Do patient characteristics explain the differences in outcome between medically treated patients in SAMMPRIS and WASID?

Seemant Chaturvedi, MD[1], **Tanya N. Turan, MD**[2], **Michael J. Lynn, MS**[3], **Colin P. Derdeyn, MD**[4], **David Fiorella, MD, PhD**[5], **L. Scott Janis, PhD**[6], and **Marc I. Chimowitz, MBChB**[2] for the SAMMPRIS Trial Investigators

[1]Department of Neurology, University of Miami

[2]Department of Neurosciences, Medical University of South Carolina, Charleston, SC

[3]Department of Biostatistics and Bioinformatics, Emory University Rollins School of Public Health, Atlanta, GA

[4]Mallinckrodt Institute of Radiology and the Departments of Neurology and Neurosurgery, Washington University School of Medicine, St Louis MO

[5]Department of Neurosurgery, State University of New York, Stony Brook, NY

[6]National Institute of Neurological Disorders and Stroke, National Institute of Health, Bethesda, MD

Abstract

Background and Purpose—The SAMMPRIS medical group had a much lower primary endpoint rate than predicted from the preceding WASID trial. This result has been attributed to the aggressive medical therapy used in SAMMPRIS, but an alternative hypothesis is that SAMMPRIS patients were lower risk. We undertook analyses to evaluate these competing hypotheses.

Methods—Using proportional hazards regression, we compared the SAMMPRIS primary endpoint between SAMMPRIS medical patients and WASID patients meeting the same qualifying criteria adjusted for confounding baseline characteristics.

Results—The unadjusted comparison of the SAMMPRIS primary endpoint showed a significantly higher risk for WASID patients (p=0.009, logrank test) with 12 month Kaplan-Meier estimates of 21.9% in WASID and 12.6% in SAMMPRIS and hazard ratio (HR) 1.9 (95%CI=1.2–3.0). The analyses identified the following confounding factors that varied between the studies and that conferred a higher risk: lack of statin use at enrollment (HR=1.8, 95%CI=1.1–2.9, p=0.027) that was more prevalent among WASID patients (39% vs 14%, p< 0.0001) and prior infarcts in the territory of the symptomatic vessel (HR=1.8, 95%CI=1.1–2.9, p=0.023) that was more prevalent among SAMMPRIS patients (34% vs 22%, p=0.015). The HR for WASID vs SAMMPRIS adjusted for these two characteristics was 1.9 (95%CI=1.1–3.2).

Conclusion—After adjustment for confounding baseline characteristics, WASID patients had an almost two-fold higher risk of the SAMMPRIS primary endpoint, which supports the hypothesis that the lower rate of the primary endpoint in the medical arm of SAMMPRIS compared with WASID patients was due to the aggressive medical management used in SAMMPRIS.

Clinical Trials Registration—http://clinicaltrials.gov. Unique Identifier: NCT00576693

Keywords

Intracranial atherosclerosis; Clinical trials; Dyslipidemia; Atherosclerosis

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial demonstrated superiority of aggressive medical management over stenting[1]. Additionally, the rate of the primary endpoint in the medical group in SAMMPRIS was much lower than predicted from the preceding Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial. [2]

Although the much lower primary event rate among the SAMMPRIS patients has been attributed to the benefits of aggressive medical management[3], an alternative explanation is that the patients in SAMMPRIS were lower risk or different in other meaningful ways compared with patients in WASID. We explored this hypothesis by performing a statistical analysis comparing the SAMMPRIS primary endpoint between patients in the two studies in which we evaluated the impact of baseline characteristics on the differences in outcome.

Methods

Qualifying Criteria and Outcome

The qualifying criteria for the two studies have been published in detail previously[2, 4]. Since WASID enrolled patients with a broader range of stenosis (50–99% vs. 70–99% in SAMMPRIS) and a longer qualifying period from the last symptomatic stroke or TIA to enrollment (90 days vs. 30 days in SAMMPRIS), the entire population of WASID was not comparable to that in SAMMPRIS. Therefore, for this analysis, we compared all 227 patients randomized to the medical arm of SAMMPRIS with the 143 patients in WASID who met the following primary SAMMPRIS qualifying criteria: 70–99% stenosis

determined by the local investigator, < 81 years old, absence of tandem stenoses, and 30 days from qualifying event to randomization. The outcome for this analysis was the SAMMPRIS primary endpoint: any stroke or death within 30 days after enrollment or ischemic stroke in the territory of the qualifying artery beyond 30 days of enrollment.

