Journal of the American College of Cardiology Vol. 53, No. 4, 2009

Published by Elsevier Inc.
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.08.074

Persistent Impairment of Endothelial Vasomotor Function Has a Negative Impact on Outcome in Patients With Coronary Artery Disease

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Objectives We assessed the hypothesis that changes in endothelial vasomotor function in response to optimized therapy for atherosclerotic coronary artery disease predict future cardiovascular events.

Background Although endothelial vasomotor dysfunction is a predictor of cardiovascular events, it remains unclear whether reversibility of endothelial dysfunction in response to risk factor reduction provides prognostic information.

Methods This study included 251 patients with newly diagnosed coronary artery disease and an impaired flow-mediated dilation (FMD) of the brachial artery (FMD <5.5%). Measurement of FMD was repeated after 6 months for individualized and optimized therapy to reduce risk factors according to American College of Cardiology/American Heart Association guidelines. Patients were followed up for 36 months or until 1 of the following events occurred: cardiac death, nonfatal myocardial infarction, recurrent and refractory angina pectoris requiring coronary revascularization, or ischemic stroke.

Results FMD was persistently impaired (<5.5%) in 104 (41%) patients after 6 months of optimized therapy, whereas it improved (FMD ≥5.5%) in the remaining 147 (59%) patients. During 36 months of follow-up, events occurred in 27 (26%) patients with persistently impaired FMD and in 15 (10%) patients with improved FMD ($p < 0.01$ by chi-square test). Multivariate Cox hazards analysis showed that persistent impairment of FMD was an independent predictor of events (hazard ratio: 2.9, 95% confidence interval: 1.5 to 6.2, $p < 0.01$). Baseline FMD before the optimized therapy to reduce risk factor had no significant prognostic information.

Conclusions Persistent impairment of endothelial vasomotor function despite optimized therapy to reduce risk factors has an adverse impact on outcome in coronary artery disease patients. (J Am Coll Cardiol 2009;53:323–30)

Endothelial vasomotor dysfunction is an early event identified in the pathogenesis of atherosclerosis (1–4) and is mainly caused by loss of endothelium-derived nitric oxide (EDNO) (5–9). Because EDNO has strong antiatherogenic effects (5,10), endothelial dysfunction is involved in the development of atherosclerotic cardiovascular disease (CVD). Moreover, endothelial vasomotor dysfunction is recognized as a predictor of adverse cardiovascular outcomes (11–14). However, a decrease in EDNO and endothelial vasomotor dysfunction is reversible after a reduction in atherosclerotic risk factor burden by pharmacological interventions and life-style modifications (15–20). Because a reduction in risk factors improves endothelial vasomotor function, a single assessment of endothelial vasomotor function may not necessarily reflect later EDNO activity, and endothelial function measured at a single time point may not reflect long-term progression of atherosclerotic diseases. Most previous studies (12–14) that used endothelial function to predict future cardiovascular events assessed endothelial function at only a single time point; only a few studies evaluated the prognosis based on serial measure-

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Manuscript received April 10, 2008; revised manuscript received August 6, 2008, accepted August 30, 2008.

JACC Vol. 53, No. 4, 2009
January 27, 2009:323–30

Abbreviations and Acronyms

CAD = coronary artery disease

CVD = cardiovascular disease

EDNO = endothelium-derived nitric oxide

FMD = flow-mediated dilation

Hb = hemoglobin

LDL-C = low-density lipoprotein cholesterol

ROC = receiver-operator characteristic

ments of endothelial function (11,21). Modena et al. (11) first tested the prognostic role of reversing endothelial vasomotor dysfunction in post-menopausal women with mild-to-moderate hypertension. They enrolled patients with a low prevalence of other risk factors and no previous cardiovascular events, and showed that patients with improved flow-dependent dilation of the brachial artery (flow-mediated dilation [FMD]) after antihypertensive therapy had fewer events during follow-up. Thus, recovery from endothelial vasomotor dysfunction was associated with reduced cardiovascular events in their hypertensive patients. However, that report (11) did not assess the changes in other confounding variables such as diabetes mellitus that might have influenced outcome. Moreover, it remains unknown whether the association between reversible endothelial function and favorable outcome is also true in patients with coronary artery disease (CAD) and advanced atherosclerotic burden. Thus, this study examined whether changes in endothelial vasomotor function in response to optimized therapy for atherosclerotic burden provide prognostic information on future cardiovascular events in patients with CAD.

