Reduction of Iron Stores and Cardiovascular Outcomes in Patients With Peripheral Arterial Disease

A Randomized Controlled Trial

Leo R. Zacharski, MD
Bruce K. Chow, MS
Paula S. Howes, MS, APRN
Galina Shamayeva, MS
John A. Baron, MD
Ronald L. Dalman, MD
David J. Malenka, MD
C. Keith Ozaki, MD
Philip W. Lavori, PhD

Context Accumulation of iron in excess of physiologic requirements has been implicated in risk of cardiovascular disease because of increased iron-catalyzed free radical–mediated oxidative stress.

Objective To test the hypothesis that reducing body iron stores through phlebotomy will influence clinical outcomes in a cohort of patients with symptomatic peripheral arterial disease (PAD).

Design, Setting, and Patients Multicenter, randomized, controlled, single-blinded clinical trial based on the Iron (Fe) and Atherosclerosis Study (FeAST) (VA Cooperative Study #410) and conducted between May 1, 1999, and April 30, 2005, within the Department of Veterans Affairs Cooperative Studies Program and enrolling 1277 patients with symptomatic but stable PAD. Those with conditions likely to cause acute-phase increase of the ferritin level or with a diagnosis of visceral malignancy within the preceding 5 years were excluded. Analysis was by intent-to-treat.

Intervention Patients were assigned to a control group (n=641) or to a group undergoing reduction of iron stores by phlebotomy with removal of defined volumes of blood at 6-month intervals (avoiding iron deficiency) (n=636), stratified by hospital, age, and baseline smoking status, diagnosis of diabetes mellitus, ratio of high-density to low-density lipoprotein cholesterol level, and ferritin level.

Main Outcome Measures The primary end point was all-cause mortality; the secondary end point was death plus nonfatal myocardial infarction and stroke.

Results There were no significant differences between treatment groups for the primary or secondary study end points. All-cause deaths occurred in 148 patients (23%) in the control group and in 125 (20%) in the iron-reduction group (hazard ratio (HR), 0.85; 95% confidence interval (CI), 0.67-1.08; *P*=.17). Death plus nonfatal myocardial infarction and stroke occurred in 205 patients (32%) in the control group and in 180 (28%) in the iron-reduction group (HR, 0.88; 95% CI, 0.72-1.07; *P*=.20).

Conclusion Reduction of body iron stores in patients with symptomatic PAD did not significantly decrease all-cause mortality or death plus nonfatal myocardial infarction and stroke.

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ACCUMULATION OF IRON IN EXcess of physiologic requirements has been implicated in the risk of several chronic diseases through increased iron-catalyzed free radical–mediated oxidative stress.[1-8] Common diseases of aging that have been attributed to this mechanism include cardiovascular disease and cancer.[1,5,8-14]

Sullivan[15] formulated the iron-heart hypothesis of atherosclerotic cardiovascular disease to explain the age-related increase in risk of myocardial infarction (MI) in women following menopause. Serum ferritin levels average about 25 ng/mL in children and in women prior to menopause but increase in concert with increasing MI risk in women with cessation of menstrual blood loss.[15] Rates of MI increase earlier in men, in whom ferritin levels begin to increase from childhood levels in the late teens.[1,15] Increasing levels of body iron might be causative, a hypoth-

For editorial comment see p 639.

Author Affiliations: White River Junction VA Medical Center, Research Service, Department of Veterans Affairs Medical Center, White River Junction, Vt (Dr Zacharski and Ms Howes); VA Palo Alto Health Care System, Research Service, Department of Veterans Affairs Medical Center, Palo Alto, Calif (Mr Chow and Ms Shamayeva and Drs Dalman and Lavori); Department of Medicine, Dartmouth Medical School, Lebanon, NH (Drs Zacharski, Baron, and Malenka); Departments of Surgery (Dr Dalman) and Health Research and Policy (Dr Lavori), Stanford University Medical School, Palo Alto; and the University of Florida College of Medicine, Gainesville, and North Florida/South Georgia Veterans Health, Research Service, Department of Veterans Affairs Medical Center, Gainesville (Dr Ozaki).
Corresponding Author: Leo R. Zacharski, MD, Research Service (151), VA Medical Center, 215 N Hartland Rd, White River Junction, VT 05001 (leo.r.zacharski@dartmouth.edu).

esis that can be tested by reducing iron stores.

