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RESEARCH ARTICLE

Ischemic stroke in children and young adults with sickle cell disease in the post-STOP era

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Abstract

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) and Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) trials established routine transcranial Doppler ultrasound (TCD) screening, with indefinite chronic red cell transfusions (CRCT) for children with abnormal TCD as standard of care. Implementation failures and limitations to the STOP protocol may contribute to continued ischemic stroke occurrence. In the "Post-STOP" study, we sought to assess the impact of the STOP protocol on the incidence of ischemic stroke in a multicenter cohort of former STOP and/or STOP 2 trial participants. A central team abstracted data for 2851 (74%) of the 3835 children who took part in STOP and/or STOP 2. Data included TCD and neuroimaging results, treatment, laboratory data, and detailed clinical information pertaining to the stroke. Two stroke neurologists independently confirmed each stroke using pre-specified imaging and clinical criteria and came to consensus. Among the 2808 patients who were stroke-free at the start of Post-STOP with available follow-up, the incidence of first ischemic stroke was 0.24 per 100 patient-years (95% CI, 0.18, 0.31), with a mean (SD) duration of follow-up of 9.1 (3.4) [median 10.3, range (0-15.4)] years. Most (63%) strokes occurred in patients in whom the STOP protocol had not been properly implemented, either failure to screen appropriately with TCD (38%) or failure to transfuse adequately patients with abnormal TCD (25%). This study shows that substantial opportunities for ischemic stroke prevention remain by more complete implementation of the STOP Protocol.

1 | INTRODUCTION

Stroke is one of the most devastating complications of sickle cell disease (SCD). In an unscreened population in the Cooperative Study of Sickle Cell Disease (CSSCD), the overall incidence of first stroke in individuals with homozygous sickle cell disease (SCD-SS) was 0.61 per 100 patient years.¹ Subsequently, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) found that routine transcranial Doppler (TCD) ultrasound screening with chronic red cell transfusions (CRCT) for children with abnormal TCD, reduced the risk of first stroke by over 90% in this high risk group.² The follow-up study, Optimizing Primary

Stroke Prevention in Sickle Cell Anemia (STOP 2), showed that discontinuation of CRCT was associated with an unacceptably high rate of reversion to high risk of stroke, which led to the recommendation of indefinite transfusion therapy for patients with abnormal TCD.³

The STOP protocol includes annual TCD screening for children with SCD-SS and SCD-S-Beta⁰-thalassemia from ages 2 to 16 years, with more frequent monitoring if the result is not normal. Treatment with CRCT is recommended for children identified with abnormal TCD. The success of this screening and treatment strategy has been re-demonstrated in several clinical series.^{4,5} Analyses of large administrative databases also show a reduction in hospitalizations with stroke

diagnostic codes, when comparing time periods before and after the publication of the STOP study in 1998.^{6,7} Yet TCD screening and CRCT often are underutilized, and limitations of the STOP protocol also may lead to the occurrence of stroke in this patient population.⁴

To assess the impact of the STOP protocol on stroke incidence, we sought to determine the rate of centrally-confirmed ischemic stroke in a multicenter cohort of former STOP and/or STOP 2 trial participants and to assess whether these strokes were due to failures of STOP protocol implementation or to limitations of the STOP protocol itself (defined as false negative TCD screening or CRCT treatment failures). We hypothesized that the overall rate of ischemic stroke would be lower than prior to the publication of STOP, and that most strokes would be due to STOP protocol implementation failures. These data will help direct appropriate modifications to the STOP protocol and its implementation.

2 | METHODS

Institutional Review Board approval was obtained from the participating sites. Informed consent or a waiver of consent was obtained based on local requirements.

2.1 | STOP and STOP 2 studies

Between 1995 and 2005, STOP and STOP 2 were conducted at 26 sites in the US and Canada. These studies included 3835 children, ages 2 to 16 years with SCD type SS or S-beta⁰-thalassemia. All children underwent at least a single TCD with classification of results as previously described.² A subset of these children participated in an ancillary study with repeated TCD screening. Data on stroke were collected on screened subjects for the duration of the study (1995-2000).⁸ In the STOP study, children with abnormal TCD were eligible for randomization to CRCT or usual care.² In the STOP 2 study, children with prior abnormal TCD, whose TCD had reverted to normal on CRCT were eligible for randomization to continued CRCT, or withdrawal of CRCT.³ The STOP 2 study also had an observational arm for children receiving CRCT whose TCD had not reverted to normal. Participation in STOP and STOP 2 ranged from a single screening TCD to randomization.

