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 stoke (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. **(*J 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.[1] Data from administrative databases and observational registries suggest that the incidence of perioperative stroke after cardiac surgery ranges from 0.8% to 5.2%.[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.[3-5]

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.[6] 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.

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Accompanying Tables S1 through S7 and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012447

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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) statement[7] 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

Table 1. Details of Outcomes in the Included Studies

Study/Year	Study Type	Cohort Size	Perioperative Stroke	Early Stroke	Delayed Stroke
Blossom 1992[14]	R	3428	46	16	30
Boivie 2005[15]	R	2641	98	76	22
Borger 2001[16]	R	6682	98	90	8
Bull 1993[17]	P	245	5	4	1
Calafiore 2002[18]	R	4875	49	24	25
Cao 2011[19]	R	430	32	4	28
Carrascal 2014[20]	R	844	32	23	9
Chen 2015[21]	R	1010	11	5	6
Doi 2010[22]	R	611	8	0	8
Fessatidis 1991[23]	R	1487	15	12	3
Filsoufi.A 2008[24]	R	2808	63	35	28
Filsoufi.B 2008[25]	R	2985	48	25	23
Gaudino 1999[26]	R	2987	31	25	6
Goto 2003[27]	P	463	18	13	5
Hedberg 2005[28]	R	2641	77	58	19
Hedberg 2011[29]	R	9122	245	146	99
Hedberg 2013[30]	R	10 809	339	223	116
Hogue 1999[31]	P	2972	48	17	31
Imasaka 2018[32]	R	1134	20	8	12
Karhausen 2017[33]	R	6130	110	35	75
Karkouti 2005[34]	R	10 949	160	110	50
Kinnunen 2015[35]	R	1314	23	7	16
Lahtinen 2004[36]	R	2630	52	20	32
Lee 2011[37]	P	1367	33	15	18
Lisle 2008[38]	R	7201	202	46	156
Martin 1982[39]	R	253	8	4	4
Marui 2012[40]	R	2446	45	20	25
Murdock 2003[41]	R	2104	68	18	50
Nishiyama 2009[42]	P	2516	46	17	29
Peel 2004[43]	R	10 573	211	57	154
Ridderstolpe 2002[44]	R	3282	64	47	17
Salazar 2001[45]	R	5971	214	158	56
Tarakji 2011[46]	P	45 432	688	279	409
Toumpoulis 2008[47]	R	4140	138	102	36
Weinstein 2001[48]	P	2217	51	24	27
Wijdicks 1996[49]	R	8270	25	4	21

P indicates prospective; R, retrospective.

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.[10] 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.[11]

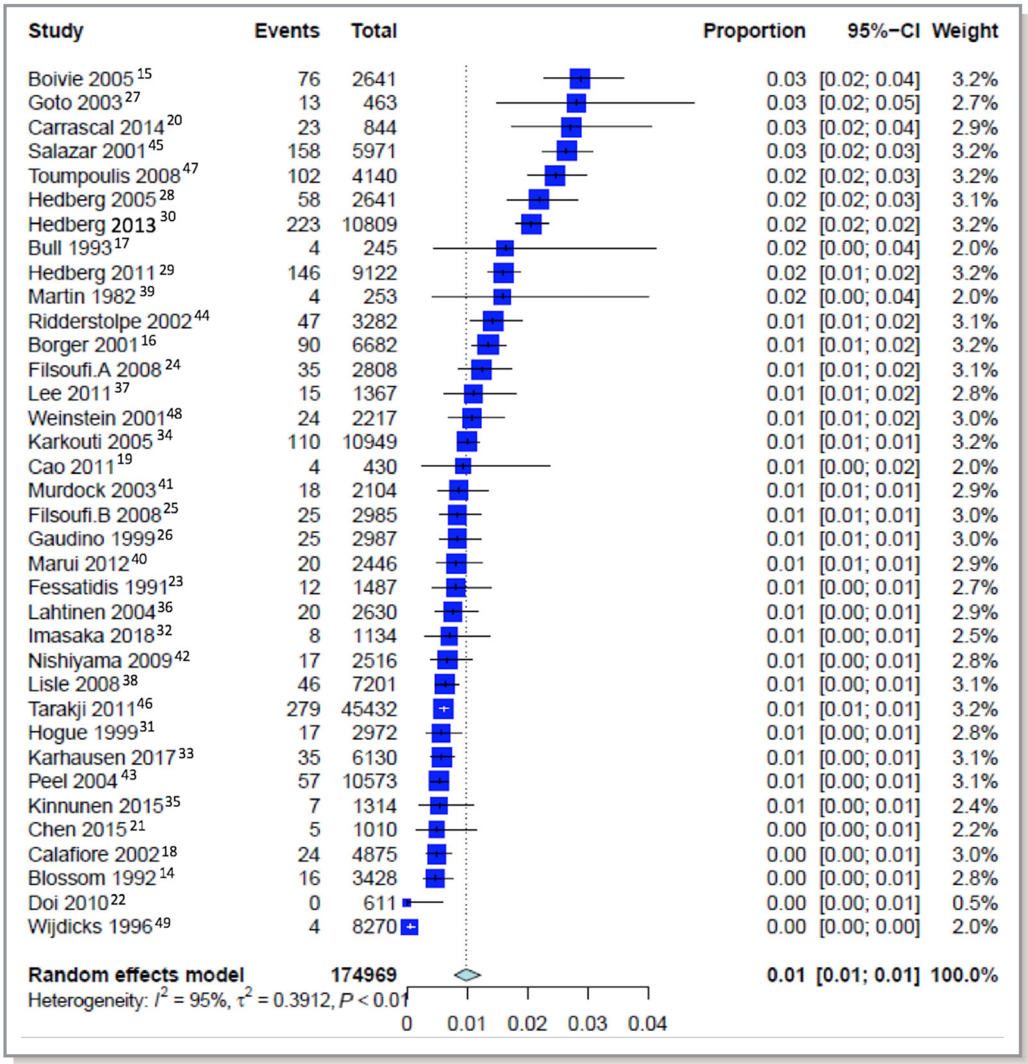

Figure 1. Pooled event rate for early stroke.

