Circulating FABP4 Is a Prognostic Biomarker in Patients With Acute Coronary Syndrome but Not in Asymptomatic Individuals

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Objective—Blood-borne biomarkers reflecting atherosclerotic plaque burden have great potential to improve clinical management of atherosclerotic coronary artery disease and acute coronary syndrome (ACS).

Approach and Results—Using data integration from gene expression profiling of coronary thrombi versus peripheral blood mononuclear cells and proteomic analysis of atherosclerotic plaque–derived secretomes versus healthy tissue secretomes, we identified fatty acid–binding protein 4 (FABP4) as a biomarker candidate for coronary artery disease. Its diagnostic and prognostic performance was validated in 3 different clinical settings: (1) in a cross-sectional cohort of patients with stable coronary artery disease, ACS, and healthy individuals (n=820), (2) in a nested case–control cohort of patients with ACS with 30-day follow-up (n=200), and (3) in a population-based nested case–control cohort of asymptomatic individuals with 5-year follow-up (n=414). Circulating FABP4 was marginally higher in patients with ST-segment–elevation myocardial infarction (24.9 ng/mL) compared with controls (23.4 ng/mL; *P*=0.01). However, elevated FABP4 was associated with adverse secondary cerebrovascular or cardiovascular events during 30-day follow-up after index ACS, independent of age, sex, renal function, and body mass index (odds ratio, 1.7; 95% confidence interval, 1.1–2.5; *P*=0.02). Circulating FABP4 predicted adverse events with similar prognostic performance as the GRACE in-hospital risk score or N-terminal pro–brain natriuretic peptide. Finally, no significant difference between baseline FABP4 was found in asymptomatic individuals with or without coronary events during 5-year follow-up.

Conclusions—Circulating FABP4 may prove useful as a prognostic biomarker in risk stratification of patients with ACS. (***Arterioscler Thromb Vasc Biol*. 2015;35:1872-1879. DOI: 10.1161/ATVBAHA.115.305365.**)

Key Words: acute coronary syndrome ■ atherosclerosis ■ biological markers ■ FABP4 protein, human ■ follow-up studies

Atherosclerosis is a chronic disease with features of inflammation across the distinct stages of development.[1] Plaque rupture and erosion with ensuing thrombus formation and occlusion of the artery lead to acute clinical complications comprising acute coronary syndrome (ACS),[2] which constitutes one of the leading causes of death worldwide.[3] Therefore, there is a great medical need to improve risk prediction in asymptomatic patients,[4] to improve early diagnosis and risk stratification of patients with ACS[5] and to monitor atherosclerotic burden during treatment.

Proteins that are secreted or released from atherosclerotic lesions or thrombi into the circulation may provide a direct and simple measure of the atherosclerotic burden in individual patients. This concept has already been examined in the diagnosis and monitoring of other diseases, for example, several types of cancers by tumor markers.[6]

For the discovery of such biomarker candidates, we combined gene expression profiling of coronary thrombi versus peripheral blood mononuclear cells and proteomic analysis of secretomes derived from atherosclerotic plaques versus

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Nonstandard Abbreviations and Acronyms	
ACS	acute coronary syndrome
AUC	area under the curve
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
FABP4	fatty acid-binding protein 4
NT-proBNP	N-terminal pro–brain natriuretic peptide
OR	odds ratio
STEMI	ST-segment–elevation myocardial infarction

healthy tissue. The few differentially expressed transcripts and proteins identified by both approaches included fatty acid–binding protein 4 (FABP4). Its expression in atherosclerotic plaques of carotid arteries was previously found to predict cardiovascular outcome[7] or naturally occurring genetic low-expression variant of FABP4 to promote plaque stability and to reduce the risk of cardiovascular events.[8]

