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EXPEDITED PUBLICATION

Impact of Coronary Artery Calcium Scanning on Coronary Risk Factors and Downstream Testing

The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) Prospective Randomized Trial

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Objectives We conducted a prospective randomized trial to compare the clinical impact of conventional risk factor modification to that associated with the addition of coronary artery calcium (CAC) scanning.

Background Although CAC scanning predicts cardiac events, its impact on subsequent medical management and coronary artery disease risk is not known.

Methods We assigned 2,137 volunteers to groups that either did undergo CAC scanning or did not undergo CAC scanning before risk factor counseling. The primary end point was 4-year change in coronary artery disease risk factors and Framingham Risk Score. We also compared the groups for differences in downstream medical resource utilization.

Results Compared with the no-scan group, the scan group showed a net favorable change in systolic blood pressure ($p = 0.02$), low-density lipoprotein cholesterol ($p = 0.04$), and waist circumference for those with increased abdominal girth ($p = 0.01$), and tendency to weight loss among overweight subjects ($p = 0.07$). While there was a mean rise in Framingham Risk Score (FRS) in the no-scan group, FRS remained static in the scan group (0.7 ± 5.1 vs. 0.002 ± 4.9, $p = 0.003$). Within the scan group, increasing baseline CAC score was associated with a dose-response improvement in systolic and diastolic blood pressure ($p < 0.001$), total cholesterol ($p < 0.001$), low-density lipoprotein cholesterol ($p < 0.001$), triglycerides ($p < 0.001$), weight ($p < 0.001$), and Framingham Risk Score ($p = 0.003$). Downstream medical testing and costs in the scan group were comparable to those of the no-scan group, balanced by lower and higher resource utilization for subjects with normal CAC scans and CAC scores ≥400, respectively.

Conclusions Compared with no scanning, randomization to CAC scanning was associated with superior coronary artery disease risk factor control without increasing downstream medical testing. Further study of CAC scanning, including pre-specified treatment recommendations, to assess its impact of cardiovascular outcomes is warranted. (Early Identification of Subclinical Atherosclerosis Using Non-Invasive Imaging Research [EISNER]; NCT00927693)
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Coronary artery calcium (CAC) scanning can predict adverse clinical events (1–4), but its direct impact on future coronary artery disease (CAD) risk and downstream medical costs, relative to that of conventional medical practice, is not yet known. To study this issue, we initiated the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial. This prospective randomized trial was designed to test the primary

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hypothesis that performing CAC scanning of asymptomatic volunteers would lead to a beneficial sustained 4-year effect on their CAD risk factors. Secondarily, we assessed the impact of CAC scanning on downstream medical resource utilization and healthcare costs.

Methods

The trial participants consisted of 2,137 subjects who were recruited between May 2001 and May 2005 at Cedars-Sinai Medical Center (CSMC) (Fig. 1). We preferentially selected middle-aged individuals with CAD risk factors and excluded subjects with a history of cardiac or cerebrovascular disease or chest pain, age ≥80 years, pregnancy, significant medical comorbidity, and prior coronary catheterization or prior CAC scanning. After recruitment, subjects were randomized into a group that was either scheduled for CAC scanning (scan group) or not scheduled for calcium scanning (no-scan group). To encourage subjects' enrollment into our study, the ratio of randomization was 2:1 for receiving a CAC scan. This research was approved by the CSMC institutional review board, and all subjects signed informed consent.

Baseline clinical assessment. Baseline measurements were obtained for the following: fasting total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting serum glucose; systolic and diastolic blood pressure measurements; height; weight; and waist circumference. Physical activity was assessed dichotomously (yes/no) according to subjects' response to the following question: "Do you exercise regularly (3 to 4 times a week) for at least 30 minutes each time?" Ten-year risk of CAD was calculated by the Framingham Risk Score (FRS) in accordance with published guidelines (5,6). Subjects with diabetes mellitus were automatically assigned a high risk FRS of 20%, or higher if so calculated (6).

Risk factor counseling. At the baseline examination, one of our nurse practitioners, each having been trained regarding the need for impartiality and consistency in counseling, conducted a private risk factor counseling session. To further standardize counseling, the nurse practitioner printed a customized risk factor management packet for each subject containing the American Heart Association guidelines on cardiac risk factors (7), subjects' results for each risk factor, and information on how to improve their risk profiles. The nurse practitioner reviewed the packet with each subject first, and then additionally also reviewed the CAC images, and CAC score and percentile score with subjects in the scan group. Subjects were instructed that the presence of any calcium constituted evidence of atherosclerosis. To preserve subject anonymity as required by our institutional review board, test results were not sent directly to subjects' physicians, but subjects were given 2 copies of their anonymized CAC scan report and were encouraged to share their results with their physician.

Coronary calcium scanning. Scanning was performed using electron beam (GE-Imatron Inc., San Francisco, California) or multislice computed tomography (Siemens Medical Systems, Forchheim, Germany). The imaging protocol involved acquiring a single scan of ~30 to 40 slices of 3 or 2.5 mm thickness (8). Foci of CAC were identified by an experienced radiographic technologist and scored using semiautomatic commercial software on a NetraMD workstation. Total calcium score was determined by summing lesion-specific scores, calculated as the product of the area of each calcified focus and peak CT number derived according to the Agatston method (9). Estimated radiation dose ranged from 1 to 2 mSv.

Abbreviations and Acronyms

- **CAC** = coronary artery calcium
- **CAD** = coronary artery disease
- **CI** = confidence interval
- **CSMC** = Cedars-Sinai Medical Center
- **FRS** = Framingham Risk Score
- **HDL** = high-density lipoprotein
- **LDL** = low-density lipoprotein
- **OR** = odds ratio

4-year clinic visit. Trial participants were asked to return for a follow-up clinic visit at 4 years, during which all assessments obtained at baseline were repeated and CAC scanning was performed in all subjects. Of the 2,137 enrolled subjects, 713 (33.4%) were randomized to the no-scan group and 1,424 (66.6%) to the scan group (Fig. 1). Of these, 584 (81.9%) no-scan and 1,256 (88.2%) scan subjects completed the follow-up clinic evaluation and questionnaire ($p < 0.001$). There were 35 (4.9%) no-scan subjects and 38 (2.7%) scan subjects who could not return for the follow-up clinic evaluation and completed the questionnaire only; these subjects were not assessed for clinic-determined risk factors at 4 years. Within the no-scan group, 52 (7.3%) were lost to follow-up, 17 (2.4%) withdrew from the trial, and 4 (0.6%) died before 4-year follow-up. Within the scan group, 61 (4.3%) were lost to follow-up, 13 (0.9%) withdrew, and 17 (1.2%) died before follow-up. There were 21 (2.9%) no-scan subjects and 39 (2.7%) scan subjects who indicated they met eligibility criteria at enrollment but later disclosed an exclusion criterion that resulted in their subsequent exclusion. Three no-scan subjects and 8 scan subjects did not undergo repeat CAC scanning at the time of their 4-year clinic visit.

