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Practice Patterns for Stroke Prevention using Transcranial Doppler in Sickle Cell Anemia: DISPLACE Consortium

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Abstract

Background: Children with sickle cell anemia (SCA) are at increased risk for stroke. In 2014, the National Heart, Lung, and Blood Institute (NHLBI) developed guidelines for stroke prevention in SCA informed by the Stroke Prevention Trial in Sickle Cell Anemia (STOP) and Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP II) trials. The guidelines specify the use of transcranial doppler (TCD) screening and intervention with chronic red cell transfusion (CRCT) in children with SCA who have TCD indication of high stroke risk. The purpose of this study was to describe real-world practice patterns of stroke risk screening and intervention in sites that participated in the Dissemination and Implementation of Stroke Prevention Looking at the Care Environment (DISPLACE) Consortium.

Procedure: Site investigators completed a survey during the formative stages of the study to evaluate their TCD practices relative to the STOP studies. Descriptive statistics and analysis of free text comments for more complex practices were evaluated.

Results: Results suggested universal acceptance of annual TCD screening and initiation of CRCT following an abnormal result among the DISPLACE Consortium, consistent with NHLBI

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recommendations. However, there was wide variation in methods for conducting TCD screenings (e.g., dedicated Doppler versus TCD imaging), classifying TCD results, and actions taken for conditional and inadequate results.

Conclusions: Annual TCD screening and initiation of CRCT are critical stroke prevention practices that were universally embraced in the consortium. Additional research would be beneficial for informing clinical practices for areas in which guidelines are absent or unclear.

Keywords

sickle cell anemia; stroke; prevention; clinical practice

Introduction

Stroke is a devastating complication associated with sickle cell anemia (SCA).[1] In the absence of intervention, it is estimated that about 10% of children with SCA will have an overt stroke.[2] Stroke prevention practices in SCA were developed based on the Stroke Prevention Trial in Sickle Cell Anemia (STOP) and Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP II) trials. These multi-center studies established that routine transcranial Doppler (TCD) screening with indefinite chronic red cell transfusions (CRCT) for children with abnormal TCD substantially reduced the rate of ischemic stroke in SCA.[3,4]

The 2014 National Heart, Lung, and Blood Institute (NHLBI) guidelines adopted these practices for clinical care.[5] These guidelines were important for defining evidence-based methods for stroke prevention; however, there is likely variation in how these recommendations are interpreted and implemented. As demonstrated in the Post STOP study, implementation of TCD recommendations for SCA varies considerably, even among sites that participated in the original STOP trials.[6] It is also unclear how specialists are applying findings in scenarios in which guidelines are absent or unclear or how providers are adopting recent clinical trial findings into their practice patterns.

The purpose of this study was to evaluate current TCD screening practices across 28 sites that participated in the Dissemination and Implementation of Stroke Prevention Looking at the Care Environment (DISPLACE) Consortium. DISPLACE is a multi-center study designed to evaluate current implementation of stroke prevention practices and subsequently design and deliver interventions to improve implementation of stroke prevention guidelines for children with SCA (ClinicalTrials.gov number). We specifically sought to illustrate the range of practices used by the consortium relative to 2014 NHLBI guidelines and STOP studies.

Brief Summary of Guidelines and STOP Study Recommendations

Table 1 provides a summary of current practice recommendations from the NHLBI guidelines and STOP studies (including STOP, STOP II, and Post STOP). The NHLBI guidelines recommend annual TCD screening for children ages 2 to 16. Children with abnormal or conditional TCD should be referred to a specialist with expertise in CRCT.[5] The STOP studies[3,4] provide specific guidance about TCD methods and follow-up care. TCD methods should be conducted as follows using dedicated Doppler: determine the

highest time averaged mean maximum (TAMM) blood-flow velocity in 2-mm increments in the middle cerebral artery (MCA; at three points), distal internal carotid artery (dICA), anterior and posterior cerebral arteries (ACA, PCA), and basilar artery. This approach is to ensure proper orientation and anatomical probe placement. For classifying results, STOP protocol defines an abnormal result as velocity ≥200 cm/sec in the MCA or dICA on either side. Conditional TCD is broadly defined as a result of ≥170 cm/sec, but <200 cm/sec. A prior STOP trial publication also created two designations of conditional TCD: low conditional (170–184 cm/sec) and high conditional (185–199 cm/sec) using dedicated Doppler.[7] There are no specific guidelines for TCD imaging (TCDi).

