# The Statin–Iron Nexus: Anti-Inflammatory Intervention for Arterial Disease Prevention

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*Objectives.* We postulated the existence of a statin–iron nexus by which statins improve cardiovascular disease outcomes at least partially by countering proinflammatory effects of excess iron stores.

*Methods.* Using data from a clinical trial of iron (ferritin) reduction in advanced peripheral arterial disease, the Iron and Atherosclerosis Study, we compared effects of ferritin levels versus high-density lipoprotein to low-density lipoprotein ratios (both were randomization variables) on clinical outcomes in participants receiving and not receiving statins.

*Results.* Statins increased high-density lipoprotein to low-density lipoprotein ratios and reduced ferritin levels by noninteracting mechanisms. Improved clinical outcomes were associated with lower ferritin levels but not with improved lipid status.

*Conclusions.* There are commonalities between the clinical benefits of statins and the maintenance of physiologic iron levels. Iron reduction may be a safe and low-cost alternative to statins. (*Am J Public Health*. Published online ahead of print February 14, 2013: e1–e8. doi:10.2105/AJPH.2012.301163)

Statins, prescribed widely for primary and secondary prevention of cardiovascular disease (CVD),[1,2] have been recommended for expanded use in apparently healthy individuals at risk for CVD.[3] On February 8, 2010 the US Food and Drug Administration approved rosuvastatin (Crestor) for

> reducing the likelihood of a heart attack or stroke or the need for a procedure to treat blocked or narrowed arteries in patients who have never been told they have heart disease but are nevertheless at increased risk of a cardiac event.[3]

The target population included men older than 50 years and women older than 60 years with elevated levels of high-sensitivity C-reactive protein and an additional CVD risk factor such as smoking, hypertension, a family history of premature CVD, or low levels of high-density lipoprotein (HDL) cholesterol.[4]

Computational studies concluded that a "treat-all" approach to CVD prevention is cost-effective.[5–7] However, misgivings over widespread statin use have been expressed on the basis of overall societal impact, including cost and toxicity, especially with the extension of treatment to children.[8–10] The wholesale cost of a 40-milligram rosuvastatin tablet at a local pharmacy recently was $4.22. Side effects of statins involve primarily liver[11] and muscle[12] damage. Statins also have been associated with risk of diabetes,[13] nonmelanotic skin cancer,[14] and adverse drug interactions.[15–17] Although statins are of proven efficacy,[1,2] CVD remains a major public health problem beckoning further innovative approaches to prevention and treatment.[18]

The clinical benefits of statins relate to their ability to reduce cholesterol levels by inhibiting the rate-limiting cholesterol biosynthetic enzyme 3-hydroxy-3-methylglutaryl-CoA reductase.[1,2] However, drugs other than statins that effectively lower lipids have not improved clinical outcomes.[19] Statins are effective in individuals with normal lipid levels[1,2] exhibiting pleiotropic properties unrelated to lipid reduction.[20,21] These properties include stimulation of new blood vessel[22] and bone formation[23] and the reduction of inflammation and oxidative stress.[24–35]

Mascitelli and Goldstein provided evidence that the beneficial effects of statins may result from their ability to favorably alter iron homeostasis.[36] Pathologic cellular iron retention has been implicated in systemic oxidative stress, vascular inflammation, and atherogenesis. Statins reduce ferritin levels in patients with advanced CVD,[37–39] renal disease,[40] and diabetes.[41] Data from a randomized trial of iron (ferritin) reduction (the Iron and Atherosclerosis Study [FeAST]) in participants with advanced peripheral arterial disease (PAD) showed significant improvement in all-cause mortality and combined death plus nonfatal myocardial infarction and stroke with iron reduction.[42] There is evidence suggesting that iron reduction may provide an alternative to statins for reducing inflammation associated with atherosclerosis.