Primary outcomes. The primary outcome of our trial was change in CAD risk profiles at 4 years among the scan subjects versus no-scan subjects, including change in global risk as assessed by the FRS.

Secondary outcomes. Secondary outcomes included comparison of the randomized groups relative to rates of downstream tests and procedures, health care costs, and occurrence of adverse clinical events. To assess costs, we applied nationwide, average Medicare diagnosis-related group reimbursement rates using the PC Pricer prospective payment system estimator. Outpatient service costs were derived by use of the outpatient prospective payment amounts (nationwide and specific locality) based on healthcare common procedure codes. The Medicare planner for retail and mail-order pharmacy charges were used to derive drug costs in our

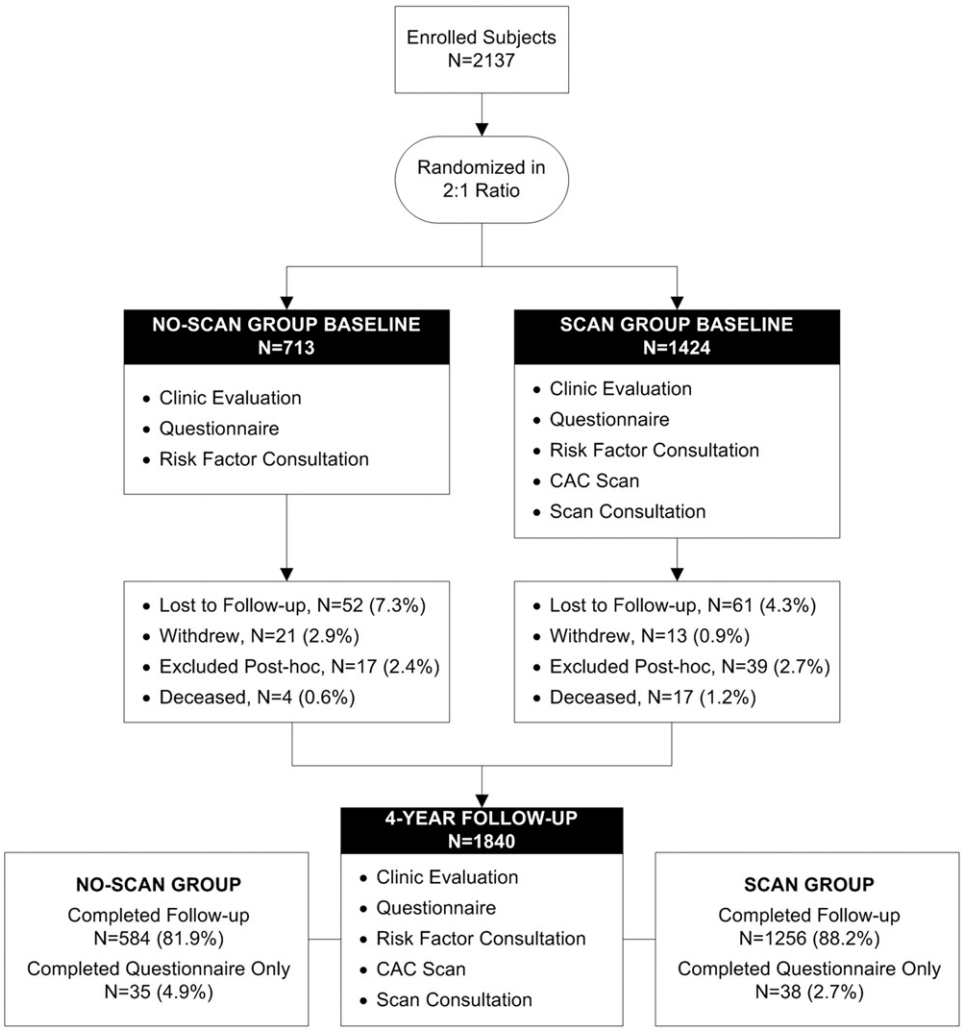

Figure 1 **Summary of Trial Design and Subject Disposition at 4-Year Follow-Up**

CAC = coronary artery calcium.

trial (10). Costs were inflation-adjusted and discounted at a rate of 3% per year. A $150 charge was assigned for CAC scanning (although it was performed at no charge). Clinical events included cardiac and all-cause death and nonfatal myocardial infarction. Cause of death status was confirmed by medical record review. Diagnosis of myocardial infarction was confirmed by enzymatic elevation and electrocardiographic changes consistent with acute infarction.

Statistical analyses. Changes in risk factors were mainly expressed as the clinical value at 4 years minus the value at baseline, with negative change indicating a reduction in risk factor. All data were analyzed using STATA version 11 (StataCorp, College Station, Texas). Continuous variables were expressed as mean ± SD or median (25th, 75th percentiles) and compared using 2-sample *t* tests for approximately normal variables or Wilcoxon rank-sum test for non-normal variables. Likewise, continuous variables in >2 groups were compared using 1-way analysis of variance or Kruskal-Wallis test for non-normal variables, and if ordered, were also tested using Cuzick's test for trend. Categorical variables were compared using Pearson's chi-square test or Fisher exact test where there were cell counts of <6. Ordered categorical variables were further assessed using the chi-square test for trend. Annual event rates were calculated as the % number of events divided by person-years. Progression of CAC scores in the scan group were assessed by comparing the CAC score at 4 years to that at baseline. Relative change in CAC scores were assessed according to the formula developed by the MESA (Multi-Ethnic Study of Atherosclerosis) study: $\ln(\text{CACy4}+25) - \ln(\text{CACbl}+25)$. We identified progression of CAC to have occurred if subjects converted from a negative to a positive scan or if subjects were ≥75th percentile for progression by the MESA formula. All clinically relevant predictors were tested using logistic regression with progression as the outcome both

alone and in conjunction with age, sex, and length of follow-up time. Furthermore, both forward and backward stepwise logistic regression were used to find the best predictors of progression, where candidate variables with a p value <0.05 were entered and those with a p value >0.10 were removed from the model. Separate models were made for baseline and treatment variables before combining into a single overall model. Models were evaluated for goodness of fit and other parameters (results not shown). A p value <0.05 was considered significant.

