

Withholding transfusion therapy in children with sickle cell disease with abnormal transcranial Doppler and normal magnetic resonance angiography: a retrospective analysis

We report the results of a retrospective analysis of our management protocol for children with sickle cell disease (SCD) and abnormal transcranial Doppler ultrasonography (TCD) velocities to prevent a cerebrovascular accident (CVA). According to this protocol, magnetic resonance angiography (MRA) imaging is performed in all children with abnormal TCD velocities and regular transfusion therapy is started only when intracranial vascular stenosis is demonstrated by MRA. Our results suggest that MRA may improve the identification of patients with an increased risk of developing a CVA and thereby reduce the proportion of children that need to start chronic transfusion therapy.

In 1992, Adams *et al.* demonstrated that 40% of pediatric SCD patients (HbSS or HbS β^0) with abnormal TCD velocities develop a CVA during an observation period of 30 months which can be prevented in 90% of these children by the initiation of chronic transfusion therapy.¹⁻³ Following this landmark study, several American guidelines, including the most recent American Society of Hematology (ASH) 2020 guideline, specify that children with HbSS or HbS β^0 should receive annual TCD screening between the ages 2 to 16 years and regular blood transfusions are recommended for at least a year in those children with abnormal TCD velocities.⁴⁻⁶

Although transfusion therapy strongly reduces the risk of a first CVA in children with SCD and abnormal TCD velocities,^{2,3} only 25-40% of all children with abnormal velocities, will develop a CVA during a follow-up of 30-70 months when not treated with transfusions.^{1,2} Thus, 60-75% of children are unnecessarily treated with transfusions for the prevention of CVA. Long-term transfusion therapy is associated with a high patient burden, iron load and its ensuing complications as well as red cell alloimmunization.^{7,8} Therefore, it is of great importance to more selectively identify patients at the highest risk of a CVA and to restrict transfusion therapy to patients who really need it.

A previous study suggested that the use of MRA in patients with abnormal TCD could narrow the group with an increased risk of developing a CVA.⁹ Based on this observation our institution adopted a management protocol that was different from the main American guidelines. In this protocol (bi)annual TCD screening is performed in all patients with HbSS or HbS β^0 , but instead of direct initiation of transfusion therapy in children with abnormal TCD velocities, regular transfusion therapy is started only when intracranial vascular stenosis is demonstrated by MRA. MRA imaging is performed in all children with abnormal

TCD velocities on two separate occasions.

In this retrospective analysis, we assessed the safety and efficacy of our protocol over a period of 22 years, aiming to determine whether patients with an abnormal TCD on two occasions and a normal MRA could safely refrain from transfusion therapy.

All HbSS and HbS β^0 patients that had undergone TCD screening at least once between the age of 2-18 years and who were managed according to this standard protocol between January 2000 and September 2022 were included in this analysis. TCD screening was performed biannually at the age of 2 to 10 years and annually at the age of 10 to 18 years. TCD screening included bilateral insonation of the MCA, the terminal ICA and the ACA through the temporal window. TCD was classified as abnormal if velocities were >200 cm/sec (non-imaging) or >180 cm/sec (imaging) and borderline values were defined as between 170 and 199 cm/sec (non-imaging) or between 155 and 179 cm/sec (imaging). If TCD velocities were either abnormal or borderline, TCD was repeated within 1 month. When this follow-up TCD showed abnormal or borderline TCD velocities again, MRA was performed within 6 weeks. MR examinations were performed on a 3-T system (Philips Intera, Philips Medical Systems, Best, the Netherlands) using an eight-channel phased array head coil. Multiple overlapping thin slab acquisition (MOTSA) 3D time of flight (TOF) MR angiography sequences were obtained for all patients (TE/TR 4/21 ms, 200 mm field of view, 1.0 mm thick sections). Sedation was used for children under the age of 7 years. The following thresholds were used to determine the severity of stenosis: mild (25-49%), moderate (50-74%), severe (75-99%), or occlusion (>99%). Chronic transfusion therapy was started only if a cerebral vascular stenosis was demonstrated by MRA. Children without vasculopathy on MRA were managed with regular TCD again. If TCD velocities remained abnormal or borderline, follow-up MRA were repeated every 2 years. The primary outcome of this retrospective analysis was the occurrence of a CVA. Due to its retrospective character, this study was not subject to the Medical Research Act (Dutch: WMO) and was therefore exempted from medical ethical review by the Dutch Medical Research Ethics Committee. Two hundred and nine SCD patients that were screened according the above-described algorithm between January 1, 2000 and September 1, 2022 were included in the study. The median age of these patients at the start of the follow-up was 4.4 (interquartile range [IQR], 2.3-8.2) years. The cumulative observation period was 2,321 patient-years.

