 10,251 T2DM patients were shown in Table 1. Patients enrolled in current study were 62.81 ± 6.65 years old of age on average. Among the 10,251 individuals, 61.45% was male and 38.55% was female. 1826 patients (17.8%) developed MACEs after a median follow-up of 9.7 years.

Table 1
Characteristics of patients among the non-MACE and MACE group.

Characteristics	Total (n = 10251)	Non-MACE(n = 8425)	MACE (n = 1826)	*P*
Age, (year)	62.81 ± 6.65	62.52 ± 6.51	64.15 ± 7.13	<0.001
Gender (%)				<0.001
Female	3952 (38.55)	3389 (40.23)	563(30.83)	
Male	6299 (61.45)	5036 (59.77)	1263(61.45)	
Live alone	8171 (79.72)	6735 (79.96)	1436(78.64)	0.211
Race/ethnicity, n (%)				<0.001
White	6393 (62.36)	5128 (60.87)	1265(69.28)	
Non-White	3858 (37.64)	3297 (39.13)	561(30.72)	
Education, n (%)				0.002
Less than high school	1521 (14.85)	1214 (14.42)	307 (16.84)	
High school graduate or GED	2704 (26.40)	2223 (26.40)	481 (26.39)	
Some college	3357 (32.77)	2740 (32.54)	617 (33.85)	
College degree or higher	2662 (25.99)	2244 (26.65)	418 (22.93)	
Previous cardiovascular event, n (%)	3609 (35.21)	2640 (31.34)	969 (53.07)	<0.001
Previous congestive heart failure, n (%)	494 (4.82)	327 (3.88)	167 (9.15)	<0.001
Previous hyperlipidemia, n (%)	7165 (69.90)	5862 (69.58)	1303 (71.36)	0.136
Previous hypertension, n (%)	7726 (75.37)	6301 (74.79)	1425 (78.04)	0.003
Cigarette-smoking status, n (%)				<0.001
Current	1429 (13.94)	1146 (13.60)	283 (15.50)	
Former	4540 (44.29)	3664 (43.49)	876 (47.97)	
Never	4282 (41.77)	3615 (42.91)	667 (36.53)	
Weight (kg)	93.51 ± 18.41	93.28 ± 18.400	94.58 ± 18.40	0.006
Body mass index (Kg/cm^2)	32.22 ± 5.40	32.21 ± 5.41	32.28 ± 5.37	0.625
Blood pressure (mmHg)				
Systolic	136.36 ± 17.11	136.00 ± 16.88	138.02 ± 18.04	<0.001

ACEI: Angiotensin-converting-enzyme inhibitor; ARB:

Characteristics	Total (n = 10251)	Non-MACE(n = 8425)	MACE (n = 1826)	*P*
Diastolic	74.88 ± 10.66	75.14 ± 10.48	73.70 ± 11.37	0.001
Medications, n (%)				
Insulin	3260 (31.80)	2559 (30.37)	701 (38.39)	0.001
Metformin	6554 (63.94)	5467 (64.90)	1087 (59.53)	0.001
Any sulfonylurea	5474 (53.40)	4530 (53.77)	944 (51.70)	0.109
Any thiazolidinedione	2258 (22.03)	1912 (22.70)	346 (18.95)	0.001
ACEI/ARB	7102 (69.28)	5835 (69.26)	1267 (69.39)	0.933
Aspirin	5579 (54.68)	4538 (54.12)	1041 (57.26)	0.016
Statin	6500 (63.66)	5314 (63.33)	1186 (65.16)	0.147
Cholesterol absorption inhibitors	207 (2.03)	169 (2.02)	38 (2.09)	0.854
Niacin and nicotinic acid	183 (1.79)	142 (1.69)	41 (2.26)	0.118
Duration of diabetes (year)	10.80 ± 7.60	10.50 ± 7.42	12.18 ± 8.21	0.001
Glycated hemoglobin (%)	8.30 ± 1.06	8.28 ± 1.05	8.41 ± 1.09	0.001
Fasting plasma glucose (mg/dL)	175.19 ± 56.17	174.04 ± 55.31	180.51 ± 59.72	0.001
Serum creatinine (mg/dL)	0.91 ± 0.23	0.90 ± 0.23	0.97 ± 0.25	0.001
eGFR (mL/min/1.73m2)				0.001
30–49 mL/min/1.73m2	271 (2.64)	192 (2.28)	79 (4.33)	
>50 mL/min/1.73m2	9980 (97.36)	8233 (97.72)	1747 (95.67)	
Plasma triglycerides (mmol/L)	2.13 ± 1.68	2.11 ± 1.65	2.26 ± 1.81	0.001
Total plasma cholesterol (mmol/L)	4.71 ± 1.13	4.71 ± 1.12	4.76 ± 1.19	0.059
Plasma LDL-C (mmol/L)	2.70 ± 0.90	2.69 ± 0.89	2.74 ± 0.94	0.024
Plasma HDL-C (mmol/L)	1.08 ± 0.31	1.09 ± 0.31	1.03 ± 0.31	0.001
Atherogenic index of plasma (AIP)	0.54 ± 0.75	0.51 ± 0.75	0.64 ± 0.74	0.001
ACEI: Angiotensin-converting-enzyme inhibitor; ARB:				

