Symptomatic intracranial arterial disease: incidence, natural history, diagnosis, and management

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Symptomatic intracranial arterial disease is a common cause of ischemic stroke, but the optimal management of this condition remains incompletely defined. Options include medical therapy, endovascular treatment with angioplasty with or without stent placement, and surgical intervention for direct or indirect revascularization. In this review we provide evidence supporting or refuting the use of each of these potential therapies. Special emphasis was placed on available data regarding endovascular and surgical treatment of sICAD.

Epidemiology and Risk Factors

In the US, sICAD accounts for approximately 8%–9% of all ischemic strokes, resulting in approximately 65,000 strokes per year. Its incidence, however, exhibits racial and ethnic differences. In Asian populations, between 30% and 50% of ischemic strokes are due to sICAD. Atherosclerosis, in association with traditional stroke risk factors, accounts for the majority of sICAD. In African Americans and Hispanics, a significantly higher proportion of strokes are attributable to intracranial atherosclerosis than in Caucasians, despite an equal incidence of the extracranial atherosclerotic stroke subtype among the 3 racial/ethnic groups.

Atherosclerosis, in association with traditional stroke risk factors, accounts for the majority of sICAD. The common nonmodifiable risk factors of sICAD are age, male sex, and race. The most common modifiable risk factors are hypertension, hyperlipidemia, ischemic heart disease, and diabetes mellitus. The less common causes of sICAD include moyamoya disease, sickle cell disease, infectious meningitis, vasculitis, dissection, and radiation therapy.

Natural History

There is a high risk of recurrent strokes, which are often disabling, in patients with sICAD. Two large prospective trials—the WASID study and the Groupe d’Etude des Stenoses Intracraniennes Atheromateuses symptomatiques (GESICA) study—have documented recurrence rates of 14% and 19% over 2 years, with the majority of strokes occurring in the 1st year. Analysis of the WASID data has identified female sex, National Institutes of Health Stroke Scale score > 1, enrollment ≤17 days after ischemic event, and ≥70% stenosis (p = 0.004) as independent risk factors for recurrent stroke. In the WASID study, 73% of patients with recurrent strokes had ischemic lesions in the territory of the symptomatic stenotic artery. Importantly, 91% of the recurrent strokes...
were nonlacunar and 44% were disabling. Also, nearly half of the strokes in the remaining 27% of patients were due to a previously asymptomatic intracranial arterial stenosis.

Optimal Diagnostic Imaging

Digital subtraction angiography is the gold standard for diagnosing intracranial stenosis. Other commonly used modalities include TCD ultrasonography, MR angiography, and CT angiography. A rigorous comparison of the diagnostic accuracy of TCD ultrasonography and MR angiography with DS angiography was provided by the SONIA trial, a prospective, multicenter study designed in collaboration with WASID.\textsuperscript{21} In this study, both TCD ultrasonography and MR angiography were found to have high negative predictive values (86% and 91%, respectively), but low positive predictive values (36% and 59%, respectively). The study concluded that both modalities could reliably exclude intracranial stenosis, but if found, would need confirmation with DS angiography. The sensitivity and specificity of CT angiography studies of intracranial stenosis vary from 78% to 100% and 82% to 100%, respectively.\textsuperscript{7,34,57,67} The negative predictive value of CT angiography varies from 84% in the SONIA trial to 99.8% in recent retrospective studies.\textsuperscript{7,21} These data suggest that, in centers with experienced neuroradiologists, CT angiography could be an accurate and useful diagnostic tool for sICAD.

