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The Relative Importance of Vascular Structure and Function in Predicting Cardiovascular Events

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OBJECTIVES We sought to assess the prognostic utility of brachial artery reactivity (BAR) in patients at risk of cardiovascular events.

BACKGROUND Impaired flow-mediated vasodilation measured by BAR is a marker of endothelial dysfunction. Brachial artery reactivity is influenced by risk factors and is responsive to various pharmacological and other treatments. However, its prognostic importance is uncertain, especially relative to other predictors of outcome.

METHODS A total of 444 patients were prospectively enrolled to undergo BAR and follow-up. These patients were at risk of cardiovascular events, based on the presence of risk factors or known or suspected cardiovascular disease. We took a full clinical history, performed BAR, and obtained carotid intima-media thickness (IMT) and left ventricular mass and ejection fraction. Patients were followed up for cardiovascular events and all-cause mortality. Multivariate Cox regression analysis was performed to assess the independent association of investigation variables on outcomes.

RESULTS The patients exhibited abnormal BAR (5.2 ± 6.1% [mean ± SD]) but showed normal nitrate-mediated dilation (9.9 ± 7.2%) and normal mean IMT (0.67 ± 0.12 mm [average]). Forty-nine deaths occurred over the median follow-up period of 24 months (interquartile range 10 to 34). Patients in the lowest tertile group of BAR (<2%) had significantly more events than those in the combined group of highest and mid-tertiles ($p = 0.029$, log-rank test). However, mean IMT (rather than flow-mediated dilation) was the vascular factor independently associated with mortality, even in the subgroup ($n = 271$) with no coronary artery disease and low risk.

CONCLUSIONS Brachial artery reactivity is lower in patients with events, but is not an independent predictor of cardiovascular outcomes in this cohort of patients. (J Am Coll Cardiol 2004;43:616–23)

In patients with coronary artery disease (CAD), coronary endothelial dysfunction has been shown to correlate with cardiovascular events (1,2). However, the techniques used for assessment of coronary reactivity are invasive and not ideal for clinical purposes, especially if serial measurements are required. An alternative approach is to non-invasively examine vascular function in a peripheral vessel, in the belief that vascular disease is a systemic process (3,4). This

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principle underpins the non-invasive assessment of brachial artery reactivity (BAR) to measure flow-mediated dilation (FMD) of the arteries (5). A number of studies have shown that abnormal arterial reactivity is associated with the classic cardiovascular risk factors (6,7) and that treatment of these risk factors can improve endothelial function (8–10).

However, the prognostic power of this technique remains poorly defined. The association between coronary and brachial reactivity is modest to good (11,12). The existing studies investigating BAR and outcomes have generally involved small or highly selected populations (13,14), and they have not addressed whether the test results provide information that is incremental to that already gathered by alternative tests. Therefore, we sought to investigate whether the measurement of brachial artery FMD could predict mortality and cardiovascular morbidity in a large group of patients at risk of vascular disease, and whether this information was incremental to that already gathered in risk assessment.

METHODS

Study design. Consecutive patients deemed at risk of CAD were prospectively enrolled from cardiology and renal outpatients from December 1998 to July 2002, for risk evaluation and subsequent follow-up. Patients were deemed at risk due to known or suspected vascular disease, renal dysfunction, or the presence of multiple cardiovascular risk factors. Exclusion criteria included a recent (up to six weeks) inpatient stay due to myocardial infarction (MI), acute coronary syndrome, coronary revascularization, heart failure, or sepsis. All patients gave written, informed consent, and the study was approved by the Human Ethics Committee of University of Queensland and Princess Alexandra Hospital.

A full clinical history and examination were undertaken

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Abbreviations and Acronyms

BAR = brachial artery reactivity
CAD = coronary artery disease
EF = ejection fraction
FMD = flow-mediated dilation
HDL = high-density lipoprotein
IMT = intima-media thickness
LV = left ventricle/ventricular
MI = myocardial infarction

by a specialist physician. Baseline demographic data, cardiovascular risk factors, and cardiovascular medications were documented, and a 12-lead electrocardiogram was reviewed. Fasting serum was collected for lipid analysis. Brachial artery reactivity was assessed as a measure of vascular dysfunction; carotid intima-media thickness (IMT) was measured as a marker of atherosclerotic burden; and standard transthoracic echocardiography was performed for assessment of left ventricular (LV) ejection fraction (EF) and mass.

