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Review Article

# Stroke in sickle cell disease and the promise of recent disease modifying agents

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ABSTRACT

Sickle cell disease (SCD) is an inherited hemoglobinopathy affecting approximately 100,000 individuals in the United States. Cerebrovascular disease is among the most common and debilitating complications of SCA, with 53% experiencing silent cerebral infarct by age 30 and 3.8% experiencing overt stroke by age 40 years. This review highlights the burden of cerebrovascular disease in SCD, including both stroke and silent cerebral infarct (SCI). We then discuss the pathophysiology of stroke and cerebral fat embolism in the absence of a patent foramen ovale. This review also reveals that options for primary and secondary stroke prevention in SCD are still limited to hydroxyurea and blood transfusion, and that the role of aspirin and anticoagulation in SCD stroke has not been adequately studied. Limited data suggest that the novel disease-modifying agents for SCD management may improve renal dysfunction, leg ulcers, and lower the abnormally high TCD flow velocity. Further research is urgently needed to investigate their role in stroke prevention in SCD, as these novel agents target the main stroke contributors in SCD - hemolysis and vaso-occlusion. This literature review also explores the role of healthcare disparities in slowing progress in SCD management and research in the United States, highlighting the need for more investment in patient and clinician education, SCD management, and research.

## 1. Introduction

Sickle cell disease (SCD) is an inherited hemoglobinopathy affecting approximately 100,000 individuals in the United States [1]. The most common form of SCD is sickle cell anemia (SCA), which arises in the presence of two copies of the hemoglobin S gene (HbS). Due to the protective effect of HbS carrier status against malaria, SCD is most prevalent in regions where malaria has historically been endemic such as in sub-Saharan Africa, where 79% of the annual global SCA incidence occurs [2]. In the United States, SCD disproportionately impacts those of African ancestry (90% of all cases), though it can affect individuals of any race [3].

HbS polymerizes when deoxygenated, yielding repetitive sickling episodes that lead to chronic hemolysis, vaso-occlusion, and eventually multiorgan dysfunction and death. Cerebrovascular disease is among the most common and debilitating complications of SCA, with 53% experiencing SCI by age 30 and 3.8% experiencing overt stroke by age 40 years. [4–6].

Transcranial doppler ultrasound (TCD) can identify children with increased risk of stroke by detecting abnormally increased cerebral blood flow velocity ($\geq$ 200 cm/s) reflective of large vessel stenosis [5,7]. Initiating regular blood transfusions in these children lowers the abnormally increased TCD velocities and stroke risk. Therefore, TCD screening is recommended in children with SCD [5]. In adults with SCD, TCD screening has not been sufficiently studied and it is not known whether it can provide same clinical benefit. Despite the high prevalence of neurologic complications in individuals with SCD, there are minimal evidence-based treatment options for primary and secondary stroke prevention in adults.

In this review, we highlight the burden of SCD related stroke and SCI in the United States. We also review the knowledge accumulated in the past decade regarding the pathophysiology and prevention of stroke in

*Abbreviations:* SCD, Sickle cell disease; SCA, sickle cell anemia; HbS, hemoglobin S; SCI, silent cerebral infarct; TCD, transcranial doppler; RBC, red blood cell; PFO, patent foramen ovale; MRI, magnetic resonance imaging; ASH, American Society of Hematology; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant; VTE, venous thromboembolism.

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SCD and explore new potential therapeutic options for primary and secondary prevention, including the role of novel disease modifying agents approved or in the pipeline for SCD management.

## 2. The epidemiology of cerebrovascular disease in SCD

### 2.1. Stroke

Stroke is a devastating SCD complication with multiple detrimental long-term impacts and a high prevalence and recurrence rate. First, overt stroke has been associated with increased levels of health anxiety, which predicts lower levels of quality of life and higher levels of depression, general anxiety, and disability [8]. Second, cognitive impairment is significantly more common in individuals with SCD and ischemic stroke compared to those without a history of stroke [9]. Third, individuals with SCD and a history of end-organ damage such as stroke demonstrate higher rates of health care utilization, including more hospital days, emergency department visits, outpatient visits, lab tests, and outpatient pharmacy claims compared to those without end-organ damage. Additionally, estimated annual Medicaid costs from January 2013 through December 2017 for patients with SCD were 4.68-fold higher within 1 year of stroke compared to those without stroke [10].

In the 1990s, the Cooperative Study of Sickle Cell investigated the epidemiology and natural history of stroke in 4082 children and adults with SCD, revealing a crude stroke prevalence of 3.75% and incidence rate of 0.46 per 100 patient years. Most strokes were ischemic (53.9%), while a lower percentage were hemorrhagic (34.2%), transient ischemic attacks (TIA, 10.5%), or both ischemic and hemorrhagic (1.3%). Overall stroke recurrence rate was 14%. This study also demonstrated that ischemic stroke has a bimodal distribution in SCD, most commonly affecting children or adults >30 years of age. Conversely, the rate of hemorrhagic stroke was highest in the 20- to 29-year age group [4]. Subsequent work published in 2009 by Strouse et al., however, showed that stroke risk was highest in middle-aged and older adults, regardless of stroke type; this discrepancy may be due to enrollment or survival bias in the earlier study [11]. Over time, stroke prevalence in children with SCD has decreased from 11% to 1.9%, largely due to the practice of TCD screening and initiation of prophylactic blood transfusions when indicated [12]. While stroke risk is highest among individuals with SCA (HbSS), it is important to note that those with other SCD genotypes (compound heterozygous types, which are often miscategorized as "milder sickle cell") are also at risk for cerebrovascular disease [13]. When comparing outcomes for genotypes SS ($n = 2436$), SC ($n = 839$), $S\beta^+$($n = 188$), and $S\beta^0$ ($n = 184$), The Cooperative Study of Sickle Cell estimated that age-adjusted stroke incidence rates were 0.61, 0.15, 0.09, and 0.08 per 100 patient years, respectively [4].

