# ASSOCIATION BETWEEN BRACHIAL ARTERY REACTIVITY AND CARDIOVASCULAR DISEASE STATUS IN AN ELDERLY COHORT: THE CARDIOVASCULAR HEALTH STUDY

**Joseph Yeboah**[a], **Kim Sutton-Tyrrell**[b], **Mary Ann Mcburnie**[c], **Gregory L. Burke**[a], **David M Herrington**[a], and **John R Crouse**[a]

[a] Departments of Internal medicine/Cardiology and Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC

[b] Departments of Internal medicine/Cardiology and Public Health Sciences, University of Washington, Seattle, WA

[c] Departments of Internal medicine/Cardiology and Public Health Sciences, University of Pittsburgh, PA

## Abstract

**BACKGROUND AND OBJECTIVES—**The association of brachial flow-mediated dilation (FMD) and cardiovascular disease (CVD) status is unclear especially in older adults whose FMD is greatly diminished. We assessed the association of FMD and the presence or absence of subclinical and clinical CVD in a population based cohort of older adults.

**METHODS AND RESULTS—**FMD was measured in 2971 adults aged 72–98 years (mean age 78.6 years) who participated in the Cardiovascular Health Study. Multiple linear regression analysis was used to examine the association between FMD and CVD status (clinical, subclinical and free of CVD). Out of 2791 with complete data, 82.7% were Caucasians and 59% females. 743 were classified as having clinical CVD, 607 as subclinical CVD and 1441 as neither clinical CVD nor subclinical CVD (CVD free). FMD was higher in the CVD free group compared with either the clinical (3.13 ± 0.05% vs 2.93 ± 0.07%, p=0.025) or the subclinical CVD group (3.13± 0.05% vs 2.95± 0.08%, p=0.05) after adjusting for covariates. There was no significant difference between the FMD of subjects with clinical and subclinical CVD (2.93 ± 0.07% vs 2.95 ± 0.08%, p=0.84). Similar but inverted associations were observed between height adjusted brachial artery diameter (BAD) and CVD status. However, FMD and BAD had poor diagnostic accuracies for identifying older adults with subclinical CVD.

**CONCLUSION—**Among older adults, those with either clinical or subclinical CVD have lower FMD than CVD free subjects. BAD showed similar but inverted associations with CVD status in

this cohort. FMD and BAD had poor diagnostic accuracies for identifying older adults with subclinical CVD.

### Keywords

Brachial flow-mediated dilation; brachial artery diameter; cardiovascular disease; elderly

## Introduction

The incidence and prevalence of cardiovascular disease is high in older adults (1, 2). Traditionally, individuals have been classified as having either clinical cardiovascular disease (CVD) or free of clinical CVD depending on whether or not they had experienced an overt CVD event. The Cardiovascular Health Study(CHS) sub-classified subjects who were free of clinical CVD into those who had subclinical CVD and those who were free of CVD based on ankle brachial index measurement, the degree of carotid artery stenosis and wall thickness, abnormal electrocardiographic and echocardiographic findings, and a positive Rose angina and claudication questionnaire (3). Subclinical CVD was as prevalent as clinical CVD and constitute about thirty-eight percent (38%) of the CHS cohort (2, 4). Subclinical CVD was related to traditional CVD risk factors, including lipoprotein levels, glucose-insulin levels, inflammatory markers, body mass index and systolic and diastolic blood pressure in both men and women (2).

Subclinical CVD (based on measurements of several vascular beds) was a better predictor of the risk of developing short-term clinical CVD than the measurements of either traditional CVD risk factors or subclinical vascular abnormalities in a single vascular bed (2, 5, 6). Subclinical CVD has also been shown to be an independent predictor of long term clinical coronary heart disease in the CHS cohort (5, 7).

Brachial flow-mediated dilation (FMD) is a validated non-invasive physiologic measure of endothelial function (8) and has been associated with cardiovascular risk factors, coronary artery disease (8, 9) and also predicts incident CVD events (10–12). Studies have shown, in relatively young populations that subjects with clinical CVD have impaired brachial FMD compared with healthy subjects (13). Studies have also shown that brachial FMD declines with age (14). However, whether the association between brachial FMD and cardiovascular disease status still exists in older adults has not been well studied. In addition brachial FMD of subjects with subclinical CVD has been less well characterized even in relatively young adults.

To investigate the association of endothelial function and CVD status in older adults and to characterize the endothelial function of subjects with subclinical CVD further, we examined the association between brachial FMD and cardiovascular disease status in a large population based cohort of older adults.

## METHODS

### Study Population

Fried at al have previously described the design and rationale of the CHS study (3). Briefly, CHS was a longitudinal multicenter study of 5888 adults aged 65 years designed to be representative of the US population. Recruitment of 5201 adults into the study began between May 1989 and May 1990 at four clinic sites (University of California Davis-Sacramento county CA, The Johns Hopkins University-MD, Wake Forest University-Forsyth county NC and University of Pittsburgh-Pittsburg PA) with the coordinating center at University of Washington Seattle, WA. Between 1992 and 1993, an additional 687 African American participants were recruited from three out of the four clinic sites (Sacramento county, Forsyth county and Pittsburgh). All participants were either medicare beneficiaries or medicare-eligible during recruitment. The Cardiovascular Health Study was approved by the institutional review boards of each of the study sites and informed consent was obtained from all participants.

