

# Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis

Yoichi Inaba · Jennifer A. Chen ·  
Steven R. Bergmann

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## Abstract

**Background** We conducted a meta-analysis of observational studies which examined the association between flow-mediated dilatation (FMD) of brachial artery, a noninvasive measure of endothelial function, and future cardiovascular events.

**Methods** Electronic databases were searched using a predefined search strategy. Data was independently abstracted on study characteristics, study quality, and outcomes by two reviewers. The multivariate relative risks, adjusted for confounding factors, were calculated from individual studies and then pooled using random-effects models. Statistical heterogeneity was

evaluated using I<sup>2</sup> statistics. Subgroup analyses and meta-regression analyses were conducted to assess the robustness of the meta-analysis. Publication bias was examined with funnel plot analysis and Egger's test.

**Results** Four population-based cohort studies and ten convenience-cohort studies, involving 5,547 participants, were included in the meta-analysis. The pooled relative risks of cardiovascular events per 1% increase in brachial FMD, adjusted for confounding risk factors, was 0.87 (95% CI, 0.83–0.91). The significant associations between brachial FMD and cardiovascular events were consistent among all subgroups evaluated, suggesting the robustness of the meta-analysis. However, the presence of heterogeneity in study quality, the remaining confounding factors, and publication bias in the available literature prevent a definitive evaluation of the additional predictive value of brachial FMD beyond traditional cardiovascular risk factors.

**Conclusions** The meta-analysis of heterogeneous studies with moderate methodological quality suggested that impairment of brachial FMD is significantly associated with future cardiovascular events. Further prospective randomized trials are warranted to confirm the efficacy of the usage of brachial FMD in the management of cardiovascular diseases.

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Y. Inaba (✉)

Division of Cardiovascular Medicine, Oregon Health and Science University, UHN62, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA  
e-mail: yoichiinaba@yahoo.com

J. A. Chen · S. R. Bergmann  
Division of Cardiology, Beth Israel Medical Center,  
New York, NY, USA

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## Abbreviations

CI	Confidence interval
FMD	Flow-mediated dilatation
SD	Standard deviation

## Introduction

The endothelium is a dynamic organ system which maintains normal vessel homeostasis by regulating vascular tone and protecting against atherogenesis. Impairment of endothelial function is not only an important initial step in the pathogenesis of atherosclerosis, but is also associated with a defective endothelial repair mechanism which may lead to further progression of vascular disease [1, 2]. In addition, there is accumulating evidence linking an inflammatory process of the vascular wall with endothelial dysfunction. It has been suggested that inflammatory activation of the endothelium is involved in the destabilization of atherosclerotic lesions and may contribute to future cardiovascular events [3].

Elucidation of the important role of the endothelium in various stages of atherosclerosis has led to the development of tests designed to evaluate the functional properties of the vascular endothelium. Since 1992, the noninvasive measurement of endothelium-dependent, brachial artery flow-mediated dilatation (FMD) has been used by numerous investigators to evaluate endothelial function [4]. Using high-resolution ultrasound, this method quantifies the change in diameter of a conduit artery in response to shear stress induced by increasing blood flow during reactive hyperemia. Mounting evidence suggest that brachial FMD is not only associated with traditional cardiovascular risk factors but also with future cardiovascular events.

The existing evidence, however, has been based on observational studies in which the risk of confounding bias is always present. In fact, some studies have found the associations to be weak or non-significant after multivariate adjustment [17, 23, 24]. In addition, the question of whether the association is consistent in different populations remains unclear. The objectives of this meta-analysis, therefore, are to critically appraise the available literature, to quantitatively summarize the result of all studies, to explore the

clinical and methodological heterogeneities between studies, and to determine whether brachial FMD can predict future cardiovascular events beyond conventional cardiovascular risk factors.

## Materials and methods

### Selection and data collection

To identify potentially relevant citations, two reviewers (YI, JAC) independently searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 1966 to November 2008 using the following Medical Subject Headings (MeSH) and text words: endothelium, brachial artery, vasodilation, endothelial dysfunction, flow-mediated, cardiovascular diseases, myocardial infarction, stroke, mortality. The search was limited to human studies and combined with the cohort study filter [5]. The exact search terms used are listed in Supplement Table 1. The reference lists of retrieved articles were manually reviewed to search for additional studies.

