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Mindy Hong Date

The Effects of Antithrombotic Medication on Patients Enrolled in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial

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B.S., Emory University, 2013

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Abstract

The Effects of Antithrombotic Medication on Patients Enrolled in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial

By Mindy Hong

Intracranial arterial stenosis is an imperative cause of stroke that can be treated with percutaneous transluminal angioplasty and stenting (PTAS) in patients who have experienced a recent transient ischemic attack (TIA) or stroke. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial aimed to determine whether angioplasty and stenting is beneficial to aggressive medical management in preventing a primary end point. The clinical trial discovered that the 30-day rate of stroke or death was much higher in the PTAS group (14.7%) than the medical management group (5.8%), and concluded that aggressive medical management was superior to PTAS in patients with intracranial stenosis. Because there has not yet been a treatment proven to be more effective than medical therapy, interventionalists hope to find an effective alternative method to treating patients with intracranial stenosis, especially in those who have failed medical management. Since patients who were taking antithrombotic medication at the time of the qualifying event can be considered to have failed medical therapy, we are interested in observing whether or not angioplasty and stenting can provide any potential benefit to these patients. In this study, we used the log-rank test and Cox proportional hazards regression to see whether or not there was a statistical difference in overall time to primary endpoint between patients who were on antithrombotic medication and patients who were not. Product-limit estimates for both medication groups were obtained through Kaplan-Meier curves. Our results showed that within the group of patients taking antithrombotic medication, the probability of experiencing a primary endpoint was significantly higher in patients assigned to the PTAS group compared to those in the medical management group ($p = 0.0428$). Furthermore, multivariate analysis regression results showed that the effect of treatment was not statistically different in the two antithrombotic medication groups. Therefore, our results emphasized that PTAS does not provide a benefit over aggressive medical management alone in patients who were taking antithrombotic medication at the time of the qualifying event.

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Introduction

Background

Intracranial arterial stenosis refers to the narrowing of an artery within the brain, a process that can potentially lead to stroke. Stenosis is normally caused by a buildup of plaque, known as atherosclerosis, within the walls of the artery, thus restricting blood flow to the brain and possibly causing more severe symptoms such as brain damage and death. There are three major ways in which intracranial arterial stenosis can lead to a stroke: 1) the plaque becomes larger and continues to narrow the artery and restrict blood flow to the brain, 2) the plaque roughens and alters the wall of the artery, resulting in the formation of blood clots which also restrict blood flow to the brain, 3) the plaque breaks away from walls and blocks the pathway in a smaller artery, also preventing blood from flowing to the brain (Ringer et al., 2010). The most common symptoms of intracranial arterial stenosis are a stroke or transient ischemic attack (TIA).

There are two main types of strokes – ischemic and hemorrhagic. An ischemic stroke accounts for 87% of all stroke cases (American Heart Association, 2012) and typically occurs as a result of an obstruction within a blood vessel that is supplying blood to the brain. A hemorrhagic stroke is most commonly caused by uncontrolled hypertension, and typically occurs when a blood vessel ruptures, causing blood to overflow into the brain. A TIA can result from a temporary clot, which can possibly lead to a temporary stroke. Signs of a stroke or TIA consist of slurred speech and facial, arm or leg weakness, especially on one side of the body, and can lead to impaired function and other brain injuries.

Intracranial arterial stenosis is a leading cause of stroke worldwide and is responsible for 8% to 10% of strokes in the United States (Mayfield Clinic, 2013), and affects specific ethnic groups, including African Americans, Asian Americans and Hispanics, more than others. Atherosclerosis is the main cause of intracranial arterial stenosis, and is usually a result of damage to the inner wall of the artery. Factors that can lead to atherosclerosis include diabetes, smoking, high blood pressure, elevated LDL cholesterol, family history, and advanced age. Regarding diagnostics, an imaging test is most commonly performed in order to identify narrowing of the intracranial arteries. An angiogram involves injecting a contrast agent into the arteries through a catheter in the groin and uses X-ray imaging to see the arteries and veins within the brain, providing essential information about the stenosis. Computed tomography angiographies also use X-rays in order to better visualize the anatomical structures inside the brain, allowing doctors to better analyze the blood vessels and soft tissues. Another diagnostic test is the transcranial Doppler ultrasound, which uses the sound wave from an ultrasound probe to measure the velocity of blood flow through the blood vessels inside the brain. Additionally, position emission topographies (PET) can also be used to analyze how glucose is metabolized in the brain, and can locate potential abnormalities (Qureshi et al., 2009).

