

Endothelial Function Assessed by Automatic Measurement of Enclosed Zone Flow-Mediated Vasodilation Using an Oscillometric Method Is an Independent Predictor of Cardiovascular Events

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Background—A new device for automatic measurement of flow-mediated vasodilation (FMD) using an oscillometric method has been developed to solve technical problems of conventional FMD measurement. This device measures enclosed zone FMD (ezFMD). The purpose of this study was to evaluate the prognostic value of endothelial function assessed by ezFMD for future cardiovascular events.

Methods and Results—We measured ezFMD in 272 participants who underwent health-screening examinations. First, we investigated cross-sectional associations between ezFMD and cardiovascular risk factors, and then we assessed the associations between ezFMD and first major cardiovascular events (death from cardiovascular causes, stroke, and coronary revascularization). Univariate regression analysis revealed that ezFMD was significantly correlated with age, triglycerides, glucose, smoking pack-years, estimated glomerular filtration rate, high-sensitivity C-reactive protein, and Framingham risk score. During a median follow-up period of 36.1 months (interquartile range 18.8–40.1 months), 12 participants died (6 from cardiovascular causes), 3 had stroke, 8 had coronary revascularization, and 10 were hospitalized for heart failure. There was no episode of acute coronary syndrome during the study period. Participants were divided into tertiles (low, intermediate, and high) based on ezFMD. Kaplan–Meier curves for first major cardiovascular events among the 3 groups were significantly different ($P=0.004$). After adjustment for cardiovascular risk factors, the low group was significantly associated with an increased risk of first major cardiovascular events compared with the high group (hazard ratio 6.47; 95% CI 1.09–125.55; $P=0.038$).

Conclusions—These findings suggest that endothelial function assessed by ezFMD may be useful as a surrogate marker of future cardiovascular events.

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Key Words: atherosclerosis • biomarker • cardiovascular events • endothelial function

Endothelial dysfunction is the initial event in atherosclerosis and plays a key role in atherogenesis, resulting in cardiovascular complications.^{1,2} It is clinically important to

assess endothelial function for early detection of atherosclerosis. Several methods have been developed to evaluate endothelial function in humans.^{3–9} Measurement of flow-

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mediated vasodilation (FMD) in the brachial artery is a noninvasive and broadly applicable method for assessing endothelial function.^{4–9} It has been shown that endothelial dysfunction evaluated by FMD is an independent predictor of cardiovascular events.^{10–14}

Although measurement of FMD is most widely used for assessment of endothelial function, change in vascular diameter measured by manual operation or by a semiautomated ultrasound system is used for calculation of FMD; therefore, this technique has relatively low reproducibility and requires a skilled operator.^{5,6} We previously developed a new device for fully automatic measurement of endothelial function using an oscillometric method to solve the technical problems of FMD measurement.^{15,16} The newly developed device measures enclosed zone FMD (ezFMD). The ezFMD can be easily measured by placement of a blood pressure cuff around the upper arm. We previously confirmed that endothelial function measured by ezFMD significantly correlated with conventional FMD and cardiovascular risk factors ($r=0.34$; 95% CI 0.22–0.44; $P<0.0001$)¹⁵; however, it is unclear whether ezFMD can predict future cardiovascular events. In the present study, we evaluated the prognostic value of endothelial function assessed by ezFMD for future cardiovascular events.

Methods

Participants

Between May 2011 and January 2015, 272 participants were enrolled from among persons who underwent health-screening examinations at Hiroshima University Hospital. All employees have an obligation to undergo health screening every year under the regulation of the society-managed health insurance union in Japan. In accordance with that regulation, we performed health-screening examinations at our institute. Participants can select to receive optional measurements of vascular function. The inclusion criterion was age ≥ 20 years. There were no exclusion criteria. We measured ezFMD in 272 consecutive subjects who agreed to participate in this study. Hypertension was defined as systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg in a sitting position on at least 3 different occasions. Diabetes mellitus was defined according to the American Diabetes Association.¹⁷ Dyslipidemia was defined according to the third report of the National Cholesterol Education Program.¹⁸ Framingham risk score was calculated with points for the following risk factors: age, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, and smoking status.¹⁹ Estimated glomerular filtration rate was calculated using the following equation: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$

($\times 0.739$ for women).²⁰ This study was approved by the ethics committee of Hiroshima University. All participants gave written informed consent for participation in the study.

Study Protocol

Endothelial function was assessed by measurement of ezFMD in all participants. The participants were instructed to abstain from eating, drinking alcohol, smoking, and taking caffeine for at least 12 hours prior to the measurements. Measurements were performed while each participant was in the supine position in a quiet, dark, air-conditioned room (constant temperature of 22–25°C). Venous blood samples were obtained from the left antecubital vein. The ezFMD measurement was taken after 30 minutes of resting in the supine position. The observers were blind to the purpose of this study.

