Perioperative Strokes Following Surgical Correction of Mitral Valves: A Systematic Review and Meta-Analysis

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**Abstract**

**Objective:** The primary aim of this meta-analysis was to quantify the impact of perioperative strokes on stroke-related mortality after open mitral valve (MV) procedures were performed. **Methods:** An electronic search of the PubMed, Embase, and the Web of Science databases was performed to retrieve articles published up to December 2015, relevant to patients undergoing MV procedures. Data were extracted from the final list of 25 studies to calculate a summary OR for 30-day stroke-related mortality. **Results:** The stroke rate in the total sample population was 1.62% (73/4,498). The 30-day all-cause mortality rate was 3.51% (158/4,498). The percentage of total deaths caused by stroke was 6.87%. The summary OR of stroke-related mortality following MV procedures was estimated to be 7.22 (95% CI 4.13–12.63, \(p < 0.001\)). A subgroup analysis was done for studies involving concomitant MV surgery and coronary artery bypass grafting. The summary estimate of the subgroup showed an OR of 8.508 (95% CI 1.552–46.622, \(p = 0.0136\)). **Conclusion:** Perioperative strokes following open MV procedures may be associated with more than 7 times greater odds of 30-day stroke-related mortality. They appear to be more commonly occurring than what is reported by current literature, making further studies investigating possible mechanisms and preventive measures a priority.

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**Keywords**

Mitral valve surgery · Perioperative stroke · In-hospital mortality · Morbidity

**Introduction**

Perioperative strokes, a significant complication following open mitral valve (MV) procedures, have grave implications on the postoperative mortality rates and the patients' quality of life [1]. Mitral regurgitation (MR) or mitral stenosis is corrected by surgical MV repair or a mechanical/ biological MV replacement (MVR) or by percutaneous mitral clip insertion depending on the etiopathogenesis, severity of clinical symptoms, and perioperative risk. As with any open cardiac surgery, thromboembolic events play a major etiological role in adverse neurological outcomes following MV procedures [1].
Mechanical and bioprosthesis methods of MVR have been shown to be associated with higher rates of perioperative thromboembolic events and in-hospital mortality compared to MV repair due to the increased platelet activation and clot formation associated with prosthetic materials [1]. Most studies have small patient populations or are single-center studies; a systematic analysis of the published literature has not been performed.

Current literature reports the maximum risk of stroke to be in the immediate postoperative period (<30 days) with the risk gradually declining to general population mortality rates following surgical correction of MV disease. Underlying the significant risk of debilitating neurological outcomes associated with MV procedures and their relationship with postoperative mortality in a large patient sample could help us investigate pharmacotherapeutic strategies that can help prevent thromboembolic events and lower perioperative stroke-related morbidity and mortality rates.

Materials and Methods

Search Criteria and Strategy

This systematic review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines (online suppl. PRISMA checklist; for all online suppl. material, see www.karger.com/doi/10.1159/000477164). An electronic search of the PubMed, Embase, and the Web of Science databases was performed to retrieve a list of articles published up to December 2015, relevant to patients undergoing open MV repair or replacement. The search was done using a combination of the following terms: mitral valve repair, mitral valve replacement, mitral valve surgery, stroke, transient ischemic attack, hemiparesis, hemiplegia, cerebrovascular accident, and mortality. The search history is provided in the supplement file.

Study Selection

The inclusion criteria included the following: (1) randomized clinical trials and prospective or retrospective cohort reviews; (2) studies conducted on patients undergoing MV repair/replacement; (3) studies inclusive of details on 30-day postoperative neurological outcomes and 30-day postoperative mortality data; (5) a total sample size of 50 or more patients (studies with a sample size of 50 or more were chosen to obtain an adequate sample size); (6) studies conducted on adult humans 18 years or older; (7) studies published in English, and (8) studies inclusive of an abstract.