Treatments

Treatments for intracranial arterial stenosis aim to reduce the overall risk of stroke and depend on the severity of symptoms. Patients are generally first treated with medications that minimize risk factors, such as high blood pressure and high cholesterol, or lifestyle programs that allow them to maintain a healthy diet and exercise routine. Medications

that lower and regulate blood pressure include beta-blockers, calcium channel blockers and diuretics. Cholesterol-lowering medications can assist in preventing additional plaque build-up in atherosclerosis, and can consist of statins, niacin and a low fat, high fiber diet. Antithrombotic medications, which focus on reducing thrombus formation, are one of the most common treatments for intracranial stenosis. Antithrombotic medication consists of two classes: anticoagulants and antiplatelet drugs (Turan et al., 2009). A anticoagulant, or a blood thinner, eases the process in which the blood passes through the narrowed arteries by targeting proteins in the blood. Examples of frequently used anticoagulants are warfarin and heparin. Antiplatelet drugs prevent possible blood clots and sudden blood constrictions from occurring by binding to receptors located along the surface of platelets. Some antiplatelet drugs include aspirin, clopidogrel, ticlopidine and dipyridamole.

Surgical procedures can be effective methods of treatment for preventing recurrent stroke if the diseased artery can be successfully bypassed. One surgical approach is cerebral artery bypass, which requires detaching a donor artery from the scalp and redirecting it in order to reroute the blood supply around the plaque. However, because of the risks associated with surgeries, they are customarily considered for patients who do not respond to medication. An interventional approach is angioplasty and stenting, an endovascular procedure that widens the diameter of the affected artery by compressing the plaque buildup. It is typically performed within the affected artery by inserting a catheter, a small and flexible tube, into the femoral artery during an angiogram. The catheter is then moved through the bloodstream towards the affected artery, and an

attached balloon is inflated in order to shrink the amount of plaque buildup, allowing more room for blood to flow through (Klopfenstein et al., 2005).

Angioplasty and stenting is a relatively successful procedure that is commonly used for treating the arteries within the heart before, but has only recently been applied within the brain. The primary goal is to reduce stenosis by approximately 50%, but many complications can result from angioplasty and stenting, including recurrent stroke, sudden constriction of a blood vessel, or tearing of the walls within the artery. As a result, angioplasty is typically considered for patients who did not respond to medication, who have at least 70% stenosis, and who have had recent recurrent stroke or TIA symptoms. The effectiveness of angioplasty and stenting as a treatment for recurrent stroke is further studied in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) clinical trial.

SAMMPRIS

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study is a randomized, clinical trial funded by the National Institute of Neurological Disorders and Strokes (NINDS) that was conducted at 50 sites in the United States. The study focused on two principal strategies used to treat affected patients with intracranial stenosis: aggressive medical therapy alone, which is a combination of antiplatelet therapy and intensive management of risk factors, and aggressive medical therapy plus percutaneous transluminal angioplasty and stenting

(PTAS). The primary goal of the trial was to determine whether or not angioplasty and stenting added any benefit to aggressive medical management alone.

In order to be eligible for the SAMMPRIS trial, patients were required to have experienced a recent TIA or non-disabling ischemic stroke (referred to as the qualifying event) within the last 30 days, in addition to 70-99% stenosis. Patients were randomized to either aggressive medical management alone or to aggressive medical management plus PTAS. Medical management was identical in both treatment groups, and included aspirin (325 mg per day) for the entire follow-up, clopidogrel (75 mg per day) for 90 days after trial enrollment, risk factor management focusing on systolic blood pressure lower than 140 mmHg and low-density cholesterol lower than 70 mg/dL, as well as a lifestyle modification program targeting risk factors such as diabetes, smoking and weight. The PTAS procedure uses the Gateway PTA Balloon Catheter and Wingspan Stent System, which are the only devices that have been approved by the Food and Drug Administration (FDA). The devices have been available for treatment since 2005 under a Humanitarian Device Exemption (HDE), which is an application that authorizes an applicant to market "a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year" (FDA, 2014). Patients randomized to PTAS were required to undergo the stenting procedure within 3 days of randomization, and a primary operator administered the process under general anesthesia (Chimowitz et al., 2011).