2.2 | Post-STOP

The design of the Post-STOP study has been previously described.⁹ The study was designed to follow the outcomes of children who participated in one or both of the STOP trials. After exit from STOP and STOP 2, these children received TCD screening and treatment according to local practices. For all participants, the date of their last encounter in STOP or STOP 2 defined the start of their Post-STOP observation period.

2.3 | Data abstraction

A team of three trained data abstraction analysts visited each study site, and reviewed all available inpatient and outpatient records for

that site's subjects. Abstraction visits occurred between January 2012 and May 2014. Retrospective data collection included information from the subject's Post STOP start date through the date of the site visit, or the last follow-up date for subjects no longer receiving care at that site. Data abstraction included all TCD data, brain neuroimaging reports, and clinical reports regarding any neurological events. Laboratory data collected included results of complete blood counts and quantitation of hemoglobin A, S and F levels (if available). Treatment data collected included prescription of CRCT and/or hydroxyurea along with the date(s) of administration. Using values from the written reports, all TCD results were classified into STOP Protocol categories according to the time averaged mean velocities in the internal carotid (ICA), middle cerebral arteries (MCA), or the ICA bifurcation in the following manner: normal (<170 cm/s), conditional (170-199 cm/s), abnormal (≥ 200 cm/s), or inadequate (readings not provided from the ICA/MCA bilaterally in the absence of an abnormal value). For Transcranial Doppler Imaging (TCDI), an abnormal TCD was defined as a velocity of 185 cm/s or higher.

2.4 | STOP protocol

Annual TCD screening was recommended after the initial STOP study for all children ages 2 to 16 years old with SCD-SS or SCD-S- β^0 -thalassemia, with more frequent TCD if the prior study was not normal. While the interval for repeating TCD that previously was not normal was not specified, guidance included more frequent monitoring (such as every 3 to 6 months) for children with conditional TCD who were at highest risk of conversion to abnormal TCD.⁸ Repeat TCD within 4 weeks, or initiation of CRCT, was recommended for abnormal TCD. No specific recommendations for following inadequate TCD were made, though alternative methods of stroke risk assessment such as MRA were often utilized in clinical practice. The STOP protocol recommended initiation of CRCT for a confirmed abnormal TCD, or single TCD with velocities of 220 cm/s or higher. Based on the STOP 2 study results published in 2005, the duration of CRCT was recommended to continue indefinitely.³

2.5 | Central adjudication of ischemic stroke

For adjudication of suspected strokes, two stroke neurologists independently evaluated neuroimaging reports [magnetic resonance imaging (MRI) and computerized tomography (CT)] and medical records. They documented the clinical event while blinded to the subject's treatment history, TCD results, and other neuroimaging results (except studies performed at the time of the event in question). Stroke (ischemic or hemorrhagic) was defined as any acute clinical event with brain injury due to vascular disease. Ischemic stroke was defined based on clinical and imaging criteria: (i) documentation in the medical records of neurological signs and symptoms (including subtle or transient neurological events), and (ii) brain imaging evidence of infarction in the appropriate anatomical location to explain the clinical event. Disagreements between the reviewers were resolved through discussion. Infarcts that were not associated with documented symptoms

referable to the lesion were classified as silent infarcts and excluded from this analysis.

2.6 | Assessment of STOP protocol implementation failure

After confirmation of ischemic stroke, TCD and treatment data were reviewed to further categorize the stroke as either failure of implementation of the STOP protocol or STOP protocol failure. Failure of STOP protocol implementation was defined in two ways: (i) Failure to screen appropriately with TCD, which included children ages 2 to 16 years who had not had a TCD within 12 months, and children older than 16 years who had not had a TCD at age 16 years and (ii) Failure to adequately transfuse patients with abnormal TCD.

Charts were reviewed for evidence of prescription of CRCT, including clinic notations, transfusion records, and laboratory data. Two hematologists independently reviewed the CBC results and hemoglobin A, S, and F quantitation to assess adherence/adequacy of CRCT for the 6-month period prior to the stroke. Disagreements in categorization were resolved by discussion.

