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Reply

The letter from Drs. Amorim and Doenst regarding an interpretation of the data presented in our recent study (1) underscores the immense complexity of discerning the interplay between the metabolic syndrome, coronary artery disease (CAD), diabetes, and heart failure.

Drs. Amorim and Doenst rightly point out that the existence of cardiac insulin resistance (cIR) in diabetes is still a matter of debate and that attributing the alterations in mitochondrial metabolism of palmitoyl-L-carnitine and glutamate that we observed in the diabetic human hearts to cIR is questionable. We agree with this statement and wish to emphasize that this interpretation of the data was one of several put forth, along with the possibility that diabetic hearts may not be responding appropriately to nutritional status and substrate availability, that key mitochondrial enzymes in the metabolic pathway for these substrates may be defective, or both. It also should be pointed out that in those studies that have reported cIR, the question of *when* cIR develops during the course of metabolic syndrome or diabetes also seems to be unresolved. Although many studies suggest that cIR is a strong predictor of the development of heart failure (2,3), other studies have shown that heart failure can cause insulin resistance (4,5), thereby clouding the cause-and-effect relationship between the two. With respect to our study, we believe that although it is possible the nondiabetic patients have cIR, the additional stress of overt diabetes has pushed the diabetic hearts closer to a phenotype resembling that of heart failure (i.e., reduced fatty acid oxidative capacity and oxidative stress). In any case, because these samples were obtained from patients in a fasted state, measurement of insulin signaling proteins in the heart samples would be of indeterminate value.

We also concur that the altered respiratory capacity seen in the diabetic human heart tissue is not the result of a defect of mitochondrial complex I, but instead believe it to be the result of specific defects in the mitochondrial enzymes responsible for the oxidation of these substrates. Recent studies in animal models of heart failure have shown defects that are strikingly similar (6,7), lending further support to the proposition that the hearts of the diabetic patients with CAD have a metabolic phenotype that is closer to heart failure than nondiabetic, age-matched individuals with CAD alone.

Finally, because these data were generated in mitochondrial preparations from atrial tissue and not ventricular tissue, it is doubtful that ischemia concomitant to CAD is playing a role, although it cannot be completely ruled out.

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Statins in Acute Coronary Syndromes and Genetic Insight

The report of Gibson et al. (1) addresses the issue of whether intensive statin therapy (atorvastatin 80 mg/day) leads to a greater reduction in major adverse cardiac events (MACE) among patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome, compared with patients randomized to moderate statin therapy (pravastatin 40 mg/day). Intensive statin therapy reduced MACE and target vessel revascularization significantly more than standard statin therapy, and the authors noted that the effect was independent of low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hs-CRP) levels and might be related to pleiotropic effects of statins. This report is similar to the original PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) results and raises 3 additional questions of clinical importance. First, was the MACE benefit primarily in favor of carriers of the KIF6 polymorphism? Second, was the time to benefit shorter in carriers of the KIF6 polymorphism? And third, why were differences in LDL-C and hs-CRP levels not associated with clinical outcome?

The event rate for the primary composite end point in the Gibson analysis was 21.5% in the atorvastatin 80-mg/day group, compared with 26.5% in the pravastatin 40-mg/day group for a

5.0% absolute risk reduction (1). In a genetic substudy of PROVE IT–TIMI 22, only carriers of the KIF6 polymorphism revealed a significant reduction in clinical events when treated with atorvastatin (16.1%), compared with the group randomized to pravastatin (26.0%), for an absolute risk reduction of 10.0%. In the non-KIF6 carrier group, the reduction in clinical events did not differ between those treated with pravastatin and those treated with atorvastatin (2). Thus, genetic analysis identified a subgroup that derived the majority of clinical event reductions, and knowledge regarding such an assessment in the Gibson et al. (1) analysis might be of clinical relevance.

Second, the original PROVE IT–TIMI 22 report indicated a difference in event reduction that became significant at approximately 180 days. However, the KIF6 genetic substudy revealed a statistically significant reduction in events at 30 days and beyond in only the KIF6 carrier subgroup and not in the noncarrier subgroup. Early benefit of statin therapy could be particularly crucial in the setting of PCI. Statins might potentially improve plaque stability, among their other pleiotropic effects, and this would be most important immediately after the intervention.

Third, in the PROVE IT–TIMI 22 genetic substudy, the median on-trial LDL-C reduction did not differ between KIF6 carriers and noncarriers. Similar to that seen in the Gibson et al. (1) report, the clinical event benefit in the genetic substudy is independent of LDL-C and hs-CRP level and change during the trial. This supports their suggestion that a pleiotropic effect is responsible for the reduction in MACE, but this effect might be most powerful in KIF6 carriers.

In conclusion, the data brought forth by Gibson et al. (1), in regard to intensive versus moderate statin treatment in acute coronary syndrome patients requiring PCI, highlight the potential importance of the pleiotropic effects of statins. Kinesin proteins have a role in intracellular transport and might contribute to these pleiotropic effects (3–6). Genetic polymorphisms such as KIF6 might play a role in differentiating subgroups that respond differently to statin therapy.

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