Predictors of Mortality in Patients With Lacunar Stroke in the Secondary Prevention of Small Subcortical Strokes Trial

Mukul Sharma, MD; Lesly A. Pearce, MS; Oscar R. Benavente, MD; David C. Anderson, MD; Stuart J. Connolly, MD; Santiago Palacio, MD; Christopher S. Coffey, PhD; Robert G. Hart, MD

Background and Purpose—The Secondary Prevention of Small Subcortical Stroke trial (SPS3) recruited participants meeting clinical and radiological criteria for symptomatic lacunes. Individuals randomized to dual antiplatelet therapy with clopidogrel and aspirin had an unanticipated increase in all-cause mortality compared with those assigned to aspirin. We investigated the factors associated with mortality in this well-characterized population.

Methods—We identified independent predictors of mortality among baseline demographic and clinical factors by Cox regression analysis in participants of the SPS3 trial. Separately, we examined the effect on mortality of nonfatal bleeding during the trial.

Results—During a mean follow-up of 3.6 years, the mortality rate was 1.78% per year for the 3020 participants (mean age, 63 years). Significant independent predictors of mortality at study entry were age, diabetes mellitus, history of hypertension, systolic blood pressure (hazard ratio [HR], 1.3 per 20 mm Hg increase), serum hemoglobin <13 g/dL (HR, 1.6), renal function (HR, 1.3 per estimated glomerular filtration rate decrease of 20 mL/min), and body mass index (HR, 1.8 per 10 kg/m² decrease). Participants with ischemic heart disease (P=0.01 for interaction) and normotensive/prehypertensive participants (P=0.03 for interaction) were at increased risk if assigned to dual antiplatelet therapy. Nonfatal major hemorrhage increased mortality in both treatment arms (HR, 4.5; 95% confidence interval, 3.1–6.6; P<0.001).

Conclusions—Unexpected interactions between assigned antiplatelet therapy and each of ischemic heart disease and normal/prehypertensive status accounted for increased mortality among patients with recent lacunar stroke given dual antiplatelet therapy. Despite extensive exploratory analyses, the mechanisms underlying these interactions are uncertain.

Clinical Trial Registration—URL: http://www.SPS3ClinicalTrials.gov. Unique identifier: NCT00059306.

(Stroke. 2014;45:00-00.)

Key Words: mortality ■ stroke, lacunar

Lacunar infarcts, or small subcortical strokes, represent 25% of all ischemic strokes, are associated with cognitive and functional impairment, and are frequently discovered on brain imaging without a prior clinical presentation (ie, covert infarcts). Hypertension is associated, and the pathology is often in the small penetrating arteries of the brain. Little is known about the predictors of mortality in those with lacunar infarcts. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial tested 2 levels of blood pressure control versus aspirin monotherapy did not show a similar association, suggesting that the results of SPS3 were unique. Although fatal hemorrhage was more common in the dual antiplatelet arm (9 versus 4 cases), the number of fatal bleeds was insufficient to explain the difference in mortality. We sought to determine the predictors of mortality in this population and hypothesized that the increased mortality might be the result of higher rates of nonfatal hemorrhage in the dual antiplatelet therapy group.

Methods

The rationale, design, participant characteristics, and main results of the SPS3 trial have been reported elsewhere. In brief, SPS3 was a randomized, multicenter clinical trial conducted in 81 clinical centers in North America, Latin America, and Spain. Patients aged ≥30 years with a recent (≤180 days) symptomatic lacunar stroke who...
were found to be approximately normally distributed and were assessed for normality and found to be approximately normally distributed with the exception of the body mass index. Body mass index was further classified as: <18.5 (underweight), 18.5 to 24.9 (normal), 25 to 29.9 (overweight), and ≥30 kg/m² (obese). Crude (univariate) hazard ratios (HRs) and the 95% confidence intervals (CIs) for each of the patient demographic and clinical characteristics were computed separately by assigned antiplatelet treatment groups. To determine independent predictors of mortality, variables univariately associated with increased risk of death (P<0.05) in 1 or both treatment groups along with assigned antiplatelet treatment group were then considered in a multivariable Cox proportional hazards regression model. Forward-stepwise regression was used to identify independent predictors, and interaction terms between assigned antiplatelet treatment and patient characteristic were investigated if the main effect term for the patient characteristic was statistically significant. HR estimates and 95% CIs were reported for variables independently predictive of mortality. Mortality and other event rates were computed by dividing the total number of deaths (or other event) by the total number of patient-years of exposure for each assigned treatment group. Confidence intervals for event rates were computed assuming a Poisson distribution. The time to major hemorrhage was calculated as the time to the first one in the case of multiple hemorrhages and analyzed as a time-dependent variable. Exposure for patients without a major hemorrhage was censored at the time of termination of study participation or at death. Statistical significance was accepted at the 0.05 level, and all tests were 2-sided. Analyses were done using SPSS 20.0 (Armonk, NY).

