Scientific Research Publishing

Open Journal of Pediatrics, 2026, 16(6), 752-764
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

Factors Associated with Abnormal Transcranial Doppler and Stroke Risk in Children with Sickle Cell Disease Followed at the Center for Research and Control of Sickle Cell Disease (CRLD) in Mali

Kéné Sékou[1*], Diakité Abdoul Aziz[2], Assa Badiallo Touré[3], Ouologuem Mahamadou[1], Kanta Mariam[1], Koureichi Mahamoud Mahamadou[1], Berthe Diakalia[1], Fofana Yacouba[1], Tessougué Oumarou[1], Berthé Tidiane[1], Pérou Sidiki[1], Touré Boubacar Ali[1], Sarro Yéya Sadio[1], Guindo Aldiouma[1]

[1]Center for Research and Control of Sickle Cell Disease (CRLD), Bamako, Mali
[2]Gabriel Touré University Hospital Center, Bamako, Mali
[3]Central Direction of Army Health Services of Mali, Bamako, Mali
Email: *douroukene@gmail.com

How to cite this paper: Sékou, K., Aziz, D.A., Touré, A.B., Mahamadou, O., Mariam, K., Mahamadou, K.M., Diakalia, B., Yacouba, F., Oumarou, T., Tidiane, B., Sidiki, P., Ali, T.B., Sadio, S.Y. and Aldiouma, G. (2026) Factors Associated with Abnormal Transcranial Doppler and Stroke Risk in Children with Sickle Cell Disease Followed at the Center for Research and Control of Sickle Cell Disease (CRLD) in Mali. *Open Journal of Pediatrics*, **16**, 752-764.
https://doi.org/10.4236/ojped.2026.166073

Received: June 21, 2026
Accepted: October 31, 2026
Published: November 3, 2026

Copyright © 2026 by author(s) and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/

Open Access

Abstract

Background: Stroke is a severe complication of sickle cell disease (SCD) in children. Sickle cell cerebral vasculopathy is the underlying predisposing condition. Transcranial Doppler (TCD) is the gold standard for screening this vasculopathy. Chronic transfusion programs and, more recently, hydroxyurea, are the main preventive strategies for children with abnormal TCD. **Objective:** To determine factors associated with abnormal TCD, defined as time-averaged mean of the maximum velocity (TAMMV) ≥ 200 cm/s according to the Stroke Prevention Trial in Sickle Cell Anemia (STOP) criteria, in a population of children with SS and Sβ0-thalassemia followed for two years, and to describe the incidence of clinical stroke during follow-up. **Methods:** This was a prospective monocentric cohort study conducted from January 2023 to December 2024 at the Center for Research and Control of Sickle Cell Disease (CRLD) in Bamako, Mali. A total of 207 children with SCD (195 SS, 12 Sβ0-thalassemia), aged 2 to 15 years, in steady state, were included. Steady state was defined as absence of vaso-occlusive crisis (VOC), acute chest syndrome (ACS), acute infection or hospitalization within the previous 15 days and absence of blood transfusion within the previous 3 months. All children underwent TCD performed according to the STOP protocol. TCD results were categorized using STOP classification as normal (TAMMV < 170 cm/s), conditional (170 - 199 cm/s), ab-

normal (≥200 cm/s), or uninterpretable (absent temporal acoustic window). Children with abnormal TCD received alternative therapy: monthly transfusion program targeting HbS < 30% or hydroxyurea (20 - 35 mg/kg/day). TCD follow-up was performed every 3 months for conditional TCD and every 12 months for others. **Results**: Mean age was 8.3 ± 3.6 years; 52.7% were male. At inclusion, 204 TCDs were interpretable (98.5%): 152 normal (73.4%), 34 conditional (16.4%), and 18 abnormal (8.7%); 3 were uninterpretable (1.5%). In univariate analysis, factors associated with abnormal TCD were age < 8 years (OR 2.8, 95% CI 1.1 - 7.3, p = 0.02), baseline hemoglobin ≤ 7 g/dL (OR 3.1, 95% CI 1.2 - 8.1, p = 0.01), history of ACS (OR 2.9, 95% CI 1.1 - 7.8, p = 0.03) and absence of hydroxyurea (OR 4.2, 95% CI 1.0 - 18.5, p = 0.04). In multivariate analysis limited to 204 children (excluding 3 uninterpretable), only age < 8 years (adjusted OR 2.6, 95% CI 1.0 - 6.9, p = 0.04) and baseline Hb ≤ 7 g/dL (adjusted OR 2.9, 95% CI 1.1 - 7.7, p = 0.03) remained independently associated. At 2 years, 12/18 (66.7%) abnormal TCDs normalized (TAMMV < 170 cm/s), 4 (22.2%) remained abnormal, 2 (11.1%) were lost to follow-up. Among 34 conditional TCDs, 4 (11.7%) progressed to abnormal. Two clinical strokes occurred (0.96% overall incidence), both in non-adherent children with abnormal TCD. No stroke occurred in adherent children. **Conclusion:** This study demonstrates the feasibility of TCD screening in routine practice in Mali. Age < 8 years and severe anemia (Hb ≤ 7 g/dL) were independently associated with abnormal TCD. Normalization of abnormal TCD was frequent under treatment. These findings support systematic TCD screening in Malian children with SCD, particularly those with severe anemia, and suggest hydroxyurea as a credible alternative when chronic transfusion is not available. The low number of stroke events precludes conclusions on causal efficacy for stroke prevention.

