Supplementary Online Content

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Association of preoperatively-diagnosed patent foramen ovale with perioperative ischemic stroke

Supplementary appendix

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Section 1. Overview

In order to ensure the stability of our findings, several additional statistical analyses were performed in addition to those reported in the primary manuscript. These methodological checks confirm that our findings are robust with regards to several considered threats to our interpretation. In what follows is a detailed description of ancillary analyses, sensitivity analyses, or exploratory analyses.

Section 2. Details to methods

2.1 Definitions of variables

eTable 1 details the list of ICD-9/10 (International Classification of Diseases, Ninth/Tenth Revisions) codes used to define the exposure, outcome, and confounder variables. The presence of a preoperatively-diagnosed PFO was determined using ICD-9/10 (International Classification of Diseases, Ninth/Tenth Revisions) diagnostic codes '745.5' and 'Q21.1'. Across all variables, patients without a billing diagnosis of such within 12 months prior to surgery were considered not exposed.

2.2 Source of medical / health information

Data were obtained from the MetaVision Anesthesia Information Management System (AIMS) (iMDsoft, Dedham, MA), the Research Patient Data Registry (RPDR), and Enterprise Performance Systems Inc (EPSi) (Allscripts Healthcare) at Massachusetts General Hospital. The AIMS prospectively collects intraoperative data including physiological parameters such as blood pressure, ventilator and respiratory indices, administered drug doses, and fluid volumes. This is matched to the patients' demographic data and pre-/post-procedural condition using RPDR, a centralized clinical data warehouse that compiles health records and billing data from various Partners hospital systems specifically for research purposes. Information on hospital length of stay, costs, and readmission were collected through EPSi.

2.3 Chart review

The outcome of a perioperative ischemic stroke within 30 days of surgery was based on ICD-9/10 diagnostic codes (eTable 1) and confirmed by chart review. Review of medical records of all patients with a diagnostic coding of ischemic stroke within 30 days after surgery were conducted by a research fellow and a neurologist. The chart review was conducted with a standardized methodology in reviewing patient notes, neurologist assessments, and findings from radiological studies such as CT or MRI brain. All reviewers were blinded to PFO status.

Details of the stroke, including the date and timing, temporal relationship with the index surgery and with hospital discharge after index surgery, the stroke subtype by Oxford Community Stroke Project (OCSP) classification,[1] and the stroke-related neurological deficit measured by National Institute of Health Stroke Scale (NIHSS)[2] were obtained from neurology consultation notes and brain imaging reports. The OCSP stroke classification and the NIHSS were collected retrospectively in the following order of priority: as scored by neurologists in neurology notes, as recorded on reports of radiological studies, and lastly, abstracted from records. 88.6% of strokes were classified and scored at the time of stroke occurrence. When the information was abstracted from records, the raters were blinded to PFO status.

Section 3. Study population

After applying inclusion and exclusion criteria, a total of 168 621 cases were available for analysis. A total of 18 423 (10.9%) were excluded from the complete case analysis due to missing values in any of the variables used in the regression model (see Section 6.9 ‘Missing data imputation’).

Of the 150 198 cases that underwent analysis, 1540 (1.0%) had a preoperatively-diagnosed PFO based on ICD-9/10 codes. Patients with PFO were older; had a lower body mass index (BMI), higher American Society of Anesthesiologists (ASA) physical classification status, and higher Charlson comorbidity index; were more likely to have history of smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, myocardial infarction, congestive heart failure, pulmonary edema, pulmonary hypertension, cardiomyopathy, congenital heart disease, atrial fibrillation, valvular heart disease, COPD, transient ischemic attack, ischemic stroke, migraine, chronic kidney disease, hypercoagulable state, deep vein thrombosis, pulmonary embolism, and systemic embolic phenomenon; had more prescriptions of beta-blockers, statins, anti-platelet agents, and anticoagulants; underwent more emergency procedures, high risk procedures, inpatient surgeries, and longer surgeries; had more intraoperative hypotensive minutes; received higher intraoperative doses of vasopressors, less intraoperative fluids, and more packed red blood cell transfusions. There was no significant difference in terms of gender, or procedural complexity measured by work RVU (Table 1).

Patients with PFO were more likely to have underlying major cardiovascular or thromboembolic conditions at the time of PFO diagnosis (eTable 2). Because these coexisting conditions could have biased such patients to the diagnosis of PFO through referral for a dedicated echocardiography study, all of these significant conditions were included in the confounder model for the primary analysis.

eTable 3 shows details of the type of surgery for patients with and without PFO. Patients with PFO underwent higher frequency counts of anesthesiology and radiology procedures, neurosurgeries, transplant surgeries, and vascular surgeries compared with patients without PFO.

Section 4. Sample size and power

Prior to conducting our analysis, we defined an odds ratio of 2.0 as a clinically meaningful association between PFO and perioperative ischemic stroke. Assuming the observed PFO rate of 1.0%, a one-sided alpha level of 0.025, and an event rate of 0.5% perioperative ischemic stroke within 30 days after surgery, we achieved 94.3% power to detect an odds ratio of 2.0 or greater.

Previous studies have examined the PFO-stroke association in smaller sample sizes, but would have had modest levels of statistical power using our event rates (eTable 4).

Section 5. Evaluation of primary regression model

In order to evaluate a multivariable model, the assumptions underlying the model and the model fit must be closely evaluated. The primary regression model for perioperative ischemic stroke was conducted using forced variable entry and evaluated using calibration tests (Hosmer-Lemeshow test) and discrimination indices (area under the curve) to ensure that the estimates could be interpreted conventionally. All continuous variables in the primary regression model were tested for linearity. Work relative values units (work RVU), intraoperative hypotensive minutes, intraoperative dose of vasopressors, and intraoperative fluid volumes were categorized in quintiles due to non-linearity of the coefficients.

Model discrimination was assessed through the concordance c-statistic, which in our case was equivalent to the area under the receiver operating characteristic curve (AUC=0.845) (eFigure 1a). Although the Hosmer-Lemeshow test suggested a statistically significant miscalibration (chi2=28.23, P=0.0004), this should be interpreted with caution due to the hypersensitivity of this test in large sample sizes.[3] Therefore, model calibration was additionally assessed through a reliability plot, which analyzed the agreement between the observed and estimated outcomes (eFigure 1b), and this evaluation indicated an acceptable fit. Model resolution was assessed by plotting a histogram of the log of the estimated values (see insert in eFigure 1a). Taken together, these findings confirmed that our primary regression model had good resolution and was well-calibrated.

Section 6. Sensitivity analyses

6.1 Primary outcome: based on chart review versus ICD-9/10 code-based

In the primary analysis, we used a chart reviewed outcome of perioperative ischemic stroke; details of the methods of obtaining the diagnosis have been reported previously (see Section 2.3 'Chart review'). The incidence of perioperative ischemic stroke confirmed by chart review in the entire study population was 850 (0.6%). In the sensitivity analysis, we explored whether the effect estimate remained unchanged when the outcome variable was defined using the same process of classification as other variables, that is by ICD-9/10 codes (eTable 1).

The incidence of the non-chart-reviewed outcome of perioperative ischemic stroke was 2155 (1.4%). The odds of experiencing a stroke in the PFO group (136/1540 [8.8%]) was greater than in the non-PFO group (2019/148 658 [1.4%]); (unadjusted odds ratio [OR], 7.04; 95% CI, 5.87-8.43; $P<.001$). In adjusted analysis, the association between PFO and perioperative stroke was also significant when using the ICD-based outcome (OR, 2.91; 95% CI, 2.38 to 3.56; $P<.001$). This resulted in estimated risks of 1.2% (95% CI, 0.1 to 1.5%) ischemic strokes in patients with PFO, and 0.4% (95% CI, 0.4 to 0.5%) in patients without PFO (adjusted absolute risk difference, 0.8%; 95% CI 0.6 to 1.1%).

6.2 Validation of exposure variable

In the primary analysis, we defined PFO based on having an ICD-9/10 code for 'patent foramen ovale' or 'atrial septal defect' (ASD). Patients with a history of PFO or ASD closure were classified into the group without PFO. Since the diagnoses of PFO and ASD are not distinguishable by ICD-9/10 codes, we chart reviewed the patients with a coding diagnosis of PFO and perioperative ischemic stroke to estimate the true frequency of PFO. Of the 49 patients with PFO who experienced a perioperative ischemic stroke, a total of 40 patients (81.6%) had a PFO diagnosed by transthoracic or transesophageal echocardiography, only 3 patients (6.1%) had an ASD.

6.3 Confounder control for preoperative ischemic cerebrovascular events

In the primary analysis, multivariable logistic regression was performed to evaluate the odds ratio of perioperative ischemic stroke in patients with PFO, controlling for confounding variables selected a priori based on data in the published literature and biological plausibility (details of the confounder model were listed in the Methods section). We did not control for preoperative ischemic cerebrovascular events since they may have also been associated with a PFO. However, in a sensitivity analysis, we tested whether the PFO-stroke association remained significant after including history of ischemic cerebrovascular events in the confounder model.

