ORIGINAL RESEARCH

Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis

Yasushi Matsuzawa, MD, PhD; Taek-Geun Kwon, MD, PhD; Ryan J. Lennon, MS; Lilach O. Lerman, MD, PhD; Amir Lerman, MD

***Background*—**Endothelial dysfunction plays a pivotal role in cardiovascular disease progression, and is associated with adverse events. The purpose of this systematic review and meta-analysis was to investigate the prognostic magnitude of noninvasive peripheral endothelial function tests, brachial artery flow-mediated dilation (FMD), and reactive hyperemia—peripheral arterial tonometry (RH-PAT) for future cardiovascular events.

***Methods and Results*—**Databases of MEDLINE, EMBASE, and the Cochrane Library were systematically searched. Clinical studies reporting the predictive value of FMD or RH-PAT for cardiovascular events were identified. Two authors selected studies and extracted data independently. Pooled effects were calculated as risk ratio (RR) for continuous value of FMD and natural logarithm of RH-PAT index (Ln_RHI) using random-effects models. Thirty-five FMD studies of 17 280 participants and 6 RH-PAT studies of 1602 participants were included in the meta-analysis. Both endothelial function tests significantly predicted cardiovascular events (adjusted relative risk [95% CI]: 1% increase in FMD 0.88 [0.84–0.91], $P<0.001$, 0.1 increase in Ln_RHI 0.79 [0.71–0.87], $P<0.001$). There was significant heterogeneity in the magnitude of the association across studies. The magnitude of the prognostic value in cardiovascular disease subjects was comparable between these 2 methods; a 1 SD worsening in endothelial function was associated with doubled cardiovascular risk.

***Conclusions*—**Noninvasive peripheral endothelial function tests, FMD and RH-PAT, significantly predicted cardiovascular events, with similar prognostic magnitude. Further research is required to determine whether the prognostic values of these 2 methods are independent of each other and whether an endothelial function–guided strategy can provide benefit in improving cardiovascular outcomes. **(*J Am Heart Assoc*. 2015;4:e002270 doi: 10.1161/JAHA.115.002270)**

Key Words: cardiovascular diseases • endothelium • meta-analysis • prognosis

The vascular endothelium is a delicate monolayer of cells lining all blood vessels, which plays important structural and functional roles in initiation and development of cardiovascular diseases (CVD). A properly functioning endothelium is key for cardiovascular health, whereas endothelial dysfunction is associated with numerous disease states. Importantly, endothelial dysfunction is not only a marker but also a contributor to atherosclerotic diseases. Specifically, endothelial dysfunction has been reported to be associated with coronary plaque progression, anatomical complexity, and vulnerability.[1] Furthermore, endothelial function has a substantial role in developing thrombotic complications.[1] Thus, a strategy based on endothelial function assessment might provide a more tailored approach to prevent cardiovascular events. A number of methods to assess endothelial function have been investigated. Initially, endothelial function was assessed in coronary arteries using an invasive method during cardiac catheterization. More recently, several noninvasive methods for assessment of endothelial function have been developed. Studies of brachial artery flow-mediated dilation (FMD) have been reported since 1992,[2] and it is the most widely used method in clinical research. Reactive hyperemia–peripheral arterial tonometry (RH-PAT) is a newly developed method. In 2002, RH-PAT was reported to be the test for peripheral vascular endothelial function,[3] and its use has been rapidly increasing. The RH-PAT technique is less operator dependent and uses a contralateral arm as its

From the Divisions of Cardiovascular Diseases (Y.M., T.-G.K., A.L.), Biomedical Statistics and Informatics (R.J.L.), and Nephrology and Hypertension (L.O.L.), Mayo Clinic, Rochester, MN.

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Correspondence to: Amir Lerman, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: lerman.amir@mayo.edu

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internal control to correct for systemic changes during testing. Both methods are based on the same principle of reactive hyperemia phenomenon: that is, increased blood flow following a period of transient arterial occlusion, which serves as an index of endothelium-dependent vasodilator function. FMD assesses the endothelial response to shear stress in the brachial artery as a result of hyperemia, whereas RH-PAT measures the actual hyperemia. However, these methods differ in target vasculature: the brachial artery diameter in FMD versus a finger arterial pulse wave in RH-PAT. The Framingham Heart Study reported no statistically significant relationship between signals obtained with RH-PAT and FMD, suggesting that these reflect distinct aspects of vascular function.[4] Although both tests have been reported to predict cardiovascular events,[5–7] their relative value for predicting cardiovascular risk has not been directly compared, to date. Previously, 2 meta-analyses on the prognostic value of FMD have been reported,[5,6] and Xu et al[7] reported another meta-analysis of the prognostic value of both FMD and RH-PAT. However, only 3 RH-PAT studies were included in their meta-analysis, and 2 methods were not directly compared. Since then, several additional prospective studies have been published focusing on the prognostic value of these tests.

Therefore, in this systematic review with meta-analysis, we aimed to update the evidence of FMD and RH-PAT as predictors of cardiovascular events, and compare the prognostic magnitude on cardiovascular risk between these 2 methods.

Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.

Data Sources and Search Strategies

A comprehensive search of several databases from each database's earliest inception to September 24, 2014 was conducted and updated on December 4. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Ovid Cochrane Database of Systematic Reviews. The strategy to search potentially relevant prospective observational studies investigating FMD or Reactive hyperemia index (RHI) as assessed by RH-PAT and cardiovascular event risk was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of endothelial function tests for cardiovascular events. The actual strategy is available in Data S1. We also manually searched PubMed, Ovid Medline, and references in pertinent articles that were identified during the screening.

Study Selection

Two investigators (Y.M. and T.G.K.) independently reviewed all records identified by these search methods. The selection was performed in 2 steps; the first step was abstract review and the second step was full text review. Studies with discrepant decisions in screening of the abstract proceeded to full text review, and discrepancies in full text review were resolved through consensus. Studies were eligible for inclusion in this systematic review if they met the following criteria: (1) study provided original data, (2) prospective observational study with follow-up time ≥6 months, (3) study reported risk estimates of endothelial function as assessed by brachial FMD or RH-PAT for cardiovascular events or mortality, (4) study of human adults, and (5) study published in English.

Data Extraction

Data from included studies were extracted independently by 2 investigators (Y.M. and T.G.K.) using predetermined forms. Discrepancies found in the verification process were resolved by discussion with a third investigator (A.L.). The following

classifications	Items	Point for each item
Selection	1) Representativeness of the exposed cohort	0 or 1
	2) Selection of the non exposed cohort	0 or 1
	3) Ascertainment of exposure	0 or 1
	4) Demonstration that outcome of interest was not present at start of study	0 or 1
Comparability	1) Comparability of cohorts on the basis of the design or analysis	0, 1, or 2
Outcome	1) Assessment of outcome	0 or 1
	2) Was follow-up long enough for outcomes to occur	0 or 1
	3) Adequacy of follow up of cohorts	0 or 1

Quality scores were calculated by adding each point for each item.