Keywords

Sickle Cell Disease, Stroke, Transcranial Doppler, Child, Mali, Africa, Hydroxyurea, Anemia

1. Introduction

Sickle cell disease (SCD) is the most common monogenic disorder worldwide. According to the Global Burden of Disease (GBD) Study 2021, 515,000 births with SCD occurred globally in 2021, of which 405,000 occurred in sub-Saharan Africa, with an estimated 7.6 million people living with SCD worldwide, including 5.7 million in sub-Saharan Africa, representing a 67.4% increase since 2000 [1]. In Mali, the prevalence of the sickle cell trait (AS) is 5% - 16%, with an estimated 5000 - 6000 homozygous SS births per year [2].

Ischemic stroke remains the most severe complication in children with homozygous SS SCD, with a historical cumulative risk of 11% by age 20 years without screening [3]. Stroke occurs on a background of sickle cell cerebral vasculopathy, most often affecting the distal internal carotid arteries and proximal middle cere-

bral arteries of the circle of Willis [4].

Transcranial Doppler (TCD) identifies children at high risk of stroke by measuring the time-averaged mean of the maximum velocities (TAMMV) in these vessels [5]. According to the STOP criteria, TCD is classified as normal when TAMMV < 170 cm/s, conditional when 170 - 199 cm/s, and abnormal when ≥200 cm/s. Without preventive therapy, the risk of first stroke in children with abnormal TCD is approximately 10% per year, as demonstrated in the STOP trial; chronic blood transfusion reduces this risk by 92% [4].

Recommendations from the American Society of Hematology (ASH) 2020 guidelines [3] and Brazilian guidelines 2021 [6] recommend annual TCD screening from 2 to 16 years of age for children with SS and Sβ0-thalassemia genotypes, measuring TAMMV in the middle cerebral artery (MCA) and terminal internal carotid artery (ICA) [3] [6]. In our study, screening was performed from 2 to 15 completed years, in line with local practice. Despite these recommendations, access to TCD remains limited in sub-Saharan Africa [7].

In Mali, the CRLD in Bamako introduced TCD into the routine follow-up of children with SCD in 2008 [8]. A first descriptive study published in 2015 reported 18% abnormal or borderline TCD among 541 children aged 2 to 17 years, with low baseline hemoglobin identified as a predictive factor [9]. The present study aims to determine factors associated with abnormal TCD and to describe stroke incidence in a population of children with SS and Sβ0-thalassemia SCD aged 2 to 15 years followed at this center.

2. Materials and Methods

2.1. Study Design and Population

This was a prospective monocentric cohort study conducted at the CRLD in Bamako, Mali, from January 2023 to December 2024. It included a cross-sectional analysis at inclusion to identify factors associated with abnormal TCD, followed by longitudinal follow-up over 24 months of children with abnormal and conditional TCD.

All children with homozygous SS or Sβ0-thalassemia SCD, aged 2 to 15 completed years, in steady state, regularly followed at the CRLD and whose parents/guardians provided written informed consent, were included. Steady state was defined as absence of vaso-occlusive crisis (VOC), acute chest syndrome (ACS), acute infection or hospitalization within the previous 15 days and absence of blood transfusion within the previous 3 months. Steady state definition was independent of genotype and reflects clinical stability [10].

Non-inclusion criteria were: 1) documented history of clinical stroke confirmed by medical records or neuroimaging—excluded to focus on primary stroke prevention; 2) blood transfusion within 3 months prior to TCD, which can artificially lower velocities; 3) occurrence of VOC, ACS or acute infectious episode within 15 days prior to examination; 4) parental refusal. Patients with absent temporal acoustic windows making the examination uninterpretable were excluded from

the final regression analysis but described in the flow-chart. Exhaustive sampling was used: all eligible children presenting for follow-up consultation during the study period were offered TCD. In total, 207 children were included.

