



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

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Rationale, Design, and Implementation of Aggressive Risk Factor Management in the SAMMPRIS Trial

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Introduction

The value of comprehensive intensive atherosclerotic risk factor control in patients with coronary artery disease (CAD) is well-established. In 2007, the COURAGE trial demonstrated that among patients with stable coronary disease, intensive management of vascular risk factors was as good as endovascular intervention plus intensive medical management for preventing cardiac ischemic events¹. Yet, despite the fact that atherosclerotic risk factor control in patients with stroke or TIA is recommended by

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guidelines², a multimodal approach to prevention has not previously been tested in patients with atherosclerotic stroke. Older atherosclerotic-stroke prevention trials comparing carotid revascularization to medical therapy, such as NASCET³ and ACAS⁴, were performed in an era before statins and angiotensin converting enzyme (ACE) inhibitors became standard of care, and therefore risk factor control was not adequate by today's standards. Even recent trials comparing carotid revascularization procedures^{5, 6} had little emphasis on risk factor control in their design and therefore had little impact on blood pressure and cholesterol measures at 1 year^{7, 8}. Among stroke prevention trials in patients with heterogeneous causes of stroke, several trials have studied the effects of specific risk factor medications^{9–11} or of intensive control of a particular risk factor, such as blood pressure¹², but no stroke prevention trials have used a multi-modal aggressive risk factor approach.

Among patients with intracranial atherosclerosis, which may be the most common cause of stroke world-wide¹³, risk factor control is also believed to be important for stroke prevention. The Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial, in which patients with symptomatic intracranial stenosis were managed with either warfarin or aspirin and usual risk factor management¹⁴, showed that patients with poorly controlled blood pressure and elevated cholesterol during follow-up had significantly higher rates of recurrent stroke and other vascular events¹⁵, suggesting that aggressive management of vascular risk factors may benefit these patients. However, the impact of multi-modal aggressive risk factor control as a primary treatment strategy in patients with intracranial stenosis had not been assessed. Endovascular treatment of intracranial stenosis was also an emerging, yet unproven therapy. Therefore, in an effort to study these two treatment strategies, the Stenting and Aggressive Medical Management for Prevention of Recurrent stroke in Intracranial Stenosis (SAMMPRIS) Trial was designed to compare aggressive medical management alone versus aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS). Thus, the SAMMPRIS trial became the first multicenter stroke prevention trial to incorporate multi-modal, protocol-driven risk factor control in the design. This paper focuses on the rationale, design, and implementation of the intensive risk factor management protocols in SAMMPRIS and describes challenges implementing these protocols during the trial and how the challenges have been managed.

Overall SAMMPRIS Design

The overall design of SAMMPRIS has been described previously¹⁶. In brief, SAMMPRIS is an ongoing investigator-initiated and designed Phase III randomized multicenter trial funded by the National Institute of Neurological Disorders and Stroke (NINDS) in which eligible patients were randomized at 50 sites to: aggressive medical therapy alone or percutaneous transluminal angioplasty and stenting (PTAS) using the Wingspan stent system plus aggressive medical therapy. The main eligibility criteria were TIA or non-disabling stroke within 30 days prior to enrollment caused by 70% – 99% stenosis of a major intracranial artery (MCA, carotid, vertebral, or basilar). The primary outcome is stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion performed during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days. Aggressive medical therapy includes aspirin 325 mg/day during the entire follow-up period (estimated mean follow-up of approximately 32 months), clopidogrel 75mg per day for 90 days after enrollment, and aggressive risk factor management primarily targeting systolic blood pressure (SBP) < 140 mm Hg (< 130 if diabetic) and low-density lipoprotein cholesterol (LDLc) < 70 mg/dl. Risk factor management of both primary and secondary targets (see Table 1) is performed by the study neurologist and coordinator at each site, assisted by an innovative, evidence-based, educational, lifestyle modification program (INTERxVENT) that is administered at regularly scheduled times to all patients throughout the study.

The target sample size in SAMMPRIS was 764 patients, but enrollment was stopped early by NINDS based on a recommendation by the independent Data Safety Monitoring Board on April 5, 2011 due primarily to safety concerns regarding the periprocedural stroke and death risk in the PTAS group¹⁷. At the time enrollment was stopped, 451 patients had been enrolled and the primary event rate in the medical arm was substantially lower than anticipated¹⁷. Follow-up with aggressive medical management of all enrolled patients will continue until March, 2013, after which the final outcome and risk factor data will be available for analysis.