SUM

Quality score
Ranged from 0 to 9

Figure 1. Scheme of risk bias assessment.

data were extracted (where available): first author, year of publication, years of enrollment of the cohort, sex composition, average age, sample size, duration of follow-up, characteristics of the population, method of endothelial function assessment, outcome characteristics (number of cardiovascular events and type of events [eg, cardiovascular death, myocardial infarction, and stroke]), unadjusted and adjusted hazard ratios (HRs) for continuous value of FMD or logarithmic value of RHI (Ln_RHI), and variables adjusted for. We adopted Ln_RHI rather than RHI because of its skewed distribution. When data were missing or results for continuous value of FMD or Ln_RHI were not reported, the original

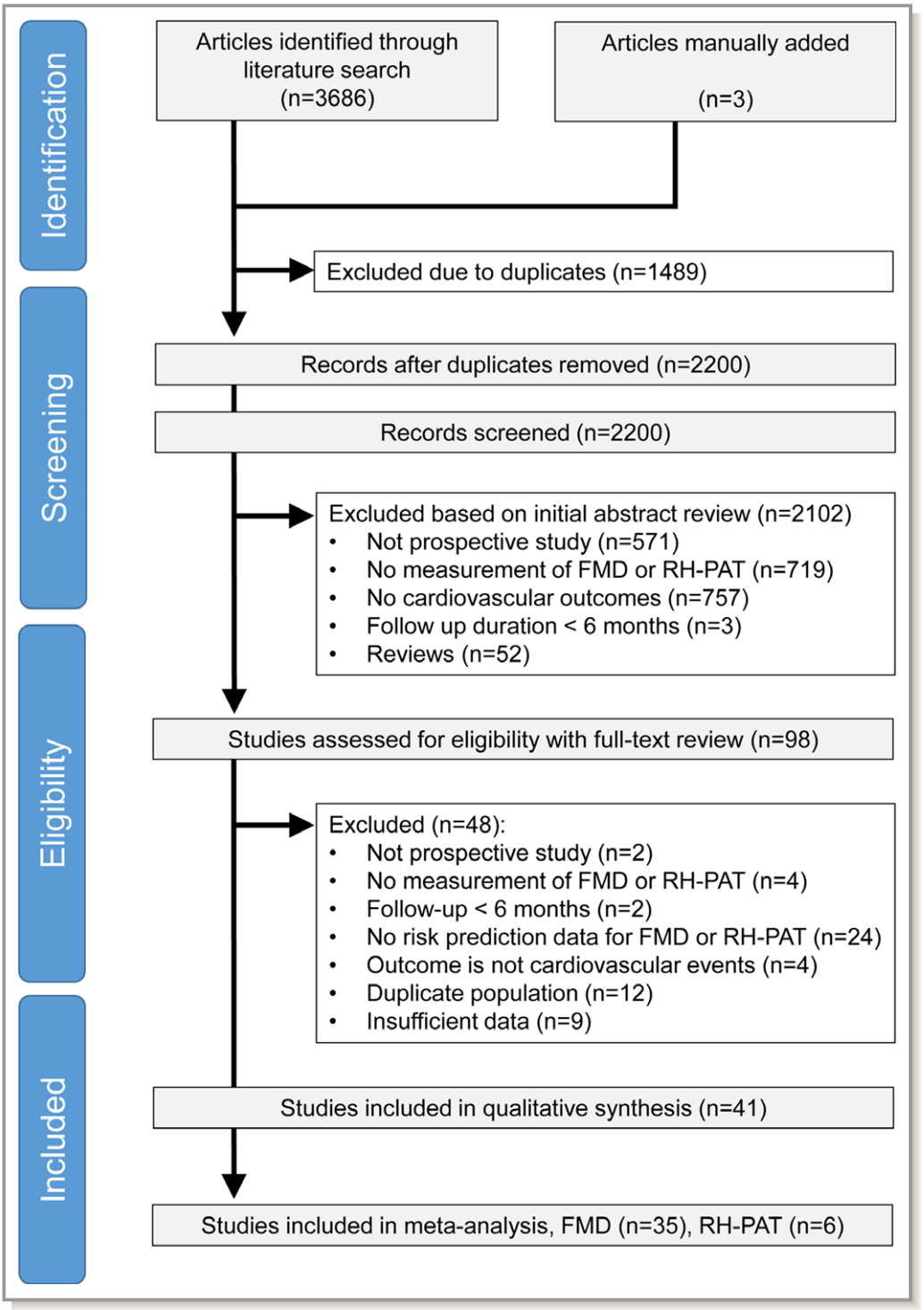

Figure 2. Flow chart of the study selection procedure. FMD indicates flow-mediated dilation; RH-PAT, reactive hyperemia–peripheral arterial tonometry.

Table 1. Characteristics of FMD Studies of Non-CVD Subjects

Study	Description of Study Subjects	Age*, y	Male	Follow-up*	No. Event	No. Population	Annual Event Rate	End Point
Yeboah, 2007[14]	Elderly	79	42%	60 mo	674	2791	4.8%	CV death, MI, coronary revascularization, stroke, CHF, PAD
Muiesan, 2008[15]	Hypertension	56	59%	95 mo	32	172	2.4%	Sudden death, MI, UA, angina, coronary revascularization, arrhythmia, stroke, TIA, CHF, PAD
Rossi, 2008[16]	Postmenopausal women	54	0%	45 mo	90	2264	1.1%	Cardiac death, MI, coronary revascularization, stroke, TIA
Suzuki, 2008[17]	General population	67	43%	81 mo	84	819	1.5%	Vascular death, MI, stroke
Morimoto, 2009[18]	CKD with hemodialysis	61	56%	43 mo	14	199	2.0%	CV death
Yeboah, 2009[19]	General population	61	49%	60 mo	182	3025	1.2%	CV death, resuscitated cardiac arrest, MI, UA, angina, coronary revascularization, stroke
Akishita, 2010[20]	Men with CV risk factors	48	100%	77 mo	20	171	1.8%	Cardiac death, CAD, stroke, PAD
Anderson, 2011[21]	Male firefighter	49	100%	86 mo	71	1574	0.6%	CV death, resuscitated cardiac arrest, MI, coronary/carotid/peripheral artery revascularization, vascular disease, stroke, TIA
Lind, 2011[22]	General population of 70 y of age	70	47%	62 mo	101	921	2.1%	All-cause death, MI, stroke
Yilmaz, 2011[23]	CKD without dialysis	46	52%	41 mo	89	304	8.6%	CV death, MI, stroke, PAD
Nagai, 2013[24]	Elderly	71	42%	41 mo	42	274	4.5%	MI, UA, angina, stroke, TIA, CHF, renal failure, aortic disease, PAD
Shechter, 2014[25]	Healthy subjects	54	63%	55 mo	48	618	1.7%	All-cause death, MI, angina, coronary revascularization, stroke, CHF
Lee, 2014[26]	CKD with peritoneal dialysis	50	48%	42 mo	25	143	4.9%	Fatal and nonfatal ACS, angina requiring coronary revascularization, stroke, TIA, CHF

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; FMD, flow-mediated dilation; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient cerebral ischemic attack; UA, unstable angina pectoris.
*Either mean or median as reported.

authors were contacted in an attempt to obtain these data. One study reported risk estimates for RHI.[8] We contacted and asked the authors to transform RHI results to logarithmic value and obtained results with Ln_RHI. The studies were classified according to CVD or non-CVD population. CVD population included patients with coronary artery disease, chest pain, heart failure, stroke, and peripheral arterial disease. Non-CVD subjects included those without established CVD (general population, healthy subjects, elderly, postmenopausal women, and patients with coronary risk factors).

