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Peri-procedural Stroke or Death in Stenting of Symptomatic Severe Intracranial Stenosis

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Abstract

Background and Purpose—There is limited data on predictors of 30-day stroke or death in patients with symptomatic intracranial atherosclerosis (sICAS) undergoing stenting. We aim to determine factors associated with stroke or death at 30 days in the stenting arm of the SAMMPRIS trial.

Methods—This is a post-hoc analysis SAMMPRIS including patients who underwent angioplasty/stenting. We compared patient specific variables, lesion specific variables, procedure specific variables, and FDA approved indications between patients with and without the primary outcome (stroke or death at 30 days). We performed logistic regression analyses to evaluate associations with the primary outcome.

Results—We identified 213 patients; 30 patients (14.1%) met the primary outcome. Smoking status and lesion length were associated with the primary outcome; the odds of stroke or death for non-smokers vs. smokers (adjusted OR 4.46, 95% CI 1.79–11.1, p = 0.001) and with increasing lesion length in millimeters (adjusted OR 1.20, 95% CI 1.02–1.39, p = 0.029). These had modest predictive value: absence of smoking history (sensitivity = 66.7% and specificity = 65.4%) and lesion length (Area Under Curve = 0.606). Furthermore, event rates were not significantly different between patients with and without the FDA approved indication for stenting (15.9% vs. 12%, p = 0.437).

Conclusion—In SAMMPRIS patients who underwent angioplasty/stenting, neither clinical and neuroimaging variables nor the FDA indication for stenting reliably predicted the primary outcome. Further work in identifying reliable biomarkers of stroke/death in patients with sICAS is needed before considering new clinical trials of stenting.

Keywords

Intracranial stenosis; intracranial atherosclerosis; stent; angioplasty; outcome

Introduction

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial demonstrated the superiority of aggressive medical treatment over stenting in patients with severe (≥ 70%) symptomatic intracranial stenosis (sICAS).[1, 2] The United States Food and Drug Administration (FDA) recently issued a statement advising against the use of the Wingspan stent unless the following conditions were met: 1) patient age 22–80 years, 2) baseline modified Rankin Scale (mRS) 3 or less, 3) 70% or more intracranial stenosis of the affected artery, 4) two or more strokes in the territory of the affected artery despite optimal medical treatment, and 5) stenting to be performed 7 days or more from the most recent ischemic stroke. The Wingspan Stent System Post Market Surveillance (WEAVE) study demonstrated improved safety of

intracranial stenting with a peri-procedural event rate of stroke or death of 2.6% when stenting was performed using the FDA approved indication and by experienced operators.[3]

While predictors of ischemic and hemorrhagic stroke in patients with sICAS undergoing stenting in SAMMPRIS have been previously described,[4] predictors of the combined outcome of stroke or death at 30 days in SAMMPRIS patients who underwent stenting have not been determined. In this study, we aim to determine factors associated with stroke or death at 30 days in the stenting arm of the SAMMPRIS trial and to compare 30-day outcomes between SAMMPRIS patients undergoing stenting who met the FDA approved indication versus those who did not.

Methods

Study population

This is a post-hoc analysis of the SAMMPRIS trial approved by the NINDS using publicly available SAMMPRIS trial data and was also approved by the Institution Review Board of Rhode Island Hospital. As per the SAMMPRIS protocol, patients with severe sICAS were randomized to aggressive medical treatment versus stenting. The primary endpoint in SAMMPRIS was stroke or death within 30 days from enrollment or revascularization and stroke within the territory of the symptomatic artery beyond 30 days. In this study, we included patients randomized to the stenting arm of SAMMPRIS (n = 224) who underwent angioplasty with or without stenting (n = 213).[4]

Study variables

Study variables were drawn from the publicly available SAMMPRIS dataset and included:

1. Patient specific variables:
    a. Baseline demographics: age, sex, race, and ethnicity.
    b. Vascular risk factors: history of hypertension (known history of hypertension or on any treatment for hypertension), history of diabetes (known history of diabetes or on any treatment for diabetes), history of lipid disorder (known history of lipid disorder or on any treatment for lipid disorder), body mass index (weight/height^2), smoking history (active or ex-smoker vs. non-smoker), physical activity in target range (moderate/severe activity vs. less than moderate activity), infection in the last 30 days (defined as any infection treated with antibiotics in the last 30 days), history of coronary artery disease (defined as coronary artery disease, myocardial infarction, angina, and coronary artery bypass surgery), history of congestive heart failure, history of peripheral vascular disease (defined as previously treated for peripheral vascular disease), and history of ischemic stroke (not qualifying event)
    c. Medications: aspirin at time of event, clopidogrel at time of event, statin within 7 days of enrollment

d. Clinical variables: National Institute of Health Stroke Scale (NIHSS) score at enrollment, systolic blood pressure at enrollment, diastolic blood pressure at enrollment, stroke as qualifying event (versus transient ischemic attack) and time from qualifying event to enrollment.

e. Laboratory variables: Baseline glucose level (mg/dL), baseline total serum cholesterol level (mg/dL), baseline serum low-density lipoprotein level (mg/dL), baseline serum high density lipoprotein level (mg/dL), and baseline glycosylated hemoglobin level.

f. Radiological variables: acute or subacute infarcts on brain imaging (brain computed tomography or magnetic resonance imaging)

2. Lesion specific variables: symptomatic artery (internal carotid, middle cerebral artery, vertebral artery, or basilar artery), symptomatic artery side (left versus right), symptomatic artery involving a perforator segment (post cavernous internal carotid artery, middle cerebral artery where the lenticulostriate perforators arise, vertebral artery at or after the posterior inferior cerebellar artery branch, and middle or distal segment of the basilar artery[5]), degree of stenosis by central adjudication at baseline, length of lesion (mm), and diameter of lesion (mm).

3. Procedure specific variables: type of anesthesia (general anesthesia versus conscious sedation), time from enrollment to stent (days), time from event to stent (days), stent diameter (mm), stent length (mm), balloon diameter (mm), balloon length (mm), first inflation pressure (atmosphere), last inflation pressure (atmosphere), number of stents, number of balloons, number of inflations, percent stenosis after procedure by central adjudication, activated clotting time within target (vs. out of target), and duration of procedure.

4. FDA indication: age 22–80 years, baseline mRS 3 or less, 70–99% stenosis (vs. < 70% or 100%), and time from last stroke to procedure of 7 days or less. We combined all available components of the indication, but could not account for patients with 2 or more strokes on optimal medical treatment because this variable could not be accurately captured using the SAMMPRIS publicly available data.

Study outcomes

The primary outcome of this study was stroke or death at 30 days. The stroke outcome was the composite of ischemic stroke (defined as a new focal neurological deficit lasting for 24 hours or more without evidence of hemorrhage on brain imaging) and hemorrhagic stroke (defined as any hemorrhage on brain imaging associated with new focal neurological symptoms lasting for 24 hours or more or seizure).

Analytical plan

Patients were stratified by the primary outcome. We compared patient specific variables, lesion specific variables, procedure specific variables, and the FDA approved indication between the two groups (with/without primary outcome)using Fisher’s exact test for

categorical variables and Student's t-test or non-parametric tests for continuous variables. We built multivariable logistic regression models that included factors associated with primary outcome on univariate analyses ($p<0.1$) to determine predictors. Analysis was done using SPSS version 25.0, and $p<0.05$ was considered statistically significant.

Results

Baseline characteristics and univariate analyses

Out of 213 patients who underwent angioplasty/stenting, stroke or death at 30 days occurred in 30 patients (14.1). The mean age in years was 61.0 ± 10.7, and 41.8% were women. The primary outcome included 20 ischemic strokes, 10 hemorrhagic strokes, and 4 deaths. All deaths occurred in patients with hemorrhagic stroke. The NIHSS at the time of the events was available in 28/30 patients and the median was 5 and interquartile range was 8.