Statistical Methods

An unadjusted comparison of the SAMMPRIS primary endpoint between the two studies, was made by estimating the cumulative probability of the outcome versus time for each study using the Kaplan-Meier method with the resulting curves compared between the studies using the log-rank test. Although we included in the analysis only the WASID patients who met the primary eligibility criteria that differed between WASID and SAMMPRIS, there could have been differences between the two selected study populations in terms of the baseline characteristics that were related to the outcome. We employed the following process to identify and adjust the comparison of the studies for such confounding factors. Baseline characteristics were compared between the two studies using Fisher's exact test for percentages, t-test for means, and the Wilcoxon rank-sum test for medians. Also, the relationship of each of the baseline characteristics (other than the study participated in) to the outcome was assessed using bivariate and multivariable proportional hazards regression in the set of patients formed by combining the two studies. We identified the baseline characteristics that were both significantly different between the studies and also significantly associated with the outcome. A proportional hazards regression model was fit that included terms for the baseline characteristics identified and also a term for the study that was participated in. The hazard ratio comparing the two studies was estimated from that model. To further adjust for any potential confounding factors, the baseline characteristics that were statistically different between the studies and not already in the model were added one at a time to the model and were retained in the model if the hazard ratio comparing the studies changed by more than 10% from the hazard ratio estimated without the newly added characteristic. If a characteristic to be added had missing data, then the hazard ratios to be compared were estimated from the same set of patients. All analyses were done using SAS 9.3. All reported p-values are two-sided and those < 0.05 are considered statistically significant.

Results

Unadjusted Comparison of Outcome between Studies

The Kaplan-Meier curves for the risk of the SAMMPRIS primary endpoint were significantly different between WASID and SAMMPRIS (Figure 1, Table 1, p = 0.009). WASID patients had greater risk of the outcome at 1, 2, and 3 years after enrollment (21.9%, 23.7%, 28.9%, respectively) compared to SAMMPRIS patients (12.6%, 14.1%, 14.9%, respectively). The unadjusted hazard ratio (WASID relative to SAMMPRIS) was 1.9 (95% CI = 1.2 – 3.0).

Comparison of Baseline Characteristics between Studies

Compared with WASID patients, SAMMPRIS patients were younger (mean age 59.5 years vs. 62.5 years; p=0.009) but had higher percentages of hypertension (89% vs. 76%;

p=0.001), old infarcts in the territory of the symptomatic artery (34% vs 22%; p = 0.015), stenosis in the 80–99% range (55% vs. 35%; p=<0.0004), and anterior circulation stenosis (68% vs. 48%; p<0.0002) and a lower percentage of patients not taking a statin at enrollment (14% vs 39%; p < 0.0001).

SAMMPRIS patients had higher mean systolic blood pressure (SBP) (146.8 mmHg vs. 139.1; p= 0.0002), higher mean diastolic blood pressure (DBP) (82.3 vs 76.5; p < 0.0001), higher mean body mass index (30.7 kg/m^2 vs. 29.4; p=0.048) but lower mean LDL (98 mg/dl vs. 125; p<0.0001) and HDL (39 mg/dl vs 44; p = 0.0004). There were no significant differences in the frequency of female gender, black race, stroke as the qualifying event, diabetes, smoking, physical activity, history of previous stroke, time from qualifying event to study entry, history of coronary artery disease, stroke scale scores or HgbA1c among patients with a history of diabetes (Table 2).

Association of Baseline Characteristics and Outcome

In bivariate analyses, the following baseline characteristics were found to be significantly related to outcome in the combined set of WASID and SAMMPRIS patients (Table 3): female gender, history of diabetes, not using statin at enrollment, modified Rankin score 1, NIH stroke scale score 1, old infarcts in the territory of the symptomatic artery, and stroke as the qualifying event all conferred a significantly higher risk of the SAMMPRIS primary endpoint.

The baseline characteristics that were both different between the studies and related to outcome and thus potential confounders were no statin use at enrollment (more prevalent among WASID patients) and old infarcts in the territory of the symptomatic artery (more prevalent among SAMMPRIS patients). In a multivariable analysis, both characteristics were found to be related to the outcome with the following hazard ratios - no statin use at enrollment: 2.0 (95% CI = 1.1 – 3.3, p = 0.019), old infarcts in the territory of the symptomatic artery 1.9 (95% CI = 1.1 – 2.9, p = 0.019).

