The Use of Screening Tests in Patients With Sickle Cell Disease: A Systematic Review, 2012

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Included Studies

Table 1. Baseline Characteristics of Included Studies

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Al-Sukhun, 2000[1]	Adults	37±10 for pulmonary hypertension (PH) group 34±11 for no PH group	152	To determine the frequency of PH in patients with sickle cell disease (SCD) and which patients are at higher risk	2, patients with SCD and PH vs. patients with SCD without PH	Inclusion: Adult patients with SCD seen at an urban academic medical center	42	NR	NR	NR	100	R, Obs	NR
Ambrusko, 2006[2]	Children	14.82±1.87 for the affected group and 12.90±1.63 for the control group	44	To study the incidence and characteristic presentation of PH in children with SCD	2, patients with SCD and tricuspid regurgitant velocity (TRV)<2.5 m/s on 1 arm (control group) vs. patients with SCD and TRV≥2.5 m/s on the other arm (affected group)	Inclusion: Patients with SCD with echocardiographic (ECHO) measurement of TRV in the steady state (defined as echocardiograms obtained as an outpatient with no history of admission for vaso-occlusive crisis (VOC), acute chest syndrome (ACS), or other acute illnesses for at least 4 weeks)	54.5 in the affected group and 45.2 in the control group	Affected group HbSS (100%), control group HbSS (67.7%)	NR	NR	100	R, Obs	NR
Armstrong-Wells, 2009[3]	Children	NR	157	To study the utilization of transcranial Doppler (TCD) screening in a retrospective cohort of all children with SCD within a large, managed care plan from Jan. 1993 to Dec. 2005	1, children (<20 yr of age) with sickle cell anemia (SCA)	Inclusion: All children (<20 yr old) with SCD enrolled in Kaiser Permanente Medical Care Program from Jan. 1, 1993, to Dec. 31, 2005	43.3	HbSS (70%), HbSβ^0-thal (30%)	NR	0	100	R, Obs	102±48 (mean±standard deviation (SD))
Barrett, 1984[4]	82% adults	Range: 16–60	108	To explore the disparity between the high frequency of cardiovascular complications in patients with SCD and the rare occurrence of myocardial infarctions (MI) in such patients	1 arm; all SCD	Inclusion: All patients with HbSS followed in the specified center	36	HbSS	NR	0	100	R, Obs	NR

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Bernaudin, 2008[5]	Children	NR	373	To define predictive factors for abnormally high velocities (>2 m/s) based on the Créteil pediatric SCA cohort composed of 373 stroke-free children with SCA	1, children with SCD	Based on the Créteil pediatric SCA cohort of stroke-free children	52	HbSS (100%)	CAR/CAR 40, Ben/Ben 24, Sen/Sen 9, Other 27 (β-globin haplotypes, studied in 293 patients)	NR	100	R, Obs	22.6
Castro, 2003[6]	Adults	37 (range: 21–59)	34	To compare survival of PHTN vs. no PHTN	2, 20 cases and 14 controls	Inclusion: Adults with SCA.	47	All HbSS except 1 HbSβ^0-thal	NR	0	99	R, Obs	119
Enninful-Eghan, 2010[7]	Children	All patients were <22 yr old	1005 (475 patients in the pre-TCD group and 530 patients in the post-TCD group)	To assess the impact of TCD ultrasonography (US) program on the incidence of 1st stroke and the rate of transfusion for stroke prevention in children with SCD	2, patients pre- and post-TCD US screening program application	Inclusion: Patients <22 yr of age with HbSS or HbSβ^0-thal enrolled in the Comprehensive Sickle Cell Center (CSCC) at the main campus of Children's Hospital of Philadelphia (CHOP). Exclusion: Patients who had had a stroke before the study period or before enrollment at the CSCC at CHOP	52 (pre-TCD), 51.3 (post-TCD)	HbSS, HbSβ^0-thal (proportions not specified)	NR	NR	100	R, Obs	192
Field, 2008[8]	Children	10.7±2.8	79 (and 255 controls)	To provide preliminary evidence that growth of lung function is attenuated in children with SCD	2, 79 patients with SCD and 255 age- and race-matched children from the Harvard Six Cities Study (H6CS)	Inclusion: Children who received inpatient and outpatient medical care exclusively at St. Louis Children's Hospital	47 in the SCD group (52 in the H6CS control group)	HbSS 100%	NR	0	24	R, Obs	3.5 yr (mean) in the SCD group. 6.4 yr (mean) in the H6CS group
Field, 2008[9]	Adults	36.2±10.6	92	To describe the changes in pulmonary function over time in adults with SCD	1, adult patients with SCD	Inclusion: Patients were required to have at least 1 pulmonary function test (PFT) performed at 20 yr of age or older. Exclusion: Persons were excluded if inadequate followup data existed, defined as <1 yr of followup at Central Middlesex Hospital	48	HbSS 72%, HbSC 16%, HbSβ^0-thal 2%, HbSβ^+-thal 7%, S-hereditary persistence of fetal hemoglobin (SHPFH) 2%, HbSD 1%	NR	0	100	R, Obs	159.6

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Gill, 2008[10]	Children	NR (all patients were <18 yr old)	263	To determine both the prevalence and age of onset of clinically significant retinopathy in the pediatric sickle cell population, and to propose a screening strategy for ophthalmologists	1, children with SCD	Inclusion: children with a sickling hemoglobinopathy referred to the Ophthalmology service at the Hospital for Sick Children with the genotypes HbSS, HbSC, and sickle hemoglobin beta thalassemia (HbSβ-thal)	NR	HbSS 62%, HbSC 28%, HbSβ-thal 10%	NR	9	100	R, Obs	12–192 (range)
Gold, 2008[11]	Children	13	65	To determine the extent of neurocognitive impairment, the prevalence of neuroradiographic abnormalities, and their relationship in neurologically asymptomatic adult patients with SCD	1, patients with SCD	Inclusion: Patients with SCD undergoing routine neuropsychological testing and magnetic resonance imaging (MRI)	60	HbSS 80%, HbSC 15%, HbSβ^0-thal 5%	NR	0	100	R, Obs	17
Goldberg, 2010[12]	% adults not reported	12.9±5.5	201	To define the mortality risk of a prolonged corrected QT (QTc) interval in patients with SCD	1, patients with SCD	NR	NR	HbSS 100%	NR	3	100	R, Obs	72
Koumbourlis, 2007[13]	Children	10.6±3.5	45	To determine whether the lung function and somatic growth in patients with SCD maintain the same pattern over time, and the relation between the 2	1, patients with SCD	Inclusion: Patients who had at least 2 PFTs performed at least 1 yr apart from each other	44	HbSS 100%	NR	NR	100	R, Obs	42.3±23.3
Koumbourlis, 2008[14]	Children	9.6 (mean)	26 (13 on each arm)	To investigate the changes in lung function and somatic growth that occur over time in children with HbSC	2, HbSC patients with SCD on 1 arm and age-, race-, and gender-matched HbSS patients with SCD on the other	Inclusion: Patients who had at least 2 PFTs performed 1 yr or more apart from each other	NR	HbSS 50%, HbSC 50%	NR	0	100	R, Obs	50 (mean) for the HbSC group, 57 (mean) for the HbSS group

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Kwiatkowski, 2003[15]	Children	10.1±4.9 yr	249	To investigate the possibility of a familial predisposition to elevated cerebral blood flow velocity	1 group all with SCD	Inclusion: All children aged between 2 and 21 years old with a confirmed genotype of SCD-SS or SCD-S/beta° thalassaemia with TCD performed over the 2-yr period between July 1998 and June 2000. Exclusion: Prior history of clinical stroke	49	HbSS, HbSβ^0-thal (proportions not reported)	NR	NC/NR	100	R, Obs	NC/NR
Kwiatkowski, 2009[16]	Children	0.65±1.2	96	To assess the prevalence of silent infarcts and cerebrovascular disease in a cohort of young children with SCD-HbSS	1, patients with SCD	Inclusion: All children with SCD who were born between Jan. 1997 and Dec. 2002 and were actively followed at CHOP. Exclusion: Patients who were receiving chronic transfusions or hydroxycarbamide were excluded	59.4	HbSS 100%	NR	0	100	R, Obs	48
MacLean, 2008[17]	Children	12.7±2.7 for patients who had spirometry. 12.9±2.6 for children who had lung volume test	413	To determine if the pattern of lung function in SCD differs from race-matched, predicted values across childhood, to describe that pattern of change, and to examine the effect of clinical covariates on lung function	1, patients with SCD	All children with SCD and lung function measurements were eligible for inclusion in this study. Pulmonary function data obtained before 1989 were excluded to coincide with the implementation of routine annual lung function testing. To be included in the analysis, children must have had at least 2 repeated measures available for spirometry or lung volume across the study period	49.4 (of those who had spirometry) and 48.6 (of those who had lung volume test)	The group who had spirometry HbSS 37.5%, HbSC 16.7%, HbSβ^+ 4.8%, other 0.3%, missing 40.7%. The group who had lung volume test HbSS 38.1%, HbSC 16.7%, HbSβ^+ 5.1%, other 0.1%, missing 39.8%	NR	0	100	R, Obs	204

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McCarville, 2008[18]	Children	Range: 2–16	NR	To evaluate the efficacy of a TCD screening program	1, patients with SCD	Inclusion: Patients with HbSS or HbSβ^0-thal, age 2–16, no history of prior stroke, no fever in the past 24 h, no acute illness in the past 2 weeks, sedation in the past 24 h, or transfusions in the past 2 mo	NR	HbSS, HbSβ^0-thal (proportions not specified)	NR	NR	100	R, Obs	Different mean duration over different study periods: Period 1: 108 period 2: 96 period 3: 30
Mueller, 2006[19]	Children	NR	142	To determine the prevalence of prolonged QT segment in children with SCD	1, patients with SCD	Inclusion: Patients with SCD with electrocardiogram (ECG) results	NR	NR	NR	0	100	R, Obs	NA
Parmar, 2009[20]	Children	NR	342	The presentation of 1st 4 yr of clinically screened children (i.e., outside Stroke Prevention Trial in Sickle Cell Anemia (STOP) and STOP II trials with SCD using TCD	1, patients with SCD	NR	NR	HbSS 92%, HbSβ^0-thal 8%	NR	NR	100	R, Obs	48
Silbermins, 2009[21]	Adults	NR	362	To determine the natural history of pulmonary arterial hypertension (PAH) in the adult SCD population	1, patients with SCD	NR	NR	NR	NR	NR	100	R, Obs	360
Steen, 1998[22]	Children	2–16	96 (47 patients with SCD and 49 controls)	To determine whether children with SCD, but without clinical evidence of cerebrovascular disease, have vasculopathy shown by quantitative magnetic resonance angiography (MRA)	2 groups, patients with SCD, *n*=47, and patients without SCD undergoing MRI for other reasons, mainly for brain tumors, *n*=49	Inclusion: Patients with SCD	NR	39% HbSS, 8% HbSC, 1% HbSβ-thal, 1% fetal hemoglobin (HbF)	NR	0	49	R, Obs	NR
Voetsch, 2010[23]	Children	7.4±4.1	79	To study the rate of stroke risk progression as measured by TCD and the effect of therapeutic interventions on its values	1, patients with SCD	NR	53.2	HbSS 100%	NR	NR	100	R, Obs	48

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Wang, 2000[24]	Children	11.4±2.6	78	To compare the results of standardized MRI of the brain and TCD US of cerebral arteries in school-aged children with SCD	1, patients with SCD	Inclusion: Patients with SCD enrolled in the Cooperative Study of Sickle Cell Disease (CSSCD) or STOP I, screened since infancy. Exclusion: Patients were excluded if the MRI was uninterpretable, TCD study was inadequate, or studies were performed >1 yr apart	53	HbSS, HbSβ-thal (proportions not specified)	NR	NR	100	R, Obs	NR
Abboud, 2004[25]	Children	8.3	100	MRA findings in patients with SCD and correlation with TCD results	2 MRA results vs. TCD results	Inclusion: Patients with SCD	44	HbSS, HbSβ^0-thal (proportions not specified)	NR	NR	100	P, Obs	NR
Adams, 1992[26]	Children	8.9±4.2	190	To demonstrate that abnormal results of TCD US identify patients with an increased risk of stroke	1, patients with SCD	Exclusion: An acute illness that might alter the ultrasound findings, such as fever or central nervous system (CNS) infection, or a history of stroke of any type. Headache was not grounds for exclusion unless associated with a loss of consciousness or focal neurologic symptoms. Children younger than 3 yr were excluded	NR	NR	NR	2.6	100	P, Obs	29±17 (mean±SD)
Adams, 1997[27]	Children	8.8±4.2	315	To determine the long-term stroke risk in children with SCD screened with TCD	1, patients with SCD	Described in a previous report	49.5	HbSS, HbSβ-thal (proportion not specified)	NR	3.5	100	P, Obs	64.4±23.8 (mean±SD)
Adams, 2004[28]	Children	Range: 2–16	2324	To examine the stroke risk relative to the TCD findings in this large cohort and determine the rate of conversion from low-risk to high-risk TCD	1, patients with SCD	Exclusion: Patients with chronic transfusion, prior stroke, human immunodeficiency virus (HIV) infection, treated seizure disorder, pregnancy, or a serum ferritin level >500 ng/mL	NR	HbSS or HbSβ^0-thal (proportion not specified)	NR	NC/NR	100	P, Obs	48±18

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Adekile, 2002[29]	Children	9.8±3.5	30	To document the prevalence of silent cerebral infarcts in children with SCD in Kuwait	1, patients with SCD	Inclusion: Patients had to be at least 6 yr old and in steady state at the time of the MRI study. Exclusion: Any child with a known underlying neurological abnormality or history of seizures	63.3	HbSS 76.6%, HbSβ^0-thal 23.4%	β^s chromo-somes with SAI haplotype; SAI and Benin haplotype	NR	100	P, Obs	NR
Aleem, 2007[30]	% adults not reported	24.5±9.2	65 (and 58 controls)	To identify cardiac abnormalities by ECHO in adolescent and adult Saudi patients with stable SCD	2, patients with SCD and age- and gender-matched healthy controls	Inclusion: All patients were evaluated in steady state Exclusion: Patients with sickle cell trait (HbSA or HbAS)	43	HbSS 91%, HbSβ^0-thal 9%	NR	NR	53	P, Obs	12
Aleem, 2008[31]	% adults not reported	23, 14–40 (median and range)	73	To evaluate the presence of renal abnormalities in adolescent and adult Saudi patients with SCD	1, patients with SCD	Inclusion: Age 14 yr or older and documented homozygous or heterozygous SCD. Patients were evaluated in steady state with no acute illness during the 2 weeks prior to the assessment. Exclusion: Patients with HbSA	46.5	HbSS 92%, HbSβ^0-thal 8%	NR	0	100	P, Obs	17
Ataga, 2006[32]	Adults	39.7	93	To evaluate the trends of development of PHTN, the association of PHTN with clinical and laboratory measures, and effect of PHTN on mortality in patients with SCD	1, patients with SCD	Inclusion: Each enrolled subject was studied in a noncrisis, steady state; had not experienced an episode of acute chest syndrome (ACS) in the 4 weeks preceding enrollment, and had no clinical evidence of congestive heart failure	39.4	HbSS 74%, HbSC 12%, HbSβ^0-thal 5%, HbSβ^+-thal 9%	NR	18.3 (17/93)	100	P, Obs	31.2 (median)
Bachir, 2009[33]	Adults	34±10	403	To evaluate whether a measurement of TRV≥2.5 m/s at ECHO accurately identifies patients with PHTN in patients with SCD	1, patients with SCD	NR	NR	HbSS 98.4%, HbSβ-thal 1.6%	NR	0.7 (3 patients died)	100	P, Obs	11

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Bernaudin, 2000[34]	Children	10.2±3.2	173 patients with SCD (76 healthy siblings served as controls for the neuro-cognitive function testing only)	To evaluate the impact of SCD on the brain and neurocognitive function	2, patients with SCD and healthy siblings as controls. (The control arm was for neurocognitive function testing only and not for the imaging studies)	NR	50.8	HbSS 89.6%, HbSC 4%, HbSβ^0-thal 4.6%, HbSβ^+-thal 1.7%	NR	NR	100	P, Obs	18
Bernaudin, 2001[35]	Children	11.5±5.9	244	To report early cerebral exploration with TCD in patients with SCD	1, patients with SCD	NR	NR	HbSS 83.6%, HbSβ^+-thal 3.6%, HbSβ^0-thal 1.6%, HbSC 9%	NR	NR	100	P, Obs	NR
Bernaudin, 2009[36]	% adults not reported	NR	320	To define the prevalence and risk factors of elevated TRV in children with SCD at steady state	1, patients with SCD	Measurements were at steady state	NR	HbSS 83.75%, HbSC 9.3%, HbSβ^0-thal 2%, HbSβ^+-thal 4%, HbSD Punjab 0.3%	NR	NR	100	P, Obs	127
Brambilla, 2007[37]	Children	Range: 2–16.9 yr	812	To provide information on the intraindividual variation in blood flow velocity among patients with SCD	1, patients with SCD	Inclusion: Patients with at least 2 interpretable TCD examinations within 6 mo were included in this analysis. Exclusion: Examinations performed over longer intervals were excluded to avoid contaminating intrasubject variation around a subject's steady-state mean with systematic changes in that mean over time	NR	HbSS, HbSβ-thal (proportions not specified)	NR	0	100	P, Obs	NR
Cheung, 2001[38]	Children	5–18	18	Correlative study on the vasculopathy of large and small vessels in patients with SCD, using TCD and computer-assisted intravital microscopy	1, patients with SCD	Inclusion: SCD patients who were 5 to 18 years of age and had been given a diagnosis of HbSS Exclusion: Patients with SCD aged 5–18 yr, if they had a history of stroke or were transfused within the previous 2 mo	NR	HbSS 100%	NR	0	100	P, Obs	NR

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Clarkson, 1992[39]	% adults not reported	Median: 20	150 (85 for followup)	To assess the prevalence of ocular complications of SCD in a random sample of patients frequenting a sickle cell care center, and describe the natural history of those complications	1, patients with SCD	Inclusion: Patients with SCD >5 yr of age	49	HbSS 73%, HbSC 19%, HbSβ-thal 8%	NR	4	100	P, Obs	80.4
Colombatti, 2010[40]	Children	6.2	37	To identify predictive factors of precocious PHTN development	2, patients with SCD and healthy controls	Inclusion: Children in steady state, defined as 4 weeks from an acute illness (pain crisis, fever, ACS, or other SCD-related complication) or transfusion. Exclusion: Children on a chronic transfusion regimen	56.7	HbSS 83.7%, HbSC 8.1%, HbSβ-thal 8.1%	NR	0	NR	P, Obs	12–24
de Souza, 2007[41]	Adults	24.4±5.4 for SCA, 27.7±3.2 for HbSA, 26.6±5.2 for patients with iron deficiency anemia (IDA) 26.3±6.3 for normal controls	10 SCA, 10 with trait, 8 with IDA, 10 normal controls	To evaluate the role of the coronary microcirculation in the development of the cardiac abnormalities found in SCA	4, SCA, HbSA IDA, normal controls	Inclusion: Patients were clinically stable, with no pain crises, hospitalizations, or blood transfusions in the 3 mo prior to the beginning of the study. No patients received hydroxyurea (HU). Patients with sickle cell trait (TRA) were asymptomatic. Exclusion: Patients with systemic and PHTN, diabetes, dyslipidemia, coronary artery disease or history of chest pain, asthma or obstructive pulmonary disease, esophageal disease, renal failure, stroke, pregnancy, presence of antibodies against HIV, alcohol consumption, and smoking	45	HbSS 26%, HbSA 26%, normal hemoglobin (HbAA) 48%	NR	0	26	P, Obs	NR

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DeBaun, 1995[42]	Children	NR	24	To evaluate the accuracy of TCD and MRA as a screening modality for cerebral infarct in patients with SCD	2, patients with SCD. Group 1: those enrolled in the Cooperative Study of SCD and were scheduled to undergo MRI. Group 2: those on a blood transfusion therapy for stoke or had recently been taken off blood transfusion and had been subjected to MRI and magnetic resonance angiogram	Children with homozygous SCA;	NR	HbSS 100%	NR	NR	100	P, Obs	NR
Delclaux, 2005[43]	Adults	30	49	To determine the cardiorespiratory factors associated with dyspnea in patients with HbSS, with a specific interest in lung vascular involvement	1, patients with SCD	Inclusion: HbSS, age >18 yr, the absence of a recent (i.e., <3 mo) occurrence of a vaso-occlusive crisis (VOC), ACS, or blood transfusion, the ability to perform a 6-min walk test, the absence of any associated cardiac or respiratory disease (other than that due to SCD), including the absence of smoking history and the absence of treatment by HU or nocturnal oxygen administration or exchange transfusion program	41	HbSS 100%	NR	0	100	P, Obs	10

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Dham, 2009[44]	Children	Range: 8–17	364	To define the incidence and causes of PHTN in pediatric patients with SCD	2 groups, patients with SCD and healthy controls	Inclusion: Subjects with SCD in this study had to have been previously identified and documented as having a variant of SCD (SS, SC, or Sβ thalassemia). Exclusion: Patients who were not in a steady-state condition, previously defined as being free of any hospitalization, emergency room visit or doctor's office visit for pain crisis, ACS, infection, or other complications of SCD for 3 weeks or more	50	HbSS 72.5%, HbSβ^0-thal 1.7%, hemoglobin SD disease, Los Angeles ($HbSD^{LA}$) 0.7%, HbSC 20.7%, HbSβ^+-thal 4.4%	NR	0	85.1	P, Obs	NR
Downes, 2005[45]	% adults not reported	Range: 5–26	473	To describe the incidence, prevalence, and natural history of proliferative sickle retinopathy (PSR)	1, patients with SCD	Inclusion: Consecutive patients with SCD screened at birth. Exclusion: Patients were excluded if eye examination was difficult to perform, e.g., patients with cerebral palsy	51	HbSS 65%, HbSC 35%	NR	NC	100	P, Obs	254

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Fontaine, 2008[46]	Adults	40±12	26	To evaluate the cardiac substrate in asymptomatic patients with SCA and to identify the potential mechanisms of sudden cardiac death in this patient population	1, patients with SCD	Inclusion: Asymptomatic African American patients aged ≥18 yr with a diagnosis of SCA and the ability to undergo the proposed procedures. Exclusion: Patients with HbSA, atrial fibrillation, a permanent pacemaker, renal failure requiring dialysis, pregnancy during time of the study, of childbearing age and have not taken effective contraceptive measures (e.g., tubal ligation), life expectancy of <1 yr, aplastic crisis, sickle cell crisis within 2 weeks of enrollment, and HIV infection	61.5	NR	NR	0	100	P, Obs	8±3
Friberg, 1986[47]	% adults not reported	8–54	110	To determine the prevalence of various retinal lesions in SCD	1 group, patients with SCD	Inclusion: Outpatients with SCD referred for comprehensive ocular examination	NR	84% HbSS, 7% HbSC, 9% HbSβ-thal	NR	0	100	P, Obs	30
Gillams, 1998[48]	% adults not reported	7.5	22	To establish the range of appearances in asymptomatic patients with SCD and to correlate brain MRI results (either subclinical abnormalities or normal brain parenchyma) with the MRA findings	1 group, patients with SCD	Inclusion: Patients with SCD who are neurologically intact	59	64% HbSS, 36% HbSC	NR	0	100	P, Obs	24

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Gladwin, 2004[49]	Adults	36±12	195 (and 41 controls)	To determine the prevalence of PHTN in adults with SCD, the mechanism of its development, and its prospective prognostic significance	2, patients with SCD on 1 arm and healthy controls on the other	Only outpatients with sickle cell hemoglobinopathy documented by high-pressure liquid chromatography in stable condition were included; patients who had a VOC within the previous 2 weeks or an episode of ACS within the previous 4 weeks were evaluated at a later time. Patients receiving transfusions were not excluded	42 (41 in the control group)	HbSS 69%, HbSC 18%, HbSβ-thal 12%	NR	2.5	82.6	P, Obs	18
Gordeuk, 2009[50]	Children	NR	361	To determine the correlation between hemolysis-associated elevation in TRV and the 6-min walk distance	1, patients with SCD	Inclusion: Enrolled patients who were at steady state	NR	NR	NR	NR	100	P, Obs	22 (median)
Gordeuk, 2011[51]	% adults not reported	Median: 13	269	To evaluate elevated TRV on exercise capacity and mortality in children and adolescents with SCD	1, patients with SCD	Inclusion: Patients with SCD who had clinical evaluation, ECHO, and 6-min walk test performed at steady state with available followup information. Exclusion: Patients with acute complications, patients who did not have followup studies	49.4	HbSS 100%	NR	38	100	P, Obs	22 (median)

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Hankins, 2008[52]	Children	Median: 7.1	274	To determine the rate of conversion conditional TCD to abnormal TCD velocities in children with SCD and how to prevent it	1, patients with SCD	Exclusion: Data were excluded from this analysis if the TCD examination was performed while the patient received hydroxycarbamide therapy, or if a blood transfusion had been administered within the previous 3 mo. Data from patients participating in blinded studies comparing therapeutic agents (e.g., hydroxycarbamide to placebo) were also excluded	NR	HbSS 97.0%, HbSβ^0-thal 3.0%	NR	NR	100	P, Obs	Median 6
Hogan, 2006[53]	Children	Patients were studied during their 1st yr of life	14 patients and 14 controls	To investigate whether infants with SCA are at risk of neurodevelopmental delay, and whether any delay is associated with SCA pathology	2, patients with SCD on 1 arm and healthy controls on the other	NR	78.5 (35.7 for the control group)	HbSS 100%	NR	0	50	P, Obs	12
Hoppe, 2003[54]	Children	13.1±2.9	231	To determine the association between some human leukocyte antigen genotypes and stroke in patients with SCA	1, patients with SCD	Inclusion: All children with adequate DNA and interpretable MRI results. Children with SCA and MRI documented cerebral infarction <15 yr old were included as case subjects. Exclusion: Children with MRI evidence of atrophy, cerebral hemorrhage, or other noninfarction abnormalities, unless accompanied by infarction	NR	HbSS 100%	NR	0	100	P, Obs	196

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Jones, 2001[55]	Children	9.5	29	To correlate transcranial arterial time-averaged mean velocities obtained from an Acuson TCD Imaging to those obtained using the TCD as the gold standard for treatment decisions based on STOP	1, patients with SCD	Inclusion: Patients with SCD	59	NR	NR	NR	100	P, Obs	NR
Jones, 2005[56]	Children	Range: 2–16 yr	1937	To compare peak systolic velocity (PSV) and end diastolic velocity (EDV) with time average mean of the maximum (TAMM) for prediction of stroke and to derive PSV cutpoints for STOP protocol definitions of conditional and abnormal TCD	1, patients with SCD	Reported elsewhere	NR	HbSS, HbSβ-thal (proportions not specified)	NR	NR	100	P, Obs	50±16
Kirkham, 2001[57]	% adults not reported	7.7, 1.0–23.1 (median, range)	95	To test the hypothesis that nocturnal hypoxemia can predict CNS events better than clinical or hematological features, or TCD US	1, patients with SCD	Inclusion: Patients who had not had a stroke	57	HbSS 74%, HbSC 14%, HbSβ^0-thal 7%	NR	NR	100	P, Obs	6·01 (0·11–8·54) yr (median and range)
Kral, 2004[58]	Children	10.12±2.62	62	To identify behavioral manifestations of executive dysfunction that are associated with cerebrovasculopathy, as measured by TCD US, in children with SCD (HbSS)	1, patients with SCD	Inclusion: Patients were participants in the multicenter STOP investigation Exclusion: Patients with a history of birth complications, traumatic brain injury, known cerebrovascular accident (CVA), or major chronic illness other than SCD	43.5	HbSS 100%	NR	0	100	P, Obs	18
Kugler, 1993[59]	% adults not reported	Group 1: 19.57±6.6. Group 2: 20.86±6.67	16	To assess neurological correlates and clinical outcomes of patients with SCD receiving serial brain MRI exams	2, patients with MRI abnormalities consistent with cerebral infarcts at baseline vs. patients without MRI abnormalities	Inclusion: Asymptomatic patients with SCD	NR	HbSS 100%	NR	13	100	P, Obs	44.4 mo

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Liem, 2010[60]	% adults not reported	15.8±3.3	30	To examine the reproducibility of ECHO-derived tricuspid valve regurgitant jet velocity (TRJV) measurements and to evaluate potential sources of disagreement associated with these measurements	1, patients with SCD at steady state	Inclusion: Patients with SCD between 10 and 25 yr old and scheduled for an ECHO at steady state Exclusion: Patients with history of VOC pain in the 2 weeks prior to the measurement. Patients on chronic transfusion or those who received transfusion support in the previous 10–12 weeks were also excluded	53	HbSS 83.3%, HbSβ^0-thal 13.3%, HbSC 3.4%	NR	NA	100	P, Obs	NA
Lima, 2002[61]	Adults	31.58	72 (and 50 controls)	To test the usefulness of a random urine specimen albumin to creatinine (A/C) ratio in predicting 12-h urinary albumin excretion (12UAE) in patients with SCD	2, patients with SCD and healthy controls	NR	47.5	NR	NR	0	59	P, Obs	6
Lorch, 2009[62]	Adults	39±14	215	To determine the predictability of mortality of mild elevations in pulmonary artery systolic pressure (PASP) on ECHO	1, patients with SCD	NR	NR	NR	NR	NR	100	P, Obs	93.6 (median)
Machado, 2007[63]	Adults	34±2.5	26	To determine the effect of VOC on pulmonary artery pressure	1, patients with SCD	Inclusion: Patients with SCD were evaluated in steady state and during VOC	50	HbSS 88.5%, HbSC 7.7%, HbSβ^0-thal 3.8%	NR	0	100	P, Obs	NA
Makani, 2009[64]	Children	7.4±4.0	105	To study the impact of high cerebral blood flow velocity and low hemoglobin oxygen saturation on neurological complications in SCA	1, patients with SCD	Inclusion: Study patients were recruited when they were well	NR	NR	NR	0.09	100	P, Obs	48
Malouf, 2001[65]	Children	2–16 yr	125	To compare the results of the nonduplex US STOP trial with those of TCD, duplex-power US by using the STOP protocol and to correlate abnormal TCD findings with MRI and MRA findings	1, patients with SCD	Exclusion: Patients with a history of stroke, hemoglobin disease other than SCA or HbSβ-thal, and/or an age outside the range of 2–16 yr	NR	96% HbSS, 4% HbSβ-thal	NR	0	100	P, Obs	12–24

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Martins, 1999[66]	% adults not reported	26.56±9.19 (26.76±7.62 for the control group	25 (and 25 controls)	Anatomical and functional assessment of the heart through Doppler and ECHO in patients with SCA	2, patients with SCD on 1 arm and healthy controls on the other	Inclusion: Patients in ambulatory followup with clinical and electrophoretic diagnosis of HbSS. Exclusion: Patients in painful or in hemolytic crisis or with infection in the previous 4 weeks were excluded from the study, as were those patients transfused in the previous 3 mo. Individuals with other diseases were also excluded from the study, as were pregnant women and individuals on drugs with a cardiovascular effect	NR	HbSS 100%	NR	NR	50	P, Obs	12
McBurney, 2002[67]	Children	11.3	151	To determine the prevalence of microalbuminuria and to establish clinical characteristics associated with microalbuminuria in children with SCA	1, patients with SCD	NR	51.6	HbSS 100%	NR	NR	100	P, Obs	39
McCarville, 2004[68]	% adults not reported	2–20	53	Comparison of TCD sonography with and without imaging in the evaluation of children with SCA	1 arm, patients with SCA	Inclusion: All patients with SCA between the ages of 2 and 20 yr. Exclusion: Patients were febrile or imaging was technically difficult	NR	NR	NR	0	100	P, Obs	NR
McKie, 2007[69]	Children	191	12.1±4.86	To define the age of onset of microalbuminuria and proteinuria and their association with age, sex, and hemoglobin (Hb) in patients with SCD, and to explore the safety and efficacy of HU and angiotensin-converting enzyme (ACE) inhibitor therapy	1, patients with SCD	Inclusion: Patients with HbSS who were seen for annual well visits from Sept. 1996 to Dec. 2002.	49.7	HbSS 100%	NR	NR	100	P, Obs	2.19 y±2.05

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Miller, 2001[70]	Children	8.3±1.9	248 patients with SCD who had not had a clinical stroke by the time of baseline MRI	To determine whether children with HbSS who have silent infarcts on MRI of the brain are at increased risk for overt stroke	1 arm	Inclusion: Patients with HbSS who (1) enrolled in the CSSCD before age of 6 mo; (2) had at least 1 study-mandated brain MRI at age 6 yr or older; and (3) had no overt stroke before a 1st MRI	NR	HbSS 100%	NR	NR	100	P, Obs	60
Mokhtar, 2010[71]	% adults not reported	17.93	70	To determine the prevalence of PHTN in patients with SCD and thalassemia in relation to clinical and laboratory parameters of hemolysis and hemosiderosis, as well as plasma N-terminal probrain natriuretic peptide, as well as to define the role of thromboembolic pulmonary artery obstruction in its etiology	2, patients with SCD vs. patients with thalassemia	Inclusion: Patients were cardiovascularly asymptomatic; no ACS within the last 3 mo	53	NR	NR	0	57	P, Obs	18±6.1
Morris, 2005[72]	Adults	36±11 (37±11 for the control group)	228 (and 36 controls)	To explore the role of arginase in SCD pathogenesis, PHTN, and mortality	2, patients with SCD on 1 arm and healthy controls on the other	NR	40 (47 in the control group)	NR	NR	3.9	86.3	P, Obs	33 (median)
Moser, 1996[73]	Children	8.3±1.8	312	To define the spectrum of abnormalities in SCD, including infarction, atrophy, and hemorrhage, that are identified by brain MRI	1, patients with SCD	Inclusion: Patients identified by newborn screening programs and enrolled in CSSCD trial.	NR	69% HbSS, 31% HbSC	NR	0	100	P, Obs	NR
Neish, 2002[74]	Children	9.3±3.7	66	To determine whether criteria for screening patients with SCA for stroke established with a nonimaging TCD US technique are applicable to studies performed with a TCD US imaging technique	1, all children with SCD who were screened between Aug. 1999 and Dec. 2000 were enrolled consecutively	Exclusion: Children undergoing transfusion therapy and those who had had a previous stroke	45.5	HbSS 79%, HbSC 17%, HbSβ-thal 4%	NR	0	100	P, Obs	NR

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Okoro, 1991[75]	Children	4–14	60 (and 305 controls)	Comparison between glomerular filtration rate (GFR) in healthy Nigerian children and in children with SCA in a steady state	2 groups, patients with SCD, *n*=60, and healthy controls, *n*=305	Inclusion: SCD and healthy controls otherwise not specified	61	HbSS 16%	NR	0	16	P, Obs	NR
Onyekwere, 2008[76]	% adults not reported	16±3.26	52	To determine the prevalence of PHTN in pediatric patients with SCD	1, patients with SCD	Inclusion: All patients had to have a history of SCD and regular followup in 1 of the 2 institutions involved in the study	52	HbSS 83%	NR	0	100	P, Obs	NR
Pashankar, 2008[77]	Children	9.41, 0.32–20.41 (mean and range)	169	To determine the prevalence and risk factors of elevated pulmonary artery pressures in children with SCD and to determine a correlation between abnormal TCD examinations and elevated pulmonary artery pressures	1, patients with SCD	Inclusion: All patients who had a screening ECHO. Exclusion: Patients with pulmonary stenosis or other structural obstruction to pulmonary blood flow	57	HbSS 53.2%, HbSC 28.9%, HbSβ^0-thal 8.28%, HbSβ^+-thal 7.1%, HbS other 2.3%	NR	0	100	P, Obs	NR
Pashankar, 2009[78]	Children	NR for the whole population. 13.9 for the 18 patients had the followup ECHO	62	To study the effect of long-term PHTN in children with SCD	1	Inclusion: Patients with SCD at steady state	NR	HbSS, HbSβ-thal; proportions not specified	NR	0.16	100	P, Obs	23 (range 19–31 mo)

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Pawlak, 2009[79]	Children	7.7±3.3	68	To establish reference values of the ratios of flow velocity of intracranial to extracranial cerebral arteries	1, patients with SCD	Inclusion: (1) HbSS, (2) ages 2–14 yr, (3) no neurologic deficits, (4) no history of stroke. Exclusion: (1) history of major head injury requiring visit to an emergency department, (2) history of seizure disorder requiring anticonvulsant therapy, (3) chronic transfusion therapy, (4) episode of SCD pain, ACS, or other important medical problem in the period between laboratory blood testing and US, (5) history of prenatal or perinatal hypoxic-ischemic brain injury (6) evidence of HIV infection	44	HbSS 100%	NR	NR	100	P, Obs	NA
Pegelow, 2002[80]	Children	8.33±1.90	415	Silent infarct prevalence, localization, recurrence, and progression	1, patients with SCD	Inclusion: All patients with SCD who were previously enrolled in the CSSCD	52.5	HbSS 64%, HbSC 29%, HbSβ^+ 5% , HbSβ^0 2%	NR	15	100	P, Obs	120
Sachdev, 2007[81]	Adults	35±11 (37±11 for the control group)	235 (41 control patients)	To characterize left ventricular (LV) diastolic function in the SCD population and to relate ECHO measures of dysfunction with PHTN and mortality	2, patients with SCD on 1 arm and age- and gender-matched controls on the other	NR	40 (41 in the control group)	NR	NR	1.2	85	P, Obs	30.8 (median)
Silva, 2011[82]	Children	Median 6.2	262	To estimate by means of TCD the risk of cerebrovascular disease in children belonging to a newborn cohort	1	Exclusion: Children with hereditary persistence of HbF	43.8	HbSS 100%	NR	0	100	P, Obs	124