In univariate analyses (Fisher's exact test and t-tests), factors associated with primary outcome were older age (64.7 ± 9.4 vs. 60.4 ± 10.8, p = 0.042), history of diabetes (60% vs. 39.3%, p = 0.045), absence of smoking history (65.4% vs. 33.3%, p = 0.001), history of congestive heart failure (10.0% vs. 1.1%, p = 0.021), history of stroke (46.7% vs. 24.0%, p = 0.014), and lesion length in mm (8.2 ± 3.3 vs. 7.0 ± 2.8, p = 0.036). Other variables, including the FDA approved indication, did not achieve statistical significance (Table 1).

Multivariable models

In multivariable logistic regression analysis including variables with $p<0.1$ on univariate analyses above, predictors of the primary outcome were smoking status (adjusted OR for nonsmokers 4.46, 95% CI 1.79–11.1, p = 0.001) and lesion length in mm (adjusted OR 1.20, 95% CI 1.02–1.39, p = 0.029) (Table 2). These predictors however, had only modest predictive value: non-smoking (sensitivity = 66.7% and specificity = 65.4%) and lesion length (Area Under Curve = 0.606).

Primary and secondary outcome vs. FDA approved indications

The FDA approved indication for stenting and its individual components, apart from the missing variable of having had two or more strokes on optimal medical treatment, were not significantly associated with the primary outcome, which was seen in 15.9% of patients with an FDA approved indication and 12.0% of patients without the approved indication (p = 0.437) (Table 3).

Discussion

In this post hoc-analysis of the SAMMPRIS trial, predictors of peri-procedural outcome were smoking status and length of the atherosclerotic lesion. These predictors had only modest predictive ability and, therefore, may not be useful in clinical practice. The FDA approved indication for stenting was also not associated with peri-procedural outcome. Further study of predictive factors during the treatment of sICAS is warranted to to better triage patients in future research and clinical care.

Mechanisms of Associations

The association between lesion length and peri-procedural complications is controversial. While some studies have shown an association between lesion characteristics and peri-procedural complication rates, other studies have failed to show such an association.[6] For instance, one study that included patients with sICAS treated with balloon angioplasty showed a significantly higher rate of events in patients with tubular and extremely angulated lesions more than 10 mm in length (Type C) as compared to other lesion types (Types A or B).[7] Other more recent studies, using intracranial stents as the primary treatment, did not find a significant association between longer lesion length and peri-procedural complication risk.[8–10] A previous post-hoc analysis of SAMMPRIS showed no significant associations between lesion length and either the hemorrhagic or the ischemic outcome in patients undergoing angioplasty with or without stenting.[4] In our study, the discriminative ability of lesion length was modest (AUC = 0.606) suggesting that it has limited ability in identifying patients who are likely to be harmed by stenting.

Furthermore, our study showed a lower event rate in current smokers and ex-smokers as compared to non-smokers. The “smoking paradox” has been demonstrated in patients undergoing cardiac stents, who had lower early mortality.[11] In addition, another study showed that smokers tend to have more platelet inhibition in response to clopidogrel than non-smokers.[12] A meta-analysis, however, showed no effect of smoking on major cardiovascular events but an increased risk of major cardiovascular and cerebrovascular events in smokers (vs. non-smokers) undergoing coronary stenting (OR: 2.09, 95% CI: 1.43–3.06).[13] In stroke patients, studies have shown that smokers had lower in-hospital mortality[14] and were more likely to achieve recanalization and reperfusion with thrombolytic therapy.[15] A post-hoc analysis of SAMMPRIS showed an association between non-smoking and increased risk of ischemic events in patients undergoing stenting (hazard ratio 8.8, 95% confidence interval 2.5 – 31.8).[4] Most of these studies, including ours, have several major limitations including small sample size and/or the possibility of bias because smokers are usually younger with fewer atherosclerotic risk factors and less atherosclerotic disease burden. In fact, there is evidence to suggest that the smoking paradox disappears after controlling for potential confounders.[16] In our study, the effect size of non-smoking was relatively large (OR = 4.46) but the predictive ability of non-smoking is limited as it has fair modest (66.7%) and specificity (65.4%) arguing that smoking history should not be used to select patients for stenting. More importantly, robust and consistent epidemiological data links smoking with long-term morbidity and mortality.[17, 18]

We found no significant difference in peri-procedural complications between patients meeting the FDA approved indication versus those who did not, suggesting that this indication may not be associated with a lower risk of peri-procedural complications. While we could not account for having two strokes on optimal medical treatment (one of the components of the FDA approved indication), there is no obvious reason to suspect that patients who fail medical treatment have lower peri-procedural complication rates with stenting as compared to those who respond to optimal medical treatment.

