Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, gender and relative high systolic blood pressure


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ABSTRACT

The most common form of neurological injury in sickle cell anemia (SCA) is silent cerebral infarction (SCI). In the Silent Cerebral Infarct Multi-Center Clinical Trial (SIT Trial), we sought to identify risk factors associated with SCI. In this cross-sectional study, we evaluated the clinical history and baseline laboratory values and performed magnetic resonance imaging of the brain in participants with SCA (HbSS or HbSβ⁰ thalassemia) between the ages of 5 and 15 years with no history of overt stroke or seizures. Neuroradiology and neurology committees adjudicated the presence of SCI. SCI were diagnosed in 30.8% (251 of 814) participants who completed all evaluations, and had valid data on all pre-specified demographic and clinical covariates. The mean age of the participants was 9.1 years, with 413 males (50.7%). In a multivariable logistic regression analysis, lower baseline hemoglobin concentration \( p < 0.001 \); higher baseline systolic blood pressure (SBP), \( p = 0.013 \); and male gender, \( p = .026 \); were statistically significantly associated with an increased risk of a SCI. Hemoglobin concentration and SBP are risk factors for SCI in children with SCA and may be therapeutic targets for decreasing the risk of SCI. This study is registered at www.clinicaltrials.gov (NCT00072761).
Introduction

Silent cerebral infarcts (SCI) have been recognized by neuroimaging in neurologically normal older adult populations since 1981 and were documented in SCA soon afterwards. As with overt stroke, SCI represent a clinical finding that is common in older adults without SCD, but they appear during early childhood in individuals with SCA. SCI are defined as a magnetic resonance image (MRI) signal abnormality visible on two views on the T-2 weighted images (axial and coronal) that must measure at least 3 mm in one dimension; further, the individual deemed to have a SCI must have an absence of focal neurological deficit compatible with the anatomical location of the brain lesion. SCI is the most common form of neurological injury among children with SCA, occurring in at least 27% prior to six years of life and 37% by 14 years of life. SCIs in children with SCA are associated with increased risk of future overt strokes and new or progressive SCI. In addition, children with SCA and SCI have been found to have poorer cognitive function than children with SCA with normal MRI of the brain or sibling controls.

Clinical and laboratory risk factors for SCI have been evaluated only sparingly. In the most rigorous study to date, the investigators from Cooperative Study for Sickle Cell Disease (CSSCD) described risk factors associated with SCI in 42 participants comparing them with 188 controls with normal MRI. In the final multivariable analysis, the authors found that SCI was associated with history of seizure, a relatively low frequency of pain episodes, and elevated WBC. Elevated SBP measurement was not associated with SCI; however, this analysis of CSSCD data had several limitations, including misclassifications of SCI that were corrected in a subsequent evaluation and a relatively small number of participants with SCI, when compared to the current study. Neurological examinations were neither routinely performed by a pediatric neurologist nor adjudicated by a central committee. Thus, a participant classified as having SCI could, in fact, have had an overt stroke. In addition, other risk factors have not been examined. Therefore, despite the observation that elevated SBP measurement is a risk factor for overt stroke in patients with SCA, the relationship between SBP
measurements and SCI has not been established. The major objective of the present study was to assess previously identified risk factors and identify new risk factors for SCI, through analysis of data from the SIT Trial clinical repository. Specifically; we tested the hypothesis that SBP measurement or other previously identified risk factors for SCI in SCA and the general population were associated with an increased risk of SCI in SCA.

**Material and Methods**

The SIT Trial is a multi-center trial designed to determine the efficacy of blood transfusion therapy for prevention of recurrent SCI in participants with SCA. To be eligible for screening, participants must: have a confirmed diagnosis HbSS or HbSβ⁰ thalassemia; be between the ages of 5 and 15 years; have no history of focal neurological deficits associated with an ischemic event or seizure disorder; have received no treatment with hydroxyurea in the previous three months; have not had a history of elevated Transcranial Doppler Scan (TCD) measurement; and not be on chronic transfusions. A detailed description of the protocol and details of the study design can be found in Casella et al.¹⁵

The SIT Trial was approved by the Institutional Review Boards of all participating institutions and is registered at www.clinicaltrials.gov (NCT00072761) and www.ISRCTN.org (ISRCTN52713285). During screening, parents of the participants completed a comprehensive questionnaire and medical records were reviewed.

