

Challenges in the Medical Management of Symptomatic Intracranial Stenosis in an Urban Setting

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Background and Purpose—Since the SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis), aggressive medical management (AMM), which includes dual antiplatelet therapy (DAPT) and high-dose statin (HDS) therapy, is recommended for patients with symptomatic intracranial atherosclerotic disease. However, limited data on the real-world application of this regimen exist. We hypothesized that recurrent stroke risk among patients treated with AMM is similar to the medical arm of the SAMMPRIS cohort.

Methods—Using a prospective registry, we identified all patients admitted between August 2012 and March 2015 with (1) confirmed ischemic stroke or transient ischemic attack; (2) independently adjudicated symptomatic intracranial atherosclerotic disease; and (3) follow-up at 30 days. We analyzed 30-day risk of recurrent ischemic stroke stratified by treatment: (1) AMM: DAPT plus HDS therapy, (2) HDS alone, and (3) DAPT alone. We also assessed 30-day risk among patients who met prespecified SAMMPRIS eligibility criteria.

Results—Among 99 patients who met study criteria (51.5% male, 54.5% black, mean age 68.2±11.2 years), 49 (48.5%) patients were treated with AMM, 69 (69.7%) with DAPT, and 73 (73.7%) with HDS therapy. At 30 days, 20 (20.2%) patients had recurrent strokes in the territory of stenosis. Compared with the risk in the medical arm of SAMMPRIS (4.4%), the 30-day risk of recurrent stroke was 20.4% in AMM patients, 21.5% in HDS patients, 22.4% in DAPT patients, and 23.2% in SAMMPRIS-eligible patients (all $P < 0.001$).

Conclusions—Recurrent stroke risk within 30 days in patients with symptomatic intracranial atherosclerotic disease was higher than that observed in the medical arm of SAMMPRIS even in the subgroup receiving AMM. Replication of the SAMMPRIS findings requires further prospective study. (*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.016254.)

Key Words: acute stroke ■ stenosis ■ therapy ■ transient ischemic attack

Intracranial atherosclerotic disease (ICAD) is a major cause of stroke worldwide and portends a high risk of recurrent stroke.¹ The SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) included aggressive medical management (AMM) characterized by use of dual antiplatelet therapy (DAPT: aspirin 325 mg plus clopidogrel 75 mg daily for 90 days), high-dose statin (HDS) therapy with rosuvastatin, and other risk factor and lifestyle modification.² The trial was stopped prematurely after finding that AMM alone was superior to stent placement plus AMM. Since the publication and in the subsequent guidelines, AMM with DAPT and HDS therapy is recommended (Class IIb; Level of Evidence B) in patients with symptomatic ICAD causing 70% to 99% stenosis.³

No trial, however, has compared AMM to non-AMM approaches and demonstrated its superiority in patients with symptomatic ICAD. Furthermore, there are limited data on the real-world application of this regimen⁴ and its effect on stroke recurrence. In a prospective cohort of patients with

symptomatic ICAD admitted to an urban academic medical center, we hypothesized that 30-day recurrent stroke risk among patients treated with AMM would be similar to that observed in the medical arm of the SAMMPRIS trial.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local Institutional Review Board. With informed consent, consecutive patients aged ≥18 years with a confirmed acute ischemic stroke (AIS) or transient ischemic attack (TIA) between August 1, 2012, and March 13, 2015, were enrolled in the Northwestern University Brain Attack Registry. Written informed consent was obtained from the patient or their legally authorized representative.

Selection of Cohort

We defined AIS as sudden onset of neurological deficits lasting >24 hours without alternative diagnosis or confirmation of AIS on diffusion-weighted imaging (DWI).⁵ In patients in whom DWI was not performed (n=2), the diagnosis was made clinically based on the

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duration of symptoms and computerized tomography imaging findings. TIA was defined as sudden onset of neurological deficits lasting <24 hours without alternative diagnosis and no acute lesion on DWI. Patients with confirmed AIS or TIA because of moderate to severe intracranial stenosis involving any of the following arteries were included: intracranial internal carotid artery, middle cerebral artery, intracranial vertebral artery, and basilar artery. Stenosis of the vessel was determined using a modified WASID method [Warfarin Aspirin Symptomatic Intracranial Disease] on CTA and DSA when available, with moderate stenosis defined as 50% to 69% stenosis and severe stenosis defined as 70% to 99% stenosis; among those with only magnetic resonance angiography performed (n=36), we measured degree of stenosis as >50% by the modified WASID method and further categorized stenosis as 50% to 69% when flow gap was not present and 70% to 99% stenosis when flow gap was present.^{6,7} Symptomatic ICAD required that the infarct on DWI or computerized tomography was in the vascular distribution of the stenotic artery without another causative mechanism found on diagnostic testing. Board-certified vascular neurologists prospectively reviewed clinical and radiographic data to determine Trial of Org 10172 in Acute Stroke Treatment subtype⁸ for each confirmed case; adjudication was made by consensus to avoid inter-rater reliability concerns.⁹ Consecutive patients with the following criteria were included: (1) AIS or TIA as previously defined and (2) independently adjudicated symptomatic ICAD.

