Assessment by Cardiovascular Magnetic Resonance, Electron Beam Computed Tomography, and Carotid Ultrasonography of the Distribution of Subclinical Atherosclerosis Across Framingham Risk Strata

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Screening for subclinical atherosclerosis has been advocated for individuals at intermediate global risk for coronary heart disease (CHD). However, the distribution of subclinical atherosclerosis test values across CHD risk strata is unknown. We studied a stratified random sample of 292 participants (mean age 59.5 years, 50% women) from the offspring cohort of the Framingham Heart Study who were free of clinically apparent cardiovascular disease. We assessed abdominal and thoracic aortic plaque burden by cardiovascular magnetic resonance (CMR), coronary artery calcification (CAC) and thoracic aortic calcification (TAC) by electron beam computed tomography, and common carotid intima-media thickness (C-IMT) by ultrasonography. We categorized the upper 20% of each measurement as a high level of atherosclerosis and evaluated these variables across clinically relevant Framingham CHD risk score strata (low, intermediate, and high risk). In age-adjusted analyses in men and women, correlations across CMR aortic plaque, CAC, TAC, and C-IMT were low (maximum r = 0.30 for CAC:TAC in women, p <0.005). In men and women, the proportion of subjects with high atherosclerosis test results for any of these measurements increased significantly across Framingham CHD risk score strata (Kruskal-Wallis test, p <0.0001). In the intermediate Framingham CHD risk score category, 14% of men and 25% of women had a high atherosclerosis result on ≥2 measurements. However, different participants were identified as having high atherosclerosis by each modality. For example, in a comparison of the overlap across CMR aortic plaque, CAC, and C-IMT, only 4% of men and 16% of women were classified as having high atherosclerosis on all 3 measurements. In conclusion, in a community-based sample, correlations among subclinical atherosclerosis test results are low, and a substantial proportion has high levels of subclinical atherosclerosis detected on ≥2 imaging tests. **(Am J Cardiol 2007;99:310–314)**

In a stratified sample of Framingham Heart Study participants free of clinical cardiovascular disease, we sought to (1) establish the inter-relations across 4 subclinical atherosclerosis measurements detected by 3 imaging techniques, i.e., abdominal and thoracic aortic plaque burden by cardiovascular magnetic resonance (CMR), coronary artery calcification (CAC) and thoracic aortic calcification (TAC) by electron beam computed tomography, and carotid intima-media thickness (C-IMT) by ultrasound; (2) define whether these techniques identify the same participants as "at risk"; and (3) examine if the distribution of imaging test results differs across coronary heart disease (CHD) risk categories.

Methods

Participants: The recruitment procedure has been previously described.[1] Briefly, the present study was designed as a pilot study to evaluate several subclinical atherosclerosis imaging tests in the Framingham Heart Study offspring cohort. The subjects represent a stratified sample of participants from the offspring cohort of the Framingham Heart Study. Initially recruited in 1971, the offspring cohort consisted of 5,124 subjects 5 to 70 years of age, and each subject has been examined approximately every 4 years.[2]

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Table 1
Baseline characteristics

Variable	Men (n = 146)	Women (n = 146)
Age (yrs)	59 ± 9	60 ± 9
Total cholesterol (mg/dl)	204 ± 37	216 ± 37
High-density lipoprotein cholesterol (mg/dl)	43 ± 13	56 ± 16
Systolic blood pressure (mm Hg)	130 ± 18	128 ± 19
Current cigarette smoker	16%	12%
Diabetes mellitus	12%	8%
Body mass index (kg/m^2)	28.9 ± 4.2	27.7 ± 6.4
Framingham CHD risk score (%)	16.9 ± 11.9	8.5 ± 6.5

Values are expressed as mean ± SD unless otherwise indicated.