Medical Management

Anticoagulation Versus Antiplatelet Therapy

Initially, the use of warfarin to prevent recurrent ischemic events in patients with sICAD was a common clinical practice.\textsuperscript{22} This treatment paradigm was supported by several retrospective studies, which demonstrated that anticoagulation may be more effective than antiplatelet therapy for prevention of recurrent stroke.\textsuperscript{12,73,79} However, this practice was challenged by the results of WASID, a large, prospective, double-blind, multicenter randomized control trial.\textsuperscript{13} In this trial, patients with TIA or nondisabling stroke in whom angiographically demonstrated stenosis of 50%–99% was found in any major intracranial artery were randomized to receive aspirin or warfarin and followed for a mean of 1.8 years. Among 569 patients enrolled in this study, there was no difference (22.1% in the aspirin group vs 21.8% in the warfarin group) in the composite primary end point (ischemic stroke, brain hemorrhage, or death from any vascular causes other than stroke). Importantly, patients treated with warfarin had a higher incidence of adverse events (death and major hemorrhage), necessitating premature termination of patient enrollment. Another multicenter randomized trial examined the efficacy of nadroparin calcium, a low-molecular-weight heparin, in Asian patients with ischemic stroke within 48 hours of symptom onset.\textsuperscript{62} Of 603 patients recruited, 353 had moderate or severe stenosis of large arteries (300 with intracranial stenosis only, 11 with extracranial stenosis only, and 42 with both intracranial and extracranial stenosis) confirmed by carotid duplex scan, TCD, or MR angiography. These 353 patients were randomized to receive either 3800 U nadroparin calcium subcutaneously twice daily or 160 mg aspirin daily for 10 days, followed by 80–300 mg aspirin daily (in all enrolled patients) for 6 months. The primary end point, good outcome at 6 months (defined as Barthel Index $\geq$ 85), did not differ between the 2 groups.

Choice of Antiplatelet Drug

Although the American Heart Association/American Stroke Association guidelines recommend single antiplatelet therapy for all patients with acute ischemic stroke,\textsuperscript{2} there have been no studies comparing a single antiplatelet agent to placebo for secondary stroke prevention in patients with sICAD. However, in a multicenter, double-blind, placebo-controlled trial (Trial of cilostazol in Symptomatic intracranial arterial Stenosis [TOSS]), investigators evaluated dual antiplatelet therapy with aspirin and cilostazol, a phosphodiesterase-3 inhibitor, in 135 patients with sICAD.\textsuperscript{44} The primary outcome measure was progression of M or basilar artery stenosis as measured by MR angiography. The cilostazol/aspirin treatment group showed less progression (6.7% vs 28.8%) and greater regression (24.4% vs 15.4%) of stenosis. However, major limitations of this study include a high dropout rate, small sample size, short follow-up, and large proportion of mild stenosis. A follow-up trial, TOSS-II, initiated to compare the effect of cilostazol versus clopidogrel monotherapy, has recently been completed.

Risk Factor Modification

During the WASID trial, multiple risk factors for stroke were monitored at baseline and throughout the 2-year follow-up period.\textsuperscript{10} Although significant lowering of total cholesterol, low-density lipoprotein, and glycated hemoglobin was seen over the study period, blood pressure did not change. On multivariate analysis, a mean systolic blood pressure $\geq$ 140 mm Hg ($p = 0.0009$), no alcohol consumption ($p = 0.002$), and cholesterol $\geq$ 200 mg/dl ($p = 0.048$) were associated with an increased risk of stroke, myocardial infarction, or death from vascular causes other than stroke. These same factors were also significantly associated with ischemic stroke alone. A closer look at the relationship of blood pressure and recurrent stroke risk demonstrated a continuous increase in risk with increasing systolic and diastolic blood pressure.\textsuperscript{76} The significance for systolic blood pressure was largely driven by the highest blood pressure group (systolic $\geq$ 160 mm Hg). A common clinical practice regarding blood pressure management following sICAD is to withhold antihypertensive therapy, allowing for permissive hypertension and prevention of hemodynamic ischemic events in the territory of the stenotic artery. The aforementioned relationship between higher blood pressure and increased recurrent stroke risk suggests that this practice is not beneficial and may instead be harmful.