Methods

Study patients. This study enrolled 251 patients from among 302 consecutive patients with newly diagnosed CAD who were admitted to Yamanashi University Hospital for coronary angiography from April 2002 to March 2004. The inclusion criteria included an impaired FMD (<5.5%) at enrollment (first FMD) and a second test of FMD repeated 6 months after the first FMD test at the enrollment. All patients had angiographic documentation of organic stenosis of >70% of at least 1 major coronary artery. Patients were excluded based on the presence of any of the following criteria: 1) acute coronary syndrome, stroke, cardiogenic shock, pulmonary edema, major surgery, trauma, or serious infectious disease within 4 weeks prior to enrollment and during 6 months between first and second FMD test; 2) New York Heart Association functional classification ≥III; 3) left main trunk disease; 4) left ventricular ejection fraction on echocardiography <30%; 5) neoplasm, chronic hepatic or inflammatory diseases; 6) chronic renal failure (serum creatinine levels >2.0 mg/dl); and 7) other serious systemic diseases. Among the 302 eligible patients with CAD, 51 patients were excluded because of FMD ≥5.5% in 38 patients, a CVD event between first and second FMD test in 3 patients, and the other exclusion criteria in 10 patients. This study also included 100 control subjects with angiographically normal coronary arteries and normal ventriculography. These control subjects were selected to match the age and sex of the patients with CAD. The FMD measurements were once performed at the enrollment of these control subjects, and their FMD values were compared with those of the CAD patients. The characteristics of the study patients and the control subjects are shown in Table 1. Written informed consent was obtained from all patients and control subjects before the study. This study was in agreement with the guidelines approved by the ethics committee at our institution.

Study protocol. Measurement of FMD in the brachial artery was performed in the morning after an overnight fast in the same manner within 3 days (first FMD) before the coronary angiography and 6 months (second FMD) after the first FMD test in all study patients with CAD. All vasodilators were withdrawn 48 h before the FMD measurements. After the first FMD measurement, all patients had individualized, optimized therapies including medications and life-style changes to reduce risk factors for CAD according to the AHA/ACC guidelines (22,23). The target for low-density lipoprotein cholesterol (LDL-C)-lowering therapy was <100 mg/dl (2.6 mmol/l), hypertension control was <140/90 mm Hg (or <130/80 mm Hg if diabetes present), and hemoglobin (Hb)A_{1C} <7.0% for diabetes control. All patients were advised to maintain or reduce waist circumference to <85 cm in men and <90 cm in women through an appropriate balance of physical activity (walking >30 min/day) and caloric intake according to the Examination Committee of Criteria for Obesity Disease in Japan (24). All patients were followed up in the hospital or with a clinic visit every month and encouraged to adhere to the life-style changes and diet recommendations. Levels of serum lipids, HbA_{1C}, and C-reactive protein were assayed, as described previously (25).

Follow-up study. After the second FMD test, all of the 251 patients with CAD were prospectively followed up every month in the hospital or with a clinic visit for up to 36 months or until the occurrence of 1 of the following clinical CVD events: cardiac death, nonfatal myocardial infarction, recurrent or refractory angina pectoris requiring coronary revascularization by percutaneous coronary intervention or coronary artery bypass surgery, or ischemic stroke. The time to the first CVD event was evaluated prospectively. Diagnosis of myocardial infarction was made by chest pain, appearance of a new Q-wave in the electrocardiogram, and elevation of plasma creatine kinase to more than twice the upper limit of normal. The cause of death was determined from hospital records. All end point data were checked for accuracy, consistency, and completeness of follow-up by the investigators (J.O., K.S.) without knowledge of the patients' baseline characteristics. The same medications prescribed during the 6 months between the first and second FMD tests and the recommended diet and life-style changes were continued in each patient throughout the follow-up period.