## METHODS

The data we collected prospectively from FeAST allowed us to compare the effects of HDL/low-density lipoprotein (LDL) ratios versus those of ferritin levels (both randomization variables) on clinical outcomes. We searched FeAST data to test our hypothesis that clinical benefits of statins might be correlated with effects on iron homeostasis rather than cholesterol levels.

The Veterans Affairs Cooperative Studies Program supported FeAST, a prospective, randomized, controlled, single-blind clinical trial of iron reduction by graded phlebotomy.[42,43] We tested the hypothesis that improved clinical outcomes might be achieved by reducing iron stores, represented by the serum ferritin, to levels typical of children and premenopausal women (about 25–50 ng/mL).[44] The consolidated standards of reporting trials diagram, study design, informed consent procedures, and other methodological details have been described in detail elsewhere.[42,43] The majority of the 1277 participants (average age = 67 years) were male, and all participants were patients with PAD who were cancer-free on entry.[42,43] We used the entry ferritin level to calculate the amount of blood to be removed to target a trough ferritin level of about 25 nanograms per milliliter in participants randomized to iron reduction. We measured ferritin levels and HDL/LDL ratios (both were randomization

variables)[43] in all participants at 6-month follow-up visits. We used 6-month ferritin levels to calculate the amount of blood to be removed to maintain the targeted reduced iron status in patients randomized to iron reduction.

We subjected the effects of variables of interest on the primary end point, all-cause mortality, to intent-to-treat analysis.[42,43] When FeAST began, statins were increasingly becoming the standard of care treatment of all patients with PAD. Although not a randomization variable, we tracked statin use prospectively over the 6-year study period.[42,43] These study design features provided a unique opportunity to explore interactions between statin use, HDL/LDL ratios, and ferritin levels during a 6-year period.

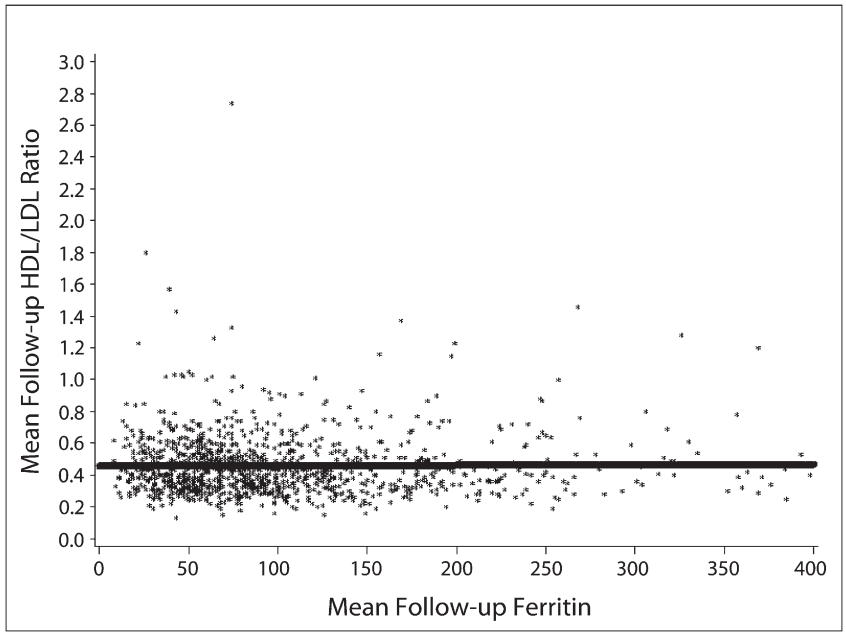
We designed FeAST to have an 85% power to detect a 30% decrease in the primary outcome with iron reduction.[43] We used time-to-event[45] curves to describe the timing of the primary end point during follow-up.[45] Because mean follow-up ferritin levels were not normally distributed, we used the median of mean follow-up ferritin level values. We calculated the mean along with the SD for continuous variables. We used the unadjusted Cox proportional hazards regression model[46] to compute hazard ratios (HRs) and 95% confidence intervals (CIs). To describe the effect of mean follow-up HDL/LDL ratios (or mean follow-up ferritin levels) on the primary end point, we plotted the log-relative hazards from the Cox proportional hazards model. We compared other types of categorical and continuous variables using the $\chi^2$ test or *t* test, respectively. We used univariate linear regression analyses to test the relationship between continuous variables. We considered differences of $P<.05$ statistically significant.

