Letters to the Editor

Continuation or Withdrawal of Beta-Blocker Therapy in Patients Admitted for Heart Failure

We read with great interest the article by Fonarow et al. (1) evaluating the effect of continuation or withdrawal of beta-blocker drugs on outcomes in patients hospitalized with heart failure. The authors performed an analysis of 2,374 patients admitted with decompensated heart failure and concluded that withdrawal of beta-blocker therapy in these patients was associated with higher mortality.

There are several baseline characteristics that substantially differ among treatment groups. In addition to differences in the prevalence of coronary risk factors and coronary artery disease, patients who were withdrawn from beta-blocker drugs had lower left ventricular ejection fraction and higher expected post-discharge mortality risk. The authors performed a propensity score analysis to adjust for potential treatment selection bias.

Propensity scores represent the conditional probability of being assigned to a treatment group given a set of potential confounders (2,3). The bias and variance of the estimated effect of the treatment under study depend on the covariates selected for propensity score estimation. The authors claim that the propensity scores in their study were calculated with the set of all possible covariates that were related to the probability of receiving beta-blocker therapy; the inclusion of all information regarding the factors that might affect the selection of the treatment is, in fact, an important mainstay of propensity score analysis. However, the authors did not indicate which variables they used for estimation of the propensity scores. Furthermore, the reasons for beta-blocker withdrawal during hospital stay were not collected; this information is essential, because beta-blocker continuation or withdrawal might depend strongly on the clinical evolution of the patient during hospital stay, which in turn might be associated with outcome. Unfortunately, the authors also failed to provide information on the accuracy of the propensity scores for predicting treatment assignment, which might be assessed by the area under the receiver operating characteristic curve of the logistic regression model.

The presence of unmeasured variables that both affect the choice of the treatment and the outcome and the generation of propensity scores from potentially inaccurate models might preclude an adequate comparison among the different groups, which might compromise the validity of the estimated effect of the intervention.

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Reply

We are grateful to Dr. Bouzas-Mosquera and colleagues for their interest in our article (1). They raise several important issues and request additional details regarding the propensity score analysis used in this study to adjust for potential treatment selection bias. As noted in the article, although most variables of prognostic importance (e.g., age, systolic blood pressure, heart rate, creatinine, sodium) were similar between patients in the group continued on beta-blocker drugs and those withdrawn, left ventricular ejection fraction was lower (2.7 unit absolute difference), and a few other variables differed in patients withdrawn from beta-blocker therapy. Although withdrawal of beta-blocker drugs was associated with a few indicators of more severe heart failure, it remained significantly and independently associated with increased mortality after adjustment for multiple covariates and propensity score. The variables used for the propensity score are posted at the OPTIMIZE-HF (Organized Program To Initiate Life-saving treatMent In hospitaliZEd patients with Heart Failure) website (2). We applied accepted modeling techniques to obtain the best fit for each variable in the model. The c-index of the propensity scores for the treatment assignment in this study was 0.649. Weitzen et al. (3) have shown that the c-index is not a good measure of the likelihood of omitted variables. One way to view this is that the best case scenario for estimating treatment differences would be under the assumption of randomization. A propensity score for this situation should have a c-index of 0.50, because no factor should be associated with receiving the randomized therapy. We have performed a sensitivity analysis (4). This indicates that an unknown covariate would need to have an odds ratio in the model of approximately 5 before we could obtain the opposite interpretation for the use of withdrawing beta-blocker drugs on post-discharge mortality. It seems fairly unlikely, although certainly possible, that a factor of such great importance was missed. We fully agree that the specific rationale for beta-blocker continuation and withdrawal during hospital stay were not collected, and this might have influenced the findings. Furthermore, despite covariate and propensity score adjustment, other measured and unmeasured factors might have influenced improvements in clinical outcomes associated with continuation or withdrawal of beta-blocker therapy. Nevertheless the findings of
this OPTIMIZE-HF study are consistent with prior studies and current heart failure guidelines. Routine discontinuation of beta-blocker therapy on hospital admission is neither necessary nor advisable, and the majority of patients hospitalized for heart failure are eligible for beta-blocker therapy to be continued.

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