Between patients who developed MACE and patients who did not, there was no significant difference in their living condition (live alone), history of hyperlipidemia, body mass index and prescription record (i.e. sulfonylurea, ACEI/ARB, statin, cholesterol absorption inhibitors, or niacin and nicotinic acid). There was no marked difference in plasma cholesterol level between the MACE group and the non-MACE group,

suggesting that it would not be a promising indicator to predict MACE. In comparison to the non-MACE group, traditional risk factors for CVD including old age, male, hypertension and smoking were more prevalent in diabetic patients with MACEs. Patients with MACEs also had significantly larger body weight, higher blood pressure, longer duration of diabetes and a higher incidence of cardiovascular event and congestive heart failure. In addition, they showed significantly higher concentration of fasting plasma glucose, HbA1c, plasma triglycerides and LDL-C than non-MACE individuals. On the other hand, plasma HDL-C was lower in patients with MACEs than those who did not develop MACEs. Subsequently, AIP, which is the marker for abnormal lipid and glucose metabolism and calculated as the ratio between LDL-C and HCL-C on a logarithmic scale, was significantly higher in diabetic patients with MACEs than those without MACEs.

The relationship between AIP and prognosis in patients with T2DM

To explore whether AIP was associated with the poor outcomes of diabetic patient, we obtained an optimal threshold of AIP that would best separate MACE and non-MACE individuals via ROC curve analysis. Our result showed that AIP had an area under curve (AUC) of 0.5512, suggesting that there was an association between AIP and the risk of MACEs (Fig. 1). Furthermore, the optimal cut-off point for AIP was 0.34 obtained from the curve. The study population was thereby assigned to two groups based on AIP: high AIP (greater than or equal to 0.34) and low AIP (less than 0.34).

Next, AIP was assessed as a continuous covariate via univariate cox proportional hazards regression. During follow-up, 1233 of the patients with high AIP developed MACEs while only 593 patients with low AIP had the same outcome (Table 2). Similar results were found in the analysis of secondary outcomes. 1263 patients with high AIP resulted in death from any cause, while such poor outcomes were observed in 695 patients with low AIP (Table 2). AIP was an independent prognostic marker and associated with primary outcomes (HR: 1.383, 95% CI: 1.254–1.525, $P < 0.001$) and secondary outcomes (all-cause death, HR: 1.205, 95% CI: 1.099–1.322, $P < 0.001$) in T2DM patients with MACEs (Table 2). More specifically, high AIP presented the highest risk in cardiovascular deaths (HR: 1.500, 95%CI: 1.270–1.765, $P < 0.001$) and nonfatal myocardial infarction (HR: 1.499, 95%CI: 1.304–1.722, $P < 0.001$) (Table 2), suggesting that it could be used as a strong predictor of the two outcomes. Kaplan-Meier curves were used to visualize the probability of primary outcomes, the probability of specific cardiovascular events including cardiovascular deaths, nonfatal myocardial infarction, nonfatal strokes (Fig. 2A-D), as well as secondary outcomes, total strokes, and congestive heart failure (Fig. 2E-G). In comparison to patients with low AIP, the probability of poor patient outcomes was significantly higher in the high AIP group ($P < 0.05$), further illustrating that AIP could be used as a good prognostic marker among patients with T2DM.

