Perioperative Complications and Long-Term Outcomes After Bypasses in Adults with Moyamoya Disease: A Systematic Review and Meta-Analysis

Hai Sun1, Christopher Wilson2, Alp Ozpinar3, Sam Safavi-Abbasi1, Yan Zhao2, Peter Nakaji1, John E. Wanebo1, Robert F. Spetzler1

BACKGROUND: Surgical revascularization for adults with moyamoya disease (MD) includes direct, indirect, or combination bypasses. It is unclear which provides the best outcomes. We sought to determine the best surgical management for adults with MD by comparing perioperative complications and long-term outcomes among 3 bypass types.

METHODS: Literature databases were searched for articles reporting revascularization bypass outcomes for adults with MD. A pooled analysis of all qualified studies and meta-analysis using only studies reporting direct comparisons of 2 bypass types were performed. Overall odds ratios (ORs) comparing 2 bypass types were computed and publication bias was assessed. Rates of perioperative and long-term hemorrhage and ischemia and favorable outcomes were compared.

RESULTS: Forty-seven studies were analyzed; 8 had level 1 or 2 evidence. Pooled analyses showed that perioperative hemorrhage rates were significantly (P = 0.02) lower with indirect compared with direct (OR, 0.03; 95% confidence interval [CI], 0.002–0.55) or combined (OR, 0.03; 95% CI, 0.002–0.53) bypasses. Meta-analysis showed that direct bypass was better at preventing long-term hemorrhage than was indirect bypass (OR, 0.26; 95% CI, 0.09–0.79; P = 0.02). Pooled analyses showed that direct is significantly better (P < 0.01) than indirect (OR, 0.51; 95% CI, 0.33–0.77) and combined (OR, 0.47; 95% CI, 0.31–0.72) bypasses in preventing long-term ischemia. Meta-analysis showed that direct was better than indirect bypass in producing long-term favorable outcomes (OR, 2.62; 95% CI, 1.19–5.79; P = 0.02), and the pooled analysis showed that combined bypass was better than indirect bypass in producing long-term favorable outcomes (OR, 1.26; 95% CI, 1.03–1.54; P = 0.02).

CONCLUSIONS: Overall, our analyses suggest that direct bypass with or without indirect augmentation provides the best outcomes for adults with MD.

INTRODUCTION

Moyamoya disease (MD) is characterized by idiopathic progressive narrowing or occlusion of the bilateral distal internal carotid arteries. Over time, compensatory collateral vasculature develops in the basal brain, which is commonly seen on angiography as a puff of smoke.1 Without treatment, adults with MD progressively accumulate neurologic and cognitive deficits and have more than double the mortality of pediatric patients with MD (10% vs. 4.3%, respectively).2 Surgical revascularization provides better outcomes for these patients than medical treatment alone.3-6 Surgical revascularization can be direct, indirect, or a combination of the 2 bypass approaches. Direct bypass is accomplished by anastomosing extracranial vessels to intracranial vessels, most often the superficial temporal artery (STA) to the middle cerebral artery (MCA) (STA-MCA bypass). However, other variations exist. Indirect bypass has variations but is generally accomplished by

Key words
- Adult moyamoya disease
- Bypass
- Cerebral blood flow
- Cerebral ischemia
- Intracranial hemorrhage
- Surgical revascularization

Abbreviations and Acronyms
CI: Confidence interval
MCA: Middle cerebral artery
MD: Moyamoya disease
OR: Odds ratio
STA: Superficial temporal artery

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incorporating well-vascularized tissue on the surface of the brain to promote angiogenesis.\(^1\)\(^{10}\) Unlike the direct method, indirect bypass begins to alter the cerebral blood flow only after angiogenesis has taken place, which may take a few months to a year.\(^1\)\(^{10}\) A combined bypass uses both direct and indirect approaches simultaneously to maximize the effect of revascularization.

In this study, we compared published studies of direct, indirect, and combined bypasses with regard to perioperative complications and long-term clinical outcomes in adults with MD. In doing so, we aim to summarize the existing knowledge to determine the best type of bypass for adults with MD.