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.[12] Supplementary analyses using a fixed-effect model were also performed, and τ^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.[13] 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).

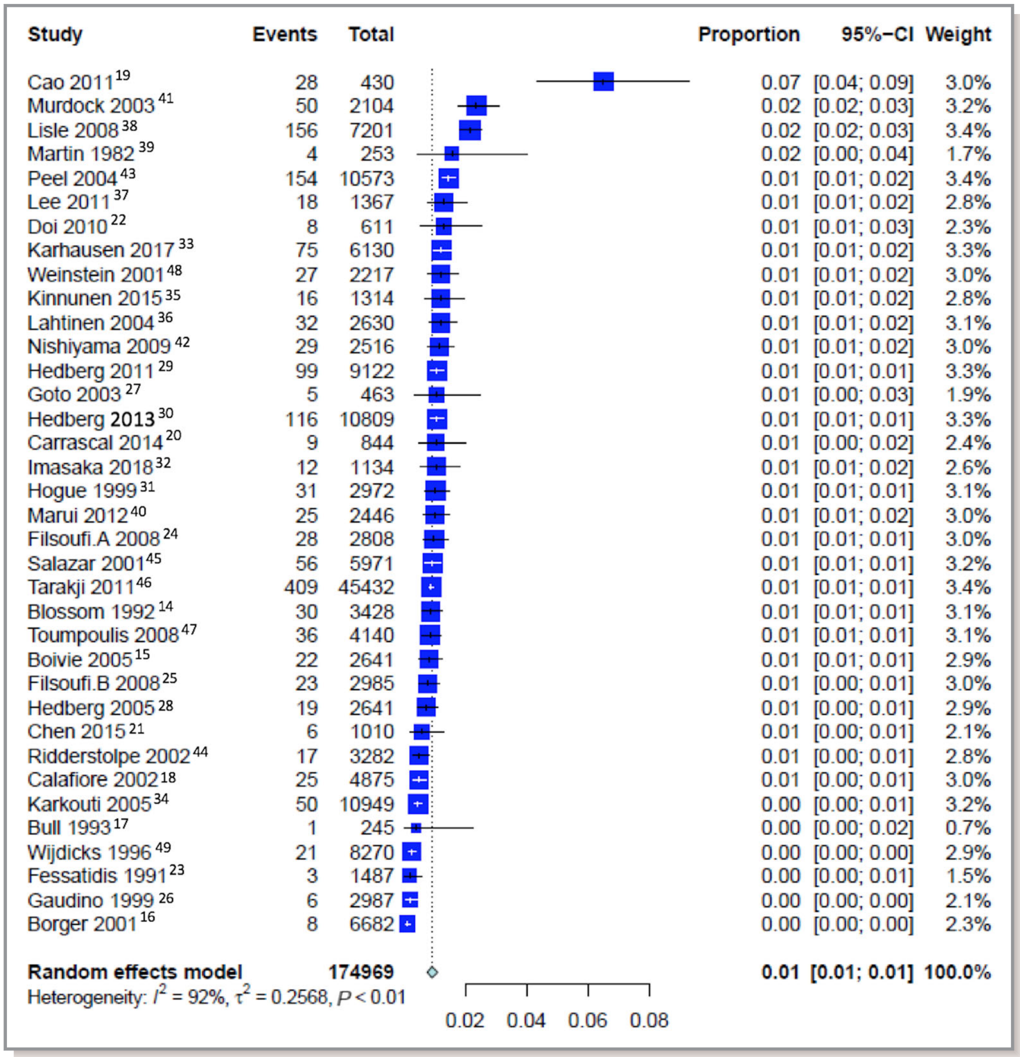

Figure 2. Pooled event rate for delayed stroke.

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: 245-45 432), 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% (1767/174 969) had early stroke, and 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).

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

Outcomes	No. of Studies	Proportion [CI]	Heterogeneity (I^2, *P* Value)	τ^2	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	···	0.6774
Pooled rate of delayed stroke	36	0.93% [0.77; 1.11]; PI=0.33-2.59	91.5%, *P*<0.0001	0.2568	···	0.6774
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 late 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.

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 stroke, early stroke, 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 2.3% to 5.2%). The incidence rate for late mortality was 10.9% (CI 7.3% to 16.2%) for patients with perioperative stroke, 11.7% (CI 7.5% to 18.3%) for early stroke, and 9.4% (CI 5.9% to 14.9%) for delayed stroke (*P*=0.50). The incidence rate for late mortality for patients without stroke 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.