Table 1 Comparisons of Baseline Clinical Characteristics at the First FMD Test

Characteristic	Patients With Persistently Impaired FMD (n = 104)	Patients With Improved FMD (n = 147)	Control Subjects (n = 100)
Age, yrs	68 ± 10	66 ± 10	64 ± 11
Male sex, %	54	61	61
Hypertension, %	73	65	63
Patients with BP ≥140/90 mm Hg, %	36	41	38
Patients with LDL-C ≥100 mg/dl, %	81	79	73
Diabetes mellitus, %	43*	34*	24
Patients with HbA_{1c} ≥7.0%, %	21*	16*	10
Current smoker, %	30	40	31
Family history of CAD, %	27*	21*	12
Multivessel CAD, %	58	57	—
Percutaneous coronary intervention, %†	94	95	—
Body mass index, kg/m^2	24 ± 3.4	24 ± 2.8	23 ± 3.3
Waist circumference, cm	86 ± 11	85 ± 8	85 ± 7
Systolic BP, mm Hg	137 ± 24	134 ± 23	133 ± 16
LDL-C, mg/dl	130 ± 36	128 ± 35	126 ± 32
HDL-C, mg/dl	48 ± 13	46 ± 11	50 ± 14
HbA_{1c}, %	6.1 ± 1.3*	6.2 ± 1.5*	5.5 ± 0.9
CRP, mg/l	4.3 ± 8.3*	4.1 ± 8.1*	2.5 ± 4.7

Data are expressed as mean ± SD or percentage of the patients. There was no significant difference in parameters between patients with persistently impaired flow-mediated dilation (FMD) of the brachial artery and improved FMD. Hypertension is defined as ≥140/90 mm Hg or taking an antihypertensive medication; diabetes mellitus is defined according to the American Diabetes Association report or as taking an antidiabetic medication; smoking is defined as ≥10 cigarettes per day for ≥10 years. *$p < 0.05$ versus control subjects. †Percutaneous coronary intervention performed at screening.

BP = blood pressure; CAD = coronary artery disease; CRP = C-reactive protein; Hb = hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Measurements of FMD in the brachial artery. Vasodilator responses in the brachial arteries were measured by use of B-mode ultrasound images with a 7.5-MHz linear array transducer (HP-5500, Phillips Corp., Tokyo, Japan) as described in our previous studies (17,25). Briefly, optimal brachial artery images were obtained between 1 and 5 cm above the antecubital crease. This location was marked, and all subsequent images were obtained at the same location. The exact distance of the measured point on the skin surface from the antecubital crease was recorded in each subject to ensure that the same segment of the brachial artery was measured at each time point during follow-up. The responses of the vessel diameter and blood flow to reactive hyperemia and nitroglycerin were expressed as percentage increases in diameter and blood flow from the baseline value, respectively. In our studies, the repeated measurement of baseline arterial diameter had an interobserver variability of 0.04 ± 0.01 mm, and an intraobserver variability of 0.02 ± 0.01 mm. When these studies were performed at the same time on 2 separate days in 20 control subjects, the difference in arterial diameter during reactive hyperemia between the 2 days in each subject was 0.05 ± 0.01 mm, yielding a mean difference of 1.1 ± 1.0% of FMD. Impairment of FMD was pre-defined as <5.5% (mean minus 1 SD of FMD in 100 healthy normal subjects in our hospital) before the start of the recruitment of CAD patients into this study.

Statistical analysis. Data were expressed as the mean ± SD or a percentage. The frequencies between 2 groups of patients and the 2 mean values were compared using the chi-square test and Student paired or unpaired *t* test, respectively. For comparisons of the mean values >3 groups, 1-way analysis of variance followed by a Scheffe test for post-hoc comparisons was employed. The mean value of vascular variables related to FMD before and during treatment was compared between the 2 groups using 2-way analysis of variance for repeated measures followed by post-hoc testing with a Scheffe test. Kaplan-Meier analysis of event-free survival during follow-up was performed with patients with CAD stratified on the basis of change in FMD. The association of FMD with future events was assessed by Cox proportional hazards analysis. The data were analyzed initially using a univariate model with covariates, including FMD and other potential confounders that had a statistically significant difference between patients with and without events. Multivariate Cox proportional hazards analysis was then applied using FMD and the covariates that were significantly associated with events in the univariate Cox proportional hazards analysis. Cox proportional hazards analysis included the confounders that had proportionalities, evaluated by Schoenfeld residuals test. In this multivariate model, interaction analysis between covariates on the outcome was performed using the likelihood test. On the basis of our preliminary observations, we proposed that the composite end point would occur in ≈30% of patients with persistently impaired FMD during 36 months of follow-up and in 10% of those with improved FMD. Thus, it was estimated that 72 patients would be

