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Intracranial Stenosis: Impact of Randomized Trials on Treatment Preferences of US Neurologists and Neurointerventionists

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Abstract

Background and Purpose—Medical and endovascular treatment options for stroke prevention in patients with symptomatic intracranial stenosis have evolved over the past several decades, but the impact of 2 major multi-center randomized stroke prevention trials on physician practices has not been studied. We sought to determine changes in US physician treatment choices for patients with intracranial atherosclerotic stenosis (ICAS) following 2 NIH-funded clinical trials that studied medical therapies (antithrombotic agents and risk factor control) and percutaneous transluminal angioplasty and stenting (PTAS).

Methods—Anonymous surveys on treatment practices in patients with ICAS were sent to physicians at 3 time points: before publication of the NIH-funded Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial (pre-WASID, 2004); 1 year after WASID publication (post-WASID, 2006); and 1 year after the publication of the NIH-funded Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) Trial (post-SAMMPRIS, 2012). Neurologists were invited to participate in the pre-WASID survey (n=525). Neurologist and Neurointerventionists were invited to participate in the post-WASID (n=598) and post-SAMMPRIS (n= 2080) survey. The 3 surveys were conducted using web-based survey tools delivered by email, and a fax-based response form delivered by email and conventional mail. Data were analyzed using the chi-square test.

Results—Pre-WASID, there was equipoise between warfarin and aspirin for stroke prevention in patients with ICAS. The number of respondents who recommended antiplatelet treatment for ICAS increased across all 3 surveys for both anterior circulation (pre-WASID=44%, post-WASID=85%, post-SAMMPRIS=94%) and posterior circulation (pre-WASID=36%, post-

DISCLOSURES:

RHW, MJL, GC, JEW, and SS have no relevant conflicts to report.

WASID=74%, post-SAMMPRIS=83%). The antiplatelet agent most commonly recommended post-WASID was aspirin, but post-SAMMPRIS it was the combination of aspirin and clopidogrel. The percentage of neurologists who recommended PTAS in > 25% of ICAS patients increased slightly from pre-WASID (8%) to post-WASID (12%), but then decreased again post-SAMMPRIS (6%). The percentage of neurointerventionists who recommended PTAS in > 25% of ICAS patients decreased from post-WASID (49%) to post-SAMMPRIS (17%).

Conclusions—The surveyed US physicians' recommended treatments for ICAS differed over the 3 survey periods, reflecting the results of the 2 NIH-funded clinical trials of ICAS and suggesting that these clinical trials changed practice in the US.

Keywords

Intracranial stenosis; Survey; Cerebral arteries; Treatment practices

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS) causes 8-10% of ischemic strokes in the US¹ and is one of the most common causes of stroke worldwide². Despite the high prevalence and high risk of recurrent stroke associated with ICAS, optimal treatment for this disease is still evolving. Over a decade ago, physician preferences regarding antithrombotic and endovascular treatment of ICAS were largely based on retrospective studies³ and expert opinion⁴, but since then, two large randomized trials have compared treatment strategies for this disease. First, the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial compared aspirin vs. warfarin among patients with symptomatic 50-99% intracranial stenosis and found that aspirin was safer and as effective as warfarin for prevention of stroke and vascular death in patients with ICAS⁵. More recently, the Stenting and Aggressive Medical Management for Prevention of Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial compared aggressive medical management vs. aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS) among patients with symptomatic 70-99% stenosis and found a high rate of periprocedural stroke after PTAS and a lower than expected rate of stroke on aggressive medical therapy⁶. The impact of these large randomized trials on clinical practice has not been quantified. Therefore, we sought to determine the impact of the results of these studies on treatment choices of US physicians managing patients with ICAS by surveying physicians before and after the publications of WASID and SAMMPRIS.

METHODS

Anonymous surveys of physician treatment choices were conducted at the following times: 1. Pre-WASID: prior to publication of WASID results (2004), 2. Post-WASID: 1 year after publication of the WASID results (2006), and 3. Post-SAMMPRIS: approximately 1 year after publication of the SAMMPRIS trial results (2012).

Pre-WASID Survey

The pre-WASID survey was conducted using a written questionnaire, sent by email or conventional mail (if no email). The survey was sent to neurologists and included WASID

investigators (n=90) and American Academy of Neurology (AAN) Stroke Section members (n=435) and it was available for 8 weeks. One reminder was sent. Completed questionnaires were faxed to the WASID Datafax server. The survey included 15 multiple choice questions (Appendix A) on the following topics: physician's practice setting, experience treating stroke, preferred antithrombotic agent for ICAS, willingness to change practice based on the WASID results, current use of PTAS for ICAS.

Post-WASID Survey

The post-WASID survey was administered using an internet-based survey tool (www.questionpro.com). The survey was sent to neurologists, including WASID investigators and AAN Stroke Section members with available email addresses (n=233), and neurointerventionists who were American Society of Interventional & Therapeutic Neuroradiology (ASITN) members with available email addresses (n=365) and it was available for 8 weeks. Not all email addresses were valid, but attempts were made to ascertain the correct contact information and remove duplicates. Email notification of the request to complete the survey and a link to the survey were sent and one reminder email was sent.

The post-WASID survey included multiple choice questions (Appendix B) on the same topics as the pre-WASID survey, but also included questions that asked respondents to choose the maximum 2-year rate of stroke in the territory of the symptomatic intracranial artery among patients treated with PTAS that would result in PTAS becoming their treatment of choice for the following 2-year stroke rates on medical therapy: 25%, 20%, 16%, and 12%. The response options reflected a 25%, 33%, 40%, 50%, and 60% relative risk reduction (RRR) from PTAS or “medical therapy would remain my treatment regardless of stenting rate”.

Post-SAMMPRIS Survey

The post-SAMMPRIS survey was administered using the internet-based Research and Electronic Data Capture (REDCap) survey tool⁷. The survey was sent to neurologists from previous email lists and AAN Stroke Section members with available email addresses (n=1400) and neurointerventionists from previous survey email lists and members of the Society of Vascular Interventional Neurologist (SVIN) and Society of Neurointerventional Surgeons (SNIS) (n=680) and it was available for one month. Attempts were made to ascertain the correct contact information and remove duplicate emails. Email notification of the request to complete the survey and a link to the survey were sent and one reminder email was sent.

