Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia (ENIGMA) Studies: The Tale of Two Large Pragmatic Randomized Controlled Trials

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> "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity…" A Tale of Two Cities, Charles Dickens, 1859

In recent years, there is an emphasis on evidence-based practice. Large randomized controlled trials (RCTs) are considered as the highest level of evidence. However, tightly controlled trials may not have generalizability.[1] In addition, when conducting large, multicenter, international trials, it may not be possible to control all variables during the perioperative course. Therefore, pragmatic study designs that allow for variations in the preoperative, intraoperative (anesthetic, analgesic, and surgical techniques), and postoperative care are increasingly being used.[2] However, the perioperative period is associated with complex interactions between the anesthetic and surgical aspects (ie, technical or care principles). Thus, there is a concern that single intervention trials in the perioperative setting may not always serve well to guide clinical practice.[3]

This article stimulates debate on the design and interpretation of large pragmatic RCTs evaluating perioperative interventions by critically examining the contradictory findings and interpretation of 2 large RCTs, the Evaluation of Nitrous oxide in the Gas Mixture for Anesthesia (ENIGMA)-I study[4] and the subsequent ENIGMA-II study.[5] Its secondary aim is to assess the current role of nitrous oxide (N_2O), one of the oldest anesthetics with amnestic, anesthetic, and analgesic properties.[6]

ENIGMA-I TRIAL

The ENIGMA-I trial was a large, international, multicenter, randomized study in adult patients undergoing major surgical procedures with expected duration of anesthesia of at least 2 hours and expected hospital stay of at least 3 days.[4]

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The premise of this study was that hyperhomocysteinemia observed with N_2O might increase postoperative cardiovascular complications.[7] Another premise of the study was that the use of higher (80%) oxygen (O_2) concentrations would reduce surgical site infections (SSI) and postoperative nausea and vomiting (PONV).

The primary aim of the study was to assess the influence of N_2O on hospital length of stay (LOS), whereas the secondary aim examined the duration of intensive care unit (ICU) stay and postoperative complications such as severe PONV, pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, awareness under anesthesia, and 30-day mortality.

Patients were randomly assigned to N_2O-free (80% O_2 in air, n = 997) or N_2O-based (30% O_2 and 70% N_2O, n = 1015) anesthesia. Patients undergoing cardiac and thoracic surgery were excluded. The anesthetic and analgesic techniques as well as the management of perioperative hemodynamics and cardiac drug administration were not standardized (ie, a pragmatic study design). Thus, there was significant variability in the use of induction drugs (propofol, thiopental, etomidate), airway devices (tracheal tube and supralaryngeal device), maintenance of anesthesia (inhaled anesthetics and total IV anesthesia), depth of anesthetic monitoring and management, opioids, prophylactic antiemetic therapy, and regional anesthesia/analgesia (epidural analgesia and other regional blocks). Also, the postoperative care was variable.

The study found that the use of N_2O did not influence LOS (primary outcome). However, patients in the N_2O-free group had significantly lower rates of major complications including severe PONV, fever, wound infection, pneumonia, and atelectasis. Also, inspired O_2 concentration did not influence the LOS and the incidence of complications. The authors concluded that the routine use of N_2O in patients undergoing major surgery should be questioned. Several secondary analyses were published subsequently including the effects of N_2O on long-term morbidity and mortality,[8] PONV,[9] cost benefits of using N_2O,[10] and effects of N_2O on chronic postsurgical pain.[11]

ENIGMA-II TRIAL

The same group of investigators performed the ENIGMA-II trial, which was a larger, international, multicenter, randomized trial in patients >45 years old with known or suspected coronary artery disease undergoing major noncardiac surgery.[5] The primary outcome measure was a composite of death and cardiovascular complications (nonfatal

myocardial infarction, stroke, pulmonary embolism, cardiac arrest) within 30 days of surgery.

Patients were randomly assigned to receive either 30% O_2 with 70% N_2O (n = 3543) or 30% O_2 in air (n = 3569) during the maintenance of general anesthesia. Similar to the ENIGMA-I study, the anesthetic and analgesic techniques were not standardized (a pragmatic study design). The study found that there were no differences between the groups with respect to mortality and postoperative complications including myocardial infarction and SSI rates as well as the need for admission to the ICU, the duration of ICU stay, and the LOS. Also, the incidence of severe PONV was similar.

The authors concluded that N_2O is safe in patients undergoing major noncardiac surgery and that the emetogenic effects of N_2O can be controlled with antiemetic prophylaxis. This study also confirmed that N_2O reduced inhaled anesthetic requirements. Further analyses of the ENIGMA-II study found no differences in the 1-year mortality and cardiac complications in patients enrolled in the N_2O and the non-N_2O groups,[12] which contradicts the secondary analyses of the ENIGMA-I long-term study that found an increased risk of myocardial infarction in the N_2O group.[8] Similarly, further analysis of the ENIGMA-II study showed that avoiding N_2O reduced severe PONV only minimally and the associated risk of PONV was eliminated by prophylactic antiemetics,[13] which also contradicts the secondary analyses of the ENIGMA-I study.[9]

DISCUSSION

The contradictory findings of the ENIGMA-I and the ENIGMA-II studies suggest that even large multicenter, international RCTs can be difficult to interpret, because of the many uncontrolled variables that may influence the outcome. Both premises of the ENIGMA study (ie, hyperhomocysteinemia can increase cardiovascular risk and hyperoxia can reduce SSI) have been shown to be controversial. A trial in patients with cardiac risks undergoing noncardiac surgery with N_2O found that acute increases in homocysteine levels were not associated with increases in perioperative cardiac troponin levels.[14] Also, a study reported that N_2O did not increase the incidence of SSI.[15] Similarly, several recent studies and meta-analyses concluded that the administration of 80% O_2 did not decrease the risk of SSI.[16–18] A recent Cochrane review found that there is insufficient evidence to support the administration of high O_2 concentrations to reduce the risk of SSI.[18] Furthermore, administration of supplemental O_2 has not been shown to reduce PONV.[19] Similar to the findings of the ENIGMA-II trial, and contrary to the ENIGMA-I trial, a systematic review and meta-analysis of 30 RCTs (n = 2297 in N_2O group versus n = 2301 in non-N_2O group) also reported that avoiding N_2O reduced risk of PONV, but overall effect was modest.[20] In addition, propofol negated the emetic effects of N_2O. The authors proposed that prophylactic antiemetic therapy might further negate the emetic effects of N_2O,[20] which was confirmed by the ENIGMA-II study.[5]

The differences in cardiac complications and SSI rates observed in the ENIGMA-I trial may represent a type I error. In contrast to the ENIGMA-I trial, several subsequent trials failed to find an increased incidence of cardiovascular complications with the use of N_2O. A propensity-matched observational trial (n = 10,755 in each group) found that the odds of 30-day mortality and morbidity were lower with the use of N_2O compared with no N_2O.[21] Similar to the ENIGMA-II study, this study found that N_2O reduced inhaled anesthetic requirements. Another propensity-matched study in patients with high cardiac risk also found that N_2O was not associated with an increased risk of adverse outcomes.[22] These findings are similar to those of the ENIGMA-II trial.

As acknowledged in the ENIGMA-II study,[5] the ENIGMA-I study design was partially flawed,[4] because the 2 groups were not comparable with regard to the inspired O_2 concentrations (30% O_2 in the N_2O group versus 80% O_2 in the N_2O-free group). Another limitation is that the ENIGMA studies did not control anesthetic and analgesic techniques, or standardize the management of perioperative hemodynamics or cardiac drug administration. However, the choice of analgesia, surgical technique, type of intervention, and well-proven anti-ileus techniques are important for several of the outcomes evaluated in these studies. Although the investigators adjusted for variability, which is supposed to reduce the probability of intergroup differences, the perioperative period is dynamic and complex during which anesthesiologists and surgeons make several adjustments, and it is difficult to evaluate the effects of a single intervention (ie, the use of N_2O) on the investigated perioperative outcomes. Therefore, statistical analyses may not adequately adjust for the interactions between these factors. Furthermore, the lack of specific information on perioperative care principles in these multicenter studies hinders sufficient interpretation and application to modern anesthetic and surgical practice.