Data Extraction

Two authors (R.U. and P.N.) independently screened all the titles and abstracts to identify and extract the studies that satisfied the inclusion criteria. Each author then subsequently created an Excel spreadsheet listing the articles to be included and excluded with a reason for elimination indicated by a number corresponding to one of the predetermined inclusion criteria, which was not fulfilled. A third author (P.D.T.) reconciled any disagreements in the inclusion/exclusion of studies following which a final list of studies was compiled. The following data were extracted from each study-author name and year, number of study patients, age and gender of study patients, number of patients who underwent isolated MV repair or replacement, number of patients who underwent combined MV repair/replacement with CABG or any other associated procedures, 30-day postoperative stroke data, and 30-day postoperative mortality data.

For this study, perioperative strokes were defined as any onset of new neurologic symptoms lasting longer than 24 h and occurring within 30 days of MV procedures. The main outcome of interest was 30-day mortality or in-hospital mortality rates among patients with perioperative strokes. Data on patients with perioperative strokes who died, patients with perioperative strokes not resulting in death, patients with no perioperative strokes who died, and patients with no perioperative strokes and no resultant deaths were collected for each study and tabulated in a 2 × 2 table, one for each category of patients.

Quality Assessment of Individual Studies

The risk of bias in the individual studies was determined based on recommendations of the Cochrane Collaboration. Twenty-four prospective and retrospective cohort studies were assessed for quality using the Newcastle-Ottawa Scale. The quality of these studies was assessed across 3 domains – selection, comparability, and outcome. According to the Newcastle-Ottawa Scale, a maximum of 4 stars may be awarded for selection, 2 stars for comparability, and 3 stars for outcome. Studies that receive 9 stars are of the highest quality. The results of the quality assessment are presented in the supplementary material (online suppl. Table 1).

Statistical Analysis

Statistical analysis was performed using version 3.1.2 of the METAFORE package for R [3]. Data extracted from each of the finalized studies were used to calculate the summary OR for 30-day stroke-related mortality outcomes in patients with perioperative
strokes versus patients without perioperative strokes following MV repair or replacement. A forest plot of the summary log ORs was constructed along with the calculation of the $I^2$ statistic to both visualize and quantify heterogeneity among the studies. For the purposes of this study, $I^2$ values of 25, 50, and 75% corresponded to low, medium, and high heterogeneity respectively. An overarching estimate of OR was calculated after relevant details were pooled from the individual studies using a random effects model. This type of model was used because this analysis involved a random sampling of patients undergoing MV repair or replacement. Publication bias was assessed using a funnel plot and Egger’s regression test.

**Results**

The electronic database search revealed a total of 1,178 studies after eliminating duplicates. A preliminary screening of all titles and abstracts excluded 895 studies based on the predetermined inclusion criteria (Fig. 1). Two hundred eighty-three articles were assessed for eligibility, of which 258 studies were excluded from the final list due to the lack of sufficient data on 30-day neurological outcomes and mortality. The total study population analyzed comprised of 4,498 patients. The mean age across the patient population was 62.76 years. One study by Seeburger et al. [4], including a population of 126 patients, provided no details on patient gender. In the remaining 24 studies, 60.6% (2,652/4,372) were found to be male patients. Overall, 1.62% (73/4,498) study patients developed perioperative strokes within 30 days of the procedure.

![Fig. 1. PRISMA chart exhibiting the elimination process for study analysis.](image-url)
Table 1. Patient data on perioperative stroke and 30-day mortality

