ASA failure

Does the combination ASA/clopidogrel confer better long-term vascular protection?

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ABSTRACT

Objective: To assess whether adding clopidogrel to acetylsalicylic acid (ASA) has a long-term protective vascular effect in patients with lacunar stroke while taking ASA.

Methods: Post hoc analysis of 838 patients with ASA failure and recent lacunar stroke from the Secondary Prevention of Small Subcortical Strokes Trial (SPS3) cohort randomly allocated to aspirin (325 mg/day) and clopidogrel (75 mg/day) or placebo. Primary efficacy outcome was stroke recurrence (ischemic and intracranial hemorrhage) and main safety outcome was major extracranial hemorrhage. Patients were followed for a mean period of 3.5 years.

Results: The ASA failure group had a significantly higher risk of vascular events including ischemic stroke when compared with the non-ASA failure group ($n = 2,151$) in SPS3 ($p = 0.03$). Mean age was 65.6 years and 65% were men. The risk of recurrent stroke was not reduced in the dual antiplatelet group, 3.1% per year, compared to the aspirin-only group, 3.3% per year (hazard ratio [HR] 0.91; 95% confidence interval [CI] 0.61–1.37). There was also no difference between groups for ischemic stroke (HR 0.90; 95% CI 0.59–1.38). The risk of gastrointestinal bleeding was higher in the dual antiplatelet group (HR 2.7; 95% CI 1.1–6.9); however, the risk of intracranial hemorrhage was not different.

Conclusions: In patients with a recent lacunar stroke while taking ASA, the addition of clopidogrel did not result in reduction of vascular events vs continuing ASA only.

Classification of evidence: This study provides Class I evidence that for patients with recent lacunar stroke while taking ASA, adding clopidogrel as compared to continuing ASA alone does not reduce the risk of recurrent stroke. *Neurology*® 2014;82:382–389

GLOSSARY

ASA = acetylsalicylic acid; **CI** = confidence interval; **HR** = hazard ratio; **SPS3** = Secondary Prevention of Small Subcortical Strokes Trial.

Some patients with cardiovascular conditions have events while treated with aspirin. This observation, termed aspirin treatment failure, can be due to multiple reasons, including poor adherence and presence of multiple vascular risk factors enhancing platelet activation.^{1–3} A laboratory resistance to aspirin has also been described in approximately 15%–20% of cerebrovascular patients.^{4,5} In these cases, alternate therapeutic approaches could include either replacing or adding another antiplatelet such as clopidogrel to aspirin.^{1,6,7} Clinicians will often switch to another antiplatelet such as clopidogrel after a new non-cardioembolic cerebral ischemic event under acetylsalicylic acid (ASA) therapy.⁷ However, this clinical practice has not been shown to be effective and lacks any direct supportive evidence. In addition, the combination of ASA and clopidogrel is not recommended for long-term secondary stroke prevention in current guidelines, based on lack of proven efficacy and increased hemorrhagic risk.^{8,9} Although recent evidence appears to suggest a potential benefit for the combination of ASA and clopidogrel in the acute setting, additional confirmatory evidence is needed.¹⁰ Previous studies^{11,12} that have assessed the combination of ASA and clopidogrel have not taken into consideration aspirin failure as a potential confounder. The Secondary

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Prevention of Small Subcortical Strokes Trial (SPS3),¹³ by identifying patients on ASA at the time of the qualifying cerebral event, provides an opportunity to assess both their level of vascular risk and benefit from long-term dual antiplatelet therapy. We thus performed a post hoc analysis of the SPS3 trial to answer these questions.