The post-SAMMPRIS survey included multiple choice questions (Appendix C) on the topics of the prior surveys, but also included questions about the definition of “failure of medical therapy”, factors that influence treatment with PTAS, and the impact of SAMMPRIS on practice. Three questions asked respondents to choose the maximum 1-year rate of stroke in the territory of the symptomatic intracranial artery among patients treated with a “new endovascular procedure” that would result in that procedure becoming their treatment of choice for the following 1-year stroke rates on aggressive medical therapy: 25%, 20%, and

16%. The response options reflected a 25%, 33%, 40%, 50%, and 60% RRR from the “new endovascular procedure” or “aggressive medical therapy would remain my treatment regardless”.

Statistical Analysis

Responses were characterized by standard descriptive statistics (i.e. percentages). Survey questions required categorical responses, with limited fields for ‘other’ answers. All comparisons between groups were done using Chi-square analysis.

RESULTS

The overall response rates for the surveys were: pre-WASID, 34% (181/525); post-WASID, 33% (199/598), and post-SAMMPRIS, 15% (302/2080). While the target groups were similar between the surveys, the number of respondents who completed more than one of the surveys is unknown due to anonymity. As shown in Table 1, in all surveys, the majority of respondents had University-based practices, were in practice 10 years or more, and at least 25% of their practice involved treating stroke patients. Respondents differed significantly in practice type and years in practice since training, with more University-based respondents in the post-WASID survey.

Medical Management

Willingness to change practice—In the pre-WASID survey, the majority of neurologists (91%) indicated that if the 3-year stroke and vascular death rate was 30% on their preferred antithrombotic treatment, they would require a 20-33% RRR from the more effective antithrombotic agent to switch from their preferred agent, whether their preferred agent was warfarin or aspirin. Only 3.6% would continue to use warfarin and 1.4% would continue to use aspirin regardless of the WASID results.

Choice of antithrombotic medication—The neurologists’ preferred antithrombotic agent differed significantly between pre-WASID and post-WASID surveys for the treatment of both anterior circulation ($p<0.001$) and posterior circulation ($p<0.001$) stenoses. As shown in Figure 1, the pre-WASID neurologists’ preferred antithrombotic treatment was equally divided between warfarin and antiplatelet agents for anterior circulation stenosis, but more neurologists preferred warfarin for posterior circulation stenosis. Compared to the post-WASID respondents, more post-SAMMPRIS respondents preferred antiplatelet agents for stenosis in the anterior circulation (85% vs. 94%, $p=0.0017$) and posterior circulation (74% vs. 83%, $p=0.0145$).

Choice of antiplatelet agent—As shown in Table 2, the antiplatelet treatment most commonly preferred for ICAS post-WASID was aspirin (44% for anterior circulation, 43% for posterior circulation), whereas post-SAMMPRIS it was the combination of aspirin and clopidogrel (45% for anterior circulation, 43% for posterior circulation). The preferred dose of aspirin was 325 mg/day in both the post-WASID and post-SAMMPRIS surveys. The dose of aspirin used in WASID (1300 mg/day) was preferred by only 11% of post-WASID respondents and virtually no post-SAMMPRIS respondents. In the post-SAMMPRIS survey,

the combination of aspirin and clopidogrel (which was used for 90 days after enrollment in SAMMPRIS) was recommended for 30 days, 90 days, and indefinitely by 5%, 45%, and 44% of respondents, respectively.

Definition and treatment of patients on “maximal medical therapy”—In the post-SAMMPRIS survey, the majority of respondents (61%) considered “maximal medical therapy” to include both “use of antithrombotic treatment” and “use of aggressive medical therapy to manage risk factors and achievement of SBP<140 and LDL<70”, which were the risk factor targets in SAMMPRIS⁸. Only 4% of respondents considered “maximal medical therapy” to include only “use of antithrombotic treatment”. For treatment recommendations in patients with symptomatic intracranial stenosis who have “failed medical therapy”, 50% of respondents reported that they “assess for compliance and/or intensity medical therapy”, whereas 45% “recommend treatment with angioplasty or stenting”.

Endovascular treatment

Neurologist PTAS recommendations—The proportion of patients for whom the neurologists recommended PTAS significantly increased from the pre-WASID to the post-WASID survey ($p<0.0001$) and then decreased in the post-SAMMPRIS survey ($p=0.0135$) to approximately pre-WASID levels, as shown in Figure 2. The majority of neurologists recommended PTAS in less than 10% of their ICAS patients in all surveys.

Neurointerventionist PTAS recommendations—In the post-WASID survey, about half of neurointerventionists (51%) reported that they recommended PTAS in 25% or less of their patients with ICAS, but in the post-SAMMPRIS survey 84% recommended PTAS in 25% or less, as shown in Figure 2. The proportion of neurointerventionists who recommended PTAS in over half of their patients with ICAS decreased from 29% post-WASID to 9% post-SAMMPRIS.

Characteristics of patients selected for PTAS—In the post-SAMMPRIS survey, the patient characteristics that were most commonly selected as influencing the decision to recommend PTAS were: symptoms attributed to hypoperfusion (81%), severe stenosis (68%), impaired collaterals (59%), and recent symptoms (54%).

Required risk-reductions to change treatment of choice—Figure 3 shows the percentage of respondents in the post-WASID and post-SAMMPRIS surveys who selected each RRR for PTAS (post-WASID) or a “new endovascular procedure” (post-SAMMPRIS) for the proposed 2-year rates of stroke in the territory of the symptomatic stenotic artery on medical treatment. For a stroke rate of 25% on medical therapy, the majority of post-WASID respondents required a minimum RRR of 33% (corresponding to a number needed to treat (NNT) of 13) from PTAS to make PTAS their treatment of choice. As the stroke rate on medical therapy decreased, the RRR required increased. In the post-SAMMPRIS survey, the majority of respondents wanted a RRR of 40% (NNT of 10 for a stroke rate of 25% on medical therapy) from the “new procedure”, which is a higher RRR compared to the post-WASID survey respondents for the same event rate of 25% on medical therapy. For a medical therapy stroke rate of 16%, the majority of post-WASID respondents required a

minimum RRR of 40% (NNT of 17) from PTAS to make PTAS their treatment of choice. In the post-SAMMPRIS survey, the majority of respondents wanted a RRR of 50% (NNT of 13 for a stroke rate of 16% on medical therapy) from the “new procedure”, which is also a higher RRR compared to the post-WASID survey respondents for the same event rate of 16% on medical therapy.

Impact on practice—In the Post-SAMMPRIS survey, 91% (100/110) of respondents who participated in SAMMPRIS and 82% (228/277) of overall respondents indicated that the SAMMPRIS results changed the way they managed patients with ICAS.