Table 2
Subclinical atherosclerosis imaging test values

Atherosclerotic Measurement	Categories of Atherosclerotic Burden		
	Low*	Middle†	High‡
Men (n = 146)			
CMR aortic plaque burden (%)	0	5.1 ± 0.44	13.0 ± 4.6
No.	83	33	30
Range	0	4.6–6.3	9.1–26.3
CAC Agatston score	14 ± 20	177 ± 81	1,106 ± 679
No.	73	43	30
Range	0–75	75–320	340–2,538
TAC Agatston score	11 ± 16	209 ± 125	2,412 ± 4,113
No.	75	44	30
Range	0–65	66–466	574–23,304
C-IMT (mm)	0.53 ± 0.05	0.65 ± 0.03	0.85 ± 0.14
No.	72	44	30
Range	0.42–0.61	0.61–0.72	0.72–1.42
Women (n = 146)			
CMR aortic plaque burden (%)	0	5.2 ± 0.3	14.3 ± 8.6
No.	88	26	32
Range	0	4.8–5.6	5.9–42.1
CAC Agatston score	0.3 ± 0.6	47 ± 36	429 ± 322
No.	73	43	30
Range	0.0–2.7	4–133	135–1,460
TAC Agatston score	13 ± 19	381 ± 290	2,770 ± 1,562
No.	73	43	30
Range	0–66	72–1141	1,270–7,129
C-IMT (mm)	0.49 ± 0.04	0.60 ± 0.02	0.74 ± 0.12
No.	73	43	30
Range	0.41–0.56	0.56–0.63	0.64–1.24

Values are expressed as mean ± SD.
* Represents lower 50% of test results.
† Represents 51st to 80th percentile of test results.
‡ Represents 81st to 100th percentile of test results.

The collection of cardiovascular risk factor information has been previously described.[2] Of the initial 3,219 participants attending examination cycle 6 (1995 to 1998), 349 were excluded from sampling due to clinical cardiovascular disease, 357 who lived outside of New England, and 7 who were not 35 to 84 years of age. The remaining 2,506 participants were stratified by gender, age quartiles, and Framingham CHD risk score quintiles. Participants were sampled randomly from each of 24 strata as previously described.[1] Thus, the participants sampled represent the spectrum of age, gender, and Framingham risk score seen in the offspring cohort.

Table 3
Correlations across subclinical atherosclerosis Imaging Measurements

Atherosclerotic Measurements	Age Adjusted	Age FCRS Adjusted
Men		
CMR: CAC	0.07	0.02
CMR: TAC	0.23*	0.19†
CMR: IMT	0.08	0.03
CAC: TAC	0.22†	0.17†
CAC: IMT	0.13	0.08
TAC: IMT	0.17†	0.11
Women		
CMR: CAC	0.19†	0.17†
CMR: TAC	0.23*	0.21†
CMR: IMT	0.11	0.08
CAC: TAC	0.30*	0.27*
CAC: IMT	0.19†	0.13
TAC: IMT	0.12	0.08

Spearman correlations between aortic plaque burden by CMR, CAC, TAC, and IMT.
* $p < 0.005$; † $p < 0.05$.

Of the 331 participants selected, 39 were excluded, including 13 who declined consent for CMR, 20 with technically inadequate CMR studies, and 6 without carotid ultrasonograms. The remaining 292 participants had successful imaging with all 3 techniques and form the basis for this report. Each of the 3 techniques was interpreted independently and completely blinded to results from other methods and risk factor status.

The institutional review board at Boston Medical Center (Boston, Massachusetts) approved the Framingham Heart Study examination and carotid ultrasonographic protocols. Institutional review boards at Boston Medical Center and Beth Israel Deaconess Medical Center (Boston, Massachusetts) approved the CMR and electron beam computed tomographic protocols. All participants gave written informed consent.