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Sample size</th>
<th>Mean patient age</th>
<th>Sample size</th>
<th>Mean patient age</th>
<th>Mean patient age</th>
<th>30-Day all-cause mortality data</th>
<th>Perioperative stroke data</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>no deaths (%)</td>
<td>total deaths (of study population)</td>
<td>no deaths (%)</td>
<td>total deaths (% of study population)</td>
<td>no stroke, %</td>
<td>patients with strokes, %</td>
</tr>
<tr>
<td>Akar et al. [12], 2002</td>
<td>102</td>
<td>63.8</td>
<td>93 (91.2)</td>
<td>9 (8.8)</td>
<td>97 (95.1)</td>
<td>5 (4.9)</td>
<td>123 (97.6)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Asai et al. [13], 2015</td>
<td>126</td>
<td>59.5</td>
<td>125 (99.2)</td>
<td>1 (0.8)</td>
<td>1022 (99.6)</td>
<td>4 (0.4)</td>
<td>90 (98.9)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Bando et al. [14], 2005</td>
<td>1,026</td>
<td>NA</td>
<td>1,011 (98.5)</td>
<td>15 (1.5)</td>
<td>90 (98.9)</td>
<td>1 (1.1)</td>
<td>93 (98.9)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Calafiore et al. [15], 2004</td>
<td>91</td>
<td>65.1</td>
<td>87 (95.6)</td>
<td>4 (4.4)</td>
<td>92 (97.9)</td>
<td>2 (2.1)</td>
<td>101 (98.1)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Cingoz et al. [11], 2004</td>
<td>94</td>
<td>NA</td>
<td>91 (96.8)</td>
<td>3 (3.2)</td>
<td>91 (99.6)</td>
<td>0 (0.4)</td>
<td>90 (98.9)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Coutinho et al. [16], 2013</td>
<td>103</td>
<td>60.1</td>
<td>96 (93.2)</td>
<td>7 (6.8)</td>
<td>802 (99.5)</td>
<td>4 (0.5)</td>
<td>71 (97.3)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>David et al. [17], 2015</td>
<td>606</td>
<td>57.2</td>
<td>601 (99.2)</td>
<td>5 (0.8)</td>
<td>602 (99.3)</td>
<td>4 (0.7)</td>
<td>224 (99.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Fukui et al. [20], 2007</td>
<td>73</td>
<td>62.9</td>
<td>70 (95.9)</td>
<td>3 (4.1)</td>
<td>71 (97.3)</td>
<td>2 (2.7)</td>
<td>1 (98.1)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Bando et al. [21], 2002</td>
<td>225</td>
<td>58.6</td>
<td>219 (97.3)</td>
<td>6 (2.7)</td>
<td>224 (99.6)</td>
<td>1 (0.4)</td>
<td>51 (98.1)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Houser et al. [5], 1990</td>
<td>52</td>
<td>67.6</td>
<td>49 (94.2)</td>
<td>3 (5.8)</td>
<td>223 (98.7)</td>
<td>3 (1.3)</td>
<td>5 (96.4)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Jonjev et al. [6], 2007</td>
<td>226</td>
<td>55.7</td>
<td>209 (92.5)</td>
<td>17 (7.5)</td>
<td>223 (98.7)</td>
<td>3 (1.3)</td>
<td>53 (96.4)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Maleszka et al. [22], 2008</td>
<td>55</td>
<td>NA</td>
<td>50 (90.9)</td>
<td>9 (9.1)</td>
<td>48 (98)</td>
<td>2 (4)</td>
<td>48 (92.3)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Malhotra et al. [7], 2014</td>
<td>50</td>
<td>55.04</td>
<td>47 (94)</td>
<td>3 (6)</td>
<td>52 (94.5)</td>
<td>3 (5.5)</td>
<td>59 (96.7)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Murakami et al. [23], 2009</td>
<td>52</td>
<td>63.8</td>
<td>47 (90.1)</td>
<td>5 (9.6)</td>
<td>52 (94.5)</td>
<td>3 (5.5)</td>
<td>52 (94.5)</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>Murashita et al. [24], 2014</td>
<td>55</td>
<td>77.6</td>
<td>51 (92.7)</td>
<td>4 (7.3)</td>
<td>59 (96.7)</td>
<td>2 (3.3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nicolini et al. [8], 2006</td>
<td>61</td>
<td>69.2</td>
<td>58 (85.1)</td>
<td>3 (4.9)</td>
<td>108 (99.1)</td>
<td>1 (0.9)</td>
<td>111 (96.5)</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Papadopoulos et al. [25], 2015</td>
<td>109</td>
<td>66.4</td>
<td>100 (91.7)</td>
<td>9 (8.3)</td>
<td>241 (99.6)</td>
<td>1 (0.4)</td>
<td>123 (97.6)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Rathore et al. [10], 2008</td>
<td>115</td>
<td>58.5</td>
<td>110 (95.7)</td>
<td>5 (4.3)</td>
<td>150 (93.8)</td>
<td>10 (6.2)</td>
<td>74 (98.7)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Santini et al. [26], 2001</td>
<td>242</td>
<td>NA</td>
<td>222 (91.7)</td>
<td>20 (8.3)</td>
<td>175 (98.9)</td>
<td>2 (1.1)</td>
<td>74 (98.7)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Seeburger et al. [4], 2010</td>
<td>126</td>
<td>NA</td>
<td>123 (97.6)</td>
<td>3 (2.4)</td>
<td>175 (98.9)</td>
<td>2 (1.1)</td>
<td>175 (98.9)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Shinn et al. [27], 2009</td>
<td>160</td>
<td>60.5</td>
<td>149 (93.1)</td>
<td>11 (6.9)</td>
<td>175 (98.9)</td>
<td>2 (1.1)</td>
<td>175 (98.9)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Sjatskig et al. [28], 2012</td>
<td>75</td>
<td>68.8</td>
<td>72 (96)</td>
<td>3 (4)</td>
<td>394 (99.9)</td>
<td>9 (0.1)</td>
<td>123 (97.6)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Stefanidis et al. [29], 2005</td>
<td>177</td>
<td>57.5</td>
<td>127 (97.5)</td>
<td>5 (2.5)</td>
<td>394 (99.9)</td>
<td>9 (0.1)</td>
<td>123 (97.6)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Stevens et al. [9], 2010</td>
<td>403</td>
<td>63</td>
<td>395</td>
<td>8</td>
<td>4,425 (97.3)</td>
<td>11</td>
<td>4,425 (97.3)</td>
<td>11</td>
</tr>
</tbody>
</table>