**METHODS**

**Study Selection**

We reviewed the MEDLINE, Web of Science, PubMed, and Cochrane databases for published articles concerning perioperative complications and long-term outcomes of surgical management of MD in adults. The search was not limited by year of publication. The terms used in the search included “moyamoya” AND (“surgical treatment” OR “cerebral revascularization”) AND “adult” AND “outcome.” Three independent reviewers (H.S., A.O., and C.W.) evaluated articles that described indirect, direct, and combined bypass techniques. The 3 reviewers screened articles by title and abstract for inclusion. Articles were excluded if they 1) were from non-peer-reviewed journals, 2) were not in English, 3) did not report a clinical study, 4) included only patients with moyamoya syndrome, 5) did not report outcomes for each type of surgical procedure, 6) did not separate pediatric from adult patients, or 7) did not report any outcomes. Articles that could not be initially excluded were assessed in full text. Reference lists of relevant articles were manually searched so that no published data were overlooked. The final list of included articles was reviewed by the director of the Barrow Moyamoya Center (J.W.). The level of evidence for each study was categorized as level 1 to level 5 using the Centre for Evidence-Based Medicine methods (www.cebm.com).

**Data Extraction**

Acquired data included rates of perioperative complications (hemorrhage and ischemia) and measures of long-term outcomes. The definition of a perioperative period varied among studies. In some studies, only complications that occurred during the same hospitalization as the revascularization were considered perioperative complications. However, in many studies, perioperative outcomes were counted if they occurred within 30 days of revascularization regardless of discharge status. To unify the studies, we considered intracranial hemorrhage or ischemia that occurred within 30 days of bypass to be perioperative complications.

The 3 long-term outcome measures assessed were rates of long-term hemorrhagic and ischemic events occurring more than 30 days after bypass and rates of favorable outcomes at last follow-up. Definitions of favorable outcomes varied among studies; both clinical improvement and angiographic improvement were included in our definition of favorable outcomes. If a study reported both clinical and angiographic improvements, clinical outcomes were included.

**Statistical Analysis**

The 5 outcome variables (perioperative hemorrhage, perioperative ischemia, long-term hemorrhage, long-term ischemia, and favorable outcomes) were compared among the 3 bypass approaches. For each outcome, the overall odds ratio (OR) and its 95% confidence interval (CI) comparing every 2 approaches across relevant studies were summarized using both pooled analysis and meta-analysis.

Although it has limitations, a pooled analysis obviates eliminating studies not directly comparing the 2 approaches of interest and thus was used to increase the power of the comparison. This analysis computes an OR and its 95% CI using the pooled and collapsed 2 x 2 contingency table that results from calculating the sum of the outcome of interest and no outcome of interest for each bypass approach.

The meta-analysis for each comparison included only studies in which the outcomes of 2 approaches of interest were both reported and then a weighted analysis of ORs from each individual study was conducted. The homogeneity of the ORs across relevant studies was tested using Cochrane Q statistics. If the homogeneity was rejected at the 0.1 level, then the ORs were treated as random effects and the overall OR was computed using the Cochran-Mantel-Haenszel method; if the homogeneity was accepted, ORs were treated as fixed effects and the overall OR was computed using the DerSimonian-Laird method. No studies were excluded because of bias, but possible sources of publication bias were evaluated using forest plots when more than 4 articles were included.

**RESULTS**

Using the designated search terms, we identified 2626 studies in the literature databases (search conducted in September 2015). On the basis of the 7 exclusion criteria, 2529 studies were excluded because of titles or abstracts. The remaining 97 articles were reviewed in their entirety by the 3 screeners applying the same 7 exclusion criteria. Of these 97 studies, 3 were excluded: 1) because outcomes were reported per hemisphere rather than per patient\(^12\); 2) because it was conducted among patients who had previously undergone revascularization\(^1\); and 3) because it was conducted on patients who were asymptomatic before procedures.\(^13\) The final analysis included 47 studies that met inclusion criteria and evaluated outcomes or complications of surgical management of MD in adult patients. A flow diagram of study selection is available online (Figure 1).