Results

Among the 3020 participants with recent lacunar stroke, the mean age was 63 years and the frequencies of hypertension, diabetes mellitus, and ischemic heart disease were 80%, 37%, and 10%, respectively. During 10758 years of follow-up for the antiplatelet trial (mean, 3.6 years; range, 0–8.2 years), there were 191 deaths (annualized rate, 1.78%). All-cause mortality was increased in the group assigned dual antiplatelet therapy compared with those assigned aspirin monotherapy (113 versus 78 deaths; HR, 1.5; 95% CI, 1.1–2.0). Mortality did not vary by assigned blood pressure target at the time the antiplatelet trial was terminated. Major bleeding was increased in the dual antiplatelet therapy arm but was not affected by blood pressure target assignment (Table 1).

Factors at Study Entry Associated With Mortality

Patient demographic and clinical characteristics examined for an association with mortality are shown in Table 2. Participants in either assigned antiplatelet group who were older (an average of 7 years), had lower body mass index, were diabetic, a history of hypertension, or reduced renal function had increased risk of death. Those assigned to dual antiplatelet therapy with a history of ischemic heart disease, lower diastolic blood pressure, less severe hypertension, aspirin use at the time of the qualifying event, and lower hemoglobin were also at higher risk.

By multivariable analysis, independent predictors at study entry of death were increasing age, lower body mass index, history of hypertension, higher systolic blood pressure, diabetes mellitus, hemoglobin <13 g/dL, and lower estimated

### Table 1. Mortality and Major Bleeding by Assigned Interventions

<table>
<thead>
<tr>
<th></th>
<th>Higher SBP Target</th>
<th>Lower SBP Target</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n</td>
<td>37</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>Aspirin</td>
<td>26</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>Clopidogrel plus asprin</td>
<td>50</td>
<td>55</td>
<td>105</td>
</tr>
<tr>
<td>Overall</td>
<td>76</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

The 3020 participants were randomized in a 2×2 factorial design to aspirin and higher SBP (systolic blood pressure) target, n=755; aspirin and lower target, n=748; clopidogrel plus aspirin and higher target, n=764; and clopidogrel plus aspirin and lower target, n=753.

†HR 1.1 for lower vs higher BP target; 95% CI, 0.86–1.5; P=0.4.
glomerular filtration rate with no statistically significant interaction between any of these factors and antiplatelet therapy assignment (Table 3). However, patients assigned to dual antiplatelet therapy with ischemic heart disease ($P=0.01$ for interaction) and normotensive/prehypertensive patients ($P=0.03$ for interaction) were at increased risk of death (Table 3; Figure). For the 71% of participants who were stage I or II hypertensive but without ischemic heart disease, the mortality rates were equal between antiplatelet arms. There was no significant imbalance in these factors between the antiplatelet assignments. Estimates of HRs were not appreciably changed by the exclusion of history of hypertension as a variable.

Table 2. Baseline Features Associated With All-Cause Death by Antiplatelet Assignment

