Effect of controlled reduction of body iron stores on clinical outcomes in peripheral arterial disease

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Background Published results from a controlled clinical trial in patients with peripheral arterial disease found improved outcomes with iron (ferritin) reduction among middle-aged subjects but not the entire cohort. The mechanism of the age-specific effect was explored.

Methods Randomization to iron reduction (phlebotomy, n = 636) or control (n = 641) stratified by prognostic variables permitted analysis of effects of age and ferritin on primary (all-cause mortality) and secondary (death, nonfatal myocardial infarction, and stroke) outcomes.

Results Iron reduction improved outcomes in youngest age quartile patients (primary outcome hazard ratio [HR] 0.44, 95% CI 0.21-0.92, $P = .028$; secondary outcome HR 0.34, 95% CI 0.19-0.61, $P < .001$). Mean follow-up ferritin levels (MFFL) declined with increasing entry age in controls. Older age ($P = .035$) and higher ferritin ($P < .001$) at entry predicted poorer compliance with phlebotomy and rising MFFL in iron-reduction patients. Intervention produced greater ferritin reduction in younger patients. Improved outcomes with lower MFFL were found in iron-reduction patients (primary outcome HR 1.11, 95% CI 1.01-1.23, $P = .028$; secondary outcome HR 1.10, 95% CI 1.0-1.20, $P = .044$) and the entire cohort (primary outcome HR 1.11, 95% CI 1.01-1.23, $P = .037$). Improved outcomes occurred with MFFL below versus above the median of the entire cohort means (primary outcome HR 1.48, 95% CI 1.14-1.92, $P = .003$; secondary outcome HR 1.22, 95% CI 0.99-1.50, $P = .067$).

Conclusions Lower iron burden predicted improved outcomes overall and was enhanced by phlebotomy. Controlling iron burden may improve survival and prevent or delay nonfatal myocardial infarction and stroke. (Am Heart J 2011;162:949-957.e1.)

The hypothesis that iron burden contributes to cardiovascular (CVD) and other diseases of aging[1-4] was tested in a prospective randomized single-blinded trial, The Iron and Atherosclerosis Study (FeAST) (see online Appendix for The FeAST group and administration), of iron (ferritin) reduction by calibrated phlebotomy in patients with advanced peripheral arterial disease (PAD).[5-8] The primary outcome was all-cause mortality, and the secondary outcome combined death plus nonfatal myocardial infarction and stroke. Time-event (Kaplan-Meier) analyses of curves representing control versus iron-reduction patients failed to show significant differences in primary and secondary outcomes in the entire study cohort.[6] However, preplanned analyses according to randomization variables at entry, including age and ferritin level, showed improved outcomes with iron reduction with younger age by quartile for the secondary end point (P for interaction = .004). Age analyzed as a continuous variable in the Cox proportional hazards regression model and log-relative hazard plots revealed that age interacted nonlinearly with treatment in both primary (hazard ratio [HR] 1.44, 95% CI 1.10-1.88, $P = .04$) and secondary (HR 1.12, 95% CI 0.90-1.40, $P < .001$) outcomes. The Cox model showed improved primary (HR 0.47, 95% CI 0.24-0.90, $P = .02$) and secondary (HR 0.41, 95% CI 0.24-0.68, $P < .001$) outcomes in youngest age quartile patients (age 43-61 years) randomized to iron reduction versus control. Thus, an interaction between age and level of body iron may have masked beneficial effects of iron reduction in the overall cohort.[6]

Levels of body iron in free-living individuals may vary according to dietary iron availability,[9,10] blood loss for various reasons, or other factors to alter iron burden and therefore outcomes. For example, an unexplained lower iron burden may have supported longer survival in

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RCT reg no. NCT00032357.
Submitted March 22, 2011; accepted August 19, 2011.
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0002-8703/$ - see front matter

doi:10.1016/j.ahj.2011.08.013

potential study candidates resulting in their availability for accrual to this study. Variable compliance with phlebotomy during follow-up in patients randomized to iron reduction may have diminished the likelihood of achieving the targeted ferritin reduction and thus influenced outcomes in this secondary prevention study. The design and intent-to-treat methodology used permitted analysis of effects of possible interactions between age and body iron burden on study outcomes.

Methods

The Consort Diagram[6] and methodological details of study protocols, informed consent, randomization and intervention, outcome ascertainment including statistical procedures and sample size calculation, and administration of this study have been reported.[5-7] Institutional review boards at each participating hospital and a national institutional review board approved the protocol. Consenting patients >21 years old with stable PAD were computer randomized by age, ferritin level, high-density lipoprotein (HDL)/low-density lipoprotein (LDL) cholesterol ratio, diabetes, smoking status, and medical center.[6,7] Patients had to have a hematocrit >35% (without iron deficiency) and a ferritin <400 ng/mL, but no predefined minimum ferritin level was specified. The entry ferritin level was used to calculate the amount of blood drawn to achieve the required decrement in serum ferritin ([initial ferritin − 25] × 10 = milliliters of blood to be removed).[5] No more than 1 U (500 mL) of blood was drawn per phlebotomy, and sessions were no more frequent than weekly. The intent-to-treat study design made no prior assumptions regarding possible interactions between age and ferritin level, compromised compliance with phlebotomy, the time required, or completeness of ferritin reduction or follow-up procedures.[6,7]

