Central Nervous System Complications and Management in Sickle Cell Disease: A Review

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Abstract

With advances in brain imaging and completion of randomized clinical trials (RCTs) for primary and secondary stroke prevention, the natural history of central nervous system (CNS) complications in sickle cell disease (SCD) is evolving. In order of current prevalence the primary CNS complications include silent cerebral infarcts (39% by 18 years), headache (both acute and chronic: 36% in children with sickle cell anemia (SCA), ischemic stroke (as low as 1% in children with SCA with effective screening and prophylaxis, but ~11% in children with SCA without screening) and hemorrhagic stroke in children and adults with SCA, 3% and 10%, respectively. In high income countries RCTs (STOP, STOP II) have demonstrated that regular blood transfusion therapy (typically monthly) achieves primary stroke prevention in children with SCA and high transcranial Doppler (TCD) velocities; after at least a year, hydroxycarbamide may be substituted (TWiTCH). Also in high income countries, RCTs have demonstrated that regular blood transfusion is the optimal current therapy for secondary prevention of infarcts for children with SCA and strokes (SWiTCH), or silent cerebral infarcts (SIT). For adults with SCD, CNS complications continue to be a major cause of morbidity and mortality, with no evidence-based strategy for prevention.

Introduction

With recent advances in medical treatment, the natural history of sickle cell disease (SCD) continues to evolve as morbidity and mortality fall. In the last 40 years significant clinical research efforts have been focused on preventing initial and subsequent central nervous system (CNS) injuries. In children and adults with SCD, from the 1970s until 2010, approximately 75% of the infarcts were ischemic and the remainder hemorrhagic.[1,2] In the 1990s , the prevalence of the first transient ischemic attack, infarctive or hemorrhagic stroke in children with SCA younger than 19 years was 11%[3] and 24% by 45 years for adults with SCA.[3] Since the 1990s, four major randomized trials to prevent CNS injuries have been completed providing evidence based guidelines for primary and secondary stroke prevention in children with SCA.[4-8]

Unfortunately in sub-Saharan African countries and India, where greater than 90% of the children with SCA are born[9], there are no evidence based primary and secondary stroke prevention strategies. Thus before their 18th birthday, approximately 50% of the children with SCA will have either an overt or silent cerebral infarct (SCI), Figure 1.

The pathophysiology of ischemic stroke and cerebral hemorrhage in SCD is not well defined[10] but over the last three decades, we have begun to understand more about clinical risk factors and potential mechanisms of brain injury, Figure 2. At least six risk factors are associated with cerebral ischemic events in SCD:

1. low oxygen content associated with

   a. lower oxygen saturation[11,12] or
   b. acute drop in hemoglobin[13,14]
2. presence of cerebral vasculopathy compromising cerebral blood flow (CBF), acting synergistically with the compensatory increase in CBF secondary to
   a. anemia and
   b. increased percentage of hemoglobin S to decrease cerebrovascular reserve. The substantial impact on hemoglobin S levels on CBF is a unique attribute of SCD and must be considered in acute management of strokes when the goal is to rapidly lower hemoglobin S levels, Figure 3[15]
3. acute infection with fever [14] increasing cerebral metabolic demands'
4. cardiovascular risk factors as in the general population: hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and renal disease, ~~the last four in adults with SCD only~~[2]
5. presence of a prior cerebral infarct with the greatest risk being within two to three years of infarct occurrence, regardless of treatment[1,13]
6. rapid increases in hemoglobin levels typically greater than 12 g/dl with either auto-transfusion from splenic or liver sequestration [16] or blood transfusion therapy.[17]

Adults with SCD have different risk factors for strokes and different prevalence of ischemic and hemorrhagic stroke than children with SCD. In a large population study, the biggest risk factor for strokes in children with SCD was hypertension; whereas, in adults with SCD, the biggest risk factors included not only hypertension, but also diabetes mellitus, hyperlipidemia, atrial fibrillation, and renal disease.[18] The

determinants of cognition in adults with SCD are not well documented. In asymptomatic adults with SCA undergoing cognitive testing, performance IQ was not associated with sex, white blood cell count, platelet count, or levels of hemoglobin F, lactate dehydrogenase, or hemoglobin ~~levels~~.[19] This review will initially focus on the epidemiology of the most common CNS complications, primarily in SCA, and then will review the evidence for primary and secondary stroke prevention in high and low income countries.

Silent Cerebral Infarcts Are Common in SCA

SCI is the most common permanent neurological injury in children with SCA, and probably in adults as well. The only current strategy to detect a SCI is a 30-60 minute ~~brain image with~~ magnetic resonance image (MRI). The most complete definition of a SCI has both a neuroimaging component and an assessment by a neurologist.[7] The imaging component requires a signal abnormality that is at least 3 mm in one dimension and that is visible in two planes on fluid-attenuated inversion recovery (FLAIR) T2-weighted images. The neurology component includes a normal neurological examination or an abnormality on examination that could not be explained by the location of the brain lesion or lesions.[7] The neurological evaluation by a neurologist is critical because individuals that are previously labeled as having a SCI may in fact have an undetected stroke, a higher risk category for future neurological morbidity.[20]

SCIs are common in infants and pre-school children. Approximately 25% of children

with SCA will have an infarct prior to their 6th birthday[21] and 39% by their 18th birthday,[22] with no evidence that the number of children with new SCI plateaus through 20 years of age, Figure 4. Well established risk factors for SCI include low baseline hemoglobin,[23] particularly before age three years,[22] relative hypertension,[23] acute anemia events[13,14,22] and evidence of cerebrovascular disease on intracranial[24,25] and extracranial[22] MR angiography (MRA). Unfortunately, the presence of multiple SCI risk factors together or independently has not led to accurate prediction of SCI. In children with SCD and SCI that do not have either SCA or hemoglobin S-β^0 thalassemia (entry criteria for the SIT Trial) management should be based on an individual basis until large multi-center studies are completed to identify optimal management strategies for this population. A more detailed review on the natural history, detection, and mimics of SCI in SCD has been recently published.[26]