Studies were included if they (1) were longitudinal studies, or nested case–control studies, (2) measured brachial FMD at baseline, (3) reported a cardiovascular event outcome, and (4) adjusted results for possible confounding factors. There were no exclusion criteria or language restrictions in this meta-analysis.

Two reviewers (YI, JAC) independently extracted data, and disagreement was resolved by consensus. For each study, the number of participants; geographical location of study; type of cohort (population-based or convenience-cohort); follow-up period; proportion of males; mean age; proportion of participants with coronary heart disease, diabetes mellitus, hypertension, hypercholesterolemia, or smoker; the mean brachial FMD with its standard deviation; the definitions of cardiovascular outcomes; the multivariable adjusted risk estimates; and the variables incorporated into the multivariable analyses were retrieved. Original study authors were contacted to obtain missing data when necessary.

### Quality assessment

The quality of observational studies was assessed independently by two reviewers (YI, JAC) using a

**Table 1** Characteristics of selected studies

Source	Participants (n)	Mean age (years)	Men (%)	Follow up (years)	Annual mortality (%)	Population	Study outcomes
Neunteufl et al. [15], Austria	73	51	52	5	0	C, Patients with chest pain and subsequent CAG	Death, MI, revascularization
Brevetti et al. [16], Italy	131	64	90	1.9	1.2	C, Patients with PAD	CV death, MI, revascularization, stroke, CHF, PVD
Gokce et al. [17] USA	199	67	82	1.2	2	C, Patients with PAD	CV death, MI, stroke
Fathi et al. [18], Australia	444	59	59	2	5.5	C, Patients with CAD, HD, or multiple CV risk factors	Death, MI, revascularization, stroke
Katz et al. [19], USA	259	54	84	2.3	2	C, Patients with CHF	CV death, cardiac transplantation
Patti et al. [20], Italy	136	63	81	0.5	0	C, Patients with CAD undergoing stenting	CV death, MI, Angina, In-stent restenosis
Frick et al. [21], Austria	398	54	100	3.3	0.3	C, Male patients with chest pain and subsequent CAG	CV death, MI, revascularization
Meyer et al. [22], Austria	75	56	89	1.5	12	C, Patients with CHF	Death, CHF
Karatzis et al. [23], Greece	98	63	100	2	1.9	C, Patients with NSTEMI	CV death, MI, stroke
Yeboah et al. [24], USA	2792	78	41	5	2.4	P, $\geq 65$ years	CV death, MI, revascularization, stroke, CHF, PVD
Shimbo et al. [25], USA	842	66	42	3	0.19	P, Northern Manhattan Study	CV death, MI, stroke
Rossi et al. [26], Italy	2264	55	0	3.8	0.03	P, Post-menopausal woman	CV death, MI, revascularization, stroke
Shechter et al. [27], Israel	435	54	75	2.7	0.2	P, Via a primary prevention clinic	Death, MI, revascularization, CHF
Muesan et al. [28] 2008, Italy	172	57	59	7.9	0.2	C, Patients with hypertension	CV death, MI, revascularization, stroke, CHF, PVD, arrhythmia

C convenience-cohort study, CAG coronary angiography, CHF congestive heart failure; CV cardiovascular, MI myocardial infarction, NSTEMI non-ST elevation myocardial infarction, PVD peripheral vascular disease, and P population-based cohort study

checklist designed by Downs and Black [6]. This tool evaluates study quality in terms of reporting (10 items, total score 11), external validity (three items, total score 3), internal validity-bias (seven items, total score 7), internal validity-confounding (six items, total score 6) and power (two items, total score 2). Then, a “risk of bias” table, which consists of confounding bias, selection bias (consecutive sampling of their cohort), detection bias (blind adjudication of clinical outcomes), and attrition bias (completeness of follow-up), was created [7]. Discrepancies in quality assessment were resolved by consensus among the authors.