Cardiovascular magnetic resonance: CMR imaging was conducted as previously described.[3] Briefly, participants underwent thoracoabdominal aortic CMR using a commercial 1.5-T whole-body CMR system (Gyroscan ACS-NT, Philips Medical Systems, Shelton, Connecticut) with a PowerTrak 6000 gradient system (peak gradient 23 mT/m, rise time 219 ms). Twenty-four, 10-mm thick, transverse slices with a 10-mm gap spanning the aortic arch to the aortoiliac bifurcation were obtained using a free-breathing electrocardiographically gated, black-blood T2-weighted turbo spin-echo sequence as previously described.[3] An average of 19 aortic images per participant was available, and ~1 image per subject was excluded from image analysis due to artifacts, residual blood signal, or insufficient signal-to-noise ratio.[3]

Reviewers blinded to all clinical data analyzed CMR plaque data. Atherosclerotic plaque was defined as characteristic luminal protrusions ≥1 mm in radial thickness.[3,4] Atherosclerotic burden was quantified for each subject by calculating aortic plaque burden as follows: aortic plaque

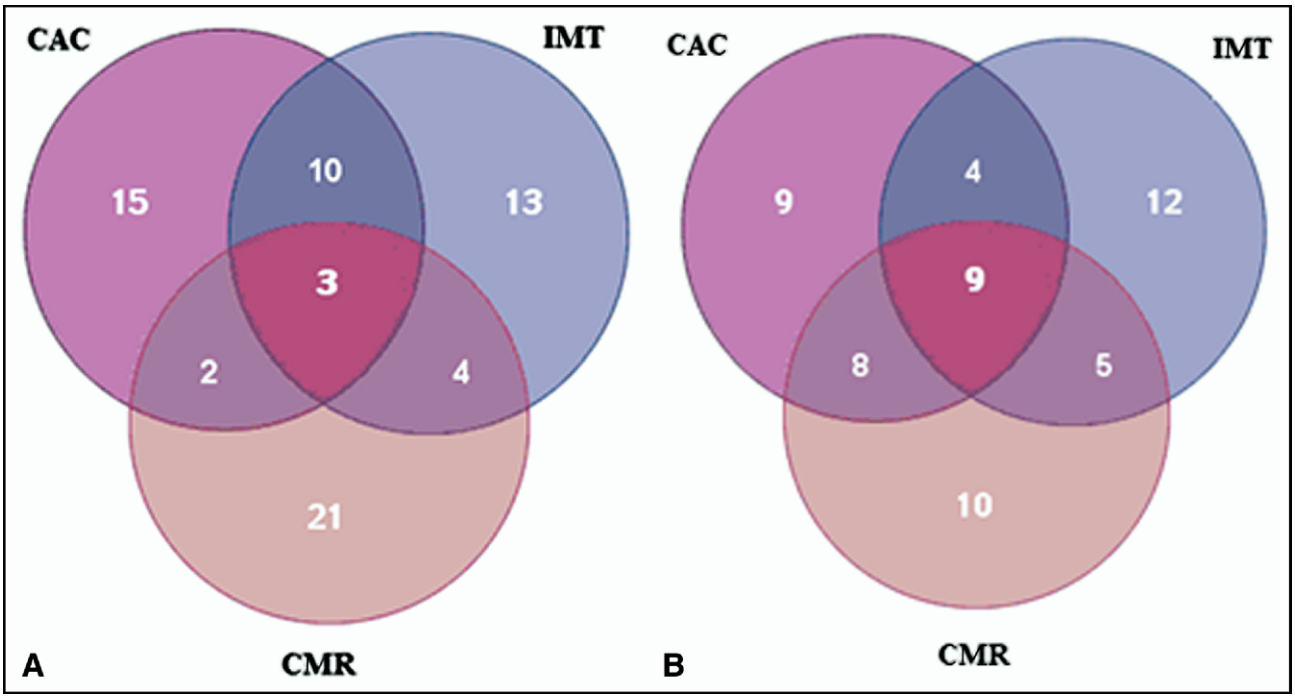

Figure 1. Overlap of high atherosclerosis test results on aortic plaque burden by CMR, CAC, and C-IMT in *(A)* men and *(B)* women. Values in the Venn diagram represent numbers of participants. In total, 68 men and 57 women had a high atherosclerosis test result on ≥1 test.

burden (percentage) = 100 × (number of aortic slices with plaque/number of total aortic slices).[3]

Carotid ultrasonography: Imaging was conducted as previously described.[5] Briefly, using a high-resolution 7.5-MHz transducer, diastolic images were obtained at the level of the distal common carotid artery on the left and right sides. Mean C-IMT measurements in the near and far walls on each side were averaged. C-IMT was defined as the mean of the mean IMT measurement of the left and right common carotid arteries.

