Journal of the American College of Cardiology Vol. 46, No. 1, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.02.089

Treatment of Asymptomatic Adults With Elevated Coronary Calcium Scores With Atorvastatin, Vitamin C, and Vitamin E

The St. Francis Heart Study Randomized Clinical Trial

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OBJECTIVES We sought to determine whether lipid-lowering therapy and antioxidants retard the progression of coronary calcification and prevent atherosclerotic cardiovascular disease (ASCVD) events.

BACKGROUND The electron beam computed tomography-derived coronary calcium score predicts coronary disease events. Small, uncontrolled studies suggest that vigorous lipid-lowering therapy slows progression of coronary calcification and prevents coronary artery disease events, but controlled, scientific demonstration of these effects is lacking.

METHODS We conducted a double-blind, placebo-controlled randomized clinical trial of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha-tocopherol) 1,000 U daily, versus matching placebos in 1,005 asymptomatic, apparently healthy men and women age 50 to 70 years with coronary calcium scores at or above the 80th percentile for age and gender. All study participants also received aspirin 81 mg daily. Mean duration of treatment was 4.3 years.

RESULTS Treatment reduced total cholesterol by 26.5% to 30.4% ($p < 0.0001$), low-density lipoprotein cholesterol by 39.1% to 43.4% ($p < 0.0001$), and triglycerides by 11.2% to 17.0% ($p \leq 0.02$) but had no effect ($p = 0.80$) on progression of coronary calcium score (Agatston method). Treatment also failed to significantly reduce the primary end point, a composite of all ASCVD events (6.9% vs. 9.9%, $p = 0.08$). Event rates were related to baseline calcium score (pre-specified analysis) and may have been reduced in a subgroup of participants with baseline calcium score >400 (8.7% vs. 15.0%, $p = 0.046$ [not a pre-specified analysis]).

CONCLUSIONS Treatment with alpha-tocopherol, vitamin C, and low doses of atorvastatin (20 mg once daily) did not affect the progression of coronary calcification. Treatment may have reduced ASCVD events, especially in subjects with calcium scores >400, but these effects did not achieve conventional levels of statistical significance. (J Am Coll Cardiol 2005;46:166–72)

In asymptomatic persons, the electron beam computed tomography (CT)-derived coronary calcium score predicts coronary artery disease (CAD) events independently of standard CAD risk factors (1–4). This observation suggests that criteria for cholesterol-lowering therapy should include the coronary calcium score in addition to standard CAD risk factors.

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We therefore conducted a randomized, double-blind clinical trial of aspirin, atorvastatin, vitamin C, and vitamin E (alpha-tocopherol) versus aspirin and matching placebos in apparently healthy men and women age 50 to 70 years with elevated coronary calcium scores. The primary purpose of this study was to determine whether treatment with a statin and antioxidant vitamins can reduce the rate of atherosclerotic cardiovascular disease (ASCVD) events in persons identified at high risk by fast CT scanning of the coronary arteries. A secondary objective of the study was to determine the effect of treatment with a statin and antioxidant vitamins on progression of coronary calcification.

METHODS

The methods have been previously published (5). To recapitulate briefly, men and women age 50 to 70 years were considered eligible provided they had no history, symptoms (Rose questionnaire [6]), or signs of ASCVD. The latter included carotid bruits, diminished femoral or distal pulses, and either Q waves or poor precordial R-wave progression on electrocardiograms.

Other exclusion criteria included indications for risk factor modification or conditions that might interfere with the conduct or conclusions of a randomized clinical trial. The former consisted of insulin-dependent diabetes, triglycerides >500 mg/dl, and in men, low-density lipoprotein (LDL) cholesterol >175 mg/dl (7). The upper limit for cholesterol in women, total cholesterol >300 mg/dl, was chosen in the absence of any proof (circa January 1996) of benefit of cholesterol-lowering therapy in women in a setting of primary prevention and to conform to local practice patterns. Interfering conditions included weight >136 kg (the upper limit of the table), any disease likely to

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Manuscript received December 12, 2004; revised manuscript received February 17, 2005, accepted February 22, 2005.

