Standard of practice: endovascular treatment of intracranial atherosclerosis

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ABSTRACT

Background Symptomatic intracranial atherosclerotic disease (ICAD) worldwide represents one of the most prevalent causes of stroke. When severe, studies show that it has a very high risk for recurrent stroke, highlighting the need for effective preventative strategies. The mainstay of treatment has been medical therapy and is of critical importance in all patients with this disease. Endovascular therapy is also a possible therapeutic option but much remains to be defined in terms of best techniques and patient selection. This guideline will serve as recommendations for diagnosis and endovascular treatment of patients with ICAD.

Methods A literature review was performed to extract published literature regarding ICAD, published from 2000 to 2011. Evidence was evaluated and classified according to American Heart Association (AHA)/ American Stroke Association standard. Recommendations are made based on available evidence assessed by the Standards Committee of the Society of NeuroInterventional Surgery. The assessment was based on guidelines for evidence based medicine proposed by the American Academy of Neurology (AAN), the Stroke Council of the AHA and the University of Oxford, Centre for Evidence Based Medicine (CEBM).

Results 59 publications were identified. The SAMMPRIS study is the only prospective, randomized, controlled trial available and is given an AHA level B designation, AAN class II and CEBM level 1b. The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial arteries (SSYLVIA) trial was a prospective, non-randomized study with the outcome assessment made by a non-operator study neurologist, allowing an AHA level B, AAN class III and CEBM level 2. The remaining studies were uncontrolled or did not have objective outcome measurement, and are thus classified as AHA level C, AAN class IV and CEBM level 4.

Conclusion Medical management with combination aspirin and clopidogrel for 3 months and aggressive risk factor modification is the firstline therapy for patients with symptomatic ICAD. Endovascular angioplasty with or without stenting is a possible therapeutic option for selected patients with symptomatic ICAD. Further studies are necessary to define appropriate patient selection and the best therapeutic approach for various subsets of patients.

BACKGROUND AND OVERVIEW

Epidemiology and natural history of ICAD

Intracranial atherosclerotic disease (ICAD) likely accounts for 10–15% of all ischemic strokes, with an increased incidence seen in Asian, Black and Hispanic populations.[1] It is particularly prevalent in Chinese populations, with estimates of ICAD in stroke populations ranging from 33% to 50%.[2] While all traditional risks factors are associated with ICAD,[3] it appears that the presence of diabetes and metabolic syndrome are particularly associated with the development of atherosclerotic disease of the intracranial vasculature.[4 5] Due to the increasing prevalence of these risk factors[6 7] and also due to this significant prevalence in non-Caucasian populations, it may represent the most common stroke etiology worldwide.[2]

Two main mechanisms contribute to stroke in the setting of ICAD, which are not mutually exclusive: thrombus at the site of stenosis with distal embolization or hemodynamic flow reduction to areas which are unable to recruit adequate collateral flow. As with other atherosclerotic lesions, plaque rupture can initiate a cascade which results in thrombus formation at the site of the lesion, resulting in occlusion of the vessel and perforating arteries which may arise from the segment.[8] Emboli from the thrombus may progress downstream and cause occlusion of distal vessels.[8] In addition, the lack of cerebral blood flow to the distal vessel may result in ischemia in watershed areas between major vessels, particularly when the collateral circulation is not adequate.[9]

Symptomatic ICAD carries a high risk of subsequent stroke. The best data to date come from the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial.[10] This randomized, double blind, controlled trial compared warfarin with aspirin for the management of ICAD in patients with 50–99% symptomatic stenosis. From this trial, 106 patients reached the endpoint of an ischemic stroke, 77 (73%) of which were in the territory of the stenotic artery.[10] The factors which were most predictive of stroke in the area of the stenotic artery included stenosis measuring 70–99%, time for qualifying event (<17 days) and female gender.[11] One of the strongest predictors was 70–99% intracranial stenosis, with stroke rates of 18% at 1 year and 19% at 2 years (compared with 6% at 1 year and 10% at 2 years for those with

<70% stenosis).[11 12] The risk of stroke is greatest in the first year following the initial event, highlighting the need for prompt assessment and management. In the WASID trial, strokes in the area of the stenotic artery were hemispheric (ie, non-lacunar) (70/77; 91%) and often disabling (34/77; 44%).[13]