<table>
<thead>
<tr>
<th>Prevalence, % or Mean (SD)</th>
<th>Crude Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin Plus Clopidogrel</td>
</tr>
<tr>
<td>Age, y</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Male sex</td>
<td>62</td>
</tr>
<tr>
<td>Race/ethnic group</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>51</td>
</tr>
<tr>
<td>Hispanic</td>
<td>30</td>
</tr>
<tr>
<td>Black</td>
<td>16</td>
</tr>
<tr>
<td>Other/multiple</td>
<td>3</td>
</tr>
<tr>
<td>Region</td>
<td></td>
</tr>
<tr>
<td>United States or Canada</td>
<td>65</td>
</tr>
<tr>
<td>Latin America</td>
<td>23</td>
</tr>
<tr>
<td>Spain</td>
<td>12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29 (6)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt;25†</td>
<td>24</td>
</tr>
<tr>
<td>25–29.9</td>
<td>41</td>
</tr>
<tr>
<td>≥30</td>
<td>35</td>
</tr>
<tr>
<td>Current tobacco smoker</td>
<td>20</td>
</tr>
<tr>
<td>Alcohol use (≥7 drinks/wk)</td>
<td>12</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>76</td>
</tr>
<tr>
<td>Screening blood pressure, mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>143 (19)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78 (11)</td>
</tr>
<tr>
<td>Severity of hypertension</td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>2</td>
</tr>
<tr>
<td>Prehypertensive</td>
<td>18</td>
</tr>
<tr>
<td>Stage I</td>
<td>40</td>
</tr>
<tr>
<td>Stage II</td>
<td>39</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>10</td>
</tr>
<tr>
<td>Prior symptomatic lacunar stroke or transient ischemic attack</td>
<td>15</td>
</tr>
<tr>
<td>Aspirin use at time of qualifying event</td>
<td>30</td>
</tr>
<tr>
<td>Statins at time of randomization</td>
<td>68</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Hemoglobin (&lt;13 g/dL)</td>
<td>33</td>
</tr>
<tr>
<td>HbA1c, % (n=987 of 1105 diabetics)</td>
<td>8.2 (2)</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>81 (20)</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>113 (40)</td>
</tr>
<tr>
<td>Assigned intensive blood pressure control</td>
<td>50</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; and LDL-C, low-density lipoprotein cholesterol.

*Indicates a significant increase in mortality risk ($P<0.05$).
†Thirteen patients had body mass index <18.5 kg/m².
‡See the Methods section for definition of severity of hypertension.
The observation of increased mortality in individuals with lacunar stroke assigned dual antiplatelet therapy was unexpected. We undertook data-driven analyses to assess the differential mortality observed with dual antiplatelet therapy in SPS3. Participants with a history of ischemic heart disease had a significantly higher mortality rate when assigned to dual antiplatelet therapy compared with those assigned to aspirin, despite evidence that dual antiplatelet therapy prevents myocardial infarction better than aspirin in populations with vascular disease. Those assigned dual antiplatelet therapy were at increased risk of death if they were normotensive/prehypertensive and had no history of ischemic heart disease. Although this may be a chance association, the definition of lacunar stroke in SPS3 was rigorous, requiring MRI confirmation, and may have selected for a unique mixture of vascular pathology with an unexpected response to the trial interventions. Bleeding was associated with mortality in the SPS3 cohort. There were more fatal and nonfatal major bleeds in the dual treatment arm, and major nonfatal bleeds correlated with mortality. The association between nonfatal major bleeding and mortality is plausible because it may lead to physician discontinuation of medications or nonadherence by patients. The proportion of patients with nonfatal major bleeding in SPS3 was 6.3% in the dual antiplatelet group and 3.5% in the monotherapy group during a mean follow-up of 43 months. These rates are similar to those observed in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial that compared dual therapy to aspirin in individuals at high vascular risk.

We lacked detailed data on exposure time for nonassigned treatments in participants who withdrew permanently from assigned antiplatelet therapy and cannot exclude antiplatelet nonadherence as an explanation of the excess mortality associated with nonfatal major hemorrhage. Nonadherence is unlikely to be the complete explanation for the difference in mortality because the increase in vascular mortality in those assigned dual antiplatelet therapy was insufficient to explain the mortality difference between antiplatelet arms (Table 5). This likely reflects an overlap of factors that affect vascular and nonvascular mortality. In addition, the assignment of cause of death by record review is inherently imprecise and a limitation of our analysis.

In general populations, obese individuals experience significantly higher all-cause mortality when compared with normal-weight individuals, whereas those overweight have significantly lower mortality, suggesting a J-shaped relationship. In SPS3 we found a linear, inverse relationship between body mass index and mortality with no interaction with treatment assignment. This may be partially explained by confounding because of smoking or pre-existing disease. Although we cannot exclude pre-existing disease, adjustment for smoking did not weaken the association between lower body mass index and mortality. A similar association has been observed.

### Table 3. Multivariable Predictors of All-Cause Death

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 y increase</td>
<td>1.6 (1.3–1.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Body mass index per 10 kg/m² decrease</td>
<td>1.8 (1.4–2.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.7 (1.1–2.7)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure per 20 mmHg increase</td>
<td>1.3 (1.1–1.5)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.0 (1.5–2.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (&lt;13 g/dL)</td>
<td>1.6 (1.2–2.1)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>eGFR per 20 mL/min per 1.73 m² decrease</td>
<td>1.3 (1.1–1.5)</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

**Final model variables considered for multivariable model were those in Table 1 with P<0.05 for 1 or both treatment groups. If main effect term was significant, then an interaction term with assigned antiplatelet was investigated. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.**

*P<0.05 for interaction.
†P<0.01 for interaction.

