

CORRESPONDENCE

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In Reply:—Thank you for your comments about our article "Prophylactic Atenolol Reduces Postoperative Myocardial ischemia." I would like to address each point in the two letters.

First, when this study was initiated, the committee for human investigation was much more concerned about the safety of adding prophylactic beta-blockade to patients with or at risk for coronary artery disease (American Society of Anesthesiology Physical Status III and IV patients), than about the risk of beta-blocker withdrawal. In previous epidemiologic studies, in a similar patient population, we were unable to demonstrate any effect of morning-of-surgery beta-blocker withdrawal.¹ Moreover, in the current patient population, there was no demonstrable effect of beta-blocker withdrawal.² This study was a prospective, randomized, placebo-controlled, double-blinded clinical trial approved by a committee for human investigation. We do not agree with the implication that we behaved unethically.

Is myocardial ischemia a marker for cardiac morbidity or a cause? A single episode of postoperative myocardial ischemia is associated with a ninefold increase in the incidence of cardiac complications before hospital discharge¹ and a twofold increase during the next 2 yr.³ Reduction in the incidence of perioperative myocardial ischemia is associated with a twofold decrease the incidence of death in the next 2 yr.⁴ It would be highly unethical to show the cause and effect relation between episodes of myocardial ischemia and cardiac morbidity by inducing myocardial ischemia in a randomized study. However, the data are very clear. Pharmacologic reductions in the incidence of myocardial ischemia are beneficial for long-term survival.⁴

Why would 1-week administration of beta-blockade during the perioperative period reduce long-term mortality? Let us conduct a thought experiment. Take two groups of people at risk for cardiac morbidity. Have one group of patients take it easy for a week. Force the patients in the other group to exercise to the point of exhaustion for 24 h a day for 7 days. It would not be hard to imagine that the incidence of myocardial ischemia in the exercise group would be higher than in the rest group. Moreover, it would not be surprising that the patients who managed to survive the forced exercise would have a higher incidence of cardiac morbidity for a few months after the initial exercise period. Intracoronary plaques may have been ruptured and the endovascular epithelium may have been injured. The delayed response to such rupture and injury have been shown in animal and ambulatory human models. Furthermore, in surgical patients, we previously showed a strong association between perioperative events and outcomes over the ensuing 2 yr,²⁻⁴ results that are consistent with the current findings. Episodes of myocardial ischemia are a marker for cardiac injury. That injury persists beyond the initial insult and leads to further cardiac morbidity. Prevention of myocardial ischemia clearly is associated with a reduction in cardiac morbidity.^{2,4}

Patients in the atenolol group were prescribed more beta-blockers, diuretics, and all hypertensives combined before surgery. They tended to have more hypertension. This difference in preoperative medication suggests that the patients in the atenolol group were either slightly more sick preoperatively or that they had more aggressive physicians. There is no evidence, as suggested in the letter to the editor, that there was a trend toward more ill patients in the placebo group. Moreover, it is incorrect that there was a higher percentage of patients with

definite coronary artery disease, previous myocardial infarction, diabetes, untreated hypertension, and major vascular surgery.

It is clear from these two studies, "Effect of Atenolol on Mortality and Cardiovascular Morbidity after Noncardiac Surgery"⁴ and "Prophylactic Atenolol Reduces Postoperative Myocardial Ischemia,"² that the use of prophylactic atenolol in patients at risk for cardiac morbidity is safe and effective. Moreover, a reduction in perioperative myocardial ischemia clearly is associated with improved survival.^{2,4}

In response to the second letter, there are several misunderstandings. All patients in the atenolol group received atenolol during the hospital stay. Furthermore, patients were analyzed by intention to treat. It would be inappropriate to design a study that did not have checks and balances regarding the dosing of potent medications with serious side effects. We refer to the ISIS trial.⁵ Withholding or reducing the dose of atenolol from a patient with bradycardia (heart rate < 50 beats/min), hypotension (systolic blood pressure < 100 mmHg), severe bronchospasm, or acute congestive heart failure is good medicine and good trial design.