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Steen, 1999[83]	Children	10.6±3.7 (11±3.7 for the control group)	50 (and 52 controls)	To test the hypothesis that patients with SCD who are free of neurological symptoms may still be at risk of disease-related damage to the brain	2, patients with SCD and healthy controls	NR	NR	HbSS 68%, HbSC 28%, Other 4%	NR	NR	49	P, Obs	NR
Steen, 1998[22]	Children	10.4	51	Can quantitative MRI of the brain in children with SCD reveal abnormalities unseen by conventional MRI (cMRI)?	2, 30 SCD vs. 24 healthy controls	Inclusion: No clinical evidence of stroke	56	NR	NR	NR	56	P, Obs	NR
Steen, 1999[84]	Children	10.6±3.7 (11±3.7 for the control group)	50 (and 52 controls)	To test the hypothesis that subtle brain abnormality can be present in pediatric patients with SCD normal by cMRI	2, patients with SCD and healthy controls	NR	NR	HbSS 68%, HbSC 28%, Other 4%	NR	NR	49	P, Obs	NR
Strouse, 2006[85]	Children	8.5±2.0	24	To study the correlation between cerebral blood flow measured by continuous arterial spin-labeling MRI and neurocognitive function in children with SCA	1, children with SCD	Inclusion: Children aged 6 to 12 years with homozygous sickle cell disease (HbSS) or sickle β-null thalassemia from our pediatric hematology clinic. Exclusion: Children with previous traumatic brain injury, seizure disorders, abnormal TCDs (>200 cm/s), stroke, other identified causes of cognitive impairment, and those receiving scheduled transfusions	NR	HbSS, HbSβ^0-thal (proportions not specified)	NR	29	100	P, Obs	42
Sylvester, 2006[86]	Adults	36, 17–67 (median, range)	33	To determine whether patients with SCD in steady state had pulmonary abnormalities seen on high-resolution computed tomography (CT) and whether any abnormalities correlated with diagnosed lung function abnormalities	1, patients with SCD	Inclusion: Patients with SCD in steady state. No history of urinary tract infection in the past 2 weeks. No history of VOC in the past month	36.3	HbSS 100%	NR	0	100	P, Obs	NR

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Sylvester, 2007[87]	Children	9 (median for the SCD group) and 8.4 (median for the control group)	86 patients with SCD and 75 controls	To create a reference range of peak expiratory flow (PEF) results of Afro-Caribbean children	2, patients with SCD on 1 arm and age- and ethnicity-matched controls on the other	Exclusion: Patients (and controls) who had a history of ACS or asthma	NR	HbSS 100%	NR	NR	100	P, Obs	NR
Sylvester, 2007[88]	Children	11 for patients with SCD; 11 for the controls (median)	24 (and 24 controls)	To determine if the lung gas transfer results of children with SCA differed from those of ethnicity- and origin-matched controls of similar age and whether they correlated to the results of other measures of lung function	2, patients with SCD on 1 arm and age- and ethnicity-matched controls on the other	Patients who were able to undertake lung gas transfer measurements are reported	58%	HbSS 100	NR	0	100	P, Obs	NR
Sylvester, 2007[89]	Children	11.7 (median)	42	To determine the occurrence and magnitude of airway hyperresponsiveness (AHR) in children with SCA who had or had not had ACS episodes	1, patients with SCA	Inclusion: Consecutive children aged < 18 yr, who had SCA and whose parents gave informed written consent	52	HbSS 100%	NR	NR	100	P, Obs	NR
Taksande, 2005[90]	Children	9.91	75 (25 with HbSS, 25 HbAA but with anemia, 25 non-anemic patients)	To investigate the systolic and diastolic LV function of children with SCA	3, patients with HbSS, HbAA patients with anemia, and patients who were not anemic	Inclusion: Subjects were crisis free for 2 weeks prior to the study and had not been transfused in the preceding 3 mo	56 (in the SCD group)	HbSS 33.3%, HbAA 66.7%	NR	0	33.3	P, Obs	7
Talbot, 1988[91]	Children	Range: 5–13	563	To investigate sickle cell retinopathy in a children cohort	1, patients with SCD	Inclusion: Children with SCD in a cohort study	NR	56% HbSS, 36% HbSC, 6% HbSβ^{+}-thal, 2% HbSβ^{0}-thal	NR	NR	100	P, Obs	NC
Telfer, 2007[92]	Children	Median 7.8	252	To investigate the outcomes in a UK neonatal cohort as a benchmark for care of children with SCD	1	Inclusion: Children identified from screening	54	HbSS 71.4%, HbSC 25.3%, HbSβ-thal 3.1%	NR	2.8	100	P, Obs	NR (2158 patient-yr)
Verlhac, 1995[93]	Children	3–17	74 (58 patients and 16 controls)	Compare findings of TCD US with findings at MRI, MRA, and conventional angiography	2, patients with SCD, *n*=58, and non-SCD controls, *n*=16	Inclusion: Consecutive patients with SCD	NR	59% HbSS, 16% HbSC, 3% HbSβ-thal	NR	NR	78	P, Obs	18

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Wigfall, 2000[94]	Children	Range: 2–21	442	To study proteinuria and its clinical correlation in children with SCD	1	Inclusion: Children with SCD Exclusion: Children with HbAS	NR	HbSS 55%, HbSC 26%, HbSβ$^+$-thal 8%, HbSβ^0-thal 4%, Other 7%	NR	NR	100	P, Obs	120
Zafeiriou, 2004[95]	Children	14.9±3.9	21	To determine the prevalence of CNS abnormalities in asymptomatic young patients with HbSβ-thal	1, patients with SCD	NR	52.3	HbSβ-thal$^+$ 90.5, HbSβ^0-thal 9.5	NR	0	100	P, Obs	NR
Gordeuk, 2008[96]	Adults	Range: 26–46	163	To check whether systemic HTN is associated with increased risk for PHTN and renal dysfunction	1, patients with SCD	Inclusion: Patients with HbSS or HbSβ^0-thal who participated in the Sickle Cell Pulmonary Hypertension Screening Study and who had values recorded for systolic blood pressure (SBP) and also values for TRV by ECHO, serum creatinine concentration, or both	45	HbSS 97%, HbSβ^0-thal 3%	NR	50	100	R-P, Obs	24
al-Naama, 2000[97]	Children	8.3±2.3 (13.8±2.5 for the control group)	30 (and 45 controls)	To determine the levels of serum uric acid, urea, and creatinine in subjects with SCD and compare them to those reported in literature	2, patients with SCD and healthy controls	NR	67% in the SCD group 46.6% in the control group	HbSS 40%, HbAA 60%	NR	NA	40	Cross	NA

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Abo-Zenah, 2009[98]	Adults	27.7±7.5	165 (and 18 controls)	To screen this sickle cell population for markers of cardiorenal risk such as albuminuria and intima-media thickness	2, 165 patients with SCD on 1 arm and 18 healthy adults on the other	Inclusion: Saudi nationality and aged 15 yr or older. Exclusion: Non-Saudi residents, individuals known to have diabetes and HTN, as well as pregnant women. Patients who attended the hospital because of gross or microscopic (positive orthotolidine test) hematuria, sickle cell crises, or because of other hemoglobinopathies such as thalassemia were also excluded; patients with urinary sediment abnormalities inferred from positive leukocyte esterase or nitrates indicative of significant bacteriuria	19.5	NR	NR	NA	100	Cross-sectional study (cross)	NA
Adebiyi, 2010[99]	% adults not reported	26.1±7.98 (and 25.55±7.07 for the control group)	90 (number of subjects in the control group not reported)	To estimate the pulmonary artery systolic and diastolic pressures in subjects with SCA seen at the University College Hospital, and to determine the frequency of PHTN among them	2, patients with SCD and healthy controls	Inclusion: Patients with SCA and in steady state. They all had Doppler echocardiographic estimation of pulmonary artery pressures.	42.2	NR	NR	NA	NR (number of subjects in the control group was not reported)	Cross	NA

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Aessopos, 2007[100]	Adults	30.3±8.1	47 patients with SCD and 40 healthy controls	To investigate aortic elastic properties and endothelial function in sickle-thalassemia	2, patients with SCD and healthy controls	Inclusion: patients with the diagnosis of sickle-thalassemia Exclusion: An age of 45 yr or older, a mean Hb level over the past 1 yr lower than 8.5 g/dL, as well as the presence of heart failure, systolic LV dysfunction (LV shortening fraction <30% or LV ejection fraction (EF) (LVEF) <55%), systemic HTN, significant PHTN (peak systolic tricuspid pressure gradient >40 mmHg), cardioactive medication, diabetes mellitus, dyslipidemia, thyroid or parathyroid dysfunction, and history of smoking	42.6	HbSβ^+-thal 64% HbSβ^0-thal 36%	NR	NA	54	Cross	NA
Aessopos, 2009[101]	Adults	34±14 for patients, control's age NR	165 (115 patients and 50 healthy controls)	To perform a global evaluation of cardiac function in a large cohort of Greek patients with HbSβ-thal and discuss our findings in comparison with the existing data in sickling syndromes	2 groups, patients with HbSβ-thal, *n*=115, and healthy matched controls, *n*=50	Inclusion: The diagnosis of HbSβ-thal. Exclusion: (1) a history of painful crises or infection throughout the 2-mo period prior to the study; (2) a history of regular or frequent blood transfusion therapy; (3) a history of severe hepatic dysfunction with ascites of noncardiac origin	43.5	HbSβ^0-thal 71.3% HbSβ^0-thal$^+$ 28.7%	NR	NA	70	Cross	NA
Aikhionbare, 1988[102]	Children	5	32 (22 patients and 10 controls)	To study endogenous creatinine clearance (CrCl) in children with SCA and its relationship with age	2, patients with SCD, *n*=22, and non-SCD controls *n*=10	Symptom free patients with HbSS, and control patients are those with HbAA who had ailments like rhinitis.	66	HbSS 69%, HbAA 31%	NR	NA	69	Cross	NA
Akgul, 2007[103]	% adults not reported	18.5±8.0 (19.6±7.2 for the control group)	73 (and 25 controls)	To examine QT dispersion in patients with SCD and to assess the effect of PHTN on QT dispersion	2, patients with SCD on 1 arm and healthy controls on the other	Inclusion: Enrolled patients were in a noncrisis, steady state and had not experienced an episode of ACS in the 6 weeks preceding enrollment	60	NR	NR	NA	100	Cross	NR

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Al-Ali, 1995[104]	% adults not reported	5–25	439	To determine the level of uric acid, creatinine, and urea in normal, glucose-6-phosphate dehydrogenase (G6PD) deficient and HbSS patients	Healthy volunteers and patients in clinic	NR	NR	NR	NR	NA	30	Cross	NA
Alameri, 2008[105]	% adults not reported	22.7±7.1	39	To examine pulmonary function, dyspnea, and exercise capacity in adult Saudi patients with SCD	1, patients with SCD	Inclusion: >14 yr of age and a steady-state clinical condition defined as no acute illness during the 4 weeks before assessment. Exclusion: A history of cardiac or pulmonary diseases (other than conditions related to SCD) and a history of smoking	49	HbSS 100%	NR	NA	100	Cross	NA
Aleem, 2010[106]	% adults not reported	23.8±7.2	67	To identify risk factors, if any, associated with proteinuria in adult patients with SCD	1, patients with SCD	Inclusion: Patients with SCD aged 14 and older in steady state (no acute illness during 2 weeks prior to assessment). Exclusion: Patients with HbSA	46.3	HbSS 91%, HbSβ^0-thal 9%	NR	NA	100	Cross	NA
al-Hazzaa, 1995[107]	Adults	27.25	71	To determine whether or not retinal changes occur in SCD in Saudi Arabian subjects with either the Benin, which exists in the south western part of the kingdom, or Asian haplotypes in the east, and to compare the findings with those in SCD in Jamaica	1, patients with SCD	NR	53.5	HbSS 86%, HbSβ-thal 14%	Benin, Asian	NA	100	Cross	NA

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Almeida, 2008[108]	Adults	23±5	25 (+ 19 healthy controls)	To determine whether quantitative myocardial contrast ECHO could detect perfusion abnormalities in young adults with stable HbSS, with a long disease history, and clinical absence of heart failure	2, patients with SCD on 1 arm and healthy controls on the other	Inclusion: Young adult patients with HbSS who are clinically stable and without symptoms of heart failure or physical signs. Exclusion: Inadequate ECHO window, more than mild valvular regurgitation/disease, pregnancy, and lactation	24, 26 for the control group	HbSS 100% (of the patient group)	NR	NA	57	Cross	NA
Alouch, 1989[109]	% adults not reported	NR	65	To evaluate renal and electrolyte profile in steady-state HbSC	1, patients with SCD. This study compares tests between different SCD genotypes	NR	NR	60% HbSS, 26% HbSC, 8% HbSβ^0-thal, 6% HbSβ^+-thal	NR	NA	100	Cross	NA
Alpert, 1981[110]	Children	10.1	217	To determine whether exercise responses are different from normal in children with SCA	2 groups, patients with SCD, *n*=47; and healthy controls *n*=170	Inclusion: Patients with SCD not otherwise specified	60% of the SCD group	22% HbSS	NR	NA	22	Cross	NA
Alvarez, 2006[111]	Children	12.2±4.7	120	To discover the prevalence and risk factors of microalbuminuria in patients with SCD	1	NR	50	HbSS 74.1%, HbSC 18.3%, HbSβ^+-thal 2.5%, HbSβ^0-thal 5.0%	NR	NA	100	Cross	NA
Alvarez, 2006[112]	% adults not reported	9–21 yr (range)	20	To examine the value of serum cystatin C as a marker for GFR in children with SCD, as compared to serum creatinine and CrCl	2, patients with SCD with albuminuria and patients with SCD without albuminuria	NR	50	HbSS 95, HbSC 5	NR	NA	100	Cross	NA
Animasahun, 2010[113]	Children	95.41±49.06 mo (95.45±50.92 mo for the controls)	60 (and 60 healthy controls)	To determine ECHO cardiac dimensions and hemodynamic parameters of children with HbSS in steady state at the Lagos University Teaching Hospital (LUTH)	2, patients with SCA on 1 arm and healthy controls matched for age and sex on the other	Inclusion: Patients with SCA in steady state which was defined absence of any crisis in the preceding 4 weeks, no recent drop in the Hb level, and absence of any symptoms or signs attributable to an acute illness	55	HbSS 50%, HbAA 50%	NR	NA	50	Cross	NA

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Aoki, 1990[114]	Children, and adults	26.5 (range 13-47)	56 (and 10 controls)	To determine the presence of microalbuminuria measured by radioimmunoassay in patients with SCD	2, patients with SCD and normal controls	Inclusion: Patients who were clinically stable	48	HbSS 73%, HbSC 20%, HbSβ-thal 7%	NR	NA	84.8	Cross	NA
Aparicio, 1990[115]	Adults	50.7	38	To compare the measurement of chromium-51-labeled ethylenediaminetetra-acetic acid (51Cr-EDTA) clearance, CrCl, serum creatinine, and beta 2 microglobulin as indicators of renal function in patients with SCD	1, *n*=38, patients with SCD	Inclusion: Patients older than 40 yr of age with SCD	45	100% HbSS	NR	NA	100	Cross	NA
Armstrong, 1996[116]	Children	Range: 6–12	194	To determine whether neuroradiographic evidence of infarct in children with SCD between ages 6 and 12 yr would result in impairment in cognitive and academic functioning	Patients enrolled in CSSCD trial	Inclusion: Patients with SCD	49	70% HbSS, 30% HbSC	NR	NA	100	Cross	NA
Arslankoylu, 2010[117]	% adults not reported	10.4±4.2	32 and 30 healthy controls	To evaluate LV and right ventricular (RV) functions by using the Doppler myocardial performance index (MPI) in children with SCA	2, 32 patients with HbSS on 1 arm and 30 healthy children on the other	NR	53 of patients Control data NR	HbSS 52%	NR	NA	52%	Cross	NA
Asaolu, 2010[118]	% adults not reported	12–30 (range)	42	To compare some biochemical parameters between patients with SCD and age-matched healthy controls	2, patients with SCD on 1 arm and healthy controls on the other	NR	28.5	NR	NR	NA	NR	Cross	NA
Asdourian, 1976[119]	Adults	NR	100	To document ocular posterior pole changes and characterizes their evolution in SCD	1, patients with SCD	SCD followed at sickle cell eye clinic	NR	41% HbSS, 36% HbSC, 15% sickle thalassemia (HbS-thal), 7% HbAS, 1% HbCC	NR	NA	100	Cross	NA

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Ataga, 2004[120]	Adults	37±13	60	To determine the prevalence of PHTN in adult patients with SCD and to identify factors associated with this life-threatening complication	1, patients with SCD	Inclusion: Enrolled patients were in the noncrisis, steady state; had not experienced an episode of ACS in the preceding 4 weeks; and had no evidence of heart failure	46.7	HbSS 80%, HbSC 10%, HbSβ^0-thal 3.3%, HbSβ^+-thal 6.7%	NR	NA	100	Cross	NA
Ataga, 2008[121]	Adults	Median for patients with SCD 39, median for controls 45	76 patients, 6 controls	To determine whether markers of coagulation activation and inflammation are associated with PHT in SCD	2, patients with SCD and healthy controls	Inclusion: Each enrolled patient with SCD was studied while in a noncrisis, steady state, had not experienced an episode of ACS in the 4 weeks preceding enrollment, and had no clinical evidence of congestive heart failure	39% of patients, 33% of controls	HbSS 74%, HbSβ^+ 9%, HbSβ^0-thal 5%, HbSC 12% (controls not included)	NR	NA	92.6	Cross	NA
Ataga, 2010[122]	Adults	Range: 24–44	94 (73 patients and 21 controls)	To determine the relationship between albuminuria and both clinical and laboratory variables in SCD	2, 73 patients with SCD and 21 healthy, race-matched control subjects	NR	35.6	HbSS 83.5%, HbSC 10.9%, HbSβ^+-thal 1.3%, HbSβ^0-thal 4.1% (controls not included)	NR	NA	77.6	Cross	NA
Ausava-rungnirun, 2006[123]	% adults not reported	9.26	80	To determine the presence of hyperemia in asymptomatic patients with SCD using Dynamic Vascular Analysis	1, patients with SCD	Inclusion: Patients with SCD who had not experienced clinical stroke or transient ischemic attack (TIA) by history and neurological examinations were eligible. Patients had TCD as part of routine outpatient clinical followup	50	HbSS 62.5%, HbSC 26.5%, HbSβ-thal 10%, hemoglobin S alpha thalassemia (HbSα-thal) 1.2%	NR	NA	100	Cross	NA
Aygun, 2009[124]	Children	9.4±4.6	65	To compare GFR measured quantitatively by plasma clearance of injected 99-technetium diethylenetriaminepenta-acetate (99mTC-DTPA) to GFR estimates using serum creatinine and cystatin C in children with SCA	1, patients with SCD	NR	63	NR	NR	NA	100	Cross	NA

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Babalola, 2001[125]	15% adults	15.3	90	To highlight a time frame for the development of PSR to enable pediatricians decide on an appropriate time of referral for ophthalmic assessment	1, patients with SCD	NR	52	98% HbSS, 2% HbSC	NR	NA	100	Cross	NA
Bahia, 2009[126]	Adults	29	80	To evaluate the intracranial lesions in adult patients with SCD using MRI and MRA	1, patients with SCD	Patients were chosen in an aleatory way to perform MRI and MRA, including both symptomatic and asymptomatic, from a cohort of patients with SCD who had undergone TCD	NR	HbSS 81.3%	NR	NA	100	Cross	NA
Balfour, 1984[127]	Children	9.9	202	To document the effects of the disease on the heart to enable more accurate prediction of the course and outcome of these patients	2 groups, SCD group, *n*=124, and healthy Black volunteers, *n*=78	Inclusion: Patients with SCD not otherwise specified	NR	90% HbSS, 10% HbSC or HbSβ-thal	NR	NA	61	Cross	NA
Balfour, 1988[128]	Adults	23	49	To document suspected abnormalities of diastolic function and to relate these abnormalities to exercise performance	11 normal Black subjects and 38 patients with SCA while they were at rest to evaluate their LV systolic and diastolic function	Inclusion: SCD not otherwise specified	67	NR	NR	NA	78	Cross	NA
Barros, 2006[129]	Adults	31.6±9.8	70	To obtain reference Cr-EDTA values as an estimation of GFR	1, patients with SCD	Inclusion: All patients were free of pain at the time of the study and had not been hospitalized or transfused for at least 3 mo before the study. The patients were not receiving any medication other than folic acid. Exclusion: Abnormal serum creatinine (serum creatinine >1.1 mg/dL, clinical albuminuria (>200 µg/min), HTN, diabetes, and pregnancy	43	HbSS 100%	NR	NA	100	Cross	NA

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Batra, 2002[130]	% adults not reported	11.7±4.7	77	To determine how the degree of anemia and transfusion status relate to cardiac findings	2, patients with SCD who are not on transfusion (group 1) and patients with SCD who are receiving transfusion (group 2)	Inclusion: Patients were recruited during their routine clinic visits. Exclusion: Patients who had ECHOs performed during a sickle cell crisis. Patients with HbSC and HbSβ-thal were also excluded	60	HbSS 100%	NR	NA	100	Cross	NA
Bayazit, 2002[131]	Children	9.2	68 (55 patients and 13 controls)	To demonstrate the abnormalities of HbSS patients' renal function in childhood	2, SCD, *n*=55, and healthy controls, *n*=13	Inclusion: All patients with SCD followed by the center	51% in the SCD group, NR in total population	HbSS 81%	NR	NA	81	Cross	NA
Becton, 2010[132]	Children	11.4±5.2	90	To determine the prevalence and examine clinical correlates of microalbuminuria/protein uria in patients with SCDs	1, children with SCD	Inclusion: Patients with SCD aged 2 to 18 yr in their steady state. Exclusion: Patients were ineligible if they were in pain at the time of their visit to the clinic, had VOC or ACS within the last 3 weeks, or had other concomitant primary kidney disease or secondary HTN. Patients with HbSA were also excluded	57	HbSS 73%, HbSC 17%, HbSβ-thal 8%, Other 2%	NR	NA	100	Cross	NA
Behera, 1979[133]	Children	1–14	60	To study the cardiac state in SCA	1, *n*=60, patients with SCD	Exclusion: Patients with HTN or any major cardiac disease	NR	NR	NR	NA	100	Cross	NA
Brady, 2009[134]	Children	Range: 5 mo to 18 yr	33	To establish a screening process that identifies patients with sickle cell lung disease	1, patients with SCD	NR	NR	NR	NR	NA	100	Cross	NA
Brass, 1991[135]	% adults not reported	23	23	To understand better the relationship between blood velocity measured by TCD and cerebral blood flow measured by the 133Xe inhalation method	1, *n*=23, patients with SCD already enrolled in a prospective study	NR	39	87% HbSS, 9% HbSC, 4% HbSβ-thal	NR	NA	100	Cross	NA

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Bulas, 2000[136]	Children	8 (mean) 3–14 (range)	22	To compare nonimaging (TCD) and transcranial duplex imaging (TCDI) findings in children potentially at risk for stroke with SCD	1, patients with SCD	Inclusion: Patients had no history of stroke	NR	NR	NR	NA	100	Cross	NA
Caldas, 2008[137]	Children	10.1±4.7 (7.9±4.5 for the control group)	107 (+ 70 controls)	To determine the systolic and diastolic function of both ventricles using load-independent parameters and to evaluate cardiac findings due to transfusion or chelation therapy in patients with SCA	2, HbSS patients with SCD on 1 arm and 70 normal children and adolescents on the other	Exclusion: Sickle cell crisis within the 3 mo previous to entry in the study, HbSC, and HbSβ-thal. Patients on chronic transfusion protocol were also included, and all of them were on iron chelation therapy with deferoxamine	46.7 of the patient group	HbSS 100%	NR	NA	60.5	Cross	NA
Castro, 2010[138]	Children	10.7 (median)	15	To evaluate the frequency of PHTN in a group of pediatric patients with SCD living at high altitude (2600 meters above sea level)	1, patients with SCD	Exclusion: Patients with cardiac disease or other disorders related to PHTN	NR	NR	NR	NA	100	Cross	NA
Cetta, 1997[139]	% adults not reported	9.8±5.4	20 (14+6)	To evaluate the utility of the RV MPI in children and young adults with SCA	2, patients were divided into 2 groups based on the LV end-diastolic dimension (LVEDD) as measured by standard M-mode techniques. Patients with LVEDD >90th percentile for body weight (*n*=14) were assigned to group A. Patients with LVEDD <90th percentile were assigned to group B (*n*=6)	NR	NR	NR	NR	NA	100	Cross	NA

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Chaudry, 2010[140]	Children	14±2.3 (14.9±2.0 for the control group)	50 (and 50 controls)	To determine the prevalence of PHTN in patients with SCD and the relation to pulmonary vascular resistance	2, patients with SCD on 1 arm and healthy controls on the other	Eligibility: Older than 10 yr, genotype HbSS or HbSC and Afro-Caribbean ethnicity in at least 1 parent. Exclusion: HIV infection, a history of stroke and congenital heart disease. All children were in a baseline state of health, defined as being free from acute illness for a minimum of 14 d prior to the study	49	HbSS 34%, HBSC 16%, HbAS 9%, HbAA 41%	NR	NA	50	Cross	NA
Chung, 1987[141]	Children	All subjects (patients and controls) were within 2 mo of their 8th birthday	10 (and 14 controls)	To determine the cardiac performance in SCD children and compare it to healthy individuals	2, patients with SCD and healthy controls	NR	58.3	HbSS 41.6%, HbAA 58.4% (controls not included)	NR	NA	41.6	Cross	NA
Cipolotti, 2001[142]	Children	9±4.9	38	To describe the cardiac size and function in patients with SCD in Segipe, Brazil, and its association to the clinical severity, duration of illness and Hb levels	1, patients with SCD	Exclusion: Patients who had an acute crisis or had received transfusions in the preceding 3 mo; and those with cardiac diseases other than SCA or chronic illnesses (e.g., HTN)	50	HbSS 100%	NR	NA	100	Cross	NA
Colombatti, 2009[143]	Children	Range: 1–12	36 (12+12+12)	Verifying if internationally accepted reference values could also apply to our population and could be used as reference screening values	3, group A with 12 SCD HbSS African patients, group B with 12 healthy African age-matched controls, group C with 12 healthy Caucasian age-matched controls	NR	33.3	HbSS 33%	NR	NA	33.3	Cross	NA
Covarrubias, 1980[144]	% adults not reported	25±7.2	14	To assess LV function in SCA	1, patients with SCD, *n*=14	Exclusion: Patients with congenital heart disease, rheumatic heart disease, HTN, renal failure, angina, documented MI, and excessive alcohol abuse	93	NR	NR	NA	100	Cross	NA
Covitz, 1983[145]	% adults not reported	15.3	34	To characterize the functional abnormality in SCD	2, patients with SCD, *n*=22, non-SCD controls, *n*=12	Inclusion: SCD not otherwise specified	NR	65% HbSS	NR	NA	65	Cross	NA

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Covitz, 1995[146]	% adults not reported	25.9±8.8	191	To obtain representative ECHO measurements of cardiac size and function in stable patients with SCD	1, patients with SCD	Inclusion: Subjects were crisis free for 2 weeks prior to the study and had not been transfused in the preceding 3 mo	39.2	HbSS 100%	NR	NA	100	Cross	NA
Dahoui, 2010[147]	% adults not reported	12.4	85	To determine the prevalence of PHTN and identify factors associated with PHTN among children and young adults with SCD in Lebanon	1	NR	54.5	HbSS 74.25%, HbSβ^+-thal 21.3%, HbSβ^0-thal 4.4%	NR	NA	0	Cross	NA
Datta, 2003[148]	Children	All patients were <14 yr of age	64	To determine the prevalence of microalbuminuria in children with SCD	1, patients with SCD	Exclusion: Patients with documented acute or chronic infection, hemodynamic instability, history of use of potential nephrotoxic medication, comorbid condition like diabetes, HTN, congestive heart failure, and family history of renal disease	NR	HbSS 81.3%	NR	NA	100	Cross	NA
de Melo, 2008[149]	Children	9.55±4.67 (9.82±4.51 for the control group)	34 (and 80 controls)	To evaluate brain hemodynamic profile of children with SCA	2, patients with SCD and healthy controls	Exclusion: Patients with antecedent of cerebrovascular disease, using HU, who had been submitted to blood transfusion or had any clinical event in the 30 previous d	53.5	HbSS 29.8%	NR	NA	29.8	Cross	NA
Dham, 2009[150]	Children	NR	19 (and 4 controls)	To analyze regional RV strain using velocity vector imaging in children with SCD and see whether it could provide insight to cardiovascular pathophysiology of SCD	2, patients with SCD and healthy controls	NR	NR	NR	NR	NA	82.6	Cross	NA
Dhamidharka, 1998[151]	Children	9.47±4.62	102	To prospectively investigate the prevalence of microalbuminuria in children with HbSS and determine factors which affect its expression	1, patients with SCD	Inclusion: Children in the steady state. Exclusion: Children with prior known proteinuria, HTN, pregnancy, or fever/ pain episode in the last 15 d	52	HbSS 100%	NR	NA	100	Cross	NA

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Elegbeleye, 1978[152]	% adults not reported	26	12 (and 40 controls)	Effects of anemia caused by SCD on pulmonary diffusing capacity	2 groups, SCD group, *n*=12 and healthy controls, *n*=40	Patients with SCD vs. healthy controls. None of the patients had chronic cardiopulmonary disease	56	23% HbSS	NR	NA	23	Cross	NA
Elshazly, 2010[153]	Adults	32±6	100	To evaluate the prevalence of PHTN in patients from eastern province Saudi Arabia and correlate the findings with the well-documented characteristics of this patient population, comparing patients with and those without HU treatment	1, patients with SCD	NR	58	NR	NR	NA	100	Cross	NA
Falk, 1992[154]	81% adults	NR	381	To determine the prevalence of proteinuria and renal insufficiency in a group of patients with SCD	1, adult patients with SCD	Inclusion: Adult patients with SCD	47	HbSS 71%, HbSC 17%, HbSβ-thal 11%, other 1%	NR	NA	100	Cross	NA
Fonseca, 2010[155]	Adults	NR	80	To estimate the prevalence, clinical and laboratory features and hemodynamic profile in patients with PHTN	1, patients with SCD	NR	NR	HbSS, % NR HbSβ-thal % NR	NR	NA	100	Cross	NA
Gerry, 1976[156]	Adults	29.5	23 (and 9 controls)	To evaluate LV function in patients with SCD	2, patients with SCD and healthy controls	Inclusion: All enrolled patients were asymptomatic. Exclusion: Patients with rheumatic heart disease, HTN, renal failure, angina pectoris, or documented MI	NR	HbSS 100 (controls not included)	NR	NA	76.7	Cross	NA
Gold, 2001[157]	Children	13 (range: 7–17)	65	To determine the extent of neurocognitive impairment, the prevalence of neuroradiographic abnormalities, and their relationship in neurologically asymptomatic adult patients with SCD	1, patients with SCD	Inclusion: All participants were in the steady state	60	HbSS 80%, HbSC 15.4%, HbSβ^0-thal 4.6%	NR	NA	100	Cross	NA

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Goldbaum, 1978[158]	% adults not reported	24.5	80	To describe retinal depression signs indicating a small retinal infarct in SCD	1, patients with SCD	Inclusion: SCD not otherwise specified	NR	HbSS, HbSC, HbSβ-thal, HbAC, HbAS (percentages not reported)	NR	NA	100	Cross	NA
Gribbons-Harris, 1998[159]	Children	8–12	10	To investigate whether the use of TC-99m hexamethylpropylene-amine oxime (HMPAO) single photon emission computer tomography (SPECT) is superior to MRI for the detection of small vessel disease in asymptomatic patients with SCA and to compare these findings with clinical evaluation	1, patients with SCD	Neurologically asymptomatic patients with SCA. Subjects with SCA were recruited by a convenience sample if they had no documented history of stroke, were aged 8–12 yr, and were not receiving chronic blood transfusions	NR	NR	NR	NA	100	Cross	NA
Guasch, 1996[160]	Adults	Range: 18–65	34	To determine the course of progressive renal insufficiency in patients with SCA and, using physiological techniques, to identify possible markers of early glomerular injury in this disease	1, patients with SCD	NR	37	HbSS 67.6%, HbSC 32.4%	NR	NA	100	Cross	NA
Guasch, 1999[161]	Adults	30.4	76	To investigate the role of the α-globin gene microdeletion, and β-globin gene cluster haplotypes on the degree of glomerular involvement in patients with SCD	1, patients with SCD	Patients were excluded if they reported pain compatible with a vaso-occlusive episode (VOE), had a fever, or were acutely ill	42	HbSS 100%	NR	NA	100	Cross	NA
Guasch, 2006[162]	Adults	Range: 19–76	300	To determine the prevalence of glomerular damage in SCD and the clinical correlates of renal insufficiency	1	Samples were not collected when patients were acutely ill (including having a fever or needing referral to the urgent care center), had symptoms suggestive of sickle cell pain crisis or urinary tract infection, or had gross hematuria	56.3	HbSS 61.3%, Non-HbSS 39.7%	NR	NA	100	Cross	NA

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Gurkan, 2010[163]	Children	12±4.5	40	To determine the prevalence of microalbuminuria and proteinuria in a pediatric SCA population and to identify clinical and laboratory variables associated with them	1, patients with SCD	Inclusion: Any patient between the ages of 5 and 20 yr with a diagnosis of SCA who was seen as an outpatient during the specified period was included in the study. Exclusion: Because the renal involvement correlates with the duration of SCA, patients younger than 5 yr were excluded	50	HbSS 81.58%, HbSC 13.16%, HbSβ-thal 5.26%	NR	NA	100	Cross	NA
Helton, 2009[164]	Children	Median: 12	21	To evaluate cerebral blood flow in white and grey matter of children with SCD	1, pediatric patients with SCD	Inclusion: Children with HbSS. Exclusion: Children requiring sedation to complete the MRI examination	71	HbSS 100%	NR	NA	100	Cross	NA
Herrera, 2002[165]	% adults not reported	24.4±7.4 (25.3±7.0 for the controls)	16 (and 20 controls)	To investigate creatinine secretion after an intravenous creatinine load in patients with SCD before they have evidence of deterioration of renal function	2, patients with SCD and healthy controls	NR	NR	HbSS 44.4%	NR	NA	44.4	Cross	NA
Hijazi, 2005[166]	Children	11.45	28 patients with SCD, 10 patients with HbH (i.e., alpha-thal), 10 healthy controls	To study pulmonary function in patients with SCD and those with HbH disease	3, patients with SCD, patients with HbH, and healthy controls	Inclusion: The patients had to be in steady state, i.e., no acute illness within the preceding 6 weeks, and they were aged ≥6 yr and able to cooperate in conducting pulmonary function studies	NR	HbSS 38.2, HbSβ^0-thal 12.7, HbH 18.2, HbAA 30.9 (controls not included)	Arab/Indian	NA	50.1	Cross	NA
Holloman, 1987[167]	Adults	27	87	An analysis of the ECGs of adult patients with HbSS	1, patients with SCD	NR	43.6	HbSS 100%	NR	NA	100	Cross	NA
Jaja, 2000[168]	Adults	21.7±0.5 (21.0±0.8 for the control group)	25 (and 15 controls)	To show whether there is a positive relationship between HbF, irreversibly sickled cells, and several lung function parameters	2, patients with SCD and healthy controls	NR	NR	HbSS 62.5%, HbAA 37.5%	NR	NA	62.5	Cross	NA

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Johnson, 2010[169]	Children	10.1	44	To test the hypothesis that cardiac abnormalities in children with SCD are related to sleep abnormalities	1, patients with SCD	Inclusion: Patients with SCD, 4 to 18 yr of age, who were enrolled in the Sleep and Asthma Cohort study and had sleep study and ECHO performed within 7 d. Exclusion: Chronic blood transfusion therapy, CPAP or overnight oxygen therapy, noncompliance with clinic followup, participation in clinical trials of blood transfusion, oxygen or HU, comorbidities known to predispose to sleep-disordered breathing, chronic lung disease, cardiac disease requiring surgical or catheter-based intervention, or HIV disease. Adenoidal or tonsillar hypertrophy was not an excluding condition	NR	HbSS 100%	NR	NA	100	Cross	NA
Jordan, 2010[170]	Children	Median: 9.2 yr	953	To describe the prevalence and range of incidental intracranial abnormalities identified through MRI of the brain in a large group of children screened for a clinical trial	1, patients with SCD	Exclusion: Children with a history or findings from a neurologic examination by a pediatric hematologist that were concerning regarding overt stroke	51.7	HbSS, HbSβ^0-thal	NR	NA	100	Cross	NA
Jyothi, 2009[171]	Children	11.4±5.2	100	To determine the prevalence and examine the risk factors associated with microalbuminuria/ proteinuria in children with SCD	1, patients with SCD	NR	57	NR	NR	NA	100	Cross	NA