First, we investigated cross-sectional associations between ezFMD and cardiovascular risk factors, and then we assessed the prognostic value of ezFMD. From March 2016 to April 2016, we collected information on potential outcomes or adverse events from medical records and from a telephone survey. We obtained complete follow-up data for all participants. We assessed the associations of ezFMD with first major cardiovascular events (death from cardiovascular causes, acute coronary syndrome, stroke, and coronary revascularization), and then we assessed the associations with death from cardiovascular causes, acute coronary syndrome, stroke, coronary revascularization, hospitalization for heart failure, and death from any causes.

Measurement of ezFMD

Oscillometric noninvasive blood pressure measurement is widely performed in a clinical setting. The theory is that the arterial wall contains no stress and that the vessel is minimally distended when external or cuff pressure is equal to arterial pressure.^{21,22} Cuff wave pressure is a signal of variation of internal cuff pressure and arises from volumetric change in the cuff, which, in turn, originates from volumetric pulse change in the artery. When arterial vessel volume increases, cuff volume decreases and cuff internal pressure increases. Repetition of changes in arterial vessel volume and cuff volume shows the oscillation signal. The magnitude of oscillation and volumetric change in the artery shows a close proportional relation. Cuff pressure associated with the largest oscillation amplitude can be considered as mean blood pressure. The vascular response to reactive hyperemia in the brachial artery is assessed for oscillation amplitude measurement of ezFMD.^{15,16} The pulse wave is measured with an OPV 1500 (Nihon Kohden Co.). Oscillometry is a

Table 1. Clinical Characteristics of the Participants on the Basis of ezFMD

| Variables | Total (n=272) | High Group (n=91) | Intermediate Group (n=91) | Low Group (n=90) | P Value for Trend |
|--|------------------|-------------------|---------------------------|------------------|-------------------|
| Age, y, mean±SD | 55±20 | 45±18 | 55±19 | 66±17 | <0.001 |
| Age >55 years, n (%) | 145 (53.5) | 25 (27.5) | 50 (55.0) | 70 (77.8) | <0.001 |
| Sex, men/women | 195/77 | 68/23 | 63/28 | 64/26 | 0.70 |
| Body mass index, kg/m ² , mean±SD | 23.1±3.7 | 22.8±3.5 | 22.5±3.3 | 23.8±4.1 | 0.06 |
| Systolic blood pressure, mm Hg, mean±SD | 120±18 | 118±17 | 122±19 | 122±18 | 0.33 |
| Diastolic blood pressure, mm Hg, mean±SD | 68±12 | 68±13 | 70±10 | 67±12 | 0.31 |
| Heart rate, beats/min, mean±SD | 68±12 | 69±13 | 67±10 | 67±12 | 0.59 |
| Medical history | | | | | |
| Hypertension, n (%) | 138 (50.7) | 25 (27.5) | 49 (53.9) | 64 (71.1) | <0.001 |
| Dyslipidemia, n (%) | 150 (55.2) | 35 (38.5) | 52 (57.1) | 63 (70.0) | <0.001 |
| Diabetes mellitus, n (%) | 57 (21.0) | 9 (9.9) | 17 (18.7) | 31 (34.4) | <0.001 |
| Previous coronary artery disease, n (%) | 52 (19.1) | 9 (9.9) | 11 (12.1) | 32 (35.6) | <0.001 |
| Previous cerebrovascular disease, n (%) | 20 (7.4) | 1 (1.1) | 6 (6.6) | 13 (14.4) | 0.002 |
| Smoker, n (%) | 121 (44.5) | 33 (36.3) | 38 (41.8) | 50 (55.6) | 0.02 |
| Smoking, pack-years, median (IQR) | 0 (0–28.1) | 0 (0–10.0) | 0 (0–23.0) | 6 (0–41.8) | <0.001 |
| Laboratory determinations | | | | | |
| eGFR, mL/min/1.73 m ² , mean±SD | 69.9±23.9 | 79.5±23.2 | 69.1±20.5 | 63.5±25.3 | <0.001 |
| Total cholesterol, mmol/L, mean±SD | 4.78±1.01 | 4.94±1.14 | 4.73±0.88 | 4.68±0.98 | 0.34 |
| Triglycerides, mmol/L, median (IQR) | 1.30 (0.87–1.89) | 1.14 (0.75–1.49) | 1.30 (0.86–2.09) | 1.39 (0.98–2.07) | 0.04 |
| HDL-C, mmol/L, mean±SD | 1.47±0.41 | 1.53±0.44 | 1.42±0.39 | 1.45±0.44 | 0.31 |
| LDL-C, mmol/L, mean±SD | 2.79±0.80 | 2.84±0.88 | 2.79±0.75 | 2.74±0.80 | 0.75 |
| Glucose, mmol/L, median (IQR) | 5.72 (5.05–6.94) | 5.27 (4.66–5.83) | 5.66 (5.05–6.94) | 6.27 (5.44–7.60) | <0.001 |
| hsCRP, µg/L, median (IQR) | 400 (200–1100) | 500 (200–1200) | 400 (200–600) | 900 (300–2400) | 0.01 |
| Medications | | | | | |
| Antiplatelets, n (%) | 72 (26.5) | 13 (14.3) | 21 (23.1) | 38 (42.2) | <0.001 |
| Calcium channel blockers, n (%) | 79 (29.0) | 10 (11.0) | 26 (28.6) | 43 (47.8) | <0.001 |
| Renin–angiotensin system inhibitors, n (%) | 84 (30.9) | 11 (12.1) | 30 (33.0) | 43 (47.8) | <0.001 |
| Statins, n (%) | 70 (25.7) | 14 (15.4) | 20 (22.0) | 36 (40.0) | <0.001 |
| Medically treated diabetes mellitus | | | | | |
| Any, n (%) | 47 (17.3) | 9 (9.9) | 14 (15.4) | 24 (26.7) | 0.01 |
| Insulin dependent, n (%) | 11 (4.0) | 2 (2.2) | 2 (2.2) | 7 (7.8) | 0.10 |
| Framingham risk score, %, median (IQR) | 7 (3–11) | 4 (2–8) | 7 (3–11) | 7 (5–13) | <0.001 |
| ezFMD, %, mean±SD | 26.6±16.7 | 44.5±13.2 | 25.1±3.7 | 10.0±7.1 | <0.001 |