Clinical evaluation. The presence of CAD was defined as a history of MI, coronary revascularization, or typical chest pain with a positive stress echocardiogram. Diabetes mellitus was defined by the use of insulin injections or oral hypoglycemic agents. Hypertension was defined as an average systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on three separate occasions or by the use of antihypertensive medications (15). Hypercholesterolemia was defined as a fasting total cholesterol level of ≥190 mg/dl (4.90 mmol/l) (16) or by the use of a statin. Smoking status was defined as current smoker or reformed/nonsmoker. Significant renal impairment was defined as chronic renal impairment, with a calculated glomerular filtration rate of <60 ml/min/1.73 m^2, or by dialysis (17).

Two-year coronary heart disease event risk in patients with no previous MI was calculated using the revised Framingham risk score (18), using the variables of gender, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and smoking status. For patients with a previous MI, a two-year coronary heart disease event rate was calculated from gender, age, total cholesterol, HDL cholesterol, systolic blood pressure, diabetes, and smoking history (19).

Biochemical analysis. Blood for biochemical analysis was obtained from fasting venous samples. Total cholesterol, HDL cholesterol, and triglycerides were determined by standard enzymatic methods. High-density lipoprotein was measured as a homogeneous assay in liquid phase. The Friedewald equation was used to calculate low-density lipoprotein.

Brachial artery reactivity. Our technique for assessment of BAR has been previously described (20). Patients were studied in the fasting state; vasoactive medications were withheld for 24 h before the study. After 5 min of rest, the brachial artery was located above the elbow, and a longitudinal image of 6 to 8 cm was taken as the resting scan. A blood pressure cuff was placed on the forearm and inflated to 300 mm Hg for 4.5 min. The cuff was deflated, and after ~1 min, the second or FMD scan was obtained, which represents the endothelial-dependent dilation due to shear-induced endothelial nitric oxide production. The second rest scan was acquired after 15 min of rest, and endothelial-independent dilation was measured by calculation of the vasodilator response to exogenous nitrate 3 min after administration of 400 μg of sublingual nitroglycerin. The percent diameter change for FMD and nitrate-mediated dilation was calculated in relation to its respective rest scan, and the ratio of flow-mediated to nitrate-mediated dilation was also calculated. Thirty-eight randomly selected images were reanalyzed for intraobserver variation, using the previously described software developed for lumen measurement (HDILab version 1.5, with the Lumen Diameter Over Time version 1.15 plugin, HDI Lab, Bothell, Washington). Intraobserver variation for FMD was 1.4 ± 1.2%, with a coefficient of variation of 5.3%. For nitrate-mediated dilation, the intraobserver variation was 2.1 ± 1.8%, with a coefficient of variation of 7.6%.

Intima-media thickness. Our method for IMT measurement has been previously reported (21). Both the left and right common carotid arteries were imaged at the level of the carotid bifurcation in the anterior, lateral, and posterior plane, using longitudinal B-mode ultrasonography. The focal zone was set at or just below the far wall, which was scanned perpendicular to the transducer face. The far wall IMT was identified as the region between the lumen-intima interface and the media-adventitia interface; care was taken to exclude localized plaque. Off-line analysis of magnified, frozen end-diastolic images was performed by an experienced observer with automatic edge-detection software (HDILab version 1.83H). Intraobserver variation in far wall mean IMT was studied in 288 images using the automated software. The intraobserver variation was 0.01 ± 0.04 mm, with a coefficient of variation of 5.0%.

Detection of ischemia. A subset of patients underwent dobutamine stress echocardiography with standard end points, as previously described (22). Wall motion was scored using the 16-segment model of the American Society of Echocardiography (23). Regional myocardial performance was scored on the basis of wall thickening as normal, mildly hypokinetic, severely hypokinetic, and akinetic or dyskinetic. Ischemia was identified by new or worsening wall motion abnormalities with stress.

Transthoracic echocardiography. Patients also underwent standard echocardiography. Ejection fraction was calculated using the modified Simpson's biplane rule (23). Left ventricular mass was calculated using the formula of Devereux and Reichek (24,25).