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Kalpatthi, 2009[172]	Children	13, 5–20 (median, range)	73	To report the prevalence of PHTN as estimated by TRV ≥2.5 m/s measured on routine ECHO in children with SCA receiving care at Medical University of South Carolina comprehensive sickle cell center	1, patients with SCD	Inclusion: Patients were at steady state	53.4	HbSS, HbSβ^0-thal (proportions not specified)	NR	NA	100	Cross	NA
Kanadasi, 2005[173]	% adults not reported	26.4±8.5	31 patients (and 31 controls)	To investigate LV diastolic function in patients with SCA without congestive heart failure by using pulsed waved tissue Doppler imaging (TDI)	2, patients with SCD on 1 arm and healthy controls on the other	Inclusion: Patients were HbSS and had no signs or symptoms of heart failure. Exclusion: Patients with rheumatic heart disease, HTN, renal failure, LV systolic dysfunction (EF <45%), or documented coronary artery disease. Patients had no sickling crisis for 2 weeks prior to the study and recent blood transfusion <3 mo	60	HbSS 50%	NR	NA	50	Cross	NA
Karasmanis, 2009[174]	% adults not reported	17.7	20	To assess the incidence of CVA in a population of exclusively patients with HbSβ-thal	1, patients with SCD	Inclusion: All patients were in steady state with no neurological signs	NR	HbSβ-thal 100%	NR	NA	100	Cross	NA
Katopodis, 1997[175]	% adults not reported	Range: 16–59)	17 (and 17 controls)	To examine renal abnormalities in Greek patients with HbSβ-thal	2, patients with SCD and healthy controls	Inclusion: Patients were not receiving any medication other than folic acid. Patients had no other active medical problems, and had been free of pain crises for at least 1 mo before the study	47	HbSβ-thal 50%	NR	NA	50	Cross	NA
Kent, 1994[176]	Adults	Range: 16–55	50	To determine the prevalence of ocular complications in patients	1, patients with SCD	NR	52	HbSS 74%, HbSC 18%, HbSβ-thal 8%	NR	NA	100	Cross	NA
Kilinc, 1993[177]	Children	7.9±2.6 for the mild SCD group, 8.0±3.7 for the severe SCD group, 8.0±2.4 for the healthy controls	30 patients (12 mild and 18 severe) and 12 healthy controls	To evaluate cardiac functions by ECHO in patients with SCA and investigate whether there was any difference between patients with mild and severe clinical courses	3, patients with mild SCD, patients with severe SCD, and healthy controls	NR	NR	NR	NR	NA	71.4	Cross	NA

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Kim, 2009[178]	Adults	33±12 for the patients with SCD (35±9 for the controls)	18 (+10 controls)	To determine whether cerebrovascular control in patients with SCD is affected by and related to hemolysis	2, 18 patients with SCD on 1 arm and 10 age- and ethnicity-matched healthy subjects on the other	Inclusion: Only patients with SCD with genotype HbSS or HbSβ^0-thal. Exclusion: A sickle cell crisis in the preceding 4 weeks, history of symptomatic cerebrovascular disease, clinical manifestation of heart failure or other cardiovascular diseases, uncontrolled HTN (blood pressure (BP) >160/100 mmHg), orthostatic hypotension, use of medication with potential influence on autonomic cardiovascular function, or a blood transfusion in the preceding 4 mo	28.5% (28% in the SCD group and 30% in the control group)	HbSS 95%, HbSβ^0-thal 5% (controls not included)	NR	NA	64	Cross	NA
Kinney, 1999[179]	Children	8.2±1.8	230	To study the risk factors of silent stroke in SCD children	1	NR	51.7	HbSS 100%	NR	NA	100	Cross	NA
Kirk, 2009[180]	Children	Range: 5–11 (12–21 in controls)	28 (+29 healthy controls)	To assess cortical thickness in patients with SCD who had no detectable abnormalities on conventional MRI/MRA	2, patients with SCD (older and younger groups) vs. healthy controls (older and younger groups)	Inclusion: HbSS pediatric patients who had a negative MRI test	NR	HbSS 100 (controls not included)	NR	NA	49	Cross	NA
Klings, 2006[181]	Adults	30.7±10.3	310	To determine the pattern of pulmonary dysfunction and their association with other systemic complications of SCD	1, patients with SCD	Inclusion: Patients were in the steady state (at least 4 weeks after a VOC). Exclusion: Subjects who were not African American, not HbSS, and without complete PFTs	41	HbSS 100	NR	NA	100	Cross	NA

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Klings, 2008[182]	Adults	30.0±9.3 for the HbSS patients, 37.3±12.2 for the patients with HbSC, 28.3±7.2 for the healthy HbAA controls	124 (+23 controls)	To determine the prevalence of PAH and PHTN related to left-sided heart disease (LHD)	2, patients with SCD on 1 arm and age- and race- matched healthy controls on the other	Recruitment was performed irrespective of cardiopulmonary symptomatology	38 (22 for the control group)	HbSS 78, HbSC 22 (controls not included)	NR	NA	84	Cross	NA
Knight-Madden, 2005[183]	Children	7.1±1.1	160 (80+80)	To test the hypotheses that asthma and bronchial hyperreactivity (BHR) are more common in children with SCD than in ethnic-matched controls and that children with SCD with atopic asthma are more likely to have recurrent episodes of ACS	2 groups, patients with SCD, *n*=80, and healthy controls, *n*=80	Inclusion: Children with HbSS aged 5–10 yr attending the Sickle Cell Clinic at the University of the West Indies, Jamaica	50%	HbSS 100% of SCD group, 0% of control group	NR	NA	50%	Cross	NA
Kontessis, 1992[184]	% adults not reported	29.8	49 (+14 healthy controls)	To assess the renal function in HbSβ-thal patients	3, HbSβ-thal vs. HbSS vs. healthy controls	NR	NR	HbSβ-thal 65%, HbSS 13%	NR	NA	78	Cross	NA
Kral, 2003[185]	Children	10.09±2.61	60	To examine the relationship between cerebral blood flow velocity, measured by TCD US, and neurocognitive functioning	1, patients with SCD	Inclusion: Patients who were between the ages of 6 yr, 0 mo and 16 yr, 11 mo and had a confirmed diagnosis of HbSS and also were participants in the larger, multicenter STOP investigation of TCD. Exclusion: Patients with a history of birth complications, traumatic brain injury, known CVA, or major chronic illness other than SCD	43.3	HbSS 100%	NR	NA	100	Cross	NA

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Kral, 2006[186]	Children	129.15±35.85 mo (mean±SD)	27	To evaluate the utility of MRI, MRA, and TCD US for predicting neurocognitive functioning in children and adolescents with SCA	1	Inclusion: Patients between the ages of 6 yr, 0 mo and 16 yr, 11 mo with a confirmed diagnosis HbSS who also were participants in the larger, multicenter STOP. Exclusion: Patients with a history of birth complications, traumatic brain injury, known stroke, or a major chronic illness other than SCA	44.4	HbSS 100%	NR	NA	100	Cross	NA
Lamers, 2006[187]	Children	Range: 9.6	107	To evaluate myocardial contractility using the end-systolic wall stress (ESSm)-velocity of circumferential fiber shortening (VCFc) relationship in patients with SCA	2, patients with SCD vs. healthy controls	Healthy AA patients and SCA patients age 3 months to 18 years were studied	57	HbSS 100 (for the SCD group)	NR	NA	53	Cross-sectional	NA
Leong, 1997[188]	Children	10.7±3.5	40 (18 had a history of reactive airway disease (RAD), 22 had no known history of RAD) (and 10 controls)	To investigate the prevalence of AHR in SCD by cold-air bronchial provocation testing, and to assess whether AHR can be present in symptom-free patients with SCD	2, patients with SCD and healthy controls	Inclusion: Patients had to be in steady state, i.e., the absence of overt pain crisis, no blood transfusion within 3 mo, and no acute wheezing or upper respiratory tract infection for at least 4 weeks. Exclusion: Patients receiving chronic transfusion therapy or anti-sickling therapy	52	HbSS 75, HbSC 17.5, HbSβ^+-thal 7.5 (controls not included)	NR	NA	80	Cross-sectional	NA

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Lester, 1990[189]	Children	7.37±0.71 (7.81±0.60 for the control group)	64 (and 99 controls)	To characterize the cardiac abnormalities in a large group of children with SCA using an ECHO as a major tool, to determine whether the cardiac findings were related to the degree of anemia or percentage of Hb S, and whether they progress with age; and to evaluate cardiac performance and determine whether a "sickle cell cardiomyopathy" was encountered during childhood	2, patients with SCD and normal controls	NR	45.3	NR	NR	NA	39.2	Cross-sectional	NA
Lewis, 1991[190]	% adults not reported	30	30 (+30 healthy controls)	To determine whether LV diastolic abnormalities are an early feature of SCA	2, patients with SCD vs. healthy controls	Inclusion: Patients with SCD, age<40 yr, absence of cardiac symptoms or clinical evidence of heart disease, systolic fractional shortening >30%, no segmental wall motion abnormalities on 2-dimensional ECHO, no clinical or ECHO evidence of PHTN or RV systolic dysfunction, and absence of sickle crisis or blood transfusion in the 3 mo preceding the study	50	HbSS 77%, HbSC 23% (controls not included)	NR	NA	50	Cross-sectional	NA
Liem, 2007[191]	Children	14.02±2.62	51	To study the correlation between hemolysis and TRJV elevation in children and young adults with SCD	1	Inclusion: Subjects on HU therapy at the time of screening. Exclusion: Subjects undergoing chronic transfusions	58.8	HbSS 80%, HbSC 12%, HbSβ^0-thal 8%	NR	NA	100	Cross	NA
Liem, 2009[192]	% adults not reported	14.2±3	76	To determine the prevalence of prolonged QTc and evaluate its relationship to clinical factors in children and young adults with SCD	1, patients with SCD	Inclusion: Patients enrolled in PHTN screening protocol	57	HbSS 78%, HbSC 16%, HbSβ^0-thal 6%	NR	24	100	Cross	NA

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Liem, 2009[193]	% adults not reported	14.3±3	78	To estimate the prevalence of TRJV elevation and determine its relationship to pulmonary function in children and young adults with SCD at baseline	1, patients with SCD	Inclusion: All children and young adults between ages 10 and 25 yr, with SCD confirmed by hemoglobin analysis. Exclusion: Patients on chronic transfusion protocol for SCD-related complications such as cerebrovascular disease	59	HbSS 77%, HbSC 17%, HbSβ^0-thal 6%	NR	NA	100	Cross	NA
Lima, 2006[194]	Adults	30±10	102	To clarify whether the clinical, laboratory and genetic aspects of SCD influence the occurrence of vessel alterations in the conjunctiva and retina	1, patients with SCD	Inclusion: Patients who presented no medical problems apart from those associated with their SCD status. Exclusion: Patients who had previously submitted to retinal laser photocoagulation, suffered from painful crises in the previous 3 mo, or received a blood transfusion during the previous 3 mo	44	HbSS 70%, HbSC 19%, HbSβ-thal 11%	Benin/Benin 23, Ben/CAR 33, CAR/CAR 20	NA	100	Cross	NA
Lippman, 1985[195]	Adults	28±9	72	To assess the prevalence of abnormal initial downward deflections of the QRS complex (Q waves) in SCD and to determine if such Q waves could be explained by, or related to, ECHO-determined anatomic or functional abnormalities	1 group, patients with SCD	Inclusion: Patients with SCD. No patient had a history of systemic arterial HTN, valvular heart disease, or congestive heart failure. Exclusion: 1 patient with documented chronic systemic arterial hypertension, 1 patient with chronic renal failure, and 2 patients with rheumatic valvular heart disease	60	76% HbSS, 24% HbSC	NR	NA	100	Cross	NA

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Manfre, 1999[196]	% adults not reported	6–48 (range)	41	To evaluate the spectrum of MR findings of the brain in asymptomatic patients affected with thalassemia intermedia or sickle cell thalassemia disease to prevent brain damage by identifying patients at risk for stroke so that transfusional or pharmacologic treatment could be implemented	1, thalassemia intermedia or sickle cell-thalassemia disease patients	Inclusion: Enrolled patients had no history of previous stroke-like episodes, seizures, infectious diseases, or any other entities causing brain atrophic changes and normal findings on neurologic examination	37.5	HbSβ-thal 62.5%	NR	NA	62.5	Cross	NA
Marouf, 2003[197]	% adults not reported	26.9±9.3	35	To determine the prevalence of silent brain infarcts in adult Kuwaiti patients with SCD and to investigate the role of coexistent alpha thalassemia (α-thal) trait and other clinical or hematological factors	1, patients with SCD	Inclusion: All patients were studied in steady state, i.e., no acute illness within the preceding 6 weeks. Exclusion: Patients with a history of seizures or any other neurological abnormality	57	HbSS 71.4%, HbSβ^0-thal 28.6%	Saudi Arabia/ India HbSβ	NA	100	Cross-sectional	NA
Marouf, 2006[198]	% adults not reported	14–60	59	To evaluate and compare cystatin C, β2-microglobulin, and creatinine as markers of renal disease in relation to the degree of proteinuria and other complications of SCD	1	Inclusion: Patients, recruited during their routine visit to hematology clinics, included those who were in steady state and crisis-free for at least 2 weeks before enrollment. Thus none of the patients was on drugs known to affect GFR, creatinine secretion, or general tubular function. None of the patients was on HU	42.3	HbSS 48%, HbSβ-thal 52%	NR	NA	100	Cross	NA
Marsenic, 2008[199]	Children	9.57±5.45	32	Characterization of glomerular permselectivity and tubular proteinuria in children with SCD	1, patients with SCD	Inclusion: Stable patients (defined as those who were not having an acute illness and a crisis of SCD) and those without other chronic illness. Exclusion: Known HTN, fever, and pregnancy	47	HbSS 100%	NR	NA	100	Cross	NA

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Melek, 2006[200]	% adults not reported	22.1±7.8 (21.0±7.4 for the control group)	59 (and 28 healthy controls)	To investigate the effect of silent infarction on neurological soft signs and to evaluate whether neurological soft signs can be used in clinical practice to evaluate the patients at risk of stroke in patients with SCD with silent infarction	2, patients with SCD and healthy controls	Exclusion: Any subjects with focal neurological signs and severe head trauma were excluded	54.2 (53.5 for the control group)	NR	NR	NA	68	Cross	NA
Miller, 2009[201]	Children	13±2.7 mo	185	To describe the urine concentrating ability in children with SCD	1, patients with SCD enrolled in the Pediatric HU Phase III Clinical Trial (BABY HUG)	Inclusion: Infants with SCD aged 9–17 mo at entry. Exclusion: Infants with <4 h of fluid deprivation	NR	NR	NR	NA	100	Cross	NA
Morgan, 1981[202]	Adults	40–64 yr (range)	25	To examine renal function in patients older than 40 yr of age with HbSS	1, patients with SCD	NR	48	HbSS 100%	NR	NA	100	Cross	NA
Morgan, 1982[203]	% adults not reported	1–66	407	To study the correlation between proteinuria and leg ulcers in patients with HbSS	1, patients with SCD,	Inclusion: Patients with SCD not otherwise specified	48	100% HbSS	NR	NR	100	Cross	NA
Morgan, 1984[204]	Adults	40	64	To investigate the contribution of glomerular failure to the hyperuricemia in SCD	1, patients with SCD attending clinic, asymptomatic	Inclusion: Asymptomatic patients with SCD	45	100% HbSS	NR	NR	100	Cross	NA
Moyssakis, 2005[205]	Adults	54±10 (53±11 for the control group)	43 (and 55 controls)	To evaluate the RV and LV systolic and diastolic function in middle-aged patients with HbSβ-thal	2, patients with SCD	Inclusion: Diagnosis of HbSβ-thal. Patients had painful crises and red cell transfusions rarely (I<5/yr), while none was receiving drugs such as digoxin, diuretics, or vasodilators	34.8 (32.7 for the control group)	HbSβ^+-thal 100 (controls not included)	NR	NA	43.8	Cross	NA
Naoman, 2010[206]	Adults	37 (29–48) median (interquartile range)	105	To describe the ECHO findings in patients with SCD and assess whether PHTN is associated with hemolysis	1, patients with SCD	Adult outpatients or inpatients with SCD undergoing echocardiographic examination in Howard University Hospital, Washington, DC in 2006 and 2007 were included.	47	HbSS 73%, HbSC 17%, HbSβ^0-thal 10%	NR	NA	100	Cross	NA

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Nebor, 2010[207]	Adults	34.8±12.1	189	To identify possible risk factors for albuminuria, an early marker of SCA glomerulopathy	1, patients with SCD	Inclusion: Patients with SCD at steady state. Exclusion: Patients with HIV, hepatitis B or C	48	HbSS 100%	α-thal in 66 patients (36%), with the deletion of either 1 (*n*=60) or 2 genes (*n*=6). Benin (73%), Bantou (13.6%), Senegal (8.3%), Cameroun (2%), Arabo-Indian (0.3%), and atypical (2.8%).	NR	100	Cross	NA
Nelson, 2007[208]	Children	12.1	53	To study the prevalence of PHTN in children with SCD	1, patients with SCD	Inclusion: Patients with SCD at steady state	52.8	(Reported for 15 patients who had high TRV) HbSS 73.3%, HbSC 6.7%, HbSβ^+ 6.7%, HbSβ^0 13.3%	NR	NA	100	Cross	NA
Nobrega, 2009[209]	% adults not reported	21.3±3.9	51	To determine the prevalence of microalbuminuria in the patients with SCD without clinical or laboratorial evidence of established renal disease and determine factors, which may be associated with microalbuminuria	1, patients with SCD	NR	55	NR	NR	NA	100	Cross	NA

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Nur, 2009[210]	Adults	26 (21–42) Median (range) for the SCD group. 33 (24–40) for the control group	23 patients with SCD and 16 controls	To assess the cerebrovascular reserve capacity in patients with SCD	2, 23 patients with SCD on 1 arm and 16 age-, gender-, and ethnicity-matched healthy controls on the other	Inclusion: Patients with SCD age ≥18 yr and HbSS. Exclusion: Patients with history of stroke, HTN (systolic >140 mmHg and/or diastolic >90 mmHg), use of cardiovascular medication, blood transfusion in the preceding 4 mo, and acute vaso-occlusive events in the preceding 4 weeks	39 (for the patient group) 44 (for the control group)	HbSS 100% (controls not included)	NR	0	59	Cross	NA
O'Driscoll, 2008[211]	Children	9 (mean)	115	To study the relationship of serum lactate dehydrogenase (LDH) levels to cerebral vasculopathy as assessed by TCD	1, patients with SCD	The authors have analyzed anonymized, routinely collected, clinical data on all children with HbSS and HbSC who underwent both LDH measurement and TCD scans in 2006	NR	HbSS 69%, HbSC 31%	NR	0	100	Cross	NA
Olowu, 2002[212]	Children	Range: 5–13 yr	54 (and 57 controls)	To assess GFR as determined by endogenous CrCl in steady-state Nigerian children with HbSS and HbAA	2, patients with SCD on 1 arm and healthy controls on the other	Inclusion: Patients with SCD were in steady state, i.e., crisis-free for at least 3 mo prior to the study	53	HbSS 48%, HbAA 52%	NR	NA	48	Cross	NA
Onadeko, 2006[213]	% adults not reported	27.1±9.7	43	To investigate DTPA clearance in steady state, otherwise healthy adult patients with SCD and correlate it with PFTs, hematologic and clinical parameters	1, patients with SCD	Inclusion: Patients were asymptomatic and crisis-free for at least 3 mo before the study. At enrollment, all subjects had normal chest radiographs. None had a history of diabetes mellitus, cardiovascular, liver, or renal disease. There was also no history of obstructive airway disease or any other respiratory problem since childhood. All subjects were nonsmokers	48.8	HbSS 56%, HbSβ^0-thal 44%	NR	NA	100	Cross	NA

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Ozbek, 2007[214]	Children	10.51±3.06 (and 10.79 ±2.46 in the control group)	31 and 30 health children as controls	To identify airway hyperreactivity using a methacholine challenge test and compare PFTs between patients with SCD and healthy controls	2, patients with SCD on 1 arm and age-matched controls on the other	Inclusion: Diagnosis of HbSS or HbSβ, the ability to perform the PFT maneuvers, and steady-state disease (which was defined as the absence of overt pain crisis for at least 1 mo before the initiation of the study, no blood transfusion within 3 mo before the study initiation, and no acute wheezing episode or upper respiratory tract infection for at least 4 weeks before the start of the study)	55 for the SCD group, 60 for the control group	HbSS 48%, HbSβ-thal 52% (controls not included)	NR	0	51	Cross	NA
Pavlakis, 1988[215]	% adults NR	20	73	To study the pathophysiology of CVA in SCD	1 arm, patients with SCD	Inclusion: Patients with SCD followed in clinic	40	NR	NR	0	100	Cross	NA
Pavlakis, 2010[216]	Children	12.6 mo	199	To study the usefulness of TCD in predicting stroke in SCA children <2 yr of age	1, patients with SCA	TCD was performed on infants with SCA-enrolled in the Pediatric HU Phase III Clinical Trial (BABY HUG trial); during screening, had no history of stroke, and were not receiving chronic blood transfusion	44	HbSS 96%, HbSβ^0-thal 2.5%, Unavailable 1.5%	NR	NA	100	Cross	NA
Pavuluri, 2009[217]	Children	NR	27 (and 34 controls)	To characterize LV and RV systolic and diastolic function and hemodynamic assessment in children and adolescents with HbSS as compared to age-matched controls to identify adaptive vs. functional abnormalities	2, patients with SCD and healthy controls	NR	NR	HbSS 44.3%, HbAA 55.7%	NR	NA	44.3	Cross	NA

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Pianosi, 1993[218]	Children	Range: 7–18	37 (+22 healthy controls)	To compare the results of PFTs in children with SCD with healthy children	2, pediatric patients with SCD vs. healthy children	Inclusion: Patients who were >6 yr of age and were willing to cooperate with testing. Exclusion: Patients with HTN, rheumatic heart disease, transfusion therapy, and peripheral vascular disease	48	HbSS 54%, HbSC 38%, HbSβ-thal 8% (of the SCD group)	NR	NA	67	Cross	NA
Quinn, 2009[219]	Children	8	181	To determine whether daytime Hb saturation correlated with TCD measurements of cerebral artery blood flow velocity	1, pediatric patients with SCD	Inclusion: All patients with HbSS or HbSβ^0-thal who had screening TCD studies for clinical care	53.8	HbSS 97.8%, HbSβ^0-thal 2.2%	NR	NA	100	Cross	NA
Qureshi, 2006[220]	% adults not reported	8.9±5.1 (9.9±5.3 for the control group)	32 (and 32 controls)	To assess the effects of SCA on the RV	2, patients with SCD and healthy controls	NR	50	HbSS 100% (controls not included)	NR	NR	50	Cross	NR
Raj, 2005[221]	Children	10.3±4.7	22	To report cardiac function in patients with SCD maintained on long-term erythrocytapheresis	2, patients with SCD on transfusion therapy and patients who are not on transfusion therapy	Inclusion: Patients with HbSS not manifesting any acute symptoms	64	HbSS 100%	NR	0	100	Cross	NA
Rees, 2008[222]	Children	Range: 2–16	96	To develop an index based on routine clinical measurements that also predicts increased intra-cerebral blood flow	1, SCD pediatric patients	Inclusion: Pediatric patients with SCD who had TCD scanning in 2006. Exclusion: Patients on regular transfusion and patients for whom steady-state data were unavailable in that year	NR	HbSS 100%	NR	NA	100	Cross	NA
Reyes, 1984[223]	Children	1.2	33	To evaluate the effects of SCA in infancy, including increased heart rate and LV diameter	1, patients with SCD	Inclusion: Asymptomatic infants and young children	NR	NR	NR	NA	100	Cross	NA
Riebel, 2003[224]	% adults not reported	9.5 yr (median)	47	To evaluate TCD US for identifying cerebrovascular disease in neurologically asymptomatic children and young adults with SCD	1, patients with SCD	NR	40.4	HbSS 71.4%, HbSβ^0-thal 14.9%, HbSβ^+-thal 2.1%, HbSC 2.1%	NR	NA	100	Cross	NA

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Sampaio Silva, 2006[225]	Adults	27.1±10.09 (29±10.47 for the control group)	56 (and 56 controls)	To determine the role of TCD in assessing stroke risk in adult patients with SCD	2, patients with SCD and healthy controls	Inclusion: Patients >16 yr of age with HbSS. Exclusion: In the control group, volunteers with a history of HTN, diabetes, migraine, cerebrovascular disorder, and smoking	59	HbSS 100% (controls not included)	NR	NA	50	Cross	NA
San, 1998[226]	Adults	22.6±7.3	54 (and 23 controls)	To evaluate the LV systolic and diastolic functions in patients SCA	2, patients with SCD and healthy controls	Inclusion: All patients were asymptomatic. Exclusion: Patients with rheumatic heart disease, HTN, renal failure, or documented MI	63	HbSS 100% (controls not included)	NR	NA	70	Cross	NA
Sanchez, 2010[227]	Children	Range: 5–8 yr	39	To investigate the association of increased cerebral blood flow velocity with specific language abilities in children with SCD	1, patients with SCD	Inclusion: Children who received voluntary developmental screenings through the Prevention and Early Intervention Program for Sickle Cell Disease. Exclusion: Patients receiving blood transfusion therapy or HU treatment due to the observed reversal of elevated TCD velocities and cognitive symptoms with these treatments. Patients with a history of overt stroke, recent illness, seizure disorder, or a major developmental disability. Participants who may have had a history of silent stroke were not excluded	41	HbSS 92%, HbSβ^0-thal 8%	NR	NA	100	Cross	NA
Schatz, 2002[228]	Children	12.13	27	To determine the relationship between the extent of injury and IQ scores in children with silent cerebral infarcts	1, patients with SCD	Inclusion: All children had a normal neurologic history and examination	59.2	HbSS 100%	NR	NA	100	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Schatz, 2006[229]	Children	12.7 (13.8 for the control group)	28 (and 16 controls)	To assess midsagittal corpus callosum size in SCD and its relationship to lesion volume, lesion location, and cognitive functioning	2, patients with SCD on 1 arm and healthy controls on the other	NR	53.5 (56 of the control group)	HbSS 100% (controls not included)	NR	NA	63.6	Cross	NA
Schmitt, 1998[230]	Adults	26.6±1.3	14 (and 16 controls)	To analyze the determinants of glomerular filtration in nonnephrotic young adult patients with SCA	2, patients with SCD and healthy controls	Inclusion: Patients with SCA had normal plasma creatinine (creatinine <1.2 mg/dL), normal BP, and albuminuria <1 g/dL. All patients were free of pain and had not been hospitalized or transfused for at least 3 mo before the study. The patients were not receiving any medication other than folic acid. They had no other medical problems. Exclusion: Renal and cardiovascular diseases were excluded	50	HbSS 100% (controls not included)	NR	NA	46.6	Cross	NA
Sedrak, 2009[231]	Children	Median =12	48	To estimate the prevalence of PHT in our pediatric sickle cell population and its possible association with various clinical and laboratory findings, including obstructive sleep apnea, and/or pulmonary dysfunction	1, patients with SCD	Inclusion: Patients with SCD seen for routine well-child visits and also those receiving chronic transfusion therapy just before a scheduled transfusion. Exclusion: Patients who experienced an acute complication within the previous 4 weeks were not enrolled until they returned to steady state	62.5	HbSS 79.2%, HbSC 10.4%, HbSβ^+-thal 6.3%, HbSβ^0-thal 4.2%	NR	0	100	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Sen, 2009[232]	Adults	27.48±7.05 (28±5.6 in control group)	31 (+31 healthy controls)	To assess pulmonary function and airway hyperresponsiveness (AHR) in adults with SCD	2, patients with SCD vs. healthy controls	Inclusion: Adult patients with SCD without asthmatic symptoms. Exclusion: Blood transfusion within the last 3 mo, a painful crisis within the previous month, wheezing or an upper respiratory tract infection within the last 2 mo, treatment other than folic acid, hepatic disease, or heart disease	42	HbSS 32%, HbSβ-thal 68% (of the SCD group)	NR	NA	50	Cross	NA
Serarslan, 2009[233]	% adults not reported	Range: 11–39	88	To determine prevalence of PHTN in patients with HbSS, and if there is any relation of PHTN with leg ulceration	2 groups, group 1 patients with SCD with leg ulcers, group 2 patients with SCD without leg ulcers	Inclusion: The study was confined to clinically well subjects	56.8	HbSS 100%	NR	NA	100	Cross	NA
Sesso, 1998[234]	% adults not reported	22, 2–49 (median, range) (28, 5–69 for the control group)	66 (and 40 controls)	To evaluate glomerular and tubular renal function in children and adults with HbSS or HbSA	2, patients with SCD on 1 arm and HbAS on the other	Exclusion: Documented acute or chronic infection, painful crisis, or hemodynamic instability	60.6	HbSS 56.6%, HbAS 43.4% (controls not included)	NR	NA	56.6	Cross	NA
Siegel, 1995[235]	Children	11	24	To evaluate flow velocity measurements in the middle cerebral artery (MCA) and/or neurologic examination for detection of cerebral infarction in SCD	1, patients with SCD	Exclusion: Children <6 yr of age.	33.3	NR	NR	NA	100	Cross	NA
Silva, 2009[236]	Adults	26.8±10.1	50	To study the frequency of MRI and MRA abnormalities in adults with SCD and to define what TCD velocities are associated with intracranial stenoses detected by MRA	1, patients with SCD	NR	40	HbSS 100%	NR	NA	100	Cross	NA
Simmons, 1988[237]	Adults	26±10	40	To assess the cardiovascular effects of SCD	1, patients with SCD	Inclusion: Adult patients with SCD, no evidence of systemic HTN	60	NR	NR	NA	100	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Sklar, 1990[238]	56% adults	18.5	368	To define normal limits for serum creatinine levels, as well as to explore the relationship between age and the prevalence and severity of renal disease in patients with SCD	1, patients with SCD	NR	49	HbSS 100%	NR	NA	100	Cross	NA
de Souza, 2007[239]	Children	13.9±2.5	50	To evaluate quality of sleep and pulmonary function in clinically stable adolescents with SCA	1, patients with SCD	Inclusion: Having been diagnosed with SCA (HbSS), being from 10 to 18 yr of age, and not having been previously diagnosed with a respiratory disease or sleep disorder. Exclusion: Patients diagnosed with other SCDs and patients presenting fever or infection within the 4 weeks preceding the polysomnography; menstruating patients	50	HbSS 100%	NR	NA	100	Cross	NA
Steen, 1996[240]	55% adults	5–41	40	To investigate the ability of quantitative MRI to show subtle brain abnormalities in patients with SCD as well as to compare T1 mapping to conventional MRI/MRA	2, SCD group, *n*=19, and healthy Black controls, *n*=21	Inclusion: Patients enrolled in the CSSCD	NR	35% HbSS, 10% HbSC, 2.5% HbSβ-thal	NR	NR	48	Cross	NA
Steen, 2003[241]	% adults not reported	9.5±5	146	To evaluate the relationship between brain injury by MRI and vasculopathy by MRA in children with HbSS	1, patients with SCD	Inclusion: Asymptomatic as well as symptomatic patients were recruited to get a broad perspective on brain injury in children with SCD. The only selection criterion was that parents keep the scheduled appointment for their child. Exclusion: Patients with genotype other than HbSS	NR	HbSS 100%	NR	NA	100	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Steen, 2003[242]	Children	9.9±4.9	185	To determine prevalence of imaging abnormalities in the brain of children with SCD and to identify clinical and methodological factors that influence prevalence estimate	1, patients with SCD	Inclusion: The protocol was broadly written so that any patients with SCD could undergo imaging, irrespective of their clinical condition. Exclusion: There were no patient exclusion criteria, since the authors were interested in the natural history of the disease	51.3	HbSS 81.6%, HbSC 14%, HbSβ-thal 3.2%	NR	NA	100	Cross	NA
Steen, 2003[243]	Children	9.5±3.9	49	To test the hypothesis that cognitive impairment in children with HbSS SCD is associated with low hematocrit (Hct) and MRI abnormalities	1, patients with SCD	Inclusion: All patients had no history of clinical stroke	55	HbSS 100%	NR	NA	100	Cross	NA
Steen, 2003[244]	Children	10, 4.2–20.2 (median and range) healthy subjects 29 median (range4.5 to 79.3)	141	To characterize the expected range of variation in T1 (spin-lattice relaxation time) of brain tissue in vivo, as a function of age, and to use these maturational norms to study children with SCD	2, patients with SCD and healthy children	Subjects included in this study were hospital employees and their family members, or else elderly volunteers from the community, all of whom were healthy by self-report. All subjects age 18 or older signed an informed consent. For subjects under age 18, an informed consent document was signed by the parent or guardian; and children with sickle cell disease	51	Reported elsewhere	NR	NA	41%	Cross	NA
Steen, 2004[245]	Children	2.2±1 (1.3±1 for the healthy controls)	46 (and 55 healthy controls)	To report the first comparison of brain T1 in healthy young children to brain T1 in young children with SCD	2, patients with SCD on 1 arm and healthy controls on the other	NR	56.5	NR	NR	0	46	Cross	NR
Steen, 2005[246]	Children	9.4±3.8 (10.0±3.6 for the control group	83 (and 43 controls)	To test a hypothesis that children with SCD have a disease-related delay in brain volumetric growth compared to healthy children	2, patients with SCD and healthy controls	NR	57	HbSS 84.3%, HBSC 13.2%, HbSβ$^+$-thal 1.2% (controls not included)	NR	NA	65.8	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Strouse, 2009[247]	Children	8.77	76	To evaluate the hypothesis that C-reactive protein and the ratio of apo-lipoprotein B/A1 and other biomarkers might be important in children with silent cerebral infarction	1, patients with SCD	NR	55.13	HbSS 96%, HbSβ^0-thal 4%	NR	NA	100	Cross	NA
Sylvester, 2004[248]	Children	10±2.4 (10±2.5 for the control group)	64 (and 64 controls)	To determine whether children with SCD have restrictive lung function abnormalities and whether the severity of such abnormalities increases with age	2, patients with SCD on 1 arm and healthy controls on the other	No child was tested within 2 weeks of an upper respiratory tract infection, and children with SCD were not tested within 1 mo of a VOC	46.8 (the same for the control group)	HbSS 100% (controls not included)	NR	0	50	Cross	NA
Thompson, 1999[249]	Children	8.3±2.1	289	To investigate the independent and combined contributions of neurocognitive and family functioning to mother-reported behavior problems in children with SCD and evaluate the factor structure of the Family Environment Scale with African American families	1, patients with SCD	Inclusion: Patients were 6 yr of age or older at the time of enrollment or turned 6 yr old while on the study	52	HbSS 68%, HbSC 32%	NR	NA	100	Cross	NA
Thompson, 2007[250]	Adults	20.8 (median) for the patient group and 21.7 (median) for the control group	65 patients and 15 controls	To investigate the relationship between BP, renal hemodynamics, and urinary albumin excretion (UAE) in subjects with HbSS disease and matched controls as a prelude to intervention studies	2, patients with SCD and healthy controls	NR	51	HbSS 100% (controls not included)	NR	0	81	Cross	NA
Tzika, 1993[251]	Children	3–20 (range)	33	To assess cerebral perfusion dynamics in patients with SCD using contrast-enhanced T2-weighted MRI	2, group A: asymptomatic patients with SCD; group B: patients with SCD with cerebrovascular disease (1 patient in group B did not have SCD)	Inclusion: Group A subjects were enrolled on the basis of absence of any clinical indication of cerebrovascular disease and a normal cMRI	NR	HbSS 97%	NR	NA	97	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
van Beers, 2008[252]	Adults	31	85	To determine the value of general laboratory testing, plain chest radiography, ECG, high-resolution CT of the thorax, PFT, and plasma N-terminal brain natriuretic peptide and brain natriuretic peptide in patients with SCD-related PHT	1, patients with SCD receiving ECHO for PHT screening	Inclusion: SCD adult ambulatory patients	32	HbSS+ HbSβ^0-thal 69%, HbSC+HbSβ^+-thal 31%	NR	NA	100	Cross	NA
van Beers, 2008[253]	Adults	31	85	To assess the potential role of pulmonary artery obstruction in the etiology of SCD-related PHT	1, patients with SCD	Inclusion: Adult patients with SCD	32	HbSS+ HbSβ^0-thal 69%, HbSC+HbSβ^+-thal 31%	NR	NA	100	Cross	NA
Van Den Tweel, 2009[254]	Children	13	36	To examine regional cerebral blood flow (rCBF) in children with SCD and compare it with rCBF in healthy children	24 neurological normal patients with SCD and in 12 healthy children matched for ethnicity and age	Inclusion: Patients with normal flow on TCD US and no history of neurological events. Exclusion: Patients with abnormal TCD US (<40 cm/s or >200 cm/s) or a history of neurological events	50	HbSS, HbSβ^0-thal (percentages NR)	NR	0	67%	Cross	NA
VanderJagt, 1997[255]	Children	6.5 (7.6 for the control group)	13 (and 17 controls)	To determine serum and urinary amino acid and creatinine levels in patients with SCD	2, patients with SCD on 1 arm and healthy controls on the other	NR	53.3	HbSS 100% (controls not included)	NR	NA	43.3	Cross	NA
VanderJagt, 2008[256]	% adults not reported	16.1	102 (and 104 healthy controls)	To assess the relationship between pulmonary function and body composition in Nigerian children and young adults with SCD	2, patients with SCD vs. healthy controls	Inclusion: Patients with SCD confirmed using cellulose acetate electrophoresis	40	NR	NR	NA	49	Cross	NA
Veille, 1994[257]	Adults	NR	55	To document noninvasively the effect of SCD on LV systolic and diastolic function during the 3rd trimester of pregnancy	2 groups, women who are pregnant and have SCD, *n*=15, and healthy women who are pregnant, *n*=40	Inclusion: Women who are pregnant and have SCD	0%	18% HbSS, 9% HbSC	NR	0	27	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Vendramini, 2006[258]	Adults	23.5 (24.3 for the control group)	26	To investigate the prevalence of AHR in adult patients with SCD	2, patients with SCD, n=26, and age-matched controls, n=28	Inclusion: A confirmed diagnosis of HbSS, HbS, or HbSC and the ability to adequately perform the PFT maneuvers. Exclusion: Blood transfusion within the previous 3 mo; wheezing or upper respiratory tract infection in the previous 6 weeks; antisickling therapy (e.g., HU); a history of smoking; a history of reactive air-way disease or of pulmonary disease (except ACS, VOC); alcohol misuse; immunodeficiency; heart disease; or liver disease	58 (50 in the control group)	HbSS 34.6%, HbSC 38.4%, HbSβ-thal 26.9% (controls not included)	NR	NR	48	Cross	NA
Vichinsky, 2010[259]	Adults	31.6±8.95 (33.1±10.06 for controls)	160 (+ 52 healthy controls)	To measure neuro-cognitive dysfunction in neurologically asymptomatic adults with SCA vs. healthy control individuals	2, asymptomatic adult patients with SCD, healthy adults as control	Inclusion: Patients with SCA (Hb level ≤10 mg/dL) aged 19 to 55 yr and of African descent. Exclusion: Patients with any history of neurologic injury, stroke, abnormal neurologic examination or imaging findings, serious cognitive impairment or depression. Patients with a chronic disorder (e.g., diabetes, chronic lung disease, HTN, liver or renal disease); recent acute illness; or medication use that could affect neurocognitive function. Patients with a history of recent transfusions and Hb level >15% were not eligible	37 (51 for the control group)	HbSS 95%, HbSβ^0-thal 5% (controls not included)	NR	NA	100 (of the patient group)	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Voskaridou, 2006[260]	Adults	42.6±10.4	87 (and 30 controls)	To evaluate whether cystatin-C (Cys-C), urine N-acetyl-β -D-lucosaminidase (NAG) excretion and serum and urinary β2-microglobulin (β2-M) may serve as early indicators of renal dysfunction in a large cohort of HbSβ-thal patients	2, patients with SCD on 1 arm and healthy controls on the other	Inclusion: All patients had stable disease at the time of evaluation, without sickle cell crises or infections, and had not been transfused for at least 3 mo before	41	HbSβ-thal 100% (controls not included)	NR	NR	74	Cross	NA
Voskaridou, 2007[261]	Adults	35	84 (and15 healthy controls)	To evaluate the incidence of PHTN and its correlation with clinical and laboratory findings in patients with HbSβ-thal	2 HbSβ-thal patients vs. healthy controls	Inclusion: Patients with HbSβ-thal. Exclusion: LV failure, evidence of a VOC in the past 15 d, atrial fibrillation or ventricular tachycardia, mitral regurgitation or mitral stenosis, and severe pericardial effusion	36	HbSβ^0-thal 61%, HbSβ$^+$-thal 39% (controls not included)	NR	NA	85	Cross	NA
Wali, 2000[262]	Children	9.37±2.51	40 (and 25 controls)	To describe the cardiovascular function in Omani children with SCD	2, patients with SCD and healthy controls	Inclusion: Subjects were crisis free for at least 2 weeks prior to the study and had not received blood transfusion in the preceding 4 mo	55	NR	NR	NA	61.5	Cross	NA
Wall, 1979[263]	Children	12	24 (12+12)	To compare lung function tests in patients with and without SCD	2 groups, SCD group, *n*=12, and height-matched Black control subjects, *n*=12	Inclusion: Patients with SCD otherwise not specified	NR	50% HbSS	NR	0	50	Cross	NA
Wang, 1998[264]	Children	18, 7–47 mo (median, range)	39	To determine whether abnormalities of the CNS are present in very young children with SCA	1, patients with SCD	Exclusion: Patients with a history of overt stroke	46	HbSS 100%	NR	NA	100	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Wang, 2008[265]	Children	13.7 mo	23	To report MRI/MRA finding in patients with SCD included in the BABY HUG trial before their randomization to HU vs. placebo	1, patients with SCD	Inclusion: All patients had MRI/MRA of the brain performed as part of their baseline CNS eligibility evaluation for BABY HUG. All subjects had HbSS and all had normal examinations performed by a pediatric neurologist. This study reports the abnormality in MRI/MRA, which were done before randomization to HU vs. placebo	56.5	HbSS 100%	NR	NA	100	Cross	NA
Ware, 2010[266]	Children	13.7±2.6 mo	191	To examine the feasibility and accuracy of GFR measurements in infants with SCA	2, HU vs. placebo	Inclusion: Children with SCD	41	HbSS, HbSβ^0-thal (proportions not recorded)	NR	NA	100	Cross	NA
Waugh, 1999[267]	14% adults	12.7	35	To study whether SCD includes a nutritional disorder in which there is a deficiency of extracellular L-arginine and plasma creatinine	2, SCD African American patients, *n*=19, and healthy African Americans, *n*=16	Inclusion: HbSS patients. Patients had not received recent blood transfusions, had not experienced severe painful crises within the previous 2 weeks, and were not on HU therapy	43	54% HbSS	NR	0	54	Cross	NA
Young, 1988[268]	Adults	27	82	To explain the patho-physiology of restrictive ventilatory defects in patients with SCD	2, patients with SCD, *n*=66, and non-SCD controls, *n*=16	NR	NR	71% HbSS, 6% HbSC, 4% HbSβ-thal	NR	0	80	Cross	NA
Zilberman, 2007[269]	Children	10.4	73 (and 81 controls)	To evaluate diastolic function in pediatric patients with SCD	2, patients with SCD on 1 arm and healthy controls on the other	Inclusion: Patients with HbSS or HbSβ-thal underwent ECHO evaluation while in a clinical steady state. Exclusion: Subjects on chronic transfusion protocol, had known congenital or acquired cardiac diseases, or had any conditions other than anemia affecting myocardial performance; subjects with inadequate acoustic windows	45	NR	NR	NA	47	Cross	NA