All results are presented as mean±SD, median (IQR), or number (%). P values for categorical variables are based on the chi-square test or Fisher exact test depending on expected frequency. P values for continuous variables were based on ANOVA if normal distribution assumption is met; otherwise, P values were based on the Kruskal–Wallis test. High group indicates ezFMD >32.3%, intermediate group indicates ezFMD 19.5% to 32.3%, and low group indicates ezFMD <19.5%. eGFR indicates estimated glomerular filtration rate; ezFMD, enclosed zone flow-mediated vasodilation; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

commonly used noninvasive method for measuring blood pressure with a sphygmomanometer cuff tied around the upper arm. After the cuff is inflated to a level higher than systolic blood pressure, it is deflated slowly, and blood pressure is estimated on the basis of oscillation signals recorded from the internal cuff pressure. At first, blood

pressure is measured 2 times on the upper arm in a supine position at rest with this device, and after interrupting blood flow for 5 minutes with the cuff, blood pressure is consecutively measured 5 times automatically. The cuff is inflated up to systolic pressure plus 50 mm Hg. For every cuff pressure deflation of 5 mm Hg, 2 oscillation signal pulses

Table 2. Univariate Analysis of the Relation Between ezFMD and Variables

| Variable | ρ | P Value |
|------------------------------------|--------|---------|
| Age, y | -0.467 | <0.001 |
| Body mass index, kg/m ² | -0.097 | 0.14 |
| Systolic blood pressure, mm Hg | -0.090 | 0.14 |
| Diastolic blood pressure, mm Hg | 0.037 | 0.55 |
| Heart rate, beats/min | -0.015 | 0.82 |
| eGFR, mL/min/1.73 m ² | 0.312 | <0.001 |
| Total cholesterol, mmol/L | 0.028 | 0.69 |
| Triglycerides, mmol/L | -0.153 | 0.02 |
| HDL-C, mmol/L | 0.066 | 0.33 |
| LDL-C, mmol/L | 0.022 | 0.74 |
| Glucose, mmol/L | -0.314 | <0.001 |
| hsCRP, μ g/L | -0.173 | 0.04 |
| Smoking, pack-years | -0.223 | <0.001 |
| Framingham risk score | -0.259 | <0.001 |

Univariate analysis of the relations among ezFMD and variables (Spearman's rank correlation analysis). eGFR indicates estimated glomerular filtration rate; ezFMD, enclosed zone flow-mediated vasodilation; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

and deflation of the cuff are repeated, and cuff pressure is released at the point when diastolic pressure is reached. The average of the oscillation amplitudes of 2 pulses is considered the typical value of oscillation amplitude at each cuff pressure step. The maximum typical value of 1 measurement sequence to calculate the compliance change is used. The ezFMD is calculated using the following equation: %ezFMD=[(peak oscillation amplitude–baseline oscillation amplitude)/baseline oscillation amplitude]×100. In the postocclusion period, the average of the third, fourth,