The current study used a subset of the registered participants in the SIT Trial. At the time that the data were finalized for assessment and analysis (September 10, 2010), 1176 participants had completed phenotypic and demographic evaluation (Figure 1). The data set used for this study is designated as the SIT Trial screening database, which includes cleaned data from these 1176 patients. After review and exclusion where silent infarct information was missing or Hb F% was obtained before 3 years of age, and where information was missing on the pre-specified covariates,
the final analysis dataset consisted of 814 participants. A priori, we wanted to determine the association between SBP and SCI. The SBP, as a single measurement, was performed as part of routine medical care during the most recent well visit.

*Silent Cerebral Infarcts*

MRI of the brain was performed and read by the Neuroradiology Committee using a protocol detailed previously in Vendt et al.\(^{16}\) Between 2004 and 2010, 1091 participants underwent baseline MRI of the brain; 1047 were performed using a 1.5-Telsa scanner and the remaining using 3.0 Telsa scanner.

A SCI-like lesion was defined by a MRI signal abnormality visible on two views on the T-2 weighted images (axial and coronal) and at least 3 mm in one dimension, based on consensus of two of three neuroradiologists. Subsequently, each SCI-like lesion was adjudicated by the neurology committee as to whether it was truly silent, after review of the local site pediatric neurologist's examination. The local neurologist was unaware of the results of the MRI. If the neurological examination was normal or there was an abnormality on the neurological examination that was not explained by the location of the MRI lesion, the participant was classified as having a SCI.

*Statistical Methods*

The relationship between the demographic and clinical covariates and the presence of SCI was assessed with a chi-square test or a t-test for categorical or continuous covariates, respectively. A multivariable logistic model was constructed with covariates in their original scale, entering all covariates in one block. Before enrollment began in the trial, we elected not to include site location as a variable in the analyses. A second reduced model included only those covariates that were nominally significant predictors (\(p < .20\)) from the first model. Separate models were created with the statistically significant covariates in their original scales or grouped into tertiles, and the latter is
presented here. Additional analysis was done to determine the effect, if any, of case selection due to eligibility criteria and missing data on the covariates, using a chi-square or t-test.

Subject Selection Effects

A total of 225 participants of the original 1176 did not have a successful MRI and thus were not eligible for this study. The reasons for unsuccessful MRI were: a) The Neuroradiology Committee could not decide whether there was a SCI or not, (n=7); b) The Neurology Committee considered that the participant had had an overt stroke, (n=13); c) The Neurology Committee could not determine whether the stroke was overt or silent, (n=1); d) Subjects withdrew from the study before the MRI was completed, (n=165); e) The MRI failed, (n=30); f) MRI data were not available at the time of the Neurology consensus committee review (n=5); or g) The Neurology Examination form was not completed at the time of the Neurology consensus committee review (n=4). An additional 137 participants could not be included in the multivariate models, because they had missing data on one or more of the pre-specified covariates (listwise deletion was used for all models) or had HbF % levels measured before 3 years of age.

RESULTS

A total of 30.8% (251 of 814) of the participants were determined to have SCI. The demographic features of the participants with and without SCI are described in Table 1. The mean SBP was 108.0 mmHg; the median SBP was also 108.0 mmHg. The standard deviation was 11.5, with a range from 66 to 151 mmHg.

Baseline Hemoglobin and SBP Measurements are Associated with SCI

When all of the clinical and laboratory covariates of interest were forced into the multivariate logistic regression model, the overall model was statistically significant (chi-square = 29.37, df = 11, p = .002). The model had a C statistic of .620. Three factors were significant at the level of p < 0.20;
hemoglobin concentration \( p = .007 \), SBP \( p = .112 \), and gender, with female gender as the reference \( p = .046 \) (Table 2).

