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ORIGINAL RESEARCH

Effects of Volatile Anesthetics on Postoperative Ischemic Stroke Incidence

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BACKGROUND: Preclinical studies suggest that volatile anesthetics decrease infarct volume and improve the outcome of ischemic stroke. This study aims to determine their effect during noncardiac surgery on postoperative ischemic stroke incidence.

METHODS AND RESULTS: This was a retrospective cohort study of surgical patients undergoing general anesthesia at 2 tertiary care centers in Boston, MA, between October 2005 and September 2017. Exclusion criteria comprised brain death, age <18 years, cardiac surgery, and missing covariate data. The exposure was defined as median age-adjusted minimum alveolar concentration of all intraoperative measurements of desflurane, sevoflurane, and isoflurane. The primary outcome was postoperative ischemic stroke within 30 days. Among 314 932 patients, 1957 (0.6%) experienced the primary outcome. Higher doses of volatile anesthetics had a protective effect on postoperative ischemic stroke incidence (adjusted odds ratio per 1 minimum alveolar concentration increase 0.49, 95% CI, 0.40–0.59, $P<0.001$). In Cox proportional hazards regression, the effect was observed for 17 postoperative days (postoperative day 1: hazard ratio (HR), 0.56; 95% CI, 0.48–0.65; versus day 17: HR, 0.85; 95% CI, 0.74–0.99). Volatile anesthetics were also associated with lower stroke severity: Every 1-unit increase in minimum alveolar concentration was associated with a 0.006-unit decrease in the National Institutes of Health Stroke Scale (95% CI, −0.01 to −0.002, $P=0.002$). The effects were robust throughout various sensitivity analyses including adjustment for anesthesia providers as random effect.

CONCLUSIONS: Among patients undergoing noncardiac surgery, volatile anesthetics showed a dose-dependent protective effect on the incidence and severity of early postoperative ischemic stroke.

Key Words: anesthetics ■ cerebral ischemia ■ retrospective studies ■ stroke ■ stroke prevention

In the United States, ≈60 000 patients undergo general anesthesia every day.[1] With an aging surgical population,[2] increasing surgical case volumes, and incidences of perioperative stroke ranging from 0.1% to 9.7%,[3] perioperative stroke prevention has become a goal of increasing importance.[4]

Intraoperative anesthetic management strategies have substantial consequences on a patient's susceptibility to ischemic stroke after surgery.[5–7]

Preclinical data suggest that volatile anesthetics have neuroprotective effects that may decrease the risk of stroke.[8–10] However, recent studies lack conclusive evidence derived from large patient cohorts.[9,11]

The primary aim of this study was to examine the effect of intraoperative volatile anesthetic dose on ischemic stroke within 30 days after noncardiac surgery in a large and diverse surgical cohort.

METHODS

Study Design and Setting

This was a hospital registry study of patients undergoing surgery with general anesthesia at Beth Israel

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CLINICAL PERSPECTIVE

What Is New?

- In this retrospective cohort study of 314 932 patients undergoing noncardiac surgery with general anesthesia, volatile anesthetics had a dose-dependent protective effect on postoperative ischemic stroke incidence and severity; the magnitude of the protective effect was dependent on the postoperative timing of stroke occurrence.
- Compared with patients undergoing propofol-based anesthesia, patients receiving volatile anesthetics had a significantly lower risk of postoperative ischemic stroke.
- Our findings were robust across several sensitivity analyses, including propensity score matching and adjustment, and in a mixed-effects model adjusting for provider variability.

What Are the Clinical Implications?

- This study supports the use of volatile anesthetics in patients who require general anesthesia and who are vulnerable to postoperative ischemic stroke.
- Since the effects were dose dependent, clinicians should know that using higher doses of volatile anesthetics, as compared with lower doses or propofol-based anesthesia, might be considered for stroke prevention.
- Optimally, our study results would be confirmed in a randomized controlled trial.

Deaconess Medical Center in Boston, Massachusetts, between October 2005 and September 2017, and at Massachusetts General Hospital in Boston, Massachusetts, between January 2007 and December 2015. The study was approved by the Beth Israel Deaconess Medical Center Institutional Review Board (protocol number 2019P000014) and the Partners Human Research Committee (reliance agreement [SMART IRB] number 1627). Requirement for informed consent was waived. Data were retrieved from data repositories at Beth Israel Deaconess Medical Center and Partners HealthCare, and subsequently combined into a deidentified data set (Data S1). The authors TTH and ME had full access to the data in this study and take responsibility for their integrity and analysis.

The data supporting our findings are available from the corresponding author upon reasonable request. This article adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational research (Data S2).

Patient Selection

Patients undergoing surgery with general anesthesia were included in the study cohort. Exclusion criteria comprised age <18 years, cardiac surgery,[12] or an American Society of Anesthesiologists physical status classification of VI (brain death) (Data S1). Patients with missing covariate data were excluded from analyses to apply the complete case method.

Exposure and Primary Outcome

The primary exposure variable was defined as median age-adjusted minimum alveolar concentration (MAC) of all minute-by-minute end-tidal measurements of volatile anesthetics (ie, desflurane, sevoflurane, and isoflurane) throughout the surgical case (Data S1).[13]

The primary outcome was postoperative ischemic stroke within 30 days, identified through *International Classification of Diseases, Ninth/Tenth Revision* (*ICD-9/ICD-10*) billing diagnoses (Table S1).

Covariate Model

Confounding factors were selected a priori utilizing a model for preoperative assessment of perioperative ischemic stroke risk developed by our group.[14] Subsequently, we expanded the model for perioperative factors based on available literature[15–17] as well as biological and clinical plausibility. The final model adjusted for patient demographics, comorbidities, and anesthesia- and procedure-related factors (Data S1).

Primary Analysis

In the primary analysis, we applied multivariable logistic regression to examine the effect of intraoperative volatile anesthetic dose on ischemic stroke within 30 days after surgery.

Secondary Analyses

In secondary analyses, we assessed the time dependency of the observed effect using a Cox proportional hazards model adjusting for the covariates included in the primary model. Therefore, the exposure was dichotomized by the median MAC among all patients (MAC >0.73 versus ≤0.73). An interaction term (volatile anesthetic dose×time after surgery) was included in the model. In a post hoc logistic regression analysis based on findings from the Cox proportional hazards model, we compared the effect of volatile anesthetics on postoperative ischemic stroke occurring earlier (within days 1–17) versus later (within days 18–30 after surgery).

Further, we analyzed the effect of volatile anesthetic dose on postoperative transient ischemic attack (TIA) and all-cause mortality within 30 days after surgery (Data S1).

Sensitivity Analyses

Multiple sensitivity analyses were performed to test the robustness of findings, discussed below.

Anesthetic Requirement

We created a propensity score for receiving high doses of volatile anesthetics (highest tertile) utilizing the covariates of the full primary logistic regression model (Data S1).[18–21] Subsequently, patients were categorized into equally sized tertiles of low, intermediate, and high propensity, respectively, and we repeated the primary analysis in each group.

Effects of Intraoperative Hypotension

To further address potential differences in patients' individual susceptibility to anesthetics, we assessed the maximum blood pressure decrease within 5 minutes of anesthesia induction with propofol (in percent from baseline before induction). Maximum mean arterial pressure (MAP) decrease was categorized (<10%, ≥10 and <20%, ≥20 and <30%, or ≥30%) and an interaction term (volatile anesthetic dose×maximum MAP decrease) was introduced into the primary model.

The primary analysis was also repeated in patients with no, short, intermediate, and prolonged duration of intraoperative hypotension, defined as 0, >0 and ≤2, >2 and ≤5, and >5 measurements of MAP <55 mm Hg during surgery, respectively.

Propensity Score Matching and Adjustment

To address potential residual confounding, 1:1 propensity score matching was performed for the variable high-dose (higher than the cohort median) volatile anesthetics, utilizing the covariates of the primary model. A calculated caliper was used for matching,[22] and variables were examined for residual imbalances. Further, we calculated the E-value for our primary finding to quantify the potential impact of unmeasured confounding. As introduced by VanderWeele and Ding,[23] the E-value is defined as the minimal magnitude of association that unmeasured confounding would need to have with both exposure and outcome in order to fully explain away the observed effect.[24]

Analysis Stratified by Baseline Stroke Risk

The full primary covariate model was utilized to estimate patients' baseline risk of postoperative ischemic stroke. The study cohort was then divided into equally sized tertiles of patients with low, intermediate, and high baseline risk, respectively, and we reran the primary analysis in every risk tertile.

Subgroup Analysis in Patients With High Procedure-Related Stroke Risk

We further examined the primary association in a subgroup of patients with high procedural risk of postoperative ischemic stroke, defined as brain and vascular surgery (including carotid endarterectomy).[3,25]

Impact of Provider Variability

Since the dosing of volatile anesthetics may depend on provider preference, we analyzed provider variability in our cohort and assessed its impact on the primary finding. Individual providers' preferences for using high doses were defined using a mixed-effects logistic regression model with volatile anesthetic doses higher than the cohort median as the outcome. All covariates of the primary model were added as fixed effects while individual providers with a total experience of ≥100 procedures were added as random effect, resulting in the predicted probability of receiving high doses for each patient. For each provider, the adjusted preference of using doses higher than the median was calculated across all cases performed by the respective provider.

To assess the impact of provider variability on our primary finding, a mixed-effects model was used on the primary logistic regression model, adding anesthesia providers as random effect.

Adjudicated Outcome Based on Chart Review

We reran the primary analysis using an adjudicated outcome variable based on medical record review performed by an interdisciplinary team as previously described by our group.[15,16] All cases with a billing diagnosis of ischemic stroke within 30 days after surgery were manually reviewed using brain scan reports, discharge summaries, and neurology consultation notes (Data S1). Additionally, stroke location according to the Oxfordshire Community Stroke Project[26], and National Institutes of Health Stroke Scales (NIHSS)[27] were assessed.

Effects of Anesthesia Depth (Bispectral Index)

To discriminate between the effect of volatile anesthetic dose and the effect of the level of unconsciousness during anesthesia, the association of the median intraoperative bispectral index (BIS) and postoperative ischemic stroke was assessed in a subgroup of patients with available data.[28] Further, an interaction term (BIS×volatile anesthetic dose) was included in the model.

Supplemental Sensitivity Analyses

Additional sensitivity analyses, including those taking into account missing follow-up[29] and covariate data, are provided in Tables S2 and S3).

Exploratory Analyses

We compared volatile anesthesia (while allowing for an induction bolus of propofol) to total intravenous anesthesia (TIVA) using propofol regarding the primary outcome.

Model fit was assessed using c-statistics (ie, area under the receiver operating characteristics curve), as well as calibration plot and Brier score (squared difference between estimated and observed outcomes).

Additional post hoc analyses are described in Data S1. Briefly, to address a suggestion of a peer reviewer, we also included all patients undergoing cardiac surgery who had previously been excluded. Further, we explored compound-specific effects of volatile agents in the respective subgroups.

Statistical Analyses

If not further specified, multivariable logistic regression utilizing the full covariate model was used for binary outcome variables. Analyses were selected a priori. Statistical significance was assumed at a 2-sided $P<0.05$.

Analyses were performed using Stata (version 15; StataCorp LLC, College Station, TX) or Rstudio (version 1.1.442; Rstudio Inc., Boston, MA).

RESULTS

Study Cohort

A total of 400 257 patients underwent surgery under general anesthesia at Beth Israel Deaconess Medical Center and Massachusetts General Hospital within the studied time frame (Figure 1). There were 23 719 patients excluded for being underage, brain-dead, or undergoing cardiac surgery, and 61 606 patients were excluded from analysis because of missing covariate data. The final study cohort comprised 314 932 cases (Table 1).[30] 298 505 patients (94.5%) received volatile anesthetics for anesthesia. The overall median MAC of volatile anesthetics was 0.73 (interquartile range, 0.50, 0.94).

Primary Analysis

Of all patients in the study cohort, 1957 patients (0.6%) had an ischemic stroke within 30 days after surgery. The median time to ischemic stroke was 4 days (interquartile range, 1, 14) (Figure S1).

A higher MAC of volatile anesthetics had a significant protective effect on ischemic stroke within 30 days after

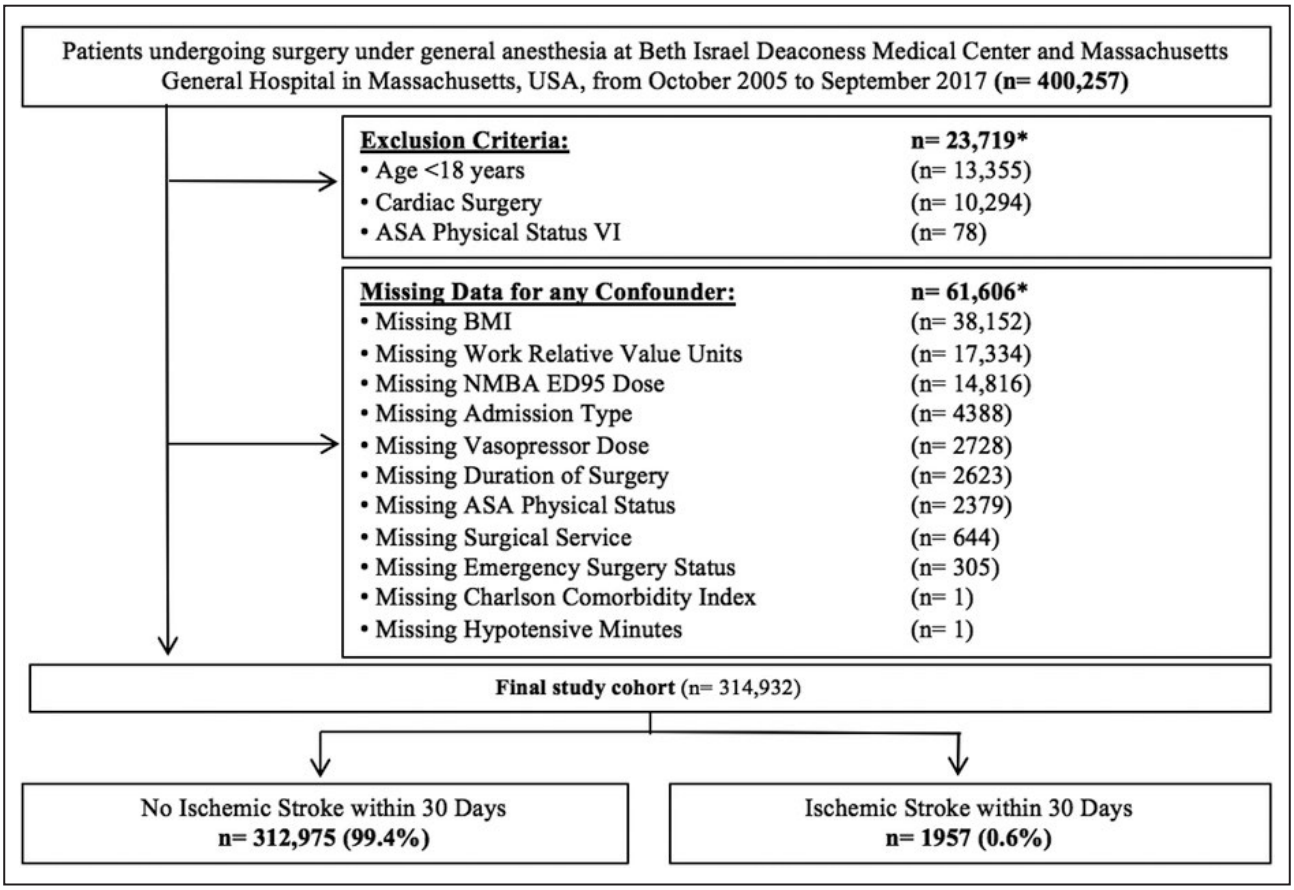

Figure 1. Study flow.