### 2.2. Silent cerebral infarct

Another serious yet insidious cerebrovascular complication of SCD is silent cerebral infarct (SCI), which is generally defined as abnormal brain magnetic resonance imaging (MRI) findings in a patient with a normal neurologic exam and no history of overt stroke [14]. Similar to overt stroke, SCIs also present significant long-term morbidity and are associated with lower academic achievement and poorer neurocognitive outcomes among children with SCD. Lower cognitive test scores have been reported in students with SCIs compared to those with normal MRI findings, and SCIs are associated with a 5.2-point decline in IQ [15,16]. Prussien et al. recently showed that while children with SCD and a history of overt stroke have demonstrated the largest deficits across various domains of cognitive function testing, those with SCD and SCIs also show medium to large deficits across all domains [17]. Individuals with compound heterozygous SCD are also at risk for SCIs with one study showing that 38% of those with $S\beta^+$ had evidence of silent infarction on brain imaging [18]. SCIs predict future overt stroke, progressive MRI abnormalities, and vascular stenosis [19,20]. Conversely, a lack of SCIs predicts a lower risk of overt stroke in children with normal TCD measurements [21]. SCIs are the most prevalent type of stroke among individuals with SCA, and appear to affect children at a very young age, with the BABY HUG trial showing that 13% of 13.7 month-olds with SCA had evidence of SCI on MRI [22]. Additionally, SCIs occur in 27.7% of those with SCA before age 6 years, 37.1% before age 14 years, and 53% before age 30 years [6,12,23]. Significant independent risk factors for SCI include baseline hemoglobin <7 before age 3 years, a high rate of acute anemic events, and isolated extracranial internal carotid artery stenosis [24].

### 2.3. Cerebral fat embolism syndrome

Cerebral fat emboli (CFE) can occur during vaso-occlusive crises (VOC) when sites of bone marrow necrosis release fat globules into the venous circulation. These fat emboli can travel to the lungs and brain, leading to respiratory failure and cerebral ischemia [25,26]. Bone marrow emboli have been detected in 44–60% of cases of acute chest syndrome through bronchoalveolar lavage evaluation for fatty macrophages [27,28]. In the presence of a patent foramen ovale (PFO), fat microglobules can enter the arterial circulation and embolize to the brain. However, there are multiple cases reported in the literature of cerebral fat emboli in SCD in the absence of a PFO [13,29,30]. It is hypothesized that in the absence of intracardiac or intrapulmonary shunts, free fatty acids may cause endothelial damage in the pulmonary capillary bed and smaller microemboli may pass into the systemic circulation via the damaged pulmonary capillary bed [31]. Interestingly, to date this phenomenon has been described more commonly in case reports and case series of compound heterozygous types of sickle cell disease [29,30,32,33]. Further research is needed to conclusively determine whether cerebral fat emboli is indeed more common in these compound heterozygous subtypes.

## 3. Stroke pathophysiology in SCD

Regardless of SCD genotype, the pathophysiology of ischemic stroke begins with sickle erythrocytes, which have a decreased affinity for oxygen compared to healthy red blood cells (RBCs) [34]. This is due to hypoxia-induced adenosine signaling leading to increased levels of 2,3-diphosphoglycerate inside RBCs [34]. In the deoxygenated state, HbS polymerizes into rigid fibers that deform RBCs into a rigid sickle shape, with two major consequences: hemolysis and vaso-occlusion [35]. These processes occur both acutely and chronically, activating a cascade of amplifying events that ultimately lead to vaso-occlusion, ischemia, and stroke as described below (Fig. 1).

During intravascular hemolysis, RBC rupture leads to the release of hemoglobin, adenine nucleotides, and arginase-1 into the blood circulation. Free hemoglobin is either removed from the blood by haptoglobin or oxidized using nitric oxide (NO) to methemoglobin, which then rapidly degrades to free heme. Free heme is subsequently scavenged by hemopexin, – a protein with a very high affinity for heme – forming heme-hemopexin complexes that are taken up by macrophages and hepatocytes via receptor-mediated endocytosis [36,37]. Therefore, haptoglobin, hemopexin, and NO are depleted in states of acute and chronic excessive hemolysis such as in sickle cell disease. This leads to accumulation of free hemoglobin and free heme, which results in endothelial damage, oxidative stress, and inflammation [38,39]. Free heme also contributes to stroke risk as it increases levels of reactive oxygen species, leading to sterile inflammation and subsequent platelet, neutrophil, reticulocyte, and endothelial activation, vaso-occlusion, and coagulation [40]. The increase in oxidative stress and reactive oxygen species is exacerbated by the decreased expression of mitochondrial antioxidant enzyme, superoxide dismutase 2 (SOD2), in the peripheral blood and endothelium in individuals with SCD. This decrease correlates with cardiomyopathy and increased hemolysis [41,42]. Additionally, the net bioavailability of NO is further reduced by erythrocyte arginase-