The STOP study aimed to maintain the hemoglobin S level below 30% on CRCT. A subsequent report showed that outside the study setting the hemoglobin S level often is maintained slightly higher, with a mean of $34 \pm 11\%$ such that in the TCD with Transfusions Changing to Hydroxyurea (TWITCH) study, hemoglobin S levels below 45% were not considered protocol violations.¹⁰ Therefore, we defined a CRCT protocol violation in Post-STOP as documented Hemoglobin S level above 45%. The CRCT treatment was first classified into one of four categories: (i) evidence of adequate red cell transfusion defined as the majority of hemoglobin S levels <45%; (ii) Evidence of transfusion but with more than 1/3 of hemoglobin S values above 45%; (iii) no evidence of chronic red cell transfusion and (iv) no laboratory values available to assess adherence to transfusion. For this study, CRCT was considered to be adequate for categories (i) and (iv) and inadequate for categories (ii) and (iii).

Treatment with hydroxyurea was noted, but hydroxyurea was not considered adequate therapy because the TWITCH study was not published until after our study end date. For subjects receiving hydroxyurea, the CBC results and hemoglobin quantitation were reviewed, where available. A rise in mean corpuscular volume (MCV) of at least 10 fL from baseline, or an MCV of 93 fL or higher if pre-hydroxyurea laboratory data were not available, and/or rise in hemoglobin F of 10% or more were considered to represent good adherence to treatment.¹¹

The STOP protocol screen failures included subjects with stroke who had a TCD within 12 months that was not abnormal, and subjects who were beyond the age of recommended TCD screening (17 years and older) who had a TCD at age 16 that was not abnormal. The STOP protocol treatment failures consisted of subjects with stroke who were receiving adequate CRCT for abnormal TCD.

2.7 | Other stroke risk factors

Additional contributing factors to stroke, including recent (within 2 weeks) hospitalization for acute chest syndrome or medical event, history of silent infarct, and other stroke risk factors (patent foramen ovale, acute anemic event) were assessed.^{1,12-14} For the group of children with normal TCD within a year or normal TCD at 16 years old, reports of magnetic resonance angiography at the time of, or after the stroke, if normal, were reviewed for evidence of vessel stenosis.

2.8 | Statistical methods

Descriptive analyses including mean, median, SD, and proportions were used to describe patient characteristics. Subjects with a history of stroke that occurred prior to the Post STOP study period were excluded in this analysis of primary stroke. In addition, only the first Post-STOP ischemic stroke was included in this report. Secondary stroke rate will be reported separately. The crude incidence rate of ischemic stroke was calculated as the number of first ischemic strokes occurring during the study period, divided by the number of person-years of observation. Follow-up was censored at the date of ischemic stroke or the date of the last follow-up visit by the patient.

3 | RESULTS

Nineteen of the 26 original study sites participated in Post-STOP, contributing a total of 3539 (92%) of the STOP and STOP 2 subjects (Figure 1). There was no significant difference in prevalence of abnormal TCD between sites that did and did not participate. Of the 3539 subjects, follow-up data were available for 2851(81%). Subjects without follow-up data available were significantly older at the end of STOP (12.1 ± 4.9 years) than subjects included in Post STOP (10.51 ± 4.6 years), but, there was no significant difference in the last STOP study TCD velocities between these groups. Forty-one children who had stroke prior to the Post-STOP study were excluded from the analyses. That included 11 children on the standard care arm in STOP, one child on the discontinue transfusion arm in STOP 2, and 29 screened children who had stroke during the STOP study or ancillary study follow-up (4/1995-11/1999). An additional two subjects with incomplete follow-up were also excluded. Thus, 2808 subjects were included in the analyses. Baseline characteristics of the study population are shown in Table 1. The mean age at the start of post-STOP was 10.5 ± 4.6 (median 10.4, range 2.0-23.2) years, and mean duration of follow-up in post-STOP was 9.1 ± 3.4 (median 10.3, range 0-15.4) years.

3.1 | Stroke incidence

A total of 60 (2.1%) first ischemic strokes occurred during the post-STOP study period (Figure 1). The mean age at the time of first stroke was 13.7 (median 13.2, range 3.5 to 28.9) years. Stroke occurred at a