Clinical criteria for the diagnosis and treatment of ICAD

The clinical presentation of symptomatic ICAD is dependent on the vessel affected. The most common arterial sites involved are the petrous, cavernous and supraclinoid internal carotid artery (ICA), the middle cerebral artery (MCA), the basilar artery (BA) and the intracranial segment of the vertebral artery. The MCA appears to be the most common location involved.[10 14] Patients may present with either transient ischemic attack (TIA) or stroke.[15] The vast majority will have cortical symptoms or signs as a part of their stroke/TIA although lacunar syndromes have been reported due to perforator occlusion.[13] It is also important to assess for the presence of hemodynamic failure, especially indicated by postural symptoms or limb shaking TIAs, as this may predict even further increased risk of recurrent stroke.[16]

Diagnostic testing

Multiple modalities are available for assessment of ICAD. Transcranial Doppler ultrasound (TCD) is a portable beside test which can be performed in most patients, including those who are critically ill. In the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial[17] (a substudy of the WASID trial), standardized TCD and an MR angiography (MRA) protocol was performed. To optimize predictive value, positive tests were defined as TCD mean velocities of 240 cm/s, 120 cm/s and 130 cm/s found in the MCA, ICA and BA, respectively.[17] The negative predictive value (NPV) of TCD was 83%, although the positive predictive value (PPV) was low (55%).[17] Time of flight MRA was assessed in the SONIA trial having a NPV of 91% and a PPV of 59%.[17] Other studies have also shown that MRA has good NPV but limited PPV, making MRA, like TCD, a good screening test but one requiring a confirmatory test if a lesion is found.[18 19] The third type of non-invasive testing is CT angiography, which has revealed higher sensitivity and specificity than MRA or TCD for the assessment of ICAD.[19 20] Perfusion imaging[21] and tests of cerebrovascular reserve[22] may also be able to subdivide patients who may be at even higher risk of deterioration and recurrent stroke. Techniques such as high resolution (3 T or greater) MRI and quantitative MRI[23 24] are under evaluation to assess the anatomic composition of apparent stenoses (plaque type, associated thrombus or dissection, hemodynamics and restenosis following treatment). The role of high resolution MRI remains to be determined but it may become more important in the assessment and treatment of ICAD patients.

Conventional digital subtraction angiography remains the gold standard for defining the location and severity of stenosis (box 1). Although catheter cerebral angiography is an invasive test, it is quite safe when performed by physicians experienced in neuroangiography.[25 26] Within the WASID study, only four of 196 patients (2.0%) had procedure related neurological adverse events, all of which were transient.[27] The convention for measurement of ICAD is by the WASID method.[28 29] The measurement is $1-(D_{min}/D_{normal}) \times 100$, where D_{min} is the minimal luminal diameter of the stenotic segment and D_{normal} is the normal vessel diameter proximal to the diseased segment for the MCA, BA and intracranial vertebral artery.[28] If the proximal vessel to its origin is not suitable for measurement, the second choice is to use the normal distal artery and if this is also unsuitable, the distal most non-tortuous segment of the feeding vessel represents the third choice.[28] When the stenosis affects the precavernous, cavernous or postcavernous portion of the ICA, D_{normal} is taken from the widest normal portion of the petrous carotid artery; if this entire segment is diseased, the most distal parallel portion of the distal cervical ICA is the second choice.[28] Utilizing this standard approach, good intra-rater (81–100%) and inter-rater (67–88%) reliability was seen.[29] It is also important to note the length of stenosis, whether the stenosis is concentric or eccentric, straight or angulated (Mori classification), and the presence of ulceration, intraluminal thrombus and immediately adjacent aneurysms, as these factors will be important for device sizing and may influence the risk of the procedure.[30]

Once symptomatic ICAD is confirmed, the aim of treatment is stroke prevention. The remainder of this document will assess the medical and endovascular therapeutic options for stroke prevention in the setting of symptomatic ICAD.

Box 1 Suggested information to be reported in patients presenting with symptomatic intracranial atherosclerotic disease

% Stenosis (measured by Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) method)
Vessel(s) affected
Minimal luminal diameter
Proximal vessel luminal diameter
Distal vessel luminal diameter
Length of stenosis
Concentric or eccentric stenosis
Presence of ulceration or thrombus
Presence of other vascular lesions (ie, aneurysms)

Technical results, clinical results and clinical outcomes

As discussed in the foregoing, standardization of reporting methods is necessary to enable meaningful and systematic analysis of clinical data based on the experiences of many operators and patient populations. According to convention used in recent trials, technical success is achieved when revascularization is accomplished at the target lesion with <50% residual stenosis on completion of angiography. If technical success is defined in a different manner, then the rationale, measurement and treatment criteria should be specified. Reported clinical results should include death and territory specific stroke (specific to treated vessel) at 30 days, 90 days, 1 year and 2 years. New procedure related neurological deficits should be indicated and differentiated as transient or permanent and disabling or non-disabling.[29] Clinical outcomes should be standardized and reported using the modified Rankin Scale or the Barthel Index. Neurocognitive measurements and scales may also be considered.