Patients were followed up at 6-month intervals regardless of whether iron reduction was performed, the amount of blood was removed, or the rapidity or degree of ferritin reduction was achieved. Trough ferritin levels (not measured) were calculated to be approximately 25 ng/mL, and peak levels measured before the next 6-monthly phlebotomy were approximately 60 ng/mL.[5] Levels in this range are considered optimal based on existing data.[2,6,8,9,11] Follow-up ferritin levels reported are the 6-monthly measured (maximum) values used to recalculate the amount of blood to be removed to achieve a decrement in ferritin to 25 ng/mL.[5] Iron reduction was not undertaken if bleeding had occurred, the physician judged the procedure to be not in the patient's interest, the patient declined, the hematocrit was <35%, or when the calculated amount of blood to be removed was <100 mL. Comorbidities were scored when the diagnosis was made clinically and the condition required treatment.[7]

Statistical methods

The clinical trial on which this analysis is based was designed to have an 85% power to detect a 30% decrease in the primary outcome with iron reduction.[6] This 6-year study began on May 1, 1999, and patient entry ended October 31, 2002; follow-up ended on April 30, 2005. Compliance with phlebotomy was assessed by the cumulative percent of the amount of blood calculated for withdrawal that was actually withdrawn across all phlebotomy episodes and by the effect of phlebotomy on the separation of ferritin values between the 2 strategies over time.

Baseline patient characteristics were compared using the χ^2 or *t* test. Time-to-event (Kaplan and Meier) curves characterized the timing of the primary and secondary end points during follow-up.[12] The general linear model was used to measure the effect of morbidities on compliance. Loess plots, locally weighted regression smoothers, illustrated age effects at entry on mean follow-up ferritin levels (MFFLs). Because MFFL values for each arm were not normally distributed, the median of MFFL values was used. The Cox proportional hazards regression model[13] was used to compute HRs and 95% CIs. To describe the effect of MFFL on the primary and secondary CVD outcomes, the log-relative hazards from the Cox proportional hazards model were plotted. Differences having $P < .05$ were considered statistically significant.

This work was supported entirely by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development Cooperative Studies Program.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final content.

Results

Of the 1,277 patients entered, 636 were randomized to iron reduction, and 641, to control. The 2 groups were comparable at entry for clinical and laboratory parameters (Table I).[6] The average entry age, 67 ± 9 (mean ± SD) years, was identical between groups and remained constant over the 3.5 years of accrual to this study. Details on entry and follow-up ferritin levels, number of phlebotomy episodes and volumes of blood removed initially and at 6-monthly intervals, factors effecting compliance with phlebotomy and dose-effect relationships to ferritin reduction, and effects of randomization variables on outcomes have been reported previously.[6,8] The average separation in ferritin values between intervention groups across all follow-up visits was 42.8 ng/mL. The observed mean follow-up was 3.50 years per patient and was comparable for iron-reduction and control patients.[6]

No differences existed between intervention groups for the occurrence of vascular disease or other variables at entry in age quartile 1 patients (age 43-61 years, data not shown). Demographic features of patients in age quartile 1 versus quartiles 2 to 4 (age 62-87 years) are compared in Table I. Age quartile 1 patients had lower homocysteine levels, were more likely to be smokers and to have an adverse (lower) HDL/LDL ratio, and less likely to have hypertension at entry compared with older patients.

Improved outcomes with iron reduction in age quartile 1 patients are shown in Table II. Kaplan-Meier analysis confirmed the significant improvement with iron reduction in these patients (primary outcome HR 0.44, 95% CI 0.21-0.92, $P = .028$ and secondary outcome HR 0.34, 95% CI 0.19-0.61, $P < .001$) (Figure 1A and B) but not in older age quartile patients (data not shown).

Table I. Comparison of patients in age quartile 1 (n = 332) and patients in age quartiles 2 to 4 (n = 945) for certain clinical variables at entry

Variable	Quartile 1	Quartiles 2-4	*P*
Age (y)	55 (4)	71 (6)	<.001
Male, n (%)	328 (98.80)	934 (98.84)	1.000
White race, n (%)	272 (82.53)	802 (84.87)	.335
Tobacco use	331 (99.7)	892 (94.39)	<.001
Alcohol use	111 (33.43)	265 (28.04)	.069
Diabetes	112 (33.73)	361 (38.2)	.165
Hypertension	235 (70.78)	742 (78.52)	.0053
BMI	28.5 (5.3)	28 (4.9)	.123
HDL/LDL ratio	0.41 (0.21)	0.45 (0.25)	<.001
Statin use at entry, n (%)	196 (59.04)	561 (59.37)	.948
Fibrinogen	392.2 (99.4)	390 (91.1)	.962
Homocysteine (μmol/L)	10.5 (2.6)	12.8 (3.8)	<.001
Ferritin at entry, ng/mL	125.4 (82.8)	120.9 (82.9)	.304

Values are presented as mean (±SD), unless otherwise specified. *BMI*, Body mass index.