### Statistical analyses

Relative risk was used as the measure of the association of FMD with future cardiovascular events. We treated hazard ratios as relative risks. We algebraically converted odds ratios to relative risks using the formula described by Zhang and Yu [8]. Summary estimates of the relative risks from all studies were obtained by averaging the natural logarithms of the relative risks from individual studies, weighted by the inverse of their variances. The standard errors of the log relative risks were calculated from reported 95% CIs or P values. We used DerSimonian and Laird random effects model to incorporate both within-study and between-study variability [9].

Brachial FMD was treated as a continuous variable in this meta-analysis. Thus, the relative risk represents the expected increase (or decrease) in risk per 1% or 1-standard deviation (SD) increase in brachial FMD. If individual studies provided only relative risks according to categories of brachial FMD at different cutoff levels, we used Greenland and Longnecker’s covariance-corrected generalized least-squares trend (GLST) estimation method to estimate one continuous relative risk [10]. These estimates were calculated from the assumption that there is a linear relationship between the natural logarithm of relative risk and brachial FMD. The median value was assigned to each brachial FMD category and estimated, if not presented, from within-study data assuming a normal distribution for brachial FMD [6].

Two articles presented only univariate relative risk and did not report the precise estimates after multivariate adjustment [18, 22]. One article was a

negative study and reported the p value as non-significant after adjustment for confounders [18]. These missing data could not be obtained from the original authors. To avoid the biased result toward positive studies by exclusion of negative studies with non-significant p values, we included these articles and adjusted the results for meta-analysis. First, we estimated the effects of multivariate adjustment on the point estimate and standard error of univariate relative risks as a correlation coefficient from other articles. We then calculated the adjusted relative risk by applying a correlation coefficient of 0.62 for the point estimate and 0.80 for the standard error to the log univariate relative risk in articles with missing data. We also performed a sensitivity analysis that excluded the 2 studies in which this adjustment was performed.

We assessed heterogeneity between studies with the  $I^2$  statistic which quantifies the variation that is due to heterogeneity rather than chance.  $I^2$  values of 25%, 50%, and 75% indicate low, moderate, and high degrees of heterogeneity, respectively [11].

We performed pre-specified subgroup analyses and meta-regression analyses to examine the robustness of our meta-analysis. We examined the following study characteristics which could affect our result: study design (population-based versus convenience-cohort), number of participants, percentage of men, mean age, annual mortality, duration of follow up, study quality, risk of bias (consecutive sampling of the cohort, blind adjudication of clinical outcomes, completeness of follow-up, and adjustment for confounding factors), and quality score. Categorical data was examined in subgroup analyses and both categorical and continuous data were examined in meta-regression analyses.

Publication bias was examined by visual inspection for funnel plot asymmetry and the Egger’s linear regression test. Adjustment for publication bias was performed using the “trim and fill” imputation method estimating the number of missing negative studies from the funnel plot [12].

All calculations were performed using STATA version 10 software (STATA Corporation, College Station, Texas, USA). We attempted to conform to MOOSE (The Meta-analysis Of Observational Studies in Epidemiology) guidelines in the report of this meta-analysis [13].