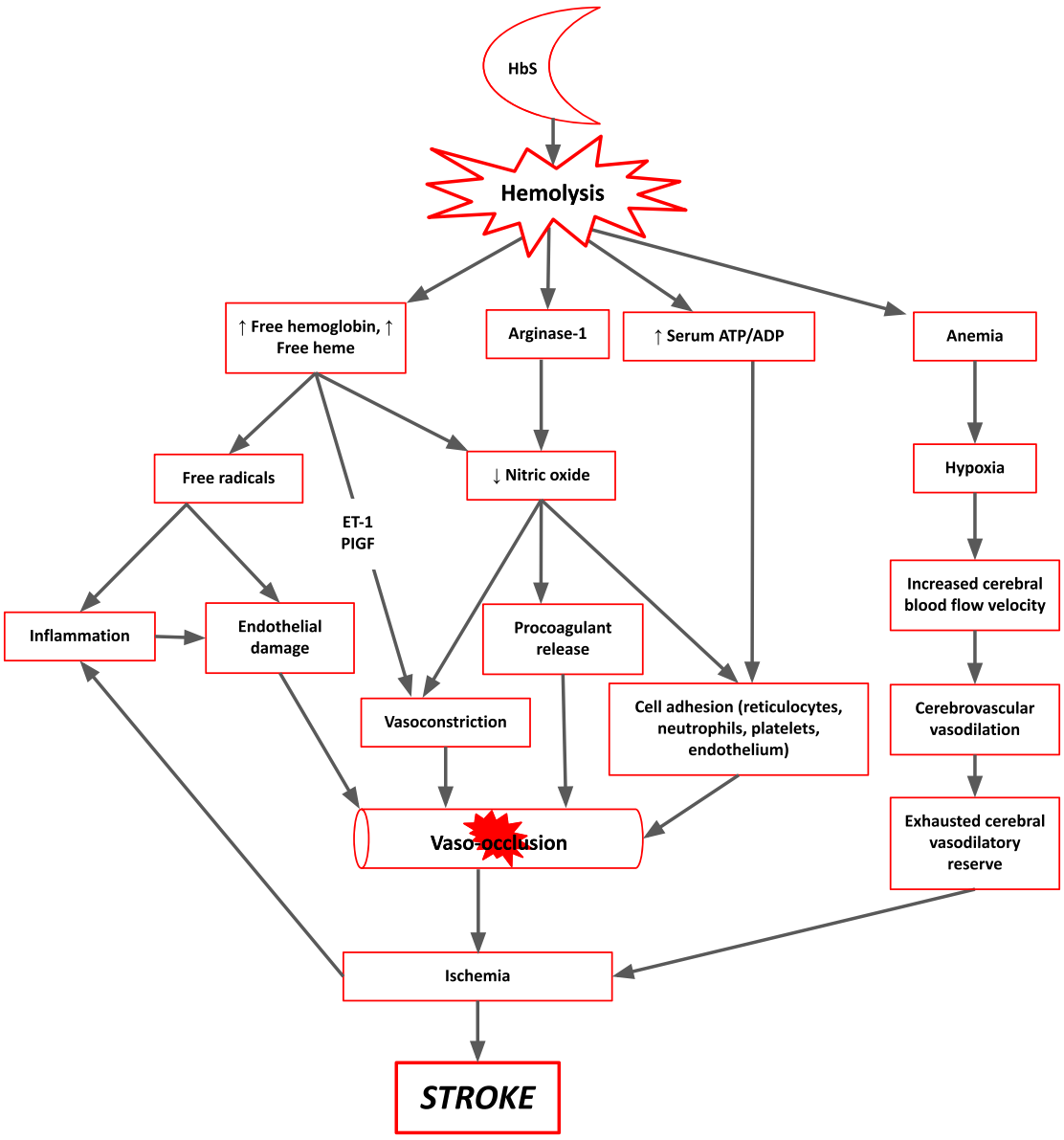


**Fig. 1.** Pathophysiology of Ischemic Stroke in SCD: Hemolyzed HbS RBCs release free hemoglobin, arginase-1, and serum ATP/ADP. The increase in free hemoglobin amplifies Fenton reaction activity, which increases free radical production, creates free heme, and consumes nitric oxide (NO). Arginase-1 further depletes NO by consuming plasma L-arginine, which is typically converted to NO via endothelial nitric oxide synthase (eNOS). Further depletion of NO results in vasoconstriction, procoagulants release, and the activation of cell adhesion molecules, which all contribute to vaso-occlusion. Moreover, free radicals created by the Fenton reaction drive inflammation and endothelial damage, which also promote vaso-occlusion. Free heme increases the production of endothelin-1 (ET-1) and placental growth factor (PIGF), exacerbating vasoconstriction. The release of ATP/ADP further promotes the activation of cell adhesion molecules and vaso-occlusion. Chronic hemolysis also creates anemia and cerebral hypoxia, promoting cerebrovascular vasodilation which is not able to adequately compensate for the hypoxia, resulting in ischemic stroke.