Abbreviations and Acronyms

ASCVD = atherosclerotic cardiovascular disease
CAD = coronary artery disease
CK-MB = creatine kinase-myocardial band
CT = computed tomography/tomographic
HDL = high-density lipoprotein
LDL = low-density lipoprotein
MI = myocardial infarction

cause death within five years, current therapy with estrogens or glucocorticoids, refusal to discontinue lipid-lowering drugs, vitamin C or vitamin E, and uncontrolled hypertension, which was defined as systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg. Low-density lipoprotein cholesterol <90 mg/dl was also an exclusion criterion. The lower limit for LDL cholesterol was chosen out of concern that local primary care physicians would become alarmed by LDL cholesterol levels <60 mg/dl, which were known to be achievable with atorvastatin at the time of study design. Such alarm might have jeopardized compliance with assigned medications or even continued participation in the study.

Electron beam CT scanning was performed at enrollment and again at two and four years with reconstruction to a 26-cm field of view. Forty contiguous 3-mm slices were scanned during a single breath hold, beginning at the carina. Scan time was 100 ms/slice, synchronized to 80% of the RR interval. At least two adjacent pixels with an attenuation coefficient >130 Hounsfield units defined a calcified lesion, and coronary calcium scores were calculated using the method of Agatston et al. (8).

Subjects with coronary calcium scores above the 80th percentile for age and gender, as defined by an internal database comprising more than 5,000 asymptomatic persons, were invited to participate in the randomized clinical trial. The threshold calcium score was 26 in women age 50 to 51 years and increased by approximately 10% every two years up to a threshold score of 128 in women age 69 to 70 years. In men, the threshold calcium score was 69 at age 50 to 51 years and increased by about 10% every two years up to a threshold score of 368 in men age 69 to 70 years (5).

Treatment consisted of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha tocopherol) 1,000 U daily versus matching placebos, administered in double-blind fashion. In addition, at the insistence of the St. Francis Hospital Institutional Review Board, all participants were given 81 mg of aspirin daily. Study participants experiencing nonfatal coronary end points who met either Scandinavian Simvastatin Survival Study (4S) (9) or Cholesterol and Recurrent Events (CARE) (10) criteria were placed on open-label atorvastatin 20 mg daily.

The primary hypothesis tested was that treatment with atorvastatin and vitamins C and E would reduce a composite of all ASCVD events in a population defined as high risk by electron beam CT scanning of the coronary arteries rather than by conventional risk factor assessment. Events of interest, verified by an independent committee of current or former coronary care unit directors at academic medical centers, blinded to the coronary calcium score, included coronary death, nonfatal myocardial infarction (MI), surgical or percutaneous coronary revascularization procedures, non-hemorrhagic stroke, and peripheral vascular (i.e., arterial) surgery. For purposes of analysis, only the first event experienced by a patient was counted. Secondary end points included all coronary events, the sum of nonfatal MI and coronary death, and all events occurring more than 90 days after randomization. The relationship of events to baseline calcium score and standard risk factors was also a prespecified analysis. A secondary hypothesis was that treatment would reduce the rate of progression of the coronary calcium score.

C-reactive protein was measured with a high-sensitivity assay, using latex immunonephelometry on a BN Prospec analyzer (Dade Behring, Newark, Delaware [11]).

This study was approved by the St. Francis Hospital Institutional Review Board and all participants gave informed consent.

Randomization. The sample size of 944 was calculated on the basis of a predicted event rate of 12% at four years in the control group, 80% power to detect a 50% reduction in events (two-sided test), and six interim analyses by the Data and Safety Monitoring Board, with O'Brien-Fleming guidelines for each interim analysis. The slightly higher actual sample (n = 1,005) was recruited in response to dropouts during the recruitment phase, that is, most dropouts occurred in the first three months after randomization, and recruitment continued until 944 committed participants were enrolled. Participants were seen in follow-up at three-month intervals.

Randomization was stratified by gender, age (50 to 54 years, 55 to 59 years, 60 to 64 years, and 65 to 70 years), ratio of LDL cholesterol to high-density lipoprotein (HDL) cholesterol (≥3.5 or <3.5), and the number of non-lipid risk factors (0 to 2 or >2). Data entry by either of two clerks placed the patient into a cell and assigned a randomly generated number to that patient. Each number corresponded to a treatment assignment. The same clerks also dispensed study medications to study nurses in prepackaged containers according to the treatment assignment (labels indicating container content, treatment or placebo, were removed by the clerks and filed). Other than the two clerks and the statistician (D.N.), no study personnel had access to or were made aware of treatment assignment.