Substantial preclinical and clinical literature supports the contribution of iron-related oxidative stress to the pathogenesis of atherosclerotic cardiovascular disease.[10-14,16,17] However, this concept remains controversial because of differences in findings between clinical studies having variable experimental design.[14,16,17] Nonetheless, this hypothesis has continued to gain support from mechanistic and clinical studies.[18-26] Several studies have suggested that iron may contribute to the pathogenesis of atherosclerosis relatively early in its course.[11,15,17,19,27-36]

We conducted a randomized controlled study of reduction of body iron stores in patients with peripheral arterial disease (PAD). Phlebotomy was the intervention chosen because reducing iron levels through phlebotomy ameliorates iron-induced lipid peroxidation[37] and because routine blood donation, an "over-the-counter" intervention, has been associated with improved health status and reduced risk of MI.[38,39]

METHODS

Patients

This study was a multicenter, randomized, controlled, single-blinded trial conducted within the Department of Veterans Affairs Cooperative Studies Program and designed to test the hypothesis that reduction in body iron stores by phlebotomy would influence clinical outcomes in patients with symptomatic but stable PAD. Experimental intervention was based on the Iron (Fe) and Atherosclerosis Study (FeAST) (VA Cooperative Study #410), a pilot study that demonstrated the accuracy of a formula for calculating the amount of blood required to be removed to achieve the desired ferritin reduction safely and without causing iron deficiency.[40]

Details of methods including participating site selection; patient entry characteristics; reasons for patient exclusion; informed consent procedures; and methods of randomization, reduction of iron stores by phlebotomy with removal of defined volumes of blood at 6-month intervals, single-blinded outcome assessment, intent-to-treat follow-up procedures, and study administration have been reported.[41] Men and postmenopausal women with symptomatic but stable PAD and an ankle-brachial blood pressure ratio (ankle/brachial index) of 0.85 or less on 2 separate occasions were included provided they were not part of another experimental protocol and were judged able to meet protocol requirements. Included patients were required to have no bleeding within the past 6 months, no abnormality of iron metabolism, and to avoid taking iron supplements and donating blood during the study. The protocol was approved by the institutional review boards at each participating institution and by a national board; all included patients provided written informed consent.[41]

Entry criteria minimized accrual of patients with acute-phase elevation of ferritin level; patients with visceral malignancy within the preceding 5 years were excluded. Patients older than 21 years with advanced but stable PAD meeting defined entry criteria were entered over 3.5 years. Participants were not excluded based on severity or site of vascular disease in addition to PAD; medication use; or comorbid conditions including diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease, or degenerative joint disease (scored on data forms when patients required treatment). Patients were required to have a hematocrit greater than 35% (in the absence of iron deficiency) and a ferritin level less than 400 ng/mL, but there was no predefined minimum ferritin level.

Demographic, medical, and lifestyle information was collected at study entry by interview and review of the medical records. Race was self-reported using standard federal categories.[42] Body mass index was calculated as weight in kilograms divided by height in meters squared, based on direct measurement. Smoking was recorded as ever vs never used inhaled tobacco products regularly. Alcohol use was recorded as the number of drinks usually consumed per week. For this report, alcohol was assessed as either used or not used currently. Angina class was based on the Goldman Scale.[43] Patient recruitment began on May 1, 1999, and ended on October 31, 2002; follow-up ended on April 30, 2005 (6-year study duration).

Randomization, Intervention, and Outcome Measures

Patients were assigned to control or iron-reduction groups through computer randomization stratified according to participating hospital, age ($\leq$60 and $>$60 years), ferritin level at entry (calculated based on the rolling mean of prior entrants), diagnosis of DM, smoking status, and ratio of high-density lipoprotein cholesterol (HDL-C) level to low-density lipoprotein cholesterol (LDL-C) level (also calculated based on the rolling mean of prior entrants). Randomization was performed using the adaptive allocation method balanced on the marginal total of each factor.

For patients in the iron-reduction group, phlebotomy was scheduled at 6-month intervals so that appropriate volumes of blood were removed repeatedly throughout follow-up to achieve trough ferritin levels of approximately 25 ng/mL and peak ferritin levels prior to the next phlebotomy episode of approximately 60 ng/mL, a range presumed to be optimal.[15,44] Compliance with intervention was assessed by 2 methods. First, the cumulative percentage of the amount of blood calculated for removal that was actually removed across all phlebotomy episodes was determined. Second, analysis of the effect of phlebotomy on the separation of ferritin levels over time between the 2 strategies was calculated. Follow-up data were obtained at 6-month intervals, at which time patients were interviewed and medical records reviewed for interim data-sheet entries by an observer blinded to intervention status. Follow-up began at the time of randomization.

The primary end point was all-cause mortality; the secondary end point was death plus nonfatal MI and stroke. Briefly, the diagnosis of nonfatal MI required the presence of definite biomarkers of MI in addition to symptoms consistent with acute MI or electrocardiographic changes consistent with MI or ischemia. The diagnosis of nonfatal stroke required evidence of ischemic or hemorrhagic brain injury manifested by either persistent impairment of motor ability, loss of vision in 1 or both eyes, or impairment of language use or speech production, each lasting 24 hours or longer; or severe headache associated with loss or alteration of consciousness, persistent neurologic signs, and/or neck stiffness (meningismus).