We therefore selected FABP4 for clinical validation as a circulating biomarker and considered 3 different situations, where a novel cardiovascular biomarker may improve clinical management of coronary artery disease (CAD). In clinical routine, electrocardiography and cardiac troponins are the gold standards for making the diagnosis of ACS.[9] As the trade-off of their high sensitivity, novel cardiac troponin assays have reduced specificity,[10] what may be improved by the determination of additional biomarkers reflecting plaque rupture. For this reason, we assessed in a cross-sectional study (designated as the diagnostic cohort) diagnostic performance of FABP4 by comparing circulating FABP4 levels of healthy individuals with those of patients with stable CAD or ACS. Another medical need is an improvement of risk prediction toward optimized or personalized targeting of preventive measures. Clinical risk prediction algorithms combining demographic, clinical, and biochemical measures are nowadays reference methods; however, they differ considerably in primary and secondary prevention settings. For instance, for primary prevention in an asymptomatic population, algorithms and scores, such as Framingham, Pooled Cohort Equations, or European Atherosclerosis Society/European Society of Cardiology score combine information on age and sex with risk factors, such as diabetes mellitus, blood pressure, and plasma lipids.[11] For secondary prevention of symptomatic patients, the GRACE or thrombolysis in myocardial infarction scores combine data on age, cardiovascular, and renal function.[12] In our study, we assessed the performance of circulating FABP4 as a prognostic biomarker for the incidence of cerebrovascular and cardiovascular events in 2 nested case–control studies: 1 with 5-year follow-up of asymptomatic individuals from the general population (designated as prospective population cohort) and another with 30-day follow-up of patients with ACS (designated as prospective clinical cohort).

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

Identification of FABP4 as a Biomarker Candidate

Data sets from 2 independent approaches were combined to identify biomarker candidates for CAD. In the first approach, using gene array technology, mRNA expression levels isolated from coronary thrombi were compared with those of peripheral blood mononuclear cells from patients with ACS. In the second approach, protein profiles of atherosclerotic plaque–derived secretomes were compared with those of

Table 1. Characteristics of the Diagnostic Cohort

Characteristics	Controls, n=313	CAD, n=68	NSTEMI, n=170	STEMI, n=269	*P* Value
Age, y	60±10	62±7	64±13	63±12	<0.001
Sex, male*	214 (68%)	59 (87%)	137 (81%)	207 (77%)	0.001
Hypertension*	159 (51%)	61 (90%)	136 (80%)	184 (68%)	<0.001
Hypercholesterolemia*	155 (50%)	58 (85%)	124 (73%)	179 (67%)	<0.001
T2DM*	38 (12%)	22 (32%)	52 (31%)	152 (57%)	<0.001
Current smoking*	103 (33%)	9 (13%)	73 (43%)	109 (41%)	<0.001
Body mass index, kg/m^2	27±4	29±5	27±4	27±5	0.034
Total cholesterol, mmol/L	5.8±1.0	4.1±1.1	4.9±1.2	5.1±1.2	<0.001
HDL, mmol/L	1.6±0.4	1.1±0.4	1.1±0.4	1.2±0.3	<0.001
LDL, mmol/L	3.6±0.9	2.3±0.8	3.1±1.1	3.4±1.6	<0.001
Triglycerides, mmol/L†	1.3 (0.6–3.0)	1.0 (0.5–4.4)	1.3 (0.5–3.5)	0.9 (0.4–2.6)	<0.001
CRP, mg/L†	1.5 (0.3–8.3)	0.9 (0.3–15.0)	3.6 (0.5–43.5)	2.2 (0.4–35.7)	<0.001
hsTnT, μg/L†	n.d.	n.d.	0.47 (0.015–3.06)	0.22 (0.12–3.34)	0.002
Glucose, mmol/L†	5.6 (4.6–8.1)	5.6 (4.3–11.2)	6.0 (4.6–11.7)	7.4 (5.2–17.2)	<0.001
FABP4, ng/mL†	23.4 (5.9–71.0)	22.5 (7.4–73.7)	20.3 (8.8–70.2)	24.9 (10.0–77.9)	0.029

CAD indicates coronary artery disease; CRP, C-reactive protein; FABP4, fatty acid–binding protein 4; HDL, high-density lipoprotein; hsTnT, high-sensitive troponin T; LDL, low-density lipoprotein; NSTEMI, non–ST-segment–elevation myocardial infarction; NT-proBNP, N-terminal pro–brain natriuretic peptide; STEMI, ST-segment–elevation myocardial infarction; and T2DM, diabetes mellitus type 2.

*n (%), χ^2 test.

