

## Original Investigation

# Effect of a Balloon-Expandable Intracranial Stent vs Medical Therapy on Risk of Stroke in Patients With Symptomatic Intracranial Stenosis

## The VISSIT Randomized Clinical Trial

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**IMPORTANCE** Intracranial stenosis is one of the most common etiologies of stroke. To our knowledge, no randomized clinical trials have compared balloon-expandable stent treatment with medical therapy in symptomatic intracranial arterial stenosis.

**OBJECTIVE** To evaluate the efficacy and safety of the balloon-expandable stent plus medical therapy vs medical therapy alone in patients with symptomatic intracranial stenosis ( $\geq 70\%$ ).

**DESIGN, SETTING, AND PATIENTS** VISSIT (the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) trial is an international, multicenter, 1:1 randomized, parallel group trial that enrolled patients from 27 sites (January 2009-June 2012) with last follow-up in May 2013.

**INTERVENTIONS** Patients (N = 112) were randomized to receive balloon-expandable stent plus medical therapy (stent group; n = 59) or medical therapy alone (medical group; n = 53).

**MAIN OUTCOMES AND MEASURES** Primary outcome measure: a composite of stroke in the same territory within 12 months of randomization or hard transient ischemic attack (TIA) in the same territory day 2 through month 12 postrandomization. A hard TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia lasting at least 10 minutes but resolving within 24 hours. Primary safety measure: a composite of any stroke, death, or intracranial hemorrhage within 30 days of randomization and any hard TIA between days 2 and 30 of randomization. Disability was measured with the modified Rankin Scale and general health status with the EuroQol-5D, both through month 12.

**RESULTS** Enrollment was halted by the sponsor after negative results from another trial prompted an early analysis of outcomes, which suggested futility after 112 patients of a planned sample size of 250 were enrolled. The 30-day primary safety end point occurred in more patients in the stent group (14/58; 24.1% [95% CI, 13.9%-37.2%]) vs the medical group (5/53; 9.4% [95% CI, 3.1%-20.7%]) ( $P = .05$ ). Intracranial hemorrhage within 30 days occurred in more patients in the stent group (5/58; 8.6% [95% CI, 2.9%-19.0%]) vs none in the medical group (95% CI, 0%-5.5%) ( $P = .06$ ). The 1-year primary outcome of stroke or hard TIA occurred in more patients in the stent group (21/58; 36.2% [95% CI, 24.0-49.9%]) vs the medical group (8/53; 15.1% [95% CI, 6.7-27.6%]) ( $P = .02$ ). Worsening of baseline disability score (modified Rankin Scale) occurred in more patients in the stent group (14/58; 24.1% [95% CI, 13.9%-37.2%]) vs the medical group (6/53; 11.3% [95% CI, 4.3%-23.0%]) ( $P = .09$ ). The EuroQol-5D showed no difference in any of the 5 dimensions between groups at 12-month follow-up.

**CONCLUSIONS AND RELEVANCE** Among patients with symptomatic intracranial arterial stenosis, the use of a balloon-expandable stent compared with medical therapy resulted in an increased 12-month risk of added stroke or TIA in the same territory, and increased 30-day risk of any stroke or TIA. These findings do not support the use of a balloon-expandable stent for patients with symptomatic intracranial arterial stenosis.

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Intracranial arterial stenosis is a common stroke etiology worldwide.<sup>1-6</sup> The recurrent stroke risk with severe symptomatic intracranial stenosis ( $\geq 70\%$ ) may be as high as 23% at 1 year, despite medical therapy.<sup>7,8</sup> Endovascular options are limited to balloon angioplasty only, self-expanding stent, balloon-expanding stent, or a combination of these therapies. The SAMMPRIS (Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis) trial showed that aggressive medical therapy alone was superior to percutaneous transluminal balloon angioplasty followed by stenting using the Wingspan self-expanding stent (Stryker) with an absolute difference of 8.9% at 30 days and 9.0% at 3 years in the primary outcome.<sup>9-11</sup> The 30-day event rates with medical therapy were nearly one-half of the reported event rates in the WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) trial and the balloon angioplasty with stenting results were nearly double the rates that were reported in prior stenting registries.<sup>7,8,12-14</sup>

In this trial (VISSIT [Vitesse Stent Ischemic Therapy]), which was initiated soon after the start of SAMMPRIS, we examined percutaneous transluminal balloon angioplasty with stenting in symptomatic intracranial stenosis, but differed in its design, sample size, and type of intracranial stent used.<sup>15</sup> The trial was a multicenter randomized study designed to evaluate the safety and effectiveness of the balloon-expandable stent in patients with cerebral or retinal ischemia attributed to intracranial stenosis. Following the release of the SAMMPRIS trial results, which reported worse-than-anticipated self-expanding stent outcome results and better-than-expected medical therapy results, the sponsor performed an unplanned analysis of the short-term outcome and stopped the trial early. Here, we report the final trial results.

