

# Update in the treatment of intracranial atherosclerotic disease

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## ABSTRACT

This review highlights the recent evolution of the imaging, medical management, surgical options and endovascular therapies for symptomatic intracranial atherosclerotic disease (ICAD). Recent imaging developments including optical coherence tomography and other modalities to assess the intracranial arteries for symptomatic ICAD are reviewed, not only to diagnose ICAD but to determine if ICAD plaques have any high-risk features for treatment. Potential future developments in the treatment of ICAD are discussed, including the development of trackable drug-coated balloons for the cerebral circulation to treat primary or restenotic arteries, new iterations of self-expanding intracranial stents with easier delivery systems, and the re-examination of indirect surgical bypass techniques for revascularisation. In addition to these important technological developments, however, is the evolving evidence regarding the best treatment window for these techniques and additional factors in medical management which can improve patient outcomes in this devastating pathology.

## INTRODUCTION

The management of symptomatic intracranial atherosclerotic disease (ICAD) has some similarities with the management of atherosclerotic coronary artery and peripheral artery disease, and some key differences. The standard management of ICAD is still in evolution, but we are beginning to obtain more refined data through recent studies to determine the best medical, endovascular and possibly surgical management of this disease. Atherosclerotic disease within the arteries is thought to begin with retention of low-density lipoprotein (LDL) particles within the inner arterial wall and inflammation causing endothelial cell dysfunction. Subsequent migration of smooth muscle cells and other cellular inflammatory processes lead to the development of an atherosclerotic plaque.

The composition of the atherosclerotic plaque may be relatively soft, or firm with additional deposition of fibrous tissue and calcium. The build-up of plaque within the cerebral arteries is known as ICAD or intracranial atherosclerotic stenosis. As in other anatomical locations, cerebral atherosclerotic disease leads to a loss of compliance and elasticity of the arteries, can lead to arterial

lumen narrowing, progressing to ischaemia or embolic events, or exhibiting ruptured plaque, which may lead to embolic events or in-situ arterial thrombosis. These factors and plaque characteristics are key in understanding the safe future endovascular treatment of ICAD.

## INCIDENCE

ICAD demonstrates variable incidence among different races. Most studies indicate Asians have the highest incidence of ICAD, followed by African-Americans, Hispanics, then Caucasians. In the USA, stroke is the fifth most common cause of death, and ICAD is estimated to represent 8%–10% of the aetiology in patients with stroke.<sup>1</sup> This is approximately 50 000–80 000 patients per year. In China, however, where stroke is the most common cause of death, ICAD has been reported as a contributory cause of stroke in 20%–46% of patients.<sup>2</sup> The CICAS (Chinese Intracranial Atherosclerosis) study showed ICAD in 46% of patients with acute stroke.<sup>3</sup> As expected, there does appear to be an increased incidence in patients who are cigarette smokers, and patients with hyperlipidaemia, diabetes, hypertension and obesity.

## DIAGNOSIS

Cerebral intra-arterial narrowing is not always secondary to ICAD, so other aetiologies must be considered in the differential diagnosis for treatment. Vasculitis many involve multiple intracranial arteries; however, usually an inflammatory or infectious cause is found. Cerebral artery dissection, either spontaneous or traumatic, typically has a more characteristic angiographic appearance and may be associated with other predisposing factors such as fibromuscular dysplasia or collagen vascular disease. Moyamoya disease is characterised by progressive supraclinoid carotid artery stenosis. These diseases may appear like ICAD in certain stages, and efforts should be made to identify the correct diagnosis prior to managing the patient like a patient



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with ICAD, since the optimal treatment paradigms are different.

Endovascular intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have recently been used in cerebral artery evaluation to determine plaque characteristics and composition, as well as perforator artery identification.<sup>4</sup> More recently, OCT has shown to have better imaging characteristics than IVUS. OCT involves coherent light from an intra-arterial catheter to perform three-dimensional imaging of the vessel wall. This technique, pioneered in the coronary arteries, can be used to characterise atherosclerotic plaque, diagnose arterial dissection, demonstrate stent apposition to the arterial wall and show tissue prolapse through the stent struts in cerebral arteries.<sup>5</sup> Likewise, the use of high-resolution MRI (HR-MRI) has helped better characterise cerebral artery plaques and active inflammatory activity, as well as anatomical relationship of atherosclerotic lesions to adjacent perforator arteries non-invasively.<sup>6</sup>

