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Nitrous Oxide and Serious Morbidity and Mortality in the POISE Trial

1. Kate Leslie, MBBS, MD, MEpi, FANZCA
   Title: Professor
   Affiliation: Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Australia; Department of Pharmacology, University of Melbourne, Melbourne, Australia
   Email: kate.leslie@mh.org.au
   Role: This author helped design the study, conduct the study, and write the manuscript
   Conflicts: Kate Leslie reported no conflicts of interest
   Attestation: Kate Leslie reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files

2. Paul Myles, MBBS, MD, MPH, FANZCA, FCARSCI, FRCA
   Title: Professor
   Affiliation: Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Melbourne, Australia; Academic Board of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia; National Health and Medical Research Council Practitioner Fellow
   Email: p.myles@alfred.org.au
   Role: This author helped design the study, conduct the study, and write the manuscript
   Conflicts: Paul Myles reported no conflicts of interest
   Attestation: Paul Myles reviewed the analysis of the data and approved the final manuscript

3. Philip J Devereaux, MD, PhD
   Title: Dr
   Affiliation: Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada
   Email: philipj@mcmaster.ca
   Role: This author helped design the study, conduct the study, and write the manuscript
   Conflicts: Philip J Devereaux reported no conflicts of interest
   Attestation: Philip J Devereaux has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

4. Andrew Forbes, MSc, PhD
   Title: Professor
   Affiliation: Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
   Email: andrew.forbes@monash.edu
   Role: This author helped analyze the data and write the manuscript
   Conflicts: Andrew Forbes reported no conflicts of interest
   Attestation: Andrew Forbes has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

5. Purnima Rao-Melancini, MSc
Title: Ms
Affiliation: Population Health Research Institute, McMaster University, Hamilton, Canada
Email: Purnima.RaoMelacini@phri.ca
Role: This author helped analyze the data and write the manuscript
Conflicts: Purnima Rao-Melancini reported no conflicts of interest
Attestation: Purnima Rao-Melancini has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

6. Elizabeth Williamson, PhD
Title: Dr
Affiliation: Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; School of Population Health, University of Melbourne, Melbourne, Australia
Email: ewi@unimelb.edu.au
Role: This author helped analyze the data and write the manuscript
Conflicts: Elizabeth Williamson reported no conflicts of interest
Attestation: Elizabeth Williamson has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

7. Shouchun Xu, MD
Title: Dr
Affiliation: Fu Wai Cardiovascular Hospital, CAMS, Peoples Republic of China
Email: scxhypt@yahoo.com.cn
Role: This author helped conduct the study and write the manuscript
Conflicts: Shouchun Xu reported no conflicts of interest
Attestation: Shouchun Xu approved the final manuscript

8. Pierre Foex, MD, DPhil, FRCA, FANZCA, FCA(SA), FMedSci
Title: Professor
Affiliation: Nuffield Division of Anaesthetics, Oxford University, Oxford, United Kingdom
Email: pierre.foex@nda.ox.ac.uk
Role: This author helped conduct the study and write the manuscript
Conflicts: Pierre Foex reported no conflicts of interest
Attestation: Pierre Foex approved the final manuscript

9. Janice Pogue, MSc
Title: Dr
Affiliation: Population Health Research Institute, McMaster University, Hamilton, Canada
Email: janice@phri.ca
Role: This author helped analyze the data and write the manuscript
Conflicts: Janice Pogue reported no conflicts of interest
Attestation: Janice Pogue has seen the original study data, reviewed the analysis of the data, and approved the final manuscript
10. Maribel Arrieta, MD
   Title: Dr
   Affiliation: Nueva Granada Military University, Bogota, Colombia; Department of Anaesthesia, Resuscitation and Pain Management, Central Military Hospital, Bogota, Colombia
   Email: maribel.ao@gmail.com
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Maribel Arrieta reported no conflicts of interest
   Attestation: Maribel Arrieta approved the final manuscript