Results

Subject characteristics. The clinical characteristics of the 2 randomized groups are shown in Table 1. The 2 groups were comparably matched in terms of age, sex, socioeconomic factors, cardiac risk factors, medication use, and FRS.

Comparison of CAD risk factors at 4 years in the randomized groups. Table 2 shows the change in CAD risk factor status in the randomized groups at 4-year follow-up. Compared with the no-scan group, the scan group had significantly greater reduction in systolic blood pressure and serum LDL cholesterol levels, reduction in waist circumference for those with increased abdominal girth at baseline, and modest tendency towards less weight gain among subjects who were overweight (body mass index ≥25 kg/m^2). There was no significant difference between the 2 groups with respect to HDL cholesterol, triglyceride, and glucose levels; smoking cessation; and new exercise activity. Notably, the 4-year mean FRS score increased in the no-scan group compared with baseline FRS (0.7 ± 5.1), but remained essentially unchanged in the scan group (0.002 ± 4.9, p = 0.003) even though they were 4 years older.

Comparison of medical resource utilization in the randomized groups. More scan than no-scan subjects had initiation of new antihypertensive medication use, and there was a modest tendency toward greater use of lipid-lowering medications. Within both groups, continuation of lipid lowering and antihypertensive medication remained high at 4 years for those on these medications at baseline. As shown in Table 2, the 2 randomized groups did not differ in 4-year utilization of stress tests, carotid ultrasound studies, noninvasive and invasive coronary angiogram studies, and revascularization procedures. The overall medical procedure costs were comparable in both randomized groups, although medication costs tended to be higher in the scan group.

Comparison of clinical events in the randomized groups. Within our study population, there were 3 cardiac deaths (annualized cardiac mortality rate of 0.04%) and 21 all-cause deaths (annualized all-cause mortality rate of 0.3%). One cardiac death (0.2%) and 4 all-cause deaths (0.6%) occurred in the no-scan group, and 2 cardiac deaths (0.2%) and 17 all-cause deaths (1.3%) occurred in the scan group (p = 1.00 for cardiac and p = 0.24 for all-cause mortality). Myocardial infarction occurred in 2 (0.3%) no-scan subjects and 10 (0.8%) scan subjects (p = 0.36). The combined number of deaths and/or myocardial infarction were 6 (1.0%) in the no-scan group and 27 (2.1%) in the scan group (p = 0.08).

Impact of baseline CAC score on 4-year CAD risk profiles. Within the scan group, increasing baseline CAC score was associated with a proportionally greater improvement in most CAD risk factors at follow-up (Table 3). An inverse dose-response relationship was observed between increasing baseline CAC scores and systolic and diastolic blood pressure, serum cholesterol, LDL cholesterol, and triglycerides. In addition, greater weight loss was noted among overweight subjects with CAC scores ≥100 at baseline, and for subjects with increased abdominal girth, the greater decline occurred among those with CAC scores ≥400 at baseline. There was also a trend toward more exercise with increasing CAC scores. The FRS rose in subjects with a zero CAC score, but decreased in subjects with evidence of CAC at baseline.

Impact of baseline CAC score on medical resource utilization. A progressive increase in new cardiac medications occurred with increasing baseline CAC scores, particularly for lipid-lowering medications. Among subjects on medications at baseline, adherence rates at 4 years were high for use of lipid-lowering and antihypertensive medications. The frequency of both noninvasive and invasive procedures as well as procedural costs also increased with increasing baseline CAC scores, but the rate of catheterization and revascularization was low in all groups. Procedural costs were low for subjects with no CAC and much higher for subjects with CAC scores ≥400.

Comparison of the no-scan group to subjects with a normal baseline CAC scan. Comparison of the no-scan randomized group to the scan subgroup with normal CAC scans (CAC score = 0) is shown in Table 4. There was no difference between these groups in 4-year CAD risk profiles, although the normal scan subjects had lower rates of initiation of new lipid medication. Similarly, adherence to baseline medications did not differ between these groups. Lower downstream rates of noninvasive tests and invasive procedure utilization were noted for subjects with normal CAC scans. Overall, incurred costs were lower in the normal scan subjects compared with the no-scan subjects, including 37% lower procedures costs (p = 0.001) and 26% lower medication costs (p = 0.005).

Assessment of CAC scores at 4 years. The CAC score at 4 years was mean 147 ± 335, or median 11 (0, 124) in the no-scan group and mean 163 ± 431 or median 12 (0, 124) in the scan group (p = 0.89). The distribution of CAC scores was similar between the no-scan and scan groups at 4 years: 43% and 42% had a zero CAC score, 29% and 31% had a CAC score of 1 to 99, 18% and 17% had CAC scores of 100 to 399, and 11% in both groups had CAC scores ≥400 (p = 0.75 for all subgroups). Overall, 385 (31%) of the 1,248 scan subjects showed conversion from a normal to abnormal CAC scan (n = 73) or change in CAC score that was >75th percentile for progression by the MESA formula (n = 273) or both (n = 39). In the baseline predictors model

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Table 1 Baseline Characteristics