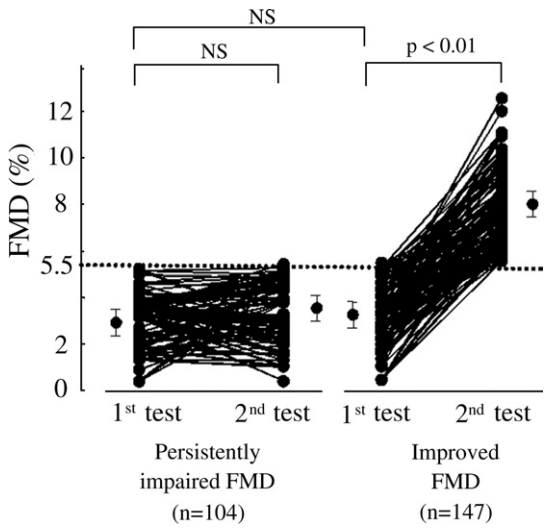

Figure 1 FMD Comparison Between First and Second Test in CAD Patients

A comparison between the first and second test of flow-mediated dilation (FMD) of the brachial artery in patients with coronary artery disease (CAD). NS = not significant.

needed in each group (n = 144, total) to detect a significant difference in events between the 2 groups with a 2-tailed α of 0.05 and a power of 0.80 ($\beta = 0.20$). A p value of <0.05 was considered statistically significant. Analyses were performed with StatView 5.0 (SAS Institute, Cary, North Carolina), and STATA version 10.0 (Stata Corp, College Station, Texas).

Results

FMD measurement. At the second FMD test, 104 patients had persistently impaired FMD (<5.5%), whereas the remaining 147 patients had significantly improved FMD (≥5.5%) (Fig. 1, Table 2). The baseline FMD at the first test was comparable between patients with persistently impaired FMD and those with improved FMD (Fig. 1, Table 2). Baseline brachial arterial diameter, baseline brachial blood flow, an increase in brachial blood flow during reactive hyperemia, and the dilator response to nitroglycerin were not significantly different between the 2 groups at either the first or the second test (Table 2). These parameters related to vascular vasomotor responses, except for FMD, were similar between patients with CAD and control subjects (Table 2). In receiver-operator characteristic (ROC) analysis, an optimal cutoff point for FMD in discriminating the CAD patients from the control subjects was 5.2% (sensitivity 87%, specificity 87%), which was located close to 5.5% (sensitivity 89%, specificity 78%), the pre-determined cutoff point for impaired FMD in the present study.

Comparison of clinical variables at first and second FMD test between CAD patients with persistently impaired FMD and those with improved FMD. Profiles of atherosclerotic risk factors at the first and second FMD tests were comparable between the 2 groups (Tables 1 and 3). Profiles of atherosclerotic risk factors were equally improved at the second FMD test from their baseline values at the first FMD test, and the target achievement rates for blood pressure control, LDL-C levels, and HbA_{1c} levels at the second FMD test were comparable between the 2 groups (Table 3). In addition, the frequencies of cardiovascular medications used at the first and second FMD tests, dosage changes, or the addition of new medications immediately after the first FMD test, and the percutaneous coronary intervention at entry were comparable between the 2 groups (Tables 1 and 4).