Rationale for Incorporating Aggressive Risk Factor Management

Aggressive management of vascular risk factors was incorporated into the SAMMPRIS design for several reasons: 1. In the WASID study¹⁴ (which included patients with stroke or TIA within the previous 90 days that was due to 50–99% intracranial stenosis) risk factors were managed by the study neurologist in association with the patient's primary care physician. National guidelines for treatment of risk factors were provided to the neurologist at each site, but no specific protocols to address risk factors were followed. Table 2 (reproduced from Chaturvedi S, et al.¹⁵) shows how often risk factors exceeded pre-specified target goals at baseline and year 1 (study period: 1999–2003) in WASID. Some progress was made in treating cholesterol and smoking within the first year, but not in lowering blood pressure. Many patients still had uncontrolled vascular risk factors, suggesting that simply providing guidelines for risk factor control was not sufficient to achieve desired targets; 2. Failure to achieve risk factor targets in WASID appeared to have important clinical consequences, since good control of blood pressure and cholesterol levels during follow-up was associated with reductions in the risk of stroke, MI and vascular death¹⁵; 3. Other secondary prevention stroke trials of patients with heterogeneous causes of stroke had shown that treatment of elevated LDLc¹¹ and blood pressure¹⁰ reduced the risk of recurrent stroke; 4. Among patients with stable coronary artery disease (CAD), intensive risk factor management alone was shown to be as good as endovascular intervention plus either usual medical management or intensive medical management in preventing cardiac ischemic events^{1, 18}; and 5. If usual medical management was compared to stenting plus usual medical management in SAMMPRIS and the stenting arm was found to be superior, stenting would become the standard of care for these patients. It would then be very difficult to perform a subsequent trial to determine if aggressive medical management alone could obviate the need for stenting. Thus, it was critical to determine within SAMMPRIS whether aggressive medical therapy obviated the need for stenting.

Rationale for Specific Risk Factor Targets

Systolic Blood Pressure

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends a target SBP of less than 140 mm Hg (< 130 mm Hg in diabetics)¹⁹ and the American Heart Association/American Stroke Association also endorses this blood pressure target for stroke patients². In WASID during a mean follow-up of 1.8 years, 23% of patients with mean SBP \geq 140 mm Hg has a recurrent ischemic stroke compared with 15% of patients with mean SBP < 140 mm Hg (HR 1.63, 95% CI: 1.11–2.40, $p=0.0120$)^{15, 20}, supporting the use of the JNC7 target in SAMMPRIS.

Low-density Lipoprotein cholesterol

At the time of WASID, the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) recommended targeting LDLc < 100 mg/dL²¹. In WASID during a mean follow-up of 1.8 years, 19% of patients with a mean LDLc \geq 100 mg/dL had

a recurrent ischemic stroke compared with 11% of patients with a mean LDLc < 100 mg/dL (HR 1.72, 95% CI: 1.04–2.85, $p=0.0326$)^{15, 20}. Since the completion of WASID, the NCEP guidelines were updated to include a target LDLc of < 70 mg/dL for very high risk patients^{22, 23}. In WASID, only 10% of patients achieved a mean LDLc < 70 mg/dL by the end of Year 2, but the data was strongly suggestive that achieving an LDLc < 70 mg/dL was highly beneficial, as 23% of patients with a mean LDLc \geq 70 mg/dL during follow-up had a primary endpoint (stroke, vascular death, or MI) compared to 7% of patients with an LDLc < 70 mg/dL ($p=0.09$)¹⁵, supporting the use of the NCEP target for very high risk patients in SAMMPRIS.

Non-High-density Lipoprotein cholesterol

Non-HDLc was selected as a secondary target in SAMMPRIS because the NCEP ATP III guidelines considered it an important secondary target and recommended achieving a target of < 100 mg/dL in high-risk patients²³, particularly in patients with triglycerides > 200 mg/dL. In WASID, there was an association between elevated non-HDLc \geq 130 mg/dL (the NCEP ATP II recommended target at the time of WASID follow-up) and a higher risk of recurrent stroke (HR 1.94, 95% CI: 1.15–3.27, $p=0.01$)^{15, 20}. Evidence at the time of the SAMMPRIS design did not support specific target levels for other cholesterol sub-fractions, such as HDLc.