Follow-up after TCD should occur as follows according to STOP, STOP II, and Post STOP recommendations. Children with abnormal TCD should either be initiated on CRCT or should have a repeat TCD within 4 weeks followed by initiation of CRCT if an abnormal result is confirmed. For children with conditional TCD, screening should occur more frequently than annually with frequency based on the child's age and TCD velocity, such that younger children and those with TCD velocities closer to 200 cm/sec receive more frequent TCDs. Finally, for inadequate TCD (when key arterial segments that indicate stroke risk, i.e., the dICA and MCA, are not clearly insonated), no specific guideline exists; however, Post STOP recognizes that repeating the TCD or using alternative methods of evaluation, such as magnetic resonance angiography (MRA), are often performed.

Methods

Sample and Setting

Respondents were site Principal Investigators (PIs) at each DISPLACE institution. All respondents were specialty providers in pediatric hematology/oncology who provide care to individuals with SCA. Sites varied in characteristics including region (rural versus urban, US geographical location), size (large versus small), and previous participation in stroke prevention studies.

Data Collection

The practice patterns survey was developed in the needs assessment stage of DISPLACE to establish a baseline understanding of current practices in our 28-site consortium (additional data on implementation rates for stroke prevention practices will be forthcoming in a separate publication). Our multidisciplinary team representing psychology, nursing, medicine, and public health developed the survey using an iterative process. The 2014 NHLBI guidelines and prior STOP publications served as a survey development framework, and 37 items were included around practices on: TCD screening, CRCT initiation, magnetic resonance imaging (MRI) and MRA, echocardiograms, developmental-behavioral screening, and immunizations. Only results from the 8 TCD screening items are presented in this report. TCD screening questions included TCD type (dedicated Doppler versus imaging), blood vessels and velocity ranges for classifying results, screening frequency, and actions taken for abnormal, conditional, and inadequate results. One additional item was included for open comments on TCD practices. The survey was administered electronically using

REDCap[8] via email to each PI. The survey was multiple-choice response with optional free-text comment items; for some items, multiple response selection was permitted.

Data Analysis

Data were exported from REDCap[8] to SAS software, version 9.4 (Copyright © 2016 by SAS Institute Inc., Cary, NC, USA.) for analysis. Descriptive statistics were calculated including measures of central tendency (mean, median, range) for continuous variables and proportions and frequencies for categorical variables. Line-by-line examination of free-text comments was also conducted to further understand the complexity of practice patterns. The most common patterns for multiple response selections were described in the Results.

Results

All 28 (100%) site PIs completed the survey. Approximately half (53%) were female, 77.8% were White, 11.1% were Asian, 7.4% were Black or African American, and 7.4% were Hispanic or Latino.

Methods for Screening and Classification of TCD Results

Results from TCD screening items are presented in Table 1. Most sites (92.9%) intend to conduct screening annually, with 7.1% conducting screening more frequently. Dedicated Doppler was used by slightly more sites than TCDi. Nearly all sites (96.4%) used the MCA to classify results as normal or abnormal, followed by the dICA (71.4%) and ACA (71.4%). The only site not specifically reporting use of the MCA to classify results stated they relied on the radiologist to decide which vessels were used. Most commonly, sites used the MCA, ACA, and dICA to classify results (25%), followed by the MCA and dICA (17.9%), and the MCA, ACA, dICA, and PCA (14.2%).

Three site PIs further explained vessels used to classify results in comments. One site PI reported using the ACA for classification based on research suggesting that ACA velocities are clinically significant (even though it is not a STOP criterion). Another site PI clarified that the posterior circulation velocities are documented (in addition to the MCA and ACA), but only the anterior circulation velocities are used for classification. The third PI explained that the radiology department at their site obtains peak systolic (PSV) velocities and, depending on the radiologist, will sometimes use PSV velocities for classification based on a previous 2005 study that found PSV to be comparable to TAMM for determining stroke risk.[9]

Sites were also asked to provide the standard TAMM values used to categorize results as normal, high/abnormal, and conditional. Table 2 presents the mean minimum and maximum TAMM cut-off values across sites for dedicated Doppler and TCDi compared with STOP protocol cut-offs.