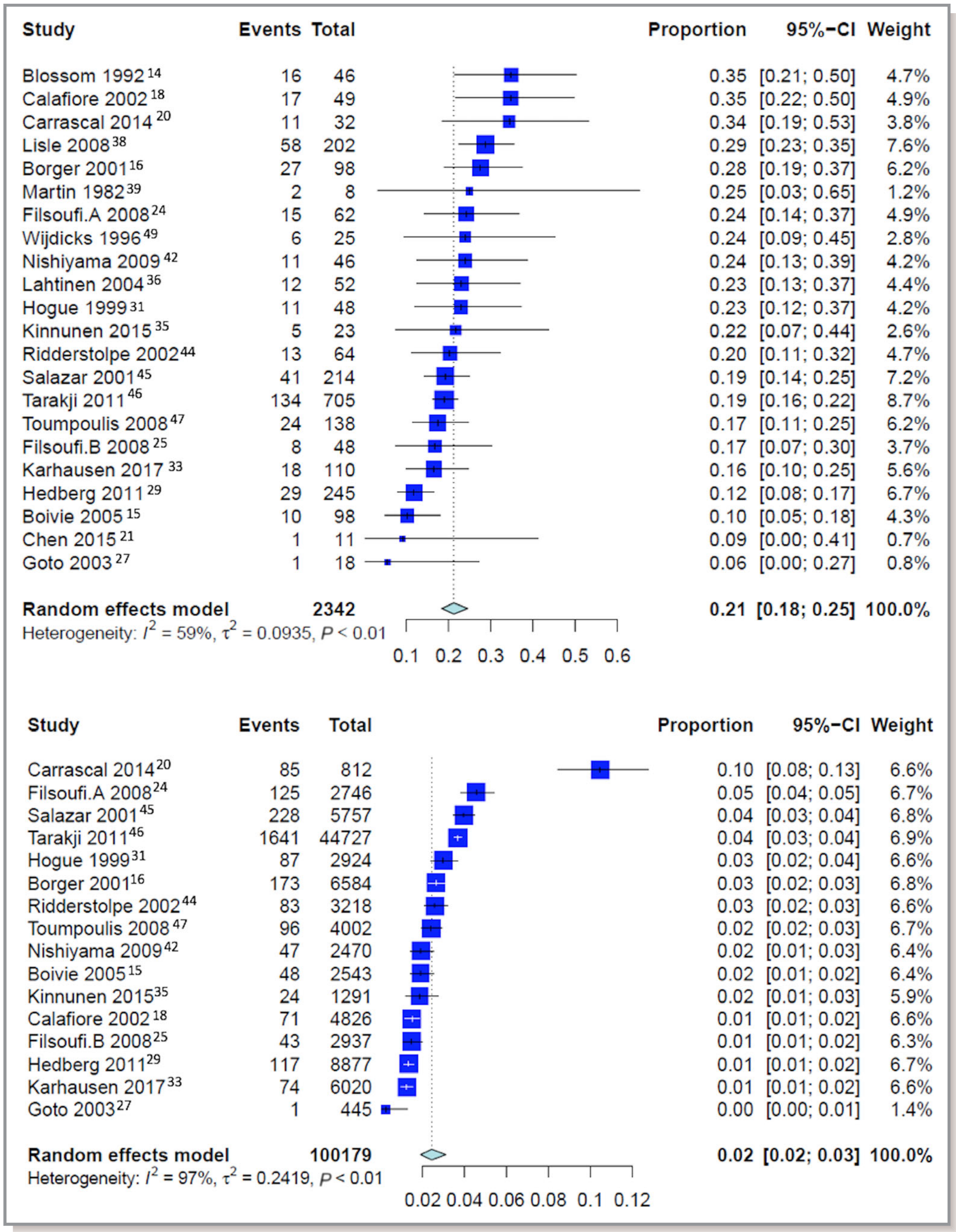

Figure 3. Pooled event rate for operative mortality in patients with (top) and without perioperative stroke (bottom).