An external data and safety monitoring board reviewed all data during the course of the study. An external end points adjudication committee blinded to intervention status adjudicated primary and secondary study end points.

Statistical Methods

The target sample size was calculated using the method of Lakatos[45,46] for a comparative time-to-event study based on the log-rank statistic. Assumptions included an annual mortality rate of 6.8% in the control group, a 30% decreased mortality in the iron-reduction group, a 5% 2-sided significance level, and 85% power. After adjusting for staggered accrual, lag in 3-month treatment effect, annual rate of losses to follow-up of 1%, and a 2.5% rate of noncompliance in year 1 and a rate of 1% thereafter, the sample size was calculated to be 1600 for a planned minimum follow-up of 2.5 years. Although randomization was stratified by hospital, age, and baseline smoking status, DM status, HDL-C/LDL-C ratio, and ferritin level, we did not incorporate stratification in the sample-size calculations and instead assumed average rates across strata. The lower than expected sample size of 1277 achieved, extension of the study from 5 to 6 years, and observed noncompliance rates of 16% in the first year and 3.2% thereafter (which were higher than expected) resulted in 68% power to detect a 30% reduction in mortality.

Formal interim analyses for efficacy were conducted as requested by the data and safety monitoring board using the method of Lan and DeMets,[47] with an O'Brien-Fleming–type spending function[48] that adjusted for multiple looks at the data while preserving a near-nominal overall significance level.

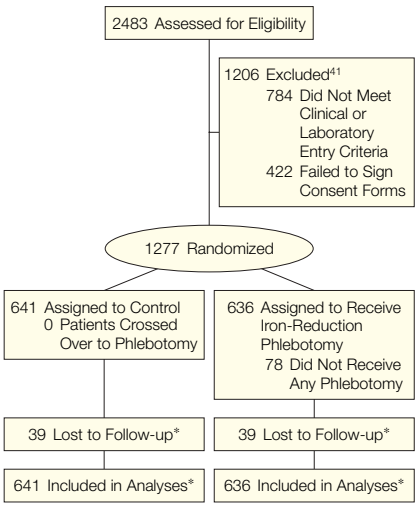
Data analysis was on an intent-to-treat basis. Since we were able to either assess patients to the end of the study or track end point status through the Department of Veterans Affairs national database located in Austin, Tex,[49] data from all randomized patients were included in the primary and secondary end point analyses, even though some patients were withdrawn from the study early.

Baseline patient characteristics were compared using the χ^2 test, t test, or analysis of variance. Survival curves were used to characterize the timing of the primary and secondary end points during follow-up according to the method of Kaplan and Meier.[50] Since accrual rate and duration, as well as control event rates, differed from prior assumptions, the achieved study precision was best revealed by the width of confidence intervals (CIs) for effect. The Cox proportional hazards regression model[51] was used to compute hazard ratios (HRs) and 95% CIs, with adjustment for covariates.

The 5 prespecified biological covariates identified at entry (age, smoking status, diagnosis of DM, HDL-C/LDL-C ratio, and ferritin level) were analyzed using corresponding product terms in the proportional hazards regression models for possible interaction with treatment assignment. The interaction analysis was an exploratory, post hoc analysis; adjustments for multiple comparisons for this interaction analysis were not performed.

To explore and describe the nonlinear effect of the age interaction with treatment on the outcomes, age was fitted in the linear tail-restricted cubic spline function with 3 knots in the Cox proportional hazards model, and the log relative hazards were plotted (using the Design and Hmisc packages in R version 2.3.1 [R foundation for Statistical Computing; available at http://www.R-project.org]). Interaction analyses of the 5 stratifiers were plotted with age, HDL-C/LDL-C ratio, and ferritin level presented as quartiles.

Figure 1. Study Flow



*Since all patients were accessible through the end of the study or trackable through the Austin database, data from all randomized patients were included in the primary and secondary end point analyses.

RESULTS

The flow of patients through this study is summarized in FIGURE 1. Because of slower than expected enrollment, patient accrual was extended to 3.5 years while retaining the 2.5-year minimum follow-up.[41]

Of the 1277 patients entered from 24 participating medical centers, 641 were randomly assigned to the control group and 636 to the iron-reduction group. Baseline patient characteristics are shown in TABLE 1. Entry ferritin levels were similar to those found in the general middle-aged and older adult population[1] and in the pilot study.[40] Control and iron-reduction groups were comparable at baseline for age; sex; race; tobacco and alcohol use; diagnosis of DM and hypertension; body mass index; HDL-C/LDL-C ratio; levels of fi-

brinogen, homocysteine, and ferritin; and cardiovascular comorbid conditions.[41] Patients generally had advanced, systemic atherosclerotic cardiovascular disease. The control group had higher proportions of white individuals and statin drug users at entry than the iron-reduction group.