Including a history of transient ischemic attack (OR, 2.32; 95% CI, 1.70 to 3.18; $P<.001$) or history of ischemic stroke (OR, 1.55; 95% CI, 1.13 to 2.14; $P=.007$) in the confounder model did not change the primary study results.

6.4 Propensity matching

In the primary analysis, we categorized patients based on having a preoperative diagnosis of PFO. However, there may be subtle processes that lead to diagnosis of a PFO that were not properly considered in the multivariable confounder model. To reduce potential diagnostic bias, we first defined a new confounder control model to create a propensity score to predict PFO. Since PFO is a congenital anomaly most commonly detected during an echocardiographic examination, the covariates were selected based on probability of subjecting a patient to an echocardiography study. They included age, sex, BMI, ASA physical status classification, Charlson comorbidity index; history of cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease (COPD), chronic lung disease, chronic kidney disease, moderate to severe liver disease; prescription within 28 days before surgery of beta-blockers, statins, anti-platelet agents, anticoagulants; emergency surgery status, inpatient surgery, high risk surgical service,[4] and work RVU. The propensity model was conducted using a logistic regression model forcing all of the predictors into the model (i.e., non-parsimonious model). The AUC was 0.79. Propensity score matching was then performed using the 'Matchit' package in R Studio, using a 1:5 matching ratio with nearest neighbor and sampling without replacement with a caliper set to 0.20.

Of the 1540 cases with PFO, 1521 (98.8%) were successfully matched at a 1:5 ratio. 6 (0.4%) had exactly four matches, 7 (0.5%) had exactly three matches, 2 (0.1%) had exactly two matches, and 1538 (99.9%) had at least one match. Because of the high success rate of finding a 1:5 match, we included individuals with less than a 1:5 match to avoid the loss of data.[5] The final propensity-score-matched cohort of 1538 patients with PFO and 7656 patients without PFO (Table 3) confirmed our primary finding of the PFO-stroke association. PFO was associated with an increased risk of stroke (49/1538 [3.2%] vs 77/7656 [1.0%]; OR, 3.16; 95% CI, 2.19 to 4.51; *P*<.001). Close examination of the matched sample revealed that several variables used in the match exhibited residual imbalances (i.e. standardized mean difference >0.10) (Table 3). To further adjust for these imbalances, these variables were forced into a post-hoc regression model in the matched sample. This analysis further confirmed the findings (OR, 1.54; 95% CI, 1.04 to 2.26; *P*=.03).

6.5 Subgroup analysis and propensity matching in patients with history of echocardiogram

We repeated the primary analysis in a subgroup including only patients with history of an echocardiogram in our institution prior to the index surgery, in order to further control for unmeasured differences that biased the referral for evaluation by echocardiogram. A total of 29 629 (19.7%) patients in the cohort had history of an echocardiogram performed in the same healthcare system based on billing codes. The primary analysis was repeated in this subgroup and confirmed the PFO-stroke association (32/1162 [2.8%] vs 335/28 467 [1.2%]; OR, 1.86; 95% CI, 1.28 to 2.72; *P*=.001).

The primary study results were replicated in further analysis with a 1:5 propensity matching of patients without and with PFO in this subgroup (using the propensity score derived in Section 6.4 'Propensity matching') (OR, 1.84; 95% CI, 1.21 to 2.76; *P*=.003).

6.6 Baseline PFO-independent risk of stroke

Previous studies have suggested that the association between PFO and stroke was stronger in patients younger than 55.[5,6] We tested if the PFO-attributable risk of stroke differs for patients at different stroke risks.

We created a probability score for the risk of perioperative ischemic stroke, independent of PFO diagnosis. The variables were comorbid conditions and surgical factors selected based on their biologically-plausible relationship with stroke, and included age; sex; BMI; ASA physical status classification; Charlson comorbidity index; history of cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, atrial fibrillation, COPD, migraine, or chronic kidney disease; prescription within 28 days before surgery of beta-blockers, statins, anti-platelet agents, or anticoagulants; emergency surgery status; inpatient surgery; high risk surgical service; duration of surgery; intraoperative hypotensive minutes; intraoperative dose of vasopressors; intraoperative fluid volumes; requirement for packed red blood cells transfusion; and work RVU. The AUC was 0.84.

The study population was subdivided by median split into two equally-sized groups – 'low stroke risk' and 'high stroke risk' – based on this baseline probability of perioperative ischemic stroke, and the PFO-stroke association was re-examined for heterogeneity across groups. 31 patients with ASA physical status class V were not included due to failure to calculate the probability score. Clinical characteristics of the two groups are presented in eTable 5.

The relative risk estimate of PFO on perioperative ischemic was modified by patients' PFO-independent baseline risk of stroke (interaction term "PFO x low stroke risk": OR, 4.59; 95% CI, 1.36 to 15.5; *P* for interaction<.014; interaction term "PFO x baseline stroke risk": OR, 1.23e-26; 95% CI, 6.70e-39 to 2.26e-14; *P* for interaction <.001). For individuals at low risk of stroke, the estimated probabilities of stroke with and without PFO were 1.4% (95% CI, 0.2 to 2.9%) and 0.1% (95% CI, 0.1 to 0.2%); (adjusted OR, 15.92; 95% CI, 4.92 to 51.53; *P*<.001). For individuals at high risk of stroke, the estimated probabilities of stroke with and without PFO were 0.8% (95% CI, 0.5 to 1.0%)

and 0.3% (95% CI, 0.3 to 0.4%); (adjusted OR, 3.80; 95% CI, 2.81 to 5.15; *P*<.001). The PFO-attributable risk of stroke in patients at low baseline stroke risk was higher (adjusted absolute risk difference, 1.3%; 95% CI, -0.3 to 2.8%) compared with patients at high baseline stroke risk (adjusted absolute risk difference, 0.5%; 95% CI, 0.2 to 0.7%).

We also performed a subgroup analysis in a cohort excluding patients with major risk factors of stroke, such as history of hypertension, myocardial infarction, atrial fibrillation, or COPD. This group consisted of 79 649 cases (53.0%) from the study population. In these patients at lower risk of stroke based on absence of major risk factors, having a PFO was associated with an increased risk of perioperative ischemic stroke (13/410 [3.2%] vs 228/79 239 [0.3%]; OR, 3.14; 95% CI, 1.66 to 5.94; *P*<.001).

6.7 Falsification analysis

To better ensure that the observed association between PFO and stroke was not due to some underlying cause unrelated to our mechanistic hypothesis, we examined three additional outcomes that are theoretically unrelated to the mechanism of PFO in falsification testing – septic shock, wound complication, and peptic ulcer disease. They were selected based on a common contributing etiology of non-thrombotic tissue ischemia. All outcomes were defined by ICD-9/10 diagnostic codes and within 30 days after surgery (eTable 1).

We performed superiority tests with high levels of power to detect even small associations. Assuming the PFO rates we observed, a one-side alpha level of 0.025, and event rates of 3.3% 1.6%, and 2.0% for septic shock, wound complications, and peptic ulcer disease respectively, we achieved 95% power to reject the null hypothesis (eFigure 2). In adjusted analyses, septic shock (15 [1.0%] vs 525 [0.4%]; OR, 0.89; 95% CI, 0.52 to 1.52; *P*=.67), wound complication (103 [6.7%] vs 6807 [4.6%]; OR, 0.90; 95% CI, 0.73 to 1.11; *P*=.35), and peptic ulcer disease (8 [0.5%] vs 492 [0.3%]; OR, 1.23; 95% CI, 0.61 to 2.49; *P*=.56) were not significantly associated with having a diagnosis of PFO (Table 2). Due to sparse data in peptic ulcer disease (only 8 outcomes in patients with PFO), multivariable logistic regression was performed with a modified confounder model, consisting age, gender, body mass index, and the three most significant predictors of perioperative stroke (based on the beta-coefficients in the primary logistic regression model) – emergency surgery status, inpatient surgery, and high risk surgical service.

6.8 Mixed effects modeling

The study included patients and data from three hospital sites – Massachusetts General Hospital, Mass General West – Waltham, and Mass General / North Shore Center for Outpatient Care. To account for the impact of variation from different healthcare facilities, we performed mixed effects logistic regression, with clustering within anesthesia provider specified as a random effect and other covariates as fixed effects. The anesthesia provider was chosen as a viable surrogate of the inter-hospital difference in practices, and was defined as the primary anesthetist responsible for the anesthetic care of the surgical case.

Data on the anesthesia provider was available for 150 188 (99.9%) of the cohort, and there were 754 individual anesthesia providers. The results of the primary analysis did not change (OR, 2.69; 95% CI, 1.97 to 3.67; P<.001), suggesting that the primary study finding was not driven by systematic differences in the practice patterns of anesthesia providers at multiple hospital sites.

6.9 Missing data imputation

The complete case method was adopted to deal with missing data in the primary statistical analysis. To better ensure that missing data did not bias the primary analysis, multiple imputation was conducted. A total of 7 variables in our primary regression model had missing data, and the pattern of missingness was examined to ensure missing at random (MAR) (eFigure 3).

