

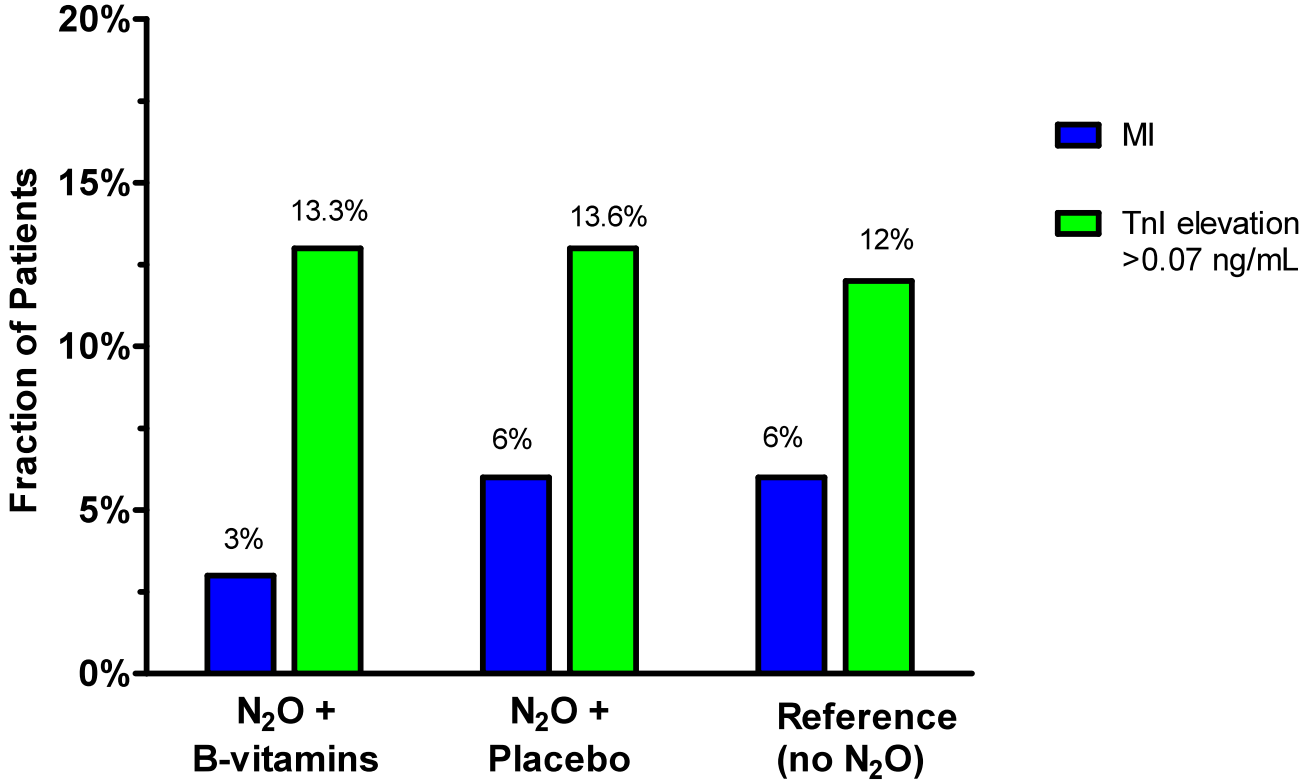
## Nitrous Oxide Anesthesia and Perioperative Myocardial Infarction

### The VINO Randomized Controlled Trial

#### Abstract

- Background** Nitrous oxide anesthesia has been associated with an increased risk for perioperative myocardial ischemia and infarction, but the evidence is conflicting. Acute increase in plasma homocysteine, which is more pronounced in among patients homozygous for the *MTHFR* C677T or A1298C allele, has been suggested as the causal mechanism.
- Methods** In a double-blind randomized controlled trial, 625 adult patients with cardiac risk factors undergoing nitrous oxide anesthesia for noncardiac surgery were randomly assigned to receive intravenous B-vitamins before and after surgery (250 patients) to reduce homocysteine concentrations or to placebo (250 patients). A reference group without nitrous oxide was concurrently enrolled (125 patients). Serial cardiac biomarkers and 12-lead electrocardiograms were obtained. Primary endpoint was the incidence of cardiac troponin I elevation within the first 72 hours after surgery. In addition, a novel high-sensitivity troponin T assay was used to measure the change between preoperative and peak postoperative level.
- Results** Patients who received B-vitamins and nitrous oxide had a smaller increase in plasma homocysteine ( $2.7 \pm 4.4 \mu\text{mol/L}$ ) than patients who received nitrous oxide/placebo ( $4.1 \pm 5.8 \mu\text{mol/L}$ ,  $p < 0.001$ ); patients who did not receive nitrous oxide had no increase. No significant differences in the incidence of cardiac troponin elevation or myocardial infarction were observed among the study arms: 13.3% and 2.8% in the nitrous oxide/B-vitamin group, 13.6% and 6.0% in the nitrous oxide/placebo group, and 12.0% and 6.4% in the reference group ( $p = 0.91$  for troponin elevation; Figure 1). The median increase in high-sensitivity troponin T was similar in all groups: +3.1 ng/L, +2.8 ng/L, +3.9 ng/L for the nitrous oxide/B-vitamin, nitrous oxide/placebo and reference group, respectively ( $p > 0.17$ ). The *MTHFR* genotype had no effect on homocysteine increase or cardiovascular outcomes.
- Conclusions** Nitrous oxide anesthesia, *MTHFR* genotype and subsequent hyperhomocysteinemia are not associated with perioperative troponin elevation and myocardial infarction. B-vitamins are efficacious in blunting nitrous oxide-induced homocysteine increase but have no effect on cardiac outcomes.

Figure 1. Incidence of primary outcome events



Blue: incidence of myocardial infarction; green: incidence of cardiac troponin elevation (defined as a postoperative troponin I increase > 99<sup>th</sup> percentile [0.07 ng/mL]).