DISCUSSION

Previous surveys have examined stroke prevention practices⁹⁻¹¹, but our surveys focused on the impact of two large randomized clinical trials on physician treatment practices for ICAS in the US. We found significant differences in treatment choices for both medical and endovascular treatment of ICAS across the 3 surveys. While we found a tendency to adopt both medical and endovascular treatments supported by the clinical trial results, not all of the more effective treatment strategies in the trials were widely adopted.

Medical management of ICAS changed over the three study periods, which extended over more than a decade. After the publication of the WASID results, most neurologists preferred antiplatelet therapy over warfarin, and the preferred antiplatelet agent in the post-WASID survey was aspirin. However, despite the fact that aspirin was the only antiplatelet agent tested in WASID, a surprising number of respondents in the post-WASID survey (more than half) preferred other antiplatelet agents or combinations of antiplatelet agents over aspirin. This finding may be due to studies that showed other antiplatelet regimens may have a role in preventing stroke in patients with large artery atherosclerosis^{12, 13}. The most commonly prescribed dose of aspirin in the post-WASID survey was 325 mg/day, despite the fact that the dose used in WASID was 1300 mg/day¹⁴. A stroke prevention guideline statement published around the time of the post-WASID survey (2006) recommended aspirin doses of 50-325 mg/day in patients with atherosclerotic stroke or TIA based on general safety and efficacy data¹⁵, suggesting that our survey results regarding aspirin dose are consistent with consensus expert opinion at the time.

The neurologists' preference for dual antiplatelet (aspirin and clopidogrel) therapy in patients with ICAS increased from the post-WASID to the post-SAMMPRIS surveys. This is likely because of the lower early recurrent stroke rates in SAMMPRIS (when patients were on a combination of aspirin and clopidogrel) compared to WASID historical controls taking either aspirin or warfarin⁶. Results from the CLAIR study also showed that combined aspirin and clopidogrel decreased the number of microembolic signals on transcranial doppler compared to aspirin alone in patients with recently symptomatic ICAS¹⁶, further supporting the use of dual antiplatelet therapy for early recurrent stroke prevention in ICAS. However, despite the fact that in the SAMMPRIS trial dual antiplatelet therapy was only used for 90 days, almost equal numbers of respondents in the post-SAMMPRIS survey recommended dual antiplatelet therapy for 90 days (45%) and indefinitely (44%). So, in both the post-WASID and post-SAMMPRIS surveys it appears that the general selection of

anti-thrombotic agents may be influenced by the clinical trial results, but that the specifics of the trial treatment protocols (e.g. specific antiplatelet agent or duration of treatment) were not strictly adopted.

The post-SAMMPRIS survey respondents' definitions of "maximal medical management" included risk factor modification as a component, with only 4% of respondents indicating that "failure of medical therapy" was limited to failure of antithrombotic agents alone. This finding probably reflects the respondents' recognition of the benefit of intensive risk factor management for improving the outcomes in medically treated patients in the SAMMPRIS trial compared to WASID historical controls⁶ as well as previous analyses of WASID and SAMMPRIS data that have demonstrated that 'failure of antithrombotic therapy' is not a useful predictor of increased risk of recurrent stroke in patients with ICAS^{17, 18}.

While the majority of neurologists recommend PTAS in < 10% of their patients with ICAS in all survey periods, the percentage of neurologists who recommended PTAS in > 10% of patients significantly increased from the pre- to the post-WASID surveys. This finding is consistent with a retrospective study that showed an increase in intracranial PTAS procedures after the publication of the WASID results¹⁹. The increased frequency of endovascular procedures for ICAS after WASID, despite lack of evidence for their efficacy for stroke prevention, may have reflected a perceived failure of medical therapies given the high risk of recurrent stroke in WASID and the availability of the Wingspan stenting system that was approved by the FDA under a humanitarian device exemption (August 3, 2005). However, in the post-SAMMPRIS survey, the percentage of neurologists who recommended PTAS in > 10% of patients returned to pre-WASID levels, likely due to the early SAMMPRIS results that showed no benefit from PTAS⁶.

The post-WASID and post-SAMMPRIS surveys asked respondents what benefit they would require from endovascular procedures (PTAS and a "new endovascular procedure", respectively) over medical therapy to make the procedure their treatment of choice for ICAS. For carotid stenosis, the North American Symptomatic Carotid Endarterectomy Trial (NASCET)²⁰ showed the 2-year risk of ipsilateral stroke in patients with symptomatic extracranial carotid stenosis was 26% on medical therapy and 9% with surgical therapy, resulting in a NNT with endarterectomy of 6 patients. In our survey of ICAS treatment preferences, for a risk of stroke on medical therapy similar to NASCET (25% at 2-years), the majority of our respondents required a NNT of 13 patients to make an endovascular procedure the treatment of choice over medical therapy. This finding suggests that physicians may incorporate the risk/benefit ratio of established stroke prevention interventions into their expected benefits of procedures or they may have an inherent threshold for benefit that they feel is optimal for similar high-risk conditions. As expected, the RRR from PTAS and the "new endovascular procedure" required by our survey respondents increased as the proposed risk of stroke on medical therapy decreased. In other words, as the rates of recurrent stroke with medical therapy decrease, the respondents require a much larger benefit from ICAS endovascular procedures to make the procedures their treatment of choice.

One of the reasons we undertook the post-WASID survey was to help design the “Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS)” Trial²¹. Historically, the hypothesized benefit of one treatment over another in many trials has been selected by estimating the treatment effect that physicians and patients would deem important to adopt a new treatment and by considering the feasibility of recruiting the required sample size. We chose to quantify the minimum benefit from PTAS that would make it the treatment of choice by surveying physicians who take care of patients with ICAS. The use of physician surveys may provide a more scientific approach for determining the clinically meaningful benefit that physicians will require to adopt a new treatment, thereby increasing the impact of clinical trials on clinical practice.

Our study has some weaknesses, including the practice type and experience differences between the pre- and post-WASID survey respondents. The post-WASID survey included more University-based respondents than the other surveys, but the majority of respondents were at University centers in all 3 surveys. Additionally, we did not survey a random sample of physicians who take care of patients with ICAS and we limited the survey to physicians in the US. Given that the approach to patients with intracranial stenosis varies in different countries such as China²², our results may not be representative of physicians who treat patients with ICAS worldwide. Finally, our survey data are self-reported and therefore subject to the inherent biases of such data, such as social desirability bias and recall bias.

In summary, our study shows that after the publications of the NIH-funded WASID and SAMMPRIS trials, there was a significant change in physician self-reported medical and endovascular treatment practices for ICAS in the US. Based on these results, we expect that future clinical trials to determine the best management of patients with ICAS will likely have a significant impact on physician practices.