Study label	Patient age group	Total population age in yr (mean)	Total number of patients in the study	Objective of this study	Number and description of study arms	Describe the inclusion/exclusion criteria	% males	Genotypes	Haplotypes	% patients lost to followup	% of patients with SCD in total study population	Design	Followup (mo, mean)
Zoneraich, 1984[270]	% adults not reported	25 (17–47)	60	To evaluate changes in LV performance in patients with SCD	30 patients with SCD matched with 30 normal subjects	Inclusion: Patients with SCD. Exclusion: Patients who were hypertensive, diabetic, uremic, or had rheumatic heart disease	33	50% HbSS	NR	0	50	Cross	NA
Zorilla, 2005[271]	% adults not reported	NR	160	To determine the prevalence of albuminuria in patients with SCD	1, patients with SCD	Urine samples were taken when the patients were feeling healthy	NR	HbSS 59.3%, Others 40.7%	NR	NA	100	Cross	NA
Bernaudin, 2005[272]	Children	(1) newborn screened population median age was 7.4 yr (2) referred children with SCD, mean age was 8.8 yr	291	Patient with normal or questionable MRA findings and TCD velocities that normalized on a transfusion program could be safely treated with HU	Case series of 291 patients with SCD; 150 have been followed since birth and 141 with SCD were referred at various ages	Inclusion: Pediatric patients with SCD	NR	81% HbSS, 14% HbSC, 1% HbSβ^0, 4% HbSβ^+	44.4% Bantou, 23.7% Benin, 9.6% Senegal, 22.2% Others	NR	100%	Case series	Up to 144 mo
Tharaux, 2005[273]	Adults	27	17 patients and 17 controls	To determine the relevance of the pathophysiological mechanisms that implicate renal ET-1 in patients with sickle cell nephropathy in the steady state	2, patients with SCD on 1 arm and healthy controls on the other	Exclusion: (1) current treatment with HU, (2) blood transfusion during the 100 d preceding the study, (3) nonsteroidal anti-inflammatory drugs used during the preceding 2 weeks, (4) body mass index (BMI)>30, (5) positive serology for HIV or hepatitis B or C (6) pregnancy, (7) HTN	41.6 (in both groups)	NR	NR	0	50	Case control	1 d

Table 2. Quality of Included Longitudinal Studies

Study label	Baseline imbalances between groups	Was outcome assessment blinded or not?	Outcome ascertainment similar in the 2 groups?	Analysis adjustment for confounding	% patients lost to followup
Abboud, 2004[25]	NA, single cohort	No	NA	Yes, for TCD velocities	NR
Adams, 1992[26]	NA, single cohort	NR	NA	Yes, for age, Hct, levels of HbF and HbS, sex	2.6
Adams, 1997[27]	NA, single cohort	Blinded	NA	Yes, for age, Hct, reticulocyte count	3.5
Adams, 2004[28]	NA, single cohort	No	NA	NR	NC/NR
Adekile, 2002[29]	NA, single cohort	NR	NA	NR	Saudi Arabia/India 90, SAI and Benin 10
Aleem, 2007[30]	Yes, quite similar	NR	Yes	NR	NR
Aleem, 2008[31]	NA, single cohort	No	NA	NR	0
Al-Sukhun, 2000[1]	NA, single cohort	NR	NA	NR	NR
Ambrusko, 2006[2]	Yes, quite similar	NR	Yes	Yes, for age, gender, frequency of occurrence of VOCs, RAD/asthma, obstructive sleep apnea	NR
Armstrong-Wells, 2009[3]	NA, single cohort	No	NA	NR	0
Ataga, 2006[32]	NA, single cohort	Blinded	NA	Yes, for age, sex, BMI	28.3 (17/60)
Bachir, 2009[33]	NA, single cohort	NR	NA	NR	0.7 (3 patients died)
Barrett, 1984[4]	NA, single cohort	NR	NA	NR	0
Bernaudin, 2000[34]	NA, single cohort	NR	NA	NR	NR
Bernaudin, 2001[35]	NA, single cohort	NR	NA	NR	NR
Bernaudin, 2008[5]	NA, single cohort	NR	NA	Yes, for sex, β-globin haplotype Hb, mean corpuscular volume, white blood cell (WBC) count, and LDH	0
Bernaudin, 2009[36]	NA, single cohort	NR	NA	Yes, for gender, α-thalassemia, G6PD deficiency, height and weight	NR
Brambilla, 2007[37]	NA, single cohort	Blinded	NA	NR	0
Castro, 2003[6]	none	No	Yes	Yes, controlled for age, sex, Hb type, and pulmonary capillary wedge pressure	0
Cheung, 2001[38]	NA, single cohort	No	NA	NR	0
Clarkson, 1992[39]	NA, single cohort	No	NA	NR	4
Colombatti, 2010[40]	Yes, quite similar	NR	Yes	Yes, for reticulocyte count and blood pressure	0
de Souza, 2007[41]	Yes, quite similar	Blinded	Yes, patient records	NR	0
DeBaun, 1995[42]	NA, single cohort	Blinded	NA	No	NR
Delclaux, 2005[43]	NA, single cohort	No	NA	Yes, for age, weight, height, and sex	0
Dham, 2009[44]	Yes, quite similar	NR	NR	Yes, for Hb concentration, LV diameter, and LA pressure	0
Downes, 2005[45]	No: They are different in genotype, gender	No	NA	Yes	NC
Enninful-Eghan, 2010[7]	Yes, quite similar	NR	Yes, by looking at medical records	NR	NR

Study label	Baseline imbalances between groups	Was outcome assessment blinded or not?	Outcome ascertainment similar in the 2 groups?	Analysis adjustment for confounding	% patients lost to followup
Field, 2008[8]	Yes, quite similar	NR	NR	Yes, for age and height	0
Field, 2008[8]	NA, single cohort	No	NA	Yes, for age, height, race	0
Fontaine, 2008[46]	NA, single cohort	No	NA	No	0
Friberg, 1986[47]	NA, single cohort	No	NA	No	0
Gill, 2008[10]	NA, single cohort	No	NA	Yes, for Hb genotype, gender, and the presence of systemic manifestations	9
Gillams, 1998[48]	NA, single cohort	No	NA	No	0
Gladwin, 2004[49]	Yes, quite similar	No	Similar	Yes, for age, cardiac output, stroke volume, the ratio for the electromagnetic wave (E wave) to the A wave, deceleration time, isovolumic relaxation time, Hb level, HbF level, LDH level, WBC count, and creatinine level	2.5
Gold, 2008[11]	NA, single cohort	Blinded	NA	NR	0
Goldberg, 2010[12]	NA, single cohort	NR	NA	NR	3
Gordeuk, 2008[96]	NA, single cohort	No	NA	NR	50
Gordeuk, 2009[50]	NA, single cohort	NR	NA	NR	NR
Gordeuk, 2011[51]	NA, single cohort	No	NA	Yes, for age, participation in a chronic transfusion program, treatment with HU, site of enrollment, duration of followup, baseline TRV	38
Gurkan, 2010[163]	NA, single cohort	NR	NR	Yes, for age, sex, GFR, Hb level, HbF%, type of SCA, BMI, history of transfusions, and reticulocyte	0
Hankins, 2008[52]	NA, single cohort	NR	NR	Yes, for age, initial TCD velocity, and the interaction between age and initial TCD velocity in the conversion from normal to conditional time-averaged mean velocity (TAMV)	NR
Hogan, 2006[53]	Yes, quite similar	Blinded	Similar	NR	0
Hoppe, 2003[54]	Yes, quite similar	Blinded	Similar	NR	0
Jones, 2001[55]	NA, single cohort	No	NA	No	NR
Jones, 2005[56]	NA, single cohort	Blinded	NA	NR	NR
Koumbourlis, 2007[13]	NA, single cohort	NR	NA	Yes, for race and gender	NR
Koumbourlis, 2008[14]	Yes, quite similar	NR	NR	Yes, for age, race, and gender	0
Kral, 2004[58]	NA, single cohort	NR	NA	NR	0
Kugler, 1993[59]	No: Group 1 had abnormal MRI findings at baseline indicative of cerebral infarcts while group 2 didn't	No	Yes, similar	NR	13
Kwiatkowski, 2003[15]	NA, single cohort	No	NA	Yes, for age, HbF, red blood cell (RBC) count	NC/NR
Kwiatkowski, 2009[16]	NA, single cohort	NR	NA	NR	0
Liem, 2010[60]	NA, single cohort	Blinded	NA	Yes, for age, weight, height, body surface area, baseline Hb, or reticulocyte count	NR
Lima, 2002[61]	Yes, quite similar	NR	Similar	NR	0
Lorch, 2009[62]	NA, single cohort	NR	NA	NR	NR

Study label	Baseline imbalances between groups	Was outcome assessment blinded or not?	Outcome ascertainment similar in the 2 groups?	Analysis adjustment for confounding	% patients lost to followup
Machado, 2007[63]	NA, single cohort	Blinded	NA	NR	0
MacLean, 2008[17]	NA, single cohort	NR	NA	Yes, for age, sex, Hb level, and β-globin genotype	0
Makani, 2009[64]	Yes, quite similar	NR	NR	Yes, for age, Hct, peripheral Hb oxygen saturation	0.09
Malouf, 2001[65]	NA, single cohort	No	NA	No	0
Martins, 1999[66]	Yes, quite similar	NR	Yes	NR	NR
McBurney, 2002[67]	NA, single cohort	No	NA	Yes, for age, Hb, WBC count, frequency of ACS, aplasia, avascular necrosis, priapism, pain whether treated as inpatient or outpatient, and pneumonia whether treated as inpatient or outpatient	NR
McCarville, 2004[68]	NA, single cohort	Blinded	yes	Yes, for blood vessels	0
McCarville, 2008[18]	Yes, quite similar	No	Not similar	NR	NR
McKie, 2007[69]	NA, single cohort	NR	NR	Yes, for age and Hb concentration	NR
Miller, 2001[70]	NA, single cohort	No	NA	Yes	NR
Mokhtar, 2010[71]	No: Patients with SCD, vs. patients with thalassemia	No	Yes, clinically, similar	Yes, for duration of illness, LDH levels, serum ferritin level, Hb level, HbF %, mean transfusion index and gender	0
Morris, 2005[72]	Yes, quite similar	NR	Yes	NR	3.9
Moser, 1996[73]	NA, single cohort	Blinded	NA	Yes, for Hb phenotype, sex, cardiovascular accident (CVA), age	0
Mueller, 2006[19]	NA, single cohort	Blinded	NA	NR	0
Neish, 2002[74]	NA, single cohort	No	NA	Yes, for age, sex, blood vessel	0
Okoro, 1991[75]	Yes, quite similar	NR	Yes	NR	0
Onyekwere, 2008[76]	NA, single cohort	No	NA	Yes, for age, sex	0
Parmar, 2009[20]	NA, single cohort	NR	NA	NR	NR
Pashankar, 2008[77]	NA, single cohort	No	NA	Yes, for age	0
Pashankar, 2009[78]	NA, single cohort	NR	NA	NR	0.16
Pawlak, 2009[79]	NA, single cohort	Blinded	NA	Yes, for age, Hb, Hct	NR
Pegelow, 2002[80]	NA, single cohort	NR	NA	Yes, for age, sex	15
Sachdev, 2007[81]	Yes, quite similar	Blinded	Yes	Yes, for age, mean arterial pressure, Hb level	1.2
Silbermins, 2009[21]	NA, single cohort	NR	NA	NR	NR
Silva, 2011[82]	Yes, quite similar	NR	NR	Yes, for reticulocyte count, total Hb, WBC count	0
Sklar, 1990[238]	NA, single cohort	No	NA	NR	NR
Steen, 1998[274]	No: They are different in disease status	No	Yes	No	0
Steen, 1998[22]	Yes, quite similar	No	Yes	No	NR
Steen, 1999[83]	Yes, quite similar	No	Yes	NR	NR
Steen, 1999[84]	Yes, quite similar	No	Yes	Yes, for age	0

Study label	Baseline imbalances between groups	Was outcome assessment blinded or not?	Outcome ascertainment similar in the 2 groups?	Analysis adjustment for confounding	% patients lost to followup
Strouse, 2006[85]	NA, single cohort	No	NA	Yes	29
Sylvester, 2006[86]	NA, single cohort	NR	NA	No	0
Sylvester, 2007[87]	Yes, quite similar	No	Yes	Yes, for Hb	0
Sylvester, 2007[89]	NA, single cohort	No	NA	NR	NR
Sylvester, 2007[88]	Yes, quite similar	NR	Yes	Yes, for age, height	NR
Taksande, 2005[90]	Yes, quite similar	No	Yes	NR	0
Talbot, 1988[91]	NA, single cohort	No	NA	No	NR
Telfer, 2007[92]	NA, single cohort	NR	NR	NR	2.8
Verlhac, 1995[93]	No: They are different in SCD status	No	Similar	Yes, for velocity, age, Hct, HbF, genetic typing alpha	NR
Voetsch, 2010[23]	NA, single cohort	NR	NA	NR	NR
Wang, 2000[24]	NA, single cohort	Blinded	NA	Yes, for gender, age, TCD velocities, neuropsychometric score, MRI result	NR
Wigfall, 2000[94]	NA, single cohort	NR	NR	Yes, for age and sex	NR
Zafeiriou, 2004[95]	NA, single cohort	NR	NA	NR	0

Table 3. Electrocardiography Results*

Study label	Design	Accuracy data for the test†	Gold standard test‡	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests/ uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Relevant subgroup data
Barrett, 1984[4]	R, Obs	No	NR	Minnesota code evidence of MI	108	0	3	40 of the 108 (37%) ECGs showed signs of LV hypertrophy (LVH), and 20 others (18.5%) had nondiagnostic ST segment and the first deflection in the ECG following the QRS complex (T wave) abnormalities. 9 showed first-degree AV block and 4 right bundle branch block	No	No	NR
Goldberg, 2010[12]	R, Obs	No	NR	Patients were defined as having prolonged QTc if the QTc measured ≥460 ms on 1 or more ECGs. Borderline QTc: 1 or more ECGs with a measurement of 440–459 ms	201	0	31	31 patients (15.9%) had prolonged QTc, and 60 (30.8%) had borderline QTc	The mortality rate in the composite of the borderline and prolonged QTc groups was 4/91 (4.4%). The mortality rate in the normal QTc group was 3/104 (2.9%). This difference was not significant (p=0.71)	No	NR
Mueller, 2006[19]	R, Obs	No	NR	A prolonged QTc interval was defined as >440 ms for children and >425 ms for adolescents	142	NR	12	The abnormal QTc intervals ranged from 444–530 ms in children and from 433–545 ms in adolescents, and half of the patients (71) had persistently prolonged QTc intervals. Values in the same patients tended to fluctuate greatly	No	No	NR
Fontaine, 2008[46]	P, Obs	No	NR	NR	25	0	22	Evidence of MI (septal) was seen in 2 patients (8%), LVH was seen in 7 (28%), ST-T wave abnormality present in 13 (52%), and an interventricular conduction delay was evident in 1 (4%). Paroxysmal supraventricular tachycardia was observed in 6 of 26 patients (23%), whereas short runs of atrial tachycardia were evident in all (100%). Nonsustained ventricular tachycardia was seen in 2 patients (8%). 1 patient had transient Mobitz I second-degree AV block and another had rate-related left bundle branch block	There were no deaths, serious arrhythmic events, or documented acute MIs during a mean followup period of 8±3 mo	No	NR

* None of the included studies assessed the accuracy of electrocardiography or compared it to a gold standard test.
† Diagnostic test accuracy relates to the ability of a test to discriminate between the target condition and health.
‡ Gold standard test refers to a diagnostic test or benchmark that is the best available under reasonable conditions.

Study label	Design	Accuracy data for the test[†]	Gold standard test[‡]	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests/ uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Relevant subgroup data
Akgul, 2007[103]	Cross	No	NR	NR	73 patients and 25 controls	0	NR	There was no statistical difference between QT minimum of the patients with SCD and the control subjects; however, mean QT, QT max, QT dispersion, mean QTc, QTc max, QTc minimum, and QTc dispersion in patients with SCD were increased compared to control subjects ($P<0.05$)	NA	Healthy subjects	Among patients with SCD, patients with PHT had higher maximum QTc and QTc dispersion than patients without PHT ($p<.0001$). However, minimum QTc showed no significant differences between the 2 patient groups
Alpert, 1981[110]	Cross	No	NR	The ECG responses that were defined as definitely ischemic were downsloping of the ST segment during the initial 60 to 80 ms with or without J-point depression, or a flat ST segment slope with J-point depression. Equivocally ischemic responses were those in which the ST segment during exercise had a slope of 0 during the initial 60 to 80 ms or J-point depression and an up-sloping ST segment	47 patients and 170 controls	NR	24	No VOCs occurred during or after exercise; neither were there any exercise-induced dysrhythmias. 7 of the children with SCA (15%) had definitely ischemic ECG responses; 16 (34%) had equivocally ischemic responses; and 24 (51%) had nonischemic responses. Of the 170 healthy children, none had definite ischemia. 1 control child had a flat ST segment slope at maximum exercise, and 4 had isolated J-point depression. Thus, the percentage of the healthy children with equivocal responses was 2.6%, while that in the patients with SCA was 34.0%	NA	Healthy Black, age-matched subjects	NR
Batra, 2002[130]	Cross	No	NR	NR	77	0	NR	ECG analysis found no statistical difference between the amplitude of the S waves in leads 1 and V_1 between groups. The initial upward deflection of the QRS complex (R wave) in lead V_6, however, was significantly taller in group 1 compared to group 2 ($p=.04$)	NA	Healthy subjects	NR
Behera, 1979[133]	Cross	No	NR	NR	60	NR	46	ECG cardiac enlargement was noted in 76.6% cases out of which RVH in 38.3%, LVH in 31.6% and combined ventricular hypertrophy was seen in 6.6% of cases. Other abnormalities were P wave in 3.3%, Q wave in 18.3%, P-R interval in 15%, S-T segment in 13.3%, T wave in 70%, incomplete right bundle branch block in 1.66% and inferior infarction in 1.66% of cases	NA	No	NR

Study label	Design	Accuracy data for the test[*,†]	Gold standard test[‡]	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests/ uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Relevant subgroup data
Caldas, 2008[137]	Cross	No	NR	NR	107	0	46	Normal ECG results were obtained in 61 patients (57.0%). 9 patients (8.5%) had LA hypertrophy. 37 patients (34.9%) had LVH. 2 patients (2.0%) had ventricular repolarization abnormalities	NA	Patients evaluated for murmurs and had normal ECHOs	Patients who were on hypertransfusion regimes had higher Hb levels (mean, 8.9 ±1.6 g/dL) than patients who were not (mean, 8.1±1.4 g/dL) (*p*=.08). In patients who were not on hypertransfusion regimes, left ventricular (LV) mass was significantly higher than in the control group for both sexes (*p*=.00). Mass and left atrial (LA) and LV dimensions were higher in patients with Hb levels <8 g/dL than in those with levels >8 g/dL
Holloman, 1987[167]	Cross	No	NR	NR	87	0	63	Abnormal ECGs were present in 63 of 87 (72%) patients. Nonspecific ST-T wave abnormalities (NS-ST-T) occurred in 43 of 87 (52%) and prolonged QT intervals in 9 of 87 (11%); these were often concurrent (*P*<.005). LVH occurred in 15 (22%) patients and was more frequently seen in men (13) than in women (*P*<.01)	NA	No	Men had measurably wider mean QRS intervals than female patients (0.09 vs. 0.08 s, P<.01)
Liem, 2009[192]	Cross	No	NR	A QTc >440 ms was considered prolonged	76	0	29	A total of 29/76 (38%) subjects had a prolonged QTc >440 ms (range 441–477 ms), the majority of whom had HbSS (23 HbSS, 2 HbSβ^0-thal, 4 HbSC). When compared to subjects without prolonged QTc, a larger proportion of subjects with baseline QTc >440 ms had a history of at least 2 episodes of ACS (66% vs. 38%, *p*=.038)	Yes, studies were repeated at steady state in only 22/29 (76%) subjects with QTc prolongation at a mean of 15.6 mo after initial screening. Of these 22 subjects, QTc remained prolonged >440 ms in 10/22 (45%). No clinical events believed to be related to QTc prolongation were reported during the followup period in this subset	No	The authors found neither a difference in HU use nor a history of other factors, including frequent VOC pain, asthma, priapism, splenectomy, exchange transfusion, or tonsilloadenoidec-tomy, in subjects with and without QTc prolongation

Study label	Design	Accuracy data for the test[*,†]	Gold standard test[‡]	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests/ uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Relevant subgroup data
Lippman, 1985[195]	Cross	No	NR	A P-R interval of <210 ms, a QRS duration of <100 ms, and a corrected Q-T interval of <420 ms were considered normal	72	NR	15	Abnormal septal Q waves (amplitude ≥0.30 mV; duration ≤29 ms) were noted in leads V_4, V_5, or V_6 in 15 of 72 patients, and 50% (36) of the population under study demonstrated ECG voltage changes consistent with LVH	No	No	NR
Raj, 2005[221]	Cross	No	NR	NR	22	0	7	ECG showed evidence of LVH in 7 patients and combined ventricular hypertrophy in 2 patients	No	No	NR
van Beers, 2008[252]	Cross	No	NR	NR	74	0	NR	In the HbSS/Sβ^0-thal patients, the median R-axis (degrees) in those with PHT and without PHT were 26 (12–49) and 43 (29–54), respectively (*P* >.05). In HbSC/HbSβ^+-thal patients, the median R-axis (degrees) in those with PHT and without PHT were 18 (25 to 42) and 46 (12–52), respectively (*P* >0.05). None of the patients had a right-axis deviation or a P-pulmonale. 2 patients had an R wave in V1 >7 mm, 1 of whom had PHT. Comparison of all other ECG parameters between patients with or without PHT did not show any significant difference	No	No	NR

Table 4. Echocardiography Results

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Gordeuk, 2008[96]	Obs, R	No	NR	TRV ≥2.5 m/s was considered elevated	163	0	The prevalence of TRV ≥2.5 m/s was 27% with SBP <120 mmHg and diastolic blood pressure (DBP) <70 mmHg, 37% with SBP 120–139 mmHg or DBP 70–89 mmHg, and 93% with SBP ≥140 mmHg or DBP ≥90 mmHg	Of the 69 patients with initial TRV<3.0 m/s who were followed up 2 yr later, TRV increased from <2.5 m/s to ≥2.5 m/s or from 2.5–2.9 m/s to ≥3.0 m/s in 13 (19%). The progression rate was 10% with normal BP, 25% with relative HTN, and 33% with elevated BP	At the 2-year follow-up evaluation, hypertension was observed in none of 19 patients who initially had SBP < 120 mmHg and DBP < 70 mmHg and in 2 of 19 (16%) of those with relative systemic hypertension at initial evaluation.	No	No
Al-Sukhun, 2000[1]	Obs, R	No	NR	PHTN was judged to be present if there were evidence of RV pressure overload (i.e., dilation of the RV with paradoxical motion of the ventricular septum) and peak TRJV of 2.5 m/s or higher	152	0	152	50 (32.9%) patients with SCD undergoing an ECHO had evidence of PH. There were no statistically significant differences between the 2 groups (PHTN vs. not) in age (mean 37+10 yr vs. 34±11 yr), gender (male/female: 19/31 vs. 45/57), or LV dysfunction (5 of 50 vs. 10 of 102). LV dilation (16 of 50 vs. 21 of 102) had a tantalizing but not statistically significant *p* value of *p*=.12	Mortality was significantly greater among patients with PHTN than those without (22 of 50 (44%) vs. 17 of 102 (17%); *p*=.0003). For those that died, median survival from the time of diagnosis of PHTN was 2 mo (range: 1 to 46 mo)	No	No
Ambrusko, 2006[2]	Obs, R	No	NR	TRV ≥2.5 m/s was considered elevated	44	0	11	TRV values range from 1.09 to 2.49 m/s for the study (control) patients, and 1.97–3.52 m/s for the study (affected) patients. Lower Hb concentration, history of cerebrovascular disease, and RAD/asthma remained in a regression model predicting TRV elevation (*p*=.0001 for entire model). This analysis yielded an odds ratio (OR) of 4.19 for each 1 g/dL decrease in Hb concentration (*p*=.009), 26.63 for cerebrovascular disease (*p*=.012), and 10.14 for RAD/asthma (*p*=.054)	No	Patients with SCD who had ECHO measurement of TRV <2.5 m/s	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Silbermins, 2009[21]	Obs, R	No	NR	NR	252	52.4	NR	Among patients with multiple ECHOs and measurable tricuspid regurgitation (TR) jet performed at steady state, we used a linear mixed model to identify a mean yearly rate of progression of 0.04 m/s (p<.001, 95% confidence interval (CI) 0.02 to 0.05). The rate of progression of TRJV at steady state was also not statistically significantly related to mortality (p=.57). Interestingly, however, patients who died had an inpatient TRJV slope of 0.08 m/s/yr, compared to patients who were alive at the end of the study period (0.03 m/s/yr, p=.04)	81 patients died during this period	No	No
Aleem, 2007[30]	Obs, P	No	NR	NR	65 patients	0	NR	The most common abnormal finding was raised PASP found in 25 (38%) of patients. 19 of the patients with raised PASP had mild PHTN, 4 of them had moderate PHTN, and only 2 had severe PHTN. The 2nd common abnormality was dilated right atrium. Valvular regurgitation was found in 21 patients. 4 patients had reduced EF	NR	Age- and gender-matched controls	No
Ataga, 2006[32]	Obs, P	No	NR	A subject was classified as having PHTN if his/her PASP exceeded the upper limits of normal in the reference ranges	60	0	17	Among the patients who initially had no evidence of PHTN (n=30), 4 (13%) have now developed PHTN (mean followup period 3.3±0.4 yr). By contrast, 3 of the 13 subjects (25%) originally diagnosed with PHT were found to have normal PASP determinations at the time of their repeat ECHOs (mean followup period of 3.2±0.6 yr). PHTN was strongly associated with an increased risk of death (relative risk (RR), 9.24; 95% CI: 1.2–73.3). There were no differences in the risk of death when different degrees of PHTN were compared (mild, moderate, or severe)	The mean duration of followup for subjects who had PHTN (n=36, 39%) was 2.4±1.6 yr, with a mean followup duration of 2.7±1.6 yr for patients without PHTN (n=57, 61%). At the time of this report, 10 of the 93 study subjects had died (11%)	No	No
Bachir, 2009[33]	Obs, P	False-positive rate=75% (72/96 did not have evidence of PHTN on right heart catheterization (RHC))	RHC	NR	385	4.5	96	96 had TRV ≥2.5 m/s (25%) and underwent RHC. There was no PHTN in 72/96 with mean pulmonary artery pressure (MPAP)=19±3 mmHg	During followup, 3 patients died, all in the group of patients with TRV ≥2.5 m/s and confirmed PHTN at RHC	No	No
Bernaudin, 2009[36]	Obs, P	No	NR	PHTN was defined as a TRJV 2.5 m/s	320	NR	NR	Elevated TRJV 2.5 m/s was found in 5/44 HbSC/HbSβ^+ (11%) at the mean age of 12.6±2.1 yr and in 57/276 HbSS/HbSβ^0 (21%) (p=not significant (NS)) at the mean age of 12.6±4.5 yr (range 3.5–20)	No	No	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Castro, 2003[6]	Obs, R	No	RHC	MPAP of >25 mmHg	20 (and 14 controls)	0	20	11 patients (55%) with PHTN died compared to 3 (21%) patients without PHTN (*p*=.05). MPAP inversely correlated with survival (10 mmHg increase was associated with 1.7-fold increase in the hour of death (95% CI=1.1–2.7; *p*=.028)). The median survival (PHTN: 25.6 mo, no PHTN: >70%) at the end of the 119-mo observation period (*p*=.044)	The median survival (PHTN: 25.6 mo, no PHTN: >70% at the end of the 119-mo observation period (*p*=.044))	Yes	No
Colombatti, 2010[40]	Obs, P	NR	NR	TRV=/>2.5 m/s	37	0	8	Out of the 37 patients, 8 (21.6%) had TRV=/>2.5 m/s (95% CI 8.3–34.9%), 7 being HbS/HbS and 1 HbSβ-thal	At followup, all 8 patients with high TRV displayed further increase and 7 more developed TRV=/>2.5 m/s	Racially/age-matched controls	No
de Souza, 2007 (TEE)[239]	Obs, P	No	NR	NR	50	0	NR	Total sleep time and rapid eye movement (REM) sleep percentage were lower, whereas REM sleep latency, the number of awakenings, movement during sleep, changes in sleep stage, sleep-disordered breathing index and obstructive apnea index were higher. There were statistically significant differences between the groups in most of the polysomnographic variables. The pulse oximetry (SpO_2) in REM sleep presented a strong positive correlation with waking SpO_2 and with SpO_2 in non-REM sleep, whereas it presented a strong negative correlation with the percentage of total sleep time during which SPO_2 was < 90%. Mean spirometric values were within normal ranges. Residual volume and the residual volume/total lung capacity/functional residual capacity ratio were elevated	No	Patients with SCA were compared to patients with HbAS and IDA and to healthy subjects	No
Delclaux, 2005[43]	Obs, P	No	NR	Systolic pulmonary arterial pressure of >30 mmHg.	49	0	13	13 patients (27%; 9 men) exhibited a mild PHTN (mean, 34±3 mmHg; maximum, 38 mmHg). The ECHO results were not significantly correlated with any parameter obtained from PFTs or from both dyspnea and fatigue assessments	No	No	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Dham, 2009[44]	Obs, P	NR	NR	TRVs=/>2.6 m/s.	310 (and 54 controls)	NR	33 (and 1 control)	TRV was measurable in 290 of 310 subjects with SCD (94%). 32 of 290 patients with SCD (11%) had TRVs >2.60 m/s, and 1 patient with SCD had a TRV >3.0 m/s. TRV was significantly elevated in patients with SCD compared to controls (2.28 vs. 2.10 m/s, *p*<.0001). Increased TRV was associated with left ventricular diastolic diameter (LVDD), Hb, and estimated LA pressure. TRV remained elevated when controlling for LV diameter and LA pressure. The mean EF in patients was 64%, compared to 65% in controls, the *p* value of .12. After adjusting for Hb concentration, it was 64 and 65 in 2 groups, respectively, with a *p* value of .06. Cardiac index (L/min/m2) was 3.2 compared to 2.2 in controls with *p* value of .0001. After adjusting for Hb concentration, it was 3.0 in both groups with a *p* value of .72	NR	Healthy control	No
Fontaine, 2008[46]	Obs, P	No	NR	LVH	26	0	17	A normal EF was observed in 23 of 26 (88%) patients. ECHO diagnosis of LVH was the most common finding in the study and was seen in 17 of 26 patients (65%). The mean LVEF was 60.6±12% (range 30–60%) and was normal for all except 2 patients, who had an LVEF of 30 and 45%. Other findings included 18 (69%) with LA enlargement; 12 (46%) had RV enlargement; 7 (27%) had 4 chamber enlargement; 14 (54%) had right atrial enlargement; and 8 (31%) had valvular dysfunction, such as aortic insufficiency, mitral regurgitation, tricuspid regurgitation, or pulmonic valve insufficiency	There were no deaths, serious arrhythmic events or documented acute MI, during a mean followup period of 8±3 mo	No	No
Gladwin, 2004[49]	Obs, P	No	RHC	PHTN was defined as a peak TRJV of at least 2.5 m/s	195 (41 controls)	0	63	The patients with SCD had significantly higher mean values for TRJV than did the controls (*p*=.003). 32% of patients with SCD had elevated PASP. Higher values TRJV were associated with increased cardiac-chamber sizes. There was a slight decrease in the EF at the highest levels of jet velocity (*p*=.10)	Yes, proportional-hazards regression analysis showed that patients with a TRJV of at least 2.5 m/s had a significantly higher mortality rate than those with a jet velocity of <2.5 m/s (*P*<.001)	Age- and sex-matched healthy controls	No
Gordeuk, 2009[50]	Obs, P	No	NR	Elevated TRV was defined as 2.60 m/s or higher	193	NR	21	21 of 193 patients had elevated TRV of 2.60 m/s or higher at baseline. Elevated baseline TRV with high hemolytic rate also predicted a decline in the 6-min walk distance by 10% or more at followup (hazard ratio 3.9; 95% CI 1.4 to 10.7; *p*=.009)	Elevated baseline TRV with high hemolytic rate predicted elevated TRV at followup (OR 7.7; 95% CI 2.5 to 24.2; *P*<.001) but elevated baseline TRV with lower hemolytic rate did not (OR 1.6; 95% CI 0.2 to 14.1; *p*=.7)	No	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Gordeuk, 2011[51]	Obs, P	NR	NR	TRV of 2.60 m/s or over and mitral valve E/Etdi ratio of 9.23 or higher	160	11	21	Among 139 participants with TRV measurable at both baseline and followup, 24 (17.3%) had an increase in the velocity of 1 SD or more: 13.6% of participants with baseline hemolytic component below the median had such an increase compared to 20.6% of participants with baseline hemolytic component above the median. The authors calculated the ratio of the mitral inflow E wave to the tissue Doppler imaging E wave (E/Etdi). Among 145 participants with E/Etdi measurable at both baseline and followup, 17 (11.7%) had an increase in E/Etdi of 1 SD or more: 10.1% of participants with baseline hemolytic component below the median had such an increase compared to 14.3% of participants with baseline hemolytic component above the median	Among patients with a negative test result, 1 died and 14 had ACS. No patients with a positive test result died or had an ACS	No	No
Liem, 2010[60]	Obs, P	No	NR	TRJV elevation was defined by a peak TRJV equal to or more than 2.5 m/s (mild: 2.5–2.9, moderate = or >3)	30	10–17	9–12 depending on the reader	30 to 40% of the patients had a mild or moderate TRJV elevation	No	No	No
Lorch, 2009[62]	Obs, P	No	NR	NR	213	0	78	78 out of 213 patients who had undergone ECHOs had PAH on ECHO	30 died during the followup period.	No	No
Machado, 2007[63]	Obs, P	No	NR	NR (used cutoff from other literature)	26 (32 events)	12.5	28.6	TRV was elevated during VOC (TRV m/s: steady-state 2.4±0.07; crisis 2.9±0.07; *P*<.001). This represents a crisis-associated increase in ECHO-estimated PASPs from 30±1.0 mmHg to 39±1.7 mmHg (*P*<.001)	TRV significantly decreased to levels close to baseline in 19 patients who had ECHOs repeated 2.4±0.7 mo after crisis resolution (*P*<.001)	No	No
Martins, 1999[66]	Obs, P	No	NR	NR	25 (and 25 controls)	0	25	There were increases in all chamber diameters and LV mass of the patients with SCA. The preload was increased (LV end-diastolic volume: 63.79±9.12 mL/m^2 in controls as opposed to 86.17±17.85 in patients with SCD, *P*<.001) and the afterload was decreased (DBP (73.60±7.30 mmHg in controls and 62.00±12.46 in patients with SCD, *P*<.001) peripheral vascular resistance (1,407.62±455.12 in controls and 774.96±269.43 in patients with SCD) and end-systolic parietal stress (55.93±15.91 in controls and 37.63±11.20 in patients with SCD, *P*<.001)) The cardiac index was increased (3.14±0.91 in controls, 5.90±1.77 in patients with SCD, *P*<.001)	No	Age-, sex-, and race-matched healthy controls	No