METHODS SPS3 was a randomized multicenter clinical trial in clinical centers in North America, Latin America, and Spain. Details for the rationale, design, and characteristics of participants have been previously described.^{13,14} In brief, patients ≥ 30 years with a recent (≤ 180 days) symptomatic lacunar stroke who were without surgically amenable ipsilateral carotid artery disease or major risk cardioembolic sources were eligible and randomized simultaneously in a 2-by-2 factorial design, either to single or dual antiplatelet therapy (double-blind) and to 1 of 2 target levels of systolic blood pressure control (< 130 mm Hg vs 130–149 mm Hg, open-label). The choice of prespecified systolic targets was justified by the lack of information about their potential benefit in secondary stroke prevention. Participants with a clinical lacunar syndrome were required to meet MRI criteria that included a diffusion-weighted imaging lesion ≤ 2.0 cm with confirmatory apparent diffusion coefficient image or a well-delineated focal hyperintensity ≤ 2.0 cm on fluid-attenuated inversion recovery or T2 that corresponded to the clinical syndrome. In addition, MRI evidence of a recent or remote cortical infarct, large (> 1.5 cm) subcortical infarct, or prior intracerebral hemorrhage excluded participation. MRI eligibility was determined by local investigators, with images submitted for central interpretation by a neuroradiologist. Additional exclusion criteria included disabling stroke (modified Rankin Scale score ≥ 4). Antiplatelet treatment between the index event and randomization was left to the treating physician.

Patients with prior lacunar stroke or TIA must have had a clinical episode antecedent to the qualifying event that was consistent with a classic subcortical ischemic stroke, and not solely an infarct on neuroimaging. Diabetics were those with a history of diabetes mellitus at the time of the qualifying stroke plus those with diabetes diagnosed at the time of stroke (fasting serum glucose ≥ 120 mg/dL) or initiation of antidiabetic medications during the first 3 months of follow-up. This definition, although different from current guidelines, was unlikely to have affected our results. Blood pressure at entry was based on the average of screening systolic blood pressure measurements taken at least 1 week apart.

Randomized assignments, stratified according to clinical center and baseline hypertensive status, were generated with the use of a permuted-block design and protected from previewing. All participants were given 325 mg of enteric-coated aspirin daily and were randomly assigned to receive 75 mg of clopidogrel daily or a matching placebo, with adherence measured by pill counts performed at follow-up visits.

Standard protocol approvals, registrations, and patient consent. Participation required written informed consent for all patients and approval by the human research subjects committee at each study center. Clinical trials registration number is NCT00059306.

The primary hypothesis was that clopidogrel added to aspirin would be superior to aspirin alone in reducing the primary outcome of stroke recurrence (any ischemic stroke or intracranial

hemorrhage). Recurrent ischemic stroke was clinically defined as a focal neurologic deficit of sudden onset persisting for more than 24 hours with hemorrhage excluded by neuroimaging. Intracranial hemorrhage included intracerebral, subdural, epidural, and subarachnoid bleeds. Strokes were counted as fatal if death occurred within 30 days or if it occurred after 30 days and was attributable to the stroke. Secondary outcomes included acute myocardial infarction and death, classified as vascular, nonvascular, or unknown cause. The primary safety outcome was major extracranial hemorrhage, defined as serious or life-threatening bleeding requiring transfusion or surgery or resulting in permanent functional sequelae or death. All reported efficacy and safety outcomes were reviewed and confirmed by a central adjudication committee that was unaware of treatment and classified ischemic strokes by presumed mechanism.

For the present analysis, participants were included if they were on aspirin only at the time of the qualifying event, defined as no antithrombotic drugs marked on the qualifying stroke form at baseline except aspirin. Patients on other antiplatelets were not included. A total of 838 participants were included who were considered aspirin failures at baseline.

The Pearson χ^2 or Fisher exact test was used to examine the association between the antiplatelet group and baseline characteristic or risk factors of interest for categorical variables, as appropriate. A 2-sample t test was performed to test if there is a significant difference between antiplatelet groups for continuous risk factors. Significance was assessed at $p = 0.05$. Factors found to be significant in univariate analysis were then included in a multivariable model.

We computed the annual outcome rates for each of the combination therapy and monotherapy groups, and then used Cox proportional hazards models to compute the hazard ratio (HR), comparing the combination therapy group to the monotherapy group. In addition, we included sex and time between the qualifying event and randomization in the Cox models since they were unbalanced between the antiplatelet groups in the ASA failure group (table 1); however, with one exception, they did not affect the results. Thus, we reported the results in table 2 (efficacy) and table 3 (safety) unadjusted.

