Early Versus Delayed Stroke After Cardiac Surgery: A Systematic Review and Meta-Analysis

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Background—Although it is traditionally regarded as a single entity, perioperative stroke comprises 2 separate phenomena (early/intraoperative and delayed/postoperative stroke). We aimed to systematically evaluate incidence, risk factors, and clinical outcome of early and delayed stroke after cardiac surgery.

Methods and Results—A systematic review (MEDLINE, EMBASE, Cochrane Library) was performed to identify all articles reporting early (on awakening from anesthesia) and delayed (after normal awakening from anesthesia) stroke after cardiac surgery. End points were pooled event rates of stroke and operative mortality and incident rate of late mortality. Thirty-six articles were included (174 969 patients). The pooled event rate for early stroke was 0.98% (95% CI 0.79% to 1.23%) and was 0.93% for delayed stroke (95% CI 0.77% to 1.11%; P=0.68). The pooled event rate of operative mortality was 28.8% (95% CI 17.6% to 43.4%) for early and 17.9% (95% CI 14.0% to 22.7%) for delayed stroke, compared with 2.4% (95% CI 1.9% to 3.1%) for patients without stroke (P<0.001 for early versus delayed, and for perioperative stroke, early stroke, and delayed stroke versus no stroke). At a mean follow-up of 8.25 years, the incident rate of late mortality was 11.7% (95% CI 7.5% to 18.3%) for early and 9.4% (95% CI 5.9% to 14.9%) for delayed stroke, compared with 3.4% (95% CI 2.4% to 4.8%) in patients with no stroke. Meta-regression demonstrated that off-pump was inversely associated with early stroke (β=−0.009, P=0.01), whereas previous stroke (β=0.02, P<0.001) was associated with delayed stroke.

Conclusions—Early and delayed stroke after cardiac surgery have different risk factors and impacts on operative mortality as well as on long-term survival. ([Am Heart Assoc. 2019;8:e012447. DOI: 10.1161/JAHA.119.012447])

Key Words: cardiac surgery • delayed stroke • early stroke • stroke

Perioperative stroke is a devastating complication after cardiac surgery, and the incidence has remained largely unchanged despite advances in surgical techniques. Data from administrative databases and observational registries suggest that the incidence of perioperative stroke after cardiac surgery ranges from 0.8% to 5.2%. In landmark trials comparing outcomes of coronary artery bypass graft (CABG) and percutaneous coronary intervention, including SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) and FREEDOM (Future REvascularization Evaluation in patients with Diabetes Mellitus), the burden of stroke has been a major limitation for surgery. Stroke may occur intraoperatively (usually detected when patients initially awaken from anesthesia) or thereafter. The 2 types of strokes have different pathophysiologic mechanisms: early/intraoperative stroke occurs primarily from aortic manipulation and atheroembolism, whereas delayed/postoperative stroke is usually related to postoperative atrial fibrillation or cerebral vascular disease. The conceptual framework of early and delayed stroke is important because it facilitates implementation and evaluation of tailored preventative strategies for both. Greater understanding of the incidence, risk factors, and sequelae of early and delayed stroke will facilitate the continued improvement in the safety of surgical intervention.
Clinical Perspective

What Is New?

- This is the first systematic review and meta-analysis to examine the incidence of early and delayed stroke after cardiac operations.

What Are the Clinical Implications?

- Early and delayed stroke after cardiac surgery have different risk factors and impacts on operative mortality as well as on long-term survival.

Here we performed a systematic review and meta-analysis to give an objective and weighted estimate of the incidence and risk of early and delayed stroke following cardiac surgery and their impact on operative and long-term patient survival.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. This systematic review and meta-analysis were performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement7 and the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines (Table S1).8

Search Strategy

A medical librarian (M.D.) performed comprehensive systematic searches to identify studies that evaluated perioperative stroke after cardiac surgery. Searches were run in April 2018 on the following databases: Ovid MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present); Ovid EMBASE (1974 to present); and The Cochrane Library (Wiley, Hoboken, NJ). The search strategy included all appropriate controlled vocabulary and keywords for identified “cardiac surgical procedures” and “intra- and postoperative stroke.” Full details regarding the search strategy for Ovid MEDLINE are provided in Table S2.

Study Selection and Inclusion Criteria

Database searches were conducted and deduplicated by a qualified librarian (M.D.). Three preliminary reviewers screened the searched database for inclusion. A fourth independent reviewer confirmed the adequacy of studies based on predefined inclusion criteria for titles and abstracts. Inclusion criteria were full-text English articles on adult patients who had undergone cardiac surgery and reported perioperative strokes and classified them as early or delayed. A full text of preliminary screened studies was then retrieved for a second round of eligibility screening. Reference lists of the included articles were also searched, and additional studies included (ie, backward snowballing). The full PRISMA flow chart outlining the study selection process is available in Figure S1. The Newcastle-Ottawa Scale for quality assessment was used for the critical appraisal of included studies (Table S3).9 Studies with scores of 6 or more were included.

Clinical Outcomes/Definitions

The primary outcome was the rate of early and delayed stroke. Secondary outcomes were (1) rate of perioperative (early+delayed) stroke; (2) operative mortality among patients with perioperative stroke, early stroke, delayed stroke, and among patients without stroke; and (3) late mortality for the above groups of patients.

We used the original articles’ definitions for early and delayed stroke. The most common definitions used were stroke observed “on awakening” or “after extubation” for early stroke and stroke occurring after a symptom-free interval for delayed stroke (Table S4).

Data Extraction and Statistical Analysis

Extracted variables included study name, publication year, study design, type of surgery, total sample size, number of patients with perioperative, early, and delayed stroke, mean age (years), percentages of women, diabetes mellitus, preoperative atrial fibrillation (AF), preoperative carotid disease, previous history of stroke or urgent or emergency surgery, peripheral vascular disease, chronic renal failure, redo surgery, in-hospital mortality in the whole sample and in different subgroups, long-term mortality, and mean follow-up.

Measurement data were reported as mean±SD. Pooled event rates with 95% CI were calculated for binary outcomes. For late outcomes the incidence rate with an underlying Poisson process with a constant event rate was used to account for different follow-up periods in different studies with the total number of events observed within a treatment group out of the total person-time of follow-up for that treatment group calculated from the study follow-up. Additionally, for long-term survival, individual patient survival data were reconstructed using an iterative algorithm that was applied to solve the Kaplan-Meier equations originally used to produce the published graphs. This algorithm uses digitalized Kaplan-Meier curve data obtained by the Graph Grabber.
software package (Quintessa, Oxfordshire, UK) to find numerical solutions to the inverted Kaplan-Meier equation. Based on the published data in each included study, 4 different levels of information might be available (“all information,” “no numbers at risk,” “no total events,” and “neither”). The censoring pattern varied based on the numbers at risk published intervals as in Williamson. For the “no number at risk” case, the censoring pattern is assumed constant over the interval, and for the “neither” case, no censoring is assumed.

