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ORIGINAL RESEARCH

Elevated Circulating Adipocyte-Fatty Acid Binding Protein Levels Predict Incident Ischemic Cardiovascular Events in a Longitudinal and Prospective AMI Aging Study

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Background: The protein known as Fatty Acid-Binding Protein 4 (FABP4), predominantly found in adipocytes, macrophages, and endothelial cells, has emerged as a pivotal biomarker linking inflammation and metabolism in the context of cardiovascular diseases.

Aim: The present investigation sought to elucidate the influence of FABP4 on the prognostic ramifications for patients experiencing ischemic vascular events, which encompass ischemic cerebrovascular occurrences, myocardial infarctions, and cardiovascular mortality.

Methods: A total of 1102 consecutive patients diagnosed with acute myocardial infarction (AMI) and aged over 55 years were prospectively enrolled from March 2017 to January 2020. Initially, participants were stratified into three groups according to the tertile levels of FABP4, followed by further categorization based on various lipid profiles and specific inflammatory markers.

Results: On follow-up (median 751 days, maximum 1506 days), a total of 158 ischemic events were recorded. 1) In multivariable models meticulously adjusted for age, gender, traditional coronary heart disease factors, Killip classification, and discharge medications, the association of elevated levels of FABP4 (Tertile 3 HR 1.618 [1.061 to 2.468], p=0.026), augmented concentrations of PTX3 (Tertile 3 HR 1.811 [1.211 to 2.710], p=0.004), or LL-37 (Tertile 3 HR 0.651 [0.433 to 0.981], p=0.040) with ischemic risk was markedly intensified. 2) Multivariate HRs associated with 1 standard deviation (SD) (mg/dL) increase in the FABP4 parameters were as follows in different subgroups. 1-SD difference in FABP4 was associated with a 23%, 23%, 21 and 29% increase in ischemic events over after fully adjusted the confounding risk factors among male, patients with hyperlipidemia, hypertension and diabetes respectively. 3) The Kaplan-Meier curve demonstrated significant differences between the tertiles of FABP4 index levels among all enrolled participants (p=0.0180).

Conclusion: This study reinforces the utility of FABP4 for enhancing risk stratification specifically among older patients diagnosed with ST-elevation myocardial infarction.

Keywords: FABP4, lipid profile, PTX3, LL-37, ischemic vascular events

Introduction

Proteins released or secreted into the bloodstream from atherosclerotic lesions may offer novel metrics for addressing the burden of atherosclerosis and mitigating cardiovascular risk in individuals. Fatty acid-binding protein 4 (FABP4), predominantly localized within adipocytes, can also be upregulated in macrophages, endothelial cells, vulnerable plaques, and ruptured atherosclerotic plaques found in the carotid arteries. This phenomenon has been substantiated

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through comprehensive genome-wide expression analyses of isolated macrophages followed by meticulous quantification of FABP4.[1] Elevated levels of FABP4 have been linked to plaque instability and an augmented risk of cardiovascular events.[2,3] The burgeoning interest in FABP4 is largely predicated on recent findings that underscore its pivotal role as a crucial nexus between inflammation and metabolism in cardiovascular diseases; it achieves this by modulating inflammatory activation within macrophages and consequently influencing the expression of inflammatory chemokines, cytokines, cyclooxygenase-2, and inducible nitric oxide synthase.[4,5] Building upon these foundational insights, circulating levels of FABP4 have been observed to rise significantly in plasma—particularly evident within blood monocytes—and brain macrophages following middle cerebral artery occlusion during experimental atherosclerosis.[6] Pharmacological inhibition of FABP4 correlates with reductions in ischemic lesion size, diminished brain edema, and preservation of blood-brain barrier integrity when administered early during stroke treatment.[7,8] Moreover, serum levels of FABP4 exhibit an increase post-stroke that correlates with mortality rates. Notably, individuals harboring allelic variants associated with reduced expression levels appear to manifest lower triglyceride concentrations—thereby potentially diminishing their cardiovascular risk profile.[9,10] Altogether, these lines of evidence further substantiate the proposition that targeting such a molecule may constitute a legitimate therapeutic strategy in the realm of cardiovascular disorders. We have previously elucidated that elevated serum levels of inflammatory biomarkers—including proprotein convertase subtilisin/kexin type 9 (PCSK9), pentraxin 3 (PTX-3), antimicrobial peptide LL-37 (LL-37), and Lipoxin A4 (LXA4)—are independently correlated with major adverse cardiovascular events.[11–13] Moreover, the modulation index of lipid metabolism encompasses resolvin D1 (RVD) alongside traditional lipid profiles. In this context, we meticulously characterized the utility of varying serum levels of FABP4, inflammation indices, and lipid metrics for predicting ischemic cardiovascular risk within a substantial population-based prospective cohort comprising elderly individuals. To achieve this objective, we scrutinized their interrelations and compared the efficacy of predictive models integrating these parameters. This endeavor was executed in two distinct phases: (1) by conducting head-to-head comparisons among FABP4 and various inflammation and lipid measures to ascertain whether FABP4 could serve as an effective predictor for ischemic risk; and (2) by assessing whether increments in FABP4 can incrementally enhance predictions regarding coronary heart disease (CHD) risk beyond established CHD risk factors, including conventional lipid measurements.

Materials and Methods

Study Sample

The Longitudinal and Prospective Aging Study China, a population-based investigation involving 1102 men and women aged 55 to 85 years, was conducted at Fuwai Hospital in Beijing, China (Diagnosis and Treatment of Acute Coronary Syndrome Group of Yan Hongbing from Fuwai Hospital - Chinese Academy of Medical Sciences (CAMS)). This national tertiary care institution specializes in cardiovascular diseases and has consecutively enrolled patients who underwent emergency coronary angiography due to an acute myocardial infarction (AMI) diagnosis between March 2017 and January 2020 (as illustrated in Figure 1). Diagnosis and classification of AMI were performed according to contemporary guidelines and universal definitions,[14] encompassing criteria based on clinical presentations, typical electrocardiographic characteristics, dynamic changes in cardiac enzymes, as well as imaging evidence. The current cohort has included all patients diagnosed with acute myocardial infarction at baseline. Patients were excluded from the final analysis if they lacked available measurements of plasma fatty acid-binding protein 4 (FABP4) or had no follow-up records. The study adhered to the principles outlined in the Declaration of Helsinki; it received approval from the ethics committee of the institute (No.2017–866), with all participants providing written informed consent during hospitalization.

Blood Samples Collection and Measurements

Venous blood samples for complete blood count, basic metabolic panel (including parameters such as creatinine and glucose), cardiac troponin I (cTnI), and N-terminal prohormone of brain natriuretic peptide (NT proBNP) were collected into tubes containing ethylene diamine tetraacetate (EDTA) prior to percutaneous coronary intervention (PCI). The

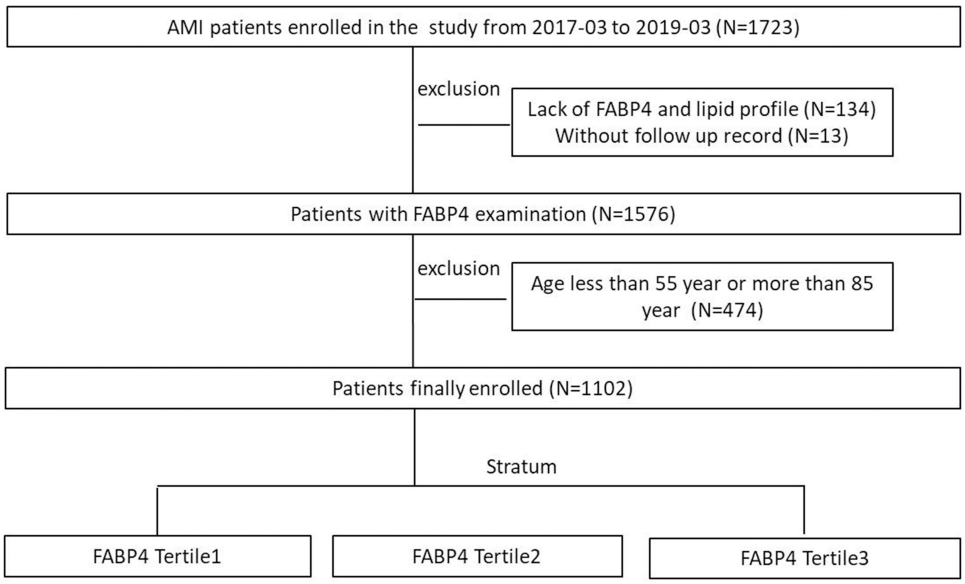

Figure 1 Flow chart.

samples were then centrifuged at 2000 × g for 15 minutes at room temperature, with the plasma subsequently frozen for PTX3 analysis and stored at −80°C until further examination. Enzyme-linked immunosorbent assays (ELISA) were performed using the MultiSkan MK3 instrumental platform (Thermo Scientific). Blood cell counts were determined utilizing an automatic hematology analyzer (XT 1800i; Sysmex Corporation). The concentrations of blood glucose and creatinine were measured with an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan), in accordance with standard protocols established by our core laboratory. For the measurement of FABP4, LL-37, PTX3, RVD, LXA, and PCSK9 levels in plasma, samples were obtained via radial or femoral access before commencing coronary angiography (CAG). These samples were collected in vacutainer tubes containing EDTA, immediately centrifuged at 2000 × g for 15 minutes at room temperature to isolate plasma, which was subsequently stored at −80 °C until further analysis. ELISA kits were utilized to measure plasma FABP4 and LL-37 levels using products from HyCult Biotechnology (HK321; Uden, Netherlands) as well as PCSK9 measurements obtained from R&D Systems (DY3888; Minneapolis, MN USA), following manufacturer instructions with comparisons made against purified human PCSK9 standards. Circulating levels of PTX3 were quantified through ELISA using reagents supplied by R&D Systems (USA). Blood samples intended for lipid profiling and other routine tests were drawn via cubital vein puncture immediately upon patient admission to the coronary care unit.