Outcomes. The primary outcome was the time to the most significant episode, in order, of death (26), MI, or admission with acute coronary syndrome, stroke, or coronary revascularization. In patients with more than one event, only the

Table 1. Patient Characteristics

	CAD (n = 150)	Dialysis (n = 134)	Multiple Risk Factors (n = 160)
Age (yrs)	64 ± 11	56 ± 15	56 ± 14
Men	102 (68%)	71 (53%)	92 (58%)
Body mass index (kg/m^2)	28 ± 6	26 ± 7	27 ± 5
Known or suspected CAD			
Previous MI	126 (84%)	—	—
Chest pain	150 (100%)	17 (13%)	8 (5%)
Revascularization	46 (31%)	—	—
Renal dysfunction			
Dialysis	43 (29%)	134 (100%)	—
Chronic renal impairment	11 (7%)	—	53 (33%)
Transplant	13 (9%)	—	79 (49%)
Risk factors			
Hyperlipidemia	86 (57%)	73 (55%)	76 (48%)
Hypertension	106 (71%)	111 (83%)	87 (54%)
Diabetes mellitus	55 (37%)	40 (30%)	33 (21%)
Smoker (current)	11 (7%)	11 (8%)	13 (8%)
Calculated 2-year risk of a cardiac event			
≥4% (high risk)	110 (73%)	12 (9%)	11 (7%)
<4% (low to intermediate risk)	40 (27%)	122 (91%)	149 (93%)
Lipids analysis			
Total cholesterol (mg/dl)	177 ± 44	183 ± 45	193 ± 42
LDL cholesterol (mg/dl)	99 ± 38	104 ± 41	102 ± 37
HDL cholesterol (mg/dl)	41 ± 15	46 ± 16	53 ± 20
Triglycerides (mg/dl)	199 ± 146	166 ± 106	188 ± 125
Medications			
Beta-blocker	100 (67%)	41 (31%)	46 (29%)
ACE inhibitor	73 (49%)	52 (39%)	68 (43%)
Calcium channel blocker	72 (48%)	44 (33%)	89 (56%)
Statin	102 (68%)	56 (42%)	71 (44%)
Nitrate	61 (41%)	13 (10%)	25 (16%)
Aspirin	120 (80%)	38 (28%)	30 (19%)
Insulin	8 (5%)	10 (8%)	7 (4%)
Oral hypoglycemic agents	48 (32%)	21 (16%)	9 (6%)

Data are presented as the mean value ± SD or number (%) of patients.
ACE = angiotensin-converting enzyme; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

most significant event was used for analysis. Outcomes were determined by assessment of the death certificate or hospital record survey or by telephone conversation with the patient or treating local medical practitioner.

Acute coronary syndrome was defined as worsening of angina class or ischemic chest pain at rest of >30 min, necessitating hospital admission with either 1) ST-segment deviation of at least 0.1 mV or new T-wave inversion in two contiguous leads; or 2) a creatine kinase rise greater than twice the upper limit of normal. ST-segment elevation MI was defined as ischemic chest pain at rest of >30 min, with new ST-segment elevation of at least 0.1 mV and a creatine kinase increment of >2 times the upper limit of normal.

Statistical analysis. All data are expressed as mean value ± SD or frequency (%), unless otherwise stated. The baseline clinical characteristics of the groups were compared using the two-tailed independent *t* test for continuous variables and the chi-square or Fisher exact test for non-continuous variables, as appropriate. Survival was illustrated with Kaplan-Meier curves, and outcomes were compared using the log-rank test. Independent predictors of events were calculated using Cox proportional hazards regression. The following variables were used first in a univariate model: age, gender, presence of known or likely CAD, renal dysfunction, previous MI, hypertension, hyperlipidemia, diabetes mellitus, current smoking, FMD, nitrate-mediated dilation, flow to nitrate dilation ratio, IMT, total, low-density lipoprotein, and HDL cholesterol, triglycerides, medications, LV mass, EF, and two-year risk score. Factors with a value of $p < 0.20$ were then entered into a forward stepwise multivariate Cox proportional hazards analysis. Statistical significance was assumed at $p < 0.05$. All statistical analyses were performed using SPSS for Windows 11.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Clinical characteristics. We studied 444 patients (age 58 ± 14 years; 265 men). The inclusion categories included multiple risk factors (n = 160 [36%]), dialysis patients without clinical evidence of CAD (n = 134 [23%]), and known CAD (n = 150 [34%]); the last group included 126 patients (28%) with previous MI and 60 (14%) with proven CAD not amenable to revascularization. Clinical details are

Table 2. Imaging Investigation Results

Brachial artery diameter at rest (mm)	3.3 ± 1.6
Flow-mediated dilation (%)	5.2 ± 6.1
Nitroglycerin-mediated dilation (%)	9.9 ± 7.2
Flow to nitroglycerin-mediated dilation ratio	0.68 ± 1.4
Mean carotid IMT (mm)	0.67 ± 0.12
Maximum carotid IMT (mm)	0.76 ± 0.16
Ejection fraction (%)	57 ± 15
Left ventricular mass (g)	253 ± 116

Data are presented as the mean value ± SD.
IMT = intima-media thickness.

summarized in Table 1. There was a high prevalence of risk factors, as well as vasoactive and statin medications. The calculated risk of a cardiac event over a two-year period was 3.9 ± 4.4%. The results of cardiac and vascular imaging are summarized in Table 2.