All analyses followed an intention-to-treat paradigm. All tests were 2-sided, and statistical significance was accepted at the 0.05 level, with no adjustment made for multiple comparisons. Analyses were performed with SAS version 9.2.

Classification of evidence. This study provides Class I evidence that for patients with recent lacunar stroke while taking ASA, adding clopidogrel as compared to continuing ASA alone does not reduce the risk of recurrent stroke during an average 3.5 years follow-up.

RESULTS Study participants. The present subgroup analysis included a total of 838 patients: 411 in the group treated with aspirin plus placebo and 427 in the group treated with aspirin and clopidogrel. Participants were followed on average for 3.5 (SD = 2.2) years. The mean ($\pm$ SD) age of the patients was 66 years (10.4) and 65% were men; 85% had a history of hypertension, 47% had diabetes, and 18% were current tobacco smokers. The median time from the date of the qualifying stroke to randomization was 77.3 days (SD = 46.3). Among participants, the mean systolic blood pressure was 144 ± 18.3 mm Hg at study entry and declined to 131 (SD = 16.2) by the time of last follow-up assessment.

Table 1 Patient characteristics by ASA use at index stroke and for antiplatelet groups within the ASA failure group

	Aspirin use at index stroke				Aspirin failure group by antiplatelet treatment		
	Aspirin	No aspirin	p Value	p Value from multivariable model	Aspirin + clopidogrel	Aspirin + placebo	p Value
Number randomized	838	2,151			427	411	
Male, %	65	62	0.11	—	62	69	0.04
Age, y, mean (SD)	66 (10.4)	62 (10.8)	<0.01	<0.0001	66 (10.6)	66 (10.2)	0.85
Smoking status, %			<0.01	0.15			0.47
Never	37	40			38	36	
Former	45	38			43	47	
Current	18	22			19	17	
Mean MMSE score at baseline, mean (SD)	28 (2.2)	28 (2.4)	0.05	—	28 (2.1)	28 (2.2)	0.60
BMI, mean (SD)	29 (6.2)	29 (7.1)	0.09	—	29 (6.4)	29 (6)	0.70
Systolic BP, mm Hg, mean (SD)	144 (18.3)	143 (19)	0.10	—	145 (18.3)	143 (18.4)	0.18
Prior symptomatic, %	18	7	<0.01	<0.0001	17	20	0.31
Hypertension, %	85	71	<0.01	0.009	87	84	0.27
Diabetes mellitus, %	47	32	<0.01	0.21	44	49	0.23
Congestive heart failure, %	1	0	0.02	0.61	1	1	0.96
Ischemic heart disease, %	21	6	<0.01	<0.0001	21	21	0.91
Hyperlipidemia, %	63	43	<0.01	<0.0001	63	64	0.88
PAD, %	5	2	<0.01	0.15	6	5	0.74
Days from qualifying stroke to randomization, mean (SD)	77 (46.3)	76 (47.3)	0.52	—	82 (48.6)	73 (43.3)	0.01
Glucose, mg/dL, mean (SD)	130 (52.4)	124 (55.7)	0.01	0.57	128 (50.6)	132 (54.1)	0.22
LDL-C, mg/dL, mean (SD)	107 (39.6)	114 (39.8)	<0.01	0.19	108 (39.7)	106 (39.5)	0.50
Creatinine, mg/dL, mean (SD)	0.99 (0.3)	0.94 (0.3)	<0.01	0.77	0.99 (0.3)	0.99 (0.3)	0.91

Abbreviations: ASA = acetylsalicylic acid; BMI = body mass index; BP = blood pressure; LDL-C = low-density lipoprotein cholesterol; MMSE = Mini-Mental State Examination; PAD = peripheral arterial disease.