The plasma concentrations of triglycerides, LDL-C, and HDL-C were measured using an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). Serum levels of lipoprotein(a) [lp(a)] were determined by the immunoturbidimetry method (LASAY Lp(a) auto, SHIMA Laboratories Co., Ltd., Tokyo, Japan). HbA1c levels were assessed with a Tosoh Automated Glycohemoglobin Analyzer (HLC-723G8, Tokyo, Japan). The level of high-sensitivity C-reactive protein was quantified using immunoturbidimetry (Beckmann Assay, Bera, CA, USA). Baseline data encompassing patient clinical demographics—including age, sex, smoking status; medical history regarding hypertension; diabetes; hyperlipidemia; chronic kidney disease; and prior percutaneous coronary intervention (PCI)—as well as laboratory results from primary PCI procedures and medical treatments were obtained from hospital records. Serum levels of FABP4, lipid profiles, and inflammatory biomarkers were analyzed through standard laboratory techniques at Fuwai Hospital.

Endpoints and Follow-Up

Ischemic vascular events were defined as a composite of ischemic stroke, non-fatal MI, and cardiovascular mortality. Stroke was diagnosed based on the presence of rapidly developing focal or widespread brain dysfunction that persisted

for more than 24 hours or resulted in death, with non-vascular causes being excluded. Non-fatal MI was identified by symptoms indicative of typical chest pain or characteristic changes in serial electrocardiograms, corroborated by positive cardiac troponin levels. A clinical follow-up was conducted after three years through direct interviews, telephone calls, and review of hospital discharge records or clinical notes in cases of death. This follow-up was performed by well-trained physicians and nurses overseeing the patients enrolled in the study. The follow-up protocol received approval from the Institutional Review Board at Fuwai Hospital. Physicians specifically trained to manage the primary endpoints—including angina pectoris, cardiac death, all-cause mortality, non-fatal MI, revascularization procedures, heart failure, ischemic stroke, hemorrhagic apoplexy, and bleeding events—identified and extracted these endpoints from various sources such as hospital records, laboratory reports, emergency documentation, medical files, and required clinical notes sent to our centers. More than two professional physicians who were blinded to both clinical data and angiographic findings independently verified all clinical endpoints.

Statistical Analysis

The distribution of outcome variables was evaluated using the Kolmogorov–Smirnov test. Continuous data are presented as the median (median ± standard deviation) for both normal and non-normal distributions. Between-group differences were assessed using an independent samples *t*-test or the Mann–Whitney *U*-test, depending on whether the data were normally or non-normally distributed, respectively. Categorical data are reported as counts (percentages) and compared using Pearson's chi-squared (χ^2) test or Fisher's exact test, as deemed appropriate. To assess the associations between FABP4 levels and the incidence of ischemic cardiovascular events, multivariable Cox proportional hazards regression models were employed with adjustment for confounding factors. Kaplan-Meier survival curves were constructed to evaluate the incidence rates of ischemic cardiovascular events among groups categorized by optimal tertile points of FABP4, while discrepancies in cumulative event rates were analyzed using the Log rank test. Statistical analyses were conducted utilizing SPSS (version 20.0; IBM Corp., Armonk, NY, USA), R Programming Language X64 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria), and MedCalc version 18.2.1 (MedCalc Software, Ostend, Belgium). A significance level of $P < 0.05$ was established for all statistical tests with two-tailed P values reported throughout.

Results

On follow-up (median 751 days, maximum 1506 days), there were 158 ischemic events (117 in men) including recurrence MI, ischemic stroke and cardiovascular death.

Population Characteristics and Intra-Correlations

Compared with male, females were more likely to have hypertension, lower incidence of myocardial infarction and PCI, lower levels of LL-37, creatinine, higher levels of FABP4, PCSK9, hs-CRP, HDL-C, LDL-C, and higher levels of all other lipid parameters among patients free of ischemic events (Table 1). Among patients with ischemic events, female was more likely to be older, higher level of FABP4, Fasting glucose and HDL-C, lower level of LL-37 and creatinine compared with male (Table 1).

As expected, FABP4 was inter-correlated with lipid profile biomarkers and inflammation biomarkers in the enrolled cohort and the subgroups (Table 2). FABP4 was positive correlated with HDL-C (r=0.0642, p=0.0332), LDL-C (r=0.0639, p=0.0340), TC (r=0.0644, p=0.0324), LXA (r=0.0745, p=0.0134) and hs-CRP (r=0.0773, p=0.0113). However, FABP4 was negative with LL-37 (r=−0.0786, p=0.009). By taking gender categorization, FABP4 was correlated with LL-37 (r=−0.0835, p=0.0170), hs-CRP (r=0.0794, p=0.0233) among male (Figure 2A) and TC (r=0.1196, p=0.0433) among female (Figure 2B). FABP4 was correlated with PCSK9 (r=−0.0860, p=0.0239), LDL-C (r=−0.0841, p=0.0272), LXA (r=−0.0901, p=0.0179), hs-CRP (r=−0.0989, p=0.0093) among patients without DM (Figure 2C). FABP4 was correlated with RVD (r=−0.1083, p=0.0280), HDL-C (r=−0.0973 p=0.0484), LPA (r=−0.1177, p=0.0168) and LL-37 (r=−0.1064, p=0.0308) among DM subgroup (Figure 2D). FABP4 was correlated with LL-37 and hs-CRP among patients with hypertension or hyperlipidemia (Figure 2E-H).

Table 1 Baseline Clinical and Procedure Characteristics of the Study Population Divided by the Occurrence of Ischemic Events

Variables	Whole Cohort (N =1102)	Free of Ischemic Events (%)		Ischemic Events (%)		P value	P' value
		Male (N =699)	Female (N =245)	Male (N =117)	Female (N =41)		
Age (years)	66.88 ± 8.33	65.31 ± 7.63	70.74 ± 8.62	66.59 ± 8.54	71.50 ± 8.68	<0.001*	0.002*
Heart rate (beats/min)	74.93 ± 21.86	74.69 ± 24.63	74.61 ± 15.62	75.93 ± 16.82	78.12 ± 15.64	0.394	0.302
SBP (mmHg)	126.00 ± 19.90	125.41 ± 19.91	127.60 ± 19.89	125.50 ± 19.05	127.98 ± 22.15	0.213	0.357
DBP(mmHg)	77.09 ± 12.60	78.42 ± 12.94	73.84 ± 10.82	77.68 ± 12.15	72.27 ± 13.43	<0.001*	0.081
Risk factors							
Hypertension[%(n)]	760 (68.97%)	461 (65.95%)	187 (76.33%)	82 (70.09%)	30 (73.17%)	0.030*	0.708
Hyperlipidemia[%(n)]	997 (90.47%)	635 (90.84%)	219 (89.39%)	106 (90.60%)	37 (90.24%)	0.504	0.947
Smoking[%(n)]	729 (66.64%)	575 (82.85%)	46 (18.93%)	102 (87.18%)	6 (15.00%)	<0.001*	<0.001*
CKD[%(n)]	109 (9.89%)	57 (8.15%)	25 (10.20%)	16 (13.68%)	11 (26.83%)	0.327	0.054
Peripheral atherosclerosis	77 (6.99%)	49 (7.01%)	15 (6.12%)	11 (9.40%)	2 (5.00%)	0.634	0.383
History of MI	220 (19.96%)	145 (20.74%)	26 (10.61%)	37 (31.62%)	12 (29.27%)	<0.001*	0.779
History of PCI	225 (20.42%)	144 (20.60%)	34 (13.88%)	39 (33.33%)	8 (19.51%)	0.021*	0.096
History of CABG	31 (2.81%)	22 (3.15%)	5 (2.04%)	3 (2.56%)	1 (2.44%)	0.371	0.965
Lipid measures/median (25th-75th percentile)							
FABP4	7.77 ± 7.00	6.81 ± 5.89	9.24 ± 8.10	8.36 ± 7.03	13.63 ± 11.59	<0.001*	0.010*
PCSK9	72.00 ± 81.82	68.27 ± 80.63	77.98 ± 77.11	74.79 ± 94.24	92.00 ± 88.94	0.011*	0.260
rvd	230.95 ± 266.93	237.76 ± 278.46	219.47 ± 272.80	215.66 ± 194.94	226.89 ± 204.00	0.371	0.798
HDL-C (mg/dl)	1.10 ± 0.31	1.07 ± 0.32	1.17 ± 0.29	1.08 ± 0.29	1.25 ± 0.34	<0.001*	0.002*
LDL-C (mg/dl)	2.58 ± 0.87	2.54 ± 0.82	2.81 ± 0.96	2.41 ± 0.88	2.44 ± 0.82	<0.001*	0.826
Triglycerides (mmol/L)	1.55 ± 0.96	1.51 ± 0.97	1.61 ± 0.86	1.63 ± 1.14	1.47 ± 0.65	0.006*	0.777
Total cholesterol (mmol/L)	4.24 ± 1.83	4.18 ± 2.13	4.54 ± 1.12	3.98 ± 1.04	4.16 ± 0.84	<0.001*	0.199
LPA (g/L)	277.65 ± 280.76	267.21 ± 269.01	288.15 ± 283.74	295.85 ± 321.87	341.06 ± 328.07	0.369	0.373
TC/HDL-C	4.17 ± 4.14	4.30 ± 5.11	4.04 ± 1.19	3.87 ± 1.26	3.53 ± 0.99	0.869	0.211
LDL-C/HDL-C	2.65 ± 4.20	2.78 ± 5.22	2.51 ± 0.98	2.36 ± 1.00	2.11 ± 0.86	0.834	0.209