Table 1. Details of Outcomes in the Included Studies

| Study/Year | Study Type | Cohort Size | Perioperative Stroke | Early Stroke | Delayed Stroke |
|------------|------------|-------------|----------------------|--------------|---------------|
| Blossom 1992 | R          | 3428        | 46                   | 16           | 30            |
| Bolvie 2005 | R          | 2641        | 98                   | 76           | 22            |
| Borger 2001 | R          | 6682        | 98                   | 90           | 8             |
| Bull 1993  | P          | 245         | 5                    | 4            | 1             |
| Calafiore 2002 | R       | 4875        | 49                   | 24           | 25            |
| Cao 2011   | R          | 430         | 32                   | 4            | 28            |
| Carrascal 2014 | R      | 844         | 32                   | 23           | 9             |
| Chen 2015  | R          | 1010        | 11                   | 5            | 6             |
| Doi 2010   | R          | 611         | 8                    | 0            | 8             |
| Fessatidis 1991 | R       | 1487        | 15                   | 12           | 3             |
| Filsoufi.A 2008 | R    | 2808        | 63                   | 35           | 28            |
| Filsoufi.B 2008 | R       | 2985        | 48                   | 25           | 23            |
| Gaudino 1999 | R         | 2987        | 31                   | 25           | 6             |
| Goto 2003  | R          | 463         | 18                   | 13           | 5             |
| Hedberg 2005 | R         | 2641        | 77                   | 58           | 19            |
| Hedberg 2011 | R         | 9122        | 245                  | 146          | 99            |
| Hedberg 2013 | R         | 10 809      | 339                  | 223          | 116           |
| Hogue 1999  | P          | 2972        | 48                   | 17           | 31            |
| Imasaka 2018 | R         | 1134        | 20                   | 8            | 12            |
| Karhausen 2017 | R       | 6130        | 110                  | 35           | 75            |
| Karkouti 2005 | R         | 10 949      | 160                  | 110          | 50            |
| Kinnunen 2015 | R         | 1314        | 23                   | 7            | 16            |
| Lahtinen 2004 | R         | 2630        | 52                   | 20           | 32            |
| Lee 2011   | P          | 1367        | 33                   | 15           | 18            |
| Lisle 2008  | R          | 7201        | 202                  | 46           | 156           |
| Martin 1982 | R          | 253         | 8                    | 4            | 4             |
| Marui 2012  | R          | 2446        | 45                   | 20           | 25            |
| Murdoch 2003 | R         | 2104        | 68                   | 18           | 50            |
| Nishiyama 2004 | P        | 2516        | 46                   | 17           | 29            |
| Peel 2004   | R          | 10 573      | 211                  | 57           | 154           |
| Ridderstolpe 2002 | R    | 3282        | 64                   | 47           | 17            |
| Salazar 2001 | R         | 5971        | 214                  | 158          | 56            |
| Tarakji 2011 | P          | 45 432      | 688                  | 279          | 409           |
| Toumpoulis 2008 | R        | 4140        | 138                  | 102          | 36            |
| Weinstein 2001 | P       | 2217        | 51                   | 24           | 27            |
| Wijdicks 1996 | R         | 8270        | 25                   | 4            | 21            |

P indicates prospective; R, retrospective.
The reconstructed patient survival data were then aggregated to obtain combined survival curves. Subgroup analysis was used to compare early and delayed stroke for primary and secondary outcomes. Meta-regression was used to assess the effect of age, sex, diabetes mellitus, preoperative AF, preoperative carotid disease, previous stroke, urgency or emergency surgery, off-pump CABG, single or multiple aortic clamping, ascending aorta atheroma or calcification, cardiopulmonary bypass time, and aortic clamp time on the rate of early and delayed stroke.

Study heterogeneity was assessed using the Cochran Q statistic and the $I^2$ test. For the primary outcomes, if heterogeneity was significant ($I^2 > 75\%$), a leave-one-out sensitivity analysis was performed. Potential publication bias was assessed using a funnel plot and the Egger regression test.

A random-effect model (inverse variance method) was used. In addition, prediction interval was calculated as described by Riley et al. Supplementary analyses using a fixed-effect model were also performed, and $\tau^2$ was provided as an inference on between-study variability; we then used meta-regression, which used covariates to explain some of this variability. A restricted maximum-likelihood model was used for meta-regression because it estimates parameters that maximize the likelihood of the error distribution while imposing restrictions to avoid overfitting, which makes it possible to obtain a better balance between the fractions of the variability captured by the fixed part versus the random part of the statistical model. Hypothesis testing for equivalence was set at the 2-tailed $P<0.05$. Analyses were performed using R (version 3.3.3, R Project for Statistical Computing, Vienna, Austria) with the statistical packages “meta” and “metafor” within RStudio (0.99.489, http://www.rstudio.com).

Figure 1. Pooled event rate for early stroke.
Results

Characteristics of Eligible Studies

We retrieved 5212 articles and 3784 articles after deduplication. Thirty-six articles met our inclusion criteria (list of the included studies provided in the supplemental references). The PRISMA flowchart is shown in Figure S1. The mean sample size for each study was 4860 patients (range: 245-432), and the mean follow-up time was 8.25 years (range 1.0-11.0 years). The mean age was 65.5 years (range: 54.0-74.0 years) (Table S5). Women represented 15% to 83% of the included patients, and diabetes mellitus, AF, carotid disease, and urgent/emergent procedures were reported in 5% to 47%, 1% to 19%, 6% to 32%, and 1% to 70% of patients, respectively. Sixty-three percent of procedures were isolated CABG (Table S5). A total of 174 969 patients were included in the analysis, of whom 2.0% (3421 of 174 969 patients) had perioperative stroke, 1.0% (1654/174 969) had delayed stroke ($P=0.68$) (Table 1).14-49

The majority of stroke patients suffered from an ischemic event (88%). Transient ischemic attacks were reported in 1.38% of cases.

Mean bypass time was 81.6 minutes, and mean cross-clamp time was 82.2 minutes.

Meta-Analysis

Rate of Stroke

The pooled event rate of perioperative stroke was 2.03% (CI 1.75% to 2.35%) (Figure S2), early stroke was 0.98% (CI 0.79% to 1.23%; Figure 1), and delayed stroke was 0.93% (CI 0.77% to 1.11%; $P=0.68$ Figure 2; Table 2). A summary of the outcomes as analyzed by means of a fixed-effect model is reported in Table S6.)
Operative Mortality

Overall pooled event rates for operative mortality was 2.2% (CI: 1.8% to 2.8%). For patients with perioperative stroke, the operative mortality was 21.3% (CI: 18.3% to 24.5%), 28.8% (CI: 17.6% to 43.3%) for patients with early stroke and 17.9% (CI: 14.0% to 22.7%) for patients with delayed stroke (P<0.001 for early versus delayed stroke; Figures 3 and 4). The pooled event rate for operative mortality without stroke was 2.4% (CI 1.9% to 3.1%) (P<0.001 compared with patients with perioperative, early, and delayed stroke; Figure 4).

Late Mortality

The weighted mean follow-up was 8.25 years. Overall incidence rate for late mortality for the entire cohort was 3.4% (CI 2.4% to 4.8%; P<0.0001 compared with patients with perioperative, early, and delayed stroke; Table 2; a summary of the outcomes as analyzed by means of a fixed-effect model is reported in Table S6).

Reconstructed individual patient survival data from Kaplan-Meier survival curves showed 1-, 3-, 5-, and 10-year survival of 80.2%, 73.0%, 63.3%, and 40.7%, respectively, in the early-stroke group and 88.1%, 85.2%, 71.3%, and 30.2%, respectively, in the delayed-stroke group (Figure S3). For patients who did not experience stroke, 1-, 3-, 5-, and 10-year survivals were 99.5%, 99.2%, 99.1%, and 97.1%, respectively.

The funnel plot of observed and imputed studies (trim-and-fill method) and leave-one-out analysis for the primary outcomes revealed absence of publication bias (the Egger intercept is −2.25±1.33 [P=0.10] for early and −1.47±1.04 [P=0.17] for delayed stroke; Figure S4). The cumulative analyses for the primary outcomes are shown in Figure 5.

