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DISPLACE Study Shows Poor Quality of Transcranial Doppler Ultrasound for Stroke Risk Screening in Sickle Cell Anemia

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Abstract:
Children with sickle cell anemia (SCA) are at increased risk of stroke when compared to age-based counterparts. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) previously demonstrated that with the use of transcranial Doppler ultrasound (TCD; Sickle Stroke Screen) and chronic red cell transfusion, the risk of stroke risk is reduced by over 90%. The STOP criteria detailed the type and method of measurement required; the time averaged mean maximum velocity (TAMMV). Unfortunately, it has been difficult to adhere to the appropriate TAMMV measurements. The objectives of this study were to assess the quality of TCD and transcranial Doppler imaging (TCDi) reports to determine report quality and accuracy. This is a sub-analysis of the DISPLACE (Dissemination and Implementation of Stroke Prevention Looking at the Care Environment) study. Over 12,000 TCD/TCDi reports were collected during this study from 28 institutions; 391 TCDs were reviewed for this sub-analysis. There was significant variation in which vessels were assessed, the velocities used to define abnormal results, and who was interpreting the scans. In 52% of reports, it was impossible to identify whether the TAMMV was what was measured. Similarly, it was only clear in 42% of reports that the TAMMV was used to interpret the exam as normal/abnormal. Given this inconsistency, we strongly recommend standardization of TCD/TCDi reporting, specialized training for those performing and interpreting the scans in the use of TCD/TCDi in patients with SCA, internal quality assurance, and institutional quality improvement work to ensure appropriate use of this potentially lifesaving technology.

Conflict of interest: COI declared - see note

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Abstract

Children with sickle cell anemia (SCA) are at increased risk of stroke when compared to age-based counterparts. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) previously demonstrated that with the use of transcranial Doppler ultrasound (TCD; Sickle Stroke Screen) and chronic red cell transfusion, the risk of stroke risk is reduced by over 90%. The STOP criteria detailed the type and method of measurement required; the time averaged mean maximum velocity (TAMMV). Unfortunately, it has been difficult to adhere to the appropriate TAMMV measurements. The objectives of this study were to assess the quality of TCD and transcranial Doppler imaging (TCDi) reports to determine report quality and accuracy. This is a sub-analysis of the DISPLACE (Dissemination and Implementation of Stroke Prevention Looking at the Care Environment) study. Over 12,000 TCD/TCDi reports were collected during this study from 28 institutions; 391 TCDs were reviewed for this sub-analysis. There was significant variation in which vessels were assessed, the velocities used to define abnormal results, and who was interpreting the scans. In 52% of reports, it was impossible to identify whether the TAMMV was what was measured. Similarly, it was only clear in 42% of reports that the TAMMV was used to interpret the exam as normal/abnormal. Given this inconsistency, we strongly recommend standardization of TCD/TCDi reporting, specialized training for those performing and interpreting the scans in the use of TCD/TCDi in patients with SCA, internal quality assurance, and institutional quality improvement work to ensure appropriate use of this potentially lifesaving technology.

Key Points

- DISPLACE study shows inconsistencies in use and reporting of transcranial doppler (TCD) for stroke risk screening in sickle cell anemia in the United States.
- A standardized reporting template, training on the use of TCD in sickle cell anemia, and institutional quality assurance is recommended.

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Introduction

Children with sickle cell anemia (SCA) are at significantly increased risk of stroke when compared to their age based counterparts, with up to an 11% chance of overt stroke prior to the age of 20 in the pre-chronic transfusion era[1]. The Stroke Prevention Trial in Sickle Cell Anemia (STOP), completed between 1995 and 1997, demonstrated that with the use of transcranial Doppler ultrasound (TCD; Sickle Stroke Screen), children at highest risk for stroke could be identified and started on chronic red cell transfusion therapy (CRCT), thus reducing the risk of stroke by over 90%[2]. This led to the adoption of the STOP protocol as standard of care, first announced in 1997 by the National Institutes of Health (NIH) in a Clinical Alert[3], in which it is recommended that patients with SCA (genotypes HbSS and HbSβ0-thalassemia) between the ages of 2 and 16 years undergo routine yearly TCD screening and patients with abnormal findings should start chronic transfusion therapy. This guideline has been reaffirmed in several subsequent reports from the National Heart, Lung and Blood Institute (NHLBI)[4] and the American Society of Hematology (ASH)[5].