†Median (5th–95th percentile), Mann–Whitney *U* test.

healthy tissue secretomes from the corresponding endarterectomized carotid arteries.[13] Comparison of 325 upregulated mRNAs from coronary thrombi with 390 proteins from the secretomes (Table I in the online-only Data Supplement) yielded 8 common hits. The FABP4 was the only protein detected in the plaque secretomes, but not in the control secretomes, its mRNA expression in coronary thrombi was 55-fold higher than in peripheral blood mononuclear cells (Table II in the online-only Data Supplement). Moreover, increased FABP4 expression in atherosclerotic plaques of carotid arteries was found to predict forthcoming adverse cardiovascular events.[7] Therefore, FABP4 was selected for clinical validation.

FABP4 Confounding Factors and Correlation With Other Diagnostic Parameters

In both the diagnostic and the prospective population cohort, bivariate analysis revealed weak to moderately positive correlations of circulating FABP4 with age, body mass index (BMI), glucose, and C-reactive protein. Notably, FABP4 in the diagnostic cohort showed stronger correlation with BMI in asymptomatic controls than in CAD patients (P=0.34 versus 0.22, both P value <0.001). There was no significant correlation of FABP4 with total cholesterol, high-density lipoprotein, low-density lipoprotein, or triglycerides in either cohort (Table III in the online-only Data Supplement). In general, circulating FABP4 levels were significantly higher in women, in individuals with BMI >25 kg/m^2, diabetes mellitus, or with hypertension when compared with men, normal weight, nondiabetic, and normotensive counterparts. Circulating FABP4 was lower in current smokers than in nonsmokers, but this difference was only significant in the diagnostic cohort (Table IV in the online-only Data Supplement).

Furthermore, circulating FABP4 showed a very weak positive correlation with high-sensitive troponin T (P=0.19 and 0.01) or C-reactive protein (P=0.16 and 0.04) in the diagnostic cohort. In the prospective clinical cohort, circulating FABP4 moderately correlated with the GRACE risk score for in-hospital death or myocardial infarction (P=0.41 and <0.001), with N-terminal pro–brain natriuretic peptide (NT-proBNP; P=0.35 and <0.001) and with creatinine (P=0.45 and <0.001; Table V in the Data Supplement).

Circulating FABP4 Levels Do Not Differ Remarkably Between Patients With ACS and Asymptomatic Controls

The cross-sectional diagnostic cohort included 820 individuals from both SPUM-ACS (Special Program University Medicine-Acute Coronary Syndrome; n=553) and CoLaus (Cohorte Lausannoise; n=267) studies. The SPUM-ACS participants were recruited at the University Hospital Zurich and included 46 healthy controls, 68 patients with stable CAD, 269 patients with ST-segment–elevation myocardial infarction (STEMI), and 170 patients with non–ST-segment–elevation myocardial infarction. Since the number of healthy controls was low in the SPUM-ACS study and these individuals were younger than patients with CAD (data not shown), additional controls were selected from the CoLaus study

