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Nitrous Oxide and Serious Morbidity and Mortality in the POISE Trial

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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.

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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 trial¹ and observational studies²⁻⁴ 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.

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Materials and Methods

The POISE Trial protocol has been described in detail elsewhere and was registered with ClinicalTrials.gov (NCT00182039).^{8,9} 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 $\mu\text{mol/L}$, 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.^{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.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.

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.^{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).¹² 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' condition¹¹ 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)¹³ 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.¹⁴

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,^{1,3,4} despite the plausible pathophysiologic rationale³ and clinical trial support¹⁵ 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,¹ although a long-term follow-up revealed a marginal increase in the risk of MI.³ In contrast, Shiba et al.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).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.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.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.

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References

1. Myles P, Leslie K, Chan M, Forbes A, Paech M, Peyton P, Silbert B, Pascoe E. Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. *Anesthesiology* 2007; 107: 221-31
2. Leslie K, Myles P, Forbes A, Chan M. The effect of bispectral index monitoring on long-term survival in the B-Aware trial. *Anesth Analg* 2010; 110: 816-22
3. Leslie K, Myles P, Chan M, Forbes A, Paech M, Peyton P, Silbert B, Williamson E. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. *Anesth Analg* 2011; 112: 387-93
4. Shiba S, You J, Saager L, Sessler D, Turan A. Nitrous oxide and postoperative outcomes after non-cardiac surgery, American Society of Anesthesiologists Annual Meeting. San Diego, 2010
5. Stiglitz D, Amaratunge L, Konstantatos A, Lindholm D. Intraoperative nitrous oxide as a preventive analgesic. *Anaesth Intensive Care* 2010; 38: 890-3
6. Myles P, Leslie K, Peyton P, Paech M, Forbes A, Chan M, Sessler D, Devereaux P, Silbert B, Jamrozik K, Beattie S, Badner N, Tomlinson J, Wallace S. Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) Trial: Rationale and design. *Am Heart J* 2009; 157-62: 488-94
7. McPeck B. Inference, generalizability and a major change in anesthetic practice. *Anesthesiology* 1987; 66: 723-4
8. POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; 371: 1839-47

9. POISE Trial Investigators. Rationale, design, and organization of the PeriOperative ISchemic Evaluation (POISE) Trial: A randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery. *Am J Heart* 2006; 152: 223-230
10. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; 70: 41-55
11. Williamson E, Morley R, Lucas A, Carpenter J. Propensity scores: From naïve enthusiasm to intuitive understanding. *Statistical Methods in Medical Research* 2012; 21: 273-93
12. Hernan M, Robins J. Estimating causal effects from epidemiological data. *Epidemiol Community Health* 2006; 60: 578-86
13. Austin P, Grootendorst P, Anderson G. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Statistics in Medicine* 2007; 26: 734-53
14. Sharon-Lise T, Normand S-L T, Landrum M, Guadagnolia E, Ayaniana J, Ryand T, Clearya P, McNeil B. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: A matched analysis using propensity scores. *Journal of Clinical Epidemiology* 2001; 54 387-98
15. Badner N, Beattie W, Freeman D, Spence J. Nitrous oxide-induced increased homocysteine concentrations are associated with increased postoperative myocardial ischemia in patients undergoing carotid endarterectomy. *Anesth Analg* 2000; 91: 1073-9
16. Myles P, Leslie K, Silbert B, Paech M, Peyton P. A review of the risks and benefits of nitrous oxide in current anaesthetic practice. *Anaesth Intensive Care* 2004; 32: 165-

17. Myles P, Chan M, Leslie K, Peyton P, Paech M, Forbes A. Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. Br J Anaesth 2008; 100: 780-6

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Table 1 Nitrous oxide baseline characteristics (n = 5,104)

