Early detection and management of extracranial arteriopathy reduces the incidence of silent cerebral infarcts in sickle cell anemia: a long-term prospective cohort study

Françoise Bernaudin,[1,2] Cécile Arnaud,[1] Annie Kamdem,[1] Jenny Youn,[1] Manuela Vasile,[3] Isabelle Hau,[4] Fouad Madhi,[4] Aline Malterre,[4] Céline Delestrain,[4] Ralph Epaud,[4] Camille Jung[2] and Suzanne Verlhac[3,5]

[1]Referral Center for Sickle Cell Disease, Department of Pediatrics, Centre Hospitalier Intercommunal, Créteil (CHIC Hospital), Creteil, University Paris XII, Paris; [2]Clinical Research Department, CHIC Hospital, Universite Paris XII, Paris; [3]Medical Imaging Department, Referral Center for Sickle Cell Disease, CHIC Hospital, Créteil; [4]Department of Pediatrics, CHIC Hospital Créteil, Universite Paris XII, Paris and [5]Medical Imaging Department, Hôpital Robert Debré, Paris, France

Correspondence: F. Bernaudin
francoise.bernaudin@chicreteil.fr

Received: March 03, 2025.
Accepted: June 11, 2025.
Early view: June 26, 2025.

https://doi.org/10.3324/haematol.2025.287720

Abstract

Previous reports about the Creteil newborn cohort (1988/April 2007) showed that the risk of silent cerebral infarcts (SCI) remained high (37.1%) at the age of 14 years in children with sickle cell anemia (SCA) and intracranial time-averaged mean maximum velocity (TAMMV) ≥200 cm/second (s), despite chronic transfusion. Systematic assessment of extracranial internal carotid artery (eICA) since June 2011 revealed that SCI risk is associated with chronic or acute anemia and eICA stenosis. Based on these results, SCA children with eICA TAMMV ≥200 cm/s or eICA stenosis were placed on chronic transfusion and considered for allogeneic stem cell transplantation (alloSCT). SCA children with 160-199 cm/s eICA TAMMV were maintained on hydroxyurea (HU). We hypothesized that detection/management of eICA arteriopathy and wider use of HU could reduce SCI incidence. Comparison between the new cohort (May 2007/December 2014; eICA-assessed before 4 years of age) with wider but not systematic use of HU and the earlier cohort (1988/April 2007; never eICA-assessed until the 2008 update) revealed a significant reduction in SCI risk (Log Rank: *P*=0.009) associated with eICA assessment but not with wider use of HU. eICA TAMMV ≥160 cm/s, even with no eICA stenosis, was a risk factor for SCI, suggesting that all SCA children with eICA TAMMV ≥160 cm/s should be placed on chronic transfusion. HU initiation at an early age was associated with lower intracranial arteriopathy incidence, but not with lower eICA arteriopathy or SCI incidence. In the overall cohort (1988-2014), including 332 SCA children, all assessed/managed for eICA arteriopathy after 2011, the cumulative SCI incidence by the age of 14 years was 25.0% (95%CI: 19.0-31.0%). SCI risk was associated with being older at first neck magnetic resonance angiography and having high mean corpuscular volume on HU. While the impact of HU on SCI incidence remains unclear, making controlled trials necessary, eICA arteriopathy management by intensive therapy is effective at improving SCI prevention.

Silent cerebral infarcts (SCI), defined by the presence of ischemic lesions on magnetic resonance imaging (MRI) and absence of clinical neurological event, are associated with cognitive deficiency in children with sickle cell anemia (SCA).[1-3] The studies conducted before the era of transcranial Doppler (TCD) screening showed that SCI may be progressive,[4] a risk factor for stroke,[5] and may be associated with low pain event rate, history of seizure, leukocyte count >11.8x10^9/L, and SEN β-haplotype.[6] In patients screened by TCD and magnetic resonance angiography (MRA) for intracranial arteriopathy, SCI were associated with low baseline hemoglobin[7-10] and intracranial stenosis.[8,11]

In the initial Créteil SCA newborn cohort (1988-2007), who underwent early TCD screening with data updated in 2008,[7] patients with intracranial time-averaged mean maximum velocities (TAMMV) ≥200 cm/second [s]) or stenosis on MRA were placed under chronic transfusion. The stroke risk at 18 years of age was only 1.9%[7] compared to 11% reported in the literature before TCD screening.[12] In contrast, a cumulative SCI incidence of 37.1% (95% confidence interval [CI]: 26.3-50.7) with no plateau was still observed by the age of 14.[7] This suggested that detection/management of

intracranial arteriopathy was not sufficient to prevent SCI. Despite the predominant involvement of the circle of Willis in SCA cerebral arteriopathy, the extracranial portion of the internal carotid artery (eICA) can be the site of stenosis and/or occlusion responsible for strokes and SCI.[13-17] Patients from two independent cohorts (Debré-Paris, Créteil) were assessed once for eICA arteriopathy, using eICA color Doppler sonography via submandibular approach[15] and neck MRA.[13-18] Results showed that eICA TAMMV ≥160 cm/s were most often isolated cases, with a prevalence of 9.2%, and highly predictive of eICA stenosis.[18,19] Moreover, in the Créteil cohort, updated in December 2013, isolated eICA stenosis with chronic and acute anemia were shown to be significant independent risk factors for SCI.[19]

Based on these results, eICA color Doppler and neck MRA were systematically added to TCD screening and MRI/MRA starting June 2011. Patients with eICA TAMMV ≥200 cm/s or eICA stenosis received chronic transfusion, with a switch to hydroxyurea (HU) for those with normalized velocities and no stenosis, as for intracranial arteriopathy. Patients with eICA TAMMV 160-199 cm/s without stenosis received HU if not already prescribed. Moreover, a wider use of HU was recommended to reduce baseline anemia and acute anemia rates.

We present here the incidence of SCI since the systematic detection/management of eICA arteriopathy in the Créteil newborn cohort. The objective of the present cohort study was to demonstrate the hypotheses that: 1) detection/management of eICA arteriopathy reduces the cumulative incidence of SCI; 2) earlier and wider use of HU impacts the cumulative incidence of abnormal velocities and SCI.

Methods

Doppler and neuro-imaging assessment

Since May 1992, our center has performed color TCD imaging during the 2nd year of life.[18] The highest TAMMV recorded in middle cerebral (MCA), internal carotid (ICA), and anterior cerebral (ACA) arteries after tracking the entire course of the vessel every 2 mm in depth without angle correction were used to classify TCD[20] as either normal (<170 cm/s), conditional (170-199 cm/s), abnormal (≥ 200 cm/s), or inadequate (unavailable temporal windows). Any patient with conditional TCD was evaluated every three months. Cerebral MRI/MRA with a 1.5T magnet with FLAIR, T1, T2, SWI, diffusion-weighted sequences, circle of Willis 3D time-of-flight (TOF) angiography was performed without sedation every two years in children over 5 years of age, or earlier under sedation if patients were chronically transfused for abnormal TCD or allogeneic stem cell transplantation (alloSCT) was programmed.

Since June 2011,[19] eICA assessment via submandibular windows using the same low frequency probe as for color TCD, and neck 3D-TOF angiography (neck MRA) were added to the follow-up.[21] Arteries were assessed for deformation and stenosis as recently reported.[22] All imaging data were reviewed by the same expert (SV).

Newborn sickle cell anemia cohort

All children with SCA regularly followed up at the referral SCA-Center of the Centre Hospitalier Intercommunal de Créteil (CHIC) were prospectively included in our database, created in 1992 (CNIL, N 2069568) and constantly updated by the Center's physicians. Data include baseline characteristics and clinical, biological, and imaging results, events, hospitalizations, annual check-ups, transfusion and transplantation dates (*Online Supplementary Figure S1*). Parental written informed consent was obtained in accordance with the Declaration of Helsinki. Use of the database was approved for this cohort study by the Créteil Institutional Review Board.

Genetic markers (sex, G6PD activity, α genes, β haplotypes) and averaged baseline biological parameters during the 2nd year of life were obtained away from transfusion or crisis and before any disease-modifying therapy. Thereafter, patients are clinically evaluated every three months and have a complete check-up every year. Start and end dates of treatment and biological parameter data are recorded.

Indications for disease-modifying and curative therapy

In 1992, the Center started prescribing HU to patients with frequent vaso-occlusive crises (VOC) and/or acute chest syndrome (ACS) who were over three years old.[7] Since 1998, patients with abnormal TCD history on chronic transfusion but normalized velocities and no stenosis were switched to HU[11] with trimestral TCD reassessment and transfusion reinitiation as soon as abnormal TCD was detected.[23] Moreover, because of the proven negative effect of anemia on cognitive performance,[2] since 2000, HU was also given to patients with normal TCD but baseline hemoglobin <7 g/dL. Thereafter, HU was also recommended to children with crises during the 2nd year of life after their first complete check-up with TCD. Of note, in this cohort born before 2015, asymptomatic children were not systematically treated with HU.

Chronic transfusion was recommended for children experiencing at least 2 acute splenic sequestrations until the recommended age for splenectomy, for those with intracranial (middle, anterior or internal carotid arteries) or eICA TAMMV ≥200 cm/s or stenosis on cerebral or neck MRA, and for those still experiencing frequent VOC/ACS on HU. Allogeneic stem cell transplantation was recommended for patients with frequent VOC/ACS despite HU or to those with cerebral vasculopathy (presence of intracranial or eICA stenotic arteriopathy or TAMMV ≥200 cm/s or SCI) if they had a matched-sibling donor (MSD). Related haplo-identical alloSCT was recommended for those with severe arteriopathy and no MSD.

Statistical analysis

Participant baseline characteristics were summarized using percentages, mean (standard deviation, SD) or median, with the 25th and 75th percentiles (Q1-Q3). 95%CI around point estimates were computed. Exact Fisher tests were used to compare proportions and Mann-Whitney tests to compare continuous distributions. Birth date defined entry into the study. Last MRI defined the end of MRI follow-up. SCI incidence represents the number of patients having SCI per 100 patient-years (PY) of MRI follow-up. For SCI Kaplan-Maier (KM) estimates, participants were censored on the date of SCI or at the last MRI/MRA without SCI. Failure time data curves were compared across groups by the Log Rank test.

Cox regression analysis with estimated hazards ratio (HR) and 95%CI was used to assess predictive risk factors for SCI among genetic markers and baseline variables recorded before the age of two years. Logistic regression analysis was used to evaluate the association between SCI risk, arteriopathy, and HU use.

