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A randomized trial comparing primary angioplasty versus stent placement for symptomatic intracranial stenosis

Adnan I Qureshi[1], **Saqib A Chaudhry**[1,*], **Farhan Siddiq**[1], **Shahram Majidi**[1], **Gustavo J Rodriguez**[1], and **M Fareed K Suri**[1]

[1] *Zeenat Qureshi Stroke Research Center, Departments of Neurology and Neurosurgery, University of Minnesota, and Hennepin County Medical Center, Minneapolis, MN 55455, USA*

Abstract

Background: Both primary angioplasty alone and angioplasty with a self-expanding stent have been compared in non-randomized concurrent clinical studies that suggest equivalent results. However, there is no randomized trial that has compared the two procedures in patients with symptomatic high grade intracranial stenosis.

Objective: The primary aim of the randomized trial was to compare the clinical and angiographic efficacy of primary angioplasty and angioplasty followed by stent placement in preventing restenosis, stroke, requirement for second treatment, and death in patients with symptomatic intracranial stenosis.

Methods: The study prospectively evaluated efficacy and safety of the two existing neurointerventional techniques for treatment of moderate intracranial stenosis (stenosis ≥ 50%) with documented failure of medical treatment or severe stenosis (≥70%) with or without failure of medical treatment.

Results: A total of 18 patients were recruited in the study (mean age [±SD] was 64.7 ± 15.1 years); out of these, 12 were men. Of these 18, 10 were treated with primary angioplasty and 8 were treated with angioplasty followed by self-expanding stent. The technical success rates of intracranial angioplasty and stent placements defined as ability to achieve <30% residual stenosis when assessed by immediate post-procedure angiography was 5 of 10 and 5 of 8 patients, respectively. The total fluoroscopic time (mean [±SD]) was lower in patients undergoing primary angioplasty 37 [±11] min versus those undergoing angioplasty followed by self-expanding stent 42 [±15] min, $P = 0.4321$. The stroke and death rate within 1 month was very low in both patient groups (1 of 10 versus 0 of 8 patients). One patient randomized to stent placement continued to have recurrent ischemic symptoms requiring another angioplasty in the vertebral artery on post-procedure Day 2.

Conclusions: The trial suggests that a randomized trial comparing primary angioplasty to angioplasty followed by stent placement is feasible. The immediate procedural outcomes with primary angioplasty are comparable to stent placement and warrant further studies.

Keywords

primary angioplasty; stent; intracranial atherosclerosis; intracranial stenosis; stroke; randomized trial

Introduction

Patients who have suffered a stroke or transient ischemic attack (TIA) attributed to stenosis (50–99%) of a major intracranial artery face a high risk for ipsilateral stroke following the initial ischemic event, despite treatment with antithrombotic medications [1]. The primary end point (ischemic stroke in any vascular territory, intracranial hemorrhage, or vascular death) occurred in 22% of the symptomatic patients in the Warfarin vs. Aspirin Symptomatic Intracranial Disease (WASID) trial [2]. The 1-year risk of ipsilateral stroke in patients with symptomatic intracranial stenosis ≥70% was 19% [3]. The Consensus Conference on Intracranial Atheroscler-

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*Correspondence to: SA Chaudhry, chaudhrys208@gmail.com

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otic Disease [4] concluded that no validated criteria exist for selecting patients for intracranial stenting. However, symptomatic patients with ≥70% intracranial stenosis and those with ischemic symptoms that can be attributed to hemodynamic changes are at high risk for recurrent ischemic events. Therefore, it is reasonable to consider these patients for endovascular treatment, clinical studies, and institutional protocols. The consensus statement also acknowledged that no clear data are available to support the effectiveness of primary angioplasty over stent placement for treatment of intracranial stenosis. Both primary angioplasty alone and angioplasty with a self-expanding stent have been evaluated in a non-randomized trial with high technical success rates.

Based on these gaps in scientific knowledge, we initiated a randomized clinical trial to compare the clinical and angiographic efficacy of angioplasty versus stent placement in preventing restenosis, stroke, requirement for second treatment, and death in patients with symptomatic intracranial stenosis. On April 11, 2011, the National Institutes of Health (NIH), based on the recommendation of the study's Data Safety Monitoring Board (DSMB), stopped enrollment in a concurrent randomized trial, Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) because of a 14% rate of 1 month stroke and/or death in patients treated with angioplasty combined with stent placement [5]. Subsequent to the premature termination of SAMMPRIS, local Institutional review Boards (IRBs) requested a temporary halt in recruitment in trial and requested a detailed interim analysis. We present the results of angioplasty versus stent placement trial based on the data acquired from patients recruited prior to IRBs request in the current report.