Table 2. Summary of the Outcomes (Random-Effect Model)

| Outcomes                                             | No. of Studies | Proportion [CI]       | Heterogeneity (I², P Value) | Perioperative Stroke vs No Stroke* | Early vs Delayed Stroke Difference* |
|------------------------------------------------------|----------------|-----------------------|-----------------------------|-----------------------------------|-------------------------------------|
|                                                     |                |                      |                             |                                   |                                     |
| Random-effect model                                  |                |                      |                             |                                   |                                     |
| Pooled rate of perioperative stroke                  | 36             | 2.03% [1.75; 2.35]; PI=0.85-4.74 | 94.1%, P=0.0001 | 0.1804                            | ...                                 |
| Pooled rate of early stroke                          | 36             | 0.98% [0.79; 1.23]; PI=0.27-3.49 | 94.7%, P=0.0001 | 0.3912                            | ...                                 |
| Pooled rate of delayed stroke                        | 36             | 0.93% [0.77; 1.11]; PI=0.33-2.59 | 91.5%, P=0.0001 | 0.2568                            | ...                                 |
| Pooled rate of operative mortality in the whole group| 20             | 2.2% [1.8; 2.8]       | 96.9%, P=0.0001 | 0.2543                            | ...                                 |
| Pooled rate of operative mortality for patients with perioperative stroke | 22             | 21.3% [18.3; 24.5]  | 58.8%, P=0.0003 | 0.0935                            | <0.0001                             |
| Pooled rate of operative mortality for patients without stroke | 16             | 2.4% [1.9; 3.1]     | 96.9%, P=0.0001 | 0.2419                            | <0.0001                             |
| Pooled rate of operative mortality for patients with early stroke | 12             | 28.8% [17.6; 43.4]  | 84.2%, P=0.0001 | 0.9440                            | <0.0001                             |
| Pooled rate of operative mortality for patients with delayed stroke | 13             | 17.9% [14.0; 22.7] | 20.1%, P=0.2407  | 0.0550                            | <0.0001                             |
| Incidence rate of late mortality in the “all” group  | 5              | 3.4% [2.3; 5.2]      | 99.3%, P=0.0001 | 0.2150                            | ...                                 |
| Incidence rate of late mortality in patients with perioperative stroke | 5              | 10.9% [7.3; 16.2]  | 84.8%, P=0.0001 | 0.1600                            | <0.0001                             |
| Incidence rate of late mortality in patients without stroke | 8              | 3.4% [2.4; 4.8]     | 99.7%, P=0  | 0.2426                            | <0.0001                             |
| Incidence rate of late mortality in patients with early stroke | 5              | 11.7% [7.5; 18.3] | 87.6%, P=0.0001 | 0.2194                            | 0.5063                              |
| Incidence rate of late mortality in patients with delayed stroke | 5              | 9.4% [5.9; 14.9]    | 71.2%, P=0.008 | 0.1771                            | 0.5063                              |

PI indicates prediction interval.
*P value for subgroup difference.
Meta-Regression

Off-pump surgery was inversely associated with early stroke ($\beta=-0.009$, $P=0.01$). Previous stroke ($\beta=0.02$, $P<0.001$) was associated with delayed stroke. Single versus multiple aortic clamping, ascending aortic atheroma or calcification, use of circulatory arrest, cardiopulmonary bypass, and aortic cross-clamp times were not associated with either early or delayed stroke (Table S7).

Discussion

To our knowledge the present work is the first systematic review and meta-analysis to examine the incidence, risk factors, and impact on clinical outcomes of early and delayed stroke after cardiac surgery.

Previous evidence was based on single-center cohorts with variable sample size, incidence of events, and follow-up duration so that a general and objective estimate of the
The incidence of the 2 types of stroke was difficult to ascertain. For this reason, the results of this meta-analysis are of substantial relevance for patient counseling, clinical decision making, and planning of research for preventive interventions.

The main findings were as follows: (1) the rates of early and late stroke were similar at ≈1% each, (2) both early and delayed stroke were associated with a significant increase in operative as well as late mortality, (3) the impact on operative mortality was significantly higher for early versus delayed stroke, (4) a prior history of stroke was associated with delayed stroke, whereas (5) off-pump CABG was inversely associated with early stroke.

Early stroke (defined as detected “on awakening” or “after extubation”) is directly linked to intraoperative events. Early strokes were inversely associated with off-pump CABG but not with any patient characteristics, suggesting the technical/surgical nature of their etiology. Cerebral embolization is known to occur mainly due to aortic manipulation (cannulation, cross-clamping, and performance of proximal aortic anastomoses during CABG). Early stroke has been reported to be usually located in the right hemisphere, consistent with the jet of the flow from the aortic cannula.

Although large randomized controlled trials have reported similar neurological outcomes after on- and off-pump CABG (30-day stroke incidence for on- versus off-pump, respectively; 0.7% versus 1.3% [P=0.28] in the ROOBY [Randomized On/Off Bypass] trial\textsuperscript{53}; 2.7% versus 2.2% [P=0.47] in the GOPCABE (German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients) trial\textsuperscript{54}; 1.1% versus 1.0% [P-value not reported] in the CORONARY (CABG Off or On Pump Revascularization Study) trial\textsuperscript{55}), in our analysis off-pump surgery was significantly and adversely associated with early stroke. Differences in sample size, treatment allocation, and surgeon expertise are the possible reasons for these differences.
Hedberg et al in a series of 10,809 patients reported that early strokes were predominantly located in the right hemisphere (\(P=0.009\)), whereas delayed stroke had a uniform spatial distribution. Authors suggested that the preponderance for right-hemispheric lesions might suggest an embolic etiology via the brachiocephalic trunk.\(^3\) Higher stroke-related mortality (odds ratio 9.16; \(P<0.0001\)) and greater rehabilitation needs for early versus delayed stroke were reported in a review of 7,201 patients.\(^3\)

Significant efforts have been aimed at intraoperative stroke reduction including minimizing or eliminating aortic manipulation, eliminating cardiopulmonary bypass, and using preoperative CT scan of the ascending aorta and duplex scanning of the carotid arteries as well as epiaortic ultrasound.\(^5\)–\(^6\)

Motallebzadeh et al randomized a total of 212 patients to receive on-pump versus off-pump coronary artery bypass and demonstrated reduced cerebral embolism with a better neurocognitive score at discharge in those undergoing off-pump surgery (\(P<0.001\) and \(P=0.01\), respectively); there were 3 nonfatal strokes in the on-pump group and 1 in the off-pump group within 30 days of surgery.\(^6\)

In a large series including more than 12,000 patients, the use of an aortic facilitating device to perform the proximal anastomosis significantly reduced the postoperative stroke rate but was inferior to no-aortic touch technique (stroke rates 0.6%, 1.2%, and 1.5% in the no-touch, clampless facilitating device, and the clamp group, respectively).\(^6\)

Consistent with these results, Vallely reported that an aortic off-pump coronary artery bypass resulted in 0.25% of neurological adverse events as compared with 1.1% in the groups with side-clamping for proximal anastomoses.\(^6\)