1, which is released upon hemolysis and depletes L-arginine, the substrate for NO synthesis [43,44]. Decreased levels of NO limit the conversion of GTP (guanosine triphosphate) to cGMP (cyclic guanosine monophosphate), which is required to relax vascular smooth muscle and enable vasodilation [39,43]. The disruption of this process therefore leads to increased vasoconstriction, which is further compounded by increased release of endothelin-1 – a potent endogenous vasoconstrictor – from endothelial cells when exposed to free hemoglobin [45].

In addition to releasing free hemoglobin, arginase-1, and heme, hemolysis also results in chronic anemia in SCD. Anemia induces hypoxia and subsequent HbS polymerization and RBC sickling, which promotes RBC adhesion and vaso-occlusion [35,46]. Given that anemia also decreases arterial oxygen content, it promotes progressive vasodilation of the cerebral vasculature to maintain adequate oxygen delivery to the brain; this mechanism is discussed in detail in a recent review [47]. This increases the rate of cerebral blood flow (CBF) to meet cerebral oxygen demand. Over time, cerebral blood vessels demonstrate reduced vascular reserve and diminished vasodilatory capacity, worsening their ability to appropriately regulate CBF [48]. In cases of severe anemia, such as during vaso-occlusive crises, cerebral vessels reach maximal vasodilation and cannot further compensate for the decrease in arterial oxygen content, resulting in cerebral ischemia and increased risk of stroke [49,50]. Even at baseline, patients with SCD have demonstrated decreased white matter oxygen delivery compared to healthy controls despite increased whole brain cerebral blood flow [51]. CBF is inversely associated with hemoglobin and positively correlated with bilirubin and LDH [48]. MRI studies have also demonstrated decreased cerebral metabolic rate of oxygen in the brain of individuals with SCD [52,53]. In

children with SCD, low hematocrit, low hemoglobin concentration, and arterial oxygen desaturation predict elevated cerebral blood flow velocities and therefore increased risk of stroke [54].

Another important pathophysiologic feature of SCD is ongoing vaso-occlusion, which can contribute to stroke. In SCD, erythrocytes demonstrate greater rigidity than normal RBCs, increasing blood viscosity and promoting vaso-occlusion [55]. Chronic hemolysis and inflammation in SCD can also lead to vaso-occlusion through increasing the expression of cell adhesion molecules. P-selectin, which mediates adhesion between sickle RBCs and the endothelium, as well as between leukocytes, platelets, and endothelial cells, is chronically activated in platelets and endothelial cells in SCD due to ongoing inflammation [56,57]. Sickle reticulocytes have also demonstrated increased expression of adhesion molecules (Lu/BCAM, ICAM-4, and LFA-3 specifically), and reticulocytosis has been established as a key predictor of stroke and abnormally elevated TCD results in infants [58,59]. In addition, platelet binding and activation play an important role in vaso-occlusion through activating neutrophils and inducing a chronic inflammatory state [60]. Platelet activation is further increased in SCD by the release of ADP from hemolyzed RBCs and the presence of free hemoglobin, which has also been associated with increased levels of P-selectin [61,62]. Recurrent vaso-occlusive episodes result in cyclic ischemia, necrosis, and reperfusion injury, which leads to blood vessel damage and endothelial dysfunction [63,64]. This creates a vicious cycle of progressively worsening vasculopathy that predisposes to further vaso-occlusion. Vaso-occlusion is also exacerbated by vasoconstriction due to NO scavenging of free hemoglobin as described above.

Individuals with SCD are predisposed to ischemic stroke given the described increase in vasoconstriction, inflammation, and endothelial dysfunction. This creates a hypercoagulable environment with increased platelet activation, cell adhesion, and procoagulant release. Biomarkers of coagulation and thrombin activation are significantly elevated in children with SCD with elevated TCD measurements, indicating an association between hypercoagulability and stroke risk [65]. Additionally, anticoagulant proteins C and S concentrations tend to be low at baseline in SCD, which has been associated with a history of stroke [64,66].

While hemorrhagic stroke is less common than ischemic stroke in SCD, its pathophysiology is likely similarly related to cyclic vascular occlusion and reperfusion injury, which lead to weakening of the endothelium. Indeed, intracranial hemorrhage is often due to bleeding of fragile vessels and abnormal neovascularization which may result from prior ischemic stroke, cerebral artery stenosis, cerebral aneurysms, or moyamoya syndrome [67–69]. Additionally, intracranial hemorrhage has been strongly associated with a prior ischemic stroke [68]. Hypertension has also been significantly associated with hemorrhagic stroke [11]. Given the robust relationship between prior ischemic stroke and hemorrhagic stroke, we anticipate that therapies targeting ischemic stroke may also reduce the risk of intracerebral hemorrhage in SCD.