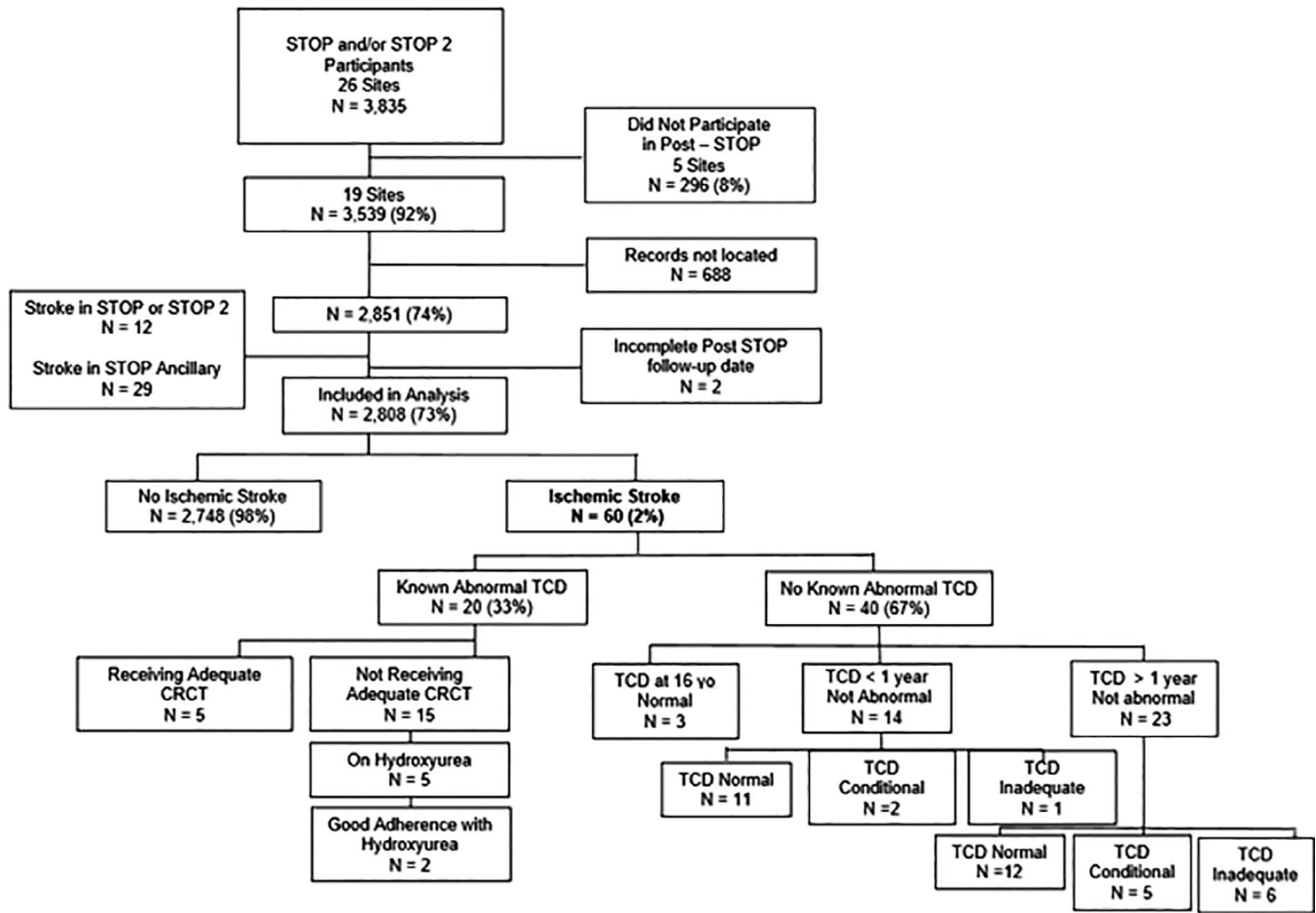


FIGURE 1 Flow chart depicting Post-STOP enrollment and occurrence of ischemic stroke by TCD screening and treatment status

TABLE 1 Patient characteristics

Baseline ^a characteristic	Total (n = 2808)	Stroke (n = 60)	No stroke (n = 2748)	P-value*
Age (mean +/- SD), years				
Age at end of STOP/STOP2 era	10.5 +/- 4.6	9.5 ± 4.1	10.5 ± 4.6	.10
Age at last TCD STOP/STOP2 era	9.6 +/- 4.2	8.7 ± 3.8	9.6 ± 4.3	.11
Sex (% female)	49.3	43.3	49.5	.35
Worst TCD category in STOP/STOP2 era (%)				.0003
Abnormal	11.9	26.7	11.5	
Conditional	16.9	25.0	16.7	
Inadequate	6.6	6.7	6.6	
Normal	64.6	41.7	65.1	
Last TCD category in STOP/STOP2 era (%)				<.0001
Abnormal	3.5	11.7	3.4	
Conditional	11.0	21.7	10.8	
Inadequate	5.6	11.7	5.4	
Normal	79.9	55.0	80.5	
Last STOP maximum TCD velocity (cm/s) ^b	144.2 +/- 28.8	160.8 ± 36.8	143.8 ± 28.6	.002
Follow-up time since last STOP/STOP2 visit, years	9.1 +/- 3.4	9.8 ± 3.1	9.1 ± 3.4	.08
Follow-up time since last STOP/STOP2 TCD, years	10.0 +/- 3.8	10.7 ± 3.8	10.0 ± 3.8	.19

^aBaseline refers to last visit recorded in STOP or STOP 2.