Statistical analysis. Differences in proportions were tested for significance using chi-square analyses. Differences in distributions of continuous variables were tested for significance using either independent sample *t* tests. In the case of the coronary calcium scores, which were highly skewed, Wilcoxon rank sum tests were used. Kaplan-Meier curves were used to estimate the probability of sustaining a clinical event for a given duration of follow-up, which enabled variable time of

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Table 1. Baseline Characteristics

	Treatment (n = 490)	Control (n = 515)	p Value
Age (yrs)	59 ± 6	59 ± 6	0.73
Male (%)	73	74	0.77
Total cholesterol (mg/dl)	224 ± 35	227 ± 34	0.72
LDL cholesterol (mg/dl)	146 ± 30	147 ± 30	0.91
HDL cholesterol (mg/dl)	51 ± 15	50 ± 14	0.30
Triglycerides (mg/dl)	136 ± 83	149 ± 97	0.08
Hypertension (%)	38	43	0.08
Diabetes mellitus (%)	9	8	0.65
Current smoker (%)	12	13	0.99
Family history of premature CAD (%)	31	29	0.54
Body mass index	29.5 ± 5.0	29.3 ± 4.9	0.59
C-reactive protein (mg/l)			
Median	1.99	2.10	0.99
25th, 75th percentiles	0.97, 4.24	0.96, 4.35	
Calcium score			
Mean	527	563	—
Median	379	370	0.77
25th, 75th percentiles	148, 636	183, 671	

Normally distributed continuous variables are presented as mean ± SD. To convert cholesterol levels to mmol/l, divide by 38.7. To convert triglyceride levels to mmol/l, divide by 88.6.
CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

follow-up (censoring) to be taken into account. Significance of differences in the Kaplan-Meier curves by treatment group were assessed using log-rank tests. Multivariable proportional hazards regression was used to assess differences in time to event by treatment group while taking into account variable time of follow-up and adjusting for standard risk factors. All hypothesis tests were conducted with an alpha level of 0.05 and were two tailed, and all end points were analyzed on the basis of intention to treat.

In January of 2002, because of lower-than-expected event rates and threatened dropout of large numbers of subjects who had been in the study for more than four years, we appealed to the Data and Safety Monitoring Board for advice on whether to continue the study. On the basis of information available at that time, the Data and Safety Monitoring Board concluded that it was unlikely that the known event rate would yield a significant difference within the next 6 to 12 months. Fearing substantial defections, we elected to terminate the study rather than have a result clouded by large numbers of dropouts. Upon notifying all study participants of our decision to end the study, we became aware of additional events.

Role of the funding source. Neither the funding source (the St. Francis Hospital Foundation), nor Pfizer Inc., which provided atorvastatin and matching placebo free of charge, had any role in study design, the collection, analysis, and interpretation of data, or the preparation or submission of this paper.

RESULTS

Between July 1996 and March 1999, 5,582 apparently healthy men and women age 50 to 70 years underwent electron beam CT scanning of the coronary arteries. Based on an internal database, 1,269 with coronary calcium scores at or above the 80th percentile for age and gender underwent physical examination, electrocardiography, and measurement of risk factors. Of these, 177 were determined to be ineligible, 87 withdrew before randomization, and 1,005 were enrolled in the study. Although stratification of randomization yielded an uneven number of participants in the active treatment (n = 490) and placebo (n = 515) groups, baseline characteristics were well matched (Table 1).

Of 185 dropouts, representing 18.4% of the study cohort, 50 occurred within 12 weeks of randomization. Thereafter, the dropout rate was 3.1% per year. All dropouts took at least some study medication, and all were included in data analysis.

Compliance, defined as consumption of at least 85% of study medications, was assessed every three months and averaged 85% for atorvastatin or its matching placebo, 88% for vitamins C and E or their matching placebos, and 79% for aspirin. Conversely, under the direction of their private physicians, 14% of subjects assigned to the control arm began taking a statin without an antecedent ASCVD event.