To test the robustness of our results, the analysis was repeated with the entire cohort using the technique of multiple imputations by chained equations.[8] The variables with missing data were imputed using all covariates included in the primary model. Using the 'MICE' package in R Studio, 5 imputations were performed with 5 iterations per imputation. Even BMI, the variable which had the largest amount of missing data out of all included variables, had only 10 232 (6.1%) missing values. The imputed cohort included all 18 423 (10.9%) cases that were dropped due to missing values in any of the variables used in the regression model. The model estimate of PFO on risk of stroke from the imputed dataset was consistent with the complete case cohort (53/1788 [3.0%] vs 906/166 833 [0.5%]; OR, 2.59; 95% CI, 1.93 to 3.48; $P<.001$).

Section 7. Exploratory analyses

7.1 Association of PFO with 30-day hospital readmission

We examined whether having a PFO was associated with other burdensome clinical outcomes (Table 2). Hospital readmission was defined as an in-patient readmission to a hospital in the Partners healthcare network. There were a total of 11 597 (7.7%) cases of 30-day readmission – 245 (15.9%) in patients with PFO and 11 352 (7.6%) in patients without PFO. In multivariable analysis, having a PFO was not significantly associated with increased rate of 30-day readmission (OR, 1.15; 95% CI, 0.99 to 1.33; *P*=.07).

We further examined whether PFO was associated with emergent or unplanned admissions in particular. Having a PFO was associated with increased rate of emergent or unplanned readmission within 30 days of surgery (218/1540 [14.2%] vs 9126/148 658 [6.1%]; OR, 1.20; 95% CI, 1.03 to 1.41; *P*=.02).

We tested if having a PFO was associated with specific causes of hospital readmission. The odds of 30-day readmission due to a principle or admitting diagnosis of PFO-related complications – including ischemic stroke, systemic embolic complications, and atrial fibrillation, was higher in patients with PFO compared with patients without PFO (13/1540 [0.8%] vs 232/148 658 [0.2%]; OR, 1.93; 95% CI, 1.01 to 3.45, *P*=.03).

7.2 Association of PFO with 30-day mortality

There was no difference in 30-day mortality (27 [1.8%] vs 917 [0.6%]; OR, 0.95; 95% CI, 0.63 to 1.43; *P*=.87) between patients with and without PFO.

We performed an additional time-to-event analysis to account for the competing risk of mortality within 30 days after surgery. After confirming satisfaction of the proportional hazards assumption, we conducted a Cox proportional hazards analysis using the same confounder model as in the primary analysis to model time to stroke up to 30 days after surgery. The analysis yielded results similar to the primary logistic regression model (hazard ratio [HR], 2.67; 95% CI, 1.97 to 3.61).

7.3 Association of PFO with perioperative ischemic stroke after discharge

The acquisition of the date of stroke by chart review allowed us to categorize strokes into strokes occurring during the index hospitalization or post-discharge strokes. Of the 850 perioperative ischemic strokes occurring within 30 days after surgery, a total of 215 (25.3%) perioperative strokes occurred after discharge – 13 (26.5%) in patients with PFO and 202 (25.2%) in patients without PFO. Patients with PFO had an increased risk of post-discharge strokes compared with patients without PFO (13/1540 [0.8%] vs 202/148 658 [0.1%]; OR, 2.74; 95% CI, 1.52 to 4.91; *P*=.001).

7.4 Association of PFO with postoperative hospital length of stay

The association between PFO and postoperative hospital length of stay was assessed utilizing a time-to-event Cox proportional hazards model stratified by stroke. There was no difference in postoperative hospital length of stay between patients with or without PFO (median length of stay, 4 vs 3; interquartile range, 2-8 vs 1-5), regardless of whether they experienced a stroke (HR, 0.93; 95% CI, 0.67 to 1.29; *P*=.67) or not (HR, 0.95; 95% CI, 0.90 to 1.00; *P*=.05).

7.5 Association of PFO with postoperative new onset atrial fibrillation

We tested whether having a PFO is associated with an increased incidence of perioperative new onset atrial fibrillation (AF) in patients without history of AF. This subgroup of patients without history of AF consisted of 136 520 cases (90.9%) from the study population. In analysis adjusted for age, sex, and BMI, there was increased perioperative new onset AF in patients with PFO compared with patients without PFO (12/1087 [1.1%] vs 589/135 433 [0.4%]; OR, 2.37; 95% CI, 1.33 to 4.23; *P*=.003).

7.6 Association of PFO with postoperative myocardial infarction

Myocardial infarctions could be related to PFO in the circumstance of coronary artery embolism. Although ICD-9/10 diagnosis codes do not allow the distinction of myocardial infarctions from embolic origin, we tested whether having a PFO is associated with an increased incidence of postoperative myocardial infarction as a whole. In adjusted analysis, the risk of myocardial infarction was increased in patients with PFO (45 [2.9%] vs 922 [0.6%]; OR, 1.60; 95% CI, 1.13 to 2.27; *P*=.008) compared with patients without PFO.

7.7 Perioperative stroke preventive measures

In order to test the hypothesis that the paradoxically higher absolute estimated probability of stroke for the low risk group of patients with PFO compared with the high risk group of patients with PFO (Section 6.6 'Baseline PFO-independent risk of stroke') was due to a difference in intensity of perioperative stroke preventive measures, exploratory analyses on the postoperative use of antiplatelet and anticoagulation therapy was performed. The logistic regression models adjusted for potential confounders including age; sex; BMI; ASA physical status classification; Charlson comorbidity index; and history of cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, atrial fibrillation, COPD, migraine, or chronic kidney disease.

In adjusted analyses, the use of antiplatelet therapy (10 210/75 084 [13.6%] vs 28 015/75 083 [37.3%]; OR, 0.41; 95% CI, 0.40 to 0.42; *P*<.001) and anticoagulation therapy (18 940/75 084 [25.2%] vs 45 957/75 083 [61.2%]; OR, 0.25; 95% CI, 0.24 to 0.26; *P*<.001) in the 30 days after surgery was significantly lower in the 'low stroke risk' group compared with the 'high stroke risk' group.

7.8 Obstructive sleep apnea and the Score for Preoperative Prediction of Obstructive Sleep Apnea (SPOSA)

There are data to support obstructive sleep apnea (OSA) as a modifiable risk factor for stroke.[9] We recently published a prediction score validated for the preoperative prediction of OSA (SPOSA).[10] In unadjusted analysis, a high SPOSA – defined as SPOSA >= 25 – was not associated with an increased risk of perioperative ischemic stroke (274/46 421 [0.6%] vs 576/103 777 [0.6%]; OR, 1.06; 95% CI, 0.92 to 1.23; *P*=.40). Adding the dichotomized SPOSA to the confounder model did not change the primary study findings of the PFO-stroke association (OR, 2.67; 95% CI, 1.96 to 3.63; *P*<.001).

7.9 Exploratory analyses conducted at the suggestion of peer reviewers

7.9.1 Adjustment for biases from echocardiography examination

To address possible residual confounding related to biases in referral for certain types of echocardiography, or to ascertainment biases due to the different diagnostic sensitivities of these echocardiography examinations for PFO, we conducted sensitivity analyses in the group of patients with history of an echocardiogram performed in the same healthcare system prior to the index surgery (refer to Section 6.5 'Subgroup analysis and propensity matching in patients with history of echocardiogram'). Amongst these patients, we identified subgroups who had undergone prior to surgery a test considered more sensitive for the diagnosis of PFO - transesophageal echocardiography (TEE) and echocardiography with agitated saline injection.

1. TEE: We identified patients who received a TEE based on Current Procedural Terminology (CPT) codes. TEE was defined by the following CPT codes: '93312', '93313', '93314', '93315', '93316', '93317', '93318', or '93355'. A total of 4094 patients in our cohort had a TEE performed in the same healthcare system at any time prior to surgery. The frequency of PFO, defined as having any ICD-9/10 diagnoses of PFO made prior to surgery, in these patients with TEE prior to surgery was 904 (22.1%). PFO was associated with an increased risk of perioperative ischemic stroke (37/904 [4.1%] vs 44/3190 [1.4%]; unadjusted OR, 3.05; 95% CI, 1.96 to 4.75; $P<.001$; adjusted OR, 2.06; 95% CI, 1.15 to 3.68; $P=.02$).

2. Echocardiography with agitated saline injection: Since CPT codes cannot be used to identify dedicated studies conducted with agitated saline ('bubbles studies'), we used text search in Partners HealthCare notes and validated this new approach using chart review. We applied a text search function to all echocardiography notes from the Partners HealthCare network retrievable through RPDR, with the following search phrases: 'agitated saline', 'bubble', 'contrast', 'cTTE', and 'cTEE', 'Definity'; to identify patients who underwent bubble studies.