## Methods

### Study Design and Objectives

Details of the trial design were published elsewhere.<sup>15</sup> A complete trial protocol with statistical analysis plan is published in *JAMA* online (in the Supplement). The trial was a randomized multicenter study with 27 participating sites (23 in the United States and 4 international sites [3 in China; 1 in Europe]).<sup>16</sup> The US Food and Drug Administration (FDA) issued an investigational device exemption to carry out the trial (G080051). Approval by each site's institutional review board or ethics committee was obtained. Written informed consent was obtained from the patient or his or her legally authorized representative. Race and ethnicity were self-reported.

### Patient Population

Patients considered for study inclusion were 18 to 85 years of age; and had symptomatic intracranial stenosis (70%-99%) involving the internal carotid, middle cerebral, intracranial vertebral, or basilar arteries with a hard transient ischemic attack (TIA) or stroke attributable to the territory of the target lesion within the past 30 days. A hard TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia that lasts for at least 10 minutes but resolves

within 24 hours. Specifically, the patient should present with focal weakness or language disturbance (other than isolated slurred speech), transient monocular blindness, or required assistance in walking. An intracranial tandem lesion with 50% to 99% stenosis was allowed.

Key exclusion criteria were the presence of a potential source of cardiac embolism, modified Rankin Scale (mRS) greater than 3, unstable neurological status (rapid worsening of the National Institute of Health Stroke Severity Scale [NIHSS] score increasing  $>4$  points within 48 hours prior to randomization), and concurrent intracranial pathology such as cerebral aneurysm, moyamoya disease, or biopsy-proven vasculitis.

### Randomization

All patients who satisfied the inclusion criteria and none of the exclusion criteria underwent a diagnostic cerebral angiogram prior to randomization and the percent stenosis was measured using the WASID criteria.<sup>17</sup> Patients meeting the clinical and angiographic criteria were randomly assigned 1:1 using a telephonic interactive voice response system (BioClinica, Inc) to either medical therapy alone (medical group) or medical therapy and neurovascular balloon-mounted stent (stent group). Randomization was stratified by enrollment site and age (18-55 years vs 56-85 years) in fixed blocks of 4. Medical group patients were discharged postrandomization or as clinically indicated. The stent group underwent the stenting procedure within 48 hours of randomization.

### Medical Therapy and Stenting Procedure

Medical therapy consisted of clopidogrel (75 mg daily) for the first 3 months after enrollment and aspirin (81-325 mg daily) for the study duration. Additionally, patients' individual medical risk factors were managed as appropriate, including statin (20-80 mg daily) to lower low-density lipoprotein cholesterol (LDL) levels to less than 100mg/dL and an antihypertensive regimen to control systolic blood pressure to 140 mm Hg or less. To qualify as a study neurointerventionalist, physicians must have placed an intracranial stent in at least 10 patients (for aneurysm or atherosclerosis) in the 12 months prior to site initiation.

### Follow-up

Patients underwent postprocedure clinical and neurological evaluation at 24 hours and on the day of discharge, including NIHSS to assess neurological deficit and mRS to assess neurological functional disability. Clinical assessment and evaluation of neurological symptoms was performed by a NIHSS-certified study investigator not involved in the procedure. Follow-up visits occurred at 30, 90, and 180 days and at 1 year.

### Primary End Points

The primary outcome end point was a composite of 2 outcomes: (1) any stroke in the same territory as the presenting event (distal to the target lesion) within 1 year of randomization; and (2) hard TIA in the same territory as the presenting event (distal to the target lesion) between 2 days and 1 year of randomization to avoid misinterpretation of postanesthesia