A multicenter randomized trial enrolling 383 patients undergoing surgical aortic valve replacement recently evaluated the potential neuroprotective role of 2 cannulation systems designed to capture aortic microemboli (Embol-X Embolic Protection Device, Edwards Life Science, Irvine, CA; and CardioGard Cannula, CardioGard Medical Ltd, Or-Yehuda, Israel). The rate of freedom from cerebral infarction at 7 days was 32.0% with suction-based extraction versus 33.3% with control (ie, standard aortic cannula) (between-group difference, −1.3%; 95% CI −13.8% to 11.2%) and 25.6% with intra-aortic filtration versus 32.4% with control (between-group difference −6.9%; 95% CI −17.9% to 4.2%); no significant differences in mortality (3.4% for suction-based extraction versus 1.7% for control; and 2.3% for intra-aortic filtration versus 1.5% for control) or clinical stroke (5.1% for suction-based extraction versus 5.8% for control; and 8.3% for intra-aortic filtration versus 6.1% for control) were detected.\(^6\)

The effectiveness of early stroke reduction strategies was recently demonstrated by the EXCEL (Evaluation of XIENCE

![Figure 5. Cumulative analysis of incidence of (A) early stroke and (B) delayed stroke.](https://example.com/figure5.png)
Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, in which surgeons were encouraged to use intraoperative adjunctive techniques for stroke reduction including epiaortic ultrasound and trans-esophageal echocardiography for assessment of ascending aortic calcification. The result was an overall incidence of stroke that did not differ between CABG and percutaneous coronary intervention (2.9% versus 2.3%, P=0.37).

In our study early stroke was associated with a 12-fold increase in operative mortality (29% versus 2% without stroke) as well as much higher increases in the risk of late death (12% versus 3% without stroke), suggesting that addressing this potential complication can significantly improve the outcomes of cardiac surgery. Of note, the impact on operative mortality was significantly higher for early versus delayed stroke.

Delayed stroke (defined as stroke occurring after a normal awakening from anesthesia) is probably mostly related to postoperative AF or to cerebrovascular disease. In our analysis delayed stroke was associated with a 7- and 3-fold increase in operative and late mortality, respectively. Late stroke was also associated with history of stroke, suggesting a greater influence of patient-related factors such as vascular disease compared with early stroke. Indeed, contemporary cardiac surgical patients are older and have greater numbers of cardiovascular comorbidities including hypertension, diabetes mellitus, advanced age, kidney disease, peripheral artery disease, and cerebrovascular disease. Validated stroke risk prediction tools such as the CHA2DS2-VASC (congestive heart failure, hypertension, age, diabetes [mellitus], and stroke/TIA–vascular disease and female gender) scoring schema indicate that a substantial portion of cardiac surgical patients are at high risk for AF-related stroke.

The main strategies for delayed stroke prevention are (1) pharmacological or nonpharmacological AF prophylaxis, (2) anticoagulation for prevention and treatment of clot formation, and (3) elimination of the left atrial appendage. AF prophylaxis includes amiodarone, β-blockers, magnesium, atrial pacing, and posterior pericardiectomy. Regarding left atrial appendage isolation, LAOSS III (the Left Atrial Appendage Occlusion Study) is an ongoing prospective, double-blind, randomized trial comparing concomitant surgical left atrial appendage occlusion and no-occlusion in patients with AF or flutter who are undergoing cardiac surgery (ClinicalTrials.gov Identifier: NCT01561651). Again, continued efforts to evaluate interventions to lower the risk of delayed stroke in prospective surgical trials are needed.

This study shares the common limitations of analyses of aggregate data. First, this analysis included a range of cardiac surgical procedures, although isolated CABG was the most common type of procedure (Table S5). There was heterogeneity in the definitions used by the different studies, in the surgical and postoperative protocols (Table S4), as well as in the follow-up approaches, in the involvement of a neurologist in the diagnosis of stroke events, and in the documentation of these events by cerebral-imaging studies. Moreover, postdischarge stroke might have been missed in some studies. Finally, most of the studies did not use continuous monitoring of postoperative cardiac rhythm, and thus, we have no solid information on the occurrence of postoperative AF, and we were unable to include this variable in our meta-regression analysis. As in all meta-analyses, ecological fallacy is a concern. Finally, it was not possible to determine whether early or late deaths were directly related to strokes.

Summary

This is the first systematic review and meta-analysis to examine the incidence of early and delayed stroke after cardiac operations. There is a 1% risk for both early and delayed stroke after cardiac surgery. Early stroke is not associated with any patient-level risk factors, suggesting a technical cause, and is associated with a significant increase in operative mortality as well as reduction in long-term survival. The impact of early stroke on operative mortality is significantly higher than that of delayed stroke. Delayed stroke is associated with previous stroke and also negatively impacts survival. Continued targeted interventions to reduce the burden of both early and delayed strokes are imperative to improve overall surgical outcomes.

Disclosures

None.

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SUPPLEMENTAL MATERIAL
Table S1. MOOSE Checklist for Meta-analyses of Observational Studies.

| Item No | Recommendation | Page No. |
|---------|----------------|----------|
|         | **Reporting of background should include** |          |
| 1       | Problem definition | 2        |
| 2       | Hypothesis statement | 2        |
| 3       | Description of study outcome(s) | 2        |
| 4       | Type of exposure or intervention used | 3        |
| 5       | Type of study designs used | 3        |
| 6       | Study population | 3        |
|         | **Reporting of search strategy should include** |          |
| 7       | Qualifications of searchers (eg, librarians and investigators) | 3        |
| 8       | Search strategy, including time period included in the synthesis and key words | 3        |
| 9       | Effort to include all available studies, including contact with authors | 3        |
| 10      | Databases and registries searched | 3        |
| 11      | Search software used, name and version, including special features used (eg, explosion) | 3        |
| 12      | Use of hand searching (eg, reference lists of obtained articles) | 3        |
| 13      | List of citations located and those excluded, including justification | 3        |
| 14      | Method of addressing articles published in languages other than English | 3        |
| 15      | Method of handling abstracts and unpublished studies | 3        |
| 16      | Description of any contact with authors | 3        |
|         | **Reporting of methods should include** |          |
| 17      | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 3        |
| 18      | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 3        |
| 19      | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater) | 3        |
| 20      | Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | 4        |
|   | Reporting of results should include                                                                 |
|---|--------------------------------------------------------------------------------------------------|
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 4 |
| 22 | Assessment of heterogeneity                                                                       | 5 |
| 23 | Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 4 |
| 24 | Provision of appropriate tables and graphics                                                       | 5 |

### Reporting of results should include

|   |   |
|---|---|
| 25 | Graphic summarizing individual study estimates and overall estimate | Figures |
| 26 | Table giving descriptive information for each study included | Tables |
| 27 | Results of sensitivity testing (eg, subgroup analysis) | 6-7 |
| 28 | Indication of statistical uncertainty of findings | 6-7 |
| 29 | Quantitative assessment of bias (eg, publication bias) | 6-7 |
| 30 | Justification for exclusion (eg, exclusion of non-English language citations) | 6-7 |
| 31 | Assessment of quality of included studies | 6-7 |

### Reporting of conclusions should include

|   |   |
|---|---|
| 32 | Consideration of alternative explanations for observed results | 8-11 |
| 33 | Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 8-11 |
| 34 | Guidelines for future research | 8-11 |
| 35 | Disclosure of funding source | 12 |

From: Stroup DF, Berlin JA, Morton SC, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA. 2000;283:2008-2012.
Table S2. The Search Strategy for Ovid MEDLINE.