The reduced model with only these three covariates was statistically significant overall (chi-square = 24.41.04, df = 3, \( p < 0.001 \)), with a C statistic of .610. Both clinical factors were statistically significant (hemoglobin concentration, \( p = 0.001 \); SBP, \( p = .018 \)). Lower hemoglobin concentrations were associated with increasing odds of SCI; higher SBP was associated with increasing odds of SCI. Patient gender remained statistically significant \( p = .030 \), with males having increased odds of SCI.

In the final model, no variance inflation factor value was above 1.34, indicating very little multicollinearity.

As an exploratory analysis, we evaluated separately indirect measures of hemolysis, such as reticulocyte and total bilirubin. We added one of the two measures to the pre-existing covariates and followed the previously determined model. Absolute reticulocyte count \( p = .065 \) was included in the reduced model, with only the variables significant at below \( p = .20 \), along with gender, hemoglobin level, and SBP measurement; however, reticulocyte count was no longer statistically significant, \( p = 0.2 \). When total bilirubin was added to the model with all of the covariates, there was no significant association between the total bilirubin and risk of SCI \( p = .990 \). We did not obtain lactate dehydrogenase levels in the study.

A model with both clinical covariates grouped into tertiles was constructed. In this model, the highest tertile for SBP and lowest tertile of hemoglobin had the greatest odds of SCI (Table 3). The model had a C statistic of .615. The third tertile was the reference category for hemoglobin (> 8.5 g/dl); the first tertile was the reference category for SBP (< 104 mmHg). Odds ratios for SCI in the first tertile of hemoglobin (< 7.6 g/dl) were 2.12 [95% confidence interval (CI) 1.45 to 3.10, \( p < .001 \)]. Odds ratios in the second tertile (7.6 to 8.5 g/dl) were 1.19 (95% CI 0.81 to 1.76, \( p = .371 \)). Odds ratios for SCI in
the second tertile for SBP (104 to 112 mmHg) were 1.55 (95% CI 1.06 to 2.27, \( p = .025 \)); for the third tertile (> 112 mmHg) odds ratios were 1.73 (95% CI 1.18 to 2.54; \( p = .005 \)). No interaction was detected between baseline hemoglobin and SBP (\( p = .90 \)). For further model understanding, we constructed a chart (Figure 2) to show the joint effect of hemoglobin and SBP measurements. The reference category was based on individuals in the highest hemoglobin and lowest blood pressure group, holding gender constant. Individuals in the lowest hemoglobin and middle and upper tertile of SBP had the highest odds of a SCI when compared to their respective reference groups.

Given the association of SBP measurement with SCI described above, we tested the hypothesis that patients with documented hypertension would also have a higher rate of SCI. Approximately 1% (6 of 783) of the participants had diagnoses of hypertension and were being treated with anti-hypertensive medication at the time of their initial evaluation, although in one case the drug had been started for another indication (Table 4). During the screening phase for the trial, five of these six participants (83%) had SCI; this percentage was higher than expected when compared to the remaining study participants (30% or 237 of 778), \( p = 0.012 \).

**Discussion**

Risk factors for SCI in SCA have been incompletely studied; however, they may provide insight into the pathogenesis and potential preventive strategies, not only in SCA, but also in the general population. We describe for the first time in a large multi-center setting that lower baseline hemoglobin concentration and relative high baseline SBP measurement, both risk factors for SCI in the general population, are associated with an increased risk of SCI in SCA in multivariable analysis. We also demonstrate that neither the incidence rates of pain nor ACS events, measures of SCA morbidity, are associated with SCI. Further, baseline WBC, HbF % and oxygen saturation levels are not associated with an increased risk of SCI in multivariable analysis. There was biological plausibility that relative high SBP was associated with end organ disease in SCA, including the brain,
based on the work of Rodgers et al.\textsuperscript{14} and others.\textsuperscript{13,17} These findings, coupled with strong evidence that elevated SBP measurement was associated with SCI in older adults without SCA,\textsuperscript{18-19} provide support for the biological basis and generalizability of our results.