*Multiple criteria may apply. ASA indicates American Society of Anesthesiologists physical status classification (as classified by the anesthesiologist); BMI, body mass index; ED95, median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; and NMBA, neuromuscular blocking agent.

Table 1. Characteristics of the Study Population by Postoperative Ischemic Stroke Status

Characteristics	No Ischemic Stroke Within 30 d (n=312 975)	Ischemic Stroke Within 30 d (n=1957)
Demographics		
Age, y	53.7±16.5	64.1±15.2
Sex, male	137 662 (44.0%)	1094 (55.9%)
Body mass index, kg/m^2	28.4±6.9	27.6±6.0
Comorbidities*		
Arterial hypertension	125 363 (40.1%)	1416 (72.4%)
Atrial fibrillation	21 311 (6.8%)	444 (22.7%)
Carotid stenosis	6976 (2.2%)	679 (34.7%)
Chronic kidney disease	20 187 (6.5%)	352 (18.0%)
Diabetes mellitus	45 628 (14.6%)	553 (28.3%)
Dyslipidemia	96 622 (30.1%)	1066 (54.5%)
Ischemic stroke	7639 (2.4%)	1357 (69.3%)
Malignancy	92 111 (29.4%)	579 (29.6%)
Migraine	11 373 (3.6%)	87 (4.4%)
Patent foramen ovale without closure	2767 (0.9%)	135 (6.9%)
Peripheral vascular disease	12 222 (3.9%)	303 (15.5%)
Smoking	51 969 (16.6%)	516 (26.4%)
Transient ischemic attack	4691 (1.5%)	399 (20.4%)
Valvular heart disease	26 679 (8.5%)	732 (37.4%)
Beta-blocker prescription within 28 d prior	44 342 (14.2%)	1096 (56.0%)
Charlson Comorbidity Index[30]	1 (0, 3)	4 (2, 6)
ASA physical status	2 (2, 3)	3 (2, 3)
Surgical factors		
Emergency surgery	13 994 (4.5%)	182 (9.3%)
Inpatient surgery	199 951 (63.9%)	1868 (95.5%)
Duration of surgery, min	155±108	194±134
Work relative value units	14.7±9.8	19.0±12.9
Surgical service		
Burn	1976 (0.6%)	22 (1.1%)
Emergent–urgent	10 721 (3.4%)	164 (8.4%)
General	57 773 (18.5%)	86 (4.4%)
Gynecology/obstetrics	31 200 (10.0%)	33 (1.7%)
Neurosurgery	21 899 (7.0%)	531 (27.1%)
Oral/maxillofacial	3297 (1.1%)	7 (0.4%)
Orthopedic	72 620 (23.2%)	160 (8.2%)
Other (dermatology, etc)	4463 (1.4%)	58 (3.0%)
Otolaryngology	8808 (2.8%)	9 (0.5%)
Plastic	18 716 (6.0%)	19 (1.0%)
Radiology	1728 (0.6%)	71 (3.6%)
Surgical oncology	15 003 (4.8%)	19 (1.0%)
Thoracic	19 986 (6.4%)	98 (5.0%)
Transplant	5704 (1.8%)	23 (1.2%)
Urology	22 176 (7.1%)	59 (3.0%)
Vascular	10 402 (3.3%)	410 (21.0%)
Anesthetic factors		
Use of volatile anesthetic	296 714 (94.8%)	1791 (91.5%)
MAC of volatile anesthetic	0.72±0.35	0.51±0.34

(*Continued*)

Table 1. Continued

Characteristics	No Ischemic Stroke Within 30 d (n=312 975)	Ischemic Stroke Within 30 d (n=1957)
MAC of nitrous oxide	0.07 (0, 0.41)	0.21 (0, 0.56)
Total opioid dose (oral morphine equivalents)	50.5 (31.3, 79.5)	62.5 (37.5, 103.3)
Total propofol dose, mg	200 (150, 260)	170 (110, 250)
Total neuromuscular blocking agent ED95 dose	1.86 (0, 3.06)	2.82 (1.69, 4.4)
Total vasopressor dose, mg (norepinephrine equivalents)	0.01 (0, 0.1)	0.17 (0.03, 0.53)
Total fluid volume administered, mL	2000 (1000, 3000)	1350 (750, 2500)
Administration of packed red blood cells	9118 (2.9%)	141 (7.2%)
Neuraxial anesthesia	10 271 (3.3%)	65 (3.3%)
Minutes with MAP <55 mm Hg	0 (0, 2)	1 (0, 3)

Values provided as frequency (prevalence in %), mean±SD, or median (interquartile range [25th–75th percentile], values separated by comma). ASA indicates American Society of Anesthesiologists; ED95, median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; MAC, minimum alveolar concentration; and MAP, mean arterial pressure.

*For comorbidity definitions, refer to Table S1.

surgery in unadjusted (odds ratio per 1 MAC increase 0.16, 95% CI, 0.14–0.19, $P<0.001$) as well as adjusted analyses (adjusted odds ratio [aOR] per 1 MAC increase 0.49, 95% CI, 0.40–0.59, $P<0.001$) (Table 2; Table S4).

Secondary Analyses

In the Cox proportional hazards regression, we found a time-dependent effect of volatile anesthetic dose and postoperative ischemic stroke (P for interaction volatile anesthetics×days after surgery <0.001): Patients receiving high volatile anesthetic doses showed a significantly lower hazard rate of ischemic stroke for up to 17 days after surgery (postoperative day 1: hazard ratio [HR], 0.56; 95% CI, 0.48–0.65; versus postoperative day 17: HR, 0.85; 95% CI, 0.74–0.99). The protective effect was found to be no longer statistically significant ($P>0.05$) at postoperative day 18 (HR, 0.88; 95% CI, 0.75–1.02). One thousand five hundred ninety-four of 1957 ischemic strokes (81.5%) occurred within 17 days after surgery. At postoperative day 23, volatile anesthetics were no longer found to have a protective effect (HR, 1.00; 95% CI, 0.83–1.21) (Figure 2). A significant protective effect of higher volatile anesthetic doses was confirmed for ischemic strokes within 17 days (aOR, 0.41; 95% CI, 0.33–0.51, $P<0.001$) but not for ischemic strokes within days 18 to 30 (aOR, 0.98; 95% CI, 0.67–1.45, $P=0.94$) in subsequent multivariable logistic regression analyses. For details of patients receiving low versus high doses, see Table S5.

Estimated risks of ischemic stroke were 0.5 for every 1000 patients receiving high doses of volatile anesthetics (highest tertile, mean [SD] MAC 1.1 [0.23]) and 0.8 for every 1000 patients receiving low doses (lowest tertile, mean [SD] MAC 0.35 [0.19]). In comparison to patients receiving low doses, patients receiving high doses were found to have a significantly lower risk of ischemic stroke after surgery (adjusted absolute risk difference, −0.03%; 95% CI, −0.04 to −0.02, $P<0.001$; relative risk reduction, 37.5%) (Table 2). For results of all other secondary analyses, please see Table 2 and Data S1.

Sensitivity Analyses

The primary effect was found to be robust across tertiles of volatile anesthetic dose (Table 3). The decreasing

Table 2. Primary and Secondary Outcomes in Patients Receiving Low Versus High Doses of Volatile Anesthetics

Outcome	Low-Dose Volatile Anesthetics (Lowest Tertile)		High-Dose Volatile Anesthetics (Highest Tertile)		High vs Low Doses		Odds Ratio (95% CI)*	
	Outcome Rate (%)	Estimated Risk (%, 95% CI)	Outcome Rate (%)	Estimated Risk (%, 95% CI)	aARD (%)	RRR (%)	Unadjusted	Adjusted
Ischemic stroke	1.1	0.08 (0.07–0.10)	0.28	0.05 (0.04–0.06)	−0.03	37.5	0.16 (0.14–0.19)	0.49 (0.40–0.59)
TIA	0.38	0.03 (0.02–0.04)	0.07	0.01 (0.009–0.018)	−0.02	66.7	0.12 (0.10–0.16)	0.35 (0.25–0.49)
Death	1.0	0.1 (0.08–0.11)	0.49	0.05 (0.04–0.06)	−0.05	50.0	0.36 (0.32–0.41)	0.48 (0.41–0.56)

Table 2 depicts results from primary and secondary analyses in patients receiving the lowest and highest tertile of volatile anesthetic dose across the study cohort, respectively. All outcomes were assessed within 30 days after surgery. Analyses were adjusted for all covariates included in the primary model. Estimated risk and risk differences were calculated using Stata packages "predict" and "margins." Rates are rounded to 2 decimal places. aARD indicates adjusted absolute risk difference; RRR, relative risk reduction; and TIA, transient ischemic attack.

*$P<0.001$ for all results listed in Table 2.

odds ratio for tertiles of intermediate and high doses, respectively, highly suggest a dose dependency of the primary effect (*P* for trend <0.001).

Anesthetic Requirement

Repeating the primary analysis in each tertile of the propensity score for receiving high-dose volatiles confirmed the primary finding: Higher doses of volatile anesthetics had a significant protective effect on ischemic stroke in patients with the highest propensity of high doses as well as in patients with intermediate and low propensity of high doses (Table 3).

Effects of Intraoperative Hypotension

In 163 241 patients with available data, no effect modification by maximum MAP decrease from baseline after induction was found (≥10 and <20%: *P* for interaction=0.58; ≥20 and <30%: *P* for interaction=0.62; ≥30%: *P* for interaction=0.81).

The primary finding was substantiated in all categories of intraoperative hypotension: Patients without intraoperative MAP <55 mm Hg (n=172 089), as well as with short (n=72 565), intermediate (n=36 980), and prolonged duration of intraoperative hypotension (n=32 973) (Table 3).

Propensity Score Matching and Adjustment

With a calculated caliper of 0.359, a total of 159 692 (50.7%) patients higher and lower than the cohort median dose of volatile anesthetics were matched according to their propensity for receiving high-dose volatile anesthetics. In the matched cohort, the primary finding was confirmed.

Since propensity matching omitted unmatched individuals from analysis, we further performed propensity score adjustment. A model was fitted including the aforementioned exposure (doses higher versus lower than median) as well as a linear and squared term of the propensity score. Our primary finding was confirmed (Table 3).

In our primary analysis, we observed an aOR of 0.49 (95% CI, 0.40–0.59). An unmeasured confounder would have to be associated with both the exposure and the outcome, respectively, with an aOR (adjusted for all measured confounders) of 3.5 (E-value) each in order to fully explain away the observed effect. To move the 95% CI such that the observed effect would no longer be statistically significant, an unmeasured confounder of the same nature would have to have an aOR of 2.78 for the primary association. Weaker confounding could not explain away the observed association.

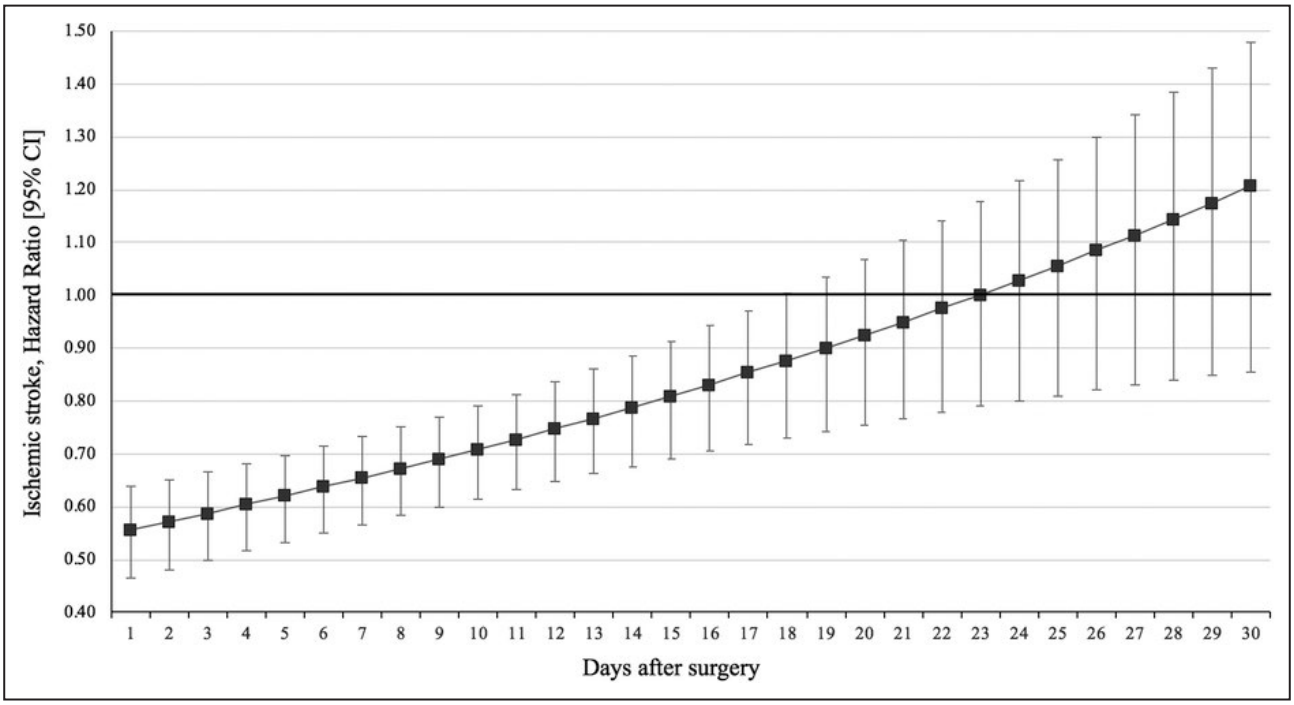

Figure 2. Hazard ratio for ischemic stroke per postoperative day.
Results of the Cox proportional hazards regression regarding the effect of volatile anesthetics higher than minimum alveolar concentration=0.73 (cohort median) on postoperative ischemic stroke, with a hazard ratio of 1.00 shown as bold line in the graph. Hazard ratios are presented per postoperative day. Patients receiving higher doses of volatile anesthetics showed significantly lower hazard of ischemic stroke for up to 17 days after surgery.