The cohort characteristics are summarized in Table 1. In this cohort, 30 of 209 patients (14.4%) had abnormal TCD velocities. The characteristics of these 30 patients are summarized in the *Online Supplementary Table S1*. Abnormal TCD velocities were detected for the first time at the median age of 5.3 (IQR, 4.0-7.6) years. MRA assessment was performed in all patients with abnormal TCD. MRA showed normal results in 14 of 30 cases (47%). Two of these patients received chronic transfusion therapy for other reasons. One patient started chronic transfusion therapy for recurrent acute chest syndrome (ACS) not responding to hydroxyurea treatment, 6.1 years after abnormal TCD velocities had been measured for the first time. In the second patient, chronic transfusions were started at the treating physician's discretion because of consistently abnormal TCD velocities without stenosis on repeated MRA (i.e., not according to the standard protocol). None of the non-transfused 12 patients with abnormal TCD velocities and a normal MRA, developed a CVA during a median follow-up of 7.5 years (IQR, 6.0-11.9). The cumulative follow-up time of these 12 patients after the first measurements of abnormal TCD velocities was 112 patient-years. Nine of the 12 patients (75%) used hydroxyurea during part of the follow-up: during 38 of 112 patient-years (34%) treatment with hydroxyurea took place. TCD velocities normalized in 11 of the 12 patients (92%). Figure 1 shows a Swimmers plot illustrating the follow-up time of the 12 patients with abnormal TCD velocities without stenosis on MRA. In three patients, repeated MRA assessments were performed because of persistently abnormal TCD velocities. None of these follow-up MRI/MRA showed a cerebrovascular stenosis or silent infarctions.

Sixteen of the 30 patients with abnormal TCD velocities appeared to have cerebrovascular stenosis on MRA. The cumulative follow-up time of these patients after the first measurements of abnormal TCD velocities was 221 years. In 15 of 16 (94%) of these patients chronic transfusion therapy was started. One patient repeatedly refused transfusion and/or hydroxyurea therapy but did not develop CVA during follow-up for 15.4 years. Two of the 15 patients on chronic transfusion therapy developed a CVA. One patient developed a fatal hemorrhagic CVA at the age of 26 years, 14.9 years after the start of transfusion therapy. A second patient developed Moyamoya disease, despite chronic transfusion therapy. This patient developed an ischemic CVA 7.7 years after the initiation of chronic transfusion therapy. Figure 2 shows a flow chart of TCD and MRA results, the treatment received and outcomes of all patients.

During follow-up, four patients of our cohort deceased. One female patient died of a hemorrhagic CVA as mentioned above. The other three patients died of non-neurological causes. Seven individuals were lost to follow-up. Six of these patients had normal TCD velocities at all occasions before they were lost to follow-up. One patient had abnormal TCD velocities in the past and no stenosis on MRA. In

this patient, TCD velocities normalized 3 years before the patient was lost to follow-up. The results of our screening algorithm contrast with the study reported by Adams *et al.* who reported a cumulative incidence rate of CVA of 0.4 (95% confidence interval [CI]: 0.27-0.59) at a follow-up of 2.4 years in a cohort of 25 patients with abnormal TCD velocities (cumulative