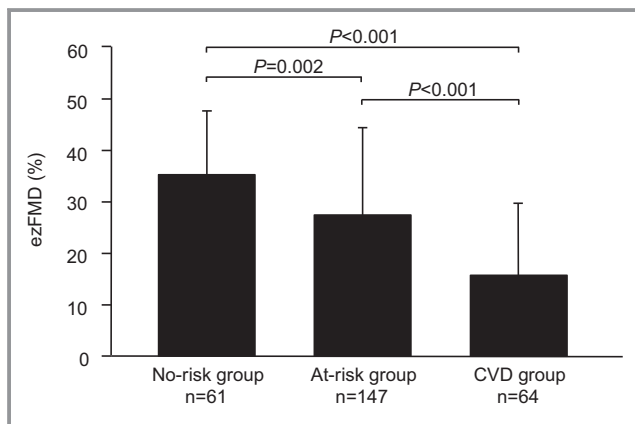


Figure 1. Bar graphs show enclosed zone flow-mediated vasodilation (ezFMD) in the no-risk, at-risk, and cardiovascular disease (CVD) groups.

and fifth of 5 measurements is used for analysis of peak oscillation amplitude.

Statistical Analysis

Results are presented as mean±SD or median (interquartile range) for continuous variables and as percentages for categorical variables. Statistical significance was set at a level of $P<0.05$. Continuous variables were compared using ANOVA or Kruskal–Wallis tests depending on normality of the data. Categorical variables were compared by means of the chi-square test or Fisher exact test depending on expected frequency. Relations between variables were determined by Spearman rank correlation analysis. The receiver operating characteristic curve analyses were carried out to assess the sensitivity and specificity of measurement of ezFMD for predicting first major cardiovascular events within 3 years using the Youden index. Time-to-event end point analyses were performed using the Kaplan–Meier method. We categorized participants into 3 tertiles according to ezFMD. A log-rank test was used to compare survival in the groups. We evaluated the associations between ezFMD and first major cardiovascular events after adjustment for age (>55 years), sex, and cardiovascular risk factors by using Cox proportional hazards regression analysis. As the sensitivity analysis, the proportional hazards assumption was confirmed by inspection of Schoenfeld residuals and log-log plotting. The data were processed using the software package Stata version 9 (StataCorp).

Results

Baseline Characteristics

The baseline characteristics of the 272 participants are summarized in Table 1. Of the 272 participants, 195 (71.7%) were men and 77 (28.3%) were women. In total, 138 (50.7%) had hypertension, 150 (55.2%) had dyslipidemia, 57 (21.0%) had diabetes mellitus, and 121 (44.5%) had a history of smoking. Of all participants who were evaluated, 52 (19.1%) had coronary artery disease and 20 (7.4%) had cerebrovascular disease. The mean ezFMD was $26.6\pm 16.7\%$.

Relationships Between ezFMD and Cardiovascular Risk Factors

Univariate regression analysis revealed that ezFMD was significantly correlated with age, estimated glomerular filtration rate, triglycerides, glucose, high-sensitivity C-reactive protein, smoking pack-years, and Framingham risk score (Table 2). The participants were divided into 3 tertiles based on ezFMD (Table 1). The high group had ezFMD of >32.3%, the

Table 3. Clinical Outcomes of All Participants on the Basis of ezFMD

| Variable | Total (n=272) | High Group (n=91) | Intermediate Group (n=91) | Low Group (n=90) | P Value for Trend |
|--|---------------|-------------------|---------------------------|------------------|-------------------|
| First major cardiovascular event, n (%) | 16 (5.9) | 2 (2.2) | 4 (4.4) | 10 (11.1) | 0.045 |
| Death from cardiovascular disease, n (%) | 6 (2.2) | 0 (0) | 1 (1.1) | 5 (5.6) | 0.02 |
| Acute myocardial infarction, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NA |
| Stroke, n (%) | 3 (1.1) | 1 (1.1) | 0 (0) | 2 (2.2) | 0.33 |
| Coronary revascularization, n (%) | 8 (2.9) | 1 (1.1) | 3 (3.3) | 4 (4.4) | 0.37 |
| Hospitalization for heart failure, n (%) | 10 (3.7) | 0 (0) | 4 (4.4) | 6 (6.7) | 0.03 |
| Death from any cause, n (%) | 12 (4.4) | 2 (2.2) | 2 (2.2) | 8 (8.9) | 0.052 |

All results are presented as number (%). *P* values for categorical variables are based on the Fisher exact test. First major cardiovascular events include death from cardiovascular disease, stroke, and coronary revascularization. High group indicates ezFMD >32.3%, intermediate group indicates ezFMD 19.5% to 32.3%, and low group indicates ezFMD <19.5%. ezFMD indicates enclosed zone flow-mediated vasodilation; NA, not applicable.