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

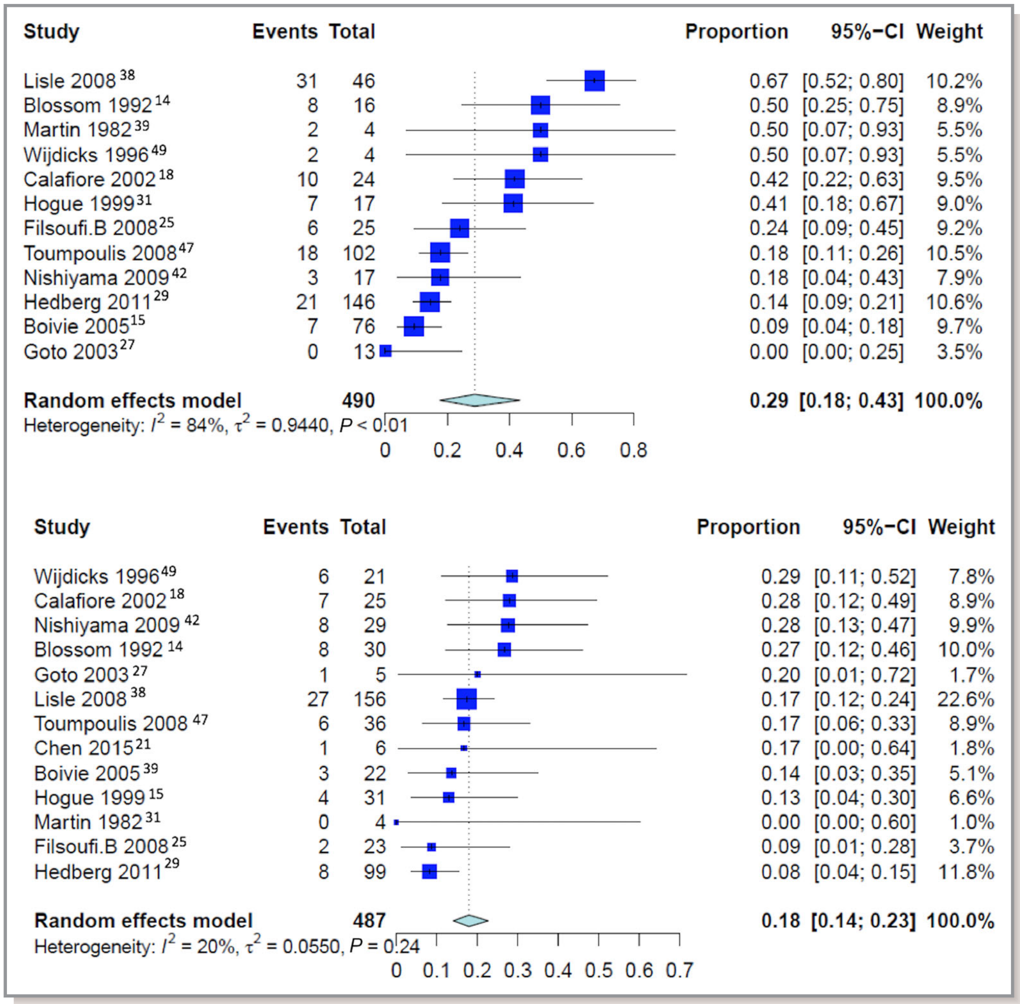

Figure 4. Pooled event rate for operative mortality for patients with early stroke (top) and late stroke (bottom).

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).[50-52] Early stroke has been reported to be usually located in the right hemisphere, consistent with the jet of the flow from the aortic cannula.[15,28]

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[53]; 2.7% versus 2.2% [P=0.47] in the GOPCABE (German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients) trial[54]; 1.1% versus 1.0% [P-value not reported] in the CORONARY (CABG Off or On Pump Revascularization Study) trial[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.

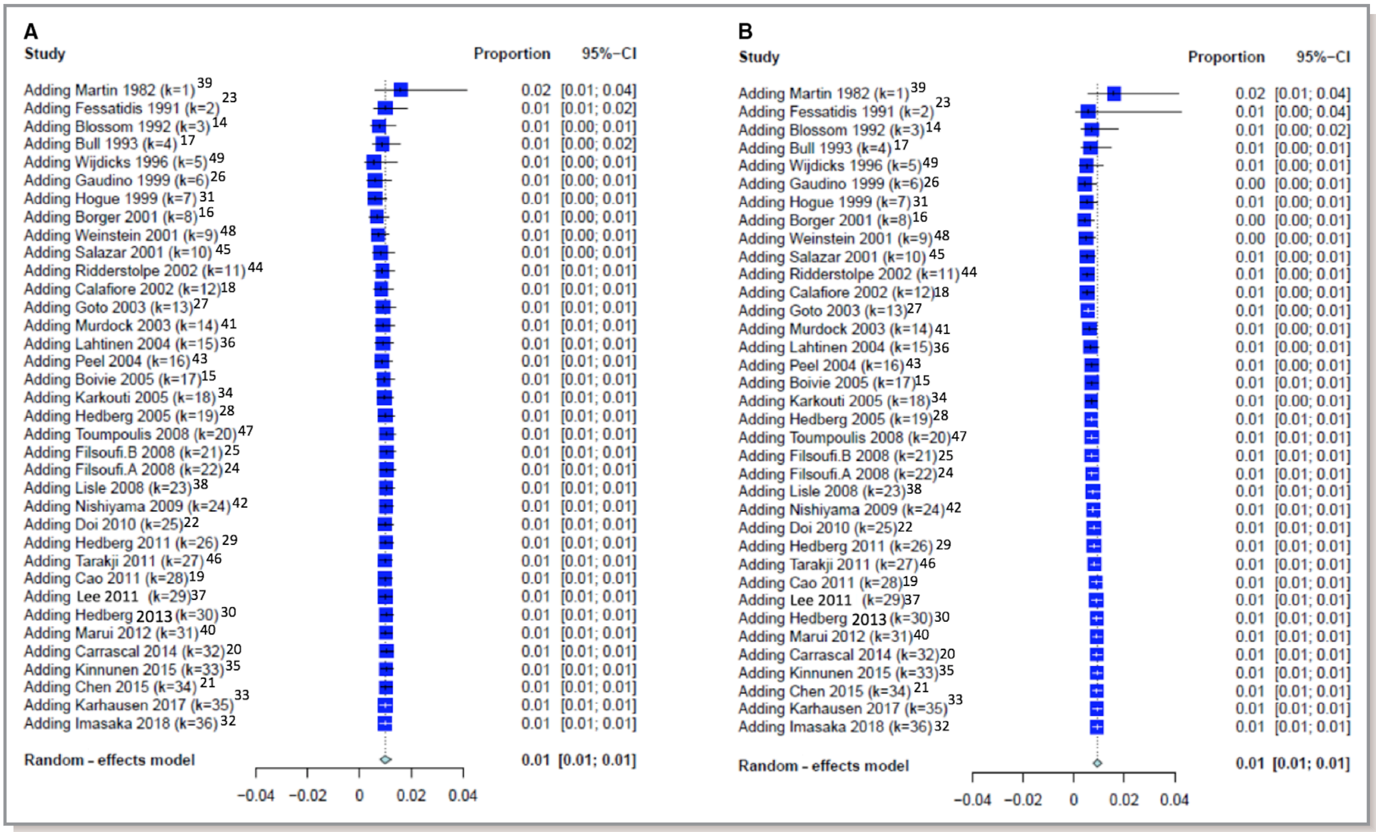

Figure 5. Cumulative analysis of incidence of (**A**) early stroke and (**B**) delayed stroke.