In defining the use of the TCD for SCA, the STOP protocol required measurement of the time-averaged mean maximum velocity (TAMMV) in the distal internal carotid artery (dICA) and proximal middle cerebral artery (MCA) with the following classifications: “normal” if all TAMMV are less than 170cm/sec, “conditional” if there is at least 1 TAMMV of 170 to 199cm/sec, and “abnormal” if there is at least 1 TAMMV greater than or equal to 200cm/sec[2]. CRCT to prevent stroke is indicated for abnormal TCD on two occasions or one TCD with TAMMV 220 cm/sec or greater. Now, more than 20 years after publication of these findings, implementation of TCD is inconsistent across United States (US) sites and lacks standardization.

The NHLBI recommended that facilities "do studies to compare their current equipment with STOP trial TCD equipment"[3]. To meet the need for training in correct TCD use, the STOP investigators provided national trainings and workshops, however these are no longer available. A standard non-imaging TCD as used in STOP was not available at all centers, therefore, some centers started to use the transcranial Doppler imaging (TCDi) technique. An early study assessing for differences between TCD and TCDi velocities published in 2001 demonstrated for the MCA that TCDi velocities were about 10% lower than those measured with TCD[6], which has subsequently been confirmed in some studies[7,8] but not in others[9–11]. In fact, the French National Authority for Health recommended use of the same thresholds for TCD and TCDi due to concern for potential over-transfusion in patients screened by TCDi[12]. In some centers, angle correction, or adjusting the velocity based on the angle between the transducer and the vessel, is performed when using TCDi[13]. The precise correlation between TCD and TCDi velocities is not clear and likely highly dependent on technique. The ASH guidelines published in 2020 continue to support the cutoff values defined in the initial STOP trial, but added recommendations for TCDi, citing the velocity used in the Silent Cerebral Infarct Transfusion (SIT) trial: mean velocity greater than or equal to 185cm/sec is abnormal[5,14].

Since the routine use of TCD for stroke risk screening in SCA was instituted in 1997, there have been several studies evaluating site-level adherence to the recommendation to obtain annual TCD assessments [15–17]. These studies used a variety of techniques for both examining barriers to TCD and facilitating improvement including the use of personalized reminders[18] and tracking patients overdue for imaging[19]. One European study identified a major barrier to routine TCD screening was the lack of trained personnel to perform the procedure. To overcome this barrier, they recruited a variety of practitioners, including clinicians with ultrasound experience,

surgeons, pediatricians, and nurses, from three centers to complete a TCD/TCDi training program. They noted that prior to this training, there was significant variation in the percentage of scans classified as abnormal among the institutions, while following training, there were no differences in the distribution of classifications[20]. Each of these studies reports on barriers to appropriate and accurate stroke risk screening for children with SCA; however, none of these studies specifically addressed the quality of the reports themselves, assessed for the correct interpretation of measurements, or insured ongoing quality assurance. Only one study assessed the accuracy of the measurements themselves[20] and no recent reports have demonstrated multi-institutional assessments of TCD quality.

The recent DISPLACE (Dissemination and Implementation of Stroke Prevention Looking at the Care Environment) study was a 28-site consortium funded by the NHLBI to evaluate barriers to TCD screening implementation and test strategies to improve adherence to TCD guidelines in SCA in the US. DISPLACE demonstrated that less than 50% of children at participating SCA centers had annual TCD screening during the baseline period (2012 - 2016)[21]. This current project is a sub-study using the DISPLACE database. In this study, we hypothesized that there would be both high variability in TCD/TCDi technique and that sites using TCDi would use inconsistent definitions to classify scans as "abnormal." In addition, we wanted to determine if sites using TCDi were making treatment decisions regarding chronic transfusion therapy based on criteria other than those established by the STOP protocol.