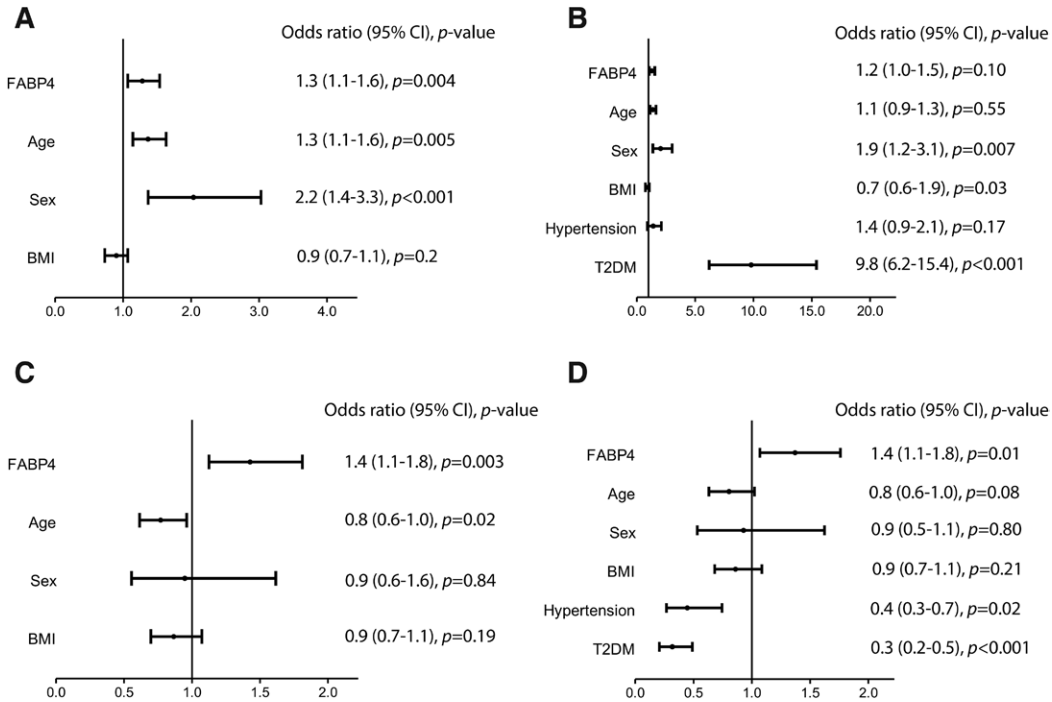

Figure 1. Odds ratios (ORs) for associations of risk factors and circulating fatty acid–binding protein 4 (FABP4) with different clinical manifestations of acute coronary syndrome in the diagnostic cohort. Multivariate logistic regression models with adjustment for several confounding factors, such as sex (male), age (years), BMI (body mass index; kg/m^2), hypertension, or diabetes mellitus, were used. Plots show odds ratios with corresponding 95% confidence intervals (CIs) and P values for the 1-SD changes in the log-transformed FAPB4, and 1-SD changes in the age and BMI (Wald statistics). Models for controls vs ST-segment–elevation myocardial infarction (STEMI; **A** and **B**) and non–STEMI vs STEMI (**C** and **D**). The vertical reference line indicates an OR of 1.0. T2DM indicates diabetes mellitus type 2.

cohort. Detailed clinical and laboratory characteristics are shown in Table 1.

One-factorial ANOVA with Games–Howell correction was applied for multiple comparisons of circulating FABP4 in asymptomatic controls, patients with stable CAD and patients with ACS, respectively. Circulating FABP4 was significantly higher (P=0.01) in patients with STEMI (median 24.9 ng/mL with 5th–95th percentile range, 11.0–77.9) compared with asymptomatic controls (median 23.4 ng/mL with 5th–95th percentile range, 5.9–71.0). Other groups did not differ significantly from each other with respect to the circulating FABP4.

The difference in the circulating FABP4 between patients with STEMI and asymptomatic controls remained significant after adjustment for age, sex, and BMI (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.1–1.6; P=0.004). However, this significance was lost after further adjustment for diabetes mellitus and hypertension (OR, 1.2; 95% CI, 1.0–1.5; P=0.1). In contrary, differences in the circulating FABP4 between patients with STEMI and non–ST-segment–elevation myocardial infarction became statistically significant in both adjusted models (OR, 1.4; 95% CI, 1.1–1.8; P=0.003 and OR, 1.4; 95% CI, 1.1–1.8; P=0.01). The details of logistic regression models are presented in Figure 1. No other differences in the circulating FABP4 became statistically significant after adjustment for the confounding factors.

Circulating FABP4 Predicts the Occurrence of Adverse Cerebrovascular and Cardiovascular Events in Patients With ACS

The prognostic performance of circulating FABP4 for future cerebrovascular or cardiovascular events was assessed in a nested case–control study of 200 patients with ACS from 4 hospitals participating in the SPUM-ACS study. These patients had a primary diagnosis of unstable angina (n=12), STEMI (n=106), or non–ST-segment–elevation myocardial infarction (n=82). During 30-day follow-up, 70 patients developed adjudicated cerebrovascular and cardiovascular events: death (34 cardiac deaths and 3 unclear deaths), recurrent myocardial infarction (n=22), or stroke (n=11). Cases were matched for age, sex, and center with 130 patients who survived 30 days without any event (Table 2).