Prognostic value of FMD in CAD patients. All of the 251 patients completed the follow-up study (from 2 to 36 months, mean 31 ± 4 months). Patients with persistently impaired FMD had 27 (26%) cardiovascular events (1 cardiac death, 4 nonfatal myocardial infarctions, 15 recurrent angina pectoris with coronary revascularization, and 7 strokes) during the follow-up period, whereas patients with improved FMD had 15 (10%) events (2 nonfatal myocardial infarctions, 10 recurrent angina pectoris with coronary revascularization, and 3 strokes; $p < 0.01$). Kaplan-Meier analysis demonstrated that a persistently impaired FMD resulted in significantly lower survival without an event than an improved FMD ($p < 0.01$ by log-rank test) (Fig. 2). Among FMD and the clinical variables listed in Table 1 at either first or second FMD test, persistently impaired

Table 2 Brachial Artery Diameter and Blood Flow

	Patients With Persistently Impaired FMD		Patients With Improved FMD		
	First Test	Second Test	First Test	Second Test	Control Subjects
Arterial diameter at rest, mm	4.1 ± 0.8	4.0 ± 0.9	4.0 ± 0.7	4.1 ± 0.8	4.1 ± 0.7
Arterial blood flow at rest, ml/min	201 ± 22	226 ± 27	203 ± 23	218 ± 28	196 ± 18
Increase in arterial blood flow, %	208 ± 18	212 ± 16	221 ± 20	210 ± 22	210 ± 20
Increase in diameter after nitroglycerin, %	18 ± 5.4	19 ± 7.2	19 ± 5.9	20 ± 6.1	21 ± 6.3
FMD, %	3.0 ± 1.5*	3.4 ± 1.3*	3.0 ± 1.0*	7.7 ± 1.3†	7.6 ± 2.0

Data are expressed as mean ± SD. *p < 0.01 versus control subjects. †p < 0.01 versus first test in patients with improved flow-mediated dilation (FMD).

Table 3 Comparison of the Clinical Characteristics at the Second FMD Test and the Percent Change in Risk Status From the First to the Second FMD Test

	Persistently Impaired FMD (n = 104)	Improved FMD (n = 147)
Risk status at the second FMD test		
Systolic BP, mm Hg	127 ± 19	129 ± 20
Patients with BP ≥140/90 mm Hg, %	24	28
LDL-C, mg/dl	102 ± 33	100 ± 30
Patients with LDL-C ≥100 mg/dl, %	45	44
HbA_{1c}, %	6.0 ± 1.1	5.8 ± 0.9
Patients with HbA_{1c} ≥7.0%, %	12	9
Current smoker, %	11	12
HDL-C, mg/dl	51 ± 14	50 ± 13
Body mass index, kg/m^2	23 ± 2.3	23 ± 2.8
CRP, mg/l	1.2 ± 2.0	1.2 ± 1.0
Percent change in risk status from the first to the second FMD test		
Systolic BP, %	−4.7 ± 15	−4.7 ± 16
Patients with BP ≥140/90 mm Hg, %	−32	−32
LDL-C, %	−17.7 ± 29	−18.1 ± 27
Patients with LDL-C ≥100 mg/dl, %	−36	−35
HbA_{1c}, %	−2.2 ± 10	−2.3 ± 11
Patients with HbA_{1c} ≥7.0%, %	−45	−46
Current smoker, %	−65	−71
HDL-C, %	4.6 ± 18	4.9 ± 17
Body mass index, kg/m^2, %	−4.2 ± 15	−4.3 ± 16
CRP, %	−28 ± 63	−30 ± 68

Data are expressed as mean ± SD or percentage of patients. There was no significant difference in parameters between patients with persistently impaired FMD and improved FMD.
Abbreviations as in Table 1.

FMD, diabetes mellitus, multivessel CAD, and family history of CAD were significantly more frequent in patients with than without an event. Furthermore, levels of HbA_{1c} at the second test were higher in patients with than without an event (data not shown). The baseline FMD at the first test was comparable between patients with and without an event (2.9 ± 1.4% vs. 3.0 ± 1.3%, respectively, p = 0.63). In a univariate Cox proportional hazards model, persistently impaired FMD, diabetes mellitus, multivessel CAD, and higher HbA_{1c} levels were significant predictors of events among the variables that had a significant difference between patients with and without events (Table 5). A multivariate Cox proportional hazards model demonstrated that persistently impaired FMD remained a significant independent predictor of future events (Table 5). The baseline FMD at the first test was not a significant predictor of a CVD event during the follow-up period in either the univariate or multivariate Cox proportional hazards model (Table 5). HbA_{1c} was excluded from the covariates in the multivariate Cox proportional hazards analysis because of a significant interaction between diabetes mellitus and HbA_{1c} levels (p value for interaction <0.001). There was no significant interaction between the other covariates including persistently impaired FMD, diabetes mellitus, multivessel CAD, and baseline FMD at first test (p value for interaction >0.1 in all).