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.[30] 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 7201 patients.[38]

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.[56-60]

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.[61]

In a large series including more than 12 000 patients, the use 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).[62] Consistent with these results, Vallely reported that anaortic 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.[63]

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.[64]

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

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 transesophageal echocardiography for assessment of ascending aortic calcification.[65] 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.[66-74] 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.[75] Validated stroke risk prediction tools such as the CHA_2DS_2–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.[76]

The main strategies for delayed stroke prevention are (1) pharmacological or nonpharmacological AF prophylaxis,[77] (2) anticoagulation for prevention and treatment of clot formation,[78] and (3) elimination of the left atrial appendage.[1] AF prophylaxis includes amiodarone, β-blockers, magnesium, atrial pacing, and posterior pericardiotomy.[77] Regarding left atrial appendage isolation, LAAOS 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

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.

Ovid MEDLINE® (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® - 1946 to Present)	
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 cerebro vascular accident* or CVA or CVAs or apoplexy or apoplexia or brain vascular accident* or vascular brain accident* or acute 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 seizure 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/

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[1]	****	*	**	*******
Boivie 2005[2]	****	*	**	*******
Borger 2001[3]	****	*	**	*******
Bull 1993[4]	****	*	**	*******
Calafiore 2002[5]	****	**	**	********
Cao 2011[6]	****	*	*	******
Carrascal 2014[7]	****	**	**	********
Chen 2015[8]	****	*	**	*******
Doi 2010[9]	****	**	*	*******
Fessatidis 1991[10]	****	*	**	*******
Filsoufi.A 2008[11]	****	**	**	********
Filsoufi.B 2008[12]	****	**	**	********
Gaudino 1999[13]	****	*	**	*******
Goto 2003[14]	****	*	**	*******
Hedberg 2005[15]	****	*	*	******
Hedberg 2011[16]	****	**	**	********
Hedberg 2013[17]	****	**	*	*******
Hogue 1999[18]	****	**	**	********
Imasaka 2018[19]	****	**	*	*******
Karhausen 2017[20]	****	**	**	********
Karkouti 2005[21]	****	**	*	*******
Kinnunen 2015[22]	****	**	**	********
Lahtinen 2004[23]	****	*	**	*******
Lee 2011[24]	****	**	*	*******
Lisle 2008[25]	****	**	**	********
Martin 1982[26]	****	*	**	*******
Marui 2012[27]	****	**	**	********
Murdock 2003[28]	****	*	**	*******
Nishiyama 2009[29]	****	**	**	********

Peel 2004[30]	****	*	*	******
Ridderstolpe 2002[31]	****	**	**	********
Salazar 2001[32]	****	*	**	*******
Tarakji 2011[33]	****	**	**	********
Toumpoulis 2008[34]	****	**	**	********
Weinstein 2001[35]	****	*	*	******
Wijdicks 1996[36]	****	*	**	*******

Table S4. Stroke Definitions in the Included Studies.

• 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 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 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 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[1]	3428	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CABG
Boivie 2005[2]	2641	66	27	NR	NR	NR	NR	NR	3	NR	NR	CABG 1882; Valve 195; CABG+Valve 200
Borger 2001[3]	6682	62	20	24	1	NR	8	17	14	3	8	CABG
Bull 1993[4]	245	NR	NR	21	6	11	12	NR	NR	NR	NR	CABG
Calafiore 2002[5]	4875	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CABG
Cao 2011[6]	430	64	24	37	3	NR	100	NR	3	NR	NR	CABG
Carrascal 2014[7]	844	74	40	20	NR	NR	8	6	10	7	6	CABG 202; CABG+Valve 209; Valve 403; Aortic 32
Chen 2015[8]	1010	67	15	NR	NR	NR	NR	27	NR	NR	NR	CABG
Doi 2010[9]	611	68	22	46	NR	NR	NR	NR	NR	15	NR	CABG
Fessatidis 1991[10]	1487	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CABG 943; Valve 496; Congenital 46
Filsoufi.A 2008[11]	2808	63	43	15	NR	NR	7	3	7	5	19	CABG+Valve 1529; Valve 1279
Filsoufi.B 2008[12]	2985	65	31	40	NR	NR	8	5	13	5	4	CABG
Gaudino 1999[13]	2987	60	44	18	NR	NR	11	NR	NR	NR	NR	CABG
Goto 2003[14]	463	70	31	35	NR	NR	17	NR	10	11	NR	CABG
Hedberg 2005[15]	2641	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	All Cardiac Surgery
Hedberg 2011[16]	9122	68	25	22	NR	NR	9	NR	NR	NR	5	CABG 8136; CABG+Valve 986

Hedberg 2013[17]	10809	NR	28	20	4	NR	9	NR	9	NR	5	All But Aortic 98,5%; Aortic 1.5%
Hogue 1999[18]	2972	68	36	28	NR	32	7	NR	NR	NR	NR	CABG (88.4); CABG/valve (15.0); Valve (26.6)
Imasaka 2018[19]	1134	NR	39	31	16	14	14	NR	NR	7	4	CABG 378; CABG+Valve 151; Valve 480; Aortic 43; Other 82
Karhausen 2017[20]	6130	NR	28	38	NR	NR	10	NR	NR	6	2	CABG
Karkouti 2005[21]	10949	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	All Cardiac Surgery
Kinnunen 2015[22]	1314	66	21	29	11	NR	4	56	12	NR	1	CABG
Lahtinen 2004[23]	2630	NR	33	31	10	NR	36	1	NR	NR	NR	CABG
Lee 2011[24]	1367	63	26	44	4	NR	9	NR	2	7	NR	CABG
Lisle 2008[25]	7201	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	All Cardiac Surgery
Martin 1982[26]	253	54	83	5	8	NR	6	NR	7	NR	NR	CABG
Marui 2012[27]	2446	67	28	47	6	11	21	6	NR	39	NR	CABG
Murdock 2003[28]	2104	60	50	46	6	NR	22	NR	30	NR	NR	CABG 1798, Valve 135, CABG+Valve 151, Other 20
Nishiyama 2009[29]	2516	67	28	46	6	NR	22	6	20	17	0	CABG
Peel 2004[30]	10573	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CABG
Ridderstolpe 2002[31]	3282	66	27	14	NR	NR	8	3	7	NR	0	CABG 2290, CABG+Valve 275, Valve 570, Aortic 60, Other 87
Salazar 2001[32]	5971	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CABG 3,974; Valve 828; CABG/valve 463;