### MEDICAL THERAPY

The early treatment of ICAD with medical therapy consisted of warfarin anticoagulant therapy. The WASID trial (Warfarin vs Aspirin for Symptomatic Intracranial Disease) compared high-dose aspirin with warfarin and demonstrated a 14% stroke and death rate at 1 year in patients presenting with transient ischaemic attack (TIA) and intracranial arterial stenosis 70% or greater, and 23% stroke and death rate in patients presenting with stroke and 70% or greater stenosis.<sup>7</sup>

The greater adoption of statins and at least 3 months of dual antiplatelet therapy in medical management of symptomatic ICAD led to the SAMMPRIS trial (Stenting vs Aggressive Medical Therapy for Intracranial Artery Stenosis). This trial used aggressive medical therapy including dual antiplatelet therapy for 3 months, then aspirin only, and use of a statin with goal LDL of 70 mg/dL or less, blood pressure control, blood glucose and haemoglobin A1C control, smoking cessation, and weight loss, and compared it with intracranial stenting with the same medical regimen. The aggressive medical therapy arm demonstrated a 30-day stroke, bleed and death rate of 5.8%, and a 1-year stroke, bleed and death rate of 12.2%.<sup>8</sup> Since this was a combination of patients who presented with TIA (36.6%) and those who presented with stroke (63.4%), we would expect by extrapolation that if only patients presenting with stroke were included in the trial, the 1-year event rate would be higher than 12.2%, since the WASID trial demonstrated a differential outcome with higher subsequent stroke rates in patients presenting with stroke compared with those presenting with TIA and the same degree of stenosis.

The medical therapy arm of the prospective randomised COSS trial (Carotid Occlusion Surgery Study) comparing surgical bypass with medical therapy alone had a mean time from stroke or TIA to enrolment of 75 days. Then postrandomisation showed a 30-day stroke and death rate

of 2% in the medical therapy arm of the trial, a 1-year stroke and death rate of 16%, and a 2-year total stroke and death rate of 22.3%.<sup>9</sup> These high recurrent stroke rates with ICAD indicate that the patients remain at significant risk for recurrent stroke in the first 2 years after stroke from symptomatic severe ICAD, and other non-medical therapies should be considered, particularly in medically refractory patients.

### SURGICAL THERAPY

The early surgical therapy for ICAD was pioneered by Sundt *et al.*<sup>10</sup> who performed open surgical endarterectomy of cerebral arteries. The cerebral arteries amenable to endarterectomy ranged from 2 to 4 mm, so technically this was a challenging procedure. Later, extracranial-intracranial (EC-IC) bypass with either the use of a donor artery from the scalp, such as the superficial temporal artery (STA),<sup>11</sup> a radial artery graft or a saphenous vein graft,<sup>12</sup> was used. The prospective randomised EC-IC bypass trial, comparing direct bypass with the STA versus medical therapy for patients with symptomatic cerebral atherosclerotic disease with either total occlusion or high-grade stenosis, failed to show a benefit with surgery.<sup>13</sup> Subsequently, another EC-IC bypass trial, COSS,<sup>9</sup> used oxygen extraction positron emission tomography scanning to determine candidates for the trial based on oxygen extraction fraction, demonstrating severely impaired collateral blood flow with hypoperfusion of the target territory. This trial also failed to show a benefit with surgical bypass.

While direct bypass had failed to show a clinical benefit in patients with symptomatic ICAD, the use of an indirect bypass with encephaloduroarteriosynangiosis (EDAS), transposing the STA adjacent to the cortical middle cerebral artery branches, has shown some initial encouraging results in a pilot National Institutes of Health (NIH)-funded trial, ERSIAS (Surgical Indirect Revascularization for Symptomatic Intracranial Arterial Stenosis).<sup>14</sup> Similar to the process of revascularisation with EDAS indirect bypass in Moyamoya disease, the indirect bypass in symptomatic ICAD has demonstrated gradual neovascularisation of the ischaemic territory through angiogenesis from the donor artery. Further studies will be needed to determine which patients may best benefit from this treatment option and whether it may be competitive with or superior to long-term medical therapy alone.