^bExcludes velocities for patients with inadequate tcd.

*P-value is for comparison of stroke versus no stroke.

mean of 5.1 (median 3.8, range < 0.1 to 17.9) years from the last TCD. The overall incidence of first ischemic stroke was 0.24 per 100 patient-years (95% CI 0.18, 0.31). Patients who developed ischemic stroke were significantly more likely to have had a history of abnormal or conditional TCD than those without stroke (Table 1). Similarly, the maximal

TCD velocity and TCD category for the last study obtained in STOP/STOP 2 was significantly higher in patients who developed ischemic stroke than patients without stroke (Table 1).

TABLE 2 Ischemic stroke by STOP protocol status (n = 60)

STOP protocol implementation failure	38 (63%)
Not appropriately screened	23 (38%)
Last TCD >12 months	
Normal	6 (10%)
Conditional	4 (7%)
Inadequate	6 (10%)
No TCD at 16 years old (stroke at >17 years old)	
Last TCD normal	6 (10%)
Last TCD conditional	1 (2%)
Abnormal TCD, not adequately transfused	15 (25%)
No transfusion	8 (13%)
Inadequate transfusion	2 (3%)
No transfusion, on hydroxyurea	5 (8%)
STOP protocol failure	22 (37%)
Screened appropriately, not identified as at risk	17 (28%)
TCD within 1 year	
Normal	11 (18%)
Conditional	2 (3%)
Inadequate	1 (2%)
Normal TCD at 16 years old	3 (5%)
Abnormal TCD, receiving adequate transfusions	5 (8%)
Total	60 (100%)

3.2 | Relationship of stroke to STOP protocol implementation failure

Table 2 provides the distribution of strokes based on STOP protocol screening and treatment status. Most strokes (63%) occurred in patients in whom the STOP protocol was not implemented correctly, either due to lack of appropriate TCD screening or insufficient CRCT for abnormal TCD. Twenty-three of the 60 (38%) strokes occurred in children who were not appropriately screened with TCD. Of these 23, 17 (74%) had not had any TCD screening in the Post-STOP period prior to the stroke. Among the 18 people in the inappropriately screened group who had stroke at 17 years or younger (median 9.7, range 5.4-17 years), the most recent TCD had been performed at a median of 2.5 (range 1.2-8.3) years prior.

Among the 20 children with known abnormal TCD, only five (25%) had evidence of adequate transfusion, and these five children accounted for only 8.3% of the strokes in this study. Five of the 20 (25%) children with abnormal TCD had been placed on hydroxyurea therapy but only two had evidence of good adherence.

3.3 | Other stroke risk factors in subjects

Additional risk factors for stroke were common among children with ischemic stroke, regardless of TCD screening status, but especially in those subjects without known abnormal TCD (Figure 2). An episode of acute chest syndrome within 2 weeks of the stroke occurred in 10 (17%) and recent hospitalization for other indications occurred in an additional 14 (23%) patients.

Among patients screened with TCD within a year of the stroke, or at age 16 years if the stroke occurred at 17 years or older, 3 of 17 (18%) had conditional or inadequate TCD at last study. Table 3

FIGURE 2 Prevalence of stroke risk factors in patients with sickle cell disease and ischemic stroke (n = 60), stratified by TCD screening and transfusion therapy prior to the stroke. Other hospitalizations were for vasoocclusive pain episode (4), meningitis (2), bacteremia/sepsis (2), Other infection (2), Priapism/Chronic renal insufficiency (1), Nephrotic syndrome (1), Steven's Johnson Syndrome (1), Sarcoidosis (1), Heart failure/heart transplant rejection (1), Hypoglycemia/diabetes (1), and Deep vein thrombosis (1)