It is disappointing that, despite the several limitations of the ENIGMA-I study described above, the authors opted to condemn N_2O with conclusions such as "the routine use of N_2O in patients undergoing major surgery should be questioned." Furthermore, they chose to emphasize several N_2O-related postoperative complications (secondary outcome measures of the study) in post hoc analyses based on these data including a retrospective cost analysis.[8–10] In fact, the cost analysis did not include the benefits observed in this study with regard to reduced persistent postoperative pain,[11] which again requires more detailed data to allow interpretation.[23]

In summary, RCTs may be the "gold standard" for evaluating linear and tightly coupled causal relationships but may not be suitable for complex multicomponent nonlinear interventions typical of the perioperative setting.[3] Therefore, the basis for assessing single interventions in the perioperative course with many uncontrolled variables may be questioned, because this may run the risk of abolishing a beneficial therapy (or overlooking adverse effects) that may be relevant in specific patient groups, and where the opportunity is lost because of too many "noise" factors. We propose that future perioperative outcome studies should be performed with a design that would have fewer variables by including a procedure-specific patient population with updated perioperative care principles (eg, analgesia, fluid management, surgical care, etc) to achieve more relevant clinical data.[24]

DISCLOSURES

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Value of Sequels

Is It Safe to Include Nitrous Oxide in Your Anesthetic?

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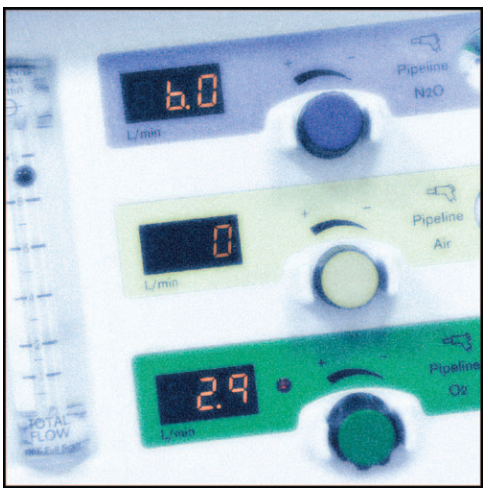
CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

THE optimal choice of anesthetic agent for the patient with cardiovascular disease undergoing noncardiac surgery has been a topic of interest for decades. On the basis of animal models, cohort studies, or small trials, experts had advocated high-dose narcotic techniques while expressing concern about the theoretical potential of developing isoflurane-induced coronary steal.[1,2] Fortunately, we have moved into the era of large-scale clinical trials that have allowed us to determine the evidence basis for the optimal agent in such patients. In this issue of ANESTHESIOLOGY, Leslie *et al.*[3] report on the long-term results of their investigation into the potential harmful effects of nitrous oxide and demonstrate no effect compared with placebo.

In the context of the movies, sequels rarely live up to the hype of the original; however, this is not the case for clinical trials. In the original Elimination of Nitrous Oxide in the Gas Mixture for Anesthesia (ENIGMA) trial investigating the effect of nitrous oxide on outcome,[4] cardiovascular morbidity was significantly higher on long-term follow-up.[5] This incidental and provocative finding was in contrast to the primary outcome of no difference in length of stay compared with placebo and therefore should be considered hypothesis generating.[4] This led the authors who designed the ENIGMA-II trial to investigate both the short- and long-term effects of nitrous oxide compared with placebo in a group of high-risk cardiovascular patients. This sequel to the original trial included a much larger sample size to address this new hypothesis and redesign of the protocol to ensure that both groups utilize the same oxygen concentration. They found no difference in the primary outcome of death and cardiovascular events in either the short-term or on long-term follow-up.[3,6] It has become increasingly clear that actions in the perioperative period may have long-term implications, and including a long-term follow-up is increasingly important.[7] Therefore, the assessment of long-term follow-up of the ENIGMA-II trial participants was critical in ensuring that the question of nitrous oxide's safety was fully addressed.



"... we can conclude that nitrous oxide is safe for the general population and in patients with cardiovascular disease undergoing noncardiac surgery when the concentration of oxygen is held constant."

The undertaking of such large-scale clinical trials is very complex, and the trial leaders should be commended for completing such a Herculean task. The authors do point out some of the limitations of their analysis given the size of the task. In particular, not all of the sites could perform the complete long-term follow-up, and even for those who could, there was a group of patients who were lost to follow-up. The authors attempted to address these issues through sophisticated statistical approaches that help ensure robustness of their conclusions. Another key issue in any such design is that the assessment of the long-term outcome includes medical record review and patient interviews. The absence of a formal screening protocol for out-of-hospital events can introduce bias given the variability in symptoms and diagnosis, but such bias will likely affect both groups similarly in such a large trial. The change in the oxygen concentration

Image: J. P. Rathmell.

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between ENIGMA and ENIGMA-II may also suggest that the original finding was not spurious but a function of the oxygen concentration. This does not negate the current findings but does suggest that more research is needed to determine whether the original protocol for general anesthesia is truly associated with worse long-term outcomes. Finally, investigators have included among their outcomes the assessment of long-term disability. This investigative group is leading the field in the assessment of disability as an important outcome to patients. They note in their article that they are currently using the World Health Organization Disability Assessment Schedule instrument.[8] Importantly, they were unable to show any difference in a disability outcome between nitrous oxide and placebo.

In summary, the investigators should be congratulated for following up on their provocative finding of long-term cardiovascular complications associated with nitrous oxide use with a large-scale sequel trial directed at addressing this question assessing both short- and long-term outcomes. On the basis of the results, we can conclude that nitrous oxide is safe for the general population and in patients with cardiovascular disease undergoing noncardiac surgery when the concentration of oxygen is held constant. ENIGMA and ENIGMA-II have demonstrated the importance of assessing short- and long-term outcomes and of following up novel associations with definitive trials in which hypothesis generation is transformed into hypothesis confirmation or refuting, as in this trial. Given the controversy surrounding nitrous oxide and clinical outcomes coupled with the availability of other fast-acting anesthetic agents, should this trial change management and result in an increase in the use of nitrous oxide? A recent study suggests that nitrous oxide is still relevant in clinical anesthesia and should be considered for certain patients, but how that fact and the current trial translates into local practice is up to the individual practitioner.[9]

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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Nitrous Oxide and Serious Long-term Morbidity and Mortality in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II Trial

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ABSTRACT

Background: The Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial randomly assigned 7,112 noncardiac surgery patients at risk of perioperative cardiovascular events to 70% N_2O or 70% N_2 groups. The aim of this follow-up study was to determine the effect of nitrous oxide on a composite primary outcome of death and major cardiovascular events at 1 yr after surgery.

Methods: One-year follow-up was conducted *via* a medical record review and telephone interview. Disability was defined as a Katz index of independence in activities of daily living score less than 8. Adjusted odds ratios and hazard ratios were calculated as appropriate for primary and secondary outcomes.

Results: Among 5,844 patients evaluated at 1 yr, 435 (7.4%) had died, 206 (3.5%) had disability, 514 (8.8%) had a fatal or nonfatal myocardial infarction, and 111 (1.9%) had a fatal or nonfatal stroke during the 1-yr follow-up period. Exposure to nitrous oxide did not increase the risk of the primary outcome (odds ratio, 1.08; 95% CI, 0.94 to 1.25; $P = 0.27$), disability or death (odds ratio, 1.07; 95% CI, 0.90 to 1.27; $P = 0.44$), death (hazard ratio, 1.17; 95% CI, 0.97 to 1.43; $P = 0.10$), myocardial infarction (odds ratio, 0.97; 95% CI, 0.81 to 1.17; $P = 0.78$), or stroke (odds ratio, 1.08; 95% CI, 0.74 to 1.58; $P = 0.70$).

Conclusion: These results support the long-term safety of nitrous oxide administration in noncardiac surgical patients with known or suspected cardiovascular disease. **(ANESTHESIOLOGY 2015; 123:00–00)**

HEALTHCARE research is increasingly focused on longer-term outcomes that are important to patients and the community.[1] For example, the long-term follow-up of the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA) trial revealed that nitrous oxide increased risk of myocardial infarction in noncardiac surgery patients (odds ratio [OR], 1.59; 95% CI, 1.01 to 2.51; $P = 0.04$).[2] This effect had not been evident at the 30-day follow-up (OR, 0.58; 95% CI, 0.22 to 1.50; $P = 0.26$).[3] However, because the patients in the ENIGMA trial were not selected on the basis of the risk for cardiovascular events and because the event rates were low, both the 30-day and long-term results required confirmation in suitably powered studies.