Hemoglobin A1c

Hemoglobin A1c (HbA1c) < 7.0% was selected as a secondary target for diabetic patients in SAMMPRIS because the American Diabetes Association²⁴ and the ASA/AHA Stroke Council²⁵ guidelines endorsed this target. In WASID, 26% of patients with a mean HbA1c \geq 7.0% had a recurrent stroke compared to 15% patients with mean HbA1c < 7.0% (HR= 1.7, 95% CI:0.81–3.58, $p=0.15$)²⁰.

Smoking Cessation

Smoking cessation was chosen as a risk factor target because the US Department of Health and Human Services Surgeon General's most recent report on the effects of smoking concluded there was sufficient evidence to establish a causal relationship between smoking and stroke²⁶, and because the AHA/ASA Stroke Council recommended strongly advising every patient with stroke or TIA who has smoked in the last year to quit²⁵.

Weight Management

Weight Management was included because the 2006 Update of the AHA Scientific Statement on Obesity and Heart Disease From the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism²⁷ listed obesity as an independent modifiable risk factor for stroke; and recommended a combination of diet, physical activity, and behavior therapy to achieve a BMI of < 25 kg/m² in patients with an initial BMI of 25.0– 27 kg/m² and 10% weight loss for those with an initial BMI > 27 kg/m².

Physical Activity

The physical activity target was included based on the AHA/ASA Stroke Prevention Guidelines statement recommendation that patients with ischemic stroke or TIA who are capable of engaging in physical activity participate in at least 30 minutes of moderate-intensity physical exercise most days²⁵.

Rationale for Incorporating a Lifestyle Modification Program

Several studies have shown a large gap between recommended target levels for risk factors and those achieved in clinical practice^{15, 28–30}. While cardiac rehabilitation programs designed to address this risk factor treatment gap exist at most large hospitals, not all healthcare facilities offer this service. Commercially available lifestyle modification programs have emerged to help patients and employees of large corporations achieve risk factor targets. These programs have improved the achievement of risk factor targets in a variety of populations, including patients who have previously suffered a stroke or TIA and those with multiple risk factors^{31–33}.

Design and Implementation of the Risk Factor Protocols in SAMMPRIS

The design of risk factor management in SAMMPRIS included the following strategies to help control risk factors: providing study medications to subjects, providing medication titration algorithms for the primary risk factors to study investigators, standardizing the measurement of primary risk factor levels, providing an innovative lifestyle management program to subjects, and central oversight of risk factor performance.

The Risk Factor Team includes the patient's study neurologist, the patient's study coordinator, and the patient's INTERxVENT lifestyle coach. The neurologist and coordinator follow protocols for the primary risk factors and collaborate with the patient's outside physicians to achieve secondary risk factor targets using national guidelines, which include general recommendations for lifestyle modification and medication use. The lifestyle coach recommends and reinforces specific healthy lifestyle behaviors.

Study Medications

Medications necessary to achieve the primary risk factor targets (LDLc and SBP) were provided to subjects free of charge to enhance compliance. In order to achieve the LDLc target of < 70 mg/dL, rosuvastatin was selected as the lipid-lowering agent for several reasons. The NCEP III²² and ASA/AHA Stroke Council guidelines²⁵ recommended statins for the treatment of hypercholesterolemia, and there was evidence that statins offered pleiotropic benefits such as stabilizing atherosclerotic plaques, enhancing endothelial function, decreasing oxidative stress and inflammation, inhibiting thrombosis, and possibly having neuroprotective effects^{34, 35}. Rosuvastatin was used in SAMMPRIS because it is more effective for LDLc reduction on a milligram-to-milligram basis than other statins^{36, 37}, FDA post-marketing surveillance of rosuvastatin showed the safety profile to be consistent with other statins³⁸, and the manufacturer agreed to donate rosuvastatin for use in SAMMPRIS patients. SAMMPRIS subjects were encouraged to start or switch to rosuvastatin at enrollment because of the early benefits of statins within 30 days of a vascular event³⁵ and for lowering the risk of stroke, MI, and death within 30 days after revascularization procedures (e.g., carotid stenting³⁹).

The antihypertensive medications provided to SAMMPRIS patients included one drug from almost every class of antihypertensive medications: diuretic (chlorthalidone), ACE inhibitor (lisinopril), potassium-sparing diuretic (spironolactone), angiotensin receptor blocker (candesartan), beta-blocker (atenolol), vasodilator (hydralazine), central alpha agonist (clonidine), and long-acting calcium channel antagonist (felodipine). These medications were selected because most were available in generic form, they were commonly used in practice, and their efficacy in stroke patients had been established in the Secondary Prevention of Small Subcortical Strokes (SPS3) study¹², on which the SAMMPRIS blood pressure protocol was based. These medications were paid for by the study and provided at

no cost to SAMMPRIS patients, but SAMMPRIS patients could use other non-study medications.