Univariable models were fitted, and all variables associated with the outcome at the 20% level were retained for introduction into a multivariable model, except for variables with strong correlation such as hematocrit / hemoglobin and neutrophils / leukocyte count. Multivariate analyses used a stepwise selection process consisting of a series of alternating forward selection and backward elimination steps. All statistical tests were two-sided; $P<0.05$ was considered statistically significant. Statistical analyses were performed with the SPSS-version-24 and MedCalc (Belgium) software packages.

Results

The CHIC SCA newborn cohort includes the previous cohort (born 1988 to April 2007), who underwent early TCD screening but who had never been eICA assessed before the August 2008 update,[7] and the new cohort (born May 2007 to December 2014) who underwent early screening for intracranial and eICA arteriopathy. Patients from both cohorts were followed at the CHIC Pediatric Center until they were 18-20 years old, and the combined overall cohort was updated in July 2019 (Figure 1).

Comparison between the two cohorts to evaluate the impact of extracranial internal carotid artery assessment on the incidence of infarction

Survival

In the previous cohort, 3 deaths occurred before the August 2008 update[7] among the 217 SCA patients born before April 2007. The new cohort included 153 SCA children (149 SS, 3 Sb0, 1 SD-Punjab). Mean and median clinical follow-up were 8.6 years (SD: 2.5) and 8.9 years (range: 1.2-12.0), respectively, providing 1,313 (PY) of clinical follow-up as of July 2019. Three deaths occurred at 2.0 years of age in 2012, one death at 1.9 years old in 2013, and one death at 7.1 years old in 2014. The incidence of death of 0.23/100 PY (95%CI: 0.10-0.62) in the new cohort was comparable to the 0.25/100 PY (95%CI: 0.07-0.63) reported in the previous cohort,[7] and both had a similar survival probability of 97.8% (95%CI: 95.2-100%) by the age of 8 years (Figure 2A).

Stroke

In the previous cohort, 3 strokes occurred, which prompted our team to modify our management protocol. One stroke in 2001 before confirmatory TCD in a 1.5-year-old patient prompted us to immediately transfuse children with abnormal TCD. The stroke in 2005 in a 4.4-year-old child with normal left-sided velocities, but no temporal window available on the right side due to severe right arteriopathy, prompted our team to perform MRI/MRA when the temporal window was not adequate. In the new cohort, no stroke occurred compared to the stroke incidence of 0.19/100 PY (95%CI: 0.04-0.5) in the previous cohort.[7] Kaplan-Meier estimates of stroke show no significant difference between the two cohorts (Log Rank: $P=0.097$) (Figure 2B).

Silent cerebral infarct incidence

The first MRI/MRA/neck MRA was performed in 145 stroke-free SCA patients at the median age of 5.1 years (range: 2.1-8.7), while the last ones occurred at 7.4 years of age (range: 2.8-12.0), providing 1,089 PY of MRI follow-up. SCI were detected in 15/145 SCA children at a median age of 5.4 years (range: 1.8-9.7) with an incidence of 15/1,089 (1.4/100 PY). The cumulative incidence of SCI in the new cohort by the age of 8 was 12.8% (6.3-19.3%) while it was 28.1% (18.9-37.3%) in the previous one (Log Rank: $P=0.009$) (Figure 2C).

Impact of extracranial internal carotid artery assessment and hydroxyurea on silent cerebral infarct incidence

Among the 129 stroke-free SCA children assessed by MRI/MRA only in the previous cohort and the 145 of the new cohort also assessed for eICA (total N=274), logistic regression analysis showed that eICA assessment/management carried out in the new cohort was strongly associated with a lower risk of SCI (OR: 0.31; 95%CI: 0.15-0.58; $P=0.001$). Of note, there was no difference in the mean and median age at HU initiation between the previous and new cohort: 5.6 years (SD: 2.6) *versus* 5.2 years (SD: 2.0), and 5.3 years (range: 0.9-12.6) *versus* 5.1 years (range: 1.3-10.4), respectively. However, a higher proportion of patients received HU in the new cohort than in the previous one, i.e., 30/145 (20.7%) *versus* 15/214 (7.0%) by the age of 4 and 80/145 (55.2%) *versus* 34/214 (15.9%) by the age of 6, respectively ($P<0.001$ for each). Moreover, mean dose of HU was higher in the new cohort (26.6 [SD: 2.5] mg/kg/day *vs*. 24.7 [SD: 2.7] mg/kg/day); $P<0.001$). Nevertheless, HU use ($P=0.49$) or HU

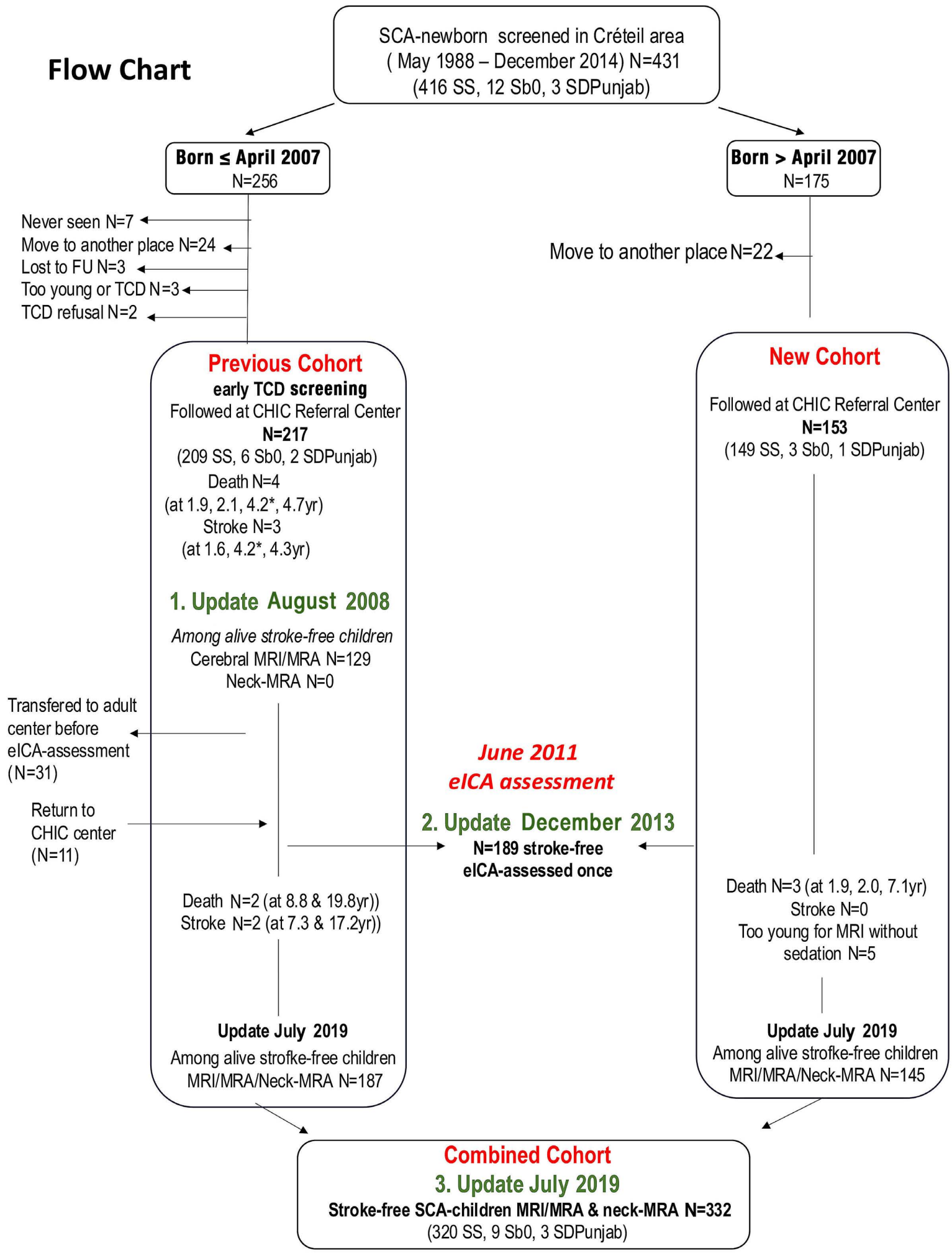


Figure 1. Flow chart of the sickle cell anemia newborn cohort. The outcome of cerebral vasculopathy in the sickle cell anemia (SCA) newborn in the previous cohort, born before April 2007 (transcranial-Doppler [TCD] screened before the age of four years), was first updated in August 2008 and reported in 2011.[7] Systematic extracranial internal carotid artery (eICA) assessment was added in June 2011. The previous cohort had never been eICA-assessed before the August 2008 update; this was compared to the new cohort born between May 2007 and December 2014 (eICA-screened before the age of four years) to evaluate the impact of eICA assessment on silent cerebral infarct (SCI) incidence. Patients in the previous and the new cohort were thereafter followed at the Centre Hospitalier Intercommunal de Creteil (CHIC) pediatric center until the age of 18-20 years. Follow-up (FU) of the combined cohorts (overall cohort) was updated in July 2019. MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; N: number.

age at initiation (*P*=0.89), and even the HU dose (*P*=0.35), were not associated with SCI risk.

Relative impact of intra- and extracranial internal carotid artery arteriopathy and hydroxyurea in the new cohort

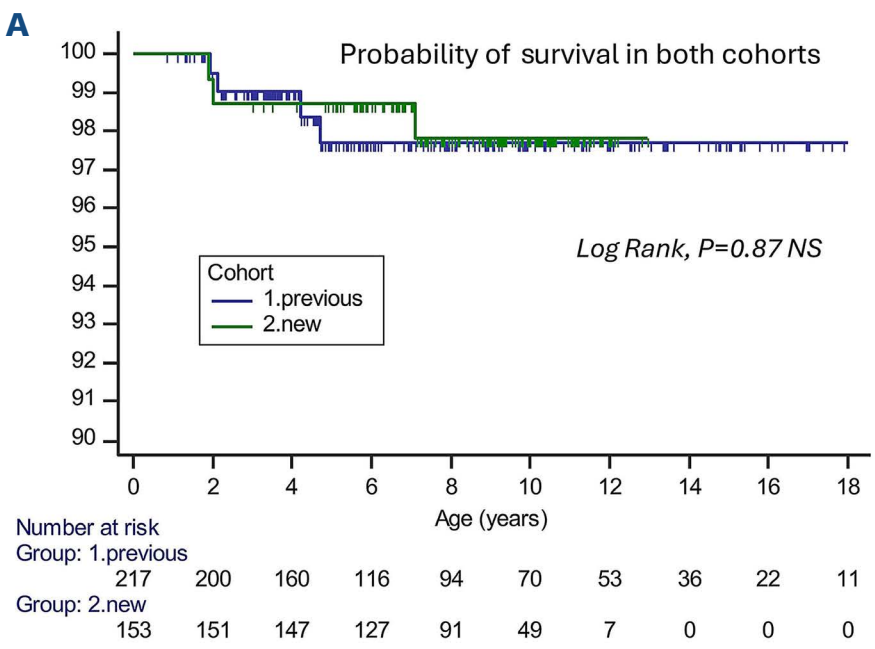
Intracranial and eICA assessment were carried out concomitantly from the 2nd year of life, allowing better evaluation of the relative impact of intracranial and eICA arteriopathy on SCI risk. Intracranial and eICA velocities increase with age until the child is 4-6 years old before gradually decreasing. Mean (95%CI) velocities in eICA were approximately 25% lower than mean MCA (Figure 3A).