intermediate group had ezFMD between 19.5% and 32.3%, and the low group had ezFMD of <19.5%. Significant differences were observed among the 3 groups in terms of age; smoking pack-years; estimated glomerular filtration rate; triglycerides; glucose; high-sensitivity C-reactive protein; prevalence of hypertension; dyslipidemia; diabetes mellitus; smoking history; history of coronary artery disease; history of cerebrovascular disease; and the use of antiplatelets, calcium channel blockers, renin-angiotensin system inhibitors, statins, and diabetic agents. Figure 1 shows ezFMD in participants with no cardiovascular risk factors (the no-risk group); with at least 1 coronary risk factor, including hypertension, dyslipidemia, diabetes mellitus, and smoking, but without established cardiovascular

disease (the at-risk group); and with cardiovascular disease (the cardiovascular disease group). The ezFMD measured in the group with cardiovascular disease was significantly lower than that in the no-risk group and in the at-risk group ($15.8 \pm 13.9\%$ versus $35.5 \pm 12.1\%$ and $27.6 \pm 17.0\%$, respectively; $P < 0.001$) (Figure 1). In the at-risk group, ezFMD was significantly lower than that in the no-risk group ($P = 0.002$) (Figure 1).

Clinical Outcomes and ezFMD

During a median follow-up period of 36.1 months (interquartile range 18.8–40.1 months), 12 participants died (6 from cardiovascular causes), 3 had stroke, 8 had coronary revascularization, and 10 were hospitalized for heart failure (Table 3). There was no episode of acute coronary syndrome during the study period. Receiver operating characteristic curve analysis revealed that ezFMD predicts cardiovascular events within 3 years with an area under the curve of 0.76 (Figure 2). The optimal cutoff value of ezFMD for first major cardiovascular events was 20.6% (sensitivity of 78.6% and specificity of 64.3%). The Kaplan-Meier curves for first major cardiovascular events among the 3 groups were significantly different ($P = 0.004$) (Figure 3). The Kaplan-Meier curves for death from cardiovascular disease ($P = 0.002$), hospitalization for heart failure ($P = 0.028$) and death from any cause ($P = 0.008$) among the 3 groups were significantly different, but the Kaplan-Meier curves for stroke ($P = 0.25$) and coronary revascularization ($P = 0.27$) among the 3 groups were not significantly different (Figure 4). Clinical outcomes of all participants on the basis of ezFMD are shown in Table 3. After adjustment for age (>55 years), sex, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, glucose, and smoking history, the low-ezFMD group was significantly associated with an increased risk of first major cardiovascular events compared with the high-ezFMD group (hazard ratio 6.47; 95% CI 1.09–125.55; $P = 0.038$) (Table 4).

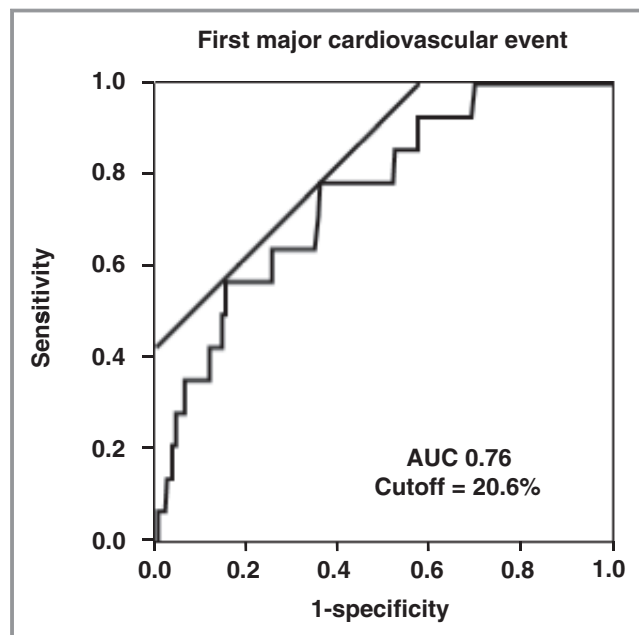


Figure 2. Receiver operating characteristic curves of enclosed zone flow-mediated vasodilation for predicting first major cardiovascular events. AUC indicates area under the curve.