11. Gregory L. Bryson, MD, FRCPC, MSc
   Title: Dr
   Affiliation: Department of Anesthesiology, The Ottawa Hospital, Ottawa, Canada
   Email: glbryson@ottawahospital.on.ca
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Gregory L. Bryson reported no conflicts of interest
   Attestation: Gregory L. Bryson approved the final manuscript

12. James Paul, MSc, MD, FRCPC
   Title: Dr
   Affiliation: Department of Anesthesia, McMaster University, Hamilton Health Sciences, Hamilton, Canada
   Email: james_paul@sympatico.ca
   Role: This author helped conduct the study and write the manuscript
   Conflicts: James Paul reported no conflicts of interest
   Attestation: James Paul approved the final manuscript

13. Michael J. Paech, MBBS, DM, DRCOG, FRCA, FANZCA, FFPMANZCA, FRANZCOG (Hon)
   Title: Professor
   Affiliation: School of Medicine and Pharmacology, University of Western Australia, Perth, Australia; Department of Anaesthesia and Pain Medicine, King Edward Memorial Hospital for Women, Perth, Australia
   Email: Michael.Paech@health.wa.gov.au
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Michael J. Paech reported no conflicts of interest
   Attestation: Michael J. Paech approved the final manuscript

14. Richard N. Merchant, MD, FRCPC
   Title: Dr
   Affiliation: Department of Anesthesia and Perioperative Medicine, Royal Columbian Hospital, New Westminster, Canada
   Email: richard.merchant@ubc.ca
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Richard N. Merchant reported no conflicts of interest
   Attestation: Richard N. Merchant approved the final manuscript
15. Peter T. Choi, MD, MSc, FRCPC
   Title: Dr
   Affiliation: Department of Anesthesiology, The University of British Columbia, Vancouver, Canada
   Email: Peter.Choi2@vch.ca
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Peter T. Choi reported no conflicts of interest
   Attestation: Peter T. Choi approved the final manuscript

16. Neal Badner, MD, FRCPC
   Title: Dr
   Affiliation: Department of Anesthesia; Perioperative Medicine, University of Western Ontario
   Email: Neal.Badner@lhsc.on.ca
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Neal Badner reported no conflicts of interest
   Attestation: Neal Badner approved the final manuscript

17. Philip Peyton, MBBS, MD, FANZCA
   Title: Associate Professor
   Affiliation: Department of Anaesthesia, Austin Hospital, Melbourne, Australia; Department of Surgery, Austin Hospital and University of Melbourne, Melbourne, Australia
   Email: phil.peyton@austin.org.au
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Philip Peyton reported no conflicts of interest
   Attestation: Philip Peyton approved the final manuscript

18. John W Sear, MA, BSc, MBBS, PhD, FFARCS, FANZCA
   Title: Professor
   Affiliation: Nuffield Department of Anaesthetics, Oxford University, Oxford, United Kingdom
   Email: john.sear@nda.ox.ac.uk
   Role: This author helped conduct the study and write the manuscript
   Conflicts: John W Sear reported no conflicts of interest
   Attestation: John W Sear approved the final manuscript

19. Homer Yang, MD, CCFP, FRCPC, CCPE
   Title: Dr
   Affiliation: Department of Anesthesia, University of Ottawa, Ottawa, Canada
   Email: hyang@ottawahospital.on.ca
   Role: This author helped conduct the study and write the manuscript
   Conflicts: Homer Yang reported no conflicts of interest
   Attestation: Homer Yang approved the final manuscript