Endovascular Treatment

With rapid advances in endovascular technology,
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along with the documented high recurrence rate in prospective studies such as WASID, the use of endovascular therapy for patients with sICAD has become increasingly common (Fig. 1). Options include angioplasty alone, balloon-expandable stents, and angioplasty followed by placement of self-expanding stents. However, all published studies examining the safety and utility of these endovascular treatments for patients with sICAD represent case series, often with limited data about long-term outcome and restenosis rates. No randomized trials comparing these treatments against medical therapy have thus far been reported, although one such study is currently underway.16 In this section, we will review this literature and highlight specific study limitations. A summary of pertinent literature has been provided in Table 1.

Primary Angioplasty

Balloon angioplasty for intracranial stenoses was first reported in 1980.69 In current practice, the technical success rate (defined as reduction of stenosis to < 50%) of angioplasty is more than 80%, and restenosis rates range from 0% to 30%.45,52 Retrospective single-center studies have reported a 30-day rate of stroke or death varying between 0% and 50%.4,14,15,24,25,32,33,45,52,53,55,56,72 However, procedures that were performed in an elective manner were associated with lower complication rates (4%–6%).15,53,56 suggesting that this wide variation in complication rates could be due to a difference in the timing of treatment after the ischemic event. Only limited long-term clinical outcome data are available. The largest study, a retrospective multicenter review of 120 patients, has reported an annual stroke rate of 4.4% (3.2% in the territory of stenosis).53 However, the actual stroke rate is still uncertain, given the retrospective nature of this study and the lack of adjudication of events by neurologists.

Angioplasty and Stent Placement

A recent meta-analysis showed that the 1-year stroke and death rates were significantly lower with angioplasty and stent placement (14%) than with angioplasty alone (20%).65 Technical success rates were also higher in the angioplasty and stent placement group (95%) than in the group with angioplasty alone (80%). However, angiographic restenosis rates were similar between the techniques (11.1% and 14%, respectively). Early reports on intracranial stent placement were single-center series that demonstrated high technical success and low complication rates.17,24,25,36,37,41,46,48,51,80,90 The larger, more recent studies additionally suggest that the rate of stroke after stent insertion in patients with 70%–99% stenosis may be substantially lower than the rate of stroke in patients in the WASID study who had 70%–99% stenosis. Data exist for 2 categories of stents: balloon-expandable and self-expanding stents.

Balloon-Expandable Stents. The initial studies of intracranial angioplasty and stent placement with balloon-mounted stents were retrospective case series in which high technical success rates (90%–98%) were reported.17,36,37,48,51,90 Thereafter, an industry-sponsored multicenter Phase I trial of a balloon-expandable bare-metal stent (Neurolink, Guidant Corp.) for intracranial stenosis provided the first prospective data. This trial, SSYLVIA, was a nonrandomized, multicenter study that evaluated the safety and performance of primary stent placement in 61 patients with the following forms of stenosis: ≥ 50% intracranial arterial stenosis (43 patients), vertebral pre-PICA stenosis (12 patients), or vertebral ostium stenosis (6 patients).68 Delivery of the stent was successful in 58 (95%) of 61 patients. Four (7.2%) of 55 patients with intracranial or pre-PICA stenosis (defined as intracranial in the WASID study) had a stroke at 30 days; there were no deaths. The frequency of stroke within 1 year (including the 30-day rate) was 6 (10.9%) of 55. All strokes were in the territory of the treated artery. The incidence of angiographically documented recurrent stenosis (≥ 50%) was 35% at 6 months. Factors that were significantly associated with restenosis included diabetes, postprocedure diameter of stenosis > 30%, and small vessel diameter. This device (the Neurolink stent) was not marketed.