Parameters	Overall (n = 1,934)	No-Scan Group (n = 623)	Scan Group (n = 1,311)	p Value
Age, yrs	58.5 ± 8.4	58.4 ± 8.2	58.6 ± 8.5	0.75
Male	1,015 (52.5%)	327 (52.5%)	688 (52.5%)	1.00
Race/ethnicity				
Caucasian	1,487 (77.0%)	493 (79.1%)	994 (76.0%)	
African-American	97 (5.0%)	26 (4.2%)	71 (5.4%)	
Asian/Pacific Islander	202 (10.5%)	62 (10.0%)	140 (10.7%)	
Hispanic/Latino	81 (4.2%)	23 (3.7%)	58 (4.4%)	
Other	64 (3.3%)	19 (3.0%)	45 (3.4%)	0.59
Level of education				
<High school	13 (0.7%)	3 (0.5%)	10 (0.8%)	
High school/tech	156 (8.3%)	43 (7.1%)	113 (8.9%)	
Some college	412 (21.9%)	137 (22.5%)	275 (21.6%)	
College	533 (28.3%)	197 (32.3%)	336 (26.4%)	
Graduate education	767 (40.8%)	230 (37.7%)	537 (42.3%)	0.87*
Annual income				
<$20,000	75 (4.2%)	26 (4.5%)	49 (4.0%)	
$20,000–$39,000	188 (10.5%)	58 (10.0%)	130 (10.7%)	
$40,000–$59,000	262 (14.6%)	77 (13.3%)	185 (15.3%)	
$60,000–$79,000	289 (16.1%)	97 (16.8%)	192 (15.8%)	
$80,000–$99,000	243 (13.6%)	78 (13.5%)	165 (13.6%)	
≥$100,000	734 (41.0%)	243 (42.0%)	491 (40.5%)	0.55*
Cardiac risk factors				
Hypertension	1,108 (57.3%)	355 (57.0%)	753 (57.4%)	0.85
High cholesterol	1,498 (77.5%)	468 (75.1%)	1,030 (78.6%)	0.09
Diabetes mellitus	158 (8.2%)	52 (8.4%)	106 (8.1%)	0.85
Past smoker	803 (41.5%)	254 (40.8%)	549 (41.9%)	0.65
Current smoker	111 (5.7%)	37 (5.9%)	74 (5.6%)	0.80
Family history of CAD	513 (26.5%)	155 (24.9%)	358 (27.3%)	0.26
Body mass index, kg/m^2	26.4 (23.9, 29.9)	26.3 (23.8, 29.7)	26.5 (23.9, 29.9)	0.23
Waist circumference, inches	36 (32.5, 39)	36 (32.3, 39)	36 (32.5, 39.3)	0.36
Medications				
BP medications	622 (32.2%)	199 (32.1%)	423 (32.3%)	0.94
ACE inhibitors	205 (10.6%)	62 (10.0%)	143 (10.9%)	0.54
Beta-blockers	168 (8.7%)	64 (10.3%)	104 (8.0%)	0.08
Calcium-channel blockers	112 (5.8%)	29 (4.7%)	83 (6.4%)	0.15
Diuretics	225 (11.7%)	78 (12.6%)	147 (11.2%)	0.39
ARBs	104 (5.4%)	31 (5.0%)	73 (5.6%)	0.60
Others	51 (2.7%)	13 (2.1%)	38 (2.9%)	0.30
Lipid medications	501 (26.0%)	169 (27.3%)	332 (25.4%)	0.37
Statins	452 (23.5%)	152 (24.6%)	300 (22.9%)	0.43
Niacin	35 (1.8%)	11 (1.8%)	24 (1.8%)	0.93
Other lipid medications	56 (2.9%)	20 (3.2%)	36 (2.8%)	0.56
Diabetic medications	79 (4.1%)	28 (4.5%)	51 (3.9%)	0.53
Aspirin	246 (12.8%)	87 (14.1%)	159 (12.2%)	0.24
Clinical laboratory values, mg/dl				
Total cholesterol	213 (187, 239)	213 (187, 238)	213 (187, 240)	0.44
HDL cholesterol	52 (42, 65)	53 (42, 65)	52 (42, 64)	0.58
LDL cholesterol	132 (110, 157)	130 (109, 155)	133 (111, 158)	0.15
Triglycerides	112 (79, 164)	113 (78, 166)	112 (79, 161)	0.99
Fasting glucose	93 (86, 101)	94 (86, 101)	93 (86, 101)	0.40
Systolic BP, mm Hg	131 (120, 143)	130 (119, 142)	131 (121, 144)	0.03
Diastolic BP, mm Hg	81 (75, 89)	81 (75, 89)	81 (76, 89)	0.41
Resting heart rate, beats/min	66 (59, 72)	66 (59, 72)	66 (60, 72)	0.73

Values are mean ± SD, n (%), or median (25th, 75th percentile). *Test for trend.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blockers; BP = blood pressure; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2 Change in Clinical Risk Factors, Medical Treatment, and Incurred Costs