Methods

All patients with angiographically documented intracranial stenosis ≥50% in severity and who failed medical treatment or those patients with stenosis severity of ≥70% (with or without trial of antiplatelet medications) and suffered an ischemic event referable to the target lesion in the last 3 months were considered for inclusion in the trial. Another requirement for inclusion was that the treating physician was unclear about the best endovascular treatment modality (i.e., primary angioplasty or stent placement) for symptomatic intracranial stenosis (clinical equipoise).

Medication failure was not considered a prerequisite for patients with severe (≥70%) stenosis because the results of WASID trial reported that such patients had a greater risk of ischemic events despite treatment with medication [3]. The inclusion and exclusion criteria are summarized in the subsequent sections.

Inclusion criteria

1. Age was greater than 18 years.
2. Patient or family agreed to the terms of follow-up evaluations as mandated by the protocol.
3. Failure of antithrombotic or anticoagulant therapy for patients with stenosis of ≥50%. defined by ipsilateral ischemic symptoms despite maximum antiplatelet therapy; specifically, by regular use of aspirin 81 mg or higher, clopidogrel 75 mg every day, or ticlopidine 250 mg twice daily, or maximum anticoagulation defined by intravenous heparin (with a activated partial thromboplastin time >1.5 times control) or oral warfarin (with an international normalized ratio greater than 2.0) [6].
4. Stenosis involved the arteries within the cranium or those encased by the cranial bones including petrous and cavernous segments of the internal carotid artery and the intradural segment of the vertebral artery.

Exclusion criteria

1. Known hypersensitivity or contraindication to use of X-ray contrast. Patients with known contrast hypersensitivity will be eligible pending treatment with steroids and histamine blockers.
2. Active bleeding, diathesis of coagulopathy, or would refuse blood transfusions.
3. History of major stroke, which is likely to confound the study endpoints.
4. Spontaneous intracerebral hemorrhage within the past 12 months.
5. Recent (<7 days) stroke of sufficient size (on computed tomographic [CT] or magnetic resonance imaging [MRI] scan) that places him/her at risk of hemorrhagic conversion during the procedure. Patients with infarction involving greater than one-third of the affected vessel distribution were excluded.
6. Hemoglobin <7 g/dL, platelet count < 100,000 cells/cc, uncorrected international normalized ratio (INR) > 1.7, or heparin-associated thrombocytopenia.
7. Neurologic illnesses within the past 3 years with neurological deficits that cannot be differ-

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entiated with TIA or stroke, including partial or secondary generalized seizure, uncomplicated migraines, tumor or other space-occupying brain lesions, subdural hematoma, cerebral contusion, other post-traumatic lesions, intracranial infections, demyelinating diseases, moderate-to-severe dementia, or intracranial hemorrhage.

8. Active participation in another clinical study.
9. Myocardial infarction (MI) within the previous 15 days.
10. Recent gastrointestinal bleeding, contraindicating anticoagulation during the endovascular procedure.
11. Proximal occlusive disease > 50%, either in the proximal carotid artery, common carotid artery, cervical internal carotid artery, or the cervical vertebral artery that would preclude safe introduction of a guiding catheter or guiding sheath.
12. Severe peripheral vascular disease which precludes successful insertion and catheterization of the arteries.
13. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a stent delivery device or balloon catheter or microwire.

Conduct of the trial

All patients with intracranial stenosis, referred to the two study investigational sites for endovascular treatment, were screened for study eligibility. A log was maintained to record the screening of each patient. All recruited patients or their families were required to sign the appropriate consent form that had been approved by the local Institutional Review Board. The two centers had considerable experience in performance of intracranial angioplasty and stent placement and each of the participating interventionalists had performed at least 25 endovascular procedures for intracranial stenosis. Eligible subjects are randomized to either the primary angioplasty or stent placement group using computer-generated randomization with allocation concealment by opaque sequentially numbered sealed envelopes, and the treating physician/interventionalist did not know the allocation at the time of consent.