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Mokhtar, 2010[71]	Obs, P	No	NR	TRV >2.5 m/s	70 (40 SCD)	NR	25 (15 SCD (37.5%) and 10 (33%) thalassemia)	The prevalence of PHTN was 37.5, 40.0 and 26.7% in SCD, B-TI, and B-TM patients, respectively. The mean TRV in patients with SCD was 2.17±0.55 m/s compared to 2.33±0.45 and 2.05±0.54 m/s in B-TI and B-TM patients, respectively (p<0.05). Patients with SCD with PHTN had significantly more frequent attacks of ACS/yr and stroke as compared to patients with SCD without PHTN (p<.05) as well as a higher HbS percentage (P<.0001). For patients with SCD, mean EF was 62.86±5.1% and mean RV systolic pressure (28.4±10.5 mmHg) and not significantly different from measures taken on the patients with thalassemia	None of the studied patients without PHTN developed PHTN during the followup period of the study	Patients with thalassemia	No
Morris, 2005[72]	Obs, P	No	NR	PHTN was prospectively defined as a TRJV of at least 2.5 m/s on Doppler ECHO	224 (and 36 controls)	15	74	TRJV 2.3±0.6 m/s for the patient group and 1.9±0.5 m/s for the control group	Between enrollment in the study and Mar. 2005, 18 patients with SCD had died, with a median survival time of 14 mo (range, 2–41 mo)	Age- and sex-matched healthy controls	No
Onyekwere, 2008[76]	Obs, P	No	NR	TRV ≥2.5 m/s was classified as having PHTN	52	0	24	24 patients (46.2%) had increased pulmonary artery pressure. 33 had a history of pulmonary disease, and 14 were evaluated shortly after hospitalization for an acute event. PHTN was less common in HbSC. Results of multiple logistic regression analysis with statistical adjustment for age and sex showed that a 1 g/dL increase in Hb concentration and a 1% increase in Hct decreased the risk of PHTN by 65% (OR 0.35 and CI 0.17 to 0.28; p=.0050) and 27% (OR 0.73 and CI 0.58 to 0.91; p=.0049), respectively. In addition, HbSS phenotype was associated with a 12-fold increase in risk for PHTN (OR 11.9 and CI 1.28 to 110.46; p=.0293)	After 9 mo of followup of those patients with PHTN, only 1 died from a pulmonary complication	No	No
Pashankar, 2008[77]	Obs, P	No	NR	PHTN was defined as PASP of at least 30 mm Hg corresponding to a TRJV of ≥2.5 m/s	62	0	19	30% (19 of 62) of the patients with SCD had a peak TRV ≥2.5 m/s, corresponding to PASP ≥30 mm Hg. 8 (12.9%) of 62 patients had had a previous stroke or abnormal TCD examinations. Of these, 7 patients were receiving chronic transfusion, and 1 patient was receiving HU. ECHOs did not reveal any evidence of PHTN in these patients. There was no correlation between the presence of elevated pulmonary artery pressures and abnormal screening TCD examination	No	No	No

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Pashankar, 2009[78]	Obs, P	NR	NR	TRV ≥2.5 m/s	62	0	19	19 of 62 children (30.6%) had elevated pulmonary artery pressures with TRJV ≥2.5 m/s on initial ECHO. 1/3 of these patients (6/19) had TRV ≥3 m/s, whereas 13/19 patients had TRV between 2.5–2.9 m/s on initial ECHO	18/19 patients had followup ECHOs. These showed normalization of TRV in 8 patients. 10 patients had persistent elevation of TRV on repeat ECHO	No	No
Sachdev, 2007[81]	Obs, P	No	NR	PHTN was prospectively defined as a peak TRJV of at least 2.5 m/s	235 (141 received the tissue Doppler) and 41 controls	0	56	There were 9 patients with concentric LVH, 7 patients with eccentric LVH, and 35 patients with concentric remodeling. In patients with a TRJV of 2.5 m/s or more, LV chamber size and mass increased (LV end-diastolic distention 52.9±5.9 vs. 50.4±4.6, *p*=.001; LV mass index 41.4±12.9 vs. 33.5±8.3, *p*<.001), although LV systolic function did not change (*p*=0.2). Only 9% of patients had evidence of systolic dysfunction with an EF <55%. The prevalence of diastolic dysfunction was assessed in 141 patients using tissue Doppler; 25 patients (18%) had evidence of mild, moderate, or severe diastolic dysfunction. Also in this group, 56 patients (40%) had TRJV of ≥2.5 m/s, and 15 patients (11%) had a TRJV of ≥3 m/s. The TRV remained a significant predictor of mortality, with an RR of 5.1. Low EF (*p*=.04) was also found to be a significant independent risk factor for death	Survival analysis included 232 patients. There were 20 deaths	Age- and gender-balanced controls	No
Taksande, 2005[90]	Obs, P	No	NR	NR	75	0	NR	Patients with anemia had higher LV internal dimension in diastole, LA dimension in systole, stroke volume, and LV mass in comparison to those who were nonanemic with a normal Hb electrophoresis pattern. On Doppler study, 'E' and 'A' wave amplitude was higher in patients with SCA than in controls. No statistically significant correlation was found between ECHO parameter (M-mode and Doppler) and severity of anemia in the patients with sickle cell	No	African American anemic patients and nonanemic controls	No
Adebiyi, 2010[99]	Cross	No	NR	PHTN was defined as a TRJV of >2.5 m/s	90	NR	11	There was no difference in the LV systolic indices between the 2 groups. There were higher pulmonary systolic and diastolic pressures among SCA subjects. The frequency of PHTN in this study was 12.2%. 2 of the subjects had TRJV above 2.9 m/s (severe)	No	Age- and sex-matched healthy controls	No

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Aessopos, 2007[100]	Cross	No	NR	NR	47 patients and 40 controls	0	NR	Indexed LA and LV diameters and LV mass were all significantly higher in patients than in controls. In what concerns diastolic LV function, 7 patients (14.9%) had an impaired relaxation pattern. Aortic diameter, measured 3 cm above aortic valve, did not differ significantly between patients and controls. In contrast, aortic strain and aortic distensibility were significantly lower (p<.05 and <.01, respectively), and aortic stiffness index was significantly higher (p<.05) in patients compared to controls	No	Age-matched healthy individuals	No
Aessopos, 2009[101]	Cross	No	None	NC	165	NR	165	Left and right chamber dimensions, LV mass, and cardiac index were significantly higher in patients compared to controls (p<.001 in most cases). 3 patients (2.9%) had reduced LVEF (<55%); mean LVEF was significantly lower in patients (p<.001). Left and RV systolic tissue Doppler indices and LV diastolic tissue Doppler indices were also impaired in patients. Systolic pulmonary artery pressure was significantly higher in patients compared to controls (p=.002); PHT was present in 28 patients (27%), while severe PHT in 3 (2.9%). In 3 patients with severe PHT, only 1 had impaired LVEF and increased pulmonary wedge pressure	No	Age-matched healthy individuals	No
Alameri, 2008[105]	Cross	No	NR	NR	39	14	NR	A mild rise in systolic pulmonary artery pressure of >30 mmHg was observed in 36% (14) of patients with SCD. There was no correlation between ECHO findings and dyspnea, 6-minute walk distance (6MWD), or pulmonary function data	No	No	No
Almeida, 2008[108]	Cross	No	NR	NR	25 (+ 19 controls)	0	NR	In comparison with the controls, patients showed larger absolute LVEDDs, septal and posterior wall thickness, and LA dimensions as well as normalized dimensions for body surface area (BSA). Patients also showed lower EF and peak systolic strain as well as higher IMP, Sa, and E/Ea. After dipyridamole, no differences in heart rate, SBP, and DBP were found between groups	No	Healthy controls with similar BSA, and resting SBP	No

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Animasahun, 2010[113]	Cross	No	NR	NR	60 patients and 60 controls	0	29 patients with SCA had abnormal LVEDD compared to only 6 in controls	The LA dimension), left ventricular end diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), IVS, left ventricular posterior wall thickness (LVPWT) were significantly larger in the subjects than controls (p<.001 for each variable). The left ventricular fractional shortening (FS) and EF were within acceptable normal limits although significantly lower in patients with SCA compared to controls (p<.001). A total of 29 patients with SCA had abnormal LVEDD compared to only 6 in controls (p<.001). Those with increased LVEDD also had lower Hb levels compared to those with normal LVEDD. However, the LV mass was higher in the subjects than the controls (p<.001). There was a significantly positive linear correlation between the direct ECHO measurements (aortic root dimension, LA, end diastolic diameter (EDD), end systolic diameter (ESD), LVPWT, interventricular septal thickness (IVS) and LV mass obtained and age in the subjects (r>0.01, p<.001). However, there was no significant positive linear association between age and the EF, FS in both subjects and controls (r>0.01, p>.5)	No	Healthy controls matched for age and sex	No
Arslankoylu, 2010[117]	Cross	No	NR	NR	32	0	NR	Compared to controls, LVEDD, LVESD, early-diastolic mitral flow velocity, and late-diastolic mitral flow velocity were significantly higher in the patients with SCA. Although, the LVEFs were in the normal ranges in patients and controls, both LV and RV MPI were significantly higher in patients than those in normal children	No	Healthy controls matched for age	No
Ataga, 2004[120]	Cross	No	NR	PHTN was diagnosed if the PASP pressure exceeded the upper limits of normal for age- and BMI-adjusted reference ranges	60	16.7	16 (2 more patients had PHTN by evidence other than TRV)	18 (30%) had PHTN, including mild HTN in 10 (17%), moderate HTN in 5 (8%), and severe HTN in 2 (3%). In a multivariate logistic model, 2 factors were associated independently with a greater risk of PHTN: lower HbF level (OR per 10% decrease=4.3; 95% CI: 1.1 to 17; p=0.04) and lower SBP (OR per 10mmHg decrease=1.8; 95% CI: 1.1 to 3.1; p=.03)	No	No	No
Ataga, 2008[121]	Cross	NR	NR	PASP was determined by Doppler ECHO (no further explanation)	76	0	26	26 patients (34.2%) had PHTN (No information was reported about the controls)	NR	Healthy subjects	No

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Balfour, 1984[127]	Cross	No	none	NC	202 (124 patients and 78 healthy controls)	NR	NR	Patients with sickle cell exhibited progressive chamber enlargement and progressively increasing LV mass. Although contractility indices were normal, when the opposing influences of volume overload due to anemia and ventricular dysfunction were separated, abnormalities of systolic time intervals were identified. LV systolic time interval ratio and LV pre-ejection period were higher in the sickle cell group and became increasingly abnormal with age	No	Healthy Black volunteers	No
Balfour, 1988[128]	Cross	No	none	NC	38 patients and 11 controls	NR	7 (abnormal ejection fraction)	ECHOs identified abnormalities of systolic and diastolic function in patients with SCA compared to the normal subjects as well as a decrease in LV end-diastolic volume during exercise. The abnormalities in diastolic and systolic function assumed greater significance at the increased heart rates associated with exercise	No	Normal Black subjects	No
Batra, 2002[130]	Cross	No	NR	NR	77	0	NR	The LV diastolic dimension and LV mass were significantly greater in group 1 than in group 2 (p=.024 and P<.001, respectively). There was normal systolic function in both groups. The LV MPI was significantly higher in group 2 as compared to group 1, indicative of impaired LV myocardial performance	No	Transfused vs. nontransfused patients with SCD	No
Caldas, 2008[137]	Cross	No	NR	NR	107 patients + 70 controls	0	NR	65 patients (60.7%) had enlarged left atria. LV dimensions were enlarged in 32 patients (29.9%). Only 2 patients had EFs <55%. Dilatation of the ascending aorta was present in 2 patients, and dilatation of the pulmonary artery in only 1 patient. RV dimension was increased in only 1 patient. LV mass was increased in 51 female patients (89.5%) and in 41 male patients (82.0%), and it was significantly larger in patients than in controls. MPI values for the LV were increased in 73 patients (68.2%) and for the RV in 18 patients (16.8%). Both E= and A= tissue Doppler waves were higher in patients than in controls (p=.00). No patient had an E' wave <0.08 m/s or an E/E' ratio >15, indicating that these patients did not have elevated filling pressures	No	Healthy subjects	In patients who were not on hypertrans-fusion regimes, LV mass was significantly higher than in the control group for both sexes (p=.00)
Castro, 2010[138]	Cross	No	NR	TRJV >2.5 m/s was considered PH	15	NR	4	4 patients (26,7%) were found to have PH	No	No	No

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Cetta, 1997[139]	Cross	No	NR	NR	20	0	NR	LVEF ranged from 51% to 73%. Group A patients mean RV MPI=0.43 (median=0.39 (range=0.24–1.00)) which was significantly (*p*=0.014) increased compared to group B patients mean RV MPI =0.27 (median=0.26 (range=0.23–0.36)). Only 1 patient had visually estimated RV systolic dysfunction. That patient's LVEF=51%. She was the oldest patient enrolled and had the highest RV MPI (1.00). Previous studies have reported that the RV MPI is 0.32±0.03 in normal children and 0.29±0.05 in normal adults	No	No	No
Chaudry, 2010[140]	Cross	No	NR	PHTN was defined as a TRV≥2.5 m/s	50 (and 50 controls)	0	20	TRV was higher in patients with SCD compared to controls: 2.28 (0.60) vs. 2.14 (0.27) m/s (*p*=0.02), and higher in HbSS compared to HbSC patients, although this was not statistically significant: 2.33 (0.37) vs. 2.16 (0.21) m/s (*p*=.08). 16 of 50 (32%) patients with SCD and 4/50 (8%) controls had a TRV ≥2.5 m/s, suggestive of PHTN. Estimated pulmonary artery pressure was higher in patients with SCD compared with controls: 26.2 (6.2) vs. 23.6 (4.5) mmHg (*p*=.018), and higher in HbSS compared with HbSC patients: 27.3 (6.8) vs. 23.8 (3.7) mmHg (*p*=.058)	Of the 14/16 patients with SCD with PHTN, only 1 had a repeat TRV <2.5 m/s, and mean repeat TRV was unchanged: 2.65 (0.18) vs. 2.63 (0.21) m/s (*p*=.74). No patient with SCD was admitted to hospital during the study	Age- and gender-matched controls	PHTN was more common in HbSS than in HbSC patients: 15/34 (44%) vs. 1/16 (6%) (*p*=.009)
Chung, 1987[141]	Cross	No	NR	NR	10 (and 14 controls)	0	NR	LV dimension index (systolic 2.89±0.31 vs. 2.33±0.42 cm and diastolic 4.70±0.35 vs. 3.64±0.48 cm, *p*=.001), diastolic volume (79.4±17.1 vs. 60.8±7.8 mL, *p*=.01), LV mass index (116.3±3.4 vs. 74.3±15.2 g/m2, *p*=.001) and cardiac index (5.51±1.32 vs. 3.38±0.85 L/min/m^2; *p*=.001) were significantly increased in patients with SCD compared to values in control subjects. However, there was no statistically significant difference between the 2 groups for EF	No	Age-matched healthy controls	No
Cipolotti, 2001[142]	Cross	No	NR	NR	38	0	NR	All measurements were significantly above the normal values. LVED was 41.26±8.50, LVES was 25.50±5.15, LA was 25.40±5.20, AO was 21.18±4.50 (all values mean±SD). There was a significant correlation between the ECHO findings and age but not with Hb or the severity index. A diffuse LV hyperkinesia was found in 30.6% of the patients	No	No	No
Covarrubias, 1980[144]	Cross	No	none	NR	14	0	NR	Mean EF was 0.76±0.07. The values of systolic time intervals and ECHO indices of LV performance were similar to those reported for normal subjects and those with comparable degrees of anemia	no	No	No

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Covitz, 1983[145]	Cross	No	None		22 patients and 12 controls	NR	NR	At maximal exercise, heart rate, cardiac output response, and work capacity were reduced; the reduction was related to the degree of anemia. LV end-diastolic volume decreased with exercise, most markedly in patients with ischemic exercise ECGs. An abnormal EF response to exercise occurred in 4 patients; electrocardiographic signs of ischemia developed in all 4, and wall motion abnormalities in 2. Those patients who had electrocardiographic signs of ischemia had a significantly lower heart rate, EF, and cardiac output response to exercise, and a lower Hct level than subjects with normal results on exercise electrocardiography		Healthy controls	No
Covitz, 1995[146]	Cross	No	NR	NR	191	0	NR	Indexed RV, LV, and LA chamber dimensions were significantly increased in patients when compared to normal subjects. Indexed aortic root dimensions were significantly increased from normal. Though the LV free wall thickness was not significantly increased in the study population, the interventricular septal thickness was significantly increased. Pericardial effusion was noted in 17 of 171 patients (10%) for whom data were available. The presence of pericardial effusion was inversely related to Hb (p=.0009) but was not related to other cardiac measurements	No	No	No
Dahoui, 2010[147]	Cross	NR	NR	TRV=/>2.5m/s.	85	0	27	Of the 85 patients, 27 (31.8%) had TRV=/>2.5 m/s. Of those, 22 (81.5%) patients had mild PHTN (2.5 <TRV<3 m/s), and 5 (18.5%) patients had moderate to severe PHTN (TRV=/>3 m/s)	NR	No	No
Dham, 2009 (Velocity Vector Imaging)[150]	Cross	No	NR	NR	19 (and 4 controls)	0	NR	On direct comparison of the RV free wall strain between SCD and control subjects, there was a trend of worse basilar RV strain (-30.6% vs. -34.0%, p=.1) and strain rate (-1.9%/s vs. -2.6%/s, p=0.2) in the SCD subjects. Strain parameters did not correlate with TRV	No	Matched-controls	No
Elshazly, 2010[153]	Cross	No	NR	PHTN was prospectively defined as TRJV of at least 2.5 m/s	100	0	15	15 had tricuspid regurgitation, with pulmonary systolic pressure ranging from36 to 60 mmHg (mean of 43.3±4.8 mmHg)	No	No	No
Fonseca, 2010[155]	Cross		Pulmonary artery catheterization	Peak velocity of regurgitant flow of tricuspid (Vrft) of at least 2.5 m/s was considered abnormal	80	0	32	40% of patients (32/80) had peak Vrft of at least 2.5 m/s. 78% (25/32) of patients with Vrft ≥2.5 m/s were submitted to catheterization and in 8 of them PHTN was confirmed	No	No	No

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Gerry, 1976[156]	Cross	No	NR	NR	23 (and 9 controls)	NR	NA	Patients with SCA had a significantly greater mean LV systolic dimension index, LVDD index, LV mass, stroke volume index, interventricular septal width, aortic root index, and LA index. No significant differences were noted between the mean velocity of circumferential fiber shortening, EF, or systolic time intervals	No	Normal subjects	No
Johnson, 2010[169]	Cross	No	NR	LV hypertrophy was defined as LV mass index above the 95th percentile for age and sex. Elevated TRV was defined as ≥2.5 m/s	44	0	20 had LV hypertrophy. Dilated LV in 26. Elevated TRV in 4	ECHO abnormalities were common among children with SCD. Specifically, 46% had LVH, all had eccentric hypertrophy. TRJV was ≥2.5 m/s in 9% of the sample. Both LV and septal myocardial performance indices were above normal thresholds in 16% of the sample. Compared to expected values, subjects also had increased estimated LV filling pressure and altered LV diastolic function	No	No	No
Kalpatthi, 2009[172]	Cross	No	NR	PHT was defined as TRV ≥2.5m/s	73	0	8	Only 8 (11%) had TRV ≥2.5 m/s. Of these 8 patients, 1 was on HU, while 5 were on chronic red cell transfusion therapy (CRTT)	No	No	No
Kanadasi, 2005[173]	Cross	No	NR	Moderate diastolic dysfunction: Doppler ratio of early (E)-to-late (atrial (A)) transmitral flow velocity (E/A) >1, deceleration time (DT) <220 ms. Severe diastolic dysfunction (restrictive pat-tern): E/A >2, DT <150 ms. (E wave: early diastole, A wave: late diastole. DT: deceleration time)	31 (and 31 controls)	0	7 patients (0 controls)	Except LVEF and RVEF, cardiac chamber dimensions, interventricular septal thickness, posterior wall thickness, and LV mass index were significantly greater in patients than in controls. In patients, E and A wave velocities were significantly increased compared to the controls. Diastolic dysfunction was detected in 7 patients (4 of them had a restrictive pattern) but was not found in controls	No	Age-matched healthy subjects	No
Kilinc, 1993[177]	Cross	No	NR	NR	30 (and 12 controls)	0	NA	LVEF in the mild SCD group was 0.369±0.082, 0.385±0.067 in the severe SCD group, and 0.355±0.057 in the healthy controls (values are given as mean±SD). LV mass (g) in the mild SCD group was 101.47±35.73, and in the severe SCD group it was 102.67±52.61, and in the control group it was 75.25±28.56. Intraventricular septal thickness in the mild SCD group was 7.69±1.70, in the severe SCD group it was 7.68±1.89, and in the control group it was 6.58±1.08	No	Healthy controls	No

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Klings, 2008[182]	Cross	NR	NR	TRJ ≥2.5 m/s	88 patients with SCD (and 23 controls)	0	42 patients with HbSS and 8 of the patients with HbSC. All normal volunteers had normal ECHOs	43% of the HbSS patients had PHTN. Of these patients with PH, 67% had a TRJ between 2.5 and 2.9 m/s and 33% had a TRJ ≥3.0 m/s. An additional 10% of HbSS patients had evidence of left-sided heart disease (LHD) including LV systolic or diastolic dysfunction or significant left-sided valvular disease. In HbSC, 28% had PHTN and 11% had LHD. None of the HbSC patients with LHD had an elevated TRJ. LHD in both populations was characterized by systolic dysfunction (characterized by either global dysfunction or a wall-motion abnormality pattern suggestive of coronary artery disease) in 40%, diastolic dysfunction in 40%, and left-sided valvular disease in 20%	NR	Age- and race-matched normal volunteers	No
Lamers, 2006[187]	Cross	No	NR	No	57 (and 50 controls)	NR	NR	The patients with SCA had increased LV dimensions in systole and diastole, and increased indexed LV mass. Load-dependent measurements of LV function (ETc, %FS, and velocity of circumferential fiber shortening (VCFc)) were lower in patients with SCA, and afterload, as measured by end-systolic wall stress (ESSm) was increased. The ESSm-VCFc relationship demonstrated reduced contractility in patients with SCA compared to control subjects. Degree and duration of anemia along with exchange transfusions did not impact contractility	No	Age-matched African-American healthy controls	No
Lester, 1990[189]	Cross	No	NR	Abnormal e ECHO dimensions were defined as values >2 SDPN (standard deviation from the predicted normal)	64	No	8~39 (according to several parameters)	Abnormal ECHO dimensions were observed in 61% of patients for LVEDD, in 41% for LVESD, and in 50% for LAmax. LV Mass/m^2 in patients with SCD was 120.4±3.24 compared to 89.9±1.81 in the control group (*P*<.001). LV cardiac index in patients with SCD was 7.54±0.24 compared to 4.47±0.13 in the control group (*P*<.001)	No	Normal Black controls	No
Lewis, 1991[190]	Cross	No	NR	NR	30 (and 30 controls)	NR	17	17 (57%) of the 30 patients with SCA had evidence of abnormal LV diastolic filling. 6 of these 17 patients had a Doppler pattern consistent with "restrictive" filling, characterized by reduced early diastolic deceleration time (<110 ms) or an increased rate of early flow velocity (>7.4 m/s^2) decline, or both, as well as decreased late diastolic velocity-time integral (2.6±0.7 vs. 3.4±0.8 cm in normal subjects; *p* <0.05). Another 11 patients showed a Doppler waveform consistent with impaired relaxation, characterized by prolonged deceleration time (>166 ms) or reduced EF slope (<3.8 m/s^2), as well as increased late diastolic velocity-time integral (4.0±0.5 vs. 3.4±0.8 cm in normal subjects; *p*=.03)	NA	Healthy subjects	No

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Liem, 2007[191]	Cross	NR	NR	TRJV ≥2.5 m/s	51	0	17	There was a significant, positive correlation between TRJV and LDH (r=0.45, *p*=.001), with higher TRJV associated with higher LDH. Modest but significant positive and negative correlations also existed between TRJV and reticulocyte count (r=0.36, *p*=.010) and AST (r=0.37, *p*=.007), and between TRJV and Hb (r=-0.33, *p*=.017), respectively	NR	No	No
Liem, 2009[192]	Cross	No	NR	Subjects were considered to have LVH if LV mass indexed for body surface area exceeded the 95th percentile for age and gender on ECHO	76	0	23	23/76 (30%) subjects had a TRJV=or >2.5 m/s. TRJV was 2.39±0.28 m/s (mean±SD). LV mass index was 105.9±27.5 g/m^2 (mean±SD)	No	No	No
Liem, 2009[193]	Cross	No	NR	TRV >2.5 m/s	78	13	26	All patients with TRV >2.5 m/s were HbSS. Only 15% of those had evidence of RV enlargement or hypertrophy either by ECHO or ECG criteria. No RV enlargement or hypertrophy was found in any of the subjects, in whom tricuspid regurgitation was not quantifiable, thus confirming the absence of tricuspid regurgitation in these individuals was a normal finding. Patients with TRV >2.5 m/s had significantly higher LDH, total WBC count, reticulocyte count, AST, and total bilirubin, as well as a significantly lower Hb	No	No	No
Lippman, 1985[195]	Cross	No	none	Prevalence of abnormal Q waves (amplitude ≥0.30 mV; duration ≤29msec))	72	0	15	Abnormal septal Q waves were noted in 15 of 72 patients, and 50% (36) of the population under study demonstrated electrocardiographic voltage changes consistent with LVH. M-mode ECHO showed that 29 of 72 patients had a thickened interventricular septum (≥1.2 cm), 16 of 72 had an abnormally thickened LV posterior wall (≥1.2 cm), and 31 of 72 had increased LV mass (>215 g). Septal excursion was decreased in 11 of the patients, and global LV function (percent fractional shortening) was slightly de-creased in 3 patients. Regional wall motion was normal in all 72 patients. 6% (4) of the patients met echocardiographic criteria for asymmetric septal hypertrophy. Linear regression analysis yielded significant positive correlations between septal dimension (r=0.38; *p*<.001) and LV mass (r=0.37; *p*<.005) when each was compared to Q wave amplitude. A significant negative correlation (r=0.40; *p*<.001) was noted between hematocrit reading and Q wave amplitude	no	No	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Moyssakis, 2005[205]	Cross	No	NR	NR	43 (and 55 controls)	0	NA	Chamber enlargement (left atrium, LV, and RV), greater LV mass index (109 (8) compared to 86 (19) g/m^2 , *p*<.01), cardiac index (4.80 (1.80) compared to 3.70 (1.20) l/min/m^2, *p*<.01) and RV wall thickness (0.32 (0.07) compared to 0.29 (0.06) cm, *p*<.05) were noted in the anemic group	No	Age- and sex-matched controls	No
Naoman, 2010[206]	Cross	No	NR	TRV ≥2.5 m/s	105	0	62	TRV was ≥2.5 m/s in 62 (59%) of the patients. TRV ≥3.0 m/s was observed in 24 (22.8)%	No	No	No
Nelson, 2007[208]	Cross	NR	NR	TRV ≥2.5 m/s	53	20	15	15 patients in our cohort had TRV ≥2.5 m/s for a PHT prevalence of 28%. 3 children had TRV >3.0 m/s for a 5% prevalence of moderate-to-severe PHT. There was a higher prevalence of PHT in children with HbSS/ HbSβ^0-thal compared to those with HbSC (RR 2.4 vs. 0.4, *p*=.28)	NR	No	No
Pavuluri, 2009[217]	Cross	No	NR	NR	27 (and 34 controls)	0	NA	Echocardiographic data from 27 patients and 34 controls showed: LV mass index (gm/m2) was 117±27.5 in cases vs. 79.9±15.5 in controls (P<.01). LVEDD, mm was 46.5±6.9 in cases vs. 43±5.2 in controls (P<.05). RVEDD, mm was 15.2±5.1 in cases vs. 13.1±4.8 in controls. LV cardiac index (l/m2) was 3.1±1.2 in cases vs. 2.1±0.5 in controls (p<.01)		Age-matched controls	No
Qureshi, 2006[220]	Cross	No	NR	NR	32 (and 32 controls)	0	NA	SCA subjects had elevated right ventricle (RV) ejection time corrected for heart rate ET_c (mean±SD, 0.369±0.030 s vs. 0.351±0.022 s; *P*<.01), diastolic area index (19.9±2.4 cm^2/m^2 vs. 13.2±2.1 cm^2/m^2; *P*<.01) and free-wall mass index (33.2±4.4 g/m^2 vs. 23.9±4.3 g/m^2; *P*<.01), whereas RV fractional area change (37±8% vs. 36±4%) was not different from controls. Although RV diastolic area index in SCA paralleled the normal range over time, RV free-wall mass index continued to gradually rise throughout childhood (r=.42; *P*<.05). tricuspid regurgitation gradients >2.5 m/s, consistent with PHTN, were found in 5 (16%) of SCA subjects, all >9 yr of age		Age-matched healthy controls	No
Raj, 2005[221]	Cross	No	NR	A TRJV of at least 2.5 m/s was used as a threshold for PHTN	22	0	4	2 patients in the non-transfused-SCD (severe) group and 2 SCD patients in the long-term erythrocytapheresis had TRJV of at least 2.5 m/s, while all NT-SCD (mild) patients had TRJV <2.5 m/s		No	No
Reyes, 1984[223]	Cross	No	NR	NR	33	NR	NA	LV diastolic dimension was significantly larger than predicted (sickle cell (S)=2.70±0.52 cm; normal (*N*)=2.47±0.29; *P*≤.005). LVPEP (LV pre-ejection period) was not significantly different (S=66.4±8.7 ms; *N*=66.6±5.1; *p*=.89). LV ejection time was significantly prolonged (S=213.3±31.8 ms; *N*=199.8±23.0; *P*<.001)	No	No	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
San, 1998[226]	Cross	No	NR	NR	54 (and 23 controls)	0	NA	LV systolic and diastolic diameters of patients with sickle cell were greater than those of controls (p<.001). All of the SCA patients had reduced systolic cardiac function (EF: 0.57±0.1 vs. 0.63±0.06 and FS: 0.30±0.06 vs. 0.34±0.04, p<.02) and abnormal diastolic LV function parameters compared to the control group (isovolumic relaxation time: 114±20 ms vs. 65±7 ms, p<.0001; E/A ratio: 1.2±0.5 vs. 1.6±0.04, p<.01). LV mass was greater in patients than in controls (222±78 g vs. 177±46 g, p<.01). LV systolic and diastolic functions were abnormal in patients with SCA, and the LV mass was greater in the patients compared to controls	No	Healthy controls with normal Hct values	No
Sedrak, 2009[231]	Cross	NR	NR	TRV ≥2.5 m/s	48	0	4	Of the 48 patients, 4 (8.3%) had TRV >2.5 m/s; all had HbSS. None of the 4 had other significant cardiac comorbidities that likely influenced TRV	NR	No	No
Serarslan, 2009[233]	Cross	NR	NR	Pulmonary hypertension was diagnosed if PA systolic pressure exceeded the upper limits of normal for age and body mass index-adjusted reference ranges	12 (and 76 controls)	0	11 (and 24 controls)	The prevalence of PHTN in group I and group II was 91.6% (n=11) and 31.6% (n=24), respectively (p=.0001). Patients with leg ulceration had increased left atrium and RV diameters at diastole and also had increased LV end-diastolic and end-systolic diameters	NA	Patients without leg ulcers	No
Simmons, 1988[237]	Cross	No	NR	NR	40	NR	NR	Valvular structures were normal despite an increased incidence of flow murmurs. Abnormalities were found more frequently in the left heart than the right, as manifested primarily by increased LV mass, and LV and LA dilatation with preservation of systolic function. PHTN, which was present in 2/3 of the sample, was minimal to moderate as assessed by Doppler technique. The effects of SCA on the heart seem to be minimal and similar to those of other anemias, predominantly confined to the left atrium and ventricle with passive elevation of pulmonary pressures. Clinical murmurs were most often physiologic; there was no association with myxomatous valvular degeneration or mitral valve prolapse	No	No	No
van Beers, 2008[252]	Cross	No	NR	TRV >2.5 m/s	78	0	25 (32%)	Only 2 patients had moderate–severe PHT in the HbSS/HbSβ^0-thal group. Diastolic dysfunction occurred more frequently in patients with PHT, although this did not reach statistical significance (P = 0.136). No intracardiac shunts or RV outflow obstruction was detected	No	No	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
van Beers, 2008[253]	Cross	No	NR	TRV >2.5 m/s	78	0	26 (33%)	No difference in the prevalence of PHT was detected between male and female patients. No intracardiac shunts or RV outflow obstruction were detected	No	No	No
Veille, 1994[257]	Cross	No	none	Comparison study, no cutoff reported	55	0	NA	Pregnant patients with SCD had a significant enlargement of the LVEDD, posterior wall, interventricular septum, and ventricular mass than the control group. Although heart rate and fractional shortening were not different between the 2 groups, stroke volume and cardiac output were higher in patients with SCD. This was mostly because of enlargement of left end-diastolic dimension. Ventricular diastolic function was different in patients with SCD, resulting in an increase in the duration of the rapid filling	no	Healthy pregnant women	No
Voskaridou, 2007[261]	Cross	No	NR	TRV >2.5 m/s or an estimated pulmonary artery pressure of at least 35 mmHg	84	NR	28 (33%)	Patients with PHTN were older than patients without PHTN. Age was also significantly correlated with both TRV and RV systolic pressure (p=.001, .002 in that order). Factors reflecting the presence of hemolysis, such as Hb concentration, reticulocyte counts, and bilirubin serum levels were significantly correlated with TRV (r=-0.386, p<.001; r=0.361, p=.001; and r=0.25, p=.022, respectively) and RVSP (r=-0.38, p<.001; r=0.345, p=.001; and r=0.26, p=.017, respectively). However, no correlations were observed between serum LDH and either TRV or RVSP	No	Healthy subjects	No
Wali, 2000[262]	Cross	No	NR	Systolic murmurs	36 (and 25 controls)	0	22	Systolic murmurs were detected in 22 (61%) of the 36 who completed the study. Clinical evidence of cardiomegaly was detected in 14 (39%) children. No other significant cardiac signs were elicited. Steady-state haemoglobin level ranged from 5.8 to 12 g/dl. Right ventricular diastolic dimension (RVDD), left ventricular diastolic dimension (LVDD), LA, septal/left ventricular posterior wall dimension (IVSd/LVPWD) ratio, and aortic root (AoR) were higher in patients than in the normal cohort. Significant differences were observed in the LVDD, RVDD and IVSd/LVPWD ratios and in the LA dimensions. RVDD (cm) was 1.98±0.30 in the cases and 1.34±0.25 in the controls, P<.01. LA (cm) was 2.73±0.54 in the cases and 2.50±0.26 in the controls, P<.05	No	Healthy age-, sex- and body surface area-matched children	No

Study label	Design	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Zilberman, 2007[269]	Cross	No	NR	RV HTN was defined as RV pressure >30 mmHg	73 patients (and 81 controls)	0	NA	Of 73 SCD subjects, 32 (42.4%) had LV dilatation, 11 (15.1%) had LVH, and 25 had elevated right ventricular pressures. Mitral inflow early velocities *E* were significantly higher in the SCD group than in the controls (116 vs. 103 cm/s, *P*<.05). Doppler tissue imaging, early diastolic Es, and systolic Ss velocities correlated positively with the LV mass/volume index in the SCD group (r ¼ 0.25, *P*<.02; r ¼ 0.34, *P*<0.03). There was a significant difference in mitral inflow/annular movement ratios E/Es (*P*<.01) and E/El (*P*<.03) between the SCD and the controls	No	Age- and race-matched subjects	No
Zoneraich, 1984[270]	Cross	No	No	NR	30 patients (and 30 controls)	0	NA	Compared to controls, there were statistically significant ECHO findings in diastolic diameter, systolic diameter, LV wall thickness in systole and diastole, interventricular septum thickness in diastole and systole, end-diastolic volume, and stroke volume indicating worsening cardiac function in patients with SCD	no	Normal subjects matched for age, sex, and social group	No