Outcome. The median duration of follow-up was 24 months (interquartile range 10 to 34). Complete information on outcomes was obtained in 437 patients (98%). The baseline characteristics of the seven patients without follow-up outcome analysis were not different from those of the remainder. The 70 events included 49 deaths (33 cardiovascular), 13 MIs, 1 stroke (leading to death), and 8 episodes of revascularization. Of the 70 events, 35 (50%) were in patients with CAD, 25 (36%) were in patients on dialysis without previous evidence of CAD, and 10 (14%) were in patients with multiple risk factors. The causes of non-cardiac death included complications of end-stage renal disease (n = 4), septicemia (n = 4), respiratory failure (n = 2), palliation for neoplasm (n = 2), meningitis (n = 1), peritonitis (n = 1), gangrene due to peripheral vascular disease (n = 1), and ischemic hepatitis (n = 1).

The *calculated* two-year cardiac risk score was 7.8 ± 4.6% for patients with CAD, 1.8 ± 1.7% for dialysis patients without previous MI, and 1.8 ± 1.5% for patients with multiple cardiovascular risk factors. The corresponding actual cardiovascular mortality event numbers (% within group) were 13 (9%), 14 (10%), and 6 (4%), revealing a higher than expected rate in the dialysis and multiple risk factor groups.

Vascular factors and outcome. Event-free survival was expressed using Kaplan-Meier curves based on tertiles of IMT, LV mass, and FMD (Fig. 1), of which IMT correlated best with the outcome. The FMD tertiles included low (<2% dilation), intermediate (2.1 to 6.3%), and high (>6.3%), with corresponding two-year event numbers being 32, 17, and 21. Log-rank analysis revealed a significant difference between the low and intermediate tertiles (p = 0.037). Further analysis revealed a significant difference in event rate between those with the most severe FMD abnormality (tertile 1) and the combined group of second and third tertiles (log-rank p = 0.029). When this analysis was restricted to all-cause mortality alone, it remained significant (log-rank p = 0.047).

Cardiovascular events were independently associated with average IMT, LV mass, nitrate use, and presence of angina

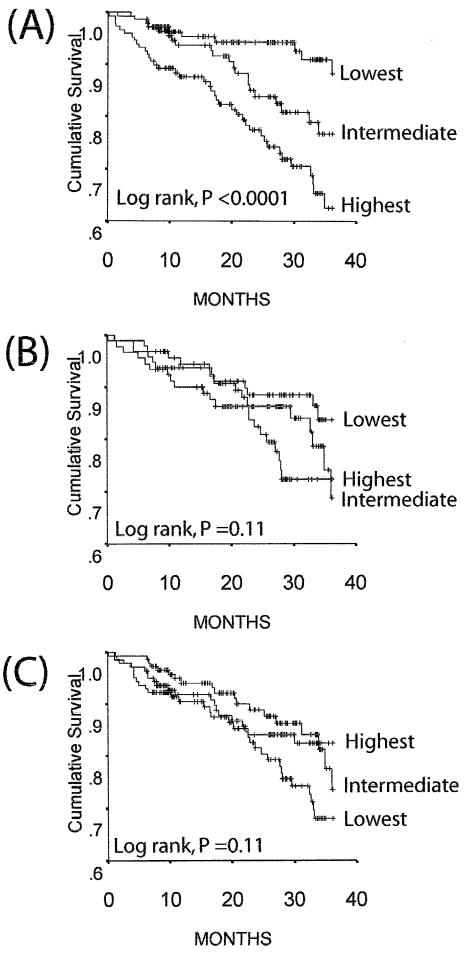

Figure 1. Kaplan-Meier curves for event-free survival associated with **(A)** intima-media thickness (lowest tertile <0.62 mm, highest >0.71 mm), **(B)** left ventricular mass (lowest tertile <181 g, highest >276 g), and **(C)** flow-mediated dilation (lowest tertile <2%, highest >6.3%).

(model chi-square 22.2, p < 0.001) (Table 3). Cardiac death was independently associated with average IMT, LV mass, and nitrate use (model chi-square 18.9, p < 0.001). All-cause death was independently associated with average IMT and LV mass (model chi-square 16.1, p < 0.001). Flow-mediated dilation was not independently associated with outcome, and no significant interaction was found between FMD and IMT, LV mass, and EF.