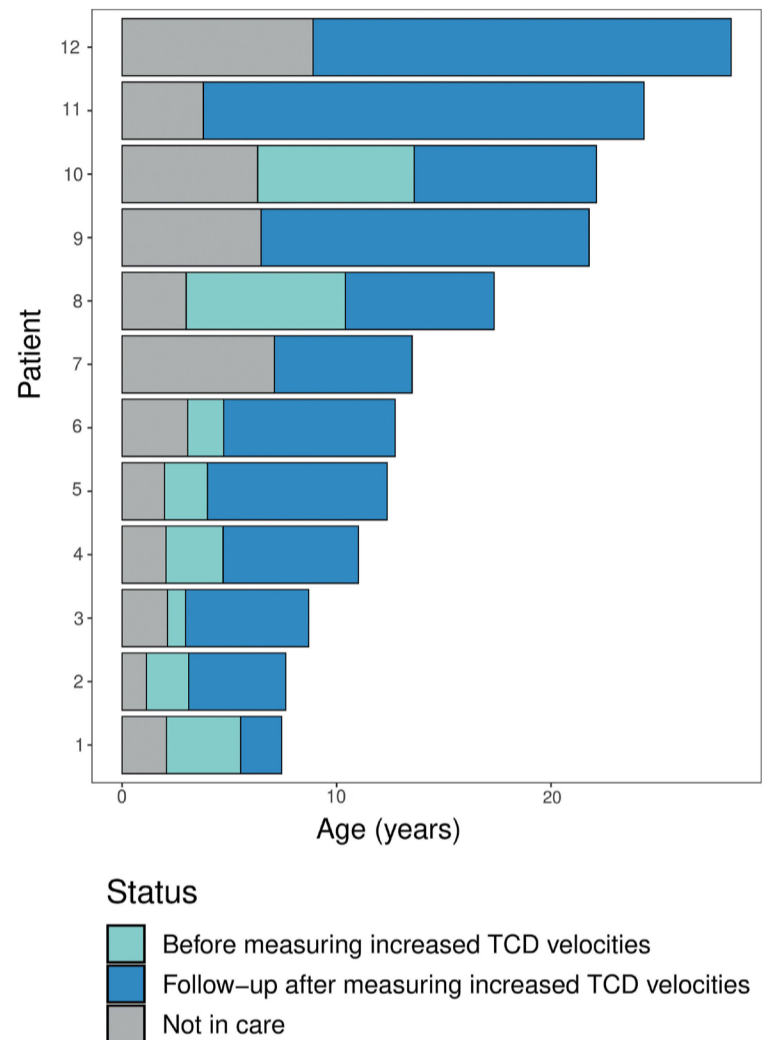


Figure 1. Swimmer plot visualizing the follow-up of the twelve patients with increased transcranial Doppler velocities, normal magnetic resonance angiography and no transfusion therapy. TCD: transcranial Doppler.

Table 1. Baseline characteristics of the study population.

Characteristics	Values
Total N of patients	209
Age in years at the start of follow-up, median (IQR)	4.4 (2.3-8.2)
Age in years at the end of follow-up, median (IQR)	17.0 (11.1-24.1)
Sex, N (%)	
Female	95 (45)
Male	114 (55)
Lost to follow-up, N (%)	7 (3)
Deceased, N (%)	4 (2)
Cumulative follow-up (patient-years)	2,321
Increased TCD velocities, N (%)	30 (14)
Hydroxyurea therapy, N (%)	136 (65)

IQR: interquartile range; TCD: transcranial Doppler.

follow-up of 60 patient years).¹ In line with our data, Seibert *et al.* reported the 8-year follow-up of nine patients (cumulative follow-up of 56 patient years), with abnormal TCD and normal MRA, who did not develop a CVA.⁹ Together these data suggest that MRA improves the identification of patients with an increased risk of developing a CVA. In the STOP study, the value of MRA was retrospectively evaluated in 53 patients randomized to standard therapy (no transfusion). Forty of these patients had a normal MRA or mild abnormalities while 13 had severe abnormalities on MRA. In contrast to our findings, five of the 40 patients with normal or mild abnormalities on MRA developed a CVA. However, three patients who developed a CVA had mild abnormalities at baseline MRA, indicating that these mild abnormalities should have been considered ‘abnormal’.¹⁰ Limitations of this retrospective analysis include the relatively small cohort of 12 children with abnormal TCD velocities and

normal MRA results, not treated with transfusion therapy. Furthermore, the use of hydroxyurea may have decreased the CVA risk in our non-transfused cohort given the effectiveness of hydroxyurea therapy in lowering TCD velocities and preventing the conversion from conditional to abnormal TCD results.¹¹⁻¹³ It is also important to acknowledge that the TCD/MRA protocol we applied in our hospital may be impossible to implement in low or middle-income countries without access to MRA. In settings where MRA is not available the original Adams protocol will need to be followed. In conclusion, this retrospective analysis of an alternative algorithm of screening pediatric SCD patients for CVA risk suggests that MRA improves the accurate identification of patients with an increased risk of developing a CVA and thereby reduces the proportion of patients requiring chronic transfusion therapy. However, whether withholding transfusion therapy in pediatric patients with an abnormal TCD

