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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,

while platelet aggregation returned to baseline after 7 to 8 weeks (5). We also demonstrated a progressive reduction in platelet sensitivity to aspirin in long-term aspirin-treated patients.

The genomic response to a pharmacological "challenge" with aspirin has also been demonstrated. After aspirin administration, a set of platelet-enriched genes and proteins associated with platelet function and cardiovascular complications have been identified. Moreover, increased platelet expression of glycoprotein IIIa with aspirin treatment has been demonstrated.

In conclusion, we suggest a better definition of the impact of prior aspirin use, because the capability of aspirin in changing protein platelet expression may be useful to better understand high on-aspirin treatment platelet reactivity.

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REPLY: Aspirin Treatment and Outcomes After Percutaneous Coronary Intervention

Results of the ISAR-ASPI Registry

We thank Dr. Pulcinelli and colleagues for their interest in our publication (1). The high proportion of patients (>90%) presenting on aspirin therapy in our cohort likely would not enable a reliable analysis of the role of the presence or absence of this therapy on the platelet response to aspirin as measured in this study.

However, the fact that a significantly lower proportion of patients taking aspirin showed high on-aspirin platelet reactivity (91.2% in patients with vs. 93.8% in those without high on-aspirin platelet reactivity; $p = 0.0006$) does not support the authors' hypothesis. In addition, as mentioned in the results section of our paper (1), prior aspirin therapy was also included in the multivariate model for the primary outcome, the composite of death or stent thrombosis at 1 year. From this model, prior aspirin therapy was associated with an adjusted hazard ratio of 0.66 (95% confidence interval: 0.45 to 0.96; $p = 0.03$) for the occurrence of the primary outcome, suggesting a protective role against ischemic events.

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Does Size Matter?

In Search of a Physiological Definition of Myocardial Atrophy

Mechanical unloading using left ventricular assist devices (LVADs) induces reverse remodeling of the failing myocardium to levels that are possibly superior to any other strategy. However, evidence of a