Electron beam computed tomographic imaging: Electron beam computed tomograms were obtained with an Imatron C-150 XP scanner (GE Medical Systems, Milwaukee, Wisconsin) in accordance with previously published protocols.[6,7] We obtained 40 to 45 3-mm axial slices during 2 breath holds from the apex of the aortic arch to the diaphragm. Image analysis for CAC used a threshold of >130 Hounsfield units. Each scan was assessed by a technologist and over-read by an experienced radiologist blinded to clinical data. CAC and TAC scores were calculated using the method described by Agatston et al.[6]

Statistical analysis: Due to different distributions of subclinical atherosclerotic measurements in men and women, all analyses were gender specific. The 10-year Framingham CHD risk score was determined for each participant according to previously published criteria[8] using risk factor information from examination cycle 6 (1995 to 1998). We computed Spearman's correlations using continuous values of CMR aortic plaque, CAC Agatston score, TAC Agatston score, and C-IMT. After initial computations using age adjustment, correlations were calculated with adjustments for age and Framingham CHD risk score.[9] Spearman's correlations were computed because CMR aortic plaque, CAC, TAC, and C-IMT had skewed distributions.

Because ≥50% of participants had no plaque on CMR images, we adopted a scheme a priori to classify atherosclerotic measurements (measurements in the top 20% were categorized as a high level of atherosclerosis, measurements in the 51st to 80th percentile as intermediate, and those in the lowest 50% as low). We separately categorized men and women based on gender-specific distributions for each imaging test.

We calculated the number of high test results for each subject (0 to 4) and then compared distributions across Framingham CHD risk score risk categories by the Kruskal-Wallis test. All analyses were performed with SAS.[9] A 2-sided p value <0.05 was considered statistically significant.

Results

Characteristics of the 292 participants (50% women) who underwent all 3 imaging techniques are listed in Table 1. Patients' average age was 59.5 years (range 36 to 78). The distribution of test values for each measurement is presented in Table 2.

Spearman's correlations across CMR aortic plaque, CAC, TAC, and C-IMT are listed in Table 3. In age-adjusted analyses in men and women, correlations across CMR aortic plaque, CAC, TAC, and C-IMT were low (maximum r = 0.30 for CAC:TAC in women, p <0.005). After adjustment for age and Framingham CHD risk score, all correlations were attenuated and correlations for CMR:TAC and CAC:TAC in men and CMR:CAC, CMR:TAC, and CAC:TAC in women remained statistically significant.