### Nonfatal Hemorrhage and Mortality

We hypothesized that nonfatal major hemorrhage would be associated with death and that assignment to dual antiplatelet therapy would be associated with a higher rate of nonfatal major hemorrhage. A major hemorrhage during the study period was independently predictive of mortality (HR, 4.5; 95% CI, 3.1–6.6; P<0.001) when added to the model with patient characteristics at study entry (Table 3). No important effect on HR estimates in that model was observed, and the increased risk of death with major hemorrhage was not increased for patients assigned dual antiplatelet therapy (P=0.7 for interaction). Of the 161 patients who had a major hemorrhage, the first was fatal for 13 patients (9 assigned dual antiplatelet therapy). Those assigned dual versus monotherapy had a higher rate of nonfatal major hemorrhage (n=96, 1.9%/patient-year versus n=52, 1.0%/patient-year; P<0.001). Regardless of assigned antiplatelet treatment, the mortality rate was higher for patients with a nonfatal major hemorrhage compared with those with no major hemorrhage (dual: 4.2% versus 1.8%/patient-year; P=0.002; mono: 3.1% versus 1.3%/patient-year; P=0.03; Table 4).
observed in recent observational studies of stroke cohorts.\textsuperscript{17,18} The mechanism for this observation, termed the obesity paradox, remains unexplained.

The overall mortality rate in SPS3 (1.78% per year) is lower than in other recent trials of secondary prevention (Prevention Regimen for Effectively Avoiding Second Strokes [PRoFESS] 3% per year, Vitamins to Prevent Stroke trial [VITATOPS] 4.7% per year, Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin in Patients With a History of Ischemic Stroke or Transient Ischemic Attack [PERFORM] 2.6% per year, European/Australasian Stroke Prevention in Reversible Ischemia trial [ESPRIT] 2.3% per year), which may be explained by a distinctive type of vascular disease underlying stroke or younger participant age.\textsuperscript{19-22} Mortality risk after lacunar infarct was 8% in the first year in a recent systematic review (n=544).\textsuperscript{23} Although this is substantially higher than we observed, there are several limitations in the observational cohorts that include relatively small numbers, poor and variable definition of lacunar stroke, variable follow-up, and a mean age of 71 years (SPS3 mean age, 63). Our analyses have been done in a population that met trial inclusion criteria with aggressive management of blood pressure and high prevalence of statin therapy, which likely contributed to lower mortality than found in the systematic review. Independent predictors of mortality in patients with MRI-defined lacunar infarcts have not been previously defined. We identified 7 independent predictors at study entry of mortality: age, lower body mass index, hemoglobin <13 g/dL, lower estimated glomerular filtration rate, history of hypertension, increased systolic blood pressure, and diabetes mellitus. Nonfatal major hemorrhage during the course of the trial was also associated with increased mortality.

A systematic review and meta-analysis of the effect of the addition of clopidrogel to aspirin on mortality identified SPS3 results as an outlier and noted that overall adding clopidrogel to aspirin does not increase mortality.\textsuperscript{8} An interaction between dual therapy and mortality has been observed in the asymptomatic and primary prevention subsets of the CHARISMA population with increased mortality risk in those assigned dual therapy.\textsuperscript{24} The SPS3 population behaves similar to the low-risk population in CHARISMA, suggesting that individuals with lacunar infarct form a distinct subset of those with established vascular disease and have increased risk of mortality on dual antiplatelet therapy.

Our study has several limitations. The population included in the study was relatively healthy stroke survivors recruited a median of 62 days after the qualifying stroke. Classification of death as vascular or nonvascular was dependent on the narrative supplied by the trial sites. We did not correct for multiple comparisons, and the results must be interpreted with caution.

In conclusion, participants in SPS3, although experiencing a lower mortality rate than previously reported lacunar stroke populations, had higher mortality when assigned dual antiplatelet therapy, which was not explained by fatal hemorrhage. It is unlikely to be explained by nonadherence to antiplatelet therapy because vascular mortality did not differ significantly between groups. Unexpected interactions were observed between dual antiplatelet therapy and absence of hypertension and history of ischemic heart disease with increased mortality in both subgroups. This observation, if confirmed in other data sets, has implications for the design of trials testing combination antiplatelet therapy and its broader use in stroke populations.