Follow-up at the end of the study was complete for all 1277 patients; total follow-up was approximately 4500 patient-years, and the observed mean follow-up was 3.50 (SD, 1.49) years per patient. Because patient outcome could be tracked through the Austin database, the total mean follow-up was 1649 (SD, 361) days, or 4.52 years per patient. The follow-up interval for control and iron-reduction patients was similar to that for the overall cohort.

The 636 patients assigned to undergo iron reduction had 3141 phlebotomy episodes (median episodes per patient, 5 [interquartile range, 3-8]; range, 0-11). The mean blood volume required for removal to achieve ferritin reduction was calculated as 970 mL; the actual volume removed was 920 mL. Initial iron reduction required a mean of 37 days and 2.3 visits. The mean volume of blood removed at 6-month intervals to maintain ferritin reduction was 411 (SD, 278) mL. Of patients assigned to undergo iron reduction, 88% had the required amount of blood removed within the first year in the study, 65% had 50% or more of the calculated amount of blood actually removed (ie, greater than 50% compliance with intervention), and the average patient had 72% of the calculated amount of blood removed over the course of follow-up.

The mean ferritin level across all follow-up visits remained unchanged from entry levels in control patients (122.5 [SD, 87.2] ng/mL) but was reduced significantly to levels considered desirable based on previous data[15,44] in those undergoing iron reduction (79.7 [SD, 71.9] ng/mL) ($P<.001$). The mean ferritin level across all 6-month follow-up visits in patients assigned to undergo iron reduction having 50% or greater compliance with phlebotomy was 58.3 (SD, 31.5) ng/mL ($P<.001$ for comparison with levels in control patients), corresponding to levels targeted by the protocol.[40,41] Compliance with phlebotomy was unaffected by severity of vascular disease and comorbid conditions at entry. Minor vasovagal events were reported in 6 patients in the iron-reduction group, all of which were attributed to volume depletion due to phlebotomy.

Table 1. Comparison of Control and Iron-Reduction Groups at Study Entry

Variable	No. (%) Control (n = 641)	No. (%) Iron Reduction (n = 636)	*P* Value
Age, mean (SD), y	67 (8)	67 (9)	.83
Men	634 (98.9)	628 (98.7)	.80
White	555 (86.6)	521 (81.9)	.02
Tobacco use	617 (96.3)	606 (95.3)	.40
Alcohol use	186 (29.0)	188 (29.6)	.85
Diabetes	235 (36.6)	239 (37.6)	.72
Hypertension	486 (75.8)	491 (77.2)	.59
BMI, mean (SD)*	28.2 (5.3)	28.1 (4.8)	.65
HDL-C/LDL-C ratio, mean (SD)	0.4 (0.2)	0.4 (0.3)	.87
Statin use	401 (62.6)	356 (56.0)	.01
Fibrinogen, mean (SD), mg/dL	391.5 (90.5)	390.2 (96.1)	.75
Homocysteine, mean (SD), µmol/L	12.3 (3.4)	12.4 (4.0)	.96
Ferritin, mean (SD), ng/mL	122.4 (83.0)	121.4 (82.3)	.86
Comorbid conditions			
Any cardiovascular	514 (80.2)	499 (78.5)	.44
Atherosclerotic heart disease only	346 (54.0)	355 (55.8)	.53
Cardiovascular disease only	229 (35.7)	238 (37.4)	.56
Peripheral arterial disease only	317 (49.5)	304 (47.8)	.57
No. of conditions			
1	223 (34.8)	205 (32.2)	.34
2	204 (31.8)	190 (29.9)	.46
3	87 (13.6)	104 (16.3)	.18

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Calculated as weight in kilograms divided by height in meters squared.