## 4. Primary and secondary stroke prevention

### 4.1. Transfusion

The most widely established and effective method of primary stroke prevention in children with SCD is TCD screening and initiation of prophylactic blood transfusions in those with abnormally elevated TCD velocities. These practices, which were established by the landmark STOP and STOP II trials, have demonstrated a 92% relative risk reduction in stroke [7,70]. The subsequent Multicenter Silent Infarct Transfusion Trial showed that children with SCA and pre-existing SCIs who received regular blood transfusions had a 58% relative risk reduction of stroke recurrence compared to observation [71]. Transfusion is also the preferred method of secondary stroke prevention in children and adults. Additionally, red cell exchange transfusion is the primary treatment for cerebral fat embolism in SCD, though mortality rate remains high [72]. Transfusion is recommended in cases of acute ischemic stroke or TIA and should be provided within 2 h of onset of neurological symptoms. In this acute setting, exchange transfusion is preferred but simple transfusion can be used if exchange transfusion is not available. Tissue plasminogen activator (tPA) can be administered for individuals with SCD in accordance with stroke guidelines for the general population, though it should not delay prompt blood transfusion [5].

Despite clear evidence of the benefits of regular TCD screening and prophylactic blood transfusions in children with SCD, they can be logistically challenging to access long-term. For example, a follow-up study of STOP participants demonstrated that only 57% of those eligible received TCD rescreening [73]. Another study interviewing caregivers of patients with SCD found that lack of knowledge, lack of self-efficacy, and fear of transfusions were major barriers to annual TCD screening [74].

Several recent studies have shed light on the mechanism by which blood transfusion reduces stroke risk in SCD. First, patients who receive chronic transfusions demonstrate decreased RBC rigidity and improved RBC mechanical sensitivity to prolonged shear stress [75]. Second, MRIs of children with SCD receiving chronic blood transfusions showed a decrease in abnormally elevated cerebral blood flow and oxygen extraction fraction, suggesting the role of transfusions in reducing cerebral metabolic stress through improving hemoglobin levels and oxygenation [76]. Third, blood transfusions appear to reduce the risk of stroke through decreasing thrombogenesis and vascular remodeling, as demonstrated by lower serum levels of biomarkers of cerebral ischemia, endothelial activation, vascular cell proliferation, and thrombosis in patients receiving chronic RBC transfusions [77]. Of note, regular blood transfusions have also demonstrated improved health-related quality of life in children with SCA as compared to those not receiving transfusion therapy [78].

The main methods of transfusion used in SCD are simple transfusion and red cell exchange (RCE), which each have their own advantages and disadvantages. Simple transfusion is more convenient in that it only requires peripheral venous access and does not necessitate specialized personnel or equipment. However, compared to exchange transfusion it presents a greater risk of volume overload, hyperviscosity, and iron overload requiring chelation therapy. Conversely, RCE is a more complex procedure that involves replacement of the patient's RBCs with donor cells and can be completed via manual (repeated phlebotomies and transfusions) or automated (using apheresis machines) methods. The apheresis machines required for automated RCE are typically only available at specialty centers given the level of training and expertise needed to operate them. Automated RCE is beneficial in that volume, hematocrit, and percent HbS post procedure can be controlled more accurately, diminishing the risk of hyperviscosity [79,80]. Apheresis machines can also be set to remove iron through a depletion protocol, decreasing iron overload. However, automated RCE may require central venous access in adult patients due to increased rates of vasculopathy. While additional evidence is needed to conclusively recommend one transfusion method over another, The American Society of Hematology (ASH) currently suggests automated RCE over manual RCE or simple transfusion for all individuals with SCD on chronic transfusion therapy [81].

Additional adverse effects of transfusions include the risk of red cell alloimmunization and acute and delayed hemolytic transfusion reactions. Even with antigen matching, red cell alloimmunization rates range from 5 to 24% in individuals with SCD [82]. Chronic transfusions are also financially costly, with a 1997–1998 retrospective review demonstrating costs of $400,000 per patient decade for transfusions with iron chelation therapy (deferoxamine); subsequent data from 2013 to 2018 found total annualized transfusion-related costs of $60,863 per patient per year on Medicaid [83,84]. However, primary stroke prevention with transfusions (regardless of transfusion type) is still cost-effective when compared with no preventive intervention [85].

Last, the role of transfusions in primary stroke prevention in adults is unclear, as the vast majority of stroke prevention studies have focused

on children with SCD. Because the utility of TCD screening is limited in adults, it is difficult to risk-stratify those that would most benefit from prophylactic transfusions as primary stroke prevention. These limitations highlight the importance of further research to assess stroke prevention in adults specifically, as well as other stroke prevention strategies beyond chronic blood transfusions.

### 4.2. Hydroxyurea

The ribonucleotide diphosphate reductase inhibitor, hydroxyurea, is the recommended treatment for reducing VOCs in SCD. Its primary mechanism of action is through inducing production of fetal hemoglobin (HbF), though it also hydrates erythrocytes, reduces neutrophil and reticulocyte count and adhesion, reduces pro-inflammatory markers, and donates nitric oxide through the soluble guanylyl cyclase/cGMP pathway [86,87].