Table 1 lists studies included and their level of evidence. From these 47 studies, 2013 patients were included in our analysis, with 796 patients who underwent direct bypass only, 508 who underwent indirect bypass only, and 719 who underwent combined bypasses. Pooled and meta-analysis were performed for the 5 outcome categories: perioperative hemorrhage, perioperative ischemia, long-term hemorrhage, long-term ischemia, and favorable outcome.

**Perioperative Hemorrhage**

The rate of perioperative hemorrhage (postoperative hemorrhage within 30 days of bypass) was evaluated in 28 studies examining 967 patients. The rates of perioperative hemorrhage by procedure type were 3.8% (n = 14) of 371 patients undergoing direct bypass (14 studies\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\)\(^24\)\(^25\)\(^26\)\(^27\)\(^28\)\(^29\)\(^30\)\(^31\)\(^32\)\(^33\)\(^34\)\(^35\)\(^36\)\(^37\)\(^38\)\(^39\)\(^40\)\(^41\)\(^42\)\(^43\)\(^44\)\(^45\)\(^46\)\(^47\)\(^48\)\(^49\)\(^50\)\(^51\)\(^52\)\(^53\)\(^54\)\(^55\)\(^56\)\(^57\)\(^58\)\(^59\)), 0% (n = 0) of 188 patients...
undergoing indirect bypass (12 studies\(^6,16,23,28,30,32,35,36,44,46,49,52\), and 3.9\% (\(n = 16\)) of 408 patients undergoing combined bypass (12 studies\(^7,17,21,25,26,32,35,36,39-41,51\)).

The pooled analysis showed that the perioperative hemorrhage rate was lower with indirect than with direct bypass (OR, 0.03; 95\% CI, 0.00–0.55; \(P = 0.02\)) and with indirect than with combined bypass (OR, 0.03; 95\% CI, 0.00–0.53; \(P = 0.02\)). There was no difference between direct and combined bypasses (Table 2).

The meta-analysis of perioperative hemorrhage rates included 5 studies comparing direct and indirect bypasses,\(^6,28,32,36,46\) 4 comparing direct versus combined,\(^7,32,39,39\) and 3 comparing indirect versus combined.\(^32,35,36\) Comparisons of perioperative hemorrhage rates between any 2 of the 3 types of bypass were not statistically significantly different (Table 3), and no publication biases were noted or applicable because of the small number of publications included.

**Perioperative Ischemia**

Perioperative ischemia (cerebral ischemic event within 30 days of bypass) was evaluated in 28 studies examining 958 patients. Rates by procedure type were 3.2\% (\(n = 11\)) of 341 patients undergoing direct bypass (13 studies\(^6,7,20,28,32,37,39,42,46-48,50-52\)), 4.8\% (\(n = 11\)) of 231 patients undergoing indirect bypass (13 studies\(^6,16,23,28,30,32,35,36,44,46,49,50,57\)), and 4.1\% (\(n = 16\)) of 386 patients undergoing combined bypass (12 studies\(^7,17,21,24-26,32,35,36,39,41,51\)).

The pooled analyses comparing any 2 of the 3 types of bypass did not yield any significant differences in perioperative ischemia rates among these approaches (Table 2).

The meta-analysis of perioperative ischemia rates included 5 studies comparing direct and indirect bypasses,\(^6,28,32,36,46\) 4 for direct versus combined,\(^7,32,39,39\) and 3 for indirect versus combined.\(^32,35,36\) No significant differences were found in

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**Figure 1.** The flow diagram shows the process of the literature search. (Used with permission from Barrow Neurological Institute, Phoenix, Arizona.)
perioperative hemorrhage rates among these approaches (Table 3). There was no indication of publication bias in our comparisons.