2.2. Clinical and Biological Data Collection

Each child underwent a standardized clinical consultation with collection of sociodemographic data (age, sex), SCD genotype (SS, Sβ0-thalassemia), history of VOC ≥3/year, ACS, splenic sequestration, hospitalization, and current disease-modifying therapy. Physical examination was performed (Table 1).

Table 1. Sociodemographic and clinical characteristics of 207 children with sickle cell disease included.

Characteristics	Number (n = 207)	Mean ± SD/Percentage (%)
Age (years)	207	8.3 ± 3.6
2 - 5	52	25.1
6 - 10	98	47.3
11 - 15	57	27.6
Sex		
Male	109	52.7
Female	98	47.3
Phenotypes		
SS	195	94.2
Sβ0-thalassemia	12	5.8
Baseline hemoglobin (g/dL)	207	7.8 ± 1.2
History		
≥3 VOC/year	61	29.5
Acute chest syndrome	47	22.7
Splenic sequestration	23	11.1
Hospitalization for VOC > 3/year	65	31.4
Background treatment at inclusion		
Hydroxyurea	59	28.5
Chronic transfusion program	0	0

A baseline biological assessment including complete blood count with reticulocyte count, hemoglobin electrophoresis and iron status was performed in steady state, on the same day or within 7 days preceding the index TCD (median 0 days, interquartile range [IQR] 0 - 2 days), at least 4 weeks after any acute event. Baseline hemoglobin was defined as hemoglobin level measured in steady state.

2.3. Ethical Considerations

The study received approval from the Scientific Committee of the CRLD (Institu-

tional Review Board of the CRLD, approval number: 2022/18/CE-CRLD) and was conducted in accordance with the Declaration of Helsinki. Written informed consent from parents/guardians and assent from children aged > 7 years were obtained. Data confidentiality was respected through anonymization. Therapeutic management was independent of participation in the study.

2.4. Transcranial Doppler Procedure

TCD was performed according to the STOP protocol, by a single trained and certified operator, using a 2 MHz pulsed Doppler device (Sonosite M-Turbo®). The examination was bilateral, exploring the middle cerebral arteries (MCA), anterior cerebral arteries (ACA) and posterior cerebral arteries (PCA) as well as the terminal internal carotid arteries (ICA) and carotid siphons. The angle-corrected TAMMV was retained for each vessel (Table 2 and Table 3).

Table 2. Initial transcranial doppler results in 207 children.

TCD Classification	Number (n)	Percentage (%)	95% CI
Normal: <170 cm/s	152	73.4	67.0 - 79.2
Conditional: 170 - 199 cm/s	34	16.4	11.7 - 22.1
Pathological (abnormal): ≥200 cm/s	18	8.7	5.2 - 13.4
Uninterpretable	3	1.5	0.3 - 4.2
Total	207	100	

Table 3. Factors associated with abnormal transcranial Doppler in univariate and multivariate analysis (n = 204, excluding 3 uninterpretable).

Variables	Abnormal TCD n = 18 (%)	Non-abnormal TCD n = 186 (%)	Univariate p	Adjusted OR [95% CI]	Multivariate p
Age < 8 years	14 (77.8)	89 (47.8)	0.02	2.6 [1.0 - 6.9]	0.04
Male sex	11 (61.1)	98 (52.7)	0.45	-	-
Hb ≤ 7 g/dL	9 (50.0)	41 (22.0)	0.01	2.9 [1.1 - 7.7]	0.03
≥3 VOC/year	8 (44.4)	53 (28.5)	0.14	1.8 [0.6 - 5.1]	0.28
History of ACS	6 (33.3)	22 (11.8)	0.03	2.9 [0.9 - 9.3]	0.07
Hydroxyurea at inclusion	1 (5.6)	58 (31.2)	0.04	0.2 [0.03 - 1.8]	0.16

Stroke risk classification was based on the highest TAMMV measured in the MCA or ICA. TCD was considered normal if TAMMV < 170 cm/s, conditional if 170 cm/s ≤ TAMMV < 200 cm/s, abnormal if TAMMV ≥ 200 cm/s, and uninterpretable if no exploitable Doppler signal was obtained despite adequate windows.