Table 1. Baseline Characteristics of the VISSIT Trial Patients

Characteristic	Medical Group (n = 53) <sup>a</sup>	Stent Group (n = 58) <sup>a</sup>
Age, mean (SD), y	61.8 (12.82)	61.8 (12.28)
Median (range), y	62.0 (30.0-84.0)	63.0 (36.0-82.0)
Male sex	32 (60.4)	41 (70.7)
Race or ethnicity		
White	38 (71.7)	42 (72.4)
Asian	7 (13.2)	7 (12.2)
Black or African American	5 (9.4)	4 (6.9)
Hispanic or Latino	2 (3.8)	5 (8.6)
Hypertension	43 (81.1)	49 (84.5)
Hyperlipidemia	32 (60.4)	29 (50.0)
Diabetes mellitus	20 (37.7)	25 (43.1)
Coronary artery disease	12 (22.6)	10 (17.2)
Peripheral vascular disease	5 (9.4)	2 (3.4)
Smoking history		
Current	12 (22.6)	11 (19.0)
Former	17 (32.1)	22 (37.9)
Never	24 (45.3)	25 (43.1)
Blood pressure, mean (SD), mm Hg		
Systolic	140.7 (17.36)	142.4 (20.33)
Diastolic	76.7 (13.02)	78.4 (10.91)
Cholesterol, mean (SD), mg/dL		
Low-density lipoprotein	98.4 (41.21)	100.6 (47.96)
High-density lipoprotein	41.0 (9.70)	40.4 (11.49)
BMI, mean (SD) <sup>b</sup>	28.8 (6.26)	28.9 (6.22)
Median (range) <sup>b</sup>	27.7 (18.1-53.6)	28.5 (19.4-56.1)
Overweight (25-29.9 BMI) <sup>b</sup>	27 (50.9)	23 (39.7)
Obese (≥30 BMI) <sup>b</sup>	15 (28.3)	18 (31.0)
Qualifying event		
Stroke	34 (64.2)	36 (62.1)
TIA	22 (41.5)	24 (41.4)
Arterial stenosis, mean (SD), %	80.4 (7.5)	78.9 (7.3)
Median (range), %	79.0 (70-98)	79.0 (57-97)
Time from qualifying event to randomization, d		
Mean (SD)	15.2 (10.34)	12.3 (9.64)
Median (range)	15.0 (0-42)	9 (0-41)
NIHSS score, mean (SD) [range] <sup>c</sup>	1.5 (1.6) [0-6]	1.9 (2.4) [0-11]
Median (IQR) <sup>c</sup>	1 (0-2)	1 (0-3)
mRS score of 3 <sup>d</sup>	4 (7.5)	7 (12.1)

Abbreviations: BMI, body mass index; IQR, interquartile range; mRS, Modified Rankin's Disability scale; NIHSS, National Institutes of Health Stroke Severity Scale; TIA, transient ischemic attack.

<sup>a</sup> Data are reported as No. (%) unless otherwise indicated.

<sup>b</sup> BMI was calculated as weight in kilograms divided by height in meters squared.

<sup>c</sup> NIHSS score is based on a 42-point scale (0 indicates normal-42 indicates coma or death).

<sup>d</sup> mRS score is based on a 7-point scale (0 indicates normal-6 indicates death).

neurological fluctuation as TIA. Primary end point success was achieved if neither of these outcomes occurred.

### Safety Outcome Measures

The primary safety outcome was a composite of stroke in any territory within 30 days of randomization, hard TIA in any territory between 2 and 30 days, all-cause mortality through 30 days postprocedure, and intracranial hemorrhage within 30 days of randomization.