Clinical correlates of adverse events. To further elucidate the factors associated with events, the cohort was subdivided according to the presence or absence of known CAD and their respective two-year risk for a coronary event. Univariate predictors of an event are displayed in Table 4. A multivariate model was produced in the subgroups with more than one univariate predictor (CAD with risk ≥4% and no CAD with risk <4%). The independent predictors of an event for CAD in the high-risk group included hyperlipidemia and nitrate use (model chi-square 10.6, p = 0.005). For the group with no CAD and low risk, the independent predictors were average IMT and EF (model chi-square 31.0, p < 0.001). Independent predictors in the low-risk population alone were average IMT, LV mass,

Table 3. Univariate and Multivariate Predictors of Any Event by Cox Regression

	Univariate		Multivariate	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (yrs)	1.03 (1.01–1.05)	0.004	—	—
Male gender	0.84 (0.53–1.3)	0.48	—	—
Known or suspected CAD				
Previous MI	2.13 (1.33–3.41)	0.002	—	—
Chest pain	2.36 (1.40–3.95)	0.001	1.94 (1.02–3.71)	0.04
Revascularization	0.74 (0.34–1.64)	0.46	—	—
Renal dysfunction				
Dialysis	1.13 (0.70–1.84)	0.62	—	—
Pre-dialysis	0.62 (0.28–1.37)	0.23	—	—
Transplant	0.32 (0.08–1.35)	0.12	—	—
Two-year risk score (%)	1.08 (1.03–1.13)	0.001	—	—
Hypertension	1.63 (0.89–2.98)	0.11	—	—
Hyperlipidemia	1.06 (0.66–1.70)	0.81	—	—
Diabetes mellitus	1.62 (1.01–2.60)	0.052	—	—
Current smoker	0.58 (0.21–1.60)	0.29	—	—
Beta-blocker	1.05 (0.65–1.68)	0.85	—	—
Calcium channel blocker	1.30 (0.81–2.08)	0.27	—	—
ACE inhibitor	1.12 (0.75–1.92)	0.45	—	—
Long-acting nitrate	2.35 (1.45–3.79)	0.001	2.18 (1.14–4.19)	0.02
Statin	1.35 (0.84–2.18)	0.21	—	—
Aspirin	1.77 (1.10–2.85)	0.02	—	—
Oral hypoglycemic	2.02 (1.20–3.38)	0.008	—	—
Insulin	1.30 (0.56–3.00)	0.54	—	—
Total cholesterol	1.00 (0.99–1.00)	0.30	—	—
LDL cholesterol	1.00 (0.99–1.00)	0.43	—	—
HDL cholesterol	1.01 (0.99–1.02)	0.89	—	—
Triglycerides	1.00 (1.00–1.01)	0.86	—	—
Flow-mediated dilation (%)	0.96 (0.92–1.01)	0.07	—	—
Nitrate-mediated dilation (%)	0.97 (0.94–0.99)	0.04	—	—
Flow to nitrate ratio	1.01 (0.87–1.18)	0.86	—	—
Average IMT (per one-tenth mm increase)	1.37 (1.14–1.63)	0.001	1.35 (1.07–1.69)	0.01
Left ventricular mass (per 10 g)	1.02 (0.99–1.04)	0.09	1.03 (1.01–1.05)	0.03
Ejection fraction (%)	0.98 (0.96–0.99)	0.004	—	—

CI = confidence interval; HR = hazards ratio; other abbreviations as in Tables 1 and 2.

previous MI, and aspirin use (model chi-square 30.0, $p < 0.001$). In the high-risk group, nitrate use remained predictive (model chi-square 9.4, $p = 0.009$).

A further univariate analysis based on clinical presentation (subsets of CAD, dialysis patients without previous MI, and those with multiple risk factors) is displayed in Table 5. Multivariate predictors of an event in groups with more than one univariate predictor revealed that in patients with CAD, independent predictors included hypertension and the use of beta-blockers, nitrates, and statins (model chi-square 27.8, $p < 0.001$). For patients on dialysis without CAD, they included IMT, EF, age, and the use of hypoglycemic tablets (model chi-square 35.4, $p < 0.001$). For patients with multiple risk factors, LV mass remained independently significant (model chi-square 6.5, $p = 0.02$).