Table 2
Univariate cox regression analysis of primary and secondary outcome

Outcomes	Total (n = 10251)	Low AIP (n = 4039)	High AIP (n = 6212)	Univariate		
				HR	95% CI	P
Primary outcome	1826 (17.81)	593 (14.68)	1233 (19.85)	1.383	1.254–1.525	<0.001
Cardiovascular cause death	669 (6.53)	205 (5.08)	464 (7.47)	1.500	1.270–1.765	<0.001
Nonfatal myocardial infarction	936 (9.13)	287 (7.11)	649 (10.45)	1.499	1.304–1.722	<0.001
Nonfatal stroke	488 (4.76)	171 (4.23)	317 (5.10)	1.219	1.012–1.468	0.037
Secondary outcomes (Any cause death)	1958 (19.10)	695 (17.21)	1263 (20.33)	1.205	1.099–1.322	<0.001
Total stroke	516 (5.03)	178 (4.41)	338 (5.44)	1.248	1.041–1.496	0.017
Congestive heart failure	696 (6.79)	227 (5.62)	469 (7.55)	1.372	1.171–1.608	<0.001

Data are expressed as OR ± 95% CIs (reported in parentheses) as assessed by univariate cox regression analysis.

Then, the hazard ratio of AIP for different patient outcomes was adjusted for confounding risk factors. Three multivariate regression models were established, each with a different number of confounders taken into consideration. Model 1 was adjusted for age, gender, history of cardiovascular events, smoking, BMI, and duration of diabetes, AIP showed a hazard ratio of 1.333 for MACEs (95% CI: 1.205–1.474, *P*<0.001) and a lower hazard ratio of 1.184 for all-cause mortality (95% CI: 1.077–1.303, *P*<0.001) (Table 3). Model 2 was adjusted for additional variables on top of Model 1, including history congestive heart failure, eGFR, HbA1c, plasma triglycerides, total plasma cholesterol, and plasma HDL-C. Model 3 was based on Model 2, with additional confounders in regard to prescription records, including the use of insulin, biguanide, sulfonylurea, thiazolidinediones, statin, other lipid-lowering medications, niacin, and fibrate. The association between AIP and MACEs remained to be true with a hazard ratio of 1.171 under model 2 and 1.194 under model 3 (Model 2: 95% CI: 1.030–1.333, *P* = 0.016; Model 3: 95% CI: 1.049–1.360, *P* = 0.007) (Table 3). Association was also observed between AIP and cardiovascular deaths or nonfatal myocardial infarction (Table 3). However, after adjustment for confounders, AIP showed hazard ratios less than 1 for nonfatal stroke, total stroke, congestive heart failure, and all-cause mortality, representing weak or no association (Table 3).

Table 3
Multivariate cox regression analysis of primary and secondary outcome.

Outcome	Model 1			Model 2			Model 3		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Primary outcome (MACEs)	1.333	1.205–1.474	<0.001	1.171	1.030–1.333	0.016	1.194	1.049–1.360	0.007
Cardiovascular cause death	1.422	1.201–1.683	<0.001	1.237	0.995–1.538	0.056	1.264	1.015–1.573	0.036
Nonfatal myocardial infarction	1.447	1.255–1.669	<0.001	1.252	1.045–1.499	0.015	1.284	1.071–1.539	0.007
Nonfatal stroke	1.190	0.984–1.441	0.073	1.078	0.841–1.381	0.590	1.090	0.849–1.399	0.680
Secondary outcomes (all-cause mortality)	1.184	1.077–1.303	<0.001	1.037	0.917–1.173	0.559	1.065	0.942–1.206	0.315
Total stroke	1.232	1.023–1.484	0.028	1.132	0.888–1.444	0.316	1.143	0.895–1.459	0.284
Congestive heart failure	1.264	1.074–1.487	0.005	1.035	0.840–1.276	0.746	1.017	0.823–1.255	0.879

Data are expressed as OR ± 95% CIs (reported in parentheses) as assessed by multivariate cox regression analysis; HR: hazard ratio; CI: confidence interval. Covariates included in multivariate cox regression models were model 1: age, gender, previous cardiovascular event, smoking, BMI, and duration of diabetes. Model 2: age, gender, previous cardiovascular event, smoking, BMI, duration of diabetes, previous congestive heart failure, eGFR, HbA1c, plasma triglycerides, total plasma cholesterol, and plasma HDL-C. Model 3: age, gender, previous cardiovascular event, smoking, BMI, duration of diabetes, previous congestive heart failure, eGFR, HbA1c, plasma triglycerides, total plasma cholesterol, plasma HDL-C, insulin, biguanide, sulfonylurea, thiazolidinediones, statin, other lipid-lowering medications, niacin, and fibrate.