												CABG/CEA 52; CABG/Other 76; Aortic 310; Transplant 94; Other 174
Tarakji 2011[33]	45432	68	21	23	2	NR	6	3	16	3	19	CABG
Toumpoulis 2008[34]	4140	64	31	35	NR	6	7	70	NR	3	NR	CABG
Weinstein 2001[35]	2217	71	35	33	19	NR	NR	NR	6	NR	NR	CABG
Wijdicks 1996[36]	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 stoke ¶	Early vs delayed stroke difference ¶
FIXED EFFECT MODEL					
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	----	<0.0001
Pooled rate of operative mortality in the whole group	20	3.39% [3.28; 3.50]	96.9%, P<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 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**

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	**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<.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.

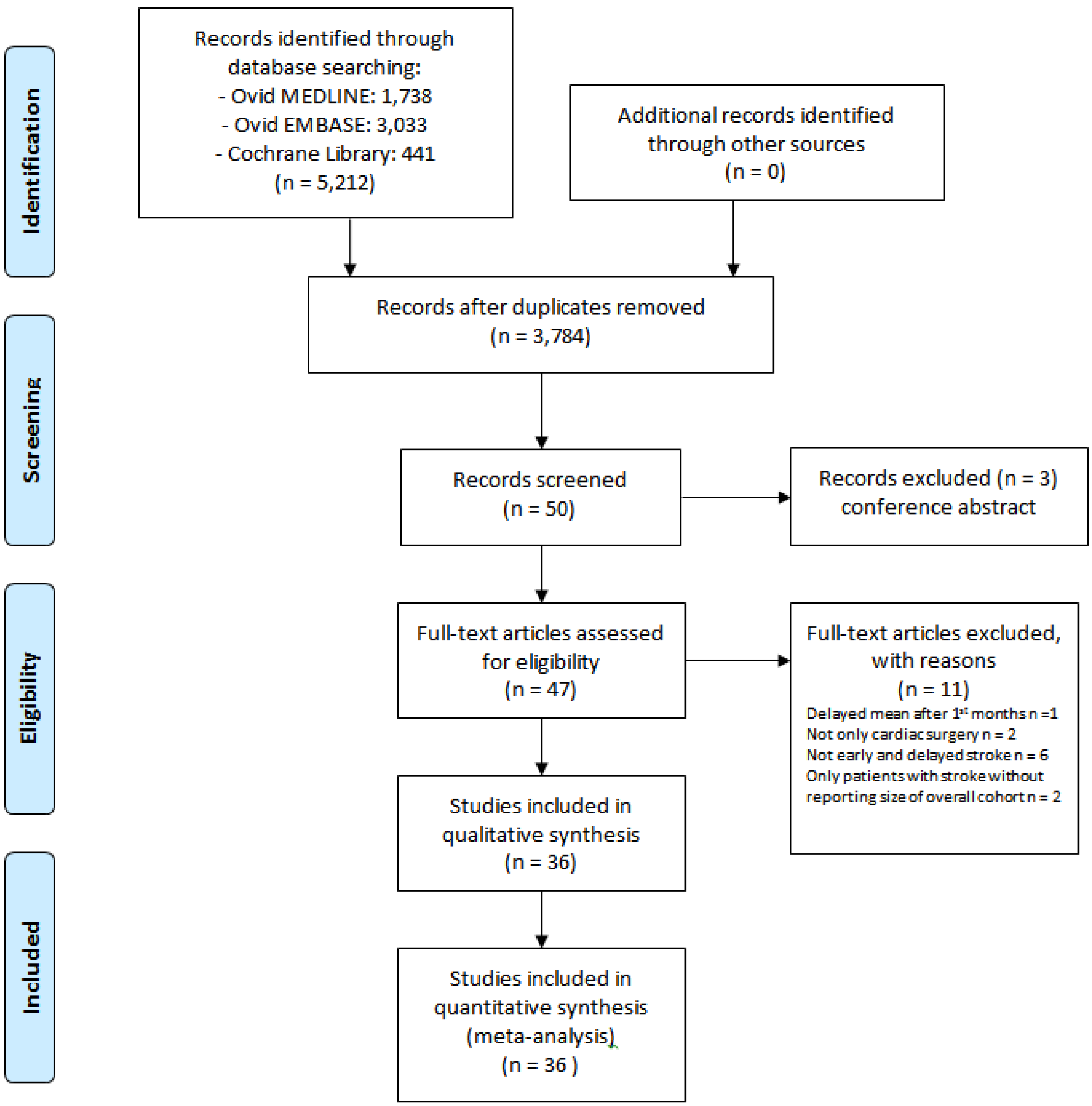


Figure S2. Pooled event rate for perioperative stroke.