Methods

Data Source

The DISPLACE study has been described previously[21,22]. Briefly, DISPLACE was a dissemination and implementation study performed to improve TCD stoke risk screening in children with sickle cell anemia in the US. The initial phase of the study was an in-depth retrospective chart review that required each participating site to identify all children with SCA treated at their sites from 2012 - 2016 and upload multiple laboratory and radiographic reports (including TCDs) from each child from all available years to determine site-level adherence to TCD screening. These results from part 1 demonstrated that more than 50% of children with SCA were not getting appropriate TCD screening and also identified updated findings regarding the decreased frequency of abnormal TCDs that coincided with the increased earlyinitiation of hydoxyurea.[21] During part 1, over 12,443 TCD reports were collected from 28 institutions and uploaded into a customized database. An IRB waiver was obtained and data from these reports were used for this DISPLACE sub-study.

Data Collection

To facilitate evaluation, a computer-generated algorithm was used to randomly select 400 TCD/TCDi reports for this sub-study. The algorithm ensured that reports were included from all 28 sites across all different years and patient age groups. The initial hypothesis of this sub-study was that there would be increased variability in interpretation of TCDi when compared to TCD. As such, it was determined that for an alpha of 0.05, approximately 400 reports would be needed, for a 95% confidence interval with precision of 0.1, assuming a sample proportion of 0.5 (most conservative assumption).

Data were manually extracted from the TCD/TCDi reports for patients aged 2 to 8 years of age at the time of their study. This age group was targeted given the highest prevalence of stroke for patients with SCD is in the first decade of life [23] in addition to previous DISPLACE

data showing the highest rate of first abnormal TCD in the 4-8 year age range[21]. Data collected from each report included the institution, year, blood vessel(s) assessed, whether numerical values for TCD velocities were recorded, the presence of low values, if peak systolic velocities were assessed, the interpretation of the TCD study, if the interpretation was based on TAMMV or another measurement, and if follow up recommendations were provided in the report. As most reports did not specifically state whether TCD or TCDi was used, these data were separately extracted from information manually entered by each participating site directly into the DISPLACE study database. Drs. Davidow and Miller reviewed this data.

Additionally, a REDCap[24] survey (version 11.2.1) of DISPLACE study principal investigators (PIs) was conducted**.** PIs were asked to recall information from the study period (2012 - 2016). Questions included the use of TCD versus TCDi, the type of machine, how technicians were trained, who reads the TCDs, velocity cutoffs used for classification of normal, abnormal, or conditional, and vessels included in interpretation. A similar survey had been previously performed[25], but was deidentified, so answers could not be directly linked to a specific institution's TCD reports.

Statistical Analysis

Microsoft Excel© was used for statistics. Counts and frequencies were calculated for categorical variables. Measures of central tendency were calculated for continuous variables.

An IRB waiver from the Nemours Children's Hospital IRB was obtained.

Results

TCD/TCDi Reports

A total of 391 TCD reports were reviewed from 26 different institutions (28 were included in the DISPLACE study; however, two sites did not upload useable reports). Due to variability in the number of reports uploaded to the DISPLACE database by each institution, the number of reports reviewed for this sub-study from each institution varied. Within this sub-cohort of 391 reports (as 9 uploaded reports were outside of the age range or were not TCD reports), the median age of patients at the time of their TCD was 5 years (range: 2 – 8 years) and the median year the studies were completed was 2013 (range 2000 to 2016). The reports evaluated included both TCD and TCDi (47% and 53% respectively), which is in a different proportion than the entire DISPLACE study (66.2% TCD vs. 32.8% TCDi)[21]. This difference was intentional as the goal for this sub-study was to compare equal numbers of TCD and TCDi reports.