Discussion

The present study showed that persistent impairment of endothelial vasomotor function despite therapies to reduce atherosclerotic risk factors was an independent predictor of future cardiovascular events in CAD patients. In contrast, the baseline FMD before therapies to reduce risk factors did not provide significant prognostic information in CAD patients in the present study. Thus, serial measurements of FMD may be useful for risk stratification in CAD patients. Patients with persistently impaired FMD may need more intensive therapy or risk factor modification to reduce future cardiovascular events. There may be several reasons for the negative predictive value of the baseline FMD (the first FMD) in the present study. The selection of patients with CAD, who had an impaired FMD at baseline, may partly account for the negative predictive value of baseline FMD in this cohort of CAD patients.

Endothelial vasomotor function reflects the atherosclerotic risk burden at the same time of its measurement (1–4,6–8). However, endothelial function is changed by modification of atherosclerotic risk burden (15–20). To date, most patients with CAD have optimized therapy for reduction of atherosclerotic risk factors according to guidelines and evidence established from many clinical trials. The antiatherosclerotic treatment suppresses the atherosclerotic burden in parallel with an improvement of endothelial function (15,16). Thus, the pre-

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Table 4 Comparison of Medication Usage

	Persistently Impaired FMD (n = 104)	Improved FMD (n = 147)
Medications at the first FMD test, %		
Statin	14	10
ACE-I/ARB	6	10
Calcium-channel blocker	21	22
Beta-blocker	5	5
Aspirin	50	42
Ticlopidine*	29	30
Sulfonylurea	7	10
Insulin	5	2
Medications increased or newly added after the first FMD test, %		
Statin	52	53
ACE-I/ARB	59	55
Calcium-channel blocker	34	36
Beta-blocker	19	20
Aspirin	50	58
Ticlopidine*	68	66
Sulfonylurea	1	1
Insulin	2	1
Medications at the second FMD test, %		
Statin	61	60
ACE-I/ARB	62	60
Calcium-channel blocker	51	52
Beta-blocker	22	20
Aspirin	100	100
Ticlopidine*	92	90
Sulfonylurea	7	10
Insulin	6	3

There was no significant difference in parameters between patients with persistently impaired flow-mediated dilation (FMD) and improved FMD. *Clopidogrel was not available until May 2006 in Japan.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

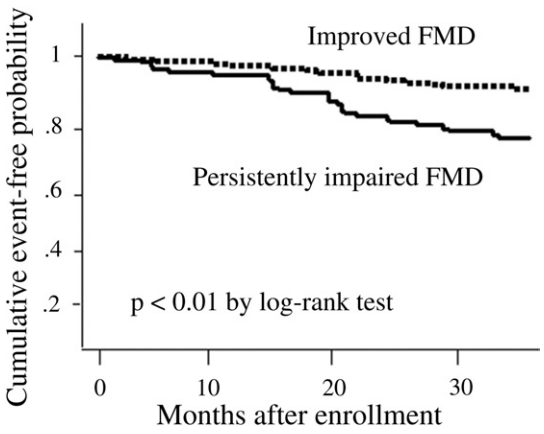

Figure 2 Kaplan-Meier Curves of Event-Free Survival

Kaplan-Meier curves of event-free survival on the basis of change in flow-mediated dilation (FMD) in response to risk factor reduction during the follow-up period (mean, 31 ± 4 months) in 251 patients with coronary artery disease (104 patients had persistently impaired FMD, and 147 patients had improved FMD). The cutoff value (<5.5%) for the impairment of FMD was predetermined from the mean minus 1 SD of FMD in 100 normal subjects in our hospital.