Adjusted Comparison of Outcome between Studies

When adjusted for no statin use at enrollment and old infarcts in the territory of the symptomatic artery, the estimated hazard ratio for WASID vs SAMMPRIS was 1.9 (95% CI = 1.1 – 3.2, p = 0.016) demonstrating a higher risk of the outcome among WASID patients (Table 4). To determine if there were additional confounding factors, the baseline characteristics other than no statin use at enrollment and old infarcts in the territory of the symptomatic artery that were significantly different between the studies (Table 2): age, history of hypertension, symptomatic artery, percent stenosis, systolic and diastolic blood pressure, BMI, LDL, and HDL were individually added to the model and the effect on the hazard ratio was noted. None of those factors changed the hazard ratio by more than 10%. The percent change ranged from 0.8% to 7.8%.

Discussion

The 1, 2 and 3-year rates of the primary endpoint were 42%, 41% and 48% lower respectively in SAMMPRIS medically-treated patients compared with WASID patients who

met the SAMMPRIS entrance criteria. Our analysis sought to explore whether SAMMPRIS patients had a lower rate of major vascular events due to a lower burden of vascular risk factors compared with WASID patients.

SAMMPRIS patients were younger, had lower LDL at baseline (because of higher statin use), and had a higher frequency of anterior circulation stenosis. Younger age and lower cholesterol have been associated with a lower risk of stroke in patients with intracranial stenosis[5, 6], however, WASID showed no increased risk of stroke with posterior circulation stenosis in medically treated patients[7]. On the other hand, SAMMPRIS patients had higher frequencies of hypertension, mean SBP, mean body mass index, more severe stenosis (80–99%) and old infarct in the territory of the symptomatic artery. Raised SBP and severe stenosis were strongly associated with an increased risk of stroke in patients with intracranial stenosis in WASID[6–8].

Among the baseline characteristics evaluated, we identified lack of statin use at baseline and old infarcts in the territory of the stenotic artery as confounding factors in that they were significantly different in frequency between WASID and SAMMPRIS patients and were associated with a worse outcome. After adjusting for these factors, WASID patients were still at a two-fold higher risk of the primary endpoint. This result support the hypothesis that the lower risk of the primary endpoint in SAMMPRIS patients is due to the differences in medical management between the two studies.

In addition to differences in risk factor control, changes in antithrombotic therapy between the two studies may have played a role. The SAMMPRIS regimen utilized dual antiplatelet therapy with aspirin and clopidogrel for 90 days compared to either aspirin monotherapy or warfarin in WASID. Dual antiplatelet therapy has been shown to reduce stroke in patients with recent minor stroke or transient ischemic attack in the Clopidogrel in High-Risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial[9]. In addition, a recent meta-analysis found that when treatment was initiated within three days of the index TIA or stroke, dual antiplatelet therapy reduced the risk of stroke by 31% compared to antiplatelet monotherapy[10].

This study has some limitations. The increased frequency of hypertension in SAMMPRIS might reflect changes in the JNC definition of hypertension after the start of WASID[11]. However, this is an unlikely explanation given that SAMMPRIS patients had significantly higher SBP at baseline compared with WASID patients. In addition, the studies were done in different time periods and other variations in secular treatment patterns during the course of these two trials may have existed, which could explain some of the differences in event rates in these two trials[12].

In conclusion, compared with WASID patients who met the SAMMPRIS qualifying criteria, SAMMPRIS patients were slightly younger but had a higher burden of other poor prognostic features. Analyses comparing the SAMMPRIS primary endpoint between the two studies adjusted for confounding factors demonstrated a higher risk of the outcome among WASID patients. These data suggest that the lower rate of stroke in the medical arm of SAMMPRIS

compared with WASID patients with the same qualifying criteria is likely related to the aggressive medical management used in SAMMPRIS.