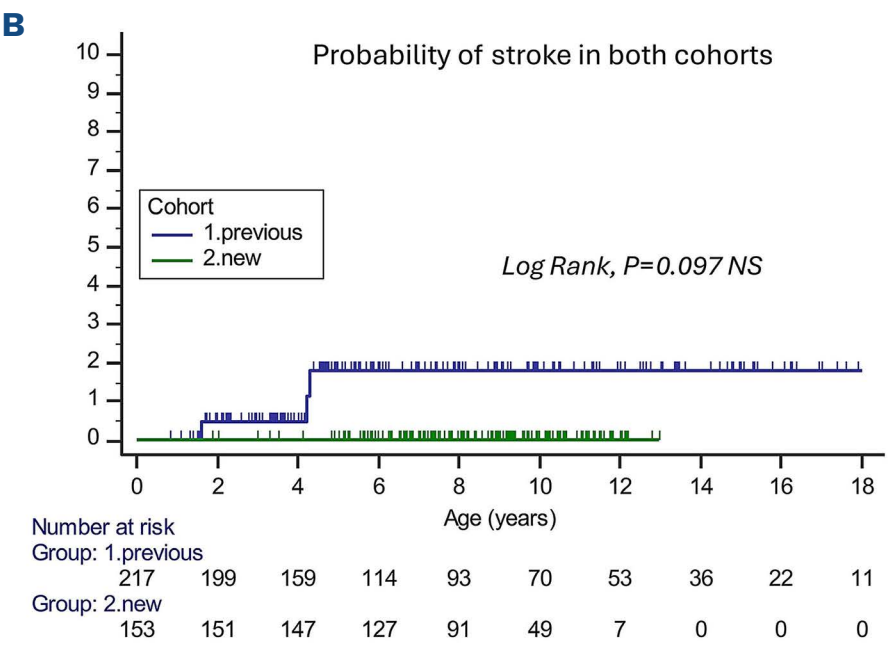
Intracranial TAMMV ≥200 cm/s was present in 39/145 (26.9%) SCA children, 10/39 (25.6%) having stenosis, while in the remaining 106 patients, only 2 had stenosis but TAMMV <200 cm/s (*P*<0.001). Thus, 41 children (39+2) with either intracranial TAMMV ≥200 cm/s or stenosis were placed on chronic transfusion for intracranial arteriopathy. Cumulative incidence of intracranial TAMMV ≥200 cm/s reached a plateau at age 8 (31.8% [95%CI: 23.1-40.5%]) in the new cohort, similar to that observed in the previous cohort (29.6% [95%CI: 22.8-38.0%]).

Isolated eICA TAMMV ≥200 cm/s was present in 8/104 children among the 104 patients without intracranial arteriopathy. eICA stenosis was present in 9/104, of whom 3 had eICA TAMMV ≥200 cm/s, 5 had 160-199 cm/s, and one <160 cm/s. Following our local protocol, children with eICA TAMMV ≥200 cm/s or eICA stenosis were placed on chronic transfusion (N=14), while those with eICA TAMMV 160-199 cm/s without eICA stenosis (N=13) were maintained on HU. Figure 3B shows the cumulative incidence of intracranial TAMMV ≥200 cm/s and that of isolated eICA TAMMV ≥160 cm/s.

Logistic regression analysis (Table 1) showed that SCI risk was not associated with intracranial or eICA TAMMV ≥200 cm/s in SCA children on chronic transfusion. In contrast, the risk for SCI was significantly higher in children with isolated eICA TAMMV of 160-199 cm/s and no eICA stenosis who were maintained on HU according to our local protocol (OR:4.9 [95%CI: 1.3-18.5]; *P*=0.019). Figure 3C shows a significantly higher cumulative incidence of SCI in patients with isolated eICA TAMMV ≥160 cm/s than in those with intracranial TAMMV ≥200 cm/s or normal velocities (Log Rank: *P*=0.012).

While early HU initiation in symptomatic or 'at risk' patients was strongly associated with a lower risk of intracranial





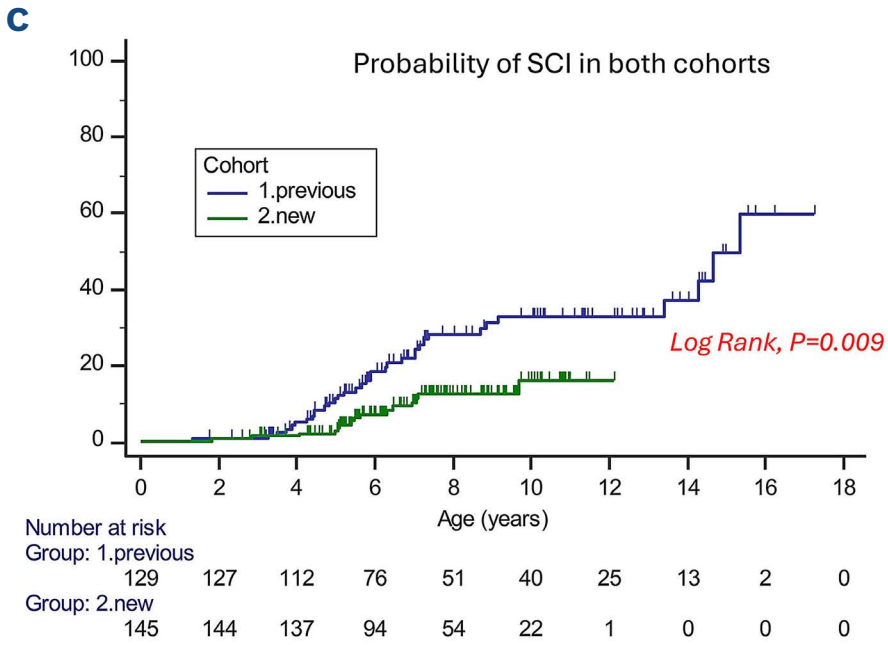


Figure 2. Comparison of probability of survival, overt stroke, and silent cerebral infarcts between the previous cohort, born before April 2007, and the new cohort, born between May 2007 and December 2014. The previous cohort, born before April 2007, had not undergone extracranial internal carotid artery assessment (eICA) before the August 2008 update. The new cohort, born between May 2007 and December 2014, had undergone early assessment / management for eICA arteriopathy and their data were updated in July 2019. (A) Probability of survival in both cohorts. (B) Probability of overt stroke in both cohorts. (C) Probability of silent cerebral infarcts (SCI) in both cohorts. NS: not significant.

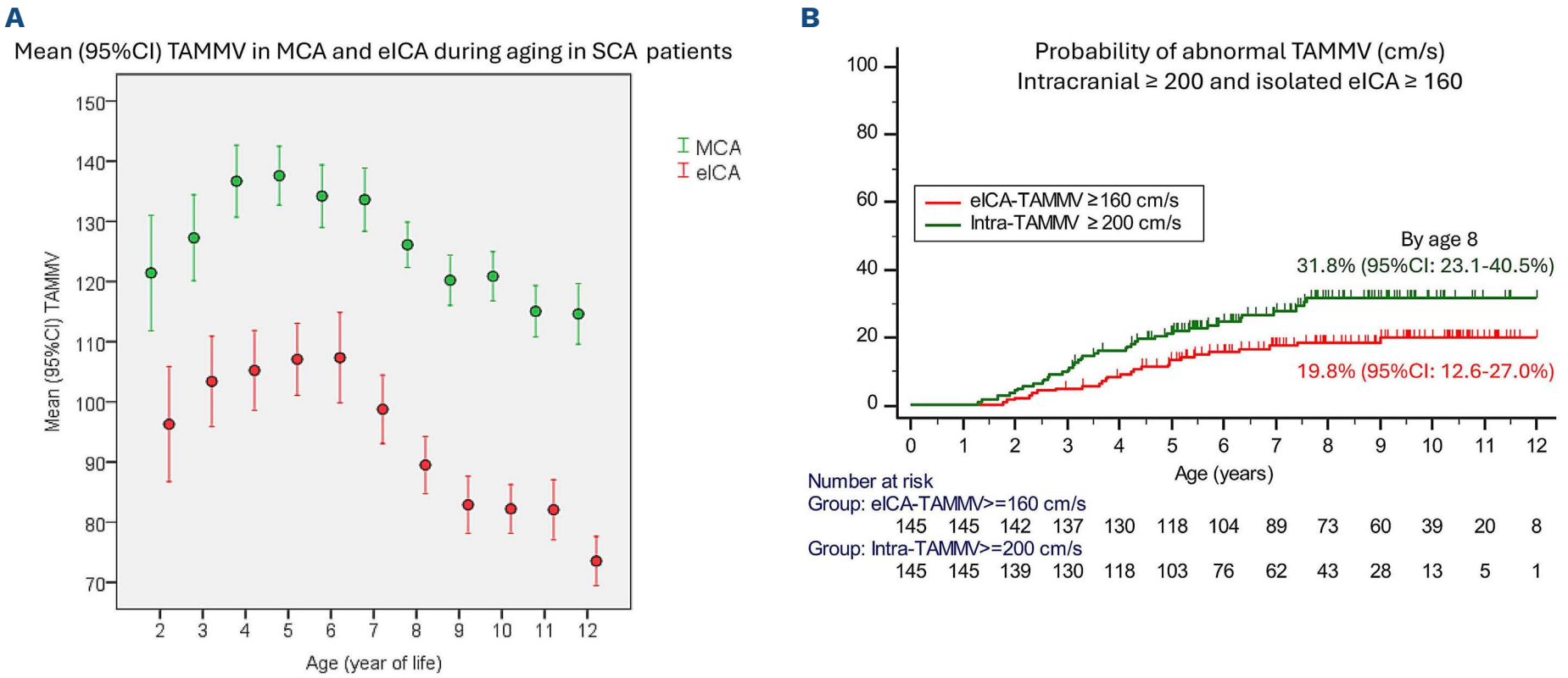


Figure 3. New cohort concomitantly early assessed for intra- and extracranial internal carotid artery arteriopathy. (A) Mean (95% confidence interval [CI]) time averaged mean maximum velocity (TAMMV) at annual check-up during aging in right/left middle cerebral artery (MCA) and extracranial internal carotid artery (eICA). (B) Cumulative incidence of intracranial TAMMV ≥200 cm/second (s) and isolated eICA TAMMV ≥160 cm/s. The cumulative incidence of intracranial TAMMV ≥200 cm/s and that of isolated (in absence of intracranial arteriopathy) eICA TAMMV ≥160 cm/s reached a plateau at 8 years of age of 31.8% (95%CI: 23.1-40.5%), and 19.9% (95%CI: 12.7-27.1%), respectively. Thus, the cumulative incidence of abnormal intracranial and isolated eICA velocities reached 51.7%