Actions Taken According to Results

Abnormal.—For follow-up after abnormal TCD, 24 sites (85.7%) selected the response “initiate CRCT.” However, 3 additional sites responded in comments that CRCT would be

initiated, leaving only 1 site that did not indicate CRCT initiation for an abnormal TCD. Of these 27 sites, 7 sites (25.9%) indicated the only response to an abnormal TCD would be to initiate CRCT. Eighteen sites (66.7%) would obtain MRI/MRA and initiate CRCT, and 6 sites (22.2%) would obtain an MRI/MRA, repeat the TCD, and initiate CRCT.

Eight sites (28.6%) indicated they would repeat the TCD after abnormal results were obtained, and before making any change in treatment. Of these 8 sites, 3 sites (37.5%) would repeat the TCD in 1 to 2 weeks, 1 site (12.5%) would repeat the TCD in 2 to 4 weeks, and 4 sites (50%) did not specify a time frame. The site above that did not report initiating CRCT for abnormal results noted they would obtain an MRI/MRA and repeat the TCD but did not indicate subsequent actions. Two site PIs described actions that would be taken if CRCT was refused by the family in comments. In both cases, providers would recommend hydroxyurea (HU).

High-range Conditional.—For conditional TCD results in the higher ranges (closer to but below the abnormal range), nearly all sites (27; 96.4%) would follow up with a repeat TCD before change in therapy. However, 19 sites (67.9%) would initiate HU if the patient was not already on HU. Of these 19 sites, 13 sites (68.4%) would also order an MRI/MRA, and 12 sites (63.2%) would initiate HU, order an MRI/MRA, and repeat the TCD. The remaining 6 sites (21.4%) would initiate HU and repeat the TCD, but would not obtain an MRI/MRA. Eight sites (28.6%) responded that the only action would be to repeat the TCD. Six of these eight sites (75%) would repeat the TCD in 12 to 16 weeks and 2 (25%) would repeat the TCD in 6 to 8 weeks. One site PI clarified in comments that if results were confirmed on a repeat TCD, the provider would either initiate HU or CRCT; if abnormalities were detected on the MRI/MRA, CRCT would be recommended; if the MRI/MRA was normal, HU would be initiated with close TCD monitoring.

Low-range Conditional.—For conditional TCD results in the lower ranges (closer to but above the normal range), the most common response was to repeat the TCD before change in therapy (20 sites; 71.4%). Of these 20 sites, 9 sites (45%) would only repeat the TCD. Five sites (25%) would initiate HU and obtain an MRI/MRA in addition to repeating the TCD, 4 sites (20%) would only initiate HU in addition to repeating the TCD, and 2 sites (10%) would obtain an MRI/MRA and repeat the TCD. Of the eight sites that would not repeat the TCD, 4 (50%) would initiate HU and obtain an MRI/MRA, 2 (25%) would only initiate HU, 1 site (12.5%) indicated they would initiate HU, but also indicated they would make no change in therapy, and 1 (12.5%) would make no change in therapy.

Inadequate—The most commonly reported follow up action for inadequate TCD results was to repeat the TCD (17 sites; 60.7%). Nine sites (32.1%) responded that the only action would be to repeat the TCD, with 7 sites (25%) repeating the TCD in 2 to 12 weeks and 2 sites (7.1%) repeating the TCD in 6 months to 1 year. Eight sites (28.6%) indicated the only follow-up action would be to obtain an MRI/MRA. Seven additional sites (25%) would obtain an MRI/MRA, but would also repeat the TCD in 2 to 12 weeks. In comments, two site PIs indicated the decision would be influenced by the patient's age. One site PI reported that the TCD would be repeated every 3 months until an adequate reading was obtained for a

patient 2 to 3 years old. If results continued to be inadequate at age 3, a sedated MRI/MRA would be performed.

Methods for Determining Inadequate Result

PIs were also asked how "inadequate" was defined at their institutions. The most frequent definition was no obtainable velocity on one or both MCAs (unless one side measured flow ≥200 cm/sec; 9 sites; 32.1%). The next most common responses were selected by 5 sites (17.9%) each and were 1.) no measurable velocities in any of the main arteries and 2.) any of the following: no measurable velocities on one or both MCAs, no measurable velocities in any main arteries, or no measurable velocities in all main arteries. Three sites selected "other" and provided a definition in comments. One site PI responded that the decision depends on the patient's age and "what we get." The second site PI clarified that results are classified as inadequate when the MCA, dICA, and ACA are not imaged. The third site PI explained that results are considered inadequate if velocities are not obtained in one or both MCAs, but also if the PCA or ACA is not visualized.