Ischemic Lesions of the Brain May Be Temporary or Evolve to Infarcts

Children with SCA are at increased risk for cerebral lesions likely to be ischemic, but not necessarily progressing to infarction. Diffusion weighted imaging (DWI) allows detection of acute ischemic events that occurred within the previous ten days. As part of the screening protocol to detect SCI in the SIT Trial[7] children (n=652) received MRI of the brain with DWI.[27] In this asymptomatic group of children, the incidence of acute silent cerebral ischemic events (ASCIEs) was 47.3 per 100 patient-years (95% CI, 22.7- 87.2),[27] nearly seven times higher than the anticipated incidence of infarct recurrence in children with pre-existing SCI,[28] but only one of two children with follow-up MRI of the brain had an infarct. These results strongly suggest that brain ischemia

in children with SCA is common and potentially reversible. Undoubtedly, as MRI scanners continue to improve in magnet strength, resulting in improvement in detecting cerebral infarcts, the prevalence of ischemic brain injury and SCI will also increase[29] and the epidemiology of both injuries will change. However, MRI of the brain in children and adults with SCD cannot replace a thorough neurological examination because in the general population, as many as 33% of the individuals with ~~a~~ confirmed strokes ~~may~~ have negative DWI MRI of the brain.[30]

Acute and Chronic Headaches Are Challenging to Manage in SCD

Headache is one of the most common neurologic symptom in SCD, both acutely[31] and chronically.[32] In acute headache, hemorrhagic stroke (see supplement for images) must be considered. In Hines'[31] study of acute care visits by children with SCA, headache was the chief complaint in 3.8% (102 of 2685). In this group of children presenting with acute headaches, 6.9% (7 of 102) had clinically significant CNS pathology requiring immediate medical management (3 venous thrombosis, 3 intracranial hemorrhage, 1 ischemic stroke).[31] Acute CNS events associated with headaches were more likely with older age, history of stroke, transient ischemic attack, or seizure, neurologic symptoms, and focal neurologic findings.[31] Unfortunately, no clinical features were identified to clearly separate those who did or did not require immediate medical management. Neuroimaging was performed in 42.2% of visits, and acute CNS events were identified in 16.3% of studies. Distinguishing whether the headache is chronic or a new symptom requiring emergent imaging is critical. The decision to obtain a MRI of the brain involves eliciting a thorough personal and family

history of chronic migrainous symptoms and careful examination of level of consciousness, vision and any focal signs. For nocturnal or early morning headaches, space-occupying lesion or idiopathic intracranial hypertension[33] must be excluded. For these reasons, we believe a neurologist should be consulted for severe new onset acute headaches.

MRI is not essential for children with SCA and chronic headache, including migraines. In the largest retrospective cross-sectional study in children with SCA (n=872), recurrent headaches (36.1%) and migraines (15.1%) were both common, but neither were associated with SCI.[34] Referral to a neurologist is advised for assessment of chronic headache and management with diet[35], psychological support and prophylactic medication (Pizotifen, Propranolol, Topiramate or Valproic acid). We do not recommend using triptans for acute migrainous headaches because of the risk of cerebral ischemia. Although headache is common, unfortunately, no specific evidence based guidelines for management have been developed for SCD.

Hemorrhagic Stroke and Aneurysms Are More Common in Adults

Intracerebral, intraventricular, subarachnoid (SAH), subdural and extradural hemorrhages have all been described in patients with SCD, (see supplement for images).[36] Hemorrhage, typically subarachnoid, has the highest incidence in young adults (20-30 years),[3,37] but is not uncommon in children.[3] Eleven of 325 children with SCD (3.4%) ~~with SCD~~ followed at the University of Illinois between 1975 and 1989 had SAH.[38] In a French cohort, 2.8% (7 of 251) of children with

SCD had either an intracranial hemorrhage or an un-ruptured aneurysm.[39,40]

Risk factors for cerebral hemorrhage are poorly defined, but include hypertension associated with the use of corticosteroids[36] or phenylephrine[41], recent transfusion[36], splenic sequestration[42] and hyper-viscosity associated with higher hemoglobin levels.[16]

Cerebral hemorrhage in adults is commonly related to aneurysm formation (see supplement for images).[43] In a large study (n=709), the prevalence of aneurysm was 1.2% and 10.8% in children and adults with SCD, respectively.[44] The aneurysms which rupture are typically relatively small (2-9 mm),[44] and located at the bifurcations of major vessels.[43,44]

Individuals with SCD and intracranial hemorrhage require immediate transfer to a tertiary hospital where a multidisciplinary team includes a neurosurgeon with vascular interventional neuroradiologist, neurosurgeon, neurologist and hematologist. We are unaware of any contra-indication to management of hemorrhage as for the general population.[44]

Extradural and Subdural Intracranial Hemorrhage May Occur Without Trauma

One of the most under-recognized complications of SCD is extradural or subdural hematoma in the absence of significant head trauma,[45,46] probably related to hypervascular areas of bone[47], bone infarction[48-50] or venous thrombosis[31] (see supplement for images). Bony infarction in the orbit may be associated with periosteal

hemorrhage and compressive optic neuropathy with risk of visual loss, while subgaleal hemorrhage, which may be substantial as there is a large potential space, may also occur.[51] These lesions are typically managed with appropriate supportive care and transfusion, but may require surgery.[52]

Seizures and Epilepsy Must Be Distinguished and Managed Appropriately

In the era prior to implementing primary stroke prevention strategy, between 7% and 10% of individuals with SCD ~~will~~ experience at least one seizure.[53,54] In the Jamaican cohort Study of Sickle Cell Disease, the five-year cumulative incidence of febrile convulsions was 2.2%.[54] Even in the context of a febrile or systemic illness, in patients with SCD, we recommend brain MRI for first seizure to exclude the possibility of a potentially treatable underlying cause, such as arterial ischemic stroke, sinovenous thrombosis, reversible posterior encephalopathy syndrome, fat embolism or cerebral abscess (see supplement for images). A history of seizures has been associated with SCI.[55]

Epilepsy (recurrent seizures) is two to three times more common than in the general population, and is associated with earlier death.[54,56] The majority of patients have focal abnormality on neuroimaging or electroencephalography[57] and cerebrovascular disease (see supplement for images).[58] Given the high rate of moyamoya in individuals with SCD, we do not recommend hyperventilation during electroencephalography because of the risk of ischemia.[59]

Central Nervous System Vasculopathy Is Associated with Stroke and SCI

Stenosis and occlusion of the large arteries of the circle of Willis have been recognized in SCD for more than 40 years on pathology[60] and contrast arteriography.[61] More recently less invasive techniques, including Transcranial Doppler ultrasound (TCD) and Magnetic Resonance Arteriography (MRA) have been used to detect and follow any improvement or progression, but they do not directly visualize the vessel diameter or wall and interpretation requires considerable skill. Higher hemoglobin levels provide better MRA images.