Clinical implications

In this study, we used data from the SAMMPRIS trial to show that baseline clinical and imaging factors associated with peri-procedural events may have limited value for predicting the risk of 30-day stroke or death. Accurately identifying patients to exclude from stenting based on baseline clinical and imaging factors is complex and our data suggests that it requires additional study. The identification of patients who are likely to fail medical treatment is an important goal because they should be targeted for enrollment in future trials of sICAS angioplasty/stenting.[19]

Mechanisms of stroke in patients with sICAS include distal embolization, perforator disease, or impaired distal perfusion.[20] While medical treatment may be effective in stabilizing atherosclerotic plaque and reducing the risk of distal embolization or perforator disease, it has been suggested that it is unlikely for this treatment to acutely improve distal blood flow.[19, 21, 22] Therefore, patients with sICAS and impaired distal perfusion may be a subgroup of patients who are likely to have neurological deterioration or recurrent stroke despite optimal medical treatment. This has been shown in the Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERITAS) study, where patients with symptomatic vertebrobasilar disease and impaired distal flow had significantly higher event rates with medical treatment than those with normal distal flow (probability at 2 years: 30% vs. 13%; hazard ratio 11.55, 95% confidence interval 1.88–71.00, $p = 0.008$).[23] Furthermore, a post-hoc analysis of SAMMPRIS showed a higher risk of events in patients with anterior circulation borderzone infarcts (a pattern associated with hypoperfusion)[24, 25] when compared to perforator or core infarcts.[26] In addition, a small single center study showed an increased risk of recurrent cerebrovascular events in patients with anterior circulation stenosis and impaired distal perfusion with tissue at risk defined as time to maximum (Tmax) more than 6 seconds vs. less than seconds (50% vs. 13%, p = 0.05).[27] This study, however, has major limitations including its retrospective nature, the possibility of selection bias, and a small sample size. Thus, the optimal definition of impaired distal perfusion in patients with sICAS in the anterior circulation remains controversial and requires further validation.[28] Patients with sICAS and impaired distal perfusion may be a group who are likely to fail medical treatment and whose event rate on medical treatment may be higher than the peri-procedural complication rates of angioplasty/stenting. This may constitute a group where the benefit of stenting may outweigh the inherent risk. In fact, a post-hoc analysis of the SAMMPRIS trial showed that patients with borderzone infarcts had fewer events with stenting (n = 55 with borderzone infarcts) compared to medical treatment (n = 53 with borderzone infarcts) (18.2% vs. 26.4%, p = 0.2) but this finding did not achieve statistical significance.[26]

Strengths and Limitations

This study has several major limitations including the relatively small number of events, which may not have provided sufficient power to detect associations. In addition, since this is a post-hoc analysis, the findings should be interpreted with caution due to the potential for bias. For instance, the time from randomization to stenting, although similar between the two groups, may have been subject to bias. Furthermore, it is possible that the event rates in SAMMPRIS do not reflect current event rates with stenting due to increased operator

experience with stenting in general.[3] In fact, the 30-day complication rates in WEAVE were much lower than in SAMMPRIS.[3] It is very difficult to draw conclusions on the reasons for this, however. While operator experience has been suggested, in the SAMMPRIS trial, there were no significant differences in event rates among operators with varying degrees of experience with the wingspan system.[29] Another important challenge in comparing complication rates between the two studies is that the two patient populations (SAMMPRIS vs. WEAVE) were different and the treatment was administered at a different frame and thus patient selection and treatment timing may have been contributing factors. Moreover, we could not investigate differences in stroke or death at 30 days between three of the FDA approved indications: mRS 3 or less and age 22–80 and having two or more strokes on optimal medical treatment as all patients enrolled in the SAMMPRIS trial met the first two indications, and we were unable to reliably account for the third indication using the publicly available SAMMPRIS data. In addition, due to the exploratory nature of this study and the small number of events, the effect of multiple comparisons and possible overfitting of the models are additional limitations. However, our adjusted model has 6 terms, which is not enough to overfit a model with 30 outcome events. Likewise, we did not correct for multiple comparisons because we did not want to increase false negatives in this scenario and all of the covariates in our adjusted model (Table 2) are biologically plausible. On the other hand, this study has several strengths including using randomized controlled trial data, independent central outcome adjudication, and central core laboratory and imaging adjudication.