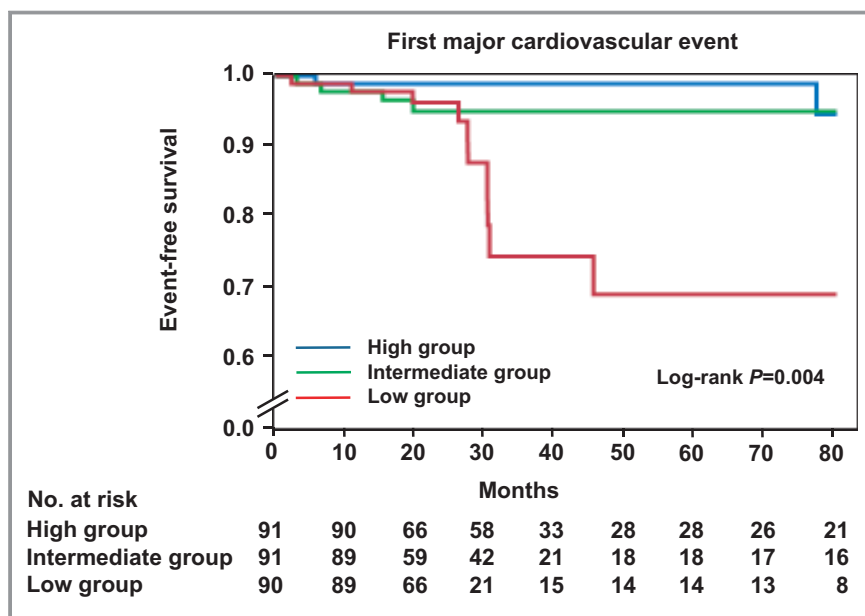


Figure 3. Kaplan–Meier curves of cumulative event-free survival of first major cardiovascular events (death from cardiovascular causes, stroke, and coronary revascularization) according to enclosed zone flow-mediated vasodilation (ezFMD). High group indicates ezFMD >32.3%, intermediate group indicates ezFMD 19.5% to 32.3%, and low group indicates ezFMD <19.5%.

Discussion

In the present study, we demonstrated that ezFMD was significantly correlated with Framingham risk score and was decreased in relation to cumulative cardiovascular risk factors. We confirmed the prognostic value of ezFMD for first major cardiovascular events. These findings suggest that endothelial function evaluated by ezFMD may be a surrogate marker for predicting cardiovascular events and may be a therapeutic target for cardiovascular disease.

Aging, smoking, obesity, hypertension, dyslipidemia, and diabetes mellitus are well-known risk factors of endothelial dysfunction.^{1–4,7–9,23–25} We previously showed that ezFMD was significantly correlated with cardiovascular risk factors and endothelial function assessed by FMD in relatively young participants.¹⁵ The relevance of ezFMD in older adults remains unclear. In the present study, we confirmed that ezFMD correlated with cardiovascular risk factors, including age; smoking pack-years; triglycerides; glucose; high-sensitivity C-reactive protein; estimated glomerular filtration rate; prevalence of hypertension, dyslipidemia, and diabetes mellitus; history of coronary artery disease; and history of cerebrovascular disease. In addition, ezFMD was significantly correlated with Framingham risk score, which is designed to estimate the 10-year risk of coronary heart disease. These findings suggest that measurement of ezFMD is useful for evaluating endothelial function and is a therapeutic marker for atherosclerosis.

Endothelial dysfunction is the earliest event in atherosclerosis, leading to cardiovascular complications.^{1,2} Several investigators, including us, have reported that endothelial function evaluated by FMD can serve as an independent predictor of cardiovascular events.^{10–14} In this study, first major cardiovascular events were significantly more frequent in participants with smaller ezFMD values than in those with large values. In addition, after adjustment for age, sex, body mass index, and cardiovascular risk factors, there was a significant association between ezFMD and increasing risk of first major cardiovascular events. These findings suggest that ezFMD also has predictive power for future cardiovascular events.

Because ezFMD is measured by pulsatile arterial volume changes, ezFMD may be affected by changes in blood flow volume into the arm during measurement. In this study, 84 of the 272 participants underwent measurements of FMD and blood flow velocity of the brachial artery by pulsed wave Doppler on different days. Reactive hyperemia ratio was calculated using the following equation: reactive hyperemia ratio (%) = [(peak flow velocity – baseline flow velocity) / baseline flow velocity] × 100. There was a significant relationship between ezFMD and FMD ($r=0.52$, $P<0.001$) (Figure 5A), but ezFMD was not associated with reactive hyperemia ratio ($r=0.07$, $P=0.52$) (Figure 5B); however, we cannot exclude the possibility that blood volume affects ezFMD.

We previously showed that ezFMD is significantly correlated with cardiovascular risk factors and endothelial function

