Original Paper

Clopidogrel plus Aspirin for Symptomatic Intracranial Atherosclerotic Stenosis: A Pilot Study

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Key Words

Acute ischemic stroke · Transient ischemic attack · Intracranial atherosclerotic disease · Dual antiplatelet therapy

Abstract

Background and Purpose: There are limited data on the optimal duration of dual antiplatelet therapy for secondary stroke prevention in patients with symptomatic intracranial atherosclerotic disease. **Methods:** Consecutive patients presenting with high-grade (70–99%) symptomatic intracranial stenosis from January 1, 2011, to December 31, 2013, and evaluated within 30 days of the index event were eligible for this analysis. All patients underwent treatment with aspirin plus clopidogrel for a target duration of 12 months along with aggressive medical management based on the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) protocol; all patients were given gastrointestinal prophylaxis for the duration of their aspirin and clopidogrel treatment. Clinical and safety outcomes of our cohort were compared with the medical arm of the SAMMPRIS trial cohort (n = 227). **Results:** Our cohort included 25 patients that met the inclusion criteria. Achievement of blood pressure and LDL cholesterol targets were similar between our cohort and the SAMMPRIS cohort. At 1 year, the rates of stroke, myocardial infarction or vascular death were 0% in our cohort and 16% in the SAMMPRIS cohort (p = 0.03). At 1 year, major bleeding rates were similar between our cohort and the SAMMPRIS cohort (4 vs. 2.2%, p = 1.0). **Conclusion:** A prolonged course of dual antiplatelet therapy for symptomatic intracranial atherosclerotic disease may be associated with less vascular events with no increase in hemorrhagic complications.

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Introduction

Intracranial atherosclerotic disease (ICAD) represents a significant number of acute ischemic stroke (AIS) cases both in the US and worldwide [1–8]. Progress in understanding the best management paradigm for both symptomatic and asymptomatic ICAD has been made in the previous decade; however, questions remain on defining optimal medical management. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial failed to show a benefit of anticoagulation over antiplatelets with aspirin (ASA) in patients with transient ischemic attack or stroke caused by angiographically verified 50–99% (moderate to severe) stenosis of a major intracranial artery [9]. The recurrent stroke risk with severe symptomatic intracranial stenosis ($\geq 70\%$) was as high as 23% at 1 year in the WASID trial, despite best medical therapy known at the time of the study [7]. This led to the emergence of endovascular therapy with percutaneous transluminal angioplasty and stenting (PTAS), which was shown in multiple registries to have a lower rate of recurrent strokes of 7–14% at 6 months with an acceptable periprocedural morbidity of 6.1% [10–12]. This did not hold true when PTAS was compared with the more recent best medical therapy constituting dual antiplatelet therapy (DAPT) with ASA and clopidogrel for 90 days after enrollment and high-dose statins in two separate trials [13, 14].

The SAMMPRIS (Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis) trial showed that aggressive medical therapy alone was superior to aggressive medical therapy with PTAS utilizing the Wingspan self-expanding stent (Stryker®), with an absolute difference of 8.9% at 30 days and 9.0% at 3 years in the primary outcome (stroke or death within 30 days after enrollment or after the revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days) [13–16]. Similarly, the VISSIT (the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) trial showed that PTAS using a balloon-expandable stent for 70–99% intracranial stenosis resulted in an increased 12-month risk of added stroke or TIA in the same territory, and increased 30-day risk of any stroke or TIA compared to the same aggressive medical therapy regimen used in the SAMMPRIS trial. The duration of DAPT in both the SAMMPRIS and the VISSIT trials for 90 days was chosen to avoid confounding errors between the two studied arms and due to lack of evidence on the optimal duration of DAPT in symptomatic ICAD therapy. The optimal duration of DAPT was better defined in the cardiology literature for coronary artery disease (CAD) without ST elevation and showed that longer DAPT, 3–12 months, with ASA and clopidogrel had beneficial effects but with slight increased risk of major bleeding [17]. The aggressive medical therapy based on the SAMMPRIS trial and a prolonged DAPT for at least 12 months along with gastrointestinal (GI) prophylaxis was adapted in our stroke center for severe symptomatic ICAD management. The objective of our study was to compare the safety and effectiveness of using prolonged DAPT in our cohort with the previously published data of the SAMMPRIS cohort.