Table 3. Results of Sensitivity Analyses

Type of Analysis	Subgroup of Patients	aOR, 95% CI	*P* Value
Tertiles of volatile anesthetic dose	Receiving low doses	1.0 (reference level)	
	Receiving intermediate doses	0.78, 0.68–0.89	<0.001
	Receiving high doses	0.61, 0.51–0.72	<0.001
Anesthetic requirement	Low propensity of receiving high doses	0.48, 0.35–0.65	<0.001
	Intermediate propensity of receiving high doses	0.50, 0.36–0.70	<0.001
	High propensity of receiving high doses	0.60, 0.40–0.91	0.02
Effects of intraoperative hypotension	No hypotension	0.54, 0.41–0.72	<0.001
	Short duration of hypotension	0.48, 0.32–0.72	<0.001
	Intermediate duration of hypotension	0.49, 0.28–0.87	0.02
	Prolonged duration of hypotension	0.38, 0.23–0.64	<0.001
Propensity score matching	Propensity of doses higher vs lower than median	0.66, 0.57–0.75	<0.001
Propensity score adjustment	Propensity of doses higher vs lower than median (vs without propensity score adjustment)	0.64, 0.57–0.72 (0.68, 0.60–0.78)	<0.001 (<0.001)
Analysis stratified by baseline stroke risk	Low baseline risk of stroke	0.99, 0.27–3.55	0.98
	Intermediate baseline risk of stroke	0.82, 0.32–2.07	0.67
	High baseline risk of stroke	0.46, 0.38–0.56	<0.001
Subgroup analysis in patients with high procedure-related stroke risk	Undergoing brain or vascular surgery	0.58, 0.43–0.79	<0.001
Impact of provider variability	Mixed-effects model adjusting for anesthesia provider	0.70, 0.60–0.83	<0.001
Adjudicated outcome based on chart review	Full study cohort	0.39, 0.30–0.50	<0.001

Table 3 depicts results from the sensitivity analyses performed in order to test the robustness of the primary finding. All sensitivity analyses use the primary outcome (ischemic stroke within 30 days after surgery). Analyses were adjusted for all covariates included in the primary model. aOR indicates adjusted odds ratio.

Analysis Stratified by Baseline Stroke Risk

The primary finding was also confirmed in patients within the highest tertile of baseline risk of postoperative ischemic stroke but not in patients within the intermediate- and low-risk group (n=104 977 each; Table 3).

Subgroup Analysis in Patients With High Procedure-Related Stroke Risk

Further, the protective effect of volatile anesthetics on postoperative ischemic stroke incidence was robust in a subgroup of 24 195 patients (7.7%) with high procedural risk of stroke, such as brain and vascular surgery (Table 3).

Impact of Provider Variability

After excluding cases performed by anesthesiologists with a total experience of <100 cases, 70 277 patients remained for analysis. In this cohort, 862 individual providers were documented. The predicted preference for individual providers to use volatile anesthetic doses higher than the cohort median ranged from 3.1% to 93.9%, demonstrating high provider variability (Figure S2). The primary finding remained robust when adjusting for provider variability in a mixed-effects model (Table 3).

Adjudicated Outcome Based on Chart Review

Medical record review verified 686 of 1957 (35.1%) ischemic strokes billed through *ICD-9/10* codes within 30 days after surgery, which translates to an ischemic stroke incidence of 0.2%. Of these verified strokes, 127 (18.5%) patients had a partial anterior circulation and 170 (24.5%) a total anterior circulation stroke. One hundred seventy-eight (26.0%) patients had a posterior circulation infarct, while 38 (5.5%) patients showed lacunar infarctions. One hundred seventy-three (25.2%) patients had an ischemic stroke of unclassifiable location. Repetition of the primary analysis utilizing the verified ischemic stroke outcome confirmed our primary findings (Table 3).

Fifty patients (7.3%) with verified ischemic stroke presented missing NIHSS data. Four hundred fifty-nine (66.9%) patients presented with mild (NIHSS ≤5) and 177 (25.8%) with moderate–severe neurological symptoms (NIHSS >5).[31] The median NIHSS among all verified ischemic strokes with complete information was 3 points (interquartile range, 1, 6.5). In a post hoc

exploratory analysis, every 1-unit increase in MAC of volatile anesthetics was associated with a 0.006-unit decrease in NIHSS (β −0.006; 95% CI, −0.01 to −0.002, *P*=0.002). Further, in a multinomial logistic regression model, volatile anesthetics had a dose-dependent protective effect on both patients with mild neurological symptoms (β −0.82; 95%, CI −1.18 to −0.46, *P*<0.001) and patients with moderate–severe neurological presentation (β −0.58; 95% CI, −1.17 to −0.01, *P*=0.054). There was no significant interaction between volatile anesthetics and intraoperative hypotension in either of the 2 groups (*P* for interaction=0.53 in patients with mild symptoms, and 0.76 in patients with moderate–severe symptoms).

Effects of Anesthesia Depth (BIS)

BIS was not associated with postoperative ischemic stroke in a subgroup of 14 862 patients with available data (aOR, 0.995; 95% CI, 0.97–1.02, *P*=0.75). No significant interaction of volatile dose and BIS was found regarding the primary outcome (*P* for interaction=0.70).

Exploratory Analyses

In our cohort, 204 522 (64.9%) patients received volatile anesthesia with the option of propofol as induction bolus. Some patients (13 918; 4.4%) underwent TIVA using propofol without volatile anesthetics. 96 492 patients in our cohort (30.6%) received a combined or different type of anesthesia and, thus, were not considered in this exploratory analysis. In comparison to TIVA, patients undergoing volatile anesthesia had significantly lower odds of experiencing the primary outcome (aOR, 0.71; 95% CI, 0.55–0.90, *P*=0.005).

The covariate model for postoperative ischemic stroke showed excellent discriminative ability independent of the exposure with an area under the receiver operating characteristics curve of 0.95 (Figure S3).

A reliability plot demonstrated excellent calibration of the covariate model (Figure S4). The Brier score for the covariate model was 0.007 and reliability was 0.002, reflecting excellent accuracy and calibration.

DISCUSSION

In this cohort of 314 932 adult patients undergoing noncardiac surgery with general anesthesia, volatile anesthetics were found to have a dose-dependent protective effect on postoperative ischemic stroke incidence and severity.

In our study, the protective effect of volatile anesthetics on ischemic stroke was stronger in patients who developed an early postoperative stroke, which supports a pharmacologically plausible effect: Volatile anesthetic preconditioning may prevent early cascades of brain ischemia from evolving into a clinically relevant ischemic stroke. A plausible mechanism is the dose-dependent frequency inhibition of cortical spreading depolarizations, which have been reported to occur for several days after ischemia.[32–34] Preclinical literature describes protective effects of volatile preconditioning for up to 3 days.[9] In this study, significant effects are seen until postoperative day 17. It is possible that anti-inflammatory and anti-thrombogenic effects, as well as remote preconditioning, are at play as well.[35–37]

This hypothesis is in line with the results of a retrospective cohort study by Sivasankar et al, who reported that the use of volatile anesthetics led to significantly lower degrees of poststroke disability in a cohort of patients undergoing revascularization procedures after stroke.[38] Our study adds to these findings that a protective effect may also be relevant for stroke prevention.

Our data further suggest that volatile anesthesia is associated with lower odds of postoperative ischemic stroke when compared with TIVA using propofol. This corresponds with a randomized controlled trial of patients undergoing carotid endarterectomy by Kuzkov et al showing that, compared with propofol, sevoflurane suppressed intraoperative asymmetry of cerebral oxygenation and improved postoperative cognition.[39] Similarly, in a randomized controlled trial of 128 patients undergoing cardiac surgery with cardiopulmonary bypass, Schoen et al found that sevoflurane-based anesthesia (compared with propofol) attenuated the effects of intraoperative desaturation on postoperative neurocognition.[40]

Strengths and Limitations

A major strength of this study is the generalizability of results derived from a large, diverse, and multicentric surgical cohort. While residual confounding cannot be ruled out because of the study's observational nature, the covariate model was shown to have excellent discriminative ability with an area under the receiver operating characteristics curve of 0.95. Misclassification of the outcome based on billing codes and varying coding practices between hospitals was likely random and unrelated to the exposure. Potential bias was addressed by medical record review of the outcome variable, which did not change our conclusions.

One might speculate that younger and healthier patients are more likely to receive higher doses of volatile anesthetics while having an overall low baseline risk of stroke and, thus, low outcome rates. Therefore, we examined subgroups of patients with varying probability of receiving higher doses. We observed the dose-dependent effect of volatile anesthetics on ischemic stroke to be robust across patients with different propensity of receiving high doses. Another marker

of anesthetic requirement may be the hemodynamic response to an induction dose of an intravenous anesthetic, typically propofol. Our data showed that the patient's hemodynamic susceptibility to anesthetics did not modify the observed primary effect.

This study focuses on the preconditioning effect of volatile anesthetics and is not designed to explore the effects of volatile anesthetics on patients with ongoing stroke. While we are enthusiastic about our results, we would caution extrapolation of these results to other settings, such as endovascular stroke treatment.

Clinical Implications

The early postoperative period corresponds with a particularly high risk of having an ischemic stroke.[41] Additionally, recognition of stroke during inpatient stays may be delayed because of comorbidities and hospital practice, while treatment options early after surgery may be limited.[25,42] Our data support the use of volatile anesthetics to prevent clinically relevant ischemic strokes during this highly vulnerable period.

This study found that the protective effect of volatile anesthetics might be of particular relevance in patients requiring general anesthesia while carrying a high baseline risk of postoperative ischemic stroke. In anticipation of potential ischemic events in such patients, prophylactic neuroprotection should be considered.[43] We believe that certain patient populations who have a high risk of surgery-related ischemic stroke (such as patients undergoing vascular or neurosurgical procedures) may have their risk mitigated with the use of volatile anesthetics. Simultaneously, our data encourage the preferential use of volatile anesthesia over TIVA using propofol in patients at particular risk of postoperative ischemic stroke. Since the observed effect was dose dependent, clinicians should be aware that, compared with lower doses or propofol-based anesthesia, using higher doses of volatile anesthetics might be helpful for stroke prevention.

Future randomized controlled trials, especially in patients undergoing high-risk procedures such as neurosurgery and vascular surgery, will be needed to confirm our findings.

In summary, volatile anesthetics had a dose-dependent protective effect on the incidence and severity of ischemic stroke within 30 days after noncardiac surgery in this diverse cohort of 314 932 adult patients. The effect was found to be of specific importance during the early postoperative period.

ARTICLE INFORMATION

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Supplementary Material

Datas S1–S2
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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Data sources

Data were collected from two major hospital systems in Massachusetts, USA – Beth Israel Deaconess Medical Center (BIDMC) and Partners HealthCare network.
At BIDMC, patient data were retrieved from the Perioperative Information Management System (PIMS), the Anesthesia Information Management System (AIMS), Casemix, the Admission Discharge Transfer (ADT) database, the Miscellaneous (MISC) database, the Online Medical Record (OMR) database, and the Center for Clinical Computing (CCC) database for anesthesia billing. While anesthesia-related data such as intraoperative medication doses and physiologic information were stored in AIMS, surgical data such as surgical times and surgical service were taken from PIMS. General encounter information as well as International Classification of Diseases (ICD) codes were obtained from Casemix and the ADT database. Death dates were gathered from the MISC database. The OMR database contains information regarding preoperative medications, and the CCC database stores for anesthesia billing Current Procedural Terminology (CPT) codes of procedures.
At Partners HealthCare, anesthetic data were retrieved from AIMS, while demographic information and billing codes from the hospital electronic medical records were obtained from Partners' Research Patient Data Registry (RPDR), a centralized clinical data registry built for research purposes. Enterprise Performance Systems Inc. (EPSi), a financial and performance improvement planning system, contains data on admissions to all hospitals within the Partners HealthCare network in Boston and outlying cities.
All patient data from the aforementioned sources were combined into strictly deidentified datasets within the respective hospital network and subsequently appended to arrive at a single combined dataset.

Exclusion criteria

Exclusion criteria comprised age <18 years, American Society of Anesthesiologists (ASA) physical status classification of VI (brain death), or cardiac surgery. Patients undergoing cardiac surgery were excluded due to the common application of extracorporeal circulation corresponding with a unique risk profile for postoperative ischemic stroke.[12] We thus decided not to combine cardiac surgery patients with patients undergoing other types of surgery.