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Appendix A



Survey of Treatment Practices for Symptomatic Intracranial Arterial Stenosis

Please check (X) only one answer unless otherwise specified.

- Which of the following best describes the setting of your clinical practice?
 - A. Community-based private practice
 - B. University-hospital based
 - C. Other (specify): _____
- Which of the following represents your number of years of clinical experience?
 - A. 1 - 2 years
 - B. 3 - 5 years
 - C. 6 - 10 years
 - D. More than 10 years
- What proportion of patients in your clinical practice do you treat for stroke?
 - A. 76 - 100%
 - B. 51 - 75%
 - C. 26 - 50%
 - D. 15 - 25%
 - E. Less than 15%
- Which non-invasive test do you use to initially diagnose intracranial stenosis? (check only one box)
 - A. MRA
 - B. TCD
 - C. CTA
 - D. Other (specify): _____
 - E. Combination of above (specify): _____
- Do you require catheter angiography to confirm intracranial stenosis before starting long-term antithrombotic therapy?
 - A. Yes
 - B. No
- Which of the following is your preferred antithrombotic agent for the long-term treatment of symptomatic stenosis of the middle cerebral artery or carotid siphon?
 - A. Warfarin
 - B. Antiplatelet therapy
 - C. Combination therapy (specify): _____
 - D. Other (specify): _____
- If you answered 'B' or 'C' to #6, which of the following is/are your preferred antithrombotic agent(s)? (X all that apply)
 - A. Aspirin
 - B. Plavix
 - C. Aggrenox
 - D. Other (specify): _____
- Which of the following is your preferred antithrombotic agent for the long-term treatment of symptomatic stenosis of the basilar or intracranial vertebral artery?
 - A. Warfarin
 - B. Antiplatelet therapy
 - C. Combination therapy (specify): _____
 - D. Other (specify): _____
- If you answered 'B' or 'C' to #8, which of the following is/are your preferred antithrombotic agent(s)? (X all that apply)
 - A. Aspirin
 - B. Plavix
 - C. Aggrenox
 - D. Other (specify): _____

Please continue to page 2.



Survey of Treatment Practices for Symptomatic Intracranial Arterial Stenosis

Questions #10-14 refer to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study, which is an ongoing NIH-funded clinical trial comparing the efficacy of warfarin versus aspirin for preventing stroke and vascular death in patients who have symptomatic intracranial arterial stenosis.

- If the results of WASID were to show that warfarin is superior to aspirin, to what degree would this finding impact your choice of antithrombotic therapy for treating this disease?
 - A. Greatly
 - B. Moderately
 - C. Minimally
 - D. Not at all
- If the results of WASID were to show that aspirin is superior to warfarin, to what degree would this finding impact your choice of antithrombotic therapy for treating this disease?
 - A. Greatly
 - B. Moderately
 - C. Minimally
 - D. Not at all
- If the results of WASID were to show that aspirin and warfarin were equally effective, to what degree would this finding impact your choice of antithrombotic therapy for treating this disease?
 - A. Greatly
 - B. Moderately
 - C. Minimally
 - D. Not at all
- If your preferred antithrombotic agent for treating symptomatic anterior or posterior circulation intracranial arterial stenosis is WARFARIN, please answer the following: If the 3-year rate of stroke and vascular death is 30% among patients treated with warfarin in WASID, what would the 3-year rate of stroke and vascular death have to be among patients treated with aspirin in order for you to change your therapeutic regimen to aspirin or other antiplatelet therapy?
 - A. 24% (e.g., 20% relative risk reduction)
 - B. 20% (e.g., 33% relative risk reduction)
 - C. 18% (e.g., 40% relative risk reduction)
 - D. 15% (e.g., 50% relative risk reduction)
 - E. 12% (e.g., 60% relative risk reduction)
 - F. I would continue to use warfarin regardless of the rate on aspirin.
- If your preferred antithrombotic agent for treating symptomatic anterior or posterior circulation intracranial arterial stenosis is ANTIPLATELET THERAPY, please answer the following: If the 3-year rate of stroke and vascular death is 30% among patients treated with aspirin in WASID, what would the 3-year rate of stroke and vascular death have to be among patients treated with warfarin in order for you to change your therapeutic regimen to warfarin?
 - A. 24% (e.g., 20% relative risk reduction)
 - B. 20% (e.g., 33% relative risk reduction)
 - C. 18% (e.g., 40% relative risk reduction)
 - D. 15% (e.g., 50% relative risk reduction)
 - E. 12% (e.g., 60% relative risk reduction)
 - F. I would continue to use antiplatelet therapy regardless of the rate on warfarin.
- In what proportion of patients who have symptomatic intracranial arterial stenosis do you use angioplasty or stenting as a therapeutic strategy?
 - A. More than 50%
 - B. 26 - 50%
 - C. 10 - 25%
 - D. Less than 10%

Upon completion, please fax both pages of this survey (without a cover page) to:
404-727-1297

Appendix B

Treatment Practices for Symptomatic Intracranial Stenosis (2006)