NA, not available.
and a 30-day mortality rate of 0.26% (1/384). The calcu-

lating procedures. These 2 studies with a sample size of 384

patients had a perioperative stroke rate of 3.12% (12/384)

performed concurrently with other val-

cular or coronary artery procedures or atrial fibrillation

surgery and this lack of adequate patients undergoing iso-

lated MV procedures limited an extensive analysis of

perioperative outcomes.

Discussion

This meta-analysis defines that surgical MV proce-

dures have a perioperative stroke rate of 1.62% with the

30-day mortality rate found to be 4 times higher in pa-

patients with perioperative strokes (15.1 vs. 3.32%). The cal-

culated OR indicates that patients with perioperative

strokes procedures have 7.22 times higher risk of 30-day

stroke-related mortality compared to patients without

perioperative strokes.

Studies report stroke rates ranging widely from 1 to 8%

following MV surgery and when compared to the results

of our study, rates are on lower end of the spectrum [2].

This discrepancy between reported stroke rates from the

literature and actual clinical experience by surgeons could

be explained by the incidence of subclinical silent infarcts

detectable only on post-surgery MRI [30]. Although rap-

id advancements in anesthetic and surgical techniques

have led to progressive improvements in outcomes with

declining postoperative mortality rates following valve

operations, postoperative ischemic neurological complica-

tions remain just as daunting as they were a decade ago

[2]. A handful of studies have reported the role of sub-

clinical infarcts following MV surgery; however, further

investigation into the incidence of these lesions and their

long-term implications on quality of life appears crucial

[30].