Therefore, we conducted the ENIGMA-II trial to explore the risks and benefits of nitrous oxide in noncardiac surgery

What We Already Know about This Topic

- The pathophysiological effects of nitrous oxide might lead to major cardiovascular events after noncardiac surgery
- Nitrous oxide increased the risk of myocardial infarction in the long-term follow-up of the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA) trial but that trial did not specifically recruit patients at risk of cardiovascular events

What This Article Tells Us That Is New

- Nitrous oxide did not increase the risk of a composite primary outcome of death and major cardiovascular events at 1 yr in 5,844 patients with cardiovascular disease recruited to the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial
- These results support the long-term safety of nitrous oxide administration in noncardiac surgical patients with known or suspected cardiovascular disease

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page XXX. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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patients with known or suspected cardiovascular disease.[4] There were no significant differences between patients receiving and not receiving nitrous oxide in terms of their 30-day risk of a composite primary outcome of death or major cardiovascular events.[5] The aim of the current study was to determine the effect of nitrous oxide administration on the composite primary outcome and secondary outcomes (death, disability, myocardial infarction, and stroke) at 1 yr after surgery in the ENIGMA-II patients.

Materials and Methods

The ENIGMA-II trial was an international, parallel-group, patient- and observer-blinded, randomized trial. A total of 7,112 noncardiac surgery patients, older than 45 yr and at risk of perioperative cardiovascular complications, were enrolled. ENIGMA-II was registered at ClinicalTrials.gov (number: NCT00430989; principal investigator: P.S.M.; date of registration: January 31, 2007). The protocol[4] and results[5] of the 30-day follow-up have been published. The trial steering committee prospectively approved the protocol for the 1-yr follow-up, including the detailed statistical analysis plan. Ethics committee approval for the 1-yr follow-up study was obtained at 39 of the 45 participating sites, and patients at these 39 sites consented to the 30-day and 1-yr follow-ups before randomization. Participating sites, investigators, and names and locations of ethics committees are listed in the appendix.

Protocol

Participating patients were randomly assigned to 70% N_2O in 30% O_2 or 70% N_2 in 30% O_2 groups. Perioperative care was otherwise at the discretion of the attending anesthesiologists. Patients were monitored with 12-lead electrocardiographs preoperatively and on postoperative days 1 and 3 and with cardiac biomarkers (troponin or, if unavailable, creatine kinase-myocardial band) at 6 to 12 h and 1 to 3 days after surgery. Other investigations were ordered as clinically indicated during the 1-yr follow-up period.

One-year follow-up was conducted *via* medical record review and telephone interview. The medical record was interrogated for the date and cause of death and the occurrence of myocardial infarction or stroke, any time between 30 days and 1 yr after surgery. The telephone interview was conducted with the patient or their relatives or doctors if the patient had died, was incapacitated, was unavailable, or was unsure about the occurrence of myocardial infarction or stroke.

The primary outcome for the 1-yr follow-up was a composite of death and cardiovascular events (nonfatal myocardial infarction, cardiac arrest, pulmonary embolism, and stroke). The main preprescribed secondary endpoint was disability or death (the inverse of disability-free survival). Disability was defined as a Katz index of independence in activities of daily living score less than 8.[6]

Other secondary outcomes were death, fatal or nonfatal myocardial infarction, and fatal or nonfatal stroke. These were defined by patient, relative, or doctor report or by fulfillment of the following criteria, as recorded in the medical record: myocardial infarction was defined by an increased cardiac biomarker level plus at least one of the ischemic symptoms, pathological Q waves, electrocardiographic changes indicative of ischemia, coronary artery intervention, new wall motion abnormality on echocardiography or a fixed defect on radionucleotide scanning, or autopsy finding of new or recent myocardial infarction.[7] The troponin threshold that was considered abnormal was each site's laboratory's 99th percentile (upper reference limit) of a healthy reference population.[8] Stroke was defined as a new neurologic deficit persisting for 24 h or longer, confirmed by a neurologist or computed tomography or magnetic resonance imaging.

Statistical Analysis

The following preoperative and intraoperative characteristics were selected prospectively as covariates in the models: age, sex, body mass index (BMI), American Society of Anesthesiologists' (ASA) physical status, good exercise capacity (≥ 4 metabolic equivalents), history of coronary artery disease, emergency surgery, vascular surgery, randomized treatment (nitrous oxide or no nitrous oxide), propofol maintenance, regional local anesthetic block, volatile anesthetic administration (minimum alveolar concentration [MAC] equivalents), bispectral index (BIS) monitoring, and duration of anesthesia.

The patients followed up at 1 yr were not necessarily a truly representative sample of the original ENIGMA-II cohort, so a logistic regression model was fitted to estimate the probability that each patient was followed up at 1 yr. For each outcome model, observations were weighted by the inverse of these probabilities. Patients who died or experienced myocardial infarction or stroke within the 30-day follow-up of ENIGMA-II were given a weight of 1. Unweighted models were fitted as sensitivity analyses.

Mortality rates were computed for each category of each covariate and were expressed as deaths per 1,000 person-years. Univariate Cox proportional hazard models were used to define hazard ratios (HRs) and 95% CIs for death. Multivariable Cox

of Epidemiology and Preventive Medicine, Monash University, and National Health and Medical Research Council Practitioner Fellow, Melbourne, Australia (P.S.M.); Department of Epidemiology and Preventive Medicine (J.K., A.F.), Monash University, Melbourne, Australia; Department of Anaesthesia, Austin Hospital, and Department of Surgery, University of Melbourne, Melbourne, Australia (P.J.P.); Department of Anaesthesia, Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China (M.T.V.C.); Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Perth, Australia, and School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia (M.J.P.); Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio (D.I.S.); Department of Anesthesia, University of Toronto, and Department of Anaesthesia, Toronto General Hospital, Toronto, Ontario, Canada (W.S.B.); Population Health Research Institute, Hamilton Health Sciences and McMaster University, and Departments of Medicine, Clinical Epidemiology, and Biostatistics, McMaster University, Hamilton, Ontario, Canada (P.J.D.); and Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, and Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia (S.W.).

proportional hazard models for death were constructed, and assessments of proportionality of hazard functions were performed. Preoperative variables were first adjusted for each other. Then, nitrous oxide, propofol maintenance, regional local anesthetic block, and BIS monitoring were adjusted for each other and preoperative variables. Finally, volatile anesthetic administration less than the median MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia were adjusted for each other, preoperative variables, nitrous oxide, and BIS monitoring (propofol maintenance was not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration).

Because the date of outcomes other than death was sometimes imprecise or missing, logistic regression was used to compute ORs and 95% CIs for the primary composite outcome, the main secondary outcome of disability or death, and further secondary outcomes of death, myocardial infarction, and stroke. Multivariable models were constructed using the technique described in the previous paragraph. The preplanned assessment of the interaction of each variable with nitrous oxide was performed by using interaction terms in the weighted and unweighted regression models. An additional analysis for stroke was conducted that included a history of previous stroke or transient ischemic attack.

Analyses were conducted using Stata 12 (Stata Corporation, USA). All *P* values are two sided, and *P* value less than 0.05 was considered statistically significant.

Results

One-year follow-up occurred between June 2009 and October 2014, with a median follow-up time of 386 days (interquartile range, 366 to 458 days). The centers participating in the 1-yr follow-up study recruited 6,651 (95%) of the 6,992 patients who were assessed for the primary outcome at 30 days.[5] Follow-up data were available for 5,844 (88%) of these patients (fig. 1).

A total of 435 patients (7.4%) died; 99 died before 30 days and 336 subsequently (fig. 2) (between treatment $P = 0.18$). The causes of death were cancer (37.5%), myocardial infarction (4.4%), stroke (4.4%), other cardiovascular death (14.3%), respiratory failure (7.8%), sepsis (13.0%), other causes (8.7%), and unknown (9.9%). In total 641 patients (10.5%) were recorded as having disability or had died (206 [3.5%] had disability), 514 patients (8.8%) were recorded as having a fatal or nonfatal myocardial infarction, and 111 patients (1.9%) were recorded as having a fatal or nonfatal stroke during the 1-yr follow-up period.