(*Continued*)

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Table 1 (Continued).

Variables	Whole Cohort (N =1102)	Free of Ischemic Events (%)		Ischemic Events (%)		P value	P' value
		Male (N =699)	Female (N =245)	Male (N =117)	Female (N =41)		
Other laboratory examinations/median (25th-75th percentile)							
PTX3	10.44 ± 21.98	10.07 ± 23.20	9.41 ± 9.34	12.01 ± 18.55	18.58 ± 47.82	0.591	0.478
LXA	7.04 ± 5.42	6.98 ± 5.55	7.17 ± 4.82	6.69 ± 5.25	8.30 ± 6.83	0.255	0.179
LL37	23.35 ± 13.95	24.33 ± 13.73	21.54 ± 13.93	23.25 ± 14.93	17.83 ± 12.93	0.001*	0.026*
hs-CRP (mg/L)	6.71 ± 9.56	6.64 ± 11.46	6.78 ± 4.66	6.67 ± 4.81	7.61 ± 5.00	0.044*	0.290
Creatinine (mmol/L)	91.25 ± 39.23	92.49 ± 29.61	80.38 ± 51.91	105.28 ± 49.53	94.94 ± 46.64	<0.001*	0.030*
Fasting glucose (mmol/L)	8.52 ± 3.96	8.18 ± 3.65	8.87 ± 3.82	8.78 ± 4.58	11.45 ± 6.18	<0.001*	0.012*
cTnI at baseline level	5.93 ± 14.07	5.62 ± 13.94	5.54 ± 12.21	8.38 ± 17.15	6.44 ± 16.45	0.097	0.781
cTnI at peak level	22.50 ± 26.59	22.52 ± 25.86	20.22 ± 25.50	25.22 ± 29.62	28.25 ± 34.59	0.162	0.890
NT-proBNP at baseline level	1307.38 ± 3053.80	897.41 ± 2308.44	1693.45 ± 2999.88	1981.51 ± 3435.68	4124.23 ± 7911.68	<0.001*	0.031*
NT-proBNP at peak level	3551.27 ± 5952.38	2626.58 ± 4200.67	4460.44 ± 6665.75	4590.66 ± 7461.78	10,894.63 ± 12,488.18	<0.001*	<0.001*
Discharge medication regimen							
Aspirin[%(n)]	1035 (95.22%)	665 (95.82%)	229 (94.63%)	108 (95.58%)	33 (86.84%)	0.440	0.061
Statin[%(n)]	1048 (96.41%)	672 (96.83%)	234 (96.69%)	107 (94.69%)	35 (92.11%)	0.918	0.560
Clopidogrel[%(n)]	596 (54.83%)	360 (51.87%)	156 (64.46%)	59 (52.21%)	21 (55.26%)	<0.001*	0.744
Ticagrelor[%(n)]	474 (43.61%)	325 (46.83%)	85 (35.12%)	51 (45.13%)	13 (34.21%)	0.002*	0.239
Beta-Blockers[%(n)]	907 (83.44%)	572 (82.42%)	209 (86.36%)	94 (83.19%)	32 (84.21%)	0.155	0.883
PPI	621 (57.18%)	381 (54.90%)	161 (66.53%)	59 (52.21%)	20 (54.05%)	0.002*	0.846
Drug of anticoagulation	36 (3.31%)	19 (2.74%)	9 (3.72%)	5 (4.42%)	3 (8.11%)	0.440	0.387
Endpoints							
All caused mortality	97 (8.80%)	23 (3.29%)	15 (6.12%)	40 (34.19%)	19 (46.34%)	0.052	0.166
Recurrence HF	27 (2.45%)	10 (1.43%)	11 (4.49%)	4 (3.42%)	2 (4.88%)	0.005*	0.674
Recurrence revas	180 (16.33%)	101 (14.45%)	28 (11.43%)	41 (35.04%)	10 (24.39%)	0.236	0.209
Bleeding events	441 (40.02%)	298 (42.63%)	94 (38.37%)	38 (32.48%)	11 (26.83%)	0.244	0.501

Notes: Continuous data are presented as median (median±standard deviation). Categorical data are presented as number (%). If it is a continuous variable, it can be obtained by Kruskal Wallis rank sum test. If the counting variable is less than 10, it can be obtained by Fisher exact probability test. *P<0.05.

Abbreviations: DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diabetes blood pressure; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; HDL, high density lipoprotein; LDL, low density lipoprotein; TnI, troponin; CK-MB, creatine kinase isoenzymes; LPA, Lipase activator; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; hs-CRP, high sensitive C-reactive protein; LAD, left anterior descending artery; LCX left circumflex artery; RCA right coronary artery; SVD single vessel disease; DVD double vessel disease; TVD triple vessel disease; AHA, American Heart Association; MACE, major adverse cardiovascular events; MI, myocardial infarction. FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA4, Lipoxin A4, LL-37, Antimicrobial peptide, RVD, Resolvin D1.

Table 2 Correlations* for Plasma FABP4, Lipid Profile Biomarkers and Inflammation Biomarkers Among the Analyzed Subjects

		FABP4	PCSK9	RVD	HDL-C	LDL-C	TG	TC	LPA	TC/HDL-C	LDL-C/HDL-C	LXA	PTX-3	LL-37	Hs-CRP
FABP4	r	-													
	p	-													
PCSK9	*r*	−0.0242	-												
	p	0.4217	-												
rvd	*r*	−0.0402	−0.0830	-											
	p	0.1825	0.0059*	-											
HDL-C	*r*	0.0642	−0.0442	−0.0644	-										
	p	0.0332*	0.1430	0.0325*	-										
LDL-C	*r*	0.0639	−0.0477	0.0486	0.0871	-									
	p	0.0340*	0.1132	0.1067	0.038*	-									
TG	*r*	0.0583	0.1265	0.0916	−0.1981	0.1349	-								
	p	0.0530	<0.001*	0.0023*	<0.001*	<0.001*	-								
TC	r	0.0644	−0.0163	0.0080	0.1606	0.5254	0.1321	-							
	p	0.0324*	0.5878	0.7921	<0.001*	<0.001*	<0.001*	-							
LPA	r	0.0352	0.1048	−0.0085	0.0365	0.1278	−0.0434	0.0962	-						
	p	0.2434	0.005*	0.7779	0.2262	<0.001*	0.1503	0.0014*	-						
TC/HDL-C	r	0.0154	0.0171	0.0263	−0.2720	0.1513	0.1099	0.2934	0.0938	-					
	p	0.6102	0.5717	0.3832	<0.001*	<0.001*	0.0003*	<0.001*	0.0018*	-					
LDL-C/HDL-C	r	0.0038	0.0070	0.0259	−0.1616	0.1277	0.0671	0.0552	0.0760	0.3883	-				
	p	0.8987	0.8165	0.3908	<0.001*	<0.001*	0.0259*	0.0671	0.0117*	<0.001*	-				
LXA	r	0.0745	0.1123	−0.0898	−0.0073	0.0157	−0.0647	0.0041	0.0144	0.0412	−0.0109	-			
	p	0.0134*	0.002*	0.002*	0.8098	0.6028	0.0318*	0.8909	0.6321	0.1721	0.7176	-			
PTX-3	r	−0.0150	0.0622	−0.0076	0.0331	−0.0242	−0.0647	−0.0149	0.0154	−0.0125	−0.0117	0.0960	-		
	p	0.6188	0.0391*	0.7998	0.2728	0.4221	0.0317*	0.6219	0.6105	0.6796	0.6978	0.0014*	-		
LL-37	r	−0.0786	0.2065	−0.1547	−0.1900	0.0972	0.1621	0.0250	−0.0325	0.0524	0.0208	−0.0505	−0.0057	-	
	p	0.009*	<0.001*	<0.001*	<0.001*	0.0012*	<0.001*	0.4073	0.2808	0.0822	0.4895	0.0939	0.8499	-	
hs-CRP	r	0.0773	0.0327	−0.0145	−0.0302	0.0057	0.0364	0.0097	0.0458	0.0150	−0.0058	0.0517	0.0524	0.0254	-
	p	0.0113*	0.2787	0.6311	0.3166	0.8507	0.2279	0.7487	0.1290	0.6182	0.8482	0.0862	0.0822	0.3998	-