Medication titration algorithms

Given the relative inexperience of neurologists compared with internists and cardiologists in managing risk factors, specific step-by-step medication titration algorithms were designed to achieve the primary risk factor targets. These algorithms are provided in Figures 1 and 2. In summary, for LDLc control, each subject was to begin or switch (if on another statin) to rosuvastatin 20 mg per day at the baseline visit, followed by an increase to 40 mg at the 30-day visit if the LDLc was higher than 70 mg/dL. For SBP control, the SAMMPRIS blood pressure algorithm was based on the SPS3 blood pressure algorithm with some modifications. If the subject's baseline blood pressure was not below target level, the patient was started on antihypertensive medications (ACE inhibitor or diuretic or both were the initial recommendations). Study subjects return every 30 days until their blood pressure is in target. If the study neurologist is unable to lower the participant's LDLc or SBP to achieve target by following the algorithms, further assistance was provided by the central risk factor management team and conveyed to the sites by email or teleconference.

Medication Dispensing

Another unique challenge for successfully addressing risk factor management in a clinical trial is to provide conveniently available risk factor medications to patients. Initially, medications were dispensed through a centralized Pharmacy Coordinating Center (PCC), which handled the procurement, labeling, distribution, inventory management, and monitoring of all drugs used in the trial. SAMMPRIS sites (either the coordinators or site investigational pharmacies) received study medications from the PCC and tracked dispensing to study patients with the use of a web-based inventory system. However, due to unpredictability in study medication use, inventory issues (such as expired medications and running out of study medications) at the individual sites became a challenge.

Since SAMMPRIS study medications are FDA-approved, commercially available medications, they do not require the same amount of oversight as with investigational medications. Therefore, medication dispensing was switched to a national commercial pharmacy chain that was available near all SAMMPRIS sites. The SAMMPRIS trial billing information and the list of SAMMPRIS-provided medications were entered into the commercial pharmacy's Pharmacy Benefit System, which typically routes charges to pharmaceutical insurance providers, allowing for SAMMPRIS to be billed directly for study medications and requiring no out-of-pocket cost to study patients. This novel system of dispensing medications, besides more closely mimicking clinical practice, resulted in decreased overhead costs since it did not require payment for shipping and there was no wasting of expired medications.

Standardizing the Measurement of Primary Risk Factor Levels

Providing accurate measurements of the primary risk factor levels in SAMMPRIS is important so that LDLc and SBP levels can be reliably correlated with outcomes at the end of the trial. LDLc and SBP can have significant variability between clinical sites. The standard LDLc values reported at most medical laboratories are calculated using the Friedwald equation⁴⁰. These calculated LDLc values are impacted by levels of other blood lipids, making them more variable, particularly in the postprandial period, than a direct LDLc measurement⁴¹. Similarly, blood pressure monitoring devices also have significant variability in accuracy, with varying grades of performance⁴². Therefore, in SAMMPRIS, the accuracy of the primary risk factor measures was optimized and standardized by using a

central lipid laboratory that performs direct LDLc measurement and by providing a highly-rated blood pressure monitoring device for use at all sites.

Secondary risk factor measures were assessed using local site laboratory tests (hemoglobin A1c), central lipid laboratory values (non-HDLc), local site scales (weight), and patient-completed scales (PACE Current Physical Activity Status Score⁴³ and PACE Smoking Score⁴⁴).

Lifestyle Modification Program

The lifestyle modification program INTERxVENT R, was selected because it is nationally available, is delivered with 1-on-1 counseling via the telephone throughout the United States, and has been demonstrated to be clinically effective in a variety of populations, including patients with prior history of stroke or TIA, and patients with multiple risk factors^{31–33}. The use of a nationally available service provides an additional level of standardization of risk factor education and counseling across all SAMMPRIS sites.

INTERxVENT is provided to SAMMPRIS patients at no cost for the duration of the trial at scheduled intervals (every 2 weeks for first 12 weeks, then monthly thereafter) and includes: 1. Baseline evaluation of health and readiness to change; 2. Computer-generated risk factor goals incorporating SAMMPRIS targets; 3. Computer-generated treatment plans, with a focus on lifestyle intervention (including physical activity, nutrition, weight management, and tobacco cessation); 4. Treatment plan implementation, with brief (15 – 30 minute), behaviorally-oriented counseling sessions by coaches (non-physician healthcare professionals under the direction of a medical director) to help each patient acquire the skills, motivation, and support needed to implement and adhere to their individualized treatment plan (including medication compliance); 5. Follow-up and ongoing revision of treatment plan; 6. Computerized compliance tracking; and 7. Outcomes assessment.