Index Evaluation of Subjects

Demographics, initial National Institutes of Health Stroke Scale score during index hospitalization, risk factors and comorbidities, hospital course, and treatments were collected prospectively. Hypertension, diabetes mellitus, dyslipidemia, prior stroke, and cardiac disease (history or angina, myocardial infarction, coronary bypass or intervention, or congestive heart failure) were defined by documented history, active medications, or clinical or laboratory findings at presentation. We also collected baseline low-density lipoprotein and glycosylated hemoglobin levels at index hospitalization. Baseline brain and vascular imaging were independently reviewed by 2 investigators (R.S. Sangha and S. Prabhakaran) for the presence of acute infarcts on DWI or computerized tomography along with location, degree of stenosis, and vascular territory, blinded to outcome data.

AMM Protocol

Eligible patients with symptomatic ICAD were treated according to guidelines during the study period (Note: a change in guidelines supporting DAPT occurred in 2014).³ The use of DAPT along with HDS therapy was determined per attending stroke physician discretion. Patients also received standard inpatient counseling regarding diet and lifestyle modifications during the index hospitalization. Blood pressure medications were initiated during hospitalization whenever possible with titration toward <140/90 mm Hg (<130/80 mm Hg in diabetics) over a period of 2 to 4 weeks. Patients were instructed and scheduled to follow-up in vascular neurology clinic or with their primary care provider to ensure blood pressure medications were titrated toward this goal. Statin medications were started to target a low-density lipoprotein goal of ≤70 mg/dL. For patients at goal of 70 mg/dL at the time of hospitalization, prestroke statin dosing was continued or low-dose statin medication was started, with monitoring of lipid levels by the primary care physician or stroke neurologist in the outpatient setting.

Outcomes

Recurrent AIS in the territory of the symptomatic stenotic artery within 30 days of index event was the primary outcome. We prospectively monitored for poststroke in-hospital medical complications,¹⁰ including recurrent ischemic stroke (IS) after index AIS or TIA. Recurrent IS after hospitalization was determined via telephonic interview supplemented by using an electronic surveillance system of hospital records at any of 3 health system hospitals, with confirmation by manual review of the medical record in all instances of reported recurrent AIS or TIA.

Statistical Analysis

Data are expressed as number (percent), mean (standard deviation), or median (interquartile range) as appropriate. Baseline characteristics of our cohort to the SAMMPRIS cohort were compared using Fisher exact test, with a *P* value of <0.05 considered to be significant. We calculated the 30-day risk of recurrent AIS in the territory of the stenotic artery and 95% confidence intervals using the Wald method and compared these rates with those reported in the SAMMPRIS trial using χ^2 tests. We assessed risk of recurrent AIS in 3 categories of medical management: (1) AMM defined as DAPT plus HDS therapy; (2) HDS therapy without DAPT; and (3) DAPT without HDS therapy; we also assessed the risk in those meeting the following SAMMPRIS criteria: age (30–80 years), severe degree of stenosis, and prestroke modified Rankin scale ≤3. In secondary analyses, we compared risks across demographic and risk factor groups and in 2 subgroups recently identified in SAMMPRIS as having elevated risk: those with prior infarcts and not on statin therapy at baseline.¹¹ We performed univariable and multivariable logistic regression for predictors of the outcome or dependent variable (recurrent stroke within 30 days), including demographic, clinical, imaging, laboratory, and treatment variables. A *P* value <0.05 was considered significant in univariate comparisons; however, using the Bonferroni method, we selected a *P* value <0.0125 for the comparison of recurrent stroke risks across 4 prespecified subgroups in our primary analysis. All analyses were conducted using Statistical Package for Social Sciences version 23.0 (IBM, Armonk, NY).