Table II. Comparison of control (n = 169) and iron-reduction (n = 163) patients in age quartile 1 (n = 332) for major outcome variables

Outcome variable	Control	Iron reduction	*P*
Primary end point: all-cause mortality	28 (16.6)	13 (8)	.020
Secondary end point: combined death, MI, and stroke*	49 (29)	21 (12.9)	<.001
Death	28 (16.6)	13 (8)	.020
Nonfatal MI only	17 (10.1)	9 (5.5)	.154
Nonfatal stroke only	11 (6.5)	5 (3.1)	.200

Values are presented as n (%). *MI*, Myocardial infarction.
*Certain patients had >1 end point.

The effect of several entry variables on compliance with phlebotomy is shown in Table III. Occurrence of vascular disease and comorbidities had no effect on compliance. However, compliance was significantly reduced in patients with higher entry ferritin levels ($P < .001$) and older age ($P = .035$).

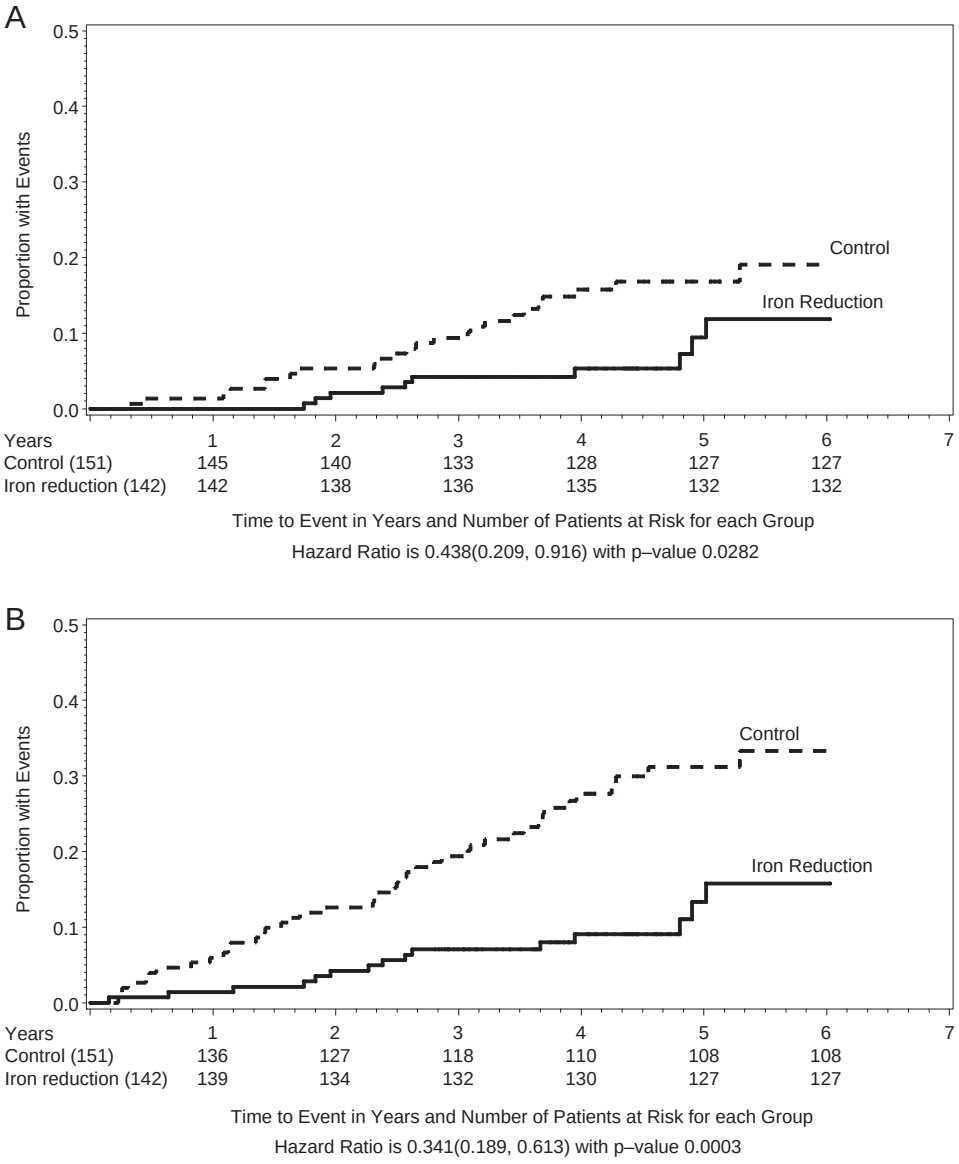
The effect of entry age on MFFL is shown in Figure 2. Mean follow-up ferritin levels declined with increasing age in control patients, suggesting that lower body iron burden may have allowed patients with vascular disease in general to survive to older age such that they were available for entry to the study. Intervention would obscure a similar effect of age on MFFL in iron-reduction patients. Mean follow-up ferritin levels were lower in iron-reduction compared with control patients but rose with increasing age, reflecting decreased compliance with phlebotomy with increasing entry age and ferritin level (Figure 2, Table III). These opposing patterns revealed greater ferritin reduction in younger iron-reduction patients and convergence of MFFL between intervention groups with increasing age (Figure 2).