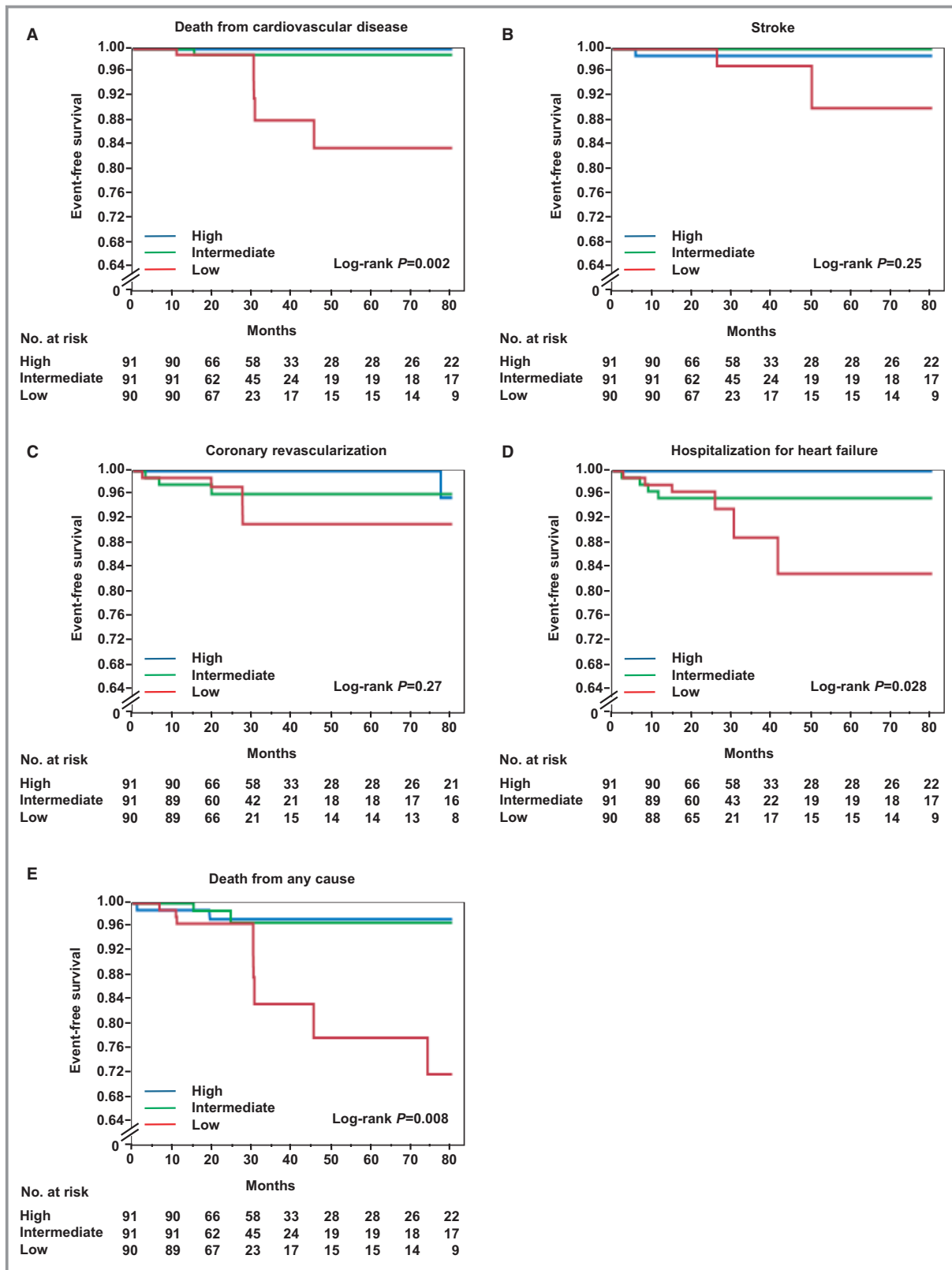


Figure 4. Kaplan–Meier curves of cumulative event-free survival of death from cardiovascular causes (A), stroke (B), coronary revascularization (C), hospitalization for heart failure (D), and death from any cause (E), according to the enclosed zone flow-mediated vasodilation (ezFMD). High group indicates ezFMD >32.3%, intermediate group indicates ezFMD 19.5% to 32.3%, and low group indicates ezFMD <19.5%.

Table 4. Association Between ezFMD and First Major Cardiovascular Events During Follow-up

| Variable | Unadjusted HR (95% CI) P Value | Adjusted* HR (95% CI) P Value |
|--------------------|-----------------------------------|----------------------------------|
| High group | 1 (reference) | 1 (reference) |
| Intermediate group | 2.49 (0.49–18.00) 0.28 | 1.78 (0.22–37.10) 0.61 |
| Low group | 7.87 (2.03–51.73) 0.002 | 6.47 (1.09–125.55) 0.038 |

First major cardiovascular events include death from cardiovascular disease, stroke, and coronary revascularization. High group indicates ezFMD >32.3%, intermediate group indicates ezFMD 19.5% to 32.3%, and low group indicates ezFMD <19.5%. ezFMD indicates enclosed zone flow-mediated vasodilation; HR, hazard ratio.