Notes: *P for correlation is <0.05. Spearman test was performed for nonnormally distributed variables. Otherwise, Pearson correlation was performed. *P<0.05.

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; LPA, Lipase activator;TC, total cholesterol; TG, Triglycerides; hs-CRP, high sensitive C-reactive protein; FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA4, Lipoxin A4, LL-37, Antimicrobial peptide, RVD, Resolvin D1.

Incidence of Ischemic Events Associated with FABP4 Measures and Other Biomarkers

In multivariable models (Table 3) adjusted for age, gender, traditional CHD factors, killip classification and discharge medication, the association of higher level of FABP4 (T3 HR 1.618 [1.061 to 2.468], p=0.026), higher levels of PTX3 (T3 HR 1.811 [1.211 to 2.710], p=0.004), or LL-37 (T3 HR0.651 [0.433 to 0.981], p=0.040) with ischemic risk was increased, whereas the association of PCSK9 (T3 HR1.138 [0.767 to 1.689], p=0.522), RVD (T3 HR1.286 [0.858 to 1.927], p=0.224) and LXA4 (T3 HR1.347 [0.493 to 1.118], p=0.154) was not.

Continuous hazard ratio across FABP4 for ischemic vascular events by controlling the confounding factors which include gender, age, the history of diabetes mellitus, history of hypertension and history of hyperlipidemia are shown in Figure 3. The restrictive cubic spline analysis showed that the increase of FABP4 was constantly associated with higher risk of ischemic vascular events.

Table 4 shows the association of the level of FABP4 with ischemic events in enrolled patients according to the subgroup of gender and subgroup of with vs without hypertension/ hyperlipidemia/DM and gender. In the subgroup of male, the high tertile of the FABP4 was a risk factor against the incidence of ischemic events compared with the low tertile of the FABP4 in the fully adjusted Cox regression models (HR, 1.780; 95% CI, 1.09–2.90; P=0.0201). Similarly, in the subgroup of hyperlipidemia, the high tertile of the FABP4 has the same tendency in the fully adjusted Cox regression

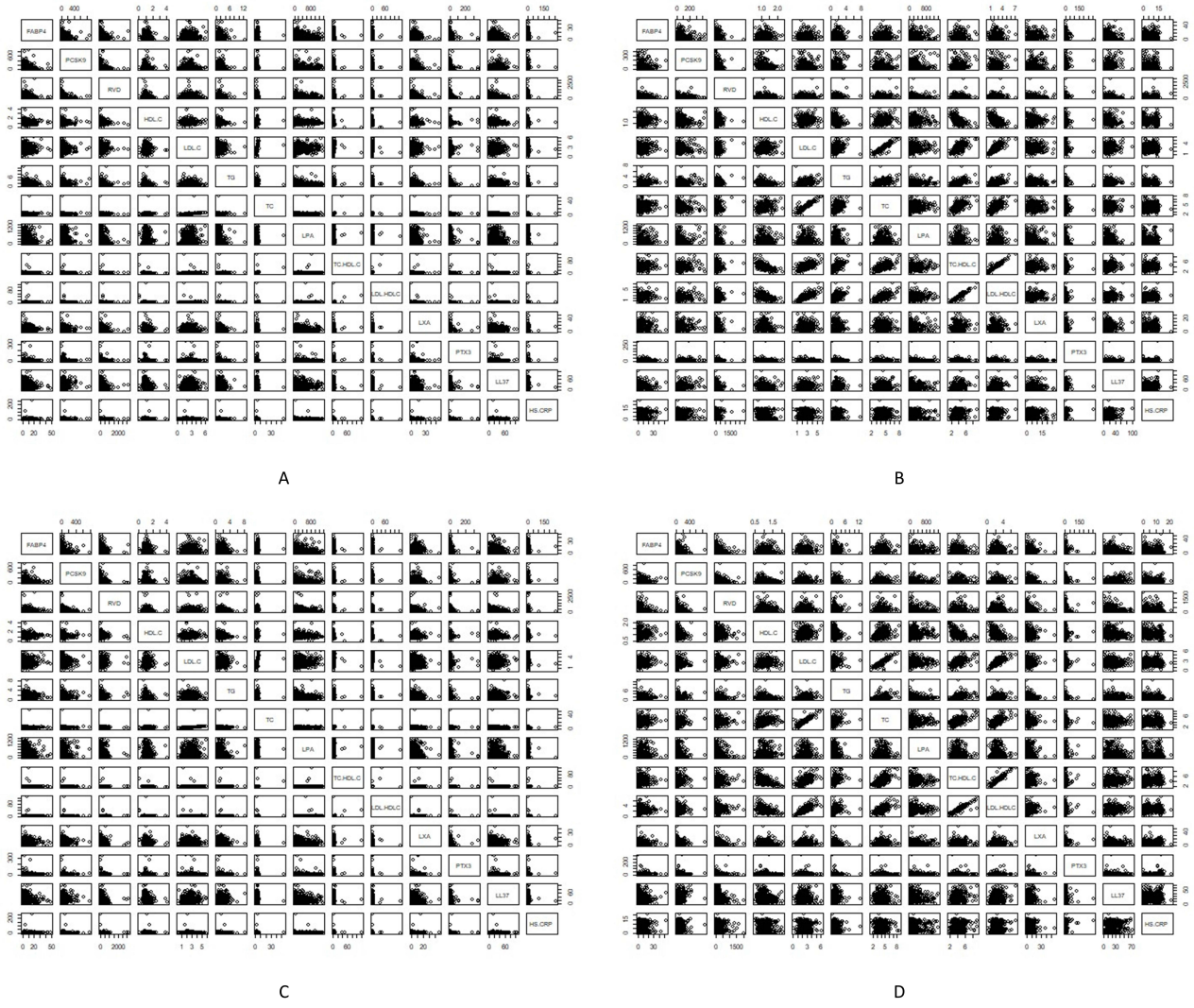

Figure 2 Continued.