After initial review of the TCD and TCDi reports, there was such substantial variation across all institutions (in the content of both TCD and TCDi reports) that a conclusion regarding how reports were categorized as abnormal could not be determined. Instead, the decision was made to focus the analyses on the quality and completeness of the information included in the reports, the accurate and consistent description of what measurements were taken, and the interpretation of the results. The majority of TCD/TCDi reports were classified as normal (67%, 262) with 13% (52) conditional and 4% (14) abnormal, consistent with the original findings from the DISPLACE part 1 cohort. In addition, 1% (5) were documented as inadequate and 15% (58) were unclassified or not interpreted using STOP-defined terminology. Further information regarding the TCD reports is summarized in **Table 1**.

Review of these 391 TCD reports identified deficiencies in reporting TCD modality (TCD vs TCDi), technique, and vessels examined. Upon data entry into the DISPLACE study database, sites were required to select if a report represented a TCD or TCDi. However, of those that were listed as being performed with TCDi, 96% did not state that a TCDi was used in the radiology report itself. Second, of the 391 TCD/TCDi reports reviewed, 6% (24) of reports did not include numerical velocities, while 8% (32) had some numerical values but not for all vessels that the body of the report listed as being evaluated. Furthermore, over half of the reports (52%, 200) did not clearly identify the velocity measurement as the TAMMV, the key variable per STOP criteria. Thirty percent (116) of reports did not assess or did not report on the distal ICA (dICA) velocity.

There were also deficiencies in reporting study interpretation clearly. **Only 42% (162) of reports clearly stated that classification of normal versus abnormal result was based on the TAMMV**, and only 32% of reports (123) clearly reported which vessels were used to classify the study as normal/abnormal. Notably, some reports included verbiage saying classification was based on STOP criteria but did not give sufficient details in the report to determine if the correct vessels were used.

Survey Results

The surveys to assess the TCD screening practices from 2012-2016 are summarized in **Table 2**. Responses were received from 23 of the 26 institutions for whom TCD reports were included. Fifty-seven percent (13) reported using TCDi and one institution reported using both TCD and TCDi. Of those sites using TCDi, 43% (6) used angle correction. There was substantial variability with regard to which vessels were examined for both TCD and TCDi, ranging from one to five vessels per hemisphere, with three institutions reporting that it was

"whatever the radiologist decides". Radiologists interpreted TCDs at most sites (70%) and neurologists and hematologists were identified as the responsible physicians in the remainder. When asked how ultrasound technicians were trained in TCD assessment, 39% (nine sites) noted using peer to peer training while 35% (eight sites) underwent formal STOP training for at least some of their technicians. See **Table 2** for further details.

As part of this survey, site PIs were also asked what velocity measurements were used to classify TCD/TCDi scans as normal/abnormal/conditional. Of those using non-imaging TCDs, the classifications were consistent with those used for the STOP study for 80% (8/10) of respondents. Five of the 10 institutions also had defined "low" values that were not included as a STOP study outcome measure. For the 14 sites using TCDi, there was substantial variability in the lower velocity classification used to define a "conditional" result which varied from 150 to 170cm/sec and for the lower limit velocity for "abnormal" ranging from 180 to 201cm/sec.

Discussion

The STOP study revolutionized care for pediatric patients with SCA, identifying a non-invasive method to monitor for children at high risk of stroke and identifying a life-saving intervention (CRCT)[2]. However, despite this significant finding, several subsequent studies have shown poor implementation of TCD screening for a variety of reasons, including missed opportunities for referral and inconsistent technique[16,20]. Furthermore, there is no consistent means of ensuring that centers perform TCDs accurately. Only one European study performed quality assessment of the technical capabilities of people performing stroke risk screening using TCD[20]. This study initially sought to evaluate the quality of TCD reports across multiple institutions in the US with the hypothesis that there would be more variability in the interpretation of TCDi than TCDs. Instead, this study identified a startling lack of

standardization across all sites including which vessels were measured, how the measurements were performed (with or without angle correction for TCDi), how the reports were interpreted, and who was reading and interpreting the report. The reports were so discrepant that it was not possible to assess whether measurements were accurately interpreted.