Eight years into the study (1997–1998), the 3032 participants who returned for their yearly visit were approached for participation in a brachial FMD ancillary study. Of the 3032 subjects, 130 were excluded from the brachial FMD ancillary study (74-history of mastectomy, 20-history of Raynauld's disease and 36-other miscellaneous reasons). Sixty-one (61) participants refused the ultrasound examination and an additional 49 discontinued the scan (19-discomfort during the exam, 9-equipment problems and 21-other reasons). In all 2791 participants, age 72–98 years underwent the brachial artery ultrasound measurement. This ancillary study was approved by the institutional review boards of each study site and participants provided informed consent.

### Definition of cardiovascular disease status

Clinical CVD in the CHS was defined as any of the following: history of atrial fibrillation or Pacemaker placement, peripheral vascular surgery, congestive heart failure, stroke, transient ischemic attack, myocardial infarction, coronary artery bypass graft surgery or percutaneous coronary intervention which has been adjudicated by a formal CHS committee. A composite measure of subclinical CVD is defined as the presence of any of the following: (a) major electrocardiographic abnormalities based on the Minnesota Code and individual ventricular conduction defects, major Q/QS wave abnormalities, left ventricular hypertrophy, isolated major ST/T wave abnormalities and first degree AV blocks (b) an ankle-arm-systolic BP ratio of 0.9 or less, (c) a percentage of stenosis of the internal carotid artery (based on ultrasonographic findings) of more than 25% or an intima-medial thickness of the internal or common carotid artery higher than the 80$^{th}$ percentile of the CHS distribution, (d) abnormalities in echocardiographic findings, (e) abnormality in ventricular wall motion, (f) low ejection fraction (LVEF < 45%), or (g) positive response to the Rose angina or claudication questionnaire without clinical history of angina or claudication (5). The CHS CVD status classification was heterogenous and not strictly based on the degree/progression of atherosclerosis. We re-classified the cohort into three groups based on the degree/progression of atherosclerosis as follows: a) clinical CVD – clinical claudication, myocardial infarction, stroke, TIA, CABG or angioplasty. b) Subclinical CVD – percent

stenosis of the internal carotid artery of more than 25% or an intima-medial thickness of the internal or common carotid artery higher than the 80th percentile in CHS, major electrocardiographic abnormalities based on Minnesota code, positive response to the Rose angina or claudication questionnaire without clinical history of angina or claudication and c) free of clinical and subclinical CVD. We then re-tested the association of our newly defined CVD status and brachial FMD.

### Clinical Evaluation and Biochemical Analysis

All participants provided a medical history and underwent clinical examination at baseline and yearly thereafter. Standardized questionnaires were used to determine medical history, medication use and cardiovascular risk assessment at baseline and then at yearly visits.

Hypertension in CHS was defined as seated average systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg, history of hypertension or antihypertensive medication usage. Diabetes mellitus was defined as fasting blood glucose 126 mg/dl, history of diabetes mellitus or use of insulin/oral hypoglycemics. Cigarette smoking is defined as current smoking or history of cigarette smoking. Race was defined by self-report with the following 5 choices: white, black, American Indian/Alaskan Native, Asian/Pacific Islanders or other. For the sake of simplicity, race was re-categorized into three categories: whites, blacks and others.

Blood for biochemical analysis was obtained from fasting venous samples and total cholesterol was determined using standard enzymatic methods (15). All the covariates used in this analysis were collected at the eight (1998) CHS clinic visit except data on body mass index and height which was collected during the seventh (1997) CHS clinic visit, carotid artery ultrasound measurements (stenosis and IMT) that was obtained on the ninth CHS clinic visit (1999) and Echocardiographic examination findings that was done on the fourth CHS clinic visit(1993).

### Flow-Mediated Brachial Artery Vasodilation

A detailed description of the scanning and reading protocol has been previously published (16). Briefly, sonographers underwent centralized training in brachial FMD measurement at Wake Forest University School of Medicine and were certified after performing at least 20 acceptable scans on volunteers. Participants had no caffeine, cigarettes or food at least eight hours prior to the examination. All the examinations took place at approximately the same time (morning) in a room with an ambient temperature of 72°F. Participants underwent examination after 15 minutes rest in the fasting state. With each participant supine and using an automated sphygmomanometer, the left arm was used to monitor blood pressure and pulse at five minute intervals throughout the exam. A standard pediatric cuff was positioned around the right arm, 2 inches below the antecubital fossa. A 10 MHz Biosound Phase 2 ultrasound system (BiosoundEsaote, Indianapolis Ind.) was used to acquire images of the right brachial artery. After obtaining baseline images of the right brachial artery for 2 minutes, the pediatric cuff was inflated to 50mmHg above the participant's systolic blood pressure to occlude the right brachial artery. The pediatric cuff was kept inflated for 4 minutes. Images of the right brachial artery were captured continuously for 2 minutes after

cuff deflation. Video tapes of the acquired images of the brachial artery were analyzed at the Wake Forest University Cardiology Image Processing Laboratory using a previously validated semi-automated system. All brachial diameter images were captured in diastole (ECG gated R-wave). The semi-automated readings of these digitized images generated the baseline and maximum diameters of the brachial artery from which the absolute change in baseline diameter and % brachial FMD was computed.

Correlations for repeated measures of baseline diameter, maximum diameter and %FMD using 80 CHS participants scanned on two separate days more than 2 weeks apart, were 0.94, 0.94 and 0.67 respectively (16). The reproducibility of the method including cuff placement below the antecubital fossa and the automated analysis was tested with repeated examinations less than one week apart among 127 CHS participants. The mean ± SD difference in percent change in diameter (brachial FMD) was $0.02 \pm 1.54\%$ and $R^2$ was 0.7(17)

### Non invasive measurement of cardiovascular disease

Carotid artery intima-media thickness was measured by means of an average of the near and far wall B-mode ultrasound distance measurements (18, 19). The degree of internal carotid artery stenosis was estimated by means of B-mode ultrasound images and Doppler-derived flow velocities (20). Echocardiographic abnormalities with respect to ejection fraction and wall motion abnormalities were obtained using M-mode images (21). Ankle brachial (arm) indexes were determined by means of a ratio of the highest obtained posterior tibial blood pressure divided by the right brachial artery blood pressure (22).