### Long-Term Hemorrhage

Long-term hemorrhage rates (any intracranial hemorrhage occurring >30 days after revascularization) were evaluated by 30 studies with 1292 patients. Rates by procedure type were 3.6% (n = 23) of 636 patients undergoing direct bypass (17 studies6,15,18-20,28,31,32,35,37,42,47,48,50,52,53,59), 4.6% (n = 12) of 259 patients undergoing indirect bypass (12 studies16,18-20,23,28,30,32,34,44,52,56), and 4.3% (n = 17) of 397 patients undergoing combined bypass (9 studies17,19,21,25,26,32,40,51,60).

The pooled analyses comparing any 2 of the 3 bypass types did not yield any significant differences in long-term hemorrhage rates among these approaches (Table 2).

The meta-analysis of long-term hemorrhage rates included 6 studies comparing direct and indirect bypasses,18-20,28,33,52 2 for direct versus combined,19,32 and 2 for indirect versus combined.17,20 Direct bypass conferred a significantly lower rate of long-term hemorrhage than did indirect bypass (OR, 0.26; 95% CI, 0.09–0.79; P = 0.02) (Figure 2A). No difference was found in rates of long-term hemorrhage between direct and combined bypasses or between indirect and combined bypasses (Table 3), and no publication biases were noted.

### Long-Term Ischemia

Long-term ischemia rates (any cerebral ischemic event occurring >30 days after revascularization) were evaluated by 30 studies with 1213 patients. Rates by procedure type were 3.9% (n = 26) of 666 patients undergoing direct bypass (18 studies6,15,18-20,22,28,31,32,35,37,39,40,42,47,48,50,52,53,59), 7.4% (n = 20) of 269 patients undergoing indirect bypass (10 studies26,28,29,30,32,34,35,39,52,53), and 7.9% (n = 22) of 278 patients undergoing combined bypass (9 studies21,24-26,32,39,41,51).

### Table 1. Distribution of Level of Evidence Among Included Studies

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Number of Studies (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual randomized controlled trial, 1b</td>
<td>1 (2)</td>
<td>Miyamoto et al., 2014</td>
</tr>
<tr>
<td>Individual cohort, 2b</td>
<td>4 (9)</td>
<td>Gonzalez et al., 2015, Jiang et al., 2014, Liu et al., 2013, Yoshida et al., 1999</td>
</tr>
<tr>
<td>Outcomes research, 2c</td>
<td>2 (4)</td>
<td>Guzman et al., 2009, Han et al., 2011</td>
</tr>
<tr>
<td>Systematic review of case-control studies, 3a</td>
<td>1 (2)</td>
<td>Kazumata et al., 2014</td>
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</table>

### Table 1. Continued

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Number of Studies (%)</th>
<th>References</th>
</tr>
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<td>Kinugasa et al., 1993</td>
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<tr>
<td>Kobayashi et al., 1991</td>
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</tr>
<tr>
<td>Kurama et al., 2015</td>
<td>3</td>
<td></td>
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<tr>
<td>Mesiwala et al., 2008</td>
<td>4</td>
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<tr>
<td>Miyamoto et al., 1998</td>
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<td></td>
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<tr>
<td>Miyamoto et al., 1998</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sakamoto et al., 2007</td>
<td>7</td>
<td></td>
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<tr>
<td>Starke et al., 2009</td>
<td>8</td>
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<td>Tu et al., 1997</td>
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<tr>
<td>Yoshikawa et al., 1998</td>
<td>10</td>
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<tr>
<td>Expert opinion, 5</td>
<td>1 (2)</td>
<td>Lougheed et al., 1971</td>
</tr>
</tbody>
</table>
The pooled analysis showed a statistically significantly lower long-term ischemia rate in patients with direct bypass versus indirect bypass (OR, 0.51; 95% CI, 0.33–0.77; P < 0.01). Similarly, direct bypass conferred lower odds of long-term ischemia than did combined bypass (OR, 0.47; 95% CI, 0.31–0.72; P < 0.01) (Table 2). However, no difference was found between indirect and combined bypasses (Table 2).