1. What type of physician are you?
 - a. Neurologist
 - b. Neurointerventional Radiologist
 - c. Neurosurgeon
 - d. Other
2. Did you participate in WASID?
 - a. Yes
 - b. No
3. Which of the following best describes the setting of your clinical practice?
 - a. Community-based private practice
 - b. University-hospital based
4. Which of the following represents your number of years of clinical experience since your specialty training was completed?
 - a. 1-2 years
 - b. 3-5 years
 - c. 6-10 years
 - d. 11-15 years
 - e. more than 15 years
5. Approximately, what proportion of patients in your clinical practice do you treat for stroke?
 - a. 76-100%
 - b. 51-75%
 - c. 26-50%
 - d. 15-25%
 - e. less than 15%
6. Which of the following is your preferred antithrombotic agent for the long-term treatment of symptomatic stenosis of the MIDDLE CEREBRAL ARTERY (MCA) or CAROTID SIPHON?
 - a. Warfarin
 - b. Antiplatelet therapy
 - c. Combination therapy (Warfarin & Antiplatelet)
 - d. Other
7. Which of the following is your preferred antiplatelet agent for MCA or CAROTID SIPHON stenosis?
 - a. Aspirin
 - b. Plavix
 - c. Aggrenox
 - d. Combination Antiplatelet
 - e. Other
8. What is your preferred COMBINATION of antiplatelet agents for MCA or CAROTID SIPHON stenosis? (check all that apply)
 - Aspirin
 - Plavix
 - Aggrenox
 - Other
9. What dose of aspirin do you typically prescribe for MCA or CAROTID SIPHON stenosis?
 - a. 81 mg/day
 - b. 325 mg/day
 - c. 650 mg/day
 - d. 1300 mg/day
 - e. Other
10. Which of the following is your preferred antithrombotic agent for the long-term treatment of symptomatic stenosis of the BASILAR or INTRACRANIAL VERTEBRAL ARTERY?
 - a. Warfarin
 - b. Antiplatelet therapy
 - c. Combination therapy (Warfarin & Antiplatelet)
 - d. Other
11. Which of the following is your preferred antiplatelet agent for BASILAR or VERTEBRAL ARTERY stenosis?
 - a. Aspirin
 - b. Plavix
 - c. Aggrenox
 - d. Combination Antiplatelet
 - e. Other
12. What is your preferred COMBINATION of antiplatelet agents for BASILAR or VERTEBRAL ARTERY stenosis? (check all that apply)
 - Aspirin
 - Plavix
 - Aggrenox
 - Other
13. What dose of aspirin do you typically prescribe for BASILAR or VERTEBRAL ARTERY stenosis?
 - a. 81 mg/day
 - b. 325 mg/day
 - c. 650 mg/day
 - d. 1300 mg/day
 - e. Other
14. In what proportion of patients who have symptomatic intracranial arterial stenosis do you currently use ANGIOPLASTY or STENTING as a therapy?
 - a. More than 50%
 - b. 26-50%
 - c. 10-25%
 - d. Less than 10%
 - e. None
15. For the following 2-year rates of stroke in the territory of the intracranial artery among patients treated with best MEDICAL THERAPY, please choose the MAXIMUM 2-year rate of stroke in the territory among patients treated with STENTING that would result in stenting becoming your treatment of choice. The 2 year stenting stroke rates in the choices below already include an initial procedural stroke rate of 6-8%.

If the 2 year stroke risk with medical therapy is 25%, the 2 year risk with stenting would have to be:

 - a. 19% (i.e. 25% relative risk reduction or NNT = 17)
 - b. 17% (i.e. 33% relative risk reduction or NNT = 13)
 - c. 15% (i.e. 40% relative risk reduction or NNT = 10)
 - d. 12.5% (i.e. 50% relative risk reduction or NNT = 8)
 - e. 10% (i.e. 60% relative risk reduction or NNT = 7)
 - f. Medical therapy would remain my treatment regardless of stenting rate.
16. If the 2 year stroke risk with medical therapy is 20%, the 2 year risk with stenting would have to be:
 - a. 15% (i.e. 25% relative risk reduction or NNT = 20)
 - b. 13% (i.e. 33% relative risk reduction or NNT = 14)
 - c. 12% (i.e. 40% relative risk reduction or NNT = 13)
 - d. 10% (i.e. 50% relative risk reduction or NNT = 10)
 - e. 8% (i.e. 60% relative risk reduction or NNT = 8)
 - f. Medical therapy would remain my treatment regardless of stenting rate.
17. If the 2 year stroke risk with medical therapy is 16%, the 2 year risk with stenting would have to be:
 - a. 12% (i.e. 25% relative risk reduction or NNT = 25)
 - b. 11% (i.e. 33% relative risk reduction or NNT = 20)
 - c. 10% (i.e. 40% relative risk reduction or NNT = 17)
 - d. 8% (i.e. 50% relative risk reduction or NNT = 13)
 - e. 6% (i.e. 60% relative risk reduction or NNT = 10)
 - f. Medical therapy would remain my treatment regardless of stenting rate.
18. If the 2 year stroke risk with medical therapy is 12%, the 2 year risk with stenting would have to be:
 - a. 9% (i.e. 25% relative risk reduction or NNT = 33)
 - b. 8% (i.e. 33% relative risk reduction or NNT = 25)
 - c. 7% (i.e. 40% relative risk reduction or NNT = 20)
 - d. 6% (i.e. 50% relative risk reduction or NNT = 17)
 - e. 5% (i.e. 60% relative risk reduction or NNT = 14)
 - f. Medical therapy would remain my treatment regardless of stenting rate.

Appendix C: Intracranial Stenosis Treatment Post-SAMMPRIS

The following is an anonymous survey about your treatment preferences for intracranial stenosis. Please answer all of the following questions and note that responses to certain questions will prompt follow up questions. Thank you!

- 1 What type of physician are you? (Check 1 only)
 - a. Neurologist but not an interventionist
 - b. Neurology Interventionist
 - c. Neuroradiologist
 - d. Neurosurgeon
 - e. Other
 If Other, please indicate: _____
- 2 Did you participate in WASID? (Check 1 only) Yes No
- 3 Did you participate in SAMMPRIS? (Check 1 only) Yes No
- 4 Which of the following best describes the setting of your clinical practice? (Check 1 only)
 - a. Community-based private practice
 - b. University-hospital based
 - c. Other
 If Other, please explain: _____
- 5 Which of the following represents the number of years of clinical experience since your specialty training was completed? (Check 1 only)
 - a. 1-2 years
 - b. 3-5 years
 - c. 6-10 years
 - d. 11-15 years
 - e. more than 15 years
- 6 Approximately, what proportion of patients in your clinical practice do you treat for stroke? (Check 1 only)
 - a. 76-100%
 - b. 51-75%
 - c. 26-50%
 - d. 15-25%
 - e. less than 15%

Antithrombotic treatment of MCA or carotid siphon stenosis:

- 7 Which of the following is your preferred antithrombotic agent for the long-term treatment of symptomatic stenosis of the MIDDLE CEREBRAL ARTERY (MCA) or CAROTID SIPHON? (Check 1 only)
 - a. anticoagulation with warfarin or newer anticoagulant
 - b. antiplatelet therapy alone
 - c. combination anticoagulant + antiplatelet
 - d. other
 If Other, please explain: _____

Which of the following is your preferred antiplatelet agent for symptomatic MCA or CAROTID SIPHON stenosis? (Check 1 only)

- a. aspirin alone
- b. clopidogrel alone
- c. combination aspirin + clopidogrel
- d. Aspirin and dipyridamole
- e. other

If Other, please explain: _____

What DOSE of aspirin do you typically prescribe for MCA or CAROTID SIPHON stenosis? (Check 1 only)

- a. 81 mg/day
- b. 325 mg/day
- c. 650 mg/day
- d. 1300 mg/day
- e. other

If Other, please explain: _____

How long do you prescribe combination aspirin + clopidogrel after presentation? (Check 1 only)

- a. 7 days
- b. 30 days
- c. 90 days
- d. indefinitely
- e. other

If Other, please explain: _____

Antithrombotic treatment of vertebral or basilar stenosis:

8 Which of the following is your preferred antithrombotic agent for the long-term treatment of symptomatic stenosis of the BASILAR or VERTEBRAL ARTERIES? (Check 1 only)

- a. anticoagulation with warfarin or newer anticoagulant
- b. antiplatelet therapy alone
- c. combination anticoagulant + antiplatelet
- d. other

If Other, please explain: _____

Which of the following is your preferred antiplatelet agent for BASILAR or VERTEBRAL ARTERIES stenosis? (Check 1 only)

- a. aspirin
- b. clopidogrel
- c. combination aspirin + clopidogrel
- d. Aspirin and dipyridamole
- e. other

If Other, please explain: _____

What DOSE of aspirin do you typically prescribe for symptomatic BASILAR or VERTEBRAL ARTERY stenosis? (Check 1 only)

- a. 81 mg/day
- b. 325 mg/day
- c. 650 mg/day
- d. 1300 mg/day
- e. other

If Other, please explain: _____

How long do you prescribe combination aspirin + clopidogrel after presentation? (Check 1 only)

- a. 7 days
- b. 30 days
- c. 90 days
- d. indefinitely
- e. other

If Other, please explain: _____

Endovascular treatment:

9 In what proportion of patients who have symptomatic intracranial arterial stenosis do you currently recommend ANGIOPLASTY or STENTING as therapy? (Check 1 only)

- a. More than 50%
- b. 26-50%
- c. 10-25%
- d. less than 10%
- e. None

What procedure do you recommend? (Check 1 only)

- a. angioplasty only
- b. angioplasty and stenting with self-expanding stent
- c. angioplasty and stenting with balloon-expandable stent
- d. other

If Other, please explain: _____

10 In your practice, what do you consider "failure of maximal medical therapy?" Stroke despite: (Check 1 only but combinations of a, b, and c provided as options too.)

- a. use of antithrombotic treatment
- b. use of aggressive medical therapy to manage risk factors regardless of BP and LDL levels achieved
- c. use of aggressive medical therapy to manage risk factors AND achievement of SBP < 140 and LDL < 70
- d. both a. and b.
- e. both a. and c.
- f. other

If Other, please explain: _____

- 11 How do you treat patients who have failed medical therapy?
- Assess for compliance and/or intensify medical therapy
 - Recommend angioplasty or stenting
 - Other
- If Other, please explain: _____
- 12 Which patient characteristics make you MORE likely to recommend ANGIOPLASTY or STENTING? (Select the 4 most important) (Please answer even if you don't usually recommend endovascular treatment)
- recent symptoms
 - stroke rather than TIA presentation
 - severe stenosis
 - anterior circulation location of stenosis
 - impaired collaterals
 - symptoms attributed to hypoperfusion through
 - stenotic artery
 - presence of diabetes
 - presence of smoking
 - young age
 - gender
 - race or ethnicity
 - patient requests treatment

Impact of the SAMMPRIS Trial on your practice:

- 13 Have the results of SAMMPRIS changed the way you manage patients with symptomatic intracranial stenosis? (Check 1 only) yes no
- If no, please explain: _____

In what area(s) has the results of SAMMPRIS changed the way you manage patients with this disease? (check all that apply)

- Stopped recommending endovascular treatment
 - Combine antiplatelet medications
 - Use of statins for treating LDL < 70
 - Blood Pressure medications to target SBP < 140 (< 130 in diabetics)
 - Incorporating a lifestyle program
 - Other
- If Other, please explain: _____

Potential benefit of new endovascular treatments:

For the following 1-year rates of stroke in the territory of the intracranial artery among patients treated with AGGRESSIVE MEDICAL THERAPY, please choose the MAXIMUM 1-year rate of stroke in the territory among patients treated with a new endovascular procedure that would result in the procedure becoming your treatment of choice. Assume that the peri-procedural risk of stroke is responsible for half of the total 1-year risks provided for the endovascular treatment. *Note: for answers NNT = number needed to treat.

- 14 If the 1 year stroke risk with aggressive medical therapy is 25%, the 1 year risk with the new procedure would have to be: (Check 1 only)
- Aggressive medical management would remain my treatment regardless
 - 10% (i.e. 60% relative risk reduction or NNT =7)
 - 12.5% (i.e. 50% relative risk reduction or NNT= 8)
 - 15% (i.e. 40% relative risk reduction or NNT =10)
 - 17% (i.e. 33% relative risk reduction or NNT =13)
 - 19% (i.e. 25% relative risk reduction or NNT =17)
- 15 If the 1 year stroke risk with aggressive medical therapy is 20%, the 1 year risk with the new procedure would have to be: (Check 1 only)
- Aggressive medical management would remain my treatment regardless
 - 8% (i.e. 60% relative risk reduction or NNT = 8)
 - 10% (i.e. 50% relative risk reduction or NNT =10)
 - 12% (i.e. 40% relative risk reduction or NNT =13)
 - 13% (i.e. 33% relative risk reduction or NNT =14)
 - 15% (i.e. 25% relative risk reduction or NNT =20)
- 16 If the 1 year stroke risk with aggressive medical therapy is 16%, the 1 year risk with the new procedure would have to be: (Check 1 only)
- Aggressive medical management would remain my treatment regardless
 - 6% (i.e. 60% relative risk reduction or NNT =10)
 - 8% (i.e. 50% relative risk reduction or NNT =13)
 - 10% (i.e. 40% relative risk reduction or NNT =17)
 - 11% (i.e. 33% relative risk reduction or NNT =20)
 - 12% (i.e. 25% relative risk reduction or NNT =25)