Results

Among 99 consecutive patients (mean age 68.2±11.2 years; 51.5% male; 38.4% white; 54.5% black; 7.1% Hispanic) included for analysis after exclusion and loss to follow-up (Figure 1), the intracranial internal carotid artery (37.4%) and middle cerebral artery (30.3%) were the most commonly involved territories. Severe stenosis was noted in 69.7%, with the remainder having moderate stenosis. Table 1 provides the clinical and radiographic characteristics of the analyzed cohort compared with the medical arm of SAMMPRIS. Our

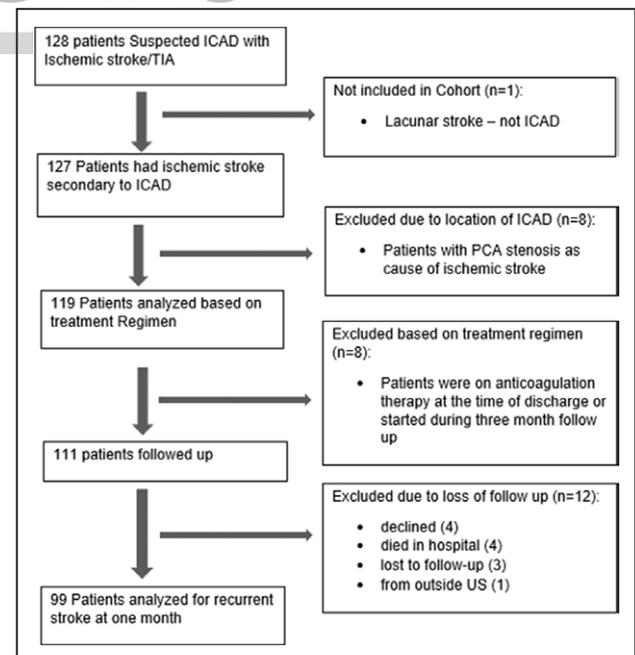


Figure 1. Flowchart of study cohort assembly. ICAD indicates intracranial atherosclerotic disease; PCA, posterior cerebral artery; and TIA, transient ischemic attack.

Table 1. Baseline Characteristics of Patients in the Cohort Compared With the SAMMPRIS Cohort

Variable	Cohort (n=99)	SAMMPRIS (n=227)	P Value
Mean age (SD), y	68.2 (11.2)	59.5 (11.8)	<0.001
Male, n (%)	51 (51.5)	82 (36.1)	0.013
Race, n (%)			<0.001
White	38 (38.4)	161 (70.9)	
Black	53 (53.5)	50 (22.0)	
Other	8 (8.1)	16 (7.0)	
Hypertension, n (%)	81 (81.8)	203 (89.4)	0.088
Diabetes mellitus, n (%)	56 (56.6)	103 (45.4)	0.082
Hemoglobin A1c, n (%)			
<5.7%, n (%)	28 (28.3)	...	
5.8%–7.9%, n (%)	42 (42.4)	...	
>7.9%, n (%)	29 (29.3)	...	
Dyslipidemia, n (%)	79 (79.8)	203 (89.4)	0.031
LDL level, n (%)			
<70 mg/dL, n (%)	20 (20.2)	...	
70–100 mg/dL, n (%)	33 (33.3)	...	
>100 mg/dL, n (%)	46 (46.5)	...	
Coronary artery disease, n (%)	22 (22.2)	59 (26.0)	0.559
Prior history of ischemic stroke or TIA, n (%)	45 (45.5)	58 (25.6)	<0.001
Current smoking, n (%)	23 (23.2)	69 (30.4)	0.235
Statin therapy, n (%)	53 (53.5)	196 (86.3)	
NIHSS score >1, n (%)	62 (62.6)	88 (38.8)	<0.001
Location of ICAD, n (%)			0.002
Middle cerebral artery	30 (30.3)	105 (46.3)	
Intracranial vertebral artery	16 (16.2)	22 (9.7)	
Intracranial internal carotid artery	37 (37.4)	49 (21.6)	
Basilar artery	16 (16.2)	51 (22.5)	
Degree of stenosis of ICAD, n (%)			<0.001
Moderate	30 (30.3)	N/A	
Severe	69 (69.7)	227 (100)	
Prior infarcts in the territory, n (%)	30 (40.8)	75 (33.0)	0.700
Discharge medications			<0.001
DAPT	67 (67.5)	227 (100)	
HDS	65 (65.4)	227 (100)	
DAPT plus HDS therapy	48 (48.4)	227 (100)	

DAPT indicates dual antiplatelet therapy; HDS, high-dose statin; ICAD, intracranial atherosclerotic disease; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; SAMMPRIS, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; and TIA, transient ischemic attack.