METHODS

The working group was composed of members of the Society for NeuroInterventional Surgery Standards and Guidelines Committee (see general document), and the recommendations presented represent a consensus statement from this working group.[31] A computerized search of Pubmed (National Library of Medicine database) including articles from 1 January 2000 to 1

May 2011 was conducted. Search terms included 'intracranial', 'atherosclerosis', 'stenosis', 'cerebral', 'stroke', 'transient ischemic attack', 'stent', 'angioplasty', 'stent assisted angioplasty', in various combinations. To have more reliable outcome data, case series with more than 10 patients were included. Publications were graded using the previously described methodology of the Stroke Council of the American Heart Association (AHA),[32 33] the University of Oxford's Centre for Evidence Based Medicine (CEBM)[34] and the American Academy of Neurology (AAN),[35] and levels of evidence and recommendations were based on the framework outlined by the American College of Cardiology Foundation/AHA.[36]

SUMMARY OF EVIDENCE REGARDING TREATMENT

Medical management

The medical management of ICAD is similar to that of atherosclerosis in other arterial beds and is important regardless of whether or not intervention is undertaken. The WASID trial helped to define the use of anticoagulant and antithrombotic medication to treat ICAD. No difference in ischemic stroke was seen between the two groups (15% in the aspirin group and 13% in the warfarin group at 2 years) but a higher rate of hemorrhage was observed in the warfarin group (8.3% vs 3.2% in the aspirin group). This has led to the general recommendation that aspirin should be used instead of warfarin for the management of this condition. In trials comparing aspirin with other antiplatelet agents or with dual antiplatelet therapy, the proportion of patients with ICAD was not specified,[37–39] and no studies in the ICAD population have been performed. The first prospective, randomized, controlled trial comparing medical therapy versus endovascular intervention was the Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial.[40] In SAMMPRIS, a combination of aspirin 325 mg daily and clopidogrel 75 mg daily for the first 3 months after enrolment, followed by aspirin 325mg daily, was used with or without endovascular stenting of the symptomatic lesion. The trial stopped enrolling after 451 (59%) of the originally planned 764 patients were enrolled after a review by the Data Safety Monitoring Board discovered a significantly higher rate of complications in the stenting arm compared with the medical therapy alone arm (14% vs 5.8%).[40] The rate of stroke and death seen in the medical arm was much lower than the expected rate. During SAMMPRIS trial planning, it was estimated that a 15% RR reduction would occur, with a projected rate of stroke and death of 24% in the medical arm at 2 years. These data strongly suggest that the use of aspirin 325 mg and clopidogrel 75 mg daily in the first 3 months, followed by aspirin 325 mg daily alone, along with aggressive risk factor modification, should be performed.[40] It is also important to address other atherosclerotic risk factors, including hypertension, hyperlipidemia, diabetes, smoking, diet and sedentary lifestyle. In the WASID trial, very few patients reached target blood pressure and low density lipoprotein (LDL) values (50% of patients had systolic blood pressure (SBP) >140 mm Hg and 58% had LDL >100 mg/dl).[41] While modification of vascular risk factors in stroke patients has been shown to reduce subsequent stroke risk, making this an extremely important aspect of management,[42–44] the proportion of patients with symptomatic ICAD in these larger stroke studies is unknown and likely small. The first study to specifically address vascular risk factors in patients with ICAD was SAMMPRIS. Aggressive management of blood pressure to achieve a target SBP of <140 mm Hg (<130 mm Hg in patients with diabetes) and statin therapy with rosuvastatin to achieve a target LDL of <70 mg/dl (1.81 mmol/l) was undertaken along with control of other risk factors (diabetes, smoking cessation), and a specific lifestyle modification program was performed. Mean SBP was reduced from 146.8 to 134.8 mm Hg and mean LDL was reduced from 97.7 to 72.8 mg/dl in the medical management alone group, although the exact number of patients achieving target was not reported.[40] In the stenting group, mean SBP was reduced from 143.9 to 133.1 mm Hg, and mean LDL was reduced from 96.3 to 75.9 mg/dl. Smoking cessation and the proportion of patients getting moderate to vigorous exercise also improved in both groups.[40] Patients who have been enrolled will continue to receive aggressive risk factor control for a minimum of 1 year and a maximum of 3 years. This study is ongoing and more data on the length of treatment and outcome will be available in the years to come.

It is important to note that the apparent reduction in stroke risk with the SAMMPRIS regimen has not been proven in a randomized trial in this population; these data, taken with the WASID data, represent consecutive cohort studies. In addition, it is not clear which medical intervention or interventions are responsible for the reduction in risk. Given data from the primary and secondary stroke risk reduction studies mentioned above, it is likely that statin therapy, control of blood pressure and dual antiplatelets all play a role.