A later study by Jiang et al.38 reported a 7.2% rate of stroke or symptomatic brain hemorrhage at 1 year after stent placement in patients with ≥ 70% intracranial stenosis. However, the stent used in this study is not available in the US. Studies have also reported the use of coronary drug-eluting stents in the cerebral circulation, with the aim of reducing in-stent stenosis.1,31 However, because of their stiffness, the currently available coronary stents are difficult to deliver consistently in the tortuous cerebral circulation. More recently, single-center studies have reported the initial experience with 2 new balloon-mounted stents specifically designed for intracranial use. One study evaluated the use of the Apollo stent (MicroPort Medical) in 46 patients and demonstrated a technical

Fig. 1. Angiograms showing an endovascular stent placed in a 61-year-old man who presented with stroke in the right MCA territory. Left: Severe stenosis of the vertical petrous segment of the ICA was identified (black arrow). Flow limitation with filling of ECA branches (white arrow) simultaneously with intracranial branches was present. Note the absence of filling of the ACA. Right: After angioplasty and placement of a self-expanding stent (Wingspan, Boston Scientific), near-complete restoration of normal luminal diameter was achieved (black arrow). The guidewire is visible crossing the stenosis and terminating in an M1 branch. Improved flow is evidenced by the presence of the A1 segment of the ACA (white arrowhead) and filling of the intracranial branches ahead of the ECA (white arrow).
TABLE 1: Literature review and summary of various management strategies for patients with sICAD*

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Authors &amp; Year(s)</th>
<th>Type of Study</th>
<th>No. of Cases</th>
<th>Treatment Method</th>
<th>Technical Success Rate (%)†</th>
<th>Stroke Incidence (%)</th>
<th>Restenosis Rate At 30 Days</th>
<th>Restenosis Rate At 1 Yr</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kasner et al. (WASID), 2006</td>
<td>prospective, multicenter RCT</td>
<td>569</td>
<td>aspirin or warfarin</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>probability of stroke at 1yr: 11%</td>
</tr>
<tr>
<td>2</td>
<td>multiple14,15,28,32,33,45,52,55,67; 1993–2003</td>
<td>retrospective, single center</td>
<td>10–70</td>
<td>primary angioplasty</td>
<td>75–100</td>
<td>0–50</td>
<td>0–14</td>
<td>0–30</td>
<td>early stroke rate for elective procedures: 4%–6%</td>
</tr>
<tr>
<td>3</td>
<td>Marks et al., 2006</td>
<td>retrospective, multicenter</td>
<td>120</td>
<td>primary angioplasty</td>
<td>60</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>16 had angioplasty &amp; stent insertion; annual stroke rate 4.3%</td>
</tr>
<tr>
<td>4</td>
<td>Siddiq et al., 2008</td>
<td>retrospective, multicenter</td>
<td>95</td>
<td>primary angioplasty</td>
<td>85</td>
<td>8.4</td>
<td>12</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>multiple17,36,37,48,51,90; 2003–2005</td>
<td>retrospective, single center</td>
<td>18–106</td>
<td>balloon-expandable stents</td>
<td>90–98</td>
<td>2–10</td>
<td>2–10</td>
<td>0–13</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Siddiq et al., 2008</td>
<td>retrospective, multicenter</td>
<td>96</td>
<td>balloon-expandable stents</td>
<td>96</td>
<td>9.2</td>
<td>13</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SSYLVIA study, 2004</td>
<td>prospective, multicenter</td>
<td>61</td>
<td>balloon-expandable stents (Neurolink)</td>
<td>95</td>
<td>7</td>
<td>11</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Jiang et al., 2007</td>
<td>prospective, single center</td>
<td>46</td>
<td>balloon-expandable stents (Apollo)</td>
<td>91</td>
<td>7</td>
<td>11</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Kurre et al., 2008</td>
<td>prospective, single center</td>
<td>14 (21)‡</td>
<td>balloon-expandable stents (Pharos)</td>
<td>86</td>
<td>14</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Bose et al., 2007</td>
<td>prospective, single center</td>
<td>45</td>
<td>self-expanding stents (Wingspan)</td>
<td>98</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Fiorella et al., 2007; Albuquerque et al., 2008</td>
<td>prospective, multicenter</td>
<td>78</td>
<td>self-expanding stents (Wingspan)</td>
<td>99</td>
<td>6</td>
<td>NR</td>
<td>32§</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Zaidat et al., 2008</td>
<td>prospective, multicenter</td>
<td>129</td>
<td>self-expanding stents (Wingspan)</td>
<td>97</td>
<td>10</td>
<td>NR</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>multiple19,10; 1984 &amp; 2009</td>
<td>retrospective, single center</td>
<td>11–105</td>
<td>direct bypass</td>
<td>97–100</td>
<td>0–3</td>
<td>NR</td>
<td>NA</td>
<td>only sICAD</td>
</tr>
<tr>
<td>14</td>
<td>multiple37,70,87; 1976–2003</td>
<td>retrospective, single center</td>
<td>65–403</td>
<td>direct bypass</td>
<td>87–99</td>
<td>0–6</td>
<td>NR</td>
<td>NA</td>
<td>intracranial arterial disease with multiple origins</td>
</tr>
<tr>
<td>15</td>
<td>EC–IC Bypass Trial, 1985</td>
<td>prospective, multicenter RCT</td>
<td>1377</td>
<td>direct bypass</td>
<td>96</td>
<td>4.5</td>
<td>20</td>
<td>NA</td>
<td>approx 30% of patients w/ sICAD</td>
</tr>
<tr>
<td>16</td>
<td>Komotar et al., 2009</td>
<td>retrospective, single center</td>
<td>12</td>
<td>indirect bypass</td>
<td>NR</td>
<td>27</td>
<td>42</td>
<td>NA</td>
<td>17% had increased perfusion to ischemic area on SPECT scans</td>
</tr>
</tbody>
</table>