The primary endpoint for study was a composite endpoint that included the event that PTAS was intended to prevent, an ischemic stroke in the territory of the qualifying artery, as well as potentially harmful short-term effects of the PTAS procedure. A primary endpoint was defined to be: 1) any stroke or death within 30 days after enrollment, 2) any stroke or death within 30 days after a revascularization procedure of the qualifying lesion during follow-up, or 3) ischemic stroke in the territory of the qualifying artery beyond 30 days. Secondary endpoints included any stroke or death, myocardial infarction, major non-stroke hemorrhage, functional outcome at the end of follow-up, and cognitive outcome.

The SAMMPRIS clinical trial began in November 2008. Out of the 451 patients enrolled, 227 were randomized to the medical management group and 224 to the PTAS group. However, enrollment was stopped in April 2011 because results showed that the 30-day rate of stroke or death was significantly higher in the PTAS group (14.7%) than the medical management group (5.8%) ($p = 0.002$), and that there was very little evidence showing a benefit from the stenting procedure (Chimowitz et al., 2011). However, follow-up of the study continued until the last patient enrolled had been followed for two years, and results over the entire follow-up period after enrollment indicated that the probability of occurrence of a primary endpoint differed significantly between the two treatment groups ($p = 0.009$) (Chimowitz, et al., 2011). In order to show the longer-term results of the study, the SAMMPRIS trial extended the follow-up of all randomized patients in the clinical trial to a termination date of 2 years after the last patient was enrolled. Results showed that the cumulative probability of the primary endpoints was

still smaller in the medical management group than the PTAS group ($p = 0.0252$), and that the occurrence of adverse events, specifically any stroke ($p = 0.0468$) or major hemorrhage ($p = 0.0009$), was also higher in the PTAS group versus the medical management group (Derdeyn et al., 2013). Thus, the study revealed that even over an extended follow-up period, the use of aggressive medical management is still superior to the PTAS procedure in high-risk patients with atherosclerotic intracranial arterial stenosis.

Although the results of the SAMMPRIS trial came to the general conclusion that stenting provided very little, if any, benefit to preventing recurrent stroke in patients with intracranial stenosis, interventionalists hope to find an alternative effective method of treatment for patients who have failed medical management. Since patients who were taking antithrombotic medication at the time of the qualifying event can be considered to have failed medical therapy, there is a possibility that angioplasty and stenting may prove effective for these patients. As a result, in this study, we aim to examine whether or not there is a significant difference in the probability of experiencing a primary endpoint between each treatment group in both patients who are taking antithrombotic medication and patients who are not, and to see if angioplasty and stenting is a more effective method of treatment than aggressive medical management in these subgroups.

Methods

The SAMMPRIS clinical study enrolled a total of 451 patients, who were categorized into two groups – patients who were taking antithrombotic medication at the time of the qualifying event and patients who were not. A patient was considered to be taking

antithrombotic medication if he or she took any of the following: warfarin, aspirin, ticlopidine, clopidogrel, dipyridamole, heparin (intravenous and subcutaneous routes) or other medication. Because patients who had their qualifying event while taking an antithrombotic were considered to have failed medical therapy, stenting was thought to have be potentially effective for these patients. As a result, we compared the two antithrombotic groups to see whether or not there are any statistical differences in characteristics that may contribute to benefitting from the stenting procedure.

The baseline characteristics that were compared between the two antithrombotic groups included age, gender, ethnic origin, history of hypertension, history of diabetes, history of lipid disorder, smoking history, history of coronary artery disease, history of stroke with the exception of the qualifying event, type of qualifying event, time from qualifying event to study enrollment, type of symptomatic qualifying artery, and level of stenosis of symptomatic qualifying artery. Basic descriptive statistics the baseline characteristics were assessed through exploratory data analysis. Percentages for categorical characteristics, such as gender and history of coronary heart disease, were compared using either Fisher's exact test or Pearson's chi-square test. For continuous characteristics, two-sample Student t-tests were applied to compare means, through which the pooled variance was used if population variance were equal. Otherwise, the Satterthwaite method was used.