TCD results have critical implications for medical decision-making for children with SCA and our study reveals a significant lack of quality assurance and consistency in the reporting of stroke risk screening, using both TCD and TCDi. Most notably, many reports did not clearly identify which blood vessels were used to assess stroke risk, did not report on the correct velocity measurement (or lacked the information to determine if the correct velocity was measured), or made interpretations based on velocities other than TAMMV, the measurement validated in the STOP trial. Additionally, most reports reviewed in this study did not make note of whether a TCD or TCDi was performed, and for TCDi, it was frequently unclear if angle correction was performed which can affect cut-offs for normal, conditional, and abnormal. Corroborating these findings, survey data from the participating DISPLACE sites showed significant variation in the training methods used for those performing TCD. Though radiologists were the most common physician interpreting results, some sites noted neurologists or hematologists assuming this role. The training of the interpreting physician was not assessed.

This study revealed a significant lack of quality assurance in TCD technique and interpretation across 26 pediatric SCA centers in the United States suggesting variability of result quality that could result in missed opportunities to prevent strokes. To address this, we have several recommendations for improved clarity of TCD reporting at pediatric SCA centers. First, we recommend creation of a standardized template for TCD/TCDi reports to be used across institutions which includes the following key data: 1) Specific type of TCD (TCD or TCDi)

being used, 2) Defined measurement (time-averaged mean maximum velocity abbreviated as either TAMMV or TAMMX) for each vessel examined (MCA, dICA, ACA, etc), 3) Numerical values noted for the TAMMV of each vessel that is assessed, 4) A clear impression statement indicating whether the TCD/TCDi is normal, abnormal, or conditional, with a clear definition of what values were used to categorize the results as such, and 5) A statement regarding the adequacy of the study. We additionally recommend consideration for the inclusion of comments about asymmetry[26] and low values[27]. As there is some evidence to suggest utility in measuring peak systolic velocities[28], for sites measuring them we recommend inclusion in the body of the report but exclusion from the impression so as to prevent misinterpretation. Similarly, the assessment of additional vessels such as the ACA[29] or the external portion of the ICA (eICA)[30,31] deserve further study. The format of these reports should be standardized in all electronic health records using a standardized data dictionary (as used by the National Alliance of Sickle Cell Centers) to facilitate both longitudinal assessment of individual patients and intra and inter-center comparative quality assessment. Data should also be entered into the electronic health record in an easily extractable format to facilitate multi-institution reviews. Please see **Figure 1** for our recommended standardized template. The standardization of measurements and methods used for interpretations are critical to allow comparison of data for use in research to advance the field especially as novel medications and transformative therapies are being developed.

Regarding TCDi measurements, it has been shown in several studies that one can expect the velocities to be about 10% lower than TCD, however this has not been confirmed; thus, there are no established guidelines regarding interpretation. Sites using TCDi varied significantly in their definitions of conditional and abnormal velocities with or without angle correction. In the US, we recommend compliance with the ASH guidelines for TCDi, using a TAMMV greater than or

equal to 185cm/sec to define abnormal[5] until further studies or internal quality assurance suggests another threshold should be used as discussed below.

We also recommend choosing one brand of TCD or TCDi that is used for all patients with SCA being cared for at an institution to allow consistency within the institution as well as internal quality assurance. Most ideally, the exact same machine would be used for all patients undergoing TCD/TCDi for stroke risk screening at an institution given variability even amongst different equipment from the same manufacturer. While calibration of each machine for the performance of stroke risk screening for children with SCA would be optimal, there is not a recognized, guideline-approved method for this practice at this time. The equipment should undergo re-calibration as recommended by the manufacturer to maintain the best precision. Triggers to evaluate the process and thresholds used within an institution could include a lack of abnormal scans (as this suggests the threshold for abnormal may be too high), a change in percentage of abnormal results, and a clinical review of every patient who has a stroke that had undergone a TCD. The percentage of abnormal scans should be compared continuously both within and between SCA centers as the rates of abnormal TCD and frequency of stroke have changed as treatments have evolved. Hematologists, sonographers, and radiologists at SCA centers should work together to evaluate their practices and outcomes to improve local performance and outcomes.