Circulating FABP4 was significantly higher in patients who developed adverse cerebrovascular and cardiovascular events during the follow-up compared with control patients without any event: 39.9 ng/mL (5th–95th percentile range, 15.0–307.7) versus 26.4 ng/mL (5th–95th percentile range, 13.8–97.9), respectively, P=0.001. These differences remained statistically significant after adjustment for age, sex, creatinine level, and BMI (OR, 1.7; 95% CI, 1.1–2.5; P=0.02; Figure 2).

The prognostic performance of FABP4 for predicting adverse cerebrovascular or cardiovascular events during the follow-up was further assessed by comparison with the

Table 2. Matching for Controls and Cases in the Prospective Clinical Cohort of Patients With Acute Coronary Syndrome During 30-d Follow-Up (n=200)

Characteristic	Controls, n=130	Cases, n=70	*P* Value
Clinical presentation*			
UA	8 (6%)	4 (6%)	0.20
NSTEMI	59 (45%)	23 (33%)	
STEMI	63 (49%)	43 (61%)	
Age, y	71±12	72±11	0.71
Sex, male*	91 (70%)	50 (71%)	0.83
Hypertension*	95 (73%)	46 (66%)	0.28
T2DM*	24 (18.5%)	21 (30%)	0.06
Current smoking*	31 (24%)	23 (33%)	0.13
BMI, kg/m^2	27±4	27±5	0.26
Total cholesterol, mmol/L	4.7±1.3	4.5±1.2	0.38
HDL, mmol/L	1.2±0.4	1.2±0.3	0.59
LDL, mmol/L	2.9±1.2	2.8±1.0	0.93
Triglycerides, mmol/L	1.3±0.8	1.1±0.7	0.11
CRP, mg/L†	2.9 (0.5–73.5)	5.8 (0.4–97.9)	0.04
hsTnT, μg/L†	0.306 (0.012–3.008)	0.743 (0.018–5.323)	0.01
NT-proBNP, ng/L†	797 (43–7314)	1340 (76–28 094)	0.01
Creatinine, μmol/L†	77.0 (52.5–142.7)	88.5 (56.2–202.7)	0.001
FABP4, ng/mL†	26.4 (13.8–97.9)	39.9 (15.0–307.7)	0.001
In-hospital death or myocardial infarction GRACE score	212±50	248±68	<0.001

BMI indicates body mass index; CRP, C-reactive protein; FABP4, fatty acid–binding protein 4; HDL, high-density lipoprotein; hsTnT, high-sensitive troponin T; LDL, low-density lipoprotein; NSTEMI, non–ST-segment–elevation myocardial infarction; NT-proBNP, N-terminal pro–brain natriuretic peptide; STEMI, ST-segment–elevation myocardial infarction; T2DM, diabetes mellitus type 2; and US, unstable angina.

*n (%), χ^2 test.

†Median (5th–95th percentile), Mann–Whitney *U* test.

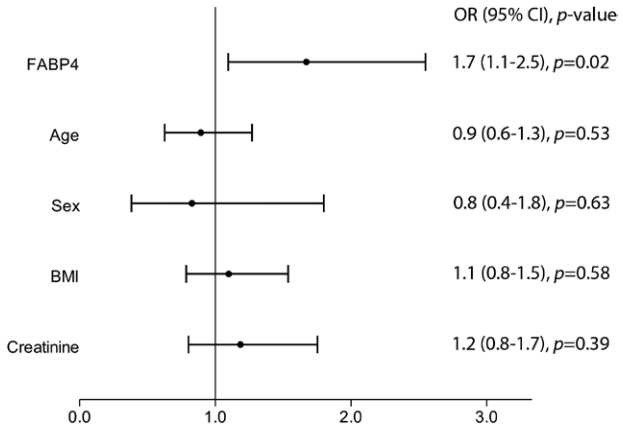

Figure 2. Odds ratios (ORs) for associations of confounding factors and circulating fatty acid–binding protein 4 (FABP4) in patients with adverse cerebrovascular and cardiovascular events during 30-day follow-up after the index acute coronary syndrome event. Multivariate logistic regression model with adjustment for several confounding factors, such as sex (male), age (years), BMI (body mass index; kg/m^2), and creatinine (μmol/L) were used. Plot shows ORs with corresponding 95% confidence intervals (CIs) and *P* values for the 1-SD changes in the log-transformed FAPB4 and creatinine values, and 1-SD changes in the age and BMI (Wald statistics). The vertical reference line indicates an OR of 1.0.