Effect of treatment on lipids. Treatment induced a 43% reduction in LDL cholesterol ($p < 0.0001$), a 17% reduction in triglycerides ($p < 0.0001$), and a 30% reduction in total cholesterol ($p < 0.0001$) at six weeks. Significant changes from baseline ($p < 0.0001$) were maintained over the course of the study. Differences in LDL cholesterol ($p < 0.0001$), triglycerides ($0.02 > p \geq 0.0001$), and total cholesterol ($p < 0.0001$) between the treatment and control groups also persisted throughout the study, despite the crossover of a total of 21% of control arm subjects to treatment with a statin.

Effect of treatment on ASCVD events (Fig. 1, Table 2). At a mean of 4.3 years of follow-up, 34 treatment group

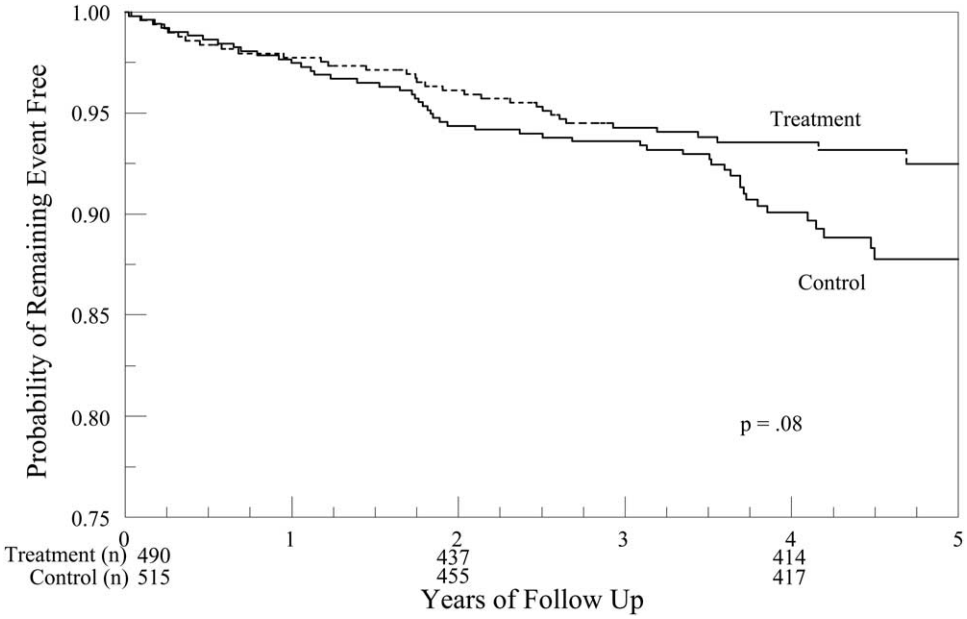

Figure 1. Kaplan-Meier survival curves for all atherosclerotic disease events.

subjects (6.9%) and 51 control group subjects (9.9%) had experienced at least one ASCVD event ($p = 0.08$). Treatment reduced all CAD events by 28% ($p = 0.13$), the sum of nonfatal MI and coronary death by 44% ($p = 0.14$), and all ASCVD events occurring more than 90 days after initiation of therapy by 33% ($p = 0.07$).

Effect of treatment on progression of coronary calcification (Table 3). Mean increase in calcium score at four years was 331 ± 421 U in the treatment group compared with 323 ± 385 U in the control group ($p = 0.80$).

Determinants of ASCVD events. Baseline coronary calcium score (median [interquartile range]) was higher in subjects who sustained ASCVD events (581 [346, 1,148]), than in those who did not (361 [175, 625], $p < 0.0001$). The coronary calcium score (mean ± SD) also increased more from the baseline examination to the two-year examination in subjects who subsequently experienced ASCVD events than in those who remained event free (256 ± 430 vs. 120 ± 286, $p = 0.01$).

In multivariate analysis, including standard CAD risk factors, C-reactive protein, and baseline coronary calcium score, only the calcium score was significantly associated with disease events ($p < 0.0001$). Change in calcium score, which was highly correlated with baseline calcium score, did not predict events after adjustment for these variables.

C-reactive protein did not predict events independently of the calcium score ($p = 0.47$), nor was there a significant interaction between C-reactive protein and calcium score on treatment effect.

Among study participants with baseline calcium score >400 (47% of the study population), treatment reduced the incidence of all ASCVD events by 42% (20 of 229 [8.7%] vs. 36 of 240 [15.0%], $p = 0.046$).