Nitrous oxide did not increase the risk of the primary outcome (OR, 1.08; 95% CI, 0.94 to 1.25; $P = 0.27$) (table 1). Age, BMI, ASA physical status, exercise capacity, coronary artery disease, emergency surgery, propofol maintenance, regional local anesthetic block, and duration of anesthesia were significant predictors of the primary outcome. The adjusted ORs were largely unaffected by weighting to adjust for missing data (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 1). The

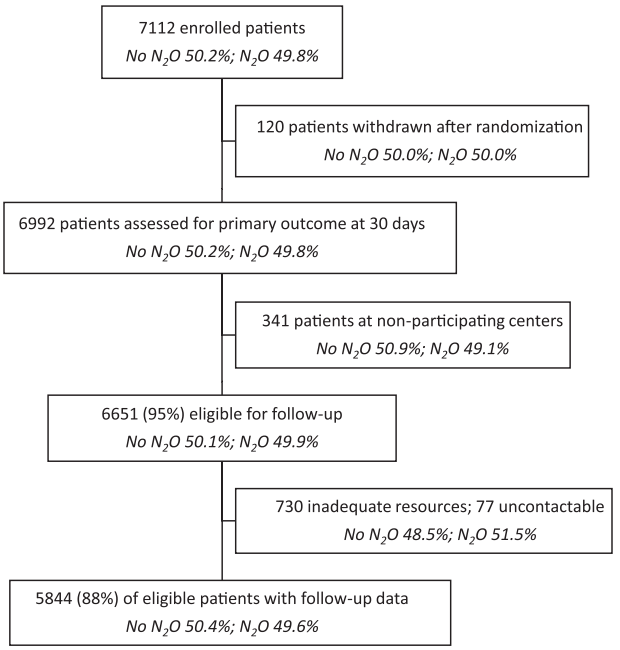

Fig. 1. Flow diagram.

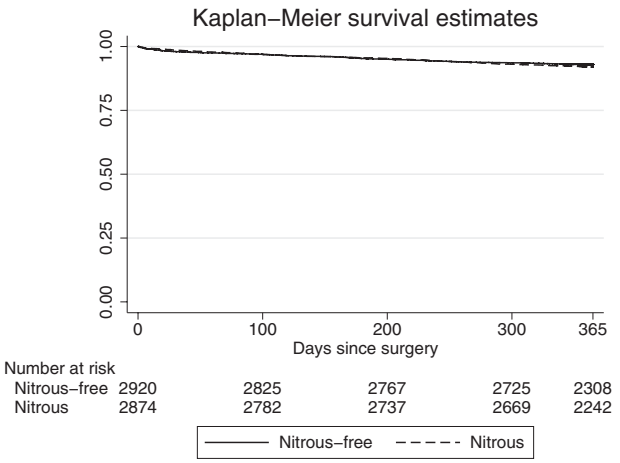

Fig. 2. Kaplan–Meier survival curve for death for randomized treatment groups ($P = 0.18$).

interaction between nitrous oxide and age was statistically significant ($P = 0.046$) in the weighted model for the primary outcome, but this did not otherwise change the main result (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 2).

Nitrous oxide did not increase the risk of disability or death (OR, 1.07; 95% CI, 0.90 to 1.27; $P = 0.44$) (table 2). Age, BMI, exercise capacity, emergency surgery, and duration of anesthesia were significant predictors of death. The adjusted ORs were largely unaffected by weighting to adjust for missing data (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 3). There was no significant interaction between nitrous oxide administration and any covariate in either the weighted or unweighted models for disability or death (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 4).

Table 1. ORs for the Composite Primary Outcome of Death or Major Cardiovascular Events (Nonfatal Myocardial Infarction, Cardiac Arrest, Pulmonary Embolism, and Stroke)*

	n	n (%) with Outcome	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)†	*P* Value
Age (yr)				< 0.0005		< 0.0005
< 50	166	17 (10.2)	1.00 (reference)			
50–59	842	102 (12.1)	1.24 (0.71–2.15)		1.23 (0.70–2.16)	
60–69	1,610	234 (14.5)	1.48 (0.87–2.52)		1.44 (0.84–2.46)	
70–79	2,353	396 (16.8)	1.78 (1.06–3.01)		1.71 (1.00–2.92)	
≥ 80	871	226 (25.9)	3.16 (1.85–5.40)		2.67 (1.55–4.61)	
Sex				0.21		0.28
Male	3,767	608 (16.1)	1.00 (reference)			
Female	2,075	367 (17.7)	1.10 (0.95–1.27)		1.09 (0.93–1.27)	
Body mass index				< 0.0005		< 0.0005
< 18.5	155	50 (32.3)	1.89 (1.32–2.72)		1.79 (1.22–2.62)	
18.5–24.9	1,909	381 (20.0)	1.00 (reference)			
25–29.9	2,052	303 (14.8)	0.70 (0.59–0.83)		0.69 (0.58–0.82)	
≥ 30	1,726	241 (14.0)	0.66 (0.55–0.79)		0.65 (0.54–0.79)	
ASA physical status				< 0.0005		< 0.0005
1–2	1,798	217 (12.1)	1.00 (reference)			
3	3,633	643 (17.7)	1.51 (1.28–1.79)		1.45 (1.21–1.74)	
4	411	115 (28.0)	2.56 (1.97–3.32)		2.24 (1.69–2.99)	
Exercise capacity ≥ 4 METS				< 0.0005		0.002
Yes	4,378	659 (15.1)	1.00 (reference)			
No	1,464	316 (21.6)	1.51 (1.30–1.76)		1.28 (1.09–1.51)	
Coronary artery disease				0.001		0.028
Yes	2,213	420 (19.0)	1.00 (reference)			
No	3,629	555 (15.3)	0.79 (0.68–0.91)		0.85 (0.73–0.98)	
Emergency surgery				< 0.0005		0.014
No	5,598	915 (16.3)	1.00 (reference)			
Yes	244	60 (24.6)	1.73 (1.27–2.35)		1.49 (1.08–2.04)	
Vascular surgery				0.063		0.63
No	3,575	563 (15.7)	1.00 (reference)			
Yes	2,267	412 (18.2)	1.14 (0.99–1.32)		1.04 (0.89–1.21)	
Nitrous oxide				0.35		0.27
No	2,944	481 (16.3)	1.00 (reference)			
Yes	2,897	493 (17.0)	1.07 (0.93–1.23)		1.08 (0.94–1.25)	
Propofol maintenance				0.017		0.035
Yes	188	44 (23.4)	1.00 (reference)			
No	5,653	930 (16.5)	0.65 (0.46–0.93)		0.68 (0.47–0.97)	
Regional LA block				< 0.0005		< 0.0005
Yes	1,600	317 (19.8)	1.00 (reference)			
No	4,241	657 (15.5)	0.73 (0.63–0.85)		0.73 (0.63–0.86)	
BIS monitoring				0.056		0.28
Yes	2,516	539 (16.2)	1.00 (reference)			
No	3,325	435 (17.3)	1.15 (1.00–1.32)		1.08 (0.94–1.25)	
MAC equivalents				0.077		0.89
≥ 0.72	2,819	445 (15.8)	1.00 (reference)			
< 0.72	2,816	487 (17.3)	1.14 (0.99–1.31)		0.99 (0.83–1.18)	
Duration of anesthesia (h)				< 0.0005		< 0.0005
< 2	703	80 (11.4)	1.00 (reference)			
2–3	1,761	237 (13.5)	1.22 (0.94–1.60)		1.26 (0.96–1.67)	
3–4	1,394	217 (15.6)	1.48 (1.13–1.94)		1.52 (1.14–2.02)	
4–5	837	150 (17.9)	1.71 (1.28–2.28)		1.83 (1.35–2.48)	
≥ 5	940	248 (26.4)	2.65 (2.02–3.48)		2.90 (2.17–3.86)	

* Each observation weighted by the probability of being nonmissing at 1 yr. † Preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block, and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide, and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration).

ASA = American Society of Anesthesiologists; BIS = bispectral index; LA = local anesthetic; MAC = minimum alveolar concentration; METS = metabolic equivalents; OR = odds ratio.