Time was determined by calculating the number of days between each patient's study enrollment to primary endpoint, and was then adjusted in order to obtain the time in

months. In the event that the patient did not have a primary endpoint, the date of last contact was used as the end date. The Kaplan-Meier curve and corresponding product-limit estimates at each time point were generated, and the probability of events was calculated at 6, 12 and 24 months for each antithrombotic medication group. In order to compare the distributions between the two antithrombotic groups, the log rank test was used. Finally, a multivariate analysis of the variables *treatment* (aggressive medical therapy or PTAS) and *antithrombotic* (whether or not patient was taking antithrombotic medication) was performed using the Cox proportional hazard regression model. In order to determine if the effect of treatment is different in the two antithrombotic medication groups, the interaction term of *treatment* and *antithrombotic* was included in the model. Additionally, the interaction term between *time* (time from study enrollment to primary endpoint or last contact) and *treatment* was incorporated in the regression model to accommodate for non-proportional hazards.

Significance levels were set at 0.05 for all tests. The SAS statistical package version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for all data management and analyses techniques.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics data were collected from the patients enrolled in the SAMMPRIS trial and are summarized in Table 1. Out of the 451 patients enrolled in the clinical trial, 284 (63.0%) were taking antithrombotic medications and 167 (37.0%)

were not. The characteristics included age, gender, ethnic origin, history of hypertension, history diabetes, history of lipid disorder, smoking history, history of coronary artery disease, history of stroke with the exception of a qualifying event, type of qualifying event, time from qualifying event to study enrollment, type of symptomatic qualifying artery, and level of stenosis of symptomatic qualifying artery. The mean (± standard deviation) age of patients in the antithrombotic medication group was 61.3 ± 11.0 years old, versus 58.4 ± 11.6 years old in the group of patients who were not taking antithrombotic medication. The mean age of people taking antithrombotic medication at the time of the qualifying event (61.3 years) was significantly higher than for patients not taking medications (58.4 years) ($p = 0.009$). There were more males in the group of patients on antithrombotic medication (62.3%) than those who were not on medication (56.9%), but the difference was not statistically significant ($p = 0.2544$). Ethnic origin was self-reported and consisted of three primary categories: white, black or other. In both medication groups, the population was predominantly white, with 73.2% in patients on antithrombotic medication and 68.3% in patients not on medication, but there was no significant difference between the ethnic groups.

The percentage of hypertensive patients the antithrombotic group (91.5%) was higher than those for the no antithrombotic group (85.6%), and there was a distinct trend towards significance between the two groups ($p = 0.07$). There was no apparent difference in significance between medication groups regarding smoking history ($p = 0.2238$), which was divided into the following categories: never smoked , used to smoke, and currently smoking. Patients who were taking medications reported a slightly higher

history of diabetes, but the difference was not significant ($p = 0.1793$). In addition, patients who were taking antithrombotic medication at the time of the qualifying event had a significantly higher rate of lipid disorder (92.6%) compared to those who were not taking medication (80.2%) ($p = 0.0002$). Results from Pearson's chi-square tests showed that the difference between antithrombotic medication groups for history of coronary heart disease, qualifying event (either stroke or TIA), and stroke other than the qualifying event were all significant ($p < 0.0001$). In regard to symptomatic qualifying arteries, out of the 451 enrolled patients, there were 94 who indicated internal carotid artery (20.8%), 197 for middle cerebral artery (43.7%), 60 for vertebral artery (13.3%), and 100 for basilar artery (22.2%). The differences between each symptomatic qualifying artery were statistically significant ($p = 0.005$). Finally, because patients were required to have at least 70% stenosis in order to be eligible for SAMMPRIS, the levels of stenosis of symptomatic qualifying artery were separated into 70-79%, 80-89% and 90-99%, and the percent of patients in each category are 46.5%, 41.9% and 11.5%, respectively. The mean percentage stenosis for patients in the antithrombotic medication group (80.3 ± 6.4) was not different than that of patients who were not taking medication (80.8 ± 6.9) ($p = 0.8331$).