Discussion

The results of this initial practice patterns survey from the DISPLACE Consortium suggest near universal adoption of the NHLBI guidelines for annual TCD screening and initiation of CRCT following an abnormal result across sites. However, methods for classifying TCD results and follow-up practices when TCD results were conditional or inadequate varied considerably across sites.

For TCD methods, a substantial number of sites (42.9%) were using TCDi. Although there are no formal guidelines for TCDi, follow-up studies were conducted following the STOP trial to compare dedicated Doppler to TCDi.[10–13] Although study sample sizes were small, each found TCDi velocities were significantly lower than dedicated Doppler (approximately 10 – 15% lower, but as much as 20% lower depending on the vessel). Conversely, Nelsh et al.[14] found agreement in categorization of results using dedicated Doppler and TCDi in 81% of results. Practice standards vary as to whether lower parameters are applied for categorizing TCDi results. According to some investigators[15], there is consensus that parameters set in STOP protocol for dedicated Doppler can be applied to TCDi. However, McCarville et al.[10] recommended parameters for classifying TCD results using TCDi that are 10% lower than STOP protocol for dedicated Doppler, i.e., TAMM values of 180 cm/sec or more for abnormal, and 153 – 179 cm/sec for conditional. Comparable lower parameters were applied for TCDi in the Silent Cerebral Infarct Transfusion (SIT) multi-center clinical trial.[16,17]

Among our study sites using TCDi, the range for classifying results as conditional was 163 – 188 cm/sec and the mean cut-off for abnormal was 190 cm/sec. Further, some sites using TCDi reported using STOP protocol values for classifying results. These findings likely reflect inconsistency in the literature described above and highlight the need for clearer guidance for using TCDi to detect stroke risk in children with SCA. It was also notable to see the ranges used for classification of conditional versus abnormal TCD. The slight variation in some sites for the taxonomy of normal, conditional, and abnormal may also

suggest some confusion around the cut-offs described in the 2014 NHLBI guidelines even with dedicated Doppler.

Sites also varied in which cerebral vessels were used to classify results. STOP protocol provides guidance for which vessels to examine; however, stroke risk classification is made only from the MCA and dICA. While nearly all sites used the MCA to classify stroke risk, about 1/4 of sites were not using the dICA. This finding may be the result of relative ease of obtaining a velocity in the MCA versus the dICA. Many sites were also incorporating other vessels into their classification, with the ACA examined about as much as the dICA. As one of the site PIs reported, some literature suggests the potential importance of the ACA in identifying children with SCA at high stroke risk.[18]

As noted above, nearly all sites reported they would initiate CRCT if a child had an abnormal TCD screening, with some sites also confirming the result via repeat TCD within 4 weeks before starting CRCT. Both of these methods would be consistent with idealized implementation described in Post STOP.[6] Some sites described additional practices that were not addressed in guidelines or STOP literature, including obtaining an MRI/MRA and initiating HU. Sites are likely using MRI/MRA to identify potential cerebrovascular abnormalities in children with abnormal TCD, including previous undetected overt or silent stroke or blood vessel stenosis. This information may also be used by sites who are implementing the protocol from the TCDs with Transfusions Changing to Hydroxyurea (TWiTCH) trial.[19] This multi-site study determined that children with abnormal TCD, but no significant cerebrovascular abnormalities on MRI/MRA (i.e., no history of stroke, no severe vasculopathy) could be safely transitioned to HU after one year of transfusions to maintain TCD velocities and prevent stroke.[19]

Follow-up practices were more variable for children with conditional TCD, for which there are no established guidelines. Post STOP recommended repeating TCDs more frequently than annually for children with conditional TCD, with consideration of the child's age and TCD velocity when determining frequency. Webb and Kwiatkowski[20] made more specific recommendations regarding frequency. For low conditional TCD, the authors recommended repeating within 3 to 6 months. For high conditional TCD, the authors recommended repeating the TCD within 6 weeks if the child is <10 years of age and repeating within 3 months if the child ≥10 years or older. The authors further recommended considering an MRI/MRA for children with high conditional TCD who are <10 years of age. The rationale for repeating the TCD is the potential conversion risk to from conditional to abnormal (or stroke), with previous studies suggesting conversion rates of 29% in the original STOP cohort for stroke and 23% for abnormal TCD in a subsequent study.[7,21]