	Unweighted - % (N)				Propensity score weighted - %			
	No nitrous oxide (n=3,616)	Nitrous oxide (n=1,488)			No nitrous oxide (n=3,616)	Nitrous oxide (n=1,488)		
Characteristic	% (N)*	% (N)*	StDiff (%)	P value**	% (N)*	% (N)*	StDiff (%)	P value**
Age (years)	69.7 (10)	68.2 (10.5)	14.9	<0.001	69.3 (10.2)	69.2 (10.3)	0.8	0.85
Age group (years)								
45-54	8.8 (318)	13.1 (195)	13.8	<0.001	9.9	10.5	1.8	0.97
55-64	22.3 (806)	23.2 (345)	2.1		22.5	22.5	0.0	
65-74	36.4 (1318)	33.7 (501)	5.8		35.9	34.8	2.3	
75-84	27.8 (1005)	26.4 (393)	3.1		27.3	27.4	0.4	
85+	4.7 (169)	3.6 (54)	5.2		4.4	4.8	1.7	
Sex (female)	37.5 (1355)	35.3 (526)	4.4	0.15	36.6	35.8	1.5	0.71
Past history								
Coronary artery disease	39.2 (1419)	44.1 (656)	9.8	<0.001	39.9	42.6	5.4	0.18
Peripheral vascular disease	38.2 (1383)	35.7 (531)	5.3	0.09	38.2	38.2	0.1	0.99
Stroke thought due to atherothrombotic disease	14.9 (540)	16.1 (240)	3.3	0.28	15.3	15.6	0.8	0.83
Transient ischemic attack history	11.5 (415)	11.8 (175)	0.9	0.77	11.8	12.9	3.4	0.39
Hospitalized for congestive heart failure	2.4 (86)	2.8 (41)	2.4	0.43	2.5	2.8	2.3	0.56
Documented heart failure	5.6 (204)	4.4 (66)	5.5	0.08	5.3	5.4	0.3	0.95
Preoperative serum creatinine >175 µmol/L	4.5 (162)	5.2 (78)	3.5	0.248	4.5	3.4	5.7	0.06
Diabetes on oral hypoglycaemic agent or insulin	27.5 (993)	26.9 (401)	1.2	0.71	27.4	26.5	2.0	0.63
Hypertension	64.1 (2317)	61.5 (915)	5.3	0.08	63.4	65.5	4.5	0.24
Smoking Status								
Never	36.0 (1301)	37.4 (556)	2.9	0.42	35.9	37.1	2.4	0.49

Current	21.3 (770)	19.8 (294)	3.8		20.9	22.0	2.7	
Former	42.7 (1545)	42.9 (638)	0.3		43.2	40.9	4.6	
Preoperative medications								
Aspirin	35.7 (1291)	33.5 (499)	4.6	0.14	35.8	34.4	3.0	0.45
Clopidogrel	3.9 (141)	5.2 (77)	6.1	0.04	4.4	4.7	1.6	0.71
LMWH/unfractionated heparin	7.7 (277)	5.3 (79)	9.6	<0.001	7.4	9.9	8.9	0.10
ACEI/ARB	46.7 (1689)	40.4 (601)	12.8	<0.001	44.7	45.1	0.8	0.84
Statin	35.2 (1274)	33.3 (496)	4.0	0.20	34.8	33.5	2.7	0.48
Diuretic	21.7 (783)	19.2 (285)	6.2	0.05	20.8	22.7	4.7	0.27
Calcium channel blocker	20.1 (726)	24.5 (365)	10.7	<0.001	21.4	21.0	0.78	0.83
Long-acting nitrates	5.8 (210)	10.3 (153)	16.5	<0.001	7.0	6.4	2.3	0.51
Non-study beta-blockers	0.6 (20)	0.5 (8)	0.2	0.95	0.5	0.5	0.9	0.76
Digoxin	2.7 (99)	2.5 (37)	2.5	0.61	2.6	2.7	0.2	0.97
Amiodarone	1.4 (49)	1.1 (16)	1.5	0.42	1.3	1.6	3.0	0.57
Oral anticoagulants	3.2 (115)	2.8 (41)	2.5	0.42	3.0	2.9	1.0	0.76
Type of surgery								
Major vascular	39.2 (1419)	38.4 (572)	1.6	<0.001	39.9	38.7	2.5	0.68
Other vascular	7.3 (264)	5.0 (75)	9.4		6.6	8.2	5.9	
Orthopedic	12.5 (451)	12.8 (191)	1.1		12.7	11.7	3.1	
Intra-abdominal	28.3 (1025)	24.8 (369)	8.0		26.7	27.8	2.3	
Other	12.6 (457)	18.9 (281)	17.2		14.0	13.6	1.0	
Region								
Australia and New Zealand	13.2 (479)	15.0 (223)	5.0	<0.001	13.7	13.4	1.0	0.98
Central and South America	19.7 (711)	2.6 (39)	56.3		14.7	16.7	5.5	
Canada	51.2 (1852)	43.3 (644)	15.9		48.9	47.7	2.4	
Southeast Asia, China and Hong Kong	9.0 (325)	18.1 (269)	26.8		11.7	11.3	1.1	
Europe	5.1 (185)	4.0 (60)	5.2		4.8	4.8	0.2	
India	1.8 (64)	17.0 (253)	54.1		6.2	6.1	0.4	
Emergency surgery	10.5 (380)	8.3 (124)	7.5	0.02	9.9	10.1	0.6	0.90