Table 2. Comparison of Control and Iron-Reduction Groups for Primary (All-Cause Mortality) and Secondary (Death Plus Nonfatal MI and Stroke) Outcome Events

Outcome	Total (N = 1277)	Control (n = 641)	Iron Reduction (n = 636)	HR (95% CI)	*P* Value
Primary end point	273 (21.4)	148 (23.1)	125 (19.7)	0.85 (0.67-1.08)	.17
Secondary end point	385 (30.1)	205 (32)	180 (28.3)	0.88 (0.72-1.07)	.20
MI	119 (9.3)	58 (9)	61 (9.6)	1.01 (0.70-1.47)	.95
Stroke	61 (4.8)	29 (4.5)	32 (5)	1.22 (0.71-2.10)	.46

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

End Point Analyses

No statistically significant difference between treatment groups was observed for either the primary end point (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.67-1.08; $P=.17$) or the secondary end point (HR, 0.88; 95% CI, 0.72-1.07; $P=.20$) (TABLE 2). Kaplan-Meier curves for the primary and secondary study end points for the control and iron-reduction groups are shown in FIGURE 2. Excluding patients in both groups with entry ferritin levels of less than 60 ng/mL and in those in the iron-reduction group with less than 50% adherence did not change the HR for treatment in either the primary or secondary end points. Neither the cumulative incidence nor the time to occurrence of other nonfatal peripheral, coronary, and

cerebral vascular events during follow-up differed between groups.

Subgroup Analyses

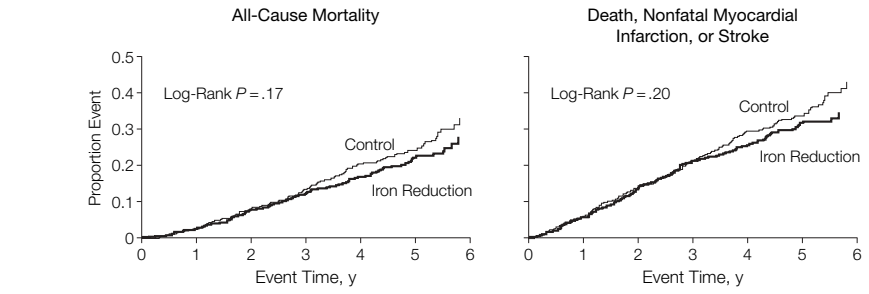
Post hoc analyses were performed to determine whether effects of iron reduction differed across subgroups defined by the 5 factors used at entry to stratify the randomization (FIGURE 3). These interaction plots appear to suggest improvement with iron reduction in patients without diabetes and in smokers, and graded improvement based on highest HDL-C/LDL-C ratio quartile, lowest ferritin level quartile, and youngest age quartile. Although these trends were similar for the primary and secondary end points, these results are exploratory and unadjusted for multiple comparisons.

Further post hoc analyses were conducted for the primary and secondary study end points, treating age as a continuous variable (FIGURE 4). Comparison of treatment groups revealed that age interacted nonlinearly with treatment in both the primary ($P=.04$) and secondary ($P<.001$) end points. Compared with control patients, those in the youngest age quartile alone assigned to undergo iron reduction had a reduction in the primary end point (unadjusted HR, 0.47; 95% CI, 0.24-0.90; $P=.02$) and a reduction in the secondary end point (unadjusted HR, 0.41; 95% CI, 0.24-0.68; $P<.001$). Thus, iron reduction appeared to improve outcome to a significantly greater extent in younger compared with older patients.

COMMENT

The hypothesis that accumulated iron contributes to disease risk through iron-catalyzed free radical–mediated damage to critical biomolecules and through altered cellular function rests on secure biochemical grounds.[1-8,52] However, the relationship between iron and disease has, as aptly expressed by Wood,[16] remained "in hiding" because of inconsistent find-

Figure 2. Kaplan-Meier Analyses of the Primary (All-Cause Mortality) and Secondary (Death plus Nonfatal Myocardial Infarction or Stroke) Study End Points for the Entire Study Cohort, by Intervention Group

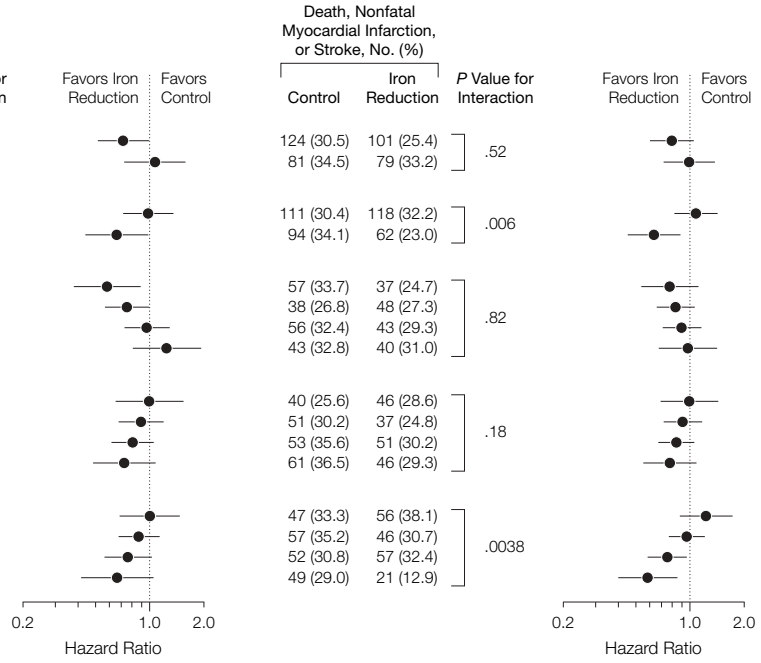


No. at Risk

Control	641	622	586	502	343	193	641	600	549	451	297	163
Iron Reduction	636	617	585	506	347	179	636	597	546	452	311	152

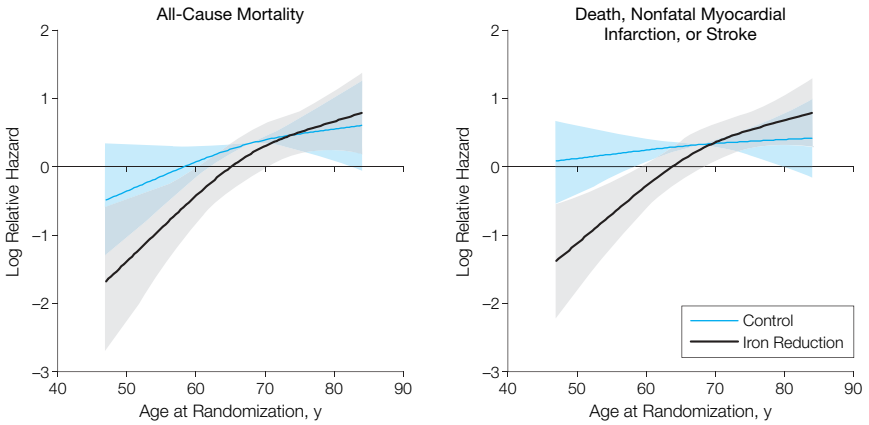
Figure 3. Association Between 5 Prespecified Randomization Variables at Study Entry and the Primary (All-Cause Mortality) and Secondary (Death plus Nonfatal Myocardial Infarction or Stroke) Study End Points

Characteristic	No. of Patients: Control	No. of Patients: Iron Reduction	Mortality, No. (%): Control	Mortality, No. (%): Iron Reduction	*P* Value for Interaction	Death, Nonfatal Myocardial Infarction, or Stroke, No. (%): Control	Death, Nonfatal Myocardial Infarction, or Stroke, No. (%): Iron Reduction	*P* Value for Interaction
Diabetes								
No	406	398	94 (23.2)	69 (17.3)	.25	124 (30.5)	101 (25.4)	.52
Yes	235	238	54 (23.0)	56 (23.5)		81 (34.5)	79 (33.2)	
Smoker								
No	365	367	84 (23.0)	82 (22.3)	.06	111 (30.4)	118 (32.2)	.006
Yes	276	269	64 (23.2)	43 (16.0)		94 (34.1)	62 (23.0)	
HDL/LDL Ratio								
≥0.506	169	150	48 (28.4)	23 (15.3)	.13	57 (33.7)	37 (24.7)	.82
0.381-0.505	142	176	26 (18.3)	34 (19.3)		38 (26.8)	48 (27.3)	
0.289-0.380	173	147	39 (22.5)	31 (21.1)		56 (32.4)	43 (29.3)	
≤0.288	131	129	29 (22.1)	31 (24.0)		43 (32.8)	40 (31.0)	
Ferritin, ng/mL								
≤169-<400	156	161	26 (16.7)	33 (20.5)	.15	40 (25.6)	46 (28.6)	.18
104-≤168	169	149	39 (23.1)	25 (16.8)		51 (30.2)	37 (24.8)	
60-≤103	149	169	40 (26.8)	35 (20.7)		53 (35.6)	51 (30.2)	
≤59	167	157	43 (25.7)	32 (20.4)		61 (36.5)	46 (29.3)	
Age, y								
75-87	141	147	39 (27.7)	39 (26.5)	.10	47 (33.3)	56 (38.1)	.0038
69-74	162	150	43 (26.5)	35 (23.3)		57 (35.2)	46 (30.7)	
62-68	169	176	38 (22.5)	38 (21.6)		52 (30.8)	57 (32.4)	
43-61	169	163	28 (16.6)	13 (8.0)		49 (29.0)	21 (12.9)	



HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Error bars indicate 95% confidence intervals.

Figure 4. Association Between Age and the Log Relative Hazard for the Primary (All-Cause Mortality) and Secondary (Death plus Nonfatal Myocardial Infarction or Stroke) Study End Points



Solid lines indicate the log relative hazards of the control and iron-reduction groups; tinted areas, 95% confidence intervals ($P = .04$ for difference in primary end point; $P = .001$ for secondary end point). See "Methods" for details.

ings between clinical studies having variable experimental design.[10-14,16,17] Examples of such design differences include the use of the percentage of transferrin saturation[1,18,53] or non–transferrin-bound iron levels[54] for disease correlations which, unlike the ferritin level, are not confirmed measures of body iron stores suitable for epidemiologic studies[1]; admixture of patients with and without genetic predisposition to increased iron accumulation[55]; differences in the mix of numerous other confounding and uncontrolled risk factors between studies[14,16,17,56,57]; and failure to analyze outcome according to age and other potential interacting variables.[11,15,17,19]

Data reported from this randomized clinical trial may explain previous conflicting reports. Preplanned analyses of the primary (all-cause mortality) and secondary (death plus nonfatal MI and stroke) end points performed on the entire study cohort showed no effect of iron reduction. However, there was a significant interaction with age (1 of 5 prespecified biological stratifying factors), suggesting that a beneficial effect might exist in younger patients, an observation that coincides with findings of others.

Sullivan[15] emphasized differential coronary risk between male and female individuals before the fifth decade of life. Haidari et al[19] found a significant relationship between the serum ferritin level and risk of coronary artery disease in male patients younger than 50 years. Ramakrishna et al[11] reviewed evidence consistent with a contribution of iron to atherosclerosis but at a relatively early age.

Possible effects of iron reduction on cardiovascular outcomes in younger individuals may be interpreted in light of growing interest in the importance of risk factors in early atherogenesis.[27-36] Juonala et al[28] reported data for 3596 Finnish individuals studied in 1980 at ages 3 to 18 years. These individuals were restudied in 2001 at ages 24 to 39 years. Risk factors present at the earlier examination (obesity, elevated blood pressure, increased skinfold thickness, high levels of LDL-C and triglycerides, low levels of HDL-C, and smoking) predicted poor vascular health as represented by reduced arterial elasticity when these individuals were restudied. Vascular health deteriorated progressively between ages 24 and 39 years, and deterioration in men preceded deterioration in women. Data from the Bruneck Study[58,59] demonstrated 2 distinct age-related risk profiles. Common risk factors, including levels of body iron stores, were operative in early atherosclerosis, while other risk factors, such as hypercoagulability and DM, were operative in later-stage disease. Age was the strongest risk predictor of atherosclerosis, and the sex difference in the incidence of atherosclerosis disappeared after adjustment for body iron stores. Thus, potentially preventable and reversible free-radical damage relatively early in the course of atherogenesis may lead to advanced disease that is unresponsive to reduction in iron burden.[60-62]

Interactions between age and iron stores in early atherogenesis invite further study, eg, using strategies that measure effects of iron reduction on vessel wall thickness[58,59] or arterial elasticity.[31] Zheng et al[23] showed significantly improved arterial elasticity in high-frequency blood donors (mean ferritin level, 17 ng/mL) compared with lower-frequency blood donors (mean ferritin level, 52 ng/mL). While the mean age of individuals studied was about 60 years, the relatively low ferritin levels in both groups (due to routine blood donation) are much more typical of individuals in their teens and twenties and, especially, premenopausal women,[1] suggesting that vascular health might be preserved into later life by maintaining low iron levels over time.

The present study has several limitations. Because of the lower than expected accrual, the study was underpowered overall and particularly underpowered to definitively assess outcomes in younger patients and smokers. While interactions between iron reduction and other variables, such as age and smoking, were apparent, data were inadequate to determine definitively whether 1 or more of these variables interacted biologically with iron-reduction therapy. The study was single-blinded, and primary and secondary end points were adjudicated by a committee external to the study. Nonetheless, concerns remain about possible bias, particularly in subgroup

analyses. Patients with very high ferritin levels were excluded from the study, and the efficacy of iron reduction in individuals with extreme levels of iron stores is unknown.

The FeAST data highlight opportunities for further research. Potentially toxic iron levels appear to exist in asymptomatic individuals. This observation corresponds to the fact that ingested iron accumulates imperceptibly; iron cannot be recognized as noxious by taste, smell, or the amount ingested. Thus, iron stores increase slowly over years or decades to levels not obviously related temporally to disease that seems to appear capriciously. Patterns in and extent of elevated iron levels over time may account not only for differences in disease risk according to age and sex[15] but also for increased disease risk in black individuals, whose iron levels exceed those of white individuals.[1] Mean ferritin levels decline in individuals older than age 70 years, consistent with the concept that lower levels of body iron may be conducive to greater longevity.[1]

The FeAST data show that it should be possible to test definitively whether controlling iron levels may reduce disease risk. Additional research is needed to further define ferrotoxic diseases, stratify risk reduction with intervention, and clarify mechanisms, particularly in younger patients.