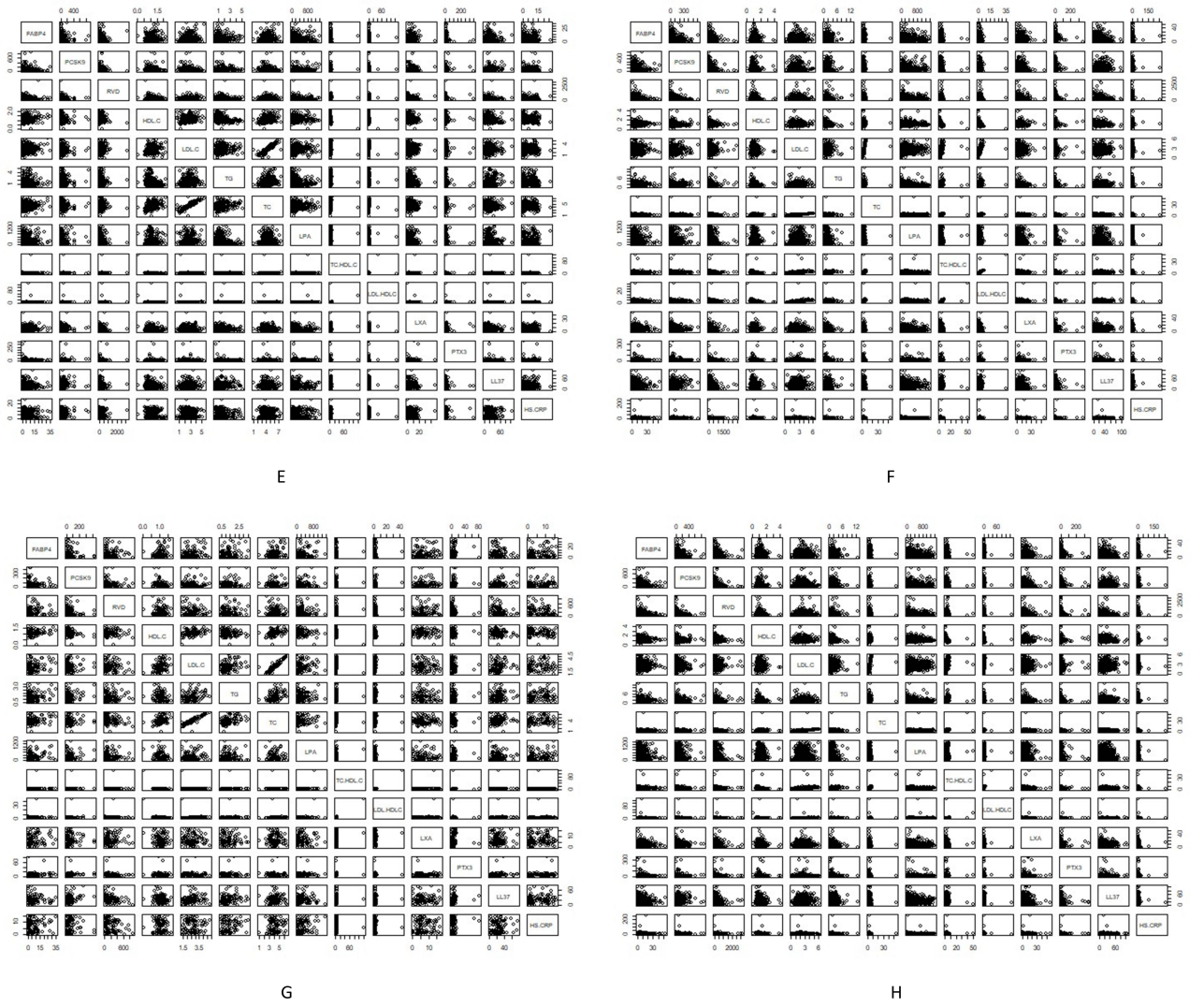

Figure 2 Correlations for Plasma FABP4, lipid profile biomarkers and inflammation biomarkers Among the Analyzed sub-cohort. (**A**), FABP4 was correlated with LL-37 (r=−0.0835, p=0.0170), hs-CRP (r=0.0794, p=0.0233) among male. (**B**), FABP4 was correlated with TC (r=0.1196, p=0.0433) among female. (**C**), FABP4 was correlated with PCSK9 (r=−0.0860, p=0.0239), LDL-C (r=−0.0841, p=0.0272), LXA (r=−0.0901, p=0.0179), hs-CRP (r=−0.0989, p=0.0093) among non-DM cohort. (**D**), FABP4 was correlated with RVD (r=−0.1083, p=0.0280), HDL-C (r=−0.0973 p=0.0484), LPA (r=−0.1177, p=0.0168) and LL-37 (r=−0.1064, p=0.0308) among DM cohort. (**E**), FABP4 was correlated with HDL-C (r=−0.1131, p=0.0365), LDL-C (r=−0.1601, p=0.0030), TC, LXA (r=−0.1083, p=0.0280) among patients without hypertension. (**F**), FABP4 was correlated with LL-37, hs-CRP among hypertension cohort. (**G**), FABP4 was correlated with HDL-C, TG, TC, LPA, hs-CRP among patients without hyperlipidemia. (**H**), FABP4 was correlated with LXA, LL-37, hs-CRP among hyperlipidemia cohort.

Abbreviations, FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA4, Lipoxin A4, LL-37, Antimicrobial peptide LL-37, RVD, Resolvin D1, TC, total cholesterol, HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride;, LPA, Lipase activator; hs-CRP, high sensitive C-reactive protein.

models (HR, 1.840; 95% CI, 1.18–2.88; P=0.0074). Multivariate HRs associated with 1 SD (mg/dL) increase in the FABP4 parameters were as follows in different subgroups. 1-SD difference in FABP4 was associated with a 23%, 23%, 21 and 29% increase in ischemic events over after fully adjusted the confounding risk factors among male, patients with hyperlipidemia, hypertension and diabetes respectively (Table 4). However, the significant correlation was not reflected among subgroups of female, patients without hyperlipidemia, hypertension and diabetes.

Kaplan-Meier curves showing cumulative ischemic vascular events rates for up to median 2.058 years stratified by the tertiles level of FABP and other biomarkers characteristic among enrolled patients. Among all enrolled patients, the K-M curve showed significant differences between the tertiles of FABP4 index levels (p=0.0180) (Figure 4A), PTX-3 (p=0.001) (Figure 4B) and LL-37 (p=0.030) (Figure 4C). However, the difference was not significant among the patients divided by LXA (p=0.870) (Figure 4D), PCSK9 (p=0.490) (Figure 4E), RVD (p=0.870) (Figure 4F).

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Table 3 Associations Between Biomarkers and Incident Ischemic Cardiovascular Events in Multivariate Cox Regression Analyses. Statistically Significant (P < 0.05) Associations are Bolded

		Hazard ratio	95% confidence Interval for HR	Regression Coefficients	Standard Errors Of Regression Coefficients	P for Value
Mutually adjusted and also for age, gender, hypertension, hyperlipidemia, diabetes mellitus (N=1102)	**FABP4**					
	Tertile 1	1	–	–	–	–
	Tertile 2	1.298	0.848–1.986	0.261	0.217	0.2303
	Tertile 3	1.663	1.109–2.493	0.509	0.207	0.0138 *
	PCSK9					
	Tertile 1	1	–	–	–	–
	Tertile 2	1.021	0.685–1.521	0.021	0.203	0.918
	Tertile 3	1.193	0.819–1.738	0.177	0.192	0.357
	RVD					
	Tertile 1	1	–	–	–	–
	Tertile 2	1.105	0.748–1.634	0.099	0.199	0.616
	Tertile 3	1.323	0.898–1.948	0.280	0.198	0.157
	PTX3					
	Tertile 1	1	–	–	–	–
	Tertile 2	1.021	0.675–1.547	0.021	0.212	0.920
	Tertile 3	1.778	1.216–2.598	0.575	0.194	0.003*
	LXA4					
	Tertile 1	1	–	–	–	–
	Tertile 2	0.995	0.680–1.455	−0.005	0.194	0.979
	Tertile 3	0.872	0.590–1.289	−0.137	0.199	0.492
	LL-37					
	Tertile 1	1	-	-	-	-
	Tertile 2	0.770	0.530–1.120	−0.261	0.191	0.172
	Tertile 3	0.627	0.424–0.928	−0.466	0.199	0.020*

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Additionally adjusted for height, weight, heart rate at baseline, systolic blood pressure, diastolic blood pressure, Killip classification, aspirin, Ticagrelor, Clopidogrel (N=1060)	**FABP4**					
	Tertile 1	1	-	-	-	-
	Tertile 2	1.339	0.865–2.071	0.292	0.223	0.191
	Tertile 3	1.618	1.061–2.468	0.481	0.215	0.026*
	PCSK9					
	Tertile 1	1	-	-	-	-
	Tertile 2	1.091	0.721–1.652	0.088	0.211	0.679
	Tertile 3	1.138	0.767–1.689	0.129	0.202	0.522
	RVD					
	Tertile 1	1	-	-	-	-
	Tertile 2	1.123	0.745–1.681	0.116	0.206	0.574
	Tertile 3	1.286	0.858–1.927	0.251	0.207	0.224
	PTX3					
	Tertile 1	1	-	-	-	-
	Tertile 2	1.178	0.765–1.815	0.164	0.221	0.458
	Tertile 3	1.811	1.211–2.710	0.594	0.206	0.004*
	LXA4					
	Tertile 1	1	-	-	-	-
	Tertile 2	1.076	0.628–1.376	−0.073	0.200	0.716
	Tertile 3	1.347	0.493–1.118	−0.298	0.209	0.154
	LL-37					
	Tertile 1	1	-	-	-	-
	Tertile 2	0.850	0.578–1.250	−0.162	0.197	0.409
	Tertile 3	0.651	0.433–0.981	−0.429	0.209	0.040*

Note: *P<0.05.

Abbreviations: FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA4, Lipoxin A4, LL-37, Antimicrobial peptide, RVD, Resolvin D1.