DISCUSSION

In this study of apparently healthy men and women age 50 to 70 years with elevated coronary calcium scores, treatment with aspirin 81 mg daily, atorvastatin 20 mg daily, vitamin E 1,000 U daily, and vitamin C 1 g daily versus aspirin 81 mg daily and matching placebos induced substantial and sustained reductions in LDL cholesterol and triglycerides but failed to achieve conventional levels of statistical significance in the reduction of either all ASCVD events or CAD events. In contrast to earlier reports (12–14), treatment also failed to retard the progression of coronary calcification, a

Table 2. Effect of Treatment on Clinical Events

Events	Treatment	Control	p Value
Primary end point			
All ASCVD*	34/490 (6.9%)	51/515 (9.9%)	0.08
Secondary end points			
All coronary	31/490 (6.3%)	45/515 (8.7%)	0.13
Non-fatal MI/coronary death	9/490 (1.8%)	17/515 (3.3%)	0.14
All ASCVD after 90 days	30/486 (6.2%)	47/511 (9.2%)	0.07

*All atherosclerotic cardiovascular disease (ASCVD) events includes coronary death, non-fatal myocardial infarction (MI), coronary revascularization procedures, non-hemorrhagic stroke, and peripheral revascularization procedures. All secondary end points were pre-specified. A p value <0.05 notes statistical significance for the primary end point.

Table 3. Effect of Treatment on Coronary Calcium Score

	Treatment	Control	p Value
Baseline			
n	490	515	
Mean	528	563	—
Median	379	370	0.96
25th, 75th percentiles	184, 636	183, 671	—
Year two			
n	417	431	—
Mean	647	723	—
Median	482	505	—
25th, 75th percentiles	231, 820	251, 901	
Change (year two minus baseline)			
Absolute	137 ± 310	155 ± 358	0.86
Percent	38 ± 75	36 ± 58	0.86
Year four			
n	281	288	
Mean	846	922	—
Median	623	673	—
25th, 75th percentiles	335, 1,077	343, 1,138	—
Change (year four minus baseline)			
Absolute	331 ± 421	323 ± 385	0.80
Percent	81 ± 89	73 ± 93	0.76

Because baseline calcium scores were not normally distributed, p values are based on the distribution of calcium scores (median, interquartile range [Wilcoxon rank sum test]), rather than mean values. Change in calcium scores was normally distributed and the p value is based on comparison of the mean values and their respective variances.

powerful correlate of disease events (15). Do these results mean that current therapy cannot ameliorate the prognosis of asymptomatic middle-aged persons with elevated coronary calcium scores? We think not, but the answer to this question requires consideration of several aspects of study design.

This study tested two cells of a two by two factorial: atorvastatin and antioxidant vitamins versus neither. Neither monotherapy with atorvastatin nor antioxidants alone was tested. This feature of study design was intentional and represented a balance between, on the one hand, the high level of interest in antioxidants at the time of the design of the study (16) and, on the other hand, both the expectation that concurrent, large, randomized clinical trials would define the relative effects of statins and antioxidant vitamins in intermediate- to high-risk populations and the practical realities of screening approximately 10,000 subjects in order to obtain the 2,000 subjects with high coronary calcium scores who would have been required for all four cells of a 2 × 2 factorial design. Although evidence in support of the toxic effects of oxidized LDL cholesterol remains strong (17), alpha-tocopherol and ascorbic acid in doses similar to those given in the present study appear to have no effect on the incidence of ASCVD events (18,19). Thus, the addition of antioxidant vitamins to atorvastatin in this study probably had no effect on event rates.

A second relevant feature of study design was the definition of high risk. At the time that the study protocol was designed, we had evidence in symptomatic persons that for any given coronary calcium score, younger persons had more coronary disease, defined angiographically, than older persons (Guerci et al., unpublished data, 1995). Accordingly, we established lower calcium score thresholds in younger persons than in older subjects.

This turned out to be an error, that is, age was not a significant determinant of events. As a result of this error, the study population contained substantial numbers of low-risk subjects, in whom treatment had little effect. Conversely, in just 469 subjects with calcium scores above 400, treatment reduced the event rate by 42%.