Institution: Department of Anaesthesia and Pain Management, Royal Melbourne Hospital,
Melbourne, Australia; Department of Pharmacology, University of Melbourne, Melbourne, Australia; Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Melbourne, Australia; Academic Board of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia; National Health and Medical Research Council, Canberra, Australia; Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; Population Health Research Institute, McMaster University, Hamilton, Canada; School of Population Health, University of Melbourne, Melbourne, Australia; Fu Wai Cardiovascular Hospital, CAMS, People’s Republic of China; Nuffield Division of Anaesthetics, Oxford University, Oxford, United Kingdom; Nueva Granada Military University, Bogota, Colombia; Department of Anaesthesia, Resuscitation and Pain Management, Central Military Hospital, Bogota, Colombia; Department of Anaesthesiology, The Ottawa Hospital, Ottawa, Canada; Department of Anesthesia, McMaster University, Hamilton Health Sciences, Hamilton, Canada; School of Medicine and Pharmacology, University of Western Australia, Perth, Australia; Department of Anaesthesia and Pain Medicine, King Edward Memorial Hospital for Women, Perth, Australia; Department of Anesthesia and Perioperative Medicine, Royal Columbian Hospital, New Westminster, Canada; Department of Anaesthesiology, The University of British Columbia, Vancouver, Canada; Department of Anesthesia and Perioperative Medicine, University of Western Ontario; Department of Anaesthesia, Austin Hospital, Melbourne, Australia; Department of Surgery, Austin Hospital and University of Melbourne, Melbourne, Australia; Nuffield Department of Anaesthetics, Oxford University, Oxford, United Kingdom; Department of Anesthesia, University of Ottawa, Ottawa, Canada

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**Corresponding Author:**
Kate Leslie, MBBS, MD, MEpi, FANZCA

Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Australia; Department of Pharmacology, University of Melbourne, Melbourne, Australia

Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Parkville, VIC, 3050, Australia

Phone: +61-3-93427540

FAX: +61-3-93428623

Email: kate.leslie@mh.org.au

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This study was conducted with written informed consent from the study subjects.

This report describes an observational clinical study.

This report describes cohort observational clinical study. The author states that the report includes every item in the STROBE checklist for cohort observational clinical studies.

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Abstract

**Background:** The aim of this post-hoc sub-analysis of the POISE trial was to determine whether nitrous oxide was associated with the primary composite outcome of cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest within 30 days of randomization.

**Methods:** The POISE Trial of perioperative beta-blockade was undertaken in 8,351 patients. Nitrous oxide anesthesia was defined as co-administration of nitrous oxide in patients receiving general anesthesia, with or without additional neuraxial blockade or peripheral nerve blockade. Logistic regression, with inverse probability weighting using estimated propensity scores, was used to determine the association of nitrous oxide with the primary outcome, myocardial infarction, stroke, death and clinically significant hypotension.

**Results:** Nitrous oxide was administered to 1,489 (29%) of the 5,133 patients included in this analysis. Nitrous oxide had no significant effect on the risk of the primary outcome (112 [7.5%] vs. 248 [6.9%]; OR, 1.08; 95% CI, 0.82-1.44; 99% CI, 0.75-1.57; P = 0.58), myocardial infarction (89 [6.0] vs. 204 [5.6]; OR, 0.99; 95% CI, 0.75-1.31; 99% CI, 0.69-1.42; P = 0.94), stroke (6 [0.4%] vs. 28 [0.8%]; OR, 0.85; 95% CI, 0.26-2.82; 99% CI, 0.17-4.11; P = 0.79), death (40 [2.7%] vs. 100 [2.8%]; OR, 1.04; 95% CI, 0.6-1.81; 99% CI, 0.51-2.15; P = 0.88) or clinically significant hypotension (219 [14.7%] vs. 544 [15.0%]; OR, 0.92; 95% CI, 0.74-1.15; 99% CI, 0.70-1.23; P = 0.48).

**Conclusions:** In this post-hoc sub-analysis, nitrous oxide was not associated with an increased risk of adverse outcomes in POISE Trial patients. This analysis was limited by the
observational nature of the data and lack of information on the concentration and duration of nitrous oxide administration. Further randomized controlled trial evidence is required.
**Introduction**

Nitrous oxide is commonly used during non-cardiac surgery and, in view of the large number of patients exposed worldwide every year, good evidence for its beneficial or harmful effects is desirable. However, the available large randomized trial\(^1\) and observational studies\(^2\)-\(^4\) report conflicting results which limit reliable conclusions about the value of nitrous oxide.