Among DISPLACE sites, practices were similar for children with conditional TCD velocities in both the lower and higher ranges and included repeating the TCD, initiating HU, and obtaining an MRI/MRA (as well as combinations of these practices). Repeating the TCD was nearly universal when the child's TCD was closer to 200 cm/sec versus 170 cm/sec. In addition, one site would consider initiating CRCT with TCD velocities closer to 200 cm/sec. Sites may be recommending HU therapy based on previous work suggesting the potential for HU to decrease TCD velocities[22]. Overall, the variation in practices for

conditional TCD suggests the need for prospective data on the effects of repeating TCDs at varying intervals, including whether repeating TCDs captures children who convert to abnormal and ultimately prevents stroke.

Currently, no guidelines regarding inadequate TCD exist, though providers frequently repeat the TCD or use an alternate imaging evaluation method.[6] DISPLACE study sites most frequently repeated the TCD with wide variation in the timeframe and/or obtained an MRI/MRA. STOP protocol recommended repeating a TCD that was inadequate within 2 to 12 weeks.[7] Site PIs also reported a range of methods for defining an inadequate result. According to STOP protocol, inadequate was defined as a study without attainable readings from the right and left MCA/dICA, unless one side was abnormal.[7] A recent study conducted in the United Kingdom (UK) applied more stringent criteria than STOP to better characterize inadequate TCD findings in children with SCA. This protocol defined inadequate as any study in which none of the 10 vessels could be measured for any reason.[15] Most frequently, our study site PIs defined inadequate in accordance with STOP protocol; however, approximately two-thirds of sites used other methods, which may represent adoption of protocols similar to those used in the UK.

Conversion from normal, conditional, or inadequate to an abnormal result was infrequent (1%) in the STOP study.[7] In addition, stroke risk for individuals with an inadequate result was significantly lower than those with an abnormal result. Among individuals in STOP studies who experienced stroke, fewer (9%) had an inadequate TCD immediately prior to the stroke event than normal, conditional, or abnormal.[7] In their in-depth exploration of inadequate TCD results, Greenwood et al.[15] found nearly 75% of individuals with an inadequate scan had a subsequent normal scan; less than 5% had a subsequent abnormal scan and none had subsequent stroke. A poor temporal window and lack of patient cooperation were the most common causes for an inadequate result. Findings from these studies suggest inadequate TCD results are uncommonly associated with stroke risk and are often the result of technical issues; however, best practices for follow-up after an inadequate result remain unclear.

This study's findings should be interpreted in the context of limitations. Practice patterns in this study were specific to sites who agreed to be part of DISPLACE. There may be characteristics (such as having a higher level of university support to engage in research) that make them less generalizable to other sites. Sites were chosen to represent a range of characteristics, including clinic population size, region, and previous affiliation with STOP studies. We also chose to collect information via survey; however, it was difficult to fully represent nuances described in free text comments as well as the range of multiple selection responses.

In conclusion, these findings illustrate areas of commonality and variation when comparing stroke prevention practices described in research studies versus real-world implementation. The areas of agreement likely reflect the strong evidence base behind the NHLBI guidelines and STOP studies; however, the variation observed in other areas illustrates the need for further study to inform clearer practice guidelines. In particular, providers need specific guidance about the use of TCDi to classify stroke risk in children with SCA. It would also be

beneficial to have guidance on unusual findings from TCD, such as vessel abnormalities other than the MCA and dICA or inadequate TCD. Finally, guidance for clinical practices apart from CRCT following conditional and abnormal results would be beneficial, such as protocols for repeating TCD, use of MRI/MRA, and HU.