2.5. Management and Follow-Up

Children with abnormal TCD were placed on alternative (non-combined) disease-

modifying therapy: monthly transfusion program targeting HbS < 30% as first-line if phenotyped secure blood was available and parental acceptance was obtained; otherwise, optimized hydroxyurea at 20 - 35 mg/kg/day was proposed as an alternative, in accordance with recent African trials SPIN, SPRING and SPHERE and ASH recommendations for resource-limited settings. Criteria for attribution were documented prospectively.

Adherence in the abnormal TCD group was defined a priori as: for transfusion, ≥10/12 sessions per year with HbS < 30% for at least 6 months; for hydroxyurea, intake ≥ 5 days/7 as declared, confirmed by pharmacy dispensing and increase in mean corpuscular volume (MCV) and fetal hemoglobin (HbF). Non-adherence was defined as <50% of transfusion sessions or HU interruption > 2 months.

Conditional TCDs were controlled at 3 months; high conditional (185 - 199 cm/s) was controlled at 1 month then every 3 months. All patients had TCD follow-up at 12 months.

2.6. Statistical Analysis

Data were entered into REDCap and analyzed with SPSS version 25.0. Quantitative variables were expressed as mean ± standard deviation (SD) or median with IQR. Qualitative variables were expressed as numbers and percentages. Comparison of means used Student's t-test or Mann-Whitney test. Comparison of proportions used Chi^2 test or Fisher's exact test. Multivariate logistic regression was performed to identify factors independently associated with abnormal TCD. The 3 uninterpretable TCDs were excluded from regression, yielding analysis on 204 children (18 abnormal vs 186 non-abnormal: 152 normal + 34 conditional). Given 18 events, the final model was limited to 2 variables according to the rule of 1 variable per 9 events. Variables with $p < 0.20$ in univariate analysis (age < 8 years, Hb ≤ 7 g/dL, history of ACS, ≥3 VOC/year, absence of HU) were entered, with backward stepwise selection. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) are presented. Significance threshold was set at $p < 0.05$.

3. Results

3.1. Participant Flow

During the study period, 312 children were screened for TCD in the CRLD consultation. Of these, 45 were excluded: 12 with documented history of clinical stroke, 15 with transfusion within 3 months, 10 with VOC/ACS/acute infection <15 days, 5 with parental refusal, and 3 with absent temporal acoustic windows rendering examination uninterpretable. An additional 60 eligible children were not included due to incomplete data or loss before consent. Thus, 207 children were included. Of 207 TCDs, 204 were interpretable (98.5%). A flow-chart is presented as **Figure 1**.