### ENDOVASCULAR THERAPY: BALLOON ANGIOPLASTY

Historically there were early reports on balloon angioplasty of intracranial arteries performed via surgical exposure for arterial access.<sup>15</sup> While these early attempts demonstrated some angiographic successes, this treatment paradigm did not gain popular acceptance and has for the most part been abandoned. The development of less compliant balloons which were suitable for the revascularisation of atherosclerotic arteries was pioneered by Dotter<sup>16</sup> in the peripheral circulation. However,

angioplasty alone in cerebral arteries has often resulted in arterial recoil and restenosis, requiring subsequent repetitive treatments. Early reports on the use of angioplasty balloons for ICAD involved balloons designed for coronary arteries. However, the cerebral arteries histologically do not have the same structural integrity. Cerebral arteries have a much thinner muscularis layer compared with coronary or other peripheral arteries. Cerebral arteries also lack an external elastic layer that coronary or peripheral arteries exhibit. Therefore, aggressive dilation of a cerebral artery with an intraluminal non-compliant angioplasty balloon may result in vascular rupture or dissection. Nevertheless, balloon angioplasty alone has been recommended by several investigators as a less invasive endovascular treatment for ICAD.<sup>17 18</sup> Such studies have demonstrated a low periprocedural complication rate but significant residual stenosis, often requiring repeat treatments, and high recoil and dissection rates resulting in unclear long-term results.

The more recent use of drug-coated balloons for treatment of ICAD remains controversial. While the idea of inhibiting restenosis with a drug-coated balloon is appealing, there are questions on long-term effects of this type of treatment, particularly since the cerebral artery walls are much thinner than similar diameter coronary arteries. Preliminary reports have been mixed, with one study using a paclitaxel-coated balloon leading to a 31.8% periprocedural complication rate.<sup>19</sup> Another small recent study demonstrated a good periprocedural safety, but poor efficacy in stenotic artery revascularisation, with a mean postangioplasty residual stenosis of 50%.<sup>20</sup> However, other studies have shown more reasonable periprocedural complication rates with lower restenosis incidence, including a series of 30 patients treated by Han *et al*<sup>21</sup> with a periprocedural complication rate of 6.7% and a short-term restenosis rate at a mean of 7 months of 3.2%.

### ENDOVASCULAR THERAPY: INTRACRANIAL STENTING

The early treatment of ICAD with angioplasty and stenting involved the use of balloon-expandable coronary stents.<sup>22</sup> The first stent specifically designed for intracranial stenting was a balloon-expandable stent that was fairly successful in the SSYLVA clinical trial (Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries), but was never manufactured and marketed subsequently.<sup>23</sup>

The Wingspan stent was the first self-expanding stent, specifically designed for treatment of symptomatic ICAD. Currently, it is the only Food and Drug Administration (FDA)-approved stent for the treatment of symptomatic intracranial ICAD. The initial Humanitarian Device Exemption (HDE) approval trial treated 44 patients with the stent and demonstrated excellent periprocedural safety results, with a 4.5% complication rate, and this was subsequently marketed under the HDE application.<sup>24</sup> There were two subsequent registries, each enrolling over 150 patients with the delivery of Wingspan stents, the

US Wingspan stent registry and the NIH Wingspan stent registry.<sup>25–28</sup> These both demonstrated approximately 6% periprocedural complication rate and represented the initial clinical experience with the stent in the USA. Subsequent large clinical series were reported by multiple centres in both single-centre registries and multicentre trials.<sup>29–36</sup>

The SAMMPRIS trial was a prospective randomised trial comparing the Wingspan stent with aggressive medical management alone; however, the use of the stent was in an Investigational Device Exemption FDA application with expanded indications including early treatment and treatment of patients with TIAs alone, as opposed to stroke presentation solely.<sup>8</sup> With this indication, approximately 8% of patients were stented on-label and the remainder would not have met the original HDE application indications. This study demonstrated a markedly higher periprocedural complication rate of 14.7%, and these results hindered the use of the stent following the trial. The FDA subsequently mandated a postmarket surveillance study of the Wingspan stent, following the poor SAMMPRIS results. The WEAVE trial (Wingspan Stent System Post Market Surveillance) was designed to determine the safety of the stent when used strictly on-label by experienced interventionalists.<sup>37</sup> The trial enrolled 152 on-label patients, which was the largest on-label trial performed in the USA to date, and excellent results were seen. The periprocedural complication rate of 2.6% was also the lowest complication rate obtained in prior trials. The trial inclusion protocol and patient management protocol were very strict, and these clinical outcomes were adjudicated by core stroke neurologists.

In retrospect, one of the primary differences between the various registries and trials is that there were much lower periprocedural complication rates when patients were stented 2 or 3 weeks following their last stroke as opposed to 7 days or less, as they were in the SAMMPRIS trial. The poor results in the SAMMPRIS trial, however, were not due to the long-term effects of the stenting. The initial high periprocedural complication rate of 14.7% was insurmountable compared with long-term complications of medical treatment only. In a separate analysis by Yu and Jiang<sup>38</sup> of the SAMMPRIS data, looking only at patients beyond 30 days following stenting or the initiation of medical therapy alone, there was a threefold higher rate of disabling or fatal strokes in a medical therapy group compared with the stenting group, with a 6.2% event rate in the medical group and 2.2% in the stenting group. This implies that if angioplasty and stenting can be performed with a low periprocedural complication rate, then the long-term benefit of the stent provides some protection from disabling stroke and death compared with medical therapy alone.