The meta-analysis of long-term ischemia rates included 5 studies comparing direct and indirect bypasses,23,26,28,31,39 2 comparing direct versus combined,32,39 and 1 comparing indirect versus combined.18 We found no differences in the rates of long-term ischemia between direct and indirect bypasses or between direct and combined bypasses. The study18 that compared the rate of long-term ischemia between indirect and combined bypass patients showed no statistically significant difference between these cohorts (Table 3). No publication bias existed.

**Favorable Outcome**

Long-term favorable outcome were assessed in 45 studies that included 1918 patients. We excluded 2 of the 47 total studies from the analyses for long-term favorable outcomes: 1 did not report favorable outcomes by bypass modality18 and the other included pediatric patients in long-term outcomes data.49 The definition of favorable outcome varied among studies. Most studies used the improvement of preoperative symptoms or functional status as the indication for favorable outcome. Among the 45 studies analyzed, favorable outcomes included the reduction of preoperative symptoms in 15 studies6,7,25-29,32-34,41,43,47,52,57 (33%), complete resolution of preoperative symptoms in 10 studies31,32,38,39,42,51,53,58,61 (22%), ability to live independently in 8 studies16,24,35,37-39,42,51,53,58 (18%; generally modified Rankin Scale score of 0–2), stabilization of preoperative symptoms in 6 studies36,46,48,56,59,61 (13%), postoperative angiographic improvement in 3 studies20,40,55 (7%), and other less common intellect or functional scores to define postoperative improvements in 3 studies20,21,22 (7%).

The rates of long-term favorable outcome by procedure type were 80% (n = 578) of 725 patients undergoing direct bypass (22 studies6,7,15,19,20,22,28,29,31,32,36,37,39,40,41,43,46-48,50,52,53,59), 78% (n = 403) of 520 patients undergoing indirect bypass (22 studies22,23,27-30,32,34-36,40,44,46,52,55,57,58,61), and 81% (n = 547) of 673 patients undergoing direct bypass (18 studies17,19,21,24-26,29,33,35,38,39,41,43,51,54,57). The pooled analyses showed no difference in favorable outcome rates between undergoing patients direct or indirect bypass or between patients undergoing direct and combined bypass patients.

### Table 2. Pooled Analysis Summary

<table>
<thead>
<tr>
<th>Comparison by Outcome and Bypass Type (Number of Patients)</th>
<th>Number of Studies</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect (188) vs. direct (371)</td>
<td>12 vs. 14</td>
<td>0.03</td>
<td>0.00–0.55</td>
<td>0.02</td>
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<tr>
<td>Direct (371) vs. combined (408)</td>
<td>14 vs. 12</td>
<td>0.96</td>
<td>0.57–1.61</td>
<td>0.8</td>
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<tr>
<td>Indirect (188) vs. combined (408)</td>
<td>12 vs. 12</td>
<td>0.03</td>
<td>0.00–0.53</td>
<td>0.02</td>
</tr>
<tr>
<td>Perioperative ischemia</td>
<td></td>
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</tr>
<tr>
<td>Direct (341) vs. indirect (231)</td>
<td>13 vs. 13</td>
<td>0.67</td>
<td>0.37–1.22</td>
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<tr>
<td>Direct (341) vs. combined (386)</td>
<td>13 vs. 12</td>
<td>0.77</td>
<td>0.44–1.34</td>
<td>0.4</td>
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<tr>
<td>Indirect (231) vs. combined (386)</td>
<td>13 vs. 12</td>
<td>1.16</td>
<td>0.66–2.02</td>
<td>0.6</td>
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<tr>
<td>Long-term hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct (636) vs. indirect (259)</td>
<td>17 vs. 12</td>
<td>0.77</td>
<td>0.47–1.28</td>
<td>0.3</td>
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<tr>
<td>Direct (636) vs. combined (397)</td>
<td>17 vs. 9</td>
<td>0.84</td>
<td>0.53–1.32</td>
<td>0.4</td>
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<tr>
<td>Indirect (259) vs. combined (397)</td>
<td>12 vs. 9</td>
<td>1.09</td>
<td>0.64–1.95</td>
<td>0.8</td>
</tr>
<tr>
<td>Long-term ischemia</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Direct (666) vs. indirect (269)</td>
<td>18 vs. 10</td>
<td>0.51</td>
<td>0.33–0.77</td>
<td>0.002</td>
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<tr>
<td>Direct (666) vs. combined (278)</td>
<td>18 vs. 9</td>
<td>0.47</td>
<td>0.31–0.72</td>
<td>0.0004</td>
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<tr>
<td>Indirect (269) vs. combined (278)</td>
<td>10 vs. 9</td>
<td>0.93</td>
<td>0.59–1.46</td>
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<tr>
<td>Favorable outcome</td>
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<tr>
<td>Direct (725) vs. indirect (520)</td>
<td>22 vs. 22</td>
<td>1.15</td>
<td>0.94–1.39</td>
<td>0.2</td>
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<tr>
<td>Direct (725) vs. combined (673)</td>
<td>22 vs. 18</td>
<td>0.91</td>
<td>0.75–1.09</td>
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<tr>
<td>Combined (673) vs. indirect (520)</td>
<td>18 vs. 22</td>
<td>1.26</td>
<td>1.03–1.54</td>
<td>0.02</td>
</tr>
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</table>