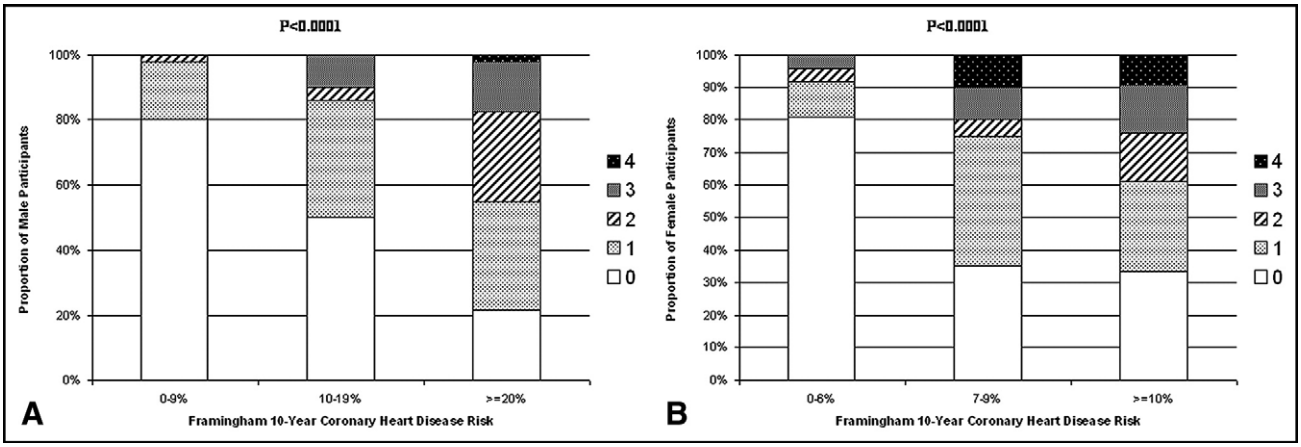

Figure 2. Proportions of *(A)* men and *(B)* women with a high atherosclerosis result on 0, 1, 2, 3, or 4 atherosclerosis tests (CMR, TAC, CAC, C-IMT) stratified by 10-year Framingham CHD risk score ($p < 0.001$ for the 2 comparisons).

We sought to determine whether the same participants were classified as at risk by the 4 atherosclerotic imaging tests. For this analysis, we categorized an atherosclerotic test result as high atherosclerosis if the value was in the top 20% of the gender-specific distribution. Of the 292 participants studied, 68 men and 57 women had ≥1 high atherosclerosis test result. The overlap of high atherosclerosis test results for CMR aortic plaque, CAC, and C-IMT in men and women is shown in Figure 1. Of the 68 men with a high atherosclerosis test result, only 3 (4%) were categorized as having high atherosclerosis on all 3 measurements (Figure 1). Of the 57 women with a high atherosclerosis test result on ≥1 measurement, only 9 (16%) were categorized as having high atherosclerosis on all 3 measurements (Figure 1).

The proportion of men and women who had 0, 1, 2, 3, or 4 high atherosclerosis test results across Framingham CHD risk score strata is displayed in Figure 2. In men and women, the proportion of participants with 0, 1, 2, 3, or 4 high test values differed significantly across the 3 Framingham CHD risk score strata (Kruskal-Wallis test, $p < 0.0001$). In women, the proportion of participants with ≥2 high atherosclerotic measurements increased across Framingham CHD risk score categories (8% in low, 25% in intermediate, and 39% in high Framingham CHD risk score strata). Similar results were seen in men. In men in the intermediate Framingham CHD risk score category (34% of men), 14% of participants had a high atherosclerosis result on ≥2 measurements, 36% on 1 measurement, and 50% on 0 measurement (Figure 2). Similar results were seen in women (Figure 2).

Discussion

In a community-based sample free of clinical cardiovascular disease, we evaluated subclinical atherosclerosis by 4 different imaging techniques: abdominal and thoracic aortic plaque burden by CMR, CAC and TAC by electron beam computed tomography, and C-IMT by ultrasonography. Our principal findings were (1) correlations across atherosclerotic measurements in the various major vascular beds were low; (2) subclinical atherosclerosis tests identified different participants at risk; and (3) in subjects with an intermediate Framingham CHD risk score, a substantial proportion (14% of men, 25% of women) had a high atherosclerosis test value on ≥2 imaging tests. These results suggest that a combination of imaging tests may be useful in risk stratification, and this hypothesis warrants testing in larger studies.

Participants at intermediate global risk for CHD represent a substantial proportion of the population.[10] Based on Bayesian principles, it has been suggested that atherosclerosis imaging tests offer greatest value in individuals at intermediate CHD risk on an office-based global risk assessment.[11] However, to date there are limited data on imaging test results in a general population at intermediate risk.

In men at intermediate CHD risk, we found that 36% of subjects had a high level of atherosclerosis on 1 measurement and 14% had a high level of atherosclerosis on ≥2 measurements. These results suggest that atherosclerosis is reasonably prevalent on imaging tests and therefore may be particularly useful in subjects at intermediate risk. Our findings warrant further trials to confirm the concept that a "positive" test result in patients with intermediate CHD risk may trigger more aggressive preventive strategies, whereas a "negative" test result may lead to reassurance and advice on healthy lifestyle habits.[11] Important issues that should be addressed in such trials will include cost effectiveness, standardization of test measurements, risks and discomforts of testing, risk of radiation, and cost/burden of detecting incidental medical findings.