*Also adjusted for age (>55 years), sex, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, glucose, and smoking history.

evaluated by FMD.¹⁵ It is clinically important to evaluate endothelial function. FMD is widely used and is useful for knowing the degree of atherosclerosis, the efficacy of

treatment for atherosclerosis, and the possibility of cardiovascular events. Measurement of FMD, however, remains a research tool rather than a clinical tool because of the high cost of an ultrasound device and skill-biased technical change.^{5,6} Although there was a lot of variability in ezFMD as well as FMD,¹⁵ measurement of ezFMD has good potential for screening with minimal technical requirements for assessing endothelial function, and the cost of measuring ezFMD is much lower than that using an ultrasonography system.

Study Limitations

First, the number of events, especially stroke, during the follow-up period was relatively small; however, our results clearly showed that ezFMD predicts future cardiovascular events. Further studies are needed to confirm the prognostic value of ezFMD in a multicenter study including a larger population. Second, we measured ezFMD just 1 time, when the participants were enrolled. It is well known that endothelial function can be modified by interventions including aerobic exercise, body weight reduction, and pharmacological therapy.² Several investigators have shown that repeated assessment of vascular function has much greater predictive power of cardiovascular disease progression and cardiovascular outcomes.^{26,27} Repeated measurement of ezFMD will enable specific conclusions concerning the role of ezFMD in future cardiovascular events to be drawn. Third, several medications such as renin–angiotensin system inhibitors and statins affect endothelial function.^{2,6} In the present study, measurement of ezFMD was performed without withholding these medications. Because we enrolled participants who underwent health-screening examinations, it would have been inappropriate to withhold medications. A previous study demonstrated that administration of vasoactive medication did not significantly influence the value of endothelial function evaluated by FMD.²⁸ Nevertheless, we cannot deny the possibility that medication affects ezFMD. Fourth, mean blood pressure should change during measurement of ezFMD. Changes in mean blood pressure may cause failure in detection of maximal oscillation amplitude; therefore, the cuff used for measurement of ezFMD is inflated to a level higher than systolic blood pressure to measure oscillation amplitude at mean blood pressure. Finally, the oscillometric method has been validated and calibrated for participants with sinus rhythm.²⁹ The variability of heart rate and stroke volume caused by arrhythmia may affect ezFMD. In this study, ezFMD was measured under sinus rhythm. Further studies are needed to determine whether ezFMD is a useful method for evaluating endothelial function in patients with arrhythmia.

In conclusion, endothelial function evaluated by a fully automated device for measurement of ezFMD was shown to

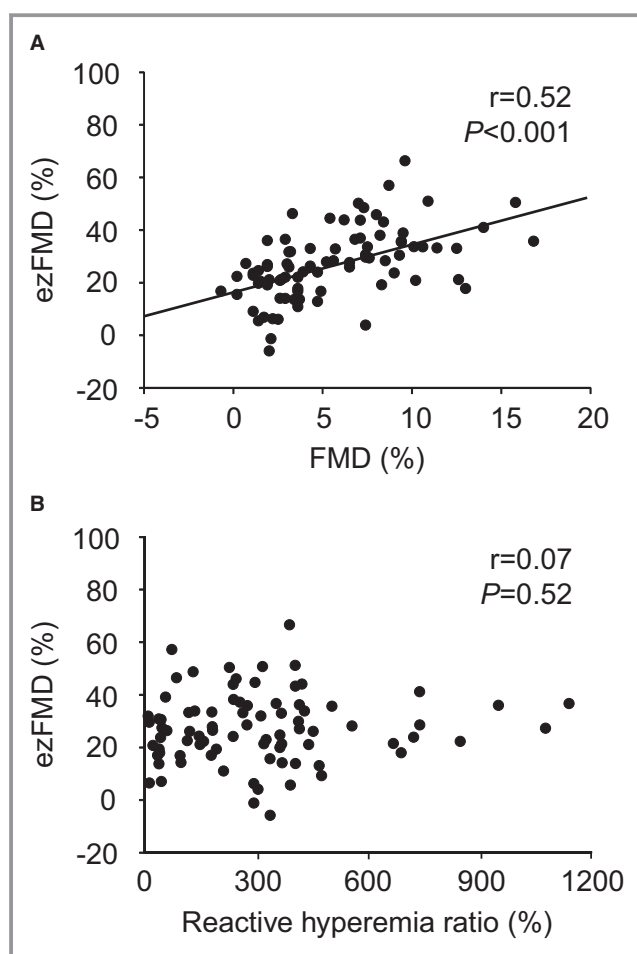


Figure 5. Scatter plots show the relationships between enclosed zone flow-mediated vasodilation (ezFMD) and flow-mediated vasodilation (FMD) (A) and reactive hyperemia ratio (B).

be an independent predictor of cardiovascular events, suggesting that ezFMD may be useful as a surrogate marker of future cardiovascular events. Further large clinical trials are required to confirm the usefulness of ezFMD.

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Disclosures

None.

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