## Results

### Study selection

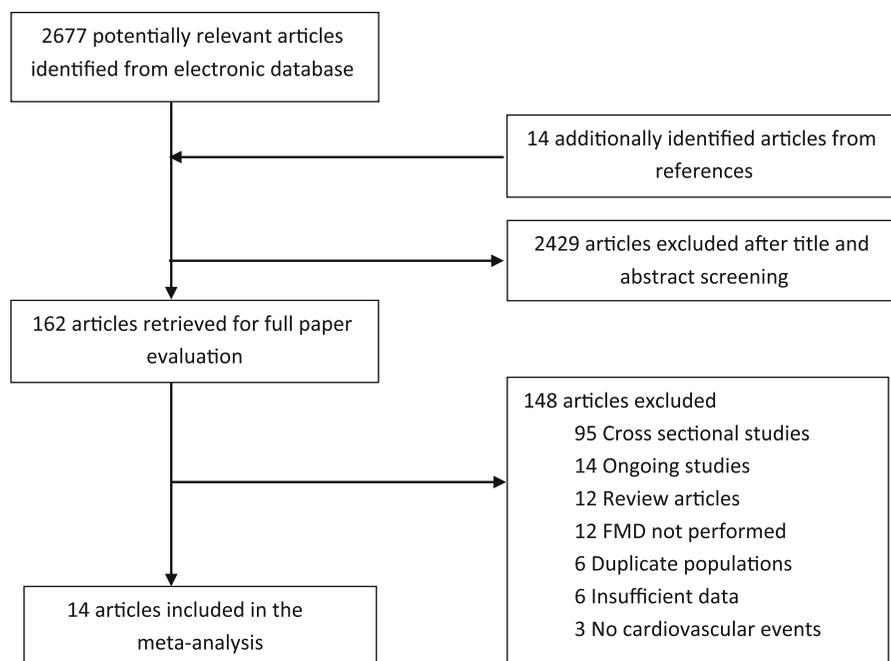
Our initial search identified 2677 articles and 14 additional articles were identified from references (Fig. 1). After title and abstract screening, we retrieved 162 articles for full paper evaluation. We then excluded 148 articles: 95 were cross-sectional study design, 12 were review articles, 14 were ongoing studies, 6 were duplicate study populations, 12 did not perform brachial FMD, 3 lacked measurement of cardiovascular events, and 6 did not include sufficient data for meta-analysis. One study was excluded because the investigators examined the association between risk of cardiovascular events and an improvement of FMD after antihypertensive therapy, not baseline FMD. Among the 6 excluded studies due to insufficient data, there was only one negative study in which FMD did not predict future cardiovascular events. The study was excluded because it was published as a letter to the editor and did not present enough information to be included [14]. All five other studies showed a significant association between FMD and future clinical events. The final set consisted of 14

articles [15–28]. The inter-observer agreement for the study selection was excellent with kappa value of 0.93.

Thirteen studies were prospective, and 1 retrospective, cohort studies with duration of follow-up between 6 months and 7.8 years. Four were population-based cohort studies and 10 were convenience-cohort studies, among which 8 were cohort studies of patients with preexisting disease and 2 were cohort studies of people with suspected coronary artery disease. Details of included studies are summarized in Table 1.

### Study quality and risk of bias

All studies were determined to be appropriate for inclusion in the meta-analysis. The risk of bias and the study quality of the included studies are shown in Supplement Table 2 and Supplement Table 3. Twelve studies (86%) described independent, consecutive sampling of their cohort. Seven studies (50%) clearly reported a blind adjudication of clinical outcomes. Seven studies (50%) reported the number of patients lost to follow-up: 3% or fewer participants in 3 studies and no participants in 4 studies were lost to follow-up. However, completeness of follow-up was unclear in 7 studies (50%). All



**Fig. 1** Flow chart for study selection. FMD denotes flow-mediated dilatation

studies adjusted the result for most cardiovascular risk factors by either logistic regression or Cox regression. However, six studies (43%) were determined to still have high risk of bias because of the presence of remaining confounding factors which were not included in the final multivariate analysis. Only four studies (29%) adjusted for all traditional risk factors included in the Framingham risk score. The method for adjustment of confounding factors in the included studies is shown in Supplement Table 4. Overall, eight studies (57%) were determined to have high quality, five studies (36%) intermediate quality, and one study (7%) low quality.

