SUPPLEMENTAL MATERIAL
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. 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. 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), betablocker prescription within 28 days prior to surgery, and a patient history of ischemic stroke, patent foramen ovale (PFO) without closure, migraine, 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. While reviewing the patient charts, the neurologic deficit caused by the stroke was measured by assessing the National Institute of Health Stroke Scale (NIHSS), and stroke subtypes were classified according to the Oxfordshire Community Stroke Project (OCSP) classification. 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., 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).

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. Premenopausal status was defined as age <55 years in female patients.
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** | | Explain the scientific background and rationale for the investigation being reported | 4 |
| **Objectives** | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | Present key elements of study design early in the paper | 5 |
| **Study design** | 4 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5; Supplement 1, p. 2 |
| **Setting** | 5 | 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 |
| **Participants** | 6 | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5, Figure 1 |
| | | 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 | |
| | | (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed | Not applicable |
| | | Case-control study—For matched studies, give matching criteria and the number of controls per case | |
| **Variables** | 7 | 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 |
| **Data sources/ measurement** | 8* | Describe any efforts to address potential sources of bias | 7-9; Supplement 1, p. 3-4 |
| **Bias** | 9 | Explain how the study size was arrived at | 5, 11, Figure 1 |
| **Quantitative variables** | 10 | 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

| (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 | Not applicable |
| 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 | |
| (g) 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
- (b) Give reasons for non-participation at each stage
- (c) Consider use of a flow diagram

| Descriptive data |
|------------------|
| 14*              |

- (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
- (b) Indicate number of participants with missing data for each variable of interest
- (c) **Cohort study**—Summarise follow-up time (eg, average and total amount)

| Outcome data |
|--------------|
| 15*          |

- **Cohort study**—Report numbers of outcome events or summary measures over time
- **Case-control study**—Report numbers in each exposure category, or summary measures of exposure
- **Cross-sectional study**—Report numbers of outcome events or summary measures

| 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
- (b) Report category boundaries when continuous variables were categorized
- (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

| Other analyses |
|----------------|
| 17             |

Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

### Discussion

| Discussion |
|------------|
| 18         |

- Summarise key results with reference to study objectives

| 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

| Interpretation |
|----------------|
| 20             |

Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

| Generalisability |
|------------------|
| 21                |

Discuss the generalisability (external validity) of the study results

### Other information

| Other information |
|-------------------|
| 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

*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 | Oclusion and stenosis of carotid artery                                     |
|                                  | ICD-10     | I63.239      | Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries |
| Charlson Comorbidity Index       | ICD-9/ICD-10 | 140.X/C00.X  | Malignant neoplasm of lip                                                  |
| Cancer, including leukemia and lymphoma, and metastatic tumor | 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 sarcoma                                                           |
| 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                     | C55.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                               |
|             | 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                              |
|             | 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                                                                 |
|---------------------------------|-----------|------------|-----------------------------------------------------------------------------|
| Congestive heart failure        | 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 | 402.01/402.11,402.91/110.0X | Hypertensive heart disease with heart failure                                |
|                                 | ICD-9/ICD-10 | 404.01/404.11,404.91/113.0X | 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 | 404.03/404.13,404.93/113.2X | 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                           |
| Diabetes mellitus with and      | ICD-9/ICD-10 | 331.2/G31.1 | Senile degeneration of brain, not elsewhere classified                      |
| 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     |
| 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 | Paraplegia (paraparesis) and quadriplegia (quadriparesis) |
| Comorbidity | Code type | Code     | Description                                      |
|-------------|-----------|----------|--------------------------------------------------|
| Comorbidity | 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/K74.4X | Fibrosis and cirrhosis of liver                   |
|             | ICD-10       | K76.0X    | Fatty (change of) liver, not elsewhere classified |
|             | ICD-9/ICD-10 | 570.0/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,     | 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/I21.1X | 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    | ICD-9/ICD-10 | 440.X/I70.X | Atherosclerosis                                                              |
| disease                | 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                   |
| Renal disease          | ICD-9/ICD-10 | 403.01/403.11,4 | Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease |
|                        | ICD-9/ICD-10 | 03.91/I12.0X | Hypertensive heart and chronic kidney disease without heart failure          |
|                        | 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                                                                 |
|--------------------------|---------------|-------------------------|-----------------------------------------------------------------------------|
| Comorbidity              |               |                         |                                                                             |
|                          | ICD-9         | 404.03,404.13,4 04.93   | 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 erythematoses                                                |
|                          | 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 rheumatic                                                       |
|                          | 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/I63.3X           | 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     | 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 |
|                          | CPT           | 33647                   | Repair of atrial septal defect and ventricular septal defect, with direct or |
|                          | CPT           | 33660                   | Repair of incomplete or partial atrioventricular canal (ostium primum atrial |
|                          | CPT           | 93580                   | Percutaneous transcatheter closure of congenital interatrial communication  |
|                          |               |                         | (i.e., Fontan fenestration, atrial septal defect) with implant              |
| Peripheral vascular      | ICD-9/ICD-10  | 440.2, I70.2            | Peripheral arterial disease                                                 |
| 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

| Cases | Pattern* | # 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 0 1 1 1 1 1 | 2274      |
| <1%   | 1 1 1 1 0 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 0 1 0 1 1 1 | 211       |
| <1%   | 1 1 1 1 0 1 0 1 0 1 | 204       |
| <1%   | 1 1 1 1 0 1 0 1 0 1 | 130       |
| <1%   | 1 1 1 0 1 0 1 0 1 0 | 128       |
| <1%   | 1 1 1 0 1 0 1 0 1 0 | 126       |
| <1%   | 1 1 0 1 0 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/m²                                | 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                           | 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

| 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

| Anesthetic Factors                                             | No missing data | Missing data |
|----------------------------------------------------------------|-----------------|--------------|
| 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/m²               |     |
| 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 Index³⁰         |     |
| 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/m²                               | 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 Index³⁰                        | 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

| 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

| Anesthetic Factor                                   | Low dose | High dose |
|-----------------------------------------------------|----------|-----------|
| 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 (25th-75th percentile), values separated by comma].
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.
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.