Methods

Data Collection

All patients presenting to our University Medical Center with high-grade (70–99%) symptomatic intracranial stenosis from January 1, 2011, to December 31, 2013, and evaluated within 30 days of an ischemic stroke or transient ischemic attack (TIA) in the index artery territory were included in this analysis. The University Institutional Review Board granted the approval for this analysis to be performed. We prospectively identified consecutive patients with 70–99% symptomatic ICAD during the period from January 1, 2011, to December 31, 2013, in our institution. While patients were identified prospectively, the data collection was collected through retrospective chart review. Our local protocol for all stroke patients includes

cerebrovascular imaging obtained with contrast-enhanced MRA or CTA; cerebral angiography is performed in a subset of patients. Baseline clinical data were obtained through retrospective chart reviews of electronic medical records and review of radiographic images. All information pertaining to age, baseline demographics, past medical history, admission glucose, admission National Institutes of Health Stroke Scale (NIHSS) score and vascular risk factor indices [LDL, glycated hemoglobin A1C, smoking status, and blood pressure (BP) values] at 90 days was collected for the purposes of this analysis.

Imaging Interpretation

All patients underwent contrasted MR angiography, CT angiography or cerebral angiography. The severity of ICAD was measured by a neuroradiologist, and we utilized the WASID criteria to identify the site of measurements [18]. Intracranial hemorrhage was classified using the European Cooperative Acute Stroke Study (ECASS) definition [19] and evaluated by CT. Symptomatic intracranial hemorrhage was defined as parenchymal hematomas type 1 or type 2 with space-occupying effects within the infarcted area.

Patient Selection

All symptomatic high-grade (70–99%) ICAD patients were selected for this study and were treated with aggressive vascular risk factor modification based on the SAMMPRIS trial protocol along with prolonged DAPT for at least 12 months from the time of the index vascular event including GI prophylaxis. The stroke risk factors were managed to targets based on the SAMMPRIS medical management regimen (BP <130/80 in diabetics, <140/90 in nondiabetics, LDL <70 mg/dl, A1c <7%). We encouraged all patients to maintain a BP log and adjusted BP medications based on home and in-office readings to achieve target. All patients were placed on high-potency statins at baseline and had repeat lipid panels obtained at least 30 days or more after the initiation of their statin. Patients with uncontrolled diabetes were referred to an endocrinologist who managed patients to a target A1c of <7%. All patients were counseled on dietary modification toward a Mediterranean diet, regular exercise targeting >150 min per week of moderate exercise and tobacco cessation for active smokers.

Outcome Measures

The primary endpoint was the rate of recurrent stroke in any vascular territory, myocardial infarction (MI), or vascular death. The safety outcome was the rate of any major hemorrhage, defined as any subdural or epidural hemorrhage or a systemic hemorrhage requiring hospitalization, blood transfusion, or surgery. Outcomes including recurrent stroke symptoms, adherence to the medication regimen, bleeding events and other side effects were collected at each follow-up visit up to 12 months from the index cerebrovascular event and were compared with the medical arm cohort of the SAMMPRIS trial cohort (n = 227).

Statistical Analysis

IBM SPSS software version 20 was utilized to perform the desired statistical analysis. A two-sample t test and Mann-Whitney U test were performed to compare each normally and nonnormally distributed continuous variable between the two cohorts. Fisher's exact test was also used to compare categorical variables.

