# Transcranial Doppler Velocities Conversion Rate Based on Increasing Hemoglobin Concentration: Analysis From the SCCRIP Cohort Study



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## BACKGROUND

- Sickle cell disease (SCD) is a rare, debilitating disease marked by pathophysiological features that include hemolytic anemia, vaso-occlusion, and progressive end-organ damage.[1-6]
- The most devastating complication of pediatric SCD is the development of central nervous system events, such as overt stroke or silent cerebral infarcts, that can produce significant physical and neurocognitive deficits.[7,8]
- Transcranial Doppler ultrasonography (TCD) measures cerebral artery blood flow velocity in children with SCD, and elevated TCD velocity levels are a reliable and clinically validated predictor of stroke risk.[6,9,10]
  - Children with conditional TCD levels (defined as ≥170 to <200 cm/s) are at increased risk of stroke compared with those with normal TCD levels (<170 cm/s).[11]
- The low hemoglobin (Hb) levels indicative of anemia have been shown to be associated with abnormal TCD levels and an increased risk of stroke and silent cerebral infarcts.[12-14]
  - However, the extent to which Hb concentration influences TCD level has not been extensively studied outside the clinical trial setting.

## OBJECTIVE

- To quantify the rise in Hb obtained during hydroxyurea (HU) therapy against the change observed in TCD levels to provide an estimate for the magnitude of Hb rise that predicts an individual's conversion from the conditional TCD level (moderate risk of stroke) to the normal TCD level (low risk of stroke), using recently collected real-world longitudinal data.

## METHODS

### Study Design

- A prospective and retrospective observational study was conducted using medical records from the Sickle Cell Clinical Research and Intervention Program (SCCRIP).[15]
  - The SCCRIP database includes full medical records of ~1300 patients from 5 sites, with an average of 5 years of follow-up.

### Inclusion Criteria

- Children (aged ≤16 years) with HbSS or HbS$\beta^0$-thalassemia.
- Patients initiating HU before December 31, 2017.

### Exclusion Criteria

- Patients receiving chronic red blood cell transfusions.
- Patients with missing baseline (BL) TCD values.

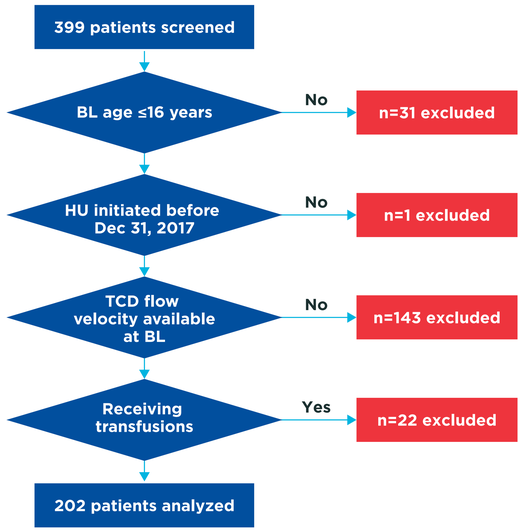
### Analyses

- Cross-sectional correlations between TCD levels and Hb levels at 1, 2, and 4 years after HU initiation were assessed using a Spearman correlation test.
  - TCD and Hb levels measured before HU initiation were defined as BL levels.
- Among patients with conditional TCD levels at BL, changes in TCD levels at 1 and 2 years after HU initiation were assessed by changes in Hb levels from BL (0 to <0.5, ≥0.5 to <1, ≥1 to <2, and ≥2 g/dL).
- The impact of Hb levels on TCD velocity was assessed by a mixed-model repeated measures approach using longitudinal panel data, controlling for demographic and clinical characteristics.

## RESULTS

- In total, 399 children were screened for the study, with 202 patients selected for analysis (**Figure 1**).

**Figure 1. Patient Selection Flow Chart**




BL, baseline; HU, hydroxyurea; TCD, transcranial Doppler ultrasonography.

- Demographics and baseline characteristics are shown in **Table 1.**
- At BL, 80.2% (n=162) of patients had normal TCD levels, whereas 16.3% (n=33) had conditional TCD levels.
- Mean (SD) Hb level was 8.4 (1.0) g/dL at BL for all patients.
  - For those with conditional TCD levels, Hb was 8.3 (0.7) g/dL at BL.