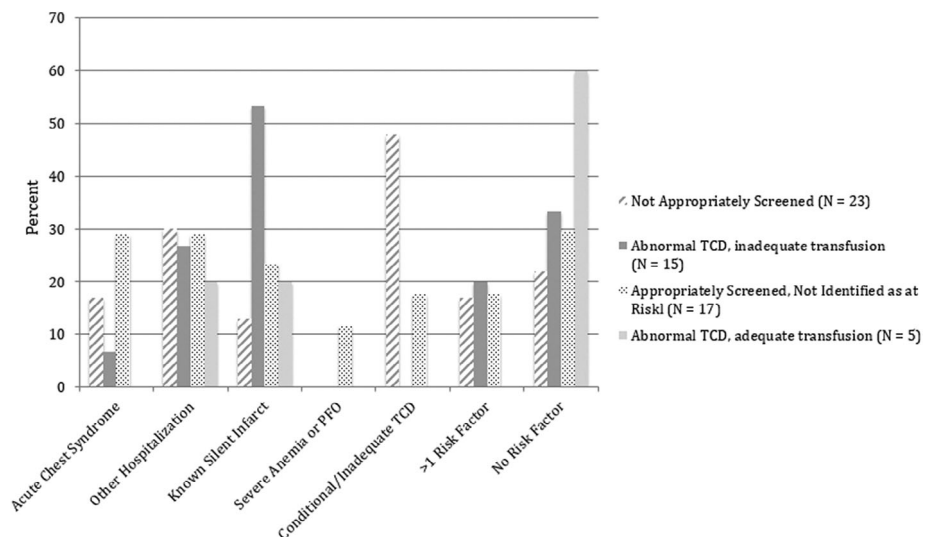


TABLE 3 Description of stroke events among subjects with recent normal TCD

Age (years)	Time from most recent TCD (months)	Prophylactic treatment	Highest TCD category (value); time from highest TCD to stroke	History of silent infarct	MRA results	Recent medical illness (within 2 weeks)	Event neurological symptoms and/or exam	Infarct description
3.46	2.8	None	Normal	ND	Normal	Yes, ACS	At 24 hours, no gross deficit, plantar responses flexor bilaterally	R frontal infarct with hemorrhage and L gyrus rectus infarct
7.59	6.7	None	Conditional (181 cm/s); 8.5 months	ND event MRI without evidence of prior SCI	Event: possible narrowing proximal intracranial arteries 6 months after event - Normal	Yes, severe ACS (intubation)	Bilateral upper and lower extremity weakness	R ACA & L ACA/MCA watershed distribution infarction + SAH.
9.95	5.8	None	Conditional (173 cm/s); 5.97 y	ND event MRI without evidence of prior SCI	Event: Motion artifact, irregular B A1, M1, ICA 5 y after event - Normal	No	Right hemiparesis, ataxia	Acute infarction L basal ganglia
12.53	11.2	None	Normal	ND event MRI with evidence of prior SCI	2.5 y after event - Normal	Yes, ACS	Complex partial seizure, decreased hand grip strength bilaterally	B frontal lobe, left cingulate gyrus and parietal infarcts
12.91	7.7	None	Conditional (171 cm/s); 1.1 y	No	Normal	No	Headache, Somnolence, Left hemiparesis	R frontoparietal watershed infarcts
13.37	7	Hydroxyurea (good adherence)	Normal	ND	Normal	No	—	Bilateral infarcts, R MCA distribution, R temporal and B watershed (ACA/MCA, MCA/PCA)
14.66	8	None	Conditional (182 cm/s); 6.15 y	ND	Normal	No (nephrotic syndrome, end stage renal disease, hypertensive)	Altered mental status	B multifocal subacute infarcts
14.83	7.5	None	Normal	Yes	Decreased flow bilateral ACA	Yes, VOE history of PFO	Seizure, altered mental status	R thalamic, temporal and parieto-occipital infarct
15.78	9.2	None	Inadequate; 10.7 y	No	Normal	No	Headache, Left hemiparesis	Cerebral sinovenous thrombosis with R venous infarction
16.75	1	None	Normal	Yes	High grade stenosis of supraclinoid RICA, mild stenosis supraclinoid LICA	Yes, VOE	Seizure, Left hemiparesis	R parietal infarct with hemorrhagic transformation

(Continues)

TABLE 3 (Continued)

Age (years)	Time from most recent TCD to stroke (months)	Highest TCD category (value); time from highest TCD to stroke	Prophylactic treatment	History of silent infarct	MRA results	Recent medical illness (within 2 weeks)	Event neurological symptoms and/or exam	Infarct description
17.96	7.9	Normal	Hydroxyurea (poor adherence); prior CRCT discontinued 2 y prior due to DHTR	Yes, progressive	Moderate focal RICA narrowing; LICA occlusion	No	Left hand/finger episodic tic-like movements; normal strength and sensation	Acute R fronto-parieto-occipital infarcts