To minimize the effect of less specific data returned from the text search method, we performed a chart review of 200 randomly-selected patients from the cohort with an echocardiography performed in the Partners HealthCare system - 100 each with and without 'bubble studies', respectively. Each case was independently analyzed by two scientists blinded to the result of the automated text search, by reviewing the echocardiography reports obtained within the Partners HealthCare system at any point prior to surgery. The results show an excellent agreement (94.0%) between the output from the automated text search and the results by chart review. The minimal level of disagreement was due to the higher granularity of timestamps during individual clinical chart review, which allowed for further identification of bubble studies performed prior to surgery on the same day.

A total of 4043 patients in our cohort had a bubble study performed at Partners HealthCare at any time prior to surgery. The frequency of PFO in this subgroup was 1139 (28.2%). PFO was associated with an increased risk of perioperative ischemic stroke (45/1139 [4.0%] vs 67/2904 [2.3%]; unadjusted OR, 1.74; 95% CI, 1.19 to 2.56; $P=.005$; adjusted OR, 1.86; 95% CI, 1.26 to 2.74; $P=.002$).

3. TTE with bubbles vs TEE with bubbles: The rates of TTE with bubbles vs TEE with bubbles in patients with and without PFO were 4.4:1 and 3.3:1, respectively. Following inclusion of the mode of echocardiography into the primary multivariable model, the unique PFO-stroke association remained significant (OR, 2.52; 95% CI, 1.85 to 3.44; $P<.001$).

Of the 4043 patients with a bubble study prior to surgery, a total of 1140 patients had the bubble study during a TEE. In this subgroup, the frequency of PFO was 460 (40.4%), with a similarly significant association between a preoperative diagnosis of PFO and an increased risk of perioperative ischemic stroke (26/460 [5.7%] vs 10/680 [1.5%]; unadjusted OR, 4.01; 95% CI, 1.92 to 8.41; $P<.001$; adjusted OR, 4.01; 95% CI, 1.91 to 8.42; $P<.001$). A total of 3948 patients had a bubble study during a TTE. In this subgroup, the frequency of PFO was 1115 (28.2%). PFO was also associated with a significantly increased risk of stroke in this subgroup (43/1115 [3.9%] vs 65/2833 [2.3%]; unadjusted OR, 1.71; 95% CI, 1.15 to 2.53; $P=.007$; adjusted OR, 1.83; 95% CI, 1.23 to 2.71; $P=.003$).

Of note, due to the relatively small number of outcomes observed under (2) and (3), we did not apply the full confounder model (38 covariates). Instead, we built a propensity score for the PFO-independent baseline risk of stroke, which includes all significant comorbidities and procedural risk factors for perioperative stroke (see Section 6.6 'Baseline PFO-independent risk of stroke' in the Supplement). For this approach, we used a model-based adjustment and forced this score into the primary model.

4. Additional falsification testing: We identified an echocardiographic finding – tricuspid valve disorders – that should not be directly associated with increased stroke risk, and analyzed its association with perioperative stroke in the complete case cohort as well as the cohort with history of echocardiography. Since tricuspid valve disorders is collinear with 'valvular heart disease' – one of the confounders included

in the primary model, the variable ‘valvular heart disease other than tricuspid valve disorders’ was used instead in the falsification analysis. Tricuspid valve disorders were not associated with an increased risk of perioperative stroke either in the complete case cohort (72/4919 [1.5%] vs 778/145 279 [0.5%]; adjusted OR, 0.99; 95% CI, 0.75 to 1.30; *P*=.93), nor in the subgroup that received an echocardiogram (67/4548 [1.5%] vs 300/25 081 [1.2%]; adjusted OR, 0.89; 95% CI, 0.66 to 1.19; *P*=0.43).

7.9.2 Adjustment for the heterogeneous stroke risk of different surgical services

The study included adult patients undergoing surgical procedures with different stroke risks (eTable 3). Only cardiac surgeries were excluded from the cohort. In order to further exclude procedures where occurrence of perioperative stroke may be a direct risk of the procedure, we performed a separate analysis excluding patients who underwent neurosurgeries and vascular surgeries. In multivariable adjusted analysis of this “low risk procedure” cohort (n=131 079) using the primary confounder model, the PFO-stroke association was replicated (24/1203 [2.0%] vs 353/129 876 [0.3%]; OR, 2.42; 95% CI, 1.56 to 3.75; *P*<.001).

7.9.3 Adjustment for data availability in the same healthcare system

Data available regarding preoperative diagnoses of patients may be related to the duration of their care in the same healthcare system. In the primary analysis, we adopted the complete case method, where we excluded all cases with missing data in any of the covariates. Of the 150 198 cases included in the complete case cohort, 9352 (6.2%) had records only starting from the surgical admission, 140 846 (93.8%) had records prior to the surgical admission - of whom 82 848 (55.2% of the cohort) had records beyond 1 year prior to surgery. As a sensitivity measure, we performed an additional analysis in patients who were treated in the Partners HealthCare network for more than 1 year prior to surgery. In this subgroup, the PFO-stroke associated remained significant (25/1096 [2.3%] vs 408/81 752 [0.5%]; OR, 2.10; 95% CI, 1.38 to 3.22; *P*=.001).

7.9.4 Propensity matching with adjusted caliper width

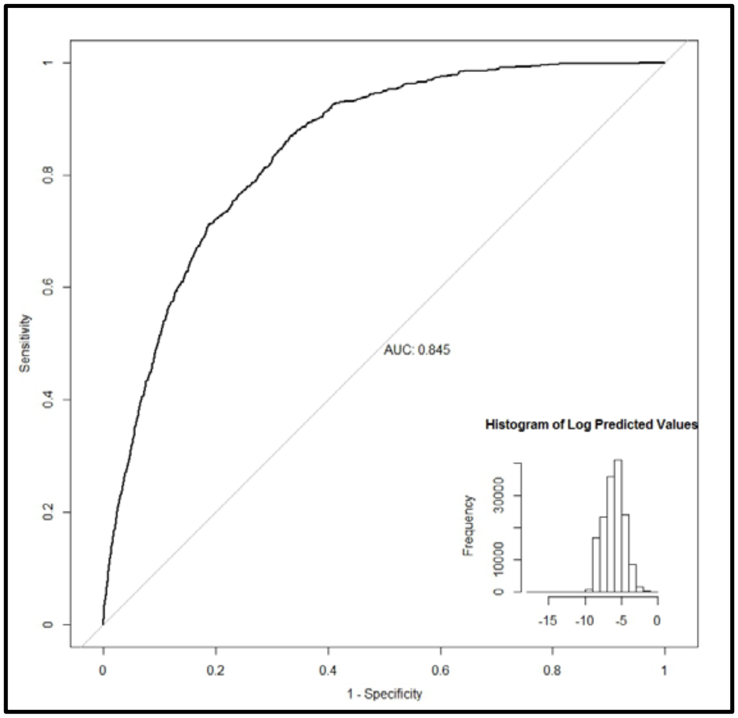
The choice of caliper width used in propensity matching has received considerable attention in the literature but still poses uncertainty amongst practicing analysts (i.e. bias versus proper CI coverage). In the initial propensity matching, we used a caliper width of 0.20 as this seemed to represent a balance between bias and precision in the matched sample.

Since we have ample match candidates for our cases, we re-estimated our matching procedure using a narrower caliper. Propensity score matching was performed using the ‘Matchit’ package in R Studio, using a 1:5 matching ratio with nearest neighbor and sampling without replacement with a caliper set to 0.10.

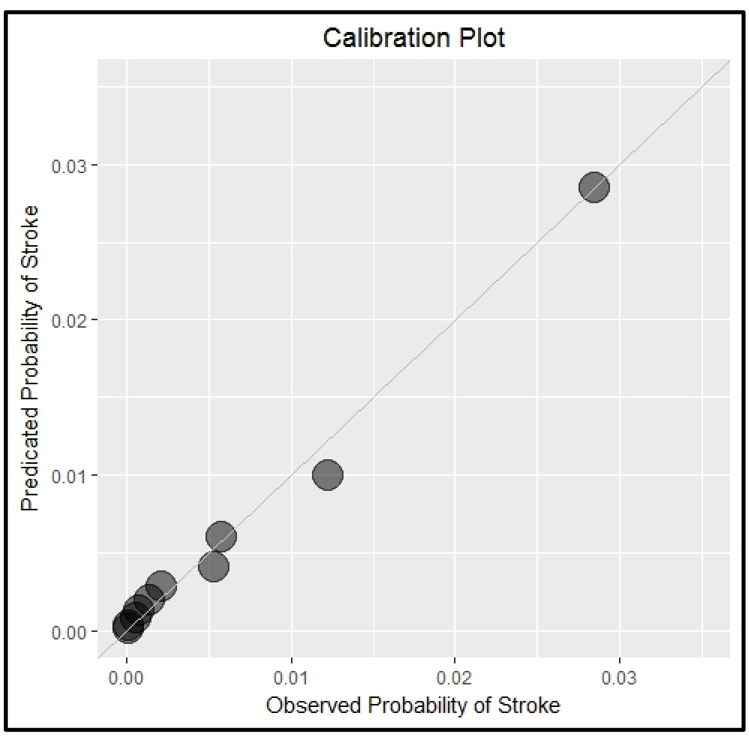
Of the 1540 cases with PFO, 1518 (98.6%) were successfully matched at a 1:5 ratio. 6 (0.4%) had exactly four matches, 2 (0.1%) had exactly three matches, 8 (0.5%) had exactly two matches, and 1536 (99.7%) had at least one match. The final propensity-score-matched cohort of 1536 patients with PFO and 7638 patients without PFO confirmed the findings obtained using the wider caliper. PFO was associated with an increased risk of stroke (49/1536 [3.2%] vs 88/7638 [1.2%]; OR, 2.83; 95% CI, 1.97 to 4.01; *P*<.001).