In summary, the patients who were on antithrombotic medication were older and had higher rates of lipid disorder, coronary artery disease, qualifying event, and a history of stroke other than qualifying event.

Analysis for the Primary Endpoint

Out of the 284 patients who were taking antithrombotic medication, 56 experienced a primary endpoint. Of those 56 patients, 21 were from the medical therapy group and 35 were from the PTAS group. When examining the event rates of patients on antithrombotic medication (Table 2), it can be seen that the probability of having a primary endpoint is higher in the PTAS group at every time point. The probability of experiencing a primary endpoint in the PTAS group is 18.8% versus 8.7% in the medical management group at 6 months, 20.9% versus 13.3% at 12 months, and 21.6% versus 15.6% at 24 months. From the product-limit primary endpoint estimates shown in the Kaplan-Meier curve for patients who were on antithrombotic medication (Figure 1), it can clearly be seen that the stenting procedure is less effective compared to aggressive medical management alone throughout the entire time period. Furthermore, results from the log-rank test indicate that within the group of patients taking antithrombotic medication, the probability of having a primary endpoint for subjects in the PTAS group is significantly higher than subjects in the aggressive medical management group ($p = 0.0428$).

Out of the 167 patients who were not taking antithrombotic medication, 30 experienced a primary endpoint. Of those 30 patients, 13 were from the medical therapy group and 17 were from the PTAS group. When examining the event rates of patients not on antithrombotic medication (Table 3), it can be seen that the probability of having a primary endpoint is once again higher in the PTAS group at every time point. The probability of experiencing a primary endpoint in the PTAS group is 15.0% versus 9.25%

in the medical management group at 6 months, 17.5% versus 11.6% at 12 months, and 18.8% versus 11.6% at 24 months. From the product-limit primary endpoint estimates shown in the Kaplan-Meier curve for patients who were not on antithrombotic medication (Figure 2), it can be seen that the stenting procedure is less effective compared to aggressive medical management alone throughout the entire time period, especially during earlier time points. The event rates for patients not on antithrombotic medication indicate that the probability of experiencing a primary endpoint is higher in the PTAS group than the medical management group, but results from the log-rank test indicate that the difference is not significant ($p = 0.0428$).

The Cox proportional hazards regression results are summarized in Table 4. The estimates for *treatment*, *antithrombotic*, the interaction variable for *antithrombotic* and *treatment*, and the interaction variable for *time* and *treatment* are 2.69, 0.17, -0.49, and -0.15, respectively. The interaction variable for *antithrombotic* and *treatment* was not statistically significant ($p = 0.2927$), indicating that the effect of treatment is not statistically different between the two antithrombotic groups and suggesting that stenting does not provide any benefit over medical therapy.

Discussion

Contrary to what was originally hypothesized, the initial results of the SAMMPRIS clinical trial concluded that aggressive medical therapy was superior to angioplasty and stenting with the Wingspan stent system, which was shown to be associated with a significantly high risk of stroke or death in the population of high-risk patients with

intracranial stenosis. Shortly afterwards, the study followed up on patients in an effort to observe whether or not there was a long-term benefit to the stenting procedure. However, results eventually indicated that even after an extended follow-up period (median duration 32.4 months), the early benefit of aggressive medical treatment compared with angioplasty and stenting in high-risk patients with intracranial arterial stenosis still persisted. Because there has not yet been a treatment proved to be more effective than medical therapy, interventionalists are hope to find an alternative method to treating patients with intracranial stenosis who have failed medical management. Since patients who were taking antithrombotic medication at the time of the qualifying event can be considered to have failed medical therapy, this study focused on examining the effect of both treatments in these patients. When comparing the event rates in both antithrombotic medication groups, the probability of experiencing a primary endpoint was higher in patients assigned to the stenting group at all time points. In addition, the log rank test provided evidence that the probability of patients in the PTAS group having a primary endpoint was significantly higher than patients in the aggressive medical management group ($p = 0.0428$). Finally, the Cox proportional hazards model showed that the interaction term between *antithrombotic* and *treatment* was not significant ($p = 0.2927$), accentuating the fact that the effect of treatment was not statistically different in the two antithrombotic medication groups. Thus, the results of this study indicated that PTAS did not have any advantage over continuing with aggressive medical management alone, further emphasizing the conclusion of the initial SAMMPRIS study.