Finally, without successful and ongoing TCD/TCDi training for technologists and interpreting physicians, results from these scans may be unreliable. Though some institutions in DISPLACE reported having technologists trained in formal STOP training courses, most training is peer to peer and currently, there are no formal sickle cell-specific training opportunities. The authors feel these trainings should be re-introduced by either the National Alliance of Sickle Cell Centers or through a professional diagnostic medical sonography organization. A standardized

training curriculum would improve both technical performance of TCD/TCDi and interpretation. Physicians interpreting TCD/TCDi should have specialized training in the use of TCD/TCDi for stroke risk screening. Hematology organizations and radiology organizations should work together to improve mutual understanding of TCD performance standards and the critical clinical significance. Recommendations are summarized in Table 3.

Although this study is multi-institutional and included the review of nearly 400 TCD reports, there are still limitations. The sites included in DISPLACE represent approximately 30% of all pediatric SCA centers across the United States and did not include international centers. The TCDs included were performed between 2000 and 2016, and institutional practices may have changed since these were completed; though notably, there was no relevant differences in the quality of reports from early time points versus later ones. When surveys were sent to DISPLACE PIs, they were requested to recall what their institution was doing during the study period (2012 – 2016); however, recall bias may have impacted the results toward reporting what the facilities are currently using. Evidence against recall bias however, are previously published; original deidentified survey results from DISPLACE similarly showed that there was significant variation in cutoffs used for TCDi and vessels used in classification[25].

In conclusion, though the STOP study clearly defined the importance of annual stroke risk screening with TCD for children with SCA, there continue to be barriers to implementation. Appropriate interpretation relies on accurate and consistent study performance, and continuous quality assessment is necessary. As such, this paper serves as a call to action for immediate re-calibration of TCD/TCDi assessment and reporting including the need for standardized templates for electronic health records, re-instatement of formal training for both those performing and interpreting scans, and ongoing comparative quality analysis. We also recommend inclusion of

TCD quality assurance in future definitions of Pediatric Sickle Cell Disease Centers of Excellence, by the National Alliance of Sickle Cell Centers and consideration for inclusion of TCD-related quality assessment in US News and World Report rankings to incentivize institutions to invest in improvement. Accomplishing these goals will require engagement of the relevant stakeholders, identification of barriers to implementation, and funding. With these interventions, we can continue to work towards meeting the recommended screening and interventions instituted by the NHLBI more than 25 years ago and optimize outcomes.

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Table 1 – Summary of TCD Reports

TCD Reports			
	median (range)		
Patient Age	5 (2 - 8)		
TCD Year	2013 (2000 - 2016)		
TCD Type*	**Count (%)**		
TCD	183 (47%)		
TCDi	207 (53%)		
Vessels Assessed**	**Yes**	**No**	**Total**
MCA	377 (100%)	0	377
ACA	327 (89%)	42 (11%)	369
PCA	306 (84%)	60 (16%)	366
dICA	275 (76%)	86 (24%)	361
Basilar	185 (51%)	179 (49%)	364
Bifurcation	146 (41%)	212 (59%)	358
Vertebral	203 (29%)	255 (71%)	358
	Yes	**No**	**Partial**
Numerical Velocities Supplied	335 (86%)	24 (6%)	32 (8%)
	Yes	**No**	**Unknown**
Classification Based on TAMMV	162 (42%)	23 (6%)	200 (52%)
	Yes	**No**	**Unknown**
Peak Velocities Assessed***	123 (33%)	246 (37%)	
Peak Velocities Noted in Impression	52 (42%)	71 (58%)	

*TCD type as entered directly into database by investigator uploading report to DISPLACE database, not based on what is reported in report itself.