Exposure definition

Measurements of the end-tidal concentrations of sevoflurane, isoflurane, and desflurane were recorded as mean per minute by the anesthetic apparatus and stored in AIMS. Subsequently, minute-by-minute measurements were summarized as median throughout time of exposure to volatile anesthetics. All median doses were then brought to an equivalent minimum alveolar concentration (MAC, minimum alveolar concentration at 1 atmosphere that prevents movement in 50% of patients exposed to surgical incision) at the patient age of 40 years. Finally, each patient's MAC was adjusted for the respective patient age, considering that the MAC differs for

patients at different ages.[13] In the analyses, we examined the incremental effect of intraoperative volatile anesthetics on postoperative ischemic stroke per 1-unit increase in MAC.

Covariate model

Analyses were adjusted for the following covariates: Patient factors included age, sex, body mass index (BMI), as well as comorbidities – the latter including ASA physical status classification, Charlson Comorbidity Index (CCI),[30] betablocker prescription within 28 days prior to surgery, and a patient history of ischemic stroke, patent foramen ovale (PFO) without closure,[15,16] migraine,[17] carotid artery stenosis, transient ischemic attack, chronic kidney disease, peripheral vascular disease, arterial hypertension, atrial fibrillation, valvular heart disease, dyslipidemia, smoking, cancer, and diabetes mellitus. For details on comorbidity definitions, see Table I. Surgical covariates comprised duration of surgery, work relative value units (RVUs, as a proxy for surgical complexity), ASA emergency surgery status, inpatient surgery, and surgical service, while anesthetic factors incorporated intraoperative hypotension (defined as minutes with mean arterial pressure (MAP) below 55 mmHg), use of neuraxial anesthesia, total amount of fluids and packed red blood cell (PRBC) units administered throughout the case, and total doses of short- and long-acting opioids (defined as oral morphine equivalents), non-depolarizing neuromuscular blocking agents (NMBA, expressed as multiples of NMBA dose needed to reduce twitch height by 95% (ED95)), propofol, and intraoperative vasopressors (defined as norepinephrine equivalents).
History of ischemic stroke, transient ischemic attack and patent foramen ovale (without closure) were considered positive if billed within any time prior to surgery. If not further specified, all other comorbidity variables had to be billed within one year before surgery to ensure currentness of covariate data. Variables were categorized in accordance with the linearity assumption: BMI, CCI, and PRBC units were categorized utilizing clinically reasonable cutoff points. Duration of surgery, work RVUs, fluids, intraoperative drug doses, and intraoperative hypotension were categorized into equally sized quintiles, respectively.

Medical record review

Relying on ICD-9/10 billing codes for the definition of postoperative ischemic stroke may result in falsely high or low outcome rates due to coding errors or site-specific coding practices. Thus, a medical record review was conducted in all patients with a positive outcome based on ICD-9/10 billing codes. At both sites, patient charts were studied to confirm or discard the billing-based outcome. Brain scan reports (magnetic resonance imaging or computed tomography), discharge summaries, and neurology consultation notes were considered in this review. The review itself was performed by an interdisciplinary team of research fellows led by a neurologist and an anesthesiologist, using methods that have previously been established and published by our group.[15,16]
While reviewing the patient charts, the neurologic deficit caused by the stroke was measured by assessing the National Institute of Health Stroke Scale (NIHSS),[27] and stroke subtypes were classified according to the Oxfordshire Community Stroke Project (OCSP) classification.[26] In our review, a stroke was determined to be unclassifiable in the OCSP classification whenever a classification as lacunar or total anterior/ partial anterior/ posterior circulation stroke was not possible. This might be the case if the clinical presentation of the respective patient did not meet

the criteria for one distinct location, i.e. if neurology notes did not offer complete data regarding the clinical presentation. Additionally, a stroke could be marked as unclassifiable if radiology notes were missing or remained unclear about the exact vascular categorization according to the OCSP.

Supplemental sensitivity analyses

In addition to those mentioned in the main manuscript, more sensitivity analyses were performed to investigate the observed primary effect:

1) To account for missing follow-up data, a subgroup analysis was performed in patients with medical records available at the respective healthcare network for a minimum of 30 days after surgery.
   According to Tsai et al.,[29] patients living further away from the index hospital, are less likely to be admitted to the same hospital again. Thus, we performed a sensitivity analysis including only patients residing within 20km from Boston.
2) We performed multiple imputation by chained equations to account for potential bias due to missing covariate data, and the primary analysis was repeated in the imputed study cohort.
3) All patients who died within 30 days after surgery were excluded to avoid competing risks regarding the primary outcome.
4) In a separate analysis, all patients undergoing neurosurgery were excluded.
5) Anticoagulant prescription within one month prior to surgery was added to the primary covariate model as additional confounder.
6) To account for repeat surgeries of individual patients within the timeframe of the study cohort, only the first surgery of a patient was considered for analysis.
7) Further sensitivity analyses were performed in subgroups of patients with atrial fibrillation, carotid artery stenosis, and previous ischemic stroke, respectively.
8) As surgical positioning may impact risk of perioperative ischemic stroke, we tested the primary association for an interaction with surgical positioning (beach chair/ sitting position).[44]
9) Finally, we tested the primary association for an interaction with menopause status to give credit to preclinical studies challenging the protective effect of volatile preconditioning in premenopausal mice.[45] Premenopausal status was defined as age <55 years in female patients.[46]

SECONDARY ANALYSES

Transient ischemic attack within 30 days

610 (0.19%) patients had a billing diagnosis of TIA within 30 days after surgery. Higher doses of volatile anesthetics had a significant protective effect on incidence of TIA after surgery (aOR 0.35, 95% CI 0.25 to 0.49, $p<0.001$).

30-Day mortality

Among all patients included, 2232 (0.71%) died within 30 days after surgery. Patients receiving higher doses of volatile anesthetics showed significantly lower rates of all-cause mortality (aOR 0.48, 95% CI 0.41 to 0.56, $p<0.001$).

SUPPLEMENTAL SENSITIVITY ANALYSES

1) Missing follow-up data

Including only 267,237 patients (84.9%) with follow-up data to their respective healthcare network for at least 30 days after surgery, the primary finding was confirmed (aOR 0.50, 95% CI 0.41 to 0.61, p<0.001). The results were also robust among 145,123 patients residing within 20km from Boston (aOR 0.49, 95% CI 0.36 to 0.65, p<0.001).

2) Validation after multiple imputation

Overall, the 61,606 patients excluded for missing data regarding any covariate of our primary model were similar, except for rates of atrial fibrillation (patients with missing data 11.0% vs. patients without missing data 6.9%) and emergency surgery (12.8% vs. 4.5%, respectively). In a separate sensitivity analysis, we excluded patients with diagnosed atrial fibrillation and undergoing emergency surgery (n= 280,488). Conclusions derived from our primary analysis did not change (aOR 0.50, 95% CI 0.40 to 0.63, p<0.001).
We examined the pattern of missingness to assure that data was missing at random (MAR, Table II). For more demographic information on patients with vs. patients without missing data, please see Table III.
BMI was the covariate with the highest proportion of missing values (38,152, 10.1%), followed by work RVUs (17,334, 4.6%) and NMBA dose (14,816, 3.9%). The imputed cohort included all 61,606 (16.4%) cases with initially missing data.
When repeating the primary logistic regression in the imputed cohort (n=376,538), the finding stayed robust (aOR 0.51, 95% CI 0.42 to 0.61, p<0.001).

3) Exclusion of patients who died within 30 days after surgery

2232 patients (0.71%) died within 30 days after surgery. In the remaining cohort of 312,700 patients, results regarding the primary outcome stayed robust (aOR 0.48, 95% CI 0.40 to 0.59, p<0.001).

4) Exclusion of patients undergoing neurosurgery

Excluding all patients undergoing neurosurgery (n= 22,430), the conclusions derived from our primary analysis did not change (aOR 0.52, 95% CI 0.41 to 0.65, p<0.001).

5) Anticoagulant prescription prior to surgery

Additionally confounding for prescription of anticoagulants within 30 days prior to surgery did not significantly influence our findings (aOR 0.49, 95% CI 0.40 to 0.59, p<0.001).

6) Accounting for repeat surgeries

Considering only the first surgery per patient for analysis confirmed the primary finding in a subgroup of 222,329 patients with an ischemic stroke rate of 0.6% (aOR 0.55, 95% CI 0.44 to 0.70, $p<0.001$).

7) Comorbidity status

The dose-dependent protective effect of volatile anesthetics on postoperative ischemic stroke was substantiated in patients with atrial fibrillation (n= 21,755; aOR 0.47, 95% CI 0.30 to 0.72, p= 0.001), patients with carotid artery stenosis (n= 7655; aOR 0.54, 95% CI 0.37 to 0.79, p= 0.002), as well as patients with previous ischemic stroke (n=8996; aOR 0.51, 95% CI 0.39 to 0.65, $p<0.001$), respectively.

8) Surgical positioning

Among 128,752 patients with available information regarding surgical positioning, 5909 patients underwent surgery in either beach chair or sitting position. There was no significant interaction between volatile anesthetic dose and surgical positioning regarding postoperative ischemic stroke (p for interaction= 0.45).

9) Menopause status

92,845 women (29.5% of patients) aged <55 years were identified. There was no significant interaction between volatile anesthetic dose and menopause status regarding our primary outcome (p for interaction= 0.39).

EXPLORATORY ANALYSES

Inclusion of patients undergoing cardiac surgery

Additionally adjusting for intraoperative use of cardiopulmonary bypass, the primary analysis was repeated in an extended cohort including all patients undergoing cardiac surgery that had previously been excluded due to exclusion criteria. Subsequently, we tested the primary effect of volatile anesthetics on ischemic stroke for an interaction with cardiac surgery.
Including all patients undergoing cardiac surgery (final cohort: n= 323,426), we observed an outcome rate of 0.62% (2000 patients). In this cohort, volatile anesthetics were associated with a lower incidence of ischemic stroke (aOR 0.50, 95% CI 0.41 to 0.60, p<0.001). There was no significant interaction between volatile anesthetics and cardiac surgery regarding the primary outcome (p for interaction= 0.78).

Individual volatile agents iso-, sevo-, and desflurane

Among 49,432 patients receiving isoflurane or no volatile anesthetics, higher doses of isoflurane had a significant protective effect on ischemic stroke within 30 days after surgery (aOR 0.56, 95% CI 0.37 to 0.85, p= 0.007). A similar observation was made in the sevoflurane group (n= 223,817; aOR 0.51, 95% CI 0.40 to 0.66, p<0.001). Among 41,007 patients receiving desflurane or no volatile gas, there was no significant effect (aOR 0.80, 95% CI 0.40 to 1.59, p= 0.53), which might have been due to the smaller sample size and less degrees of freedom. When combining the multivariate confounder model into a propensity score and adjusting the logistic regression for the propensity score as a covariate among the same sample of patients, higher doses of desflurane were found to have a significant protective effect on ischemic stroke within 30 days after surgery (aOR 0.29, 95% CI 0.19 to 0.46, p<0.001).

Postoperative anticoagulation

A logistic regression model was built to assess volatile anesthetics for a potential dose-dependent association with postoperative anticoagulation.
81,036 patients (25.7%) received anticoagulants within 30 days after surgery. Patients with higher doses of volatile anesthetics were found to be less likely to receive anticoagulants within 30 days after surgery (aOR 0.95, 95% CI 0.92 to 0.98, p= 0.002).

Data S2. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5; Supplement 1, p. 2
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5, Figure 1
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7; Supplement 1, p. 2-3; Table I
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6; Supplement 1, p. 2-3
Bias	9	Describe any efforts to address potential sources of bias	7-9; Supplement 1, p. 3-4
Study size	10	Explain how the study size was arrived at	5, 11, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Supplement 1, p. 3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-10; Supplement 1, p. 3-4

(*b*) Describe any methods used to examine subgroups and interactions	6-10; Supplement 1, p. 3-4
(*c*) Explain how missing data were addressed	Supplement 1, p. 4, 6, Tables II&III
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
(*e*) Describe any sensitivity analyses	7-9; Supplement 1, p. 3-4

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, Figure 1
		(b) Give reasons for non-participation at each stage	11, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, Table 1; Supplement 1, Table IV
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1; Supplement 1, p. 6, Table II
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11; Supplement 1, Figure I
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, Table 2; Supplement 1, p. 3
		(*b*) Report category boundaries when continuous variables were categorized	Supplement 1, p. 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12, Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-16, Tables 2&3; Supplement 1, p. 5-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S1. Comorbidity and outcome definitions based on International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) codes

Comorbidity	Code type	Code	Description
Arterial hypertension	ICD-9/ICD-10	401.X/I10.X	Essential hypertension
Atrial fibrillation	ICD-9/ICD-10	427.3X/I48.X	Atrial fibrillation and flutter
Carotid artery stenosis	ICD-9/ICD-10	433.1X/I65.2X	Occlusion and stenosis of carotid artery
	ICD-10	I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries
Charlson Comorbidity Index[30]			
Cancer, including leukemia and lymphoma, and metastatic tumor	ICD-9/ICD-10	140.X/C00.X	Malignant neoplasm of lip
	ICD-9/ICD-10	141.X/C01.X	Malignant neoplasm of base of tongue
	ICD-9/ICD-10	141.X/C02.X	Malignant neoplasm of other and unspecified parts of tongue
	ICD-9/ICD-10	143.X/C03.X	Malignant neoplasm of gum
	ICD-9/ICD-10	144.X/C04.X	Malignant neoplasm of floor of mouth
	ICD-10	C05.X	Malignant neoplasm of palate
	ICD-9/ICD-10	145.X/C06.X	Malignant neoplasm of other and unspecified parts of mouth
	ICD-10	C07.X	Malignant neoplasm of parotid gland
	ICD-9/ICD-10	142.X/C08.X	Malignant neoplasm of other and unspecified major salivary glands
	ICD-10	C09.X	Malignant neoplasm of tonsil
	ICD-9/ICD-10	146.X/C10.X	Malignant neoplasm of oropharynx
	ICD-9/ICD-10	147.X/C11.X	Malignant neoplasm of nasopharynx
	ICD-10	C12.X	Malignant neoplasm of pyriform sinus
	ICD-9/ICD-10	148.X/C13.X	Malignant neoplasm of hypopharynx
	ICD-9/ICD-10	149.X/C14.X	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
	ICD-9/ICD-10	150.X/C15.X	Malignant neoplasm of esophagus
	ICD-9/ICD-10	151.X/C16.X	Malignant neoplasm of stomach
	ICD-9/ICD-10	152.X/C17.X	Malignant neoplasm of small intestine
	ICD-9/ICD-10	153.X/C18.X	Malignant neoplasm of colon
	ICD-9/ICD-10	154.X/C19.X	Malignant neoplasm of rectosigmoid junction
	ICD-9/ICD-10	154.X/C20.X	Malignant neoplasm of rectum
	ICD-9/ICD-10	154.X/C21.X	Malignant neoplasm of anus and anal canal
	ICD-9/ICD-10	155.X/C22.X	Malignant neoplasm of liver and intrahepatic bile ducts
	ICD-9/ICD-10	156.X/C23.X	Malignant neoplasm of gallbladder
	ICD-10	C24.X	Malignant neoplasm of other and unspecified parts of biliary tract
	ICD-9/ICD-10	157.X/C25.X	Malignant neoplasm of pancreas
	ICD-9/ICD-10	159.X/C26.X	Malignant neoplasm of other and ill-defined digestive organs
	ICD-9/ICD-10	160.X/C30.X	Malignant neoplasm of nasal cavity and middle ear
	ICD-9/ICD-10	160.X/C31.X	Malignant neoplasm of accessory sinuses
	ICD-9/ICD-10	161.X/C32.X	Malignant neoplasm of larynx
	ICD-9/ICD-10	162.X/C33.X	Malignant neoplasm of trachea
	ICD-9/ICD-10	162.X/C34.X	Malignant neoplasm of bronchus and lung
	ICD-10	C37.X	Malignant neoplasm of thymus