### Meta-analysis

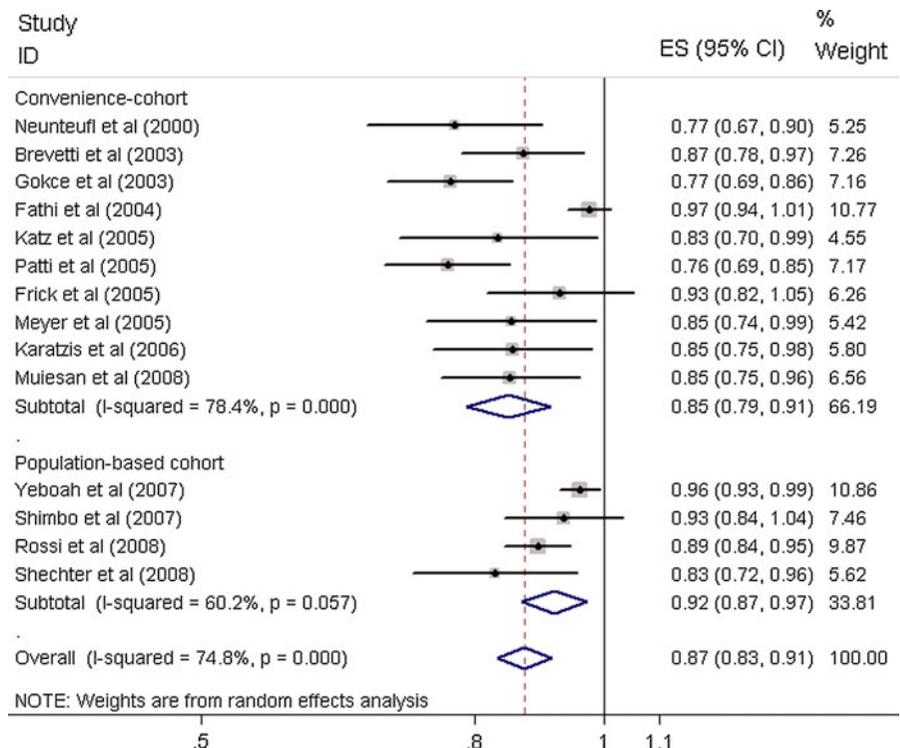
Original risk estimates as presented in each study, the degree of adjustment for data standardization process in the present meta-analysis, and adjusted multivariate relative risks per 1% increase in FMD are presented in Supplement Table 4. The pooled multivariate relative risks of cardiovascular events per 1% and per 1-SD increase in FMD was 0.872 (95% CI, 0.832–0.914) (Fig. 2) and 0.593 (95% CI, 0.490–0.718) (Fig. 3), respectively. This suggests that 1%

decrease and 1-SD decrease in FMD was associated with 13% and 41% increase in risk of future cardiovascular events, respectively. Significant heterogeneity existed between studies ( $I^2 = 74.8%$  and  $79%$ , respectively). The exclusion of 2 studies, in which the multivariate relative risks were estimated because of missing data, showed a similar result.

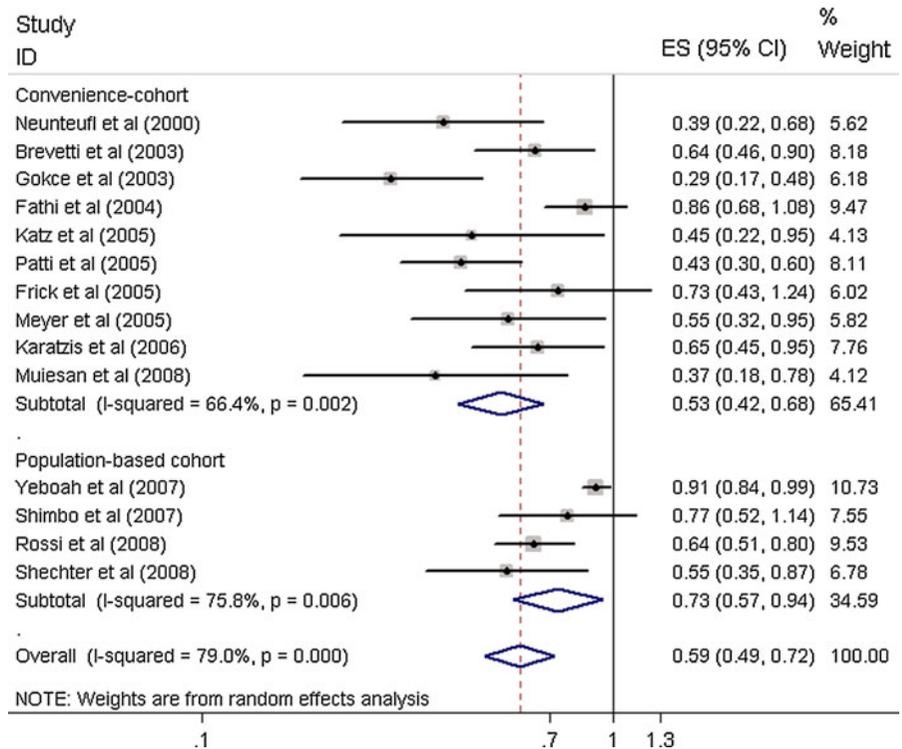
An important source of heterogeneity was identified with meta-regression analysis. The relative risks of cardiovascular events per FMD 1% increase were significantly associated with number of study participants ( $P = 0.052$ ) and quality score ( $P = 0.043$ ). This suggests that smaller studies or lower quality studies are more likely to show the significant association between FMD and cardiovascular events. On the other hand, no significant associations were shown with percentage of men, mean age, duration of follow up, or annual mortality. In subgroup analyses, significant association between FMD and cardiovascular events was demonstrated among all subgroups evaluated, suggesting the robustness of the meta-analysis (Table 2).