GRACE risk score (predictor for in-hospital death or myocardial infarction) and NT-proBNP levels. On Cox proportional hazard analysis, FABP4 (hazard ratio, 1.40; 95% CI, 1.04–1.87; *P*=0.026), GRACE risk score (hazard ratio, 1.44; 95% CI, 1.08–1.92; *P*=0.014), and NT-proBNP (hazard ratio, 1.35; 95% CI, 1.02–1.81; *P*=0.039) almost equally contributed to the prediction of adverse events during the 30-day follow-up. The receiver operating characteristic analysis of FABP4 as a prognostic marker revealed an area under the curve (AUC) of 0.65 (95% CI, 0.56–0.75; *P*=0.001), which was nearly identical to that obtained for the GRACE risk score (AUC, 0.67; 95% CI, 0.57–0.76; *P*<0.001). The combination of FABP4 and GRACE scores did not further improve the prediction of the outcome (AUC, 0.67; 95% CI, 0.57–0.76; *P*<0.001). The AUC for NT-proBNP (AUC, 0.61; 95% CI, 0.53–0.71; *P*=0.045) was lower, but the combination of FABP4 and NT-proBNP reached the highest AUC of 0.68 (95% CI, 0.60–0.77; *P*=0.045; Figure 3).

Circulating FABP4 at Baseline Does Not Predict the Development of Cardiovascular Events in the Asymptomatic Population

The prognostic performance of circulating FABP4 for future cardiovascular events was assessed in the prospective nested case–control cohort of 414 asymptomatic participants from the population-based CoLaus study. During 5-year follow-up, 112 individuals experienced an adjudicated cardiovascular event: 22 cardiovascular deaths, 54 myocardial infarction, and 36 symptomatic CAD followed by percutaneous or surgical revascularization. These cases were matched by sex, age, and health status with 302 controls who did not manifest any CAD event (Table 3). No significant difference in circulating FABP4 was found between individuals with or without incidence of cardiovascular event: 23.7 ng/mL (5th–95th percentile range, 5.9–76.8) versus 23.3 ng/mL (5th–95th percentile range, 9.3–71.4), *P*=0.75.

Discussion

The purpose of this project was the identification of novel CAD biomarkers by integration of proteomic and gene expression profiling data sets obtained from atherosclerotic plaque secretomes and coronary thrombi, respectively. The proteomic study aimed for the identification of proteins that are released from the plaque into the circulation during the progression or rupturing of atherosclerotic plaque. We previously showed that the composition and phenotype of mononuclear cells in coronary thrombi differ significantly from