### Data and Safety Monitoring Board

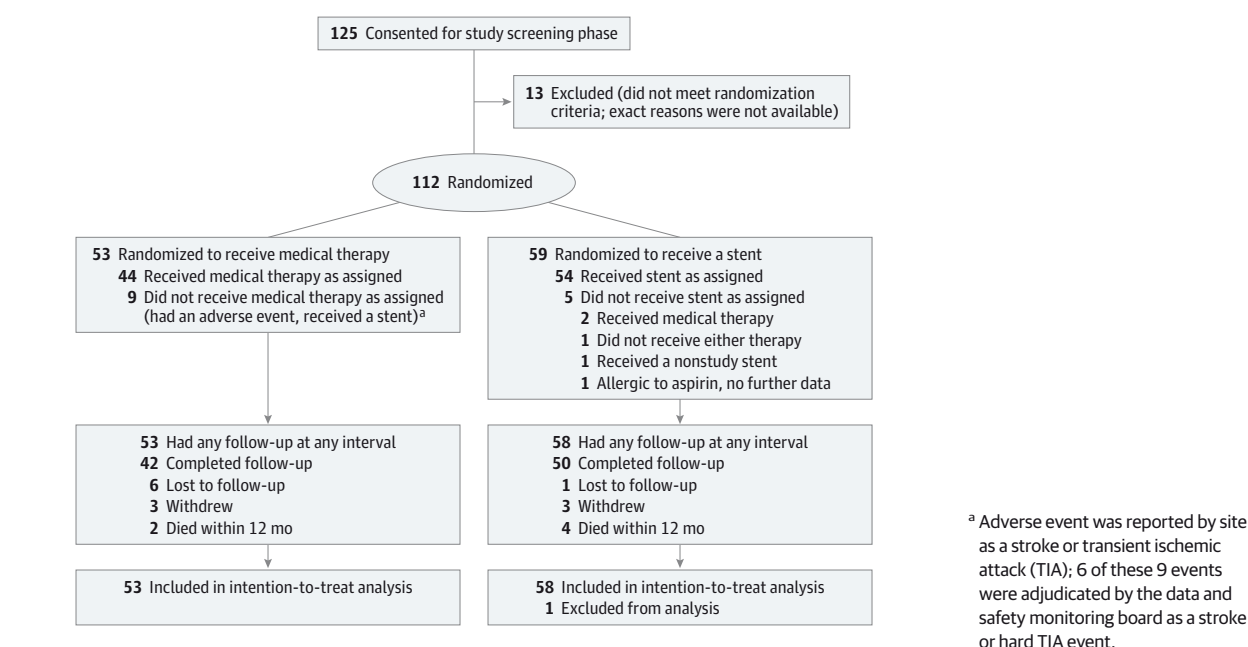
A data and safety monitoring board (DSMB) composed of a neurointensivist, a vascular neurologist, an interventional neuroradiologist, and a biostatistician not otherwise involved with

the study, was responsible for overseeing the safety and ethical conduct of the trial. The DSMB adjudicated all potential hard TIA, stroke, and death outcome events. The DSMB met 4 times to review events (February 24, 2010; February 10, 2011; August 1, 2012; and August 31, 2013).

### Statistical Analyses

Baseline demographic characteristics were presented for both groups (Table 1) using proportions for binary variables and means, standard deviation, and median with range for continuous variables. Primary end point success rates (no stroke in the same territory within 12 months or hard TIA in the same territory between 2 days and 12 months) were estimated at 12 months and corresponding 95% CIs for these success rates were

Figure 1. Design of the VISSIT Trial and Flow of Participants



estimated by Kaplan-Meier survival analysis and compared across treatment groups using the log-rank test. All clinical outcomes were compared using the intent-to-treat population. When comparing clinical outcomes, missing data were assumed to occur at random and patients with missing data were excluded from the analysis. Statistical analysis was performed with SAS version 9.3 (SAS Institute Inc). All *P* values for statistical testing were 2-sided and *P* values of less than .05 were deemed to be statistically significant. Fisher exact test *P* values were used for comparing proportions, and *t* test *P* values were used for comparing means.

### Sample Size Estimation and Conditional Power Analysis

At the start of the trial, statistical power to demonstrate a superior primary end point success rate (ie, no stroke or hard TIA) for the stent group vs the medical group was anticipated to be approximately 90% with a total sample size of 172 patients and 2-sided  $\alpha = .05$  based on anticipated success rates of 89% and 69% in the stent group and medical group, respectively. Allowing for a combined 30% crossover, stent failure, withdrawal, and loss to follow-up rate, as many as 250 participants were to be enrolled.

Given the study's actual results at early termination with 111 patients enrolled, a conditional power analysis of a null study result if the enrollment had been completed is presented at the end of the Results section.

## Results

Upon consideration of the poor outcome associated with stenting in the SAMMPRIS trial, an early unplanned analysis was performed by the sponsor, and trial enrollment was then terminated

due to the low likelihood of detecting superiority of stenting over medical therapy with the current trial design.<sup>10,11</sup>

Final results in this article represent all data received during enrollment (February 2009 to June 2012) and follow-up (through May 2013), as well as adjudication data from the final DSMB meeting in August 2013. The study database was locked on September 27, 2013.