Section 8. Figures and tables

eFigure 1a. Receiver operating characteristic (ROC) curve of the primary regression model for perioperative ischemic stroke.

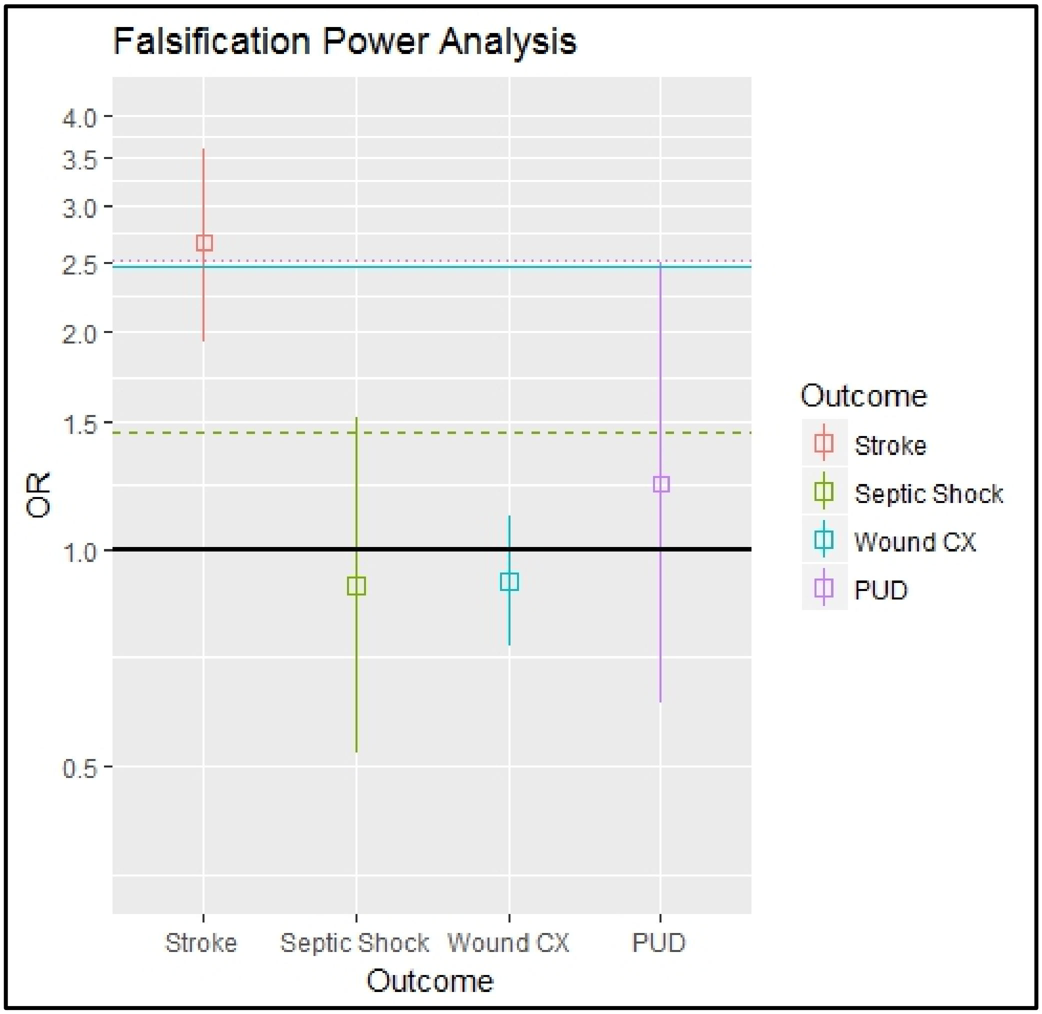


eFigure 1b. Calibration plot of the primary regression model.



Each data marker represents a decile of the predicted probability of stroke.

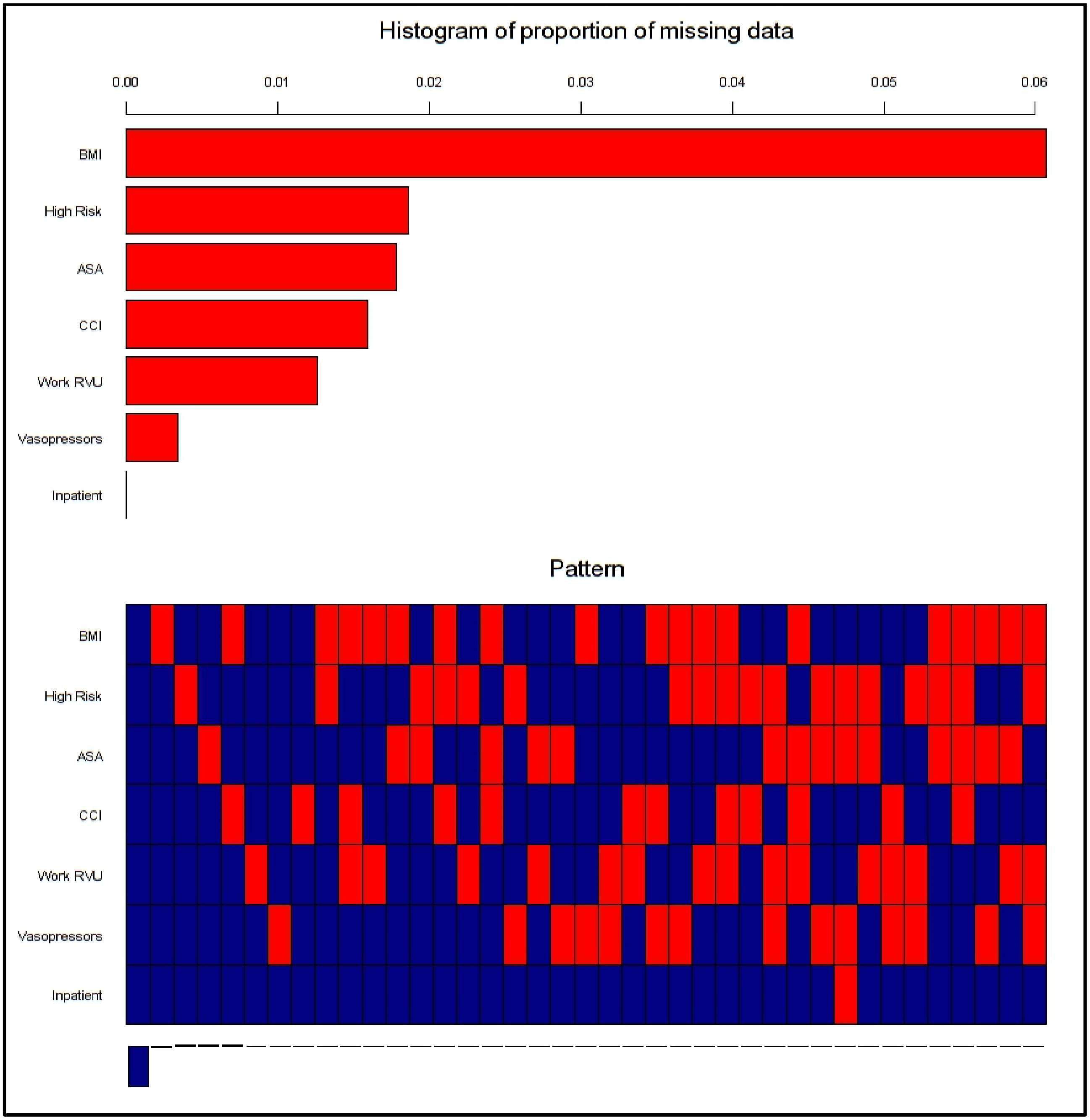
eFigure 2. Power analysis for falsification tests.



Abbreviations: Wound CX, wound complication; PUD, peptic ulcer disease.

The three postoperative outcomes (green, blue, and purple) for falsifications tests were selected based on a common contributing etiology of non-thrombotic tissue ischemia, but biologically unlikely related to the presence or absence of PFO. The stroke outcome (red) is depicted for visual comparison. The colored horizontal lines in the figure depict the smallest association for which there was 95% power to reject the null hypothesis, based on the observed event rate for each of these three outcomes. The point estimates (open squares) and error bars represent the adjusted odds ratios together with 95% confidence intervals for the three falsification tests. For example, there was 95% power to detect an odds ratio as small as 1.4 for the outcome of septic shock (green horizontal line), yet the adjusted odds ratio for the PFO-septic shock association was 0.89 (95% CI, 0.52 to 1.52). Despite being well-powered, none of the falsification tests were statistically significant, nor were the effect sizes likely to be clinically significant.

eFigure 3. Histogram of variables with missing data and the pattern of missingness.