Continued on following page.

by 8 years of age. (C) Cumulative incidence of silent cerebral infarct (SCI) according to intracranial TAMMV ≥ 200 cm/s, eICA-TAMMV ≥ 160 cm/s or normal TAMMV. (D) Cumulative incidence of intracranial TAMMV ≥ 200 cm/s according to age at hydroxyurea (HU) initiation (before or after 6 years of age). (E) Cumulative Incidence of Isolated eICA-TAMMV ≥ 160 cm/s according to age at HU initiation (before or after 6 years of age). (F) Cumulative incidence of SCI according to age at HU initiation (before or after 6 years of age). NS: not significant.

TAMMV ≥200 cm/s or stenosis (OR: 0.32 [95%CI:0.15-0.69]; *P*=0.004), it was not associated with a lower risk for eICA arteriopathy (Table 1). There was a significant reduction in the SCI cumulative incidence for intracranial TAMMV ≥200 cm/s (Log Rank: *P*=0.007) but no reduction for patients with eICA TAMMV ≥160 cm/s and SCI when HU was initiated before age 6 (Figure 3D-F).

Overall cohort

The overall cohort includes patients born before May 2007 and those born between May 2007 and December 2014. The mean and median clinical follow-up in the 431 SCA patients was 12.0 years old (SD: 5.1) and 12.2 years old (interquartile range [IQR]: 7.8-16.3), respectively, providing 5,505 PY of clinical and biological follow-up.

In the previous cohort, after the 2008 update, 2 patients died at 8.8 years of age in 2013 and 19.8 years of age in 2015. Thus, 9 deaths occurred in the overall cohort, with an overall incidence of death of 0.16/100 PY (95%CI: 0.09-0.21), resulting in an estimated survival probability at age 18 of 98.0% (95%CI: 96.6-99.4%). Two strokes were observed. One occurred in 2011 in a 7.3-year-old girl with no prior intra/eICA arteriopathy who developed a severe VOC with spontaneous extradural hematoma and pari-

Table 1. Univariate logistic regression analysis of the association of the risk of silent cerebral infarct with intracranial and extracranial arteriopathy in the new cohort.

Associated risk factors	N	Silent cerebral infarcts N=15, 10.3%			Age at HU initiation, per year increase		HU initiated <6 years of age N=78	
		N (% SCI)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Intracranial TAMMV ≥200 cm/s	39	4/39 (10.3)	1.0 (0.3-3.5)	0.933	1.25 (0.99-1.57)	0.055	0.34 (0.16-0.74)	0.006*
Intracranial stenosis	12	1/12 (8.3)	1.3 (0.1-10.8)	0.812	1.57 (1.02-2.43)	0.041*	0.15 (0.03-0.71)	0.017*
Intracranial TAMMV ≥200 cm/s or stenosis	41	4/41 (9.8)	1.1 (0.3-3.6)	0.884	1.34 (1.06-1.68)	0.012*	0.32 (0.15-0.69)	0.004*
Kinking	60	7/60 (11.7)	1.3 (0.4-3.7)	0.661	1.1 (1.1-1.3)	0.492	0.69 (0.35-1.33)	0.269
In absence of intracranial arteriopathy								
eICA TAMMV ≥200 cm/s	8	1/8 (12.5)	1.2 (0.1-11.0)	0.837	1.3 (0.9-1.8)	0.194	0.68 (0.16-2.98)	0.613
eICA stenosis	9	3/9 (33.3)	5.1 (1.1-23.2)	0.033*	1.3 (0.9-1.8)	0.134	0.69 (0.30-1.58)	0.386
eICA TAMMV ≥200 cm/s or eICA stenosis	14	3/14 (21.4)	2.7 (0.7-11.1)	0.166	1.3 (0.9-1.7)	0.135	0.61 (0.20-1.87)	0.391
eICA TAMMV ≥160 cm/s	26	7/28 (25.0)	5.1 (1.7-15.6)	0.004*	1.1 (0.9-1.5)	0.224	0.69 (0.29-1.61)	0.390
eICA TAMMV 160-199 cm/s	18	6/18 (33.3)	6.0 (1.8-19.6)	0.003*	1.1 (0.8-1.4)	0.527	0.58 (0.22-1.54)	0.277
eICA-TAMMV ≥160 or eICA stenosis	28	7/28 (25.0)	4.5 (1.5-13.9)	0.008*	1.1 (0.9-1.4)	0.271	0.69 (0.30-1.58)	0.386
eICA TAMMV 160-199 and no eICA stenosis	13	4/13 (30.8)	4.9 (1.3-18.5)	0.019*	1.0 (0.7-1.4)	0.909	0.71 (0.23-2.24)	0.564
Age in years at HU initiation per one year increase	111	NA	1.2 (.9-1.6)	0.269	NA	NA	-	-
HU initiated <6 years of age	78	7/78 (9.0)	0.7 (0.2-2.1)	0.560	NA	NA	-	-
HU dose per one mg/kg/day increase	111	NA	0.9 (0.8-1.1)	0.347	NA	NA	-	-

CI: confidence interval; eICA: extracranial internal carotid artery; HU: hydroxyurea; N: number; NA: not available; OR: odds ratio; s: second; SCI: silent cerebral infarct; TAMMV: time-averaged mean maximum velocity; y: years. **P*<0.05 was considered statistically significant by univariate logistic regression analysis.

etal compressive ischemia. The second stroke occurred in an adolescent without identified intra- or extracranial arteriopathy during the first 17 years of life, who, in 2017, at 17.2 years of age, developed acute headaches, vomiting, cerebellar syndrome, and multiple cerebellar acute ischemic lesions related to a transitory inflammatory vertebral arteriopathy.

As no stroke occurred in the new cohort, the overall incidence of strokes in the overall cohort was 0.09/100 PY (95%CI: 0.04-0.14) and the estimated stroke probability by age 18 was 1.8% (95%CI: 0.0-3.6%). The cumulative incidence of intracranial TAMMV ≥200 cm/s and isolated eICA TAMMV ≥160 cm/s are shown in Figure 4A.

Stroke-free sickle cell anemia children assessed for intracranial and extracranial internal carotid artery arteriopathy

At the July 2019 update, 187 from the previous cohort and 145 from the new cohort (total N=332) stroke-free SCA children had been assessed/managed for intracranial and eICA arteriopathies. The first cerebral MRI/MRA and those with neck MRA were performed at the median age of 5.3 years old (IQR: 4.3-6.7) and 7.3 years old (IQR: 5.2-11,9), respectively. The last MRI/MRA/neck MRA, performed at the median age of 11.1 years old (IQR: 7.6-15.1), provided 3,853 PY of MRI follow-up. HU was administered to 241/332 (72.6%) at the median age of 5.6 years old (range: 0.9-17.9). Chronic transfusion was initiated in 231/332 (69.6%) at the median age of 4.2 years old (range: 0.5-17.2). AlloSCT was performed in 60/332 (18.1%) at the median age of 6.5 years old (range: 3.4-20.4).

Silent cerebral infarcts were detected in 63/332 SCA patients (19.0%) at the median age of 6.4 years old (range: 1.8-18.0). The SCI incidence during MRI follow-up was 1.64/100 PY. The SCI cumulative incidence by age 14 was 25.0% (95%CI: 19.0-31.0%) (Figure 4B). Forty-eight patients had SCI at the first MRI, and 15 developed SCI thereafter (*Online Supplementary Table S1*). The probability of SCI at and post first MRI was higher in patients with eICA TAMMV ≥160 cm/s than in the other patients (Log Rank: *P*=0.021) (Figure 4C).

Predictive risk factors for silent cerebral infarcts

Univariate Cox regression analysis (Table 2) showed that, among baseline biological parameters, low hemoglobin and hematocrit, high reticulocyte count, high MCV, and high total bilirubin and lactate dehydrogenase levels were significant predictive risk factors for SCI. Multivariate analysis retained reticulocyte count (HR: 1.003 per 1x10^9/L increase [95%CI: 1.000-1.006]; *P*=0.029) and total bilirubin (HR: 1.016 per 1 mmol/L increase [95%CI:1.001-1.031]; *P*=0.034) as significant and independent predictive risk factors for SCI.

Associated risk factors for silent cerebral infarcts

Risk of SCI was not associated with intracranial arteriopathy but strongly associated with eICA stenosis (OR: 3.6 [95%CI: 1.6-8.3]; *P*=0.003) and eICA TAMMV ≥160 cm/s (OR: 2.5 [95%CI: 1.3-4.9]; *P*=0.007). Furthermore, SCI risk was associated with age at first neck MRA (OR: 1.03 per 1 year increase [95%CI:1.02-1.14]; *P*=0.013), but not with age at HU initiation (*P*=0.456) or with HU dose (*P*=0.772).

Relationship between therapies and silent cerebral infarct incidence

During the period without SCA-modifying therapy (1,904 PY), the incidence of SCI was 43/1,904 (2.3/100 PY). At initiation of HU, SCI was already present in 23/241 patients, while 23 other SCA children developed SCI thereafter during the 832 PY on HU, providing an incidence of SCI on HU of 2.8/100 PY (Figure 4D). At the time of chronic transfusion initiation, 43/231 patients already showed SCI, while during the 780 PY on chronic-transfusion, only 2 patients developed SCI, resulting in an incidence of 2/780 (0.3/100 PY) (Figure 4E). AlloSCT was performed in 60/332 (18.1%) SCA patients at the median age of 6.5 years (range: 3.4-20.4). SCI were present in 12/60 (20%) but no new patient developed SCI during the 337 PY post alloSCT among the 54 patients with available post alloSCT MRI (Figure 4F).