There have been various other publications demonstrating the poor clinical design of SAMMPRIS. Subsequent analyses included criticisms of the inexperience of the investigators, the early treatment with stenting of

**Table 1** Major Wingspan stent trials with mean time to treatment and complication rates

	Publication	Patients stented (n)	Percentage stented on label for stroke	Periprocedural complications (%)	Time to stent from stroke or TIA (days)
HDE trial	<i>Stroke</i> , 2007 <sup>24</sup>	44	93	4.5	22
US registry	<i>Stroke</i> , 2007 <sup>27</sup> <i>Stroke</i> , 2011 <sup>28</sup>	158	57	6.9	Not reported
NIH registry	<i>Neurology</i> , 2008 <sup>25</sup>	160	61	6.2	10
SAMMPRIS	<i>New England Journal of Medicine</i> , 2011 <sup>8</sup>	208	8.2	14.7	7
Jiang	<i>Stroke</i> , 2011 <sup>30</sup>	100	71	5.0	34
Miao	<i>Stroke</i> , 2015 <sup>29</sup>	141	56	4.3	19 for TIA/32 for stroke
Zhao	<i>Journal of Stroke and Cerebrovascular Diseases</i> , 2016 <sup>33</sup>	278	Not reported	4.3	21
Gao	<i>American Journal of Neuroradiology</i> , 2016 <sup>35</sup>	100	50	2.0	21
Ma	<i>Stroke and Vascular Neurology</i> , 2018 <sup>34</sup>	141	56	4.0	22
WEAVE	<i>Stroke</i> , 2019 <sup>37</sup>	152	100	2.6	22

HDE, Humanitarian Device Exemption; NIH, National Institutes of Health; SAMMPRIS, Stenting vs Aggressive Medical Therapy for Intracranial Artery Stenosis; TIA, transient ischaemic attack; WEAVE, Wingspan Stent System Post Market Surveillance.

patients with stroke, the potential inadequate antiplatelet therapy and the inclusion of other off-label patients.<sup>39 40</sup>

Following SAMMPRIS, there have been several single-centre and multicentre trials and registries that have demonstrated much safer periprocedural results with the Wingspan stent, provided that the time to treatment was delayed 2–3 weeks following the last stroke.<sup>29–36</sup> In a multicentre trial comparing a balloon-expandable stent with the Wingspan self-expanding stent in over 300 patients, Ma *et al.*<sup>34</sup> demonstrated a 4% periprocedural complication rate, and a total 1-year follow-up stroke, TIA, bleed and death rate of 7.9% in the Wingspan-treated group.

The WEAVE trial was different from the SAMMPRIS trial in that 100% of the patients in the WEAVE trial were treated on-label with the Wingspan stent. WEAVE did not enrol patients with stroke 7 days or earlier following their index event. It did not allow lesions greater than 14mm in length or target vessels less than 2mm. It did not allow patients presenting only with TIA or vertebrobasilar insufficiency without stroke. Also, there was formal training of the interventionalists regarding the best practices that have been learnt from previous trials. Patient selection was key and the premedication regimen with the antiplatelet therapy at least started 5 days prior to the stenting was very strict. Interventionalists were also instructed in the best practice techniques of control of the exchange wire, use of support catheters, intra-arterial vasolytic use and underdilating the angioplasty balloon in perforator-rich areas. Also, the recommendation to decrease the systolic blood pressure to less than 140 postoperatively was strictly

enforced. Finally, the experience of the operators in the WEAVE trial was superior to SAMMPRIS. The goal experience for the interventionalist in the WEAVE trial was greater than 25 Wingspan stents placed, and the mean was 37 Wingspan stents prior to enrolling a patient in the trial. In contrast, the SAMMPRIS trial interventionalists had a mean experience of 10 Wingspan stents, and some treated as few as three patients in their career. The impact of the experience of the interventionist was also demonstrated in the WEAVE trial, as those interventionists who had a case experience of 50 Wingspan stents or greater had no index events in the periprocedural period, and those with less than 50 had a 4.8% periprocedural complication rate.<sup>37</sup>