| Line # | Search term (Searched on 04/11/2018) |
|--------|-------------------------------------|
| 1      | (Intraoperative Complications/ or Postoperative Complications/) and exp Stroke/ |
| 2      | ((intraoperative or intra-operative or peroperative or per-operative or perioperative or peri-operative or early or postoperative or post-operative or post-surgical or postsurgical or delayed) adj4 (stroke or strokes or cerebrovascular accident* or cerebrovascular lesion or acute focal cerebral vasculopathy or brain blood flow disturbance or brain accident or brain attack or brain insult or brain insultus or brain ischaemic attack or brain ischemic attack or cerebral insult cerebral vascular accident or cerebral vascular insufficiency or cerebrovascular arrestor cerebrovascular failure or cerebrovascular injury or cerebrovascular insufficiency or cerebrovascular insult or ischaemic cerebral attack or ischaemic cerebral attack or ischemic cerebral attack or ischemic seizure or brain infarction* or brain venous infarction* or cortical infarction or hemisphere infarct* or hemispheric infarct* or brain stem infarction* or brainstem infarction* or Claude Syndrome or Weber Syndrome or Millard-Gublar Syndrome or Top of the Basilar Syndrome or Benedict Syndrome or Foville Syndrome or cerebral infarct* or cerebrovascular infarct* or subcortical infarction* or posterior choroidal artery infarction* or anterior choroidal artery infarction* or lacunar syndrome* or lacunar infarct*)) tw. |
| 3      | 1 or 2 |
| 4      | Cardiac Surgical Procedures/ |
|   |                                                                                       |
|---|---------------------------------------------------------------------------------------|
| 5 | (cardiac surgery or cardiac surgical procedure* or heart surgery or heart valve surgery or heart surgical procedures* or cardiac operation* or heart operation* or cardiosurgery or myocardial resection).tw. |
| 6 | Coronary Artery Bypass/                                                              |
| 7 | (CABG or aortic coronary bypass or aorticocoronary anastomosis or Total arterial revascularization or total arterial revascularisation or Multiple arterial revascularization or multiple arterial revascularisation).tw. |
| 8 | ((aortocoronary or aorta or coronary) adj2 (anastomosis or bypass or shunt or graft)).tw. |
| 9 | Coronary Artery Bypass, Off Pump/                                                    |
| 10| **Internal Mammary-Coronary Artery Anastomosis/**                                   |
| 11| **Myocardial Revascularization/**                                                    |
| 12| (cardiac muscle revascularisation or cardiac muscle revascularization or coronary revascularisation or coronary revascularization or heart muscle revascularisation or heart myocardium revascularisation or heart revascularisation or heart revascularization or internal mammary arterial anastomosis or internal mammary arterial implantation or internal mammary artery anastomosis or internal mammary artery graft or internal mammary artery implant or internal mammary artery implantation or internal mammary coronary artery anastomosis or Coronary Internal Mammary Artery Anastomosis or myocardial revascularisation or myocardial revascularization or myocardium revascularisation or myocardium revascularization or transmyocardial laser revascularisation or transmyocardial laser revascularization or vineberg operation).tw. |
| 13| (Aortic Valve Repair or Aortic Valve Replacement or aorta valve replacement or aorta valve transplantation or aortic valve transplantation or aortic valve xenotransplantation).tw. |
| 14| **Cardiac Valve Annuloplasty/**                                                      |
|   | Description                                                                                     |
|---|------------------------------------------------------------------------------------------------|
|15 | (Cardiac Valve Annuloplasty or Cardiac Valve Annuloplasties or Valvular Annuloplasties or Valvular Annuloplasty or Heart Valve Annuloplasty or Heart Valve Annuloplasties or Cardiac Valve Annulus Repair or Heart Valve Annulus Repair or Cardiac Valve Annular Repair or Heart Valve Annular Repair or Cardiac Valve Annular Reduction or Cardiac Valve Annulus Shortening or Cardiac Valve Annulus Reduction).tw. |
|16 | Mitral Valve Annuloplasty/                                                                       |
|17 | (Mitral Valve Annuloplasties or Mitral Valve Annuloplasty or Mitral Annuloplasty Mitral Annuloplasties or Mitral Valve Annulus Repair or mitral valve surgery or mitral valve replacement or mitral valve repair).tw. |
|18 | Heart Valve Prosthesis Implantation/                                                            |
|19 | heart valve prosthesis implantation.tw.                                                        |
|20 | or/4-19                                                                                        |
|21 | 3 and 20                                                                                       |
|22 | limit 21 to English language                                                                   |
Table S3. Critical Appraisal of Included Studies Using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies.

| Study/Year        | Selection | Comparability | Outcome/Exposure | Total Score |
|-------------------|-----------|---------------|------------------|-------------|
| Blossom 1992      | ****      | *             | **               | **********  |
| Bolvie 2005       | ****      | *             | **               | **********  |
| Borger 2001       | ****      | *             | **               | **********  |
| Bull 1993         | ****      | *             | **               | **********  |
| Calafiore 2002    | ****      | **            | **               | **********  |
| Cao 2011          | ****      | *             | **               | **********  |
| Carrascal 2014    | ****      | **            | **               | **********  |
| Chen 2015         | ****      | *             | **               | **********  |
| Doi 2010          | ****      | **            | *                | **********  |
| Fessatidis 1991   | ****      | *             | **               | **********  |
| Filsoufi.A 2008   | ****      | **            | **               | **********  |
| Filsoufi.B 2008   | ****      | **            | **               | **********  |
| Gaudino 1999      | ****      | *             | **               | **********  |
| Goto 2003         | ****      | *             | **               | **********  |
| Hedberg 2005      | ****      | *             | *                | **********  |
| Hedberg 2011      | ****      | **            | **               | **********  |
| Hedberg 2013      | ****      | **            | *                | **********  |
| Hogue 1999        | ****      | **            | **               | **********  |
| Imasaka 2018      | ****      | **            | *                | **********  |
| Karhausen 2017    | ****      | **            | **               | **********  |
| Karkouti 2005     | ****      | **            | *                | **********  |
| Kinnunen 2015     | ****      | **            | **               | **********  |
| Lahtinen 2004     | ****      | *             | **               | **********  |
| Lee 2011          | ****      | **            | *                | **********  |
| Lisle 2008        | ****      | **            | **               | **********  |
| Martin 1982       | ****      | *             | **               | **********  |
| Marui 2012        | ****      | **            | **               | **********  |
| Murdock 2003      | ****      | *             | **               | **********  |
| Nishiyama 2009    | ****      | **            | **               | **********  |
| Study               | Rating | Method | Quality | Conclusion |
|---------------------|--------|--------|---------|------------|
| Peel 2004\(^{30}\) | ****   | *      | *       | *****      |
| Ridderstolpe 2002\(^{31}\) | **** | **     | **      | ********   |
| Salazar 2001\(^{32}\) | **** | *      | **      | ********   |
| Tarakji 2011\(^{33}\) | **** | **     | **      | ********   |
| Toupoulis 2008\(^{34}\) | **** | **     | **      | ********   |
| Weinstein 2001\(^{35}\) | **** | *      | *       | ********   |
| Wijdicks 1996\(^{36}\) | **** | *      | **      | ********   |
**Table S4.** Stroke Definitions in the Included Studies.