Surgical therapy for ICAD

Surgical therapy for ICAD in the form of extracranial to intracranial bypass (typically superficial temporal artery (STA) to MCA) has been evaluated in two large randomized clinical trials. The extracranial to intracranial bypass trial randomized 1377 patients to best medical care (ASA 325 mg four times daily and blood pressure control) against medical therapy plus bypass of the STA to the MCA in patients with atherosclerotic narrowing or occlusion of the ipsilateral ICA or MCA.[45] The 30 day surgical mortality and major stroke morbidity rates were 0.6% versus 2.5% in the medical therapy and medical therapy plus bypass arms, respectively.[45] More recently, the Carotid Occlusion Surgery Study (COSS) attempted to improve patient selection by targeting those with hemodynamic ischemic symptoms (as defined by positron emission tomography measurement of oxygen extraction fraction). The trial was terminated after enrolment of 195 patients due to likely futility, with primary the endpoint (any stroke or death within 30 days or ipsilateral ischemic stroke within 2 years) seen in 21.0% in the surgical group and in 22.7% in the non-surgical group.[46] Due to this evidence, the role of STA-MCA bypass for ICAD is extremely limited.

Quality of the data for angioplasty and stenting of ICAD

Fifty-nine publications were identified and are summarized in table 1. The SAMMPRIS study[40] is the only prospective, randomized, controlled trial available, and is given AHA level B, AAN class II level and CEBM level 1. The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial arteries (SSYLVIA) trial was a prospective, non-randomized study with the outcome assessment made by a non-operator study neurologist, allowing a AHA level B, AAN class III level and CEBM level 2. The remaining studies were uncontrolled or did not have objective outcome measurement, and are thus classified as AHA level C, AAN class IV and CEBM level 4.

Angioplasty alone

Angioplasty has been reported in many retrospective studies to have reasonable success rates with periprocedural complication

Table 1 Studies of endovascular therapy for intracranial atherosclerotic disease

Author (year of publication)	Treated lesion locations	Comparison group	No of patients (No of lesions)	Mean % pretreatment stenosis	Endovascular therapy performed (%)	Technical success rate (%)	Periprocedural complication rate (%)	Stroke, death rate (%)
SAMMPRIS (2011)[40]	Anterior and posterior circulation	Aggressive medical therapy	451	81	SES (Wingspan)	93	19.2	30 days—14.7 (Medical—5.8)
Yu *et al* (2011)[47]	MCA, ICA, BA, VA	MCA vs other locations	MCA—35 Others—25	MCA—78.4 Others—72.5	SES (Wingspan)	MCA—97.1 Others—100	MCA—2.4 Others—4	30 days MCA—5.7 Others—12
Tang *et al* (2011)[48]	ICA, MCA, BA, VA	Medical therapy	53 (56)	79.7	BMS—91.5 SES—8.5	98.1	17.0	1 year 22 (Medical tx—23)
Nguyen *et al* (2011)[49]	ICA, MCA, ACA, BA, VA	None	74	78.7	Angioplasty alone	92	5	30 days—5 90 days—8.5
Qureshi *et al* (2011)[50]	ICA, MCA, BA, VA	None	92	74.6	Angioplasty—46.7 SES—25 BMS and DES—28.3	NR	9.8	30 days—9.8
Chamczuk *et al* (2010)[51]	Anterior and posterior circulation	None	66	75.5	SES—63.6 BMS—24.3 DES—12.1	95.5	6.6	Immediate—6.1
Lanfranconi *et al* (2010)[52]	Anterior and posterior circulation	None	34	NR	SES (Wingspan, Neuroform)—44.1 BMS—55.9	100	17.9	30 days—20.6
Suri *et al* (2010)[53]	Anterior and posterior circulation	Age <80 vs Age ≥80	Age <80—29 Age ≥80—15	Age <80—80 Age ≥80—82	NR	NR	Age <80—7 Age ≥80—23	1 year Age <80—10 Age ≥80—23
Povedano *et al* (2010)[54]	BA, VA	Medical	25	NR	SES, BMS, DES (proportions NR)	NR	NR	1 year—8 (Medical—16)
Costalat *et al* (2010)[55]	ICA, MCA, BA, VA	None	42	73.9	Angioplasty—21.5 SES—45.2 BMS—33.3	97.6	21.4	30 days—7.1
Zhao *et al* (2009)[56]	Anterior and posterior circulation	None	27 (29)	71.8	SES (Wingspan)	100	14.8	30 days—11.1
Intrastent (2010)[57]	ICA, MCA, BA, VA	None	372 (388)	NR	NR	90.2	NR	12.4
Vajda *et al* (2010)[58]	ICA, MCA, BA, VA	None	25 (30)	61	BMS (Coroflex Blue)	97	7	NR
Blasel *et al* (2010)[59]	Anterior and posterior circulation	None	40	76.2	BMS	95	NR	12.5
Samaneigo *et al* (2009)[60]	Anterior and posterior circulation	Medical	53	NR	SES and BMS	NR	5.6	7.5 (Medical—13.8)
Miao *et al* (2009)[61]	MCA	None	113	80.8	BMS	96.5	NR	4.4
Siddiq *et al* (2008)[62]	Anterior and posterior circulation	Angioplasty alone vs stent placement	190 (193) Angioplasty—95 Stent—98	Angioplasty—89.2 Stent—90.1	Angioplasty Stents—not specified	Angioplasty—85 Stent—96	Angioplasty—8 Stent—9	2 years Angioplasty—8 Stent—11
Kurre *et al* (2008)[63]	ICA, MCA, BA, VA	None	21	81.3	BMS—Pharos	90.5	19.0	30 days—9.5
Mazighi *et al* (2008)[64]	ICA, MCA, BA, VA	None	53 (69)	85	Angioplasty BMS DES	98.6	NR	30 days—10.1
Suh *et al* (2008)[65]	ICA, MCA, BA, VA	None	100	69.3	BMS	99	NR	6 months—10
Zaidat at al. NIH Wingpan registry (2008)[66]	ICA, MCA, BA, VA	None	129	82	SES (Wingspan)	96.7	6.2	30 days—9.6 6 months—14.0
Ralea *et al* (2008)[67]	BA, VA	None	12 (14)	75.4	BMS SES	100	NR	30 days—8.3
Puetz *et al* (2008)[68]	ICA, MCA, BA, VA	None	36	81.1	BMS DES	92	NR	30 days—10.5