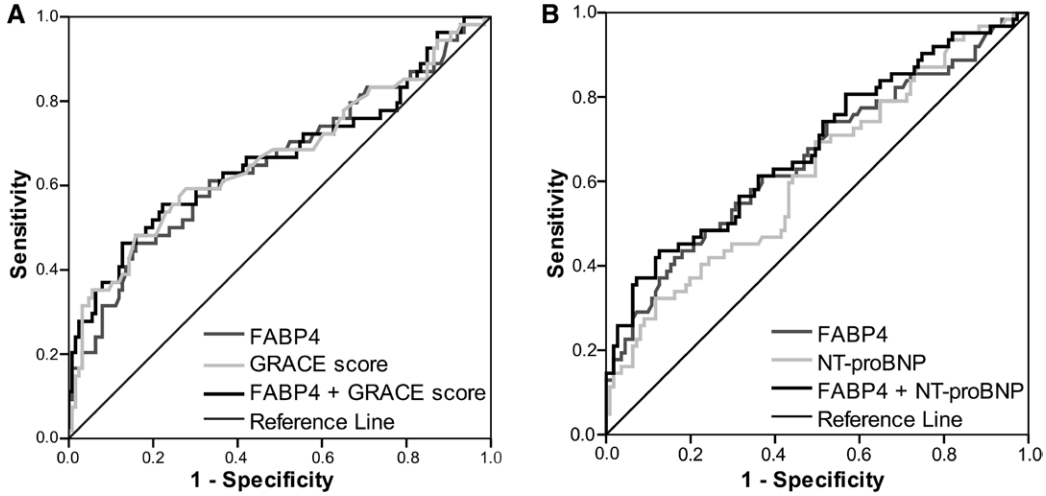

Figure 3. Fatty acid–binding protein 4 (FABP4) predicts adverse cerebrovascular and cardiovascular events during 30-day follow-up after an index acute coronary syndrome event. **A**, The calculated areas under the curve (AUCs) for FABP4, GRACE risk score, and their combination as predictors of adverse events was 0.65 (95% confidence interval [CI], 0.56–0.75; *P*=0.001), 0.67 (95% CI, 0.57–0.76; *P*<0.001), and 0.67 (95% CI, 0.57–0.76; *P*<0.001), respectively. **B**, The calculated AUCs for N-terminal pro–brain natriuretic peptide (NT-proBNP) was 0.61 (95% CI, 0.53–0.71; *P*=0.045) and for the combination of FABP4 and NT-proBNP was 0.68 (95% CI 0.60–0.77, *P*=0.045).

Table 3. Matching Controls and Cases in the Prospective Population Cohort During 5-y Follow-Up (n=414)

Variable	Controls, n=302	Cases, n=112	*P* Value
Age, y	60.9±9.8	61.2±9.4	0.77
Sex, men*	208 (69%)	81 (70%)	0.50
Hypertension*	185 (61%)	70 (63%)	0.82
T2DM*	43 (14%)	21 (19%)	0.26
Current smoking*	118 (39%)	41 (37%)	0.65
BMI, kg/m^2	27.9±4.6	28.4±5.4	0.38
Total cholesterol, mmol/L	5.8±1.1	5.7±1.0	0.18
HDL, mmol/L	1.5±0.4	1.4±0.4	0.03
LDL, mmol/L	3.6±1.0	3.5±0.9	0.23
Triglycerides, mmol/L	1.6±0.8	1.7±0.9	0.10
hsCRP, mg/L†	1.7 (0.4–10.5)	2.3 (0.3–17.3)	0.04
FABP4, ng/mL†	23.7 (5.9–76.8)	23.3 (9.3–71.4)	0.75

BMI indicates body mass index; FABP4, fatty acid–binding protein 4; HDL, high-density lipoprotein; hsCRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; and T2DM, diabetes mellitus type 2.

*n (%), χ^2 test.

†Median (5th–95th percentile), Mann–Whitney *U* test.

those of peripheral blood mononuclear cells obtained from patients with ACS.[14,15] Therefore, differential gene expression profiling was performed to identify molecular characteristics of thrombus-associated mononuclear cells that could also serve as ACS biomarkers. Comparison of both data sets revealed several common targets. One of them, FABP4 (also known as AFABP or aP2) was found in the plaque secretome but not in the control secretome and its expression in coronary thrombi was 55-fold higher than in peripheral blood mononuclear cells.

FABP4 is abundantly produced in adipocytes, but significant amounts of FABP4 are also found in macrophages, which are pathogenic constituents of atherosclerotic plaques. Furthermore, a naturally occurring genetic low-expression variant of FABP4 was found to promote plaque stability and reduce the risk of cardiovascular events.[8] On the contrary, FABP4 expression is increased in vulnerable and ruptured plaques as shown by genome-wide expression analysis of isolated macrophages[16] and quantification of FABP4 in vulnerable human plaques.[7] Extensive studies in FABP4-deficient mice or FABP4 inhibitor–treated animals also demonstrated that FABP4 promotes insulin resistance and the development of diabetes mellitus and modulates lipid metabolism.[17] Moreover, FABP4 seems to play an important role in the development of atherosclerosis. For instance, in the absence of any significant differences in serum lipids and insulin sensitivity, FABP4/ApoE-double–knockout mice developed markedly less atherosclerosis than control ApoE-knockout mice. Interestingly, the reduction of atherosclerotic lesions was similar in macrophage-specific FABP4 deficiency and whole-body FABP4-deficient mice.[18] These data indicate that macrophage-derived FABP4 may exert local pathogenic effects in atherosclerosis independent from its established role in systemic glucose or lipid metabolism.