Progressively increased risk of both primary and secondary outcomes was observed with increasing MFFL in iron-reduction patients using log-transformed data (primary outcome HR 1.11, 95% CI 1.01-1.23, $P = .028$ and secondary outcome HR 1.10, 95% CI 1.0-1.20, $P = .044$) (Figure 3A and B). Because body iron burden may vary for reasons other than protocol participation,[9,10] the log-relative hazard for the primary and secondary outcomes was plotted against the MFFL for all patients combined (n = 1,277). This analysis showed progressively increased risk with higher MFFL that was statistically significant for the primary but not the secondary outcome (primary outcome HR 1.11, 95% CI 1.01-1.23, $P = .037$ and secondary outcome HR 1.06, 95% CI 0.97-1.17, $P = .177$, respectively) (Figure 4A and B). Mean follow-up ferritin levels were calculated for all patients, and the median of the means calculated for the entire population (median 78 ng/mL, n = 1,277). Kaplan-Meier plots for the primary and secondary outcomes comparing patients falling above versus below this median showed improved outcomes with lower MFFL for all patients combined (primary outcome HR 1.48, 95% CI 1.14-1.92, $P = .003$; secondary outcome HR 1.22, 95% CI 0.99-1.50, $P = .067$, respectively) (Figure 5A and B). The MFFL in patients randomized to iron reduction having no primary or secondary outcome event over the 6-year follow-up was 76.5 ng/mL (95% CI 71-82).

Discussion

In the FeAST study, preplanned analyses by randomization variables including entry age and ferritin level showed significantly improved outcomes in middle-aged subjects randomized to iron reduction but not in the overall cohort.[6] Analyses reported here demonstrate an interaction between age and both entry and MFFL that might have masked benefits of iron reduction on primary and secondary outcomes. Significantly improved outcomes were found in age quartile 1 patients (age 43-61 years) randomized to iron reduction (Table II, Figure 1A and B). Mean follow-up ferritin levels declined with increasing age at entry in control patients (Figure 2); lower ferritin levels appeared to be associated with greater longevity. Phlebotomy significantly reduced MFFL in iron-reduction compared with control patients, but in contrast to the trend in control patients, MFFL rose with increasing entry age reflecting reduced compliance with phlebotomy associated with increasing entry age and ferritin level (Figure 2, Table III). More successful ferritin reduction with phlebotomy in younger iron-reduction subjects may explain both the improvement in clinical end points in younger individuals and the inability to detect significant benefits in the overall cohort.[6] Significantly improved outcomes with lower MFFL were found

Figure 1



Kaplan-Meier analyses of outcomes for patients in age quartile 1. **A** and **B**, primary outcome HR 0.44, 95% CI 0.21 to 0.92, $P = .028$ and secondary outcome HR 0.34, 95% CI 0.19 to 0.61, $P <$,001, respectively. Numbers below the horizontal axis represent the number of patients observed at each follow-up interval.

in iron-reduction patients (Figure 3A and B). Similar trends were observed in the entire study cohort that were statistically significant for the primary end point (Figure 4A and B). A protective effect of lower iron burden was also found in Kaplan-Meier analysis comparing patients having MFFL above versus below the median for the entire cohort (78 ng/mL) (Figure 5A and B). Iron reduction patients having no outcome event over the entire duration of the study had an MFFL of 76.5 ng/mL. Beneficial effects of lower MFFL in the total cohort were more pronounced with iron-reduction intervention and could not be explained by other characteristics of the study population (Table I). These data show a dose/effect relationship between the MFFL and clinical outcomes upon removal of the amount of iron represented by 1 or 2 U of blood.