\textbf{Sources of Funding}

The study was supported by the National Institute of Neurological Disorders and Stroke (U01 NS38529-04A1).

\begin{table}
\centering
\caption{Relationship of Severity of First Bleeding Event During Trial and Death According to Antiplatelet Assignment}
\begin{tabular}{lcc}
\hline
 & Aspirin & Clopidogrel Plus Aspirin \\
\hline
No. of Deaths/n & Rate (% per patient-year) & Rate (% per patient-year) \\
\hline
Fatal hemorrhage & 4/4 & 9/9 \\
Nonfatal major hemorrhage & 8/52 & 3.1 & 18/96 & 4.2 \\
No major hemorrhage & 66/1447 & 1.3 & 86/1412 & 1.8 \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Cause of Death by Treatment Assignment}
\begin{tabular}{lcccc}
\hline
 & & & & \\
 & Aspirin & Clopidogrel Plus Aspirin & HR (95% CI) & \\
All participants & & & & \\
All deaths & 78 & 113 & 1.5 (1.1 to 2.0) & \\
Vascular* & 25 & 45 & 1.9 (1.1 to 3.0) & \\
Nonvascular & 31 & 39 & & \\
Uncertain cause & 22 & 29 & & \\
Ischemic heart disease±stage I/II hypertension at entry & & & & \\
All deaths & 11 & 30 & 2.9 (1.4 to 5.8) & \\
Vascular* & 4 & 14 & 3.8 (1.2 to 12) & \\
Nonvascular & 4 & 9 & & \\
Uncertain cause & 3 & 7 & & \\
Normotensive/prehypertensive and no ischemic heart disease at entry & & & & \\
All deaths & 8 & 28 & 3.3 (1.5 to 7.3) & \\
Vascular* & 0 & 11 & >60 (0.51 to >1000) & \\
Nonvascular & 6 & 9 & & \\
Uncertain cause & 2 & 8 & & \\
Stage I/II hypertension and no ischemic heart disease at entry & & & & \\
All deaths & 59 & 55 & 0.98 (0.68 to 1.4) & \\
Vascular* & 21 & 20 & 1.0 (0.54 to 1.8) & \\
Nonvascular & 21 & 21 & & \\
Uncertain cause & 17 & 14 & & \\
\hline
\end{tabular}
\end{table}
Disclosures

Drs Benavente and Hart report received grant support from National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) as coprincipal investigators of the Secondary Prevention of Small Subcortical Stroke trial; Dr Coffey is a consultant for ZZ Biotech LLC and received grant support from NIH/NINDS and the Michael J. Fox Foundation; Dr Connolly reports honoraria for Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, and Portola. The other authors report no conflicts.

References

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Supplemental Material

I. Definition of Death and Vascular Death in SPS3

Death: Persistent and irreversible absence of brain or brainstem function. Death can be the initial study event (i.e. due to cancer) or secondarily result from another event. The cause of death should be determined as vascular or non-vascular.

Vascular Death: Vascular death may be classified as Cerebral or Non-Cerebral.

Cerebral Vascular Death is defined as death that occurs within 30 days of an ischemic or hemorrhagic stroke. The stroke should be confirmed by CT, MRI, or post mortem examination. Death from a complication of stroke (e.g., pneumonia, sepsis) within 30 days of the stroke will be included as a cerebral vascular death.

Non-Cerebral Vascular Death is defined as sudden death that is attributed to cardiac ischemia (see below) or death within 30 days of one of the following well-documented vascular events.

- Myocardial infarction
- Pulmonary embolus (documented by high probability V/Q scan or angiogram)
- Ruptured abdominal aortic aneurysm (documented by angiogram, CT, ultrasound, or surgery)
- Complications of acute ischemia of a limb or internal organ (documented by typical clinical presentation [limb ischemia] or angiogram [limb or organ ischemia])
- Systemic hemorrhage (documented by typical clinical presentation, i.e., shock, drop in hematocrit, identification of bleeding source by imaging studies)

If the above in-vivo documentation is absent, post-mortem evidence that one of these conditions was the primary cause of death will suffice.

Sudden death attributed to cardiac ischemia (without proven myocardial infarction) is defined as death of sudden onset that cannot be explained by a known non-vascular process (acute or chronic) or subarachnoid hemorrhage. Examples that would not constitute sudden death attributable to cardiac ischemia are cardiac arrhythmias attributed to other causes, e.g., hypokalemia, tricyclic overdose.