Several studies have compared hydroxyurea to blood transfusions for primary and secondary stroke prevention. The randomized controlled trial "TCD With Transfusions Changing to Hydroxyurea" (TWiTCH) demonstrated that among children with SCD and abnormal TCD velocities and without severe vasculopathy on brain MRA, hydroxyurea was non-inferior to blood transfusions for primary stroke prevention [88]. Of note, in this study participants were on transfusion for at least one year (average of 4 years) before switching to hydroxyurea. However, the "Stroke With Transfusions Changing to Hydroxyurea" trial (SWiTCH), which compared standard treatment with transfusions and chelation to alternative treatment with hydroxyurea and phlebotomy, showed hydroxyurea to be less effective in secondary stroke prevention without providing superior iron unloading [89]. Additionally, in a pooled analysis of studies evaluating secondary stroke prevention, the incidence rates of stroke recurrence on regular blood transfusion therapy, hydroxyurea, and no therapy were 1.9, 3.8, and 29.1 events per 100 patient years, respectively [90].

Based on results from the TWiTCH Trial, the American Society of Hematology (ASH) 2020 guidelines state that hydroxyurea can be used for primary stroke prevention in the following limited circumstances: (i) children with abnormal TCD results who received transfusion therapy for a year or more as primary prevention and want to stop transfusion (hydroxyurea at the maximum tolerated dose can be considered in this case); (ii) children with abnormal TCD screening results living in low-resource settings where chronic blood transfusion therapy is inaccessible or unaffordable (hydroxyurea therapy with a low dose of at least 20 mg/kg/day or maximum tolerated dose is recommended in this case) [5]. For secondary prevention of stroke, the ASH panel states that hydroxyurea therapy is inferior to blood transfusions but superior to no therapy at all [5].

### 4.3. Antiplatelet and anticoagulant therapies

Given the well-established hypercoagulability of SCD, anticoagulants present an appealing strategy for stoke prevention. Although the literature assessing these therapies specifically for primary and secondary stroke prevention in SCD is sparse, some progress has been made in assessing anticoagulants' safety and efficacy for other indications in SCD, such as in the prevention of VOCs or venous thromboembolism (VTE) [91–98]. The existing literature suggests that anticoagulants may reduce the frequency and severity of VOCs, though not all studies have demonstrated this beneficial effect and a minority have reported an increased risk of bleeding events [91–98]. Notably, a recent study comparing vitamin K antagonists, low-molecular-weight heparin (LMWH), and direct oral anticoagulants (DOACs) in patients with SCD complicated by VTE demonstrated no difference in VTE recurrence among the three anticoagulants but the lowest risk of bleeding with DOACs [98]. In terms of bleeding risk, it appears that individuals with SCD may be at increased bleeding risk at baseline as compared to the general population, though it is unclear whether anticoagulant use disproportionately increases this risk. For example, a retrospective cohort analysis of 135 patients with SCD VOCs indicated that outcomes of VTE prophylaxis in this group were similar to other hospitalized patients without SCD, suggesting a minimal difference in bleeding risk when VTE prophylaxis is indicated [99]. However, a retrospective, population-based study of 6423 individuals hospitalized with SCD identified a 21.0% cumulative incidence of bleeding by age 40 years. Of note, gastrointestinal (GI) bleeding was the most common (representing 41.6% of all bleeding events), and 60% of all GI bleeds were from an upper GI source. While the study did not specifically capture whether patients were on anticoagulation at the time of the bleeding event, it is possible that many included in the study received anticoagulation for VTE prophylaxis during their hospitalization. The authors noted that bleeding incidence appeared to increase with age and other risk factors, including recent VTE, prior ischemic stroke, frequent hospitalizations, and osteonecrosis of the femoral head. Additionally, prior ischemic stroke was significantly associated with hemorrhagic stroke, raising concern about the potential risks of using anticoagulation in the post-stroke period [68].

There is also limited literature investigating the utility of antiplatelet medications in preventing SCD-related stroke. Indeed, most studies of these treatments in SCD focus on their use in VOCs or pain control and were conducted during the 1980s–1990s [100–103]. While an early study suggested that aspirin was associated with promising hematologic parameters (significantly increased hemoglobin concentration, oxygen saturation, and $pO_2$), subsequent studies have failed to show any clear beneficial effect of aspirin on the frequency or severity of VOCs or other SCD complications [100–103]. Similarly, a multinational trial of prasugrel failed to demonstrate any significant decrease in the rate of VOC events [104]. However, recent studies of aspirin in the general population suggest it may have a protective effect against intracranial aneurysm rupture, which may have applications in SCD given that the prevalence of aneurysm in adults with SCD approaches 11% [105–107]. Additionally, one small retrospective study of individuals with SCD and a history of stroke demonstrated that aspirin as an adjunct to chronic blood transfusion was relatively safe with only one patient experiencing a hemorrhagic event; however, the use of aspirin did not significantly affect mean survival time [108]. Another antiplatelet agent, ticagrelor, has also been studied in SCD and demonstrated safety in infants and toddlers with a low risk of bleeding [109]. Phase 1 and 2 studies of ticagrelor in adults have also demonstrated tolerability and safety; phase 3 studies are currently underway [110]. Atorvastatin has also demonstrated antiplatelet activity through directly inhibiting platelet Nox2 (a marker of NADPH oxidase activation), and a study of simvastatin in individuals with SCD demonstrated a reduction in inflammatory markers and the frequency of pain crises, especially when used in conjunction with hydroxyurea [111,112]. Selective serotonin reuptake inhibitors (SSRIs) also have anti-platelet effects but are associated with an increased risk of hemorrhagic stroke in the elderly [113,114]. In SCD specifically, the use of SSRIs in combination with opioids has been associated with lower rates of emergency room visits for VOC pain, though the exact mechanism of this beneficial effect is unclear [115].

