erated in the presence of iron (4) and this has been used as a possible explanation for the higher incidence of ischemic heart disease in young and middle-aged men compared to premenopausal women, as ferritin concentrations are three times higher in men than in premenopausal women (5). In contrast, more recently published data, like the studies by Aronow (6), Moore et al. (7), and Ascherio and colleagues (8), do not support the hypothesis of a relationship between serum ferritin and atherosclerosis risk.

It is noteworthy that the putative role of iron in the development of atherosclerosis is based primarily on clinical and epidemiological studies. However, only few reports investigating correlations between serum concentration of ferritin and anatomic diagnosis of coronary atherosclerosis assessed by coronary arteriography are available in the published data. We (9) could recently demonstrate that, in patients referred for coronary angiography, higher ferritin concentrations and transferrin-saturation levels (as measures of the amount of circulating iron available to tissues) are not associated with an increased extent of coronary atherosclerosis (as assessed angiographically). In that study (9), estimates of the relative risk of coronary heart disease for the quintile with the highest concentration of serum ferritin as compared with the lowest quintile were 0.83 (95% confidence interval, 0.63 to 1.24).

Another important point seems to be that all the iron indicators used to relate iron status to coronary artery disease (CAD) are affected by inflammation. As a result, an association between CAD and higher serum ferritin levels could be confounded by inflammation (10). A shortcoming of the study by Gaenzer et el. (1) is the lack of information on inflammatory markers such as C-reactive protein.

In summary, early functional and structural vascular abnormalities in patients with hereditary hemochromatosis may predict both extent of coronary atherosclerosis and the risk of cardiovascular events in this particular patient group, but in subjects without hereditary hemochromatosis our results and data from others do not support the hypothesis that body iron stores, as measured by serum ferritin and transferrin saturation, are related to the risk of CAD. In patients with hereditary hemochromatosis, enhancement of atherogenesis may involve additional mechanisms beyond iron.

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REPLY

We agree with Dr. Auer and colleagues that ferritin levels in our study (1) may be both a reflection of increased iron stores linked to primary iron overload and an indication of a chronic inflammation, as ferritin expression is also regulated by inflammatory cytokines (2,3).

To rule out the possibility that increased ferritin levels in hemochromatotic patients are a reflection of an ongoing inflammatory response we performed conventional serum tests for C-reactive protein (CRP), which were all normal in the hemochromatotic subjects included in our study. However, we cannot rule out that by using a high-sensitive CRP assay we could have found low-grade inflammation not detected by the conventional test (4), which would have been of interest because, at least in diabetics, elevated levels of CRP have been associated with early structural changes of arteries (5) and because iron is known to increase formation of hydroxyl radicals during an inflammatory process (6), which will then exert harmful effects toward the endothelium.

However, in our study, changes in endothelial-dependent dilation (EDD) very well correlated with transferrin saturation in a way that higher transferin saturation (TfS) was associated with increased oxidative stress, increased intima-media thickness, and decreased EDD. This observation argues against an important role of inflammation in our setting. This notion is based on the fact that, during inflammation, drastic changes in iron homeostasis and distribution occur, which frequently lead to the development of anemia of chronic disease (7). This condition is characterized by high ferritin levels and low transferrin saturation, the later just being the opposite of what is observed in hemochromatotic patients, even in our study.

Finally, our data demonstrate a close relationship among iron overload, impaired EDD, and increased intima-media thickness, which may not be primarily referred to an underlying inflammatory condition. Nonetheless, determination of high-sensitive CRP will be attractive to see whether iron overload may induce low-grade inflammation in hemochromatotic patients.

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Cost-Effectiveness of a Heart Failure Management Program From the Societal Perspective?

I read with great interest the study by Capomolla et al. (1), which was recently published in this *Journal*. The investigators assessed the cost-effectiveness of an interdisciplinary heart failure management program delivered by day-hospital compared with usual care. In times of increasing pressures to contain health care resource consumption, the study by Capomolla and colleagues represents an important contribution to the literature.

The investigators state that their cost-effectiveness analysis was conducted from the societal perspective, whereas it actually represents an analysis from the health care perspective. When defining the perspective of an economic evaluation, the following key issues need to be considered in order to be in line with a societal viewpoint:

The type of costs in economic evaluation. In an analysis from the societal perspective, all costs are included. In addition to health care costs, productivity costs should have been assessed (2,3). This is important if the age of the study population is relatively young. The average age in the study by Capomolla et al. (1) was 56 years. The researchers might have therefore missed a significant proportion of the costs from a societal perspective, thereby probably underestimating the cost-effectiveness of the interdisciplinary heart failure management program, a program that might help to avert future production losses in that it enables the sick person to work again or work until later in his or her life.

Time horizon of the analysis. From an economic perspective, the appropriate time horizon for a trial would include all of the time when there is resource use related to heart failure (4). Because heart failure is a chronic disease, a life-long treatment/management is necessary. Accordingly, to agree with a societal perspective, the follow-up period of 12 ± 3 months of the within-trial evaluation might have been expanded within a modeling framework. In such a simulation study, one would describe the course of the disease with and without the intervention for a patient's lifetime. The simulated societal costs and (untruncated) life-expectancy resulting from the two strategies would then be compared in an incremental analysis.

The utility of health states. The utility values were elicited from patients using the time trade-off technique. In a societal cost-effectiveness analysis, it is not the patients' utilities but the utilities that society attributes to the health states experienced by the patient that should be included in the study. That is, a random sample of the general public should have been asked to estimate utilities from the societal perspective. Alternatively, the EuroQoL questionnaire (5), a generic measure of quality of life, could have been administered to the patients in the study. Value sets are available that can be used to attach societal utility values to the health states described by the patient in the EuroQoL questionnaire.

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REPLY

We thank Dr. Sendi for the methodological considerations of our study.

The type of costs in economic evaluation. In our economic analysis we considered both direct health costs and indirect costs (as missing profit). The choice of evaluating the former costs was a consequence of the management strategy. In the analysis of