Results

A total of 25 consecutive patients presented to our University Stroke Center and met our study inclusion criteria. The mean age was 68 ± 8 years, 77% were male, 58% white, 92% with hypertension, 100% with dyslipidemia, 15% with CAD, and 18 (72%) had stroke as their qualifying index event. The site of symptomatic ICAD included the middle cerebral artery (MCA) in 9 patients (36%), the intracranial segment of the vertebral artery in 4 patients (16%), and the basilar artery (BA) in 12 patients (48%). Comparison of baseline characteristics between our cohort and the SAMMPRIS medical management arm are shown in table 1. The mean age was greater in our cohort compared to the SAMMPRIS medical arm cohort (68.5 ± 8 vs. 59.5 ± 11.8 ; $p = 0.0002$). A history of active smoking at the time of the symptomatic event was lower in our cohort (4 vs. 30.4%; $p = 0.0038$), and the

Table 1. Comparison of demographic and clinical characteristics between our cohort and the SAMMPRIS medical arm cohort

Characteristic	Our cohort (n = 25)	SAMMPRIS medical arm cohort (n = 227)	p value
Age, years	68.5±8.0	59.5±11.8	0.0002
Male sex	20 (80)	145 (63.9)	0.12
Race (black)	10 (40)	50 (22)	0.08
Race (white)	16 (60)	161 (70.9)	0.26
Race (other)	0	16 (7)	0.38
Hypertension	23 (92)	203 (89.4)	1
Diabetes mellitus	12 (48)	103 (45.4)	0.83
Dyslipidemia	25 (100)	203 (89.4)	0.14
Current smoker	1 (4)	69 (30.4)	0.0038
Former smoker	7 (28)	80 (35.2)	0.52
Never smoker	17 (68)	78 (34.4)	0.0018
CAD	4 (16)	59 (26)	0.34
QE stroke	18 (72)	152 (67)	0.66
QE TIA	7 (28)	75 (33)	0.66
On antithrombotic at time of QE	12 (48)	141 (62.1)	0.2
Symptomatic artery ICA	0	49 (21.6)	0.006
Symptomatic artery MCA	9 (36)	105 (46.3)	0.4
Symptomatic artery BA	12 (48)	51 (22.5)	0.0126
Symptomatic artery VA	4 (16)	22 (9.7)	0.3

QE = Qualifying event; ICA = internal carotid artery; VA = vertebral artery. Data are presented as mean ± SD or n (%).

percentage of lifetime nonsmoker was higher in our cohort (68 vs. 34.4%; $p = 0.0018$). Our cohort had less involvement of the internal carotid artery as the symptomatic artery (0 vs. 22%; $p = 0.006$) and more involvement of the BA (48 vs. 23%; $p = 0.0126$). Other baseline characteristics including sex, race, hypertension, dyslipidemia, diabetes mellitus, CAD and history of antithrombotic use at the time of the qualifying event were similar between the two cohorts.

The achievement of BP and LDL cholesterol targets at the 90-day follow-up in our cohort was similar to what was achieved in the SAMMPRIS medical arm cohort at 120 days from randomization (table 2). Twelve patients in our cohort (48%) and 103 patients in the SAMMPRIS medical arm cohort (45%) had a documented history of diabetes mellitus. The glycated hemoglobin level was similar between our cohort at the 90-day follow-up and the SAMMPRIS medical cohort at 120 days. However, persistence of smoking status in our cohort at 90 days was lower than what was reported for the patients that were evaluated at 120 days in the SAMMPRIS cohort (0 vs. 20%; $p = 0.0098$).

We had a 100% follow-up of our patients, and at 12 months the combined outcome of recurrent stroke in any vascular territory, MI, or vascular death was lower than in the SAMMPRIS cohort (0 vs. 16%, $p = 0.0312$; table 3). The major bleeding rates at 12 months were similar between the 2 groups, with our cohort having 1 (4%) major bleeding event and the SAMMPRIS cohort having 5 (2.2%) events ($p = 1.0$). The major bleeding event in our cohort was a single GI bleeding event requiring transfusion, which occurred while the patient was taking concomitant nonsteroidal anti-inflammatory medication in addition to DAPT.