Our results are different from the largest study to date evaluating risk factors for SCI among participants with SCA.\textsuperscript{12} In the CSSCD study, several variables, including seizure history, pain event rate, lower hemoglobin, high WBC, elevated pocked red blood cell counts, SEN beta-S globin gene haplotype (a measure of reduced splenic function) were associated in univariate analysis; however, only seizure history, low pain rate, higher WBC, and the presence of a SEN beta-S globin gene haplotype were associated with risk of SCI in the final multivariable analysis.\textsuperscript{12} Several possible explanations exist to explain the differences between the current and previous studies. First, the current study has greater than six times more participants with SCI. Second, the two studies did not have the same eligibility criteria. The CSSCD was an infant cohort without selection based on previous co-morbid condition; in contrast, the SIT Trial participants that were screened for SCI were enrolled between 5 and 15 years of age, and participants were excluded if they had an active non-febrile seizure disorder or a stroke, or severe disease which led to treatment with hydroxyurea or blood transfusion therapy; consequently, our results can only be generalized to children with SCA who meet these criteria.

Our finding that low hemoglobin concentrations are associated with SCI in SCA is consistent with the findings in other populations without SCA in which SCI occurs, but which also have relative low hemoglobin concentrations, such as in patients receiving dialysis\textsuperscript{20} and patients with $\beta$-thalassemia intermedia.\textsuperscript{21-22} Although, the etiology of SCI is unknown, the consistent finding that anemia is a risk factor strongly implicates cerebral hemodynamic insufficiency as a central component. All patients with chronic anemia have a compensatory mechanism in the brain (auto-regulation) that occurs with vasodilation of the cerebral vasculature and manifests initially as increased cerebral
blood flow.\textsuperscript{23-24} Despite this compensatory mechanism, acute drops in hemoglobin are temporally associated with overt stroke\textsuperscript{25-26} and SCI\textsuperscript{27} in SCA. Given the strong association between anemia and SCI, the most likely explanation for the majority of SCI events in individuals with SCA is a continuous state of delicate balance in supply and demand of oxygen to the brain; thus, any decrease in supply or increase in demand may result in ischemia or infarction in this vulnerable group of patients. Alternatively the low hemoglobin may be a proxy for a higher rate of relative hemolysis, with subsequent endothelial dysfunction.\textsuperscript{28-29} We were unable to assess endothelial dysfunction, and our indirect measures of hemolysis (total bilirubin and reticulocyte count) were not associated with SCI in this cohort. Other potential mechanisms that are likely to be important, and associated with hemodynamic insufficiency, include vascular stenosis, venous sinus thrombosis and posterior reversible encephalopathy syndrome, often referred to as PRES.\textsuperscript{30}

Additional support for the precarious balance between oxygen delivery and demand that may result in SCI is the observation that infants with SCA may begin to develop their anemia as young as 10 weeks of age\textsuperscript{31} and that at 3 months of age, the mean hemoglobin of infants with HbSS is approximately 1.5 g/dl below expected for children without SCA of the same age.\textsuperscript{31} The lower hemoglobin levels may explain in part why SCIs have been detected in an infant as young as 7 months\textsuperscript{32} and in several infants less than 15 months of age.\textsuperscript{33} The vast majority of SCI occur in children less than 6 years of age,\textsuperscript{4} when the hemoglobin levels decline continuously until levels` reach steady state.\textsuperscript{31} In addition to our findings that low hemoglobin levels are associated with SCI, two single center studies of children with SCA have demonstrated similar findings. Using a multivariable analysis from a retrospective cohort, Bernaudin et al. demonstrated that low hemoglobin was associated with an increased rate of SCI.\textsuperscript{5} In univariate analysis, lower hemoglobin levels were associated with SCI in Kwiatkowski’s study of young children with SCA.\textsuperscript{4,14} Ultimately, studies of interventions to improve baseline hemoglobin concentration, such as hydroxyurea, will be necessary to evaluate this strategy for the primary prevention of SCI.
The biological basis for the association between relative high SBP measurements and SCI is not known. The etiology of the lower blood pressure in SCA is not clear, but may be explained in part by compensatory systemic vasodilatation to increase oxygen delivery that occurs in adults and children with chronic anemia. We postulate that, in SCA, as with low hemoglobin, elevated SBP results in a compromise in the compensatory auto-regulation mechanism. Consistent with this concept is that the highest odds of SCI occurred in the group of children with both the highest SBP and the lowest hemoglobin measurements when compared to all other groups, Figure 2.