Table 2. ORs for Disability or Death*

	n	n (%) with Outcome	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)†	*P* Value
Age (yr)				< 0.0005		< 0.0005
< 50	165	13 (7.9)	1.00 (reference)			
50–59	837	74 (8.8)	1.13 (0.61–2.13)		1.13 (0.60–2.15)	
60–69	1,591	132 (8.3)	1.01 (0.55–1.84)		0.99 (0.53–1.84)	
70–79	2,330	258 (11.1)	1.36 (0.75–2.46)		1.26 (0.69–2.31)	
≥ 80	862	159 (18.4)	2.47 (1.35–4.53)		2.01 (1.08–3.74)	
Sex				0.85		0.11
Male	3,728	404 (10.8)	1.00 (reference)			
Female	2,057	232 (11.3)	1.02 (0.85–1.21)		0.86 (0.71–1.03)	
Body mass index				< 0.0005		< 0.0005
< 18.5	154	43 (27.9)	2.24 (1.53–3.28)		2.01 (1.35–3.00)	
18.5–24.9	1,895	270 (14.2)	1.00 (reference)			
25–29.9	2,024	185 (9.1)	0.63 (0.51–0.77)		0.63 (0.51–0.77)	
≥ 30	1,712	138 (8.1)	0.54 (0.43–0.67)		0.55 (0.43–0.69)	
ASA physical status				0.01		0.13
1–2	1,784	170 (9.5)	1.00 (reference)			
3	3,598	400 (11.1)	1.12 (0.93–1.36)		1.10 (0.89–1.36)	
4	403	66 (16.4)	1.63 (1.19–2.22)		1.43 (1.01–2.04)	
Exercise capacity ≥ 4 METS				< 0.0005		< 0.0005
Yes	4,338	389 (9.0)	1.00 (reference)			
No	1,447	247 (17.1)	2.07 (1.74–2.47)		1.97 (1.64–2.38)	
Coronary artery disease				0.59		0.72
Yes	2,183	246 (11.3)	1.00 (reference)			
No	3,602	390 (10.8)	0.95 (0.80–1.13)		0.97 (0.81–1.16)	
Emergency surgery				< 0.0005		< 0.0005
No	5,542	582 (10.5)	1.00 (reference)			
Yes	243	54 (22.2)	2.45 (1.78–3.38)		1.95 (1.38–2.76)	
Vascular surgery				0.17		0.009
No	3,550	408 (11.5)	1.00 (reference)			
Yes	2,235	228 (10.2)	0.88 (0.74–1.05)		0.77 (0.64–0.94)	
Nitrous oxide				0.45		0.44
No	2,915	311 (10.7)	1.00 (reference)			
Yes	2,869	325 (11.3)	1.07 (0.90–1.26)		1.07 (0.90–1.27)	
Propofol maintenance				0.092		0.21
Yes	183	28 (15.3)	1.00 (reference)			
No	5,601	608 (10.9)	0.70 (0.46–1.06)		0.75 (0.49–1.17)	
Regional LA block				0.022		0.034
Yes	1,590	196 (12.3)	1.00 (reference)			
No	4,194	440 (10.5)	0.81 (0.67–0.97)		0.81 (0.67–0.98)	
BIS monitoring				0.44		0.40
No	3,290	358 (10.9)	1.00 (reference)			
Yes	2,494	278 (11.1)	1.07 (0.90–1.27)		1.08 (0.90–1.29)	
MAC equivalents				0.26		0.51
≥ 0.72	2,789	287 (10.3)	1.00 (reference)			
< 0.72	2,794	322 (11.5)	1.10 (0.93–1.31)		0.93 (0.76–1.15)	
Duration of anesthesia (h)				< 0.0005		< 0.0005
< 2	701	57 (8.1)	1.00 (reference)			
2–3	1,750	159 (9.1)	1.17 (0.86–1.61)		1.18 (0.85–1.64)	
3–4	1,387	151 (10.9)	1.42 (1.03–1.95)		1.48 (1.06–2.07)	
4–5	824	98 (11.9)	1.56 (1.11–2.19)		1.65 (1.15–2.37)	
≥ 5	921	144 (15.6)	2.02 (1.46–2.78)		2.15 (1.52–3.02)	

* Each observation weighted by the probability of being nonmissing at 1 yr. † Preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block, and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide, and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration).

ASA = American Society of Anesthesiologists; BIS = bispectral index; LA = local anesthetic; MAC = minimum alveolar concentration; METS = metabolic equivalents; OR = odds ratio.

Nitrous oxide did not increase the risk of death (HR, 1.17; 95% CI, 0.97 to 1.43; $P = 0.11$) (table 3). Age, BMI, ASA physical status, exercise capacity, emergency surgery, vascular surgery, and duration of anesthesia were significant predictors of death. The adjusted HRs were largely unaffected by weighting to adjust for missing data (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 5). The interactions between nitrous oxide and exercise capacity ($P = 0.035$), and nitrous oxide and MAC equivalents ($P = 0.026$), were statistically significant in the unweighted model for death (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 6).

Nitrous oxide did not increase the risk of myocardial infarction (OR, 0.97; 95% CI, 0.81 to 1.17; $P = 0.78$) (table 4). Age, ASA physical status, exercise capacity, coronary artery disease, emergency surgery, vascular surgery, regional local anesthetic block, BIS monitoring, and duration of anesthesia were significant predictors of myocardial infarction. The adjusted ORs were largely unaffected by weighting to adjust for missing data (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 7). The interaction between nitrous oxide and BIS monitoring was statistically significant in the weighted model for myocardial infarction ($P = 0.045$) (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 8).

Nitrous oxide did not increase the risk of stroke (OR, 1.08; 95% CI, 0.74 to 1.58; $P = 0.70$) (table 5). Age and vascular surgery were significant predictors of stroke. The adjusted ORs were largely unaffected by weighting to adjust for missing data (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 9). There was no significant interaction between nitrous oxide administration and any covariate in either the weighted or unweighted models for stroke (Supplemental Digital Content 1, http://links.lww.com/ALN/B204, table 10). A history of previous stroke or transient ischemic attack was a significant predictor of stroke within 1 yr of surgery (adjusted OR, 2.43; 95% CI, 1.64 to 3.61; $P < 0.005$). Adjusted ORs for other covariates were largely unaffected by inclusion of a history of previous stroke or transient ischemic attack (results not shown).

Discussion

We found that nitrous oxide did not increase the incidence of a composite of death or major cardiovascular complications at 1 yr after surgery in patients enrolled in the ENIGMA-II trial. These results are consistent with our findings at 30 days postoperatively and further support the safety of nitrous oxide administration in patients with known or suspected cardiovascular disease.

The ENIGMA-II trial was established on the premise that the pathophysiological effects of nitrous oxide might lead to major cardiovascular events after noncardiac surgery.[4,9] These effects include the inhibition of methionine synthase with resulting hyperhomocysteinemia[10,11] and endothelial dysfunction,[12,13] especially in patients with genetic[14] or dietary[15] predispositions. However, the recent Vitamins in Nitrous Oxide (VINO) randomized trial[16] did not confirm earlier findings[17] of myocardial ischemia among patients exposed to nitrous oxide or an ameliorating effect of vitamin B_{12} and folate administration on postoperative troponin increases. The VINO study and our ENIGMA-II analyses provide strong evidence to refute the hypothesis that the hyperhomocysteinemia associated with nitrous oxide administration leads to adverse cardiovascular outcomes.

The ENIGMA-II 1-yr follow-up results contrast with our finding in the long-term follow-up of the ENIGMA study[2] of an increased long-term risk of myocardial infarction in patients who were randomly assigned to nitrous oxide group. There were important differences between ENIGMA and ENIGMA-II: (1) the inclusion criteria (unselected in ENIGMA and selected for cardiovascular risk factors in ENIGMA-II); (2) the percentage of inspired oxygen administered (30% in the nitrous oxide group and 80% in the no nitrous group in ENIGMA and 30% in both groups in ENIGMA-II); and (3) the duration of follow-up (3.5 yr [range, 0 to 5.7 yr] in ENIGMA and 1.06 yr [range, 0 to 3.89 yr] in ENIGMA-II). Most likely, though, differences in long-term outcomes simply reflect the smaller sample size of the ENIGMA follow-up (n = 1,660), leading to a spurious finding in that study.[18]

The incidences of death (7.4%), disability (3.5%), myocardial infarction (8.8%), and stroke (1.9%) in this study are consistent with the inclusion criteria for ENIGMA-II and previously published studies of noncardiac surgery patients with cardiovascular disease.[19–23] In relation to myocardial infarction in particular, these studies point to substantial scope for improved outcomes through primary prevention, early detection, treatment, and prevention of complications.[24] Unfortunately, no primary prevention measures for perioperative myocardial infarction in noncardiac surgical patients are conclusively proven to be both effective and safe,[25–28] including the omission of nitrous oxide.