Communication between INTERxVENT and the patient's healthcare providers presented another challenge in the SAMMPRIS trial. In clinical practice, INTERxVENT sends recommendations for risk factor control to the physician who orders the service (typically a primary care doctor) via mail or fax. However, in SAMMPRIS, the study neurologist and coordinator are the recipients of INTERxVENT recommendations. Since many of the study sites are at large academic centers with complex mail delivery systems, there could have been considerable delay in sites receiving the recommendations. Therefore, the SAMMPRIS electronic data capture system (iDataFAX) was used to provide reliable and timely delivery of INTERxVENT recommendations to the sites. INTERxVENT faxes their recommendations into iDataFAX, which stores them and automatically notifies the site coordinator that the recommendations are available for retrieval. This novel delivery method also allows the SAMMPRIS Clinical Coordinating Center (CCC) to monitor the interaction between INTERxVENT and the sites.

Central Monitoring of Risk Factor Performance

Another strategy to maximize risk factor control in SAMMPRIS is to combat physician treatment inertia by providing sites feedback on their risk factor performance. Community physician audit and feedback programs have been shown in several studies to improve hypertension control in clinical practice^{45, 46}. The SAMMPRIS CCC adopted a similar strategy for risk factor oversight, providing both auditing and feedback of site performance and patient-specific recommendations.

Overall site risk factor performance is monitored by generating weekly reports of each site's achievement of risk factor targets (i.e. the percentage of the site's patients who are in-target for each risk factor). Poorly performing sites are identified and reports on individual patients

at those sites are reviewed. Systematic problems in site protocol compliance are identified and additional site coordinator and neurologist training is implemented, if needed. On a monthly basis, sites receive a report detailing their risk factor performance relative to the overall performance in the trial as well as the performance at each of the other SAMMPRIS sites, in order to promote site-to-site comparisons. Other tools used to monitor risk factor performance include automated weekly reports with lists of patients who: 1. have LDLc values ≥ 70 mg/dL; 2. are overdue for repeat LDLc or SBP measurement; and 3. are overdue for safety labs (e.g. liver function tests, serum creatinine, and serum potassium).

Individual patient-specific risk factor recommendations are also provided to sites, typically for patients with particularly challenging risk factors either at the site's request or if a patient is noted to be consistently out-of-target. These recommendations are generated by the Risk Factor Management Committee Members who have specific expertise in managing key risk factors. Recommendations are conveyed to the sites by email or teleconference. All patient-specific communication between the CCC and SAMMPRIS sites are recorded centrally to ensure consistency and follow-up of prior recommendations.

In addition to this regular oversight of risk factor control at each site by the CCC, the Risk Factor Management Committee meets annually to evaluate the overall success of risk factor management in the trial and to recommend updates in the risk factor guidelines and protocols if necessary.

Discussion

The SAMMPRIS trial employs a multi-modal approach to risk factor control that has not been used in previous stroke prevention trials. Although follow-up of SAMMPRIS-enrolled patients continues, early analyses of risk factor measures show substantial improvement using the aggressive medical management strategies described above¹⁷. Within the first 30 days, mean SBP decreased by over 5 mm Hg and mean LDLc decreased by over 20 mg/dL⁴⁷, with both of these primary risk factor measures continuing to improve at year 1¹⁷. Improvements in secondary risk factor targets were also seen, with significantly better control of non-HDL cholesterol and HbA1c, weight loss, improved exercise, and smoking cessation compared to baseline⁴⁷.

These improvements in risk factor control may have contributed to better-than-expected outcomes at this point in the medical management arm of SAMMPRIS. Among WASID patients who met the SAMMPRIS entry criteria (70–99% intracranial stenosis and qualifying event of stroke or TIA within 30 days) and were treated with usual management of risk factors and aspirin or warfarin, the 30-day stroke and death rate was 10.7%, whereas the 30-day rate of stroke and death in the aggressive medical management arm of SAMMPRIS was 5.8%. While the use of dual antiplatelet therapy in SAMMPRIS likely contributed to the early benefit of aggressive medical management, it is possible that intensive risk factor control also played a role in lowering the 30-day event rate compared to WASID. Such early pleiotropic effects of risk factor medications, such as high dose statins, have been shown to reduce 30-day cardiovascular risk in patients with acute coronary syndromes³⁵. Based on currently available follow-up data in SAMMPRIS, aggressive medical management appeared, as well, to lower the 1-year rates of events. In WASID, patients who met SAMMPRIS entry criteria had a primary endpoint rate of 25% at year 1, but SAMMPRIS patients receiving aggressive medical management alone had a primary endpoint rate of 12.2% at year 1¹⁷. Dual-antiplatelet therapy was only given for 90 days after enrollment, followed by aspirin monotherapy, yet the primary endpoint rate continued to remain lower than expected at year 1, suggesting intensive risk factor control is an important contributor to the better than expected 1-year outcome in the SAMMPRIS patients