Comorbidity	Code type	Code	Description
	ICD-9/ICD-10	170.X/C41.X	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
	ICD-9/ICD-10	172.X/C43.X	Malignant melanoma of skin
	ICD-10	C45.X	Mesothelioma
	ICD-9/ICD-10	176.X/C46.X	Kaposi's sarkoma
	ICD-10	C47.X	Malignant neoplasm of peripheral nerves and autonomic nervous system
	ICD-9/ICD-10	158.X/C48.X	Malignant neoplasm of retroperitoneum and peritoneum
	ICD-9/ICD-10	171.X/C49.X	Malignant neoplasm of other connective and soft tissue
	ICD-9/ICD-10	174.X, 175.X/C50.X	Malignant neoplasm of breast
	ICD-10	C51.X	Malignant neoplasm of vulva
	ICD-10	C52.X	Malignant neoplasm of vagina
	ICD-9/ICD-10	180.X/C53.X	Malignant neoplasm of cervix uteri
	ICD-9/ICD-10	182.X/C54.X	Malignant neoplasm of corpus uteri
	ICD-9/ICD-10	179.X/C55.X	Malignant neoplasm of uterus, part unspecified
	ICD-9/ICD-10	183.X/C56.X	Malignant neoplasm of ovary
	ICD-9/ICD-10	184.X/C57.X	Malignant neoplasm of other and unspecified female genital organs
	ICD-9/ICD-10	181.X/C58.X	Malignant neoplasm of placenta
	ICD-9/ICD-10	187.X/C60.X	Malignant neoplasm of penis
	ICD-9/ICD-10	185.X/C61.X	Malignant neoplasm of prostate
	ICD-9/ICD-10	186.X/C62.X	Malignant neoplasm of testis
	ICD-9/ICD-10	187.X/C63.X	Malignant neoplasm of other and unspecified male genital organs
	ICD-9/ICD-10	189.X/C64.X	Malignant neoplasm of kidney, except renal pelvis
	ICD-10	C65.X	Malignant neoplasm of renal pelvis
	ICD-10	C66.X	Malignant neoplasm of ureter
	ICD-9/ICD-10	188.X/C67.X	Malignant neoplasm of bladder
	ICD-10	C68.X	Malignant neoplasm of other and unspecified urinary organs
	ICD-9/ICD-10	190.X/C69.X	Malignant neoplasm of eye and adnexa
	ICD-10	C70.X	Malignant neoplasm of meninges
	ICD-9/ICD-10	191.X/C71.X	Malignant neoplasm of brain
	ICD-9/ICD-10	192.X/C72.X	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
	ICD-9/ICD-10	193.X/C73.X	Malignant neoplasm of thyroid gland
	ICD-10	C74.X	Malignant neoplasm of adrenal gland
	ICD-9/ICD-10	194.X/C75.X	Malignant neoplasm of other endocrine glands and related structures
	ICD-9/ICD-10	195.X/C76.X	Malignant neoplasm of other and ill-defined sites
	ICD-9/ICD-10	201.X/C81.X	Hodgkin lymphoma
	ICD-10	C82.X	Follicular lymphoma
	ICD-10	C83.X	Non-follicular lymphoma
	ICD-10	C84.X	Mature T/NK-cell lymphomas
	ICD-10	C85.X	Other specified and unspecified types of non-Hodgkin lymphoma
	ICD-10	C88.X	Malignant immunoproliferative diseases and certain other B-cell lymphomas
	ICD-9/ICD-10	203.X/C90.X	Multiple myeloma and malignant plasma cell neoplasms
	ICD-9/ICD-10	204.X/C91.X	Lymphoid leukemia
	ICD-9/ICD-10	205.X/C92.X	Myeloid leukemia
	ICD-9/ICD-10	206.X/C93.X	Monocytic leukemia
	ICD-9/ICD-10	207.X/C94.X	Other leukemias of specified cell type
	ICD-9/ICD-10	208.X/C95.X	Leukemias of unspecified cell type

Comorbidity	Code type	Code	Description
	ICD-10	C96.X	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
	ICD-10	C97.X	Malignant neoplasms of independent (primary) multiple sites
	ICD-9	238.6	Neoplasm of uncertain behavior of plasma cells
	ICD-9	200.X	Lymphosarcoma and reticulosarcoma
	ICD-9	202.X	Other malignant neoplasms of lymphoid and histiocytic tissue
	ICD-9	164.X	Malignant neoplasm of thymus, heart, and mediastinum
	ICD-9	163.X	Malignant neoplasm of pleura
	ICD-9	165.X	Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
	ICD-9/ICD-10	196.X/C77.X	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
	ICD-9/ICD-10	197.X/C78.X	Secondary malignant neoplasm of respiratory and digestive organs
	ICD-9/ICD-10	198.X/C79.X	Secondary malignant neoplasm of other and unspecified sites
	ICD-9/ICD-10	199.X/C80.X	Disseminated malignant neoplasm, unspecified
Cerebral vascular disease	ICD-9/ICD-10	435.X/G45.X	TIA and related syndromes
	ICD-10	G46.X	Vascular syndromes of brain in cerebrovascular diseases
	ICD-9/ICD-10	362.34/H34.0X	Transient retinal artery occlusion
	ICD-9/ICD-10	430/I60.X	Nontraumatic subarachnoid hemorrhage
	ICD-9/ICD-10	431/I61.X	Nontraumatic intracerebral hemorrhage
	ICD-9/ICD-10	432.X/I62.X	Other and unspecified nontraumatic intracranial hemorrhage
	ICD-10	I63.X	Cerebral infarction
	ICD-10	I64.X	Stroke, not specified as infarction or bleeding
	ICD-9/ICD-10	433.X/I65.X	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
	ICD-9/ICD-10	434.X/I66.X	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
	ICD-9/ICD-10	437.X/I67.X	Other cerebrovascular diseases
	ICD-10	I68.X	Cerebrovascular disorders in diseases classified elsewhere
	ICD-9/ICD-10	438.X/I69.X	Sequelae of cerebrovascular disease
	ICD-9	436.X	Acute but ill-defined cerebrovascular disease
Chronic pulmonary disease	ICD-9/ICD-10	416.8/I27.8X	Other pulmonary heart disease (excluding Eisenmenger defect)
	ICD-9/ICD-10	416.9/I27.9X	Pulmonary heart disease, unspecified
	ICD-9/ICD-10	490/J40.X	Bronchitis, not specified as acute or chronic
	ICD-9/ICD-10	491.X/J41.X	Simple and mucopurulent chronic bronchitis
	ICD-9/ICD-10	491.X/J42.X	Unspecified chronic bronchitis
	ICD-9/ICD-10	492.X/J43.X	Emphysema
	ICD-9/ICD-10	496.X/J44.X	Other chronic obstructive pulmonary disease
	ICD-9/ICD-10	493.X/J45.X	Asthma
	ICD-10	J46.X	Status asthmaticus
	ICD-9/ICD-10	494.X/J47.X	Bronchiectasis
	ICD-9/ICD-10	500.X/J60.X	Coalworker's pneumoconiosis
	ICD-9/ICD-10	501.X/J61.X	Pneumoconiosis due to asbestos and other mineral fibers
	ICD-9/ICD-10	502.X/J62.X	Pneumoconiosis due to dust containing silica
	ICD-9/ICD-10	503.X/J63.X	Pneumoconiosis due to other inorganic dusts
	ICD-9/ICD-10	505.X/J64.X	Unspecified pneumoconiosis
	ICD-10	J65.X	Pneumoconiosis associated with tuberculosis
	ICD-10	J66.X	Airway disease due to specific organic dust (e.g. Byssinosis, cannabinosis)

Comorbidity	Code type	Code	Description
	ICD-9/ICD-10	495.X/J67.X	Allergic alveolitis/hypersensitivity pneumonitis due to organic dust (e.g. Farmer's lung, bagassosis)
	ICD-9/ICD-10	506.4/J68.4X	Chronic respiratory conditions due to chemicals, gases, fumes and vapors
	ICD-9/ICD-10	508.1/J70.1X	Chronic and other pulmonary manifestations due to radiation
	ICD-10	J70.3X	Chronic drug-induced interstitial lung disorders
	ICD-9	508.8	Respiratory conditions due to other specified external agents
	ICD-9	504.X	Pneumonopathy due to inhalation of other dust
Congestive heart failure	ICD-9/ICD-10	398.91/I09.9X	Rheumatic heart disease, unspecified
	ICD-9/ICD-10	402.01,402.11,402.91/I11.0X	Hypertensive heart disease with heart failure
	ICD-9/ICD-10	404.01,404.11,404.91/I13.0X	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
	ICD-9/ICD-10	404.03,404.13,404.93/I13.2X	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
	ICD-10	I25.5X	Ischemic cardiomyopathy
	ICD-10	I42.0X	Dilated cardiomyopathy
	ICD-10	I42.5X	Other restrictive cardiomyopathy
	ICD-9/ICD-10	425.5/I42.6X	Alcoholic cardiomyopathy
	ICD-10	I42.7X	Cardiomyopathy due to drug and external agent
	ICD-9/ICD-10	425.4/I42.8X	Other cardiomyopathies
	ICD-9	425.7	Nutritional and metabolic cardiomyopathy
	ICD-9/ICD-10	425.9/I42.9X	Cardiomyopathy, unspecified
	ICD-9/ICD-10	425.8/I43.X	Cardiomyopathy in diseases classified elsewhere
	ICD-9/ICD-10	428.X/I50.X	Heart failure (LV/systolic/diastolic/combined/etc)
	ICD-10	P29.0X	Neonatal cardiac failure
Dementia	ICD-10	F00.X	Dementia in Alzheimer's disease
	ICD-10	F01.X	Vascular dementia
	ICD-9/ICD-10	294.1/F02.X	Dementia in diseases classified elsewhere
	ICD-10	F03.X	Dementia, unspecified
	ICD-10	F05.1X	Delirium in dementia
	ICD-10	G30.X	Alzheimer's disease
	ICD-10	G31.3X	Other degenerative diseases of the nervous system, unspecified
	ICD-9	290.X	Senile and presenile organic psychotic conditions
	ICD-9/ICD-10	331.2/G31.1	Senile degeneration of brain, not elsewhere classified
Diabetes mellitus with and without chronic complications	ICD-10	E10.0X	Type 1 DM
	ICD-10	E10.1X	Type 1 DM with ketoacidosis
	ICD-10	E10.6X	Type 1 DM with other specified complications
	ICD-10	E10.8X	Type 1 DM with unspecified complications
	ICD-10	E10.9X	Type 1 DM without complications
	ICD-10	E11.0X	Type 2 DM with hyperosmolarity
	ICD-10	E11.1X	Type 2 DM with hyperosmolarity with coma
	ICD-10	E11.6X	Type 2 DM with other specified complications
	ICD-10	E11.8X	Type 2 DM with unspecified complications
	ICD-10	E11.9X	Type 2 DM without complications
	ICD-10	E12.0X	DM associated with malnutrition
	ICD-10	E12.1X	DM associated with malnutrition with coma
	ICD-10	E12.6X	DM associated with malnutrition with other specified complications
	ICD-10	E12.8X	DM associated with malnutrition with unspecified complications