Finally, asymmetry of funnel plot analysis suggested the presence of publication bias (Egger's test:  $p < 0.001$ ). After adjusting for publication bias with

**Fig. 2** Forest plots of the relative risks per 1% increase in the brachial FMD. Results were stratified as either population-based cohort studies or convenience-cohort studies



**Fig. 3** Forest plots of the relative risks per 1-SD increase in the brachial FMD. Results were stratified as either population-based cohort studies or convenience-cohort studies



the “trim-and fill” method, the relative risk per 1% and per 1-SD increase in FMD was 0.922 (95% CI, 0.903- 0.940) and 0.783 (95% CI, 0.734- 0.835), showing a smaller but still significant association.

**Discussion**

The present meta-analysis shows that impairment of brachial artery FMD, a noninvasive measure of endothelial function, is significantly associated with future cardiovascular events beyond conventional cardiovascular risk factors. The inclusion of 14 cohort studies, involving 5,547 participants, increased the statistical power and added precision to the estimates of effect: 1% decrease and 1-SD decrease in FMD was associated with 8% and 22% increase in risk of future cardiovascular events, respectively. As brachial FMD was treated as a continuous variable in the meta-analysis, the risk estimates are clinically applicable in different vascular laboratories where the methods for measurement of brachial FMD vary widely. Even though the populations included in the meta-analysis were heterogeneous, the associations of brachial FMD with future cardiovascular events were

consistent across a broad range of populations, suggesting that the vascular endothelium plays a critical role in various phases of the atherosclerotic disease process.

According to the “response-to-injury” hypothesis, disturbance of the anatomic and functional integrity of the vascular endothelium is the stimulus for the initiation of atherosclerosis [1]. Several studies have shown that endothelial dysfunction, in response to genetic and environmental risk factors, develops long before clinically apparent vascular complications. For example, brachial FMD is attenuated in children who have been exposed to environmental tobacco smoke [29] and also in Framingham Offspring participants without clinical cardiovascular disease but with metabolic risk factors [30].

Recently, it has become clear that endothelial dysfunction reflects not only the extent and degree of injury on the vascular wall, but also a disruption in the integrity of the vascular remodeling and repair mechanism. The Young Finns Study shows that the number of risk factors was associated with increased carotid IMT in subjects with impaired FMD but not among those with preserved FMD [31]. This suggests that endothelial function reflects the propensity of

**Table 2** Subgroup analyses of associations of FMD with future cardiovascular events

Subgroup	Summary relative risk <sup>a</sup> (95% CI)
<b>Study design</b>	
Population-based cohort	0.91 (0.86–0.97)
Convenience-cohort	0.84 (0.77–0.90)
<b>Cardiovascular outcome</b>	
Death, MI, revascularization	0.82 (0.72–0.93)
Death, MI, stroke	0.85 (0.75–0.96)
Death, MI, revasc, stroke	0.91 (0.87–0.95)
<b>Number of participants</b>	
<200	0.81 (0.77–0.85)
≥200	0.93 (0.89–0.96)
<b>Mean age</b>	
<60	0.88 (0.82–0.93)
≥60	0.84 (0.76–0.93)
<b>Annual mortality</b>	
<1%	0.85 (0.81–0.91)
≥1%	0.88 (0.82–0.94)
<b>Study quality</b>	
Low	0.84 (0.79–0.90)
High	0.88 (0.83–0.93)
<b>Confounding bias</b>	
High or intermediate	0.84 (0.78–0.90)
Low	0.88 (0.83–0.93)
<b>Selection bias (consecutive sampling)</b>	
Unclear	0.81 (0.73–0.90)
Low	0.87 (0.83–0.92)
<b>Detection bias (blind adjudication of clinical outcomes)</b>	
Unclear	0.84 (0.78–0.92)
Low	0.88 (0.82–0.95)
<b>Attrition bias (completeness of follow-up)</b>	
Unclear	0.85 (0.80–0.90)
Low	0.88 (0.82–0.93)