Parameters	Study Group at Baseline	No-Scan Group	Scan Group	p Value
CAD risk factors				
Baseline SBP, mm Hg	All subjects	130 (119, 142)	131 (121, 144)	0.03
Change in SBP, mm Hg	All subjects	−5 (−16, 6)	−7 (−18, 3)	0.02
Baseline DBP, mm Hg	All subjects	81 (75, 89)	81 (76, 89)	0.41
Change in DBP, mm Hg	All subjects	−4 (−12, 4)	−5 (−12, 3)	0.50
Baseline cholesterol, mg/dl	All subjects	213 (187, 238)	213 (187, 240)	0.44
Change in cholesterol, mg/dl	All subjects	−16 (−44, 7)	−21 (−49, 6)	0.08
Baseline LDL, mg/dl	All subjects	130 (109, 155)	133 (111, 158)	0.15
Change in LDL, mg/dl	All subjects	−11 (−41, 10)	−17 (−44, 7)	0.04
Baseline HDL, mg/dl	All subjects	53 (42, 65)	52 (42, 64)	0.58
Change in HDL, mg/dl	All subjects	−1 (−7, 5)	−1 (−6, 5)	0.28
Baseline triglycerides, mg/dl	All subjects	113 (78, 166)	112 (79, 161)	0.99
Change in triglycerides, mg/dl	All subjects	−9 (−37, 14)	−10 (−42, 14)	0.40
Baseline glucose, mg/dl	All subjects	94 (86, 101)	93 (86, 101)	0.40
Change in glucose, mg/dl	All subjects	−2 (−8, 6)	0 (−8, 7)	0.16
Baseline weight, lbs	BMI ≥25 kg/m^2	186 (167, 210)	188 (166, 209)	0.66
Change in weight, lbs	BMI ≥25 kg/m^2	1 (−5, 8)	0 (−6, 7)	0.07
Baseline WC, inches	M >40, W >35	41 (38, 43)	41.3 (38, 43.5)	0.19
Change in WC, inches	M >40, W >35	1 (−2, 3)	0 (−3, 2)	0.01
Quit smoking	Smokers	16/36 (44%)	34/69 (49%)	0.64
Exercise ≥3 times/week	Nonexercisers	95/266 (36%)	214/582 (37%)	0.77
Baseline FRS	All subjects	6 (2, 12)	6 (2, 12)	0.45
Change in FRS*	All subjects	0 (0, 2)	0 (−1, 2)	0.003
New meds				
Lipid meds	No lipid meds	109/441 (25%)	284/963 (29%)	0.06
BP meds	No BP meds	77/419 (18%)	214/877 (24%)	0.02
Diabetic meds	No diabetic meds	15/595 (3%)	40/1260 (3%)	0.44
Aspirin	No aspirin	39/525 (7%)	92/1130 (8%)	0.62
Meds adherence				
Lipid meds	On lipid meds	145/168 (86%)	281/325 (86%)	0.96
BP meds	On BP meds	173/192 (90%)	388/414 (94%)	0.11
Diabetic meds	On diabetic meds	26/28 (93%)	45/51 (88%)	0.71
Aspirin	On aspirin	26/84 (31%)	43/158 (27%)	0.54
Performed procedures				
Resting ECG	All subjects	380 (61.0%)	767 (58.5%)	0.30
Stress nuclear	All subjects	62 (10.0%)	169 (12.9%)	0.06
Stress echocardiography	All subjects	102 (16.4%)	195 (14.9%)	0.39
Any stress test†	All subjects	211 (33.9%)	454 (34.6%)	0.74
Cardiac CT	All subjects	44 (7.1%)	101 (7.7%)	0.62
Carotid ultrasound	All subjects	88 (14.1%)	167 (12.7%)	0.40
Cardiac catheterization	All subjects	18 (2.9%)	43 (3.3%)	0.71
Coronary revascularization	All subjects	11 (1.8%)	30 (2.3%)	0.46
Medical costs (in U.S. $)				
Procedure costs	All subjects	712 (523, 901)	904‡ (739, 1,056)	0.56
Medication costs	All subjects	2,937 (2,620, 3,254)	3,149 (2,924, 3,374)	0.09
Lipid-lowering meds	All subjects	721 (625, 817)	748 (682, 813)	0.06
BP meds	All subjects	761 (659, 863)	892 (819, 966)	0.02
Diabetic meds	All subjects	545 (415, 675)	533 (444, 623)	0.87
Aspirin	All subjects	26 (20, 33)	27 (22, 31)	0.92
All costs	All subjects	3,649 (3,263, 4,035)	4,053 (3,739, 4,367)	0.09

Values are median (25th, 75th percentile) or n (%). *Mean ± SD change in FRS was 0.7 ± 5.1 versus 0.002 ± 4.9 in the no-scan versus scan groups, respectively. †Stress nuclear, stress echocardiography, or treadmill exercise electrocardiography (ECG). ‡Includes a $150 charge for coronary artery calcium scanning.

BMI = body mass index; CT = computed tomography; DBP = diastolic blood pressure; FRS = Framingham Risk Score; M = men; meds = medications; SBP = systolic blood pressure; W = women; WC = waist circumference; other abbreviations as in Table 1.

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Table 3 Change in Clinical Risk Factors, Medical Treatment, and Incurred Costs According to CAC Score