Continued

Table 1 Continued

Author (year of publication)	Treated lesion locations	Comparison group	No of patients (No of lesions)	Mean % pretreatment stenosis	Endovascular therapy performed (%)	Technical success rate (%)	Periprocedural complication rate (%)	Stroke, death rate (%)
Freitas *et al* (2007)[69]	Anterior and posterior circulation	None	32 (33)	68.8	BMS (Pharos)	92	6.2	30 days—15.6
Fiorella *et al* (2007)[70]	Posterior circulation	None	44 (47)	82.5	BMS	95.7	26.1	6 months—31.8
Jiang *et al* (2007)[71]	Anterior and posterior circulation	None	46 (48)	NR	BMS (Apollo)	91.7	NR	30 days—8.7
Bose *et al* (2007)[72]	ICA, MCA, BA, VA	None	45	74.9	SES (Wingspan)	97.8	NR	30 days—4.5 6 months—7.1
Jiang *et al* (2007)[73]	ICA, MCA, BA, VA	None	181	NR	BMS	91.0	NR	30 days—11.8
Fiorella *et al* US mulitcenter Wingspan registry (2007)[74]	ICA, MCA, BA, VA	None	78 (82)	74.6	SES (Wingspan)	98.8	15.3	30 days—6.1
Jiang *et al* (2007)[75]	ICA, MCA, BA, VA	Moderate (50—69% stenosis) vs severe (≥70%)	Moderate—92 (94) Severe—121 (126)	NR	BMS	92.3	NR	30 days, 1 year, 2 year Moderate—4.3, 7.2, 8.2 Severe—4.8, 5.3, 8.3
Turk *et al* (2007)[76]	M1 MCA, A1 and A2 ACA, P1 PCA	None	4	NR	SES	100	0	0
Steinfort *et al* (2007)[77]	Posterior circulation	None	13	67	DES	100	NR	30 days—7.7
Qureshi *et al* (2006)[78]	ICA, MCA, BA, VA	None	21	68	DES	85.7	16.6	30 days—5.6
Wojak *et al* (2005)[79]	ICA, MCA, ACA, PCA BA, VA	None	60 (71)	NR	Angioplasty—73.8 BMS—26.2	86.9	9.5	30 days—4.8
Marks *et al* (2006)[80]	ICA, MCA, PCA BA, VA	None	120 (124)	82.2	Angioplasty—87.1 Stents (not specified)—12.9	40.7	NR	30 days—5.8
Gupta *et al* (2006)[81]	ICA, BA, VA	None	26	NR	DES	90	NR	30 days—12
Abou-Chebl *et al* (2006)[82]	Anterior and posterior circulation	None	48	85	BMS	100	14.6	30 days—10.5
Abou-Chebl *et al* (2005)[83]	ICA, MCA, BA, VA	None	8	84.4	DES (Cipher and Taxus)	100	25	1 year—12.5
Boulos *et al* (2005)[84]	ICA, MCA, BA, VA	None	13	NR	DES	100	0	18 months—7.7
Lylyk *et al* (2005)[85]	ICA, MCA, PCA BA, VA	None	104	NR	BMS DES	98	10	30 days—9.5
Henkes *et al* (2005)[86]	ICA, MCA, BA, VA	None	15	72	SES (Wingspan)	100	6.6	30 days—6.6
Chow *et al* (2005)[87]	BA, VA	None	39	75	BMS DES	97.4	NR	30 days—28.2
Suh *et al* (2005)[88]	ICA, MCA, BA, VA	None	35	78.6	Angioplasty—54.3 Stents (not specified)—45.7	97	NR	30 days—11
Marks *et al* (2005)[89]	ICA, MCA, PCA BA, VA	None	36 (37)	84.2	Angioplasty	50	NR	30 days—8.3
Lee *et al* (2005)[90]	MCA	None	17	67.6	BMS	94.1	68.8	30 days—18.8
Hatano *et al* (2005)[91]	Posterior circulation	None	15	NR	BMS	100	0	0
Kessler *et al* (2005)[92]	Posterior circulation	None	16	84	BMS	81.2	NR	30 days—25
Kim *et al* (2005)[93]	Posterior circulation	None	17	76.1	BMS	100	12	30 days—5.3
Qureshi *et al* (2005)[94]	ICA, MCA, BA, VA	None	24	84	Angioplasty BMS	Angioplasty—100 Stent—71.4	NR	30 days—7
Weber *et al* (2005)[95]	Posterior circulation	None	22	92.3	BMS	100	NR	30 days—14
Yu *et al* (2005)[96]	BA	None	18	79.6	BMS	100	NR	16.7