### Statistical Analysis

Data are reported as mean± SE for continuous variables and frequencies for categorical variables. ANOVA and chi-square tests were used to compare the means of covariates across CVD status.

General linear models (multiple linear regression analyses) were used to determine the association between brachial artery measures (baseline diameter, maximum diameter, absolute change in baseline diameter and % brachial FMD) and CVD status. We present analyses with and without adjustment for factors found to be associated with FMD in this study or previous studies including: age, gender, race/ethnicity, total cholesterol, β-blocker use, ACE inhibitor use, HMG CoA reductase inhibitor use, diabetes mellitus, smoking and hypertension. Consistent with other studies, subject's height was better associated with brachial artery diameters than BMI in our analysis. Height was therefore included in the multivariate model instead of BMI to account for the differences in baseline diameter due to body size. All comparisons were pre-specified and therefore we did not adjust for multiple comparisons.

The area under curve (AUC) of a receiver operator curve reflects the sensitivity and specificity and hence the overall accuracy of a model (23). To examine the accuracy of brachial FMD in diagnosing subclinical CVD in the elderly, we assessed whether the addition of brachial FMD to a logistic model consisting of the traditional CV risk factors will increases the area under curve.

Statistical significance was inferred at a two-sided p-value  0.05. Analysis was done using SAS version 9.1(SAS Institute Cary, NC)

## RESULTS

The 2791 subjects included in this analysis had a mean age of 78.6 years; 59% were females and 83% were Caucasians. Based on the CHS classification, 743 of the subjects had clinical CVD, 607 subjects had subclinical CVD and 1441 subjects were free of clinical and subclinical CVD (free of CVD). Age, gender, blood pressure, total cholesterol, diabetes mellitus, smoking, β blocker use, ACE inhibitor use and HMG CoA reductase inhibitor use were significantly different between the three groups (Table 1)

Brachial FMD (percent change in baseline diameter) was not significantly different between the clinical and subclinical CVD groups in both the adjusted and unadjusted models. However the brachial FMD of the group free of CVD was significantly higher in both the adjusted and unadjusted models compared with either the clinical or the subclinical CVD group (Table 2).

Repeating the analysis with our newly defined criteria (atherosclerosis based) yielded similar findings. Subjects with clinical CVD (N=625) had a significantly lower brachial FMD compared with those free of CVD (N=1493) ($2.88 \pm 0.08$ vs $3.13 \pm 0.05$ %, p=0.01) after adjusting for age, gender, race/ethnicity, total cholesterol, hypertension, diabetes mellitus, cigarette smoking, β blocker use, ACE inhibitor use and HMG CoA reductase inhibitors use. The brachial FMD of subjects with clinical CVD was however not significantly different from those with subclinical CVD ($2.88 \pm 0.08$ vs $2.97 \pm 0.07$ %, p=0.40) after adjusting for covariates. There was a trend towards significance for lower brachial FMD in subjects with subclinical CVD compared with those free of CVD ($2.97 \pm 0.07$ vs $3.13 \pm 0.05$ %, p=0.07).

In the stratified analyses, older adults with age less than or equal to the median (78 years) had significantly higher brachial FMD compared with those with age greater than the median. Females had significantly higher brachial FMD compared with males, Caucasians also had significantly higher brachial FMD compared with blacks and older adults without history of hypertension had significantly higher brachial FMD compared with older adults with history of hypertension (Table 3). Brachial FMD was not associated with diabetes mellitus, cholesterol level, cigarette smoking status, ACE inhibitor use, HMG CoA reductase inhibitor use and β blocker use in the adjusted regression model (Table 3). Similar associations were seen with baseline brachial diameter and CV risk factors/medication use (Table 3).

As shown in table 2, the baseline brachial artery diameter was largest in the group with clinical CVD and was significantly larger compared with either the subclinical CVD group or the group free of CVD in the unadjusted model. However after adjusting for the covariates including height, the baseline diameter was not significantly different between the clinical and the subclinical CVD groups. Maximum brachial artery diameter was also significantly higher in the group with clinical CVD compared with either the subclinical

CVD or the CVD free group. However after adjusting for covariates including height, the maximum brachial artery diameter was not significantly different between the clinical and the subclinical CVD groups (Table 2).

The absolute change in baseline diameter was significantly different between the clinical CVD and the CVD free group in the unadjusted model. However after adjusting for covariates, there was no significant difference between the absolute change in diameter between any pair of the three groups (Table 2).

Figure 1 curve A is an ROC curve showing the AUC when traditional cardiovascular risk factors such age, gender, total cholesterol, HDL, smoking, hypertension and diabetes mellitus were included in the model for the diagnosis of subclinical CVD in this elderly cohort. The AUC or the c-statistic was calculated as 0.841. The c-statistic (AUC) when brachial artery diameter alone (curve B) is in the model was 0.593 and the c-statistic when brachial FMD alone (curve C) is in the model was 0.552 respectively (Figure 1). Addition of brachial FMD to the model containing the classical CV risk factors enumerated above increased the AUC to 0.842 (net AUC =0.01. p value for net increase was not significant)

Addition of brachial artery diameter to the model containing the classical CV risk factors enumerated above did not increase the AUC at all (AUC=0.841).