Risk Bias Assessment

We followed the recommendations for bias assessment of nonrandomized studies, as suggested by the Cochrane collaboration,[9] and information on the methodological quality of each included study was recorded and quality assessment was performed using the Newcastle-Ottawa Scale (NOS)[10] by 2 independent investigators (Y.M. and T.G.K.). Disagreement was resolved by discussion with a third investigator (A.L.). The score assessed major classifications: selection (4 items), comparability (1 item), and outcome (3 items) (Figure 1). A maximum score of 1 was graded for each item, except that related to comparability, which allowed for 2. Total scores were calculated by adding each score for each item. For quality, total scores ranged from 0 (lowest) to 9 (highest), and studies with ≥7 points were considered as good quality. The presence of CVD was defined as the most important covariate that would define comparability. Studies that controlled for the presence of CVD received 1 score, whereas studies that controlled for another important confounder (age, sex, hypertension, diabetes, or dyslipidemia) received an additional score. Since the risk of patients with established coronary heart disease are at 4- to 6-folds higher than those without CVD,[11] we defined

Table 2. Characteristics of FMD Studies of CVD Subjects

Study	Description of Study Subjects	Age*, y	Male	Follow-up*	No. Events	No. Population	Annual Event Rate	End Point
Neunteufl, 2000[27]	Chest pain	51	52%	60 mo	27	73	7.4%	All-cause death, MI, coronary revascularization
Brevetti, 2003[28]	PAD	64	90%	23 mo	39	131	15.5%	CV death, MI, UA, coronary revascularization, stroke, TIA, PAD
Fathi, 2004[29]	CAD CKD with dialysis CV risk factors	58	60%	24 mo	70	444	7.9%	All-cause death, MI, UA, coronary revascularization, stroke
Katz, 2005[30]	Chronic HF with NYHA class II-III	54	84%	28 mo	17	149	4.9%	All-cause death, heart transplantation
Karatzis, 2006[31]	NSTE-ACS	63	100%	25 mo	20	98	9.9%	CV death, ACS, stroke
Huang, 2007[32]	PAD	66	74%	10 mo	50	267	22.5%	CV death, MI, UA, stroke, CHF
Hu, 2008[33]	Chest pain	62	58%	16 mo	36	279	9.7%	CV death, MI, UA, stroke, CHF
Takase, 2008[34]	Chest pain	62	77%	50 mo	15	103	3.5%	Cardiac death, MI, UA, CHF
Shechter, 2009[35]	Chronic HF with NYHA class IV	64	92%	14 mo	30	82	31.4%	All-cause death, MI, CHF
Ulriksen, 2009[36]	Chest pain	54	76%	50 mo	90	223	9.7%	CV death, MI, UA, coronary revascularization
Wang, 2009[37]	STEMI	62	66%	12 mo	29	101	28.5%	Cardiac death, MI, UA, coronary revascularization, stroke, CHF
Akamatsu, 2010[38]	PAD, aortic aneurysm	71	93%	47 mo	18	93	4.9%	CV death, MI, UA, coronary revascularization, stroke, aortic disease, PAD
Santos-García, 2011[39]	Stroke	73	58%	48 mo	32	120	6.7%	CV death, MI, coronary revascularization, stroke, PAD
Chan, 2012[40]	Stroke	67	69%	30 mo	12	127	3.8%	CV death, ACS, coronary revascularization, stroke, CHF, PAD
Takishima, 2012[41]	Chronic HF	66	68%	33 mo	33	245	4.9%	Cardiac death, CHF
Careri, 2013[42]	NSTE-ACS	62	73%	32 mo	14	60	8.8%	Cardiac death, ACS, angina
Nakamura, 2013[43]	CAD	63	71%	52 mo	69	547	2.9%	Cardiac death, MI, UA, stroke
Savic-Radojevic, 2013[44]	Chronic HF	59	62%	13 mo	11	120	8.4%	All-cause death
Sedlak, 2013[45]	Women with chest pain	58	0%	115 mo	83	377	2.3%	All-cause death, MI, stroke, CHF
Tarro Genta, 2013[46]	Chronic HF	65	86%	17 mo	19	71	18.9%	Cardiac death, heart transplantation, LVAD implantation
Sawada, 2013[47]	CAD	69	76%	6 mo	25	111	45.0%	All-cause death, MI, target vessel revascularization
Hafner, 2014[48]	PAD	67	67%	50 mo	49	184	6.4%	CV death

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; FMD, flow-mediated dilation; HF, heart failure; LVAD, left ventricular assist device; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NYHA, New York Heart Association; PAD, peripheral arterial disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient cerebral ischemic attack; UA, unstable angina pectoris.
*Either mean or median as reported.

sufficient follow-up duration separately. Studies of patients without CVD at enrollment with median follow-up time >5 years were assigned a score of 1, whereas studies of patients with CVD at enrollment with follow-up time >1 year were assigned a score of 1. Studies with a follow-up rate >80% were assigned a score of 1.

Statistical Methods

The risk estimates of each study were reported as HR or risk ratio (RR). We considered HRs as estimates of RRs. If, in addition to original HRs, the studies reported separate HRs for sex, population health status (CVD and non-CVD), or outcome

(overall cardiovascular events and hard cardiovascular events, which consist of cardiovascular death, myocardial infarction, and stroke), these separate HRs were also pooled for subsequent subgroup analyses. If the original author only provided results for categorical values of FMD or Ln_RHI, we converted it into 1 continuous RR using Greenland and Longnecker's covariance-corrected generalized least-square trend estimation method.[12] In this meta-analysis, RR represents the increase in risk per 1% increase in brachial FMD or per 0.1 increase in Ln_RHI. Standard errors, which were calculated from CIs, were used for weighing the studies. A random-effects model was used for calculating the pooled overall risk estimate. The heterogeneity among studies was evaluated by the Cochran's Q-statistic and the I^2-statistic. Values of 25%, 50%, and 75% value for I^2-statistic represented low, moderate, and high heterogeneity, respectively.[13] To assess the robustness of our meta-analysis, we examined the following study characteristics in subgroup analyses: study population (CVD population versus non-CVD population, age, and sex), sample size, duration of follow-up, annual event rate, FMD technique (forearm versus upper arm occlusion), study quality, and study outcome (cardiovascular mortality and hard cardiovascular events). Owing to the limited number of RH-PAT studies, no subgroup analyses were performed. In order to assess the impact on cardiovascular outcomes between FMD and RH-PAT, a pooled SD for each of FMD and Ln_RHI in all included studies of CVD population was calculated using following equation, and RRs for the pooled SD increase in FMD and Ln_RHI were compared.

$$\text{Pooled SD} = \sqrt{\left\{\sum_{i=1}^{k}(n_i-1)U_i+\sum_{i=1}^{k}n_i(\bar{X}_i-\bar{X}_t)^2\right\}\div(n_t-1)}$$

κ, number of groups; n_i, number of patients in each group; n_t, total number of patients; U_i, unbiased estimate of population variance; $\bar{X}_i$, mean value of each group; and $\bar{X}_t$, pooled mean value.

Finally, publication bias was evaluated by examining the asymmetry of funnel plot. All P values are 2 tailed and $P<0.05$ was considered statistically significant. All analyses were performed using the Review Manager, version 5.3.5 (Cochrane Collaboration, Oxford, UK) and R software, version 3.2.0.

Results

Study Retrieval

The process of study selection is shown in Figure 2. According to our systematic search strategy, 2197 titles were identified from electronic databases, and 3 studies were retrieved via hand searching. After screening the title and abstract, 98 studies were eligible for full text review; of these, 57 were excluded, resulting in 35 FMD studies[14–48] and 6 RH-PAT studies[8,49–53] being eligible for this meta-analysis. Overall, these studies comprised data from a total of 17 280 participants with FMD, and 1602 with RH-PAT.