There are a few limitations to the SAMMPRIS clinical trial. Since enrollment in the study was stopped early for safety reasons, only 451 patients were enrolled. A larger sample size would most likely reduce potential bias in the data. In addition, many of the baseline characteristics were self-reported, which could generate self-serving bias. Even though a longer follow-up period study was conducted for the initial results from SAMMPRIS, a longitudinal follow up of event rates could provide clinically significant information. Although it is possible that a longer follow-up could potentially show less benefit from aggressive medical therapy, this possibility is unlikely because there is no indication that the efficacy gap between the two assigned treatment groups narrows over time in patients who are taking antithrombotic medication.

Despite the limitations, the results in this study provide a useful emphasis on the conclusion that aggressive medical management is superior to PTAS with the Wingspan system, and also generates a useful benchmark on which more SAMMPRIS-related studies can be conducted.

Appendix

Tables

Table 1: Baseline Characteristics

Characteristic	Antithrombotic Medication (N = 284)	No Antithrombotic Medication (N = 167)	p-value
Age (in years)	61.3 ± 11.0	58.4 ± 11.6	0.009*
Men	177 (62.3%)	95 (56.9%)	0.2544
Ethnic Origin			0.4996
Black	62 (21.8%)	42 (25.1%)	
White	208 (73.2%)	114 (68.3%)	
Other	14 (4.9%)	11 (6.6%)	
History of hypertension	260 (91.5%)	143 (85.6%)	0.07
Diabetes	129 (45.4%)	63 (37.7%)	0.1793
History of lipid disorder	263 (92.6%)	134 (80.2%)	0.0002*
Smoking history			0.2238
Never	108/284 (38.0%)	60/166 (36.1%)	
Former	106/284 (37.3%)	53/166 (31.9%)	
Current	70/284 (24.6%)	53/166 (31.9%)	
History of coronary artery disease	92 (32.4%)	14 (8.4%)	< 0.0001*
History of stroke other than QE	100 (35.2%)	18 (10.8%)	< 0.0001*
Qualifying events (QE)			0.0811
Stroke	134 (47.2%)	74 (44.3%)	
TIA	150 (52.8%)	93 (55.7%)	
Days from QE to randomization (median, IQR)	7.5 (13.5)	11 (14.0)	0.776
Symptomatic qualifying artery			0.0811
Internal carotid	59 (20.8%)	35 (21.0%)	0.005*

Middle cerebral	108 (38.0%)	89 (53.3%)	
Vertebral	45 (15.8%)	15 (9.0%)	
Basilar	72 (25.4%)	28 (16.8%)	
Stenosis of symptomatic qualifying artery			0.8331
Mean % stenosis	80.3 ± 6.4	80.8 ± 6.9	
70-79% stenosis	134 (47.2%)	75 (44.9%)	
80-89% stenosis	119 (41.9%)	70 (41.9%)	
90-99% stenosis	31 (10.9%)	21 (12.6%)	

Table 2: Event Rates in Patients on Antithrombotic Medication

Time	**Medical Management**	**PTAS**
6 months	8.7% (4.0% - 13.5%)	18.8% (12.4% - 25.2%)
12 months	13.3% (7.5% - 19.0%)	20.9% (14.2% - 27.5%)
24 months	15.6% (9.5% - 21.7%)	21.6% (14.9% - 28.3%)

* Data are in % (95% confidence interval), PTAS = percutaneous transluminal angioplasty and stenting

Table 3: Event Rates in Patients Not on Antithrombotic Medication

Time	**Medical Management**	**PTAS**
6 months	9.25% (3.1% - 15.4%)	15.0% (8.2% - 21.8%)
12 months	11.6% (4.9% - 18.4%)	17.5% (9.2% - 25.8%)
24 months	11.6% (4.9% - 18.4%)	18.8% (10.2% - 27.3%)

