males respond differently than females. More than 80 anatomic, chemical, and physiological similarities between animals deficient in copper and people with ischemic heart disease have been identified (4,5).

Perhaps low DHEA in their subjects (1) was a subtle, indirect sign of copper deficiency. People who believe that high concentrations of DHEA are beneficial may find that copper supplements are less expensive and less hazardous than DHEA supplements. A supplement containing copper produced improvement in heart failure.

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Recognizing Sex Similarities in Cardiovascular Disease Research

We read the interesting article by Tivesten et al. (1), which concluded that low serum dehydroepiandrosterone (DHEA) and its sulfate predict an increased risk of coronary heart disease in men. This study examined a cohort of 2,416 elderly men, and previously we evaluated DHEA-S in 270 women. In our National Heart, Lung, and Blood Institute-Women's Ischemia Syndrome Evaluation study (2), we found among postmenopausal women undergoing coronary angiography for suspected myocardial ischemia, that lower circulating DHEA-S predicted higher cardiovascular disease (CVD) mortality and all-cause mortality, similar to the Tiversten et al. findings among men. Furthermore, this relationship was independent of other major CVD risk factors but was attenuated for presence or severity of angiographic coronary artery disease. Our findings suggested that DHEA-S levels and CVD mortality could be mechanistically linked to atherosclerosis.

A large portion of THE Tivesten et al. (1) discussion focused on possible mechanisms for DHEA/-S to reduce risk of cardiovascular events and we believe that our research findings are an important addition to support this discussion. Although Tivesten et al. (1) cited studies that included women, the discussion only mentioned men, and did not mention our sex-specific study (2). It is important that contemporary research not perseverate the historical "male-pattern" biomedical model where studies in women are either ignored, as was the case in the Tivesten et al. article, or made to fit into male diagnostic and therapeutic standards (3,4). It is similarly important to evaluate and demonstrate areas where women and men have similar findings, as the Tivesten et al. and our prior WISE study demonstrate.

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REPLY: Recognizing Sex Similarities in Cardiovascular Disease Research Copper, Coronary Heart Disease, and Dehydroepiandrosterone

Aspects of gender and biological sex are important to address in research, and we thank Dr. Shufelt and colleagues for their letter. Certainly it would have been suitable to address the association between dehydroepiandrosterone (DHEA), its sulfate, and cardiovascular risk in women in the discussion of our paper (1), even if women were not included in the MrOS cohort. The data by Shufelt et al. (2) are interesting and suggest an association between low DHEA-S and cardiovascular risk in women as in men, whereas other studies have suggested a U-shaped association in women (3).

We also thank Dr. Klevay for sharing his hypothesis regarding copper, coronary heart disease, and DHEA, proposing that low DHEA may be a sign of copper deficiency.

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Aspirin Treatment and Outcomes After Percutaneous Coronary Intervention

Results of the ISAR-ASPI Registry

We read with great interest the paper by Mayer et al. (1) demonstrating an association between high on-aspirin treatment platelet reactivity and cardiovascular complications in patients undergoing percutaneous coronary intervention. We would like to congratulate the investigators for this pivotal study and suggest that they consider prior aspirin use as another variable contributing to adverse outcomes. In fact, we believe that the larger number of patients with high on-aspirin treatment platelet reactivity in the ISAR-ASPI (Intracoronary Stenting and Antithrombotic Regimen—Aspirin and Platelet Inhibition) registry compared with other populations using tests specific for COX-1 activity (2,3) may be due to the higher percent of patients receiving aspirin treatment at the time of hospital admission.

Such consideration follows our demonstration that human megakaryocytes have an adaptive response to aspirin, leading to up-regulation of platelet multidrug resistance protein 4 (MRP4) (4). Aspirin effects are reduced in patients undergoing coronary artery bypass grafting because of platelet MRP4 overexpression, because aspirin is an MRP4 substrate. Moreover, with long-term drug exposure, eukaryotic cells may trigger specific genes leading to cellular mechanisms modulating their effects.

Because MRP4 inhibition reduces collagen-induced platelet activation, we hypothesized that platelets with MRP4 overexpression may be hyperresponsive.

A reduction of aspirin-dependent platelet inhibition over time is well established. In fact, aspirin-treated healthy volunteers, either at high (1,300 mg/day) or low (100 mg/day) concentrations, showed reduced platelet aggregation in the early weeks of treatment,