Most of the studies of anticoagulants and antiplatelet agents reviewed were limited by either their small sample sizes, lack of an appropriate control group, or varying degrees of incomplete adverse event information, making it difficult to draw conclusions for or against the use of antithrombotic therapies in managing complications of SCD. In addition, because there are no large, randomized controlled trials assessing aspirin or anticoagulation for SCD stroke prevention specifically, little is known regarding the risk-benefit tradeoff of such therapies for this indication. The lack of studies on antithrombotic medications in SCD stroke may be attributed to the lower incidence of stroke compared to VOCs and other SCD complications, requiring a longer study period to capture the impact of antithrombotic therapy [116]. Moreover, antithrombotic treatment may also be limited to date in SCD given the risk of intracranial hemorrhage in SCD and the fact that

hemorrhagic stroke is more common than ischemic stroke in younger individuals aged 20–29 [4]. Additional research is warranted to further elucidate the safety and utility of antithrombotic therapy for stroke in SCD.

### 4.4. Novel disease-modifying agents and curative treatments for stroke prevention in SCD

Several other therapies are under evaluation or recently approved for SCD management, though their utility in stroke prevention has not yet been established. Voxelotor, an HbS polymerization inhibitor, works by binding to hemoglobin alpha chains to stabilize the oxygenated hemoglobin state and has been shown to significantly increase hemoglobin levels, decrease markers of hemolysis, and improve leg ulcers [117,118]. Amino acid L-glutamine and anti-P-selectin monoclonal antibody crizanlizumab were also recently approved by the FDA and both work by reducing the number of sickle cell crisis episodes [119]. Blocking P-selectin has also demonstrated protection from ischemia-reperfusion induced acute renal failure in mice [120]. *E*-selectin inhibitors have also been studied in SCD, with GMI 1070 rivipansel demonstrating decreased biomarkers of endothelial activation, leukocyte activation, and hypercoagulability in a Phase 1 mouse model study [121]. A phase 3 study of rivipansel in VOC management failed to meet its primary or secondary efficacy endpoints in humans, though additional analysis demonstrated shortened IV opioid use and hospital stay specifically when rivipansel was administered early during VOCs [122]. Given the described mechanisms of action, these agents could potentially be effective in stroke prevention, though to our knowledge there are currently no completed clinical trials assessing these therapies for primary and/or secondary stroke prevention in SCD. On http://ClinicalTrials.gov, there are presently a handful of trials recruiting participants to assess the effects of voxelotor and crizanlizumab on cerebrovascular outcomes, though they are largely in children with sickle cell disease (NCT02850406, NCT05018728, NCT04218084, NCT05228834, NCT05334576). Additionally, one trial of L-glutamine assessing its impact on transcranial doppler flow velocity is recruiting pediatric participants (NCT05371184). There are currently no rivipansel trials in progress on http://ClinicalTrials.gov.

Additional medications in the pipeline for SCD treatment seek to address the damaging effects of acute and chronic hemolysis, such as through augmenting or supplementing the role of hemopexin as a heme scavenger. A study of a sickle mouse model demonstrated that exogenous hemopexin treatment decreases the inflammatory phenotype of macrophages, thereby decreasing the production of damaging cytokines and reactive oxygen species [123]. Other pipeline medications include red cell pyruvate kinase (PKR) activators etavopivat and mitapivat, which work by increasing PKR activity (increased ATP and decreased 2,3-diphosphoglycerate) and hemoglobin-oxygen affinity and have demonstrated safety and proof of mechanism [124,125]. Both agents have active ongoing clinical trials at this time, either in phase 2/3 or phase 3: NCT05144256, NCT05031780, NCT04624659. Phosphodiesterase-9 inhibitor IMR-687 was another drug under investigation, but its development was recently discontinued after phase 2b clinical trial interim results showed no significant difference in median annualized VOC rate in the high-dose group compared to placebo [126,127].

Matched related hematopoietic stem cell transplant (HSCT), currently the only curative treatment for SCD, has demonstrated long-term hematologic improvements and low graft failure rate [128]. HSCT from matched sibling donors provides a 93% overall survival, though outcomes are more favorable when transplant is performed prior to the age of 16 due to the high toxicity of the conditioning regimen [129]. In addition, children who received HSCT have demonstrated TCD velocities that were significantly lower compared to those receiving standard of care 1 year following transplant [130]. HSCT may also decrease the risk of stroke recurrence [131]. Another study showed stabilization of intelligence quotient (IQ) following HSCT [132]. ASH guidelines recommend consideration of HSCT in all patients with SCD and neurologic injury if they have a matched related sibling donor [133]. HSCT is an active area of research in SCD with numerous clinical trials currently recruiting participants.

In recent years, gene therapy has emerged as a promising treatment for SCD, though it is still in development. Unlike HSCT, gene therapy uses autologous hematopoietic stem cells and is therefore not limited by the need for a matched donor. At least seven pharmaceutical companies are currently working on various forms of gene therapy for SCD, with LentiGlobin currently the farthest along in development at phase 3 (NCT04293185). These patients demonstrated decreased levels of hemolysis markers and resolution of all severe VOCs [134]. Data on the impact of gene therapy on TCD or stroke is currently not yet available.