Preoperative medication including a combination of aspirin (325 mg daily) and clopidogrel (75 mg daily) started 3 days prior to the procedure. If clopidogrel could not be initiated 3 days prior to the procedure, a loading dose of 300 mg was used. The patients underwent the allocated procedure according to local institutional practices. In general, an introducer sheath was placed in the femoral artery using percutaneous access. Heparin was intravenously administered as a bolus dose to achieve an activated coagulation time (ACT) in the range of 250 to 350 s. A guide catheter was placed in the distal cervical internal carotid artery or cervical vertebral artery. The selected balloon catheter or stent delivery device was advanced over a 0.014-inch microguide wire and navigated to the site of stenosis. Primary angioplasty (submaximal) was performed using the semi-compliant Gateway™ PTA Balloon Catheter (Boston Scientific Corporation, Natick, MA). The protocol for stent placement was identical to that described above for primary angioplasty, except that the terminal device was a self-expanding stent; specifically, the Wingspan® Stent System (Boston Scientific Corporation, Natick, MA). The goal of the procedure was to reduce the stenosis to ~30% or less. Post-procedure, a combination of aspirin (325 mg daily) and clopidogrel (75 mg daily) was used for at least a month followed by aspirin indefinitely. The clinical outcomes were to be evaluated at 1 month-, 6 month-, and 1 year following treatment. A repeat cerebral angiogram was to be performed if possible at 6 months to evaluate the presence of restenosis or de novo stenosis. Attention was directed toward modification of risk factor profile of patients in regard to cigarette smoking and/or hypertension.

Outcomes assessed

The angiographic severity of stenosis was measured by the treating physician using the WASID criteria [2]. The outcomes were defined as follows: stroke, defined by sudden onset of neurologic deficit that persisted for more than 24 h and further categorized into minor (a modified Rankin scale of 2 or less at discharge) or major stroke; TIA, defined by ischemic symptoms lasting < 24 h; MI, defined by clinical history of chest pain, electrocardiographic changes, and serum cardiac enzymes; and, death, with an effort made to obtain the relevant records from the hospital or patient's family physician including death certificate to determine the cause of death. The outcomes were ascertained by vascular neurologists with certification in determination of National Institutes of Health Stroke Scale score. Bleeding complications were classified as major (intracranial hemorrhage or decrease in hemoglobin of >5 g/dL), minor (decrease in hemoglobin of 3–5 g/dL), or insignificant [7]. Crossover to the alternate treatment was recorded if the treating physician decided to place a stent in a patient allocated to primary angioplasty in the event that a satisfactory result is not achieved with primary angioplasty alone or a complication occurs, such as dissection; or, avoiding stent place-

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ment after angioplasty in a patient allocated to the stent group due to thrombosis or other intraprocedural events.

Statistical considerations

Analysis was performed according to the actual treatment received due to the small number of patients. The study was considered exploratory and formal sample size estimation was not performed. The study was underpowered to test for equivalence between treatment interventions. For adequate power to test equivalence of treatments, we would require a total of 1000 patients to achieve an 80% power assuming that the rate of primary outcome in the stent-treated group is 17% and a clinical significance difference is 7%.

Results

A total of 23 patients were screened for the study over 18 months. Of these, 18 patients were recruited in the study; mean age [±SD] was 64.7 ± 15.1 years, 12 were men. Further, 3 patients had intracranial stenosis 50–69% in severity with medication failure while 15 patients had intracranial stenosis ≥70%. However, 5 patients of the 23 patients were not recruited in the study because of (intracranial stenosis <50% (n = 3), tandem lesion (n = 1), and stenosis/occlusion of 100% (n = 1). The indications were recruitment were recent TIA (n = 9), minor ischemic stroke (n = 6), and major ischemic stroke (n = 3) in the randomized patients. Hypertension (n = 15), diabetes mellitus (n = 6), hyperlipidemia (n = 15), cigarette smoking (n = 7), coronary artery disease (n = 3), congestive heart failure (n = 1), and atrial fibrillation (n = 3) were underlying cardiovascular risk factors. Further, 8 patients had suffered a previous stroke or TIA in another distribution.