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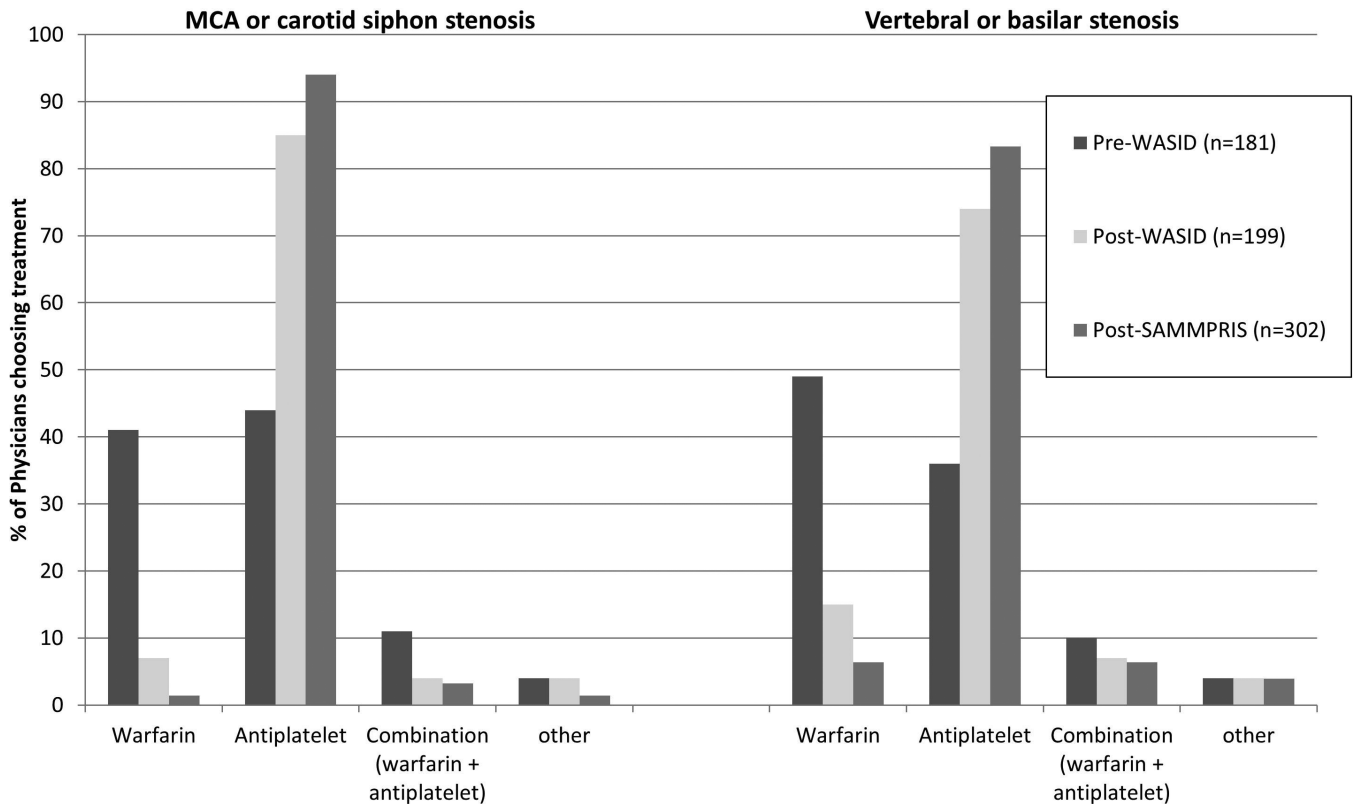


Figure 1. Antithrombotic medication treatment preferences for symptomatic intracranial stenosis in 3 surveys

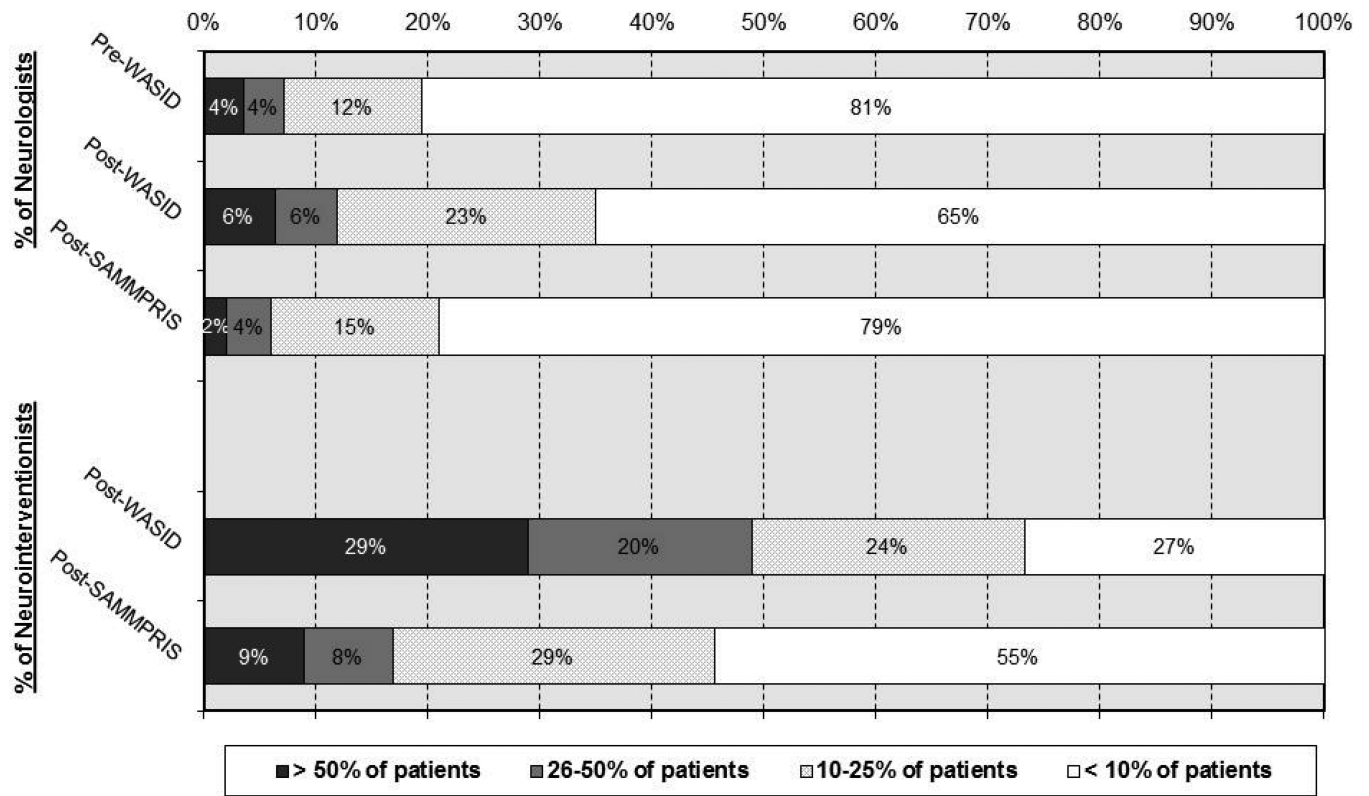


Figure 2. Percentage of respondents who recommend angioplasty and stenting for a given proportion of patients with ICAS