### Patients

A total of 27 sites (23 in the United States and 4 international sites [3 in China; 1 in Europe]) received internal review board/ethics committee approval; and 20 sites enrolled at least one patient. Of the 125 patients who consented to trial participation, 112 were randomized (59 in the stent group, 53 in the medical group). One patient randomized to the stent group was subsequently found to meet an exclusion criterion (allergic to aspirin) before stent placement; this patient did not receive a stent, no further data was provided, and the patient was therefore excluded (Figure 1). A total of 111 randomized patients who met all inclusion criteria and no exclusion criteria were included in the intent-to-treat (ITT) population (53 were randomized to the medical group and 58 to the stent group). Of those patients randomized to the stent group, 54 had the trial stent placed at the target lesion per protocol and 2 received medical therapy only without stent placement. Of those randomized to the medical group, 44 received treatment per protocol and 9 received the trial stent during the study after an adverse event (stroke or TIA) was reported by the site (6/9 were adjudicated by the DSMB as a stroke or hard TIA event).

The 2 groups were balanced with respect to baseline characteristics and medical comorbidities (Table 1). The mean age was 61.8 years in both groups. The most common risk factors were hypertension in more than 80% of patients in both groups,

Table 2. 30-Day and 1-Year Primary, Secondary, and Safety End Points in the Intent-To-Treat Population

	Proportion, (%) [95% CI]		Difference (95% CI) <sup>a</sup>	P Value
Outcome	Medical Group (n = 53)	Stent Group (n = 58)		
Safety outcomes within 30 d				
Any stroke within 30 d or hard TIA between 2 d and 30 d of randomization	5/53 (9.4) [3.1-20.7]	14/58 (24.1) [13.9-37.2]	14.7 (1.2-28.2)	.05
Any ischemic stroke within 30 d postrandomization	3/53 (5.7) [1.2-15.7]	10/58 (17.2) [8.6-29.4] <sup>b</sup>	11.6 (0-23.1)	.08
Any hard TIA from day 2 through day 30 postrandomization	2/53 (3.8) [0.5-13.0]	0/58 (0) [0-5.0]	-3.8 (-8.9 to 1.4)	.23
Intracranial hemorrhage within 30 d of randomization	0/53 (0) [0-5.5]	5/58 (8.6) [2.9-19.0] <sup>b</sup>	8.6 (1.4-15.8)	.06
Primary effectiveness end points				
Stroke in the same territory (distal to the target lesion) within 1 y or hard TIA in the same territory between 2 d and 1 y of randomization	8/53 (15.1) [6.7-27.6]	21/58 (36.2) [24.0-49.9]	21.1 (5.4-36.8)	.02
Stroke in the same territory within 1 y of randomization	5/53 (9.4) [3.1-20.7]	20/58 (34.5) [22.5-48.1]	25.1 (10.5-39.6)	.003
Hard TIA between 2 d and 1 y of randomization	3/53 (5.7) [1.2-15.7]	1/58 (1.7) [0-9.2]	-3.9 (-11.0 to 3.1)	.35
Secondary end points at 12 mo <sup>c</sup>				
Disabling stroke at 1 y (mRS>3)	3/42 (7.1) [1.5-19.5]	7/50 (14.0) [5.8-26.7]	6.9 (-5.5 to 19.2)	.34
NIHSS at 12 mo, No.	41	48		
Mean (SD)	0.46 (0.90)	1.35 (2.02)		.02
Median (IQR) [range]	0 (0-1) [0-4]	0.5 (0-2) [0-10]	0.89 (0.21-1.57)	
NIHSS worse by 4 points, baseline-12 mo	0/53 (0) [0-5.5]	3/58 (5.2) [1.1-14.4]	5.2 (-0.5 to 10.9)	.25
mRS worse, baseline-12 mo	6/53 (11.3) [4.3-23.0]	14/58 (24.1) [13.9-37.2]	12.8 (-1.1 to 26.7)	.09
Stent placement success (across target lesion, 0%-20% residual stenosis)		27/50 (54.0) [39.3-68.2]		
Restenosis				
≥50% <sup>d</sup>		9/34 (26.5) [12.9-44.4]		
≥70% <sup>d</sup>		1/34 (2.9) [0.1-15.3]		
Other safety end points				
Death from any cause within 30 d of randomization	0/53 (0) [0-5.5]	3/58 (5.2) [1.1-14.4]	5.2 (-0.5 to 10.9)	.25

Abbreviations: IQR, interquartile range; ITT, intent-to-treat; mRS, Modified Rankin's Disability scale; NIHSS, National Institutes of Health Stroke Severity scale; TIA, transient ischemic attack.

<sup>a</sup> Some data may not sum because of rounding.

<sup>b</sup> One patient in the stent group experienced both an intracranial hemorrhage within 30 days of randomization and an ischemic stroke within 30 days postrandomization.