## RESULTS

Statins were used at entry by 59.0% of participants.[43] Mean ferritin levels at entry were significantly lower in patients taking statins (117.53 ng/mL; SD = 80.07) compared with patients not taking statins (128.65 ng/mL; SD = 86.39; $P=.037$).[38,39] Statin use at entry was significantly more frequent in participants randomized to control, 62.6%, than in participants randomized to iron reduction, 56.0% ($P=.01$).[43] The mean HDL/LDL ratio at entry in patients not receiving statins was 0.41 (SD = 0.28), whereas the mean HDL/LDL ratio in patients receiving statins was, as expected, significantly higher at 0.46 (SD = 0.20; $P<.001$). Linear regression analysis showed no relationship between ferritin levels and HDL/LDL ratio at entry for the total cohort ($P=.83$), for statin users ($P=.69$), or for participants not receiving statins ($P=.75$). Statin use tracked at 6-month follow-up visits increased over time and again occurred more frequently in control participants, 84.2%, than in iron reduction participants, 79.4% ($P=.031$). Statin use was recorded at 72.7% of visits of control participants and 66.5% of visits of iron reduction participants ($P=.011$). Increasing statin prescriptions over time for all PAD patients likely explains the observation that the mean follow-up HDL/LDL ratios for control (0.45; SD = 0.20) and iron reduction (0.46; SD = 0.18) participants approached the ratios observed in statin users (0.46; SD = 0.20) at entry.

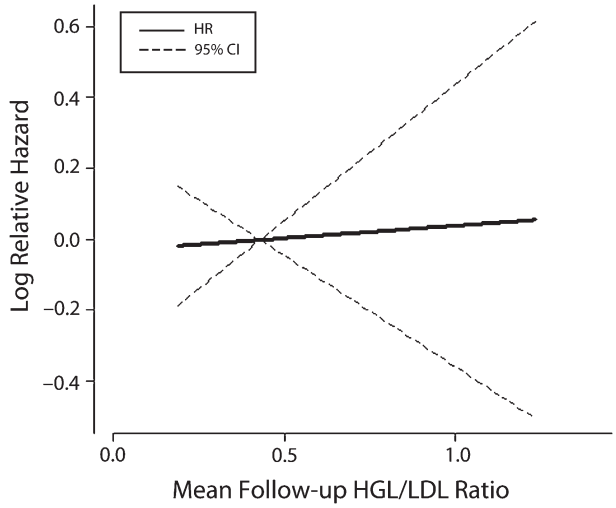
Iron reduction by phlebotomy significantly lowered mean follow-up ferritin level ($P<.001$).[42,43] As found for entry values, linear regression analysis showed no relationship between mean follow-up HDL/LDL ratios and mean follow-up ferritin levels either for all participants combined ($P=.89$; Figure 1) or for participants randomized to iron reduction ($P=.58$). Using linear regression analysis, we noted a significant association between mean follow-up ferritin level and the log-relative hazard for all-cause mortality as described previously for the entire study cohort ($P=.037$) as well as for participants randomized to iron reduction ($P=.028$).[42]

By contrast, from the Cox proportional hazard regression model, we did not find a relationship between the mean follow-up HDL/LDL ratios versus the log-relative hazard for all-cause mortality for the entire cohort (HR = 1.01; 95% CI = 0.89, 1.16; $P=.84$; Figure 2). Previous Kaplan–Meier analysis of mortality for the entire study cohort comparing patients having mean follow-up ferritin level above versus below the median of the means also showed significantly improved survival for participants with lower ferritin levels ($P=.003$).[42] Kaplan–Meier analysis of mean follow-up HDL/LDL ratios comparing patients having ratios above versus below the median of the means showed no effect of increasing mean follow-up HDL/LDL ratio on mortality (Figure 3).




