Effects of Atenolol on Postoperative Myocardial Ischemia

To the Editor—We commend Wallace et al. for the excellent study about the effects of atenolol on postoperative myocardial ischemia. However, we have major concerns. First, it is highly unethical to randomize chronically beta-blocked patients with coronary artery disease into a group that will not receive beta-blockers before major surgery. Multiple studies have shown the deleterious effects from abrupt beta-blocker withdrawal, including tachycardia, ischemia, and infarction caused by upregulation of β-receptors. Although the authors noted no complications from abrupt beta-blocker withdrawal, it was poor practice to deliberately subject patients to this added risk.

Second, although the authors found that beta-blockers were associated with a decrease in perioperative ischemia and a decrease in long-term mortality, one must be careful not to conclude that decreasing perioperative ischemia decreases long-term mortality. Ischemia, as diagnosed by ST depression, is often caused by a supply/demand imbalance of oxygen delivery to the myocardium. This is in contrast to mortality from myocardial infarction, which is more likely caused by plaque rupture with sudden complete occlusion of an epicardial vessel. It is difficult to physiologically conceptualize that decreasing myocardial ischemia perioperatively will result in a decrease in future mortality. Therefore, although an episode of ischemia may be a predictive marker of a possible myocardial infarction, prevention of an ischemia period, perioperatively or otherwise, has not been proven to decrease the incidence of myocardial infarction.

It is most likely that the beneficial effects of beta-blockers have not been fully elucidated, and prevention of myocardial infarction goes beyond preventing ischemia alone. For example, although beta-blockers decrease mortality after myocardial infarction, no other antiischemic medications have had similar results.

Finally, the authors’ conclusion that perioperative treatment with atenolol reduces long-term mortality is in question. Although there was no difference in the use of cardiovascular medications between the two groups in the 2-yr postoperative period, there is no information regarding any difference in other interventions (e.g., PTCA, CABG) that may have also contributed to a difference in survival between the groups. Also, there was a trend toward more ill patients in the placebo group, which had a higher percentage of patients with definite coronary artery disease, previous myocardial infarction, diabetes mellitus (an independent predictor of death during 2-yr follow-up), untreated hypertension, and who underwent major vascular surgery. Although these trends were not statistically significant, the power was too low to conclude that the placebo group was not more ill than the atenolol group.

We agree with the recommendation to introduce perioperative beta-blockade in high risk patients for major surgery; however, we do not yet agree that the reduction in transient perioperative ischemia will have long-term benefits.

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Beta Blockade in Non-cardiac Surgical Patients

To the Editor—I read with interest the article by Wallace et al.1 about beta-blockade in noncardiac surgical patients. Although β-adrenoceptor antagonists have been beneficial in many previous studies of non-surgical patients with coronary artery disease identified by the accompanying editorial by Wallier,2 the current study by Wallace et al.1 had a number of methodologic and statistical problems that rendered their conclusions difficult to interpret.

First, the study drug atenolol was withheld from patients with bradycardia, hypotension, and other clinical conditions in which the use of beta-blockade was contraindicated. This peculiar study design would result in misclassification error (patients randomized to atenolol who did not receive it or who received only a partial dose), thus confounding the reported association. It is possible that the patients did well solely because of slower heart rates separate from the study drug. A better study design would be to exclude patients from participating in the study if they were “bradycardic” or “hypotensive” so study randomization could be preserved and misclassification error could be minimized.

Second, a previous report3 about 2-yr mortality that used the same group of patients showed, by multivariate models, that the presence of diabetes mellitus was the most important risk factor for 2-yr mortality. The effect of atenolol was not significant (hazard ratio of 0.5 and confidence interval crossing 1) after controlling for the presence of diabetes. This interpretation was never provided by the authors in the previous report nor in the current report. The observation that diabetic patients are more sick with greater mortality is entirely consistent with clinical observations. The authors need to include the incidence of postoperative myocardial ischemia and diabetes mellitus in the multivariate logistic regression model.

Third, the incidence of intraoperative hypertension (systolic blood pressure > 180 mmHg) and tachycardia (heart rate > 100 beats/min) was high (32% and 55%, respectively in the atenolol group) considering that these patients had “received” an active treatment aimed at decreasing these two hemodynamic parameters. Similar data had never been provided for the recovery room, the first 24–48 h, and the subsequent study period.

Fourth, the authors indicated that “beta-blockers were withheld from patients in both the atenolol and the placebo groups” preoperatively. For how much time was beta-blockade withheld? Because most patients were recruited the day before surgery, it would be unlikely that beta-blockade withholding was for a long duration. Because more patients in the atenolol group were administered preoperative beta-blockade than in the placebo group, it would be entirely possible that these patients were more “protected” perioperatively. More importantly, these same patients would probably continue beta-blockade postoperatively after hospital discharge, thus contributing to reduced long-term mortality, regardless of perioperative beta-blockade. In addition, the results of the current study might simply be explained by the finding that diabetic patients were less likely to receive beta-blockade preoperatively or postoperatively after hospital discharge. The authors should provide the incidence of long-term beta-blockade in the diabetic versus nondiabetic group to determine the effect of interaction of these two variables.

Finally, another important study limitation omitted by the authors is that no women participated in this study. Although one might suspect that beta-blockade should work to a similar extent in men and women, this could not be shown by this study and should be discussed.

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