The association between AIP and MACEs in the different subgroups of the study population.

Next, to explore the association between AIP and MACEs in more detail, we categorized the study population based on patient demographics and medical records including gender, age, race/ethnicity, history of cardiovascular diseases (CVD), treatment given and trial enrolled, HbA1c level and incidence of depression. Subsequently, we performed stratified analyses to test for interactions and stratified confounders in the association between AIP and MACEs in the different subgroups (Table 4, **Supplemental Fig. 1**). Our results showed that gender might play roles in the association between AIP and MACEs, leading to a stronger prediction of MACEs by AIP among women. However, we did not detect any interaction among different demographic factors and clinical records in male patients. On the other hand, gender seemed to also interact with the association between AIP and nonfatal myocardial infarction. Taken together, the stratified analyses suggested that AIP might be a stronger prognostic marker among elderly women. Furthermore, we

evaluated the association between AIP and nonfatal myocardial infarction and similar results were found across different population subgroups (Table 4, **Supplemental Fig. 2**).

Table 4
Hazard ratios for the primary outcome and death from any Cause in prespecified Subgroups.

Outcome	Low AIP		High AIP		HR[a]	95%CI	P	P for interaction[b]
	Events/n	%	Events/n	%				
Primary outcome								
Gender								**0.024**
Male	389/2207	17.63	874/4092	21.36	1.230	1.091–1.386	0.001	
Female	204/1832	11.14	359/2120	16.93	1.566	1.318–1.859	<0.001	
Age								0.912
<65	298/2416	12.33	690/4073	16.94	1.426	1.245–1.634	<0.001	
≥65	295/1623	18.18	543/2139	25.39	1.410	1.224–1.625	<0.001	
Race/ethnicity								0.557
White	336/1987	16.91	929/4406	21.08	1.286	1.135–1.457	<0.001	
Non-White	257/2052	12.52	304/1806	16.83	1.368	1.159–1.615	<0.001	
CVD history								0.254
Yes	300/1260	23.81	669/2349	28.48	1.241	1.083–1.422	0.002	
No	293/2779	10.54	564/3863	14.60	1.391	1.208–1.602	<0.001	
Glycemia arm								0.716
Standard	301/2021	14.89	629/3102	20.28	1.408	1.227–1.615	<0.001	
Intensive	292/2018	14.47	604/3110	19.42	1.358	1.181–1.562	<0.001	
Trail								0.131
BP	311/2295	13.55	468/2438	19.20	1.473	1.277-1.700	<0.001	

[a] Low AIP as reference, the Hazard Ratio of High AIP for primary outcome or nonfatal myocardial infarction in each subgroup in gender, age, race/ethnicity, CVD history, Glycemia arm, Trail, HbA1c and Depression. [b] Interaction between categorical factor AIP and gender, age, race/ethnicity, CVD history, Glycemia arm, Trail, HbA1c and Depression, respectively.