## DISCUSSION

In this cross-sectional study of 2791 population based older adults, brachial FMD was similar in subjects with clinical and those with subclinical CVD. Subjects free of CVD however, had significantly higher brachial FMD compared with either the clinical or the subclinical CVD group. We also observed that baseline brachial artery diameter exhibited similar but inverted associations with CVD status and CV risk factors as brachial FMD in older adults. The magnitude of differences observed between those with clinical CVD and those free of CVD is quite small. This however is to be expected especially since healthy older subjects have lower FMD than younger subjects. One would therefore expect smaller margin of possible further depression of FMD in older adults with clinical CVD compared with those free of CVD.

Very limited data exist comparing the brachial artery reactivity of subjects with clinical CVD with those free of clinical CVD. Most of the current knowledge on this topic was obtained by inference from prior studies where subjects without clinical CVD were used as controls (13, 24–26). However, most of these studies were clinical trials with limited statistical power for such a comparison. In addition, previous studies were carried out in relatively young subjects. Our study is by far the largest to assess this association, suggests that even though the brachial FMD of older adults is greatly diminished compared with younger adults, the association between brachial FMD and CVD status is maintained into older adulthood.

The results of our subsequent analysis in which the cohort was re-classified based on the presence or absence of clinical/subclinical atherosclerosis was similar to the results obtained when the CHS classification was used. This suggests that the association between brachial

FMD and CVD status observed using the CHS classification may not be due to the heterogeneity of that classification.

The absolute change in diameter of the brachial artery was not significantly different between any of the three CVD status groups after adjusting for covariates. The association of baseline brachial diameter and CVD status mirrored that of brachial FMD but not absolute change in diameter and CVD status. Thus baseline brachial diameter which is more reproducible and easy to measure provided similar information as brachial FMD in this cohort of older adults.

Although progression of atherosclerosis often leads to narrowing of the lumen of blood vessels and symptomatic cardiovascular disease, a growing body of evidence suggests that arteries have the potential to enlarge in response to atherosclerosis and thus compensate for the narrowing of the lumen (27–31). Glagov et al demonstrated this "compensatory remodeling" in specimens of the left main coronary artery obtained at autopsy (27). Other studies have suggested that this compensatory remodeling may be expressed widely within the arterial system (32). Thus in some part of the arterial system compensatory remodeling may manifest as dilation of the artery and may manifest as constriction of the artery in other parts of the arterial system. For example, Terry et al showed that the inter-adventitial diameter of the common carotid artery was larger in subjects with coronary artery disease compared with subjects free of coronary artery disease. However, the converse was true for the internal carotid artery (33). In the Rotterdam study, each one standard deviation larger carotid lumen diameter was associated with a 15% increased risk of incident myocardial infarction (34). A number of population based studies have also found increases in common carotid diameter to be associated with elevated cardiovascular risk factors (29–31, 35–37). Thus, an increase in carotid arterial diameter has been suggested to reflect the adaptive response of the arterial wall to cardiovascular risk factors. Our study suggests that remodeling in the brachial artery due to atherosclerosis may be similar to that seen in the common carotid artery and manifest as larger brachial artery diameters in subjects with clinical/subclinical CVD compared with subjects free of CVD.

In addition to body size/height, the diameter of arteries may be partly determined by vascular tone. Current literature suggests that vascular tone is under the influence of signal molecules produced by the vascular endothelium (38, 39). Although the exact mechanism by which signal molecules modulate vascular tone is not fully understood, the following postulated mechanism seems plausible. It appears that the type of signal molecule produced by the vascular endothelium may depend on the type of blood flow in the vessel (40, 41). Under normal conditions, blood flow is laminar and this may be the stimulus for the release of vasoconstrictor substances such as endothelin-1. However under turbulent blood flow, such as the blood flow after the release of the cuff during brachial FMD measurements, vasodilator substances such as nitric oxide may be the dominant signal molecule produced by the vascular endothelium. A diseased vascular endothelium will produce less vasoconstrictor substances during laminar blood flow resulting in a larger diameter at baseline and will also produce less vasodilator substances during turbulent blood flow resulting in less vasodilation. The baseline brachial artery diameter and the percent vasodilation of the brachial artery may both be a reflection of vascular endothelial health.

Current traditional cardiovascular risk factors performed very well as a diagnostic tool for identifying older adults with subclinical CVD in this cohort (Figure 1). Brachial FMD and brachial artery diameter had poor diagnostic accuracy when used alone to identify older adults with subclinical CVD in this cohort. In addition, neither brachial FMD nor brachial artery diameter added significantly to the diagnostic accuracy of current traditional cardiovascular risk factors for the diagnosis of subclinical CVD. Thus even though brachial FMD is significantly impaired in older adults with subclinical CVD compared with those free of subclinical CVD, its has no value as a diagnostic tool in clinical practice for detecting older adults with subclinical CVD in the presence of the current traditional CV risk factors. There is however a possibility that an advantage in using these surrogates of endothelial function may be uncovered in longitudinal studies evaluating CVD events rather than in observational/cross-sectional studies such as the present study. Studies evaluating the diagnostic accuracy of brachial FMD/brachial artery diameter for subclinical CVD are needed in relatively younger populations.

Our study has the following limitations: Endothelium-independent vasodilation with nitroglycerin was not examined in our participants due to the advanced age (72–98 years) and the risk-benefit considerations of nitroglycerin administration in a population based cohort study. We cannot be certain that the relationship between FMD and CVD status in our study was entirely due to endothelium-dependent vasodilation.

Covariates that have been shown in prior studies to be associated with endothelial function or showed a significant association with brachial FMD in our univariate analyses were included in the adjusted model. Height which has been shown in prior studies to be associated with carotid artery diameter, also showed significant associations with the baseline and maximum diameter in this study. Height was therefore included in the adjusted models for baseline and maximum diameter. Even though several confounders were included in our adjusted models, our results may still be due to other covariates not account for in the multivariable model (residual confounding).

Covariates used in this analysis were all not collected on the same CHS clinic visit. For example body mass index and height used in the analysis were from the 1997 visit. Using covariates obtained at different times in a cross-sectional study can affect the results and may have contributed to our findings.

This cross sectional study was conducted in older adults and therefore our results and inferences may not hold true for younger individuals.

## Conclusion

Older adults with history of clinical CVD and those with subclinical CVD have similar brachial FMD and height adjusted brachial artery diameter. Older adults free of CVD however has higher brachial FMD and smaller height adjusted brachial artery diameter compared to those with either clinical/subclinical CVD. Brachial FMD does not improve the diagnostic accuracy of traditional CV risk factors in identifying older adults with subclinical CVD.

## Acknowledgments

## References

1. Arnold AM, Psaty BM, Kuller LH, Burke GL, Manolio TA, Fried LP, Robbins JA, Kronmal RA. Incidence of cardiovascular disease in older Americans: the Cardiovascular Health Study. J Am Geriatr Soc. 2005; 53:211–218. [PubMed: 15673343]

2. Kuller L, Borhani N, Furberg C, Gardin J, Manolio T, O'Leary DH, Psaty BM, Robbins J. Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. Am J Epidemiol. 1994; 139:1164–1179. [PubMed: 8209875]

3. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991; 1:263–276. [PubMed: 1669507]

4. Chaves PH, Kuller LH, O'Leary DH, Manilio TA, Newman AB. Subclinical cardiovascular disease in older adults; insights from the Cardiovascular Health Study. Am J Geriatr Cardiol. 2004; 13:137–51. [PubMed: 15133417]

5. Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin JM, Haan MN, O'Leary DH, Savage PJ, Tell GS, Tracy R. Subclinical disease as an independent risk factor for cardiovascular disease. Circulation. 1995; 92:720–726. [PubMed: 7641349]

6. Kuller LH, Velentgas P, Barzilay J, Beauchamp NH, O'Leary DH, Savage PJ. Diabetes mellitus: subclinical cardiovascular disease and risk of incident cardiovascular disease and all-cause mortality. Arterioscler Thromb Vasc Biol. 2000; 20:823–829. [PubMed: 10712409]

7. Kuller LH, Arnold AM, Psaty BM, Robbins JA, O'Leary DH, Tracy RP, Burke GL, Manolio TA, Chaves PH. 10 – year Follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. Arch Intern Med. 2006; 166:71–78. [PubMed: 16401813]

8. Celermajer DS, Sorensen KE, Gooch VM. Non-invasive detection of endothelial dysfunction in children and adults at risks of atherosclerosis. Lancet. 1992; 340:1111–5. [PubMed: 1359209]

9. Widlanksy ME, Gokce N, Keaney JF, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol. 2003; 42:1149–60. [PubMed: 14522472]

10. Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Menzoian JO, Vita LA. Risk stratification for postoperative cardiovascular events via non-invasive assessment of endothelial function: a prospective study. Circulation. 2002; 105:1567–72. [PubMed: 11927524]

11. Brevetti G, Silvestro A, Schiano V, Chiarello M. Endothelial dysfunction and cardiovascular risk prediction in peripheral artery disease: additive value of flow-mediated dilation to ankle-brachial pressure index. Circulation. 2003; 108:2093–8. [PubMed: 14530195]

12. Gokce N, Keaney JF Jr, Hunter LM. Predictive value of non-invasively determined endothelial dysfunction for long term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol. 2003; 41:1769–75. [PubMed: 12767663]

13. Zhang X, Zhao S, Li X, Zhou Q. Endothelium-dependent and independent functions are impaired in patients with coronary artery disease. Atherosclerosis. 2000; 149:19–24. [PubMed: 10704610]

14. Parker BA, Ridout SJ, Procter DN. Age and flow-mediated dilation: A comparison of dilatory responsiveness in the brachial and popliteal arteries. Am J Physiol Heart Circ Physiol. 2006 Jul 21. (epub ahead of print).

15. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. Clin Chem. 1995; 41:264–270. [PubMed: 7874780]

16. Herrington DM, Liexiang Fan, Matella D, Ward A, Pusser EB, Crouse JR, Burke GL, et al. Brachial flow-mediated vasodilator responses in population-based research: methods,

reproducibility and effects of age, gender and baseline diameter. Journal of Cardiovascular Risk. 2001; 8:319–28. [PubMed: 11702039]

17. Herrington DM, Espeland MD, Crouse JR, Robertson J, Riley WA, McBurnie MA, Burke GL. Estrogen replacement and brachial artery flow-mediated vasodilation in older women. Arterioscler Thromb Vasc Biol. 2001; 21:1955–1961. [PubMed: 11742870]

18. O'Leary DH, Polak JF, Kromal RA. Distribution and correlates of sonographically detected carotid artery disease in Cardiovascular Health Study. Stroke. 1992; 23:1752–1760. [PubMed: 1448826]

19. O'Leary DH, Polak JF, Kromal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid artery intimal and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999; 340:14–21. [PubMed: 9878640]

20. O'Leary DH, Polak JF, Wolfson SK Jr. The use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study. Stroke. 1991; 22:1155–1163. [PubMed: 1926258]

21. Gardin JM, Wong ND, Bommer W. Echocardiographic design of a multi-center investigation of free-living elderly subjects: the Cardiovascular Health Study. J Am Soc Echocardiogr. 1992; 5:63–72. [PubMed: 1739473]

22. Newman AB, Siscovick DS, Manolio TA. The ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Circ. 1993; 88:837–845.

23. Delong ER, Delong DM, Clarke – Pearson DL. Comparing the areas under two or more correlated receiver operating characteristics curves: a non parametric approach. Biometrics. 1998; 44:857–845.

24. Chen PL, Sheu WH, Chen YT, Ho YP, Hu HH, Hsu HY. Changes of brachial flow-mediated dilation in different ischemic stroke subtypes. Neurology. 2006; 26:1056–8. [PubMed: 17000977]

25. Hamabe A, Takase B, Uehata A, Kurita A, Ohsuzu F, Tamai S. Impaired endothelial – dependent vasodilation in the brachial artery in variant angina pectoris and the effect of intravenous administration of vitamin C. Am J Cardiol. 2001; 87:1154–9. [PubMed: 11356389]

26. Shivalkar B, Dhondt D, Goovaerts I, van Gaal L, Bartunek J, van Combrugge P, Vrints C. Flow-mediated dilation and cardiac function in type 1 diabetes mellitus. Am J Cardiol. 2006; 97:77–82. [PubMed: 16377288]

27. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987; 316:1371–1375. [PubMed: 3574413]

28. Clarkson TB, Prichard RW, Morgan TM, et al. Remodeling of the coronary arteries in human and nonhuman primates. JAMA. 1994; 271:289–294. [PubMed: 8295288]

29. Crouse JR, Goldbourt U, Evans G, et al. Arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) Cohort: in vivo quantification of the carotid artery enlargement. Stroke. 1994; 25:1354–1359. [PubMed: 8023349]

30. Bonithon-Kopp C, Touboul PJ, Berr C, Magne C, Ducimetiere P. Factors of carotid artery enlargement in a population of Aged 59–71 years: The EVA study. Stroke. 1996; 27:654–660. [PubMed: 8614925]

31. Kiechl S, Willeit J. for the Brunneck Study Group. The natural course of atherosclerosis, II: vascular remodeling. Arterioscler Thromb Vasc Biol. 1999; 19:1491–1498. [PubMed: 10364080]

32. Pasterkamp G, Schoneveld AH, van Wolferen W, et al. The impact of atherosclerotic arterial remodeling on percentage of lumen stenosis varies widely within the arterial system: a postmortem study. Arterioscler Thrombo Vasc Biol. 1997; 17:3057–3063.

33. Terry JG, Tang R, Espeland MA, Crouse JR, et al. Carotid arterial structure in patients with documented coronary artery disease and disease-free control subjects. Circulation. 2003; 107:1146–1151. [PubMed: 12615793]

34. Bots ML, Grobbee DE, Hofman A, Witteman JCM. Common Carotid Intima-Media Thickness and Risk of Acute Myocardial Infarction: The Role of Lumen Diameter. Stroke. 2005; 36(4):762–767. [PubMed: 15746451]

35. Kawamoto B, Tomita H, Oka Y, Ohtsuka N. Association between risk factors and carotid enlargement. Intern Med. 2006; 45:503–9. [PubMed: 16702741]

36. Polak JF, Kronmal RA, Tell GS, O'Leary DH, Savage PJ, Gardin JM, Rutan GH, Borhani NO. Compensatory increase in common carotid artery diameter. Relation to blood pressure and artery

intima-media thickness in older adults Cardiovascular Health Study. Stroke. 1996; 27(11):2012–2015. [PubMed: 8898807]

37. Jensen-Urstad K, Jensen-Urstad M, Johansson J. Carotid artery diameter correlates with risk factors for cardiovascular disease in a population of 55-year-old subjects. Stroke. 1999; 30(8):1572–1576. [PubMed: 10436103]

38. Marasciulo FL, Montagnani M, Potenza MA. Endothelin-1: the ying and yang on vascular function. Curr Med Chem. 2006; 13:1655–65. [PubMed: 16787211]

39. Villar IC, Francis S, Webb A, Hobbs AJ, Ahluwalia A. Novel aspects of endothelial-dependent regulation of vascular tone. Kidney Int. 2006; 70:840–53. [PubMed: 16837917]

40. Resnick N, Yahar H, Shay-Saht A, Shushy M, Schubert S, Zilberman LC, Wofovitz E. Fluid shear stress and vascular endothelium: for better or for worse. Prog Biophys Mol Biol. 2003; 81:177–99. [PubMed: 12732261]