**Total evaluable for each vessel includes only those that identified the vessels used. Total number is not the same for each row.

***Does not equal 100% as not all reports included numerical values or stated what they were measuring.

Table 2 – Summary of Survey Results

Survey Results						
Institution	**TCD/TCDi reported used on survey**	**Interprets Scans**	**Vessels Used for Interpretation**	**Cutoffs Used (cm/sec)**		**Training of Technicians Performing TCD**
				Conditional	**Abnormal**	
1	TCD	Hematologist	MCA, dICA, ACA	170-199	200+	Peer to Peer
2	TCD	Neurologist	MCA	170-184	185+	Peer to Peer
3	TCD	Neurologist	MCA, dICA	170-199	200+	Formal STOP training course
4	TCD	Neurologist	MCA, dICA	170-199	200+	Formal STOP training course
5	TCD	Neurologist	MCA, ACA	170-215	215+	Formal STOP training course
6	TCD	Neurologist	MCA, dICA, PCA, ACA	170-199	200+	Other
7	TCD	Neurologist	MCA, dICA, whatever radiologist decides	170-199	200+	Peer to peer
8	TCD	Radiologist	MCA, dICA, ACA	170-199	200+	Other formal training
9	TCD	Radiologist	MCA, dICA, PCA, ACA, Basilar	170-199	200+	Peer to Peer
10	TCD and TCDi	Radiologist	MCA	170-199 155-184	200+ 185+	Other formal training
11	TCDi	Neuroradiologist	MCA, dICA	150-179	180+	Formal STOP training course and Peer to Peer
12	TCDi	Radiologist	MCA	160-179	180+	Other formal training
13	TCDi	Radiologist	MCA, dICA	155-184	185+	Formal STOP training course and Peer to Peer
14	TCDi	Radiologist	MCA, dICA, PCA	165-184	185+	Peer to Peer
15	TCDi	Radiologist	MCA, dICA, PCA	150-184	185+	Peer to Peer
16	TCDi	Radiologist	MCA, PCA, ACA	165-184	185+	Peer to Peer
17	TCDi	Radiologist	MCA, PCA, ACA	151-184	185+	Formal STOP training course, other formal training, peer to peer
18	TCDi	Radiologist	MCA, dICA, PCA, ACA	150-184	185+	Formal STOP training course
19	TCDi	Radiologist	MCA, dICA, PCA, ACA	165-185	186+	Formal STOP training course
20	TCDi	Radiologist	MCA, dICA, PCA, ACA	155-184	185+	Other formal training, Internal training, Other
21	TCDi	Radiologist	MCA, ACA, PCA, whatever radiologist decides	170-199	200+	Peer to Peer
22	TCDi	Radiologist	whatever radiologist decides	170-200	201+	Peer to Peer
23	TCDi	Radiologist and Hematologist	MCA, dICA	155-184	185+	Other