In the largest study to date (n=516), MRA-defined vasculopathy occurred in 10.3% of asymptomatic children with SCA without prior stroke. The presence of MRA defined cerebral vasculopathy was associated with SCI; although, the vast majority (84%) of children with SCA and SCI did not have MRA defined vasculopathy.[24] Among children with SCA and strokes, MRA is abnormal in 50-60% of children.[62,63] Among children with SCA and progressive vasculopathy, 100% had evidence of new cerebral infarct within 5.5 years.[62]

Despite the routine use of TCD to identify children with SCA at risk for overt strokes, several nuances of its use exist. First there are two different methods for imaging the intracranial vessels, the imaging and non-imaging techniques.[64] Both are routinely used with most pediatric radiology departments preferring the imaging technique and most research studies using the non-imaging technique. The relative benefits and challenges with each technique are discussed in depth elsewhere. [64]

The most important ~~fact~~ is that the threshold for transfusion used in the non-imaging technique is time averaged maximum velocity (TAMV) of 200 cm/sec which is well defined and may also be appropriate for the imaging technique,[65] while other investigators in a clinical trial setting have lowered the threshold of time averaged maximum velocity (TAMX in imaging machine) ≥185 cm/sec.[7] For imaging TCD, until a rigorous head to head study is done comparing these two techniques, we prefer the more conservative strategy, namely to lower the threshold for treatment to 180 to 185 cm/sec.

Another subtlety in the use of TCD is that in approximately 10% of the children, velocities are low or absent[66,67] perhaps related to vasculopathies such as moyamoya or extracranial vasculopathy.[68] However, MRA define vasculopathy without strokes ~~of the brain does not~~ predict future strokes or SCI and cannot be reliably applied as a substitute for the lack of a TCD measurement to stratify children with SCA into high or low risk future stroke groups

Treatment

In Children with SCA and Silent Cerebral Infarcts, Regular Blood Transfusion Decreases Infarct Recurrence

No strategy has been established for primary SCI prevention. The only current strategy is to prevent infarct recurrence in children with SCI. Despite the importance of detecting SCI because of the high rate of future strokes,[69] and SCIs,[28] as well a drop of a Full Scale IQ loss of 5 points[70] Figure 5, all of the studies to date have been from

high income countries because of the expense of performing MRI of the brain.

The Silent Cerebral Infarct Transfusion (SIT Trial; NCT00072761) was the only trial designed to determine whether blood transfusion therapy can prevent progression of infarct recurrence (stroke or SCI) in children with SCA and pre-existing SCI. Participants included children with SCA (5 to 15 years of age) and SCIs. In the RCT, 196 children with SCA and SCI were randomly allocated to receive either observation (standard therapy) or regular blood transfusion (experimental therapy) for 36 months. In participants receiving regular blood transfusion, there was 58% relative risk reduction in cerebral infarct recurrence (stroke or new or progressive SCI) when compared to the children in the observation arm.[7] When compared to observation, the benefit of blood transfusion therapy included an improvement of overall quality of life,[71] as well as a statistically significant decrease in the incidence of priapism, new onset symptomatic avascular necrosis of the hip, severe vaso-occlusive pain events that resulted in hospitalization and acute chest syndrome.[7] The number of children with SCA and SCI who needed to be transfused to prevent one recurrent infarct was 13.[7] However, the benefit of blood transfusion therapy to prevent infarct recurrence was incomplete. Some children in the transfusion therapy arm went on to develop infarct recurrence, Figure 6. Thus, the high burden of regular blood transfusion may decrease the enthusiasm for infarct recurrence prevention using regular blood transfusion therapy in children with pre-existing SCI.

Primary stroke prevention in children in high income countries is successful.

The single greatest advance in preventing neurological injury in children with SCA is initiating the use of TCD screening to identify a group of children at risk for future strokes, primary stroke prevention. The pivotal RCT demonstrated that children with elevated TCD measurements > 200 cm/sec receiving regular blood transfusion therapy (defined as ~~blood~~ transfusion ~~therapy~~ ~~between~~ three to six weeks with a goal of keeping the maximum hemoglobin S level < 30%) when compared to standard therapy (observation),will have an approximate 92% relative risk reduction in the rate of overt strokes. The number with elevated TCD measurements receiving transfusion therapy to prevent one stroke was seven.[4] When available, we prefer the use of erythrocytapheresis as the approach to regular transfusions because of the lower rate of iron accumulation.[72]

In tertiary care ~~medical~~ centers providing medical care for children with SCA, adherence to routine screening of children with SCA using TCD measurements coupled with regular blood transfusion therapy has dramatically reduced the rate of strokes. In one large tertiary care center the incidence rate of overt strokes declined a log fold ~~before and~~ after the introduction of routine screening with TCD with blood transfusion therapy, 0.67 and 0.06 strokes per 100 patient-years~~, respectively~~.[73]

SWiTCH [6] was a secondary stroke prevention trial in children with SCA. The primary objective of the trial was to complete a non-inferiority randomized trial of hydroxyurea and phlebotomy compared with blood transfusion therapy and chelation for 134 children with prior stroke who had already undergone at least 18 months of regular

transfusion.[6] The primary endpoint was a composite of recurrent stroke and liver iron concentration (LIC) measured by MRI. There were no strokes in the 66 participants randomly allocated to transfusions and chelation (standard therapy), but 7 (10%) in the 67 participants randomly allocated to hydroxyurea therapy and phlebotomy (experimental therapy). The trial was stopped for futility because there was no difference in LIC.[6]

Based in part on consistent findings of studies demonstrating that hydroxyurea therapy lowers TCD measurements, Figure 8, the TWiTCH trial (NCT01425307)[8] was funded. The main objective was a primary stroke prevention trial for children with SCA who had received at least 12 months of blood transfusion therapy for TCD velocities above 200 cm/sec. Children with SCA and prior elevated TCD velocities were randomly allocated to continue blood transfusion therapy and chelation (standard therapy (n=61) or start hydroxyurea therapy and phlebotomy (experimental therapy (n=60). Participants randomly allocated to the hydroxyurea and phlebotomy arm also simultaneously received blood transfusion therapy until the hydroxyurea MTD was reached (median approximately 6 months overlap). Treatment was scheduled to last for 24 months after random allocation, at which point the primary outcome, TCD ~~velocity~~, between the two arms were compared. After the first interim analysis, the trial was ended early because the non-inferiority was demonstrated (margin of 15 cm/s).