Author Contribution: Mr Chow and Ms Shamayeva had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Zacharski, Chow, Howes, Baron, Dalman, Malenka, Ozaki, Lavori.
Acquisition of data: Zacharski, Chow, Howes, Shamayeva, Dalman, Ozaki.
Analysis and interpretation of data: Zacharski, Chow, Howes, Shamayeva, Baron, Dalman, Malenka, Ozaki, Lavori.
Drafting of the manuscript: Zacharski, Chow, Lavori.
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Study supervision: Zacharski, Chow, Howes, Shamayeva, Baron, Dalman, Malenka, Ozaki, Lavori.
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VA Cooperative Study #410 Personnel and Centers: *Study Chairman's Office:* Leo R. Zacharski, MD (Study Chairman), Paula Howes, MS, APRN (National Study Coordinator), M Heath. *Executive Committee:* L. R. Zacharski, MD (Chairman), B. K. Chow, P. Howes, C. K. Ozaki, MD, R. L. Dalman, MD, J. A. Baron, MD, D. L. Makenka, MD. *Data and Safety Monitoring Board:* B. Massie, MD (Chairman), P. Carson, MD, T. Colton, PhD, K. Detre, PhD, M. Gaziano, MD, S. Gottlieb, MD. *Endpoints Adjudication Committee:* J. F. Plehn, MD (Chairman), M. D. Tischler, MD, P. S. Rahko, MD, D. C. Hess, MD, T. J. DeGraba, MD, L. C. Pettigrew, MD. *National Human Rights Committee:* C. Giese (Chairperson). *The Palo Alto Cooperative Studies Program Coordinating Center:* P. Lavori, B. Chow, G. Shamayeva, L. Planting, L. Sheridan, B. Ventura. *Participating VA Medical Centers (listed in descending order of the number of patients enrolled):* Little Rock, Ark (M. Moursi, C. McDonald, J. Englehart, D. Doggett); Madison, Wis (J. Hoch, J. Burks, B. Dunlap); Houston, Tex (A. Blaustein, C. Pellegrino, C. Rowe, L. Lacy, R. Scott); Gainesville, Fla (C.K. Ozaki, A. Irwin, P. Irwin); Reno, Nev (R. DePalma, H.T. Cafferata, P. May, V. Hayes, K. Solomon, F. McKeon); Pittsburgh, Pa (M. Amidi, A. Sonel, M. Bell, J. Moorhead, M. DiTommas); Leavenworth, Kan (D. Courtney, M. Cook, J. Moppin); Long Beach, Calif (I. Gordon, L. Willis, W. Wong, K. Zalecki, D. Guizado, E. Berry, J. Ng); Hines, Ill (J. Third, A. White, J. Azolin, M. Ryan, A. Zuluaga, A. Vondruska); Palo Alto, Calif (R.L. Dalman, A. Hoffman, S. Thunen, S. Marinos, D. Yu); White River Junction, Vt (R.J. Powell, D. Balestra, D. O'Rourke, E. Belles, P. Howes); Louisville, Ky (S. Wagner, K. Doeshuk, M. Olligus, M. Alshaher, T. Abdul-Baki); Salt Lake City, Utah (S. Galt, M. Elstad, G. Treiman, L. Bhiranghi, C. Korowski, M. Jalilvand, D. Jost, S. Hatton-Ward, S. Granger); Lexington, Ky (T. Schwarcz, E. Endean, N. Lewis, J. Warner-Carpenter, P. Rowan, B. Broughton); San Juan, Puerto Rico (L.R. Ospina, J. Santos, A. Deleon, C. Pedrosa); Milwaukee, Wis (R. Cambria, G. Seabrook, A. Scott, S. Framberg, C. Kallio); Boston, Mass (W. Johnson, M. Watkins, J. Hamilton, A. Wrobel, B. Dionian), Durham, NC (J. Gray, C. Peterson, N. Lee, K. Swails); Cleveland, Ohio (S. Busuttil, J. Jean-Claude, D. Fox, K. Kallen, J. Miklacic, R. Jones, L. Tucker); Providence, RI (J. Slaiby, N. Crandell, L. Marquis, M.J. Roy); Birmingham, Ala (D. Whitley, L. Adams, J. Bailey-Griffin, J. Poirier, M. Egan, K. Mitchell, C. Inman); New York, NY (S. Sedlis, R. Burris, M. May, E. Anteola, M. Keary); West Haven, Conn (B. Sumpio, B. Borromeo, A. Dardick); Indianapolis, Ind (D. Cikrit, B. Solooki, C. Adams).
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