*Note.* HDL = high-density lipoprotein; LDL = low-density lipoprotein. There was no association between mean follow-up ferritin levels and mean follow-up HDL/LDL ratios ($P = .89$).

**FIGURE 1—Linear regression analysis for the overall cohort (n = 1277): the Iron and Atherosclerosis Study (FeAST), Multiple US Veterans Administration Centers, 1999–2005.**



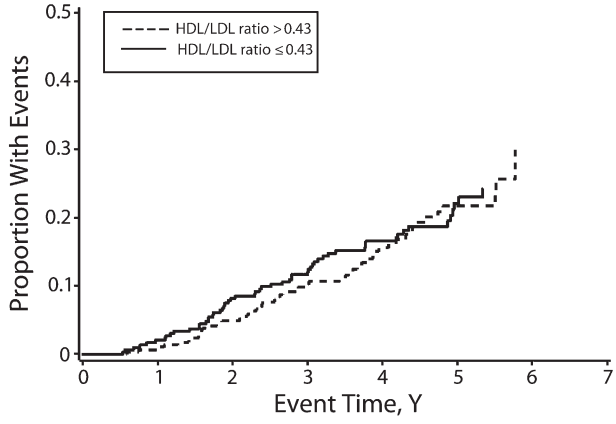

*Note.* CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein. HR = 1.01 (95% CI = 0.89, 1.16; *P* = .84).

**FIGURE 2—Mean follow-up HDL/LDL ratio and log-relative hazard for all-cause mortality for the overall cohort (n = 1277): the Iron and Atherosclerosis Study (FeAST), Multiple US Veterans Administration Centers, 1999–2005.**

## DISCUSSION

We found that improved cholesterol fractions and reduced ferritin levels with statin treatment appear to occur by noninteracting mechanisms (Figure 1). Reduced ferritin levels related significantly to improved outcomes in FeAST,[42] whereas improved HDL/LDL ratios had no effect on outcomes (Figures 2 and 3). To some extent, statin use during this trial may have contributed to outcomes; however, control participants would likely have benefitted more because they received statins significantly more frequently than did iron reduction participants. Improved outcomes with iron reduction regardless of statin use[42] suggest that iron reduction rather than altered lipid status was the more powerful—or possibly the sole—contributor to improved outcomes in FeAST. It also seems likely that statin benefits relate, at least in part, to reduction of iron-catalyzed oxidative stress and inflammation rather than to improved lipid status.[25–28,47–53]

We compared effects on clinical outcomes of follow-up levels of cholesterol fractions versus ferritin levels[42,43] and found that reduction of iron stores improved outcomes whereas improvement of cholesterol levels over time did not. Favorable effects of statins on iron homeostasis suggested the existence of a relationship, a statin–iron nexus, possibly accounting for statin benefits in the absence of hyperlipidemia.[36] The existence of this relationship appears to be supported by basic, pathophysiologic, and epidemiological observations as well as by clinical trial data.




*Note.* HDL = high-density lipoprotein; LDL = low-density lipoprotein. There was no difference between patients having mean follow-up HDL/LDL ratios above vs below the median of the means for the cohort (hazard ratio = 0.97; 95% confidence interval = 0.66, 1.41; *P* = .857).