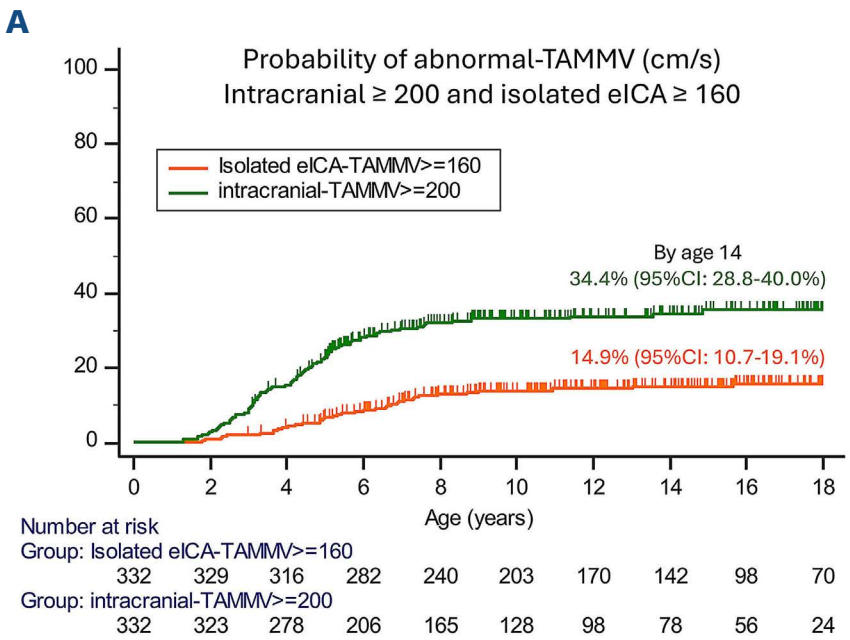
Associated risk factors for silent cerebral infarcts in patients on hydroxyurea

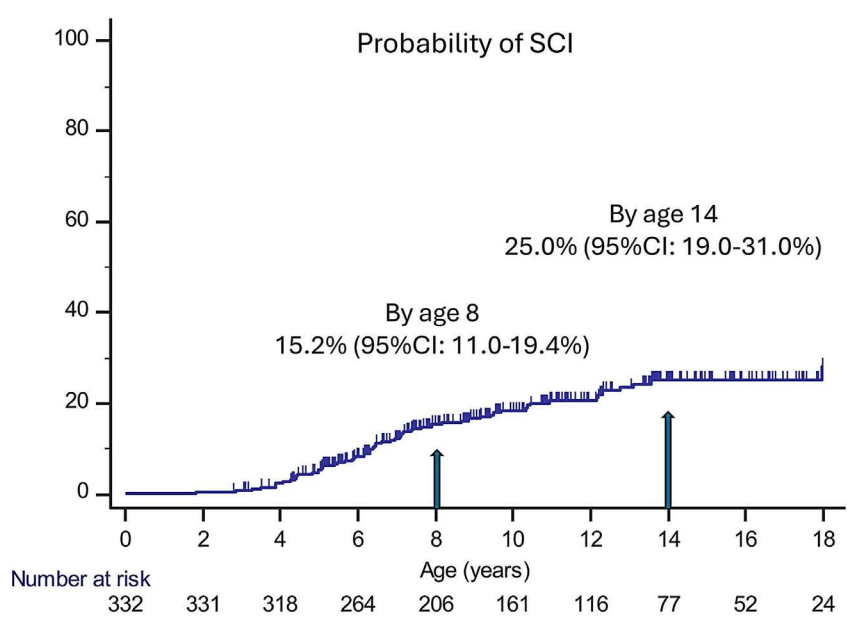
Among the 241 SCA patients taking HU, the biological parameters recorded under HU were available for 234 patients; 41 had SCI, while 193 did not (Table 3). Multivariate logistic regression analysis retained leukocyte count (OR: 1.126 per 1x10^9/L increase [95%CI: 1.027-1.234]; *P*=0.011) and MCV (OR: 1.053 per 1 fL increase [95%CI: 1.020-1.087]; *P*=0.001) as significant, independent risk factors for SCI on HU. Of note, MCV >105 fL increased the SCI risk by a factor of 5.0 (95%CI: 2.1-11.8; *P*<0.001).

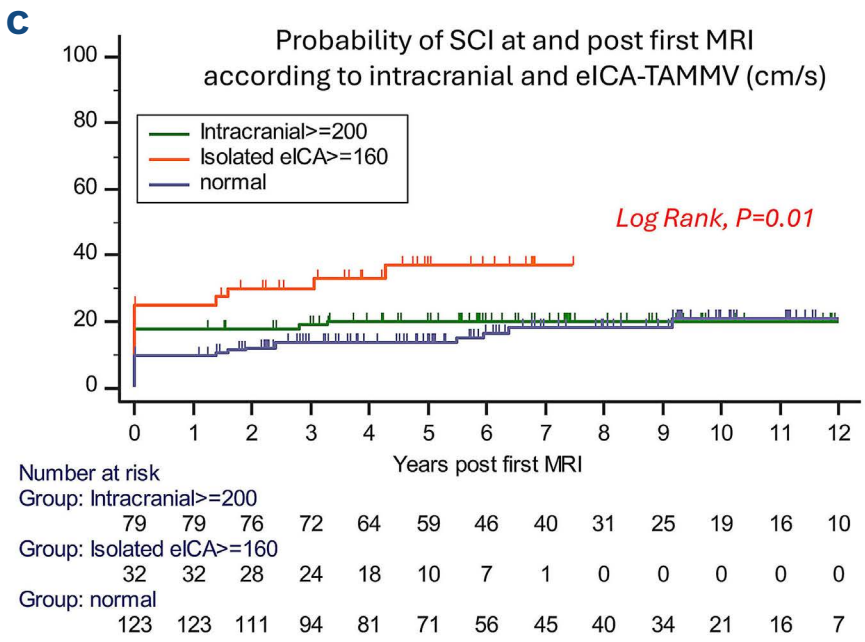
Discussion

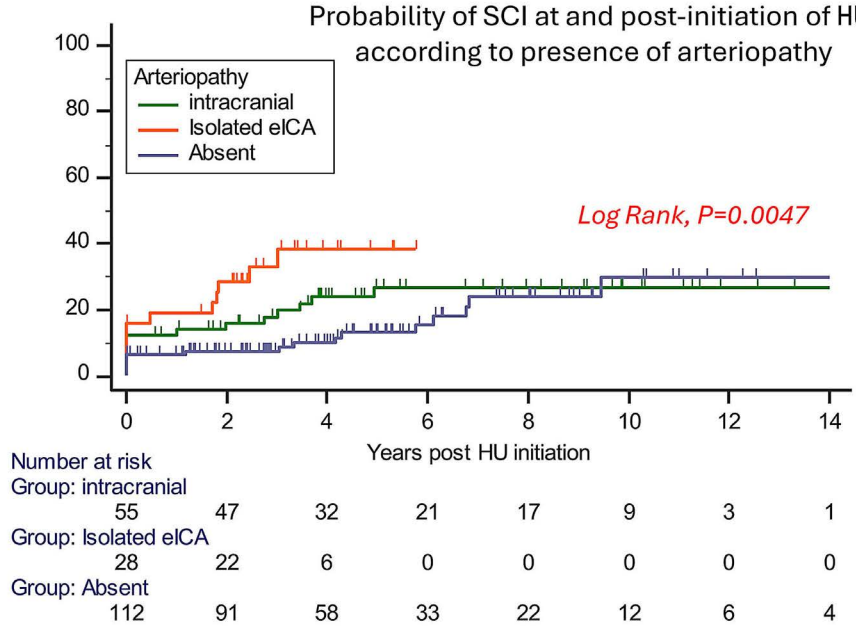
The present SCA cohort is the first to report the cumulative incidence of stroke and SCI in SCA patients, longitudinally assessed and managed for intracranial and eICA arteriopathy.

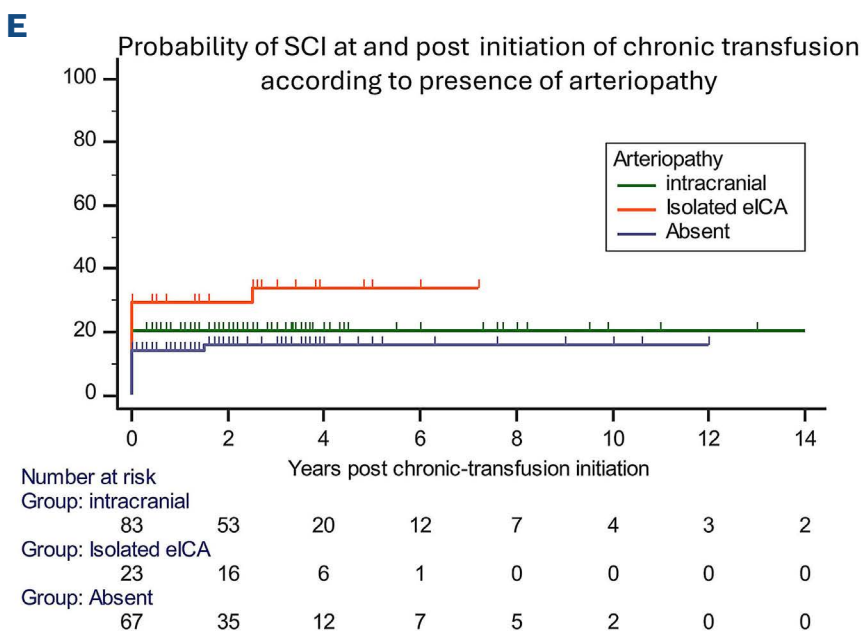
Stroke is the most devastating complication in patients with SCA. Before TCD screening, an overall incidence of 0.61/100 PY was reported,[12] with a stroke risk of 11% by the age of 20.[12] The STOP protocol,[20,24,25] using chronic transfusion in children at risk of stroke detected by TCD, significantly reduced the risk of stroke from 0.88/100 PY in 1991-1998 to 0.17/100 PY in 2000.[26] However, recent studies report higher incidence of first stroke in the post-STOP era (0.24/100 PY[27] and 0.4/100 PY[28]), demonstrating the difficulties of effectively implementing TCD assessment and the STOP protocol in the real-world.[29,30] In the present single-center cohort study, stroke risk remained low in the overall cohort who