Continued

Table 1 Continued

Author (year of publication)	Treated lesion locations	Comparison group	No of patients (No of lesions)	Mean % pretreatment stenosis	Endovascular therapy performed (%)	Technical success rate (%)	Periprocedural complication rate (%)	Stroke, death rate (%)
Kim *et al* (2004)[97]	MCA	None	14	88	BMS	85.7	NR	30 days—33.3
Jiang *et al* (2004)[98]	MCA	None	40 (42)	80.7	BMS	97.6	NR	30 days—10
SSLVIA (2004)[29 99 100]	ICA, MCA, PCA, BA, VA	None	43	69.9	BMS (Neurolink)	100	NR	30 days—9.3
Rochemont *et al* (2004)[101]	ICA, MCA, BA, VA	None	18 (20)	82	BMS	90	6	30 days—6
Gupta *et al* (2003)[102]	ICA, MCA, BA, VA	None	18 (21)	85.5	BMS	90.5	50	30 days—50
Levy *et al* (2001)[103]	BA, VA	None	11	NR	BMS	100	NR	30 days—36.6
Mori *et al* (2000)[104]	Anterior and posterior circulation	None	10 (12)	81	BMS	83.3	0	11 months—0
Gomez *et al* (2000)[105]	BA	None	12	71.4	BMS	100	16.6	30 days—8.3

ACA, anterior cerebral artery; BA, basilar artery; BMS, balloon mounted stents; DES, drug eluting stents; ICA, internal carotid artery; MCA, middle cerebral artery; NR, not reported; PCA, posterior cerebral artery; SES, self-expanding stents; VA, vertebral artery.

rates reported of 4–40%.[12 106] Initial series of angioplasty alone had higher complication rates but the technique of submaximal angioplasty, where the angioplasty balloon is undersized relative to the target vessel, appears to have lowered complications. Among more recent larger series of angioplasty alone, Marks *et al* (n=35) reported a 5.8% 30 day stroke or death rate, Wojak (n=80) reported 4.8%, Siddiq (n=67) reported 8% and Nguyen (n=55) reported 5%. The advantages of angioplasty alone include easier navigability of balloons versus stent delivery systems and the potential need for shorter duration of dual antiplatelet therapy. Concerns about angioplasty include acute intimal dissection (a phenomenon which can also be seen with stent delivery), vessel rupture (although rates of rupture are much lower with submaximal angioplasty), immediate recoil of the vessel and poor postprocedure residual stenosis. These concerns have limited its use among interventionalists. In the case of acute dissections, rescue stenting may also be required. In a study by Marks *et al*, dissection of the treated vessel occurred in 11 of 36 treated patients although none of these patients had clinical sequelae.[89] High restenosis rates of 24–40% have also been reported.[80] More date regarding long term stroke free survival of patients treated with angioplasty alone is needed.