*Bold type indicates statistically significant findings.*
However, combined bypass conferred a significantly higher rate of favorable outcome than did indirect bypass alone (OR, 1.26; 95% CI, 1.03–1.54; P = 0.02) (Table 2).

The meta-analysis of favorable outcome rates included 10 studies comparing direct and indirect bypasses,19,20,22,28,29,32,36,40,46,52 5 for direct versus combined,19,29,32,36,39 and 6 for indirect versus combined.19,29,32,35,36,55 Direct bypass conferred a significantly higher rate of favorable outcome than did indirect bypass alone (OR, 2.62; 95% CI, 1.19–5.79; P = 0.02) (Table 3 and Figure 2B). There was no difference between direct and combined bypasses in the same comparison or between indirect and combined bypasses (Table 3). The comparison of indirect and combined bypasses may be subject to publication bias, but the other comparisons were not.

### DISCUSSION

The goal of this study was to determine possible differences in rates of perioperative complications and long-term outcomes between 3 bypass approaches used to treat adults with MD. On the basis of this meta-analysis, we aimed to determine a preferred surgical approach. These analyses were conducted for a disease with considerable heterogeneity and among studies with diverse designs.

### Perioperative Complications

Although surgical treatments for MD carry the anesthetic and surgical complications common to other neurosurgeries, revascularization techniques carry increased risks of perioperative hemorrhage and ischemia for patients with MD. It has long been suspected that direct bypass may confer higher rates of perioperative complications than does indirect bypass because of several factors. First, compared with indirect revascularization, direct anastomosis is more technically challenging; second, direct anastomosis requires temporary cortical vessel occlusion, which can lead to perioperative ischemia; and third, direct anastomosis can lead to hyperperfusion syndrome, resulting in perioperative hemorrhage.62 Horn et al.59 studied the risk of perioperative ischemia related to temporary vessel occlusion in 20 consecutive adults who underwent direct STA-MCA bypasses. The duration of temporary vessel occlusion ranged from 25 to 42 minutes, and 2 patients (10%) had diffusion changes on postoperative MRI. Neither of these 2 patients was symptomatic. Mesiwala et al.57 reported a perioperative stroke rate of 7.7% after direct bypass. In the series reported by Guzman et al.,6 6 of 222 adult patients with MD who underwent direct bypass had ischemic stroke, whereas none of 11 patients who underwent indirect bypass had