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[14]	18	463	0.04	[0.02; 0.06]	0.5%	2.4%
Carrascal 2014[7]	32	844	0.04	[0.03; 0.05]	0.9%	2.7%
Boivie 2005[2]	98	2641	0.04	[0.03; 0.05]	2.8%	3.0%
Salazar 2001[32]	214	5971	0.04	[0.03; 0.04]	6.2%	3.1%
Toumpoulis 2008[34]	138	4140	0.03	[0.03; 0.04]	4.0%	3.1%
Murdock 2003[28]	68	2104	0.03	[0.03; 0.04]	2.0%	3.0%
Martin 1982[26]	8	253	0.03	[0.01; 0.06]	0.2%	1.9%
Hedberg 2013[17]	339	10809	0.03	[0.03; 0.03]	9.8%	3.2%
Hedberg 2005[15]	77	2641	0.03	[0.02; 0.04]	2.2%	3.0%
Lisle 2008[25]	202	7201	0.03	[0.02; 0.03]	5.9%	3.1%
Hedberg 2011[16]	245	9122	0.03	[0.02; 0.03]	7.1%	3.1%
Lee 2011[24]	33	1367	0.02	[0.02; 0.03]	1.0%	2.7%
Weinstein 2001[35]	51	2217	0.02	[0.02; 0.03]	1.5%	2.9%
Filsoufi.A 2008[11]	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[30]	211	10573	0.02	[0.02; 0.02]	6.2%	3.1%
Lahtinen 2004[23]	52	2630	0.02	[0.01; 0.03]	1.5%	2.9%
Ridderstolpe 2002[31]	64	3282	0.02	[0.02; 0.02]	1.9%	3.0%
Marui 2012[27]	45	2446	0.02	[0.01; 0.02]	1.3%	2.9%
Nishiyama 2009[29]	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[19]	20	1134	0.02	[0.01; 0.03]	0.6%	2.5%
Kinnunen 2015[22]	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[33]	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%
Karkouti 2005[21]	160	10949	0.01	[0.01; 0.02]	4.7%	3.1%
Blossom 1992[1]	46	3428	0.01	[0.01; 0.02]	1.4%	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]	0.9%	2.7%
Fessatidis 1991[10]	15	1487	0.01	[0.01; 0.02]	0.4%	2.3%
Calafiore 2002[5]	49	4875	0.01	[0.01; 0.01]	1.5%	2.9%
Wijdicks 1996[36]	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: $I^2 = 94\%$, $\tau^2 = 0.1804$, $p < 0.01$

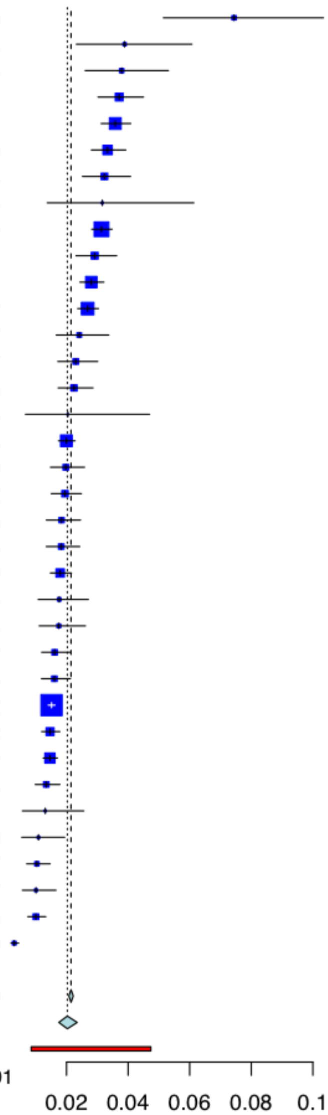


Figure S3. Reconstructed Kaplan-Meier survival curves from derived individual patient data (IPD) for A) No stroke versus perioperative stroke and B) No stroke versus early and delayed stroke. Solid/dotted line represents aggregation of all available Kaplan-Meier curves with 95% CI.