| Early Definitions                        | Delayed Definitions                        |
|------------------------------------------|--------------------------------------------|
| In 23 studies, early strokes were defined as strokes observed at awaking or extubation, while delayed strokes were defined as strokes occurring after a symptom-free interval after awaking or extubation. | In 23 studies, early strokes were defined as strokes observed at awaking or extubation, while delayed strokes were defined as strokes occurring after a symptom-free interval after awaking or extubation. |
| In 7 studies, early strokes were defined as strokes that occurred within 24 hours after cardiac surgery, while delayed strokes after 24 hours. | In 7 studies, early strokes were defined as strokes that occurred within 24 hours after cardiac surgery, while delayed strokes after 24 hours. |
| In 2 studies, early were strokes occurring intraoperatively, while delayed were those occurring postoperatively | In 2 studies, early were strokes occurring intraoperatively, while delayed were those occurring postoperatively |
| In 1 early strokes were defined as stroke at recovering from anesthesia or within 12h, while delayed strokes were defined as strokes occurring after 12 hours | In 1 early strokes were defined as stroke at recovering from anesthesia or within 12h, while delayed strokes were defined as strokes occurring after 12 hours |
| In 1 study early strokes were strokes occurring by 1st POD, while delayed strokes were defined as strokes occurring between POD 2 and 30. | In 1 study early strokes were strokes occurring by 1st POD, while delayed strokes were defined as strokes occurring between POD 2 and 30. |
| In 1 study early strokes were strokes presenting on day 0, while delayed strokes were defined as strokes occurring afterwards | In 1 study early strokes were strokes presenting on day 0, while delayed strokes were defined as strokes occurring afterwards |
| In 1 study early strokes were strokes presenting within 3rd POD, while delayed strokes were defined as strokes occurring afterwards | In 1 study early strokes were strokes presenting within 3rd POD, while delayed strokes were defined as strokes occurring afterwards |

POD, Post-operative day
Table S5. Demographics of the included studies.

| Study/Year     | Cohort | Age (Yr) | Females (%) | DM (%) | AF (%) | Carotid disease (%) | Prior Stroke (%) | Urgent/Emergent (%) | PVD (%) | CKD (%) | Redo (%) | Type of Surgery (%) |
|----------------|--------|----------|-------------|--------|--------|----------------------|------------------|----------------------|---------|---------|----------|---------------------|
| Blossom 1992   | 3428   | NR       | NR          | NR     | NR     | NR                   | NR               | NR                   | NR      | NR      | NR       | CABG                |
| Boivie 2005    | 2641   | 66       | 27          | NR     | NR     | NR                   | NR               | NR                   | 3       | NR      | NR       | CABG 1882; Valve 195; CABG+Valve 200 |
| Borger 2001    | 6682   | 62       | 20          | 24     | 1      | NR                   | 8                | 17                   | 14      | 3       | 8        | CABG                |
| Bull 1993      | 245    | NR       | NR          | 21     | 6      | 11                   | NR               | NR                   | NR      | NR      | NR       | CABG                |
| Calafiore 2002 | 4875   | NR       | NR          | NR     | NR     | NR                   | NR               | NR                   | NR      | NR      | NR       | CABG                |
| Cao 2011       | 430    | 64       | 24          | 37     | 3      | NR                   | 100              | NR                   | 3       | NR      | NR       | CABG                |
| Carrascal 2014 | 844    | 74       | 40          | 20     | NR     | NR                   | 8                | 6                    | 10      | 7       | 6        | CABG 202; CABG+Valve 209; Valve 403; Aortic 32 |
| Chen 2015      | 1010   | 67       | 15          | NR     | NR     | NR                   | NR               | 27                   | NR      | NR      | 15       | CABG                |
| Doi 2010       | 611    | 68       | 22          | 46     | NR     | NR                   | NR               | NR                   | 15      | NR      | NR       | CABG                |
| Fessatidis 1991| 1487   | NR       | NR          | NR     | NR     | NR                   | NR               | NR                   | NR      | NR      | NR       | CABG 943; Valve 496; Congenital 46 |
| Filsoufi.A 2008| 2808   | 63       | 43          | 15     | NR     | NR                   | 7                | 3                    | 7       | 5       | 19       | CABG+Valve 1529; Valve 1279 |
| Filsoufi.B 2008| 2985   | 65       | 31          | 40     | NR     | NR                   | 8                | 5                    | 13      | 5       | 4        | CABG                |
| Gaudino 1999   | 2987   | 60       | 44          | 18     | NR     | NR                   | 11               | NR                   | NR      | NR      | NR       | CABG                |
| Goto 2003      | 463    | 70       | 31          | 35     | NR     | NR                   | 17               | NR                   | 10      | 11      | NR       | CABG                |
| Hedberg 2005   | 2641   | NR       | NR          | NR     | NR     | NR                   | NR               | NR                   | NR      | NR      | NR       | All Cardiac Surgery |
| Hedberg 2011   | 9122   | 68       | 25          | 22     | NR     | NR                   | 9                | NR                   | NR      | NR      | 5        | CABG 8136; CABG+Valve 986 |
| Study            | Registry & Location | Total | Aorta | Other | CABG | CABG/Valve | Valve | All Surgery |
|------------------|---------------------|-------|-------|-------|------|------------|-------|-------------|
| Hedberg 2013     |                     | 10809 | 28    | 20    | 4    | NR         | 9     | 9           | 9 | NR | 5 | All But Aortic 98.5%; Aortic 1.5% |
| Hogue 1999       |                     | 2972  | 68    | 36    | 28   | NR         | 32    | 7           | NR | NR | NR | CABG (88.4); CABG/valve (15.0); Valve (26.6) |
| Imasaka 2018     |                     | 1134  | NR    | 39    | 31   | NR         | 16    | 14          | 14 | NR | 7 | CABG 378; CABG+Valve 151; Valve 480; Aortic 43; Other 82 |
| Karhausen 2017   |                     | 6130  | NR    | 28    | 38   | NR         | 10    | NR          | NR | 6   | 2 | CABG |
| Karkouti 2005    |                     | 10949 | NR    | NR    | NR   | NR         | NR    | NR          | NR | NR | NR | All Cardiac Surgery |
| Kinnunen 2015    |                     | 1314  | 66    | 21    | 29   | 11         | NR    | 4           | 56 | 12  | NR | CABG |
| Lahtinen 2004    |                     | 2630  | NR    | 33    | 31   | 10         | NR    | 36          | 1  | NR | NR | CABG |
| Lee 2011         |                     | 1367  | 63    | 26    | 44   | 4          | NR    | 9           | NR | 2   | 7 | CABG |
| Lisle 2008       |                     | 7201  | NR    | NR    | NR   | NR         | NR    | NR          | NR | NR | NR | All Cardiac Surgery |
| Martin 1982      |                     | 253   | 54    | 83    | 5    | 8          | NR    | 6           | NR | 7   | NR | CABG |
| Marui 2012       |                     | 2446  | 67    | 28    | 47   | 6          | 11    | 21          | 6  | NR | 39 | CABG |
| Murdock 2003     |                     | 2104  | 60    | 50    | 46   | 6          | NR    | 22          | NR | 30  | NR | CABG 1798, Valve 135, CABG+Valve 151, Other 20 |
| Nishiyama 2009   |                     | 2516  | 67    | 28    | 46   | 6          | NR    | 22          | 6  | 20  | 17 | CABG |
| Peel 2004        |                     | 10573 | NR    | NR    | NR   | NR         | NR    | NR          | NR | NR | NR | CABG |
| Ridderstolpe 2002|                     | 3282  | 66    | 27    | 14   | NR         | NR    | 8           | 3  | 7   | NR | CABG 2290, CABG+Valve 275, Valve 570, Aortic 60, Other 87 |
| Salazar 2001     |                     | 5971  | NR    | NR    | NR   | NR         | NR    | NR          | NR | NR | NR | CABG 3,974; Valve 828; CABG/valve 463; |
| Study (Year)          | Sample Size | Age | Gender | Comorbidity | CABG | CEA | PVD | Transplant | Other |
|----------------------|-------------|-----|--------|-------------|------|-----|-----|------------|-------|
| Tarakji 2011         | 45432       | 68  | 21     | 23          | 2    | NR  | 6   | 3          | 16    | 3   | 19   | CABG |
| Toumpoulis 2008      | 4140        | 64  | 31     | 35          | NR   | 6   | 7   | 70         | NR    | 3   | NR   | CABG |
| Weinstein 2001       | 2217        | 71  | 35     | 33          | 19   | NR  | NR  | NR         | 6     | NR  | NR   | CABG |
| Wijdicks 1996       | 8270        | NR  | NR     | NR          | NR   | NR  | NR  | NR         | NR    | NR  | NR   | CABG |