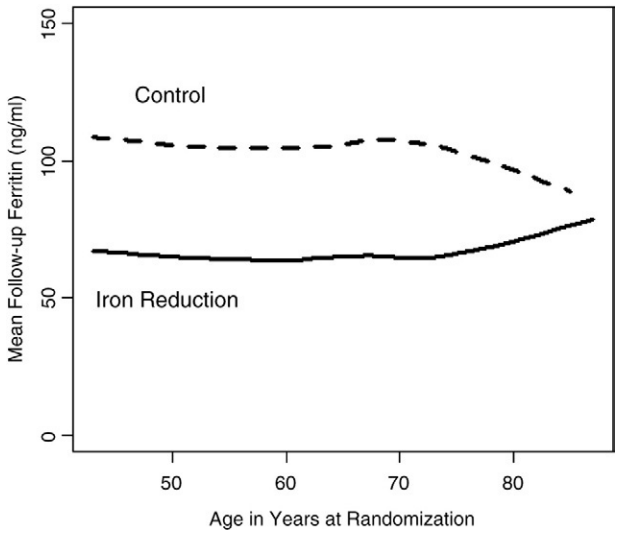
Other data suggest an interaction between age, body iron burden, and disease. For example, curves

Table III. Effect of certain variables at entry on subsequent compliance with phlebotomy

Parameter	Nonstandardized β	−95% CI	+95% CI	P
Ferritin	−0.114	−0.145	−0.082	<.0001
Age	−0.316	−0.609	−0.024	.035
Complications of PVD	2.898	−2.282	8.077	.273
Atherosclerotic heart disease	0.439	−4.972	5.850	.874
Cerebrovascular disease	4.193	−1.247	9.633	.131
Diabetes mellitus	−0.553	−5.789	4.684	.836
COPD	−6.376	−12.772	0.021	.051
Degenerative joint disease	−1.229	−6.593	4.134	.654
Hypertension	1.404	−4.856	7.663	.661

Linear regression analysis; n = 635 (1 value was missing from 1 patient who was not included in this analysis). *COPD*, Chronic obstructive pulmonary disease; see text for details.

Figure 2



Loess smoothing plots showing convergence of MFFLs with increasing age at entry in patients randomized to iron reduction versus control (see text).

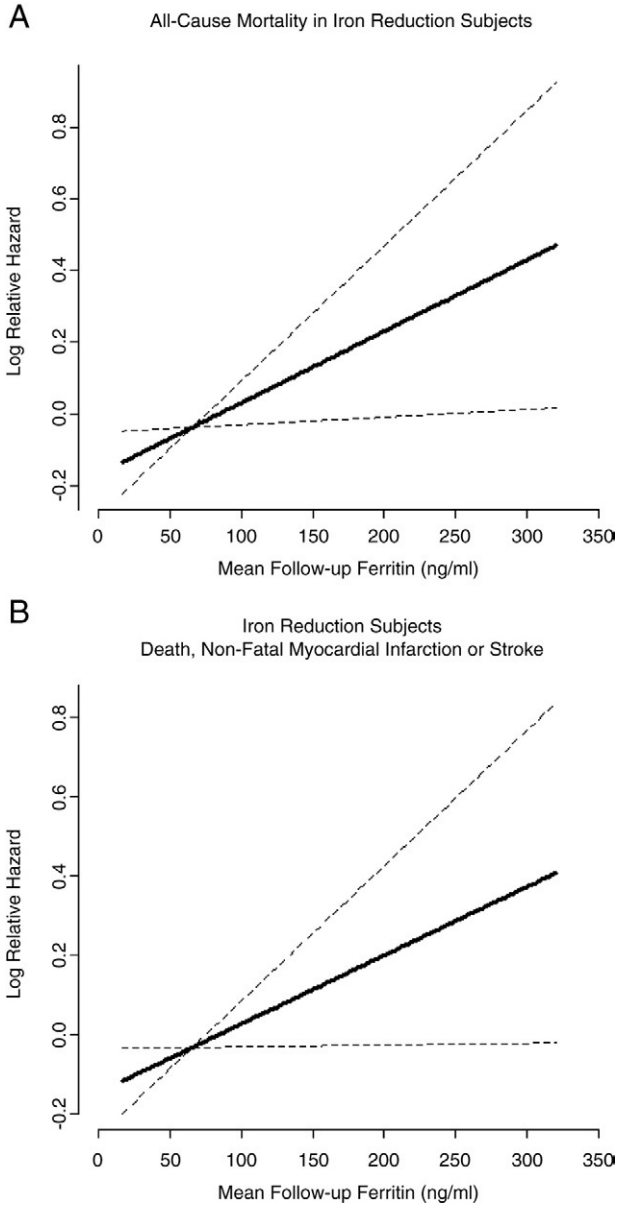
describing ferritin levels by age and sex derived from National Health and Nutrition Examination Survey (NHANES) III data showed that mean ferritin levels in males rose after the adolescent growth spurt and plateaued at approximately 148 ng/mL between ages 30 and 70 years.[2] Ferritin levels declined thereafter to approximately 80 ng/mL by age >90 years. Declining ferritin levels with advancing age in males resembled data on (primarily male) control patients reported here suggesting that lower ferritin levels are characteristic of longevity.

Epidemiologic data on free-living men of age >79 years compared morbidity and measures of oxidative stress and iron status between a high-risk cohort from northern Europe versus a low-risk cohort from southern Europe (the Mediterranean effect).[9] Dietary iron excess (attributed to iron-containing vitamin supplements, alcohol excess, and food composition) was associated with significantly higher ferritin levels, measures of oxidative stress, and disease burden in elderly northern European men.[9] Ferritin levels in high-risk northern Europeans (approximately 135 ng/mL) resembled those at baseline in the present study, whereas ferritin levels in low-risk southern Europeans (approximately 69 ng/mL) resembled those in iron-reduction patients. Benefits of lower iron burden may therefore be achievable in free-living populations by avoiding excess dietary iron.