Table 5. Pulmonary Function Tests Results

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Subgroup data
Field, 2008[8]	R, Obs	Forced expiratory volume at 1 sec (FEV1), forced vital capacity (FVC), FEV1/FVC	No	NR	NR	79 from the SCD group and 255 from control group	0	NR	Growth of lung function was less in children with HbSS compared with healthy children in the Harvard Six Cities Study (H6CS) cohort. The growth curves for FEV1 were lower in boys and girls with HbSS when compared to the HbCS cohort, *p*=.031 and *p*=.002, respectively. FVC and FEV1/FVC growth curves showed gender differences between the cohorts. The growth curve for FVC was similar for boys with and without HbSS (*p*=.139); whereas, the growth curve for FVC in girls with HbSS was significantly different when compared to girls in the general population (*P*<.001). The growth curve for FEV1 /FVC also differed in girls with HbSS vs. those in the Harvard 6 Cities Study (H6CS) cohort (*p*=.038), while in boys there was no difference in FEV1/FVC growth curves between the 2 groups (*p*=.666)	No	Healthy controls	The authors found gender differences among children with HbSS. FEV1 and FVC measurements for boys with HbSS did not differ from those in the general population until ages 12 and 10 yr, respectively. In contrast, FEV1 and FVC values were less in girls with HbSS compared to girls in the general population at all measured ages
Field, 2008[9]	R, Obs	NA	No	NR	NR	92 (49 of these patients underwent repeated PFTs	0	38 had FEV1 below normal. 65 had FVC below normal	Lung function significantly declined over time in adults with SCD. After age 20 yr, the rate of decline in FEV1 among men and women with SCD was 49 c^3/yr. There was no difference in the decline of FEV1 between individuals with HbSS compared to a group composed of the phenotypes HbSC, HbSβ^+-thal, HbSβ^0-thal, HbS-hereditary persistence of HbF, and HbSD (*p*=.29). Smoking cigarettes also did not significantly affect the decline in FEV1 (*p*=.07).There was no association between increased rate of pain and subsequent restrictive (OR 1.0, 95% CI 0.6–1.6, *p*=0.97), or obstructive physiology (OR 0.5, 95% CI 0.2–1.1, *p*=0.09), or abnormal FEV1 (OR 1.4, 95% CI 0.9–2.3, *p*=0.14); there was also no association between increased rate of ACS and subsequent restrictive (OR 1.9, 95% CI 0.6–6.1, *p*=0.28), or obstructive physiology (OR 1.1, 95% CI 0.8–1.5, *p*=0.67), or abnormal FEV1 (OR 1.0, 95% CI 0.7–1.4, *p*=.93)	Yes	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Subgroup data
Koumbourlis, 2007[13]	R, Obs	Pulmonary function tests consisting of spirometry/ maximal expiratory flow-volume curves obtained with a Sensormedics 6200 body plethysmograph. The following indices were recorded from the first and last test for further analysis: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), the ratio FEV1/FVC, forced expiratory flow at 25–75% of FVC (FEF25–75), and in patients who underwent body plethysmo-graphy the total lung capacity (TLC), vital capacity (VC), and residual lung volume (RV).	No	The determina-tion of the pattern of lung function was made in accor-dance with the guidelines of the American Thoracic Society for the interpreta-tion of lung function testing	''Normal'' When the FVC, the FEV_1, and the $FEF_{25–75}$ were equal or higher than the lower level of normal (LLN) and proportional to each other. ''Obstructive'' When the ratio FEV_1/FVC and/or the $FEF_{25–75}$ were lower than the calculated LLN and/or when the expiratory flow-volume curve was concave and the $FEF_{25–75}$ was disproportionately lower compared to the FVC. ''Restrictive'': FVC was lower than the LLN predicted value with proportional decrease in the FEV_1 and $FEF_{25–75}$ but with normal or increased FEV_1/FVC ratio	45	0	Obstructive 10 Restrictive 10	The lung volumes slightly decreased but remained borderline normal in lung volume and spirometric measurements. All spirometric indices were within the normal range but significantly decreased (*P*<.001) at the time of the 2nd test indicating development of lower airway obstruction FEV1: 87±21 vs. 80±15; FEV1/FVC: 89±7 vs. 85±6; forced expiratory flow (FEF) 25–75: 89±32 vs. 76±24). "Normal" pattern of lung function was initially found in 56% of the patients, but in only 29% in the 2nd test. In contrast, those with "obstructive" pattern increased from 22 to 44%, and those with "restrictive" pattern from 22 to 27%	No	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Subgroup data
Koumbourlis, 2008[14]	R, Obs	Spirometry/ maximal expiratory flow volume curves	No	NR	The determination of the pattern of lung function was made in accordance with the guidelines of the American Thoracic Society for the interpretation of lung function testing	26	0	NA	All patients with HbSC initially had a normal pattern of lung function, but by the time of the 2nd test, 3 (23%) had developed an obstructive pattern. Compared to the patients with HbSS, the lung function in the HbSC group was and remained significantly better in both testing periods. FEV1 (% pred) dropped from 101±20 to 93±17 in the HbSC group as compared to a drop from 85±18 to 78±14 in the HbSS group (P-value (HbSC vs. HbSS) <0.02 on the 1st test and <0.01 on the 2nd test). FVC (% pred) dropped from 96±19 to 92±16 in the HbSC group as compared to a drop from 84±19 to 79±16 in the HbSS group	No	Age-, race-, and gender-matched HbSS patients	No
MacLean, 2008[17]	R, Obs	FEV1, FVC, FEV1/FVC, total lung capacity (TLC), FEF 25–75	No	NR	Evidence of airway obstruction was defined as an FEV1/ FVC % predicted <80%. A TLC <70% was considered indicative of a restrictive airway pattern	312 received spirometry, 294 received lung volume test	0	NA	The longitudinal analysis of pulmonary function in children with SCD demonstrated significant differences from predicted values for FEV1, FVC, and FEF 25–75. The FEV1/FVC ratio did not differ from predicted values. The rate of decline in TLC showed a similar pattern to that of FEV1, FVC, and FEF 25–75. At 8 yr of age, 96.5% of children had normal lung function, 0.9% showed an obstructive pattern, and 2.6% showed a restrictive pattern. At 17 yr of age, 81.3% of children had normal lung function, none showed obstruction, and 18.7% showed a restrictive pattern. The mean RV/TLC ratio at 8 yr of age was 0.30, and declined to 0.21 at 17 yr of age	No	No	For each 1 yr increase in age; FVC declined by 88 mL for males and 79 mL for females; FEV1 declined by 89 mL for males and 89 mL for females; FEF 25–75 declined by 133 mL for males and 145 mL for females; and TLC declined by 151 mL for males and 135 mL for females
Delclaux, 2005[43]	P, Obs	Borg scale evaluation during a 6-min walk test, modified Medical Research Council, echocardiography, and biological evaluation	No	NR	NR	49	0	NA	PFT results depicted a very mild restrictive pattern (mean total pulmonary capacity, 86±11% predicted) and an impairment of the diffusing capacity of the lung for carbon monoxide (DLCO) (mean DLCO corrected for the degree of anemia, 69±13% predicted)	No	No	When comparing patients with or without PHTN, no significant difference was shown in terms of dyspnea test and PFT results, and exhaled nitric oxide parameters

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Subgroup data
Mokhtar, 2010[71]	P, Obs	A VQ for suspected thromboembo-lism as a possible etiology for PH	No	NR	Authors used the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria	70 (40 SCD)	NR	28 (40%) of entire population and 18 (45%) in patients with SCD	All patients with sickle cell with PHTN (*n*=15) had abnormalities in the V/Q scan (15/40), where 3 patients had high-, 4 had intermediate-, and 8 had low-probability scan results. All patients with thalassemia with PHTN (*n*=10) had abnormalities in the V/Q scan (10/30). Patients without PHTN (*n*=45) also underwent V/Q scans where only 8 patients had abnormal V/Q scan results and 37 had normal results (37/45). A statistically high significant difference was detected between patients with PHTN and those without regarding the presence of abnormal V/Q results in patients with SCD ($p<.0001$), as well as in patients with thalassemia ($p<.0001$). High-probability V/Q scan results were detected in 3 patients with SCD and 1 B-TI patient having PHTN. The 3 patients with SCD had a past history of ACS complicated by lung infarction, while the B-TI patient had a past history of pulmonary embolism	No	Patients with β-thalassemia	No
Sylvester, 2006[86]	P, Obs	All HRCT examinations were carried out using a dual detector helical computed tomography (CT) scanner FEV_1, FVC, and peak expiratory flow were measured using a heated pneumotacho-graph and FEV_1/FVC was calculated. Lung volumes were assessed by measurement of TLC, functional residual capacity, vital capacity, and residual volume	No	NR	Adults were diagnosed as having a restrictive abnormality if their TLCpleth was 80% of that predicted for standing height, an obstructive abnormality if their FEV1/FVC was 81.4% in males and 82.3% in females, and a mixed obstructive/restrictiv e lung function abnormality if both TLC and FEV1/FVC were reduced to these values	33	0	NA	9 patients had a restrictive lung function abnormality, 5 had an obstructive abnormality, and 4 had a mixed restrictive/ obstructive abnormality. FEV1: 83 (46–122) FVC: 82 (45–109) FEV1/FVC: 0.85 (0.75–0.96) (median (% of predicted for standing height) and range)	No	No	No

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Sylvester, 2007[88]	P, Obs	PFTs and lung gas transfer	No	NR	NR	24 patients and 24 controls	0	NA	Children with SCA compared to the controls had lower FEV1 (p<.0001) and FVC (p<.0001), but their FEV1/FVC ratios and lung volumes measured both by plethysmography and helium dilution were not significantly different from those of the controls. Children with SCA compared to the controls also had significantly lower mean diffusing capacity for carbon monoxide (DL_{CO}) (p<.0001), gas transfer per unit lung volume K_{CO} (p=.003), vital capacity measured during the single breath technique (p=.01), but similar DL_{COc} (DL_{CO} was corrected for the lower haemoglobin levels) and greater mean K_{COc} (p=.001). The K_{COc} results of the children with SCA did not correlate significantly with TLCpleth (p=.36), FEV1 (p=.39) or FVC (p=.36), but did correlate significantly with PEF (p=.02, r=−0.58). 11 of the children with SCA had either an obstructive (n=6) or a restrictive (n=5) lung function abnormality; none of the controls had a lung function abnormality	No	Ethnicity-matched subjects	No
Sylvester, 2007[89]	P, Obs	Airway responsiveness challenge test	No	NR	A positive result to either challenge was deemed to have occurred if the FEV1 fell by at least 10% from the prechallenge baseline	42	0	6	The median pre- and post- (following the cold air challenge) FEV1 of the children with ACS and children without ACS did not differ significantly. 6 of the 42 children (14%) had a positive response to the cold air challenge, all were in the non-ACS group (1 was asthmatic). FEV1 (% predicted for height) Pretest: 77 (60–87) for patients who had had ACS, 80 (53–99) for patients who had not had ACS. Posttest: 75 (60–87) for patients who had had ACS and 77 (47–90) for patients who had not had ACS (not significant in either, pre and post)	No	No	No
Alameri, 2008[105]	Cross	FEV1, FVC, DL_{CO}, TLC, 6-min walk test (6MWT) and echocardio-graphy	No	NR	NR	39	0	Varying by parameter	40% of SCD patients had a mild dyspnea at rest, and this increased to 61% at the end of the 6MWT. Pulmonary function testes were abnormal in 51%. The 6MWT was shorter in SCD patients compared to controls (368±67 vs. 407±47m, *p*=0.005). No hematological variables correlated with outcome variables	No	6MWT data was compared with BMI-matched healthy subjects	No
Ataga, 2004[120]	Cross	Doppler Echocardio-graphy, pulmonary function tests, and hematologic tests	No	NR	NR	60	0	18	The prevalence of pulmonary hypertension was 30% (18/60). Ten patients had mild pulmonary hypertension (up to 44 mm Hg), 5 had moderate pulmonary hypertension (45 to 74 mm Hg), and 2 had severe pulmonary hypertension (75 mm Hg). In a logistic regression model, both lower fetal hemoglobin level and lower systolic blood pressure were associated with the presence of pulmonary hypertension	No	No	No

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Brady, 2009[134]	Cross	Bronchodilator spirometry, pulse oximetry, and physical exam (H&P)	NA	NR	RAD/asthma was defined as post-bronchodilator improvement FEV1 >11%, history of asthma symptoms or use of asthma medications. Restrictive lung disease was defined as vital capacity or TLC <80%	25-Spirometry 33-pulse oximetry and H&P	0	Varying by parameter	2 patients (6.6%) had evidence of restriction. RAD/asthma was identified in 25 patients (75%). Five patients had evidence of pulmonary hypertension (15%) by echocardiogram. Eight patients (24%) were hypoxemic and referred for further testing	No	No	No
Elegbeleye, 1978[152]	Cross	Diffusing capacity for carbon monoxide, FVC, RV and TLC	No	None, comparison between groups study	Between groups comparison	52	0	NR	Patients with HbSS have a disproportionately high DL (diffusing capacity for carbon monoxide) value in the presence of severe anemia compared to controls	No	Normal subjects	No
Hijazi, 2005[166]	Cross	Pulmonary function test (PFT)	No	NR	NR	55 (28 SCD. 17 healthy control and 10 HbH control)	0	NA	The mean FVC and VC were significantly lower in the HbSS patients than in the healthy control group. Similarly, the mean FVC and VC were significantly lower than in those of the HbH group (p<0.001 for VC and p<0.01 for FVC). The FEV1/FVC ratio was similar among all the groups. The mean VC, FVC, and FEV1 values were significantly lower in the HbSS group than that of the HbH group (p<.01).	No	2 control groups, age- and sex-matched healthy subjects and HbH patients	No
Jaja, 2000[168]	Cross	FVC, FEV1, and peak expiratory flow rate (PEFR)	No	NR	NR	10 (and 15 controls)	0	NA	In the patients with SCA, predicted FVC, FEV1, and PEF rate (PEFR) are significantly higher (*P*<.01, P<.01, *P*<.001 in each case) than measured values. Measured FVC, FEV1, and PEFR in SCA subjects are significantly lower (*P*<.001 in all cases) than values obtained from the healthy controls. However, FEV1 percentage is similar in all groups. In SCA subjects, %HbF and %ISC correlated negatively with each of the measured parameters	No	Age- and sex-matched non-SCD subjects	No
Klings, 2006[181]	Cross	PFT	No	NR	Predicted values for FEV1, FVC, FEV1/ FVC, TLC, RV, and DLCO were calculated on the basis of algorithms that accounted for sex, age, and height in the African American population	310	0	279	Abnormal pulmonary function was observed in 90% (279 of 310) of the subjects. Overall, the population was characterized by restrictive physiology with decreased TLC (70.20 ±14.69% predicted) and DLCO (56.57±20.11%). The means for FEV1 (83.03±16.06% predicted) and FVC (84.37±16.01% predicted) were considered to be low–normal, with an FEV1 / FVC of 98.36±9.15%. The decreased DLCO persisted after adjustment for the patients' Hb concentration (64.54±19.93% predicted)	38% reported an incident episode of ACS during the followup period	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Subgroup data
Knight-Madden, 2005[183]	Cross	FEV1	No	No	BHR was diagnosed if there was a decrease of at least 10% in FEV1 after the exercise challenge	80 and 80 controls	51%	17/38	BHR diagnosed by exercise or bronchodilator testing was more common in children with SCD than in controls (SCD *n*=19 (44%); controls *n*=9 (20%), *p*=0.02). 41 children with SCD had 66 episodes of ACS (26 had a single episode)	No	Ethnicity-matched subjects	No
Leong, 1997[188]	Cross	Cold-air bronchial provocation testing	No	NR	NR	40 patients and 10 controls	0	NA	The baseline values for FVC, FEV1, FEV1/FVC, and RV/TLC in the RAD group were no different from those in the non-RAD group and the control group. The TLC was significantly lower in the RAD group, in comparison with the non-RAD and control groups (*p*<.01). In the RAD group, the TLC was 88.9±14.0% of race-corrected predicted values, the FVC was 91.2±12.6%, and FEV1 was 85.3±16.2%. The mean maximal % fall in FEV1 after cold air challenge (CACh) (*n*=13) was 18.5±9.6% and was >10% in 11 of 13 patients. The mean increase in FEV1 after bronchodilator therapy (*n*=5) was 11.5±8.3%, and it was >12% in 4 of 5 patients. In the non-RAD group the baseline TLC was 101.6±11.7 FVC was 95.5±10.2%, and FEV1 was 93.3±13.2%. The mean maximal % fall in FEV1 after CACh (*n*=19) was 14.1±8.8% and was >10% in 13 of 19 patients. The mean increase in FEV1 after bronchodilator therapy (*n*=3) was 14.7±11.3%, and was 12% or greater in 1 of 3 patients. In the control group, the baseline TLC was 105.7±12.1%, FVC was 96.2±11.1%, and FEV1 was 92.2±10.3%. The mean maximal % fall in FEV1 was 5.0±2.5%, and was >10% in none of 10 patients. The prevalence of AHR in the control group, the RAD group, and the non-RAD group was 0, 83%, and 64%, respectively (*P*<.0001). The overall prevalence in the SCD group was 73%	No	Siblings of non-RAD SCD group	No
Liem, 2009[193]	Cross	Spirometry, DLCO measurement	No	NR	(1) Obstruction if either FEV1/FVC or FEF 25–75 was below the limits of normal (LIN); (2) restriction TLC was below the LIN; and abnormal gas exchange if DLCO adjusted for Hb was <80% predicted	78	8	35 (spirometry) and 36 (DLCO)	Obstructive changes were found in 15/73 (21%), restrictive changes in 16/72 (22%), and mixed changes in 4/72 (6%). 51% of study participants demonstrated a decrease in DLCO <80% predicted. Diffusion constant corrected for alveolar volume was normal in all but 3 subjects. Patients with TRV >2.5 m/s had significantly lower % predicted FEV1, % predicted FVC and oxygen saturation (*P*<.05). TRV also inversely correlated with % predicted FVC and oxygen saturation only (*P*<.05)	No	No	No

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Onadeko, 2006[213]	Cross	PFT	No	NR	80% of the predicted value was considered normal	43	0	22	The following are the percentages of patients showing values <80% for individual PFTs: FEV1 36.6%, FVC 31.7%, FEV1/ FVC 4.9%, PEF 56.1%, TLC 7.3%, and TLCO (total lung diffusing capacity for carbon monoxide) 41.5%. When the study group was divided according to their DTPA clearance, 10 (23.3%) had enhanced, 11 (25.6%) normal, while 22 (51.2%) delayed clearance. When correlation coefficients were computed between DTPA clearance and other PFTs, there was significant negative correlation with FEV1 (r=-0.398, p=.01), FVC (r=-0.524, p=.000) and TLC (r=-0.43, p=.005)	No	No	The enhanced group had the highest mean values for all PFTs and when the values were analyzed with ANOVA, only FVC showed a significant difference (*p*=.025). However, when the mean values in the enhanced group were compared to the mean values in the 2 other groups combined and subjected to 't' test, there were significant differences in FEV1 (*p*=.03), FVC (*p*=.006), TLC (*p*=.03), and TLCO (*p*=.04). Of the 43 patients in the study, 15 (34.9%) had mild, 19 (44.2%) moderate while 9 (20.9%) severe VOC. In these 3 groups, 6 (40%), 12 (63.2%) and 4 (44.4%) had delayed DTPA clearance

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Ozbek, 2007[214]	Cross	Methacholine challenge test (MCT)	No	NR	The test was ended when 20% reduction in the baseline FEV1 was recorded	31 (and 30 controls)	0	25	Children in the patient group had lower a FVC (p=.001) and FEV1 (p=.001) at baseline. A positive response to the MCT was found in 25 children in the patient group (77.5%). 18 of those subjects (72%) had a PC20 of <1 mg/mL, and 11 (61%) had a history of ACS as well. There were only 6 patients (3 with HbSS and 3 with HbSβ-thal) who had a negative MCT result, and none of those subjects had a history of ACS	No	Age-matched healthy children	The authors divided the patients into 2 subgroups: those with HbSS and those with HbSβ-thal. When those 2 subgroups were compared, no statistically significant difference was found in the FVC, FEV1, FEV1/FVC, and FEF 25–75 measurements before and after bronchodilator treatment (P>.05 for all). When comparing patients who had ACS with those without ACS, the % predicted of the FEV1 and the FEV1/ FVC ratio were statistically significantly higher in those without ACS. However, no statistically significant difference in MCT results was found when comparing subgroups with or without ACS (p=.06)
Pianosi, 1993[218]	Cross	PFT	No	NR	NR	37 (+22 controls)	NR	NR	PFTs measured FVC, the diffusion capacity of carbon monoxide, and the plethysmographic determination of lung volumes. The FVC and FEV1, expressed as the percentage of the predicted value, were significantly less for those with HbSS with or without a history of ACS than for control subjects (p<.05), but the FEV1/FVC ratio, an index of airway obstruction, was normal in all groups. TLC was also significantly lower in patients with HbSS with or without a history of ACS than in control subjects (p<.05), but the ratio of residual volume TLC, another index of airway obstruction, was normal	No	Sex-, race-, and height-matched subjects	No
Sedrak, 2009[231]	Cross	TRV	NR		TRV values ≥2.5 m/s are correlated with PHT and increased mortality	48	0	4	Pulmonary function testing demonstrated restrictive lung disease in patient 2 and normal function in the others with elevated TRV. Of 29 patients with TRV <2.5 m/s who had testing, 9 (31%) patients had normal lung function, 16 (55%) had restrictive lung disease, 3 (10.3%) had obstructive lung disease, and 1 (3.4%) had both obstructive and restrictive disease	NR	No	No

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Sen, 2009[232]	Cross	FVC, FEV1, FEV1/FVC ratio, FEF 25%–75%, PEFR, TLC, DLco and MPT	No	NR	PFTs were evaluated as ''normal'' (TLC, FVC, FEV1 values (at least 80% of predicted) and FEV1/FVC ratio >70%), ''obstructive'' (FEV1/FVC ratio <70% and normal or increased TLC), ''restrictive'' (TLC and/or FVC value <80% of predicted together with normal FEV1/FVC ratio (at least 70%)), or ''mixed'' (decrease in FEV1/FVC ratio and TLC value). For DLCO, values below 80% of predicted values were defined as a "decrease in carbon monoxide diffusion capacity"	31 (+31 healthy controls)	NR	Varying by parameter	15 patients (48%) had restrictive, 6 (19%) had both restrictive and obstructive, and 4 (13%) had obstructive ventilatory disease. FVC, FEV1, FEF rate at 25% to 75% of FVC (FEF 25–75%), PEFR, TLC, and DLCO values were significantly lower in the patient group than in the controls (*P*<.05). No significant difference in PFT results was found between patients with and without a history of ACS	No	Matched subjects	No
de Souza, 2007[239]	Cross	Nocturnal polysomno-graphy and spirometry	NR	NR	NR	50	0		FVC=80±10% (ranging from 60 to 101%), FEV1=81±10% (ranging from 61 to 105%), FEV1/FVC=88±6% (ranging from 75 to 100%), FEF 25–75=84±21% (ranging from 46 to 133), TLC=103±16% (ranging from 65 to 144%), RV=162±49% (ranging from 62 to 275%), RV/TLC=33±9% (ranging from 10 to 51%), and FRC=130±38% (ranging from 61 to 223). It was possible to divide the patients into 4 groups: normal (57%); restrictive (8%); obstructive (29%); and lower FVC/higher RV without obstruction (6%). A positive bronchodilator response (>200 mL) was observed in 64% of the patients presenting the obstructive pattern	NA	No	The patients were subdivided into 2 groups regarding pulse oximetry (SpO_2) during REM sleep: group I (42 patients), with SpO_2 ≤93%; and group II (5 patients), with SpO_2 >93%. There were statistically significant differences between the groups in >50% of the polysomnographic variables

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Sylvester, 2004[248]	Cross	FEV1, FVC, PEF	No	NR	Children were diagnosed as having a restrictive abnormality if TLCpleth, FEV1 and FVC were at least 1.64 standardized residuals below the reference range but FEV1/ FVC was in the normal range, and an obstructive abnormality if FEV1 but not FVC was at least 1.64 standardized residuals below the normal range	64 patients and 64 ethnic matched controls	0	4 restrictive, 3 obstructive, 2 mixed restrictive/ obstructive	The children with SCD had lower FRCHe (p=0.04), FEV1 (p=.0008), FVC (p=.001), and PEF (p=.0004), but their FEV1/FVC ratios were not significantly different from those of the controls. FEV1: prebronchodilator: 1.5 (0.5) in patients with SCD 1.9 (0.7) in healthy controls (mean and SD); post-bronchodilator: 1.6 (0.5) in patients with SCD and 2.0 (0.7) in controls; FVC: prebronchodilator: 1.7 (0.6) in patients with SCD and 2.1 (0.8) in controls; postbronchodilator: 1.8 (0.6) in patients with SCD and 2.1 (0.8) in controls; FEV1/FVC (%): prebronchodilator: 89 (7.4) in patients with SCD and 90 (6.8) in controls; postbronchodilator: 90 (8.5) in patients with SCD and 91 (8.3) in controls	No	Ethnicity-matched subjects	No
van Beers, 2008[252]	Cross	General laboratory testing, plain chest radiography, ECG, high-resolution computer tomography (HRCT) of the thorax, PFT, and plasma N-terminal brain natriuretic peptide (NTproBNP) and brain natriuretic peptide (BNP)	No	NR	TRV ≥2.5 m/sec)	74	NR	45	41 patients (55.4%) appeared to have a restrictive pulmonary function whereas 4 patients (5.4%) had evidence of obstructive lung disease. 29 patients (39.2%) had normal PFTs. No statistically significant differences in PFTs were detected in patients with or without PHT in the HbSS/HbSβ^0-thal patients	No	No	No
van Beers, 2008[253]	Cross	Ventilation-perfusion (VQ) scintigraphy`	No	NR	According to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria	83	0	Varying by parameter	49 patients (92%) had a low-probability VQ scan result, 3 (6%) had intermediate probability and 1 (2%) had a high-probability scan in the HbSS/HbSβ^0-thal group. In the HbSC/HbSβ^+-thal group, 22 patients (94%) had a low-probability result, 1 (3%) patient had an intermediate probability result, and another patient had a high-probability result. In the 77 patients who received an ECHO and a VQ scan, no significant difference was observed in pulmonary perfusion between patients with and patients without PHT	No	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Subgroup data
VanderJagt, 2008.[256]	Cross	Spirometry	No	NR	Results were compared to those from the control group	102 (+104 controls)	NR	NR	Age-adjusted data revealed 19–26% lower fat free mass (FFM) for male (*P*<.001) and female (*P*<.001) subjects with SCD relative to the controls. FVC, FEV1 and PEF were also significantly reduced in male and female children and young adults with SCD compared to their control counterparts. For both male and female patients and controls, FVC, FEV1, and PEF correlated positively with FFM (*P*<.001). PEF for the female subjects with SCD diverged progressively with increasing age relative to the controls and the rate of change was significantly lower (*P*<.001)	No	Healthy, age- and gender-matched subjects	No
Vendramini, 2006[258]	Cross	Spirometry, measurements of DLCO and the MCT	No	NR	Normal: when the TLC and/or the FVC, the FEV1, and the FEF 25–75 were within the normal range (i.e., TLC, FVC, and FEV1 >80% of predicted value; FEF 25–75 >75% predicted value). Obstructive: when the ratio FEV1/FVC was >75% with FEF 25–75 disproportionately lower relative to FVC and the expiratory flow volume curve concave. Restrictive: when TLC and/or FVC were lower than 80% of the predicted normal value with a proportional decrease in FEV1 and FEF 25–75 and a normal FEV1/FVC ratio (>80%)	26 patients and 28 controls	0	Varying by parameter	6 patients (24%) exhibited a restrictive ventilatory defect. When compared to the control group, the SCD group showed significantly reduced FVC. 6 patients (24%) had the obstructive pattern; normalization after bronchodilator treatment was observed in 2. Compared to the predicted value, the DLCO value was reduced in the SCD groups. A positive methacholine challenge was found in 11 patients in the SCD group (42%) and in 4 healthy controls (14%)	No	Healthy, asymptomatic subjects	No

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Wall, 1979[263]	Cross	Measurements of DLCO, pulmonary capillary blood volume, the membrane component of diffusing capacity, arterial blood gases on breathing room air, and 100% O_2	No	None, comparison between groups	NR	12 patients and 12 controls	NR	NR	The lung volumes and expiratory flows of subjects with SCA were no different from those of the control subjects. Diffusing capacity for CO was maintained in the normal range despite the severe anemia by increases in pulmonary capillary blood volume and the membrane component of diffusing capacity. All subjects with SCA had mild hypoxemia and abnormal increases in calculated shunt	No	Height-matched control	No
Young, 1988[268]	Cross	See below	No	None	NC/NR	82	NR	NC	The % predicted values for spirometric measurements in SCD were less than that of the control subjects. Mean airway resistance in the patients with SCD was greater than that in control patients (2.61±1.07 vs. 2.18±0.57 cm H20/L/s, respectively, P<.05). When corrected for lung size (specific airway conductance), no difference was found. The decrease in mean dynamic lung compliance of patients was significant when compared to control patients (0.1l1 vs. 0.1l9 L/cm H20, *P*<.01). Mean compliance corrected for lung size and mean specific compliance was also decreased: 0.04 vs. 0.097 cm H20, *P*<.01, respectively. The % predicted static lung volumes of SCD were likewise decreased when compared to controls with the exception of the residual volume. Functional residual capacity measured in the body plethysmography was likewise decreased in the patients, 2.77 vs. 3.42 L in controls, *P*<.05. The mean % predicted diffusing capacity and SD for patients was decreased, 69.1±13.9 vs. 100.1±24.9 for controls, *P*<.01	No	Age-, race-, and gender-matched healthy subjects	No

Table 6. Renal Function Tests Results

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Gordeuk, 2008[96]	Retro-spective prospec-tive	Serum creatinine	No	NR	Elevated serum creatinine concentration was taken to be ≥1.0 mg/dL	163	0	Varying by parameter	TRV was ≥2.5 m/sec in 27% of the patients with SBP < 120mmHg and DBP<70 mmHg, in 37% with SBP 120–139 mmHg or DBP 70–89mmHg, and in 93% with SBP 140 mmHg or DBP 90 mmHg or higher (P < 0.0005 for trend). Serum creatinine concentration was 1.0 mg/dL or higher in 7% of patients with SBP < 120 mmHg and DBP < 70 mmHg, in 17% with SBP 120–139 mmHg or DBP 70–89 mmHg and 50% with SBP 140 mmHg or DBP 90 mmHg or higher (P < 0.0005 for trend)	At the 2-yr followup evaluation, HTN was observed in none of 19 patients who initially had SBP <120 mmHg and DBP <70 mmHg and in 2 of 19 (16%) of those with relative systemic HTN at initial evaluation	Age-matched African-American subjects	The prevalence of serum creatinine ≥1.0 mg/dL was 7% with SBP <120 mmHg and DBP <70 mmHg, 17% with SBP 120–139 mmHg or DBP 70–89 mmHg, and 50.0% with SBP ≥140 mmHg or DBP ≥90 mmHg
Gurkan, 2010[163]	R, Obs	Microalbumin-uria, proteinuria	NR	NR	Microalbuminuria: Urine albumin/ creatinine >30 Mcg/mg Proteinuria: Urine protein/creatinine >0.2 mg/mg	40	0	Micro-albuminuria: 6 Proteinuria: 2	Multivariate analysis revealed a significant correlation between microalbuminuria and LDH level (*p*=.04) and an equivocal correlation between microalbuminuria and history of splenectomy (*p*=.05) when controlled for age, sex, eGFR, Hb level, HbF%, type of SCA, BMI, history of transfusion, and reticulocyte count Univariate analyses revealed a significant correlation between LDH level and proteinuria (Pearson r=0.48, *p*=.035)	NR	No	No
Sklar, 1990[238]	R, Obs	Serum creatinine, proteinuria	No	NR	NR	368	0	Varying by parameter	78 patients (20.6%) had proteinuria and 17 patients (4.6%) had renal insufficiency. Renal insufficiency was accompanied by proteinuria in 11 of 17 cases (*P*<.001)	Since completion of data collection, a total of 5 patients progressed to end-stage renal disease and required chronic dialysis. 3 of them eventually died from complications of renal failure	No	No
Tharaux, 2005[273]	Case control	Plasma ET-1, albuminuria	No	NR	NR	17 patients and 17 controls	0	Of 17 patients with SCD, 8 had abnormal microalbu-minria	The mean level of plasma ET-1 for patients with SCD in steady state was 66.7±27.5 pg/mL, not significantly higher than that of control subjects, 31.1±5.3 pg/mL (*p*=.06). The difference in mean plasma ET-1 levels was significant after overnight water deprivation in patients with SCD (38.1±5.2 pg/mL), compared to controls (29.07±4.2 pg/mL) (*P*<.05). Mean albuminuria was significant (3.1±0.7 g/mol of creatinine or 35.2±8.1 mg/g of creatinine) in the SCD group	No	Sex-, age-, ethnicity- and BMI-matched subjects	No

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Aleem, 2008[31]	P, Obs	Blood urea nitrogen (BUN), serum creatinine, urine dipstick	No	NR	Significant proteinuria was defined as at least 1+ protein in the urine on dipstick examination. Protein excretion of >0.150 g per 24 h was considered abnormal	73	0	30 (with proteinuria)	The median BUN was 2.8 mmol/L (range 0.8–38), and median serum creatinine was 48 µmol/L (range 26 to 1,026). Low serum creatinine was common and present in 28 patients (38%). Median CrCl was 92.1 mL/min. Median protein excretion in 24-h for the patient cohort was abnormal (0.1601 g/d, range 0.037–14.47). The most common abnormality was proteinuria found in 30 patients (41%)	No	No	No
Lima, 2002[61]	P, Obs	Albumin to creatinine ratio (A/C)	Sensitivity 100.0%, specificity of 87.2%, and accuracy of 91.7%	12 h UAE	NR	72 (and 50 controls)	0	NR	A/C values correlated with 12UAE values (r=0.87; *p*<.001) after log/log transformation of the data. The mean value of A/C was higher in patients with raised UAE values than in those with normal UAE values (*p*<.001). In addition, the mean A/C values in patients with normal UAE values were higher than in controls (*p*<.001). Values of A/C >0.45 and <0.45 were indicative of raised and normal UAE values, respectively	Yes, comparisons of the percentage change of 12UA and A/C values from the first collection to the repeat measurements were made in patients undergoing ACE inhibitor treatment to evaluate whether the degree of change of A/C and 12UA occurred in the same direction. No correlation was found with either the 2nd (r=−0.227; *p*=.46) or the 3rd (r=0.515; *p*=.13) measurements	Healthy subjects	No
McBurney, 2002[67]	P, Obs	Microalbumin-uria	No	NR	Urine microalbumin/ creatinine ratios >2.65 mg/µmol (30 µg/mg), but <26.5 mg/µmol (300 µg/mg) were classified as microalbuminuria	151	0	27	The prevalence of microalbuminuria was 19% (27/142 patients). The mean age of children with microalbuminuria was 13.23 yr	In 24 of the 27 children with an abnormal urine microalbumin screen, at least 1 followup urine test was obtained at a mean of 8.8±7.5 mo later. 19 of 24 patients had persistence of microalbuminuria or progression to proteinuria (>26.5 mg albumin/µmol creatinine), whereas 5 had normal readings on followup	No	No

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McKie, 2007[69]	P, Obs	Microalbumin-uria/proteinuria (MA/P)	The test strips are 93.7% sensitive and 94.2% specific for the detection of microalbu-minuria	Quantitation of the amount of microalbuminuria present relative to the creatinine (Umalb/cr)	Positive results classified at concentrations of 20, 50, or 100 mg/L	191	0	37	Hb and age differed significantly between those with and without MA/P. The mean Hb was 7.71 g/dL for children with MA/P compared to a mean of 8.54 g/dL in children without MA/P (p=.0004). The mean age of children with MA/P was 14.95 yr in contrast to a mean age of 11.31 yr for children without MA/P (P<.0001). The youngest patient with MA/P was 5 yr of age. Although most of the children with proteinuria were male (7 of 9 patients), sex was not significantly related to the presence of MA/P when the entire group was considered. Of those children with MA/P, 45.9% (17/37) were female and 54.1% (20/37) were male	Data collected longitudinally demonstrated development of MA/P in 14 of 154 children at a mean age. 9 patients were found to have persistent proteinuria (>300 µg/mg at 2 or more visits) during the study (prevalence 4.5%)	No	No
Okoro, 1991[75]	P, Obs	GFR	No	No	NR	365	NR	Comparison between means only	For the healthy children who served as controls, the mean (SD) GFR was 112 (35) mL/min/1.73m^2. The peak GFR was recorded in boys at 9 yr and girls at 13 yr. In the children with SCA in a steady state, the mean (SD) GFR was 111 (36), a figure similar to that of normal control	No	Healthy siblings	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Wigfall, 2000[94]	P, Obs	Urinary protein	NA	NR	Persistent proteinuria was defined as ≥1+protein on urinalysis for at least 6 mo	442	NR	20	Urinary protein excretion was elevated (>1+ for at least 6 mo) in 20 (4.5%) of the 442 patients (4.5%) including 15 (6.2%) children with HbSS, 4 (7.8%) with HbSβ-thal, and 1 (0.9%) with HbSC. The prevalence of proteinuria for patients with HbSS increased with age, ranging from 0% in the younger children to 12% in the older teenagers	In the 7 to 12 yr age range, children with proteinuria were more likely to have been hospitalized because of pain (50%) than those without proteinuria (16%, *p*=.007). In the 13 to17 yr age range, patients with proteinuria were more likely to have cholelithiasis (60% vs. 18%, *P*<.05) or stroke (20% vs. 0%, *P*<.0001). For patients aged 18 to 21 yr, those with proteinuria were more likely to have had ACS (75% vs. 24%, *p*=.03) and to be hospitalized because of pain (75% vs. 26%, *p*=.04	No	No
Abo-Zenah, 2009[98]	Cross	UAE and eGFR (estimated GFR)	The quantitative measure-ments of 24-h UAE by a colorimetric test has a 98% specificity	NR	NR	133	0	32	Increased UAE rate, by 24-h UAE determination (380 (272.2–489.6) mg/24 h; mean and 95% CI of the mean) was detected in 32 of the screened 133 patients (6 males and 26 females). In this study, the increased UAE (24% of the total study population) took the form of microalbuminuria (168.8±59.7 mg/d) in the majority (63.6%) and macroalbuminuria (752.7±205.4 mg/d) in a smaller percentage (36.4%) of patients	No	No	No
Aikhionbare, 1988[102]	Cross	Serum creatinine	No	None	NR	32	0	NR	Mean serum creatinine for HbSS was 71.2±33 μmol/L and was 53.9±22 μmol/L for HbAA. The difference was nonsignificant. The mean endogenous CrCl of 99.1 mL/min/1.73m^2 obtained in HbSS patients was lower than the mean value of 107 mL/min/1.73m^2 obtained in the control subjects with HbAA, though the difference was not significant	No	Healthy HbAA subjects	No