* Approx = approximately; NA = not applicable; NR = not reported; RCT = randomized controlled trial.  † Technical success was defined as residual stenosis < 50% after angioplasty or stent placement, or patent bypass.  ‡ The technical success rate and stroke incidence are reported for the 14 patients who underwent elective intracranial stent placement. Clinical outcome in the remaining 7 patients with acute ischemic stroke who underwent urgent intracranial stent insertion was variable, depending on the severity of the ischemic event.  § The restenosis rate was obtained from the follow-up study by Albuquerque et al., and the remaining data were obtained from Fiorella et al. Both papers are from the same study.
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success rate of 91.7%. However, delivery of the stent was limited in some cases by vessel tortuosity, and there was a relatively high rate of restenosis (28%). The other study used the Pharos intracranial stent (Micrus) in 21 patients. Seven of these patients received urgent intervention after acute stroke for hemodynamic instability and progressive worsening of stroke or after thrombolysis. The remaining 14 patients underwent elective treatment after a TIA or minor stroke. In these 14 patients, a technical success rate of 85.7% and a procedure-related complication rate of 28.5% was observed.31

Self-Expanding Stents. The Wingspan stent (Boston Scientific)—a bare-metal, self-expanding stent designed specifically to treat intracranial stenosis—was approved by the FDA in 2005 for use under a humanitarian device exemption in patients with intracranial stenosis “who are refractory to medical therapy.” This approval was based on a European/Asian study of 45 patients with symptomatic 50%–99% stenosis who had recurrent stroke on anti-thrombotic therapy. The main results of the study were that the stent was successfully delivered in 44 (98%) of 45 patients, the 30-day rate of stroke or death was 4.4%, and the 12-month rate of ipsilateral stroke or death was 9.3%. Only 3 (7.5%) of 40 patients had restenosis at 6 months, and none were symptomatic. Of the 45 patients, 29 had 70%–99% stenosis. Of these 29 patients, 3 (10.3%) had a stroke in the territory or died within 1 year.