Balloon mounted stents

Balloon mounted stents, mainly developed for use in the coronary circulation, have also been utilized for ICAD. These may offer the advantage of the protection of the stent during angioplasty of the stenotic lesion, particularly to reduce the risk of acute vessel closure due to dissection. Initial retrospective trials also reported reasonable technical success rates with varied complication rates. The first major prospective non-randomized trial was the SSYLVIA trial,[99] using a balloon expanding bare metal stent. This stent was placed in a total of 61 patients, 43 of whom had symptomatic ICAD. Technical success was seen in 95% of cases, with an overall complication rate of 7.2% at 30 days.[99] Technical results appear to be improved over time, with less residual stenosis at the conclusion of the procedure compared with those reported for self-expanding stents.[61 63] Restenosis also appears to be lower after placement of balloon mounted stents compared with self-expanding stents.[100] However, concerns remain with the complication rates with balloon mounted stents,[70] particularly in the BA and MCA, where significant numbers of perforating arteries are present and plaque compression and redistribution could theoretically promote their occlusion.

Recently the Pharos Vitesse neurovascular stent system (Codman Neurovascular, Raynham, Massachusetts, USA) has been developed as the first balloon mounted stent designed specifically for the intracranial circulation. In a study of 21 patients from Germany,[63] technical success was seen in 90.5% of patients with a 30 day stroke rate of 9.5% and no mortality. The stent is also being evaluated in a randomized control trial, the Vitesse Intracranial Stent Study for Ischemic therapy (VISSIT),[107] which recently stopped enrolling patients but will continue follow-up, which is to be completed in mid 2013.

Drug eluting stents

Drug eluting stents (DES) have also been explored for management of ICAD, particularly as high rates of in-stent restenosis (ISR) were noted with treatment with bare metal stents. However, current DES devices are stiff and can be difficult to navigate in the intracranial circulation. Consequently, their role in the management of ICAD, at present, is limited. Nevertheless, lower rates of ISR have been noted with these devices. In

a report of the use of DES for extracranial and intracranial cerebral circulation, 29 patients with ICAD were included. In three patients with ICAD, the DES could not be placed, yielding a technical failure rate of 10%.[81]

Self-expanding stents

At present, the only FDA approved stent for the management of ICAD is the Wingspan (Stryker Neurovascular, Fremont, California, USA) stent. This nitinol stent received approval in 2005, and has been used in a substantial number of interventions in the USA. Two concurrent registries were performed following approval of the device. The US Wingspan registry, funded by Boston Scientific, tracked patients in whom the device was placed in five US centers. Initially, periprocedural results were reported, with a technical success rate of 98.8%. The mean reported residual stenosis was 27.2%±16.7%. Five (6.1%) periprocedural complications were seen, four resulting in death.[74] Later, the group published their long term results. Of a total of 129 lesions treated, 36 (27.9%) developed ISR, defined as >50% stenosis by the WASID method.[108] ISR was more frequently seen in younger patients and in the anterior circulation, with rates in the supraclinoid ICA reaching as high as 59%.[109] It is possible that these stenoses did not represent atherosclerotic disease but rather some type of inflammatory process.

The National Institutes of Health funded registry yielded similar results. The technical success rate reported in this trial was 96.7%, with a periprocedural complication rate of 6.2%.[66] Periprocedural complications occurred more frequently in the posterior circulation, at low volume centers, and at earlier times from the qualifying event when stroke was the presenting symptom.[110] ISR reported by this group was 25%.[66]

The SAMMPRIS study is the first prospective, randomized, controlled trial to be conducted for patients with symptomatic ICAD. Patients (aged 30–80 years) were included in the study if they had a TIA or stroke within 30 days of enrolment and had an intracranial stenosis measuring 70–99% by the WASID methodology. Major exclusion criteria included tandem extracranial or intracranial stenoses, presence of intraluminal thrombus or progressive neurological signs within the previous 24 h of possible enrolment. Patients were randomized to aggressive medical therapy (aspirin 325 mg daily plus clopidogrel 75 mg daily for 90 days, followed by ASA 325 mg daily thereafter, blood pressure control to target <140/90 mm Hg or <130/80 mm Hg if diabetic, and lipid lowering therapy with rosuvastatin 20 mg daily to target LDL <70 mg/dl) versus aggressive medical therapy plus angioplasty and stenting with the Gateway balloon and Wingspan stent system. Interventionalists performing the procedure were selected by a credentialing committee.[111] The primary endpoint was stroke or death within 30 days of enrolment or any additional intracranial revascularization procedure (ie, angioplasty for symptomatic ISR) or ischemic stroke in the territory of the qualifying artery between days 31 and the end of the follow-up period.