Comorbidity	Code type	Code	Description
	ICD-10	E12.9X	DM associated with malnutrition without complications
	ICD-10	E13.0X	Other specified DM with hyperosmolarity
	ICD-10	E13.1X	Other specified DM with ketoacidosis
	ICD-10	E13.6X	Other specified DM with other specified complications
	ICD-10	E13.8X	Other specified DM with unspecified complications
	ICD-10	E13.9X	Other specified DM without complications
	ICD-10	E14.0X	DM, not elsewhere classified, with coma
	ICD-10	E14.1X	DM, not elsewhere classified, with ketoacidosis
	ICD-9/ICD-10	250.8/E14.6X	Unspecified DM with other specified complications
	ICD-9/ICD-10	250.9/E14.8X	Unspecified DM with other specified complications
	ICD-10	E14.9X	DM, not elsewhere classified, without complications
	ICD-9	250.1	DM with ketoacidosis
	ICD-9	250.0	DM without complications
	ICD-9	250.2	DM with hyperosmolarity
	ICD-9	250.3	DM with other coma
	ICD-10	E10.2X	Type 1 DM with kidney complications
	ICD-10	E10.3X	Type 1 DM with ophthalmic complications
	ICD-10	E10.4X	Type 1 DM with neurological complications
	ICD-10	E10.5X	Type 1 DM with circulatory complications
	ICD-10	E10.7X	Type 1 DM with multiple complications
	ICD-10	E11.2X	Type 2 DM with kidney complications
	ICD-10	E11.3X	Type 2 DM with ophthalmic complications
	ICD-10	E11.4X	Type 2 DM with neurological complications
	ICD-10	E11.5X	Type 2 DM with circulatory complications
	ICD-10	E11.7X	Type 2 DM with multiple complications
	ICD-10	E12.2X	DM associated with malnutrition with renal complications
	ICD-10	E12.3X	DM associated with malnutrition with ophthalmic complications
	ICD-10	E12.4X	DM associated with malnutrition with neurological complications
	ICD-10	E12.5X	DM associated with malnutrition with peripheral vascular complications
	ICD-10	E12.7X	DM associated with malnutrition with multiple complications
	ICD-10	E13.2X	Other specified DM with kidney complications
	ICD-10	E13.3X	Other specified DM with ophthalmic complications
	ICD-10	E13.4X	Other specified DM with neurological complications
	ICD-10	E13.5X	Other specified DM with circulatory complications
	ICD-10	E13.7X	Other specified DM with multiple complications
	ICD-10	E14.2X	DM, not elsewhere specified, with renal complications
	ICD-10	E14.3X	DM, not elsewhere specified, with ophthalmic complications
	ICD-10	E14.4X	DM, not elsewhere specified, with neurological complications
	ICD-10	E14.5X	DM, not elsewhere specified, with peripheral vascular complications
	ICD-10	E14.7X	DM, not elsewhere specified, with multiple complications
	ICD-9	250.4	Diabetes with renal complications
	ICD-9	250.5	Diabetes with ophthalmic complications
	ICD-9	250.6	Diabetes with neurological complications
	ICD-9	250.7	Diabetes with peripheral circulatory disorders
Hemi- and paraplegia	ICD-10	G04.1X	Tropical spastic paraplegia
	ICD-10	G11.4X	Hereditary spastic paraplegia
	ICD-10	G80.1X	Spastic diplegic cerebral palsy
	ICD-10	G80.2X	Spastic hemiplegic cerebral palsy
	ICD-10	G81.X	Flaccid hemiplegia
	ICD-9/ICD-10	344.0X/G82.X	Paraplegia (paraparesis) and quadriplegia (quadriparesis)
	ICD-9/ICD-10	344.2X/G83.0X	Diplegia of upper limbs

Comorbidity	Code type	Code	Description
	ICD-9/ICD-10	344.3X/G83.1X	Monoplegia of lower limb
	ICD-9/ICD-10	344.4X/G83.2X	Monoplegia of upper limb
	ICD-9/ICD-10	344.5X/G83.3X	Monoplegia, unspecified
	ICD-9/ICD-10	344.6X/G83.4X	Cauda equina syndrome
	ICD-9/ICD-10	344.9/G83.9X	Paralytic syndrome, unspecified
	ICD-9	344.1	Paraplegia, unspecified
	ICD-9	342.X	Hemiplegia, hemiparesis
	ICD-9	343.X	Infantile cerebral palsy
HIV	ICD-9/ICD-10	042.X/B20.X	HIV disease resulting in infectious and parasitic disease
	ICD-9/ICD-10	042.X/B21.X	HIV disease resulting in malignant neoplasms
	ICD-9/ICD-10	043.X/B22.X	HIV disease resulting in other specified diseases
	ICD-9/ICD-10	044.X/B24.X	Unspecified HIV disease
Liver disease	ICD-10	B18.X	Chronic viral hepatitis
	ICD-9/ICD-10	571.0/K70.0X	Alcoholic fatty liver
	ICD-10	K70.2X	Alcoholic fibrosis and sclerosis of liver
	ICD-9/ICD-10	571.2/K70.3X	Alcoholic cirrhosis of liver
	ICD-10	K70.9X	Alcoholic liver disease, unspecified
	ICD-10	K71.3X	Toxic liver disease with chronic persistent hepatitis
	ICD-10	K71.4X	Toxic liver disease with chronic lobular hepatitis
	ICD-10	K71.5X	Toxic liver disease with chronic active hepatitis
	ICD-10	K71.7X	Toxic liver disease with fibrosis and cirrhosis of liver
	ICD-9/ICD-10	571.4/K73.X	Chronic hepatitis, not elsewhere classified
	ICD-9/ICD-10	571.5/K74.X	Fibrosis and cirrhosis of liver
	ICD-10	K76.0X	Fatty (change of) liver, not elsewhere classified
	ICD-9/ICD-10	570.X/K76.2X	Central hemorrhagic necrosis of liver
	ICD-9/ICD-10	573.4/K76.3X	Infarction of liver
	ICD-10	K76.4X	Peliosis hepatis
	ICD-9/ICD-10	573.8/K76.8X	Other specified diseases of liver
	ICD-9/ICD-10	573.9, 571.9/K76.9X	Liver disease, unspecified
	ICD-9/ICD-10	V42.7/Z94.4X	Liver transplant status
	ICD-9	070.22	Chronic viral hepatitis B with hepatic coma without hepatitis delta
	ICD-9	070.23	Chronic viral hepatitis B with hepatic coma with hepatitis delta
	ICD-9	070.32	Chronic viral hepatitis B without delta-agent
	ICD-9	070.33	Chronic viral hepatitis B with delta-agent
	ICD-9	070.44	Chronic viral hepatitis C with hepatic coma
	ICD-9	070.54	Chronic viral hepatitis C without hepatic coma
	ICD-9	070.6	Unspecified viral hepatitis with hepatic coma
	ICD-9	070.9	Unspecified viral hepatitis without mention of hepatic coma
	ICD-9	573.3	Hepatitis, unspecified
	ICD-9	571.6	Primary biliary cirrhosis
	ICD-9	572.x	Liver abscess and sequelae of chronic liver disease
	ICD-9/ICD-10	456.0/I85.0	Esophageal varices with bleeding
	ICD-9/ICD-10	456.1/I85.9	Esophageal varices without mention of bleeding
	ICD-9/ICD-10	456.2/I98.2	Esophageal varices in diseases classified elsewhere
	ICD-10	I86.4	Gastric varices
	ICD-10	K70.4	Alcoholic hepatic failure
	ICD-10	K71.1	Toxic liver disease with hepatic necrosis
	ICD-10	K72.1	Chronic hepatic failure
	ICD-10	K72.9	Hepatic failure, unspecified
	ICD-10	K76.5	Hepatic veno-occlusive disease
	ICD-10	K76.6	Portal hypertension
	ICD-10	K76.7	Hepatorenal syndrome
	ICD-9/ICD-10	410.X/I21.X	Acute myocardial infarction

Comorbidity	Code type	Code	Description
Myocardial infarction	ICD-10	I22.X	Recurring myocardial infarction
	ICD-9/ICD-10	412.X/I25.2X	Old/healed myocardial infarction
Peptic ulcer disease	ICD-9/ICD-10	531.X/K25.X	Acute gastric ulcer with hemorrhage
	ICD-9/ICD-10	532.X/K26.X	Acute duodenal ulcer with hemorrhage
	ICD-9/ICD-10	533.X/K27.X	Acute peptic ulcer, site unspecified, with hemorrhage
	ICD-9/ICD-10	534.X/K28.X	Acute gastrojejunal ulcer with hemorrhage
Peripheral vascular disease	ICD-9/ICD-10	440.X/I70.X	Atherosclerosis
	ICD-9/ICD-10	441.X/I71.X	Aortic aneurysm and dissection
	ICD-9/ICD-10	443.1/I73.1	Thromboangiitis obliterans (Buerger's disease)
	ICD-9/ICD-10	443.8X/I73.8X	Other specified peripheral vascular diseases
	ICD-9/ICD-10	443.9/I73.9	Peripheral vascular disease, unspecified
	ICD-9/ICD-10	447.1/I77.1	Stricture of artery
	ICD-10	I79.0X	Aneurysm of aorta in diseases classified elsewhere
	ICD-10	I79.2X	Peripheral angiopathy
	ICD-9/ICD-10	557.1/K55.1X	Chronic vascular disorders of intestine
	ICD-10	K55.8X	Other vascular disorders of intestine
	ICD-9/ICD-10	557.9/K55.9X	Vascular disorders of intestine, unspecified
	ICD-9/ICD-10	V43.4/Z95.8X	Presence of other cardiac and vascular implants and grafts
	ICD-10	Z95.9X	Presence of cardiac and vascular implant and graft, unspecified
	ICD-9	442.X	Other aneurysm
	ICD-9	443.2X	Other arterial dissection
Renal disease	ICD-9/ICD-10	403.01,403.11,403.91/I12.0X	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease
	ICD-9/ICD-10	404.02,404.12,404.92/I13.1X	Hypertensive heart and chronic kidney disease without heart failure
	ICD-10	N03.2X	Chronic nephritic syndrome with diffuse membranous glomerulonephritis
	ICD-10	N03.3X	Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
	ICD-10	N03.4X	Chronic nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis
	ICD-10	N03.5X	Chronic nephritic syndrome with diffuse mesangiocapillary glomerulonephritis
	ICD-10	N03.6X	Chronic nephritic syndrome with dense deposit disease
	ICD-10	N03.7X	Chronic nephritic syndrome with diffuse crescentic glomerulonephritis
	ICD-10	N05.2X	Unspecified nephritic syndrome with diffuse membranous glomerulonephritis
	ICD-10	N05.3X	Unspecified nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
	ICD-10	N05.4X	Unspecified nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis
	ICD-10	N05.6X	Unspecified nephritic syndrome with dense deposit disease
	ICD-10	N05.7X	Unspecified nephritic syndrome with diffuse crescentic glomerulonephritis
	ICD-10	N18.X	Chronic kidney disease
	ICD-9/ICD-10	586.X/N19.X	Unspecified kidney failure
	ICD-9/ICD-10	588.X/N25.0X	Disorders resulting from impaired renal tubular function
	ICD-9/ICD-10	V56.X/Z49.0X	Encounter for care involving renal dialysis
	ICD-10	Z49.1X	Extracorporal hemodialysis
	ICD-10	Z49.2X	Other hemodialysis
	ICD-9/ICD-10	V42.0/Z94.0X	Kidney transplant status
	ICD-10	Z99.2X	Dependence on renal dialysis
	ICD-9	V45.1	Postsurgical renal dialysis status

Comorbidity	Code type	Code	Description
	ICD-9	404.03,404.13,404.93	Hypertensive heart and chronic kidney disease with heart failure
	ICD-9	582.X	Chronic glomerulonephritis
	ICD-9	583.0-583.7	Nephritis and nephropathy
	ICD-9	585.X	Chronic kidney failure
Rheumatic disease	ICD-9/ICD-10	714.0, 714.1/M05.X	Rheumatoid arthritis with rheumatoid factor
	ICD-10	M06.X	Other rheumatoid arthritis
	ICD-10	M31.5X	Giant cell arteritis with polymyalgia rheumatica
	ICD-9/ICD-10	710.0/M32.X	Systemic lupus erythematodes
	ICD-9/ICD-10	710.3/M33.X	Dermatopolymyositis
	ICD-9/ICD-10	710.1/M34.X	Systemic sclerosis
	ICD-10	M35.1	Other overlap syndromes
	ICD-9/ICD-10	725.X/M35.3X	Polymyalgia rheumatica
	ICD-10	M36.0X	Dermato(poly)myositis in neoplastic disease
	ICD-9	446.5	Giant cell arteritis (temporal arteritis)
	ICD-9	714.8	Other specified inflammatory polyarthropathies
	ICD-9	710.2	Sicca syndrome
Chronic kidney disease	ICD-9/ICD-10	585.X/N18.X	Chronic kidney disease
	ICD-9/ICD-10	586.X/N19.X	Renal failure, unspecified
Dyslipidemia	ICD-9	272.X	Dyslipidemia
	ICD-10	E78.X	Disorders of lipoprotein metabolism and other lipidemias
Ischemic stroke	ICD-9/ICD-10	433.X1/I63.X	Occlusion and stenosis of precerebral arteries with cerebral infarction
	ICD-9	434.X1	Occlusion of cerebral arteries with cerebral infarction
	ICD-9/ICD-10	437.1/I67.81, I67.89	Other generalized ischemic cerebrovascular disease
	ICD-9/ICD-10	437.9/I67.9	Unspecified cerebrovascular disease
Migraine	ICD-9/ICD-10	346.X/G43.X	Migraine
Patent foramen ovale	ICD-9/ICD-10	745.5/Q21.1	Atrial septal defect
Atrial septal defect closure	ICD-9	35.51	Repair of atrial septal defect with prosthesis, open technique
	ICD-9	35.52	Repair of atrial septal defect with prosthesis, closed technique
	ICD-9	35.61	Repair of atrial septal defect with tissue graft
	ICD-9	35.71	Other and unspecified repair of atrial septal defect
	CPT	33641	Repair atrial septal defect, secundum, with cardiopulmonary bypass, with or without patch
	CPT	33647	Repair of atrial septal defect and ventricular septal defect, with direct or patch closure
	CPT	33660	Repair of incomplete or partial atrioventricular canal (ostium primum atrial septal defect), with or without atrioventricular valve repair
	CPT	93580	Percutaneous transcatheter closure of congenital interatrial communication (i.e., Fontan fenestration, atrial septal defect) with implant
Peripheral vascular disease	ICD-9/ICD-10	440.2, I70.2	Peripheral arterial disease
	ICD-9/ICD-10	440.3, I70.3, I70.5, I70.6, I70.7	Atherosclerosis of bypass graft of the extremities
	ICD-9/ICD-10	440.4, I70.92	Chronic total occlusion of artery of the extremities
	ICD-9	443.9	Peripheral vascular disease, unspecified
Smoking	ICD-9/ICD-10	305.1/ F17.X	Nicotine dependence
	ICD-9/ICD-10	V15.82/ Z87.891	Personal history of nicotine dependence
	ICD-9	435.X	Transient ischemic attack

Comorbidity	Code type	Code	Description
Transient ischemic attack	ICD-10	G45.0	Vertebro-basilar artery syndrome
	ICD-10	G45.1	Carotid artery syndrome (hemispheric)
	ICD-10	G45.8	Other transient cerebral ischemic attacks and related syndromes
Valvular heart disease	ICD-9/ICD-10	394.X/I05.X	Rheumatic mitral valve disease
	ICD-9/ICD-10	395.X/I06.X	Rheumatic aortic valve disease
	ICD-9/ICD-10	397.X/I07.X	Rheumatic tricuspid valve disease
	ICD-9/ICD-10	396.X/I08.X	Multiple valve disease
	ICD-9/ICD-10	424.0/I34.X	Nonrheumatic mitral valve disorders
	ICD-9/ICD-10	424.1/I35.X	Nonrheumatic aortic valve disorders
	ICD-9/ICD-10	424.2/I36.X	Nonrheumatic tricuspid valve disorders
	ICD-9/ICD-10	424.3/I37.X	Nonrheumatic pulmonary valve disorders

ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; CPT, Current Procedural Terminology.