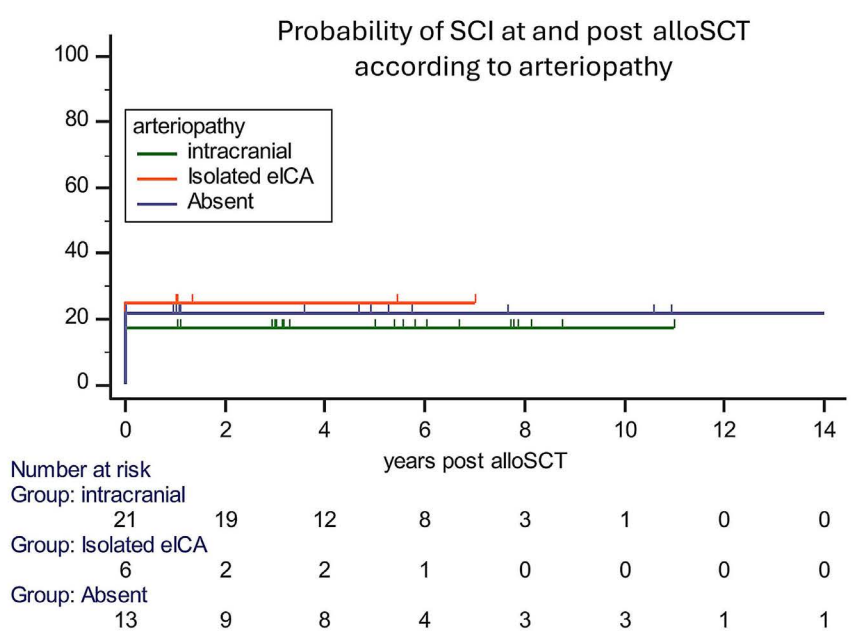


Figure 4. Overall cohort assessed and managed for extracranial internal carotid artery arteriopathy (N=332). (A) Cumulative incidence of intracranial time averaged mean maximum velocity (TAMMV) ≥200 cm/second (s) and isolated extracranial internal carotid artery (eICA) arteriopathy ≥160 cm/s. (B) Cumulative incidence of silent cerebral infarcts (SCI). (C) Cumulative incidence of SCI at and post first magnetic resonance imaging (MRI) according to TAMMV values in intracranial and eICA. (D) Cumulative incidence of SCI at and post initiation of hydroxyurea (HU). (a) At HU initiation, 23 sickle cell anemia (SCA) patients already had SCI. (b) Following HU initiation, 23 other SCA patients developed SCI: (i) 7 had intracranial arteriopathy, of whom 4 developed abnormal transcranial Doppler (TCD) despite ongoing HU, and 3 had recurrence of abnormal TCD after switch from chronic transfusion to HU; (ii) 5 had isolated eICA-arteriopathy, of whom 4 had eICA TAMMV 160-199 cm/s and developed SCI on HU, while one received chronic transfusion for eICA stenosis but developed SCI after switch to HU; (iii) 10

Continued on following page.

had no arteriopathy and developed SCI on HU. (E) Cumulative incidence of SCI at and post initiation of chronic transfusion: (i) one was on chronic transfusion for recurrent splenic sequestration and developed SCI related to severe eICA stenosis with seizure; (ii) one had no arteriopathy but severe frequent vaso-occlusive crisis (VOC) despite ongoing chronic transfusion. (F) Cumulative Incidence of SCI at and after alloSCT SCI was present in 12/60 (20%) at allogeneic stem cell transplantation (alloSCT) but no new patient developed SCI during the 337 patient-years post alloSCT among the 54 patients with available post alloSCT MRI.

had undergone early TCD screening (0.09/100 PY), and no stroke related to intracranial arteriopathy occurred after 2005. Several reasons can explain this result, e.g., the same Doppler expert conducted screening in the entire study (SV), and there was a uniform monocentric management based on our Center's experience. In line with the STOP-1 study, children with abnormal TCD were placed on chronic transfusion,[20] but given the strong associa-

Table 2. Univariate and multivariate Cox regression analysis of predictive risk factors for silent cerebral infarct in the overall combined sickle cell anemia cohort.

	Overall, N=370		**Stroke-free MRI assessed, N=332 Silent cerebral infarcts, N=63**		
Univariate Cox regression analysis					
Genetic markers	**N**	**%**	**Events/N pt. (%)**	**HR (95% CI)**	***P***
Sex					
Male	179	48.5	37/161 (23.0)	1.5 (0.9-2.5)	0.098
Female	191	51.5	26/171 (15.2)	1	
G6PD activity					
Normal	161	88.5	48/269 (17.8)	1	
Deficiency	21	11.5	11/40 (27.5)	1.87 (0.97-3.61)	0.061
Alpha-thalassemia					
Absent	105	56.1	40/191 (20.9)	1.35 (0.89-2.03)	0.154
Present	82	43.9	22/132 (16.7)	1	
eICA kinkings					
Absent	-	-	40/223 (17.9)	-	
Present	-	-	23/109 (21.1)	1.37 (0.82-2.30)	0.231
Baseline biological parameters	**N**	**Median (Q1-Q3)**	**Events**	**HR (95% CI) per Unit increase**	***P***
Hemoglobin level, g/dL	330	8.1 (7.4-9.0)	NA	0.76 (0.61-0.96)	0.019*
Hematocrit, %	259	24.3 (22.0-27.3)	NA	0.90 (0.84-0.98)	0.011*
Reticulocyte count, 10^9/L	255	277 (218-358)	NA	1.002 (1.001-1.005)	0.024*
Leukocyte count, 10^9/L	260	13.3 (10.3-16.8)	NA	1.04 (0.99-1.09)	0.131
Neutrophil count, 10^9/L	252	4.8 (3.4-7.1)	NA	1.03 (0.95-1.11)	0.430
Platelet count, 10^9/L	259	329 (256-421)	NA	1.001 (0.998-1.003)	0.613
Mean corpuscular volume, fL	219	77.1 (71.4-82.5)	NA	1.033 (1.002-1.064)	0.034*
Total bilirubin, mmol/L	195	28.0 (19.0-41.0)	NA	1.020 (1.006-1.033)	0.004*
Lactate dehydrogenase, IU/L	219	618 (463-866)	NA	1.001 (1.000-1.001)	0.043*
Fetal hemoglobin, %	251	15.3 (9.7-21.3)	NA	0.971 (0.938-1.005)	0.098
Multivariate Cox regression analysis among baseline biological parameters					
Reticulocyte count, 10^9/L	-	-	-	1.003 (1.000-1.006)	0.029*
Total bilirubin, mmol/L	-	-	-	1.016 (1.001-1.031)	0.034*

For this analysis, the biological parameters are the average of those obtained at baseline during the 2nd year of life before any intensive therapy (hydroxyurea, chronic-transfusion or allogeneic stem cell transplantation). CI: confidence interval; eICA: extracranial internal carotid artery; HR: hazard ratio; MRI: magnetic resonance imagery; N: number; NA: not available; pt: patients; Q1-Q3: 25th and 75th percentiles; SCA: sickle cell anemia. *P<0.05 was considered statistically significant.

tion between stenosis and risk of infarct,[8,11] MRI/MRA was systematically performed and chronic transfusion given to patients with stenosis. The resulting low risk of stroke validates our strategy, including immediately transfusing patients with abnormal TCD,[7,11,23] systematically performing MRI/MRA, restarting chronic transfusion in patients reverting to abnormal TCD after switching to HU,[23] and transplanting or keeping patients with stenosis on chronic transfusion.[23] Although cases of stroke associated with stenosis/occlusion of eICA have been reported in the literature,[13-17,31,32] no stroke related to eICA arteriopathy was observed in the present cohort in which children with eICA TAMMV ≥200 cm/s or eICA stenosis were placed on chronic transfusion.

While overt stroke and silent infarcts were strongly associated with intracranial arteriopathy during the pre-TCD era,[31,33-35] early management with chronic transfusion since the STOP study no longer resulted in any significant association between intracranial arteriopathy and SCI incidence. In contrast, we confirm here that eICA arteriopathy is the main risk factor for SCI, and we show the significant reduction in SCI incidence by early detection of eICA arteriopathy and initiation of chronic transfusion for eICA TAMMV ≥200 cm/s or eICA stenosis. Interestingly, we also show that eICA TAMMV of 160-199 cm/s without stenosis, which was not an indication for chronic transfusion in our protocol, and which was managed by initiation or maintenance of HU, is a strong risk factor for SCI. This indicates that all patients with eICA TAMMV ≥160 cm/s should be given chronic transfusion and that those with an HLA-identical donor should be considered for alloSCT, as for intracranial TAMMV ≥200 cm/s. It is also worth noting that, in this cohort, that has been systematically evaluated every two years by MRI/MRA/neck MRA without sedation since the age of 5 (or earlier in chronically transfused patients), no SCI enlargement and no stroke were observed in patients with a history of SCI, contrary to several reports mentioning this risk.[1,4,5] This suggests the importance of systematic stenosis detection/management for the prevention of SCI.

Although HU has been shown to reduce VOC, ACS, and transfusion requirements in SCA patients in both high-

Table 3. Logistic regression analysis to compare the risk of silent cerebral infarct of patients on hydroxyurea between those with silent cerebral infarct *versus* those without silent cerebral infarct.