Parameters	Study Group at Baseline	CAC Score 0 (n = 631)	CAC Score 1–99 (n = 400)	CAC Score 100–399 (n = 171)	CAC Score ≥400 (n = 109)	p Value (Trend)
CAD risk factors						
Baseline SBP, mm Hg	All subjects	128 (118, 140)	132 (122, 144.5)	138 (122, 149)	140 (125, 150)	<0.001
Change in SBP, mm Hg	All subjects	−4 (−16, 5)	−9 (−20, 2)	−10.5 (−21, 1)	−9 (−24, 2)	<0.001
Baseline DBP, mm Hg	All subjects	80 (74, 88)	82 (76, 90)	83 (78, 90)	82 (78, 90)	<0.001
Change in DBP, mm Hg	All subjects	−4 (−11, 5)	−7 (−14, 3)	−5 (−14, 2)	−8 (−12, −1)	<0.001
Baseline cholesterol, mg/dl	All subjects	214 (190, 239)	211 (186.5, 242)	215 (188, 240)	210 (184, 237)	0.51
Change in cholesterol, mg/dl	All subjects	−15 (−42, 9)	−21 (−50, 5)	−30 (−54, −7)	−39.5 (−78, 0)	<0.001
Baseline LDL, mg/dl	All subjects	133 (111, 156)	133 (109, 160)	135 (109.5, 157)	135 (111, 158)	0.85
Change in LDL, mg/dl	All subjects	−12 (−37, 10)	−18.5 (−50.5, 7)	−25 (−55, −4)	−29 (−62, 3)	<0.001
Baseline HDL, mg/dl	All subjects	54 (44, 67)	51 (40, 62)	50 (41, 64)	49 (42, 59)	0.001
Change in HDL, mg/dl	All subjects	−1 (−7, 5)	−2 (−6, 5)	0 (−6, 5)	0 (−5, 4)	0.46
Baseline triglycerides, mg/dl	All subjects	106 (78, 154)	113 (79, 165.5)	120 (82, 180)	124 (86, 162)	0.003
Change in triglycerides, mg/dl	All subjects	−8 (−35, 14)	−8 (−40, 19)	−16 (−53, 8)	−25 (−67, 4)	<0.001
Baseline glucose, mg/dl	All subjects	91 (85, 98)	94 (86, 103)	94 (87, 102)	97 (89, 108)	<0.001
Change in glucose, mg/dl	All subjects	−1 (−8, 6)	−1 (−8, 6)	1 (−7, 9)	0 (−10, 11)	0.34
Baseline weight, lbs	BMI ≥25 kg/m^2	186 (165, 206)	188.5 (169, 208)	197 (169, 222)	186 (160, 214)	0.15
Change in weight, lbs	BMI ≥25 kg/m^2	1 (−5, 8)	0 (−6, 6.5)	−2 (−9, 3.5)	−3 (−10, 3)	<0.001
Baseline WC, inches	M >40, W >35	41 (37.8, 43)	41.3 (39, 43)	42 (41, 43.5)	43 (39.6, 45.8)	0.002
Change in WC, inches	M >40, W >35	−0.5 (−3.8, 2)	0.3 (−2, 2)	1 (−1, 2)	−1 (3.3, 0.5)	0.56
Quit smoking	Smokers	15/27 (56%)	13/24 (54%)	3/11 (27%)	3/7 (43%)	0.22
Exercise ≥3 times/week	Nonexercisers	92/284 (32%)	75/188 (40%)	30/74 (41%)	17/36 (47%)	0.03
Baseline FRS	All subjects	4 (2, 8)	8 (4, 16)	10 (4, 16)	16 (8, 20)	<0.001
Change in FRS	All subjects	0 (−1, 2)	0 (−2, 2)	0 (−2, 2)	0 (−2, 2)	0.003
New meds						
Lipid meds	No lipid meds	94/505 (19%)	96/274 (35%)	50/116 (43%)	44/68 (65%)	<0.001
BP meds	No BP meds	91/459 (20%)	63/249 (25%)	34/112 (30%)	26/57 (46%)	<0.001
Diabetic meds	No diabetic meds	12/617 (2%)	13/377 (3%)	5/165 (3%)	10/101 (10%)	<0.001
Aspirin	No aspirin	28/560 (5%)	31/349 (9%)	17/146 (12%)	16/75 (21%)	<0.001
Meds adherence						
Lipid meds	On lipid meds	96/120 (80%)	105/117 (90%)	50/54 (93%)	30/34 (88%)	0.04
BP meds	On BP meds	157/167 (94%)	135/144 (94%)	53/58 (91%)	43/45 (96%)	0.97
Diabetic meds	On diabetic meds	14/14 (100%)	19/23 (83%)	6/6 (100%)	6/8 (75%)	0.18
Aspirin	On aspirin	15/65 (23%)	12/42 (29%)	4/24 (17%)	12/27 (44%)	0.13
Performed procedures						
Resting ECG	All subjects	341 (54.0%)	236 (59.0%)	112 (65.5%)	78 (71.6%)	<0.001
Stress nuclear	All subjects	38 (6.0%)	59 (14.8%)	34 (19.9%)	38 (34.9%)	<0.001
Stress echocardiography	All subjects	70 (11.1%)	57 (14.3%)	38 (22.2%)	30 (27.5%)	<0.001
Any stress test	All subjects	155 (24.6%)	144 (36.0%)	85 (49.7%)	70 (64.2%)	<0.001
Cardiac CT	All subjects	44 (7.0%)	28 (7.0%)	14 (8.2%)	15 (13.8%)	0.04
Carotid ultrasonography	All subjects	76 (12.0%)	43 (10.8%)	30 (17.5%)	18 (16.5%)	0.07
Catheterization	All subjects	7 (1.1%)	10 (2.5%)	10 (5.9%)	16 (14.7%)	<0.001
Revascularization	All subjects	1 (0.2%)	4 (1.0%)	9 (5.3%)	16 (14.7%)	<0.001
Medical costs (in U.S. $)						
Procedure costs	899 (733, 1,066)	447 (352,543)	705 (450,960)	1,130 (778, 1,483)	3,774 (2,302, 5,247)	<0.001
Meds costs	3,131 (2,904, 3,357)	2,176 (1,922, 2,429)	3,689 (3,265, 4,113)	3,769 (3,058, 4,480)	5,534 (4,457, 6,613)	<0.001
Lipid-lowering meds	825 (755, 895)	581 (491,671)	1,025 (886,1,163)	991 (790, 1,191)	1,232 (979, 1,485)	<0.001
BP meds	896 (822, 970)	722 (623,820)	1,072 (924,1,219)	866 (671, 1,061)	1,318 (1,045, 1,590)	<0.001
Diabetic meds	529 (439, 619)	367 (259,476)	617 (436,798)	569 (325, 813)	1,077 (652, 1,502)	<0.001
Aspirin	27 (22, 31)	16 (11, 21)	31 (22, 41)	31 (18, 45)	66 (42, 89)	<0.001
All costs	4,030 (3,714, 4,346)	2,623 (2,343, 2,903)	4,394 (3,856, 4,931)	4,900 (3,992, 5,807)	9,309 (7,200, 11,418)	<0.001

Values are median (25th, 75th percentile) or n (%).

CAC = coronary artery calcium; other abbreviations as in Tables 1 and 2.