Acknowledgments

References

1. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. New England Journal of Medicine. 2011; 365:993–1003. [PubMed: 21899409]

2. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. New England Journal of Medicine. 2005; 352:1305–1316. [PubMed: 15800226]

3. Turan TN, Lynn MJ, Nizam A, Lane B, Egan BM, Le NA, et al. Rationale, design, and implementation of aggressive risk factor management in the stenting and aggressive medical management for prevention of recurrent stroke in intracranial stenosis (sammpris) trial. Circulation. Cardiovascular quality and outcomes. 2012; 5:e51–60. [PubMed: 22991350]

4. Chimowitz MI, Lynn MJ, Turan TN, Fiorella D, Lane BF, Janis S, et al. Design of the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis trial. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association. 2011; 20:357–368. [PubMed: 21729789]

5. Wong KS, Li H. Long-term mortality and recurrent stroke risk among chinese stroke patients with predominant intracranial atherosclerosis. Stroke. 2003; 34:2361–2366. [PubMed: 12947158]

6. Chaturvedi S, Turan TN, Lynn MJ, Kasner SE, Romano J, Cotsonis G, et al. Risk factor status and vascular events in patients with symptomatic intracranial stenosis. Neurology. 2007; 69:2063–2068. [PubMed: 18040012]

7. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation. 2006; 113:555–563. [PubMed: 16432056]

8. Turan TN, Cotsonis G, Lynn MJ, Chaturvedi S, Chimowitz M. for the WASID Investigators. Relationship between blood pressure and stroke recurrence in patients with intracranial arterial stenosis. Circulation. 2007; 115:2969–2975. [PubMed: 17515467]

9. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. New England Journal of Medicine. 2013; 369:11–19. [PubMed: 23803136]

10. Wong KSL, Wang Y, Leng X, Mao C, Tang J, Bath PMW, et al. Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: An updated systematic review and meta-analysis. Circulation. 2013; 128:1656–1666. [PubMed: 24030500]

11. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The jnc 7 report. JAMA. 2003; 289:2560–2571. [PubMed: 12748199]
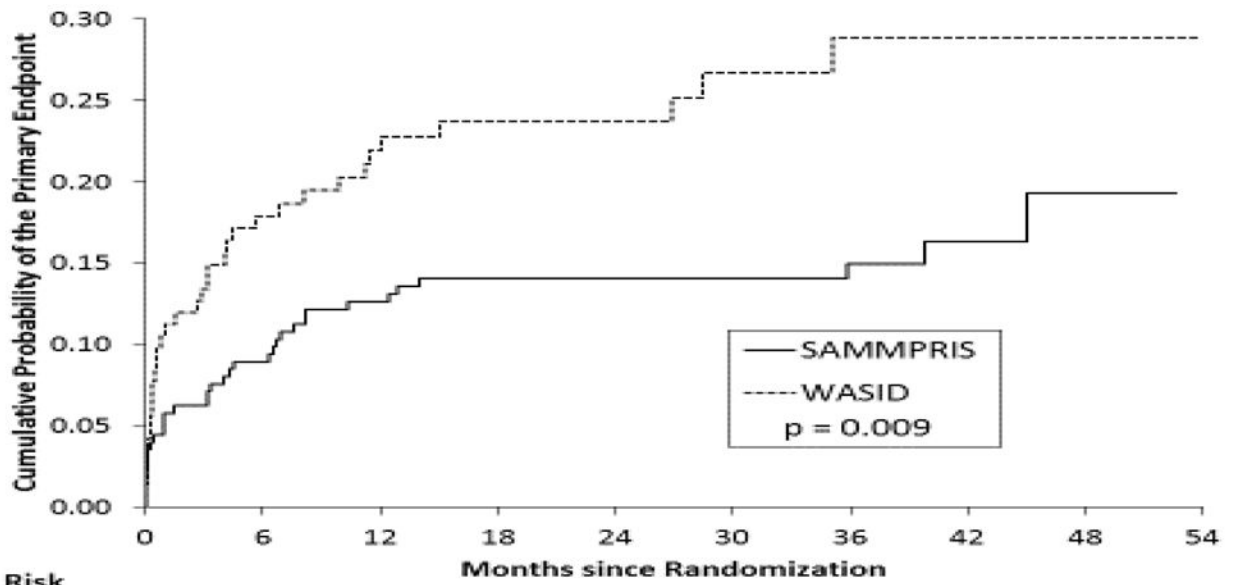
12. Egan BM, Zhao Y, Axon R. Us trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. JAMA. 2010; 303:2043–2050. [PubMed: 20501926]

Figure 1.
Kaplan-Meier estimates of the cumulative probability of the SAMMPRIS primary endpoint for SAMMPRIS medical patients and WASID patients meeting SAMMPRIS eligibility criteria.