	Patients on HU, N=234				Mann-Whitney *P*	OR (95% CI) Per one unit increase	*P*
	SCI pos, N=41		SCI neg, N=193				
	N	Median (Q1-Q3)	N	Median (Q1-Q3)			
Univariate logistic regression							
Hemoglobin level, g/dL	41	8.4 (7.7-9.4)	192	8.9 (8.1-9.7)	0.031*	0.737 (0.547-0.992)	0.044*
Hematocrit, %	35	24.8 (22.5-25.6]	187	26.3 (23.6-29.5)	0.060	0.854 (0.703-1.038)	0.113
Reticulocyte count, 10^9/L	41	186 (110-263)	184	162 (107-228)	0.237	1.002 (0.999-1.005)	0.287
Leukocyte count, 10^9/L	41	8.2 (5.2-10.7)	190	7.3 (5.6-9.7)	0.274	1.081 (0.995-1.174)	0.064
Neutrophil count, 10^9/L	41	3.6 (2.4-5.3)	190	3.6 (2.2-4.9)	0.733	1.068 (0.978-1.167)	0.142
Platelet count, x10^9/L	41	315 (230-406)	192	306 (224-409)	0.876	1.000 (0.998-1.003)	0.923
Mean corpuscular volume, fL	40	94.5 (85.3-106.8)	192	89.5 (81.0-98.4)	0.024*	1.042 (1.011-1.073)	0.007*
Total bilirubin, mmol/L	40	37.0 (20.0-47.0)	190	25.0 (17.0-40.0)	0.007*	1.0140(0.996-1.024)	0.157
Lactate dehydrogenase, IU/L	37	530 (378-666)	177	448 (339-578)	0.046*	1.001 (1.000-1.003)	0.058
Fetal hemoglobin, %	41	16.7 (10.9-22.3)	192	17.0 (10.6-23.3)	0.878	1.001 (0.964-1.039)	0.965
MCV >100 fL	-	-	-	-	-	2.54 (1.20-5.41)	0.015*
MCV >105 fL	-	-	-	-	-	4.98 (2.11-11.8)	<0.001*
MCV >110 fL	-	-	-	-	-	7.81 (2.34-26.3)	0.001*
Multivariate logistic regression							
Leukocyte count, x10^9/L	-	-	-	-	-	1.126 (1.027-1.234)	0.011*
Mean corpuscular volume, fL	-	-	-	-	-	1.053 (1.020-1.087)	0.001*

Biological parameters available for patients on hydroxyurea (HU). CI: confidence interval; fL: femtoliter; MCV: mean corpuscular volume; N: number; neg: negative; OR: odds ratio; pos: positive; Q1-Q3: 25th and 75th percentiles; SCI: silent cerebral infarct. *P<0.05 was considered statistically significant.

Summary of results

1. Previous cohort not eICA assessed at 2008 update *versus* new cohort assessed/managed for eICA-arteriopathy

Comparison

	Previous cohort May-1988/Apr-2007	New cohort May-2007/Dec-2014	*P*
eICA assessment/management	**no**	**yes**	**<0.001***
Hydroxyurea (HU) use			
Mean (SD) age at HU initiation	5.6yr (2.6)	5.2yr (2.0)	.460
Mean (SD) dose of HU mg/kg/day	24.7 (2.7)	26.6 (2.5)	**<.001***
Patients (%) on HU by age 6	15.9%	55.2%	**<.001***
SCI probability (95%CI) by age 8	**28.1%** (18.9-37.3%)	**12.8%** (6.3-19.3%)	**.009***

Risk factors for SCI in previous and new cohort

Univariate logistic regression		
	OR (95%CI)	***P***
eICA assessment/management	0.31 (0.15-0.58)	**.001***
Hydroxyurea (HU) use	1.24 (0.67-2.31)	.486
Age at HU initiation/one yr increase	1.01 (0.84-1.23)	.89
Dose of HU/one mg/kg/d increase	1.02 (0.89-1.17)	.77

The new cohort differs from the previous one in the detection and management of eICA arteriopathy, and in the wider use of hydroxyurea at a higher dose despite a similar age at treatment initiation but the significant reduction of SCI-risk (P=.009) observed in the new cohort compared with the previous one is associated with the detection and management of eICA-arteriopathy but not with the wider use of hydroxyurea, age at initiation or dose

2. New cohort early eICA-assessed/managed with chronic-transfusion when eICA-TAMMV≥200 cm/s or stenosis

a. SCI-risk according to intracranial or eICA-arteriopathy

	OR (95% CI)	***P***
Intracranial (TAMMV≥ 200 cm/s or stenosis)	1.1 (0.3-3.6)	.884
Isolated eICA (TAMMV≥200 cm/s or stenosis)	2.7 (0.7-11.1)	.166
Isolated eICA (TAMMV≥160 cm/s or stenosis)	4.5 (1.5-13.9)	**.008***
Isolated eICA TAMMV 160-199 & no eICA- stenosis	4.9 (1.3-18.5)	**.019***

b. Impact of age at HU initiation on arteriopathy & SCI-risks

	HU initiated < 6y	
	OR (95% CI)	***P***
Intracranial (TAMMV≥ 200 cm/s or stenosis)	0.32 (0.15-0.69)	**.004***
Isolated eICA (TAMMV≥200 cm/s or stenosis)	0.61 (0.20-1.87)	.391
Isolated eICA (TAMMV≥160 cm/s or stenosis)	0.63 (0.27-1.46)	.282
SCI	0.56 (0.47-4.02)	.560

Intracranial or eICA-TAMMVs≥200 cm/s or eICA-stenosis rapidly treated with chronic-transfusion were no longer risk factors for SCI, while eICA TAMMVs 160-199 cm/sec without stenosis, maintained on hydroxyurea were significant risk factors for SCI. This suggests placing all patients with eICA-TAMMV ≥ 160 cm/s on chronic transfusion, even in the absence of stenosis.

Initiation of hydroxyurea before age 6 was effective in preventing abnormal-TCD occurrence but did not prevent eICA-TAMMV ≥ 160 cm/s and SCI occurrence in this cohort without systematic recourse to hydroxyurea.

3. Overall cohort

Predictive Risk Factors for SCI among baseline biological parameters
Multivariate Cox regression analysis

	HR (95%CI)	***P***
Reticulocyte count per 1x10^9/L increase	1.003 (1.000-1.006)	**.029***
Total Bilirubin per 1 mmol/L increase	1.016 (1.001-1.031)	**.034***

Associated Risk Factors for SCI
Univariate logistic regression analysis

	OR (95%CI)	***P***
Age at first neck-MRA per one year increase	1.03 (1.02-1.14)	**.013***

In patients on hydroxyurea (n=234)
Multivariate logistic regression analysis

Leukocyte count per one x 109/L increase	1.126 (1.027-1.234)	**.011***
Mean Corpuscular Volume per one fL increase	1.053 (1.020-1.087)	**.001***

Baseline severe hemolytic anemia is predictive of SCI risk, making hydroxyurea a good candidate to reduce the risk of SCI, and justifying its earlier use before age 2. However, the assessment of eICA by color-Doppler-US and neck-MRA is necessary to detect eICA-TAMMV≥160 cm/s or stenosis requiring the initiation of chronic transfusion for SCI-prevention.

The impact of hydroxyurea on the risk of SCI is complex, beneficial through improvement in hemolytic anemia and reduction in leukocyte and reticulocyte counts, but potentially deleterious in small vessels through increased MCV in the absence of sufficient improvement in deformability.

The incidence of eICA-arteriopathy and SCI remains to be assessed in children born since 2015 in whom hydroxyurea was introduced before age 2.

Figure 5. Summary of results. The main results obtained in the different cohorts and the messages they deliver to improve the management of cerebral vasculopathy and reduce the incidence of silent cerebral infarct (SCI).

and low-income countries,[36-38] its impact on preventing SCI is unclear. No robust randomized trials testing HU for the prevention for SCI have been reported, except for a trial that was limited to 12 randomized patients.[39] Our observational cohort reports a lower SCI incidence on chronic transfusion than on HU and the absence of SCI incidence after successful alloSCT, confirming previous reports from multicenter studies.[40-42] As severe anemia and hemolysis are risk factors for SCI, and given that both parameters can be reduced by HU, we expected HU to have a preventive impact on the risk of SCI, but this could not be demonstrated in this study. We only found a favorable impact of HU on the incidence of abnormal TCD, which was reduced, as already reported in numerous studies,[1,43-45] but HU did not significantly reduce the eICA TAMMV ≥160 cm/s incidence. As we found that the main risk factor for patients with eICA TAMMV ≥160 cm/s is the presence of eICA kinking, it is not surprising that HU was less efficient in reducing intracranial velocities. However, we previously showed that kinking may develop during infancy as a function of anemia severity, suggesting that HU via hemoglobin increase could have long-term benefits, reducing kinking and SCI risk.[22] HU was not administered to asymptomatic children in patients born before December 2014; thus, it is possible that early systematic initiation of HU in asymptomatic patients could have reduced the risk of kinking and SCI. Even in patients without arteriopathy, HU was not associated with lower SCI risk, but this may be biased by HU only being administered to symptomatic patients. However, the maximum tolerated dose was reached. Understanding why HU was not effective in preventing SCI is elusive at this point, but several suggestions can be made. The HU-induced increase in fetal hemoglobin (HbF) levels is associated with improved oxygen uploading in lungs, and reduced polymerization and sickling, but the high affinity of HbF for oxygen may reduce oxygen delivery to the brain and could be a risk factor for SCI. However, no significant association was found between HbF levels and risk of SCI in patients on HU, making this hypothesis untenable. Furthermore, we found that high baseline MCV is a risk factor for SCI and that, among HU patients, those with SCI had higher MCV than those without, as previously reported in another cohort study.[46] Thus, in small vessels, HU could be a risk factor for SCI by increasing MCV in the absence of sufficient deformability improvement. Connes *et al*. tested numerous SCA patients on HU with oxygen-gradient ektacytometry[47] and reported that approximately 20% of SCA patients may have an increase in MCV without significant improvement in red blood cell deformability (*F Bernaudin, personal communication, 2025*). This suggests the usefulness of testing drugs that could improve hemolytic anemia without increasing MCV, such as hemoglobin oxygen affinity modulators[48] or erythrocyte pyruvate-kinase activators,[49] for SCI prevention. Figure 5 shows a summary of the main results and the messages they deliver to improve the management of cerebral vasculopathy and reduce the incidence of silent cerebral infarct.

This cohort study has some limitations. This is a single-center, longitudinal, prospective, observational, SCA cohort study with no control group. Thus, causality cannot be established, and determination of effectiveness or assessment of net benefits cannot be inferred, in contrast with randomized controlled trials. Furthermore, the algorithm used in this cohort study cannot be applied in low-income countries where the cost, availability, and safety of blood products are of concern. Moreover, as HU was only given to symptomatic or 'at risk' patients, results from this cohort cannot be compared to those in which HU was given to asymptomatic children. Nonetheless, this study offers the advantages of long-term and accurate data collection in a cohort from one referral center where management care and procedures have been standardized.

In summary, HU was associated with the reduction of abnormal TCD incidence, but not with a reduction of SCI in this cohort without systematic recourse to HU. Controlled trials are still needed to assess the impact of systematic initiation of HU on the prevention of SCI. On the other hand, this study argues for the routine use of cervical color-Doppler ultrasonography and neck MRA to detect eICA arteriopathy, a significant risk factor for SCI. Chronic transfusion and alloSCT to manage eICA TAMMV ≥200 cm/s or eICA stenosis were the best protocols to reduce SCI risk. Prompt initiation of chronic transfusion is also recommended for eICA TAMMV 160-199 cm/s, a risk factor for SCI, even in the absence of stenosis.