Conclusion

In this analysis of the SAMMPRIS trial, none of the factors (including failure to meet the FDA approved indication for stenting), reliably predicted stroke or death at 30 days in patients undergoing stenting. We propose that future clinical trials investigating the benefit of stenting in severe sICAS be based on identifying and selecting a subgroup of patients who is likely to fail aggressive medical treatment and whose risk on medical treatment is higher than the peri-procedural risk of stenting.

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Table 1.

Baseline characteristics in patients with or without primary outcome at 30 days

	Stroke or death at 30 days (N = 30)	Non-Stroke or death at 30 days (N = 183)	P-value
Patient associated variables			
Age (mean SD)	64.7 ± 9.4	60.4 ± 10.8	0.042
Sex (% women)	56.7% (17)	39.3% (72)	0.109
Body Mass Index (mean +/− SD)	30.0 ± 5.2	30.6 ± 6.3	0.636
Ethnicity (% Hispanic/Latino)	10.0%% (3)	8.7% (16)	0.736
Race			0.231
Caucasian (%)	86.7% (26)	69.9% (128)	
African American (%)	10.0% (3)	25.7% (47)	
Asian	0% (0)	2.2% (4)	
History of Hypertension (%)	90.0% (27)	89.1% (163)	1.000
History of Diabetes (%)	60.0% (18)	39.3% (72)	0.045
History of Hyperlipidemia (%)	90.0% (27)	86.9% (159)	1.000
Active or Ex-smoking (%)	33.3% (10/30)	65.4% (119/182)	0.001
Moderate/Vigorous Physical activity (%)	16.7% (5/30)	23.2% (42/181)	0.488
Infection within 30 days (%)	6.7% (2)	13.1% (24)	0.546
History of coronary artery disease (%)	23.3% (7)	19.1% (35)	0.622
History of congestive heart failure (%)	10.0% (3)	1.1% (2)	0.021
History of peripheral vascular disease* (%)	3.3% (1)	3.8% (7)	1.000
History of ischemic stroke (%)	46.7% (14)	24.0% (44)	0.014
Taking aspirin at the time of event (%)	63.3% (19)	52.5% (96)	0.325
Taking Plavix at the time of event (%)	20.0% (6)	21.3% (39)	1.000
Statin within 7 days of enrollment (%)	83.3% (25)	84.2% (154)	0.611
Baseline modified Rankin Scale (median, IQR)	1 (2)	1 (2)	0.912
NIHSS score (median, IQR)	0 (3)	1 (2)	0.960
Glucose (mean +/− SD)	141.7 ± 66.3	122.9 ± 48.8	0.066
HbA1C (mean +/− SD)	7.9 ± 2.4	6.9 ± 1.8	0.051
Total Cholesterol (mean +/− SD)	164.4 ± 65.3	152.3 ± 41.8	0.191
LDL cholesterol (mean +/− SD)	102.9 ± 51.5	95.1 ± 35.9	0.318
HDL cholesterol (mean +/− SD)	37/5 ± 11.5	37.6 ± 10.5	0.953
Systolic Blood Pressure (mean +/− SD)	146.4 ± 23.4	143.3 ± 19.6	0.458
Diastolic Blood Pressure (mean +/− SD)	76.3 ± 10.1	78.0 ± 10.6	0.458
Stroke as qualifying event (%)	53.3% (16)	64.5% (118)	0.308
Time from qualifying event to enrollment	10.9 ± 8.0	10.3 ± 7.8	0.693
Acute or subacute infarcts in the arterial territory (%)	53.6% (15/28)	63.8% (113/177)	0.302
Lesion related variables			
Symptomatic artery			0.522