Among the 18 subjects, 9 were randomized to primary angioplasty and 9 were randomized to angioplasty followed by self-expanding stent. The stenosis was located in the internal carotid artery (n = 3), middle cerebral artery (n = 8), vertebral artery (n = 2), and basilar artery (n = 5). The severity mean % [±SD] of angiographic stenosis prior to procedure was 78 ± 9%. The demographic, clinical, and angiographic characteristics according to treatment received are presented in Tables 1 and 2. All patients received the primary allocated treatment with one cross over in the patients allocated to stent placement. However, 1 patient randomized to stent placement (patient 2, Table 1) did not receive the stent because the treating physician felt that successful stent placement was unlikely and likely to be associated with an unnecessary risk of complications. The number of patients requiring more than one angioplasty was 0 of 10 and 1 of 8 in angioplasty and stent treatment treated patients, respectively. The total fluoroscopic time (mean [±SD]) was somewhat lower in patients undergoing primary angioplasty 37 [±11] min versus those undergoing angioplasty followed by self-expanding stent 42 [±9] min, P = 0.309. The total contrast used (mean in ml [±SD]) during the procedure was 146 ± 50 for angioplasty and 137 ± 41 for stent-treated patients. The technical success rates of intracranial angioplasty and/or stent placements defined as ability to achieve <30% residual stenosis when assessed by immediate post-procedure angiography was 6 of 10 and 5 of 8 patients treated with primary angioplasty or stent placement, respectively. The ability to achieve <50% residual stenosis when assessed by immediate post-procedure angiography was 9 of 10 and 8 of 8 patients treated to primary angioplasty or stent placement, respectively. No systemic bleeding complications were observed in any patient.

The stroke and death rate within 1 month was very low in both patient groups (1 of 10 versus none of 8 patients) treated to primary angioplasty or stent placement, respectively. An 80-year-old man with a history of hypertension, hyperlipidemia, and atrial fibrillation (requiring long-term anticoagulation) presented with ischemic stroke in the basilar artery distribution and severe stenoses in the junction between the intracranial right vertebral artery and the basilar artery on MR angiography. The left vertebral artery was hypoplastic and did not contribute to the intracranial posterior circulation. Cerebral angiography demonstrated severe stenosis located at the junction between the right intracranial vertebral artery and basilar artery, measuring 75% in severity by WASID criteria. Primary angioplasty was performed using 2.5 mm × 9 mm and 2.75 mm × 9 mm Gateway balloons. On post-procedure Day 5, the patient developed new left-sided hemiparesis and a CT scan demonstrated right anterior cerebral artery distribution infarction. The next day, worsening of hemiparesis and level of consciousness was seen associated with new hemorrhagic conversion of infarction with intraparenchymal hemorrhage involving the right frontal lobe with extension into the third and lateral ventricles and mass effect. Patient was treated with external cerebrospinal fluid drainage and hypertonic saline. Due to lack of any perceived improvement, the family decided to withdraw care and patient died on post-procedure Day 10. The second patient presented with recurrent ataxia associated with left internal carotid artery cavernous stenosis that the main contribution to posterior circulation due to previously diagnosed chronic basilar artery occlusion. The patient was randomized to stent treatment and under-

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Table 1.

The baseline demographic and clinical characteristics of patients treated with primary angioplasty and follow-up data

#	Age/ sex	Qualifying event	Risk factors	Baseline NIHSS	Lesion location	Pre-treatment stenosis (in %)	Post-treatment stenosis (in %)	Stent used	Contrast used	Procedure time/min	Length of stay	1-month events	Time to last follow-up/days	Events during follow up	mRS on last contact
1	63/F	TIA	HTN, TIA/stroke, cigarette smoking	0	ICA-supra clinoid	65	35	N/A	130 cc, opti-240	91	1	None	60	None	0
2	59/F	TIA	AF	0	BA-Mid	99	40	N/A	200 cc, opti-240	69	8	None	92	None	0
3	56/M	TIA	HTN, CAD, HL, DM, TIA/stroke, cigarette smoking	0	BA-Mid	75	50	N/A	105 cc, opti-240	35	1	None	92	None	0
4	84/M	Minor stroke	HTN, CAD, CHF, HL	0	MCA-M1	70	20	N/A	120 cc, opti-240	163	4	None	323	None	0
5	44/M	TIA	HTN, HL, , DM, TIA/stroke,	1	MCA- M1	90	30	N/A	220 cc, opti-240	106	3	None	420	None	0
6	56/F	Minor stroke	HTN, HL, TIA/ stroke	0	MCA- M1	65	17	N/A	105 cc, opti-240	67	2	None	780	None	1
7	52/M	TIA	Cigarette smoking	0	MCA- M1	75	30	N/A	200 cc, opti-240	113	1	None	29	None	0
8	80/M	Minor stroke	HTN, AF, HL, TIA, stroke	0	Intra cranial VA	75	50	N/A	160 cc, opti-240	111	1	Post procedural fatal ICH	13	Death	6
9	88/F	TIA	HL	2	MCA- M1	75	30	N/A	65 cc, opti-240	63	4	None	178	None	2
10	72/M	Pontine stroke	HTN, CAD, HL	7	proximal BA	75	48	N/A	150 cc, opti-240	123	2	None	17	None	2