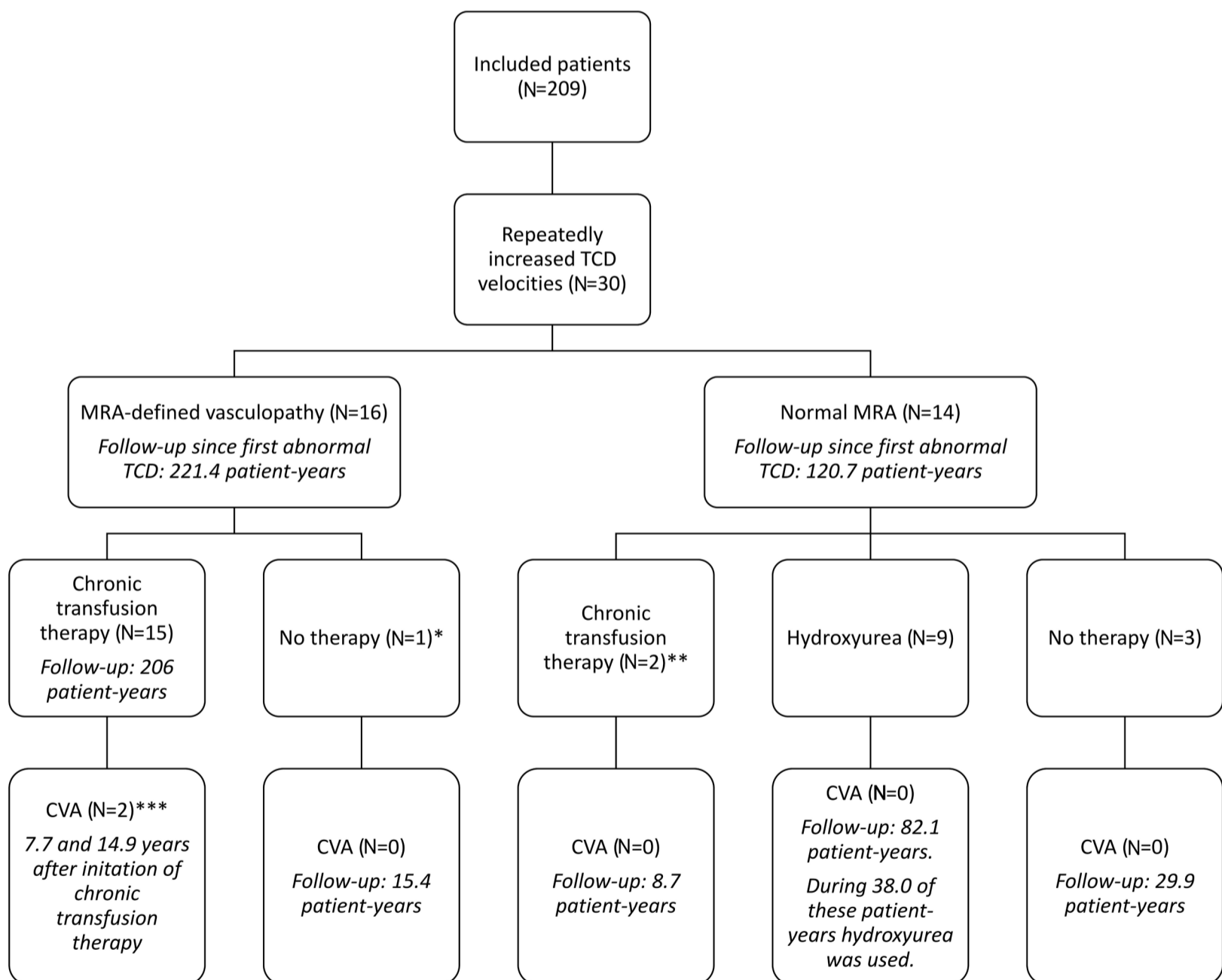


Figure 2. Flow chart transcranial Doppler/magnetic resonance angiography results, treatment and outcomes. *Patient repeatedly refused transfusion therapy. **Chronic transfusion therapy was started because of recurrent acute chest syndrome, 6.1 years after increased transcranial Doppler (TCD) velocities were measured for the first time (N=1) or because of repeatedly increased TCD velocities despite normal magnetic resonance angiography (MRA) results (N=1). ***Patient 1: first MRA showed severe cerebral vasculopathy, including multiple stenoses. The hemorrhagic cerebrovascular accident (CVA) occurred 14.9 years after the initiation of chronic transfusion therapy. Patient 2: CVA occurred 7.7 years after start of chronic transfusion therapy.

and a normal MRA is non-inferior compared to a protocol of transfusion therapy in all children with abnormal TCD velocities, can only be studied in a prospective randomized trial.

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Contributions

LL performed data curation, formal analysis, investigation, methodology, project administration, software, validation, visualization, writing-original draft. BB performed data curation, investigation, validation, writing-review and editing. KF performed data curation, investigation, methodology, validation, writing-review and editing. HH performed conceptualization, data curation, investigation, methodology, project administration, software, supervision, validation, writing-review and editing.

Data-sharing statement

Original data are available on request addressed to the corresponding author.