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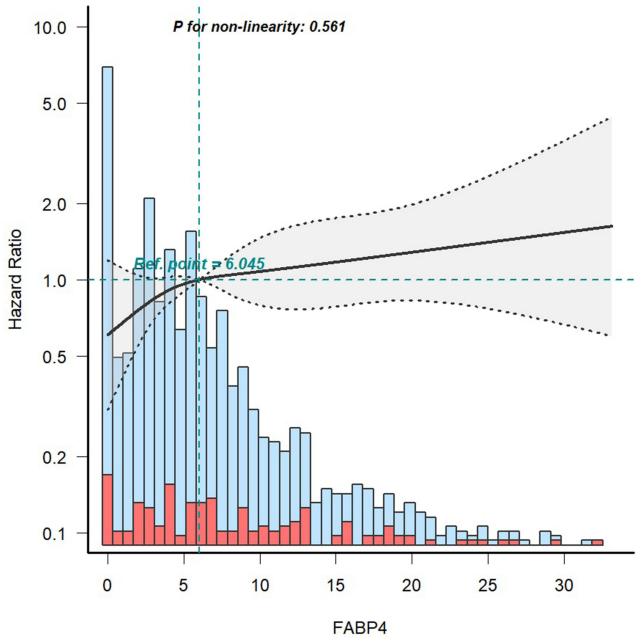

Figure 3 Continuous hazard ratios across FABP4 for ischemic vascular events by controlling the confounding factors. The controlling factors include gender, age, the history of diabetes mellitus, history of hypertension and history of hyperlipidemia. The black line represents the hazard ratio changed by FABP4 and grey represents confidence interval. The blue bar represents the proportion of different level of FABP4.
Abbreviations, HR, hazard ratio; FABP4, Fatty acid-binding protein 4.

Discussion

We evaluated the efficacy of FABP4 and multiple plasma biomarker parameters in predicting future ischemic events in older cohort during median 2.058 years of follow-up, taking into account a variety of CHD risk factors. In a multivariate model adjusted simultaneously for several CHD risk factors, FABP4 appeared to be the primary predictor among older cohort. For clinical practice, using the FABP4, a single parameter that combines the novel biomarkers measurements provides a powerful predictive model independently of several established risk factors. The magnitude of HRs across tertiles is dependent on the absolute risk among women in the bottom tertile and on the independent variation of each FABP4 parameter. Furthermore, association with CHD with a 1-SD increase might standardize this variation. We explored the ability of the FABP4 to discriminate events from nonevents on the background of all other biomarkers and covariates, an approach that may be more applicable in a clinical context.

FABP4 is primarily produced in adipocytes; however, significant amounts of FABP4 are also detected in macrophages, which contribute to the pathogenic composition of atherosclerotic plaques. Quantification studies have shown elevated levels of FABP4 in vulnerable human plaques,[1] and genome-wide expression analyses of isolated macrophages[2] indicate that the expression of FABP4 is increased in ruptured and vulnerable plaques. Conversely, a naturally occurring low-expression variant of FABP4 has been associated with enhanced plaque stability and reduced risk of cardiovascular events.[15] Globally, extensive research efforts have focused on FABP4-deficient mice or animals treated with FABP4 inhibitors, confirming that FABP4 promotes insulin resistance and modulates lipid metabolism as well as diabetes mellitus progression.[16] Compared to control ApoE-knockout mice, FABP4/ApoE double-knockout mice exhibited a significantly reduced tendency for atherosclerosis progression without any notable differences in serum lipids or insulin sensitivity.[17] These findings suggest that FABP4 plays a specific role in the development of atherosclerosis; moreover, macrophage-derived FABP4 may exert marked local pathogenic effects independent from its established roles in systemic glucose or lipid metabolism. The impact of FABP4 on vascular stability following ischemic stroke is particularly noteworthy since bleeding, edema, and blood-brain barrier (BBB) damage often lead to clinical deterioration and adverse outcomes. This has implications for acute phase treatment strategies and secondary prevention planning. Further investigations into the mechanisms by which BBB permeability and brain hemorrhages induced by FABP4 occur

Table 4 Associations Between FABP4 and Incident Ischemic Cardiovascular Events in Multivariate Cox Regression Analyses

Variables	Total	Crude model		Adjusted model I		Adjust model II		Adjust model III	
		Crude HR (95% CI)	Crude P value	Adj I. HR (95% CI)	Adj. P value	Adj. HR (95% CI)	Adj. P value	Adj. HR (95% CI)	Adj. P value
Male	816								
FABP4 per SD		1.25 (1.05, 1.50)	0.0122*	1.19 (0.99, 1.44)	0.0602	1.22 (1.01, 1.47)	0.0382*	1.23 (1.02, 1.48)	0.0336*
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		1.41 (0.88, 2.26)	0.1565	1.56 (0.97, 2.52)	0.0674	1.60 (0.99, 2.60)	0.0540	1.63 (1.00, 2.66)	0.0483*
$FABP4_{high}$		1.80 (1.13, 2.86)	0.0136*	1.68 (1.04, 2.70)	0.0328*	1.76 (1.09, 2.85)	0.0211*	1.78 (1.09, 2.90)	0.0201*
P for trend		1.34 (1.06, 1.68)	0.0132*	1.30 (1.03, 1.63)	0.0250*	1.33 (1.06, 1.68)	0.0147*	1.32 (1.04, 1.66)	0.0203*
Female	286								
FABP4 per SD		1.30 (1.06, 1.58)	0.0108*	1.20 (0.98, 1.49)	0.0841	1.17 (0.95, 1.45)	0.1389	1.15 (0.94, 1.41)	0.1787
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		0.96 (0.37, 2.59)	0.9718	0.93 (0.35, 2.50)	0.8825	0.93 (0.34, 2.51)	0.8861	1.09 (0.38, 3.07)	0.8768
$FABP4_{high}$		1.51 (0.69, 3.31)	0.3023	1.29 (0.57, 2.94)	0.5439	1.28 (0.56, 2.93)	0.5612	1.26 (0.53, 2.99)	0.6061
P for trend		1.29 (0.87, 1.91)	0.1995	1.23 (0.83, 1.84)	0.3009	1.20 (0.81, 1.80)	0.3643	1.11 (0.74, 1.67)	0.6171
With hyperlipidemia	997								
FABP4 per SD		1.28 (1.13, 1.47)	0.0002*	1.22 (1.06, 1.40)	0.0056*	1.23 (1.07, 1.41)	0.0041*	1.23 (1.07, 1.42)	0.0037*
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		1.28 (0.81, 2.01)	0.2934	1.38 (0.87, 2.18)	0.1724	1.40 (0.88, 2.21)	0.1539	1.43 (0.90, 2.27)	0.1323
$FABP4_{high}$		1.91 (1.25, 2.91)	0.0027*	1.83 (1.18, 2.83)	0.0070*	1.88 (1.21, 2.93)	0.0048*	1.84 (1.18, 2.88)	0.0074*
P for trend		1.39 (1.13, 1.72)	0.0019*	1.36 (1.10, 1.69)	0.0046*	1.39 (1.12, 1.72)	0.0029*	1.34 (1.07, 1.66)	0.0090*
Without hyperlipidemia	105								
FABP4 per SD		1.10 (0.72, 1.68)	0.6673	1.08 (0.68, 1.72)	0.7451	1.21 (0.71, 2.06)	0.4884	0.96 (0.54, 1.72)	0.8940
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		1.73 (0.53, 5.69)	0.3646	1.88 (0.55, 6.45)	0.3132	1.93 (0.56, 6.66)	0.2997	4.05 (0.81, 20.17)	0.0882
$FABP4_{high}$		0.70 (0.20, 2.48)	0.5776	0.55 (0.14, 2.10)	0.3834	0.60 (0.14, 2.50)	0.4815	0.14 (0.02, 1.23)	0.0764
P for trend		0.87 (0.49, 1.53)	0.6200	0.83 (0.46, 1.50)	0.5368	0.88 (0.46, 1.66)	0.6896	0.60 (0.27, 1.33)	0.2090

(*Continued*)

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Table 4 (Continued).