Table 4 Comparison of No-Scan Subjects and Scan Subjects With a CAC Score of 0

Parameters	Study Group at Baseline	No-Scan Group	CAC Score 0	p Value
CAD risk factors				
Baseline SBP, mm Hg	All subjects	130 (119, 142)	128 (118, 140)	0.14
Change in SBP, mm Hg	All subjects	−5 (−16, 6)	−4 (−16, 5)	0.73
Baseline DBP, mm Hg	All subjects	81 (75, 89)	80 (74, 88)	0.14
Change in DBP, mm Hg	All subjects	−4 (−12, 4)	−4 (−11, 5)	0.09
Baseline cholesterol, mg/dl	All subjects	213 (187, 238)	214 (190, 239)	0.31
Change in cholesterol, mg/dl	All subjects	−16 (−44, 7)	−15 (−42, 9)	0.45
Baseline LDL, mg/dl	All subjects	130 (109, 155)	133 (111, 156)	0.29
Change in LDL, mg/dl	All subjects	−11 (−41, 10)	−12 (−37, 10)	0.87
Baseline HDL, mg/dl	All subjects	53 (42, 65)	54 (44, 67)	0.14
Change in HDL, mg/dl	All subjects	−1 (−7, 5)	−1 (−7, 5)	0.42
Baseline triglycerides, mg/dl	All subjects	113 (78, 166)	106 (78, 154)	0.17
Change in triglycerides, mg/dl	All subjects	−9 (−37, 14)	−8 (−35, 14)	0.81
Baseline glucose, mg/dl	All subjects	94 (86, 101)	91 (85, 98)	<0.001
Change in glucose, mg/dl	All subjects	−2 (−8, 6)	−1 (−8, 6)	0.27
Baseline weight, lbs	BMI ≥25 kg/m^2	186 (167, 210)	186 (165, 206)	0.60
Change in weight, lbs	BMI ≥25 kg/m^2	1 (−5, 8)	1 (−5, 8)	0.87
Baseline WC, inches	M >40, W >35	41 (38, 43)	41 (37.8, 43)	0.91
Change in WC, inches	M >40, W >35	1 (−2, 3)	−0.5 (−3.8, 2)	0.003
Quit smoking	Smokers	16/36 (44%)	15/27 (56%)	0.38
Exercise ≥3 times/week	Nonexercisers	95/266 (36%)	92/284 (32%)	0.41
Baseline FRS	All subjects	6 (2, 12)	4 (2, 8)	<0.001
Change in FRS	All subjects	0 (0, 2)	0 (−1, 2)	0.22
New meds				
Lipid meds	No lipid meds	109/441 (25%)	94/505 (19%)	0.02
BP meds	No BP meds	77/419 (18%)	91/459 (20%)	0.59
Diabetic meds	No diabetes meds	15/595 (3%)	12/617 (2%)	0.50
Aspirin	No aspirin	39/525 (7%)	28/560 (5%)	0.10
Meds adherence				
Lipid meds	On lipid meds	145/168 (86%)	96/120 (80%)	0.15
BP meds	On BP meds	173/192 (90%)	157/167 (94%)	0.18
Diabetic meds	On diabetes meds	26/28 (93%)	14/14 (100%)	0.55
Aspirin	On aspirin	26/84 (31%)	15/65 (23%)	0.29
Performed procedures				
Resting ECG	All subjects	380 (61.0%)	341 (54.0%)	0.01
Stress nuclear	All subjects	62 (10.0%)	38 (6.0%)	0.01
Stress echocardiography	All subjects	102 (16.4%)	70 (11.1%)	0.007
Any stress test	All subjects	211 (33.9%)	155 (24.6%)	<0.001
Cardiac CT	All subjects	44 (7.1%)	44 (7.0%)	0.95
Carotid ultrasonography	All subjects	88 (14.1%)	76 (12.0%)	0.28
Cardiac catheterization	All subjects	18 (2.9%)	7 (1.1%)	0.02
Coronary revascularization	All subjects	11 (1.8%)	1 (0.2%)	0.003
Medical costs (in U.S. $)				
Procedure costs	All subjects	712 (523, 901)	447 (351, 543)	0.001
Meds costs	All subjects	2,937 (2,620, 3,254)	2,176 (1,922, 2,429)	0.005
Lipid-lowering meds	All subjects	721 (625, 817)	581 (491, 671)	0.02
BP meds	All subjects	761 (659, 863)	722 (623, 820)	0.78
Diabetic meds	All subjects	545 (415, 675)	367 (259, 476)	0.02
Aspirin	All subjects	26 (20, 33)	16 (11, 21)	0.02
All costs	All subjects	3,649 (3,263, 4,035)	2,623 (2,343, 2,903)	0.001

Values are median (25th, 75th percentile) or n (%).
Abbreviations as in Tables 1, 2, and 3.

resulting from stepwise logistic regression, predictors of CAC progression included age (odds ratio [OR]: 1.20 per 5 years; 95% confidence interval [CI]: 1.1 to 1.3; $p < 0.001$), male sex (OR: 2.02; 95% CI: 1.6 to 2.6; $p < 0.001$), family history of CAD (OR: 1.47; 95% CI: 1.1 to 1.9; $p = 0.006$), hypertension (OR: 1.38; 95% CI: 1.1 to 1.8; $p = 0.01$), hyperlipidemia (OR: 1.44; 95% CI: 1.05 to 2.0; $p = 0.03$), and history of diabetes (OR: 1.69; 95% CI: 1.1 to 2.7; $p = 0.03$). In the final treatment plus baseline model, lipid-lowering medication use by year 4 was the strongest predictor of CAC score progression (OR: 1.51; 95% CI: 1.2 to 2.0; $p = 0.002$).

Discussion

To assess the impact of CAC scanning on CAD risk, we randomly assigned asymptomatic subjects to groups undergoing CAC scan versus no CAC scan and compared the groups for 4-year changes in CAD risk. In total, 7 modifiable CAD risk factors were assessed: blood pressure, lipid profiles, serum glucose, weight, waist circumference, exercise, and smoking. Subjects who underwent CAC scanning experienced a favorable improvement in risk, including greater reduction in mean systolic blood pressure and serum LDL cholesterol level, and reduced waist circumference for those with increased abdominal girth at baseline. The overweight subjects within the scan group also showed a tendency toward more weight loss compared with their no-scan counterparts. The 2 groups did not differ in exercise activity, smoking behavior, or glucose measurements at 4 years, but the frequencies of smokers and diabetic patients in our study were both low. Four-year progression of CAD risk, as summarized by FRS, rose in the no-scan group but was static in the scan group, due to the favorable improvements in systolic blood pressure and lipid status. Importantly, risk factor profiles improved in both the scan and no-scan groups after recruitment into our trial, but the magnitude of improvement was greater in the scan group.

Overall rates of downstream medical testing and procedures did not differ among the scan and no-scan groups, resulting in comparable medical procedure costs during follow-up. Estimated medication costs were mildly higher in the scan group.

There was no substantive difference in the rates of myocardial infarction or fatal events between the 2 randomized groups; however, the rates of events were low and statistical power was insufficient to adequately assess this issue. Practical study of how CAC scanning might affect clinical events may require studying patients, rather than healthy volunteers, who may be pre-selected to be at higher risk of clinical events compared with our subjects (11).

Change in CAD risk factors, downstream tests, and incurred costs according to baseline CAC score. Within the scan group, there was a direct proportional relationship between the magnitude of baseline CAC and the degree of reduction of systolic and diastolic blood pressure, serum cholesterol, LDL, and triglyceride levels. In addition, a reduction in waist size occurred among subjects with increased abdominal girth and high CAC scores, and modest weight loss occurred among overweight subjects with CAC score elevation. Factors not varying according to CAC score included HDL cholesterol, glucose measurements, and smoking cessation. The composite FRS at 4 years increased compared with the baseline FRS among the scan subjects with a zero CAC score and decreased among subjects with elevated CAC scores.