Nitrous oxide may reduce potent hypnotic and opioid requirements intraoperatively and improve acute and chronic pain outcomes postoperatively.\(^5\) However, the effect of nitrous oxide on perioperative cardiac, pulmonary, and thrombotic outcomes is unclear.\(^1\)-\(^4\) Nitrous oxide use may increase the risk of myocardial infarction (MI) via increased plasma homocysteine concentrations and endothelial dysfunction after surgery.\(^3\) Investigating the effectiveness of anesthetic management using randomized trials is challenging\(^6\),\(^7\) and so analysis of large prospectively collected datasets is warranted.\(^4\)

The POISE Trial randomized 8,351 patients with or at risk of ischemic heart disease having non-cardiac surgery to 30 days of extended-release metoprolol succinate or placebo.\(^8\) Metoprolol was associated with a decreased risk of non-fatal MI (4.2% versus 5.7%; \(p = 0.002\)) but an increased risk of stroke (1.0% versus 0.5%; \(p = 0.005\)) and death (3.1% versus 2.1%; \(p = 0.03\)) compared with placebo. POISE required complete prospective collection of many relevant indices throughout the 30-day study period. With the significant adverse event rates and the substantial use of nitrous oxide in the trial, this dataset provides an opportunity to further explore the effects of nitrous oxide on major outcomes, even though this was not the original aim of POISE. The primary aim of this post-hoc sub-analysis,
therefore, was to determine the effects of nitrous oxide on the incidence of a composite outcome of cardiovascular death, non-fatal MI and non-fatal cardiac arrest occurring within 30 days after randomization in the POISE Trial patients.
Materials and Methods

The POISE Trial protocol has been described in detail elsewhere and was registered with ClinicalTrials.gov (NCT00182039). In summary, patients were eligible for this multi-center, blinded, randomized controlled trial, if they were aged ≥45 years, were undergoing non-cardiac surgery with an expected hospital length of stay ≥24 h, and fulfilled at least one of the following criteria: history of coronary artery disease, peripheral vascular disease, stroke, hospitalization for congestive heart failure, undergoing major vascular surgery or any three of seven criteria (intrathoracic or intraperitoneal surgery, history of congestive heart failure, transient ischemic attack, diabetes, serum creatinine >175 µmol/L, age >70 years or undergoing emergency surgery). Patients were excluded if they met the following criteria: heart rate <50 beats per minute, second or third degree heart block, asthma, already receiving a beta-blocker, coronary artery bypass surgery within five years and no cardiac ischemia since, low-risk surgical procedures, on verapamil or previous randomization into the trial. All centers obtained institutional review board approval and all patients provided informed consent for the original trial. Patients were only recruited once and data relate to the index surgery and not any other surgery. Patients who were related to another participant were not excluded. Institutional review board pendency was not maintained, and approval to add investigators who assisted with these analyses was not sought (these investigators did not have access to identifiable data nor individual case report forms).

A total of 8,351 patients from 190 hospitals in 23 countries were randomly assigned to extended-release metoprolol succinate or placebo, starting 2-4 h before surgery and continuing for 30 days. Study medication was only administered if the heart rate was ≥50 beats per minute and the systolic blood pressure was ≥100 mm Hg. Patients were
monitored with cardiac biomarker assays and electrocardiographs during the 30-day follow-up period and cardiovascular outcomes were adjudicated centrally by a blinded committee. The dosage and monitoring regimens were described in detail previously.\textsuperscript{8,9}

The primary outcome was a composite of cardiovascular death, non-fatal MI and non-fatal cardiac arrest occurring within 30 days of randomization. Secondary outcomes included MI and stroke. Clinically significant hypotension was defined as a systolic blood pressure of <90 mm Hg requiring fluid resuscitation, an inotropic agent or study drug discontinuation or intraaortic balloon pump.\textsuperscript{9} Testing the effect of nitrous oxide on these outcomes was not the primary purpose for which the POISE Trial was designed.

Nitrous oxide anesthesia was defined as co-administration of nitrous oxide in patients receiving general anesthesia, with or without additional neuraxial blockade or nerve blockade.

\textbf{Data analysis}

Baseline characteristics were summarized as number (\%) for categorical variables and mean (standard deviation) for continuous variables, and were compared between intervention groups using chi-squared tests and analysis of variance, respectively.