Table 1

Probability[*] of the SAMMPRIS Primary Endpoint For SAMMPRIS Medical Patients and SAMMPRIS-Eligible WASID Patients

Months after Randomization	Study	
	SAMMPRIS (n=227) Probability of Primary Endpoint (95% CI)	WASID (n=143) Probability of Primary Endpoint (95% CI)
1	5.8% (3.4% – 9.7%)	10.5% (6.5% – 16.9%)
6	8.9% (5.9% – 13.5%)	17.9% (12.5% – 25.4%)
12	12.6% (8.9% – 17.8%)	21.9% (15.8% – 29.9%)
24	14.1% (10.1% – 19.4%)	23.7% (17.4% – 31.9%)
36	14.9% (10.7% – 20.6%)	28.9% (21.1% – 38.8%)
p-value[†]	0.009	

[*] Kaplan-Meier estimates of the cumulative probability of a primary endpoint at the specified months after randomization.

[†] p-value for the log-rank test comparing the Kaplan-Meier curves of the two studies.

Table 2

Baseline Characteristics for the SAMMPRIS Medical Group vs SAMMPRIS-Eligible WASID Patients[*]

Characteristic	SAMMPRIS Medical Group (n=227)	WASID (n=143)	p-value[†]
Age (years)	59.5 ± 11.8	62.5 ± 10.0	0.009
Female Gender	82 (36%)	55 (38%)	0.66
Black Race	49 (22%)	37 (26%)	0.38
History of Hypertension	203 (89%)	109 (76%)	0.001
History of Diabetes	97 (43%)	62 (43%)	0.91
Previous or Current Smoker	149 (66%)	101 (71%)	0.36
History of Coronary Artery Disease	59 (26%)	41 (29%)	0.63
History of Ischemic Stroke (not the qualifying event)	58 (26%)	34 (24%)	0.71
Not Using Statin at Enrollment	31 (14%)	56 (39%)	< 0.0001
Modified Rankin Grade 1	159 (70%)	95 (66%)	0.49
NIH Stroke Scale > 1	88 (39%)	50 (35%)	0.51
Physical Activity Out of Target[‡]	161 (71%)	105 (73%)	0.64
Old Infarcts in the Territory of the Symptomatic Artery	75/222 (34%)	28/130 (22%)	0.015
Qualifying Event was a Stroke	152 (67%)	90 (63%)	0.43
On Antithrombotic Therapy at Qualifying Event	140 (62%)	75 (52%)	0.084
Time from Qualifying Event to Randomization (days)	7 (4 – 19)	8 (5 – 14)	0.87
Symptomatic Artery			
Internal Carotid Artery	49 (22%)	26 (18%)	
Middle Cerebral Artery	105 (46%)	43 (30%)	
Vertebral Artery	22 (10%)	24 (17%)	< 0.0001
Basilar Artery	51 (22%)	38 (27%)	
Combination	0	12 (8%)	
Symptomatic Artery in Posterior Circulation	73 (32%)	74 (52%)	0.0002
Percent Stenosis of Symptomatic Artery [§]	81 ± 7	78 ± 7	0.0006
Categories of Percent Stenosis of Symptomatic Artery [§]			
70–79%	102 (45%)	94 (66%)	
80–89%	97 (43%)	40 (28%)	0.0004
90–99%	28 (12%)	9 (7%)	

Characteristic	SAMMPRIS Medical Group (n=227)	WASID (n=143)	p-value[†]
Systolic BP (mmHg)	146.8 ± 21.8	139.1 ± 17.8	0.0002
Diastolic BP (mmHg)	82.3 ± 12.0	76.5 ± 9.5	< 0.0001
BMI (kg/m^2)	30.7 ± 6.3	(n=140) 29.4 ± 5.7	0.048
LDL (mg/dl)	(n=226) 97.7 ± 36.6	(n=120) 125.4 ± 39.7	< 0.0001
HDL (mg/dl)	(n=226) 38.8 ± 10.1	(n=124) 43.8 ± 13.4	0.0004
HgbA1c (%) (For patients with a history of diabetes)	(n=91) 7.6 (6.9 – 10.2)	(n=42) 8.0 (6.5 – 10.3)	0.89

[*] Values are mean ± standard deviation or number (%) or median (inter-quartile range).

[†] Comparisons of the baseline characteristics of the two studies were made using either an independent groups t-test (for means), Fisher's exact test (for percentages) or the Wilcoxon rank sum test (for medians).