Characteristics and Quality Assessment of the Included Studies

The characteristics of included FMD studies and RH-PAT studies are shown in Tables 1 through 3, and abstracted in Table 4. A total of 16 studies took place in East Asia (China, South Korea, and Japan), 13 studies in Europe (Austria, Denmark, Greece, Italy, Serbia, Spain, and Sweden), and 8 in North America (Canada and United States). Among 35 FMD studies, 13 were derived from a non-CVD population,[14–26] and

Table 3. Characteristics of RH-PAT Studies

Study	Description of Study Subjects	Age*, y	Male	Follow-up*	No. Events	No. Population	Annual Event Rate	End Point
Rubinshtein, 2010[49]	Chest pain	54	52%	70 mo	86	270	5.5%	CV death, MI, coronary revascularization, hospitalization for any cardiac cause
Akiyama, 2012[50]	HFPEF	72	50%	20 mo	59	321	11.0%	CV death, MI, UA, coronary revascularization, stroke, CHF
Matsue, 2013[51]	HFPEF	75	44%	10 mo	32	159	24.2%	Heart failure–related death, CHF
Matsuzawa, 2013[52]	Chest pain	67	69%	34 mo	105	528	7.0%	CV death, MI, UA, coronary revascularization, stroke, HF, aortic disease, PAD
Ikonomidis, 2014[8]	CAD	60	86%	34 mo	12	111	3.8%	All-cause death, MI
Matsue, 2014[53]	CAD	67	74%	31 mo	22	213	4.0%	Death due to CAD, MI, angina

CAD indicates coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; HFPEF, heart failure with preserved ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; RH-PAT, reactive hyperemia–peripheral arterial tonometry; UA, unstable angina pectoris.
*Either mean or median as reported.

22 from a CVD population[27–48] (2 studies[14,29] reported results of non-CVD and CVD samples separately). Contrarily, all RH-PAT studies derived from a CVD population.[8,49–53] The years of publication ranged from 2007 to 2014, sample size from 60 to 3025, mean age from 46 to 79, and mean follow-up duration from 6 to 115 months. FMD studies of CVD subjects had smaller sample sizes, higher male prevalence, shorter follow-up duration, and higher annual event rate, compared with FMD studies from non-CVD populations. In comparison with FMD studies, the number of RH-PAT studies has been increasing recently. Although the overall quality of studies was good, 6 FMD studies[16,18,23,26,45,47] received a low quality score (≤6). Clinical heterogeneity, in particular differences in end points, had to be taken into consideration.

Table 4. Summary of Study Characteristics

	FMD Studies of Non-CVD Subjects N=13	FMD Studies of CVD Subjects N=22	RH-PAT Studies N=6
Year of publication			
Median	2010	2010	2013*
IQR	2008–2012	2007–2013	2012–2014
Range	2007–2014	2000–2014	2010–2014
Sample size			
Median	618	124†	242
IQR	186–1919	97–251	147–373
Range	143–3025	60–547	111–528
Mean age, y			
Median	56	63	67
IQR	50–69	59–66	59–73
Range	46–79	51–73	54–75
Male prevalence, %			
Median	50	72†	60
IQR	42–61	61–84	48–77
Range	0–100	0–100	44–86
Mean follow-up duration, mo			
Median	60	29†	33
IQR	43–79	16–50	18–43
Range	41–95	6–115	10–70
Annual event rate, %			
Median	2.0	8.1†	6.3
IQR	1.4–4.7	4.9–16.4	4.0–14.3
Range	0.6–8.6	2.3–45.0	3.8–24.2
Quality score			
Median	7	8	8
IQR	6–8	7–9	7–9
Range	4–9	5–9	7–9
Low quality score (≤6)			
N (%)	4 (31)	2 (9)	0 (0)

CVD indicates cardiovascular disease; FMD, flow-mediated dilation; IQR, interquartile range; RH-PAT, reactive hyperemia–peripheral arterial tonometry.
*P<0.05 compared with FMD studies of CVD subjects by Wilcoxon test.
†P<0.05 compared with FMD studies of non-CVD subjects by Wilcoxon test.

Pooled Overall Risk Estimate of FMD and RH-PAT

Twenty-six studies* reported an unadjusted risk estimate of FMD, and 28** reported an adjusted value, whereas 5 RH-PAT studies[49–53] reported both, and one[8] reported only an adjusted value. Both adjusted and unadjusted pooled RRs were significant for both FMD (per 1% increase: unadjusted RR 0.88, 95% CI 0.86–0.91, adjusted RR 0.88, 95% CI 0.84–0.91, Figures 3 and 4) and Ln_RHI (per 0.1 increase: unadjusted RR 0.76, 95% CI 0.65–0.88, adjusted RR 0.79, 95% CI 0.71–0.87, Figures 5 and 6). Except for the adjusted RR estimates for Ln_RHI, significant between-study heterogeneity was observed.

Subgroup Analysis of FMD Studies

Subgroup analyses were performed only in FMD studies, but not in RH-PAT studies due to the small number of studies (Table 5). Sensitivity analyses were restricted to the studies in which an end point included cardiovascular death, and the studies with hard cardiovascular events as end point showed similar results when compared with the full analyses. The prognostic value of FMD was consistently significant in each subgroup. However, there were significant between-subgroup heterogeneities regarding baseline CVD status, sex, follow-up duration, annual event rate, sample size, and study quality. In the CVD population, the prognostic value of FMD for cardiovascular events was higher when compared to the non-CVD population (RR [95% CI] 0.84 [0.79–0.88] versus 0.92 [0.89–0.96], P=0.005). Additionally, in studies with male prevalence ≥half (versus <half), follow-up duration <median (versus ≥median), annual event rate ≥median (versus <median), sample size <median (versus ≥median), and quality score <median (versus ≥median), the association between FMD value and cardiovascular outcomes was stronger.

Comparison Between FMD and PAT

In comparison to FMD studies of non-CVD subjects, those of CVD subjects had higher male prevalence, smaller sample size, lower event rate, and shorter follow-up duration

*References 14, 16, 17, 19, 21, 23–26, 29, 31–33, 36–48.
**References 14–20, 22–28, 30–39, 42, 43, 46, 47.