**FIGURE 3—Kaplan–Meier analysis for all-cause mortality in the overall cohort (n = 1277): the Iron and Atherosclerosis Study (FeAST), Multiple US Veterans Administration Centers, 1999–2005.**

### Statins, Iron Homeostasis, and Inflammation

Statins may improve CVD outcomes by correcting abnormal cellular iron homeostasis through the induction of heme oxygenase (HO)-1 and inhibition of hepcidin expression.[36] The rate-controlling enzyme of heme catabolism, HO-1, counteracts oxidative endothelial damage leading to the inception and progression of atherosclerosis.[54–56] HO-1–mediated heme degradation is key to mobilization and extrusion of macrophage iron. HO-1 inhibition results in cellular loading of redox-active iron.[56] An extensive literature shows that the anti-inflammatory properties of statins result from their ability to induce HO-1 expression.[47–53] Statins may be effective in CVD in part because they increase HO-1 expression[47–53] to protect arteries from further oxidative damage by mobilizing and removing plaque iron.[57]

Hepcidin, the key hormonal regulator of iron distribution, binds to the cell membrane iron export protein, ferroportin, causing internalization and degradation of the hepcidin–ferroportin complex, resulting in macrophage iron retention.[58] Reduced hepcidin levels enhance iron export, thus reducing macrophage iron.[58] Foam cell formation and subsequent atherosclerosis require retention of macrophage iron and cholesterol.[59–62] Patients at risk for

vascular disease express elevated hepcidin levels with increased macrophage iron; both hepcidin and macrophage iron levels are associated with the presence of carotid plaques.[63] Pharmacologic inhibition of hepcidin experimentally also enhances efflux of macrophage cholesterol and iron to inhibit foam cell formation and atherosclerosis.[64] Hepcidin overexpression promotes plaque destabilization and increased inflammatory cytokine release, intracellular lipid and iron accumulation, oxidative stress, and macrophage apoptosis in an experimental model of accelerated atherosclerosis.[65] Adverse effects of hepcidin can be negated by blocking hepcidin expression as well as by iron chelation.[65] Statins reduced hepcidin levels,[66] whereas iron administration increased hepcidin levels.[67]

Numerous studies have shown that iron in physiologic excess promotes oxidative stress,[30–35] which is inhibited by statins.[24–28] Statins exert antioxidant and anti-inflammatory effects by inhibiting the generation of reactive oxygen species.[4,25–28,68,69] Iron excess catalyzes reactive oxygen species production[30–32] and is both pro-oxidant and proinflammatory.[30–32,60,61,70–74] Excess iron is implicated in the pleiotropic effects of statins, including regulation of angiogenesis,[75] microvascular function,[76] bone formation and dissolution,[77] lipid oxidation,[78] and C-reactive protein levels.[37–39] Statins inhibit experimental atherosclerosis,[79] whereas iron administration increases[69] and iron chelation inhibits[80] experimental atherosclerosis. Macrophage cholesterol uptake and retention are cardinal features of atherogenesis,[81] whereas enhanced cholesterol efflux reverses atherosclerosis.[82] Statins enhance macrophage cholesterol efflux[83–86] and inhibit foam cell formation.[59] By contrast, iron excess drives macrophage scavenger receptor expression,[60] cholesterol accumulation,[60] and foam cell formation.[70,80]

## Commonality of Effects of Statins and Low Iron Status

An extensive literature further suggests commonalities between statin effects and lower iron status. The data sources we reviewed included MEDLINE, Scopus, and the Cochrane Library. We searched these sources for prior reports of statin–iron relationships and possible mechanisms underlying ferritin reduction in participants receiving statins, using the following terms: statin–cardiovascular mortality mesh, iron metabolism–HO mesh, hepcidin, macrophage iron, foam cell atherosclerosis ferroportin, and ferritin. We evaluated design methodology, criteria for defining data quality and report selection, and corresponding terminology using prior guidelines.[87,88]

Level A data from prospective randomized trials of statins[1,2] and iron reduction[42] on CVD outcomes exist, but we did not find any level A data on the comparative benefits of statins versus iron reduction on clinical outcomes. Level B evidence surfaced that may be classified as "patient-oriented evidence that matters"; effects on morbidity, mortality, or quality of life; or "disease-oriented evidence." Disease-oriented evidence consisted of reports of changes in measures of response or other parameters observed in well-designed experimental, clinical, and epidemiological studies.[87,88] We excluded descriptive, observational, and epidemiological studies lacking appropriate interventions, measurements, or comparator populations. The results of this search, summarized in Table 1, show strong congruity of benefits of statins and lower iron status.