Some potential limitations need to be considered. First, our study design is cross sectional. The present study was not designed to assess the ability of these tests to predict risk of CHD or other cardiovascular outcomes. To fully define the incremental value of each imaging technique in risk prediction beyond established CHD risk factors, prospective studies using each technique are needed and are underway. Second, the validity of specific cutpoints for a high level of atherosclerosis may be questioned. However, the range for the high atherosclerosis category in our sample reflects test thresholds previously suggested to confer an increased risk of CHD. For example, in the present study, men with a CAC Agatston score ≥340 were classified as having a high level

of atherosclerosis, and CAC scores in this range have been previously associated with an increased risk of CHD.[12] For the high atherosclerosis category in men, mean C-IMT was 0.85 mm. C-IMT values in this range have been associated with an increased risk of myocardial infarction and stroke in elderly adults.[13,14] Third, although our sample represents the largest study to date in the literature to include aortic CMR, the sample in this pilot study is limited, and our results need to be confirmed in larger cohorts. Fourth, our sample was entirely white, so these results may not be generalizable to other ethnicities/races. Fifth, our method of CMR plaque assessment may have underestimated plaque burden as advancements in CMR scanning and interpretation technology have improved imaging resolution. Sixth, correlations across atherosclerotic measurements may be somewhat attenuated by our choice to exclude patients with a clinical history of cardiovascular disease at examination cycle 6.

1. Wang TJ, Larson MG, Levy D, Benjamin EJ, Kupka MJ, Manning WJ, Clouse ME, D'Agostino RB, Wilson PW, O'Donnell CJ. C-reactive protein is associated with subclinical epicardial coronary calcification in men and women: the Framingham Heart Study. *Circulation* 2002; 106:1189–1191.
2. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham Offspring Study. *Am J Epidemiol* 1979;110:281–290.
3. Jaffer FA, O'Donnell CJ, Larson MG, Chan SK, Kissinger KV, Kupka MJ, Salton C, Botnar RM, Levy D, Manning WJ. Age and sex distribution of subclinical aortic atherosclerosis: a magnetic resonance imaging examination of the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 2002;22:849–854.
4. Chan SK, Jaffer FA, Botnar RM, Kissinger KV, Goepfert L, Chuang ML, O'Donnell CJ, Levy D, Manning WJ. Scan reproducibility of magnetic resonance imaging assessment of aortic atherosclerosis burden. *J Cardiovasc Magn Reson* 2001;3:331–338.
5. Wang TJ, Nam BH, D'Agostino RB, Wolf PA, Lloyd-Jones DM, MacRae CA, Wilson PW, Polak JF, O'Donnell CJ. Carotid intima-media thickness is associated with premature parental coronary heart disease: the Framingham Heart Study. *Circulation* 2003;108: 572–576.
6. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832.
7. Achenbach S, Ropers D, Mohlenkamp S, Schmermund A, Muschiol G, Groth J, Kusus M, Regenfus M, Daniel WG, Erbel R, Moshage W. Variability of repeated coronary artery calcium measurements by electron beam tomography. *Am J Cardiol* 2001;87:210–213.
8. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–1847.
9. SAS/STAT User's Guide, Version 8.1. Cary, NC: SAS Institute, 2000.
10. Ford ES, Giles WH, Mokdad AH. The distribution of 10-year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. *J Am Coll Cardiol* 2004;43:1791–1796.
11. Wilson PW, Smith SC Jr, Blumenthal RS, Burke GL, Wong ND. 34th Bethesda Conference: Task force #4—how do we select patients for atherosclerosis imaging? *J Am Coll Cardiol* 2003;41:1898–1906.
12. Kondos GT, Hoff JA, Sevrukov A, Daviglus ML, Garside DB, Devries SS, Chomka EV, Liu K. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. *Circulation* 2003;107: 2571–2576.
13. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 1997;146:483–494.
14. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340: 14–22.