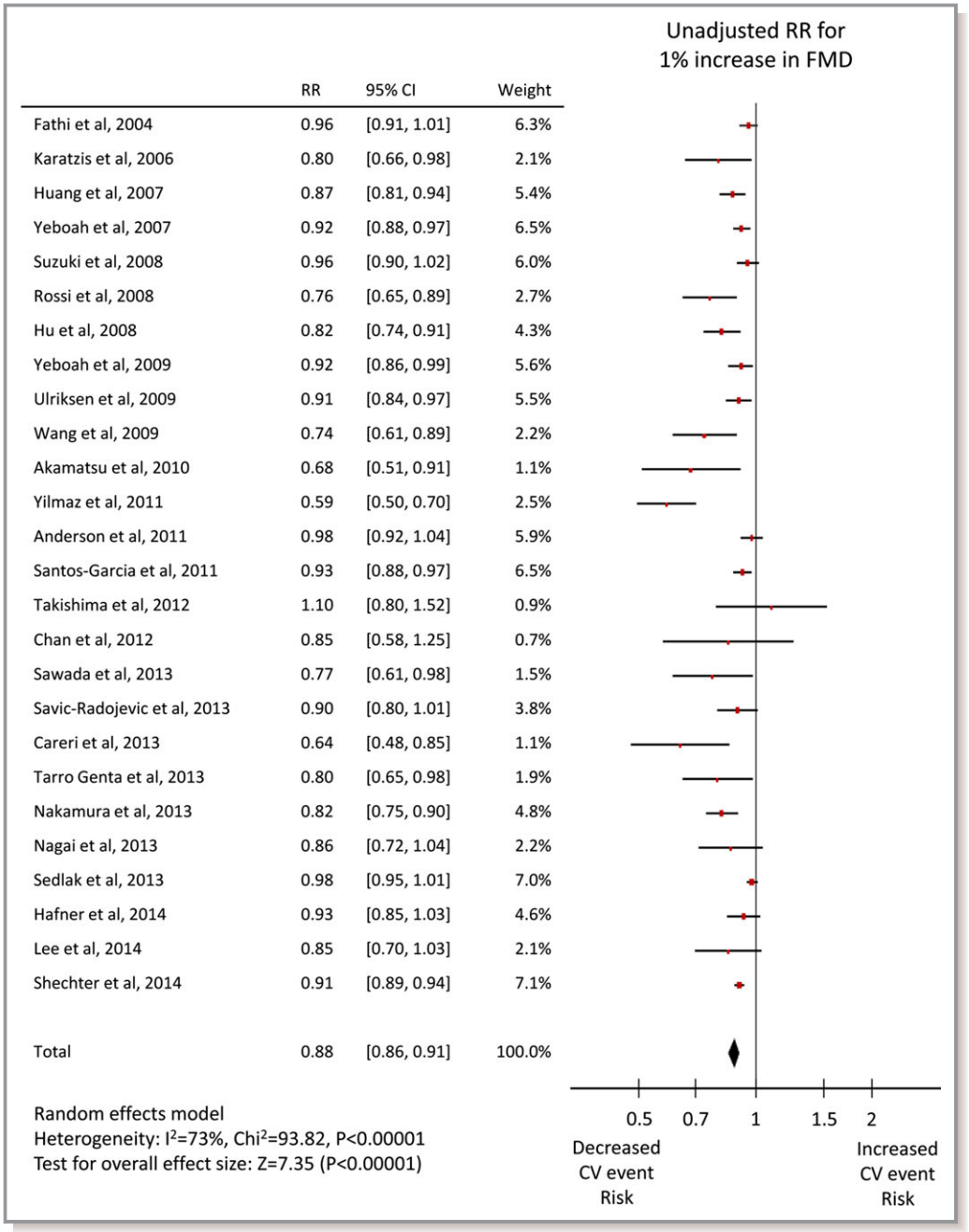

Figure 3. Forest plot of unadjusted risk ratio of FMD for cardiovascular events. CV indicates cardiovascular; FMD, flow-mediated dilation; RR, risk ratio.

(Table 4). Furthermore, all RHI studies were derived from CVD subjects and had good quality. Among studies of CVD population, characteristics of studies including male prevalence, sample size, follow-up duration, and event rate were not significantly different between FMD and RHI. Therefore, in order to compare these 2 methods, we restricted FMD studies to those of CVD population and good quality. Although the risk ratios for 1% increase in distal occlusion FMD and proximal occlusion FMD were not different as shown in Table 5, the distribution of mean values between distal and proximal occlusion FMD were different (P=0.02), which would affect pooled SD. Thus, we divided studies into 3 groups: proximal occlusion FMD, distal occlusion FMD, and Ln_RHI. Pooled mean±SD of proximal occlusion FMD, distal occlusion FMD, and Ln_RHI, which was calculated from all studies of CVD population, were 6.4±5.2, 4.3±4.6, and 0.56±0.26, respectively. Table 6 shows the pooled risk estimates for a 1 SD increase in proximal occlusion FMD (unadjusted RR [95% CI] 0.60 [0.44–0.80], adjusted 0.61 [0.44–0.85]), distal occlusion FMD (unadjusted RR [95% CI] 0.47 [0.35–0.63],

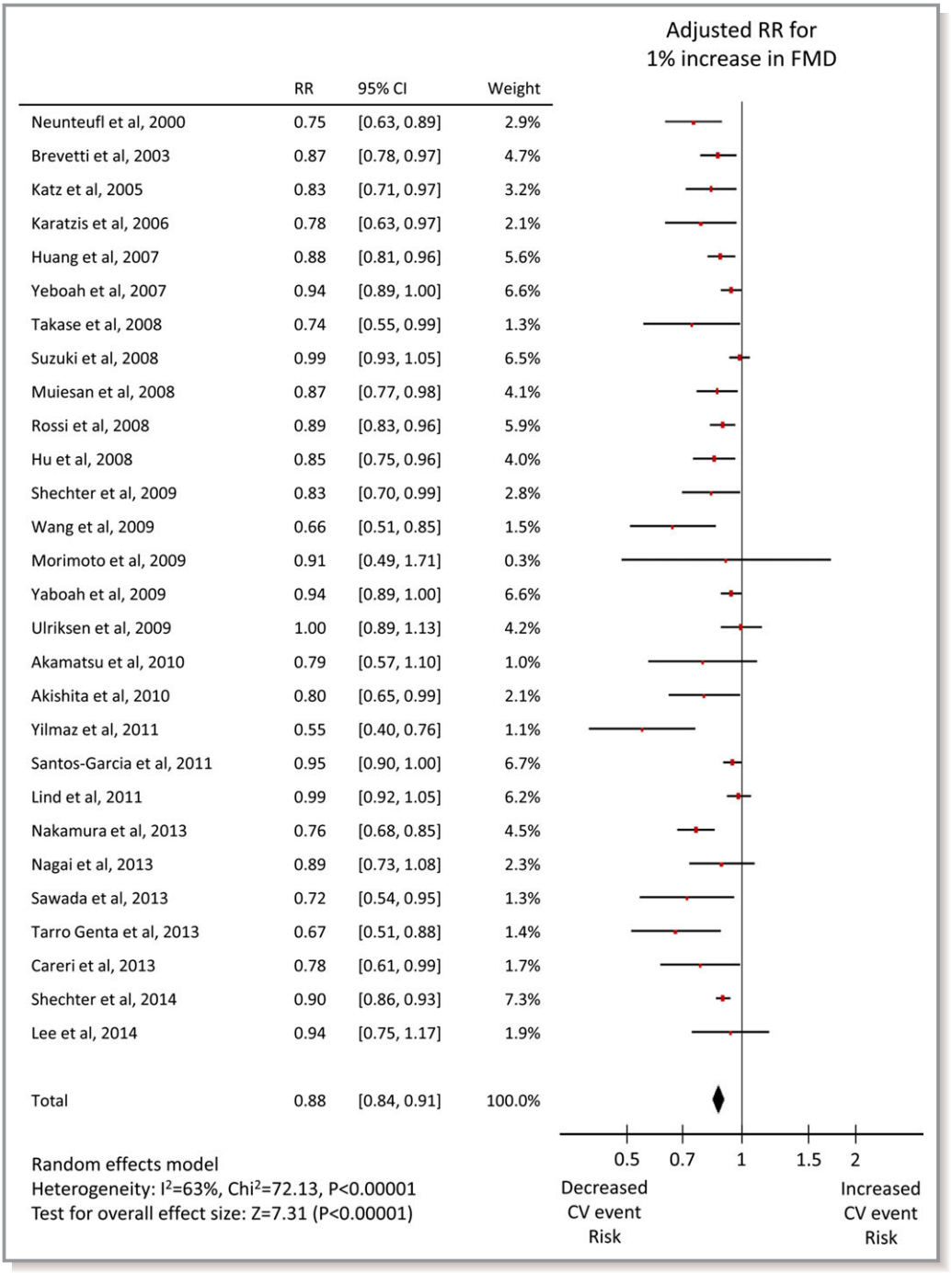

Figure 4. Forest plot of adjusted risk ratio of FMD for cardiovascular events. CV indicates cardiovascular; FMD, flow-mediated dilation; RR, risk ratio.

adjusted 0.47 [0.32–0.67]), and Ln_RHI (unadjusted RR [95% CI] 0.48 [0.33–0.72], adjusted 0.54 [0.42–0.71]). Pooled RRs for these 3 methods were not significantly different.