Table S2. Distribution and patterns of missing data before multiple imputation

	Pattern*										
Cases	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**# missing**
84%	1	1	1	1	1	1	1	1	1	1	318,769
6%	1	1	1	1	1	1	1	1	1	0	21,814
4%	1	1	1	1	1	1	1	1	0	1	15,147
3%	1	1	1	1	1	1	1	0	1	0	10,945
1%	1	1	1	1	1	1	0	1	1	1	3837
<1%	1	1	1	1	1	0	1	0	1	0	2274
<1%	1	1	1	0	1	1	1	1	1	1	1781
<1%	1	1	1	1	0	1	1	1	1	1	1443
<1%	1	1	1	1	1	1	1	1	0	0	902
<1%	1	1	1	1	1	1	1	0	0	0	777
<1%	1	1	1	1	0	1	1	1	1	0	614
<1%	1	1	0	1	1	1	1	1	1	1	478
<1%	1	1	1	1	0	1	1	0	1	0	300
<1%	1	1	1	1	1	0	1	0	1	1	211
<1%	1	1	1	1	1	1	0	1	0	1	204
<1%	1	1	1	1	1	1	0	1	1	0	130
<1%	1	1	1	0	1	0	1	0	1	0	128
<1%	1	1	1	1	0	1	1	1	0	1	126
<1%	1	1	1	0	1	1	1	1	1	0	121
<1%	1	0	1	0	1	1	1	1	0	1	101

Table S2 displays the 20 most common distributions of missing data. Data was extracted using *misstable pattern* command on Stata. 1 displays complete information regarding the respective variable, while 0 represents missing information.

* Missing variable with corresponding numbers:

1 Intraoperative hypotension
2 ASA emergency surgery status
3 Surgical service
4 ASA physical status classification
5 Duration of surgery
6 Intraoperative vasopressor dose
7 Inpatient surgery
8 NMBA dose
9 Work RVUs
10 BMI

ASA, American Society of Anesthesiologists; NMBA, neuromuscular blocking agent; RVUs, relative value units; BMI, body mass index.

Table S3. Characteristics of patients by missing data status

Characteristics	No missing data (n= 314,932)	Missing data (n= 61,606)
Ischemic stroke within 30 postoperative days	1957 (0.6%)	561 (0.9%)
Demographics		
Age, years	53.8 ± 16.5	55.1 ± 17.5
Sex, male	138,756 (44.1%)	30,252 (49.1%)
Body Mass Index, kg/m^2	28.4 ± 6.9	27.9 ± 6.7
*Comorbidities**		
Arterial Hypertension	126,779 (40.3%)	26,429 (42.9%)
Atrial Fibrillation	21,755 (6.9%)	6777 (11.0%)
Carotid Stenosis	7655 (2.4%)	1520 (2.5%)
Chronic Kidney Disease	20,539 (6.5%)	6124 (9.9%)
Diabetes	46,181 (14.7%)	12,038 (19.5%)
Dyslipidemia	97,688 (31.0%)	18,800 (30.5%)
Ischemic Stroke	8996 (2.9%)	2555 (4.1%)
Malignancy	92,690 (29.4%)	15,229 (24.7%)
Migraine	11,460 (3.6%)	1515 (2.5%)
Patent Foramen Ovale without Closure	2902 (0.9%)	610 (1.0%)
Peripheral Vascular Disease	12,525 (4.0%)	4284 (7.0%)
Smoking	52,485 (16.7%)	9217 (15.0%)
Transient Ischemic Attack	5090 (1.6%)	1257 (2.0%)
Valvular Heart Disease	27,411 (8.7%)	6803 (11.0%)
Betablocker Prescription within 28 Days Prior	45,438 (14.4%)	7327 (11.9%)
Charlson Comorbidity Index[30]	1 (0, 3)	1 (0, 3)
ASA† Physical Status	2 (2, 3)	2 (2, 3)
Surgical Factors		
Emergency Surgery	14,176 (4.5%)	7852 (12.8%)
Inpatient Surgery	201,819 (64.1%)	39,579 (64.2%)
Duration of Surgery, minutes	155 ± 108	144 ± 111
Work Relative Value Units	14.7 ± 9.9	13.6 ± 9.8
Surgical Service		
Burn	1998 (0.6%)	297 /0.5%)
Emergent-Urgent	10,885 (3.5%)	2960 (4.9%)
General	57,859 (18.4%)	8542 (14.0%)
Gynecology/ Obstetrics	31,233 (9.9%)	4041 (6.6%)
Neurosurgery	22,430 (7.1%)	3838 (6.3%)
Oral/ Maxillofacial	3304 (1.1%)	562 (0.9%)
Orthopedic	72,780 (23.1%)	12,366 (20.3%)

Characteristics	No missing data (n= 314,932)	Missing data (n= 61,606)
Other (Dermatology, etc.)	4521 (1.4%)	1095 (1.8%)
Otolaryngology	8817 (2.8%)	1099 (1.8%)
Plastic	18,735 (6.0%)	4870 (8.0%)
Radiology	1799 (0.6%)	374 (0.6%)
Surgical Oncology	15,022 (4.8%)	686 (1.1%)
Thoracic	20,084 (6.4%)	4934 (8.1%)
Transplant	5727 (1.8%)	1928 (3.2%)
Urology	22,235 (7.1%)	7913 (13.0%)
Vascular	10,812 (3.4%)	4210 (6.9%)
Anesthetic Factors		
Use of Volatile Anesthetic	298,505 (94.8%)	58,067 (94.3%)
MAC† of Volatile Anesthetic	0.72 ± 0.35	0.69 ± 0.35
MAC† of Nitrous Oxide	0.06 (0, 0.40)	0.03 (0, 0.40)
Total Opioid Dose (Oral Morphine Equivalents)	51.0 (31.3, 79.5)	50.0 (25.0, 77.5)
Total Propofol Dose, mg	200 (150, 260)	200 (140, 250)
Total Neuromuscular Blocking Agent ED95† Dose	1.87 (0, 3.08)	1.28 (0, 2.82)
Total Vasopressor Dose, mg (Norepinephrine Equivalents)	0.01 (0, 0.11)	0 (0, 0.09)
Total Fluid Volume Administered, ml	2000 (1000, 3000)	2000 (1250, 3400)
Administration of Packed Red Blood Cells	9259 (2.9%)	4163 (6.8%)
Neuraxial Anesthesia	10,336 (3.3%)	977 (1.6%)
Minutes with MAP† <55 mmHg	0 (0, 2)	0 (0, 3)

* For comorbidity definitions, refer to Table S1.
† ASA, American Society of Anesthesiologists; MAC, minimum alveolar concentration; ED95, median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; MAP, mean arterial pressure.
Values provided as frequency (prevalence in %), mean ± SD, or median [IQR (25th-75th percentile), values separated by comma].

Table S4. P-values for all covariates in the primary analysis

Characteristics	p
Demographics	
Age, years	0.69
Sex, female	0.066
Body Mass Index, kg/m^2	
18.5-24.9	0.052
25-29.9	0.098
30-34.9	0.024
>35	0.67
*Comorbidities**	
Arterial Hypertension	0.64
Atrial Fibrillation	0.41
Carotid Stenosis	<0.001
Chronic Kidney Disease	<0.001
Diabetes	0.003
Dyslipidemia	0.029
Ischemic Stroke	<0.001
Malignancy	<0.001
Migraine	0.49
Patent Foramen Ovale without Closure	0.012
Peripheral Vascular Disease	<0.001
Smoking	0.002
Transient Ischemic Attack	0.13
Valvular Heart Disease	<0.001
Betablocker Prescription within 28 Days Prior	<0.001
Charlson Comorbidity Index[30]	
1-2	<0.001
3	<0.001
4-7	<0.001
8-19	<0.001
20-26	0.29
ASA† Physical Status	0.008
Surgical Factors	
Emergency Surgery	<0.001
Inpatient Surgery	<0.001
Duration of Surgery, minutes	
Quintile 2	0.97
Quintile 3	0.34
Quintile 4	0.054
Quintile 5	0.74

Characteristics	**p**
Work Relative Value Units	
Quintile 2	0.001
Quintile 3	<0.001
Quintile 4	0.60
Quintile 5	0.59
Surgical Service	
Burn	0.008
Emergent-Urgent	<0.001
General	<0.001
Gynecology/ Obstetrics	<0.001
Neurosurgery	<0.001
Oral/ Maxillofacial	0.006
Orthopedic	<0.001
Other (Dermatology, etc.)	<0.001
Otolaryngology	<0.001
Plastic	<0.001
Radiology	0.059
Surgical Oncology	<0.001
Thoracic	<0.001
Transplant	<0.001
Urology	<0.001
Vascular	<0.001
Anesthetic Factors	
MAC† of Nitrous Oxide	
Quintile 2	0.001
Quintile 3	0.013
Quintile 4	0.040
Quintile 5	0.17
Total Opioid Dose (Oral Morphine Equivalents)	
Quintile 2	0.45
Quintile 3	0.17
Quintile 4	0.011
Quintile 5	0.55
Total Propofol Dose, mg	
Quintile 2	0.62
Quintile 3‡	-
Quintile 4	0.47
Quintile 5	0.33
Total Neuromuscular Blocking Agent ED95† Dose	
Quintile 2	0.11
Quintile 3	<0.001

Characteristics	p
Quintile 4	<0.001
Quintile 5	<0.001
Total Vasopressor Dose, mg (Norepinephrine Equivalents)	
Quintile 2	0.82
Quintile 3	0.008
Quintile 4	0.002
Quintile 5	<0.001
Total Fluid Volume Administered, ml	
Quintile 2	0.034
Quintile 3	<0.001
Quintile 4	<0.001
Quintile 5	<0.001
Administration of Packed Red Blood Cells	
>0	0.007
>1	0.48
>2	0.034
Neuraxial Anesthesia	0.46
Minutes with MAP† <55 mmHg	
Quintile 2‡	-
Quintile 3	0.62
Quintile 4	0.024
Quintile 5	0.23

***** For comorbidity definitions, refer to Table S1.
† ASA, American Society of Anesthesiologists; MAC, minimum alveolar concentration; ED95, median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; MAP, mean arterial pressure.
‡ No observations were made within this quintile.

Lowest categories were used as reference level, respectively.

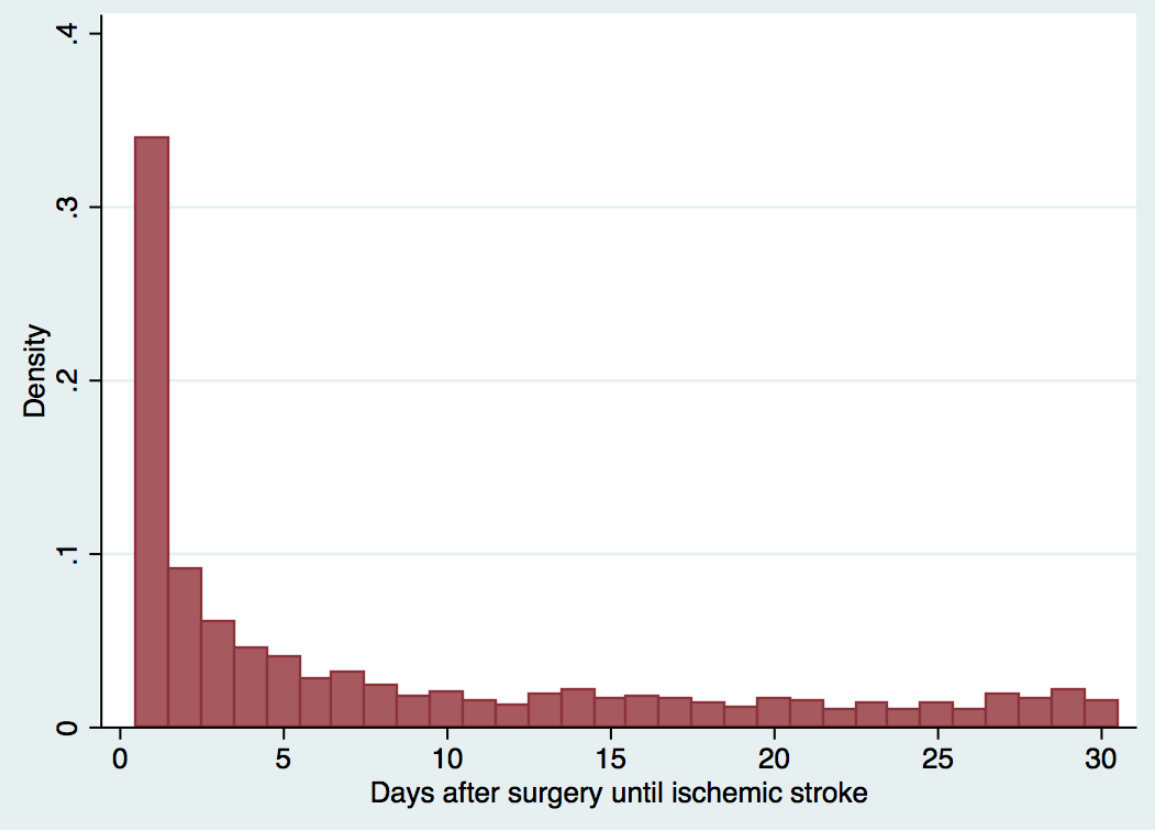
Table S5. Characteristics of the study population by volatile anesthetic dose