	Stroke or death at 30 days (N = 30)	Non-Stroke or death at 30 days (N = 183)	P-value
ICA	20.0% (6)	18.6% (34)	
MCA (M1 segment)	30.0% (9)	43.7% (80)	
Vertebral	20.0% (6)	16.4% (30)	
Basilar	30.0% (9)	21.3% (39)	
Affected side (% left)	65.2% (14/21)	54.9% (79/144)	0.354
Perforator segment involved (%)	63.3% (19/30)	50.6% (92/182)	0.238
Degree of stenosis by central reader (mean +/− SD)	75.4 ± 9.0	73.9 ± 9.3	0.120
Length of lesion (mean +/− SD)	8.2 ± 3.3	7.0 ± 2.8	0.036
Lesion length > 10 mm (%)	33.3% (10)	11.5% (21)	0.004
Diameter of lesion (mean +/− SD)	0.58 ± 0.27	0.63 ± 0.30	0.390
Procedure related variables			
Type of anesthesia (% conscious sedation)	0.0% (0/33)	1.1% (2/183)	1.00
Time from enrollment to stent	1.4 ± 1.3	1.6 ± 2.4	
Time from qualifying event to stent	11.7 ± 8.2	11.9 ± 8.4	0.764
Stent Diameter (mean +/− SD)	3.5 ± 0.7	3.4 ± 0.7	0.595
Stent length (mean +/− SD)	16.7 ± 3.2	15.6 ± 3.3	0.117
Balloon Diameter (mean +/− SD)	2.4 ± 0.6	2.4 ± 0.6	0.927
Balloon Length (mean +/− SD)	13.4 ± 4.1	12.8 ± 3.5	0.339
First inflation pressure (mean +/− SD)	6.5 ± 1.4	6.3 ± 1.6	0.666
Last inflation pressure (mean +/− SD)	8.1 ± 1.8	7.2 ± 2.9	0.350
Number of Stents Placed (median, IQR)	1 (0)	1 (0)	0.280
Number of Balloons Introduced (median IQR)	1 (0)	1 (0)	0.923
Number of Inflations (median IQR)	1 (1)	1 (1)	0.858
Activated clotting time within target (%)	55.2% (16/29)	49.4% (87/176)	0.689
Percent stenosis after stenting (mean +/− SD)	36.1 ± 17.0	37.0 ± 14.0	0.748
Duration of procedure (mean +/− SD)	99.8 ± 54.8	102.3 ± 54.1	0.818
FDA approved indications			
Age 22–80 years	100% (30)	100% (183)	1.000
Baseline mRS 3 or less	100% (30)	100% (183)	1.000
Stent 7 days or more from event	66.7% (20)	69.9% (128)	0.831
70–99% stenosis on central adjudication	86.7% (26)	73.8% (135)	0.169

Table 2.

Unadjusted and adjusted logistic regression models to predict primary outcome at 30 days

	Unadjusted OR 95% CI, p value	Adjusted OR 95% CI, p-value
Age (per year increase)	1.04 (1.00–1.08), p = 0.044	1.04 (1.00–1.09), p = 0.055
History of Diabetes	2.31 (1.05–5.09), p = 0.037	1.59 (0.65–3.87), p = 0.312
Non-smoking (vs. current/ex-smoking)	3.78 (1.67–8.56), p = 0.001	4.46 (1.79–11.1), p = 0.001
History of congestive heart failure	10.06 (1.61–62.96), p = 0.014	5.48 (0.72–41.5), p = 0.099
History of stroke	2.76 (1.25–6.11), p = 0.012	2.29 (0.94–5.55), p = 0.068
Length of lesion (per mm increase)	1.15 (1.01–1.31), p = 0.039	1.20 (1.02–1.39), p = 0.029

Table 3.

Outcomes of patients based on the FDA indication for stenting

	FDA on-label stenting* (n = 113)	FDA off-label stenting (n 100)	P-value
Combined outcome 30	15.9% (18)	12% (12)	0.437
Ischemic Stroke 30	9.7% (11)	9% (9)	1.000
Death at 30 days	2.7% (3)	1% (1)	0.624

*Two or more strokes despite medical therapy is not accounted for, n = number of patients