Therefore, we selected FABP4 for further validation as a diagnostic and prognostic biomarker for atherosclerotic CAD. Our validation studies confer 3 major findings on circulating FABP4 as a diagnostic and prognostic biomarker.

Firstly, circulating FABP4 was not associated in a clinically meaningful manner with the presence of stable CAD or its acute manifestations. In line with our results, Cabré et al[19] demonstrated that circulating FABP4 levels are not significantly associated with clinical or subclinical atherosclerosis but are markedly increased in patients with metabolic syndrome. In contrast to the studies in whites, several studies in Asian populations showed significant associations of circulating FABP4 with CAD. For instance, circulating FABP4 correlated positively with carotid intima-media thickness in Chinese women,[20] with atherosclerotic burden measured by intravascular ultrasound,[21] or with CAD in nonelderly Japanese men.[22] These discrepant findings between white and Asian populations on the association of circulating FABP4 with CAD might be partially explained by different genetic and environmental background. For instance, the prevalence of hypertension, hypercholesterolemia, or overweight and obesity is higher in whites than in Asians.[23,24] It has to be noted that these conditions are associated with higher FABP4 levels, as found in this and other studies.[25,26]

Secondly, circulating FABP4 was significantly elevated in patients with ACS who experienced adverse cerebrovascular or cardiovascular events within 30 days after the index ACS event. Furthermore, FABP4 showed the same prognostic power to predict adverse events as the GRACE in-hospital risk score or NT-proBNP. Although the highest concentration of FABP4 was observed in patients with ACS who experienced cardiac death (data not shown), our nested cohort is too small to claim a differential prognostic role of FABP4 in the prediction of fatal and nonfatal events. It is interesting to note that a significant association of FABP4 with cerebrovascular or cardiovascular events was also observed in a prospective 10-year long follow-up study of patients with CAD.[27] In this study, high baseline levels of FABP4 were associated with a higher risk for subsequent adverse events in unadjusted analyses and significantly predicted cardiovascular death even after adjustment for established cardiovascular risk factors and lipid-lowering drugs.

Finally, circulating FABP4 had no association with incidence of cardiovascular events in our prospective population cohort. In a similar study of Hong Kong Chinese, circulating FABP4 was found to predict the development of CAD after adjustment for the traditional risk factors. Despite independent association with an integrated discrimination improvement of 0.25%, FABP4 helped only marginally to improve the performance of the predictive model with established risk factors.[28]

The following limitations of our study have to be considered. Our data do not imply any causal relationship between circulating FABP4 and development of adverse events after

the index ACS. The sample size of our prospective clinical cohort was rather modest, and additional studies with larger numbers are required to confirm our findings and to validate the prognostic performance of FABP4.

In conclusion, circulating FABP4 was associated with neither stable CAD nor ACS, and thus is unlikely to serve as a clinically relevant diagnostic biomarker. Neither does it seem to be a relevant predictive biomarker in an asymptomatic population. However, in patients with ACS, FABP4 may serve as a prognostic marker to identify patients at risk for adverse cerebrovascular or cardiovascular events.

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Disclosures

None.

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Significance

Blood-borne biomarkers reflecting atherosclerotic plaque burden have great potential to improve the clinical management of atherosclerotic coronary artery disease and acute coronary syndromes. Fatty acid–binding protein 4 was identified as a biomarker candidate using data integration from gene expression profiling of coronary thrombi versus peripheral blood mononuclear cells and proteomic analysis of atherosclerotic plaque–derived secretomes versus healthy tissue–derived secretomes. In general, elevated fatty acid–binding protein 4 is associated with the incidence of adverse secondary cerebrovascular or cardiovascular events during 30-day follow-up after the index acute coronary syndrome, independent of age, sex, renal function, and body mass index. Moreover, fatty acid–binding protein 4 predicts adverse events with similar prognostic performance as the GRACE in-hospital risk score or N-terminal pro–brain natriuretic peptide. Circulating fatty acid–binding protein 4 may prove useful as a prognostic biomarker in risk stratification of patients with acute coronary syndrome.