Variables	Total	Crude model		Adjusted model I		Adjust model II		Adjust model III	
		Crude HR (95% CI)	Crude P value	Adj I. HR (95% CI)	Adj. P value	Adj. HR (95% CI)	Adj. P value	Adj. HR (95% CI)	Adj. P value
With hypertension	760								
FABP4 per SD		1.22 (1.06, 1.42)	0.0067*	1.19 (1.02, 1.39)	0.0287*	1.20 (1.03, 1.40)	0.0216*	1.21 (1.03, 1.41)	0.0184*
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		1.18 (0.70, 1.97)	0.5400	1.23 (0.73, 2.06)	0.4394	1.24 (0.74, 2.09)	0.4138	1.23 (0.73, 2.07)	0.4327
$FABP4_{high}$		1.62 (1.01, 2.61)	0.0458*	1.52 (0.94, 2.46)	0.0882	1.58 (0.97, 2.57)	0.0670	1.54 (0.94, 2.51)	0.0844
P for trend		1.29 (1.02, 1.63)	0.0369*	1.26 (1.00, 1.60)	0.0545	1.29 (1.01, 1.64)	0.0383*	1.26 (0.99, 1.60)	0.0615
Without hypertension	342								
FABP4 per SD		1.41 (1.06, 1.87)	0.0182*	1.30 (0.95, 1.77)	0.1008	1.26 (0.91, 1.75)	0.1577	1.23 (0.89, 1.69)	0.2072
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		1.57 (0.75, 3.29)	0.2280	1.91 (0.89, 4.09)	0.0947	1.95 (0.91, 4.19)	0.0870	4.05 (0.81, 20.17)	0.0882
$FABP4_{high}$		1.90 (0.91, 3.93)	0.0857	1.74 (0.79, 3.80)	0.1677	1.75 (0.79, 3.88)	0.1644	1.83 (0.81, 4.13)	0.1455
P for trend		1.37 (0.96, 1.95)	0.0841	1.32 (0.92, 1.91)	0.1349	1.31 (0.90, 1.90)	0.1533	1.31 (0.90, 1.90)	0.1569
With DM	412								
FABP4 per SD		1.19 (0.98, 1.44)	0.0792	1.26 (1.06, 1.52)	0.0110*	1.29 (1.07, 1.54)	0.0063*	1.29 (1.07, 1.56)	0.0073*
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		1.35 (0.69, 2.62)	0.3793	1.31 (0.67, 2.55)	0.4233	1.53 (0.78, 3.00)	0.2175	1.57 (0.80, 3.11)	0.1921
$FABP4_{high}$		1.99 (1.09, 3.63)	0.0247*	1.78 (0.96, 3.30)	0.0663	2.05 (1.08, 3.86)	0.0271*	1.88 (1.00, 3.56)	0.0515
P for trend		1.42 (1.06, 1.91)	0.0204*	1.41 (1.04, 1.90)	0.0273*	1.46 (1.07, 1.99	0.0166*	1.36 (1.00, 1.85)	0.0485*
Without DM	690								
FABP4 per SD		1.32 (1.12, 1.57)	0.0010*	1.13 (0.92, 1.40)	0.2445	1.14 (0.92, 1.40)	0.2301	1.15 (0.93, 1.42)	0.2065
$FABP4_{low}$		–	–	–	–	–	–	–	–
$FABP4_{mid}$		1.57 (0.75, 3.29)	0.2280	1.44 (0.82, 2.52)	0.2023	1.48 (0.84, 2.59)	0.1721	1.51 (0.86, 2.68)	0.1550
$FABP4_{high}$		1.90 (0.91, 3.93)	0.0857	1.50 (0.86, 2.60)	0.1523	1.54 (0.89, 2.69)	0.1252	1.54 (0.87, 2.71)	0.1382
P for trend		1.25 (0.97, 1.63)	0.0899	1.22 (0.93, 1.59)	0.1439	1.24 (0.95, 1.62)	0.1181	1.21 (0.92, 1.59)	0.1699

Notes: data presented are HRs and 95% CI. Adjust I model adjusts for age and current smoking; Adjust II model adjusts for adjust I plus height, weight, heart rate at baseline; Adjust III model adjusts for adjust II + systolic blood pressure, diastolic blood pressure and killip classification. *P<0.05.

post-ischemia have revealed substantial literature demonstrating that the activity of FABP4 influences c-Jun N-terminal kinase signaling pathways and metalloproteinase 9. These appear to be critical effectors within the detrimental cascade initiated by up-regulation of FABP4 during stroke events.[18,19] Thus, we selected FABP4 for further validation as a diagnostic and prognostic biomarker for atherosclerotic CAD among older cohort. Our investigations revealed several pivotal findings concerning circulating FABP4, establishing it as a diagnostic and prognostic biomarker intimately linked to ischemic vascular outcomes. In this study, high baseline levels of FABP4 were associated with a higher risk for subsequent adverse events in unadjusted analyses and significantly predicted ischemic events (including ischemic stroke/ recurrence MI/ cardiovascular death) in the elderly who conducted the primary PCI even after adjustment for established cardiovascular risk factors and lipid-lowering drugs. Similarly, the study from in Hong Kong Chinese cohort has demonstrated that circulating FABP4 could predict the development of CAD after adjustment for the traditional risk factors and FABP4 helped marginally to improve the performance of the predictive model with established risk factors.[20]

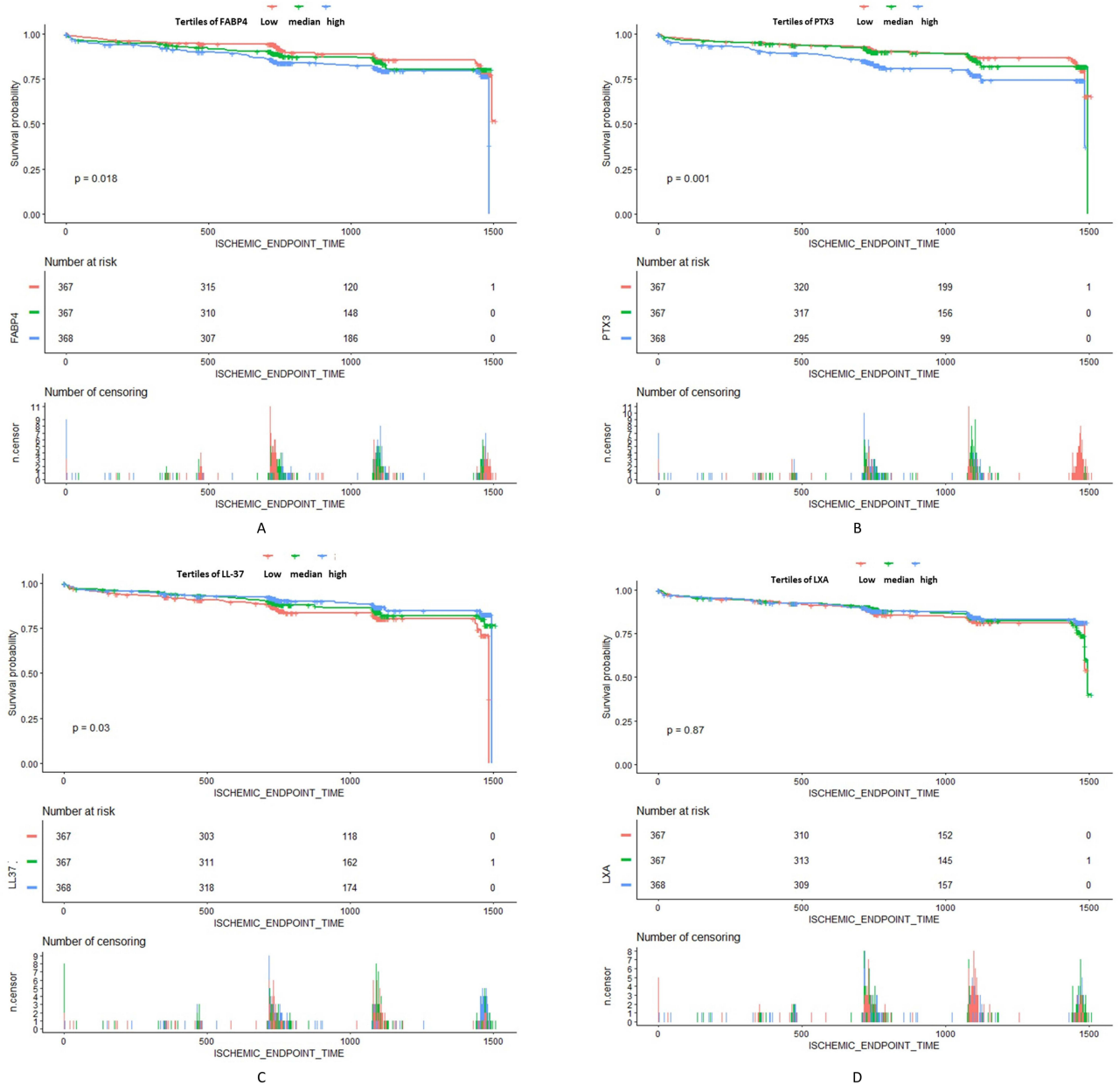

Figure 4 Continued.