Baseline characteristics for patients taking ASA at the time of their index cerebral ischemic event (aspirin failure group) compared to those who were not taking ASA in the main SPS3 trial shows that globally the aspirin failure group was significantly older and had a greater proportion of patients with vascular risk factors, thus representing a different cohort (table 1). This translated into a higher vascular risk after adjusting for history of subcortical TIA and ischemic stroke at baseline; the risk of recurrent strokes (ischemic or hemorrhagic) was marginally higher in the ASA failure group (3.2%/year) compared to the rest of the study participants (2.3%/year, $p = 0.08$) (see table 4). For ischemic stroke, the rates were 2.9%/year vs 1.9%/year, respectively, $p = 0.03$. All major vascular events including vascular death were more common in the ASA failure group (although not statistically significantly so); however, major bleeding was not different between ASA failures and those not taking ASA at the time of their index event.

Table 1 displays the baseline characteristics for the ASA failure group by antiplatelet treatment. The

demographics and risk factors were well-balanced between the treatment groups except for sex and days from qualifying stroke to randomization. The participants in the aspirin/placebo group were more likely to be male than those in the aspirin/clopidogrel group. The average days from qualifying event to randomization in the aspirin/clopidogrel group was longer than for the aspirin/placebo group.

Among ASA failures, the estimated average rate of adherence to the assigned antiplatelet regimen was 94% over the study period. Permanent discontinuation of assigned antiplatelet therapy occurred in 31% of patients in the dual antiplatelet group and in 34% of patients receiving aspirin only ($p = 0.39$). This is comparable to other studies.¹² Among patients who did not complete the study ($n = 99$), 16% were lost to follow-up, and 77% withdrew consent. Lipid-lowering agents were prescribed for 78% of patients during the study and 74% received statins equally in both groups.

Recurrent stroke. The efficacy results for the ASA failure group are presented in table 2 and in the figure, without any adjustments for covariates.

Table 2 Main efficacy outcomes^a for ASA failure group

	Aspirin failure group					
	Aspirin + placebo (n = 411)		Aspirin + clopidogrel (n = 427)		HR (95% CI)	p Value
	N	Rate, %/y	N	Rate, %/y		
All stroke (ischemic and hemorrhage)	49	3.3	45	3.1	0.91 (0.61–1.37)	0.66
Ischemic stroke	45	3.0	41	2.8	0.90 (0.59–1.38)	0.64
Intracranial hemorrhage	4	0.27	4	0.27	1.02 (0.25–4.01)	0.98
Myocardial infarct	15	0.96	15	0.95	0.99 (0.49–2.04)	0.99
Major vascular events ^b	60	4.1	57	3.9	0.94 (0.66–1.36)	0.75
Deaths (all)	22	1.38	46	2.87	2.13 (1.28–3.54)	0.004
Vascular	9	0.56	20	1.25	2.21 (1.01–4.86)	0.05
Nonvascular	8	0.50	17	1.06	2.21 (0.95–5.12)	0.07
Uncertain	5	0.31	9	0.56	1.84 (0.62–5.49)	0.28

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio.

^aTime to first event in the specific category; rates are annualized. Total patient-years of exposure for the primary outcome (all strokes) were 1,493 for those assigned to aspirin alone and 1,472 for those assigned to clopidogrel plus aspirin.

^bStroke, myocardial infarct, or vascular death.

There was no evidence that the risk of recurrent stroke was different among those randomized to aspirin plus clopidogrel compared to those randomized to aspirin only. A total of 94 participants had a recurrent stroke: 45 in the ASA/placebo group vs 41 in the dual antiplatelet group had an ischemic stroke and 4 in each group had an intracranial hemorrhage (HR 0.91; 95% confidence interval [CI] 0.61–1.37), illustrated in the figure. Further, there were no differences in the rate of recurrent ischemic stroke (HR 0.90; 95% CI

0.59–1.38), intracranial hemorrhage (HR 1.02; 95% CI 0.25–4.01), or any other major vascular events between the 2 groups. In the group receiving dual antiplatelet therapy, there was no reduction in the composite outcome of stroke, myocardial infarction, or vascular death.