<sup>c</sup> Denominators for some secondary end points may be less than the number of intention-to-treat patients because only patients with follow-up data were analyzed; missing data are treated as missing at random.

<sup>d</sup> Degree of restenosis was assessed by angiogram. There were 34 out of 58 patients in the stent group who had a 12-month core laboratory assessment.

hyperlipidemia, overweight, and diabetes. The mean degree of stenosis was 80.4% in the medical group and 78.9% in the stent group. The majority of patients in both groups presented with a stroke (64.2% in the medical group and 62.1% in the stent group), with a mean time of 15.2 and 12.3 days from the qualifying event to randomization in the medical and stent groups, respectively.

## Primary Outcome

### 1-Year Outcome

In total, there were 29 patients in the ITT population with a stroke in the same territory within 12 months of randomization or a hard TIA in the same territory between day 2 and 1 year. Among these 29 patients with a primary outcome event (stroke or hard TIA) at the end of the 1-year follow up period, 8 patients (15.1%) were in the medical group and 21 patients

(36.2%) were in the stent group (risk difference, 21.1% [95% CI, 5.4%-36.8%];  $P = .02$ ) (Table 2).

The Kaplan-Meier estimate of event-free survival at 12 months in the ITT population was 83.7% (95% CI, 69.9%-91.5%) in the medical group vs 62.2% (95% CI, 48.2%-73.5%) in the stent group, (log-rank test  $P$  value = .01) (Figure 2). In this analysis, 33 patients in the stent group and 36 in the medical group remained at risk at the beginning of the 12-month follow-up window (10.5 months, prior to which time all primary end point stroke or hard TIA events had occurred).

## Secondary and Safety Outcomes

### Thirty Day Outcome

In the ITT analysis, the 30-day safety end point of any stroke within 30 days or hard TIA within 2 to 30 days was 9.4% (5/53) in the medical group and 24.1% (14/58) in the stent group (risk



difference, 14.7%; [95% CI, 1.2%-28.2%]  $P = .05$ ) (Table 2). Hard TIA occurred in 2 patients (3.8%) in the medical group compared with none in the stent group, (risk difference, -3.8%; [95% CI, -8.9% to 1.4%]  $P = .23$ ). Ischemic stroke was observed in 3 patients (5.7%) in the medical group and in 10 patients (17.2%) in the stent group (risk difference, 11.6%; [95% CI, 0%-23.1%]  $P = .08$ ). Intracranial hemorrhage occurred in 5 patients (8.6%) in the stent group and in 0 in the medical group ( $P = .06$ ). One patient in the stent group experienced both an intracranial hemorrhage and a subsequent ischemic stroke and was included in these data.

### Mortality

The 30-day all-cause mortality was 3 of 58 patients (5.2%) in the stent group and 0 in the medical group (risk difference, 5.2%; [95% CI, -0.5% to 10.9%]  $P = .25$ ). The 3 deaths were related to hemorrhagic stroke in 2 patients (both 1 day after the stent procedure) and to ischemic stroke in 1 patient (within 20 days of randomization). One additional death occurred in the stent group after 30 days, related to suicide in a patient with a known history of depression. Two deaths occurred in the medical group related to malignancy at 2 and 11 months postrandomization.

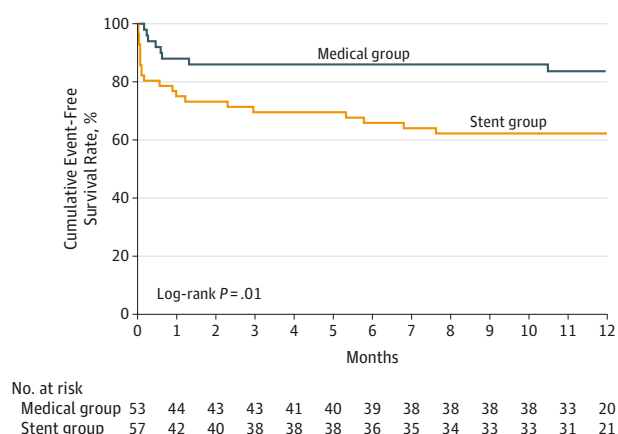
### Secondary Outcomes

Disabling stroke (mRS >3) at 12 months occurred in 3 of 42 patients (7.1%) in the medical group vs 7 of 50 (14.0%) in the stent group ( $P = .34$ ). There were no significant differences in the results of NIHSS, mRS, or EuroQol-5D follow-up assessments at 12 months between the groups. In 12 of 58 patients (20.7%) in the stent group, stent placement across the lesion was deemed unsuccessful for 1 or more of the following reasons: the stent could not be placed due to vessel tortuosity, misplacement across the target stenotic lesion, or arterial injury during placement of the supportive system. Successful placement of the stent across the lesion with residual 0% to 20% stenosis poststenting was achieved in 54% (Table 2). Restenosis of at least 50% and at least 70% was seen in 9 of 34 patients (26.5%) and in 1 of 34 patients (2.9%), respectively.