Disclosures

FB has been a consultant to AddMedica, BlueBird Bio, Global Blood Therapeutics, and Terumo, and is an advisor to Vertex and Pfizer. All of the other authors have no conflict of interests to disclose.

Contributions

FB designed and performed the research, collected the data, performed the statistical analyses, interpreted the data, and wrote the manuscript. SV designed the study, performed Doppler ultrasound scans and MRI/MRA, analyzed and interpreted data, and co-wrote the manuscript. CA, AK and CJ designed the study, collected and interpreted data, and co-wrote the manuscript. FB, CA, AK, IH, FM, AM, CD and RE participated in the management of patient care. MV and SV performed Doppler ultrasound scans and MRI/MRA. All authors critically reviewed and approved the manuscript.

Acknowledgments

The authors would like to thank the patients and their parents for their participation, all the nurses and physi-

cians at the Centre Hospitalier Intercommunal de Créteil (CHIC), France, and at the bone marrow transplant units who contributed to the management of patient care, and Dr. Martine Torres for her critical reading of the manuscript and editorial assistance. This study was presented in abstract form at the EHA meeting in Madrid, Spain (June 13-16, 2024) and at the 19th Annual Sickle Cell & Thalassemia Conference in London, UK (October 2-5, 2024).

Funding

This work was supported in part by institutional grants "Programme Hospitalier de Recherche Clinique" (IDF05001 and NCT01340404) from the French Ministry of Health.

Data-sharing statement

For original data, please contact francoise.bernaudin@chicreteil.fr and camille.jung@chicreteil.fr

References

1. DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020;4(8):1554-1588.
2. Bernaudin F, Verlhac S, Freard F, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. J Child Neurol. 2000;15(5):333-343.
3. Schatz J, Brown RT, Pascual JM, Hsu L, DeBaun MR. Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. Neurology. 2001;56(8):1109-1111.
4. Pegelow CH, Macklin EA, Moser FG, et al. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. Blood. 2002;99(8):3014-3018.
5. Miller ST, Macklin EA, Pegelow CH, et al. Cooperative Study of Sickle Cell Disease. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. J Pediatr. 2001;139(3):385-390.
6. Kinney TR, Sleeper LA, Wang WC, et al. Silent cerebral infarcts in sickle cell anemia: a risk factor analysis. The Cooperative Study of Sickle Cell Disease. Pediatrics. 1999;103(3):640-645.
7. Bernaudin F, Verlhac S, Arnaud C, et al. Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. Blood. 2011;117(4):1130-1140; quiz 1436.
8. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. Br J Haematol. 2009;146(3):300-305.
9. Debaun MR, Sarnaik SA, Rodeghier MJ, et al. Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, gender and relative high systolic blood pressure. Blood. 2012;119(16):3684-3690.
10. Debaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood. 2012;119(20):4587-4596.
11. Bernaudin F, Verlhac S, Coïc L, Lesprit E, Brugières P, Reinert P. Long term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler. Pediatric Radiol. 2005;35(3):242-248.
12. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288-294.
13. Gerald B, Sebes JI, Langston JW. Cerebral infarction secondary to sickle cell disease: arteriographic findings. AJR Am J Roentgenol. 1980;134(6):1209-1212.
14. Calviere L, Viguier A, Guidolin B, Tall P, Larrue V. Cervical artery stenoses in sickle cell disease. Eur Neurol. 2007;58(2):120-121.
15. Gorman MJ, Nystrom K, Carbonella J, Pearson H. Submandibular TCD approach detects post-bulb ICA stenosis in children with sickle cell anemia. Neurology. 2009;73(5):362-365.
16. Deane CR, Goss D, Bartram J, et al. Extracranial internal carotid arterial disease in children with sickle cell anemia. Haematologica. 2010;95(8):1287-1292.
17. Telfer PT, Evanson J, Butler P, et al. Cervical carotid artery disease in sickle cell disease: clinical and radiological features. Blood. 2011;118(23):6192-6199.
18. Verlhac S, Balandra S, Cussenot I, et al. Extracranial carotid arteriopathy in stroke-free children with sickle cell anemia: detection by submandibular Doppler sonography. Pediatr Radiol. 2014;44(5):587-596.
19. Bernaudin F, Verlhac S, Arnaud C, et al. Chronic and acute anemia and extracranial internal carotid stenosis are risk factors for silent cerebral infarcts in sickle cell anemia. Blood. 2015;125(10):1653-1661.
20. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5-11.
21. Verlhac S. University Hospital Robert Debré Paris. Tutorial : Cerebral Doppler in Sickle Cell Anemia. https://onedrive.live.com/?redeem=aHR0cHM6Ly8xZHJ2Lm1zL2YvcyFBcmpNWUZPMnV3R0JwRFJmRUloMTk3Y3dhbXA3P2U9dm53Ukpy&cid=8101BBB65360CCB8&id=8101BBB65360CCB8%214669&parId=8101BBB65360CCB8%214660&o=OneUp Accessed June 5, 2025.
22. Bernaudin F, Arnaud C, Kamdem A, et al. Incidence, kinetics, and risk factors for intra- and extracranial cerebral arteriopathies in a newborn sickle cell disease cohort early assessed by transcranial and cervical color Doppler ultrasound. Front Neurol. 2022;13:846596.
23. Bernaudin F, Verlhac S, Arnaud C, et al. Long-term treatment follow-up of children with sickle cell disease monitored with abnormal transcranial Doppler velocities. Blood. 2016;127(14):1814-1822.
24. Adams RJ, McKie V, Nichols F, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med. 1992;326(9):605-610.
25. Adams RJ, McKie VC, Carl EM, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann Neurol. 1997;42(5):699-704.
26. Fullerton HJ, Adams RJ, Zhao S, Johnston SC. Declining stroke rates in Californian children with sickle cell disease. Blood. 2004;104(2):336-339.
27. Kwiatkowski JL, Voeks JH, Kanter J, et al. Post-STOP Study Group. Ischemic stroke in children and young adults with sickle cell disease in the post-STOP era. Am J Hematol. 2019;94(12):1335-1343.
28. Oluwole O, Brunson AM, Adesina OO, et al. Rates of strokes in

Californians with sickle cell disease in the post-STOP era. Blood. 2024;144(24):2517-2527.
29. Kanter J, Phillips S, Schlenz AM, et al. Transcranial Doppler screening in a current cohort of children with sickle cell anemia: results from the DISPLACE study. J Pediatr Hematol Oncol. 2021;43(8):e1062-e1068.
30. Davidow KA, Miller R, Phillips SM, et al. DISPLACE study shows poor quality of transcranial Doppler ultrasound for stroke risk screening in sickle cell anemia. Blood Adv. 2024;8(13):3444-3452.
31. Rothman SM, Fulling KH, Nelson JS. Sickle cell anemia and central nervous system infarction: a neuropathological study. Ann Neurol. 1986;20(6):684-690.
32. Verlhac S, Ithier G, Bernaudin F, et al. Evolution of extracranial internal carotid artery disease in children with sickle cell anemia. Stroke. 2022;53(8):2637-2646.
33. Pavlakis SG, Bello J, Prohovnik I, et al. Brain infarction in sickle cell anemia: magnetic resonance imaging correlates. Ann Neurol. 1988;23(2):125-130.
34. Seibert JJ, Glasier CM, Kirby RS, et al. Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: an 8-year study. Pediatr Radiol. 1998;28(3):138-142.
35. Verlhac S, Bernaudin F, Tortrat D, et al. Detection of cerebrovascular disease in patients with sickle cell disease using transcranial Doppler sonography: correlation with MRI, MRA and conventional angiography. Pediatr Radiol. 1995;25 Suppl 1:S14-19.
36. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crisis in sickle cell anemia. N Engl J Med. 1995;332(20):1317-1322.
37. Thornburg CD, Files BA, Luo Z, et al; BABY HUG Investigators. Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood. 2012;120(22):4304-4310; quiz 4448.
38. Tshilolo L, Tomlinson G, Williams TN, et al. REACH Investigators. Hydroxyurea for children with sickle cell anemia in Sub-Saharan Africa. N Engl J Med. 2019;380(2):121-131.
39. Casella JF, Furstenau DK, Adams RJ, et al Hydroxyurea to prevent brain injury in children with sickle cell disease (HU Prevent)-a randomized, placebo-controlled phase II feasibility/ pilot study. Am J Hematol. 2024;99(10):1906-1916.
40. Bernaudin F, Socie G, Kuentz M, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. Blood. 2007;110(7):2749-2756.
41. Walters MC, Hardy K, Edwards S, et al. Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease. Biol Blood Marrow Transplant. 2010;16(2):263-272.
42. Bernaudin F, Verlhac S, Peffault de Latour R, et al. DREPAGREFFE Trial Investigators. Association of matched sibling donor hematopoietic stem cell transplantation with transcranial Doppler velocities in children with sickle cell anemia. JAMA. 2019;321(3):266-276.
43. Lagunju I, Brown BJ, Sodeinde O. Hydroxyurea lowers transcranial Doppler flow velocities in children with sickle cell anaemia in a Nigerian cohort. Pediatr Blood Cancer. 2015;62(9):1587-1591.
44. Adegoke SA, Macedo-Campos RS, Braga JAP, Figueiredo MS, Silva GS. Changes in transcranial Doppler flow velocities in children with sickle cell disease: the impact of hydroxyurea therapy. J Stroke Cerebrovasc Dis. 2018;27(2):425-431.
45. Hankins JS, McCarville MB, Rankine-Mullings A, et al. Prevention of conversion to abnormal transcranial Doppler with hydroxyurea in sickle cell anemia: a Phase III international randomized clinical trial. Am J Hematol. 2015;90(12):1099-1105.
46. Nottage KA, Ware RE, Aygun B, et al. Hydroxycarbamide treatment and brain MRI/MRA findings in children with sickle cell anaemia. Br J Haematol. 2016;175(2):331-338.
47. Boisson C, Nader E, Renoux C. Shear-stress-gradient and oxygen-gradient ektacytometry in sickle cell patients at steady state and during vaso-occlusive crises. Cells. 2022;11(3):585.
48. Estepp JH, Kalpatthi R, Woods G, et al. Safety and efficacy of voxelotor in pediatric patients with sickle cell disease aged 4 to 11 years. Pediatr Blood Cancer. 2022;69(8):e29716.
49. Saraf SL, Hagar RW, Idowu M, et al. Multicenter, phase 1 study of etavopivat (FT-4202) treatment for up to 12 weeks in patients with sickle cell disease. Blood Adv. 2024;8(16):4459-4475.