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Al-Ali, 1995[104]	Cross	Uric acid, creatinine and urea	No	NR	NR	181 (G6PD-normal) 206 (G6PD-deficient)	NR	NA	Hematological indices for normal controls are similar to those in other populations, but HbSS with or without G6PD deficiency has a mean hemoglobin concentration of 10.3±1.8 and 10.9±1.1g/dl, which are higher than other populations	No	HbAA and HbAS subjects	No
Aleem, 2010[106]	Cross	Measure 24-h urine protein level	NR	NR	Protein excretion of >0.150 g/24 h was considered abnormal	67	0	27	27 patients (40.3%) had proteinuria of >0.150 g/24 h. None of the parameters analyzed correlated with proteinuria	No	No	Comparison of different parameters between the patient groups with and without proteinuria
al-Naama, 2000[97]	Cross	Uric acid, urea, and creatinine levels	No	NR	NR	30 patients and 45 controls	0	NA	Uric acid levels in patients with SCD were 8.5±1.5 (mean±SD), significantly higher than controls (5.19±0.64) *P*<.0001. Urea levels in patients with SCD were 23±3.1, significantly lower than controls (32.37±4.94) *P*<.0001. Creatinine levels in patients with SCD were 0.85±0.15, significantly lower than controls (1.55±0.32) *P*<.0001	No	Age- and sex-matched HbAA subjects	No
Aluoch, 1989[109]	Cross	Serum creatinine	No	None	No	65	0	NR	Serum creatinine (μmol/L) level in HbSS (54.9±42.1), HbSβ^0-thal (52.2±12.7), HbSβ^+-thal (51.7±16), HbSC (60.7±15). There was no statistical difference between the groups	No	No	No
Alvarez, 2006[111]	Cross	Albuminuria, serum creatinine	NR	NR	Macroalbuminuria or proteinuria >300 mg/g creatinine, microalbuminuria 30–300 mg albumin	120	0	19	From the total of 120 patients, 19 (15.8%) had macroalbuminuria detected by random urine screening with increased albumin excretion (mean urine albumin 6.95 mg/dL ±0.56, range 3.23–24.3) and elevated albumin/creatinine ratios 30–300 mg/g creatinine, including 1 >300 mg/g creatinine, (mean ratio 79.8±0.62, range 34–337). Serum creatinine fluctuated between 0.3 and 0.8 mg/dL, mean 0.51±0.12 in 46 patients studied. The mean CrCl for all 46 patients was 177±47 mL/min/1.73 m^2, range 97–400	NR	No	The patients who did not have macroalbuminuria (*N*=35), had a CrCl of 179±50 (97–400) and those who had albuminuria (*N*=11), had a clearance of 173±41 (128–256) indicating no significant difference in hyperfiltration between both groups (*p*=.73)

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Alvarez, 2006[112]	Cross	Serum cystatin C levels	No	NR	NR	20	0	NA	The mean serum creatinine for the whole group was 0.58±0.18 mg/Ll. The mean serum cystatin C for the whole group was 0.89±0.27 mg/L. The mean measured and estimated CrCl for the 20 patients were 149±41 and 176±66 mL/min/1.73 m^2 and not significantly different (*p*=.056). Patients with tubular or glomerular proteinuria had a higher mean serum cystatin of 1.25±0.34 mg/L, whereas patients with microalbuminuria had a normal mean of 0.84±0.15, and patients without albuminuria had a mean serum cystatin of 0.78±0.16 (*p*=.004). The mean GFR estimated from serum cystatin was 63±18 mL/min/1.73 m^2 for the patients with either tubular or glomerular proteinuria, 94±21 for the patients with MA, and 103±25 for the normal group (*p*=.03) according to Hoek's formula	No	Normal subjects	No
Aoki, 1990[114]	Cross	UAE, CrCl	No	NR	UAE >30 mg/L was considered abnormal	56 (and 11 controls)	0	18	16 HbSS patients (40%) and 1 HbSC (9%) and 1 HbSβ (25%) patient presented mean UAE above normal values (30 mg/L). CrCl was measured in all individuals and was significantly higher in patients with SCD than in normal controls	No	Normal subjects	No
Aparicio, 1990[115]	Cross	CrCl	No	None	NR	21	0	NR	Mean CrCl was 51.5±24.7 mL/min. CrCl was linearly associated with 51Cr-EDTA clearance (r=0.84, *p*<.01. On average, CrCl values were 24.4 mL/min (32%0) below those obtained by the isotope method, the difference between paired values being highly significant (Student's t test=4.51, *p*<.0002)	no	No	No
Aparicio, 1990[115]	Cross	Serum creatinine	No	None	NR	21	0	NR	Mean serum creatinine was 145±136 µmol/L. The reciprocal of serum creatinine and of serum β^2 microglobulin showed a good correlation with 51Cr-EDTA clearance (r=0.81 and 0.79, respectively; *p*<.001 for both)	no	No	No
Asaolu, 2010[118]	Cross	Serum creatinine, serum urea	No	NR	NR	42	0	NA	Serum creatinine level in the SCD group was 100.55±8.13 (mean±SD) as compared to 80.15±1.11 in the control group. Serum urea in the SCD group was 10.50±6.28 as compared to 5.50±2.10 in the control group	NO	Healthy subjects	No

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Ataga, 2010[122]	Cross	Albuminuria	NR	NR	Normoalbuminuria (<30 mg/g creatinine), microalbuminuria (30–299 mg/g creatinine) or macroalbuminuria (≥300 mg/g creatinine)	73	NR	39	Normoalbuminuria was observed in 34 patients with SCD (46.6%), microalbuminuria in 24 patients with SCD (32.9%) and macroalbuminuria in 15 patients with SCD (20.5%). There was a modest correlation between age and albuminuria (r=0.32, 95% CI: 0.09–0.51; *p*=.006), although there was no significant difference when the ages of patients with SCD with macroalbuminuria, microalbuminuria, and normoalbuminuria were compared (43 yr vs. 40 yr vs. 35 yr; *p*=.12)	NR	Healthy subjects	No
Aygun, 2009[124]	Cross	GFR, serum creatinine	No	NR	Proteinuria: ≥300 mg protein/g creatinine Microalbuminuria:30-299 mg protein/gm creatinine	65	0	2:Protein-uria 7:Micro-albuminuria	The mean serum creatinine was 0.34±0.10 mg/dL (range 0.1–0.6 mg/dL). The mean 99mTC-DTPA GFR value was elevated at 155.8±38.9 mL/min/1.73 m^2 (range: 91–308 mL/min/1.73 m^2, normal for age 104±20 mL/min/1.73 m^2). A total of 63 patients had quantitative microalbumin measurements: 7 (11.1%) had microalbuminuria (30–299 mg protein/g creatinine) and 2 (3.2%) had frank proteinuria (≥300 mg protein/g creatinine). Mean 99mTC-DTPA GFR values were higher in the 9 patients with microalbuminuria or proteinuria as compared to 54 without microalbuminuria (184.2 vs. 152.7 mL/min/1.73 m^2, *p*=.077)	No	No	No
Barros, 2006[129]	Cross	Cr-EDTA measure-ments of the GFR	No	NR	NR	70	0	NA	The mean GFR (±SD) obtained for the 70 patients was 111.5 (23.1) mL/min. UAE was normal (0–20 µg/min) in 47 patients (67%) and 23 (33%) had microalbuminuria (>20–200 µg/min). The Spearman correlation coefficient demonstrated a significant relationship between 51Cr-EDTA clearance and patient age (r=–0.44, *p*=.0001), but not between 51Cr-EDTA and urinary albumin (r=–0.17, *p*=.1546) or Hct (r=0.079, *p*=.5121)	No	No	The analysis of the different age groups showed the 20–29 yr group as having the highest 51Cr-EDTA clearance mean value, with a progressive reduction in the older groups

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Bayazit, 2002[131]	Cross	CrCl	No	None	No	66	NR	NR	CrCl for patients was 131.7±23.5, as compared to 147.1±32.0 for controls (*p*=NS). FeNa, FeUa, Urine protein/Cr ratio, urinary N-acetyl-B-D- glucosaminidase and urinary malondialdehyde were not statistically significantly different between the 2 groups. Fractional excretion of potassium, tubular phosphate reabsorption, urine volume osmolality, and urine specific gravity were statistically different between the groups suggesting worsening renal function in the patients with SCD	No	Healthy subjects	No
Becton, 2010[132]	Cross	Albuminuria/ proteinuria	No	NR	Microalbuminuria was defined by an average urine A/C ratio of 30–300 mg/g, and proteinuria was defined by A/C ratio >300 mg/g on 2 spot urine specimens obtained 6 mo apart	90	NR	14	14 patients (16%) had microalbuminuria with a mean MA/Cr excretion of 78.1±56.9 mg/g compared to 5.1±6.7 for the remaining subjects with no microalbuminuria (*p*<.01). The mean calculated GFR was 187.9±64.2 mL/min/1.73 m^2	No	No	No
Datta, 2003[148]	Cross	Urine albumin concentration	No	NR	A value >20 mg/min (by single radial immunodiffusion) was considered positive	64	0	12	18.8% of the study population had significant microalbuminuria. 14.3% of patients <9 yr of age had significant microalbuminuria, whereas in patients >9 yr of age it was 33.3%. There was a significantly higher microalbumin excretion in patients >9 yr of age as compared to younger patients (*p*<.05)	No	No	No
Dhamidharka, 1998[151]	Cross	Microalbumin, creatinine	No	NR	Microalbuminuria: urinary albumin/ creatinine >20 mg/Cr	102	0	27	Microalbuminuria was present in 27 of 102 (26.5%) of the overall study group. Age was the only continuous variable to differ for the normal and abnormal groups (*P*<.0001). Most of the children with microalbuminuria were in the 10- to 18-yr age group. Creatinine clearance as estimated by Schwartz formula was elevated in all children. However, the degree of elevation of Ccr was not related to the prevalence of microalbuminuria	No	No	No

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Falk, 1992[154]	Cross	24 h urine collection to measure protein, GFR + blood sample for creatinine	No	NR	NR	381	NR	26 (creatinine) and 101 (urine protein)	26 adults (7%) but none of the children had elevated serum creatinine concentrations. 13 of these patients had a serum creatinine concentration of 177 µmol/L or less, 6 patients had values between 185 and 530 µmol/L, and 7 patients had high end-stage renal disease treated with dialysis. Among the 381 patients, 282 had no proteinuria or only trace proteinuria; 47 had proteinuria of 1+, 28 of 2+, 16 of 3+, and 10 of 4+. Proteinuria of at least 1+ was more common in patients with HbSS (p=.002)	Given for 10 patients who consented to renal biopsy, in a pre- and postenalapril setting. The mean decrement was 57 percent below base line (range, 23 to 79 percent). When measured again two to three weeks after treatment with enalapril was discontinued, the mean protein excretion was 75 percent of the base-line value (P = 0.168). In three patients, however, protein excretion continued to decrease. The decrease was most pronounced in the patient whose protein excretion was 10.8 g per day at base line.	Healthy subjects	No
Guasch, 1996[160]	Cross	Serum creatinine, GFR	No	NR	NR	34	0	NA	Serum creatinine was abnormally increased only at GFRs <30mL/min/1.73 m^2. Renal plasma flow was disproportionately higher than GFR, so that filtration fraction was low in all groups. Albuminuria was accompanied, even in patients with normal GFR, by a reduction in ultrafiltration coefficient (16±3 in albuminuria vs. 25±3 in controls, P<.05). A more severe loss of ultrafiltration coefficient and glomerular permselectivity occurred in chronic renal failure	No	No	Patients were divided according to GFR and albumin excretion rate (AER): sickle cell anemia controls (normal GFR and AER, N=10), albuminuria (increased AER, but normal GFR, N=7) and chronic renal failure (CRF, low GFR, N=17)

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Guasch, 1999[161]	Cross	Urine albumin	No	NR	Macroalbuminuria (albumin excretion rate >300 mg/g creatinine)	76	0	22	There was a tendency for a higher serum creatinine in patients with no deletions compared to patients with deleted α-globin genes (SCr, 1.0±0.2 vs. 0.8±0.1 mg/dL, respectively). The prevalence of macroalbuminuria approached 40% in adult patients without α-globin gene micro-deletions, whereas only 13% of adult HbSS patients with α-globin gene microdeletions had macroalbuminuria. In contrast to the protective effects of α-globin gene microdeletions, the CAR β-globin gene haplotypes were not associated with differences in the prevalence of macroalbuminuria	No	No	No
Guasch, 2006[162]	Cross	Albuminuria, CrCl	NR	NR	Normoalbuminuria (albumin excretion rates AER <30 mg/g creatinine), micro-albuminuria (AER 30 to 299 mg/g creatinine), or macroalbuminuria (AER ≥300 mg/g creatinine); CrCl <90 mL/min	300	0	174 Albuminuria 69 CrCl	In HbSS, increased AER occurs in 68% (125) of patients. Macroalbuminuria is present in 26%, and microalbuminuria is present in 42%; only 32% of adults with HbSS have normoalbuminuria. In other sickling hemoglobinopathies, the prevalence of increased AER is lower than in HbSS. Abnormal AER occurs in 42% (49) of patients, with macroalbuminuria occurring in 10% and microalbuminuria occurring in 32% Renal insufficiency, defined as a CrCl <90 mL/min, was present in a similar percentage of individuals with HbSS (38 (21%) of 184) vs. other sickling disorders (31 (27%) of 116; NS). However, the percentage of patients with renal insufficiency and advanced kidney failure (chronic kidney disease stage 3 or higher) was higher in HbSS (11 (29%) of 38) vs. other sickling disorders (2 (6%) of 31; *p*=.06)	NR	No	There were no gender differences in the prevalence of albuminuria

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Herrera, 2002[165]	Cross	Tubular stress test	No	NR	NR	16 (and 20 controls)	0	NA	Patients with SCD had higher GFR and CrCl and lower serum plasma creatinine (Pcr) and tubular secretion of creatinine (TScr) in the baseline studies than the control individuals. Patients' (controls') GFR, Ccr, Pcr, and TScr at baseline were: 125±23.1 (101±16.9, *P*<.001), 143±23.7 (123±15.6, *P*<.001), 54±15.7 (86±10.2, *P*<.001), and 21.4±18.1 (35.9±15.8, *P*<.05), respectively. The GFR did not change during the tubular stress test in patients with SCA nor in controls. In contrast, the Ccr increased significantly in patients with SCA and in controls with respect to pretest baseline levels, but the increment in Ccr found in the patients with SCA is significantly less (*P*<.05) than the increment observed in controls. There were similar increments in Pcr with respect to pretest values	No	Healthy subjects	No
Jyothi, 2009[171]	Cross	Urine protein	No	NR	Microalbuminuria is defined if urine micro-albumin to creatinine ratio is >30 µg/mg as previously described	100	0	14	14 (14%) patients had microalbuminuria. Hb levels were statistically different between patients with or without microalbuminuria (8.8±1.1, 9.8±1.4, respectively) and significantly correlated with microalbuminuria (rho=-0.24, *p*=.03)	No	No	No
Katopodis, 1997[175]	Cross	Renal function testing: electrolytes in serum and urine, concentrating or diluting ability, urine acidification, GFR and hormones	No	NR	NR	17 (and 17 controls)	0	Varying by parameter	The mean (±SD) GFR for patients was 94±4 mL/min and did not differ significantly from controls. 4 patients had GFR <80 mL/min, while 4 >40 yr of age had a GFR >120 mL/min. CrCl was significantly higher in patients than in controls. All patients had some degree of inability to maximally concentrate the urine. 7 patients (41%) also had a decreased ability to maximally dilute their urine	No	Healthy subjects	No
Kontessis, 1992[184]	Cross	24 h urinary specific gravity and osmolality, CrCl	No	NR	NR	49 (+14 healthy)	NR	NR	A statistically significant negative correlation (*n*=19, r=-0.48, *p*<.05) was noted between CrCl and age for the patients >30 yr of age. There was no correlation between Hb and CrCl; but rather a statistically significant negative correlation was found between CrCl and HbF (*n*=29, r=-0.428, *p*<.05)	NR	Healthy subjects	No

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Marouf, 2006[198]	Cross	Proteinuria	NR	NR	Protein excretion >150 mg/24 h was considered to indicate significant proteinuria	59	0	8	Significant proteinuria was present in 8 of the patients (13.6%). Urine protein excretion (24-h urine protein) was significantly correlated with age (r=0.33, *p*=.049). Patients with proteinuria had lower Hb concentration (*p*=.027) than patients without proteinuria	NR	No	No
Marsenic, 2008[199]	Cross	Urinary protein as a marker of glomerular permselectivity	No	NR	NR	32	0	13	Total protein excretion was elevated in 41% (13/32) of patients. The increased total protein excretion was accompanied by increased micro-albuminuria in 38.5% (5/13), increased RBP excretion in 15% (2/13) and increased immunoglobulin G (IgG) excretion in 23% (3/13). However, 46% (6/13) had increased total protein excretion without in-creased excretion of any of the tested proteins. Increased microalbuminuria was present in 25% (8/32) of all patients, and it was accompanied by increased total protein excretion in 62% (5/8) and increased IgG excretion in 62% (5/8) of patients	No	No	Increased total protein excretion was evenly distributed among age groups, 38.5% (5/13) were 0–6 yr old, 38.5% (5/13) were 7–13 yr old, and 23% (3/13) were 14–19 yr old. 60% of patients on HU had no proteinuria, while 42% of patients receiving transfusion had no proteinurea
Miller, 2010 [201]	Cross	Fluid deprivation test	No	NR	Failure to produce urine that is more concentrated than serum	178	3.8	42	The mean urine osmolality was 407±151 (mOsm/kg) H_2O (range 58–794) and was significantly greater than the mean serum osmolality of 286±6 mOsm/kg H_2O (range 275–312) (*P*<.0001). 142 (77.2%) infants were hypersthenuric. There was an average increase of 13.2 mOsm/kg H_2O (95% CI: 4.5–22.0, *p*=.003) in urine osmolality for every hour of fluid deprivation and 23.0 mOsm/kg H_2O (95% CI: 17.0–29.0, *P*<.001) for every 1.0 mg/dL increase in serum urea nitrogen	No	No	No

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Morgan, 1981[202]	Cross	Serum urea and creatinine concentrations. 24-h urine collections for creatinine and protein excretion	No	NR	NR	24	0	NA	Serum creatinine concentration exceeded the upper normal limit (124 µmol/L; 1–4 mg/100 mL) in 3 patients (12.5%), and serum urea exceeded the upper normal limit (5.5 mmol/L; 33 mg/100 mL) in 7. Serum urea concentrations were higher than those of a group of 25 randomly selected patients with HbSS aged 18–39 yr (geometric mean 5.5 v 2.9 mmol/L (33.1 vs. 17.5 mg/100 mL); $p<.001$), but there was no significant difference in serum creatinine values. CrCl varied widely (mean 116 mL/min/1.73 m^2; range 11–204 mL/min/1.73 m^2) and was below 80 mL/min/1.73 m^2 in 6 patients, who were considered on this basis to have renal insufficiency	No	No	No
Morgan, 1982[203]	Cross	Proteinuria	No	None	NR	470	NR	50	Prevalence of proteinuria increased through life; 22% of those >30 yr and 46% of those >50 yr were affected. It was uncommon in childhood	no	No	No
Morgan, 1984[204]	Cross	Proteinuria	No	None	>300 mg/d	64	NC	18	18 patients (28%) had proteinuria. Serum urate concentrations ranged between 0.24 and 0.91 mmol/L	no	No	No
Nebor, 2010[207]	Cross	Urinary protein level	NR	NR	Microalbuminuria was defined as urine albumin level from 20 to 200 mg/mL and macroalbuminuria as urine albumin >200 mg/mL	189	0	94	53 patients had microalbuminuria, 41 patients had macroalbuminuria and 85 patients were normoalbuminuric	No	No	No
Nobrega, 2009[209]	Cross	Urine protein	No	NR	NR	51	0	14	The microalbuminuria prevalence in this study was 27, 4%	No	No	No
Olowu, 2002[212]	Cross	Creatinine clearance	No	NR	NR	54 (and 57 controls)	0	NA	The mean GFRs±SD (mL/min/1.73 m^2) for SCD children and normal controls were not significantly different ($p>.05$). In the entire age group (5–13 yr) of children with SCD, the mean GFRs±SD for the 27 males and 27 females were 152±109 and 155±96, respectively. The 2 means were not significantly different		Healthy subjects	The GFR did not differ significantly between the age groups in both patients and normal controls

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Schmitt, 1998[230]	Cross	Glomerular function testing	No	NR	Albuminuria was defined as urinary albumin >30 mg/24 h	14 (and 16 controls)	0	7	7 patients were albuminuric (mean, 269.8±119.3 mg/24 h) and 6 were nonalbuminuric (12.7±2.1 mg/24 h); data not available for 1 patient; Patients with SCA had significantly higher GFR values and a marked increase in effective renal plasma flow , resulting in a significant decrease in filtration fraction	No	Healthy subjects	GFR did not differ between the albuminuric and nonalbuminuric patients (145.7±11 mL/min/ 1.73 m^2 v 141.3±15 mL/min/1.73 m^2)
Sesso, 1998[234]	Cross	Serum creatinine, CrCl, urine albumin	No	NR	NR	66 (and 40 controls)	0	NR	The percentage of individuals with microalbuminuria was significantly higher in HbSS than HbAS patients (30 vs. 8%, *P*<.0001). However, the presence of hematuria was quite similar in both groups (26 vs. 30%). Serum creatinine (mg/dL) (median and range) 0.70 (0.4–1.1) In HbAS subjects and 0.60 (0.3–1.3) in HbSS subjects *P*<.01. Microalbuminuria (mg/L) 6.8 (0.8–364.0) in HbAS subjects and 10.5 (0.7–2022.0) in HbSS subjects *P*<.05	No	Healthy subjects	No
Thompson, 2007[250]	Cross	Serum creatinine, GFR, CrCl	No	NR	NR	65 (and 15 controls)	0	NA	Serum creatinine and urea levels were lower in subjects with HbSS, but the differences in uric acid, sodium, potassium, or albumin levels between the 2 study genotypes did not reach statistical significance. Filtration fraction was significantly lower in male subjects with HbSS compared to male controls but did not differ in female subjects compared to female controls. Urine-specific gravity was lower in subjects with HbSS compared to controls. CrCl was systematically lower than GFR in controls (mean difference, -13.5 mL/min (0.2 mL/s); 95% limits of agreement, -43.2 to 16.1). In contrast, CrCl was systematically greater in subjects with HbSS	No	Healthy subjects	No
VanderJagt, 1997[255]	Cross	Serum creatinine	No	NR	NR	13 (and 17 controls)	0	NA	The serum creatinine concentrations and the calculated CrCl were not significantly different for the 2 groups. Patients with SCD (35.1±9.9 in patients with SCD and 47.3±13.7 in controls). The mean concentration of total protein in the urine of the patients with SCD was slightly lower, but not significantly, in the patients with SCD compared to controls (9.1±18 in patients with SCD and 12.7±44 in controls)	No	Healthy subjects	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Subgroup data
Voskaridou, 2006[260]	Cross	Cys-C, β_2-M, and NAG excretion, CrCl, urine protein	No	NR	NR	87 (and 30 controls)	0	NA	Mild (300–1,000 mg/24 h) and moderate (1,001–3,000 mg/24 h) proteinuria was present in 25 (28.7%) patients. CrCl <80 mL/min/1.73 m^2 was found in 31 (35.6%) patients, while 13 (14.9%) patients had CrCl levels of above 120 mL/min/1.73 m^2. Abnormal serum Cr levels presented in only 6 patients (6.8%), while increased values of Cys-C, NAG, and serum β2-M were observed in 28 (32.1%), 65 (74.7%), and 61 (70.1%) patients, respectively. HbSβ-thal patients had a dramatic increase of Cys-C, NAG, and serum β_2-M levels compared to controls, while there was no difference between patients and controls in terms of serum creatinine	No	Healthy subjects	No
Ware, 2010 (BABY HUG)[266]	Cross	GFR measured by 99mTC-TPA plasma clearance	No	NR	NR	176	8	NR	Average DTPA GFR was 125.2±34.4 (range 40.2–300.9, normal 91.5±17.8 mL/min/1.73 m^2), while Schwartz estimates were higher at 184.4±55.5 mL/min/1.73 m^2. DTPA GFR was correlated with Schwartz GFR (r^2=0.0658, *p*=.0012); also with age, weight, height, and kidney volume (all *P*<.002); but not with Hb, HbF, WBC count, reticulocytes, medical events, or splenic function	No	No	No
Waugh, 1999[267]	Cross	Pcr	No	None	No, comparison study	19 (and 16 controls)	NC	NA	Pcr levels were significantly lower in subjects with SCA. Mean values were 0.56±0.19 mg/dL (49.5±16.8 µmoles/L) in the males and 0.42±0.10 mg/dL (37.1±8.8 µmoles/L) in the females. In male and female controls, Pcr levels averaged 0.97±0.26 mg/dL (85.7±23.0 µmoles/L) and 0.79±0.19 mg/dL (69.8±16.8 µmoles/L), respectively	No	Healthy subjects	No
Zorilla, 2005[271]	Cross	Urine albumin	No	NR	Normalbuminuria <30 mg/g, microalbuminuria <30–300 mg/g, macroalbuminuria >300 mg/g	160	0	Varying by parameter	Abnormal albuminuria levels occurred in 68% of the patients with HbSS and in 42% of patients with other HbS variants	No	No	No

Table 7. Ocular Examination Results

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests and/or uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Please report any relevant subgroup data
Gill, 2008[10]	R, Obs	Fundoscopy (Only those cases with a clinical suspicion of PSR were evaluated with fluorescein angiography)	No	NR	Nonproliferative retinopathy (NPR) includes salmon-patch hemorrhages, iridescent sorts, black sunbursts, and arteriovenous anastomoses. Sign of PSR is a sea fan neovascularization.	263	24	51 PSR:7 NPR:44	The prevalence of clinically significant PSR was only 7 cases (2.7%). 6 cases (8.2%) were seen in HbSC, 1 case (0.6%) in HbSS, and no cases in HbSβ-thal. The age of onset of retinopathy (proliferative and nonproliferative), including all 3 genotypes, was variable, occurring at a mean of 12.8 yr. The mean age of onset of clinically significant PSR was 14 yr. Neither gender nor the presence of systemic manifestation was predictive for the prevalence or age of onset of retinopathy	No	No	NR
Clarkson, 1992[39]	P, Obs	Visual acuity, fundoscopy	No	NR	Neovascular proliferative disease based on the Goldberg classification	150 (85 followed)	NR	27 (stage III PR)	The anterior segment findings were limited to the conjunctival sign, noted in 59% and iris atrophy, noted in 1 patient (0.7%). The conjunctival sign was seen significantly more often in patients with HbSS (70%); $p<.01$. Macular changes were noted in relatively small numbers. Most significant findings included macular hole (1.3%), epiretinal membrane (2%), and macular pucker (1.3%). There was generalized vascular tortuosity of the major retinal vessels in 11% of patients, significantly more so ($P<.05$) in HbSS patients. Prevalence of non-PSR; hemorrhage, iridescent spot and black sunburst spot, was found to be 6%, 8%, and 35% of patients. Prevalence of PSR stages III, IV, and V was 18%, 5.3%, and 2% in that order	85 patients were followed for a mean of 6.7 yr. Prevalence of retinal hemorrhage decreased from 8% to 6%, iridescent spot stayed at 10%, and black sunburst spot increased from 41% to 46%. Prevalence of PSR stages II, IV, and V from 19% to 31% in HbSS patients and from 48% to 74% in HbSC patients	No	Non-PSR changes were found in patients with each of the different genotypes. Retinal hemorrhages and their sequelae, iridescent spot, were present more often in HbSC patients (17% and 28%) than in HbSS patients (2.8% and 3.7%) and HbS-thal (8.3% and 0%). Black sunburst spots were also found more frequently in HbSC patients than in HbSS or HbS-thal. Proliferative changes (stage III) occurred in 45% of HbSC patients, 11% of HbSS patients, and 17% in HbS-thal patients. Vitreous hemorrhage (stage IV) was found in 21%, 1.8% of HbSC and HbSS patients. Retinal detachment (stage V) occurred in 10% of HbSC patients

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests and/or uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Please report any relevant subgroup data
Downes, 2005[45]	P, Obs	Assessment included visual acuity, fundus examination through dilated pupils, and fluorescein angiography in all subjects, unless allergic to fluorescein	No	None	Leaking blood vessels on fluorescein angioscopy or angiography	100	NR	59	PSR had developed in 59 patients (14 HbSS, 45 HbSC), unilaterally in 36 patients and bilaterally in 23. Incidence increased with age in both genotypes, with crude annual incidence rates of 0.5 cases (95% CI, 0.3–0.8) per 100 HbSS subjects and 2.5 cases (95% CI, 1.9–3.3) per 100 HbSC subjects. Prevalence was greater in HbSC, and by the ages of 24 to 26 yr, PSR had occurred in 43% subjects with HbSC and in 14% subjects with HbSS. Irretrievable visual loss occurred in only 1 of 82 PSR-affected eyes, and 1 required detachment surgery and recovered normal visual acuity	This is long-term followup	No	NR
Friberg, 1986[47]	P, Obs	Comprehen-sive ophthalmologic evaluation	No	None	NR	110	NR	Varying by parameter	The most prevalent retinal abnormality was the black sunburst, occurring in 46% of HbSS patients, 63% of HbSC patients, and 37% of HbS-thal patients. Data reported in this study suggest that retinal lesions become more prevalent up to the fifth decade of life	No	No	NR
Moriarty, 1988[275]	P, Obs	Fundoscopy	No	None	Visual acuity loss is visual acuity ≤6/18	342	NR	72 (eyes)	Visual acuity loss attributable to sickle cell retinopathy occurred in 10% of untreated eyes. Visual loss was strongly associated with PSR (p<.001) and most commonly resulted from vitreous hemorrhage, tractional retinal detachment, and epiretinal membranes. The incidence of visual loss was 31 per 1,000 eye-yr observation among eyes with proliferative disease compared to 1.4 per 1,000 eye-yr observation among eyes with nonproliferative disease	No	No	NR

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests and/or uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Please report any relevant subgroup data
Talbot, 1988[91]	P, Obs	Serial retinal examinations were performed in children aged 5 yr and older and fluorescein angiography/ angioscopy in children 6 yr and older	No	None	Peripheral retinal vessel closure was diagnosed if there were continuing retinal nonperfusion extending posteriorly from the ora to at least the equator	446	NC/NR	Varying by parameter	Peripheral retinal vessel closure was present in approximately 50% of children with HbSS and HbSC at age 6 yr and increased to affect 90% of children by age 12 yr. PR was rare, occurring only once in an 8-yr-old boy with HbSC, despite 592 patient-yr of observation in children older than this age	No	No	NR
al-Hazzaa, 1995[107]	Cross	Retinal examination and fluorescein angiography	No	NR	NR	71	0	Varying by parameter	Peripheral retinal vascular changes were common, and a qualitatively abnormal vascular border believed to imply risk of PSR was significantly more common in southwestern HbSS patients and PSR was shown in 1 of these. There were no differences in visual acuity, the presence of peripheral retinal patches, or the circumferential or posterior extent of peripheral retinal vessel closure between HbSS and sickle cell β^0 thalassemia or between HbSS in the 2 regions. Compared to the Jamaican Cohort Study, >1,800 of the peripheral retinal vasculature was seen significantly less frequent, suggesting factors inhibiting vascular remodeling in Saudi patients in early life	No	No	NR
Asdourian, 1976[119]	Cross	Retinal examination and fluorescein angiography	No	None	NC	100	0	29/100 (29%)	Various abnormalities of the posterior pole vasculature were seen in 29% of the patients. Continuous remodeling of the macular and perimacular vasculature occurred. Visual acuity was variably affected and sometimes remained intact	No	No	NR
Babalola, 2001[125]	Cross	Eye assessment	No	NR	NR	90	0	Varying by parameter	24% had some form of SCD-related posterior ocular signs, 5.6% of which was preproliferative or proliferative	No	No	NR

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests and/or uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Please report any relevant subgroup data
Goldbaum, 1978[158]	Cross	Indirect ophthalmoscopy	No	None	Abnormality in the reflection from the internal limiting lamina produced by depression of the inner surface of the retina	80	NR	16/80 (20%)	16 of the total 80 patients (20%) with SCD had depressions in the posterior lobe	No	No	NR
Kent, 1994[176]	Cross	Fundus examination with mydriatics as well as fundus fluorescein angiography unless specifically contraindi-cated	No	NR	Retinopathy was classified into 4 different grades	49 (1 patient was excluded because of the presence of retinitis pigmentosa)	0	Varying by parameter	Only 7 eyes had visual acuity of ≤6/18. 1 eye with an acuity of no perception of light had a dense cataract and a tractional retinal detachment and 1 eye had perception of light with a long-standing retinal detachment. The other 3 eyes had macular problems. 32 eyes were grade I; 45 eyes were grade II; 9 eyes were grade III, while 12 eyes were grade IV. 17 eyes out of the total number had evidence of PSR. Bilaterality was a feature in 3 male patients and 2 female patients	No	No	There was a markedly in-creased prevalence of grade I retinopathy among eyes of patients with HbSS (HbSS:HbSC= 3:1), while grade II was much more common with HbSC (HbSS:HbSC= 26:14)
Lima, 2006[194]	Cross	Fundoscopy, fluorescein angiography	No	NR	Biomicroscopic evaluation was performed under a slit-lamp, and conjunctival vessel features were classified in 5 groups. Fluorescein angiography findings were classified into 5 groups according to the degree of PSR observed	102	0	Varying by parameter	Conjunctival vessel alterations of grades 1, 2, 3, and 4 were identified in 1 (11%), 20 (20%), 38 (37%), and 29 (28%) of 102 patients with SCD, respectively. Retinal vessel alterations (RVA) of grades 1, 2, 3, and 4 were seen in 32 (31%), 3 (3%), 1 (1%), and 2 (2%) patients, respectively. Logistic regression analysis and means comparison indicated that conjunctival vessel alteration was more frequent in patients with reduced levels of Hb (OR=1.4, 95% CI=1.1–1.8, *p*=.013), and haematocrit (OR=1.1, 95% CI=1.1–1.2, *p*=.017). Retinal vessel alteration was not influenced by Hb (*p*=.479) or Ht (*p*=.270) levels, as indicated by logistic regression analysis and means comparison	No significant changes in conjunctival vessel alteration and RVA were found in 13 patients previously selected by high levels of albuminuria, after 12 mo of enalapril treatment	No	Similar frequencies of conjunctival vessel alteration and RVA were seen in patients with serum creatinine ≤1.2 mg/dL or >1.2 mg/dL, in patients with normal or elevated albuminuria, and in patients with GFR <120.0 or ≥120.0 mL/min/ 1.73 m^2

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests and/or uninterpretable results	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Controls arm(s)	Please report any relevant subgroup data
Marsh, 1982[276]	Cross	Visual acuity	No	None	NR	34	0	Varying by parameter	Visual acuity measured by Snellen's test type was 6/6 in 50/68 (74%) eyes and 6/12 or better in 65/68 (96%) eyes. Acuity was 6/24 in 1 eye affected by vitreous hemorrhage and 6/36 in 2 eyes with long-standing aphakia. There was a tendency for reduced acuity to be more common in older than younger patients, acuity of <6/6 occurring in 4/20 patients <30 yr compared to 8/14 patients older than this age. This difference just failed to reach statistical significance (p=.06)	No	No	NR