Table 2. Documented Reasons for Nonadherence to AMM During Index Hospitalization

	Number of Patients
Reasons for not prescribing DAPT, n (%)	32
Intracranial hemorrhage	4 (12.5%)
History of gastrointestinal bleeding	1 (3.1%)
Clinical trial enrollment	1 (3.1%)
Large burden of infarct and risk of hemorrhagic conversion	1 (3.1%)
Recent surgery	3 (9.4%)
Prior to 2014 revised guidelines	22 (68.8%)
Reasons for not prescribing HDS, n (%)	34
At goal LDL ≤70 mg/dL	25 (73.5%)
Prior intolerance to HDS	3 (8.8%)
History of liver disease	1 (2.9%)
History of rhabdomyolysis	1 (2.9%)
Prior documented statin intolerance	1 (2.9%)
Interaction with other medications	1 (2.9%)
Unknown	2 (5.9%)

AMM indicates aggressive medical management; DAPT, dual antiplatelet therapy; HDS, high-dose statin; and LDL, low-density lipoprotein.

cohort was older, had more severe strokes, and had greater proportions of men, blacks, and diabetes mellitus but less dyslipidemia than the SAMMPRIS cohort. Medical management in our cohort included DAPT (67.7%), HDS therapy (65.7%), and both (48.5%). Documented reasons for nonadherence to AMM regimen are provided in Table 2.

The risk of recurrent AIS in the territory of the stenotic artery after the index event was 20.2% (95% confidence interval, 13.5%–29.2%) at 30 days: 9.1% (95% confidence interval, 4.9%–16.4%) during the index hospitalization versus 11.1% (95% confidence interval, 6.3%–18.8%) after hospital discharge. Those with and without recurrent stroke did not differ based on age, sex, ethnicity, risk factors, stroke severity, baseline low-density lipoprotein and HgA1c levels, prior infarcts, and degree of stenosis in symptomatic artery (Table 3). In multivariable analysis, including sex, race (black versus nonblack), diabetes mellitus, stenosis location (vertebrobasilar versus other), stenosis grade (severe versus moderate), prior infarcts, baseline statin use, and AMM at discharge, no factor was independently associated with 30-day recurrent stroke.

Among 3 prespecified groups of medical management, the risk of recurrent AIS was not different ($P=0.518$). Each medical management subgroup had higher 30-day risk of recurrent AIS in the territory of the stenotic artery than observed in the medical arm of SAMMPRIS (Figure 2): AMM (20.8% versus 4.4%; $P<0.001$); HDS therapy without DAPT (23.5% versus 4.4%; $P<0.001$); and DAPT without HDS therapy (26.3% versus 4.4%; $P<0.001$). The SAMMPRIS-eligible patients in our cohort also had a higher risk (23.2% versus 4.4%; $P<0.001$) compared with that in SAMMPRIS.

Table 3. Comparison of 30-Day Recurrent Stroke Risk by Demographic, Clinical, Serological, and Imaging Factors

Variable	Recurrent Stroke (n=20)	No Recurrent Stroke (n=79)	P Value
Mean age (SD), y	65.9 (10.6)	68.8 (11.3)	0.303
Male, n (%)	14 (70.0)	37 (46.8)	0.068
Race, n (%)			0.445
White	7 (35.0)	31 (39.2)	
Black	10 (50.0)	43 (54.4)	
Other	3 (15.0)	5 (6.3)	
Hypertension, n (%)	16 (80.0)	65 (82.3)	0.813
Diabetes mellitus, n (%)	8 (40.0)	49 (62.0)	0.075
Hemoglobin A1c, n (%)			0.894
<5.7%, n (%)	6 (30.0)	22 (27.8)	
5.8%–7.9%, n (%)	9 (45.0)	33 (41.8)	
>7.9%, n (%)	5 (25.0)	24 (30.4)	
Dyslipidemia, n (%)	19 (95.0)	68 (86.1)	0.275
LDL level, n (%)			0.313
<70 mg/dL, n (%)	4 (20.0)	16 (20.3)	
70–100 mg/dL, n (%)	4 (20.0)	29 (36.7)	
>100 mg/dL, n (%)	12 (60.0)	34 (43.0)	
Coronary artery disease, n (%)	5 (25.0)	17 (21.5)	0.738
Prior history of ischemic stroke or TIA, n (%)	8 (40.0)	37 (46.8)	0.583
Current smoking, n (%)	3 (15.0)	20 (25.3)	0.329
Statin therapy, n (%)	9 (45.0)	44 (55.7)	0.392
NIHSS score >1, n (%)	13 (65.0)	49 (62.0)	0.806
Vertebrobasilar location, n (%)	5 (25.0)	27 (34.2)	0.433
Severe stenosis, n (%)	16 (80.0)	53 (67.1)	0.262
Prior infarcts in the territory, n (%)	9 (45.0)	31 (39.7)	0.670
Aggressive medical management, n (%)	10 (50.0)	38 (48.1)	0.879
Dual antiplatelet therapy, n (%)	15 (75.0)	52 (65.8)	0.433
High-dose statin therapy, n (%)	14 (70.0)	51 (64.6)	0.647