In the current analysis, 2 studies [9, 10] reported iso-

lated MV repair with a perioperative stroke rate of 3.12%

and a summary OR of 9.36, and one study with isolated

MVR [11]. The remaining studies involved one or more

associated procedures like CABG, maze procedures, or

aortic valve procedures depending on the patients’ associ-

ated symptoms or the surgeons’ judgment and restricted

further subgroup analyses. Patients with ischemic MR
due to coronary artery disease usually undergo MV repair

or replacement concurrently with CABG. CABG has

been associated with a perioperative stroke rate of 1–5%

and the predisposing factors are consistent with the risk

factors for perioperative stroke following MV procedures


Table 2. Individual ORs

<table>
<thead>
<tr>
<th>Author and year</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akar et al. [12], 2002</td>
<td>0.85 (0.04–16.53)</td>
</tr>
<tr>
<td>Asai et al. [13], 2015</td>
<td>148.20 (4.77–4,607.42)</td>
</tr>
<tr>
<td>Bando et al. [14], 2005</td>
<td>7.22 (0.37–140.0)</td>
</tr>
<tr>
<td>Calafiore et al. [15], 2004</td>
<td>6.41 (0.23–180.45)</td>
</tr>
<tr>
<td>Cingoz et al. [11], 2004</td>
<td>8.62 (0.29–251.65)</td>
</tr>
<tr>
<td>Coutinho et al. [16], 2013</td>
<td>12.20 (0.39–379.89)</td>
</tr>
<tr>
<td>Davarpassad et al. [17], 2015</td>
<td>2.52 (0.11–57.42)</td>
</tr>
<tr>
<td>David et al. [18], 2013</td>
<td>12.07 (0.58–252.35)</td>
</tr>
<tr>
<td>Fukui et al. [20], 2007</td>
<td>3.91 (0.16–98.04)</td>
</tr>
<tr>
<td>Bando et al. [21], 2002</td>
<td>11.21 (0.42–302.09)</td>
</tr>
<tr>
<td>Houser et al. [5], 1990</td>
<td>59.40 (1.89–1,859.22)</td>
</tr>
<tr>
<td>Jonjev et al. [6], 2007</td>
<td>1.69 (0.08–33.97)</td>
</tr>
<tr>
<td>Maleszka et al. [22], 2008</td>
<td>1.76 (0.07–41.65)</td>
</tr>
<tr>
<td>Malhotra et al. [7], 2014</td>
<td>2.60 (0.10–65.41)</td>
</tr>
<tr>
<td>Murakami et al. [23], 2009</td>
<td>0.88 (0.04–18.62)</td>
</tr>
<tr>
<td>Murashita et al. [24], 2014</td>
<td>50.0 (3.08–810.54)</td>
</tr>
<tr>
<td>Nicolini et al. [8], 2006</td>
<td>28.50 (1.27–638.92)</td>
</tr>
<tr>
<td>Papadopoulos et al. [25], 2015</td>
<td>3.49 (0.13–91.78)</td>
</tr>
<tr>
<td>Rathore et al. [10], 2008</td>
<td>8.92 (0.75–105.79)</td>
</tr>
<tr>
<td>Santini et al. [26], 2001</td>
<td>34.23 (1.34–868.78)</td>
</tr>
<tr>
<td>Seeberger et al. [4], 2010</td>
<td>4.92 (0.21–114.55)</td>
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<tr>
<td>Shinn et al. [27], 2009</td>
<td>7.61 (1.65–35.08)</td>
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<td>Sjatskig et al. [28], 2012</td>
<td>6.81 (0.23–199.15)</td>
</tr>
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<td>Stefanidis et al. [29], 2005</td>
<td>6.20 (0.26–145.1)</td>
</tr>
<tr>
<td>Stevens et al. [9], 2010</td>
<td>6.91 (0.76–62.95)</td>
</tr>
</tbody>
</table>

strokes (3.32%). The summary estimate across the final

list of studies analyzed showed an OR of 7.22 (95% CI

4.13–12.63, p < 0.0001). The ORs for the individual

studies are presented in Table 2. Forest plot of the summary

and individual ORs are shown in Figure 2. No asymme-

try was shown in the funnel plot or Egger’s regression test

(z = 0.1338, p = 0.8936; Fig. 3).