The management of children with both elevated TCD measurement and MRA defined severe cerebral vasculopathy cannot be determined from the TWiTCH trial.

Regardless of vasculopathy status of children with elevated TCD measurements, the event rate of strokes is very low, ~~<1 in 100 patient years~~, while receiving blood transfusion therapy. [74] Further, in approximately 20% of the children with elevated TCD measurements, the TCD measurements will remain elevated several years after regular blood transfusion has begun with no evidence that this group is more likely to develop future strokes when compared to the group that dropped their TCD measurement < 200 cm/sec after blood transfusion therapy.

Given the success of hydroxyurea therapy for primary prevention of strokes and the relative low risk to benefit ratio when compared to hematopoietic stem cell transplant (HSCT), we would recommend continuing blood transfusion therapy or switching to hydroxyurea therapy over HSCT for the perceived high risk group of children with MRA defined vasculopathy and elevated TCD measurements. To date there is no evidence that TCD measurement in individuals with SCA above 16 years of age is beneficial. In the only study to date, Valadi et al. evaluated 110 adults with SCA and controls and did not find any values that were elevated.[75]

Primary Stroke Prevention in Low and Middle Income Countries Is Just Beginning

No definitive approach has been applied for primary stroke prevention in children with SCA living in Africa or India, where the majority of the children ~~born with SCD live~~. Two strategies in Africa have been employed, a standard care protocol using hydroxyurea therapy,[76] initially using a moderate fixed dose of hydroxyurea therapy of 20 mg/kg (SPIN, NCT01801423).[77] The feasibility trial included children with SCA between 5 and

12 years of age with elevated TCD velocities. The early results indicated that the families are willing to participate in a formal trial.[77] Further in a short follow up of participants and a comparison group (< 18 months), there were initially no unwarranted toxicities when compared to a group of children with SCA that were screened, had TCD velocities < 200 cm/sec, and were followed prospectively. Perhaps most importantly, the early results suggest that children initially started on hydroxyurea therapy, instead of blood transfusion therapy, can have significant drops in their TCD measurements <200 cm/sec 3 months after starting therapy.[77]

The essential question for primary stroke prevention in low and middle income countries is what dose of hydroxyurea therapy maximizes the benefit and minimizes the toxicity. In a setting of high rates of life threatening bacterial infections and malaria, treatment with hydroxyurea therapy, a myelosuppressive agent, may result in an increased rate of infections or other complications. Given the low family income in urban northern Nigeria, < $700 per year,[78] the out of pocket costs of a routine complete blood count (CBC), approximately $5, for assessment of hydroxyurea therapy may be prohibitive. Thus limiting the financial burden for CBC surveillance for hydroxyurea related toxicity may decrease the financial barrier without potentially sacrificing safety. Based on the promising early results of the feasibility trial in Kano, Nigeria, SPIN, NCT01801423,[77] the National Institute of Neurological Diseases and Stroke funded a randomized clinical trial to determine the efficacy of 20 mg/kg/day versus 10 mg/kg/day of hydroxyurea therapy for primary stroke prevention in children with SCA living in Nigeria and Ghana (NCT02560935). For now, in low income countries where TCD

screening is initiated for primary stroke prevention and blood transfusion therapy is not routinely used, preliminary data suggest that a fixed dose of hydroxyurea therapy at 20 mg/kg/day is a reasonable starting point for treatment[77].

Blood Transfusion Therapy for Stroke Prevention Is Palliative in High Income Countries Standard treatment for secondary stroke prevention is blood transfusion therapy. However, even when blood transfusion therapy is initiated, 45% of the children with SCA will have infarct recurrence (both stroke and SCI) over a course of 5.5 years,[21] providing evidence that alternative options must be considered for this high risk population. Figure 7 depicts the unsatisfactory results of the treatment options for secondary infarct recurrence prevention in children with SCA and overt strokes.

Given the evidence that blood transfusion therapy is palliative for secondary stroke prevention,[62] we believe after an initial stroke, alternative treatment options should be considered. Current evidence strongly suggests that HSCT decreases the rate of stroke recurrence;[79,80] however, most children and adults do not have a viable donor. A range of revascularization procedures have become an option for patients with internal carotid artery occlusion and moyamoya collaterals.[81] Regrettably no RCT has been introduced to rigorously assess standard care of regular blood transfusion therapy versus neurosurgery and regular blood transfusion therapy. Given the unknown risk to benefit ratio of HSCT and revascularization procedures for secondary stroke prevention, we strongly recommend that single or multi-institutional studies be

registered with clinicaltrials.gov so we can collectively learn from these variations in practices with no clear superior strategy for secondary stroke prevention.

Strategies Are Just Emerging for Secondary Prevention of Strokes in Low and Middle Income Countries

Given the challenges of routine blood transfusion therapy in low and middle income countries, no definitive strategy has emerged for secondary stroke prevention. However several investigators in these settings have elected to use hydroxyurea therapy as opposed to no therapy. Using pooled analysis comparing blood transfusion therapy to hydroxyurea therapy and no therapy, the expected stroke recurrence incidence rates were 1.9 (95 CI 1.0-2.9), 3.8 (95% CI 1.9-5.7) and 29.1 (95% CI 19.2-38.9) events per 100 patient years, respectively.[20] A secondary stroke prevention trial (NCT pending) is now funded in Nigeria to determine the efficacy of stroke recurrence using 20 mg/kg/day versus 10 mg/kg/day of hydroxyurea therapy. The completion of the trial is not expected to occur for an additional four years. In the meantime, we believe that the available data suggest that treatment with hydroxyurea therapy for secondary prevention of strokes is a reasonable alternative when compared to no therapy at all.

Summary

As a direct result of completed RCTs (STOP, STOP II, SIT, and TWiTCH) in children with SCA, a new standard of care has emerged for primary and secondary stroke prevention. Based on the preponderance of evidence, the use of hydroxyurea therapy

clearly decreases TCD measurements, the main modifiable risk factor for overt strokes. Further bolstering the evidence of the impact of hydroxyurea therapy on decreasing TCD measurements, the TWiTCH trial has demonstrated the non-inferiority of hydroxyurea therapy to blood for primary stroke prevention in children with SCA with high TCD velocities without vasculopathy on MRA who have already been transfused for a year. In low and middle income countries, where the majority of children with SCA are born, and blood transfusion therapy is not routinely available, primary and secondary stroke prevention RCTs are underway to determine the optimal hydroxyurea dose that maximizes benefits and limits toxicity, while potentially minimizing laboratory surveillance. Very few observational studies and no RCTs in adults with SCD have been undertaken for primary and secondary CNS complications (strokes, hemorrhage, and aneurysms). Although there have been significant strides in preventing CNS complications in the last 25 years, future research will need to focus on adults with SCD and individuals with SCD other than SCA, a group still at considerable risk for CNS morbidity.