Outcome	Low AIP		High AIP		HR[a]	95%CI	P	P for interaction[b]
	Events/n	%	Events/n	%				
Lipid	282/1744	16.17	765/3774	20.27	1.263	1.102–1.448	0.001	
HbA1c								0.072
<8.0	243/1971	12.33	548/2898	18.91	1.553	1.335–1.806	<0.001	
≥8.0	350/2068	16.92	685/3314	2067	1.260	1.108–1.433	<0.001	
Depression								0.257
Yes	122/802	15.21	363/1619	22.42	1.519	1.238–1.865	<0.001	
No	470/3235	14.53	870/4593	18.94	1.325	1.184–1.482	<0.001	
Nonfatal myocardial infarction								
Gender								0.064
Male	190/2207	8.61	457/4092	11.17	1.318	1.112–1.561	0.001	
Female	97/1832	5.29	192/2120	9.06	1.747	1.369–2.230	<0.001	
Age								0.761
<65	146/2416	6.04	373/4073	9.16	1.566	1.293–1.896	<0.001	
≥65	141/1623	8.69	276/2139	12.90	1.498	1.223–1.835	<0.001	
Race/ethnicity								0.648
White	170/1987	8.56	501/4406	11.37	1.362	1.144–1.621	<0.001	
Non-White	117/2052	5.7	148/1806	8.19	1.462	1.147–1.864	0.002	
CVD history								0.158
Yes	152/1260	12.06	356/2349	15.16	1.287	1.064–1.555	0.009	

[a] Low AIP as reference, the Hazard Ratio of High AIP for primary outcome or nonfatal myocardial infarction in each subgroup in gender, age, race/ethnicity, CVD history, Glycemia arm, Trail, HbA1c and Depression. [b] Interaction between categorical factor AIP and gender, age, race/ethnicity, CVD history, Glycemia arm, Trail, HbA1c and Depression, respectively.

Outcome	Low AIP		High AIP		HR[a]	95%CI	P	P for interaction[b]
	Events/n	%	Events/n	%				
No	135/2779	4.86	293/3863	7.58	1.572	1.282–1.928	<0.001	
Glycemia arm								0.891
Standard	151/2021	7.47	341/3102	10.99	1.513	1.249–1.832	<0.001	
Intensive	136/2018	6.74	308/3110	9.90	1.485	1.214–1.817	<0.001	
Trail								**0.025**
BP	143/2295	6.23	257/2438	10.54	1.747	1.424–2.144	<0.001	
Lipid	144/1744	8.26	392/3774	10.39	1.266	1.046–1.532	0.016	
HbA1c								0.600
<8.0	112/1779	6.30	255/2602	9.80	1.568	1.255–1.958	<0.001	
≥8.0	175/2260	7.74	394/3610	10.91	1.450	1.214–1.733	<0.001	
Depression								0.203
Yes	61/802	7.61	208/1619	12.85	1.729	1.300–2.300	<0.001	
No	226/3235	6.99	441/4593	9.60	1.394	1.188–1.637	<0.001	

[a] Low AIP as reference, the Hazard Ratio of High AIP for primary outcome or nonfatal myocardial infarction in each subgroup in gender, age, race/ethnicity, CVD history, Glycemia arm, Trail, HbA1c and Depression. [b] Interaction between categorical factor AIP and gender, age, race/ethnicity, CVD history, Glycemia arm, Trail, HbA1c and Depression, respectively.

Discussion

In this retrospective analysis of T2DM patients with high CVD risk, we found that AIP is a parameter related to abnormal lipid and glucose metabolism. The MACEs of the high AIP group were significantly higher than that of the low AIP group, and these differences mainly caused by cardiovascular death and non-fatal myocardial infarction. In the subgroup analysis, we found that AIP has a consistent effect on the prognosis of T2DM patients. Therefore, AIP can be used as a predictor of the long-term prognosis of patients with type 2 diabetes.

Currently, diabetes is affecting the health and living conditions of hundreds of million people, with a global prevalence of roughly 9.3%[27]. In 2019, it was reported that diabetes directly accounted for about 1.5 billion deaths[27]. ASCVDs, or diseases that involve cholesterol buildup in the arteries, are the leading cause of morbidity and mortality among individuals with diabetes in the world[1]. Diabetic patients would typically develop more severe ASCVDs at an earlier age in comparison to non-diabetic individuals[2, 3]. It is therefore critical to identify an effective prognostic and diagnostic marker to enhance preventive care in high-risk individuals. Originally, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial studied 10,251 randomized patients with long-standing T2DM, aiming to understand the effect of intensive glycemic control, intensive blood pressure control, and multiple lipid management in preventing ASCVD[21]. Previously, AIP, a parameter that measures lipid and glucose metabolism, has been considered as a prognostic marker for CVD[6]. A recent study also revealed that AIP could be associated with body fat level in T2DM patients[28]. However, few studies have investigated the relationship between AIP and MACEs in T2DM patients. In our post hoc analysis of the ACCORD trial, we found the AIP, plays an important role in the long-term prognosis of T2DM patients. By analyzing the AIP of 10,251 randomized T2DM patients, we found the optimal cutoff value for AIP to be 0.34. We reported that patients with AIP higher than 0.34 were at significantly higher risk of developing MACEs than those in the low AIP group. More specifically, AIP showed greater prognostic power in predicting cardiovascular deaths and nonfatal myocardial infarction. Furthermore, the study population was subcategorized based on demographic and clinical parameters, and AIP had consistent effect in predicting patient outcomes in different subgroups.