who were treated with medical management alone. Although historical comparisons between WASID and SAMMPRIS patients do not prove that the SAMMPRIS aggressive medical management strategy improved outcomes, analyses to determine the impact of risk factor control on outcomes (e.g. comparison between the event rates of patients who did achieve risk factor targets versus those who did not achieve targets in the medical arm of SAMMPRIS) will be performed at the end of follow-up to help address this question.

Another important issue is the practicality and ability to generalize the use of the SAMMPRIS risk factor management strategy in clinical practice. Most of the strategies used in SAMMPRIS to control vascular risk factors are available and used outside of clinical trials. For example, cardiac rehabilitation clinics are available at many medical centers and are recommended by the American Heart Association National Guidelines for the Management and Prevention of Coronary Heart Disease⁴⁸. Monitoring of physician performance for achievement of prevention measures also occurs in clinical practice. In programs known as “pay for performance”, which are common in the U.S. and now worldwide⁴⁹, healthcare reimbursement is linked to achievement of quality measures. Similarly, performance feedback programs, with ongoing education and training, are also being used to improve control of risk factors in high-risk populations^{45, 46}. In addition, most of the risk factor management in SAMMPRIS is coordinated by the study coordinators (typically nurses) using medication titration algorithms with neurologist oversight, similar to the increasing number of Lipid-Management Clinics that utilize physician-extenders commonly seen in clinical practice. Finally, although some risk factor medications were provided at no cost to the study participants, the method of distributing the medication (via a commercial pharmacy) largely duplicates the methods used in clinical practice. Therefore, aspects of the SAMMPRIS aggressive medical management strategy can be implemented in ‘real-life’ patients. In fact, a recent single-center study of the feasibility of implementing a SAMMPRIS-like intensive medical management protocol showed that blood pressure and LDLc targets could be achieved in clinical practice and were associated with good outcomes⁵⁰.

While the early SAMMPRIS results suggest that the SAMMPRIS aggressive medical management strategy can be and should be implemented in these high-risk patients, the next challenge is to ensure that aggressive medical management will be implemented in practice. The resources provided to SAMMPRIS study patients (e.g. free risk factor medications, close follow-up by study investigators, and individualized lifestyle management) are not currently available to many patients in the U.S. health-care system. In addition to variability of resources, additional challenges to implementation of the SAMMPRIS aggressive medical management strategy include patient language and cultural barriers, variability in healthcare provider training and education, and variability in healthcare system access and policies. Despite these challenges, the strategies used for risk factor management in SAMMPRIS provide a framework for implementing aggressive risk factor management in clinical practice. Additionally, the success in achieving multiple risk factor targets in SAMMPRIS sets the bar for future stroke prevention and implementation trials.