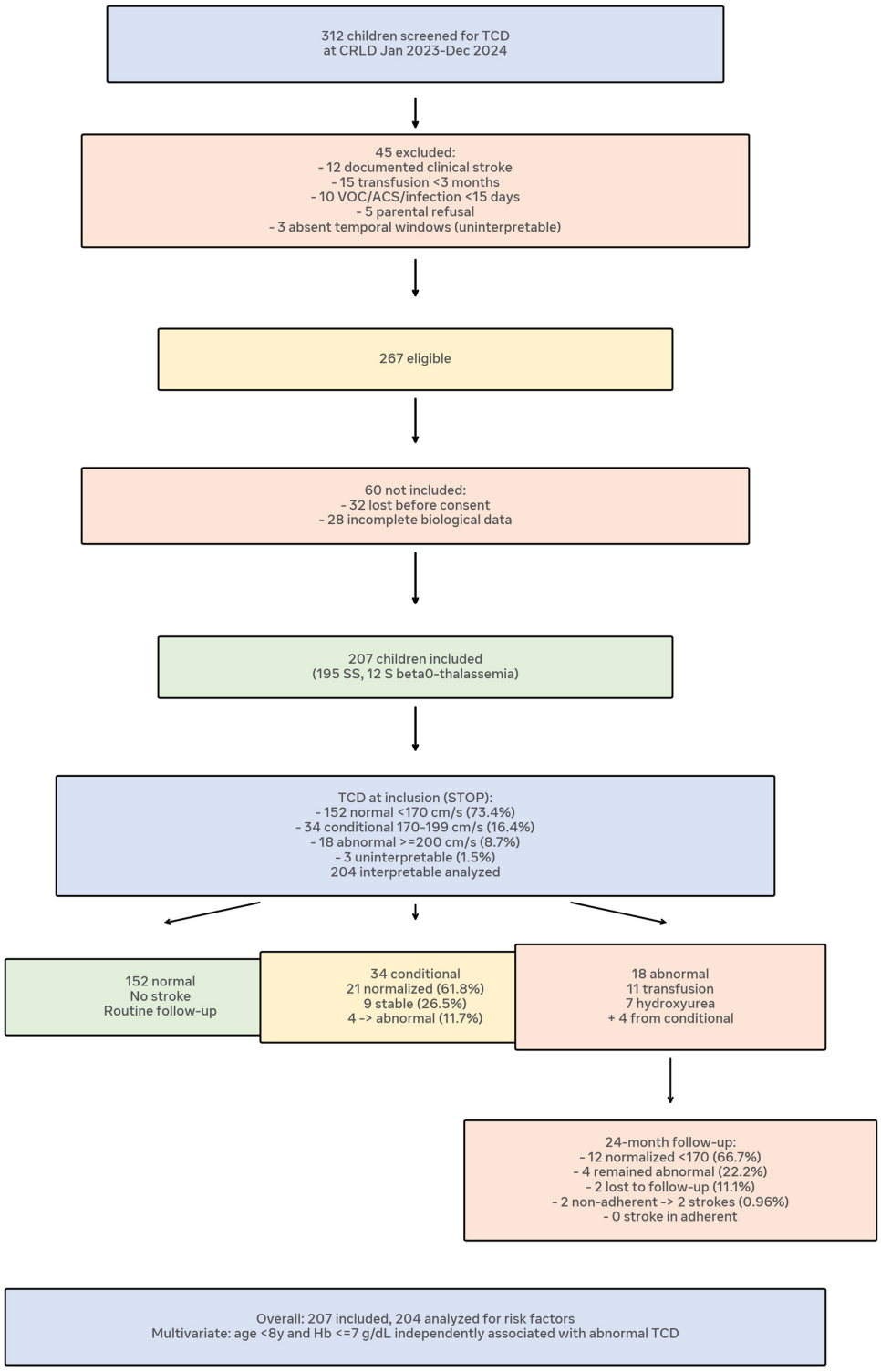


Figure 1. Participant flow-chart. CRLD = Center for Research and Control of Sickle Cell Disease; VOC = Vaso-occlusive crisis; ACS = Acute chest syndrome; TCD = Transcranial Doppler; STOP = Stroke Prevention Trial in Sickle Cell Anemia.

Figure 1: Flow-chart of study participants

Flow-chart of screening, exclusion, inclusion and 24-month follow-up of

children with sickle cell disease undergoing transcranial Doppler (TCD) at CRLD, Mali, January 2023 - December 2024. TCD classification according to STOP criteria: normal < 170 cm/s, conditional 170 - 199 cm/s, abnormal ≥ 200 cm/s.

3.2. Baseline Characteristics

Mean age was 8.3 ± 3.6 years, range 2 - 15 years. Sex ratio was 1.1 (109 males, 52.7%, 98 females, 47.3%). SS phenotype represented 94.2% (n = 195) and Sβ0-thalassemia 5.8% (n = 12). Mean baseline hemoglobin (steady state, pre-TCD) was 7.8 ± 1.2 g/dL. Notable history included ACS in 22.7% (n = 47), splenic sequestration in 11.1% (n = 23), and hospitalization for VOC > 3 times/year in 31.4% (n = 65). At inclusion, 28.5% (n = 59) were on hydroxyurea. Mean TAMMV in the MCA was 148 ± 32 cm/s.

3.3. TCD Results at Inclusion

Distribution according to STOP classification (n = 207): normal TCD 152 (73.4%, 95% CI 67.0 - 79.2), conditional 34 (16.4%, 11.7 - 22.1), abnormal 18 (8.7%, 5.2 - 13.4), uninterpretable 3 (1.5%, 0.3 - 4.2). In the 18 patients with abnormal TCD, mean TAMMV was 221 ± 18 cm/s.

3.4. Factors Associated with Abnormal TCD

In univariate analysis (n = 204, excluding uninterpretable), factors significantly associated with abnormal TCD were age < 8 years (OR 2.8, 95% CI 1.1 - 7.3, p = 0.02), baseline Hb ≤ 7 g/dL (OR 3.1, 95% CI 1.2 - 8.1, p = 0.01), history of ACS (OR 2.9, 95% CI 1.1 - 7.8, p = 0.03), and absence of hydroxyurea treatment (OR 4.2, 95% CI 1.0 - 18.5, p = 0.04). In multivariate analysis, only age < 8 years (aOR 2.6, 95% CI 1.0 - 6.9, p = 0.04) and baseline Hb ≤ 7 g/dL (aOR 2.9, 95% CI 1.1 - 7.7, p = 0.03) remained independently associated. History of ACS showed a trend (aOR 2.9, 95% CI 0.9 - 9.3, p = 0.07).