Compared with patients without T2DM, patients with T2DM tend to have more cardiovascular risk factors including hyperlipidemia. However, previous studies reported that there was no significant difference in LDL-C levels between diabetic and nondiabetic patients[29]. Moreover, LDL-C levels were not promising indicators of poor prognosis among diabetic patients[8]. On the other hand, AIP, or the ratio between triglyceride to high-density lipoprotein-cholesterol on a logarithmic scale, quantifies one's ability to metabolize glucose and lipid and was found to be independent of LDL-C[7]. More specifically, AIP was shown to be a more promising predictor of atherosclerosis than low LDL-C levels[8, 30] and could be use used in coordination with the traditional risk factors[9, 12].

The current study confirmed that AIP could be used as an independent predictor for prognosis of type 2 diabetes patients in the long-term follow-up, suggesting that it could more accurately reflect the comprehensive situation of lipids and glucose metabolism among diabetic patients. Consistent with our findings, Zheng *et al*. [7]also reported that high AIP indicated higher risk of MACEs among diabetic patients after percutaneous coronary intervention (PCI) in a single-center observational cohort study. Moreover, AIP may also be used as a powerful complementary index to assess cardiometabolic risks in children and adolescents[31]. In addition, other studies suggested that AIP was also a simple and useful tool in identifying insulin resistant patients at higher cardiometabolic risk[32], more effective than the visceral adiposity index, which was used traditionally[33]. Overall, AIP is an independent clinical marker critical to the prognosis of cardiovascular events in different subpopulation, including patients with T2DM.

Previous studies showed that the mean values of AIP ranged from − 0.24 to 0.55 in general population[8]. AIP can be divided into three different ranges, each representing a level of risk for CVD: AIP < 0.11 (low risk),

0.11 < AIP < 0.21 (intermediate risk) and AIP > 0.21 (high risk)[34, 35]. Meanwhile, patients with T2DM have higher AIP than the general population; as a result, our study used different cut-off values for AIP in our analysis. In our study, the optimal cut-off point for AIP was 0.34 among patients with T2DM, which aligned better with another study (N = 2356) that used 0.318 as the threshold for analysis; the slight difference could be due to the size difference in study population[7].

Lastly, AIP correlates to lipoprotein particle size and could be used as a marker for plasma atherogenicity[8]. Here we reported that the prognosis of the high AIP group was significantly worse than that of the low AIP group, and the difference was mainly due to MACEs including cardiovascular deaths and nonfatal myocardial infarction. From these results, we speculated that AIP was most likely a reflection of atherosclerosis, the primary underlying cause of CVD that can lead to stroke and acute coronary syndrome. AIP was thereby associated with acute coronary syndromes, CVD and its risk factors[8, 30]. In patients with T2DM, incidence of MACEs lowered in patients with lower AIP after PCI, possibly as a result of low rate of revascularization[7]. Therefore, AIP could be used as powerful marker for cardiovascular events in patients with T2DM, and further research is needed to unveil the molecular mechanism behind the correlation between AIP, MACEs, T2DM.

This study has some limitations. First, this is a post-hoc, exploratory analysis of the ACCORD trial, and there might be confounding factors included in the original study that we could not control for. Second, patients included in the study were mainly Caucasians; subsequently, our conclusions might not apply to other populations. Despite that these limitations might interfere with the clinical application of AIP threshold found in our study, our results have showed that it is absolutely necessary to strictly manage the levels of lipid and glucose among T2DM patients. Third, parameters used to calculate AIP was collected during the study, and changes in AIP were not monitored during follow-up. Hence, further studies are needed to evaluate the clinical application of AIP among patients with T2DM.