<table>
<thead>
<tr>
<th>Table 2. Comparison by Outcome and Bypass Type (Number of Patients)</th>
<th>Number of Studies</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value*</th>
<th>Publication Bias</th>
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<tr>
<td>Perioperative hemorrhage</td>
<td>Direct (273) vs. indirect (48)</td>
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<td>0.16–4.27</td>
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<td>0.62</td>
<td>0.09–4.52</td>
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<tr>
<td></td>
<td>Indirect (23) vs. combined (10)</td>
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<tr>
<td>Perioperative ischemia</td>
<td>Direct (273) vs. indirect (48)</td>
<td>5</td>
<td>0.44</td>
<td>0.11–1.74</td>
<td>0.24</td>
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<td></td>
<td>Direct (33) vs. combined (19)</td>
<td>4</td>
<td>1.62</td>
<td>0.33–8.49</td>
<td>0.57</td>
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<tr>
<td></td>
<td>Indirect (23) vs. combined (10)</td>
<td>3</td>
<td>1.16</td>
<td>0.23–12.93</td>
<td>0.60</td>
</tr>
<tr>
<td>Long-term hemorrhage</td>
<td>Direct (138) vs. indirect (58)</td>
<td>6</td>
<td>0.26</td>
<td>0.09–0.79</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Direct (10) vs. combined (9)</td>
<td>2</td>
<td>0.91</td>
<td>0.08–10.79</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Indirect (25) vs. combined (9)</td>
<td>2</td>
<td>1.51</td>
<td>0.21–10.77</td>
<td>0.68</td>
</tr>
<tr>
<td>Long-term ischemia</td>
<td>Direct (137) vs. indirect (78)</td>
<td>5</td>
<td>1.02</td>
<td>0.40–2.57</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Direct (11) vs. combined (17)</td>
<td>2</td>
<td>3.24</td>
<td>0.23–45.51</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Indirect (18) vs. combined (8)</td>
<td>1</td>
<td>1.46</td>
<td>0.05–39.66</td>
<td>0.82</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>Direct (225) vs. indirect (207)</td>
<td>10</td>
<td>2.62</td>
<td>1.19–5.79</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Direct (46) vs. combined (48)</td>
<td>5</td>
<td>1.05</td>
<td>0.42–2.60</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Combined (100) vs. indirect (42)</td>
<td>6</td>
<td>0.58</td>
<td>0.28–1.25</td>
<td>0.17</td>
</tr>
</tbody>
</table>

* Bold type indicates statistically significant findings.
ischemic changes. Several studies have reported mortalities associated with direct bypass,\(^{31,48,50,52}\) whereas indirect bypass seemed safer. Despite evidence provided by these reports, our meta-analysis did not show any significant difference in rates of either perioperative hemorrhage or perioperative ischemia among direct, indirect, or combined bypass procedures. However, the pooled analysis showed that patients with indirect bypasses had significantly lower rates of perioperative hemorrhage than did patients undergoing either direct or combined bypasses (Table 2). Our analyses suggest that, with adequate training and sufficient experience in performing the direct bypass, the neurosurgeon can minimize the rates of perioperative complications despite the aforementioned factors. Technical proficiency may lead to a shorter period of temporary vessel occlusion during anastomosis. The hyperperfusion syndrome related to direct bypass for patients with MD is a rare phenomenon that warrants further studies.

**Direct Bypass Is Superior**

Despite the findings regarding perioperative complications, our analyses showed that the collective evidence from existing studies favors direct bypass with or without the augmentation of the indirect approach over the indirect bypass alone in treating adults with MD. This finding is supported by our meta-analysis comparing direct with indirect bypasses on the rates of long-term hemorrhage and long-term favorable outcome (Figure 1). In addition, the pooled analyses showed that direct bypass is better than indirect bypass in preventing long-term ischemia and that combined bypass is better than indirect bypass in producing long-term favorable outcomes (Table 2).