Thereafter, 2 multicenter registries provided additional data on the Wingspan stent. The first report included 78 patients with 82 symptomatic intracranial stenoses (50%–99%) from 5 centers. A technical success rate of 98.8% and a periprocedural rate of 6.1% for major neurological complications were observed. The second report was the NIH Wingspan registry of 129 patients with 70%–99% symptomatic intracranial stenosis at 16 centers. The technical success rate was 96.7% and the frequency of any stroke, intracerebral hemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14% at 6 months. These data compare favorably with the outcome in the WASID study and form the basis of the ongoing randomized trial evaluating angioplasty and stent treatment (using the Wingspan system) versus best medical management (SAMMPRIS trial). Follow-up data from the Wingspan registries demonstrate a restenosis (≥ 50% on follow-up angiogram) rate of 25%–32%. However, the restenosis is usually asymptomatic. An interesting phenomenon is that the incidence of restenosis appears to be higher in younger patients, especially those with supraclinoid carotid artery stenosis, and this raises a question about the underlying occlusive vasculopathy in this population. The location of stenosis and demographic characteristics are similar to those in patients with North American moyamoya phenomenon, thereby suggesting that these patients may have a similar underlying occlusive vasculopathy but lack the proliferative signals that result in moyamoya collateral formation.

Extracranial-Intracranial Bypass

Based on several retrospective case series which demonstrated high bypass patency rates and low incidence of perioperative complications in patients with ischemic cerebrovascular disease, the STA-MCA bypass became a commonly used therapeutic approach in the 1970s and 1980s for patients with sICAD that was refractory to medical treatment. However, after the discouraging results of the International Cooperative Extracranial-Intracranial Bypass Trial were published in 1985, the STA-MCA bypass, and less common techniques for establishing a direct EC-IC bypass (for example, radial artery or saphenous vein high-flow bypass), became infrequently used for sICAD. Some groups have suggested that assessment of cerebral hemodynamics with sophisticated imaging techniques may identify a subgroup of patients with sICAD who have hemodynamic impairment that would benefit from surgical revascularization. Others have begun to explore potentially less morbidity-causing indirect revascularization techniques to treat patients with sICAD. In this section, we will review the published literature on both direct and indirect revascularization for sICAD.

Direct Bypass

Several single-institution case series examining the technical success and perioperative safety of direct EC-IC bypass for ischemic cerebrovascular disease have been published. The majority evaluated patients with a variety of cerebrovascular conditions including sICAD (but also ECA occlusion, moyamoya disease, and/or carotid artery dissection), whereas a minority specifically examined patients with sICAD. In series that reported on EC-IC bypass for ischemic cerebrovascular disease including sICAD, the overall bypass patency, perioperative morbidity, and perioperative mortality rates vary from 87% to 99%, 0% to 6%, and 0% to 8%, respectively. Very few studies have exclusively examined the safety and efficacy of direct bypass in patients with sICAD. Weinstein et al. reported a series of 105 patients who underwent STA-MCA bypass procedures for sICAD, documenting 97% bypass patency, 2.8% perioperative morbidity (from stroke), and 1% perioperative mortality. The long-term outcome after surgery (annual stroke rate of 1.5%) appeared to be better than the natural history of medically treated patients with sICAD. More recently, Tsai et al. reported a series of 11 patients who underwent STA-MCA bypass for sICAD (all MCA stenosis or occlusion). These authors documented 100% bypass patency, 0% perioperative morbidity, and 0% perioperative mortality. The late stroke rate in long-term follow-up was not reported. Importantly, all the aforementioned studies were retrospective, and none included adjudication of cerebrovascular events by neurologists.

The landmark International Cooperative Extracranial-Intracranial Bypass Trial remains the largest prospective third-party adjudicated study examining the safety and efficacy of STA-MCA bypass for patients with ischemic cerebrovascular disease including sICAD. Patients enrolled in this study included those with a history of recent TIA or minor ischemic strokes and angiographic evidence of one of the following: 1) stenosis or occlusion of the MCA or its branches; 2) stenosis of the ICA at or above the C-2 vertebral body (that is, at a place inaccessi-
able to carotid endarterectomy); or 3) ICA occlusion. Overall, approximately one-third of the patients included in this study had sICAD. Patients were randomized to STA-MCA bypass or nonsurgical management. All patients received 325 mg aspirin perorally 4 times per day throughout the trial unless contraindicated or not tolerated. The primary study end points were postrandomization fatal or nonfatal stroke. The STA-MCA bypass patency was found to be 96%. The incidence of perioperative cerebral or retinal ischemic events and major strokes was 12.2% and 4.5%, respectively, and the perioperative mortality rate was 1.1%. Importantly, the incidence of fatal and nonfatal strokes was higher in patients randomized to STA-MCA bypass versus those randomized to medical therapy alone. This trend was also noted in patients with sICAD, particularly in those with intracranial stenosis rather than occlusion. Specifically, the incidence of fatal and nonfatal stroke for patients with severe ICA or MCA stenosis was 40.2% in the surgical group versus 30.5% in the medical group. This finding has been attributed to postbypass stasis at the stenotic arterial segment (probably the result of competing antegrade flow from the native artery vs retrograde flow from the arterial bypass) that would promote thromboembolic complications. These overwhelmingly negative results significantly reduced the use of the STA-MCA bypass for patients with sICAD in whom medical therapy had “failed.”