A third weakness of study design was the low dose of atorvastatin. This dose was selected out of concern over the possibility of toxicity associated with higher doses of atorvastatin at a time when there was little published experience with the drug. In addition, we were concerned that study participants' private physicians would become alarmed over declines in LDL cholesterol to levels below 60 mg/dl. Such declines, which were known to be readily achievable with higher doses of atorvastatin even at the time of study design, might have jeopardized the blind or continued participation in the study. As a consequence, LDL cholesterol was reduced only by 40%. Higher doses of atorvastatin would have further reduced LDL cholesterol and might also have further reduced the event rate (20–22).

Fourth, we had originally intended to make aspirin part of the treatment regimen. However, our Institutional Review Board, aware of preliminary evidence of the high risk associated with elevated coronary calcium scores (23), mandated administration of aspirin to both the treatment and control groups. This decision likely reduced the control group event rate (24), favoring the null hypothesis.

Additional support for the conclusion that the morbidity and mortality associated with a high coronary calcium score can be reduced significantly with statins and aspirin comes

from cross-sectional studies of survivors of first MI. Such persons, who are known to benefit from treatment with statins and aspirin (9,10,24), typically have coronary calcium scores similar to or slightly higher than the median value of 375 observed in this study (1,25).

Last but not least, the 30% reduction in the primary end point is similar to the reduction of ASCVD events seen in other large randomized clinical trials of statins, a class of drugs with unquestionable efficacy in this application. This study had power of just 0.61 to detect a 30% reduction in events.

The failure of treatment to reduce the rate of progression of the coronary calcium score was surprising, as a small prospective study had indicated that reduction of LDL cholesterol to <100 mg/dl halted progression of coronary calcification (12). Whether these conflicting results are due to treatment with different statins (atorvastatin vs. cerivastatin), antioxidant vitamins, or other factors, is unknown. With different animal species, different diets, and different protocols, the experimental pathology literature also does not provide a clear answer to the question of stabilization of calcification of atherosclerotic plaque during long-term cholesterol-lowering therapy (26–29).

In view of previous reports of the relationship between change in calcium score and acute MI (15), the failure of change in calcium score to predict ASCVD events seems to be a function of power. Unable to distinguish coronary calcium from coronary stents with certainty, and unwilling to exclude some CAD events (i.e., percutaneous transluminal coronary angioplasty with stent), but not others from analysis, this analysis was restricted to subjects who experienced a first event after the year two follow-up scan (n = 34).

The lack of interaction between baseline C-reactive protein and treatment was also surprising, given the powerful effect noted in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS), a study with almost seven times as many patient years of observation (30). Given the much larger patient population in the AFCAPS/TEXCAPS trial, the lack of association between C-reactive protein levels and treatment effect in the present study seems most likely due to lack of power.

In summary, although atorvastatin, 20 mg daily, vitamin C 1 g daily, and vitamin E 1,000 U daily failed to significantly reduce ASCVD events in apparently healthy middle-aged men and women with elevated coronary calcium scores, several lines of evidence indicate that this study was underpowered and that the study population was undertreated, at least with respect to the dose of atorvastatin. Extrapolation from the results also suggests that a significant difference would probably have been observed with a higher-risk population chosen exclusively on the basis of a higher calcium score.

Acknowledgments

We would like to thank Pfizer Inc., for providing atorvastatin and matching placebo. We also thank the following individuals: Russell P. Tracy, PhD, University of Vermont, for validation of CRP measurements; Katherine McGrath, RN, and Joan Scordo, RN, for their invaluable contributions to patient recruitment and retention; and Bernadette Murray for her patient and able preparation of this manuscript. The authors also thank the following individuals: Data and Safety Monitoring Board: Simeon Margolis, MD, (Chair) Johns Hopkins Hospital, Baltimore, MD; David M. Herrington, MD, Wake Forest University School of Medicine, Winston-Salem, NC; Thomas H. Lee, MD, Brigham and Women's Hospital, Boston, MA; Kerry Lee, PhD, Duke University Medical Center, Durham, NC; Benjamin Littenberg, MD, University of Vermont School of Medicine, Burlington, VT. Endpoints Adjudication Committee: David H. Miller, MD, Weill Medical College of Cornell University (Chair); Richard I. Levin, MD, New York University; David A. Vorchheimer, MD, Mt. Sinai School of Medicine, all in New York, NY.

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