The iron hypothesis[1] has been challenged primarily on 2 counts. One is that atherosclerosis risk is not increased in subjects with hereditary hemochromatosis.[14] However, deficiency of hepcidin in hemochromatosis enhances both iron transport across the intestinal endothelium and export from macrophages, which must retain iron to form foam cells necessary for atherogenesis.[15-17] Reduced CVD risk in hemochromatosis may, to some extent, be genotype specific,[18,19] and hemochromatosis patients remain at risk for iron-related cardiomyopathy,[19] endothelial dysfunction,[20] and arrhythmias.[21]

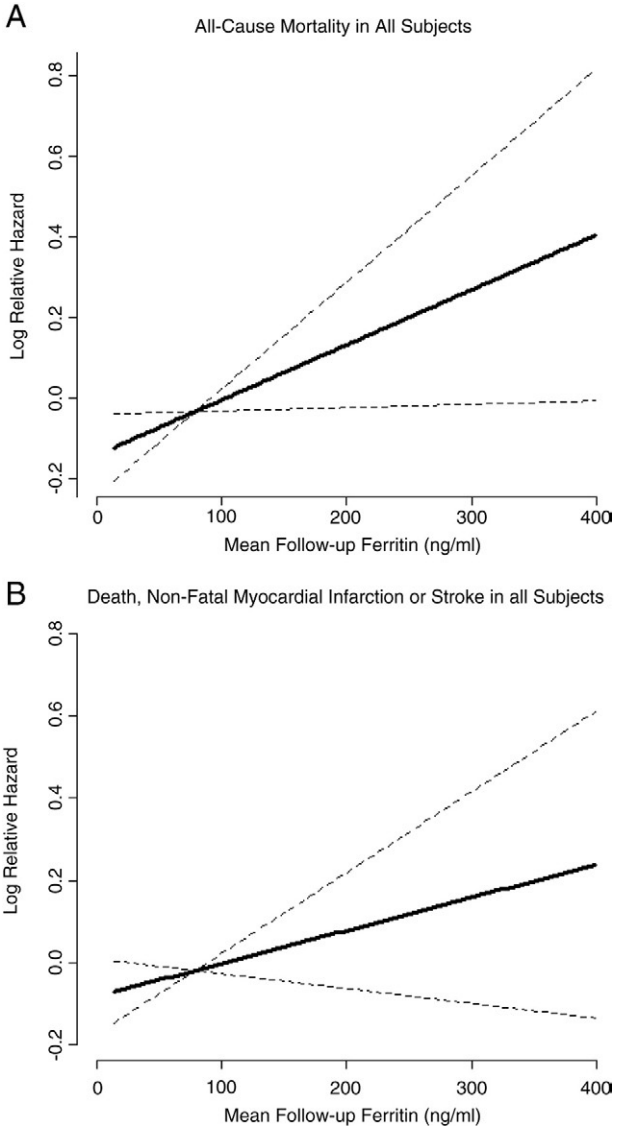
A second challenge has come from certain epidemiologic studies that may have underestimated the impact of iron burden on CVD risk.[22,23] Sun et al[22] reported no association between coronary risk and iron status in women in the Nurses Health Study. However, iron estimates were determined at a single time point (mean age at sampling 60.3 years) (Table I) at the beginning of a 9-year observation period. The mean entry ferritin level, 105.4 ng/mL, is typical of at-risk postmenopausal women[2] and may have changed unpredictably from baseline over the 9-year follow-up. No information was provided on effects of the well-known postmenopausal rise in body iron burden[2] or of interventional reduction of body iron burden on CVD events in at-risk patients.[22] Similar deficiencies exist in the report of Menke et al,[23] who found no correlation between mortality and measures of iron

Figure 3



Association between MFFL and log-relative hazard for study outcomes in patients randomized to iron reduction (n = 636). **A** and **B**, primary outcome HR 1.11, 95% CI 1.01 to 1.23, *P* = .028 and secondary outcome HR 1.10, 95% CI 1.0 to 1.20, *P* = .044, respectively. Solid lines represent the log-relative hazard and, the dashed lines, the 95% CI.