Authorship

Drs. DeBaun and Kirkham contributed equally to writing this paper. There are no conflicts of interest to disclose.

Figure 1: In sub-Saharan African countries and India, where primary prevention is not routinely practiced, the pie chart depicts the prevalence of overt strokes and silent cerebral infarct in ~~a~~ 1,000 children born with sickle cell anemia followed for 18 years (based on an assumption that 11%[3] will have a stroke and 39% will have silent cerebral infarcts prior to the 18th birthday, [21] see text for details).

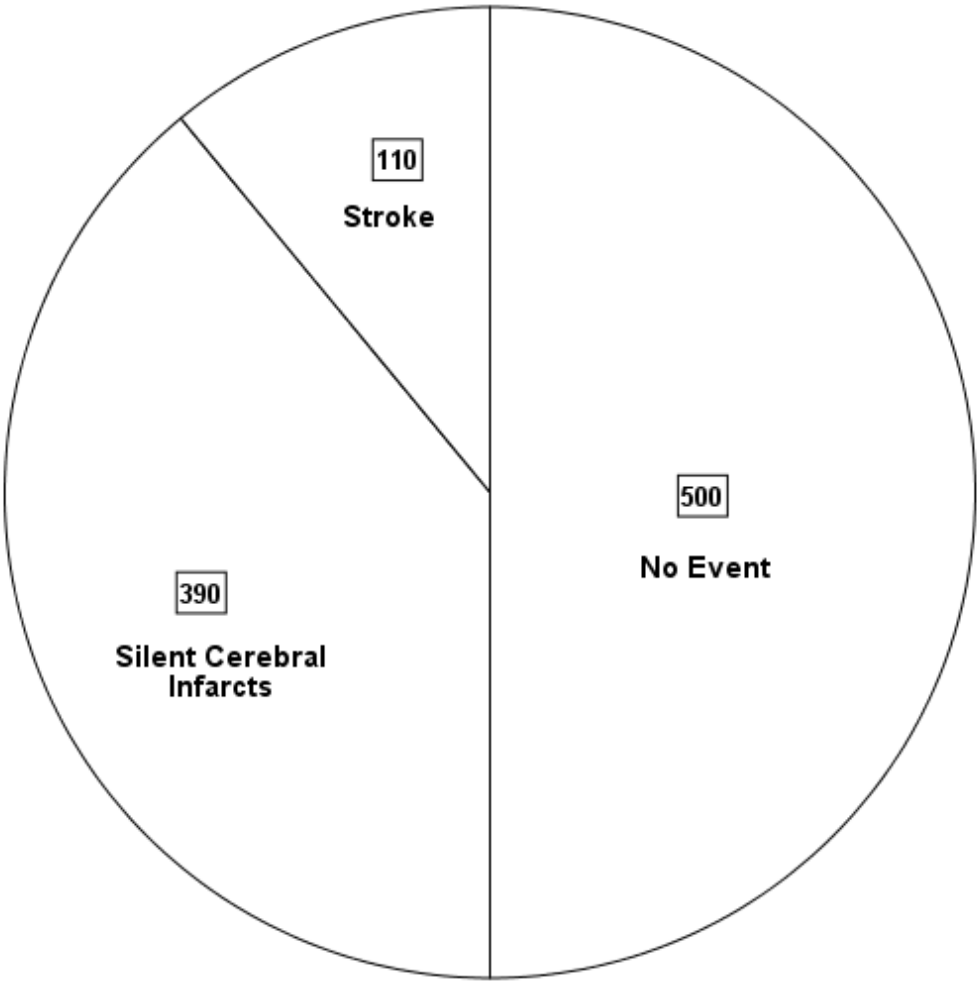


Figure 2. Established risk factors for ischemic injury of the brain in children and adults with sickle cell anemia.