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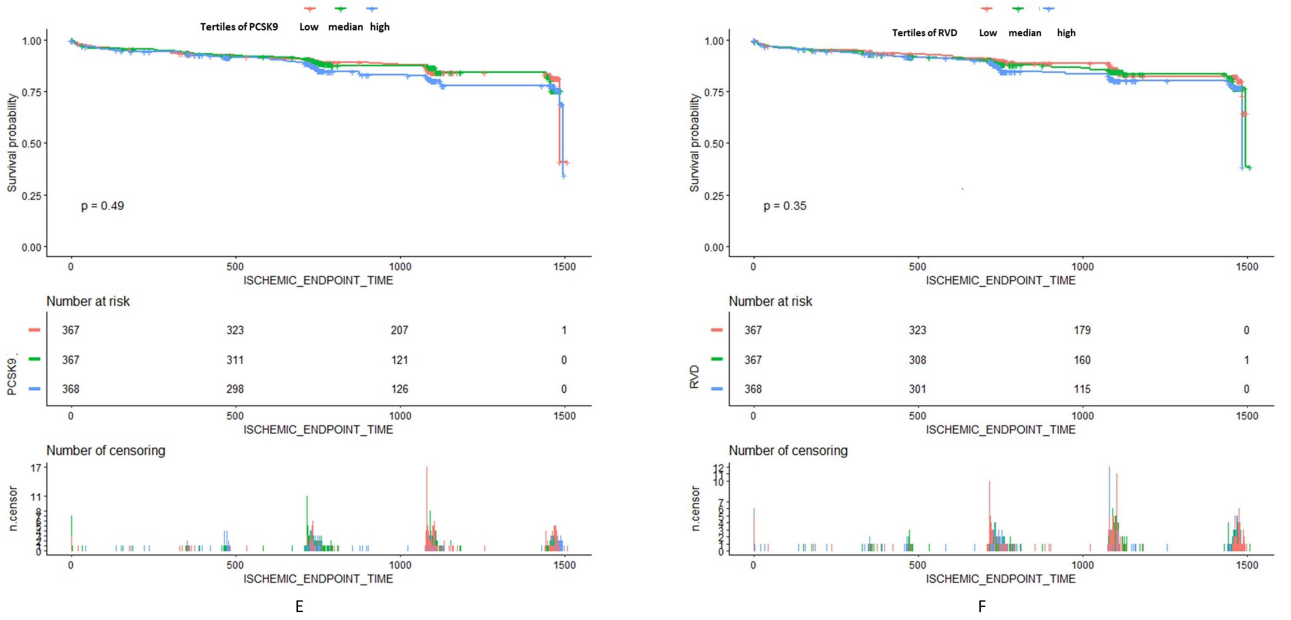

Figure 4 Kaplan-Meier curves showing cumulative MACE rates for up to median 2.058 years stratified by the tertiles level of FABP4/PTX3/LL-37/LXA/RVD characteristic among patients with AMI. Among all enrolled patients, the K-M curve showed significant differences between the tertiles of FABP4 index levels (p=0.0180) (**A**), PTX-3 (p=0.001) (**B**) and LL-37 (p=0.030) (**C**). However, the difference was not significant among the patients divided by LXA (p=0.870) (**D**), PCSK9 (p=0.490) (**E**), RVD (p=0.870) (**F**).
Abbreviations, FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA, Lipoxin A, LL-37, Antimicrobial peptide LL-37, RVD, Resolvin D1.

As noted previously, prior prospective study[21] has demonstrated that circulating FABP4 was remarkable elevated in patients with ACS who experienced adverse cerebrovascular or cardiovascular events within 30 days after the index ACS event and showed the same prognostic power to predict adverse events as the GRACE in-hospital risk score. Deterioration in cerebrovascular or cardiovascular events has been found to be associated with FABP4 in a prospective 10-year long follow-up study of patients with CAD.[22] It is interesting to note that a great correlation of circulating A-FABP4, represent an important pathophysiological mediator of atherosclerosis, with cerebrovascular or cardiovascular events was also observed in a prospective 10-year long follow-up study of patients with CAD which may point to a new target of treatment options.[22] Increased serum FABP4 level has roles in the development of metabolic syndrome, dyslipidemia, insulin resistance, and cardiovascular disease.[20,23–29] Furthermore, previous study has showed that circulating level of FABP4 showed the great prognostic power to predict adverse events as the GRACE in-hospital risk score or NT-proBNP.[15] Due to the different genetic and environmental background, circulating FABP4 associated with carotid intima-media thickness in Chinese women positively or with CAD in nonelderly Japanese men.[30–32] However, correlation above-mentioned was in contrast to the studies in whites.[33] In Table 3, we explored the ability of the FABP4 to discriminate events from nonevents on the background of lipids profile and inflammation covariates, an approach that may be more applicable in a clinical context. Nevertheless, our analysis could only demonstrate the close correlations among FABP4 and incident ischemic cardiovascular events but provide no evidence for any causal relationships.

We found that a 1-SD difference in FABP4 was associated with a 23%, 23%, 21 and 29% increase in ischemic events over after fully adjusted the confounding risk factors among male, patients with hyperlipidemia, hypertension and diabetes mellitus respectively. Previous literature[34] has demonstrated that FABP4 triggers the ubiquitination and subsequent proteasomal degradation of peroxisome proliferator-activated receptor γ which is a master regulator of adipogenesis and insulin responsiveness. The review from Masato Furuhashi[35] has introduced the significant roles of FABP4 as a lipid chaperone in physiological and pathophysiological conditions and the possibility of FABP4 being a therapeutic target for metabolic and cardiovascular diseases are discussed. Further studies are obviously to investigate the mechanism of FABP4 effecting the metabolism and immunization. Youdong Pan[36] et al have shown that mouse CD8+ Tissue-resident memory T cells generated by viral infection of the skin differentially express high levels of FABP4 that

mediate lipid uptake and intracellular transport. They further show that T-cell-specific deficiency of Fabp4 impairs exogenous free fatty acid uptake by CD8+ tissue-resident memory T cells and greatly reduces their long-term survival in vivo. Rs77878271 is a functional, low-expression variant in the promoter of the FABP4 gene. As noted previously, some prior prospective study[37] has indicated that compared with the general population, the low-expression G allele of low-expression variant rs77878271 increased CVD risk and a 1-SD unit decrease in FABP4 increased risk of CAD 2.4-fold, suggesting that genetically low FABP4 levels may be detrimental in the context of type 1 diabetes among patients with type 1 diabetes. In addition, serum FABP4 has been proposed as a novel biomarker for worse cardiometabolic health and kidney complications in type 2 diabetes due to its independent associations with kidney function decline.[38–40] Notely, our study population is predominantly elder patients over 55yr, our results may not directly relate to other age groups. In conclusion, among AMI patients older than 50, elevation of FABP4 had a markedly increased risk of ischemic vascular events. This study demonstrated the usefulness of FABP4 to enhance risk stratification in patients with STEMI especially among older.

Limitation

The following limitations of our study should be considered. Our study was limited by the low incident ischemic vascular disease event rate in our cohort, which precluded sex-specific subgroup analyses of FABP in predicting ischemic vascular disease. The low rate of endpoints might be explained by the fact that mortality of MI is highest during the pre- and early in-hospital phase. On the other hand, our findings could not be extrapolated to other ethnic groups or those subjects with higher CVD risk. Adding FABP to well-established ischemic vascular risk factors resulted improvements to the overall predictive value of the models in classification performance analyses. Thus, our long-term follow-up study supports a clinical assessment of serum FABP for cardiovascular risk stratification and reflects the pathophysiological interpretations of the results. Further studies are needed to allow detailed and a priori-specified comparisons of FABP to other potential cardiovascular risk markers including other lipid profile and inflammation biomarkers. Furthermore, interventional researches which aim to reduce serum FABP in humans are still lacking. Moreover, extrapolation to current patients should be done with caution, bearing in mind that recruitment of individuals for this study are Chinese in the single center. Usage of these modern drugs such as thiazolidinediones could change the associations described in the present study in current patient populations. Finally, outcome assessment may have been imperfect because of the large catchment areas which rely on external information in our study. Taken together, these findings strongly support the role of FABP in mediating ischemic vascular diseases. Long-term interventional studies involving therapeutic agents are warranted including reducing FABP expression or acting such as FABP inhibitors in order to determine this causal relationship.

The Novelty of the Current Study

- We have previously demonstrated that high serum level of inflammation biomarkers includes proprotein convertase subtilisin/kexin type 9 (PCSK9), pentraxin 3 (PTX-3), antimicrobial peptide LL-37 (LL-37) and Lipoxin A4 (LXA4) levels are independently associated with major adverse cardiovascular events.
- The current study aimed to investigate the effects of FABP4 on the prognostic impacts of aging patients with ischemic vascular events. Therefore, we selected patients over 55 years old.
- The difference between the findings of the study published from our research (https://doi.org/10.3390/biom12101482): We characterized the utility of different level of serum FANP4, inflammation indexes and lipid measures for predicting ischemic cardiovascular risk in a large, population-based prospective cohort of elder. We examined their correlation and compared the performance of prediction models incorporating these measures. The magnitude of HRs across tertiles is dependent on the absolute risk among women in the bottom tertile and on the independent variation of each FABP4 parameter. We explored the ability of the FABP4 to discriminate events from nonevents on the background of all other biomarkers and covariates, an approach that may be more applicable in a clinical context.

Consent for Publication and Data Availability

Written informed consent for publication was obtained from all participants. The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

It is from the ethics committee of the department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, China.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no potential conflicts of interest in this work.

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