Ischemia and adverse events. Patients undergoing stress testing as well as vascular imaging had a higher calculated two-year risk score for a cardiac event (4.1 ± 4.4% vs. 3.2 ± 3.5%, $p = 0.02$), and 124 (45%) of 277 developed ischemia. In this subset, univariate predictors of an event (hazard ratio, 95% confidence interval) included ischemia (2.5, 1.4 to 4.4; $p = 0.002$), age (1.03, 1.01 to 1.05; $p = 0.01$), previous MI (2.0, 1.2 to 3.5; $p = 0.01$), diabetes mellitus (2.1, 1.2 to 3.6; $p = 0.009$), hypoglycemic tablets (2.4, 1.3 to 4.3; $p = 0.004$), nitrate use (2.2, 1.3 to 3.9; $p = 0.005$), aspirin use (2.0, 1.1 to 3.6; $p = 0.02$), two-year risk score (1.08, 1.03 to 1.13; $p = 0.003$), FMD (0.93, 0.87 to 0.98; $p = 0.01$), nitrate-mediated dilation (0.95, 0.92 to 0.99; $p = 0.01$), IMT (1.5, 1.2 to 1.8; $p < 0.001$), LV mass (1.03, 1.01 to 1.05; $p = 0.02$), and EF (0.98, 0.96 to 0.99; $p = 0.005$). The independent predictors of an event in this subgroup included previous MI, nitrate use, FMD, IMT, and LV mass (model chi-square 33.8, $p < 0.001$).

DISCUSSION

In a group of patients with significant risk of cardiovascular events, those with the most severe disturbance of FMD had greater subsequent cardiac morbidity and mortality than those with normal or mildly abnormal FMD. However, mortality was independently predicted by IMT and LV mass rather than FMD. In the subgroup of patients with no CAD and low risk of an event, in whom further risk stratification might be most useful, average IMT and EF

Table 4. Univariate Predictors of an Event Based on the Presence of Coronary Disease and Two-Year Risk of a Cardiac Event

	Risk of CAD				No CAD Risk				Whole Group Risk			
	<4% (n = 40)		≥4% (n = 110)		<4% (n = 271)		≥4% (n = 23)		>4% (n = 311)		≥4% (n = 133)	
Event Rate (%)	9 (23)		26 (24)		28 (10)		7 (30)		37 (12)		33 (25)	
Variable	HR	p Value	HR	p Value	HR	p Value	HR	p Value	HR	p Value	HR	p Value
Two-year risk score	2.9	0.028	—	—	—	—	—	—	1.3	0.03	—	—
Hypertension	—	—	4.2	0.05	—	—	—	—	—	—	—	—
Hypercholesterolemia	—	—	0.4	0.02	—	—	—	—	—	—	—	—
Nitrate use	—	—	2.8	0.015	—	—	—	—	—	—	2.5	0.01
Age	—	—	—	—	1.03	0.035	—	—	1.03	0.009	—	—
Hypoglycemic medication	—	—	—	—	2.6	0.04	—	—	—	—	—	—
Aspirin use	—	—	—	—	2.3	0.029	—	—	—	—	—	—
Nitrate-mediated dilation	—	—	—	—	0.94	0.026	—	—	0.95	0.02	—	—
Left ventricular mass	—	—	—	—	1.04	0.003	—	—	1.03	0.013	—	—
Ejection fraction	—	—	—	—	0.95	<0.001	—	—	—	—	—	—
Beta-blocker use	—	—	—	—	—	—	5.9	0.02	—	—	—	—
Aspirin use	—	—	—	—	—	—	—	—	1.9	0.048	—	—
Previous MI	—	—	—	—	—	—	—	—	2.7	0.025	—	—
LDL cholesterol	—	—	—	—	—	—	—	—	—	—	0.99	0.05
Flow-mediated dilation	1.01	0.75	0.97	0.39	0.94	0.10	0.91	0.33	0.97	0.24	0.96	0.21
IMT	1.4	0.28	0.98	0.92	1.7	<0.001	1.1	0.72	1.6	<0.001	1.01	0.96

Abbreviations as in Tables 1 to 3.

were the independent predictors of an event. The only subgroup in which FMD proved to be an independent predictor of events (along with IMT and LV mass) was that which had also undergone stress testing.

Importance of vascular dysfunction. The endothelium exerts control over vascular tone and function through the influence of paracrine substances that aid in the development of an anti-atherogenic milieu with the inhibition of platelet aggregation, smooth muscle cell proliferation, and leukocyte adhesion (27). Abnormalities of endothelial function, and hence vascular dysfunction, commence at an early age and precede the development of overt atherosclerosis (5). Endothelial dysfunction is influenced by cardiovascular risk factors (28) and has been shown to be influenced by therapy.