Preoperative heart rate (beats per minute)	77.1 (12.5)	78.4 (12.7)	10.3	<0.001	78 (12.6)	78 (12.1)	0.8	0.82
Preoperative systolic blood pressure (mm Hg)	138.6 (19.9)	139.6 (20.0)	5.4	0.08	139 (19.9)	139 (20.4)	1.7	0.69
Randomized to metoprolol	49.1 (1776)	51.2 (762)	4.2	0.17	49.6	48.4	2.4	0.56

*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

	No nitrous oxide (N = 3,616)		Nitrous oxide (N = 1,488)		Unadjusted		Propensity score adjusted	
	N	%	N	%	OR (CI)	P value*	OR (CI)	P value*
Primary**	248	6.9	112	7.5	1.11 (95%: 0.88,1.39)	0.397	1.08 (95%: 0.82,1.44)	0.58
					(99%: 0.82,1.50)		(99%: 0.75,1.57)	
Myocardial infarction	204	5.6	89	6.0	1.06 (95%: 0.82,1.38)	0.636	0.99 (95%: 0.75,1.31)	0.94
					(99%: 0.76,1.49)		(99%: 0.69,1.42)	
Stroke	28	0.8	6	0.4	0.52 (95%: 0.21,1.26)	0.146	0.85 (95%: 0.26,2.82)	0.79
					(99%: 0.16,1.66)		(99%: 0.17,4.11)	
Death	100	2.8	40	2.7	0.97 (95%: 0.67,1.41)	0.878	1.04 (95%: 0.6,1.81)	0.88
					(99%: 0.60,1.58)		(99%: 0.51,2.15)	
Hypotension	544	15.0	219	14.7	0.98 (95%: 0.82,1.16)	0.780	0.92 (95%: 0.74,1.15)	0.48
					(99%: 0.78,1.22)		(99%: 0.70,1.23)	

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

Region	No nitrous oxide	Nitrous oxide	Propensity score adjusted	
	N (%)	N (%)	OR (95% CI)	P value
Australia/New Zealand	479 (68.2)	223 (31.8)	0.74 (0.38, 1.46)	0.39
Central/South America	711 (94.8)	39 (5.2)	0.80 (0.18, 3.54)	0.77
Canada	1,852 (74.2)	644 (25.8)	1.18 (0.85, 1.64)	0.33
South east Asia/China/Hong Kong	325 (54.7)	269 (45.3)	1.03 (0.51, 2.08)	0.93
Europe	185 (75.5)	60 (24.5)	2.20 (0.82, 5.92)	0.12
India	64 (20.2)	253 (79.8)	1.20 (0.33, 4.35)	0.78
Overall	3,616 (70.9)	1,488 (29.2)	1.08 (0.82,1.44)	0.58
P interaction				0.61

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