Use of nitrous oxide was left to the discretion of the attending anesthesiologists; that is, such use was not randomly assigned. Patient characteristics were therefore imbalanced between intervention groups, and so we used a propensity score technique to account for potential confounding. The propensity score is the probability of receiving the intervention, modelled as a function of observed variables, and can be used in various ways to adjust for confounding due to observed characteristics.\textsuperscript{10,11} We adopted an inverse probability
weighted approach, which uses the propensity score to create a `pseudo-population’ in which all measured characteristics are balanced between the intervention groups, hence removing any confounding by these characteristics (but not necessarily by unmeasured or unknown confounders). This is akin to the balance that is expected to be observed amongst measured variables in a randomized trial; however, it is not akin to the balance one would expect with unknown prognostic variables in a large randomized trial. A key assumption in the use of such methods is that every patient must have a non-zero probability of receiving each studied intervention. For nitrous oxide, patients not receiving a general anesthetic were excluded.

The propensity score for nitrous oxide use was estimated using a logistic regression model in which the outcome was the intervention group. An iterative procedure was used to select independent variables to include in the model, initially including main effects for all characteristics listed in Tables 1 and 2, adding interaction terms until no further imbalance could be removed. All analyses were repeated using a more comprehensive propensity score model including all region-by-covariate interactions, in order to investigate and account for geographical differences in intervention allocation.

We then imposed the ‘common support’ condition in which we excluded any patients in the intervention group who had an estimated propensity score higher than that of any patient in the no-intervention group, and any patients in the no-intervention group with a propensity score lower than that of any patient receiving the intervention. This removed subjects for whom no comparable subject existed in the other intervention group, since the effect of the intervention cannot be estimated for such patients.
Each subject was inversely weighted by the probability of that subject receiving the intervention that they did indeed receive (calculated using the propensity score). Within the weighted sample (the `pseudo-population’), measured patient prognostic characteristics should be balanced between the intervention groups. This was assessed using standardized differences (the difference in the percentage [or mean] of each characteristic between intervention groups, divided by an estimate of the standard deviation and expressed as a percentage) calculated both for the original sample and the weighted sample. It has been suggested that a standardized difference of 10% or greater represents a meaningful imbalance.

Odds ratios (OR) and 95% confidence intervals (CIs) for the effect of nitrous oxide on the primary composite outcome, MI and stroke were estimated using logistic regression models for each outcome including the intervention group as the sole independent variable by applying a weighted analysis as described above. Characteristics that remained imbalanced in the weighted sample were additionally included as independent variables in the logistic regression model to remove any residual confounding by these variables.

To assess between-region variability in effect, an interaction between intervention and geographical region was additionally included in the weighted logistic regression model. Estimated associations with the outcome primary for nitrous oxide by region were also calculated.

To assess the sensitivity of results to a few individuals with large weights, we excluded the 1% of subjects with the largest weights and repeated all the analyses. Subjects with missing data for surgery type or baseline heart rate or systolic blood pressure were excluded from all analyses. Analyses were conducted using Stata version 11.1. A P <0.05 was considered statistically significant.
Results

For nitrous oxide, 5,104 patients remained after exclusions were made for patients who did not receive general anaesthesia (n = 3,139), for those with missing data (n = 30), and for the common support condition (n = 78).

Patients receiving nitrous oxide were more likely to have ischemic heart disease and were less likely to be having intra-abdominal or emergency surgery than those not receiving nitrous oxide (Table 1). There was also significant regional variation in the administration of nitrous oxide, ranging from 5% in Central/South America to 80% in India. Imbalances between the intervention groups in the initial sample were reduced to minimal levels by the propensity score weighting (Tables 1). In particular, the groups were well balanced for the randomized beta-blocker treatment.