Table 2. Comparison of vascular risk factors goals between our cohort at 90 days and the SAMMPRIS medical arm cohort at 120 days

Risk factor	Our cohort (n = 25)	SAMMPRIS medical arm cohort (n = 227)	p value
Blood pressure			
Patients evaluated	20 (80)	179 (79)	
SBP	137.6±12	134.8±17	0.47
DBP	78.9±11	77.3±10	0.50
Lipids			
Patients evaluated	6 (24)	175 (77)	
LDL	64±49	72.8±26	0.43
Glycated hemoglobin			
Patients evaluated	3 (25)	47 (46)	
HgA1C	5.83±1	7.5±2	0.16
Smoking			
Patients evaluated	25 (100)	181 (80)	
Current smoker	0	37 (20.4)	0.01

SBP = Systolic BP; DBP = diastolic BP; HgA1C = glycated hemoglobin. Data are presented as mean ± SD or n (%).

Table 3. Endpoint and safety outcome

Outcome	Our cohort (n = 25)	SAMMPRIS medical arm cohort (n = 227)	p value
Endpoint outcome (12 months)	0	36 (16)	0.03
Safety outcome (12 months)	1 (4)	5 (2.2)	1.00

Data are presented as n (%). Endpoint outcome – the rate of recurrent stroke in any vascular territory, MI or death from a vascular pathophysiology; safety outcome – the rate of any major hemorrhage.

Discussion

Our analysis provides real-world experience that aggressive medical management similar to the SAMMPRIS trial protocol is effective at reducing the risk of recurrent stroke [10–14, 16]. Similar to studies after MI, our results suggest a superiority of longer-duration DAPT compared to the 90-day period studied in the SAMMPRIS and the VISSIT trials in reducing the primary outcome of ischemic stroke, MI or vascular death at 1 year [17]. The prolonged period of DAPT was not associated with a significant increase in the risk of major hemorrhage, which may be related to the utilization of H2 blocker agents for GI prophylaxis, which were a standard part of our treatment while patients were on DAPT.

The SAMMPRIS optimal medical management protocol, which included 90 days of DAPT along with rigorous risk factor modification, showed a significant reduction in the long-term risk of ischemic stroke, MI or vascular death at 1 year (12.2%) compared to the patients with similar baseline characteristics who underwent PTAS utilizing the Wingspan self-expanding stent (Stryker®) with the same medical management (20.0%) [13]. This benefit was seen within 30 days of enrollment and was lower than in symptomatic 70–99% ICAD patients from the WASID cohort (10.7 vs. 5.8%) [9, 13]. Although this early decrease in vascular events in

the SAMMPRIS group could be related to a more rigorous risk factor modification including LDL-lowering therapy, the rapid reduction in the vascular event risk is more likely to be explained by the effects of DAPT given their rapid onset of action and the lack of early cardiovascular risk reduction from statin therapy after MI [20].

The data to support such superiority of DAPT compared to monotherapy in ICAD patients presenting with TIA and ischemic stroke are limited. Aspirin and clopidogrel, as compared with aspirin alone, was found to reduce the frequency of ipsilateral distal microemboli detected by transcranial Doppler ultrasound in patients with recent (within 3 months) symptomatic extracranial carotid stenosis in the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial [21], and in patients with recent (within 7 days) symptomatic internal carotid or MCA stenosis (intracranial stenosis in 93%) in the Clopidogrel plus Aspirin for Infarction Reduction in Acute Stroke or Transient Ischemic Attack Patients with Large Artery Stenosis and Microembolic Signals (CLAIR) study [22–23]. Although reduction of microemboli detection by transcranial Doppler in patients on DAPT is a reasonable surrogate marker, it might not translate into clinical efficacy of reducing stroke or TIA with clopidogrel plus aspirin dual therapy in patients with symptomatic ICAD.