Table 3 – Summary of Results and Recommendations

Current Guidelines	DISPLACE Findings	Recommendations/Considerations for Future Study
1. Measurement of the TAMMV in the MCA and dICA to evaluate stroke risk[2]	1. 52% either did not measure or did not clearly document measuring the TAMMV 2. 30% did not measure both the MCA and dICA 3. 68% did not clearly identify which vessels were used to interpret the study	1. Standardized data dictionary and reporting template as seen in Figure 1 to reinforce the appropriate velocities to measure and interpret 2. Documentation of additional vessels assessed to facilitate future studies regarding their role in stroke risk screening
2. Definition of abnormal for TCD AND indication for CRCT: TAMMV ≥ 200cm/sec x 2 or > 220cm/sec once[2,5]	1. Sites were uniformly defining abnormal as > 200cm/sec for TCD 2. 58% did not clearly use the TAMMV to interpret the study 3.. Indications for CRCT not directly addressed in this study.	3. Repeat exam for any abnormal velocity 200-220cm/sec as recommended by ASH guidelines[5] 4. Consider lab evaluation and clinical exam at time of abnormal result
3. Definition of abnormal for TCDi AND indication for CRCT: TAMMV ≥ 185cm/sec x2 or > 205cm/sec once[5]	1. Significant heterogeneity in the definition of conditional and abnormal for TCDi 2. 43% of sites utilizing TCDi used angle correction	1. Do not use angle correction as this most closely matches original STOP trial 2. Start with following ASH recommendations in the US until new data are available. 3. Use internal quality assurance processes to adjust velocity cut offs as needed for best care
Training and calibration: No current guidelines in US	1. Training of ultrasonographers and physicians interpreting studies is variable.	1. Create joint Hematology and Radiology interest group 2. Develop new required training program for all those performing and reading TCDs for stroke risk screening in sickle cell disease 3. Each institution should be consistent in the device used for TCD measurements 4. Recommend routine maintenance or re-calibration of imaging devices to ensure continued precision 5. Internal quality assurance processes that will identify variations in technique and results

Table/Figure Legends

Table 1 Abbreviations: TCD, transcranial Doppler ultrasound; TCDi, transcranial Doppler ultrasound imaging technique; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; dICA, distal internal carotid artery; TAMMV, time-averaged mean of the maximum velocity

Table 2 Abbreviations: TCD, transcranial Doppler ultrasound; TCDi, transcranial Doppler ultrasound imaging technique; MCA, middle cerebral artery; dICA, distal internal carotid artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; STOP, the Stroke Prevention Trial in Sickle Cell Anemia

Table 3 Abbreviations: DISPLACE, Dissemination and Implementation of Stroke Prevention Looking at the Care Environment; TAMMV, time-averaged mean of the maximum velocity; MCA, middle cerebral artery; dICA, distal internal carotid artery; TCD, transcranial Doppler ultrasound; CRCT, chronic red cell transfusion therapy; ASH, American Society of Hematology; TCDi, transcranial Doppler ultrasound imaging technique; STOP, Stroke Prevention Trial in Sickle Cell Anemia; US, United States;

Figure 1 shows a proposed standardized template for TCD/TCDi reports. Abbreviations: Hgb, hemoglobin; TCD, transcranial Doppler ultrasound; TCDi, transcranial Doppler ultrasound imaging technique; STOP, the Stroke Prevention Trial in Sickle Cell Anemia; TAMMV/TAMMX, time-averaged mean of the maximum velocity; L, left; R, right; MCA, middle cerebral artery; dICA, distal internal carotid artery; ACA, anterior cerebral artery; PCA posterior cerebral artery; eICA, extracranial internal carotid artery; ASH, American Society of Hematology

Figure 1

Clinical history: This is an (age) year old patient with Hgb (type of sickle cell disease) presenting for routine stroke risk screening.

Imaging Technique: To include TCD versus TCDi, machine used, if angle correction employed for TCDi

Findings: Please define what measurement was done. The time-averaged mean maximum velocity is required per the STOP protocol. This can be abbreviated as TAMMV or TAMMX but writing out the full definition leads to the least confusion. If the peak systolic velocities are also measured, recommend including that in a table format as well.

Vessels as defined by STOP that should be assessed in all patients:

Date	L MCA	R MCA	L dICA	R dICA

Additional vessels whose assessment may be of value but were not included in STOP:

Date	L ACA	L PCA	L Vertebral	L Bifurcation	L eICA

Date	R ACA	R PCA	R Vertebral	R Bifurcation	R eICA

Date	Basilar Artery

Impression:

1) Classification per STOP criteria for TCD. For TCDi, classification as per ASH guidelines, with institutional ability to determine their own cut offs based on their best available evidence. Include the defined cutoffs and vessels as used by the institution for classification.

2) Comments on asymmetry or low values.

3) Recommendation for when to repeat the TCD.