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Table 2.

The baseline demographic and clinical characteristics of patients treated with stent placement and follow-up data

#	Age/ sex	Qualifying event	Risk factors	Baseline NIHSS score	Lesion location	Pre-treatment stenosis and characteristic (in %)	Post-treatment stenosis (in %)	Stent used	Contrast used	Procedure time/min	Length of stay	1 month events	Time to last follow-up/ days	Events during follow Up	mRS on last contact
1	46/F	Minor stroke	HTN, DM, HL, cigarette smoking	0	MCA-M1-M2	75	35	Wingspan stent (3 × 9 mm)	170 cc, opti-240	69	1	None	32	None	0
2	83/ M	Minor stroke	HTN, AF, DM, HL, TIA/stroke	2	Intra cranial VA	90	0	Wingspan stent (4*20 mm)	130 cc, opti-240	81	7	None	40	None	3
3	66/F	Stroke	HTN, HL, cigarette smoking	0	MCA-M1	75	40	Wingspan stent (3.5*15 mm)	200 cc, opti-240	192	5	None	480	None	0
4	53/ M	Minor stroke	HTN, HL	2	ICA-supra clinoinoid	85	20	Wingspan stent (4.5*20 mm)	70 cc, opti-240	43	7	Continued episodes of ataxia requiring another angiplasty	297	None	2
5	61/ M	TIA	HTN, HL, TIA/ stroke	0	MCA-M1	80	30	Wingspan (3 mm × 15 mm)	130 cc, opti-240	121	1	None	510	None	0
6	49/ M	Stroke	HTN, HL, cigarette smoking	1	ICA-supra clinoid	67	40	Wingspan (4.5 mm × 20 mm)	170 cc, opti-240	134	1	None	392	None	3
7	60/ M	TIA	HTN, HL, DM	0	BA-mid	80	5	Wingspan (3.5 mm × 15 mm)	120 ml, opti-240	116	2	None	180	None	0
8	93/ M	TIA	HTN, HL, DM, cigarette smoking	5	BA-prox	90	30%	Wingspan stent (4*15 mm)	110 cc, opti-240	123	6	None	12	None	2

went stent placement in the cavernous portion of left internal carotid artery using Gateway balloon (3 mm × 9 mm) and Wingspan stent (4.5 mm × 20 mm). The patient left against medical advice the next day and was readmitted on post-procedure Day 2 due to continued episodes of ataxia and new hiccups. CT scan did not demonstrate any new ischemic changes. The patients underwent angioplasty for multifocal stenoses in the vertebral artery. The patient remained symptom free for 10 months. Due to occurrence of restenosis and progression of stenosis in the right vertebral artery, the patient underwent angioplasty and stent placement in the extracranial right vertebral artery V2 segment (severity of 70%).

The time from primary treatment to last clinical assessment (in months, mean ± SD) was 6.1 ± 8 and 8.1 ± 7 in patients treated with primary angioplasty or stent placement, respectively. A total of 11 patients underwent repeat cerebral angiogram. Angiographic restenosis was observed in 3 of 11 patients who underwent follow-up angiography (0 of 4 in angioplasty-treated- and 3 of 7 in stent-treated patients). There was one minor ischemic stroke observed in the posterior circulation distribution in a patient treated for left internal carotid artery lesion after 10 symptom-free months.

