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In Reply:

We welcome the opportunity to respond to Dr. Saika's letter and clarify two aspects of the article, adherence to the intention-to-treat principle and the role of novel high-sensitivity cardiac troponin in the diagnosis of perioperative myocardial injury and infarction.

Intention-to-treat Analysis

As Dr. Saika correctly points out, the intention-to-treat principle is the accepted standard in the statistical analysis of randomized, controlled trials. The intention-to-treat principle was invented to circumvent two main problems during drug trials where the treatment continued over longer periods of time, namely patients stopping the treatment early (attrition) and patients switching from one trial arm to the other (crossover) in a nonrandom manner. Intention-to-treat principle allowed clinicians to determine *effectiveness* of a novel treatment under more realistic conditions rather than judging the merits of a novel drug by its maximum *efficacy* under ideal conditions. The Vitamins in Nitrous Oxide trial analysis fully adhered to the intention-to-treat principle.[1] The intervention in the Vitamins in Nitrous Oxide trial was an infusion of B-vitamins or placebo. The 57 patients who were excluded from the analysis were withdrawn from the study *before* receiving any treatment and therefore had to be excluded. What typically happened with these patients was that they were informed about the study, agreed to participate, signed the consent form, and then—before any intervention occurred—the surgery was cancelled, or the anesthesia team refused to use nitrous oxide, or the patient changed his mind. Thus, the intention-to-treat principle was not applicable to these withdrawn patients. Of the true intention-to-treat population (n = 500), 5 of 250 patients (2%) in the B-vitamin arm and 3 of 250 patients in the placebo arm (1.2%) did not receive nitrous oxide. Given these small numbers, we do not expect a strong influence on the study results.

High-sensitivity Cardiac Troponins in the Diagnosis of Perioperative Myocardial Injury and Infarction

This is without a doubt a topic of high interest to the perioperative community and an area of active investigation. In a recently published ancillary study of the Vitamins in Nitrous Oxide trial, we were able to expand on these findings.[2] On the basis of the three points of evidence, we have to disagree with the statement that perioperative increase in high-sensitivity cardiac troponin level reflects an inflated diagnosis of myocardial infarction. First, among higher-risk patients, that is, patients with pre-existing coronary artery disease, the risk for major perioperative cardiac events is high: the POISE trial found a 6.9% 30-day event rate for myocardial infarction, cardiac death, or nonfatal cardiac arrest.[3] Second, by using continuous perioperative 12-lead Holter monitoring, Landesberg *et al.*[4] showed nicely that more than 20% of their patient population developed myocardial ischemia. Therefore, perioperative myocardial infarction is likely under- not over-reported. Third, according to the Third Universal Diagnosis of Myocardial Infarction, the diagnosis of myocardial infarction requires both an increase/decrease pattern of a cardiac biomarker with at least one value above the 99th percentile and evidence for new ischemic electrocardiograph changes, such as ST-segment increase or depression, in continuous leads in a setting consistent with myocardial ischemia.[5] Most clinical 12-lead electrocardiographs are performed as spot measurements easily missing temporary ischemic events. However, cardiac troponin represents a cumulative measure of myocardial damage, and its kinetics allows the detection of myocardial injury and infarction that occurred several hours before the measurement. Thus, we believe that novel high-sensitivity cardiac troponin assays will allow us to detect more cases of perioperative myocardial infarction. This notwithstanding, there are definitely instances where perioperative cardiac troponin increase may be caused by nonischemic factors such as acute renal failure.[6] Thank you for giving us the opportunity to clarify these points.

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Competing Interests

The authors declare no competing interests.

Peter Nagele, M.D., M.Sc., Frank Brown, B.Sc., Amber Francis, B.S.N, R.N., Mitchell G. Scott, Ph.D., Brian F. Gage, M.D., M.Sc., J. Philip Miller, A.B. Washington University School of Medicine, St. Louis, Missouri (P.N.). nagelep@wustl.edu

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