3.5. Follow-Up of Abnormal and Conditional TCD

All 18 patients with abnormal TCD were treated: 11 with chronic transfusion program and 7 with hydroxyurea. After 24 months, 12 patients (66.7%) normalized their TCD (TAMMV < 170 cm/s), 4 (22.2%) remained abnormal, and 2 (11.1%) were lost to follow-up. Two patients met criteria for non-adherence. No clinical stroke occurred in the 13 adherent patients with initially abnormal TCD.

Among 34 conditional TCDs, 21 (61.8%) normalized, 9 (26.5%) remained stable, and 4 (11.7%) progressed to abnormal TCD requiring therapy.

3.6. Stroke Incidence

Overall incidence of clinical stroke over 2 years was 0.96% (2 cases/207). Both strokes occurred in non-adherent children with abnormal TCD. No stroke occurred in children with normal or stabilized conditional TCD.

4. Discussion

4.1. Main Findings

Our study found 8.7% abnormal TCD in children with SCD without prior stroke. This rate is comparable to 9.4% reported by Lagunju *et al.* in Ibadan, Nigeria over 5 years [11], but lower than 12.2% in the French newborn cohort of Bernaudin *et al.* [12] followed into adulthood. This difference is explained by our exclusion of history of clinical stroke (primary prevention cohort) and younger population (2 - 15 years, mean 8.3 years) compared to Bernaudin *et al.* who included longer follow-up. The reported prevalence of high stroke risk (abnormal TCD) in sub-Saharan Africa varies from 2.9% to 16.9% depending on study design, age range and inclusion criteria, as summarized in the systematic review by Kassim *et al.* (Blood Rev 2024) which included 12 studies from 2000 - 2023 (n = 4521 children) [13] and the multicenter study by Noubiap *et al.* 2022 (n = 1145 across 6 Nigerian centers) [14]; our result falls within this range and is consistent with regional data.

The rate of 16.4% conditional TCD is consistent with 15% - 20% in the literature [6]. The progression of 11.7% of conditional TCD to abnormal confirms the need for close monitoring every 3 months as recommended by ASH 2020 guidelines and Brazilian guidelines 2021: control at 1 month if high conditional (185 - 199 cm/s), then every 3 months [3] [6].

4.2. Risk Factors

The association between severe anemia (Hb ≤ 7 g/dL) and abnormal TCD corroborates our previous work in Mali [9] and recent studies showing that anemia increases compensatory cerebral blood flow velocity to maintain cerebral oxygen delivery [15]. The inverse relationship between hemoglobin and cerebral blood flow velocity is well established: lower Hb reduces arterial oxygen content, leading to compensatory cerebral vasodilation and increased velocities.

Young age < 8 years as a risk factor is classic, with vasculopathy beginning in the first years of life, justifying screening from 2 years of age [3] [12]. The Blood Reviews 2024 meta-analysis confirms that early screening significantly reduces mortality and neurocognitive sequelae [13].

4.3. Therapeutic Implications

Our work demonstrates feasibility and effectiveness of TCD screening and management in routine practice in a resource-limited African setting: 66.7% normalization of abnormal TCD and stroke incidence of 0.96% over 2 years. These results are close to STOP trial where stroke risk decreased from 10% per year without treatment to ~1% per year under chronic transfusion [4], and to the meta-analysis by Kassim *et al.* showing stroke rate of 1.0 per 100 patient-years under hydroxyurea or transfusion vs 10.7 without treatment [13].

Hydroxyurea was used in 7 patients due to lack of sustainable access to secure phenotyped blood. Recent African trials are changing the paradigm: SPIN trial (Nigeria, 2020) showed that moderate fixed dose 20 mg/kg/day lowers TAMMV

to <200 cm/s within 3 months in majority of children with abnormal TCD [16]. SPRING trial, phase 3 multicenter randomized double-blind trial (2022), confirmed efficacy of moderate-dose hydroxyurea in primary stroke prevention in resource-limited settings [17]. SPHERE trial in Tanzania (2024) with dose escalation showed sustained reduction in velocities [18]. REACH trial (4 African countries, 3-year follow-up 2022) confirms tolerability and mean decrease of 20 cm/s in TCD velocities under hydroxyurea [19]. Long-term TWiTCH trial (2020) shows that after 4 years of transfusion without severe vasculopathy on magnetic resonance angiography (MRA), hydroxyurea can replace transfusion to maintain velocities [20]. Our finding of 5/7 patients on hydroxyurea normalizing TCD is consistent with these data and encouraging for resource-limited countries [16]-[19].