The relation between FMD or Ln_RHI level and cardiovascular event risk is shown in Figure 7. An ≈1 SD increase in FMD or Ln_RHI was associated with reduced cardiovascular event risk by half, whereas a 1 SD decrease was associated with doubling of risk.

Publication Bias

Based on a visual inspection of the funnel plots, there may be publication bias among the included studies. The funnel plot showed asymmetrical distribution of FMD studies, indicating that publication bias may exist (Figure 8A and 8B). The small number of RH-PAT studies limits inference from the funnel plots (Figure 9A and9B).

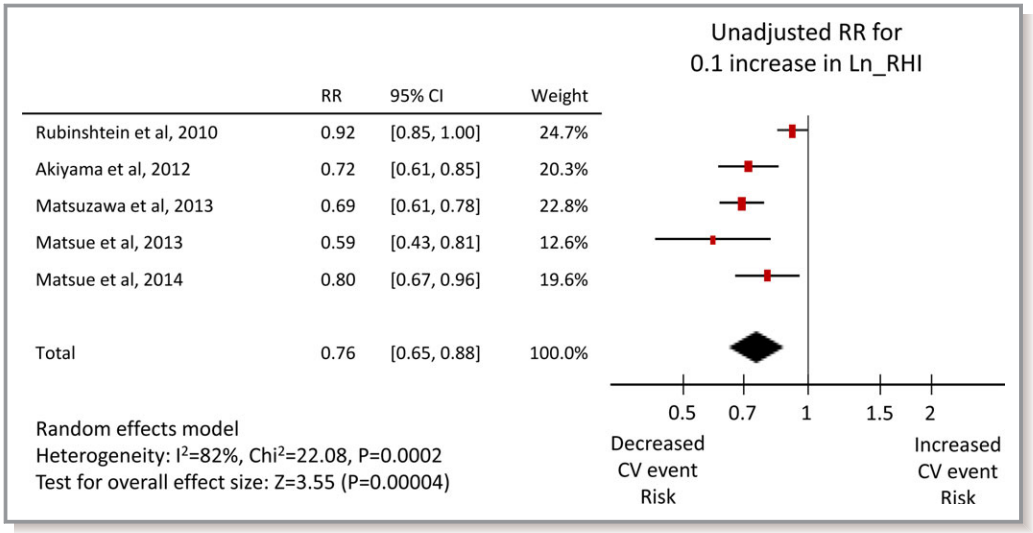

Figure 5. Forest plot of unadjusted risk ratio of Ln_RHI for cardiovascular events. CV indicates cardiovascular; Ln_RHI, logarithmic value of reactive hyperemia index; RR, risk ratio.

Discussion

In this systematic review and meta-analysis, we included 35 FMD and 6 RH-PAT papers reporting the prognostic utility of peripheral endothelial function. We confirmed that peripheral endothelial function as assessed by FMD or RH-PAT is a significant predictor of future cardiovascular events. According to the subgroup analysis of FMD studies, this prognostic utility was consistent across diverse population subgroups, although between-study and between-subgroup heterogeneity were found. The prognostic magnitudes of these 2 methods in CVD population were similar. A 1 SD deterioration in endothelial function could double the risk of cardiovascular events; conversely, a 1 SD improvement could halve it.

Our findings are in line with previous meta-analyses that reported a significant association between brachial FMD or finger-tip RH-PAT and cardiovascular event risk.[5–7] The only meta-analysis of RH-PAT studies was reported by Xu et al in 2014,[7] which included 3 studies and 865 patients. Since then, 3 more RH-PAT studies have been published, and as a result almost twice as many (1602) subjects with RH-PAT assessment were included in our meta-analysis. Recent studies showed that the results of RH-PAT are better evaluated as a logarithmic value rather than RHI itself due to its abnormal

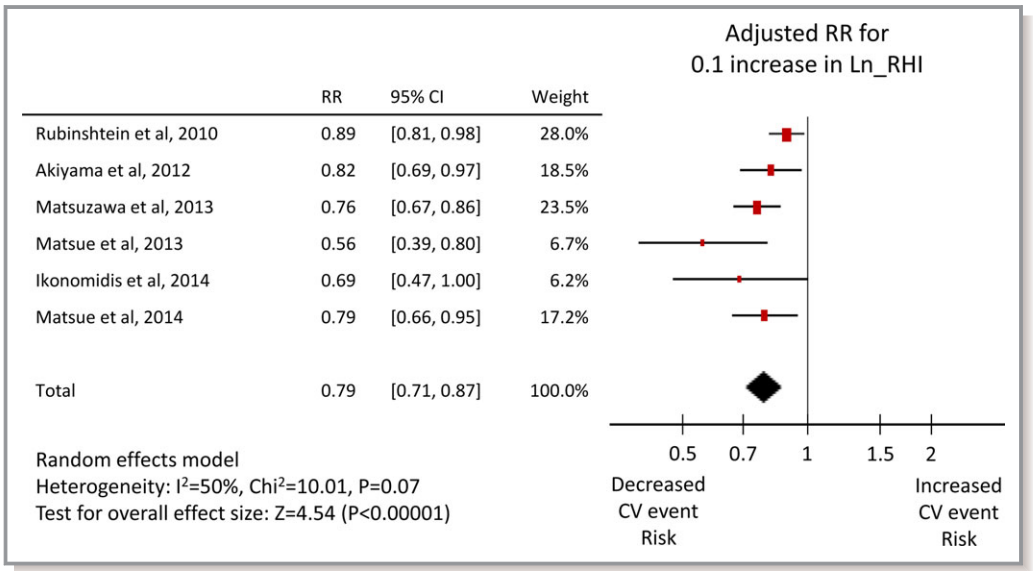

Figure 6. Forest plot of adjusted risk ratio of Ln_RHI for cardiovascular events. CV indicates cardiovascular; Ln_RHI, logarithmic value of reactive hyperemia index; RR, risk ratio.