Conclusion

Taken together, by analyzing a large-scale clinical trial that involved 10,251 randomized T2DM patients, our study suggested that AIP could be a strong prognostic marker to assess the risk of cardiovascular events in patients with T2DM. Specifically, diabetic patients with high AIP were more likely to experience cardiovascular events. The information obtained from this study has provided more insights on the discovery and clinical guidance of a new MACE bioindicator to be used among high-risk populations.

Declarations

Acknowledgements

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Availability of data and material

The datasets used and analyzed during the current study are available from the ACCORD/ACCORDIN Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center. The contents of this report do not necessarily reflect the opinions or views of the ACCORD/ACCORDIN study authors or the NHLBI.

Code availability

Not applicable

Authors' contributions

This study was completed in collaboration with the following authors: YW and ST defined the study theme and methods. LF, YZ, and JS analyzed the data. LF wrote the paper. ZX, ZZ, ST, and SZ edited the paper. All authors read and approved the final manuscript.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

All the authors listed above approved the manuscript for publication.

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Figures

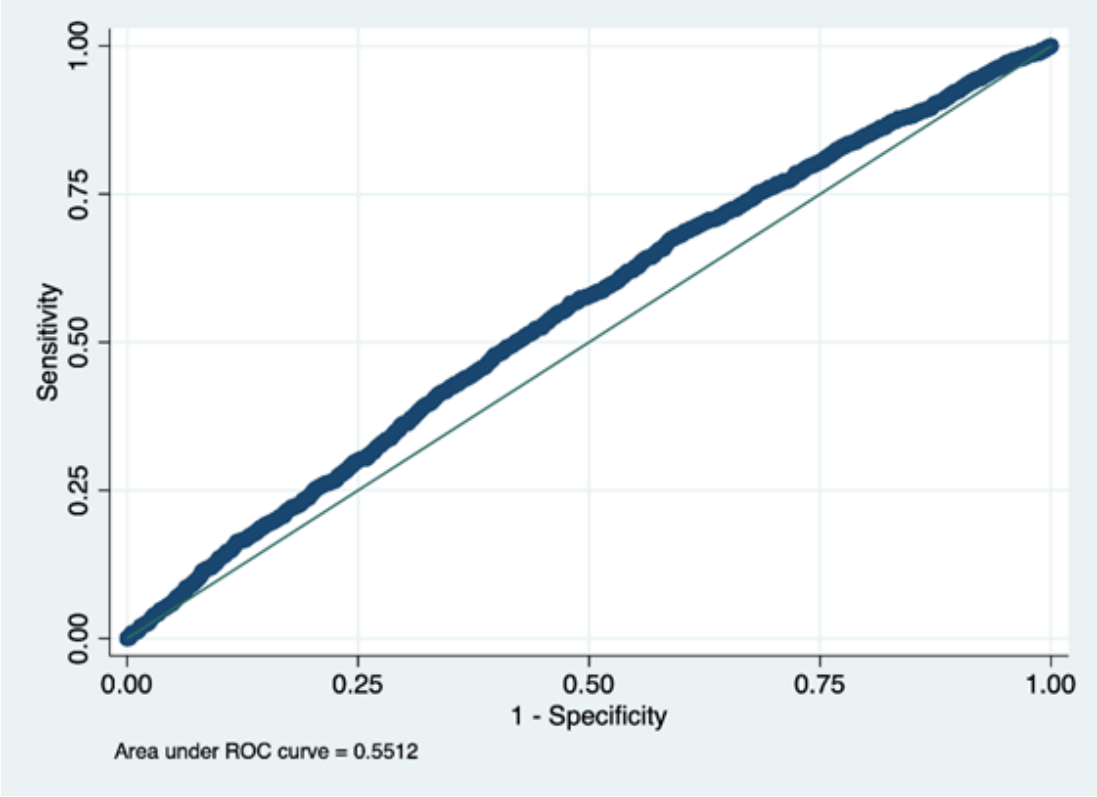

Figure 1

Area Under the Curve (AUC) for AIP in differentiate MACEs outcome in the cohort.