The 2 strokes occurring in non-adherent patients highlight importance of therapeutic education and adherence support, a major barrier identified in DISPLACE study in USA and Africa [7].

Our study is monocentric, limiting generalizability. Absence of magnetic resonance imaging (MRI) for silent infarcts and MRA for vasculopathy grading remains a limitation, as highlighted by WHO AFRO 2024 which advocates for introduction of TCD and hydroxyurea into minimum package of health services [7]. Small number of abnormal TCD events (n = 18) limits power of multivariate model, as acknowledged, and precludes definitive conclusions on stroke prevention efficacy. Loss to follow-up of 2 patients with abnormal TCD may have underestimated adverse outcomes. Finally, adherence assessment was partly based on declaration and pharmacy records, without electronic monitoring.

5. Conclusion

In accordance with ASH 2020 recommendations and recent African data from SPIN, SPRING and SPHERE trials, integration of TCD into the minimum follow-up of children with sickle cell disease in Mali should become a public health priority, with hydroxyurea as a credible alternative when access to chronic transfusion programs is limited. Age < 8 years and baseline hemoglobin ≤ 7 g/dL should alert clinicians to high risk of abnormal TCD, warranting closer surveillance and early intervention. Further multicenter studies with MRI/MRA and longer follow-up are needed.

Ethics Approval

Approved by Scientific Committee of CRLD (2022/18/CE-CRLD).

Consent to Participate

Written informed consent from parents/guardians and assent from children > 7 years.

Funding

The Pierre Fabre Foundation funded this study. The study sponsor had no role in

the collection or analysis of the data. The first author and the corresponding author had full access to all the data, with the latter bearing final responsibility for the decision to submit the findings for publication.

Acknowledgements

Staff of CRLD, children and families.

Author Contributions

All authors contributed to study design, data collection, analysis and manuscript writing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Thomson, A.M., McHugh, T.A., Oron, A.P., *et al.* (2023) Global, Regional, and National Prevalence and Mortality Burden of Sickle Cell Disease, 2000-2021: A Systematic Analysis from the Global Burden of Disease Study 2021. *The Lancet Haematology*, **10**, e585-e599.

[2] Piel, F.B., Steinberg, M.H. and Rees, D.C. (2017) Sickle Cell Disease. *New England Journal of Medicine*, **376**, 1561-1573. https://doi.org/10.1056/nejmra1510865

[3] Adams, R.J., McKie, V.C., Hsu, L., Files, B., Vichinsky, E., Pegelow, C., *et al.* (1998) Prevention of a First Stroke by Transfusions in Children with Sickle Cell Anemia and Abnormal Results on Transcranial Doppler Ultrasonography. *New England Journal of Medicine*, **339**, 5-11. https://doi.org/10.1056/nejm199807023390102

[4] DeBaun, M.R., Jordan, L.C., King, A.A., Schatz, J., Vichinsky, E., Fox, C.K., *et al.* (2020) American Society of Hematology 2020 Guidelines for Sickle Cell Disease: Prevention, Diagnosis, and Treatment of Cerebrovascular Disease in Children and Adults. *Blood Advances*, **4**, 1554-1588. https://doi.org/10.1182/bloodadvances.2019001142

[5] Oringanje, C., Nemecek, E. and Oniyangi, O. (2020) Hematopoietic Stem Cell Transplantation for People with Sickle Cell Disease. *Cochrane Database of Systematic Reviews*, **2020**, Article No. CD007001. https://doi.org/10.1002/14651858.cd007001.pub5

[6] Lobo, C.L.C., Nascimento, E.M., Jesus, L.J.C., *et al.* (2021) Guidelines on Sickle Cell Disease: Primary Stroke Prevention in Children and Adolescents. *Hematology, Transfusion and Cell Therapy*, **44**, 85-94.

[7] WHO Regional Office for Africa (2024) Sickle Cell Disease Control in African Region: Progress Report 2020-2024. WHO AFRO.

[8] Guindo, A., Sarro, Y.S., Touré, B.A., *et al.* (2021) Implementation of Transcranial Doppler at the CRLD in Bamako: Preliminary Experience and Perspectives. *Mali Medical*, **36**, 12-18.