LDL indicates low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

Discussion

In a single-center, urban, longitudinal cohort study, we observed higher rates of recurrent AIS within 30 days when compared with the SAMMPRIS trial even in those treated with AMM consisting of DAPT plus HDS therapy. Furthermore, we found no baseline demographic, serological, clinical, or imaging predictors of recurrent stroke. Our findings suggest that real-world application of AMM may be suboptimal and may not reproduce the results from the SAMMPRIS trial. We attribute this to multiple factors, including (1) difficulty in uniformly implementing AMM, especially lifestyle modification, (2) selection bias that may have excluded some patients with high risk of early

recurrence in SAMMPRIS, and (3) possible genetic, clinical, and environment/socioeconomic differences between our cohort and the SAMMPRIS medical cohort.

Lifestyle intervention with close monitoring was a key component of AMM in the SAMMPRIS trial. In addition to DAPT, HDS therapy, and blood pressure management, AMM included lifestyle coaching and modifications. Indeed, in a subgroup analysis of SAMMPRIS, compliance with the lifestyle modification program resulted in improved risk factor control.¹² Other studies in patients with stable coronary artery disease also demonstrated that intensive risk factor management alone was equivalent to endovascular intervention plus intensive medical management in preventing cardiac ischemic events, suggesting that lifestyle modifications should be a major component in the management of atherosclerotic disease.¹³

In the SAMMPRIS trial, a lifestyle coach was provided to patients, and they underwent close monitoring and frequent follow-up with the study investigators. Absent the clinical trial environment, however, compliance with and affordability of medications may be more difficult to achieve. Others have noted that replicating the results of clinical trials are met with real-world challenges.¹⁴ In clinical practice, lack of access to resources and motivation are significant barriers for optimal medical management. Indeed, patients who are more actively engaged in their medical condition and treatment may be more willing to participate in clinical trials and, thus, more adherent to the medications and treatments in comparison to the general population.¹⁵ Similar difficulty in reproducing trial results has been observed in heart failure patients.¹⁶ Furthermore, when preventive or treatment regimens are complex and require lifestyle modification of existing habits, nonadherence can be as high as 70%.¹⁷ Past studies have also shown that counseling on diet and exercise alone achieve little improvement in risk factor profiles.¹⁸ Though a small study applying AMM in 22 patients noted high rates of risk factor control and no recurrent events at 1 year,⁴ our study suggests that AMM, including lifestyle modification, but without a program such as the INTERxVENT program (innovative, evidence-based, educational, lifestyle modification program) used in SAMMPRIS, may be difficult to replicate without the trial infrastructure and improved affordability.

We included a broader range of patients with symptomatic ICAD in our study. The inclusion of patients who may have been unstable because of active plaques or hemodynamic failure could have contributed to higher rates of IS, especially in the first week in our study compared with the SAMMPRIS trial. The SAMMPRIS trial did not enroll patients with fluctuating symptoms or with deterioration within 24 hours prior to randomization. In the WASID trial, patients whose index event occurred 17 days or before randomization had a significantly higher risk of recurrent IS than patients who were randomized after 17 days.¹⁹ Although the median time from stroke to enrollment in the SAMMPRIS was 7 days, we speculate that some high-risk patients with early recurrent ISs may have been excluded or not considered for the trial, leading to an underestimate of actual recurrent IS risk in patients with symptomatic ICAD. While others have identified clinical and imaging factors associated with increased recurrent AIS risk, including prior infarcts in the territory of the stenotic artery