The World Health Organization defines disability as "difficulties in any area of functioning as they relate to environmental and personal factors."[29] We chose to use the Katz score, which measures physical functioning, to determine the disability in the ENIGMA-II trial.[6] Among the widely used scales, we now recommend the World Health Organization Disability Assessment Schedule for this purpose, as it includes cognition, interpersonal relationships, participation in society, self-care, work and household roles, and mobility.[30]

Many covariates were associated with increased risk of the primary and/or secondary outcomes of this study, including increasing age,[2,19,31–33] low BMI,[19,31,32,34] higher ASA physical status,[2,19,31–33] lower exercise capacity,[35] coronary artery disease,[2,32] emergency surgery,[2,19,33] propofol maintenance,[2] regional local anesthetic block,[36] lack of BIS monitoring, and longer duration of anesthesia.[2,19] Although analyses were sequentially adjusted for pre- and intraoperative factors, it is possible that some of these associations resulted from selection

Table 3. HRs for Death*

	Death Rate (95% CI)	Univariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)†	*P* Value
Age (yr)			< 0.0005		< 0.0005
< 50	47 (24–109)	1.00 (reference)			
50–59	57 (43–78)	1.21 (0.56–2.60)		1.23 (0.57–2.64)	
60–69	58 (48–72)	1.23 (0.59–2.57)		1.25 (0.60–2.60)	
70–79	76 (66–89)	1.61 (0.78–3.32)		1.49 (0.72–3.06)	
≥ 80	136 (113–166)	2.83 (1.36–5.90)		2.27 (1.09–4.74)	
Sex			0.81		0.17
Male	75 (67–85)	1.00 (reference)			
Female	77 (66–91)	1.02 (0.84–1.25)		0.86 (0.70–1.07)	
Body mass index			< 0.0005		< 0.0005
< 18.5	283 (204–401)	2.47 (1.73–3.53)		2.18 (1.50–3.17)	
18.5–24.9	113 (99–130)	1.00 (reference)			
25–29.9	55 (45–67)	0.49 (0.39–0.62)		0.50 (0.39–0.63)	
≥ 30	44 (35–56)	0.39 (0.30–0.51)		0.40 (0.30–0.53)	
ASA physical status			0.001		0.001
1–2	69 (58–84)	1.00 (reference)			
3	73 (65–83)	1.06 (0.85–1.32)		1.20 (0.95–1.52)	
4	128 (98–172)	1.86 (1.33–2.58)		2.06 (1.42–2.97)	
Exercise capacity ≥ 4 METS			0.001		0.017
Yes	69 (61–77)	1.00 (reference)			
No	98 (83–116)	1.42 (1.16–1.75)		1.30 (1.05–1.61)	
Coronary artery disease			0.39		0.38
Yes	71 (61–84)	1.00 (reference)			
No	79 (70–89)	1.10 (0.90–1.35)		1.10 (0.89–1.35)	
Emergency surgery			< 0.0005		0.001
No	72 (65–79)	1.00 (reference)			
Yes	181 (131–257)	2.51 (1.79–3.54)		1.86 (1.29–2.67)	
Vascular surgery			0.017		0.001
No	83 (74–94)	1.00 (reference)			
Yes	65 (55–77)	0.78 (0.64–0.96)		0.68 (0.54–0.84)	
Nitrous oxide			0.13		0.10
No	70 (61–81)	1.00 (reference)			
Yes	82 (72–93)	1.16 (0.96–1.40)		1.17 (0.97–1.43)	
Propofol maintenance			0.13		0.13
Yes	111 (73–177)	1.00 (reference)			
No	75 (68–83)	0.71 (0.45–1.11)		0.70 (0.45–1.11)	
Regional LA block			0.044		0.10
Yes	88 (74–105)	1.00 (reference)			
No	71 (64–80)	0.81 (0.66–0.99)		0.84 (0.68–1.04)	
BIS monitoring			0.44		0.10
Yes	78 (69–89)	1.00 (reference)			
No	73 (63–85)	0.93 (0.76–1.13)		1.00 (0.82–1.22)	
MAC equivalents			0.006		0.61
≥ 0.72	65 (56–76)	1.00 (reference)			
< 0.72	85 (75–98)	1.32 (1.08–1.60)		1.07 (0.84–1.36)	
Duration of anesthesia (h)			< 0.0005		< 0.0005
< 2	47 (34–68)	1.00 (reference)			
2–3	54 (45–67)	1.15 (0.78–1.70)		1.18 (0.79–1.77)	
3–4	72 (59–88)	1.50 (1.02–2.22)		1.54 (1.02–2.31)	
4–5	89 (71–113)	1.87 (1.25–2.81)		1.90 (1.24–2.92)	
≥ 5	133 (111–160)	2.79 (1.91–4.08)		2.76 (1.85–4.11)	

* Each observation weighted by the probability of being nonmissing at 1 yr. † Preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block, and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide, and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration).

ASA = American Society of Anesthesiologists; BIS = bispectral index; HR = hazard ratio; LA = local anesthetic; MAC = minimum alveolar concentration; METS = metabolic equivalents.

Table 4. ORs for Myocardial Infarction*

	n	n (%) with Outcome	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)†	*P* Value
Age (yr)				< 0.0005		< 0.0005
< 50	161	9 (5.6)	1.00 (reference)			
50–59	815	44 (5.4)	0.97 (0.46–2.04)		0.92 (0.43–1.96)	
60–69	1,549	133 (8.6)	1.57 (0.78–3.16)		1.42 (0.70–2.90)	
70–79	2,239	203 (9.1)	1.69 (0.84–3.37)		1.58 (0.78–3.20)	
≥ 80	821	120 (14.6)	2.94 (1.45–5.95)		2.38 (1.16–4.90)	
Sex				0.76		0.25
Male	3,596	323 (9.0)	1.00 (reference)			
Female	1,989	186 (9.4)	1.03 (0.85–1.25)		1.13 (0.92–1.39)	
Body mass index				0.38		0.31
< 18.5	135	15 (11.1)	1.10 (0.63–1.93)		1.02 (0.56–1.86)	
18.5–24.9	1,784	179 (10.0)	1.00 (reference)			
25–29.9	1,981	167 (8.4)	0.84 (0.67–1.05)		0.81 (0.64–1.02)	
≥ 30	1,685	148 (8.8)	0.88 (0.70–1.11)		0.87 (0.69–1.11)	
ASA physical status				< 0.0005		< 0.0005
1–2	1,717	82 (4.8)	1.00 (reference)			
3	3,481	358 (10.3)	2.21 (1.73–2.84)		1.78 (1.37–2.32)	
4	387	69 (17.8)	3.95 (2.80–5.57)		2.67 (1.84–3.86)	
Exercise capacity ≥ 4 METS				< 0.0005		0.001
Yes	4,196	328 (7.8)	1.00 (reference)			
No	1,389	181 (13.0)	1.77 (1.46–2.15)		1.42 (1.16–1.74)	
Coronary artery disease				< 0.0005		< 0.0005
Yes	2,118	260 (12.3)	1.00 (reference)			
No	3,467	249 (7.2)	0.55 (0.46–0.67)		0.65 (0.54–0.79)	
Emergency surgery				0.018		0.033
No	5,361	479 (8.9)	1.00 (reference)			
Yes	224	30 (13.4)	1.62 (1.09–2.41)		1.55 (1.04–2.33)	
Vascular surgery				< 0.0005		0.001
No	3,414	256 (7.5)	1.00 (reference)			
Yes	2,171	253 (11.7)	1.56 (1.30–1.88)		1.40 (1.15–1.70)	
Nitrous oxide				0.66		0.78
No	2,815	262 (9.3)	1.00 (reference)			
Yes	2,769	246 (8.9)	0.96 (0.80–1.15)		0.97 (0.81–1.17)	
Propofol maintenance				0.14		0.33
Yes	176	21 (11.9)	1.00 (reference)			
No	5,408	487 (9.0)	0.70 (0.43–1.12)		0.78 (0.47–1.28)	
Regional LA block				< 0.0005		< 0.0005
Yes	1,528	174 (11.4)	1.00 (reference)			
No	4,056	334 (8.2)	0.69 (0.57–0.84)		0.68 (0.56–0.83)	
BIS monitoring				< 0.0005		0.017
Yes	2,419	253 (8.0)	1.00 (reference)			
No	3,165	255 (10.5)	1.47 (1.22–1.76)		1.26 (1.04–1.52)	
MAC equivalents				0.95		0.57
≥ 0.72	2,700	247 (9.1)	1.00 (reference)			
< 0.72	2,688	240 (8.9)	0.99 (0.82–1.20)		0.94 (0.75–1.17)	
Duration of anesthesia (h)				< 0.0005		< 0.0005
< 2	677	40 (5.9)	1.00 (reference)			
2–3	1,700	131 (7.7)	1.29 (0.90–1.85)		1.36 (0.94–1.97)	
3–4	1,342	113 (8.4)	1.51 (1.05–2.17)		1.50 (1.02–2.19)	
4–5	795	79 (9.9)	1.70 (1.15–2.50)		1.85 (1.24–2.77)	
≥ 5	874	124 (14.2)	2.47 (1.72–3.55)		2.79 (1.91–4.08)	

* Each observation weighted by the probability of being nonmissing at 1 yr. † Preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block, and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide, and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration).