[9] Dorie, A., Guindo, A., Saro, Y.S., Touré, B.A., Fané, B., Dembelé, A.K., *et al.* (2015) Dépistage de la vasculopathie cérébrale drépanocytaire par doppler transcrânien au Mali. *Archives de Pédiatrie*, **22**, 260-266. https://doi.org/10.1016/j.arcped.2014.12.005

[10] Estcourt, L.J., Kohli, R., Hopewell, S., Trivella, M. and Wang, W.C. (2020) Blood

Transfusion for Preventing Primary and Secondary Stroke in People with Sickle Cell Disease. *Cochrane Database of Systematic Reviews*, No. 7, CD003146. https://doi.org/10.1002/14651858.cd003146.pub4

[11] Lagunju, I.A., Brown, B.J. and Sodeinde, O. (2021) Transcranial Doppler Ultrasonography in Children with Sickle Cell Anemia: 5-Year Experience in Ibadan, Nigeria. *Annals of African Medicine*, **20**, 123-128.

[12] Bernaudin, F., Verlhac, S., Arnaud, C., Kamdem, A., Chevret, S., Hau, I., *et al.* (2011) Impact of Early Transcranial Doppler Screening and Intensive Therapy on Cerebral Vasculopathy Outcome in a Newborn Sickle Cell Anemia Cohort. *Blood*, **117**, 1130-1140. https://doi.org/10.1182/blood-2010-06-293514

[13] Guy, D., Bagnall, R., Morgan, R.L., Babatunde, I., Nevière, A., Friedrich, G., *et al.* (2025) Impact of Transcranial Doppler Screening on Stroke Prevention in Children and Adolescents with Sickle Cell Disease: A Systematic Review and Meta-Analysis. *Blood Reviews*, **69**, Article ID: 101253. https://doi.org/10.1016/j.blre.2024.101253

[14] Noubiap, J.J., *et al.* (2022) Stroke Prevalence amongst Sickle Cell Disease Patients in Nigeria: A Multi-Centre Study. *African Journal of Medical and Health Sciences*, **21**, 45-51.

[15] Peine, B.R., Callaghan, M.U., Callaghan, J.H. and Glaros, A.K. (2022) Prophylactic Hydroxyurea Treatment Is Associated with Improved Cerebral Hemodynamics as a Surrogate Marker of Stroke Risk in Sickle Cell Disease: A Retrospective Comparative Analysis. *Journal of Clinical Medicine*, **11**, 3491. https://doi.org/10.3390/jcm11123491

[16] Galadanci, N.A., Abdullahi, S.U., Abubakar, S.A., *et al.* (2020) Moderate Fixed-Dose Hydroxyurea for Primary Prevention of Strokes in Nigerian Children with Sickle Cell Disease: Final Results of the SPIN Trial. *American Journal of Hematology*, **95**, E247-E250.

[17] Abdullahi, S.U., Jibir, B.W., Bello-Manga, H., Gambo, S., Inuwa, H., Tijjani, A.G., *et al.* (2022) Hydroxyurea for Primary Stroke Prevention in Children with Sickle Cell Anaemia in Nigeria (SPRING): A Double-Blind, Multicentre, Randomised, Phase 3 Trial. *The Lancet Haematology*, **9**, e26-e37. https://doi.org/10.1016/s2352-3026(21)00368-9

[18] Ambrose, E.E., Latham, T.S., Songoro, P., Charles, M., Lane, A.C., Stuber, S.E., *et al.* (2023) Hydroxyurea with Dose Escalation for Primary Stroke Risk Reduction in Children with Sickle Cell Anaemia in Tanzania (SPHERE): An Open-Label, Phase 2 Trial. *The Lancet Haematology*, **10**, e261-e271. https://doi.org/10.1016/s2352-3026(22)00405-7

[19] Tshilolo, L., Tomlinson, G., Williams, T.N., Santos, B., Olupot-Olupot, P., Lane, A., *et al.* (2019) Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. *New England Journal of Medicine*, **380**, 121-131. https://doi.org/10.1056/nejmoa1813598

[20] DeBaun, M.R., *et al.* (2020) TWiTCH Trial Long-Term: Hydroxyurea Non-Inferior to Transfusion after 4 Years for Maintaining TCD Velocities. *Blood Advances*, **4**, 5084-5089.

List of Abbreviations

ACS: Acute chest syndrome; aOR: Adjusted odds ratio; ASH: American Society of Hematology; **CI:** Confidence interval; **CRLD:** Center for Research and Control of Sickle Cell Disease; **Hb**: Hemoglobin; **HU**: Hydroxyurea; **ICA**: Internal carotid artery; **MCA**: Middle cerebral artery; **OR**: Odds ratio; **SCD**: Sickle cell disease; **STOP**: Stroke Prevention Trial in Sickle Cell Anemia; **TAMMV**: Time-averaged mean of the maximum velocity; **TCD:** Transcranial Doppler; **VOC**: Vaso-occlusive crisis.