MI myocardial infarction, *Revasc* revascularization

<sup>a</sup> Relative risk was the risk of future cardiovascular event per 1% increase in flow-mediated dilatation of brachial artery

arteries to develop atherosclerosis in response to exposure to cardiovascular risk factors. The importance of the repair mechanism in the pathogenesis of vascular disease has been further highlighted by the demonstration that circulating endothelial progenitor cells may play an important role in the preservation of endothelial function. Preserved brachial FMD is strongly associated with an increased number of

endothelial progenitor cells regardless of Framingham risk scores [32].

Furthermore, recent evidence suggests that assessment of endothelial function can identify the “vulnerable” patient at high risk for the recurrence of cardiovascular complications after an acute coronary syndrome [33]. This suggests a close link between inflammatory activation of vascular endothelium, which coincides with the transition from stable coronary artery disease to acute coronary syndromes, and endothelial dysfunction. The concept of endothelial inflammatory activation is further supported by a recent randomized controlled trial in which intensive treatment of periodontitis, a common potential source of low-grade inflammation, resulted in an improvement in brachial FMD [34].

Our extensive review, however, found important weaknesses in the current literature. First, there was significant heterogeneity in study quality. Although we included studies which adjusted results for possible confounding factors, only four studies (29%) adjusted for full components of the Framingham risk score. In addition, six studies (43%) did not include the remaining confounding factors into the final multivariate analysis (Supplement Table 3). As subgroup analyses suggested that studies with less stringent adjustments and lower study quality showed a stronger association of FMD with cardiovascular events, this bias may overvalue the pooled estimate of our meta-analysis. Second, primary outcomes in most studies included soft events such as coronary revascularization, unstable angina, or heart failure. In addition, we could not estimate the relative risk for specific hard events such as cardiovascular death because few studies presented the relative risk of mortality adjusted for confounding factors. Therefore, the pooled estimate of this meta-analysis may have limited value for clinical application. Third, there was significant publication bias although the trim and fill method accounting for the missing negative studies showed a similar significant association of FMD with future cardiovascular events.

Finally, there are several technical and methodological limitations for the routine clinical use of FMD. First, methodologies used for the measurement of FMD are not standardized among various vascular laboratories. Thus, there are no universal cut-off values for FMD, making it difficult to compare the results between different laboratories. Second, there

is a large variation in intersession FMD likely due to physiologic fluctuations. Thus, single measurements of FMD may have limited utility. Third, high-quality ultrasound systems, capable of quantifying a hyperemic response of 0.2 to 0.3 mm difference in a brachial artery, are necessary for reproducibility and validity of the technique. Thus, high cost and technical difficulties prevent its wide clinical application. Finally, lack of an accepted diagnostic gold standard for endothelial function makes the evaluation of diagnostic accuracy of brachial artery FMD difficult.

Further prospective randomized trials are warranted to confirm that the use of brachial FMD for risk stratification, disease monitoring, or decision-making for therapeutic interventions, improves cardiovascular outcomes.

## Conclusion

In conclusion, the current literature, which consists of 14 studies, of which 57% are high methodological quality studies, showed that the impairment of brachial FMD is significantly associated with future cardiovascular events. The consistent results across a broad range of populations provide strong evidence that the vascular endothelium plays a critical role in various phases of the atherosclerotic disease process. However, the presence of heterogeneity in study quality, the remaining confounding factors, and publication bias in the available literature prevent a definitive evaluation of the additional predictive value of brachial FMD beyond traditional cardiovascular risk factors. Further prospective randomized trials are warranted to confirm the efficacy of the usage of brachial FMD in the management of cardiovascular diseases.

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