### Conditional Power Posthoc Analysis Results

At the start of the trial, statistical power to demonstrate a superior primary end point success rate for the stent group vs the medical group was anticipated to be approximately 90% with a total sample size of  $N = 172$  patients and a 2-sided 5%  $\alpha$  based on anticipated success rates (ie, no stroke or hard TIA) of 89% and 69% in the stent vs medical groups, respectively. Since the current study results suggest harm (ie, stroke or hard TIA occurred in 36.2% for the stent group vs 15.1% for the medical group; see Table 2), a posthoc conditional power analysis was conducted to determine the likelihood of a positive trial if the trial had continued to full enrollment. Three scenarios were modeled in this conditional power analysis: (1) further patients would have followed the original study assumptions; (2) further patients would have had a null treatment effect; and (3) further patients would have continued the trend of current study results. With a full enrollment sample size of  $N = 172$ , this conditional power analysis demonstrated that the likeli-

Figure 2. Kaplan-Meier Estimate of Event-Free Survival Rates in Treatment Groups Intent-to-Treat Population



Log-rank test was used to test the hypothesis that event-free survival rates (primary end point) between groups were the same.

hood of a successful trial (ie, that stent placement reduced the risk of stroke or TIA compared with medical treatment) was less than 1% in any of these scenarios, and moreover that the likelihood of a null finding was approximately 94% for the first scenario (of following the original trial assumption), 38% for the second scenario (of further patients having a null treatment effect), and 2% for the third scenario (of continuing the same trend as the current trial results).

## Discussion

To our knowledge, this is the first randomized, multicenter, prospective, balloon-mounted stent trial for symptomatic intracranial stenosis. Although differing in its design and the type of stent used, this study yielded similar results to the SAMMPRIS trial, which investigated the self-expanding stent study.<sup>10,11</sup> In the current trial, worse outcome was shown with the balloon-expanding stent than medical therapy in symptomatic intracranial arterial stenosis.

The present trial demonstrated a higher than expected rate of periprocedural events in the stent group, 24.1% within 30 days and 36.2% at 1-year follow-up vs 9.4% and 15.1% in the medical group, with an absolute difference of 14.7% and 21.1%, respectively. The higher than expected event rates observed in the stent group may, in part, be related to the preliminary data and assumptions that drove both the study design and statistical power calculation, which was based on extrapolation from carotid stenting and endarterectomy data.<sup>15,18,19</sup> Using these data, the 1-year risk of primary composite outcome was estimated to be 11% in the stent group vs 31% in the medical group. The preliminary postmarketing retrospective stent registries and WASID trial medical therapy data that drove the self-expanding stent trial design were also optimistic.<sup>7,8,12-14</sup> Both the United States<sup>12</sup> and the National Institutes of Health Multicenter Self-Expanding Stent Registries,<sup>13</sup> demonstrated

acceptable event rates (6.1% and 9.6%, respectively). These results led to power and sample size calculation in the previously published self-expanding stent trial; however, the actual results were much different.<sup>10,11</sup>

Furthermore, these assumptions were also based on promising results from the previously published balloon-mounted stenting studies. In the SSYLIVIA trial, the 1-year stroke rate was 14% vs the 34.5% in the current trial, with technical success rate of 95% vs 79% in our trial. However, the SSYLIVIA balloon-mounted stent nonrandomized study was a study of 61 consecutive patients with a milder degree of stenosis, it used a different stent design, and the majority of the lesions were in the extracranial vasculature.<sup>20</sup> In the ASSIST balloon-mounted symptomatic intracranial stenosis study, 48 lesions were treated, it had a deployment success rate of 91.7%, and a cumulative probability of stroke and death within 30 days of 11.0%.<sup>21</sup> A retrospective study using a similar stent to the one used in our trial examined 92 patients with symptomatic intracranial stenosis and showed deployment success rate of 98.9%, with a 30-day event rate of 6.5% (95% CI, 3.7% to 13.5%) consisting of 3 periprocedural events, 3 strokes, and 1 fatal hemorrhage.<sup>22</sup> However, despite encouraging results from these studies, they are not comparable to this trial. These studies had a different study design, population, and stent type. Moreover, the majority were based on self-reported data and lack independent raters or event adjudicator.<sup>23,24</sup>