There was a strong proportional relationship between baseline CAC score and the frequency of initiating cardiac medications. Downstream medical testing also increased in proportion to baseline CAC score. Both procedural and medical costs were substantially higher in the subjects with a CAC score ≥400 compared with subjects having a CAC score of 100 to 399. Noninvasive stress testing predominated among downstream tests. Overall, approximately two-thirds of subjects with CAC scores ≥400 underwent some form of cardiac stress testing, but the frequency of 4-year rates of cardiac catheterization and coronary revascularization were substantially lower. Because of the design of our trial, we were uniquely able to assess how knowledge of a normal CAC scan influenced the forward trajectory of medical treatment and costs compared with usual medical care. Overall, there was a 25% greater reduction in medication costs in the normal CAC scan subjects compared with the no-scan group, and a 37% reduction in procedure costs. Since the normal scan subjects constituted ~50% of our scan subjects, whereas the subjects with CAC scores ≥400 constituted only ~8% of our scan subjects, these directionally opposite effects were sufficient to result in the comparable incurred costs within our scan and no-scan groups.

Assessment of CAC scores at 4 years. There was no difference in mean CAC scores or the distribution of CAC scores in the no-scan versus scan group at 4 years. Within the scan group, we found that both baseline CAD risk factors and the use of lipid-lowering medication were predictors of CAC score progression. These findings parallel that of the MESA study (12). While some early studies reported that the use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) was associated with a reduced rate of CAC progression during serial scanning (13,14), subsequent studies have reported either no difference in CAC progression (15–17) or even increased rate of CAC progression among subjects using such medication (12,18). Of note in this regard is experimental work suggesting that statins may have the ability to promote calcification of coronary plaques (19). While further study is indicated, the apparent multifactorial causation for plaque progression limits the use of CAC score progression as a therapeutic index.

Comparison to prior studies. Only 1 prior randomized trial, conducted by O'Malley et al. (20), has assessed the impact of CAC scanning on subjects' risk profiles and health behavior, and there are no prior trials concerning the

impact of CAC scanning on downstream tests and costs. In the trial conducted by O'Malley et al. (20), subjects underwent CAC scanning, but the results were then withheld in one-half of subjects. In contrast to our study, these investigators found no impact of CAC scanning on subjects' clinical profile. However, their study was primarily limited to young military personnel with a mean age of only 42 years, and 85% had normal CAC scans, thus limiting the comparability of their findings to our own.

Study limitations. Our subjects were highly educated, fairly affluent, and sufficiently motivated to volunteer for our research study, and were thus more likely than a general population to adhere to risk factor modification therapies. Indeed, the ~90% 4-year continuation rate for using lipid-lowering and antihypertensive medication in our study is atypically high compared with studies involving patient populations (21). In addition, our study and the prior study by O'Malley et al. (20) are similarly limited in that they involved the offering of free CAC scans to volunteer subjects. This incentive offering may not be reflective of the care path that patients may encounter when confronted with out-of-pocket CAC scan costs from the onset or when the scan is ordered by a physician. For these reasons, caution should be applied in generalizing our findings to populations at large.

Because of the limited assessment of health behaviors in our study, we could not determine the extent to which CAC scanning drove reduced CAD risk profiles due to improvement in subjects' health behaviors as opposed to more intensive use and adherence to medications. An objective measure of dietary habits was lacking in our study, and our assessment of exercise activity relied on a crude self-report measurement rather than on objective measurements, such as can be garnered by pedometer use. Further, the nature of our study design, involving only a 1-time counseling session, might not be ideal for inducing behavioral lifestyle changes that are more difficult to accomplish compared with taking medications. Thus, future study might compare if and what intensity of behavioral interventions improves the ability of CAC scanning to improve patients' lifestyle health behaviors.

The impact of CAC scanning on diabetes and smoking could not be adequately assessed in our trial, owing to our small number of subjects with these risk factors. In addition, we cannot exclude that the nature of our study design led to psychological effects whereby subjects who were randomized to the scan group—and thus received a free CAC scan at both onset and at 4 years—felt more motivated to participate in our trial, and those who were randomized to the no-scan group felt discouraged that CAC scanning would be deferred for 4 years. Potentially, this dynamic might explain the greater loss to follow-up that was noted among the no-scan subjects.

Another important methodological limitation was that due to anonymity restrictions imposed by our institutional review board, we could not provide CAC scan results directly to our subjects' physicians. As a result, their involvement only occurred indirectly. However, this limitation may have served to actually minimize the potential impact of CAC scanning upon risk factor management in our study. Conversely, our study design may have limited our ability to assess the financial impact of CAC scanning in clinical practice, as the actual course of action following calcium scanning may be potentially different when testing is ordered by a physician rather than being initiated by subjects seeking to assess their cardiovascular risk. For example, after their ordering of a CAC scan, physicians may feel more compelled than volunteer subjects to do follow-up stress testing in patients with intermediate to high CAC scores for fear of medicolegal consequences for a missed work-up for myocardial ischemia. Accordingly, more prospective study is required to assess the financial impact of CAC scanning upon downstream testing and medical costs in actual clinical practice.

Clinical implications. The results of our trial are consistent with the hypothesis that CAC scanning can improve cardiac management without incurring significant increase in downstream medical costs. Further work should similarly assess patients who are suitable candidates for CAC scanning based on clinical consensus and current guidelines (22–24). Notably, the finding that our study did not lead to increased downstream testing is potentially clinically significant, revealing that physicians may be applying a "gatekeeper" function to CAC scanning with respect to ascertaining the need for subsequent more expensive noninvasive testing. This potential use may be based on the repeated observation of a threshold relationship between the magnitude of CAC abnormality and the likelihood of observing inducible myocardial ischemia (8,25–28). The results of our study indicate a need for future large-scale clinical trials to determine whether our findings are applicable to different patient populations and to determine whether the salutatory effect of CAC scanning on CAD risk profiles translates to reductions in adverse clinical events. Such trials should evaluate outcomes following CAC scanning not only according to the efficacy and intensity of medications used to control CAD risk factors, but also according to the quality and intensity of behavioral interventions instituted after CAC scanning.

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