dictive value of the endothelial vasomotor function for future cardiovascular events may be considerably influenced by the antiatherosclerotic treatment initiated after the measurement of the endothelial function. From this point of view, all of the present patients consisted of the newly diagnosed CAD patients, and most of them did not have full medications against atherosclerotic CVD at baseline FMD measurement (first FMD test). However, the improvement of risk factor profiles after the 6 months of optimized antiatherosclerotic therapy was associated with normalization of FMD at the second FMD test to that observed in control subjects in patients with improved FMD. In these patients, the baseline FMD hardly reflected the atherosclerotic risk burden after the antiatherosclerotic treatment. This may be another reason for the negative predictive value of the baseline FMD. Therefore, it is reasonable that a change in endothelial function in response to antiatherosclerotic treatment may be a better predictor of future cardiovascular events than the measurement of pretreatment endothelial function at a single time point.

Risk factor modification was not optimal in some of the patients in the present study owing to the so-called treatment gap, including suboptimal dosages of drugs and poor patient compliance. The failure of attainment of the target LDL-C levels in some of the present patients may be partly caused by relatively suboptimal dosages of statin due to advanced age or very high LDL-C levels at the baseline. However, it was unlikely that insufficient risk factor reduction was the only cause for lack of improvement of endo-

Table 5 Univariate and Multivariate Cox Proportional Hazards Analyses of Risk Factors for Cardiovascular Events

	Univariate			Multivariate		
	HR	95% CI	p Value	HR	95% CI	p Value
Persistently impaired FMD	3.1	1.5–6.2	0.001	2.9	1.5–6.2	0.002
Diabetes mellitus*	2.3	1.2–4.5	0.01	2.0	1.1–3.9	0.04
Multivessel CAD	2.1	1.0–4.3	0.04	2.0	0.9–4.3	0.06
HbA_{1c} at second test*	1.5	1.1–4.7	0.01			
Family history of CAD	2.0	0.9–4.1	0.052			
Baseline FMD at first test	1.1	0.8–1.4	0.62	1.1	0.8–1.4	0.59

*HbA_{1c} was excluded from the covariates in the multivariate Cox proportional hazards analysis because it was intimately associated with diabetes mellitus.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

thelial function in the present patients, because the goal attainment rates of risk factors to the target levels were similar between patients with persistent impairment FMD and those with improved FMD. Undetermined risk factors or genetic predisposition may play a role in the failure of endothelial function to improve in response to therapy (26,27).

It is known that the risk factor reduction to target levels after optimized therapy does not necessarily prevent future cardiovascular events in all CAD patients. Endothelial functional status is not determined solely by the individual risk factor burden but, rather, may be regarded as an integrated index of all atherogenic and atheroprotective factors present in an individual patient, including known as well as unknown variables. Thus, measurement of endothelial vasomotor function, a comprehensive analysis of atherosclerotic burden, may provide a better predictive value of future cardiovascular events than the analysis of each of the traditional risk factors alone.

Study limitations. This study is preliminary and considerably limited by the small number of study patients, and that reduces the power of the statistical analyses. A large prospective trial is required to understand the precise role of persistent endothelial vasomotor dysfunction in the pathogenesis and progression of atherosclerotic disease. Also, standardized and reproducible techniques for FMD measurement need to become available for multicenter trials. The cutoff point of 5.5% for impaired FMD in the present study may not be necessarily applied to other FMD studies because the FMD value is considerably influenced by technical issues, age, sex, brachial arterial diameter, and so on (2–4). However, the cutoff point of 5.5% for impaired FMD seems to be reasonable in the present study because this pre-defined cutoff point was close to an optimal cutoff point of 5.2%, as determined by ROC analysis, for baseline FMD in discriminating CAD patients from control subjects included in the present study.

Conclusions

Persistent endothelial vasomotor dysfunction in the brachial artery may be related to future cardiovascular events despite well-established antiatherosclerotic therapy for CAD patients. Periodic measurement of FMD may be useful for risk stratification of CAD patients.

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Key Words: endothelium ■ prognosis ■ coronary artery disease ■ risk factor.