REPLY: Statistical Analyses of Arginine–Nitric Oxide Metabolites and Cardiac Dysfunction

We thank Drs. Fogel, Verma, and Obiagwu for their thoughtful comments, and particularly for identifying the Wilcoxon signed-rank test as the correct test for the Table 3 analysis (1). This is the test we performed. We regret incorrectly describing it as the Wilcoxon rank-sum test and have submitted an erratum.

We appreciate the opportunity to clarify our use of linear regression to estimate cross-sectional associations between clinical covariates and baseline levels of each of the 6 biomarkers (Table 2 [1]). As background, in response to reviews, we acknowledged that the log-ratio transformation did not fully normalize the data for each biomarker. Due to space limitations, residual plots were omitted; these showed several markers with good approximations to normality, and others with modest deviations from normality. We speculated that deviations from normality might reduce the efficiency of our estimates, leading to higher type II errors (1). Our data were not zero-inflated. Rather, our citation of Judkins and Porter (2) was primarily intended to bring attention to literature regarding the impact of deviations from normality for ordinary least squares (OLS), the basis of multiple linear regression. Even with nonnormally distributed data, classic results from mathematical statistics indicate OLS-based estimates are unbiased, and in large samples, type I error rates are valid, and coverage of confidence intervals is near the nominal level (2,3). In practice, the definition of a "large" sample, and hence the performance of OLS, depends on the extent of the deviation from normality, along with variation in the size of strata determined by using the regression model.

To increase statistical power, we considered using rank-based regression for those markers with deviations from normality (4). By selecting a different approach for each biomarker, Table 2 (1) would have included multiple modeling approaches, and we were concerned about readers having difficulty with interpretability. Each approach (linear regression for all biomarkers or a combination of methods based on an assessment of the distribution of residuals for each biomarker) has benefits and limitations. In our judgment, based on the statistical literature and assessment of residual plots, our scientific findings are robust to our choice of approach.

Lastly, plots of residuals versus fitted values suggested evidence of minor heteroscedasticity in 1 biomarker. Additional post hoc analyses (not shown) using robust standard errors to correct for potential heteroscedasticity were consistent with our original findings.

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Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Putt and Finkelman contributed equally to this work.

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The Anticoagulation Conundrum of Mechanical Heart Valves in Pregnancy

Should DOACs Be Considered?

After reading the elegant review by Steinberg et al. (1) on maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves (MHVs), we remain undecided on the best anticoagulation regimen for these patients. We would like to offer in response to this review a counterintuitive proposition that may serve as a compromise between the maternal risks associated with low-molecular-weight-heparins (LMWHs) and the fetal risks associated with vitamin K antagonists (VKAs): direct oral anticoagulants (DOACs).

Evidence for use of DOACs in patients with MHVs, a population in whom the mainstay of therapy is VKA, remains unfavorable. However, DOACs may very well be more effective than LMWHs in preventing thrombotic complications in this setting (2) as it is in others. In addition, the data currently available on fetal