## The Epidemiological Data

Middle-aged and older (i.e., aged 30–69 years) men and postmenopausal women that the Food and Drug Administration identified for statin benefit[3] coincide with the age at which serum ferritin levels become maximal[44,125] and the age at which men benefitted most from iron reduction.[42] Plots of ferritin levels by age and gender derived from National Health and Nutrition Examination Survey III data show that, following the adolescent growth spurt, mean ferritin levels in males rise and plateau at about 140 to 150 nanograms per milliliter between the ages of 30 and 70 years.[44,125] Ferritin levels in older age decline, averaging about 80 nanograms per milliliter by age 90 years, a phenomenon consistent with a possible survival benefit of lower iron stores. Ferritin levels in premenopausal women, in whom disease risk is minimal,[126,127] remain in the childhood range, between about 25 and 50 nanograms per milliliter.[44] Ferritin levels in women then rise between the ages of 40 and 60 years to plateau at about 90 to 100 nanograms per milliliter with menopause[44] synchronously with increased disease risk.[126,127]

Epidemiological studies show that low levels of body iron, measures of systemic oxidative stress, and C-reactive protein characterize individuals consuming a Mediterranean-style diet.[89] These individuals exhibit a lower morbidity and greater longevity than does the Northern European population.[89] Lower ferritin levels typical of frequent blood donors are also associated with a reduced risk of cardiac events and overall superior health.[128,129]

**TABLE 1—Clinical and Pathophysiologic Commonality in Benefits of Statins and Low (Physiologic) Iron Status: 1999–2005**

| Observation | References | |
|---|---|---|
| | Iron Effects | Statin Effects |
| Global improvement of cardiovascular outcomes | 42, 89, 90 | 1, 2, 91-93 |
| Favorable carotid artery disease status | 94-96 | 91, 92 |
| Improved insulin resistance | 97-99 | 100 |
| Reduced procoagulant activity | 101-104 | 105-107 |
| Improved vasomotor function | 76, 80, 108 | 109-111 |
| Amelioration of postischemic reperfusion injury | 112 | 113 |
| Improved myocardial perfusion | 114 | 115 |
| Improved outcome following coronary artery procedures | 112, 114, 116, 117 | 115, 118, 119 |
| Amelioration of cardiac arrhythmias | 120, 121 | 122, 123 |
| Improved myocardial function in cardiomyopathy | 120 | 124 |
| Lower high-sensitivity C-reactive protein levels | 37-39, 89 | 29, 100 |
| Lower ferritin levels | 42, 43, 89, 90 | 37-41 |

Lower ferritin levels in premenopausal women and elderly men coincide with evidence that those questioning statin efficacy in these individuals have provided.[130]

## The FeAST Data

FeAST trial findings described previously support an association between lower ferritin levels and greater longevity.[42] Regression plots of follow-up ferritin levels versus study outcomes in control and iron reduction participants combined showed significant protective effects of lower iron burden against death and nonfatal myocardial infarction and stroke.[42] Favorable effects were more pronounced with iron reduction.[42] The Food and Drug Administration[3] recommends statin treatment for patients with additional risk factors for CVD. Several clinical CVD risk factors interact with elevated iron stores. These include excessive alcohol use,[131] diabetes,[132] hypertension,[133] high body mass index,[134] and high blood lipid levels.[135] Effects of such variables on CVD risk may have been ameliorated by iron reduction.