ASA = American Society of Anesthesiologists; BIS = bispectral index; LA = local anesthetic; MAC = minimum alveolar concentration; METS = metabolic equivalents; OR = odds ratio.

Table 5. ORs for Stroke*

	n	n (%) with Outcome	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)†	*P* Value
Age (yr)				< 0.0005		< 0.0005
50–59	809	9 (1.1)	0.23 (0.11–0.50)		0.27 (0.13–0.57)	
60–69	1,529	25 (1.6)	0.35 (0.21–0.60)		0.40 (0.23–0.69)	
70–79	2,206	43 (1.9)	0.43 (0.27–0.69)		0.49 (0.31–0.79)	
≥ 80	799	33 (4.1)	1.00 (reference)			
Sex				0.27		0.14
Male	3,447	65 (1.9)	1.00 (reference)			
Female	1,896	45 (2.4)	1.25 (0.85–1.83)		1.37 (0.90–2.07)	
Body mass index				0.005		0.062
< 18.5	127	7 (5.5)	2.18 (0.96–4.96)		1.87 (0.79–4.42)	
18.5–24.9	1,707	44 (2.6)	1.00 (reference)			
25–29.9	1,911	39 (2.0)	0.82 (0.53–1.28)		0.86 (0.55–1.34)	
≥ 30	1,598	20 (1.3)	0.49 (0.29–0.84)		0.58 (0.33–1.01)	
ASA physical status				0.030		0.19
1–2	1,648	25 (1.5)	1.00 (reference)			
3	3,329	72 (2.2)	1.47 (0.93–2.33)		1.35 (0.83–2.19)	
4	366	13 (3.6)	2.49 (1.26–4.94)		2.01 (0.94–4.32)	
Exercise capacity ≥ 4 METS				0.042		0.38
Yes	4,023	73 (1.8)	1.00 (reference)			
No	1,320	37 (2.8)	1.52 (1.01–2.27)		1.22 (0.79–1.88)	
Coronary artery disease				0.60		0.31
Yes	2,040	39 (1.9)	1.00 (reference)			
No	3,303	71 (2.1)	1.11 (0.75–1.66)		1.25 (0.81–1.91)	
Emergency surgery				0.34		0.59
No	5,141	104 (2.0)	1.00 (reference)			
Yes	202	6 (3.0)	1.51 (0.65–3.49)		1.27 (0.54–3.00)	
Vascular surgery				< 0.0005		0.002
No	3,278	48 (1.5)	1.00 (reference)			
Yes	2,065	62 (3.0)	2.04 (1.39–2.99)		1.98 (1.30–3.02)	
Nitrous oxide				0.89		0.70
No	2,701	54 (2.0)	1.00 (reference)			
Yes	2,641	56 (2.1)	1.03 (0.70–1.50)		1.08 (0.74–1.58)	
Propofol maintenance				0.43		0.35
Yes	165	5 (3.0)	1.00 (reference)			
No	5,177	105 (2.0)	0.69 (0.28–1.73)		0.65 (0.26–1.61)	
Regional LA block				0.34		0.21
Yes	1,464	34 (2.3)	1.00 (reference)			
No	3,878	76 (2.0)	0.82 (0.54–1.23)		0.77 (0.51–1.16)	
BIS monitoring				0.20		0.084
Yes	2,318	70 (2.3)	1.00 (reference)			
No	3,024	40 (1.7)	0.77 (0.52–1.15)		0.70 (0.47–1.05)	
MAC equivalents				0.45		0.99
≥ 0.72	2,575	50 (1.9)	1.00 (reference)			
< 0.72	2,585	55 (2.1)	1.16 (0.79–1.71)		1.00 (0.61–1.64)	
Duration of anesthesia (h)				0.41		0.18
< 2	658	14 (2.1)	1.00 (reference)			
2–3	1,637	28 (1.7)	0.78 (0.41–1.47)		0.77 (0.39–1.49)	
3–4	1,296	27 (2.1)	0.92 (0.49–1.74)		0.90 (0.46–1.76)	
4–5	751	11 (1.5)	0.72 (0.34–1.53)		0.65 (0.28–1.50)	
≥ 5	818	25 (3.1)	1.26 (0.66–2.42)		1.43 (0.71–2.85)	

* Each observation weighted by the probability of being nonmissing at 1 yr. † Preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block, and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide, and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration).

ASA = American Society of Anesthesiologists; BIS = bispectral index; LA = local anesthetic; MAC = minimum alveolar concentration; METS = metabolic equivalents; OR = odds ratio.

bias or residual confounding, in particular the interventions at the discretion of the attending anesthesiologist where the factors that impacted on the decision to use the intervention may not have been captured completely. For example, lack of BIS monitoring was associated with an increased long-term risk of myocardial infarction in this follow-up study but was not associated with major cardiovascular events in longer-term follow-up studies of patients who were randomly assigned to receive or not receive BIS-guided anesthesia.[19,32] Therefore, this result should be interpreted with caution.

This study is one of the largest randomized controlled trials to follow noncardiac surgery patients with risk factors for major cardiovascular events over an extended postoperative period.[2,19] Our results provide a robust estimate of the incidence of death and effect of nitrous oxide on survival after surgery. The different directions of effect on death at the 30-day[5] and 1-yr follow-ups (toward a protective effect at 30 days and toward a harmful effect at 1 yr) likely arise from random error. The study is limited with respect to myocardial infarction and stroke because patients were not specifically screened for these events during the period between 30 days and 1 yr, and we relied on medical record, patient or surrogate reports. The number and scope of covariates available for adjustment in the model further limit the study. Finally, a number of centers were unable to participate in the 1-yr follow-up study due to limited resources, resulting in a 5% rate of missing 1-yr outcomes. Although we adjusted for missing 1-yr outcomes in our analyses, and results were similar in weighted and unweighted analyses, a subtle effect cannot be ruled out.

In conclusion, nitrous oxide administration did not increase the incidence of a composite of death or major cardiovascular events during a 1-yr follow-up period in patients randomly assigned to the ENIGMA-II trial. Nitrous oxide can be safely administered to patients with known or suspected cardiovascular disease undergoing noncardiac surgery.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: kate.leslie@mh.org.au. Raw data available at: kate.leslie@mh.org.au.

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Appendix: Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II Investigators Participating in the 1-yr Follow-up Study

Australia (ANZCA Clinical Trials Network Members)

Alfred Hospital

Investigators: P. Myles, S. Wallace, W. Galagher, C. Farrington, and A. Ditoro.

Ethics Committee: Alfred Hospital Ethics Committee, Research and Ethics Unit, Alfred Health, P. O. Box 315, Prahran, Victoria 3181, Australia.

Austin Hospital

Investigators: P. Peyton, S. Baulch, and S. Sidiropoulos.

Ethics Committee: Austin Health Human Research Ethics Committee, Research Ethics Unit, Austin Hospital, P. O. Box 5555, Heidelberg, Victoria 3084, Australia.

Dandenong Hospital

Investigators: R. Bulach and D. Bryant.

Ethics Committee: Southern Health Research Directorate, Monash Medical Centre, 246 Clayton Road, Clayton, Victoria 3168, Australia.

Fremantle Hospital

Investigators: E. O'Loughlin and V. Mitteregger.