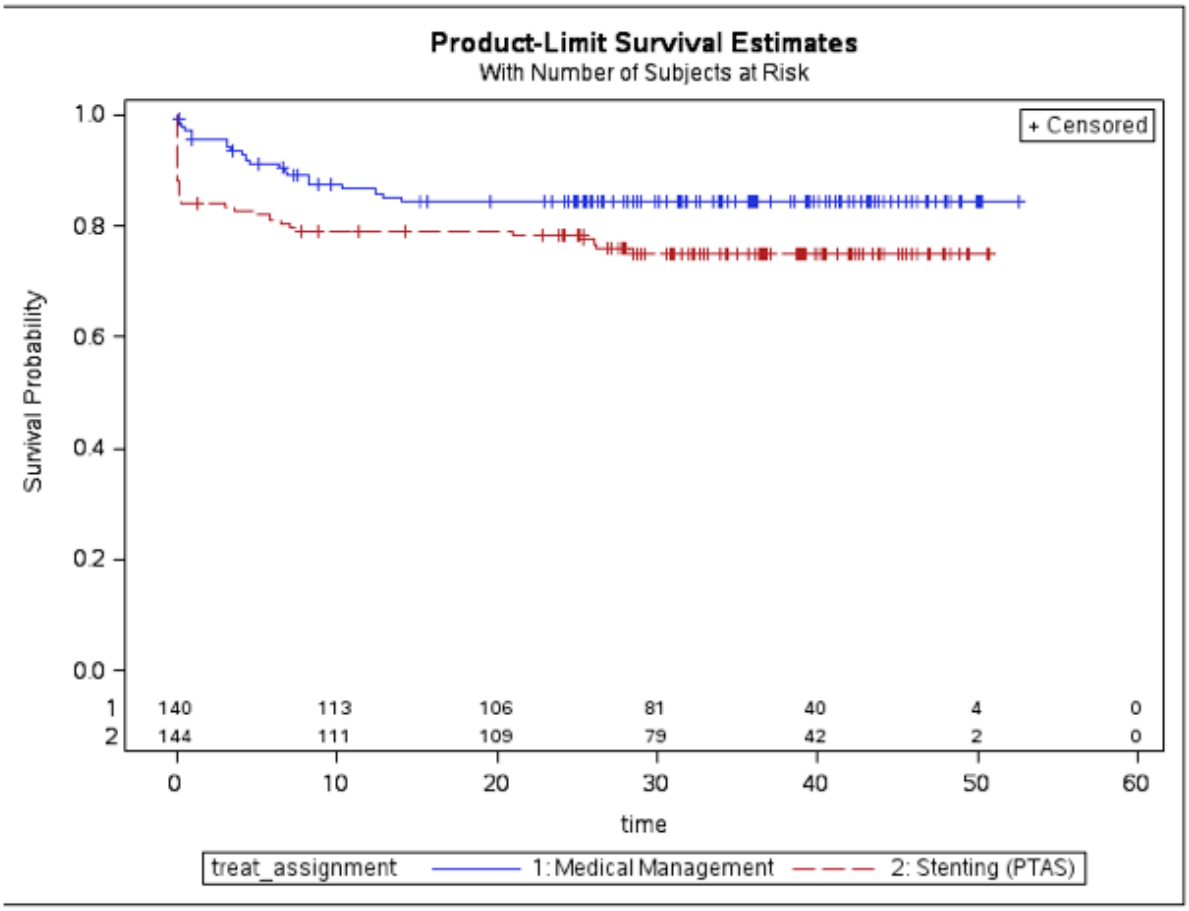
* Data are in % (95% confidence interval), PTAS = percutaneous transluminal angioplasty and stenting

Table 4: Cox Proportional Hazards Regression

Parameter	**Estimate**	**Standard Error**	**p-value**
treatment	2.68540	0.41772	< 0.0001*
antithrombotic	0.17482	0.29576	0.5545
antithrombotic * treatment	-0.48602	0.46191	0.2927
time * treatment	-0.14646	0.01872	< 0.0001*