Although significant prognostic information can be determined by coronary angiography (29,30), this technique does not assess the functional reactivity of the vessels. Furthermore, angiography is invasive and may miss significant atherosclerosis present in the vessel wall before eventual encroachment on the lumen occurs (31). An assessment of vessel function may give additive prognostic information to that derived from angiography.

Vascular reactivity and outcome. Vascular responsiveness has been shown to correlate with outcome. Schächinger et al. (1) demonstrated a greater incidence of cardiovascular events (cardiovascular death, unstable angina, MI, revascularization, and ischemic stroke) in patients with an abnormal coronary vascular response to acetylcholine or nitroglycerin, thus providing the first evidence of the prognostic significance of coronary vascular dysfunction. In patients with mild CAD, Suwaidi et al. (2) demonstrated no cardiac events (cardiac death, MI, and revascularization) in those with normal or mild coronary endothelial dysfunction, whereas those with severe endothelial dysfunction had a 14% cardiac event rate ($p < 0.05$ vs. normal endothelial function).

Because brachial artery FMD correlates with coronary reactivity (11,12), similar results might be expected, but this evidence base is not well established. In a study of 73 patients undergoing coronary angiography for the investigation of chest pain, brachial FMD <10% was associated with increased cardiovascular events over a mean follow-up period of five years (50% vs. 15%, $p = 0.002$) (13). Another study looked at the cardiovascular event rate in 400 postmenopausal hypertensive women according to their level of improvement of brachial artery FMD after treatment for hypertension (14). Over a mean follow-up period of 67 months, event rates were lower in patients whose FMD improved after six months of treatment for hypertension (0.5 per 100 person-years), compared with those who did not show an improvement (3.5 per 100 person-years, $p < 0.0001$). A short-term study involving a high-risk group of patients undergoing vascular surgery (32) showed lower FMD in those with an event ($4.9 \pm 3.1\%$ vs. $7.3 \pm 5.0\%$, $p < 0.001$), which remained an independent predictor ($p = 0.007$).

Others have used forearm plethysmography for assessment of peripheral vascular function. Perticone et al. (33) subclassified a group of 225 hypertensive patients into tertiles on the basis of their forearm blood flow response to acetylcholine. After a mean follow-up of 31.5 months, there

Table 5. Univariate Predictors of an Event Based on the Presence of Coronary Artery Disease, Dialysis, or Multiple Risk Factors

	CAD (n = 150)		Dialysis Without CAD (n = 134)		Multiple Risk Factors (n = 160)	
Event Rate (%)	35 (23)		25 (19)		10 (6)	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Age (yrs)	1.00 (0.98–1.04)	0.77	1.04 (1.01–1.07)	0.007	1.02 (0.97–1.07)	0.40
Male gender	0.56 (0.29–1.09)	0.09	1.00 (0.45–2.18)	0.99	1.41 (0.36–5.47)	0.62
Two-year risk score (%)	1.05 (0.98–1.12)	0.15	1.16 (0.94–1.43)	0.16	1.21 (0.86–1.71)	0.27
Hypertension	2.71 (1.05–6.99)	0.04	1.63 (0.49–5.44)	0.43	0.49 (0.14–1.76)	0.28
Hyperlipidemia	0.83 (0.42–1.61)	0.57	1.43 (0.63–3.24)	0.39	0.91 (0.25–3.33)	0.89
Diabetes mellitus	1.41 (0.73–2.74)	0.31	1.54 (0.69–3.42)	0.29	1.95 (0.49–7.74)	0.34
Current smoker	1.02 (0.31–3.33)	0.98	0.04 (0.01–18.5)	0.31	0.70 (0.09–5.61)	0.74
Beta-blocker	0.47 (0.24–0.91)	0.03	1.53 (0.69–3.42)	0.30	1.52 (0.39–6.00)	0.55
Calcium channel blocker	1.69 (0.86–3.33)	0.13	0.82 (0.34–2.00)	0.66	1.66 (0.46–6.07)	0.44
ACE inhibitor	1.64 (0.83–3.23)	0.15	0.71 (0.31–1.65)	0.43	1.07 (0.30–3.85)	0.92
Long-acting nitrate	2.76 (1.37–5.55)	0.004	1.24 (0.37–4.15)	0.73	1.21 (0.26–5.79)	0.81
Statin	0.55 (0.28–1.08)	0.08	3.18 (1.37–7.37)	0.007	1.01 (0.28–3.67)	0.98
Aspirin	0.60 (0.29–1.26)	0.18	2.65 (1.21–5.81)	0.02	2.26 (0.55–9.28)	0.26
Oral hypoglycemic	1.41 (0.72–2.78)	0.32	2.82 (1.17–6.79)	0.02	0.04 (0.01–3651)	0.59
Insulin	1.04 (0.25–4.35)	0.96	1.59 (0.47–5.29)	0.46	2.71 (0.30–24.84)	0.38
Total cholesterol	1.00 (0.99–1.01)	0.58	1.00 (0.99–1.01)	0.91	0.99 (0.97–1.01)	0.19
LDL cholesterol	0.99 (0.98–1.00)	0.08	1.01 (1.00–1.02)	0.30	0.98 (0.96–1.01)	0.18
HDL cholesterol	1.01 (0.99–1.03)	0.22	0.99 (0.96–1.02)	0.38	1.01 (0.98–1.05)	0.42
Triglycerides	1.00 (1.00–1.01)	0.39	1.00 (0.99–1.00)	0.18	1.00 (1.00–1.01)	0.93
Flow-mediated dilation (%)	0.99 (0.93–1.04)	0.58	0.94 (0.87–1.01)	0.08	0.91 (0.77–1.08)	0.29
Nitrate-mediated dilation (%)	0.99 (0.95–1.04)	0.68	0.95 (0.90–1.00)	0.07	0.94 (0.84–1.04)	0.23
Flow to nitrate ratio	1.07 (0.88–1.30)	0.52	0.93 (0.68–1.27)	0.65	0.67 (0.20–2.30)	0.53
Average IMT (per one-tenth mm increase)	1.06 (0.80–1.40)	0.68	1.81 (1.31–2.49)	<0.001	1.34 (0.83–2.17)	0.23
Left ventricular mass (per 10 g)	0.99 (0.96–1.03)	0.65	1.04 (1.01–1.07)	0.03	1.05 (1.01–1.10)	0.02
Ejection fraction (%)	1.00 (0.97–1.02)	0.80	0.96 (0.94–0.98)	<0.001	1.03 (0.94–1.12)	0.56