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Abbreviations list:

ACA	anterior cerebral artery
CRCT	chronic red cell transfusions
dICA	distal internal carotid artery
DISPLACE	Dissemination and Implementation of Stroke Prevention Looking at the Care Environment
HU	hydroxyurea
MCA	middle cerebral artery
NHLBI	National Heart, Lung, and Blood Institute
PCA	posterior cerebral artery
PI	principal investigator
SCA	sickle cell anemia
TCD	transcranial doppler
TCDi	transcranial doppler imaging
SIT	Silent Cerebral Infarct Transfusion
STOP	Stroke Prevention Trial in Sickle Cell Anemia
STOP II	Optimizing Primary Stroke Prevention in Sickle Cell Anemia
TAMM	time averaged mean maximum
TWiTCH	TCDs with Transfusions Changing to Hydroxyurea

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TABLE 1

Recommendations for stroke screening in sickle cell anemia and practice patterns in DISPLACE consortium

Practice Recommendations per 2014 NHLBI Guidelines and STOP Studies (STOP, STOP II, Post STOP)	**Practice Patterns in DISPLACE Consortium N = 28 (proportion; n)**
For children with HbSS and HbSβ^0: • Screen annually with TCD starting at age 2 up to age 16	Frequency of TCD Screening: • Annually (92.9%; 26) • Every 6 months (7.1%; 2)
Method using TCD standard: • Highest time-average mean blood-flow velocity in 2-mm increments in the – Middle cerebral artery (at three points) – Distal internal carotid artery – Anterior and posterior cerebral arteries – Basilar artery • Stroke risk determined from middle cerebral and internal carotid arteries No clear guidelines for using TCD imaging	Method of TCD: • Dedicated Doppler (57.1%; 16) • TCD Imaging (42.9%; 12) Cerebral vessels examined: • Middle cerebral artery (96.4%; 27) • Distal internal carotid artery (71.4%; 20) • Anterior cerebral artery (71.4%; 20) • Posterior cerebral artery (35.7%; 10) • Basilar artery (14.3%; 4) • Radiologist decides (7.1%; 2)
Abnormal TCD (≥200 cm/sec) in either the middle cerebral artery or the internal carotid artery: • Initiate CRCT **OR** • Early repeat of abnormal TCD (within 4 weeks) and initiate CRCT if abnormal confirmed	Follow-up after abnormal TCD: • Initiate CRCT (85.7%; 24) • Obtain MRI/MRA (64.3%; 18) • Repeat TCD prior to change (28.6%; 8) • Initiate hydroxyurea (7.1%; 2) • Initiate both CRCT and hydroxyurea (3.6%; 1)
Conditional TCD (170–199 cm/sec) • Screen more frequently than annually **AND** • Further increase in screening if: – Younger child age – TCD velocity closer to 200 cm/sec	Follow-up after conditional TCD (lower ranges): • Repeat TCD prior to change (71.4%; 20) • Initiate hydroxyurea (57.1%; 16) • Obtain MRI/MRA (32.3%; 11) • No change (7.1%; 2) Follow-up after conditional TCD (higher ranges): • Repeat TCD prior to change (96.4%; 27)

Practice Recommendations per 2014 NHLBI Guidelines and STOP Studies (STOP, STOP II, Post STOP)	Practice Patterns in DISPLACE Consortium N = 28 (proportion; n)
	• Initiate hydroxyurea (67.9%; 19) • Obtain MRI/MRA (46.4%;13) • Initiate CRCT (3.6%; 1) • No change (3.6%; 1)
Inadequate TCD (due to technical problems or severe arterial disease with occlusion of the arteries of interest): • No clear guideline • Repeat TCD or alternative methods of evaluation (e.g., MRA) often performed	Follow-up after inadequate TCD: • Repeat TCD (60.7%; 17) • Obtain MRI/MRA (57.1%; 16) • Initiate hydroxyurea (7.1%; 2) • No change (3.6%; 1)

CRCT = chronic red cell transfusions; DISPLACE = Dissemination and Implementation of Stroke Prevention Looking at the Care Environment

MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; NHLBI = National Heart, Lung, and Blood Institute

STOP = Stroke Prevention Trial in Sickle Cell Anemia; STOP II = Optimizing Primary Stroke Prevention in Sickle Cell Anemia;

TCD = transcranial Doppler

TABLE 2

Minimum and maximum time-averaged mean of the maximum (TAMM) cut-off values (cm/sec) by sites with means across sites for values characterized as normal, conditional, and high/abnormal by transcranial Doppler (TCD) method compared with the STOP protocol

	Normal TCD Higher End	Conditional TCD Lower End	Conditional TCD Higher End	High/Abnormal TCD Lower End
STOP Protocol	169	170	199	200
Dedicated Doppler TCD				
Mean	170	170	199	200
Min	169	170	199	200
Max	179	171	200	201
Imaging TCD (TCDi)				
Mean	163	163	188	190
Min	149	150	174	180
Max	170	170	199	200