Ethics Committee: South Metropolitan Area Health Service Human Research Ethics Committee, Fremantle Hospital and Health Service, Alma Street, Fremantle, Western Australia 6160, Australia.

Geelong Hospital

Investigators: S. Bolsin and C. Osborne.

Ethics Committee: The Barwon Health Research and Ethics Advisory Committee, The Geelong Hospital, P. O. Box 281, Geelong, Victoria 3220, Australia.

Monash Medical Centre

Investigators: R. McRae and M. Backstrom.

Ethics Committee: Human Research Ethics Committee-B, Southern Health 246 Clayton Road, Clayton, Victoria 3168, Australia.

Royal Melbourne Hospital

Investigators: K. Leslie and R. Cotter.

Ethics Committee: Melbourne Health Human Research Ethics Committee, Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia.

Royal Perth Hospital

Investigators: M. Paech and S. March.

Ethics Committee: Royal Perth Hospital Ethics Committee, Royal Perth Hospital Wellington Street, G. P. O. Box X2213, Perth, Western Australia 6847, Australia.

St. Vincent's Hospital

Investigators: B. Silbert and S. Said.

Ethics Committee: Human Research Ethics Committee-D, St. Vincent's Hospital, Grattan Street, Fitzroy, Victoria 3065, Australia.

Westmead Hospital

Investigators: R. Halliwell and J. Cope.

Ethics Committee: Sydney West Area Health Service Human Research Ethics Committee, Westmead Hospital, Hawkesbury Road, Westmead, New South Wales 2145, Australia.

Calvary Wakefield Hospital

Investigators: D. Fahlbusch and D. Crump.

Ethics Committee: Calvary Health Care Adelaide Human Research and Ethics Committee, Calvary Health Care Adelaide, 89 Strangways Terrace, North Adelaide, South Australia 5006, Australia.

Peter MacCallum Cancer Centre

Investigator: G. Thompson.

Ethics Committee: Peter MacCallum Cancer Centre Ethics Committee, Peter MacCallum Cancer Centre, St. Andrews Place, East Melbourne, Victoria 3002, Australia.

Western Hospital

Investigator: A. Jefferies.

Ethics Committee: Melbourne Health Human Research Ethics Committee, Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia.

North West Regional Hospital

Investigator: M. Reeves.

Ethics Committee: Tasmanian Human Research Ethics Committee, Health and Medical Office of Research Services, University of Tasmania, Hobart, Tasmania 7001, Australia.

Canada

McMaster University

Investigators: N. Buckley and T. Tidy.

Ethics Committee: The Hamilton Health Sciences/McMaster Health Sciences Research Ethics Board, 293 Wellington Street, Hamilton, Ontario, L8L 8E7, Canada.

Royal Victoria Hospital

Investigators: T. Schricker, R. Lattermann, and D. Iannuzzi.

Ethics Committee: SDR Committee, McGill University Health Centre, 687 Avenue des Pins, Montreal, Quebec, H3A 1A1, Canada.

Toronto General Hospital

Investigators: S. Beattie and J. Carroll.

Ethics Committee: University Health Network Research Ethics Board, 700 University Avenue, Toronto, Ontario, M5G 1Z5, Canada.

University of Alberta Hospital

Investigators: M. Jacka and C. Bryden.

Ethics Committee: Health Research Ethics Board (Biomedical Panel), Heritage Medical Research Centre, University of Alberta, Edmonton, Alberta, T6G 2S2, Canada.

London Health Sciences

Investigator: N. Badner.

Ethics Committee: The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects, The University of Western Ontario, London, Ontario, N6A 5C1, Canada.

Hong Kong

Prince of Wales

Investigators: M. T. V. Chan (ANZCA Clinical Trials Network member) and M. W. Y. Tsang.

Ethics Committee: The Joint Chinese University of Hong Kong, New Territories East Cluster Clinical Research Ethics Committee, Prince of Wales Hospital, Shatin, Hong Kong.

Tuen Mun Hospital

Investigators: B. C. P. Cheng and A. C. M. Fong.

Ethics Committee: New Territories West Cluster Clinical and Research Ethics Committee, Tuen Mun Hospital, Tuen Mun, New Territories, Hong Kong.

Pamela Youde Nethersole Eastern Hospital

Investigators: L. C. Y. Chu and E. G. Y. Koo.

Ethics Committee: New Territories West Cluster Clinical and Research Ethics Committee, Tuen Mun Hospital, Tuen Mun, New Territories, Hong Kong.

Malaysia

Hospital Kuala Lumpur

Investigators: N. Mohd and L. E. Ming.

Ethics Committee: Jawatankuasa Etika Perubatan Pusta Perubatan Universiti Malaya, Lembah Pantai, Kuala Lumpur 59100, Malaysia.

New Zealand (ANZCA Clinical Trials Network Members)

Auckland Hospital

Investigators: D. Campbell and D McAllister

Ethics Committee: New Zealand-Health and disability Ethics Committees, Multi-Region Ethics Committee, Ministry of Health, Wellington, New Zealand.

Middlemore Hospital

Investigators: S. Walker and S. Olliff.

Ethics Committee: New Zealand-Health and Disability Ethics Committees, Multi-Region Ethics Committee, Ministry of Health, Wellington, New Zealand.

Christchurch Hospital

Investigators: R. Kennedy.

Ethics Committee: New Zealand-Health and Disability Ethics Committees, Multi-Region Ethics Committee, Ministry of Health, Wellington, New Zealand.

Saudi Arabia

King Saud University Hospital

Investigators: A. Eldawlatly and T. Alzahrani.

Ethics Committee: College of Medicine Research Centre, King Saud University, P. O. Box 2925, Riyadh 1146, Saudi Arabia.

Singapore

Tan Tock Seng Hospital

Investigators: N. Chua.

Ethics Committee: National Health Group Domain Specific Review Board, 6 Commonwealth Lane, Singapore 149547, Singapore.

United Kingdom

Plymouth NHS Trust

Investigators: R. Sneyd and H. McMillan.

Ethics Committee: NRES Committee, South West-Central Bristol Bristol Research Ethics Committee Centre, Whitefriars Level 3, Block B Lewin's Mead, Bristol, BS1 2NT, United Kingdom.

Royal Lancaster Infirmary

Investigators: I. Parkinson.

Ethics Committee: NRES Committee, South West-Central Bristol Bristol Research Ethics Committee Centre, Whitefriars Level 3, Block B Lewin's Mead, Bristol, BS1 2NT, United Kingdom.

Bradford Teaching Hospital

Investigators: A. Brennan.

Ethics Committee: NRES Committee, South West-Central Bristol Bristol Research Ethics Committee Centre, Whitefriars Level 3, Block B Lewin's Mead, Bristol, BS1 2NT, United Kingdom.

Hull Royal Infirmary

Investigator: P. Balaji.

Ethics Committee: NRES Committee, South West-Central Bristol Bristol Research Ethics Committee Centre, Whitefriars Level 3, Block B Lewin's Mead, Bristol, BS1 2NT, United Kingdom.

Portsmouth Hospital

Investigators: J. Nightingale.

Ethics Committee: NRES Committee, South West-Central Bristol Bristol Research Ethics Committee Centre, Whitefriars Level 3, Block B Lewin's Mead, Bristol, BS1 2NT, United Kingdom.

King's College Hospital

Investigators: G. Kunst.

Ethics Committee: NRES Committee, South West-Central Bristol Bristol Research Ethics Committee Centre, Whitefriars Level 3, Block B Lewin's Mead, Bristol, BS1 2NT, United Kingdom.

Royal Surrey County Hospital

Investigators: M. Dickinson.

Ethics Committee: NRES Committee, South West-Central Bristol Bristol Research Ethics Committee Centre, Whitefriars Level 3, Block B Lewin's Mead, Bristol, BS1 2NT, United Kingdom.

United States of America

Beth Israel Deaconess Medical Center

Investigators: B. Subramaniam and V. Banner-Godspeed.

Ethics Committee: Committee on Clinical Investigation, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02215.

Cleveland Clinic

Investigators: D. I. Sessler, J. Liu, A. Kurz, B. Hesler, A. Y. Fu, C. Egan, A. N. Fiffick, M. T. Hutcherson, A. Turan, and A. Naylor.

Ethics Committee: Institutional Review Board, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195.

Louisville Medical Centre

Investigators: D. Obal and E. Cooke.

Ethics Committee: Institutional Review Board, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195.