Figure 4

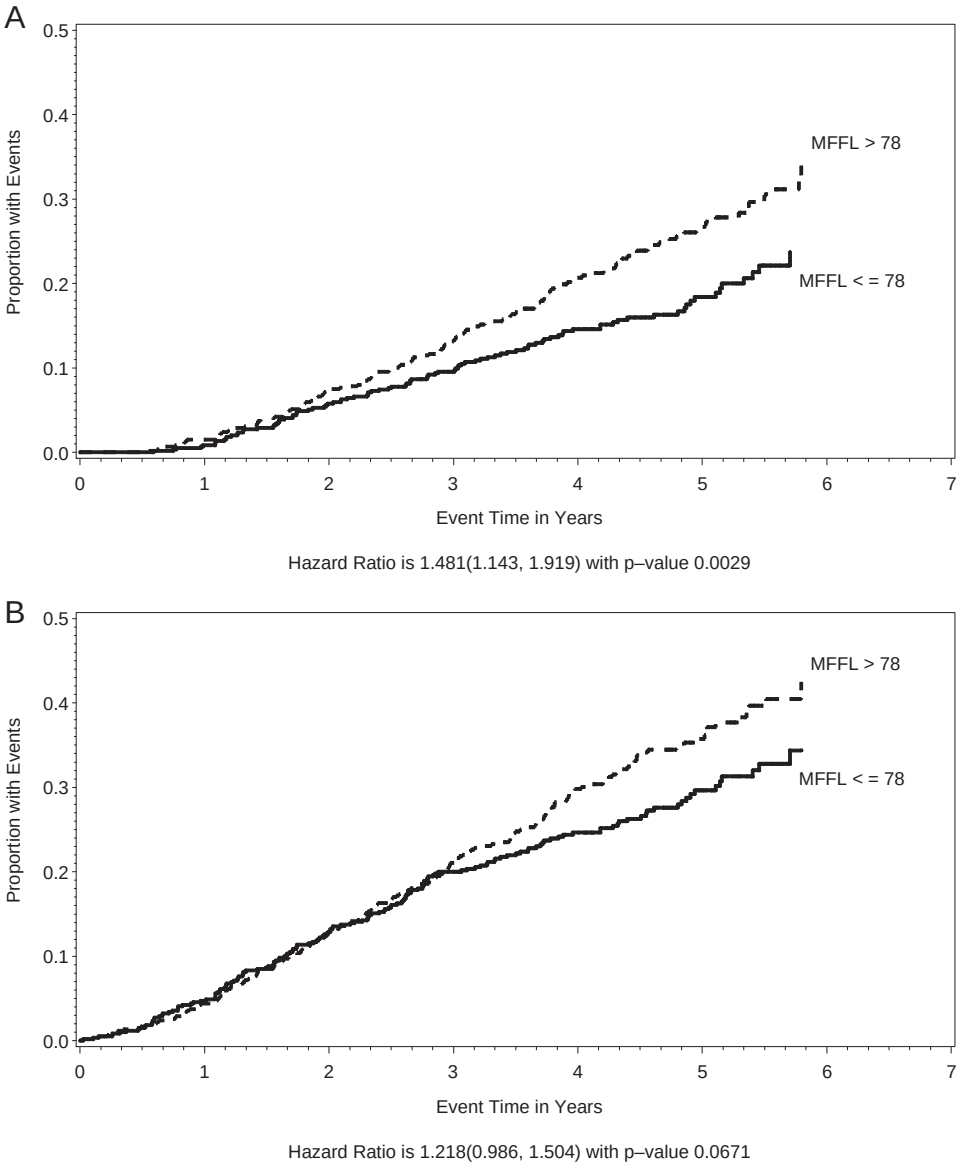


Association between MFFL and log-relative hazard for study outcomes in the entire cohort (n = 1,277). **A** and **B**, primary outcome HR 1.11, 95% CI 1.01 to 1.23, *P* = .037 and secondary outcome HR 1.06, 95% CI 0.97 to 1.17, *P* = .177, respectively. Solid lines represent the log-relative hazard, and the dashed lines, the 95% CI.

status determined 12 to 18 years earlier. Sullivan[24] reviewed the design limitations of other studies challenging the iron hypothesis and emphasized that "studies of only iron replete subjects would not be expected to reveal protective effects of iron depletion..." Mechanisms by which iron excess predisposes to CVD have been reviewed.[1,3-7,11,16,17,25,26]

This study in primarily males with PAD targeted ferritin levels between 25 and 60 ng/mL that are characteristic of children and premenopausal women.[2] Ferritin levels could be maintained in this range by removal of approximately 411 mL of blood twice per year, an amount resembling that associated with

Figure 5



Kaplan-Meier analyses of primary and secondary study outcomes (**A** and **B**, respectively) for the entire study cohort (n = 1,277) comparing patients having MFFLs above versus below the median of the means for the cohort: primary outcome HR 1.48, 95% CI 1.14 to 1.92, *P* = .003 and secondary outcome HR 1.22, 95% CI 0.99 to 1.50, *P* = .067, respectively.

improved health status in free-living blood donors.[27] This volume approximates the 780-mL average volume of blood lost per year with menstruation.[28] Neither vascular disease severity nor comorbidities at entry had an effect on compliance, and this methodology may be applicable to studies in symptomatic CVD. Conversely, blood transfusion (delivery of an iron load) increases morbidity and mortality in patients having cardiac surgery[29] and with coronary artery disease[30-32] associated with an at-risk iron burden[33]; iron reduction in these conditions might be protective. Phlebotomy ameliorates cardiac arrhythmias in hemochromatosis[21] and transfusional[21] and ambient iron overload[34] suggesting that benefits may apply to the general population. Intraoperative infusion of the iron chelator, desferrioxamine, into the coronary circulation improves the long-term outcome of patients having coronary artery bypass surgery.[35]