The benefit of direct bypass over the indirect approach likely lies in its ability to create immediate and long-lasting changes in cerebral perfusion dynamics. Hemodynamic evaluation of brain perfusion using positron emission tomography has shown increased regional cerebral blood volume in the basal ganglia of
patients with MD with corresponding reductions in cerebral blood flow and increases in oxygen extraction in the MCA territories, indicating cortical misery perfusion. These findings explain the phenomenon that clinical presentations of patients with MD include both hemorrhage and ischemia. After direct STA-MCA anastomosis, an improvement in misery perfusion and a decrease in blood flow in basal ganglia have been observed on positron emission tomography studies. Several studies have documented the area of cortical region supplied by revascularized vessels and the decrease in moyamoya vessels on postoperative angiograms. These studies found that more significant angiographic changes were observed in patients who underwent direct or combined bypasses compared with those in patients who underwent indirect bypasses. These results suggest that direct bypass may be able to directly and actively alter the pathologic cerebral blood flow pattern of patients with MD, whereas indirect bypass responds only passively to the ischemic demand with supplementary angiogenesis.

In a study conducted by Lee et al. in patients with ischemic MD, direct and combined bypasses were more effective treatments than indirect bypass surgery in preventing recurrent ischemic stroke. In patients with hemorrhagic MD, rebleeding was less likely to occur in patients who had undergone bypass surgery. However, no significant difference was observed in the rebleeding rate between patients with direct bypasses and patients with indirect bypasses. On the basis of these results, the investigators argued that direct bypass may be more effective in treating ischemic MD than hemorrhagic MD. Choi et al. reported on 44 patients with adult hemorrhagic MD who underwent revascularization in their institution. Although statistical significance was not attained, these investigators showed that both direct and combined bypasses were more effective in reducing the risk of hemorrhage than was indirect bypass. Our meta-analysis of long-term hemorrhage rate comparisons between direct and indirect bypasses included 6 studies with 296 patients. Most studies did not separate their patient cohort into ischemic and hemorrhagic types. We showed that direct bypass was indeed more effective than indirect bypass in preventing long-term hemorrhage.

Study Limitations
There are several limitations to our study related to the underlying evidence base for the treatment of MD. First, the objective of this study was to determine which revascularization approach confers the best outcome for adult patients with MD. Because of the heterogeneity of the studies on this subject, we included studies that used different long-term outcome measures. Each clinical metric used by an individual study can capture only some aspect of this otherwise heterogeneous disease. Our determination of long-term favorable outcomes made by collecting different clinical and angiographic metrics may be insufficient to characterize the true clinical outcomes of these bypass procedures. Three studies reported only the results of postoperative angiography, and the correlation between angiographic improvement and clinical improvement is unclear.

Pooled analyses have limits in strength given the Simpson paradox, which describes the phenomenon in which a trend appears in different groups of data but disappears or reverses when these groups are combined. Most of the studies included here are case series that studied only 1 type of bypass. This limits the number of studies that were included in the meta-analyses. Results from pooled analyses should also be interpreted with caution. Thus, it is reassuring that we observed a similar trend between the meta-analyses and pooled analyses.

Given the greater prevalence of MD in patients of Asian heritage, much of the body of the medical literature included in our analysis is of Japanese origin. Although this limitation is a result of the lower incidence of MD worldwide, the meta-analysis may give disproportionate weight to studies composed predominantly of patients of Asian heritage. We attempted to assess this bias and, in 1 comparison, did find that there is a possibility of publication bias.

In light of these limitations, the results from our analyses need to be substantiated by large-scale, well-designed, randomized controlled trials that involve multiple treatment centers around the world and diverse patients with different ethnic backgrounds. In the meantime, this study serves to summarize the existing literature on different revascularization approaches and provides some guidance as to how to select procedures to treat adult patients with MD.

CONCLUSIONS
Our meta-analysis of outcomes in adult patients with MD after vascular bypass procedures provides statistical evidence suggesting that direct bypass with or without indirect augmentation may have a greater likelihood of favorable outcomes than does indirect bypass alone. On the basis of these findings, we recommend that direct bypass alone or in combination with indirect approaches should be attempted when treating adult patients with MD.

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REFERENCES
HAI SUN ET AL.

REVASCULARIZATION FOR ADULT MOYAMOYA


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