[‡] Physical activity was measured in the two studies as follows: SAMMPRIS used the Physician-based Assessment and Counseling for Exercise (PACE) Current Physical Activity Status Score with a score of 1–3 considered in-target. WASID used four categories (Sedentary, Minimal, Moderate, Vigorous) with Moderate or Vigorous considered in-target. (see on-line supplement for details).

[§] Percent stenosis according to the reading of the angiogram by the study physician at the patient's clinical site.

Table 3

Bivariate Analyses of Baseline Characteristics vs the SAMMPRIS Primary Endpoint for the SAMMPRIS Medical Group and for SAMMPRIS-Eligible WASID Patients Combined

Characteristic	# Patients	HR (95% CI) [*]	p-value[*]
Age[†] (years)	370	1.0 (0.8 – 1.2)	0.96
Female Gender	370	2.0 (1.2 – 3.2)	0.004
Black Race	370	1.4 (0.8 – 2.3)	0.21
History of Hypertension	370	1.0 (0.5 – 1.9)	0.95
History of Diabetes	370	2.0 (1.2 – 3.2)	0.0055
Previous or Current Smoker	370	0.8 (0.5 – 1.4)	0.46
History of Coronary Artery Disease	370	0.9 (0.5 – 1.5)	0.71
History of Ischemic Stroke (not the qualifying event)	370	1.3 (0.8 – 2.2)	0.34
Not Using Statin at Enrollment	370	1.8 (1.1 – 2.9)	0.027
Modified Rankin Grade ≥ 1	370	1.8 (1.0 – 3.3)	0.037
NIH Stroke Scale > 1	370	1.9 (1.2 – 3.1)	0.0067
Physical Activity Out of Target[‡]	370	1.3 (0.7 – 2.2)	0.42
Old Infarcts in the Territory of the Symptomatic Artery	352	1.8 (1.1 – 2.9)	0.023
Qualifying Event was a Stroke	370	2.0 (1.2 – 3.6)	0.014
On Antithrombotic Therapy at Qualifying Event	370	0.9 (0.6 – 1.4)	0.65
Time from Qualifying Event to Randomization[†] (days)	370	0.9 (0.6 – 1.2)	0.31

Symptomatic Artery
  Internal Carotid Artery
  Middle Cerebral Artery
  Vertebral Artery
  Basilar Artery
  Combination
	370	Reference
		0.5 (0.3 – 0.9)
		0.5 (0.2 – 1.2)
		0.6 (0.3 – 1.1)
		0.6 (0.1 – 2.4)
			0.18

Symptomatic Artery in Posterior Circulation	370	0.8 (0.5 – 1.3)	0.41
Percent Stenosis of Symptomatic Artery [†]	370	1.1 (0.8 – 1.6)	0.49

Categories of Percent Stenosis of Symptomatic Artery
  70–79%
  80–89%
	370	Reference
		1.0 (0.6 – 1.7)
			0.98

Characteristic	# Patients	HR (95% CI) [*]	p-value[*]
90–99%		1.1 (0.5 – 2.4)	
Systolic BP[†] (mmHg)	370	1.0 (0.9 – 1.1)	0.53
Diastolic BP[†] (mmHg)	370	0.9 (0.8 – 1.2)	0.60
BMI[†] (kg/m^2)	367	1.0 (0.7 – 1.4)	0.84
LDL[†] (mg/dl)	346	1.04 (0.98 – 1.11)	0.19
HDL[†] (mg/dl)	350	1.06 (0.9 – 1.3)	0.63

[*] The hazard ratio and p-value from a proportional hazards regression model relating the individual characteristic to the time to a primary endpoint.

[†] The hazard ratio is calculated for a 10 unit increase in the characteristic.

Table 4

Adjusted Comparison of WASID and SAMMPRIS for the SAMMPRIS Primary Endpoint among SAMMPRIS Medical Patients and SAMMPRIS-Eligible WASID Patients[*]

Characteristic	Parameter Estimate	Standard Error	p-value	Hazard Ratio (95% CI)
WASID vs SAMMPRIS	0.64745	0.26861	0.016	1.9 (1.1 – 3.2)
Not Using Statin at Enrollment	0.31519	0.28168	0.26	1.4 (0.8 – 2.4)
Old Infarcts in the Territory	0.66134	0.25311	0.009	1.9 (1.2 – 3.2)

[*] The estimates are based on a proportional hazards regression model with 352 patients.