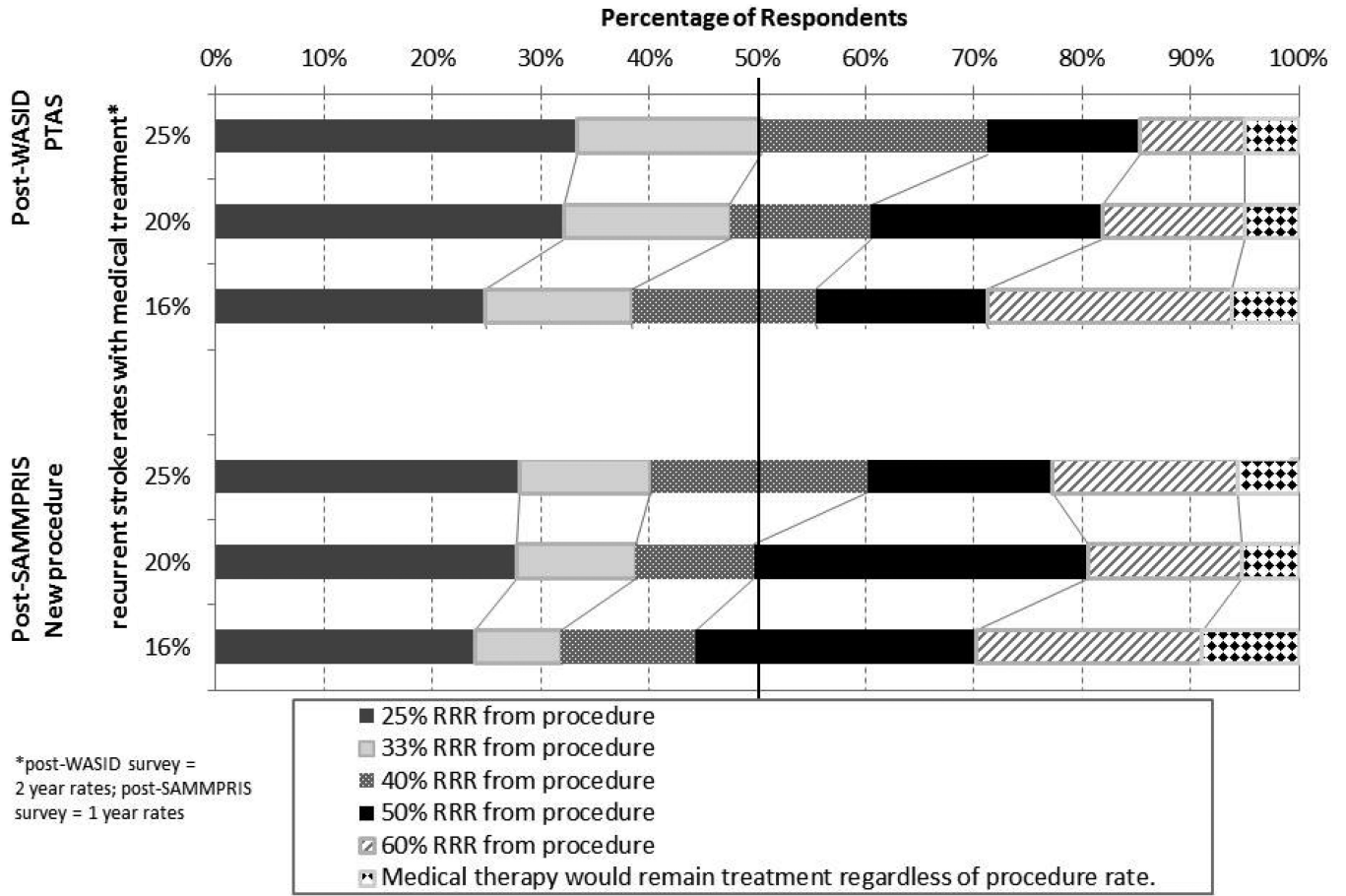


Figure 3. Relative Risk Reduction (RRR) required by respondents to make the endovascular procedure the treatment of choice over medical therapy

Table 1

Characteristics of the survey respondents

	Pre-WASID n=181		Post-WASID n=199		Post-SAMMPRIS n=302		p-value*
	No.	%	No.	%	No.	%	
type of practice							
community	43	25%	37	19%	82	27%	0.0431
university hospital	108	64%	145	76%	195	65%	
other	18	11%	9	5%	23	8%	
years clinical experience since training							
1-2	1	1%	5	3%	35	12%	<0.001
3-5	22	13%	16	8%	48	16%	
6-10	35	21%	62	32%	31	10%	
11-15**	111	66%	30	16%	50	17%	
> 15***	-	0%	78	41%	137	50%	
Proportion of patients in clinical practice treated for stroke							
76-100%	45	26%	60	31%	90	30%	0.3623
51-75%	39	23%	49	26%	70	23%	
26-50%	39	23%	33	17%	58	19%	
15-25%	37	22%	27	14%	54	18%	
< 15%	10	6%	22	12%	28	9%	
Participation in clinical trial							
WASID (yes)	55	30%	70	35%	65	22%	0.0026
SAMMPRIS (yes)	-	-	-	-	110	36%	

* Chi-square p-value comparing characteristics across the 3 surveys

*** the Pre-WASID categories were 1-2, 3-5, 6-10, and >10 years.

Table 2
 Post-WASID vs. Post-SAMMPRIS respondents preferred antiplatelet agent regimen

	MCA or carotid siphon stenosis		Vertebral or basilar stenosis	
	Post-WASID	Post-SAMMPRIS	Post-WASID	Post-SAMMPRIS
Which of the following is your preferred antiplatelet agent?				
Aspirin	75 (44%)	93 (34%)	66 (43%)	95 (38%)
Clopidogrel (Plavix)	25 (15%)	34 (12%)	24 (16%)	32 (13%)
Aspirin and Clopidogrel [*]	43 (25%)	124 (45%)	39 (25%)	110 (43%)
Aspirin and Dipyridamole (Aggrenox)	26 (15%)	19 (7%)	25 (16%)	14 (6%)
Other	1 (1%)	4 (1%)	0 (0%)	2 (1%)
	p<0.0001		p<0.0001	
What dose of aspirin do you typically prescribe?				
81 mg/day	21 (21%)	93 (43%)	17 (19%)	81 (40%)
325 mg/day	64 (65%)	118 (54%)	58 (66%)	118 (58%)
650 mg/day	2 (2%)	1 (<1%)	2 (2%)	1 (<1%)
1300 mg/day	11 (11%)	1 (<1%)	10 (11%)	1 (<1%)
Other	1 (1%)	4 (2%)	1 (1%)	4 (2%)
	p<0.0001		p<0.0001	

* In the Post-WASID survey, the selection choice was "Combination antiplatelet" and the most common combination selected was aspirin and clopidogrel. In the Post-SAMMPRIS survey, the choice was "Combination aspirin + clopidogrel".