# CORRESPONDENCE

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## Diabetes and Not Lack of Treatment with Atenolol Predicts Decreased Survival after Noncardiac Surgery

*To the Editor:*—The response provided by Wallace regarding the study on perioperative atenolol and myocardial ischemia[1] did not provide an adequate clarification of the statistical results in their previous reports.[2,3] Wallace *et al.* claimed that their previous report demonstrated that perioperative administration of atenolol decreases the incidence of death after surgery during a 2-yr follow-up period.[2] However, their study did not provide statistical support for such a claim. In a univariate analysis (*i.e.*, an analysis in which the effect of a single "independent" parameter is evaluated), the hazard (odds) ratio for death was 0.4 with a confidence interval of 0.2–0.9. This result suggested that the likelihood of death is 2.5-fold less when atenolol was given and that the effect of atenolol was statistically significant. However, in all analytic studies, confounding variables must always be considered as an alternative explanation for study findings, as was done by Mangano *et al.* In the multivariate analysis model, the hazard ratio for atenolol was 0.5 with a confidence interval of 0.2–1.1. Because the confidence interval now included 1.0, this indicated that the effect of atenolol was *not* different from that of placebo, *i.e.*, no influence of atenolol on survival. In fact, in this model, diabetes mellitus proved to be the most important predictor of death with a hazard ratio of 2.8 (confidence interval, 1.4–6.2). Stated differently, when the effects of diabetes have been considered, there is no longer an effect of atenolol.

Because the message that "patients with or at risk for coronary artery disease who are treated perioperatively with β-adrenergic blocking agents have reduced incidence of morbidity and mortality" cannot be supported by the current studies,[2,3] physicians caring for such patients should reevaluate the validity of recommending perioperative beta blockade for improved survival that was based solely on the current study findings. Furthermore, because the clinical treatment of these 200 patients after hospital discharge was completely out of the study protocol control, the effects of other confounding factors cannot be determined and assessed.

When studies involve complicated statistical modeling, it is a responsibility of the authors to understand the technique used to provide an accurate and meaningful interpretation of their results. Unfortunately, the recent popularized use of perioperative beta blockade is based on misinformation.

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*In Reply:*—Thank you for allowing me to respond to Dr. Leung's comments about the two studies.[1,2]

In February 1998, Dr. Leung wrote to ANESTHESIOLOGY with six criticisms of ANESTHESIOLOGY and *New England Journal of Medicine* articles. These criticisms included suggestions that it was inappropriate to withhold study drug from patients who might have a side effect, questions concerning the statistics in the *New England Journal of Medicine* article, requests for more postoperative hemodynamic data, questions about the withholding of beta blockade, interactions of diabetes and atenolol, and the lack of women in the study. I responded to all of these criticisms in writing, and those comments were published in ANESTHESIOLOGY.[3] Dr. Leung was dissatisfied with the results of the letter to ANESTHESIOLOGY and has sent a second letter to ANESTHESIOLOGY with more criticisms, including:

1. "Their study did not provide statistical support for such a claim."
2. ". . . this indicated that the effect of atenolol was not different from that of placebo, *i.e.*, no influence of atenolol on survival.
3. "β-adrenergic blocking agents have reduced incidence of morbidity and mortality can not be supported by the current studies."
4. ". . . the recent popularized use of perioperative beta blockade is based on misinformation."
5. "Physicians caring for such patients should reevaluate the validity of recommending perioperative beta blockade for improved survival."

We strongly disagree with Dr. Leung and her misunderstanding of the results of the two manuscripts.[1,2] The primary end-point of the atenolol[2] study was the reduction of perioperative myocardial ischemia by atenolol. Perioperative administration of atenolol for 1 week to patients at high risk for coronary artery disease significantly reduced the incidence of postoperative myocardial ischemia ($P = 0.029$). Furthermore, a secondary finding was that reductions in perioperative myocardial ischemia were asso-

ciated with reductions in the risk for death at 2 yr ($P = 0.025$). The primary end-point of the atenolol long-term study[4] was the effect of atenolol on 2-yr mortality. In patients who have or are at risk for coronary artery disease who must undergo noncardiac surgery, treatment with atenolol during hospitalization reduced mortality ($P = 0.019$) and the incidence of cardiovascular complications for as long as 2 yr after surgery ($P = 0.008$). These two studies provide clear and statistically significant evidence to support the claims that perioperative atenolol reduced incidence of morbidity and mortality and improves survival in patients at risk for cardiac morbidity.

Dr. Leung does not understand the interpretation of univariable and multivariable models presented in table 2 of the Mangano *et al.* manuscript.[4] Once statistical significance is established, it is acceptable to do a secondary analysis of the data to look for other predictors of outcomes. We demonstrated clearly that atenolol reduced the risk of death. Diabetes mellitus and ischemia increased the risk of death. In the multivariable model we demonstrated that diabetes was statistically significant, but once patients with diabetes were excluded there was not sufficient power to demonstrate the effect of atenolol. Thirty-one percent of the patients in this trial had diabetes. If one excludes 31% of the patients in a trial, power is lost. That in no way brings the results into question; it simply implies that if one excludes 31% of the patients, one also loses power to see the effect. Furthermore, Dr. Leung is incorrect in stating that $P = 0.06$ (6% type I error) is not significant when $P = 0.05$ (5% type I error) is suddenly significant. It is simply the difference between a 5% and 6% chance of a type I error. Perioperative administration of atenolol reduces the incidence of perioperative myocardial ischemia, postoperative mortality, and cardiovascular complications.

Dr. Leung's statement that the use of perioperative beta blockade is based on misinformation is incorrect. It is important to understand statistics and study design before making such a statement. Physicians should clearly evaluate any therapy. Many trials of beta-blocker use demonstrate benefits in nonsurgical patients, including the ISIS-1 (International Study of Infarct Survival),[5] the MIAMI (Metoprolol in Acute Myocardial Infarction),[6] the MAPHY (Metoprolol *versus* Thiazide Diuretics in Hypertension),[7] and the ASIST (Atenolol Silent Ischemia Study)[8] trials. We added to this abundant literature and have clearly demonstrated that perioperative beta blockade improves survival in surgical patients at risk for cardiac morbidity.

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# Catheter Tip Position and Baricity of the Local Anesthetic Have an Impact on Maldistribution in Microcatheter CSA

*To the Editor:*—We read with interest the study of Biboulet *et al.*, which shows that the orientation of the catheter tip has a major impact on the spread of local anesthetics (LA) irrespective of their baricity.[1]

These results are consistent with data from other studies using 28-gauge microcatheters and isobaric bupivacaine[2,3] and show convincingly that caudally positioned catheter tips are associated with a higher requirement of LA to reach the respective sensory level than cranially directed catheter tips. The results suggest that caudally extended catheter tip levels cause maldistribution of the LA and that cranially oriented catheter tips should be obtained in CSA.

However, the authors give no information how a cranial catheter tip position can be obtained in CSA. They do not mention the respective literature that relates to this issue. Data from a study of Ata *et al.* suggest that the paramedian lumbar approach may facilitate the spinal