Subgroup Analysis

A subgroup analysis was done for studies involving

concomitant MV surgery (either MV repair or replace-

ment) and CABG. Four primary studies with a sample

size of 389 patients were analyzed [5–8]. A perioperative

stroke rate of 2.05% (8/389) and 30-day mortality rate of

6.68% (23/389) were obtained. The summary estimate of

the risk of mortality in these 4 studies showed an OR of

8.508 (95% CI 1.552–46.622, p < 0.0001). The ORs for the individual stud-

ies are presented in Table 2. A perioperative stroke rate of

2.05% (8/389) and 30-day mortality rate of

6.68% (23/389) were obtained. The summary estimate of

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6.68% (23/389) were obtained. The summary estimate of

the risk of mortality in these 4 studies showed an OR of

8.508 (95% CI 1.552–46.622, p = 0.0136). Only 2 studies

[9, 10] involved isolated MV repair without any concom-

itant procedures. These 2 studies with a sample size of 384

patients had a perioperative stroke rate of 3.12% (12/384)

and a 30-day mortality rate of 0.26% (1/384). The calcu-

lated summary OR was 9.3686 (95% CI 1.302–67.401, p =

0.0263). One primary study [11] involved isolated MVR

with a perioperative stroke rate of 1.06%. Majority of MV

procedures were performed concurrently with other val-

cular or coronary artery procedures or atrial fibrillation

surgery and this lack of adequate patients undergoing iso-

lated MV procedures limited an extensive analysis of

perioperative outcomes.
undergoing CABG with MV procedures had a perioperative stroke rate of 2.05% and revealed a summary OR of 8.50. Patients who undergo dual valve replacement of aortic and MV s have higher risk of perioperative thromboembolism due to greater surface area for thrombogenicity and associated left ventricular dysfunction [2]. In our study, these adjunctive procedures and their additive risks could have contributed to the perioperative stroke risk.

The significant risk of 30-day stroke-related mortality following surgical correction of regurgitant MVs warrants further comprehensive clinical studies to identify factors predisposing to perioperative strokes and thereby design-preventive pharmacotherapeutic strategies. Intraoperative neuromonitoring modalities like evoked potentials, electroencephalograms, and neuroprotection medications have shown considerable utility in predicting perioperative strokes following neurosurgical procedures like carotid endarterectomy and aneurysm clipping. These modalities may be extended to MV procedures and clinical studies to further investigate their potential benefits.
applicability in preventing early stroke-related mortality may be warranted.

A few limitations are to be addressed in our study. The final list of studies analyzed from different sources and locations can differ in their guidelines for MV procedures and postoperative neurological assessment and follow-up. The study, being retrospective, does not give us information on the real incidence of stroke in this population. The MV procedures were performed concurrently with other cardiac procedures based on clinical comorbidities such as coronary artery disease or atrial fibrillation and it was difficult to distinguish patients who underwent isolated MV procedures among the sample population. This may lead to variability in the final study sample. The 30-day mortality causes could not be delineated as cardiac or non-cardiac in some of the sample patients. Associated clinical findings in 30-day stroke-related deaths could not be ascertained in some analyzed studies. Other vascular risk factors such as hypertension, diabetes, and dyslipidemia and their association with perioperative stroke risk could not be measured. The protocol for postoperative neurological evaluation could have been vastly different in each hospital and could not be accounted for.

**Conclusion**

Perioperative stroke following surgical MV procedures may be associated with more than 7 times greater odds of 30-day stroke-related mortality. Understanding the significant risk of debilitating neurological outcomes associated with MV procedures and their relationship with early postoperative mortality may help us investigate monitoring and pharmacotherapeutic strategies, which can help prevent thromboembolic or ischemic events and lower perioperative stroke-related mortality rates.

**Disclosure Statement**

The authors have no conflicts of interest to disclose. There were no sources of funding for this work.

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**References**