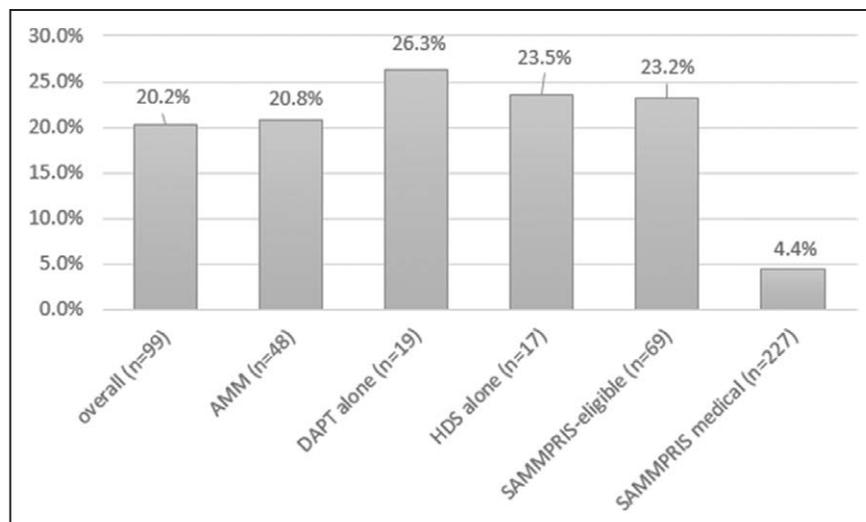


Figure 2. Thirty-day risk of recurrent stroke in the territory of the symptomatic stenotic artery overall and by subgroups and compared with the medical arm of SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis). Among 3 prespecified groups of medical management, the risk of recurrent AIS was not different ($P=0.518$). AIS indicates acute ischemic stroke; AMM, aggressive medical management; DAPT, dual antiplatelet therapy; and HDS, high-dose statin.

and no statin use at enrollment,¹¹ we were unable to confirm these findings.

Finally, we postulate that DAPT may be less effective in particular subgroups of patients. Based on the CLAIR (clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals)²⁰ and CARESS (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis)²¹ trials, short-term DAPT (≤ 3 months) has been posited to reduce the risk of IS from artery–artery embolism. Indeed, the strong unexpected results of SAMMPRIS in the medical arm have been attributed in part to DAPT.²² However, no subsequent studies have been able to confirm or refute this finding. A recent subgroup analysis of the CHANCE trial (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Event), which used a 3-week DAPT regimen after minor stroke and TIA,²³ found that DAPT provided no reduction of AIS events in the one third of patients with symptomatic ICAD. Another factor may be genetic differences that affect clopidogrel metabolism. Patients who are carriers of the CYP2C19 loss-of-function alleles are clopidogrel nonresponders.²⁴ Though we might speculate that poor responsiveness to clopidogrel was a potential explanation of our results, it is unlikely that a majority of our patients harbored the mutation.

Our findings must be viewed in the context of several limitations. First, this was a single-center prospective nonrandomized cohort study and, thus, may not generalize to other settings because our population was predominantly black, older, and urban and had a higher prevalence of diabetes mellitus than the cohort analyzed in SAMMPRIS. Second, the study did not match the exact eligibility criteria of the SAMMPRIS trial, limiting comparison as patients were included who may not have been eligible for enrollment in the SAMMPRIS trial. Third, we did not assess or enforce compliance to medications at follow-up; assessment of compliance would require a standardized method often only used in clinical trials. Fourth, some patients were not provided DAPT or HDS therapy for reasons that are outlined in Table 2. A survey of practitioners after SAMMPRIS noted that only 45% routinely used DAPT in patients with

symptomatic ICAD, suggesting that adherence to this class IIb recommendation may be far from uniform.²⁵ Fifth, we also did not measure the degree of stenosis via catheter angiography, which could lead to an inaccurate characterization of the degree of stenosis. Finally, the small sample size could result in type I error and an overestimation of risk and type II error and inability to identify predictors of 30-day recurrent stroke risk. Given these limitations and observational nature of this cohort, we refrain from drawing definitive conclusions.

In a prospective cohort, we observed that the rate of recurrent IS in patients with symptomatic ICAD was higher than that in the medical arm of the SAMMPRIS trial. Real-life application and replication of SAMMPRIS trial results are warranted. Alternatively, our data provide a rationale for improved risk factor and lifestyle management in clinical practice. Indeed, reimbursement for such activity may be necessary. Further investigation is also needed to determine the pathophysiological processes mediating recurrent IS in symptomatic ICAD, especially in the first 30 days. Understanding mechanisms of early recurrence will aid in developing targeted therapies for patients with this condition.

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