

UL1TR000064). This work was supported by grants from the Gustavus and Louis Pfeiffer Research Foundation; The Women's Guild of Cedars-Sinai Medical Center; The Ladies Hospital Aid Society of Western Pennsylvania; QMED, Inc.; the Edythe L. Broad and the Constance Austin Women's Heart Research Fellowships, Cedars-Sinai Medical Center; the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center; The Society for Women's Health Research; and The Linda Joy Pollin Women's Heart Health Program and the Erika Glazer Women's Heart Health Project, Cedars-Sinai Medical Center. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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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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<http://dx.doi.org/10.1016/j.jacc.2015.03.522>

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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,