Table 5. Subgroup Analysis of FMD Studies

Subgroup	Unadjusted RR			Adjusted RR		
	No. Studies	Pooled RR (95% CI)	*P* Value Between Subgroups	No. Studies	Pooled RR (95% CI)	*P* Value Between Subgroups
All studies	26	0.88 (0.86, 0.91)		28	0.88 (0.84, 0.91)	
Non-CVD subjects	10	0.89 (0.84, 0.94)	0.86	12	0.92 (0.89, 0.96)	0.005
CVD subjects	18	0.88 (0.85, 0.92)		17	0.84 (0.79, 0.88)	
End point includes CV death	20	0.86 (0.83, 0.90)		21	0.87 (0.83, 0.91)	
End point includes CV death, MI, and stroke	15	0.86 (0.81, 0.90)		16	0.88 (0.84, 0.92)	
Mean age ≤62 y, median	13	0.88 (0.83, 0.92)	0.53	15	0.86 (0.82, 0.91)	0.43
Mean age >62 y	13	0.89 (0.86, 0.93)		13	0.89 (0.84, 0.93)	
Male prevalence ≥half	19	0.87 (0.83, 0.90)	0.07	22	0.85 (0.81, 0.88)	<0.0001
Male prevalence <half	8	0.92 (0.88, 0.96)		7	0.95 (0.92, 0.98)	
Mean follow-up ≥43 mo, median	12	0.92 (0.89, 0.95)	0.007	15	0.91 (0.88, 0.95)	0.005
Mean follow-up <43 mo	14	0.82 (0.76, 0.89)		13	0.82 (0.77, 0.87)	
Annual event rate ≥6.4 events per y, median	13	0.85 (0.80, 0.90)	0.030	15	0.82 (0.77, 0.88)	0.010
Annual event rate <6.4 events per y	13	0.91 (0.88, 0.95)		13	0.91 (0.87, 0.95)	
Sample size ≥192, median	15	0.90 (0.86, 0.93)	0.11	13	0.91 (0.87, 0.95)	0.010
Sample size <192	11	0.84 (0.79, 0.90)		15	0.82 (0.77, 0.88)	
Forearm occlusion	19	0.87 (0.84, 0.91)	0.45	19	0.88 (0.83, 0.94)	0.77
Upper arm occlusion	7	0.90 (0.85, 0.95)		9	0.87 (0.83, 0.91)	
Lowest tertile of mean FMD value	9	0.87 (0.81, 0.94)	0.17	8	0.90 (0.85, 0.95)	0.21
Middle tertile of mean FMD value	6	0.93 (0.88, 0.97)		8	0.91 (0.86, 0.96)	
Highest tertile of mean FMD value	9	0.87 (0.82, 0.92)		9	0.84 (0.78, 0.90)	
Quality score <8 (median)	12	0.86 (0.80, 0.92)	0.30	12	0.81 (0.76, 0.87)	0.01
Quality score ≥8	14	0.90 (0.87, 0.92)		16	0.90 (0.87, 0.94)	

CV indicates cardiovascular; CVD, cardiovascular disease; FMD, flow-mediated dilation; MI, myocardial infarction; RR, risk ratio.

distribution. Thus, while the meta-analysis by Xu et al was done for 1 increase in RHI (pooled unadjusted RR 0.82 [0.76–0.89], and pooled adjusted RR 0.85 [0.78–0.93]), the present study reported for 0.1 increase in Ln_RHI (pooled unadjusted RR 0.76 [0.65–0.88], and pooled adjusted RR 0.79 [0.71–0.87]). In our study, the pooled SD was calculated for Ln_RHI as well.

In clinical research, brachial FMD has been a widely used noninvasive method that used reactive hyperemia after artery occlusion as a trigger for endothelium-dependent vasodilation. The RH-PAT technique is semi-automatic and much simpler than FMD, and can potentially provide better interobserver reproducibility. Test–retest reliability of RH-PAT has been reported to be very good.[54] Brachial arterial

Table 6. Comparison Between Proximal Occlusion FMD, Distal Occlusion FMD, and Ln_RHI

	Unadjusted		Adjusted	
	Pooled RR for Pooled SD (95% CI)	*P* Value	Pooled RR for Pooled SD (95% CI)	*P* Value
Proximal occlusion FMD Mean=6.4%, SD=5.2%	0.60 (0.44, 0.80)	0.0005	0.61 (0.44, 0.85)	0.004
Distal occlusion FMD Mean=4.3%, SD=4.6%	0.47 (0.35, 0.63)	<0.0001	0.47 (0.32, 0.67)	<0.0001
Ln_RHI Mean=0.56, SD=0.26	0.48 (0.33, 0.72)	0.0004	0.54 (0.42, 0.71)	<0.0001

FMD indicates flow-mediated dilation; Ln_RHI, logarithmic value of reactive hyperemia index; RR, risk ratio.

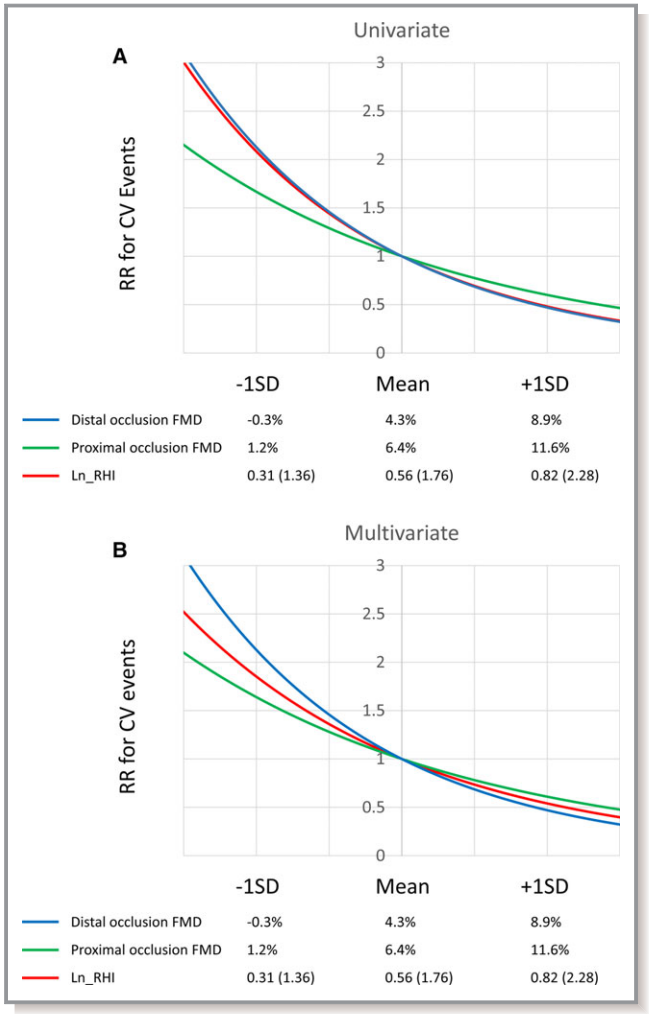

Figure 7. Relative risk for FMD and Ln_RHI values. (A) Univariate relative risk and (B) Multivariate relative risk. The relative risk for cardiovascular events in each FMD or Ln_RHI value is relative to the expected event rate with the median value of FMD or Ln_RHI. CV indicates cardiovascular; FMD, flow-mediated dilation; Ln_RHI, logarithmic value of reactive hyperemia index; RR, risk ratio.

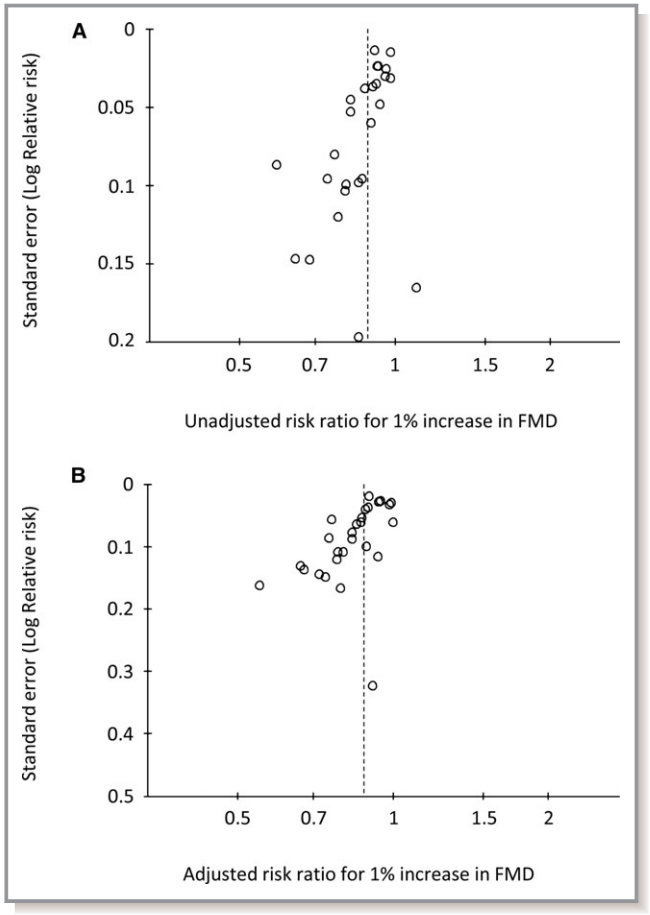

Figure 8. Funnel plot of flow-mediated vasodilation (FMD) studies. Funnel plot of univariate (A) and multivariate (B) risk ratio of FMD.