Abbreviations: ACA, anterior cerebral artery; ACS, acute chest syndrome; CRCT, chronic red cell transfusion therapy; DHTR, delayed hemolytic transfusion reaction; ICA, internal carotid artery; MICA, middle cerebral artery; ND, not done; PCA, posterior cerebral artery; PFO, patent foramen ovale; VOE, vasoocclusive pain episode.

shows the risk factors and features of stroke among the group who had a normal TCD within a year of the stroke. Eight of the 11 (73%) had no significant vessel stenosis as assessed by MRA either at the time of the stroke or afterwards. Five subjects (45%) had a history of prior conditional (4) or inadequate (1) TCD, though the most recent pre-stroke TCD study was normal. Other risk factors for stroke in this group included known silent infarct in three (27%) and patent foramen ovale in one child. Five (45%) of the ischemic strokes occurred in the setting of a recent medical illness. One subject had cerebral sinovenous thrombosis with venous infarction that would not be detected with TCD screening. Only two of the 11 children were receiving treatment with hydroxyurea, and only one of these children had evidence of good adherence with treatment. Among the three subjects who had normal TCD at 16 years of age, stroke occurred at 1.6, 3.9, and 6.2 years after that TCD. All three of these subjects had recent hospitalizations (one with acute chest syndrome, one with vasoocclusive pain, and one with Stevens Johnson syndrome), and one also had a documented patent foramen ovale. Among the 23 patients whose last TCD was more than a year before the stroke, the last TCD was conditional in 5 (22%) and inadequate in 6 (26%).

4 | DISCUSSION

This long-term follow-up study of children who participated in the STOP and/or STOP 2 studies demonstrates that most ischemic strokes in the Post-STOP era occurred in patients who were not managed by the STOP protocol. This included either failure to perform TCD screening or failure to adequately treat high-risk patients identified through screening. These STOP protocol implementation failures occurred despite these sites being trained in the protocol and equipped to perform screening and treatment. It is likely that failure to implement the STOP protocol would be more common outside of sickle cell centers. Hence, opportunities exist for system-wide improvements in implementation of the STOP protocol that could further reduce stroke risk.

The STOP protocol implementation failures included deviations from both TCD screening and treatment recommendations. Among ischemic strokes 38% occurred in children who had not been screened with TCD in the past year, despite almost half (11/23) of these children's last TCD study being conditional or inadequate. We previously showed that the overall rates of TCD re-screening at the STOP and STOP 2 study sites were surprisingly low, with only 57% of children having evidence of at least one follow-up TCD.⁹ Our current analyses support that failure to screen properly leads to preventable stroke. We also found that CRCT implementation failures occur. Three quarters of children in this study with abnormal TCD who developed stroke were not receiving adequate CRCT that could have prevented this outcome.

In this study, we are unable to assess reasons for the lack of full implementation of the STOP protocol. System level factors, such as limited TCD equipment or lack of appropriately trained personnel

could have influenced successful implementation. However, patient or family factors such as poor adherence to screening and lack of acceptance of chronic transfusion also may have contributed. Complications of transfusion, such as alloimmunization and iron overload may also limit the feasibility of continuing a chronic transfusion protocol. Wide variability in screening rates at the sites, with some sites able to achieve 90% re-screen rate,⁹ indicates that patient factors do not prevent some centers from appropriately re-screening the majority of patients. Addressing system levels factors, therefore, might be successful in enhancing implementation.

The Post-STOP study took place prior to the publication of the TWITCH study, which showed that hydroxyurea therapy for children with abnormal TCD without significant vasculopathy was noninferior to transfusions at maintaining TCD velocities, a surrogate marker for control of stroke risk.¹⁵ Thus, it is possible that as hydroxyurea use becomes more widespread for primary stroke prevention in the future, acceptance of and adherence with long-term treatment might be improved. Nonetheless, in this study, only two of five subjects with stroke who had been placed on hydroxyurea had evidence of adequate adherence, suggesting that methods to improve treatment adherence are imperative. In addition, stroke occurred in two subjects in our study with abnormal TCD with good adherence to hydroxyurea. In a French cohort of children, 29% of children with abnormal TCD who had developed normal TCD velocities on regular transfusions reverted to high-risk TCD after being switched to hydroxyurea.¹⁶ Thus, it is likely that long-term hydroxyurea therapy will not be adequate prophylactic therapy for a subset of children.