As mentioned earlier, the trial was stopped after enrolling 451 (59%) of the originally planned 764 patients. The primary endpoint within 30 days was seen in 33 patients in the angioplasty/stenting group and in 13 patients in the medical management alone group (14.7% vs 5.8%, p=0.002).[40] Following 30 days, the stroke rate in the qualifying artery had been similar (13 patients in each group), giving a 1 year rate of 20.0%, and 12.2% in the angioplasty/stenting group and medical groups, respectively (although fewer than half of the patients have reached the 1 year point).

Of the 33 strokes in the angioplasty/stenting group, the majority of the strokes (n=25) occurred within 1 day of the procedure with the remainder occurring within the first week. Ten of the strokes in the angioplasty/stenting group were symptomatic intracranial hemorrhages compared with none in the medical group. Six of these were parenchymal hemorrhages (four probably due to reperfusion, one mechanism unclear) and four were subarachnoid hemorrhages (probably due to wire perforation). The stroke rate was no different between high enrolling and low enrolling sites, nor did it diminish over the course of the trial.

The trial has stopped enrolment but will continue to follow already enrolled patients through the follow-up period, which is of critical importance to assess the rates of further stroke events in both treatment arms. The importance of the interventional treatment paradigm in the failure of this trial has yet to be determined. The reasons for the periprocedural complications will need further analysis, and factors such as periprocedural blood pressure control and possible antiplatelet resistance (which was not measured in the trial) will have to be considered, especially in future trial designs. The role of angioplasty and stenting in the management of patients with medically refractory ICAD was not addressed by this trial and future trials may have to assess this group of patients.

It is also important to note that the inclusion and exclusion criteria for SAMMPRIS study differ from the humanitarian device exemption criteria for the Wingspan stent (patients with 50–99% stenosis of a major intracranial artery with a cerebral ischemic event, refractory to medical therapy).[112]

Aspects of periprocedural management

As mentioned, periprocedural care is of critical importance in this procedure. Platelet function testing is becoming commonplace in neurovascular intervention. Various laboratory based methods are available, and point of care testing is also available through the Verify Now system (Accumetrics, San Diego, California, USA). It is estimated that between 5% and 40% of patients may be resistant to standard doses of aspirin and 5–11% of patients may be resistant to clopidogrel.[40 113] From the cardiac literature, both aspirin and clopidogrel non-responders are at increased risk of death and vascular events, particularly in the setting of coronary revascularization procedures.[114–116]

Blood pressure management during endovascular management for ICAD is important. Patients are typically treated while under general anesthesia, which will lower blood pressure. Care must be taken to maintain higher mean arterial pressures until the stenosis has been opened by angioplasty, after which it is important to lower the blood pressure to lessen the risk of reperfusion injury, although data for this strategy are extrapolated from studies of extracranial carotid artery stenting as no specific data from patients with ICAD are available.[117 118]

RECOMMENDATIONS

1. Aspirin is preferred over warfarin for the medical management of symptomatic ICAD (AHA level B, class I; CEBM level 1a, grade B).
2. The use of combination aspirin 325 mg daily and clopidogrel 75 mg daily for the first 3 months, followed by aspirin 325 mg daily, along with aggressive risk factor modification of hypertension, hyperlipidemia, diabetes and smoking cessation should be pursued in all patients with symptomatic ICAD (AHA level B, class IIa; CEBM level 1b, grade B).
3. In patients with symptomatic 70–99% intracranial stenosis who are not on maximal medical therapy, medical therapy is

recommended over angioplasty and stent therapy with the Gateway balloon and Wingspan stent system (AHA level B, class IIa; CEBM level 1b, grade B).
4. In patients with symptomatic 70–99% intracranial stenosis who have failed aggressive maximal medical therapy, angioplasty or stent therapy may be considered (AHA level B, class IIb, CEBM level 2b, grade B).
5. There is insufficient evidence to recommend between angioplasty and the use of balloon mounted, drug eluting or self expanding stent systems (AHA level C, class III; CEBM level 5, grade D). Further studies comparing these techniques and technologies are required.
6. There is insufficient evidence to advise specifically regarding periprocedural aspects of care such as blood pressure management and the use of platelet function testing (AHA level C, class III; CEBM level 5, grade D). Further studies into periprocedural care are warranted.
7. Please note that this document is not addressing the use of angioplasty with or without stenting in the setting of acute ischemic stroke. This will be reviewed in the standards document of endovascular therapy of acute ischemic stroke.[119]

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