diameter before and after reactive hyperemia-induced vasodilation is measured by ultrasound in FMD, whereas a finger pulse amplitude is recorded by a hard-shell-covered tonometry cuff in RH-PAT. Therefore, FMD is a measure of vasodilation in a conduit artery, whereas RH-PAT samples smaller resistance arteries. Although nitric oxide bioavailability plays a substantial role in the both methodologies,[55,56] other substances, such as prostaglandin, adenosine, and hydrogen peroxide, can also influence vasodilation in response to shear stress and ischemia in different manners.[57] Vasodilatory responses result from a complex interaction between a variety of these vasoactive substances and vascular smooth muscle, and can differ between conduit arteries and microvessels. Endothelium-derived nitric oxide might have a more important role in FMD technique than in RH-PAT. Although it has been reported that RH-PAT mainly reflects endothelium-derived nitric oxide,[55] further studies are needed to elucidate the detailed mechanism of RH-PAT signals. In a study of the Framingham Heart Study cohort, FMD (n=7031) and RH-PAT (n=4352) were measured. Abnormal FMD was related to advancing age, hypertension, and obesity, whereas abnormal RH-PAT was associated with obesity, increasing total/high-density lipoprotein cholesterol ratio, diabetes, and smoking. Lower systolic blood pressure was also associated with abnormal RH-PAT. Interestingly, after adjustment for risk factors and underlying CVD, RH-PAT was not significantly associated with FMD. Thus, brachial FMD and digital RH-PAT had differing relations with cardiovascular risk factors and provide distinct information regarding vascular function in conduit versus smaller digital vessels. Nevertheless, our results demonstrated that both methods provide significant predictive value for cardiovascular events and that their prognostic magnitudes in CVD population are similar. Future studies are needed to explore whether the prognostic values of these 2 for cardiovascular events are synergistic or independent of each other.

Results of brachial FMD vary across institutions, and thus, it is difficult to compare between institutions.[58] In this meta-

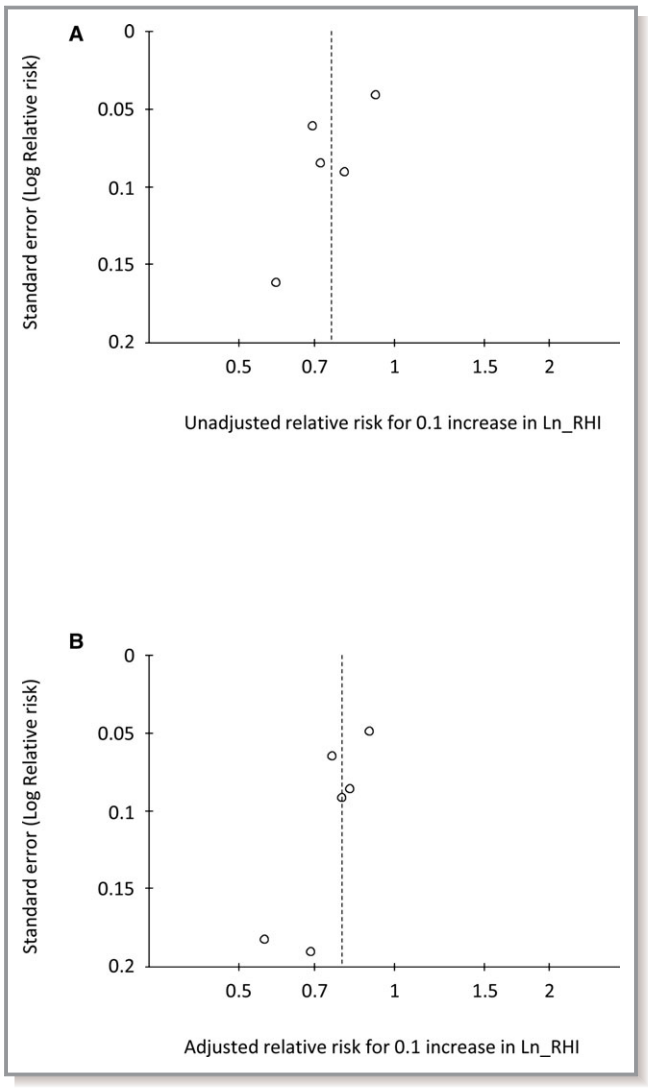

Figure 9. Funnel plot of RH-PAT studies. Funnel plot of univariate (A) and multivariate (B) risk ratio of Ln_RHI. Ln_RHI indicates logarithmic value of reactive hyperemia index; RH-PAT, reactive hyperemia–peripheral arterial tonometry.

analysis, mean values of proximal and distal FMD varied from 2.1% to 6.5% (median 3.7, interquartile range 2.5–5.4) and 4.7% to 9.1% (median 5.8, interquartile range 4.8–8.7) even when limited to CVD population, while mean values of Ln_RHI ranged from 0.28 to 0.59 (median 0.54, interquartile range 0.45–0.57) (excluding the 0.28 value results in a range of 0.50–0.59). It might be partly explained by operator dependency, technical factors, and methodological varieties of FMD measurement; therefore it is challenging to conduct a review of brachial artery FMD. On the other hand, the RH-PAT technique is less operator dependent and well standardized. We showed that cardiovascular risk change associated with a 1 SD change in test value is comparable between FMD and Ln_RHI. Specifically, a 1 SD decrease in distal occlusion FMD from the mean value corresponds to decrease from 4.3% to −0.3%, and in Ln_RHI (RHI) from 0.56 (1.76) to 0.31 (1.36). The brachial artery must not respond or constrict in order to achieve a 1 SD change.

In current clinical practice, CVD risk is estimated based on identifying and quantifying the established risk factors, while there is a notable interindividual heterogeneity in response to risk factors and therapies.[1] Furthermore, nontraditional and unknown risk factors may also have a substantial role in atherosclerosis. By measuring endothelial function, we can directly assess the functional significance of atherogenesis. Thus, noninvasive peripheral endothelial function tests seem to be feasible and effective in cardiovascular risk stratification. However, further evidence is needed, especially on RH-PAT.

Limitations

The limitations of this study must be considered. First, study subjects, sample size, follow-up duration, end points, and included covariates in multivariable analyses differed among studies. We did not have access to individual subject data to enable consistent adjustments for confounding factors. Second, only papers published in the English language were included. Third, publication bias was suspected from the funnel plots implying probable overestimation of the observed association with important practical implications for the use of endothelial function assessments. Fourth, the number of RH-PAT studies is small and no studies on non-CVD subjects with RH-PAT measures were included.

Conclusions

The current systematic review and meta-analysis found that both brachial FMD and digital RH-PAT have significant predictive value for future cardiovascular events after adjustment for other risk factors. The prognostic magnitudes of these 2 methods in CVD population were similar, and a 1 SD increase or decrease was associated with 50% lower risk or doubled risk of cardiovascular events. Future studies should explore whether the prognostic values of these 2 are independent of each other and whether endothelial function-guided therapies provide benefits in improving cardiovascular outcomes.

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Disclosures

Lerman declared consulting for Itamar Medical.

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