There was no evidence of an association between nitrous oxide and the risk of the primary outcome (OR, 1.08; 95% CI, 0.82-1.44; 99% CI, 0.75-1.57; P = 0.58), MI (OR, 0.99; 95% CI, 0.75-1.31; 99% CI, 0.69-1.42; P = 0.94) or stroke (OR, 0.85; 95% CI, 0.26-2.82; 99% CI, 0.17-4.11; P = 0.79), death (OR, 1.04; 95% CI, 0.6-1.81; 99% CI, 0.51-2.15; P = 0.88) or clinically significant hypotension (OR, 0.92; 95% CI, 0.74-1.15; 99% CI, 0.70-1.23; P = 0.48) (Table 2). Trimming the weights modified the odds ratios slightly (1.14, 1.13, 0.63, 0.88 and 0.94, respectively), however all P-values remained above 0.27 thereby retaining the conclusions from the untrimmed data. There was no evidence to support an effect of nitrous oxide on the primary outcome based on region (Table 3).
Discussion

We found no evidence that nitrous oxide had an effect on the primary outcome (cardiovascular death, non-fatal MI and non-fatal cardiac arrest), MI, stroke or clinically significant hypotension in the POISE Trial patients. We did however find marked geographical differences in the rates of nitrous oxide administration, suggesting differences in regional preferences and ongoing uncertainty of the benefits and risks of nitrous oxide. Our results should, however, be considered in the light of the study’s limitations, as outlined below.

This result is possibly due to a lack of power, but nevertheless is consistent with previous literature on this subject,\textsuperscript{1,3,4} despite the plausible pathophysiologic rationale\textsuperscript{3} and clinical trial support\textsuperscript{15} for increased myocardial ischemia in nitrous oxide patients. The trend towards an increased rate of death and MI at 30 days was not statistically significant in the ENIGMA-1 Trial,\textsuperscript{1} although a long-term follow-up revealed a marginal increase in the risk of MI.\textsuperscript{3} In contrast, Shiba et al.\textsuperscript{4} reported no effect on 30-day mortality and a decrease in hospital morbidity in nitrous oxide patients when analyzing a large administrative dataset.

We thus have uncertainty regarding this important clinical issue for anesthesiologists. Consequently, we are conducting a randomized trial of nitrous oxide–based versus nitrous oxide–free anesthesia in 7,000 noncardiac surgery patients who have or are at risk of ischemic heart disease (the ENIGMA–II Trial; www.enigma2.org.au).\textsuperscript{6} The contrasting patterns of use around the world reported in the current study illustrate the uncertainty about the risk-benefit ratio for nitrous oxide and further support the need for compelling
evidence. In the meantime, those anesthesiologists who omit nitrous oxide from their general anesthesia plan in high-risk patients should not do so on the basis that risk of important morbidity will definitely be reduced, because these results and others are not definitive.

The current analyses have several limitations. Firstly, the POISE Trial was not designed with the primary purpose of testing the effects of nitrous oxide on the primary or secondary outcomes. The patients in the POISE Trial were not randomized to nitrous oxide, and the use of this drug was at the discretion of the attending anesthesiologist. Although we included a propensity analysis in order to account for the decision to use nitrous oxide, we were limited by the data available. In addition, the original protocol was not developed with this analysis in mind. There are likely to be unmeasured and unknown factors that influenced the choice of nitrous oxide that may provide an alternative explanation for our findings.

Interest in and experience with nitrous oxide use varies amongst anesthesiologists and there are certainly institutional and regional differences. Whilst nitrous oxide use is not commonly discussed with patients, surgeons may be concerned about the effects of nitrous oxide during bowel or middle ear surgery.\textsuperscript{16} In the present study, the only data point that captured these factors was the regional variations in the use of these techniques, and we included these in our propensity score.

Secondly, we did not record the details of the nitrous oxide use when they were administered (i.e. timing of initiation, inspired nitrous oxide concentration and duration of administration). Randomized trials on this intervention need to control or record these factors. The dose of nitrous oxide determines extent of hyperhomocysteinemia and its possible consequences.\textsuperscript{17} Finally, we did not collect data on other aspects of anesthesia
care, such as the use of volatile-based or propofol-based maintenance of anesthesia, opioid use or postoperative care; on the actual operation undertaken or on the success of surgery (particularly in relation to vascular graft patency). Nitrous oxide was the only component of the general anesthetic technique that was recorded.