## Implications of the Statin–Iron Nexus

The proposal of the existence of a statin–iron nexus results from evidence that statins alter iron homeostasis[47–56] and that both statins and lower ferritin levels appear to be effective in reducing oxidative stress and associated inflammation, resulting in improved clinical outcomes. Certain statin effects appear to be mediated by mechanisms similar to iron reduction. FeAST data suggest that improved cholesterol fractions and reduced ferritin levels with statin treatment occur by noninteracting mechanisms (Figure 1). Lower ferritin levels were associated with significantly better outcomes in FeAST,[42] whereas higher, presumably better, HDL/LDL ratios were not (Figures 2 and 3).

Limitations of this report include the unavailability of dose–effect relationships between statins and measures of cholesterol fractions[19] or ferritin levels.[42,43] Studies of the comparative effects of different statins on iron homeostasis have not been performed. Head-to-head comparisons between statin treatment and iron reduction on clinical outcomes are also unavailable. The cost-effectiveness of iron reduction strategies has yet to be assessed formally as it has for statin treatment,[5,6] but iron reduction may be inferred to be less expensive. The FeAST study, conducted in the Veterans Administration Hospital System, included primarily male participants with PAD, and its generalizability to women and other populations is uncertain.

Strengths of the FeAST study include its prospective randomized controlled single-blind design, 6-year duration, intent-to-treat method of data analysis, and virtually complete follow-up.[42,43] Both the ferritin level and HDL/LDL ratio at entry were randomization variables. Comparison of effects of ferritin reduction and improvement in HDL/LDL ratios was from the same data set. Should the effectiveness of iron reduction be confirmed, concerns over statin treatment benefits versus risks[11–17] might be obviated.[136,137]

## Toward Anti-Inflammatory Treatment of Arterial Disease

Body iron (ferritin) levels, relatively low during childhood and the premenopausal years, rise with aging as dietary intake exceeds loss.[44,125,138,139] Humans have no physiologic mechanism for sensing and excreting excess iron.[30–32] Increased body iron stores occurring with unnecessary ingestion of iron supplements[138,139] may be associated with increased mortality.[90,140,141] Elevated iron stores can be prevented by dietary means[89,138–144] or corrected by blood removal[31–34,42,78,126,144] or iron chelation.[80,108,112,117] Because iron homeostasis is regulated primarily at the level of dietary intake,[89,138,139] benefits of reduced iron burden could be achievable by diet as occurs in the living Mediterranean population,[89,143] which exhibits low levels of ferritin, LDL cholesterol, and markers of lipid oxidation and reduced cardiovascular morbidity and mortality.

Efforts to implement a Mediterranean-style diet in the United States[145] may be less than fully successful because of population-wide exposure to unphysiologic iron supplements ingested involuntarily.[138,141,146] Confirmation of the efficacy of iron reduction might point the way to management of CVD using appropriate dietary measures. An analysis of public policies that affect chronic nutritional iron overdosing is beyond the scope of our study; however, the Food and Drug Administration classification of iron supplements as "generally regarded as safe" may, in the absence of iron deficiency, be open to question.[147]

The finding of a statin–iron nexus suggests the possibility of a low-cost and safe alternative to "treat-all" statin therapy.[3–7] Past confusion from negative epidemiological studies lacking appropriate comparator populations[148] could be resolved by prospective trials of iron reduction in at-risk populations. Favorable outcomes might be attained without a need for universal drug treatment to achieve a low risk range for ferritin levels approximating 75 nanograms per milliliter or lower.[42,89,90] ■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## Contributors

L. R. Zacharski and R. G. DePalma conceptualized the study. L. R. Zacharski drafted the original clinical trial protocol. L. R. Zacharski and B. K. Chow obtained funding. G. Shamayeva and B. K. Chow performed the statistical analyses. All authors contributed to critical revision of the article.


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## Human Participant Protection

The institutional review boards at all participating VA institutions and a national human participants review committee approved the study protocol. All participants provided written informed consent.

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