DM, diabetes mellitus; CKD, chronic kidney disease; PVD, peripheral vascular disease; CABG, coronary artery bypass graft; CEA, carotid endarterectomy; NR, not reported.
Table S6. Summary of the outcomes (fixed effect model).

| Outcomes                                         | No. of Studies | Proportion [Confidence interval] | Heterogeneity (I^2, P-value) | Perioperative stroke vs No stroke ¶ | Early vs delayed stroke difference ¶ |
|--------------------------------------------------|----------------|---------------------------------|-----------------------------|-------------------------------------|--------------------------------------|
| Pooled rate of perioperative stroke              | 36             | 2.15% [2.08; 2.22]              | 94.1%, P<0.0001             | ----                                | ----                                 |
| Pooled rate of early stroke                      | 36             | 1.25% [1.19; 1.30]              | 94.7%, P<0.0001             | ----                                | <0.0001                             |
| Pooled rate of delayed stroke                    | 36             | 1.08% [1.03; 1.14]              | 91.5%, P<0.0001             | ----                                | ----                                 |
| Pooled rate of operative mortality in the whole group | 20             | 3.39% [3.28; 3.50]              | 96.9%, P<0.0001             | ----                                | <0.0001                             |
| Pooled rate of operative mortality for patients with perioperative stroke | 22             | 20.76% [19.12; 22.49]           | 58.8%, P=0.0003             | <0.0001                             | ----                                 |
| Pooled rate of operative mortality for patients without stroke | 16             | 3.19% [3.08; 3.31]              | 96.9%, P<0.0001             | <0.0001                             | ----                                 |
| Pooled rate of operative mortality for patients with early stroke | 12             | 25.97% [21.80; 30.62]           | 84.2%, P<0.0001             | ----                                | 0.0049                              |
| Pooled rate of operative mortality for patients with late stroke | 13             | 17.85% [14.57; 21.67]           | 20.1%, P=0.2407             | ----                                | 0.0049                              |
| Incidence rate of late mortality in the all group | 5              | 5.78% [5.71; 5.84]              | 99.3%, P<0.0001             | ----                                | ----                                 |
| Incidence rate of late mortality in patients with perioperative stroke | 5              | 8.44% [7.83; 9.10]              | 84.8%, P<0.0001             | <0.0001                             | ----                                 |
| Incidence rate of late mortality in patients without stroke | 8              | 5.37% [5.32; 5.43]              | 99.7%, P=0                  | <0.0001                             | ----                                 |
| Incidence rate of late mortality in patients with early stroke | 5              | 8.64% [7.49; 9.95]              | 87.6%, P=0.0001             | ----                                | 0.3738                              |
| Incidence rate of late mortality in patients with delayed stroke | 5              | 7.73% [6.34; 9.43]              | 71.2%, P=0.008              | ----                                | 0.3738                              |

¶ P value for subgroup difference
Table S7. Meta-Regression for Early and Delayed Stroke (Restricted maximum likelihood model). By getting exponential of Beta (exp Beta):
- 1%↑ in prior stroke history → ↑ absolute risk of peri-operative stroke by 1.01%, P=0.001
- 1%↑ in on-pump → ↑ absolute risk of early stroke by 1.00%, P=0.006
- 1%↑ in off-pump → ↓ absolute risk of early stroke by 0.99%, P=0.012
- 1%↑ in in prior stroke history → ↑ absolute risk of delayed stroke by 1.02%, P<0.001

| Perioperative Stroke                          | Beta ±SD (P-value) | Exp (Beta) |
|-----------------------------------------------|--------------------|------------|
| Age (years)                                   | 0.0041±0.0265, P=0.8774 | 1.004      |
| Female (%)                                    | 0.0071±0.0076, P=0.3527 | 1.007      |
| Diabetes (%)                                  | 0.0015±0.0080, P=0.8470 | 1.002      |
| AF (%)                                        | -0.0111±0.0246, P=0.6530 | 0.989      |
| Carotid disease (%)                           | -0.0220±0.0144, P=0.1271 | 0.978      |
| Prior stroke (%)                              | 0.0129±0.0040, P=0.0014 | 1.013      |
| Urgent or Emergent Procedure (%)              | 0.0043±0.0041, P=0.2957 | 1.004      |
| On-pump (%)                                   | 0.0017±0.0025, P=0.4927 | 1.002      |
| Off-pump (%)                                  | -0.0014±0.0028, P=0.6152 | 0.999      |
| Single clamp (%)                              | 0.0034±0.0055, P=0.5385 | 1.003      |
| Multiple clamp (%)                            | -0.0034±0.0055, P=0.5385 | 0.997      |
| Asc Aorta atheroma or calcification (%)       | 0.0017±0.0065, P=0.7927 | 1.002      |
| Use of circulatory arrest (%)                 | NA (no enough study) | NA         |
| CPB time (in minutes)                         | 0.0007±0.0030, P=0.8220 | 1.001      |
| Aortic clamp time (in minutes)                | 0.0002±0.0038, P=0.9522 | 1.000      |

| Early Stroke                                  | Beta ±SD (P-value) | Exp (Beta) |
|-----------------------------------------------|--------------------|------------|
| Age (years)                                   | 0.0158±0.0318, P=0.6202 | 1.016      |
| Female (%)                                    | 0.0074±0.0102, P=0.4687 | 1.007      |
| Diabetes (%)                                  | -0.0178±0.0097, P=0.0678 | 0.982      |
| AF (%)                                        | -0.0153±0.0240, P=0.5256 | 0.985      |
| Carotid disease (%)                           | -0.0473±0.0252, P=0.0600 | 0.954      |
| Prior stroke (%)                              | -0.0046±0.0072, P=0.5244 | 0.995      |
| Urgent or Emergent Procedure (%)              | 0.0056±0.0074, P=0.4508 | 1.006      |
| On-pump (%)                                   | 0.0091±0.0034, P=0.0064 | 1.009      |
| Variable                                      | Beta ±SD (P-value) | Exp (Beta) |
|-----------------------------------------------|--------------------|------------|
| Off-pump (%)                                  | 0.0097±0.0038, P=0.0115 | 0.990      |
| Single clamp (%)                              | 0.0012, 0.0087, P=0.8874 | 1.001      |
| Multiple clamp (%)                            | -0.0012±0.0087, P=0.8874 | 0.999      |
| Asc Aorta atheroma or calcification (%)       | 0.0005±0.0115, P=0.9634 | 1.001      |
| Use of circulatory arrest (%)                 | NA (no enough studies) | NA         |
| CPB time (in minutes)                         | -0.0030±0.0047, P=0.5267 | 0.997      |
| Aortic clamp time (in minutes)                | -0.0035±0.0059, P=0.5600 | 0.997      |