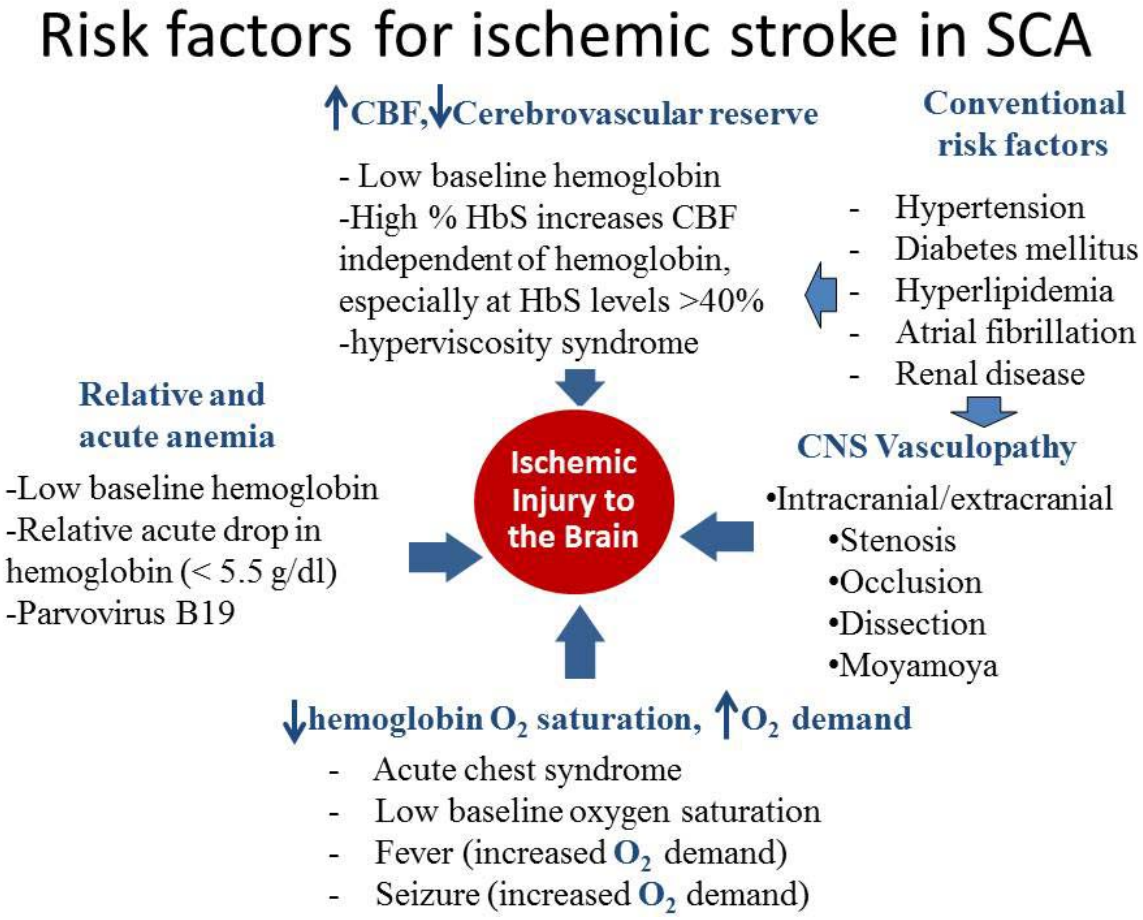


Figure 3. The critical relationship between cerebral blood flow and hemoglobin S levels in individuals with sickle cell anemia.

The study conducted by Hurlet Jensen et al.[15] describes the unique relationship between hemoglobin (Hb) and hemoglobin S levels (HbS) and cerebral blood flow (CBF) in individuals with sickle cell anemia. As hemoglobin levels increase CBF decreases (r= -0.68, p=.006). As hemoglobin S levels increases CBF increases (r=.080, p=.0003). In a stepwise multiple regression equation with Hb and HbS, only hemoglobin S was accepted and predictive of cerebral blood flow (r=0.70, p=0.01).

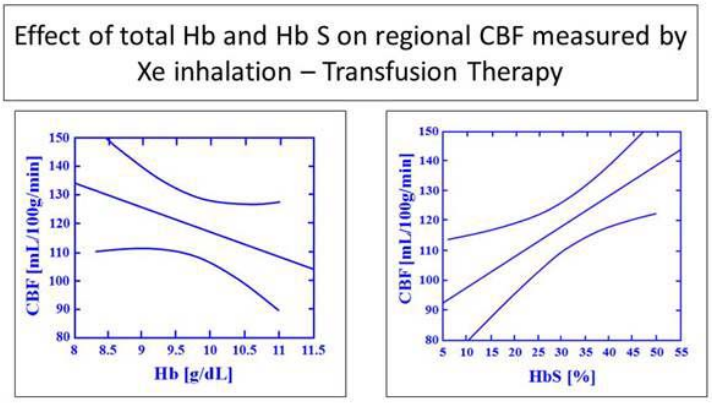


Figure 4. Prevalence of silent cerebral infarcts in children with sickle cell anemia.

The figure below displays the cumulative prevalence of silent cerebral infarcts in children with SCA based on 4 cross-sectional studies [21,22,82-85] and one longitudinal study.[22] The cumulative prevalence of silent cerebral infarcts strongly suggests that the incidence rates of silent cerebral infarcts dose not plateau in unselected children and young adults up to 20 years of age with SCA.

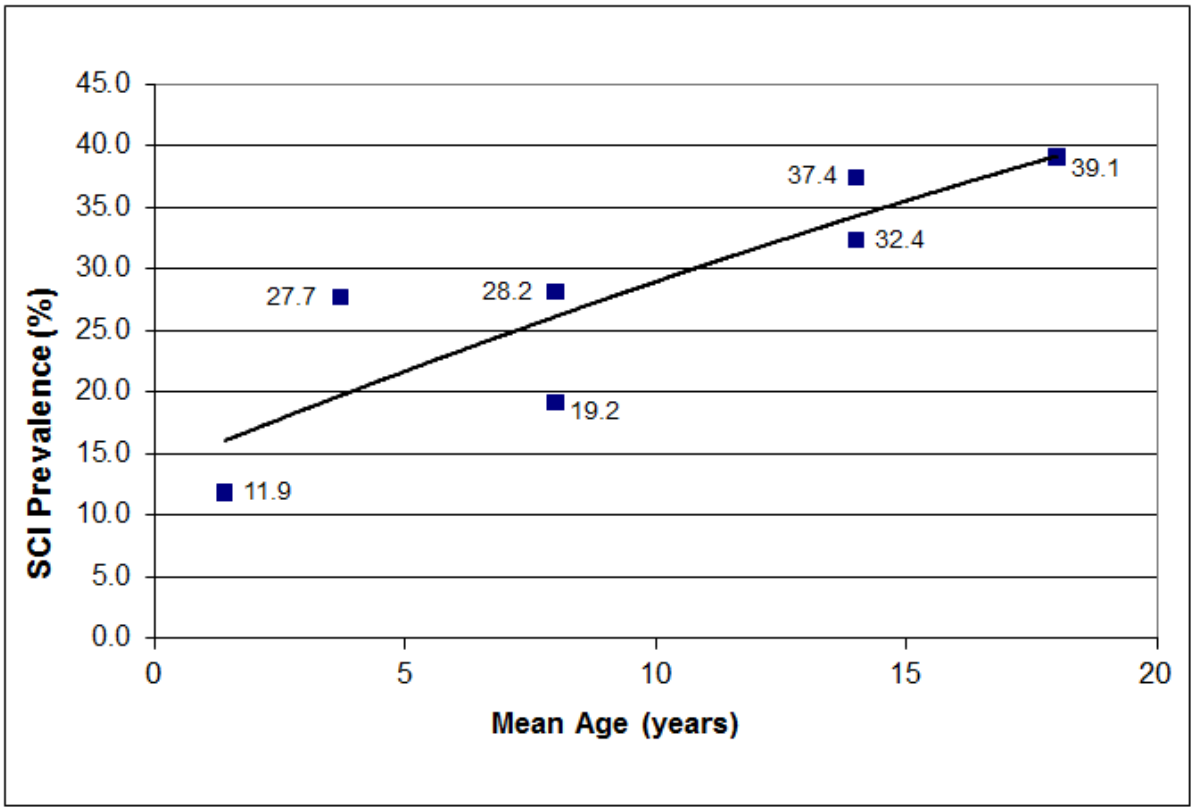


Figure 5. Meta-analyses for all studies in children with sickle cell anemia that included Full Scale IQ for those with and without SCIs.