Several factors may have contributed to the higher event rates observed in the stenting group vs the medical group in the trial. Operator experience assumptions were optimistic, and may have contributed to the higher event rates.<sup>25,26</sup> Equating stenting for the purpose of cerebral aneurysm coiling to stenting for purpose of intracranial stenosis may have not been the best parameter to assure adequate operator experience, but we do not have enough sample size to ascertain its contribution to the worse outcome.

Moreover, the high stenting event rate may have been related to the current device's technical limitation, given the inherent first-generation device's design imperfections, which requires future iterations to enhance the safety and success of newer stent technology.

Furthermore, periprocedural factors should be evaluated such as timing of the stenting, best anesthesia choice, as well as best blood pressure management following luminal reconstruction.

In addition to the operator, technical, and periprocedure factors that may have led to this outcome, medical therapy demonstrated better outcome than predicted. The 30-day and 1-year stroke rates were 5.7% and 5.8%, and 9.4% and 12.6% in the current trial and self-expanding stenting trial, respectively. One potential explanation was the implementation of a lifestyle coach and strict control of risk factors in the self-expanding stent trial.<sup>27,28</sup> The present trial did not have lifestyle coach, and no available data on the trend of risk factor control over time; however, the baseline data showed blood pressure and lipid profile within the recommended targets (Table 1). Both trials implemented short-term dual antiplatelet therapy, which has been shown to be effective in reducing the recurrent stroke rate.<sup>29,30</sup>

## Limitations

The current trial was not double-blinded due to the lack of feasibility of masking the stent group; however, end point assessment by an independent neurologist who was not involved in the procedure reduced potential bias. A clinical committee was not appointed in the trial to ensure that patients met all clinical and angiographic criteria to avoid potential vague and non-specific neurological symptoms or cases with angiographic complexity. However, this is not the standard in interventional trials, but may be considered in future trials. Operator experience in the more challenging balloon-mounted stents requires a more rigorous credentialing process given the current trial results vs any intracranial stenting experience. The trial did not include patients with intracranial stenosis refractory to medical therapy as required by the current US Food and Drug Administration (FDA) criteria.<sup>31</sup> However, when the trial was initiated, the data were supportive of randomizing patients for secondary prevention of symptomatic intracranial stenosis. Similarly, patients were not selected based on the presence of hemodynamic symptomatology.<sup>32</sup> Patients with atypical intracranial stenosis etiologies may have been enrolled despite the exclusion criteria due to the lack of confirmatory diagnostic tests such as brain biopsy. Additionally, patients with perforator stroke as an index event were not excluded and these patients may have an increased stroke risk with stenting.<sup>33</sup>

Although the results of this trial will further reduce the enthusiasm for symptomatic intracranial stenosis stenting,<sup>34</sup> potential next steps would be to identify a high-risk medical therapy subgroup. For example, patients with documented infarction in the territory while on antithrombotic therapy (35% risk of stroke and death at 2 years), vulnerable plaque, and poor collateral reserve may all have a high risk for stroke recurrence, and would be considered as a high-risk population for recurrent strokes.<sup>35,36</sup> Lower procedural risk was found with younger age and when stenting was performed after 7 days, which may guide age and procedure timing selection criteria.<sup>11</sup> The FDA has currently limited the indication of the self-expanding stent use to patients younger than 80 years, and refractory to medical therapy with 2 strokes while receiving medical therapy and 7 days following the qualifying event.<sup>37</sup>

Balloon angioplasty may be a potential target for future symptomatic intracranial stenosis prospective studies for high risk subgroups that were not enrolled in these trials; however, this approach is complex with an unknown real rate of restenosis and frequency of bailout stenting or rescue therapy.<sup>38</sup>

## Conclusions

Among patients with symptomatic intracranial arterial stenosis, the use of a balloon-expandable stent compared with medical therapy resulted in an increased 12-month risk of added stroke or TIA in the same territory, and increased 30-day risk of any stroke or TIA. These findings do not support the use of a balloon-expandable stent for patients with intracranial arterial stenosis.

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