Figures

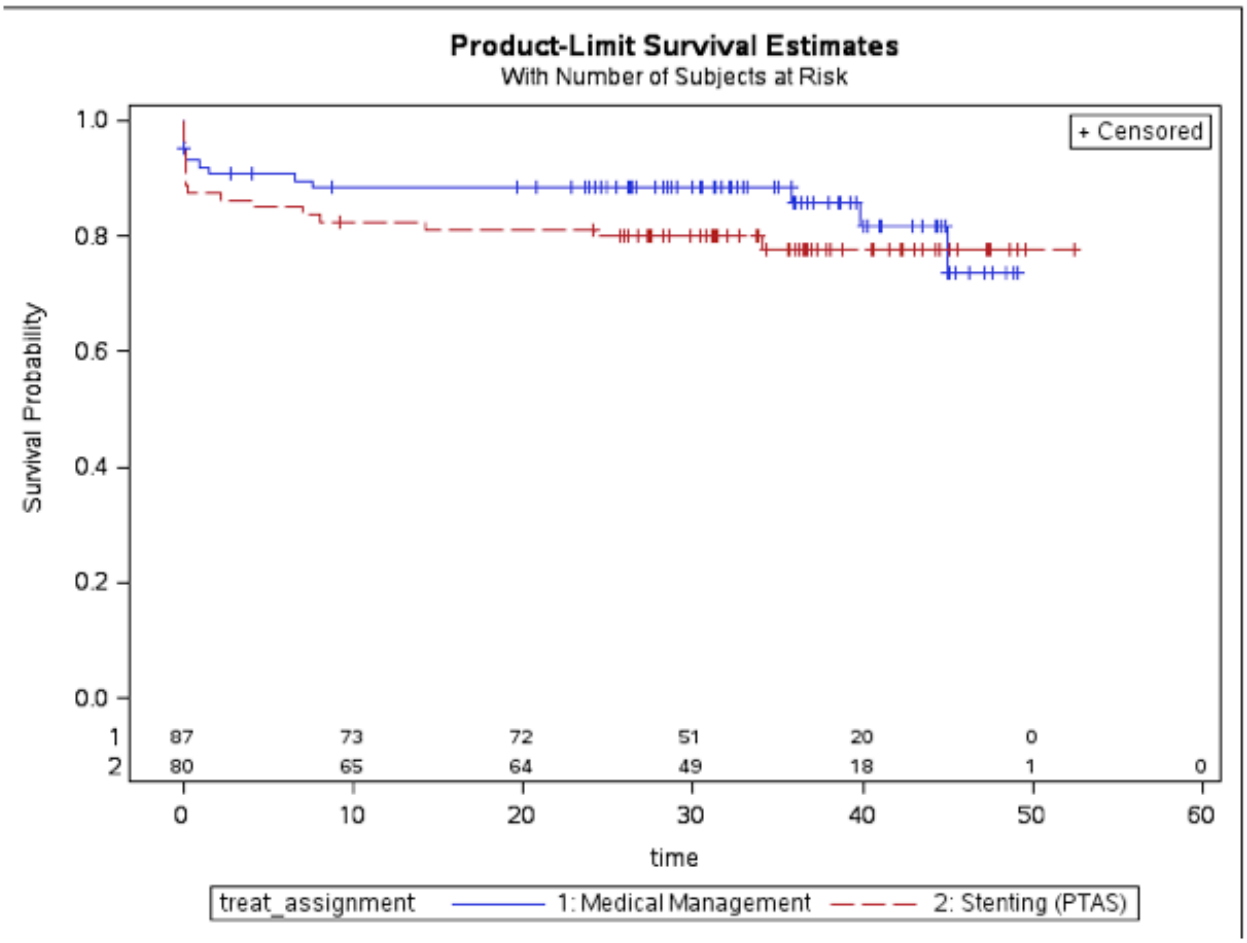
Figure 1: Kaplan-Meier Curve for the Survival Probability of the Primary End Point in Patients On Antithrombotic Medication



* Number above each time point on x-axis indicates number of patients at risk in each treatment group

Test	Chi-Square	p-value
Log-Rank	4.1052	0.0428*
Wilcoxon Rank-Sum	4.8405	0.0278*
-2log(LR)	2.6962	0.0545*

Figure 2: Kaplan-Meier Curve for the Survival Probability of the Primary End Point in Patients Not On Antithrombotic Medication



* Number above each time point on x-axis indicates number of patients at risk in each treatment group

Test	Chi-Square	p-value
Log-Rank	1.0123	0.3144
Wilcoxon Rank-Sum	1.6900	0.1936
-2log(LR)	1.0249	0.3114

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