Strengths of the present study in established PAD include its prospective randomized controlled single-blinded design, graded iron reduction by calibrated phlebotomy, 6-year duration, and intent-to-treat analysis.[5-8] Because the MFFL in iron-reduction patients having no outcome event over the entire follow-up interval was approximately 76.5 ng/mL, future studies might reasonably target maximum ferritin levels below this readily achievable level.

Limitations include the fact that almost all subjects were male, that the contribution of CVD risk factors such as hypertension and diabetes are undefined, and that applicability to females or other populations remains uncertain. There is no way to determine what ferritin levels were on initial diagnosis of CVD or what factors might have influenced changes in ferritin levels subsequently. Ferritin values over the entire range possible in a free-living population were not available for analysis. Greater benefits may have been realized with more rigorous ferritin reduction or with treatment of earlier disease. Possible interactions between iron burden and other variables (such as hemochromatosis genotype, comorbidities, use of statins, or other medications, etc) remain undefined.

Conclusions

We postulate that iron reduction may ameliorate established vascular disease[6,11,30-35] and that disease prevention may be achieved by controlling presymptomatic iron burden.[9] Low-risk ferritin levels appear to be uncommon in most free-living populations as that which exist in northern Europe[9] and the United States,[2] presumably because of iron overdosing from consumption of iron-containing vitamins and minerals and processed foods adulterated with iron.[9,10,36] Qualitative differences in diet also likely contribute importantly to iron homeostasis.[10,37,38] Beard[39] summarized data from iron balance studies consistent with the existence of a natural brake on iron absorption at ferritin levels of approximately 60 to 80 ng/mL above which absorption slows. However, most adults appear to have artificially exaggerated iron intake capable of overcoming this brake resulting in increasing ferritin levels that presumably overwhelm endogenous antioxidant mechanisms leading to increased disease risk.[10,39] Preserving optimal iron nutrition may be a safe and cost-effective strategy for managing and preventing of diseases of aging.

Acknowledgements

The authors wish to express their deep and sincere appreciation to members of the VA Cooperative Study no. 410 investigator group for their extraordinary commitment and accomplishments.

Disclosures

This material is based on work supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development Cooperative Studies Program; Study no. 410.

Conflict of interest: none declared.

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Appendix. The FeAST group and administration

Study Chairman's office: LR Zacharski, study chairperson, P Howes, National Study Coordinator, M Heath.

Executive Committee: LR Zacharski (chairperson), BK Chow, P Howes, CK Ozaki, RL Dalman, JA Baron, DL Makenka.

Data Safety and Monitoring Board: B Massie (chairperson), P Carson, T Colton, K Detre, M Gaziano, S Gottlieb.

End points Adjudication Committee: JF Plehn (chairperson), MD Tischler, PS Rahko, DC Hess, TJ DeGraba, LC Pettigrew.

National Human Rights Committee: C Giese (chairperson) and 11 members.

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, AR (M Moursi, C McDonald, J Englehart, D Doggett); Madison, WI (J Hoch, J Burks, B Dunlap); Houston, TX (A Blaustein, C Pellegrino, C Rowe, L Lacy, R Scott); Gainesville, FL (CK Ozaki, A Irwin, P Irwin); Reno, NV (R DePalma, HT Cafferata, P May, V Hayes, K Solomon, F McKeon); Pittsburgh, PA (M Amidi, A Sonel, M Bell, J Moorhead, M DiTommas); Leavenworth, KS (D Courtney, M Cook, J Moppin); Long Beach, CA (I Gordon, L Willis, W Wong, K Zalecki, D Guizado, E Berry, J Ng); Hines, IL (J Third, A White, J Azolin, M Ryan, A Zuluaga, A Vondruska); Palo Alto, CA (RL Dalman, A Hoffman, S Thunen, S Marinos, D Yu); White River Junction, VT (RJ 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, UT (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, PR (L. R. Ospina, J. Santos, A. Deleon, C. Pedrosa); Milwaukee, WI (R Cambria, G Seabrook, A Scott, S Framberg, C Kallio); Boston, MA (W Johnson, M Watkins, J Hamilton, A Wrobel, B Dionian), Durham, NC (J Gray, C Peterson, N. Lee, K. Swails); Cleveland, OH (S Busuttil, J Jean-Claude, D Fox, K Kallen, J Miklacic, R Jones, L Tucker); Providence, RI (J Slaiby, N Crandell, L Marquis, MJ Roy); Birmingham, AL (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, CT (B Sumpio, B Borromeo, A Dardick); Indianapolis, IN (D Cikrit, B Solooki, C Adams).