In addition to our findings that relative high measurement is associated with SCI, as discussed above, multiple studies in individuals with SCA document an association between relatively elevated SBP and organ damage, including overt stroke, elevated tricuspid jet velocity measurement (a proxy for pulmonary hypertension), and renal insufficiency. The consistent relationship between organ injuries and relatively elevated SBP measurements in SCA suggest an underlying common mechanism that is unlikely to be elucidated in a clinical study and may require animal models or basic physiology studies for better understanding.

Our study has several limitations. First, SBP measurements were not standardized; however, a lack of a standard blood pressure approach across multiple sites would tend to increase the variance of these measurements and bias our results toward the null hypothesis. Although, the vast majority of children with SCA were eligible to participate in the trial, the exclusion criteria eliminated some children with severe disease, including children with overt stroke or seizures, those known to have abnormal TCD velocities, and those treated with HU or chronic blood transfusion therapy. Thus, we may have limited our ability to detect other clinically significant associations, due to restriction of the study population that was eligible for the SIT Trial. We considered the potential weakness that the SBP measurement was not standardized against height, gender, and ethnic matched controls;
however, we elected not to employ this analytical strategy because children and adults with SCA have systematically lower blood pressures when compared to the general population; the general population would represent a poor reference group. We did not adjust for age, because the anticipated upper limits of normal for children between 5 and 15 years of age has a difference of less than 10 mmHg and age was not statistically significant when evaluated in the multivariable model. We did not include analysis of MRA in this manuscript, as it was not mandatory at baseline and only subgroup of patients received them.

In summary, we have provided evidence that both baseline hemoglobin concentration and relative high SBP are risk factors for SCI. Based on these findings, we cannot make definitive recommendations for preventing SCI; however, these findings provide the basis for further research focused on increasing the baseline hemoglobin concentration or attenuating factors that lead to relative high SBP measurements, as these are potentially modifiable risk factors for SCI.
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The authors have no conflicts to report.

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M. DeBaun designed research, performed research, analyzed and interpreted data, performed statistical analysis, and wrote the manuscript. J. Casella designed research, performed research, collected data, analyzed and interpreted data and wrote the manuscript. M. Rodeghier performed statistical analysis. R. Ichord wrote the manuscript. C. Minniti, T. Howard, R. Iyer, B. Inusa, P. Telfer, M. Kirby-Allen, C. Quinn, F. Bernaudin, G. Airewele, G. Woods, J. Panepinto, B. Fuh, J. Kwiatkowski, A. King, M. Rhodes, A. Thompson, M. Heiny, R. Redding-Lallinger, F. Kirkham, H. Sabio, C. Gonzalez, S. Saccente, K. Kalinyak, J. Strouse, and J. Fixler collected data and wrote the manuscript. M. Gordon and P. Miller analyzed and interpreted the data.
References:


Table 1. Potential clinical and laboratory risk factors among 814 participants with HbSS or HbS β° thalassemia between 5 and 15 years of age, with and without SCI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Silent Cerebral Infarct (n = 563) ± standard deviation</th>
<th>Silent Cerebral Infarct (n = 251) ± standard deviation</th>
<th>p Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>9.06 ± 2.43</td>
<td>9.35 ± 2.52</td>
<td>.115</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>47.4%</td>
<td>58.2%</td>
<td>.005</td>
</tr>
<tr>
<td>Frequent headaches (%)</td>
<td>34.8%</td>
<td>40.2%</td>
<td>.156</td>
</tr>
<tr>
<td>Pain event per year</td>
<td>0.63 ± 0.84</td>
<td>0.58 ± 0.88</td>
<td>.416</td>
</tr>
<tr>
<td>Acute chest syndrome event rate per year</td>
<td>0.13 ± 0.26</td>
<td>0.17 ± 0.34</td>
<td>.134</td>
</tr>
<tr>
<td>Hemoglobin g/dl</td>
<td>8.25 ± 1.10</td>
<td>7.95 ± 1.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hg F percent</td>
<td>12.53 ± 9.61</td>
<td>11.12 ± 9.86</td>
<td>.055</td>
</tr>
<tr>
<td>Baseline SBP mmHg</td>
<td>107.31 ± 11.55</td>
<td>109.41 ± 11.23</td>
<td>.016</td>
</tr>
<tr>
<td>Baseline DBP mmHg</td>
<td>60.36 ± 8.04</td>
<td>60.95 ± 7.78</td>
<td>.328</td>
</tr>
<tr>
<td>White blood cell count (10⁶/L)</td>
<td>12,342 ± 4215</td>
<td>12,561 ± 6437</td>
<td>.563</td>
</tr>
<tr>
<td>Baseline oxygen saturation percent</td>
<td>96.58 ± 2.92</td>
<td>96.12 ± 3.01</td>
<td>.040</td>
</tr>
</tbody>
</table>

HbSS: indicates sickle cell anemia
SCI: silent cerebral infarct
Hb F: fetal hemoglobin Hg: mercury
SBP: systolic blood pressure
DBP: diastolic blood pressure
§P value from an independent samples t-test or chi square test
Table 2. Logistic regression model for silent cerebral infarct using all potential covariates. The same population of participants was used as in Table I.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95.0% CI for Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>0.97</td>
<td>1.11</td>
</tr>
<tr>
<td>Gender (male reference)</td>
<td>1.37</td>
<td>1.01</td>
<td>1.87</td>
</tr>
<tr>
<td>Hemoglobin concentration</td>
<td>0.80</td>
<td>0.67</td>
<td>0.94</td>
</tr>
<tr>
<td>Hg F percent</td>
<td>1.00</td>
<td>0.98</td>
<td>1.02</td>
</tr>
<tr>
<td>Baseline Systolic blood pressure</td>
<td>1.01</td>
<td>1.00</td>
<td>1.03</td>
</tr>
<tr>
<td>Baseline Diastolic blood pressure</td>
<td>1.01</td>
<td>0.99</td>
<td>1.03</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Baseline O2 saturation</td>
<td>0.99</td>
<td>0.94</td>
<td>1.04</td>
</tr>
<tr>
<td>Acute chest syndrome event rate</td>
<td>1.36</td>
<td>0.80</td>
<td>2.29</td>
</tr>
<tr>
<td>Pain event rate</td>
<td>0.90</td>
<td>0.74</td>
<td>1.09</td>
</tr>
<tr>
<td>Frequent headaches (yes or no)</td>
<td>1.18</td>
<td>0.86</td>
<td>1.61</td>
</tr>
<tr>
<td>Constant</td>
<td>1.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Logistic regression model for silent cerebral infarct with reduced set of covariates, grouped into tertiles.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds Ratio</th>
<th>95.0% CI for Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Hemoglobin (total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt; 7.6 g/dl</td>
<td>2.12</td>
<td>1.45</td>
<td>3.10</td>
</tr>
<tr>
<td>Hemoglobin ≥ 7.6.1 g/dl and ≤ 8.5 g/dl</td>
<td>1.19</td>
<td>0.81</td>
<td>1.76</td>
</tr>
<tr>
<td>Hemoglobin ≥ 8.6 g/dl (reference)</td>
<td>1.00</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic (total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic &lt; 104 mmHg (reference)</td>
<td>1.00</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic ≥ 104 and ≤ 112 mmHg</td>
<td>1.55</td>
<td>1.06</td>
<td>2.27</td>
</tr>
<tr>
<td>Systolic ≥ 113 mmHg</td>
<td>1.73</td>
<td>1.18</td>
<td>2.54</td>
</tr>
<tr>
<td>Gender (female, reference)</td>
<td>1.42</td>
<td>1.04</td>
<td>1.93</td>
</tr>
<tr>
<td>Constant</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The reference category for hemoglobin was the third tertile (hemoglobin ≥ 8.6/dL). Participants with hemoglobin in the second tertile had a higher risk of SCI compared to the third tertile. The reference category for SBP was the first tertile (SBP < 104 mmHg). Participants in the second and third tertiles had a higher risk of SCI compared to those in the first tertile.
Table 4
Clinical characteristics of 6 participants (with either hemoglobin SS or Sβ° thalassemia) between 5 and 15 years of age who had a clinical diagnosis of hypertension in the SIT Trial