Discussion

The question of whether primary angioplasty can provide better or comparable results in lesions that are treatable by stent placement cannot be addressed without a randomized clinical trial [1]. The current trial was not intended to provide a definitive answer, but to answer the fundamental questions necessary prior to designing an adequately powered randomized trial. The current study provides proof of concept and feasibility of randomization in a group of patients that are considered appropriate candidates for either technique (clinical equipoise). Our results validate the success of inclusion and exclusion criteria used in identifying such patients. The trial also provides evidence that patients can receive the treatment without excessively high cross over or adverse event rates.

The controversy regarding whether primary angioplasty is equivalent to intracranial stent placement for intracranial stenosis is ongoing since self-expanding stents for such an application became available. In a single center study [8], the results of primary angioplasty (reserved for more complex lesions) were comparable with stent placement for intracranial stenosis (concurrent unmatched controls). In a subsequent multicenter review [9], outcomes were compared for 190 patients treated with 95 primary angioplasty procedures and 98 intracranial stents placements in three tertiary care centers. The 1-month rate of stroke and/or death was 8.4% (8/95) in the angioplasty-treated group and 9.2% (9/98) in the stent-treated group. However, primary angioplasty was preferred in these studies for patients with small vessels (<2 mm diameter), long lesions that would require multiple stents (>12 mm), tortuous proximal vessels (≤2 acute curves requiring traversing, judged by experience or trial), limited vessel length available distal to the lesion to allow stable placement of microwire, lesions located in the anterior cerebral, posterior cerebral or M2 segment lesions, or if a guide catheter could not be placed in the distal vertebral artery or internal carotid artery. These inherent differences might have affected the rates of clinical and angiographic end points independent of the treatment modality used.

The SAMMPRIS trial was halted after a 14% 1-month stroke and death rate was observed in the stent-treated group. The rate of 1-month stroke and death in the endovascular-treated patients would have to be <4% to demonstrate a relative 35% reduction in the rate of the primary end point (study hypothesis) compared with medical treatment at 2 years [10]. Such low rates of event rates are unlikely to be seen with the current generation of intracranial stents and led to consideration of primary angioplasty as the endovascular modality of choice. A retrospective analysis of 69 SAMMPRIS patients at three non-participating sites found that the 1-month stroke and death rate was 3.3% in the SAMMPRIS eligible angioplasty treated subgroup and 10.2% in the SAMMPRIS eligible stent treated subgroup [11]. The difference was seen despite the fact that the SAMMPRIS eligible stent treated subgroup was comprised of relatively younger patients compared to angioplasty-treated subgroup (mean age of 58 versus 63 years). However, the non-randomized, uncontrolled allocation of patients to either angioplasty or stent placement limited any concrete extrapolations regarding the superiority of primary angioplasty.

One issue is whether the superiority of stent placement over primary angioplasty can be assumed based on trials conducted in patients with coronary artery disease. Two meta-analyses demonstrated that there were reductions in the rates of composite end point of death, acute MI, or revascularization with stent treatment compared with primary angioplasty at 6 months. However, this difference was predominantly attributed to lower rates of restenosis and repeat revascularization [12]. Nevertheless, the technical success rates for stenting the intracra-

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nial circulation are prominently lower in the intracranial circulation compared with the coronary circulation [13]. Similarly, the rates of restenosis after stent placement in the intracranial circulation appear to be much higher (up to 30%) at 6–9 months than those observed with stent placement in the coronary circulation more [14,15]. Even in our study, 3 of the 8 patients randomized to stent placement had angiographic restenosis on follow-up angiography. The clinical significance of restenosis in the intracranial circulation and its association with subsequent ischemic events remains undetermined. However, caution needs to be exercised prior to extrapolating findings from a trial conducted in the coronary circulation and requires validation in the intracranial circulation.

The need for developing new and effective treatments for patients with symptomatic intracranial stenosis cannot be undermined. It is likely that intracranial angioplasty and/or stent placement will continue to be offered at most institutions in some limited capacity [16]. The medical community would have to decide whether enough justification exists to consider evaluation of primary angioplasty as a treatment modality for symptomatic patients with intracranial stenosis. Our results support either a phase II randomized trial between primary angioplasty and stent placement or a phase II single arm futility study to accrue appropriate data prior to proceeding to a larger scale [17]. Such data will also allow assessment of the learning curve for operators, identification of clinical and angiographic prognostic factors, ascertainment of device performances within various strata based on angiographic features, and optimal antithrombotic regimen in the peri-procedural period [18].

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