The treatment effect was examined also among patients in the non-ASA failure group, and no differences were observed with regards to the main efficacy outcomes (HR 0.92; 95% CI 0.67–1.24) (see the

Table 3 Safety outcomes^a for ASA failure group

	Aspirin failure group					
	Aspirin + placebo (n = 411)		Aspirin + clopidogrel (n = 427)		HR (95% CI)	p Value
	N	Rate, %/y	N	Rate, %/y		
All hemorrhages	19	1.2	28	1.8	1.50 (0.83–2.7)	0.17
Intracranial hemorrhages	6	0.38	5	0.31	0.85 (0.26–2.8)	0.78
Intracerebral	2	0.13	3	0.25	1.5 (0.25–8.8)	0.68
Subdural or epidural	3	0.19	2	0.13	0.70 (0.12–4.2)	0.69
Other	1	0.063	0	0	—	—
Extracranial bleeding	13	0.83	25	1.63	1.96 (1.0–3.8)	0.05
Gastrointestinal ^b	6	0.38	16	1.03	2.7 (1.1–6.9)	0.04
Fatal hemorrhages	2	0.12	2	0.13	0.96 (0.14–6.82)	0.97
Intracranial	2	0.13	1	0.06	0.48 (0.04–5.28)	0.55
Extracranial	0	0	1	0.06	—	—

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio.

^aA time-to-first-event model was used for each outcome category; rates are annualized. All adjudications were performed centrally by the Secondary Prevention of Small Subcortical Strokes Trial adjudication committee.

^bThe site of bleeding was determined by an investigator at the local study center.

Table 4 Ischemic events, major bleeding, and death by aspirin use at index event

	Aspirin (n = 838)		No aspirin (n = 2,151)		HR (95% CI)	p Value
	N	Rate, %/y	N	Rate, %/y		
All stroke (ischemic and hemorrhage)	94	3.2	164	2.3	1.26 (0.98–1.64)	0.08 ^a
Ischemic stroke	86	2.9	138	1.9	1.36 (1.03–1.79)	0.03 ^a
Intracranial hemorrhage	8	0.27	26	0.37	0.59 (0.27–1.31)	0.19 ^b
Major bleeding	47	1.52	114	1.59	0.85 (0.60–1.20)	0.35 ^c
Myocardial infarct	30	0.96	36	0.49	1.38 (0.83–2.29)	0.22 ^d
Major vascular events ^e	117	4.01	202	2.88	1.15 (0.90–1.46)	0.27 ^f
Deaths	68	2.1	118	1.6	0.95 (0.70–1.30)	0.74 ^g
Vascular	29	0.91	39	0.52	1.25 (0.76–2.07)	0.38 ^h
Nonvascular	25	0.78	43	0.58	0.93 (0.56–1.55)	0.79 ⁱ
Uncertain	14	0.44	36	0.48	0.73 (0.39–1.36)	0.32 ^j

Abbreviations: CI = confidence interval; HR = hazard ratio.

^a Adjusted for prior symptomatic subcortical stroke and TIA at baseline.

^b Adjusted for age at baseline.

^c Adjusted for subcortical TIA and age at baseline.

^d Adjusted for history of ischemic disease and β -blocker use at baseline.

^e Stroke, myocardial infarction, or vascular death.

^f Adjusted for prior symptomatic subcortical stroke, history of ischemic disease, subcortical TIA, Rankin score, β -blocker use, and age at baseline.

^g Adjusted for history of ischemic disease, history of hypertension, Rankin score, and age at baseline.

^h Adjusted for prior symptomatic subcortical stroke, history of ischemic disease, Rankin score, and age at baseline.

ⁱ Adjusted for history of ischemic disease and age at baseline.

^j Adjusted for subcortical TIA, Rankin score, and age at baseline.

figure). Further, there was no statistically significant interaction between ASA use at index stroke and antiplatelet treatment, regardless of the outcomes.

Mortality. In the ASA failure group, the risk of all-cause mortality among those randomized to the combination therapy group was higher than for those randomized to aspirin only (HR 2.13; 95% CI 1.28–3.54; $p = 0.004$). We also observed a marginal difference in the rates of vascular and nonvascular deaths between the 2 groups ($p = 0.05$ and $p = 0.07$, respectively), with those randomized to the combination treatment being more likely to experience these outcomes than those randomized to aspirin only (see table 2).