Abbreviations as in Tables 1 to 3.

was a greater cardiovascular event rate in patients in the tertile with the poorest response (57%) than in those with the greatest response (14%, p = 0.0012). Similarly, in a study of 276 patients being investigated for CAD, lower acetylcholine-induced forearm blood flow was predictive of increased event rates over a mean period of 4.5 years, which also remained an independent predictor in a Cox proportional hazards model (34). However, the results of forearm plethysmography and FMD are not necessarily analogous (35); venous dilation during plethysmography is less nitric oxide-dependent than arterial dilation. Of the two techniques, only FMD is truly non-invasive and may be more suited to clinical practice.

Study limitations. This cohort of patients was at relatively high risk, reflecting the recruitment of the group from a tertiary referral hospital with a high volume of renal failure and renal transplant patients. These results may not be generalizable to patients in primary-care settings. However, although there were a large number of events in the dialysis population, the subgroup analysis of those at low risk and without CAD also showed FMD to lack independent predictive value. Furthermore, though the mean group FMD and nitrate-mediated dilation were relatively low (5.2 ± 6.1% and 9.9 ± 7.2%, respectively), the results are analogous to other studies of patients with CAD (13,36).

To permit a definite statement regarding incremental prognostic data from BAR over coronary angiography, a large study of patients undergoing coronary angiography would be required, and thus the patient cohort would be different from that used in this study. The performance of coronary angiography was not clinically indicated for the majority of patients.

Our only measure of carotid atherosclerosis was that of IMT with plaque being specifically excluded. It is possible that measures such as plaque extent may have revealed different (possibly stronger) associations with cardiovascular events.

This study used baseline investigations only. It would have been of interest if our imaging and biochemical investigations were repeated and an assessment was made as to whether changes in these variables had any effect on outcomes. This has been attempted before by Modena et al. (14) in postmenopausal hypertensive women. It would also have been of interest to have assessed other biochemical risk parameters such as apolipoprotein B, lipoprotein(a), and high-sensitivity C-reactive protein.

Clinical implications. Although the non-invasive nature of BAR makes this feasible for serial measurements and long-term studies, its variability in response to acute stimuli (37) has made it more useful for group and intergroup

analyses in research rather than clinical applications. Although the current study shows that abnormal FMD in the brachial artery provides prognostic information on mortality and cardiovascular events in patients at moderate levels of risk, this information does not appear to be incremental to existing clinical and imaging data. However, in the subgroup of higher risk patients undergoing stress testing, FMD along with measures of structure (IMT and LV mass) proved to be an independent predictor of cardiovascular events.

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