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Medication</th>
<th>BP</th>
<th>Indication</th>
<th>MRI results</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>F</td>
<td>Enalapril</td>
<td>123/74</td>
<td>Enalapril for hypertension and congenital single kidney. Started 2 years before the diagnosis of SCI.</td>
<td>1 faint lesion in the right frontal lobe white matter. 1 lesion in the posterior corpus callosum.</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Enalapril</td>
<td>110/57</td>
<td>Enalapril for mitral valve prolapse. Started 8 years before the diagnosis of SCI.</td>
<td>5mm lesion in the left centrum semiovale.</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>Lisinopril</td>
<td>126/62</td>
<td>Lisinopril for hypertension. Started 1.5 years before the diagnosis of SCI.</td>
<td>High parietal white matter lesion on the right.</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>Atenolol</td>
<td>114/63</td>
<td>Atenolol for hypertension. Started 2 months before the diagnosis of SCI.</td>
<td>Diffuse, bihemispheric ischemic injury.</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Enalapril</td>
<td>104/58</td>
<td>Enalapril for hypertension. Started 6 years before the diagnosis of SCI.</td>
<td>2 lesions in the left frontal lobe. Bilateral posterior periventricular white matter abnormality.</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Enalapril</td>
<td>135/67</td>
<td>Enalapril for hypertension. Started 2 years before the diagnosis of SCI.</td>
<td>Does not have an infarct-like lesion.</td>
</tr>
</tbody>
</table>
Figure 1 Legend:

A flow diagram of the participants in the SIT Trial that completed all clinical forms and whose MRIs were adjudicated by both the Neuroradiology and Neurology Committee and who were available for multivariate modeling (814 subjects).
Figure 1

Participants with complete clinical information but incomplete records (n=1176)

Hg F level at age < 3 years (n=82)

Withdrew (n=80)
MRI failure (n=22)
No MRI (n=5)

Indeterminate (n=5)
Withdrew (n=6)
MRI failure (n=7)

Not adjudicated by Neurology Committee:
Withdrew (n=67)
Incomplete (n=3)

Missing data on covariates (n = 54)

Hg F level obtained at age ≥ 3 years (n = 1094)

Indeterminate (n = 1)
Missing data on covariates (n = 18)
Overt stroke (n = 12)

Indeterminate

MRI evaluated by Neuroradiology Committee (n = 987)

Evaluatex by Neurology Committee (n=282)

Valid data on all covariates

Normal MRI
No Silent Stroke (n = 563)

Silent Stroke (n = 251)
Figure 2 Legend:

Joint effect of hemoglobin total (tertiles) and systolic blood pressure (tertiles) on odds of silent cerebral infarct in 814 participants with hemoglobin SS or Sβ° thalassemia between 5 and 15 years of age.
Figure 2:
Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, gender and relative high systolic blood pressure