There were no associations between sex or time between qualifying event and randomization with any of the efficacy outcomes, with the exception of the risk of noncerebral death being lower for men than for women (HR 0.26; 95% CI 0.08–0.86).

Table 3 shows the safety outcomes by antiplatelet treatment groups for the ASA failure group. The annual rates of hemorrhagic complications, including intracranial and fatal hemorrhages, were comparable in both groups except for an increase in gastrointestinal bleeding in the ASA/clopidogrel group relative to the monotherapy group (HR 2.7; 95% CI 1.1–6.9).

DISCUSSION In this cohort of patients with a recent lacunar stroke who were taking ASA at the time of

their index event, the addition of clopidogrel to ASA did not reduce the risk of stroke recurrence or any other major ischemic events during an average follow-up of 3.5 years. This lack of protective benefit was observed even though this subgroup had a higher risk profile for ischemic stroke, with a relative risk increase of 30%, compared to the average patient in the main SPS3 trial. The HRs for the recurrence of an ischemic stroke between the ASA/clopidogrel combination vs the ASA only group was 0.82 (95% CI 0.63–1.09) for the overall SPS3 cohort vs 0.90 (95% CI 0.59–1.38) for the present high-risk ASA failure subgroup. Previous studies^{11,12} assessing the role of the combination of clopidogrel and ASA in long-term non-cardioembolic ischemic stroke prevention also reported a nonsignificant protective effect for the prevention of recurrent ischemic events while reporting an increased risk of hemorrhagic complications. These studies included patients with symptomatic cerebrovascular disease as well as a spectrum of cardiovascular conditions and presence of vascular risk factors. In addition, and similar to our results, a recent substudy from the CHARISMA trial reported a lack of protective effect from the addition of clopidogrel to aspirin in patients identified as being aspirin-resistant by laboratory measures.¹⁵ Our aspirin failure cohort was older and had a higher proportion of vascular risk factors than those who were not taking aspirin at the time of their index event in SPS3. They

Figure Probability of the primary outcome (all strokes) for ASA failure and non-ASA failure groups

The hazard ratio for the primary outcome, recurrent stroke, was 0.91 (95% confidence interval [CI] 0.61–1.37) for the acetylsalicylic acid (ASA) failure group and 0.92 (95% CI 0.67–1.24) for the non-ASA failure group.

also had a higher risk of vascular events during follow-up; this association of aspirin failure with increased vascular risk profile and worse outcome has been described previously.^{1,16–18} A possible explanation could be that vascular risk factors contributed to the aspirin failure in this cohort through heightening platelet reactivity, upregulation of inflammation, or other mechanisms. That adding clopidogrel did not apparently benefit the ASA failure group suggests that failed antiplatelet pharmacologic effect may be less important than the impact of risk factors themselves.¹

In our study, the hemorrhagic risk from gastrointestinal bleeding and overall mortality were doubled in the dual antiplatelet group. This is similar to what was reported in the SPS3 main analysis. Although a recent systematic review¹⁹ focusing on the combination of clopidogrel and ASA in diverse vascular conditions did not find an increased risk of global mortality associated with this combination, it did report a trend toward an increase in fatal hemorrhages associated with these 2 antiplatelets. The increased overall mortality associated with the ASA/clopidogrel combination reported in our study cannot be accounted for by an increase in fatal hemorrhages, as discussed previously,¹³ leaving the exact reason for this finding uncertain and possibly related either to the specific characteristics of our study population or to chance. In some studies, higher aspirin doses combined

with clopidogrel have been associated with an increase in bleeding risk,^{20,21} although we cannot exclude that this may have potentially played a role in the increased gastrointestinal hemorrhagic risk reported in our study in which 325 mg/day of enteric coated ASA was used; other studies^{11,22} using lower doses (75–162 mg/day) of aspirin with clopidogrel have reported comparable if not greater risk of hemorrhagic complications.