In conclusion, we found no evidence that nitrous oxide was associated with any of these outcomes. These results have important implications for future research.
References


7. McPeek B. Inference, generalizability and a major change in anesthetic practice. Anesthesiology 1987; 66: 723-4


<table>
<thead>
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<th>Characteristic</th>
<th>Unweighted - % (N)</th>
<th>Propensity score weighted - %</th>
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<td>Age (years)</td>
<td>69.7 (10)</td>
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## Preoperative medications

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<th>Type of Medication</th>
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<td>4.4</td>
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<td>LMWH/unfractionated heparin</td>
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<td>5.3 (79)</td>
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<td>ACEI/ARB</td>
<td>46.7 (1689)</td>
<td>40.4 (601)</td>
<td>12.8</td>
<td>&lt;0.001</td>
<td>44.7</td>
<td>45.1</td>
</tr>
<tr>
<td>Statin</td>
<td>35.2 (1274)</td>
<td>33.3 (496)</td>
<td>4.0</td>
<td>0.20</td>
<td>34.8</td>
<td>33.5</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>20.1 (726)</td>
<td>24.5 (365)</td>
<td>10.7</td>
<td>&lt;0.001</td>
<td>21.4</td>
<td>21.0</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>5.8 (210)</td>
<td>10.3 (153)</td>
<td>16.5</td>
<td>&lt;0.001</td>
<td>7.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Non-study beta-blockers</td>
<td>0.6 (20)</td>
<td>0.5 (8)</td>
<td>0.2</td>
<td>0.95</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
<td>Digoxin</td>
<td>2.7 (99)</td>
<td>2.5 (37)</td>
<td>2.5</td>
<td>0.61</td>
<td>2.6</td>
<td>2.7</td>
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<tr>
<td>Amiodarone</td>
<td>1.4 (49)</td>
<td>1.1 (16)</td>
<td>1.5</td>
<td>0.42</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>3.2 (115)</td>
<td>2.8 (41)</td>
<td>2.5</td>
<td>0.42</td>
<td>3.0</td>
<td>2.9</td>
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</table>

## Type of surgery

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Current</th>
<th>Former</th>
<th>3.8</th>
<th>20.9</th>
<th>22.0</th>
<th>2.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major vascular</td>
<td>39.2 (1419)</td>
<td>38.4 (572)</td>
<td>1.6</td>
<td>&lt;0.001</td>
<td>39.9</td>
<td>38.7</td>
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<tr>
<td>Other vascular</td>
<td>7.3 (264)</td>
<td>5.0 (75)</td>
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<td>6.6</td>
<td>8.2</td>
<td>5.9</td>
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<tr>
<td>Orthopedic</td>
<td>12.5 (451)</td>
<td>12.8 (191)</td>
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<td>12.7</td>
<td>11.7</td>
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<tr>
<td>Intra-abdominal</td>
<td>28.3 (1025)</td>
<td>24.8 (369)</td>
<td>8.0</td>
<td>26.7</td>
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</tr>
<tr>
<td>Other</td>
<td>12.6 (457)</td>
<td>18.9 (281)</td>
<td>17.2</td>
<td>14.0</td>
<td>13.6</td>
<td>1.0</td>
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</tbody>
</table>

## Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Current</th>
<th>Former</th>
<th>3.8</th>
<th>20.9</th>
<th>22.0</th>
<th>2.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia and New Zealand</td>
<td>13.2 (479)</td>
<td>15.0 (223)</td>
<td>5.0</td>
<td>&lt;0.001</td>
<td>13.7</td>
<td>13.4</td>
</tr>
<tr>
<td>Central and South America</td>
<td>19.7 (711)</td>
<td>2.6 (39)</td>
<td>56.3</td>
<td>14.7</td>
<td>16.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Canada</td>
<td>51.2 (1852)</td>
<td>43.3 (644)</td>
<td>15.9</td>
<td>48.9</td>
<td>47.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Southeast Asia, China and Hong Kong</td>
<td>9.0 (325)</td>
<td>18.1 (269)</td>
<td>26.8</td>
<td>11.7</td>
<td>11.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Europe</td>
<td>5.1 (185)</td>
<td>4.0 (60)</td>
<td>5.2</td>
<td>4.8</td>
<td>4.8</td>
<td>0.2</td>
</tr>
<tr>
<td>India</td>
<td>1.8 (64)</td>
<td>17.0 (253)</td>
<td>54.1</td>
<td>6.2</td>
<td>6.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>10.5 (380)</td>
<td>8.3 (124)</td>
<td>7.5</td>
<td>0.02</td>
<td>9.9</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p-value</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>------------</td>
<td>---------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Preoperative heart rate (beats per minute)</td>
<td>77.1 (12.5)</td>
<td>78.4 (12.7)</td>
<td>10.3</td>
<td>&lt;0.001</td>
<td>78 (12.6)</td>
<td>78 (12.1)</td>
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<tr>
<td>Preoperative systolic blood pressure (mm Hg)</td>
<td>138.6 (19.9)</td>
<td>139.6 (20.0)</td>
<td>5.4</td>
<td>0.08</td>
<td>139 (19.9)</td>
<td>139 (20.4)</td>
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<tr>
<td>Randomized to metoprolol</td>
<td>49.1 (1776)</td>
<td>51.2 (762)</td>
<td>4.2</td>
<td>0.17</td>
<td>49.6</td>
<td>48.4</td>
</tr>
</tbody>
</table>

*Except for age, heart rate and systolic blood pressure which are presented as mean (standard deviation). LMWH = low molecular weight heparin. Std Diff = standardized difference. ACEI = angiotensin converting enzyme inhibitor. ARB = angiotensin-II receptor blocker. ** Chi-squared test (categorical variables) or ANOVA (continuous variables), unweighted or weighted as appropriate.
Table 2 Estimated associations with outcome for nitrous oxide

<table>
<thead>
<tr>
<th></th>
<th>No nitrous oxide (N = 3,616)</th>
<th>Nitrous oxide (N = 1,488)</th>
<th>Unadjusted</th>
<th>Propensity score adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Primary**</td>
<td>248</td>
<td>6.9</td>
<td>112</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>204</td>
<td>5.6</td>
<td>89</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>28</td>
<td>0.8</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Death</td>
<td>100</td>
<td>2.8</td>
<td>40</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>544</td>
<td>15.0</td>
<td>219</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; *Wald-test p-value from unweighted/weighted logistic regression; ** primary outcome = cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest
Table 3 Estimated associations with the outcome primary for nitrous oxide by region

<table>
<thead>
<tr>
<th>Region</th>
<th>No nitrous oxide</th>
<th>Nitrous oxide</th>
<th>Propensity score adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>479 (68.2)</td>
<td>223 (31.8)</td>
<td>0.74 (0.38, 1.46)</td>
</tr>
<tr>
<td>Central/South America</td>
<td>711 (94.8)</td>
<td>39 (5.2)</td>
<td>0.80 (0.18, 3.54)</td>
</tr>
<tr>
<td>Canada</td>
<td>1,852 (74.2)</td>
<td>644 (25.8)</td>
<td>1.18 (0.85, 1.64)</td>
</tr>
<tr>
<td>South east Asia/China/Hong Kong</td>
<td>325 (54.7)</td>
<td>269 (45.3)</td>
<td>1.03 (0.51, 2.08)</td>
</tr>
<tr>
<td>Europe</td>
<td>185 (75.5)</td>
<td>60 (24.5)</td>
<td>2.20 (0.82, 5.92)</td>
</tr>
<tr>
<td>India</td>
<td>64 (20.2)</td>
<td>253 (79.8)</td>
<td>1.20 (0.33, 4.35)</td>
</tr>
<tr>
<td>Overall</td>
<td>3,616 (70.9)</td>
<td>1,488 (29.2)</td>
<td>1.08 (0.82, 1.44)</td>
</tr>
</tbody>
</table>

P interaction 0.61

OR = odds ratio; CI = confidence interval; Primary outcome = cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest