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**Supplemental Methods**

**Measurement of BP and subclinical CVD**

At the sixth examination cycle, BP levels were measured twice on the participant’s left arm by a Heart Study physician using a mercury column sphygmomanometer and a cuff of appropriate size, after the participant has been seated in a chair for ≥5 minutes. The assessment of subclinical disease traits is described below. To determine the ankle-brachial index (ABI), BP was measured twice on both the arms and at both the ankles, using an 8-MHz Doppler pen probe and an ultrasonic Doppler flow detector (Park Medical Electronics Inc., Shaw, Aloha, Ore), as described in the detail elsewhere.\(^1\) ABI was calculated as the average systolic BP of both ankles divided by the average systolic BP of the arms.\(^1\) Participants also underwent transthoracic echocardiography and M-Mode images were used to determine parameters of left ventricular (LV) structure, including septal wall thickness (SWT), posterior wall thickness (PWT) and LV end-diastolic diameter (LVEDD). Left ventricular mass (in g) was calculated as \(0.8(1.04([\text{LVEDD} + \text{PWT} + \text{SWT}]^3 - [\text{LVEDD}]^3)) + 0.6\) as described by Devereux et al.;\(^2\) and the sex-specific 80\(^{th}\) percentile of LV mass was used as cut-point for echocardiographic evidence of LV hypertrophy consistent with prior publications (Table S1).\(^3\) LV fractional shortening (defined as \((\text{LVEDD} - \text{LV end-systolic diameter})/\text{LVEDD}\) and visually assessed ejection fraction served as measures of LV systolic function. The excellent reproducibility of our echocardiographic measurements has been previously reported.\(^4\) In addition, a 12-lead electrocardiogram was obtained with participants in supine position. Sex-specific Cornell voltage criteria were used to assess electrocardiographic evidence of LV hypertrophy.\(^3,5\) Ultrasound of the carotid arteries was performed as described previously.\(^6\) Images of the common carotid artery and of the internal carotid artery were obtained using a 7.5-MHz transducer and a 5.0-MHz transducer, respectively.\(^6\) These images were used to calculate near- and far-wall intima media thickness (IMT). The reproducibility of these measurements was good.\(^7\) Stenoses of the carotid arteries were likewise assessed, with greater 25% stenoses indicating significant narrowing of the carotid artery. IMT values that met or exceeded the sex-specific 80\(^{th}\) percentile were defined as increased carotid artery IMT (Table
S1).³ Urinary albumin and creatinine were measured in a spot urine sample obtained in the morning. Urine albumin was assayed using an immunoturbidimetric test (Tinaquant Albumin assay, Roche Diagnostics), urinary creatinine was determined with a modified Jaffe method. Interassay coefficients of variation for urinary albumin and urinary creatinine assays were 7.2% and 2.3%, respectively.⁸

Subclinical disease score

We quantified the cumulative subclinical disease burden by generating a subclinical disease score as reported previously.³ A detailed description of the score is provided in Table S1. In essence, this score is the sum of five dichotomized indices of subclinical atherosclerosis and target organ damage: LV hypertrophy (by ECG or echocardiography); LV systolic dysfunction (by echocardiography), abnormal ultrasound of the carotid arteries (increased IMT or carotid artery stenosis), peripheral artery disease (abnormal ABI) and glomerular endothelial dysfunction (as indicated by microalbuminuria).³ Thus, the score ranged from 0 (none of the above abnormal) to 5 (all abnormal). In addition to this score, we evaluated the 5 individual components of the score. We also modeled subclinical disease as a binary variable (yes/no). The complete score and its components were available in a subgroup of 1915 participants.
**Table S1. Definitions of subclinical vascular disease**

| Characteristic                                                                 | Definition of subclinical disease component | Cut points for subclinical disease presence used in the present study |
|-------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------|
| LV hypertrophy by electrocardiography or echocardiography                     | Sum of the R-wave in a VL and the S wave in lead V3 exceeding 2.8 mV in men and 2.0 mV in women. | Presence of LV hypertrophy by Cornell criteria using electrocardiography or a height-adjusted LV mass using echocardiography that met or exceeded the sex-specific 80th percentile |
| LV hypertrophy by Cornell criteria using echocardiography                     | LV mass was calculated as 0.8(1.04([IVS+LVEDD+PW]⁻¹-[LVEDD]⁻¹))+0.6g⁻¹. LV mass values were then adjusted for height using the ratio of LV mass to height. | A fractional shortening of <0.29 by M mode, or by evidence on two-dimensional echocardiography of mild or greater systolic dysfunction on visual assessment in multiple views (corresponding to ejection fraction <50%), or by both criteria. |
| LV systolic dysfunction by echocardiography                                   | LV fractional shortening was calculated as (LVEDD-LVESD)/LVEDD¹⁰ | A standardized carotid IMT that met or exceeded the sex-specific 80th percentiles in the sample, an extreme increase of common carotid IMT, or presence of carotid artery stenosis ≥25% |
| Carotid ultrasound abnormality                                                 | A composite measure that combined the maximal common carotid artery IMT and maximal internal carotid artery IMT was obtained by averaging these two measurements after standardization (subtraction of the mean and division by the SD for the measurement)¹² | Presence of a stenosis of ≥25% in the internal or common carotid artery¹³ |
| Increased carotid artery IMT                                                  | An extreme increase of common carotid artery IMT ≥1 mm¹⁴ | |
| Extreme increase of common carotid artery IMT                                 | Presence of a stenosis of ≥25% in the internal or common carotid artery¹³ | |
| Carotid artery stenosis ≥25%                                                  | An ankle-brachial index at or below 0.9 in either leg¹³,¹⁵ | |
| Peripheral arterial disease                                                   | Defined as the ratio of the average systolic blood pressure at the ankle of each leg divided by the average systolic blood pressure in the arm with the highest blood pressure. | |
| Glomerular endothelial dysfunction                                             | An urine albumin-to-creatinine ratio ≥25 μg/mg in men, and ≥35 μg/mg in women¹⁶ | Presence of microalbuminuria according to the definition |
LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IMT, intima media thickness; LV, left ventricular; SD, standard deviation. *Copyright 2007 American Diabetes Association. From Diabetes®, Vol. 56, 2007; 1718-1726. Reprinted with permission from The American Diabetes Association.
Table S2. Baseline characteristics of the subclinical disease sample by blood pressure group

| Blood pressure (in mm Hg) group | <120/80 (N=640) | 120/80-140/90 (N=608) | <140/90 on Rx (N=223) | ≥140/90 (N=243) | ≥140/90 on Rx (N=201) | p for trend |
|---------------------------------|------------------|-----------------------|-----------------------|------------------|-----------------------|-------------|
| **Clinical and biochemical features** |                  |                       |                       |                  |                       |             |
| Age, years; mean ± SD           | 52.9 ± 8.3       | 57.3 ± 9.1            | 59.5 ± 8.3            | 61.3 ± 8.7       | 65.3 ± 8.4            | <0.0001     |
| Women n, (%)                    | 415 (64.8)       | 349 (57.4)            | 115 (51.6)            | 139 (57.2)       | 110 (54.7)            | 0.0022      |
| Systolic BP, mmHg; mean ± SD    | 109 ± 7          | 128 ± 7               | 125 ± 10              | 152 ± 13         | 155 ± 15              | <0.0001     |
| Diastolic BP, mmHg; mean ± SD   | 68 ± 6           | 77 ± 7                | 75 ± 8                | 83 ± 9           | 82 ± 10               | <0.0001     |
| Hypertension treatment, (%)     | 0 (0.0)          | 0 (0.0)               | 223 (100.0)           | 0 (0.0)          | 201 (100.0)           | <0.0001     |
| Body Mass Index, kg/m²; mean ± SD | 25.9 ± 4.1       | 27.3 ± 4.5            | 28.6 ± 5.4            | 27.7 ± 4.6       | 28.2 ± 4.4            | <0.0001     |
| Smoking, n (%)                  | 117 (18.3)       | 81 (13.3)             | 22 (9.9)              | 34 (14.1)        | 13 (6.5)              | <0.0001     |
| Diabetes, n (%)                 | 11 (1.7)         | 23 (3.8)              | 27 (12.1)             | 19 (7.8)         | 29 (14.4)             | <0.0001     |
| Total cholesterol, mg/dL; mean ± SD | 199 ± 36         | 211 ± 38              | 202 ± 34              | 214 ± 38         | 209 ± 39              | <0.0001     |
| HDL cholesterol, mg/dL; mean ± SD | 55 ± 15          | 54 ± 16               | 49 ± 16               | 53 ± 16          | 50 ± 17               | <0.0001     |

| Measures of subclinical disease |                  |                       |                       |                  |                       |             |
|---------------------------------|------------------|-----------------------|-----------------------|                  |                       |             |
| Subclinical disease score (unadjusted) mean SD | 0.29 ± 0.53 | 0.47 ± 0.69 | 0.94 ± 0.94 | 0.79 ± 0.77 | 1.17 ± 1.01 | <0.0001     |
| Prevalence of subclinical disease (score ≥1), (%) | 166 (25.9) | 222 (36.5) | 136 (61.0) | 145 (59.7) | 145 (72.1) | <0.0001     |
| LVH, echocardiographically or electrocardiographically, (%) | 69 (10.8) | 103 (16.9) | 82 (36.7) | 65 (26.8) | 80 (39.8) | <0.0001     |
| LV systolic dysfunction, (%)     | 16 (2.5)         | 17 (2.8)              | 14 (6.3)              | 6 (2.5)          | 9 (4.5)               | 0.1403      |
| Carotid ultrasound abnormality, (%) | 5 (0.8)        | 14 (2.3)              | 14 (6.3)              | 22 (9.1)         | 21 (10.5)             | <0.0001     |
| Peripheral artery diseas (ABI ≤ 0.9), (%) | 2 (0.3)        | 7 (1.2)               | 7 (3.1)               | 4 (1.7)          | 9 (4.5)               | <0.0001     |
| Microalbuminuria, (%)            | 37 (5.8)         | 32 (5.3)              | 31 (13.9)             | 28 (11.5)        | 37 (18.4)             | <0.0001     |

Rx indicates blood pressure lowering medication; BP, blood pressure; SD, standard deviation; HDL, high-density lipoprotein; GFR, glomerular filtration rate
Table S3. Hazard ratio for incident CVD in different statistical models, with and without adjustment for a propensity score

| BP group   | BP treatment | HR (95% CI)* | HR (95% CI)** | HR (95% CI)+ | HR (95% CI)** + | HR (95% CI)*** |
|------------|--------------|--------------|---------------|--------------|-----------------|----------------|
| 1 <120/80  | No           | 1            | 1             | 1            | 1               | 1              |
| 2 120/80≤140/90 | No       | 1            | 1             | 1            | 1               | 1              |
| 3 <140/90  | Yes          | 1.64 (1.25, 2.15) | 1.50 (1.13, 1.99) | 1.58 (1.18, 2.12) | 1.46 (1.09, 1.94) | 1.17 (0.79, 1.75) |
| 4 ≥140/90  | No           | 1            | 1             | 1            | 1               | 1              |
| 5 ≥140/90  | Yes          | 1.32 (0.98, 1.77) | 1.28 (0.94, 1.73) | 1.24 (0.92, 1.68) | 1.27 (0.94, 1.72) | 1.05 (0.72, 1.54) |

*adjusted for age and sex

** adjusted for age, sex, total/HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use and estimated glomerular filtration rate

+ adjusted for the propensity score only

***+ adjusted for age, sex, total/HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use, estimated glomerular filtration rate and the propensity score

*** adjusted for age, sex, total/HDL cholesterol, intake of lipid-lowering medication, smoking, and diabetes, aspirin use, estimated glomerular filtration rate, duration of hypertension and duration of hypertension treatment
Supplemental Figures

Figure S1. Multivariable-adjusted Relative Risks for presence of subclinical disease (score ≥1) by blood pressure group

Relative risk for subclinical disease

Relative Risk (95% CI)

<120/80 ≥120/80 and <140/90 <140/90 + Rx ≥140/90 ≥140/90 + Rx

BP group

1.06 1.25 1.48 1.58 2.23 1.52 2.14 1.58 2.22 1.87 1.81 1.88
Figure S2. Odds ratio for select subclinical disease abnormalities, stratified by BP group

LVH, left ventricular hypertrophy; LV, left ventricular; US, ultrasound; PAD, peripheral artery disease
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