41. Li YS, Haga JH, Chien S. Molecular basis of the effects of shear stress on vascular endothelial cells. J Biomech. 2005; 38:1949–71. [PubMed: 16084198]
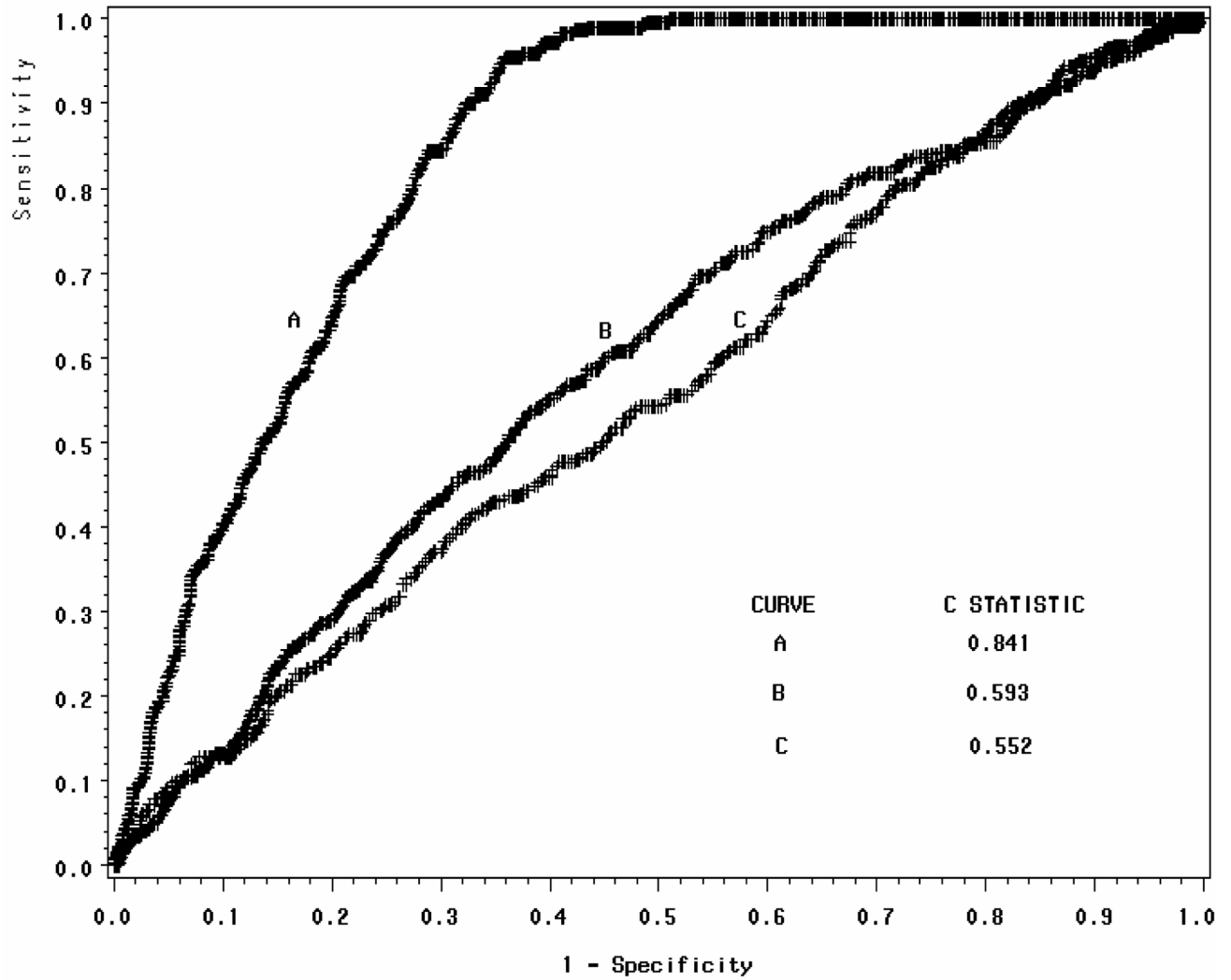
**Figure 1.**
ROC curves showing the diagnostic accuracy of traditional cardiovascular risk factors including age, gender, total cholesterol, smoking, hypertension and diabetes mellitus (curve A), baseline brachial artery diameter (curve B) and brachial FMD (curve C) in identifying older adults with subclinical cardiovascular disease.

**Table 1**

Demographics

| Variable | Clinical Disease N=743 (Mean ± se) | Subclinical disease N=607 (Mean ± se) | Free of Disease N=1441 (Mean ± se) | P value |
|---|---|---|---|---|
| Age (years) | 79.58 ± 0.16 | 78.80±0.18 | 78.09± 0.12 | <0.0001 |
| Gender (%) | | | | |
| Female | 328(44.20) | 338(55.78) | 968(67.22) | <0.0001 |
| Male | 415(58.80) | 269(44.22) | 473(32.78) | |
| Race (%) | | | | |
| White | 624(83.96) | 482(79.37) | 1204(83.54) | 0.366 |
| Black | 115(15.50) | 122(20.13) | 229(15.90) | |
| Others | 4(0.54) | 3(0.51) | 8(0.56) | |
| BMI (Kg/m$^2$) | 27.0± 0.17 | 27.26± 0.19 | 27.04± 0.12 | 0.524 |
| Cholesterol (mg/dl) | 195.22± 1.46 | 201.25± 1.60 | 206.19± 1.05 | <0.0001 |
| HDLc | 50.41 ± 14.40 | 53.12 ± 13.65 | 55.51 ± 14.21 | <0.0001 |
| LDLc | 128.53 ± 32.22 | 127.42 ± 32.81 | 128.10 ± 31.87 | 0.818 |
| Triglyceride | 150.42 ± 98.81 | 145.52 ± 84.41 | 137.33 ± 80.91 | 0.003 |
| Blood pressure (%) | | | | |
| Normal | 274(37.07) | 219(36.14) | 647(44.93) | |
| Borderline | 54(7.30) | 60(9.90) | 163(11.32) | <0.0001 |
| Hypertensive | 412(55.68) | 327(53.96) | 630(43.79) | |
| Diabetes (%) | | | | |
| No | 587(79.32) | 512(84.63) | 1288(89.57) | <0.0001 |
| Told <1yr ago | 14(1.89) | 12(1.98) | 20(1.39) | |
| Told >1yr ago | 139(18.78) | 81(13.39) | 130(9.04) | |
| Smoking (%) | | | | |
| Never | 315(42.92) | 285(47.42) | 728(51.05) | |
| Quit >1yr ago | 368(50.14) | 250(41.60) | 529(41.51) | |
| Quit <1yr ago | 14(1.91) | 14(2.33) | 13(0.91) | <0.0001 |
| Current | 37(5.04) | 52(8.65) | 93(6.53) | |
| ACE inhibit. Use (%) | 202(27.22) | 93(15.35) | 160(11.11) | <0.0001 |
| β blocker use (%) | 202(27.22) | 104(17.16) | 169(11.74) | <0.0001 |
| HMG CoA use (%) | 166(22.37) | 70(11.55) | 146(10.14) | <0.0001 |

*P values are ANOVA test for continuous variables and Chi square test for categorical variables. HDLc indicates high density lipoprotein and LDLc indicates low density lipoprotein.