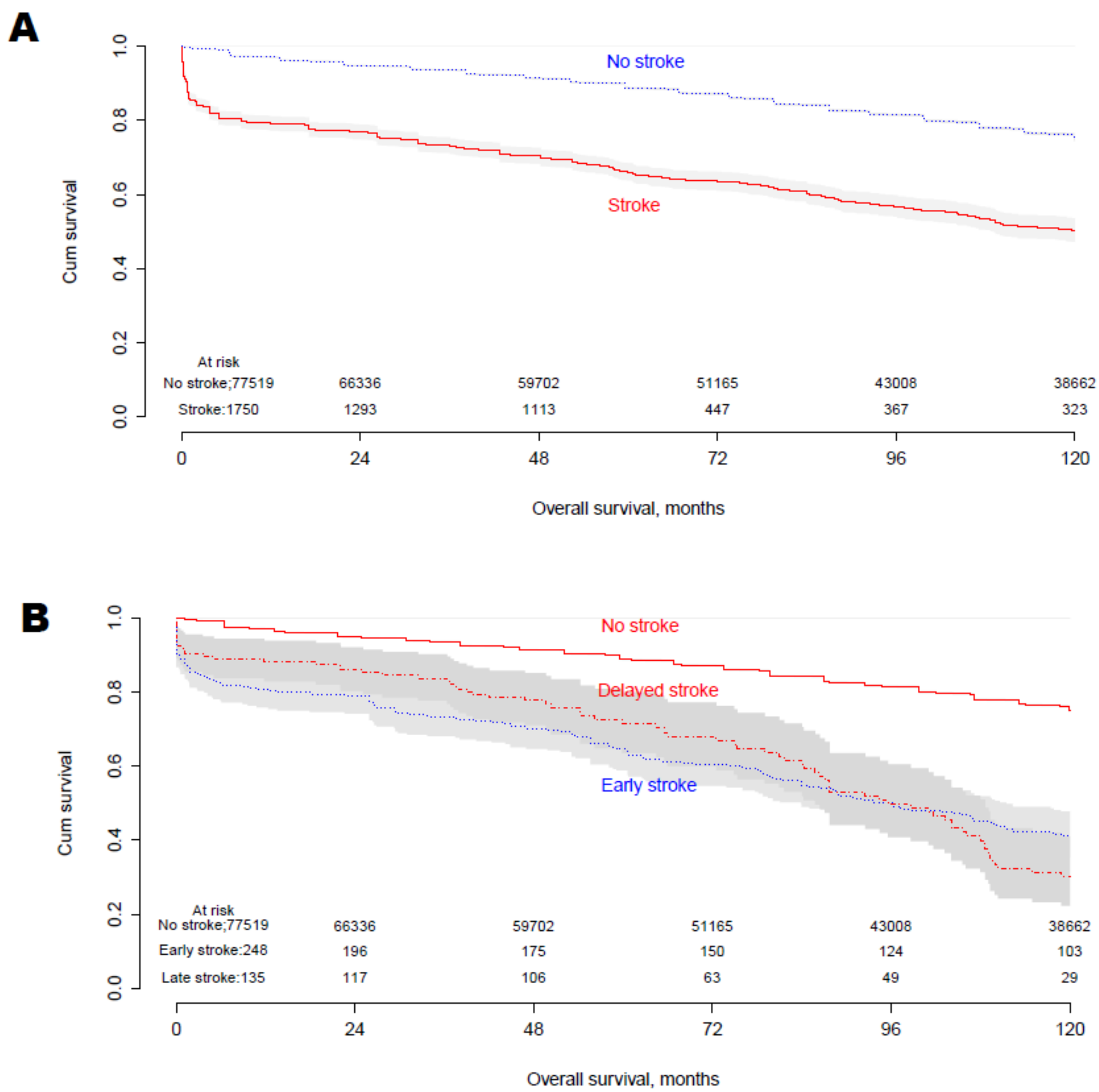
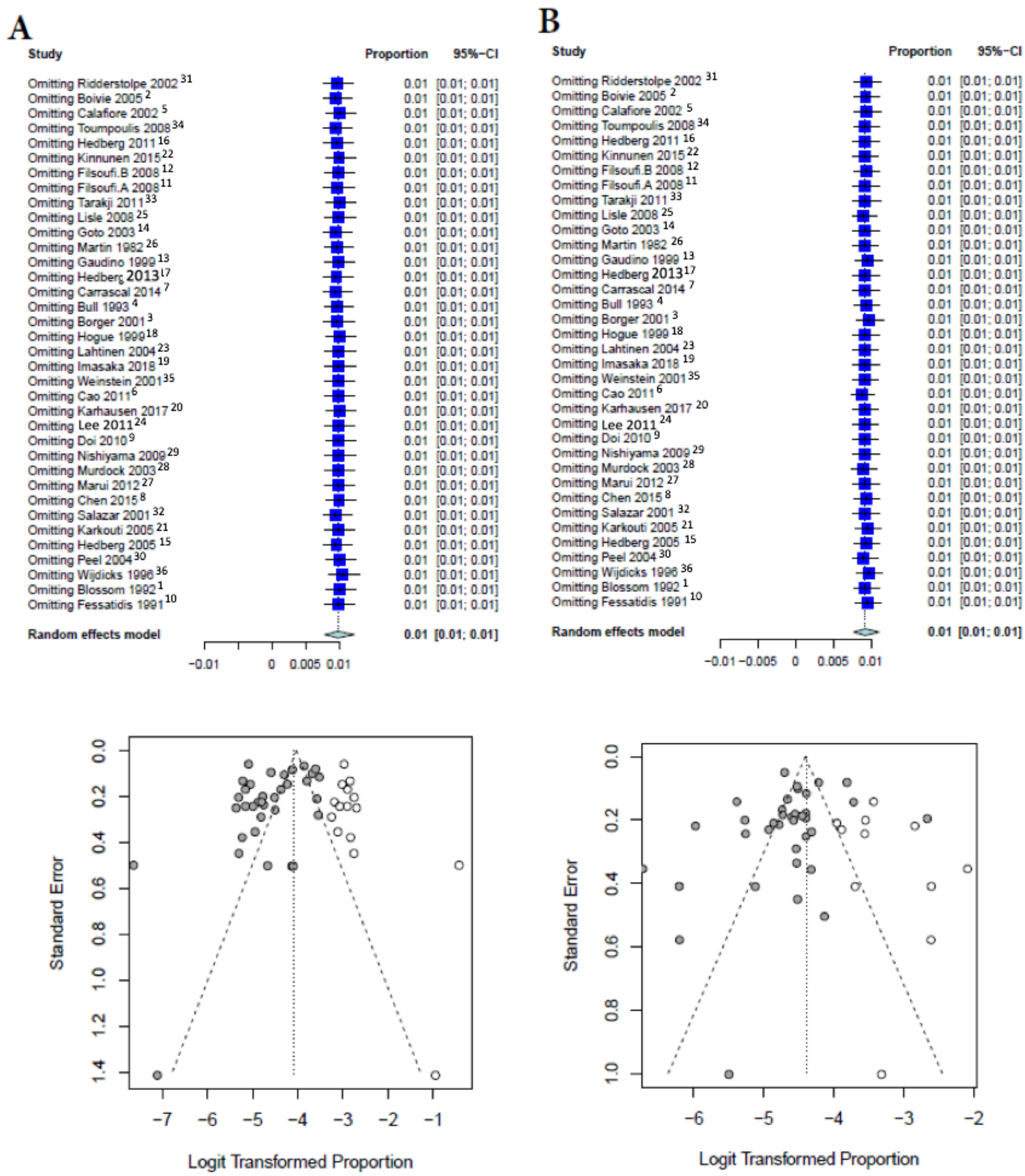


Figure S4. Leave-one-out analysis (top) and funnel plot (bottom) for incidence of A) early stroke and B) delayed stroke.



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