7 variables had missing data: body mass index (BMI), high risk surgical service (High Risk), American Society of Anesthesiologists physical status classification (ASA), Charlson comorbidity index (CCI), work relative value units (work RVU), intraoperative dose of vasopressors (Vasopressors), and inpatient surgery (Inpatient). The top panel shows the proportion (of 1.0) of missing data. The bottom panel shows the patterns of missingness (cells in blue denotes complete data, while cells in red denotes missing data for the respective variable): from the most frequent pattern of missingness on the leftmost column (no missing data in any of the 7 variables), to the least frequent on the rightmost column (missing data for the variables BMI, High Risk, Work RVU, and Vasopressors). The histogram at the very bottom depicts the corresponding frequency of each pattern of missingness.

eTable 1. International classification of diseases, ninth and tenth edition (ICD-9/10) diagnostic codes used to define exposure, outcome, and confounder variables.

Variable	ICD-9 code	ICD-10 code	Description
Patent foramen ovale / atrial septal defect	745.5	Q21.1	Patent foramen ovale or atrial septal defect
Other possible right-to-left shunt	745.4	Q21.0	Ventricular septal defect
		Q21.2	Atrioventricular septal defect
	746.89	Q24.8	Other specified congenital malformations of heart
	746.9	Q20.9	Congenital malformation of cardiac chambers and connections, unspecified
		Q24.9	Congenital malformation of heart, unspecified
	747.39	Q25.79	Other congenital malformations of pulmonary artery
Ischemic stroke	433.X1 434.X1	I63	Cerebral infarction
	437.1	I67.81	Acute cerebrovascular insufficiency
		I67.89	Other cerebrovascular disease
	437.9	I67.9	Cerebrovascular disease, unspecified
Transient ischemic attack	435.X	G45.0	Vertebro-basilar artery syndrome
		G45.1	Carotid artery syndrome (hemispheric)
		G45.8	Other transient cerebral ischemic attacks and related syndromes
Smoking	305.1	F17.XXX	Nicotine dependence
	V15.82	Z87.891	Personal history of nicotine dependence
Hypertension	401.XX	I10	Essential (primary) hypertension
Diabetes mellitus	250.XX	E10.X	Type 1 diabetes mellitus
		E11.X	Type 2 diabetes mellitus
		E13.X	Other specified diabetes mellitus
Dyslipidemia	272.X	E78.X	Disorders of lipoprotein metabolism and other lipidemias

Variable	ICD-9 code	ICD-10 code	Description
Coronary artery disease	410.XX	I21.X	STEMI and NSTEMI
		I22.X	Subsequent STEMI and NSTEMI
	411.1	I20.X	Angina pectoris
	411.8X		
	412	I25.2	Old myocardial infarction
	413.0		
	413.9		
	414.XX	I25.1XX	Atherosclerotic heart disease of native coronary artery
		I25.5	Ischemic cardiomyopathy
		I25.6	Silent myocardial ischemia
		I25.7XX	Atherosclerosis of coronary artery bypass graft(s) and coronary artery of transplanted heart with angina pectoris
		I25.8XX	Other forms of chronic ischemic heart disease
		I25.9	Chronic ischemic heart disease, unspecified
Myocardial infarction	410.XX	I21.X	STEMI and NSTEMI
		I22.X	Subsequent STEMI and NSTEMI
	411.89	I24.8	Other forms of acute ischemic heart disease
Congestive heart failure	428.XX	I50.X	Heart failure
Pulmonary edema	428.1	I50.1	Left ventricular failure
	518.4	J81.0	Acute pulmonary edema
	514	J81.1	Chronic pulmonary edema
Pulmonary hypertension	415.0	I26.0	Pulmonary embolism with acute cor pulmonale
	416.8	I27.2	Other secondary pulmonary hypertension
	416.9	I27.81	Cor pulmonale (chronic)
	416.0	I27.0	Primary pulmonary hypertension
Cardiomyopathy	425.X	I42.X	Cardiomyopathy
	425.8	I43	Cardiomyopathy in diseases classified elsewhere
Congenital heart disease	745.X	Q20.X	Congenital malformations of cardiac chambers and connections
		Q21.X	Congenital malformations of cardiac septa
		Q22.X	Congenital malformations of pulmonary and tricuspid valves
		Q23.X	Congenital malformations of aortic and mitral valves
	746.X	Q24.X	Other congenital malformations of heart
Eisenmenger’s syndrome	745.4	I27.89	Eisenmenger's syndrome
Atrial fibrillation	427.3X	I48.X	Atrial fibrillation and flutter

Variable	ICD-9 code	ICD-10 code	Description
Valvular heart disease	394.X	I05.X	Rheumatic mitral valve diseases
	395.X	I06.X	Rheumatic aortic valve diseases
	397.X	I07.X	Rheumatic tricuspid valve diseases
	396.X	I08.X	Multiple valve diseases
	424.0	I34.X	Nonrheumatic mitral valve disorders
	424.1	I35.X	Nonrheumatic aortic valve disorders
	424.2	I36.X	Nonrheumatic tricuspid valve disorders
	424.3	I37.X	Nonrheumatic pulmonary valve disorders
Chronic obstructive pulmonary disease	490	J40	Bronchitis, not specified as acute or chronic
	491.XX	J41.X	Simple and mucopurulent chronic bronchitis
		J42	Unspecified chronic bronchitis
	492.X	J43.X	Emphysema
	496	J44.X	Other chronic obstructive pulmonary disease
Migraine	346.XX	G43.X	Migraine
Chronic kidney disease	585.X	N18.X	Chronic kidney disease
	586	N19	Unspecified kidney failure
Hypercoagulable state	273.3	C88.0	Waldenstrom macroglobulinemia
	289.81	D68.5X	Primary thrombophilia
	289.82	D68.6X	Other thrombophilia
	289.89		Other specified diseases of blood and blood-forming organs
	286.9	D68.9	Coagulation defect, unspecified
Deep vein thrombosis	453.4X	I82.4XX	Acute embolism and thrombosis of deep veins of lower extremity
	453.5X	I82.5XX	Chronic embolism and thrombosis of deep veins of lower extremity
	453.79	I82.891	Chronic embolism and thrombosis of other specified veins
	453.89	I82.890	Acute embolism and thrombosis of other specified veins
	453.9	I82.9X	Embolism and thrombosis of unspecified vein
Pulmonary embolism	415.1X	I26.0X	Pulmonary embolism with acute cor pulmonale
		I26.9X	Pulmonary embolism without acute cor pulmonale
	416.2	I27.82	Chronic pulmonary embolism

Variable	ICD-9 code	ICD-10 code	Description
Systemic embolism	289.59	D73.5	Infarction of spleen
	362.3X	H34.0X	Transient retinal artery occlusion
		H34.1X	Central retinal artery occlusion
		H34.2XX	Other retinal artery occlusions
	444.21	I74.2	Embolism and thrombosis of the upper extremities
	444.22	I74.3	Embolism and thrombosis of the lower extremities
		I74.4	Embolism and thrombosis of arteries of extremities, unspecified
	444.89	I74.8	Embolism and thrombosis of other arteries
	444.9	I74.9	Embolism and thrombosis of unspecified artery
		I74.X	Arterial embolism and thrombosis
	557.0	K55.0XX	Acute vascular disorders of intestine
	557.9	K55.9	Vascular disorder of intestine, unspecified
	593.81	N28.0	Ischemia and infarction of kidney
Septic shock	785.52	R65.21	Severe sepsis with septic shock
	998.02	T81.12XX	Postprocedural septic shock
Wound complication	998.3X	T81.3XXX	Disruption of wound, not elsewhere classified
	998.59	T81.4XXX	Infection following a procedure
	998.6	T81.83XX	Persistent postprocedural fistula
	998.83	T81.89XX	Other complications of procedures, not elsewhere classified
Peptic ulcer	531	K25	Gastric ulcer
	532	K26	Duodenal ulcer
	533	K27	Peptic ulcer, site unspecified
Tricuspid valve diseases	397.0	I07.X	Rheumatic tricuspid valve diseases
		I36.X	Nonrheumatic tricuspid valve disorders

Abbreviations: STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.

eTable 2. Characterization of major cardiovascular and thromboembolic conditions at the time of PFO diagnosis.