One of the main reasons for failure of the International Cooperative Extracranial-Intracranial Bypass Trial was thought to be the absence of cerebral hemodynamic assessment to help identify patients with reduced cerebral perfusion pressure in whom STA-MCA bypass may be more beneficial.63,64,88 Subsequently, several quantitative methods have been developed to examine cerebral hemodynamic impairment in patients with ischemic cerebrovascular disease (for a review, see Grubb et al.30). Two prospective observational studies in which PET was used for assessment of hemodynamic impairment have shown that patients with recently symptomatic ischemic cerebrovascular disease and increased OEF have a markedly elevated risk of subsequent ipsilateral ischemic stroke (compared with those with normal OEF).29,30 However, only 10 of the 121 patients included in these 2 studies had sICAD (the rest had ICA occlusion). Therefore, it is difficult to draw conclusions regarding the utility of hemodynamic assessment in this patient population. Given the paucity of cerebral hemodynamic data for patients with sICAD, along with the aforementioned increased risk associated with STA-MCA bypass for patients with severe ICA or MCA stenosis,19 and the recently announced premature stopping of the Carotid Occlusion Surgery Study (a randomized controlled trial comparing STA-MCA bypass with best medical therapy for patients with recently symptomatic ICA occlusion and increased OEF30), it is unlikely that direct EC-IC bypass will be proven effective for patients with sICAD—even for those who have “failed” medical therapy and who have documented impaired cerebral hemodynamics.

Indirect Bypass

Recently, Komotar et al.32 examined the role of direct surgical bypass as a method of promoting angiogenesis and enhancing cerebral blood flow in patients with sICAD. In their series, 12 patients with sICAD and impaired cerebral hemodynamics were treated with indirect bypass: 11 underwent encephaloduroarteriosynangiosis, and 1 received bur holes with dural and arachnoid incisions. Perioperative morbidity was 27%; there were no perioperative deaths. Also, follow-up data showed that only 2 patients had increased perfusion in previously hypoperfused areas, and 5 patients suffered repeat ischemic infarction. In comparison with a meta-analysis of 4 studies of patients with symptomatic ICA occlusion and severe hemodynamic failure who were treated medically, it was observed that indirect surgical revascularization provided no protection against subsequent ischemic stroke. Based on this small retrospective case series, indirect surgical revascularization for patients with sICAD does not appear to be indicated and lacks therapeutic potential.

Conclusions

Current evidence suggests that aspirin is the preferred antithrombotic option to prevent recurrent ischemic events in patients with sICAD. Treatment of modifiable risk factors is also recommended. Consideration for angioplasty and stent placement in select patients with sICAD is also reasonable; however, at present there are no randomized trials proving its efficacy. One such trial—the SAMMPRIS38 trial—is currently underway. If results from this trial are positive, a new era of widespread use of endovascular therapy for patients with sICAD may ultimately emerge. Regarding surgical revascularization, available literature that includes only 1 large randomized multicenter trial does not support the use of direct bypass for patients with sICAD. In particular, direct bypass for patients with symptomatic severe ICA or MCA stenosis appears not only ineffective but also seems to be harmful.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Vellimana, Ford, Lee, Derdeyn. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Zipfel.

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