Characteristics	Low dose (n= 157,466)	High dose (n= 157,466)
Ischemic stroke within 30 postoperative days	1457 (0.9%)	500 (0.3%)
Demographics		
Age, years	53.6 ± 17.2	54.0 ± 15.8
Sex, male	71,225 (45.2%)	67,531 (42.9%)
Body Mass Index, kg/m^2	28.0 ± 6.8	28.7 ± 7.0
*Comorbidities**		
Arterial Hypertension	63,491 (40.3%)	63,288 (40.2%)
Atrial Fibrillation	11,374 (7.2%)	10,381 (6.6%)
Carotid Stenosis	4806 (3.1%)	2849 (1.8%)
Chronic Kidney Disease	11,425 (7.3%)	9114 (5.8%)
Diabetes	22,769 (14.5%)	23,412 (14.9%)
Dyslipidemia	48,109 (30.6%)	49,579 (31.5%)
Ischemic Stroke	5644 (3.6%)	3352 (2.1%)
Malignancy	47,085 (29.9%)	45,605 (29.0%)
Migraine	5622 (3.6%)	5838 (3.7%)
Patent Foramen Ovale without Closure	1697 (1.1%)	1205 (0.8%)
Peripheral Vascular Disease	7702 (4.9%)	4823 (3.1%)
Smoking	26,471 (16.8%)	26,014 (16.5%)
Transient Ischemic Attack	3048 (1.9%)	2042 (1.3%)
Valvular Heart Disease	15,364 (9.8%)	12,047 (7.7%)
Betablocker Prescription within 28 Days Prior	28,669 (18.2%)	16,769 (10.6%)
Charlson Comorbidity Index[30]	1 (0, 3)	1 (0, 3)
ASA† Physical Status	2 (2, 3)	2 (2, 3)
Surgical Factors		
Emergency Surgery	7532 (4.8%)	6644 (4.2%)
Inpatient Surgery	99,539 (63.2%)	102,280 (65.0%)
Duration of Surgery, minutes	141.3 ± 101.7	168.3 ± 113.2
Work Relative Value Units	13.7 ± 9.7	15.6 ± 9.9
Surgical Service		
Burn	1681 (1.1%)	317 (0.2%)
Emergent-Urgent	5043 (3.2%)	5842 (3.7%)
General	23,133 (14.7%)	34,726 (22.1%)
Gynecology/ Obstetrics	12,110 (7.7%)	19,123 (12.1%)
Neurosurgery	14,941 (9.5%)	7489 (4.8%)
Oral/ Maxillofacial	2177 (1.4%)	1127 (0.7%)
Orthopedic	39,918 (25.4%)	32,862 (20.9%)
Other (Dermatology, etc.)	2646 (1.7%)	1875 (1.2%)

Characteristics	Low dose (n= 157,466)	High dose (n= 157,466)
Otolaryngology	3543 (2.3%)	5274 (3.4%)
Plastic	8527 (5.4%)	10,208 (6.5%)
Radiology	1028 (0.7%)	771 (0.5%)
Surgical Oncology	6888 (4.4%)	8134 (5.2%)
Thoracic	12,733 (8.1%)	7351 (4.7%)
Transplant	2114 (1.3%)	3613 (2.3%)
Urology	12,192 (7.7%)	10,043 (6.4%)
Vascular	6330 (4.0%)	4482 (2.9%)
Anesthetic Factors		
MAC† of Volatile Anesthetic	0.45 ± 0.21	0.99 ± 0.23
MAC† of Nitrous Oxide	0.34 (0.01, 0.51)	0 (0, 0.08)
Total Opioid Dose (Oral Morphine Equivalents)	51.1 (31.3, 79.5)	50.0 (31.3, 76.1)
Total Propofol Dose, mg	200 (150, 300)	200 (150, 250)
Total Neuromuscular Blocking Agent ED95† Dose	1.69 (0, 2.93)	2.02 (0, 3.22)
Total Vasopressor Dose, mg (Norepinephrine Equivalents)	0.01 (0, 0.10)	0.01 (0, 0.11)
Total Fluid Volume Administered, ml	1500 (1000, 2500)	2500 (1500, 3750)
Administration of Packed Red Blood Cells	4924 (3.1%)	4335 (2.8%)
Neuraxial Anesthesia	5861 (3.7%)	4475 (2.8%)
Minutes with MAP† <55 mmHg	0 (0, 2)	0 (0, 2)

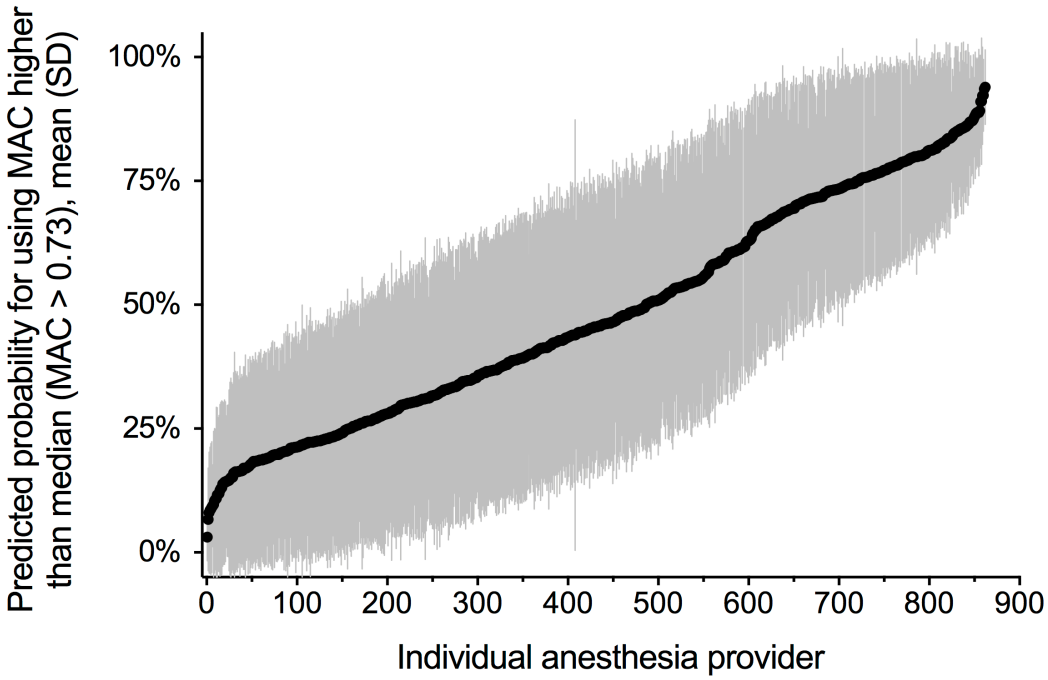
Table S5 displays the characteristics of patients receiving low dose (lower than median MAC 0.73) versus patients receiving high dose (higher than median) volatile anesthetics.
* For comorbidity definitions, refer to Table S1.
† ASA, American Society of Anesthesiologists; MAC, minimum alveolar concentration; ED95, median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; MAP, mean arterial pressure.
Values provided as frequency (prevalence in %), mean ± SD, or median [IQR (25^{th}-75^{th} percentile), values separated by comma].

Figure S1. Distribution of ischemic stroke occurrence over 30 days after surgery



A total of 1957 patients (0.6%) suffered an ischemic stroke within 30 days after surgery. The median time to ischemic stroke was 4 days (IQR 1, 14). 1594 of 1957 ischemic strokes (81.5%) happened within 17 days after surgery.
Figure S1 displays the proportional distribution of outcome occurrence over the period of interest, with each bar representing one postoperative day.

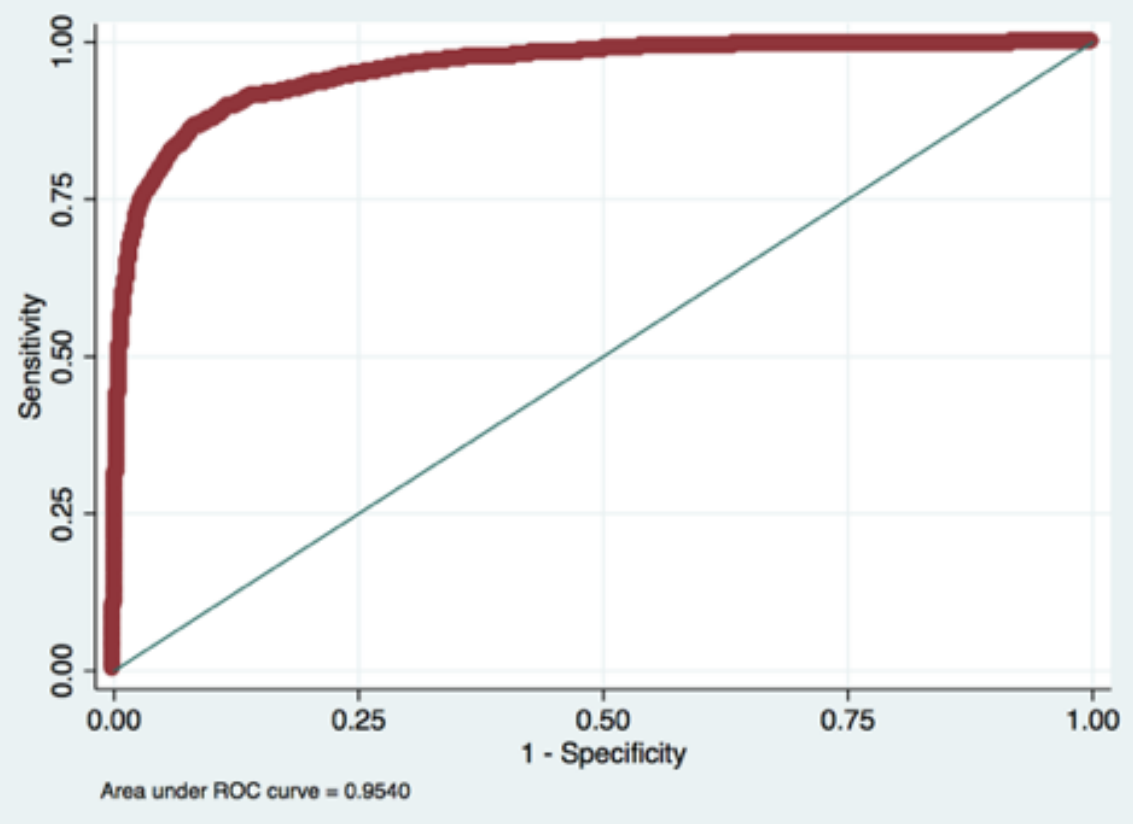
Figure S2. Provider variability in using high-dose volatile anesthetics



MAC, minimum alveolar concentration.

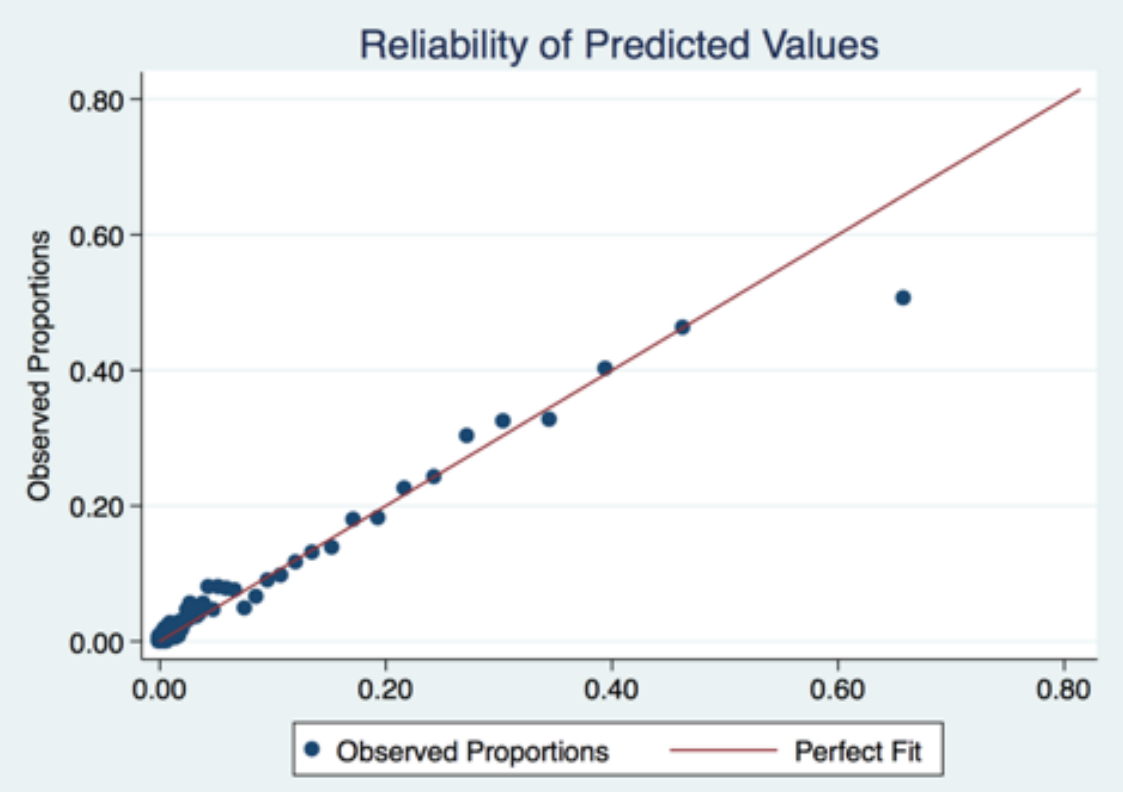
Figure S2 displays the individual anesthesia providers' preference of using volatile anesthetic doses higher than the cohort median (MAC >0.73). Only providers with a total experience of >100 cases were considered (862 individual providers). Provider variability ranged from 3.1% to 93.9%.

Figure S3. Covariate model performance (C-statistics) independent of exposure



ROC, receiver operating characteristics.
Figure S3 shows C-statistic results of the primary logistic regression model independent of the exposure (volatile anesthetic dose). Area under the ROC curve = 0.95.

Figure S4. Reliability plot for the covariate model independent of exposure



Calibration of the primary logistic regression model independent of the exposure (volatile anesthetic dose) was excellent aside from one extreme outlier.
Each data marker represents a 1000-quantile of the estimated probability of ischemic stroke within 30 days after surgery.