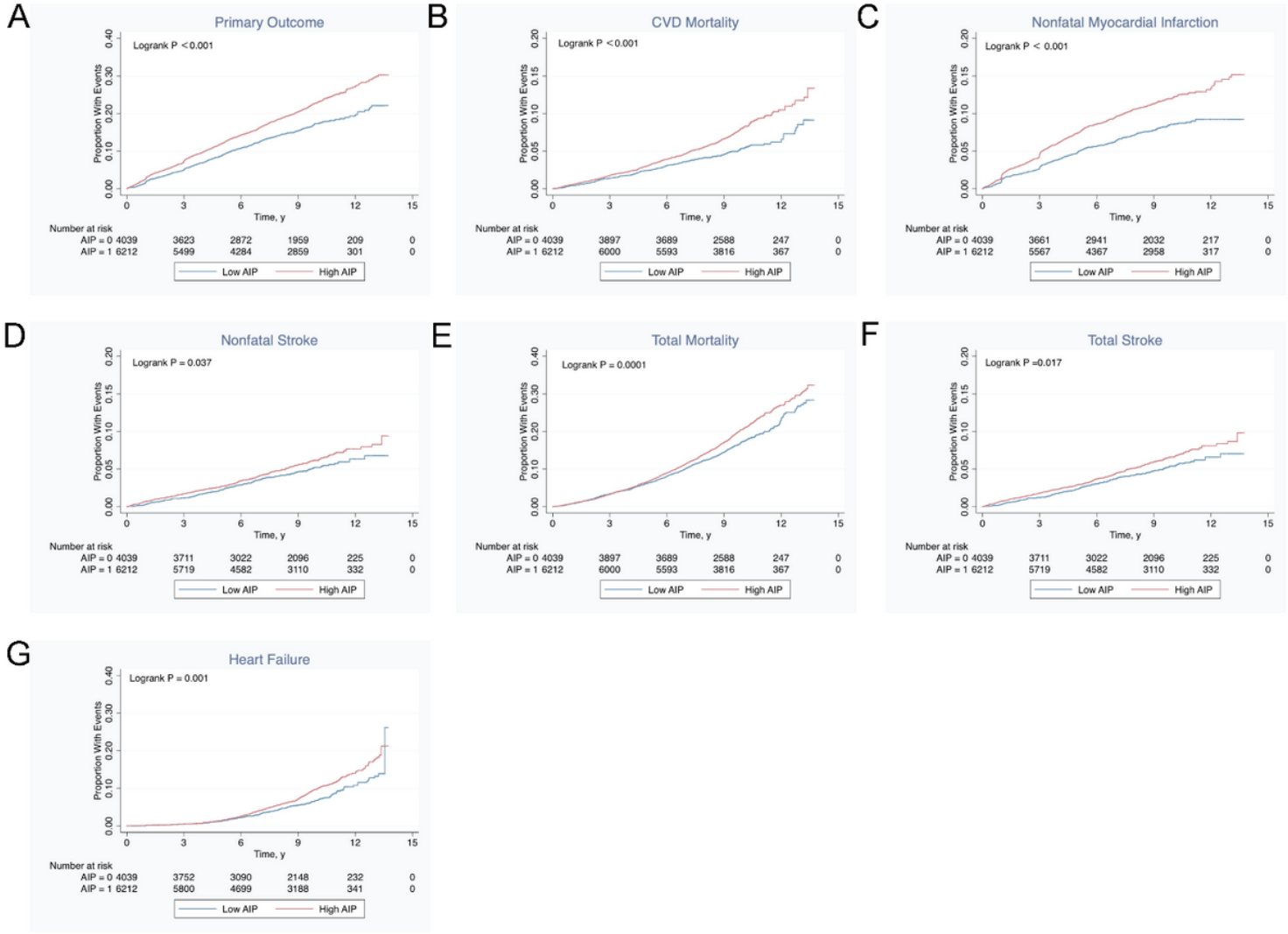

Figure 2

Kaplan–Meier Curves for the Primary and Secondary Outcomes. Low AIP vs High AIP in (A) Primary outcome, (B) CVD mortality, (C) Nonfatal Myocardial Infarction, (D) Nonfatal Stroke, (E) Total Mortality, (F) Total Stroke and (G)Heart Failure.

Supplementary Files

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- SupplementalFig1.png
- SupplementalFig2.png