The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial was a recent randomized, double-blind, placebo-controlled trial that showed DAPT with aspirin and clopidogrel for 21 days significantly reduced the risk of recurrent stroke within 90 days in patients who presented with minor ischemic stroke (NIHSS score <4) or high-risk TIA [age, BP, clinical features, duration, and diabetes (ABCD²) score ≥4] within 24 h of symptom onset compared to aspirin monotherapy (8.2 vs. 11.7%, respectively; HR = 0.68, 95% CI = 0.57–0.81, $p < 0.001$). The rate of combined events including stroke, MI or vascular death was also lower with DAPT (8.4 vs. 11.9%; HR = 0.69, 95% CI = 0.58–0.82, $p < 0.001$), while the rate of moderate or severe bleeding in CHANCE did not differ between the two groups (0.3 vs. 0.3%, $p = 0.73$) [24]. Although the CHANCE trial, which was conducted in China, did not specify the pathophysiology of the presenting cerebrovascular event or the percentage of patients with symptomatic ICAD, the distribution of stroke subtypes in China differs from that in North America in that China has a higher incidence of ICAD [19], which might indicate a more robust role of DAPT in symptomatic ICAD patients as has been evident in the SAMMPRIS and the CLAIR trials. On the other hand, the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, which was a randomized, double-blind, placebo-controlled trial that compared clopidogrel plus aspirin versus aspirin monotherapy in 3,020 patients who had a symptomatic lacunar (perforator artery) infarction confirmed by magnetic resonance imaging within 6 months of onset, failed to show any difference in the risk of recurrent stroke (ischemic or hemorrhagic stroke) between the two groups (2.5%/year in the DAPT group vs. 2.7%/year in the monotherapy group; HR = 0.92, 95% CI = 0.72–1.16, $p = 0.48$). However, the DAPT group had a higher major bleeding rate than the aspirin monotherapy group (2.1 vs. 1.1%/year, respectively; HR = 1.97, 95% CI = 1.41–2.71, $p < 0.001$) [25]. Similarly, the MATCH trial, which randomized 7,599 patients within 3 months of ischemic stroke or TIA to aspirin 81–162 mg daily/clopidogrel 75 mg daily versus clopidogrel 75 mg, failed to show an overall benefit for DAPT over monotherapy for the primary endpoint, a composite of ischemic stroke, MI, vascular death, or hospitalization for cerebral or systemic ischemia (15.7 vs. 16.7% stroke recurrence, RRR 6.4%, 95% CI –4.6 to 16.3). The MATCH trial did not show a significant difference in fatal bleeding or symptomatic intracranial hemorrhage, but there was a significant risk of life-threatening bleedings with DAPT [96 (2.6%) vs. 49 (1.3%); absolute risk increase 1.3% (95% CI 0.6–1.9)] [26]. While these studies showed no benefit with DAPT and an increase in major bleeding, the SPS3 trial included only lacunar stroke patients, and half of MATCH trial participants had lacunar stroke. Symptomatic ICAD of 70–99% severity has a significantly higher risk of recurrent ischemic stroke than lacunar

causes of stroke, and therefore the benefits of DAPT on recurrent ischemic stroke prevention in ICAD may outweigh the potential increased risk of major bleeding.

Aggressive vascular risk factor modification, along with DAPT for 90 days followed by aspirin alone, has become a standard of care in most US centers after the SAMMPRIS trial results, and it was considered reasonable based on the most recent guidelines by the American Heart Association/American Stroke Association (AHA/ASA) [27, 28].

Limitations of our study include its retrospective nature and small sample size, which resulted in differences among our patients' baseline risk factors compared to the SAMMPRIS trial. Our data suggest that prolonged DAPT may be beneficial for patients with symptomatic severe (70–99%) ICAD and warrants further evaluation. A randomized trial comparing the duration of DAPT (90 days vs. 1 year) is needed to identify the optimal duration of DAPT with aspirin and clopidogrel in patients with symptomatic intracranial stenosis.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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