## 5. Disparities in sickle cell disease care and research

SCD-related stroke prevention in the United States is contextualized by disparities in access to treatment and research funding. While sickle cell care for pediatric patients is generally strong and continues to improve, there is a lack of adult comprehensive SCD treatment centers and specialized health care providers nationwide [135]. This is compounded by the fact that 59.6% of individuals with SCD – both adults and children – use public insurance as their primary payer, compared to 34.4% of the general population, which can limit access to SCD specialty services [3,136]. For example, one study analyzing claims data found that 7% of those with Medicaid had visited a hematologist in the past year, compared to 43% of those with commercial insurance [137]. This is of clinical importance given the fact that adults with SCD who receive care from both a primary care provider and a hematologist have decreased hospitalization rates [138]. In addition, adults with public insurance have been shown to experience twice as many acute care encounters compared to those with private insurance [139]. Readmission rates for patients of all ages with SCD are high, with a reported 30-day readmission rate of 33.4% [139]. Preventive care is also inadequate even among children, with only a fraction receiving the recommended antibiotic prophylaxis or annual TCD screening [140–142]. Additionally, stigma and implicit bias impact quality of care among patients with SCD. In the United States, 90% of those with SCD are African American, and racial bias has been impacting emergency department wait times and opioid prescribing practices [3,143,144]. Individuals with SCD have been stigmatized when seeking treatment for acute and chronic pain, and many experience significant delays in receiving appropriate analgesic therapy in the Emergency Department [145,146].

The limited availability of evidence-based, clinically proven therapies for treating or preventing SCD-related stroke may be due in part to the history of significant research funding disparities for SCD. Between 2008 and 2018, SCD received a similar amount of federal research funding to cystic fibrosis (CF), despite having triple the prevalence rate [147]. These disparities in funding have also translated to a lower rate of medical innovation and insufficient treatments for SCD over the years; between 2010 and 2013, zero new drugs were approved for SCD compared to five for cystic fibrosis [148].

Despite these barriers, recent trends offer hope for the future. Since 2018, the field has seen an increase in the number of SCD-related scholarly publications as well as increased research funding. In 2019, the CDC awarded nearly $1.2 million in new funding to states to help increase data collection on SCD across the country [149]. Progress is also indicated by the increased number of drugs approved for SCD by the FDA in recent years: L-glutamine (in 2017), voxelotor (in 2019), crizanlizumab (in 2019); this represents substantial progress given that prior to 2017 the only drug approved for SCD was hydroxyurea. Investments in SCD are also being made at the state level. In California, a Sickle Cell State Action Plan was released in December 2018 and led to the state allocating nearly $15 million in 2019 to expand access to

specialty services for adults with SCD [150]. The National Institutes of Health has also made efforts to fund SCD research abroad, such as through the Sickle Africa Data Coordinating Centre initiative aimed at supporting data management and ongoing SCD research efforts in Africa [151].

## 6. Conclusion

In summary, stroke is a devastating complication of SCD, contributing to neurocognitive impairment, impacting quality of life, and increasing healthcare costs. While the effects of SCIs are more subtle, they can also lead to lifelong deficits in cognitive function and predict an increased risk of stroke. Stroke occurs in SCD via the downstream effects of two main pathophysiologic mechanisms – hemolysis and vaso-occlusion. During acute crises of vaso-occlusion, bone marrow necrosis can release cerebral fat emboli that can also contribute to stroke. Therefore, from a healthcare system perspective, improved access to SCD specialty care is warranted to optimize disease management and stroke prevention, particularly for adults with SCD. Hydroxyurea has only demonstrated benefit in stroke prevention in very limited circumstances, possibly due to the fact that it may not be started early enough in life in the majority of patients to prevent irreversible vasculopathy, which starts in infancy [12]. Additionally, patient adherence may fluctuate over time, though these speculations are yet to be studied. No other medications have been established as effective for primary and/or secondary stroke prevention in SCD. As noted above, the mainstay of primary and secondary stroke prevention in children with SCD includes optimizing sickle cell management, annual TCD screening, and chronic transfusion therapy. While these methods are effective at preventing stroke, there are limitations. Regular transfusions present risks of iron overload and liver injury, red cell alloimmunization, and hemolytic transfusion reactions. Given that the newer approved or in pipeline SCD-modifying agents act on the same targets that trigger stroke, further research is required to investigate their efficacy to prevent stroke in SCD. Additional research is also needed to explore the effect of stem cell transplant and gene therapy on stroke prevention. Moreover, structural changes are needed to improve patient education, address clinician implicit bias, and reduce barriers to care for individuals with SCD. The trend toward increased SCD research funding, clinical trials, and medication approvals indicates progress in the field and provides hope for further innovation in SCD-related stroke prevention. While the history of disparities in SCD research funding is improving, increased investment in SCD research from both private and public funding entities remains essential.

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Authors Runge, Brazel, and Pakbaz were all involved in project development, literature review, drafting of manuscript, critical review of manuscript, and final approval of version to be submitted.

## Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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