There is a clear trend from multiple recent trials and registries that performing angioplasty and stenting in the early time period, particularly 7 days or less from the qualifying stroke, results in a higher periprocedural complication rate. We have yet to define the reason for this. However, there has been speculation that with a recent stroke, there is a ruptured plaque or hot plaque which is highly inflammatory and thrombogenic and more likely to cause embolic events with the additional placement of a foreign body such as a stent.<sup>39</sup> There is also speculation that many patients may be subtherapeutic on their antiplatelet therapy in the SAMMPRIS trial because many were loaded with antiplatelet therapy 6–24 hours prior to their stenting procedure. Finally, there is a trend of thought that revascularisation of a recently stroked territory has a higher risk for reperfusion haemorrhage, particularly

**Table 2** Comparisonsvn-2019 of 1-year stroke and death rates with medical therapy and stenting 21 days or longer after qualifying event

Medical therapy	Publication	Patients (n)	One-year stroke and death rate (%)
WASID	<i>New England Journal of Medicine</i> , 2005 <sup>7</sup>	569	18
SAMMPRIS	<i>New England Journal of Medicine</i> , 2011 <sup>8</sup>	227	12.2
COSS	<i>The Journal of the American Medical Association</i> , 2011 <sup>9</sup>	98	16
Total/mean event rate		894	15.4
Stenting			
Jiang	<i>Stroke</i> , 2011 <sup>30</sup>	100	7.3
Li	<i>PloS One</i> , 2015 <sup>31</sup>	429	9.5
Wang	<i>Neuroradiology</i> , 2016 <sup>32</sup>	196	9.6
Zhao	<i>Journal of Stroke and Cerebrovascular Diseases</i> , 2016 <sup>33</sup>	278	5.8
Ma	<i>Stroke and Vascular Neurology</i> , 2018 <sup>34</sup>	141	7.9
Total/mean event rate		1134	8.0

COSS, Carotid Occlusion Surgery Study; SAMMPRIS, Stenting vs Aggressive Medical Therapy for Intracranial Artery Stenosis; WASID, Warfarin vs Aspirin for Symptomatic Intracranial Disease.

in areas that have poor collateral and are essentially an isolated circulation. This high periprocedural complication rate in patients treated early after stroke or TIA was seen in the SAMMPRIS trial, which had a mean time to treatment of 7 days, and in the subgroup analysis of the NIH Wingspan registry, which showed a higher complication rate periprocedurally in patients treated less than 10 days from their stroke compared with those stented greater than 10 days after their stroke,<sup>26</sup> whereas the HDE trial, WEAVE trial and multiple large studies from China, with a mean time to treatment of 21 days or longer post-stroke, have demonstrated significantly lower periprocedural complication rates (table 1).

Finally, if we analyse studies that demonstrate the longer-term 1-year stroke and death rate with medical therapy compared with the 1-year stroke and death rates of those trials that have stented patients in the 21-day or longer range, we see that there are significantly less strokes and death in the stented patients (table 2).

This comparative study analysis showed a mean 1-year stroke and death rate of 15.4% in the medical therapy groups and a mean 1-year stroke and death rate of 8.0% in the Wingspan stent groups. Studies were not included in the analysis if the published paper either did not state what the mean time to stenting was in the cohort or if the

mean time to treatment was less than 21 days following stroke or TIA. These data suggest that, if the periprocedural complication rate can be kept low with experienced interventionalists, best practices are used regarding periprocedural patient management, and if patients undergo delayed stenting, a mean of 21 days or longer postevent, stenting may be competitive with, or potentially superior to, medical therapy for patients presenting with 70%–99% intracranial artery stenosis, presenting with a stroke.

Currently the study results of two additional Wingspan trials are pending, the CASSISS trial (China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis) from China<sup>41</sup> and the WICAD study (Wingspan for IntraCranial Atherosclerotic Disease) from Japan. Both trials have demonstrated in early reports similar safety results with the on-label use of the stent and likely will give additional supporting data for the safe use of self-expanding stents.

## SUMMARY

The recent imaging developments of OCT and HR-MRI to assess intracranial arteries for symptomatic ICAD has helped us to diagnose ICAD and to determine if ICAD plaques have any high-risk features for treatment. Future developments in the treatment of ICAD may include further development of trackable drug-coated balloons for the cerebral circulation to treat primary or restenotic arteries, new iterations of self-expanding intracranial stents with easier delivery systems, and the re-examination of indirect surgical bypass techniques for revascularisation. Nearly as important as these technological developments, however, is to determine the best treatment window for these techniques and additional medical management factors which can improve patient outcomes in this devastating pathology.

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