In summary, the SAMMPRIS aggressive medical management strategy employed a multi-modal approach to risk factor control that has been very effective in achieving risk factor targets in study patients and likely contributed to the lower than expected rate of stroke in the medical arm. Intensive management of vascular risk factors should be incorporated into the management of patients at high risk of stroke in clinical practice and in future secondary prevention trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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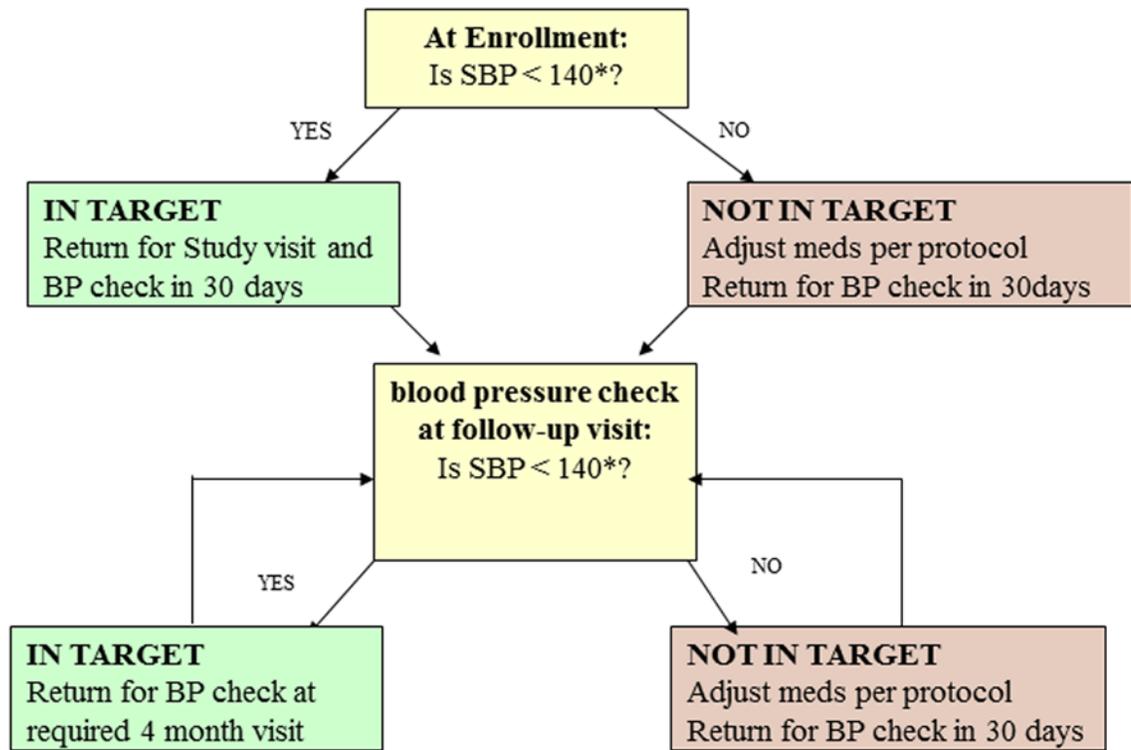
William Virgil Brown, MD has received research support from Astra Zeneca, speakers' bureau appointment payments from Abbott, Merck, Liposcience and Kowa, and honoraria from Merck, Liposcience and Pfizer. Dr. Brown has acted as a consultant to Amgen, Genzyme, Anthera, Cerenis, Pfizer, and Bristol-Myers Squibb. He has also served as an expert witness in a legal case involving Merck.