Nonetheless, limitations to the STOP protocol exist as 28% of ischemic strokes in this cohort occurred in children who were not identified by TCD screening as being high-risk. This does not generally appear to be a failure of TCD to identify significant intracranial vasculopathy, as the majority of children with recent normal TCD had no evidence of vasculopathy by MRA. It is possible that some of the STOP screening failures could be due to the presence of extracranial vasculopathy that is associated with increased stroke risk,¹⁷ which would not be detected by the STOP TCD protocol. Future studies to assess the value of adding scanning of the extracranial ICA to the STOP TCD protocol are needed. However, in this cohort, TCD screening did miss moderate or high-grade stenosis in two of 12 subjects with stroke (Table 3), perhaps because short segment stenosis can be missed or collateral vessels may be insonated.

Another possible reason for ischemic stroke occurrence in the setting of appropriate STOP screening is that the stroke occurred secondary to risk factors other than vasculopathy detectable by TCD. Additional risk factors for stroke were present in a significant proportion of patients in this cohort who had stroke. Over half (57%) of the strokes in subjects with normal TCD in the past year (5 of 11) or at 16 years old (all 3), occurred in the setting of a recent medical illness. Baseline cerebral blood flow velocity is elevated in SCD to compensate for anemia and cerebral vasoreactivity is reduced,¹⁸ predisposing to ischemia in the setting of acute blood pressure changes, worsening anemia, or hypoxemia that can accompany acute medical events. Careful attention to control of oxygenation and blood pressure and correction of severe anemia in patients with SCD in the setting of acute illnesses may further help to reduce

stroke occurrence in this patient population. Among the group with a recent normal TCD who experienced stroke, evidence of prior silent cerebral infarct was present in three patients. Silent cerebral infarct is a known risk factor for stroke that may be attenuated with regular red cell transfusions.^{14,19} Patent foramen ovale, a risk factor for stroke in the general population, was also present in two subjects, which could be amenable to repair. Thus addressing other known stroke risk factors might further reduce the incidence of stroke in children and young adults with sickle cell disease.

Finally, 8% of the strokes occurred in children with known abnormal TCD who were receiving adequate transfusion therapy. This failure rate is not surprising given that the risk of recurrent stroke has been reported to be approximately 20% with transfusions.¹² Further studies to better identify these high-risk children and the potential benefit of alternative interventions such as hematopoietic stem cell transplantation or adjunctive antiplatelet therapies for this population are needed.

The Post-STOP study has many strengths. These follow-up data were obtained on a large, multicenter cohort who had baseline standardized stroke risk assessments as part of a clinical trial. The medical care was obtained from sickle cell centers trained in the STOP protocol, which should have enhanced protocol implementation. A trained abstraction team visited each site and utilized consistent data collection tools across sites, and stroke outcomes were centrally adjudicated. Nonetheless, limitations to the study exist. Chart review may miss evidence of screening or treatment not recorded in the chart. Stroke adjudications were based on imaging reports only; we were not able to collect actual imaging studies and hence could not reliably distinguish arterial versus venous distribution of the infarcts. Complete laboratory data often were missing, which impacted the ability to determine adequacy of treatment. In subjects with abnormal TCD reported to be receiving red cell transfusions but without available laboratory data, we assumed that transfusion therapy was adequate, which may have underestimated the effectiveness of the STOP protocol. Lastly, only about half of the participating centers had integrated pediatric and adult medical records, which limited information on stroke occurrence after transition to adult care.

In conclusion, Post-STOP confirms a reduction in ischemic stroke after dissemination of the STOP Protocol that has been reported in other studies. Unfortunately, these data also confirm that the STOP Protocol is often inadequately implemented, although the reasons for this are not clear. Although most of the ischemic strokes that occurred in these experienced centers were associated with inadequate screening or therapeutic implementation, some strokes were documented in the absence of vasculopathy and were not predicted by TCD or prevented by treatment, suggesting that not all stroke in SCD is preventable by the STOP protocol, and that additional strategies might further reduce stroke rates. This study indicates that there remain substantial opportunities for ischemic stroke prevention by more complete implementation of the STOP Protocol.

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AUTHOR CONTRIBUTIONS

J.L.K. assisted in study design and data analysis and wrote the manuscript; J.K. assisted in study design, data analysis and manuscript editing; H.J.F. assisted in study design, performed stroke adjudications, and edited the manuscript; J.H.V. performed statistical analyses and edited the manuscript; E.D. and L.B. assisted with data collection and analysis and edited the manuscript; RJA designed the study, performed stroke adjudications, guided data analysis, and edited the manuscript.

CONFLICTS OF INTEREST

All authors have no relevant conflicts of interest.

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