A hazard ratio of 0.4 with a 95% confidence ratio of (0.2 to 0.9) with a probability value of 0.03 indicates that atenolol clearly was associated with a reduction in death in the univariate models. The finding that, in the multivariate model, the hazard ratio for atenolol slightly increased to 0.5 (0.2 to 1.1) ($P = 0.06$) means little. In atenolol-treated patients, the presence of diabetes was associated with a significantly increased risk of death (heart rate, 1.2 beats/min; $P = 0.76$), whereas, in patients given placebo, the presence of diabetes was associated with a quadrupling of the risk (heart rate, 4.0; $P = 0.003$). Atenolol clearly protects diabetic patients from cardiac morbidity.

This trial was not designed to determine dose-response. The finding that the incidence of intraoperative hypertension and tachycardia were high (32% and 35%, respectively) suggests that the dosage may not have achieved maximal therapeutic benefit. This dosing regimen improved long-term survival, reduced myocardial ischemia, and had minimal serious side effects. A higher dose may improve these results but also may be associated with a higher incidence of side effects.

During the 2 yr after discharge, there was no difference in the long-term cardiovascular medications administered between the two groups. There was no difference in the number of diabetic patients in the two groups. Therefore, it is highly unlikely that these results are the result of systematic interaction between the two variables.

There are a limited number of female patients at the VA hospital and this is a limitation of the study. Women tend to be smaller than men, and cardiovascular disease develops in women at a slightly older age. It is likely that lower dosage of atenolol would be needed in women. However, it is also very likely that prophylactic use of atenolol would be similarly effective in female patients at risk for cardiac morbidity.

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In Reply:—The letter from Jacqueline Leung, M.D., addresses several potential problems with the recently published investigation of Wallace *et al.*¹ Dr. Leung carefully points out that more patients randomized to the atenolol group had been medically managed with β -adrenergic antagonists before participation in the study. She hypothesizes that these same patients would probably continue beta-blocker administration postoperatively after hospital discharge, thus contributing to reduced long-term mortality, regardless of randomization to *perioperative* beta-blockade in the study. This is an important criticism. One interpretation for the discrepancy in the demographic data between groups is that those patients treated with beta-blockers before participation in this study had a greater severity of disease necessitating more medication. An equally plausible interpretation is that these patients were medically managed more aggressively, and, as Dr. Leung suggests, it is highly likely that this aggressive management continued after returning to a physician's care after surgery. Therefore, the study by Wallace *et al.*¹ may possess some flaws, but the ultimate message is clear. Patients with

coronary artery disease who are treated preoperatively, intraoperatively, and postoperatively with β -adrenergic blocking agents can have a reduced incidence of morbidity and mortality (especially to cardiovascular events). This is not by any means profound because many patients not undergoing anesthesia for surgical procedures already have benefitted from this group of drugs. More significant is the emerging role of the anesthesiologist in perioperative medicine and the rational use of these drugs in the perioperative period, which hopefully extends to long-term administration.

David C. Warltier, M.D., Ph.D.

Reference

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Predicting Malignant Hyperthermia Susceptibility

To the Editor:—Fierobe *et al.*¹ describe a patient in whom rhabdomyolysis associated with isoflurane anesthesia developed. They cited the Clinical Grading Scale² and assigned the patient a rank of 3 (total score = 18, "somewhat less than likely"). However, they failed to consider the muscle rigidity of the left arm described in their case report. This raises the rank to 4 (total score = 33, "somewhat greater than likely").

"The Clinical Grading Scale ranks the qualitative likelihood that an adverse anesthetic event represents malignant hyperthermia (MH). The assigned rank represents a lower bound on the likelihood of MH."²

The Grading Scale is meant to provide an agreed-on clinical case definition of MH. It does not rely on data from *in vitro* contracture testing when used to rank a possible MH event.

The Grading Scale is of limited usefulness when data are absent. This usually occurs because laboratory tests are not performed during the event. Clinicians are urged to perform serial arterial or venous blood gas (or both), serum potassium concentrations, and creatinine kinase measurements when a possible MH episode occurs. In the case of Fierobe *et al.*,¹ the clinical signs were present, but the authors failed to score all of them when determining the patient's probable rank.