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* < 130 if diabetic

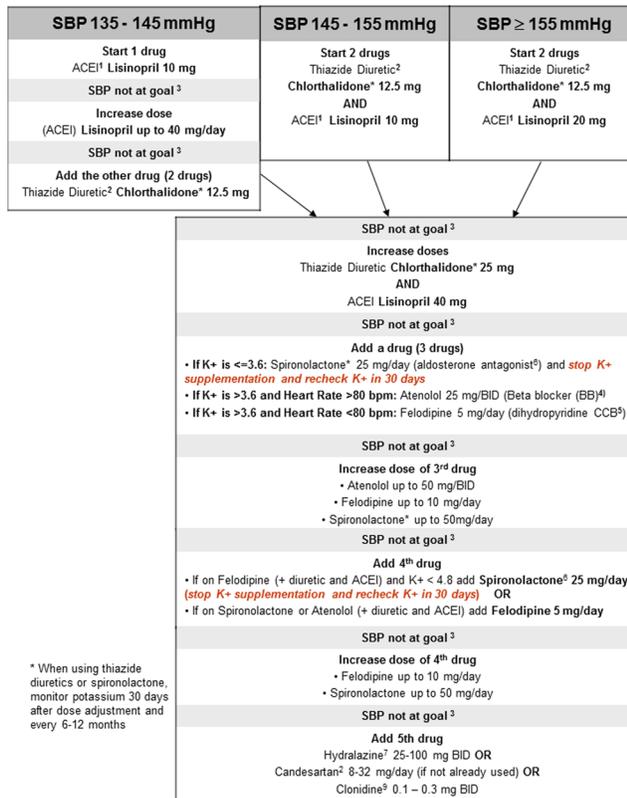
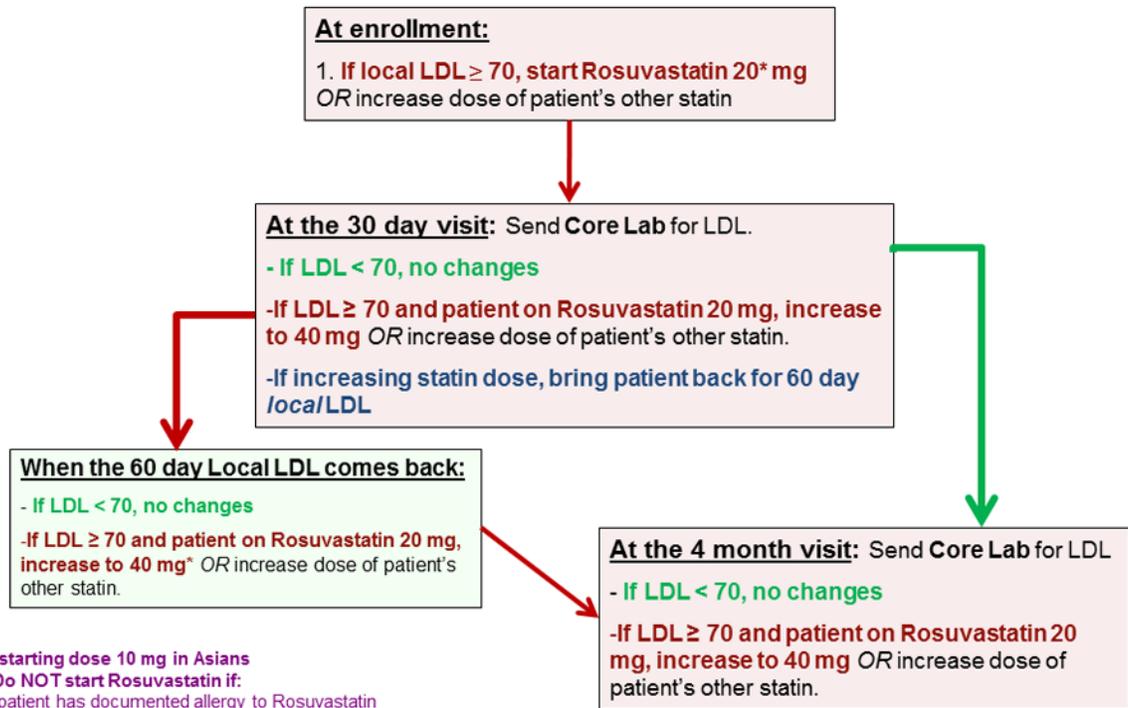


Figure 1.
 a. Blood Pressure Measurement Algorithm; b. Hypertension Treatment Algorithm



*starting dose 10 mg in Asians
Do NOT start Rosuvastatin if:
-patient has documented allergy to Rosuvastatin
OR
-estimated creatinine clearance < 30 mL/min

Figure 2.
LDLc Management Algorithm

Table 1

SAMMPRIS Risk Factor Targets and their measurement

RISK FACTOR	GOAL	MEASUREMENT
<u>Primary Risk Factors</u>		
LDLc	< 70 mg/dL	Central lab- Direct LDL measurement *
Systolic Blood pressure	< 140 mm Hg (< 130 if diabetic)	Using standardized device provided to site
<u>Secondary Risk Factors</u>		
Non-HDLc	< 100 mg/dL	Central lab
HbA1c	< 7.0%	Local lab
Smoking	Cessation	Self reported (PACE score **)
Weight Management	For initial BMI of 25 – 27 kg/m ² : target BMI < 25 kg/m ² For initial BMI > 27 kg/m ² : target 10% weight loss	Weight at each visit Height at baseline
Physical Activity	30 min of moderate exercise 3 or more times per week	Self reported (PACE score **)

* measured by homogeneous enzymatic method (www.sekisuidiagnostics.com).

** Physician-based Assessment and Counseling for Exercise (PACE) questionnaire is performed for smoking and exercise.

Table 2

Control of Vascular Risk Factors in WASID

Risk Factor	Baseline	Year 1 visit
SBP \geq 140 mm Hg	51%	49.9%
Cholesterol \geq 200 mg/dL	50%	37% *
LDLc \geq 100 mg/dL	71%	58% *
LDLc \geq 70 mg/dL	94%	88% **
HDLc $<$ 40 mg/dL	40%	33% **
Triglyceride \geq 200 mg/dL	26%	31%
Hemoglobin A1C $>$ 7% †	64%	56%
Smoking	21%	17% ***
No alcohol	55%	68% *

SBP indicates systolic blood pressure; LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol

p-values comparing percentage at baseline and 1 year.

* P<0.001

** P<0.05

*** P<0.01

† Diabetics only

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