The meta-analyses include a total of 10 publications comparing the mean difference in Full Scale IQ between those children with sickle cell anemia with and without silent cerebral infarcts (SCI). The x-axis reflects the mean Full Scale IQ difference between those with and without an SCI. The horizontal lines represent the upper and lower boundaries of the 95% confidence interval. If the 95% confidence interval overlaps zero or crosses the zero threshold then no statistical differences were observed in that study. The black and grey diamond represents the results of the fixed and random effect models. The edges of the diamonds represent the 95% confidence interval of the meta- analyses for the fixed and random effect models (adapted from Am J Hematol. 2014 Feb;89(2) :162-7).[85]

		SCD without SCI			SCD with SCI			
Reference	Study	Mean	N	SD	Mean	N	SD	MD [95% CI]
Armstrong et al 1996	1	90	105	17.42	82.8	21	13.29	-7.20 [-13.79; -0.61]
Steen et al 1998	2	78.9	12	8.9	70.6	10	12.1	-8.30 [-17.33; 0.73]
Watkins et al 1998	3	86.03	30	12	79	4	5.7	-7.03 [-14.08; 0.02]
Bernaudin et al 2000	4	86.6	104	17.1	82.6	17	15.7	-4.00 [-12.15; 4.15]
Brown et al 2000	5	81.67	30	16.68	81.91	11	14.43	0.24 [-10.17; 10.65]
Wang et al 2001	6	84.8	122	13.5	77.2	43	13.7	-7.60 [-12.34; -2.86]
Thompson et al 2003	7	90.2	93	13.1	85	29	12.6	-5.20 [-10.50; 0.10]
Kral et al 2006	8	87.59	22	11.42	90.6	5	3.05	3.01 [-2.46; 8.48]
Hijmans et al 2011	9	80	9	9	79	12	14.4	-1.00 [-11.05; 9.05]
SITT	10	99.53	51	13.08	92.94	171	12.5	-6.59 [-10.64; -2.54]

Overall Effect (MD) [95% CI]: -4.76 [-7.20; -2.33]
Test for Overall Effect: z = -3.83 (p < .001)
Test of Heterogeneity: q = 12.88, df = 9 (p = .17)

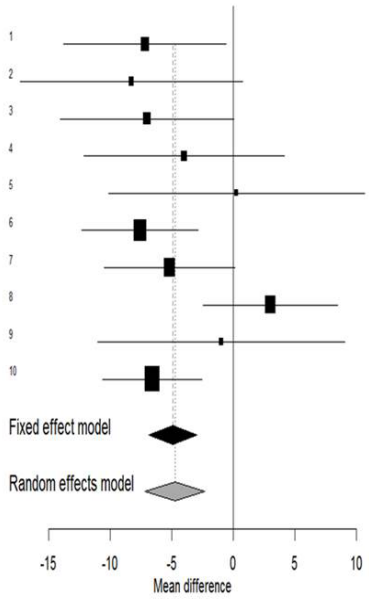


Figure 6. A hypothetical cohort of 1,000 children with sickle cell anemia and pre-existing silent cerebral infarcts followed for five years.

Events are defined as either silent cerebral infarcts or strokes for children with sickle cell anemia. The figure depicts the number of children in the cohort with infarct recurrence rate (overt and ~~silent cerebral infarct)~~ based on no therapy (4.5 events per 100 patient years) or regular blood transfusion (2.0 events per 100 patient years).[7] To provide a frame of reference on the absolute number of children with infarct recurrence, we have included the expected number of strokes in 1000 adults without sickle cell disease, but with pre-existing untreated atrial fibrillation.

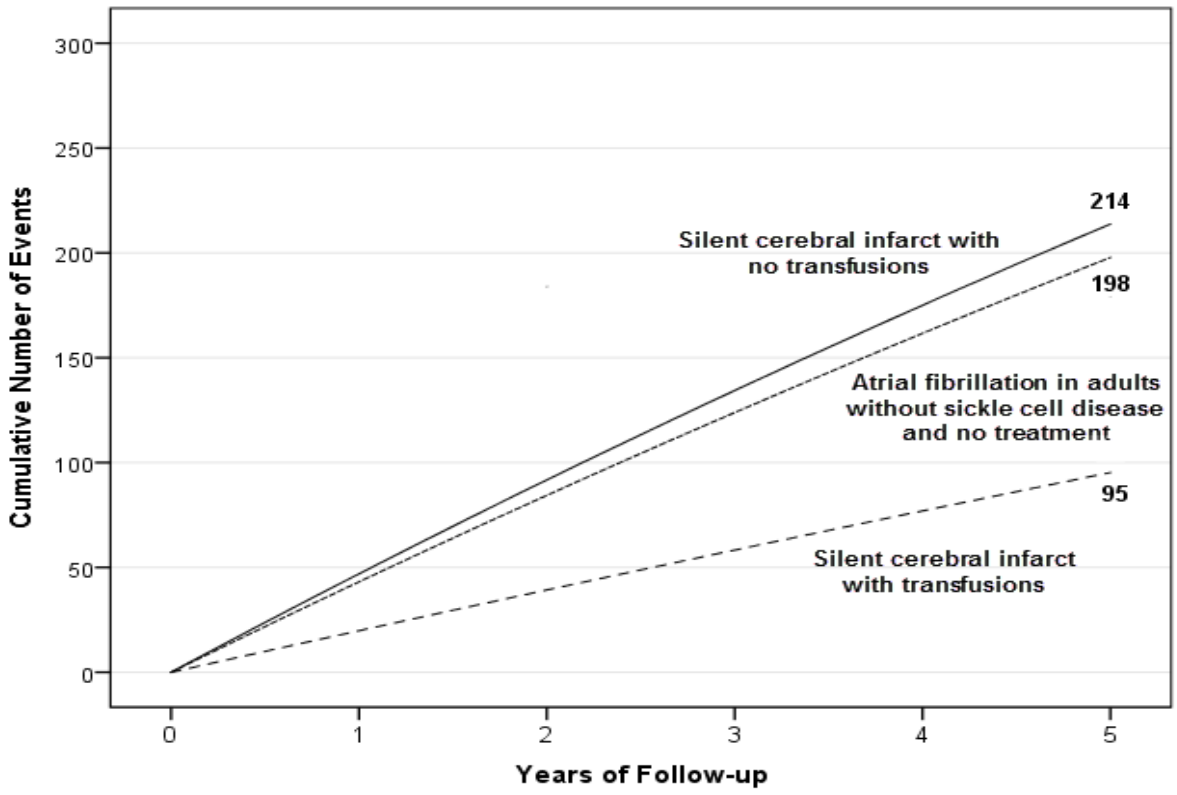


Figure 7. A hypothetical cohort of 1000 children with sickle cell anemia and strokes followed for five years receiving either no therapy, hydroxyurea therapy, or regular blood transfusion therapy.