Disease condition	ICD-9 codes	ICD-10 codes	Condition present upon PFO diagnosis, No. (%)
Atherosclerotic cardiovascular diseases			
Hypertension	401.XX	I10	1019 (66.2)
Coronary artery disease	411.1, 411.8X, 412, 413.0, 413.9, 414.XX	I21.X, I22.X, I20.X, I25.2, I25.1XX, I25.5, I25.6, I25.7XX, I25.8XX, I25.9	612 (39.7)
Myocardial infarction			
- Any	410.XX, 411.89	I21.X, I22.X, I24.8	187 (12.1)
- NSTEMI	410.7X, 411.89	I21.4, I22.2, I24.8	108 (7.0)
- STEMI	410.0X, 410.1X, 410.2X, 410.3X, 410.4X, 410.5X, 410.6X, 410.8X, 410.9X	I21.0X, I21.1X, I21.2X, I21.3, I22.0, I22.1, I22.8, I22.9	130 (8.4)
Transient ischemic attack	435.X	G45.0, G45.1, G45.8	181 (11.8)
Ischemic stroke	433.X1, 434.X1, 437.1, 437.9	I63, I67.81, I67.89, I67.9	366 (23.8)
Other major cardiovascular diseases			
Atrial fibrillation	427.3X	I48.X	439(28.5)
Congestive heart failure			
- Any	428.XX	I50.X	502 (32.6)
- Systolic heart failure	428.2	I50.2	19 (1.2)
- Diastolic heart failure	428.3	I50.3	86 (5.6)
- Combined systolic and diastolic heart failure	428.4	I50.4	3 (0.2)
Pulmonary edema	428.1, 518.4, 514	I50.1, J81.0, J81.1	514 (33.4)
Pulmonary hypertension	415.0, 416.8, 416.9, 416.0	I26.0, I27.2, I27.81, I27.0	184 (12.0)
Cardiomyopathy			
- Any	425.X	I42.X, I43	294 (19.1)
- Dilated	425.4	I42.0	270 (17.5)
- Hypertrophic	425.1	I42.1, I42.2	12 (0.8)
- Alcoholic	425.5	I42.6	5 (0.3)
Congenital heart disease	745.X, 746.X	Q20.X, Q21.X, Q22.X, Q23.X, Q24.X	93 (6.0)
Eisenmenger's syndrome	745.4	I27.89	26 (1.7)
Valvular heart disease			
- Any			976 (63.4)
- Mitral valve	394.X, 396.X, 424.0	I05.X, I34.X	706 (45.8)
- Aortic valve	395.X, 396.X, 424.1	I06.X, I35.X	453 (29.4)
- Tricuspid valve	424.2	I07.X, I36.X	115 (7.5)
- Pulmonary valve	424.3	I37.X	115 (7.5)
COPD	490, 491.XX, 492.X, 496	J40, J41.X, J42, J43.X, J44.X	343 (22.3)
Thromboembolic disease			
Hypercoagulable state	273.3, 289.81, 289.82, 289.89, 286.9	C88.0, D68.5X, D68.6X, D68.9	540 (35.1)
Deep vein thrombosis	453.4X, 453.5X, 453.79, 453.89, 453.9	I82.4XX, I82.5XX, I82.891, I82.890, I82.9X	184 (12.0)
Pulmonary embolism	415.1X, 416.2	I26.0X, I26.9X, I27.82	134 (8.7)
Systemic embolism	289.59, 362.3X, 444.21, 444.22, 444.89, 444.9, 557.0, 557.9, 593.81	D73.5, H34.0X, H34.1X, H34.2XX, I74.2, I74.3, I74.4, I74.8, I74.9,	272 (17.7)

	K55.0XX, K55.9, N28.0

Abbreviations: NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; COPD, chronic obstructive pulmonary disease.

eTable 3. Type of surgery.

Type of surgery, No. (%)	Total study population (n = 150 198)	PFO (n = 1540)	No PFO (n = 148 658)
Anesthesiology	6676 (4.4)	191 (12.4)	6485 (4.4)
Burn	1999 (1.3)	11 (0.7)	1988 (1.3)
Emergent / urgent surgery	6143 (4.1)	59 (3.8)	6084 (4.1)
General surgery	25247 (16.8)	181 (11.8)	25066 (16.9)
Gynecology	12112 (8.1)	69 (4.5)	12043 (8.1)
Neurosurgery	14051 (9.4)	219 (14.2)	13832 (9.3)
Oral / maxillofacial	3306 (2.2)	12 (0.8)	3294 (2.2)
Orthopedic surgery	26757 (17.8)	210 (13.6)	256547 (17.9)
Other	2147 (1.4)	38 (2.5)	2109 (1.4)
Otolaryngology	1046 (0.7)	3 (0.2)	1043 (0.7)
Plastic surgery	7597 (5.1)	34 (2.2)	7563 (5.1)
Radiology	1727 (1.2)	51 (3.3)	1676 (1.3)
Surgical oncology	9630 (6.4)	55 (3.6)	9575 (6.4)
Thoracic surgery	10962 (7.3)	123 (8.0)	10839 (7.3)
Transplant	2461 (1.6)	66 (4.3)	2395 (1.6)
Urology	13269 (8.8)	100 (6.5)	13169 (8.9)
Vascular surgery	5068 (3.4)	118 (7.7)	4950 (3.3)

eTable 4. Sample size and power calculation.

Study	Sample size	Prevalence of PFO	Event rate of stroke	Odds ratio	Power
Small	600	1.0%	0.5%	2.0	0.6%
Small	600	24.3%	0.5%	2.0	6.9%
Medium	1200	1.0%	0.5%	2.0	0.8%
Medium	1200	15.0%	0.5%	2.0	7.9%
Large	13 000	1.0%	0.5%	2.0	5.2%
Large	13 000	17.0%	0.5%	2.0	83.9%
Current	150 000	1.0%	0.5%	2.0	94.3%

eTable 5. Baseline and intraoperative characteristics of subgroups stratified by baseline PFO-independent risk of stroke.*

Characteristics	Total study population (n = 150 198)	Low stroke risk (n = 75 084)	High stroke risk (n = 75 083)
Baseline characteristics and comorbid conditions			
Age, mean (SD), y	55 (16)	50 (16)	59 (6)
Female sex, No. (%)	82029 (54.6)	42217 (56.2)	39796 (53.0)
Body mass index, mean (SD)	28.5 (7.1)	28.9 (7.2)	28.1 (6.9)
ASA physical status classification[a], median (IQR)	2 (2-3)	2 (2-2)	3 (2-3)
Charlson comorbidity index[b], median (IQR)	2 (0-3)	1 (0-2)	3 (1-6)
Smoking, No. (%)	30141 (20.1)	12003 (16.0)	18132 (24.1)
Hypertension, No. (%)	63955 (42.6)	19671 (26.2)	44266 (59.0)
Diabetes, No. (%)	21258 (14.2)	5812 (7.7)	15441 (20.6)
Dyslipidemia, No. (%)	48758 (32.5)	16313 (21.7)	32435 (43.2)
Coronary artery disease, No. (%)	19654 (13.1)	3876 (5.2)	15774 (21.0)
Myocardial infarction, No. (%)	2702 (1.8)	461 (0.6)	2239 (3.0)
Congestive heart failure, No. (%)	9617 (6.4)	1371 (1.8)	8243 (11.0)
Pulmonary edema, No. (%)	10299 (6.9)	1952 (2.6)	8346 (11.1)
Pulmonary hypertension, No. (%)	2212 (1.5)	323 (0.4)	1887 (2.5)
Cardiomyopathy, No. (%)	5043 (3.4)	778 (1.0)	4265 (5.7)
Congenital heart disease, No. (%)	1079 (0.7)	315 (0.4)	764 (1.0)
Eisenmenger’s syndrome, No. (%)	188 (0.1)	59 (0.1)	129 (0.2)
Atrial fibrillation, No. (%)	12234 (8.1)	2112 (2.8)	10117 (13.5)
Valvular heart disease, No. (%)	15808 (10.5)	3557 (4.7)	12244 (16.3)
COPD, No. (%)	11421 (7.6)	3604 (4.8)	7813 (10.4)
Transient ischemic attack, No. (%)	1739 (1.2)	226 (0.3)	1512 (2.0)
Ischemic stroke, No. (%)	3862 (2.6)	425 (0.6)	3435 (4.6)
Migraine, No. (%)	6050 (4.0)	1871 (2.5)	4178 (5.6)
Chronic kidney disease, No. (%)	11293 (7.5)	2613 (3.5)	8673 (11.6)
Hypercoagulable state, No. (%)	14167 (9.4)	4796 (6.4)	9365 (12.5)
Deep vein thrombosis, No. (%)	3901 (2.6)	958 (1.3)	2943 (3.9)
Pulmonary embolism, No. (%)	2454 (1.6)	589 (0.8)	1864 (2.5)
Systemic embolic phenomenon, No. (%)	8337 (5.6)	2297 (3.1)	6037 (8.0)
Prescription of medication within 28 days before surgery			
- Anticoagulants, No. (%)	46563 (31.0)	14869 (19.8)	31683 (42.2)
- Statins, No. (%)	35437 (23.6)	6651 (8.9)	28778 (38.3)
- Antiplatelet drugs, No. (%)	17879 (11.9)	2727 (3.6)	15149 (20.2)
- Beta blockers, No. (%)	20423 (13.6)	3154 (4.2)	17262 (23.0)