### Delayed Stroke

| Variable                                      | Beta ±SD (P-value) | Exp (Beta) |
|-----------------------------------------------|--------------------|------------|
| Age (years)                                   | 0.0108±0.0420, P=0.7982 | 1.011      |
| Female (%)                                    | 0.0087±0.0115, P=0.4502 | 1.009      |
| Diabetes (%)                                  | 0.0233±0.0120, P=0.0523 | 1.024      |
| AF (%)                                        | 0.0193±0.0465, P=0.6782 | 1.019      |
| Carotid disease (%)                           | 0.0059±0.0091, P=0.5185 | 1.006      |
| Prior stroke (%)                              | 0.0224±0.0056, P<0.0001 | 1.023      |
| Urgent or Emergent Procedure (%)              | 0.0005±0.0077, P=0.9510 | 1.001      |
| On-pump (%)                                   | -0.0057±0.0036, P=0.1166 | 0.994      |
| Off-pump (%)                                  | 0.0062±0.0039, P=0.1103 | 1.006      |
| Single clamp (%)                              | 0.0041±0.0091, P=0.6511 | 1.004      |
| Multiple clamp (%)                            | -0.0041±0.0091, P=0.6511 | 0.996      |
| Asc Aorta atheroma or calcification (%)       | 0.0010±0.0045, P=0.8213 | 1.001      |
| Use of circulatory arrest (%)                 | NA (no enough studies) | NA         |
| CPB time (in minutes)                         | 0.0065±0.0050, P=0.1943 | 1.007      |
| Aortic clamp time (in minutes)                | 0.0062±0.0064, P=0.3356 | 1.006      |

AF, Atrial Fibrillation; Asc, ascending; CPB, cardiopulmonary bypass; NA, not applies.
Figure S1. PRISMA flowchart.
Figure S2. Pooled event rate for perioperative stroke.

| Study            | Events | Total | Proportion | 95%–CI | Weight (fixed) | Weight (random) |
|------------------|--------|-------|------------|--------|---------------|-----------------|
| Cao 2011[^6]     | 32     | 430   | 0.07       | [0.05; 0.10] | 0.9%          | 2.7%            |
| Goto 2003[^4]    | 18     | 463   | 0.04       | [0.02; 0.06] | 0.5%          | 2.4%            |
| Carrascot 2014[^7] | 32     | 844   | 0.04       | [0.03; 0.05] | 0.5%          | 2.7%            |
| Boivie 2005[^2]  | 98     | 2641  | 0.04       | [0.03; 0.05] | 2.8%          | 3.0%            |
| Salazar 2001[^2] | 214    | 5971  | 0.04       | [0.03; 0.04] | 6.2%          | 3.1%            |
| Tournopouli 2008[^4] | 138   | 4140  | 0.03       | [0.03; 0.04] | 4.0%          | 3.1%            |
| Murdoch 2003[^8] | 68     | 2104  | 0.03       | [0.03; 0.04] | 2.0%          | 3.0%            |
| Martin 1982[^6]  | 8      | 253   | 0.03       | [0.01; 0.06] | 0.2%          | 1.9%            |
| Hedberg 2013[^7] | 339    | 10809 | 0.03       | [0.03; 0.03] | 9.8%          | 3.2%            |
| Hedberg 2005[^5] | 77     | 2641  | 0.03       | [0.02; 0.04] | 2.2%          | 3.0%            |
| Lisie 2008[^5]   | 202    | 7201  | 0.03       | [0.02; 0.03] | 5.5%          | 3.1%            |
| Hedberg 2011[^6] | 245    | 9122  | 0.03       | [0.02; 0.03] | 7.1%          | 3.1%            |
| Lee 2011[^4]     | 33     | 1367  | 0.02       | [0.02; 0.03] | 1.0%          | 2.7%            |
| Weinstein 2001[^5] | 51    | 2217  | 0.02       | [0.02; 0.03] | 1.5%          | 2.9%            |
| Filsoufi.A 2008[^1] | 63   | 2808  | 0.02       | [0.02; 0.03] | 1.8%          | 3.0%            |
| Bull 1993[^4]    | 5      | 245   | 0.02       | [0.01; 0.05] | 0.1%          | 1.5%            |
| Peel 2004[^3]    | 211    | 10573 | 0.02       | [0.02; 0.02] | 6.2%          | 3.1%            |
| Lahtinen 2004[^3] | 52    | 2630  | 0.02       | [0.01; 0.03] | 1.5%          | 2.9%            |
| Ridderstolpe 2002[^3] | 64   | 3282  | 0.02       | [0.02; 0.02] | 1.5%          | 3.0%            |
| Marui 2012[^2]   | 45     | 2446  | 0.02       | [0.01; 0.02] | 1.3%          | 2.9%            |
| Nishiyama 2009[^9] | 46    | 2516  | 0.02       | [0.01; 0.02] | 1.4%          | 2.9%            |
| Karhausen 2017[^20] | 110  | 6130  | 0.02       | [0.01; 0.02] | 3.2%          | 3.1%            |
| Imasaka 2018[^3] | 20     | 1134  | 0.02       | [0.01; 0.03] | 0.6%          | 2.5%            |
| Kinnumen 2015[^2] | 23     | 1314  | 0.02       | [0.01; 0.03] | 0.7%          | 2.6%            |
| Hogue 1999[^18]  | 48     | 2972  | 0.02       | [0.01; 0.02] | 1.4%          | 2.9%            |
| Filsoufi.B 2008[^12] | 48   | 2985  | 0.02       | [0.01; 0.02] | 1.4%          | 2.9%            |
| Tarakji 2011[^3] | 688    | 45432 | 0.02       | [0.01; 0.02] | 20.3%         | 3.2%            |
| Borger 2001[^3]  | 98     | 6682  | 0.01       | [0.01; 0.02] | 2.9%          | 3.0%            |
| Kankou 2005[^21] | 160    | 10949 | 0.01       | [0.01; 0.02] | 4.7%          | 3.1%            |
| Blossom 1992[^2] | 46     | 3428  | 0.01       | [0.01; 0.02] | 4.4%          | 2.9%            |
| Doi 2010[^9]     | 8      | 611   | 0.01       | [0.01; 0.03] | 0.2%          | 1.9%            |
| Chen 2015[^8]    | 11     | 1010  | 0.01       | [0.01; 0.02] | 0.3%          | 2.1%            |
| Gaudino 1999[^13] | 31    | 2987  | 0.01       | [0.01; 0.01] | 0.5%          | 2.7%            |
| Fessatidis 1991[^10] | 15  | 1487  | 0.01       | [0.01; 0.02] | 0.4%          | 2.3%            |
| Calafiore 2002[^3] | 49   | 4875  | 0.01       | [0.01; 0.01] | 1.5%          | 2.9%            |
| Wijdicks 1996[^38] | 25   | 8270  | 0.00       | [0.00; 0.00] | 0.7%          | 2.6%            |

**Fixed effect model** 174969 0.02 [0.02; 0.02] 100.0% —

**Random effects model** 0.02 [0.02; 0.02] — 100.0%

**Prediction interval** [0.01; 0.05]

Heterogeneity: $I^2 = 94\%$, $t^2 = 0.1804$, $p < 0.01$
Figure S3. Reconstructed Kaplan-Meier survival curves from derived individual patient data (IPD) for A) No stroke versus perioperative stroke and B) No stroke versus early and delayed stroke. Solid/dotted line represents aggregation of all available Kaplan-Meier curves with 95% CI.
**Figure S4.** Leave-one-out analysis (top) and funnel plot (bottom) for incidence of A) early stroke and B) delayed stroke.
List of the included studies

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