Our study presents several positive aspects. First, the study population was well-defined, with a diagnosis of recent lacunar infarction confirmed in all cases by neuroimaging. Although this was a post hoc analysis, the groups (ASA vs ASA/clopidogrel) were well-balanced for demographic characteristics and vascular risk factors except for sex and time from qualifying event to randomization. If anything, these imbalances would have favored the dual antiplatelet group. Secondly, because this was a randomized trial, the quality of follow-up was excellent; only 2% were lost to follow-up, reducing the risk of missing relevant outcomes; as well, the adjudication of outcomes was blinded. Adherence to antiplatelet regimen was also excellent at 94%. Third, contrary to previous studies, determination of the antiplatelet regimen at the time of the index ischemic event was recorded in our study, thus providing the opportunity to identify individuals who had experienced their event under documented ASA therapy.

Our study has limitations. First, this report is based on a post hoc analysis, so one cannot exclude the possibility that the results may have been influenced by unrecognized confounding factors. Secondly, the size of the cohort and length of follow-up were somewhat limited; this could have influenced the power of the statistical analysis. Third, because of the absence of a validated standardized method to define ASA resistance, we used the clinical ASA failure concept, defined as the occurrence of new ischemic events while taking ASA. In addition, we had limited information about the exact dosage of ASA at the time of the index event and degree of adherence. Finally, our population was restricted to patients with a lacunar infarction, so our results cannot be extrapolated to other subtypes of ischemic strokes. Presently, available evidence only supports the combination of ASA and clopidogrel in the long-term prevention of cardioembolic strokes in the context of nonvalvular atrial fibrillation but at the cost of increased hemorrhagic complications.²³

Our study is one of the first that attempted to assess the potential long-term benefit of modifying an antiplatelet regimen by adding clopidogrel after a well-documented recent cerebral ischemic event under ASA. Although a post hoc analysis of the Ticlopidine Aspirin Stroke Study¹⁸ suggested a more likely benefit from ticlopidine in patients who had been previously taking ASA, this lacks relevancy today as ticlopidine is not used routinely.

Furthermore, our study addresses statements in current stroke prevention guidelines to the effect that there is a lack of evidence supporting antiplatelet regimen modification after a cerebral ischemic event and provides a partial answer to the question about the long-term potential value of choosing an alternate antiplatelet approach in patients who have had a cerebral ischemic event while receiving aspirin.^{8,9}

Based on our results, we were unable to show a superior protective effect from the addition of clopidogrel to aspirin in patients who experienced a recent cerebral ischemic event while on aspirin. Furthermore, any potential benefit of such a combination would have to offset the potential harm in terms of increased bleeding risk and mortality.

AUTHOR CONTRIBUTIONS

Robert Côté: study concept and design, study supervision. Yu Zhang: analysis and interpretation. Robert G. Hart: critical revision of the manuscript. Leslie A. McClure: analysis and interpretation, critical revision of the manuscript. David C. Anderson: critical revision of the manuscript. Robert L. Talbert: critical revision of the manuscript. Oscar R. Benavente: critical revision of the manuscript.

STUDY FUNDING

Supported by the National Institute of Neurological Disorders and Stroke (U01 NS38529-04A1).

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received April 30, 2013. Accepted in final form September 3, 2013.

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This Week's *Neurology*[®] Podcast

ASA failure: Does the combination ASA/clopidogrel confer better long-term vascular protection? (See p. 382)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the February 4, 2014, issue of *Neurology*. In the second segment, Dr. Justin Sattin talks with Dr. Robert Cote about his paper on whether the combination of ASA/clopidogrel confers better long-term vascular protection in ASA failure. Dr. James Addington reads our e-Pearl of the week about hypoglycorrachia. In the next part of the podcast, Dr. Andy Southerland focuses his interview with

Dr. Seemant Chaturvedi on a brief review of a new oral anticoagulant (Dabigatran), reference clinical trial, indication, and dosing. Disclosures can be found at www.neurology.org.

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