Characteristics	Total study population (n = 150 198)	Low stroke risk (n = 75 084)	High stroke risk (n = 75 083)
Intraoperative characteristics			
Emergency procedure, No. (%)	5993 (4.0)	1338 (1.8)	4638 (6.2)
High risk procedure[c], No. (%)	59788 (39.8)	16478 (21.9)	43293 (57.7)
Inpatient procedure, No. (%)	111949 (74.5)	38508 (51.3)	73413 (97.8)
Work relative value units[d] (median, IQR)	14.5 (8.1-22.0)	10.5 (6.8-15.5)	19.5 (12.2-25.2)
Duration of procedure in minutes (median, IQR)	144 (92-227)	111 (74-168)	190 (122-277)
Intraoperative hypotensive minutes MAP <55mmHg (median, IQR)	0 (0-2)	0 (0-1)	1 (0-2)
Total intraoperative norepinephrine equivalent dose in mg (median, IQR)	0.0 (0.0-0.2)	0.0 (0.0-0.0)	0.1 (0.0-0.4)
Total intraoperative fluids in Ml (median, IQR)	1250 (800-2000)	1000 (750-1550)	1500 (1000-2750)
Packed red blood cell units transfused intraoperatively, No. (%)	5193 (3.5)	836 (1.1)	4346 (5.8)

*Refer to Section 6.6 “Baseline PFO-independent risk of stroke”. 31 patients with ASA physical status class V were not included due to failure to calculate the probability score for PFO-independent risk of perioperative ischemic stroke.

Abbreviations: SD, standard deviation; ASA, American Society of Anesthesiologists; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; MAP, mean arterial pressure.

[a]The American Society of Anesthesiologists physical status classification system is used to evaluate a patient’s physical state before undergoing anesthesia or surgery. The current definitions include 6 categories, from ASA I (normal healthy patient) to ASA VI (patient who is brain-dead).

[b]The Charlson comorbidity index is a method of estimating the risk of death by scoring a range of 22 comorbid diseases. Each condition is assigned a score of 1, 2, 3, or 6, and the total score is used to predict 10-year mortality.

[c]High risk procedures include surgery for burns, general surgery, neurosurgery, thoracic surgery, transplant surgery, and vascular surgery.

[d]Work relative value units are a measure of the value of the services provided by physicians, and is a marker of the procedural complexity.

eTable 6. Baseline and intraoperative characteristics of subgroups stratified by history of echocardiography prior to surgery.

Characteristics	No echocardiography (n = 120 569)	Echocardiography		
		All patients (n = 29 629)	PFO (n = 1162)	No PFO (n = 28 467)
Baseline characteristics and comorbid conditions				
Age, mean (SD), y	54 (16)	60 (16)	58 (15)	60 (16)
Female sex, No. (%)	67812 (56.2)	1427 (48.0)	633 (54.5)	13584 (47.7)
Body mass index, mean (SD)	28.4 (7.0)	28.7 (7.4)	27.9 (7.1)	28.7 (7.4)
ASA physical status classification[a], median (IQR)	2 (2-2)	3 (2-3)	3 (2-3)	3 (2-3)
Charlson comorbidity index[b], median (IQR)	1 (0-3)	3 (1-7)	4 (2-8)	3 (1-7)
Smoking, No. (%)	23139 (19.2)	7002 (23.6)	310 (26.7)	6692 (23.5)
Hypertension, No. (%)	44778 (37.1)	19177 (64.7)	766 (65.9)	18411 (64.7)
Diabetes, No. (%)	13877 (11.5)	7381 (24.9)	300 (25.8)	7081 (24.9)
Dyslipidemia, No. (%)	34469 (28.6)	14289 (48.2)	556 (47.8)	13733 (48.2)
Coronary artery disease, No. (%)	10139 (8.4)	9515 (32.1)	431 (37.1)	9084 (31.9)
Myocardial infarction, No. (%)	851 (0.7)	1851 (6.2)	98 (8.4)	1753 (6.2)
Congestive heart failure, No. (%)	2714 (2.3)	6903 (23.3)	374 (32.2)	6529 (22.9)
Pulmonary edema, No. (%)	4200 (3.5)	6099 (20.6)	322 (27.7)	5777 (20.3)
Pulmonary hypertension, No. (%)	460 (0.4)	1752 (5.9)	143 (12.3)	1609 (5.7)
Cardiomyopathy, No. (%)	800 (0.7)	4243 (14.3)	206 (17.7)	4037 (14.2)
Congenital heart disease, No. (%)	311 (0.3)	768 (2.6)	66 (5.7)	702 (2.5)
Eisenmenger's syndrome, No. (%)	80 (0.1)	108 (0.4)	14 (1.2)	94 (0.3)
Atrial fibrillation, No. (%)	4931 (4.1)	7303 (24.6)	317 (27.3)	6986 (24.5)
Valvular heart disease, No. (%)	2609 (2.2)	13199 (44.5)	683 (58.8)	12516 (44.0)
COPD, No. (%)	7047 (5.8)	4374 (14.8)	215 (18.5)	4159 (14.6)
Transient ischemic attack, No. (%)	610 (0.5)	1129 (3.8)	79 (6.8)	1050 (3.7)
Ischemic stroke, No. (%)	1427 (1.2)	2435 (8.2)	210 (18.1)	2225 (7.8)
Migraine, No. (%)	4739 (3.9)	1311 (4.4)	57 (4.9)	1254 (4.4)
Chronic kidney disease, No. (%)	5223 (4.3)	6070 (20.5)	295 (25.4)	5775 (20.3)
Hypercoagulable state, No. (%)	8619 (7.1)	5548 (18.7)	328 (28.2)	5220 (18.3)
Deep vein thrombosis, No. (%)	1939 (1.6)	1962 (6.6)	114 (9.8)	1848 (6.5)
Pulmonary embolism, No. (%)	1084 (0.9)	1370 (4.6)	84 (7.2)	1286 (4.5)
Systemic embolic phenomenon, No. (%)	5405 (4.5)	2932 (9.9)	144 (12.4)	2788 (9.8)
Prescription of medication within 28 days before surgery				
- Anticoagulants, No. (%)	32038 (26.6)	14525 (49.0)	594 (51.1)	13931 (48.9)
- Statins, No. (%)	24407 (20.2)	11030 (37.2)	456 (39.2)	10574 (37.1)
- Antiplatelet drugs, No. (%)	10579 (8.8)	7300 (24.6)	341 (29.3)	6959 (24.4)
- Beta blockers, No. (%)	11486 (9.5)	8937 (30.2)	377 (32.4)	8560 (30.1)

Characteristics	No echocardiography (n = 120 569)	Echocardiography (n = 29 629)		
		All patients (n = 29 629)	PFO (n = 1162)	No PFO (n = 28 467)
Intraoperative characteristics				
Emergency procedure, No. (%)	4487 (3.7)	1506 (5.1)	63 (5.4)	1443 (5.1)
High risk procedure[c], No. (%)	47464 (39.4)	12324 (41.6)	542 (46.6)	11782 (41.4)
Inpatient procedure, No. (%)	87242 (72.4)	24707 (83.4)	1035 (89.1)	23672 (83.2)
Work relative value units[d] (median, IQR)	15.0 (8.2-22.1)	13.2 (7.5-20.1)	14.2 (8.1-20.7)	13.1 (7.5-20.1)
Duration of procedure in minutes (median, IQR)	144 (92-225)	144 (90-235)	155 (96-251)	144 (90-234)
Intraoperative hypotensive minutes MAP <55mmHg (median, IQR)	0 (0-1)	0 (0-2)	1 (0-3)	0 (0-2)
Total intraoperative norepinephrine equivalent dose in mg (median, IQR)	0.0 (0.0-0.2)	0.1 (0.0-0.4)	0.1 (0.0-0.4)	0.1 (0.0-0.3)
Total intraoperative fluids in mL (median, IQR)	1250 (850-2000)	1100 (750-2000)	1050 (600-2134)	1100 (750-2000)
Packed red blood cell units transfused intraoperatively, No. (%)	3383 (2.8)	1810 (6.1)	89 (7.7)	1721 (6.0)

Abbreviations: SD, standard deviation; ASA, American Society of Anesthesiologists; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; MAP, mean arterial pressure.

[a]The American Society of Anesthesiologists physical status classification system is used to evaluate a patient's physical state before undergoing anesthesia or surgery. The current definitions include 6 categories, from ASA I (normal healthy patient) to ASA VI (patient who is brain-dead).

[b]The Charlson comorbidity index is a method of estimating the risk of death by scoring a range of 22 comorbid diseases. Each condition is assigned a score of 1, 2, 3, or 6, and the total score is used to predict 10-year mortality.

[c]High risk procedures include surgery for burns, general surgery, neurosurgery, thoracic surgery, transplant surgery, and vascular surgery.

[d]Work relative value units are a measure of the value of the services provided by physicians, and is a marker of the procedural complexity

Section 9. References

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