**Table 2**

Comparison of brachial artery reactivity measures between subjects with clinical, subclinical and neither clinical nor subclinical CVD (free of CVD) using the general linear model

| Variable | [a]Clinical CVD(N=743) Mean ± se | [b]Subclinical CVD(N=607) Mean ± se | [c]Free of CVD(N=1441) Mean ± se | P value (a&b) | P value (a&c) | P value (b&c) |
|---|---|---|---|---|---|---|
| Baseline Diameter(mm) | | | | | | |
| Unadjusted | 4.73± 0.03 | 4.58± 0.03 | 4.35± 0.02 | 0.001 | <0.0001 | <0.0001 |
| Adjusted* | 4.58 ± 0.03 | 4.55 ± 0.03 | 4.46 ± 0.02 | 0.480 | 0.0005 | 0.008 |
| Maximum Diameter(mm) | | | | | | |
| Unadjusted | 4.86 ± 0.03 | 4.71 ± 0.03 | 4.49 ± 0.02 | 0.001 | <0.0001 | <0.0001 |
| Adjusted* | 4.70 ± 0.03 | 4.68 ± 0.03 | 4.59 ± 0.02 | 0.560 | 0.001 | 0.009 |
| Absolute Change in diameter(mm) | | | | | | |
| Unadjusted | 0.13 ± 0.003 | 0.13 ±0.003 | 0.14 ± 0.002 | 0.536 | 0.012 | 0.151 |
| Adjusted* | 0.13 ± 0.003 | 0.13 ±0.003 | 0.13 ± 0.002 | 0.885 | 0.142 | 0.196 |
| FMD (%) | | | | | | |
| Unadjusted | 2.80 ± 0.07 | 2.92 ± 0.08 | 3.22 ± 0.05 | 0.215 | <0.0001 | 0.001 |
| Adjusted* | 2.93 ± 0.07 | 2.95 ± 0.08 | 3.13 ± 0.05 | 0.839 | 0.025 | 0.050 |

*
Adjusted for age, gender, race/ethnicity, cholesterol, HDL, hypertension, diabetes mellitus, cigarette smoking, β blocker use, ACE inhibitor use and HMG CoA reductase inhibitor use. Height was included in the adjusted model for baseline diameter and maximum diameter.

**Table 3**

Association between brachial FMD (%) and height adjusted baseline brachial diameter with cardiovascular risk factors/medication use in the adjusted linear regression model[*]

| Variable | Brachial FMD (%) (Mean ± se) | P value | Baseline Diameter (mm) (Mean ± se) | P value |
|---|---|---|---|---|
| Age (years) | | | | |
| median | 3.12 ± 0.05 | 0.009 | 4.48 ± 0.02 | 0.007 |
| > median | 2.93 ± 0.05 | | 4.55 ± 0.02 | |
| Gender | | | | |
| Females | 3.30 ± 0.05 | <0.0001 | 4.13 ± 0.02 | <0.0001 |
| Males | 2.66 ± 0.06 | | 5.04 ± 0.02 | |
| Race | | | | |
| Caucasians | 3.13 ± 0.04 | <0.0001 | 4.47 ± 0.01 | <0.0001 |
| Blacks | 2.55 ± 0.09 | | 4.72 ± 0.03 | |
| Cholesterol (mg/dl) | | | | |
| median | 3.03 ± 0.05 | 0.825 | 4.51 ± 0.02 | 0.680 |
| > median | 3.04 ± 0.05 | | 4.50 ± 0.02 | |
| Diabetes mellitus | | | | |
| No | 3.05 ± 0.04 | 0.372 | 4.49 ± 0.01 | 0.002 |
| Yes | 2.96 ± 0.10 | | 4.62 ± 0.04 | |
| Hypertension | | | | |
| No | 3.18 ± 0.06 | 0.0004 | 4.43 ± 0.02 | <0.0001 |
| Yes | 2.89 ± 0.05 | | 4.58 ± 0.02 | |
| Cigarette smoking | | | | |
| No | 3.01 ± 0.05 | 0.415 | 4.52 ± 0.02 | 0.240 |
| Yes | 2.89 ± 0.14 | | 4.46 ± 0.05 | |
| ACE inhibitor use | | | | |
| No | 3.05 ± 0.04 | 0.290 | 4.52 ± 0.01 | 0.084 |
| Yes | 2.94 ± 0.10 | | 4.46 ± 0.03 | |
| HMG CoA red. Use | | | | |
| No | 3.04 ± 0.04 | 0.790 | 4.51± 0.01 | 0.960 |
| Yes | 3.01 ± 0.10 | | 4.51 ± 0.04 | |
| β Blocker use | | | | |
| No | 3.02 ± 0.04 | 0.155 | 4.51 ± 0.01 | 0.31 |
| Yes | 3.16 ± 0.09 | | 4.48 ± 0.03 | |

[*] Each stratified analysis is adjusted for all covariates including age, gender, race, total cholesterol, HDL, hypertension, diabetes mellitus, cigarette smoking, β blocker use, ACE inhibitor use and HMG CoA reductase inhibitor use