**Table 1. Patient BL Characteristics**

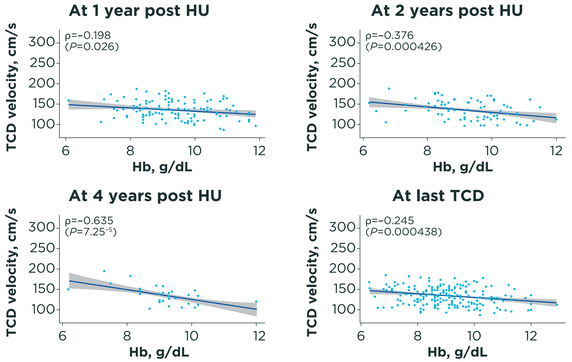
| | Patients With Conditional TCD (n=33) | All (N=202) |
|---|---|---|
| **Demographics** | | |
| Age, mean (SD), years | 6.7 (3.1) | 7.5 (3.8) |
| Female, n (%) | 20 (60.6) | 94 (46.5) |
| **Clinical characteristics** | | |
| TCD | | |
| Velocity, mean (SD), cm/s | 180.1 (7.6) | 143.7 (24.6) |
| Velocity, median (range), cm/s | 178 (170-195) | 142.5 (93-211) |
| Normal, n (%) | | 162 (80.2) |
| Conditional, n (%) | 33 (100) | 33 (16.3) |
| Abnormal, n (%) | | 2 (1.0) |
| Incomplete, n (%) | | 5 (2.5) |
| Hb, mean (SD), g/dL | 8.3 (0.7) | 8.4 (1.0) |
| Genotype, n (%) | | |
| SS/S$\beta^0$ | 32 (97.0) | 196 (97.0) |
| SC | 0 | 2 (1.0) |
| S$\beta^+$ | 0 | 2 (1.0) |
| Other | 1 (3.0) | 2 (1.0) |

BL, baseline; Hb, hemoglobin; SD, standard deviation; TCD, transcranial Doppler ultrasonography.

### Correlation of Hb Levels With TCD Levels

- In cross-sectional analysis, Hb was negatively associated with corresponding TCD levels at 1, 2, and 4 years after HU initiation (**Figure 2**).
  - Spearman correlation coefficients were −0.20, −0.38, and −0.64, respectively, with all *P* values <0.05.

**Figure 2. Cross-Sectional Relationship Between $TCD_t$ and $Hb_t$**

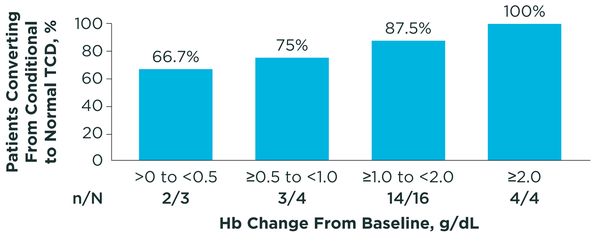



Hb, hemoglobin; $Hb_t$, hemoglobin at time *t*; HU, hydroxyurea; TCD, transcranial Doppler ultrasonography; $TCD_t$, transcranial Doppler ultrasonography at time *t*.

### Categorical Shifts Based on TCD and Hb

- The rates of shift to normal, no shift, and shift to abnormal were assessed for the 33 children with BL conditional TCD levels.
- After 1 year of HU therapy, 87.5% (23/27) of children with conditional TCD levels whose Hb increased >0 g/dL normalized their TCD level (**Figure 3**).
  - This number increased to 90% (18/20) when Hb increased ≥1 g/dL.
- The same analysis was repeated 2 years after HU initiation and yielded similar results: increases of ≥0.5 g/dL and ≥2 g/dL were associated with 88% and 100% of patients converting to normal, respectively.
- No patient with a conditional TCD level at BL converted to an abnormal TCD level at 1 or 2 years after HU initiation.

**Figure 3. Proportion of Patients Shifting From Conditional to Normal TCD Levels With Hb Increase at 1 Year**




Hb, hemoglobin; TCD, transcranial Doppler ultrasonography.

### Disclosures

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### Repeated Measures Regression Model of TCD and Hb

- Using a mixed-model repeated measures approach, Hb levels were negatively associated with TCD levels (**Table 2**).
  - A 1 g/dL difference in Hb was associated with a 14 cm/s lower TCD level among patients with BL conditional TCD (*P*<0.0001).
  - Hb levels were always statistically significantly correlated with TCD levels (*P*<0.05) when controlling for other covariates, such as age, gender, BL TCD, years since HU initiation, and other hemolysis markers.
- Results were consistent among all the included patients, regardless of BL TCD levels.

**Table 2. Regression Model of TCD and Hb**

| Model | Coefficient | | | | | |
|---|---|---|---|---|---|---|
| | | Value | SE | DF | *t* value | *P* value |
| $TCD_{i,t}=\beta_0+\beta_1 \cdot Hb_{i,t}+\mu_{i,t}$ | Intercept | 290 | 12.0 | 160 | 24 | <0.0001 |
| | $Hb_t$ | −14 | 1.3 | 160 | −11 | <0.0001 |

$\beta_0$, intercept of the regression line; $\beta_1$, slope of the regression line; DF, degrees of freedom; Hb, hemoglobin; $Hb_{i,t}$, Hb level (g/dL) measured for *i*th patient at time *t*; $\mu_{i,t}$, error term for repeated measures model; SE, standard error; *t* value, size of the estimate value in terms of SE; TCD, transcranial Doppler ultrasonography; $TCD_{i,t}$, TCD level (cm/s) measured for *i*th patient at time *t*.

## CONCLUSIONS

- In children with conditional TCD flow velocity (and, therefore, elevated stroke risk) prior to initiating HU, increases in Hb were significantly associated with a reduction in TCD level.
- Importantly, the rise in Hb was associated with a high likelihood of normalization of TCD levels when children had conditional TCD levels, which likely conveys a reduction in risk of stroke.
- Reductions in TCD flow velocity with pharmacologic therapy are similar to those demonstrated in the STOP II trial after chronic red blood cell transfusions.

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