The figure depicts the number of children in the cohort with stroke recurrence in the no treatment group, hydroxyurea therapy group and regular blood transfusion therapy group with expected incidence rates of 29.1 (95% CI 19.2-38.9), 3.8 (95% CI 1.9-5.7) and 1.9 (95 CI 1.0-2.9) events per 100 patient years, respectively.[15]

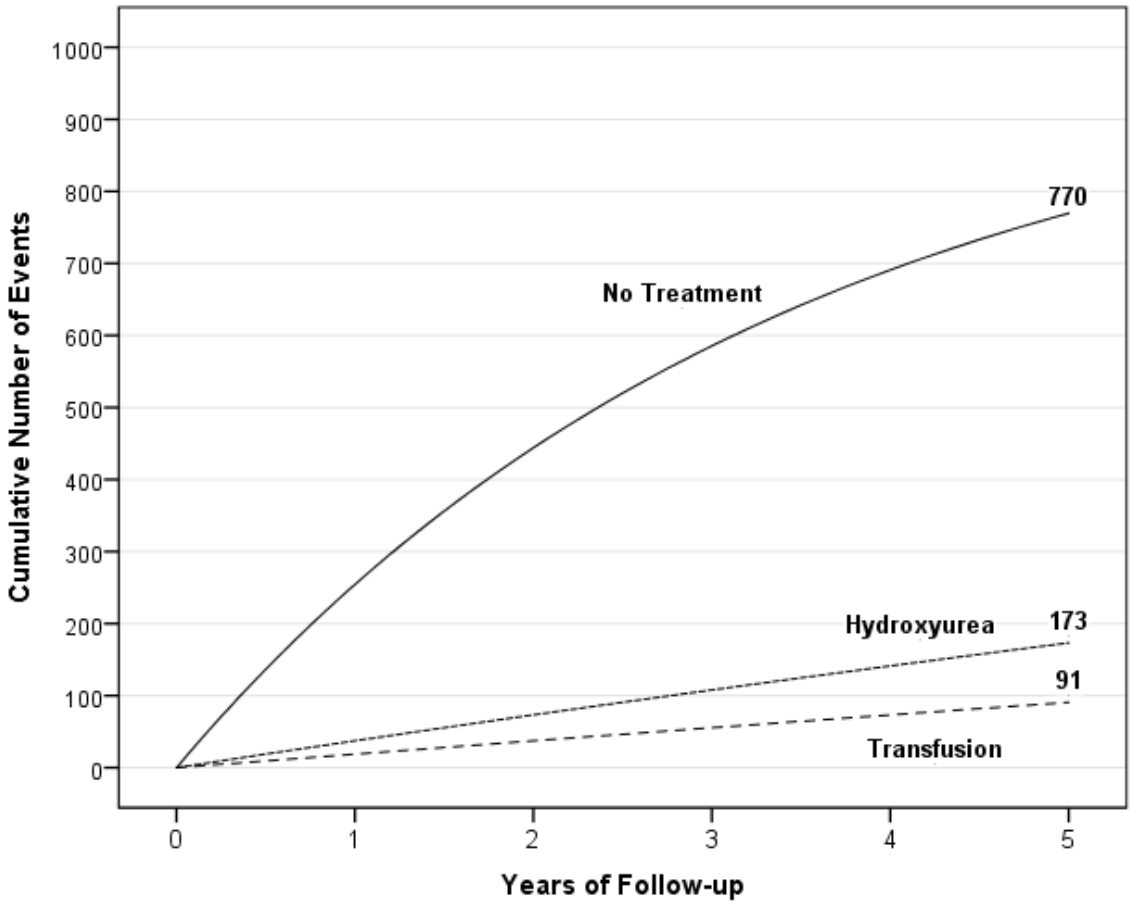
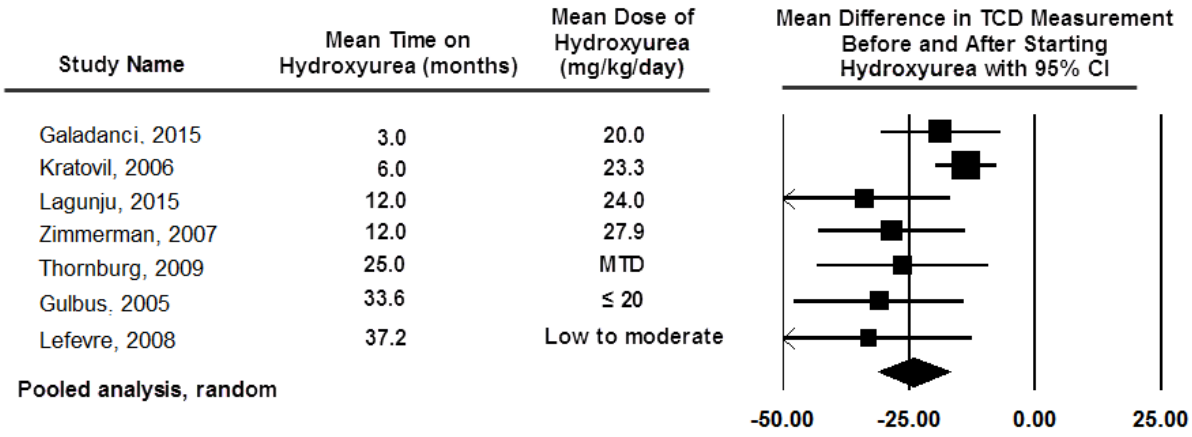


Figure 8. Pooled analysis of the seven studies documenting transcranial Doppler measurement before and after hydroxyurea therapy.

The pooled analysis based on the random effect model demonstrating the average drop in TCD measurement after starting hydroxyurea therapy of 25 cm/sec. The table also includes the observation that the decrease in TCD measurements can be seen as early as three months after starting hydroxyurea therapy with a sustained impact of hydroxyurea therapy on decreasing TCD measurements for at least 36 months. The black diamond represents the results of random effect models. The edges of the diamonds represent the 95% confidence interval of the meta-analyses for the random effect models. [85]



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