Table 8. Magnetic Resonance Imaging Results

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Relevant subgroup data
Gold, 2008[11]	R, Obs	The Wechsler Intelligence Scale for Children, the Woodcock Johnson Revised, the Purdue Pegboard Test, the Benton Tactile Perception Test, and Brain Magnetic resonance imaging (MRI)	No	NR	A radiologist and the clinic hematologist reviewed each patient's results, identified areas of cortical damage, and then assigned patients to one of the following 3 categories: overt stroke, silent infarct, or no cerebrovascular accidents (CVA).	65	0	17 had experienced a stroke. 13 had a silent infarct	Patients who had overt stroke or silent infarct displayed deficits on neuropsychological testing	No	No	No
Kwiatkowski, 2009[16]	R, Obs	MRI and angiography	No	NR	Cerebral infarction was defined as an area of abnormally increased signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging	68	0	13	At initial brain MRI, 13 of 65 (neurologically asymptomatic) children had silent infarcts (20%, 95% CI 11.1–31.8%). 34 of the 65 (52%) children had at least 1 followup brain MRI prior to the age of 6 yr. Of 28 with initial normal studies, 5 children, initially imaged at a mean age of 3.0 yr (range 2.4–3.6 yr), developed silent infarcts by followup brain MRI at a mean age of 4.8 yr (range 3.5–5.7 yr), while 23 children had repeat normal studies. Thus, the prevalence of silent infarct at the worst study obtained prior to age 6 yr was 27.7% (95% CI 17.3–40.2%). 7 of 18 children with silent infarcts at either initial (*n*=6) or followup study (*n*=1), had subsequent imaging studies before age 6 yr. 5 children with silent infarcts had persistent stable abnormalities (2 receiving transfusions), 1 had progression of silent infarcts (not receiving transfusions), and 1 developed overt stroke (prior to transfusions)	Yes	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Relevant subgroup data
Steen, 1998[274]	R, Obs	MRI:1.5 Tesla Magnetom SP63, MRA, the Wechsler Intelligence Scale for Children,	No	No	Basilar artery volume: the upper limit of normal is defined as mean adult volume+ 2 SD (≤427mm^3)	47 (and 49 controls)	NR	1 control and 17 patients	Roughly 37% of patients were classified as abnormal on the basis of conventional T1W or T2W MRI. Of the patients with SCD under age 5 yr, 21% were noted to have cranial abnormalities, whereas 44% of the patients between ages 5 and 16 had cranial abnormalities. The most common type of abnormality was single or multiple lacunae, typically located in deep white matter, which were seen in 26% of all patients with SCD	No	Similar-aged children with a wide range of medical conditions, usually including brain tumor	No
Abboud, 2004[25]	P, Obs	2-MHz pulsed Doppler US, model TME TC 2000; Nicolet, Madison, WI	No	No gold standard, 2 tests performed MRA and TCD	Arterial segments were defined to be normal or to be mildly (25%), moderately (50%), or severely (75%) stenosed or occluded	100	0	4 had mild stenosis and 21 had severe stenosis	MRA readings were interpreted as normal in 75 (75%) and as indicative of mild stenosis in 4 (4%) or severe stenosis in 21 (21%). Patients with MRA abnormalities had significantly higher cerebral blood velocities as measured by TCD	No	Healthy subjects	No
Adekile, 2002[29]	P, Obs	MRI with 1.5 Tesla unit	No	NR	NR	30	0	1	Only one patient showed hyperintense signal in the parietal white matter, consistent with small infarcts. The prevalence of silent brain infarcts in these patients is 3.3%	When the MRI was repeated 2 yr later, the infarcts were still visible, but in addition, there were 2 new infarcts	No	No
Bernaudin, 2000[34]	P, Obs	MRI	No	NR	NR	144	0	31	22% of patients (31 of 144) had abnormal MRI. 28 of those had HbSS. The silent stroke rate in this study was 15% (20 of 133), of whom 18 were HbSS. Patients with abnormal MRI results had significantly lower performance on cognitive function testing than patients with normal MRI	No	No	No
Bernaudin, 2001[35]	P, Obs	MRI	No	NR	NR	156	NR	32	Silent strokes were found in 32 patients (mean age at detection: 11.4±4.6) in 27 cases at the 1st MRI evaluation and in 5 cases ischemic lesions appeared during followup. The risk of ischemic lesions was highly increased (p<.00001) in patients with TCD >200 cm/s	No	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Relevant subgroup data
DeBaun, 1995[42]	P, Obs	MRA, Siemens 1.0- or 1.5-T scanners	MRA had a sensitivity and specificity of 100% and 92%, respectively	Neurologic examination, psychometric evaluation, MRI	Presence of a cerebral infarct was determined by an MRI and supported by neurologic and neuropsycho-metric evaluation	24	0	12	All 12 patients with abnormal MRIs had abnormal MRAs, and 11 of 12 patients with normal MRIs had normal MRAs	No	No	No
Gillams, 1998[48]	P, Obs	MRA	No	Clinical followup	Infarction was categorised by anatomical location, i.e., cortical or deep white matter infarcts (DWMI). Small, < 5 mm, focal areas of abnormal signal in the basal ganglia or periventricular white matter were not considered sufficient evidence for infarction. The MRA was evaluated for focal changes in vessel diameter or signal intensity. Changes in signal intensity were further defined as reduced but detectable, focal complete loss followed by reconstitution and complete loss of signal without reconstitution.	22	NC	4	On MR imaging, 4 patients had infarcts in 8 vascular territories (6 anterior and 2 posterior). In 3/4 of anterior vascular territories with infarction, long (≤6 mm) segments of abnormal signal were seen at the internal carotid artery bifurcation with associated reduced distal flow. Short focal areas of abnormal signal were commonly seen where vessels branched, bifurcated, or curved and were not associated with infarcts	No	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Relevant subgroup data
Hoppe, 2003[54]	P, Obs	MRI	No	NR	NR	231	0	71	Of the 231 patients with SCD included in this study, 160 (69%) had normal findings on brain MRI. 71 (31%) patients demonstrated infarctive lesions on MRI; their mean age was 9.3 yr (median, 9.0 yr) at the time of first positive MRI results. Of these, 36 (51%) had MRI evidence of large vessel involvement (with or without small vessel involvement), and 35 (49%) had exclusively small vessel involvement. Clinical history of CVA was documented in 26 (37%) of the 71 patients	No	No	No
Kugler, 1993[59]	P, Obs	MRI	No	NR	NR	16	NR	NA, all group 1 patients had abnormal MRIs at entry	In the 8 group 1 patient with abnormal MRI studies at entry, 7 of 8 patients had hyper-intensities in the subcortical white matter. In 6 of these patients, these hyperintensities were small punctate lesions. These lesions were considered to be consistent with disease of the small, deep penetrating vessels	Mean followup was 3.7 yr. In group 1; 4 patients (50%) demonstrated progressive MRI abnormalities; and 3 patients (38%) became clinically symptomatic. In group 2, findings for all patients remained normal on clinical and radiological examination	Age-matched with normal MRI studies at entry	No
Miller, 2001[70]	P, Obs	MRI	No	None	An area of abnormally increased signal on intermediate and T2-weighted pulse sequences	248	NR	6	5 (8.1%) of 62 patients with silent infarct had strokes compared to 1 (0.5%) of 186 patients without prior silent infarct; incidence per 100 patient-yr of followup was increased 14-fold (1.45 per 100 patient-yr vs. 0.11 per 100 patient-yr, *p*=.006). Of several clinical and laboratory parameters examined, silent infarct was the strongest independent predictor of stroke (hazard ratio=7.2, *p*=.027)	No	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Relevant subgroup data
Moser, 1996[73]	P, Obs	1.5-T MR scanners	No	Clinical history	Specific MR findings of atrophy and infarction/ ischemia	312	0	70	70 patients (22%) had infarction/ischemia and/or atrophy; infarction/ischemia was noted in 39 children (13%) who had no history of a stroke (the "silent" group). The prevalence rates for silent lesions were 17% for SCA and 3% for hemoglobin sickle cell disease	No	No	No
Pegelow, 2002[80]	P, Obs	MRI	No	No gold standard	NR	415	0	88 (21.2%)	88 (21.2%) of 415 children studied had a lesion on their baseline MRI. Clinical strokes, excluding TIAs, were documented in 18 (4.3%), whereas 70 (16.9%) had silent infarcts. Of 266 HbSS children, silent infarcts were found in 58 (21.8%) and strokes in 18 (6.8%) at baseline, rates that are significantly higher than the prevalence of silent infarcts and stroke found in HbSC children, 5.8% and 0%, respectively (*P*<.001 and *P*<.002)	Yes	No	No
Steen, 1998[22]	P, Obs	Quantitative MRI	No	cMRI	Asymmetric loss of white matter volume, encephalomala-cia, or lacunae	30 (and 24 controls)	0	13	In all 30 patients with SCD, qMRI T1 was lower than in 24 age- and race-matched controls, in cortical gray matter (*P*<.0006) and caudate (*P*<.0009), as well as in the ratio of gray-to-white matter T1 (*P*<.008). In the 17 patients who were shown to be normal by cMRI, qMRI T1 was still lower than in controls, in both cortical gray matter (*P*<.02) and caudate (*P*<.004). Histograms of voxel T1 show that the proportion of voxels with T1 values intermediate between gray and white matter (i.e., consistent with encephalomalacia) was 9% higher than controls in patients shown to be normal by cMRI (*P*<.05) and 15% higher than controls in patients shown to be abnormal by cMRI (*P*<.0005)		Healthy subjects of African-American hospital personnel	No
Steen, 1999[84]	P, Obs	Quantitative MRI	No	None	NR	50 (and 52 controls)	0	NA	Brain T1 was significantly lower in patients in every gray matter structure evaluated but in none of the white matter structures. Regression suggests that T1 in caudate, nucleus pulvinares, and cerebral cortex was abnormal by age 4 yr	No	Healthy age-similar subjects	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Relevant subgroup data
Steen, 1999[83]	P, Obs	cMRI, quantitative MRI (qMRI), and MRA	No	NR	Criteria of abnormality used for the T1W images included encephalomala-cia, lacunae, or atrophy	50	0	21	Overall, cMRI abnormalities were seen in 42% (21/50) of the patients with SCD. Lacunae were the most frequently noted abnormality, as they were seen in 76% of patients abnormal by cMRI. Encephalomalacia was seen in 48% of patients abnormal by cMRI. Atrophy was present in 5%. Brain T1 in patients normal by cMRI was significantly lower than controls, in caudate, thalamus, and cortex (p<.007). In patients abnormal by cMRI, T1 reductions in gray matter were larger and more significant. White matter T1 was not significantly increased except in patients abnormal by cMRI	No	Healthy, age-similar subjects	No
Strouse, 2006[85]	P, Obs	Continuous arterial spin-labeling MRI	No	NR	NR	24	0	1	1 child had silent cerebral infarct, SCI, and irregularity at the trifurcation of the left MCA. Mean CBF in the distribution of the right and left anterior cerebral arteries was 108±40 mL/100 g/min and 111±38 mL/100 g/min, and was similar for the middle and posterior cerebral arteries. This study's quantitative results suggest that there may be an inverse correlation between regional CBF and IQ	No	No	No
Zafeiriou, 2004[95]	P, Obs	MRA	No	NR	An infarct was defined as an area of abnormally increased signal intensity on T2-weighted images	21	0	8	The overall prevalence of silent infarcts was 8 of 21 (38%) or 4 of 11 of the children (36%). There was no significant difference between patients with infarcts and those without for sex, history of seizures (p=.66 and p=.53, respectively; Fisher's exact test), mean age (17.4±3.6 vs. 18±3.7), HbF (13.8±12.2 vs. 8.9±5.4). Abnormal TCD was not significantly associated with abnormal MRI (Fisher's exact test, p=.15) or MRA (Fisher's exact test, p=.74)	No	No	No
Armstrong, 1996[116]	Cross	MRI	No	none	NR	194	0	33	CNS abnormalities were identified on MRI in 17.9% of the children (22.2% of children homozygous for HbS), and a clinical history of CVA (N=9, 4.6%) was identified in only children with HbSS	no	No	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)	Relevant subgroup data
Bahia, 2009[126]	Cross	MRI, MRA	No	NR	NR	80	0	Varying by parameter	In the MRI study, 50% of the patients showed intraparenchymatous lesions. Leukoencephalopathy was the most frequent abnormality in 47.5%, encephalomalacia in 16%, lacunar infarction in 12.5%, and atrophy in 12.5%. In the MRA study, 34% of the patients presented abnormalities, 26% with vascular stenosis, and 19% with vascular occlusions. The silent lesions were observed in 45% of the MRI and 24% of the MRA	No	No	No
Gold, 2001[157]	Cross	MRI	No	NR	NR	65	0	NA	27% of patients had experienced a stroke and 13% a silent infarct. The majority (59%) of patients diagnosed with stroke or infarct sustained cortical damage to the frontal lobe	No	No	No
Gribbons, 1998[159]	Cross	Tc-99m HMPAO SPECT, MRI	No	MRI	NR	10	0	9 by SPECT 4 by MRI	9/10 patients had abnormal SPECT finding. 3 of those had MRI findings as well, while the other 6 had normal MRI findings. The tenth patient had normal SPECT but abnormal MRI findings	No	No	No
Helton, 2009[164]	Cross	Arterial spin-labeled perfusion combined with segmentation techniques	No	NR	Authors compared results to ASL findings in normal children	21	0	3	3 patients had silent infarcts on cMRI and tortuosity was identified in 9 patients. Perfusion measurements indicated that patients who were treated with HU (n=18) had a relatively normalized gray matter measure cerebral blood flow (CBF), but altered perfusion in white matter seemed to persist	No	No	No
Jordan, 2010[170]	Cross	MRI of the brain looking for incidental intracranial abnormalities	No	NR	No	953	0	63	6.6% (95% CI: 5.1%– 8.4%) of children (63 of 953 children) had 68 incidental intracranial MRI findings, as confirmed by 2 study neuroradiologists. 5 children had 2 incidental findings each. Chiari I malformations were the most common malformations seen, followed by cavum abnormalities. Cortical dysplasia, gray matter heterotopia, and various types of cysts were the other types of abnormalities seen	No	No	No

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Karasmanis, 2009[174]	Cross	MRI	No	NR	NR	20	0	2	1 overt stroke was noted (5%). 2 patients had evidence of silent infarcts on prior MRIs. In the followup, 1 of these 2 presented the same MRI condition, with no new findings added up, and the 2nd presented a normal MRI		No	No
Kinney, 1999[179]	Cross	MRI	NR	NR	Normal silent infarct present, abnormal silent infarct absent	230	0	42	42 patients (18.3%) had silent infarcts and 188 patients had normal MRI scans. There were no significant differences in the age (p=.856) or sex (p=.496) distribution between those patients with normal MRIs and those patients who had silent infarcts	NR	No	No
Kirk, 2009[180]	Cross	Brain MRI+cortical surface extraction (using a software) to assess cortical thickness	No	NR	Images were compared to healthy controls	28 (+29 controls)	NR	NR	Distinct regions of thinning were found in patients with SCD in both age groups. The number, spatial extent, and significance (P<.001) of these areas of thinning were increased in the older SCD group. Regions of interest (ROIs) were defined on the areas of highly significant thinning in the older group and then mapped onto the younger cohort; a multiparametric linear regression analysis of the ROI data demonstrated significant (P<.001) cortical thinning in SCD subjects, with the largest regions of thinning in the precuneus and the posterior cingulate. The regionally specific differences suggest that cortical thickness may serve as a marker for silent insults in SCD and hence may be a useful tool for identifying patients with SCD at risk for neurological sequelae	No	Age-matched healthy subjects	No

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Kral, 2006[186]	Cross	MRA	NR	NR	Infarction, defined as an area of abnormally increased signal on the fluid-attenuated inversion recovery series and T2-weighted pulse sequences, was classified by size (small<0.5 cm, medium=0.5–1.5 cm, large>1.5 cm) and anatomic location	27	0	5	Infarcts were identified in the basal ganglia (*n*=6) and deep white matter of the frontal lobes (*n*=3). Infarcts also were identified in the centrum semiovale (*n*=5) and deep white matter of the parietal lobes (*n*=1). Vascular stenosis was localized in the A1 segment of the anterior cerebral artery (*n*=5), the M1 segment of the middle cerebral artery (*n*=4), and the supraclinoid internal carotid artery (*n*=8). 8 patients had vascular stenosis on MRA	NR	No	No
Manfre, 1999[196]	Cross	MRI	No	NR	Atrophy was defined on personal assessment by visual inspection of a decrease in brain volume. Infarction and ischemic lesions were considered as areas of abnormally high signal intensity on long TR-weighted images	41	0	6 (thalassemia intermedia) 13 (HbS-thal)	Among the 16 thalassemia intermedia patients, 10 (62.5%) had normal MR findings, and 6 (37.5%) showed brain abnormalities on MR images. Atrophy, which was detected in 31% of these patients, was always classified as mild. Ischemic lesions were generally small (25%) and single (25%); medium and large lesions were present in only 6.5% of these patients. Among the 25 patients with HbS- thal, more than half (13 (52%)) showed brain damage. Compared to the lesions seen in the patients with thalassemia intermedia, the lesions detected in these patients were significantly larger: 24% of ischemic patients had small lesions, 16% had medium lesions, and 12% had very large lesions. Multifocal lesions were almost twice as common in this group (20%) than in the thalassemia intermedia group (12.5%)	No	No	No

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Marouf, 2003[197]	Cross	MRI	No	NR	NR	35	0	7	7 (20.0%) patients, 6 HbSS and 1 HbSβ^0-thal, showed MRI evidence of infarcts on T1- and T2-weighted images, consistent with small (<5 mm) infarcts in the deep white matter. The mean age of the patients with infarcts, 31.8±8.2 yr, was significantly (*P*<.05) higher than that in the unaffected group, 25.1±9.0 yr	No	No	Among the 25 HbSS patients in the study, α-globin genotype was determined in 21, of whom 9 were either heterozygous or homozygous for the α-thal-2 (-3.7 kb) deletion. Of these 9, 2 (22.2%) had infarcts, while of the 12 without α-thal trait, 3 (25.0%) had infarcts, showing no statistical significance (X^2=0.02, *P*>.05)
Melek, 2006[200]	Cross	MRI	No	NR	NR	59 patients (and 28 controls)	0	21	35.6% (21) of the patients showed MRI evidence of infarctions on T1- and T2-weighted images. The infarction size ranged from 6 mm to 42 mm. The mean age of patients with infarctions (25.3±7.3 yr) was significantly (*p*<.02) higher than those of the unaffected group (20.3±7.2 yr). Among the patients with SCD with silent infarction, 95.2% had at least 1 soft sign	No	Healthy subjects	No
Pavlakis, 1988[215]	Cross	1.5-Tesla magnet MRI	No	Clinical exam	NC	55	0	6	18 of the 73 had a history of stroke. 16 of the 18 stroke patients demonstrated focal MRI abnormalities consistent with arterial border zone infarctions. 55 of the 73 patients had no history of stroke. 6 of the 55 (11%) had focal MRI abnormalities suggesting previous subclinical stroke. 5 of these lesions were in border-zone regions. The distinguishing feature in 21 of the 22 patients with MRI abnormalities was the predilection for lesions in the high cortical convexity, in the general regions of arterial border zones between the major cerebral arteries and adjacent deep white matter	No	No	No

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Riebel, 2003[224]	Cross	MRI, MRA	No	NR	NR	15	0	7	Lesions due to occlusive vasculopathy were found in 7 individuals (15% of all studied patients but 47% of those with abnormal Doppler findings)	No	No	No
Schatz, 2002[228]	Cross	MRI	No	NR	Cerebral lesions were defined as a hyperintensity of 3 mm or greater on the T2-weighted MRI examinations	27	0	18	18 of 27 patients had silent infarcts. The correlation between lesion volume and ventricular volume (i.e., ventricle-to-head ratio) was only of medium size (r=.36), suggesting some independence between the 2 measures of lesion burden	No	No	For lesion volume, the small- and large-volume groups were of comparable age (12.0 and 12.8 yr, respectively) and had gender distributions (56% male and 67% male, respectively) similar to the no infarct group
Schatz, 2006[229]	Cross	MRI	No	NR	Cerebral vascular lesions were defined as hyper-intense regions of tissue 3 mm in diameter or greater evident on T2-weighted MRI exams	28 patients and 16 controls	0	8 silent infarcts, 5 overt stroke	28 children with SCD and 16 demographic controls completed MRI and neuropsychological testing. Corpus callosum (CC) size was smaller for children with silent infarcts (*n*=8) or overt stroke (*n*=8) than for those without visible infarcts (*n*=12) or control participants. Lesion volume was a robust predictor of IQ and other cognitive scores; total CC size did not typically add explanatory power for these measures. The size of the rostral body of the CC, however, independently predicted measures of distractibility, speeded production, and working memory. Posterior CC size was also decreased among many of the children with SCD, even in the absence of visible infarcts in this region	No	Demographically matched group	No

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Silva, 2009[236]	Cross	MRI, MRA	The diagnosis of middle cerebral artery or internal carotid artery intracranial stenosis with sensitivity of 100% and specificity of 73%	NR	Abnormal MRI (lacunar infarction, encephalomala-cia, leukoence-phalopathy, or atrophy)	50	0	MRI 30 MRA 36	The overall frequency of lacunar infarction, encephalomalacia, leukoencephalopathy, or atrophy was 60%. Leukoencephalopathy was the most common finding (48%). Lacunes were identified in 4% of the patients, encephalomalacia in 6%, and atrophy in 28%. 8% had previous stroke. MRA was abnormal in 72% of patients; intracranial stenoses were observed in 16% and arterial tortuosity in 64% of the patients. Patients with abnormal MRAs had significantly lower levels of HbF, Hb, and Hct than patients with normal MRAs (*p*=.03, .02, and .05, respectively)	NR	No	No
Steen, 1996[240]	Cross	1.5 T-Magnetom SP63 scanner (Siemens medical systems, Iswelin, NJ), MRA	Sensitivity of qMRI in patients with SCD was 89.5% CI 75.1–100 (17/19). Specificity was 100% CI 87–100. Overall accuracy of qMRI in thalamus 95% CI 86–100 (38/40), whereas the overall accuracy on the frontal matter was 80 CI 67–92 (31/39)	Clinical outcome and cMRI	An empirically determined signal intensity difference	19	0	12 from MRI, 5 from MRA	T1 was significantly longer in patients with SCD without stroke (*n*=13) than in control subjects (*n*=21) in the thalamus and frontal white matter. In addition, T1 values were significantly longer in patients with SCD with stroke than in patients without stroke in the genu and frontal white matter. Abnormality of the thalamus was identified by qMRI in a substantial fraction of patients read as normal by both cMRI and MRA	No	African-American hospital personnel	No

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Steen, 2003[241]	Cross	MRI, MRA	No	NR	NR	146	0	67	Of the 146 patients included in this study, 46% (67/ 146) had some form of brain injury visible by MRI. The prevalence of vasculopathy apparent by MRA was even higher, at 64% (93/146). Patients with brain injury seen by MRI were significantly more likely to have vasculopathy apparent by MRA (p<.0001). A total of only 41 patients were normal by both MRI and MRA, whereas 55 patients were abnormal by both modalities	No	No	94 patients who were not receiving treatment at the time of the imaging evaluation, 39% (37/94) were normal by both MRI and MRA; whereas, 27% (25/94) were normal by MRI but had mild vasculopathy by MRA, and 32% (30/94) were abnormal by both MRI and MRA. 52 patients who were receiving some form of treatment, only 8% (4/52) were normal by both MRI and MRA; whereas, 17% (9/52) were normal by MRI but had mild vasculopathy by MRA, and 67% (35/52) were abnormal by both MRI and MRA
Steen, 2003[242]	Cross	MRI, MRA	No	NR	NR	185	0	82	The prevalence of infarction, ischemia, or atrophy was 44% (82 of 185), and the prevalence of vasculopathy was 55% (102 of 185)	No	No	No
Steen, 2003[243]	Cross	MRI	No	NR	NR	49	0	21	Of the 49 patients with HbSS who were evaluated, 21 (43%) had abnormal MRI findings. The rate of clinically silent MRI abnormalities for these patients was somewhat higher than has been reported in some early studies, but was consistent with the incidence of abnormalities in other imaging studies. Lacunae were present in 52% of patients with any MRI abnormality and 22% of patients overall	No	No	No

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Steen, 2003[244]	Cross	Quantitative MRI to measure brain T1	No	NR	NR	141	0	NA	The caudate T1 in 40 out of 141 patients fell below the 95% CI, so we conclude that patients with SCD are more likely to have abnormal caudate T1 than are healthy children (p<.00011; binomial test). Cortical T1 in only 12 out of 140 patients fell below the 95% CI, which is still significantly more than expected (p<.001, binomial test)	No	Healthy subjects	No
Steen, 2004[245]	Cross	Quantitative MRI	No	NR	NR	46 patients (and 267 controls, 55 of them were under the age of 4 yr)	0	NA	Most white matter and gray matter tissues in infant patients (<2 yr old), had T1 values significantly higher than normal. For example, 15.0% of patient caudate T1 values were above the upper bound of the 95% CI for controls, but only 2.5% of normal values are expected to be this high (p=.0003)	No	Healthy subjects	No
Steen, 2005[246]	Cross	MRI	No	NR	NR	87 (and 43 controls)	0	NA	Total brain volume was significantly less (P<.04) in patients than in healthy control subjects. There was 4% less gray matter volume in patients (P<.01), with a greater deficit in central gray matter (basal ganglia) volume (6%, P<.01) than in cortical gray matter volume (3%, P<.03). No significant difference was noted in either white matter volume or ventricular volume between patients with SCD and control subjects. In healthy control subjects, gray matter volume decreased significantly with age (P<.005), probably due to myelination of white matter tracts. In patients with SCD, gray matter volume did not change with age	No	Healthy subjects	No
Strouse, 2009[247]	Cross	MRI	No	NR	FLAIR hyper-intensities ≥3 mm in diameter seen in at least 2 imaging planes without corresponding symptoms or signs of stroke	76	0	27	27 participants (35.5%, 1 with HbSβ^0) had silent cerebral infarcts (age 8.9±2.4 yr, 59% male) and 49 (65.2%) had normal brain MRIs (age 8.7±2.1, 53% male)	No	No	No

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Thompson, 1999[249]	Cross	MRI	No	NR	NR	244	0	52	MRIs were obtained on 244 patients. 192 were normal; 12 had apparent cerebral infarction; 33 had silent cerebral infarction; and 7 had atrophy. There were no significant differences in the rate of behavior problems as a function of MRI status (normal, 28%; clinical, 25%; silent, 27%)	No	No	No
Tzika, 1993[251]	Cross	Dynamic contrast material-enhanced T2*-weighted MRI	No	NR	NR	33	NR	NA	Group A demonstrated symmetric sequential region patterns of loss of signal intensity within 10 s of injection. Group B exhibited signal loss asymmetries that corresponded to cerebrovascular lesions on cMRI	No	No	No
Van Den Tweel, 2009[254]	Cross	3.0-Tesla MRI	no	Clinical examination	NR	36	0	14	3 patients had subtle pyramidal deficits by neurological examination and 1 control subject demonstrated mild coordination abnormalities by neurological examination. In 16 patients (67%), abnormalities were seen on T2-weighted MRI, MRA, or both. 7 patients (29%) had infarcts in the deep white matter and a normal MRA; 4 patients (17%) had stenosis (<25% in 3; 25% to 50% in 1) of 1 or more cerebral arteries and a normal MRI, and 5 (21%) had both infarcts and stenosis (<25% in 3; 25% to 50% in 2). No infarcts were detected in the control group. 2 children in the control group, including the 1 with mild coordination abnormalities, had a mild stenosis (<25%) of 1 or more cerebral arteries	No	Age- and ethnicity-matched healthy subjects	No
Vichinsky, 2010[259]	Cross	Volumetric measurements	No	NR	Lacunae were defined as regions of at least 5 mm in diameter that were hyperintense on the T2-weighted images with corresponding hypointensity on T1-weighted images	160 (+52 controls)	NA	NR	A cortical infarct was detected in 1 patient and 1 control. Lacunae were seen in 13% of patients and 2% of controls (difference, 11%; 95% CI, 4.1% to 18.4%; *p*=.05) and were mainly in the frontal lobe, parietal lobe, and basal ganglia. Atrophy was seen in 23% of patients and 16% of controls (difference, 7%; 95% CI, -5.4% to 20.4%; *p*=.40), and white matter lesions occurred in 15% of patients and 7% of controls (difference, 8%; 95% CI, -1.4% to 17.6%; *p*=.21)	No	Healthy subjects	No

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Wang, 1998[264]	Cross	MRI, MRA	No	NR	Criteria of abnormality used for the T1-weighted images included asymmetric loss of white matter volume, encephalomala-cia, and lacunae. An infarct was defined as an area of abnormally increased signal intensity on the T2-weighted images	39	0	4	Overall, 4 (11%) of the 36 asymptomatic patients examined (95% confidence interval 3% to 26%) had abnormal findings on MRI (1 with leukomalacia, 1 with severe stenosis of the supraclinoid portion of the internal carotid artery bilaterally, 2 with moderate stenosis of the posterior cerebral artery). In addition, basilar artery ectasia (dilatation) and tortuosity (increased curvature) were frequently noted. The 3 patients who had a history of seizures all had lesions observed on MRI. No correlation was seen between CNS lesions and the patients' clinical histories of hospital admissions for treatment of an vaso-occlusive event	No	No	No
Wang, 2008[265]	Cross	MRI	NR	NR	Description of MRI abnormalities	23	0	3	(1) A 14-mo-old male with a small right frontal infarct; (2) a 14-mo-old male with multiple small bilateral frontal infarcts; and (3) a 16-mo-old male with a small right frontal infarct. MRI lesions were associated with low HbF levels (p=.03) and high right-sided maximum TCD velocities (p=.05)	NR	No	No

Table 9. Transcranial Doppler Results

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)
Armstrong-Wells, 2009[3]	R, Obs	TCD	No	NR	Abnormal TCD result was defined as a velocity >200 cm/s in either the internal carotid or middle cerebral artery	157	0	11	The average annual rate of TCD screening in 157 children with SCD was 1.8 per 100 person-yr pre-1998, 5.0 from Jan. 1, 1998, to Dec. 31, 1999, and 11.4 after 1999. The only independent predictor of TCD screening was proximity to the vascular laboratory. During the entire study period, 53/157 (33.8%) of all children received a 1st TCD at some time. The annualized stroke rate pre-TCD was 0.44 per 100 person-yr, compared to 0.19 post-TCD. During the mean total followup time of 8.5 yr (SD 4.04 yr), 5 subjects had strokes	The 157 subjects were followed as children (censored at 20 yr) for a mean of 5.5 yr (SD 3.5 yr; median 4.6 yr; range 7 d to 13.9 yr). The average annual incidence rate of 1st TCD screening in children (<20 yr of age) with SCD increased significantly over the study period: before 1998, 1.8 per 100 person-yr (95% CI, 0.87–3.8); Jan. 1, 1998, to Dec. 31, 1999, 5.0 (2.4–10.5); and after 1999, 11.4 (8.3–15.6; figure). The annual rate of TCD screening was highest in 2002, at 40.0 per 100 person-yr (95% CI, 25.0–61.0), and remained high in the final year of study at 24.5 (10.2–58.8). Although 50% (78/156) of the subjects had missed at least 1 regular office appointment, only 9 of the 59 children referred for TCD screening (15%) had ever missed a TCD appointment	No
Bernaudin, 2008[5]	R, Obs	TCD	No	NR	Time-averaged mean of maximum velocities >2 m/s (middle, internal carotid, or anterior cerebral arteries) were considered as abnormal	373	0	62	Velocities ≥2 m/s were found in 62 of 373 stroke-free patients (16.6%). Prevalence of abnormally high velocities was significantly decreased by the presence of α-thalassemia, high Hb, and Hct; however, it was significantly increased by G6PD deficiency, high WBC counts, high reticulocyte counts, high mean corpuscular volume, and high LDH levels. Of the 9 variables introduced in the multivariate logistic regression model, only G6PD deficiency (OR=3.36, 95% CI 1.10–10.33; *p*=.034); absence of α-thalassemia (OR=6.45, 95% CI 2.21–18.87; *p*=.001); Hb (OR/g/dL=0.63, 95% CI 0.41–0.97; *p*=.038); and LDH levels (OR/IU/L=1.001, 95% CI 1.000–1.002; *p*=.047) remained as independent predictors of high velocities	No	No

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Enninful-Eghan, 2010[7]	R, Obs	TCD	No	NR	Conditional TCD: 170–199 cm/s; abnormal: TCD velocity ≥220 cm/s	1005	0	50	The incidence of overt stroke in the pre-TCD period was 0.67 per 100 patient-yr, compared to 0.06 per 100 patient-yr in the post-TCD period (*P*<.0001). The rate of transfusion therapy for stroke prevention increased from 0.67 per 100 patient-yr to 1.12 per 100 patient-yr since instituting our program (*p*=.008)	NR	Comparison of results before and after TCD screening institution
Kwiatkowski, 2003[15]	R, Obs	TCD	No	None	Normal (<170 cm/s), conditional (from 170 to 199 cm/s) or abnormal (=/> to 200 cm/s). The abnormal and conditional categories were combined into a single category denoted as a 'positive' result (t-ICA/MCA velocity greater than or equal to 170 cm/s)	249	0%	54	The univariate analysis revealed that a younger age, lower Hb level, lower HbF level and higher reticulocyte count were associated with a positive TCD result, while WBC count and platelet count were not. In the multivariate analysis, only Hb and age remained significantly associated with a positive TCD result. The presence of a sibling with a positive TCD result was associated with a substantially increased risk of a positive TCD result in other siblings with SCD	No	No
McCarville, 2008[18]	R, Obs	TCD	No	NR	Blood flow velocity >170 cm/s	Period 1: 0, period 2: 52/yr, period 3: 95/yr	NR	NR	During period 2, an average of 52 patients/yr was screened. In period 3, an average of 95 patients/yr was screened representing 99% of the at-risk population. 18 strokes occurred in period 1, 22 in period 2, and 3 in period 3. The 1st stroke incidence was significantly lower in period 3 compared to periods 1 and 2 (*p*=.047). Furthermore, of the 25 patients in periods 2 and 3 who had stroke, only 6 had received TCD screening (4 in period 2, 2 in period 3). These 6 either declined prophylactic transfusion therapy (*n*=2), had coexisting stroke risk factors (*n*=2), or did not return for appropriate TCD followup (*n*=2). It was concluded that TCD screening successfully decreased the incidence of 1st stroke	See reported results	Comparison of results before and after TCD screening institution
Parmar, 2009[20]	R, Obs	TCD	No	NR	NR	342	25	27	Of the 342 children screened, 40 were found to have high conditional, 27 abnormal and 25 had inadequate TCDs	No	No
Voetsch, 2010[23]	R, Obs	TCD	No	NR	Increased stroke risk was defined sonologically as mean middle cerebral artery velocity (MCAv) ≥200 m/s	79	NR	7	The average MCAv on 1st study was 134.1±27 cm/s (reference for unaffected children: 80±15 cm/s). 4 children had MCAv ≥200 cm/s on 1st TCD, 2 of which improved with transfusions. Overall, there was a nonsignificant increase in MCAv to 153.2±39.9 cm/s (*p*=.22)	Yes, 3 children (4%) with noncritical values initially, progressed to MCAv ≥200 cm/s	No

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Wang, 2000[24]	R, Obs	2-MHz pulsed Doppler US, model EME TC2000 (Nicolet, Madison, WI, USA)	No	MRI	Abnormal ≥200 cm/s; conditional ≥170 cm/s; normal <170	78	0	16	Of 61 patients who had a normal MRI examination, 11 (18%) had either conditional (5 patients) or abnormal (6 patients) TCD results. Among 17 patients in whom silent infarction was seen on MRI, only 5 (29%) had a conditional (1 patient) or abnormal (4 patients) TCD velocity. Thus, discordant results were seen in 23 patients: 12 in which the TCD result was normal and the MRI abnormal; 11 in which the TCD velocity was elevated and the MRI normal. Agreement between the 2 tests occurred in 55 patients	No	No
Adams, 1992[26]	P, Obs	TCD	No	NR	Mean velocity in the MCA ≥170 cm/s was considered positive	190	0	23	7 patients had cerebral infarction during the observational period. High velocity of cerebral blood flow was strongly associated with stroke. The highest velocities in the patients who were positive on US ranged from 172 to 280 cm/s (201±31, mean±SD), as compared to a mean of 129±22 cm/s in the negative group (p=.0001). 6 of the 7 strokes occurred among the 23 patients with abnormal US results (P<.00001 by Fisher's exact test). In this group, the relative risk of stroke was 44 (95% CI, 5.5 to 346)	No	No
Adams, 1997[27]	P, Obs	TCD	No	NR	Maximum velocity (Vmax) >200 cm/s was considered abnormal	315	0	NA	The mean MCA/ICA velocity at entry was 133±29 cm/s and the mean of the highest velocities recorded from any examination was 141±35 cm/s. 10 of the 25 patients (40%) with Vmax of 200 cm/s or greater had stroke compared to 7 of the 290 (2%) with Vmax of <200 cm/s (p<.0001). 12 of the 55 (22%) with Vmax of at least 170 cm/s vs. 5 of the 260 (2%) with Vmax of <170 cm/s had stroke (P<.0001). 5 of the 17 stroke cases had TCD velocities of <170 cm/s before stroke	17 developed stroke. 1 patient died of stroke and 6 died of other causes	No

Study label	Design	Specific test used	Accuracy data for the test	Gold standard test	How did the authors define a positive result?	*N* of patients who received this test	% incomplete tests	*N* of patients who had a positive test result	Reported test results for the patients with SCD	Long-term followup results	Control arm(s)
Adams, 2004[28]	P, Obs	2-MHz pulsed Doppler	No	History and exam plus MRI or CT or autopsy	Normal (all recordings lower than 170 cm/s); conditional (at least 170 but <200 cm/s); abnormal (TAMMvel of at least 200 cm/s in either the ICA or MCA); or inadequate	2324	NC/NR	Baseline: conditional, 409 (17.6%); abnormal, 217 (9.3%); inadequate, 140 (6%).	Risk of stroke with abnormal TCD is much higher than with normal (*P*<.001), conditional (*P*<.001), or inadequate TCD (*p*=.002) examination results. Risk with conditional but not inadequate TCD is higher than with normal TCD (*P*<.001), regardless of whether the baseline or highest TCD is used. If the baseline TCD is used, 11 (19%) of 58 stroke cases had a normal TCD, 17 (29%) had conditional, 5 (9%) had inadequate TCD, and 25 (43%) had an abnormal TCD. Substantial differences in the probability of conversion to abnormal TCD were observed, with younger children and those with higher velocity more likely to have an abnormal TCD with rescreening	There were 64 children who had stroke: 10 (16%) with intracranial hemorrhage and 54 (84%) with ischemic infarction. Eighteen of the 64 strokes were from the randomized trial (16 with cerebral infarction and 2 with intracranial hemorrhage). One of the hemorrhages occurred before randomization, and this case does not contribute to further analyses (which refer to 9 hemorrhages). The other hemorrhage in the randomized group was a subarachnoid hemorrhage. Forty-six others who were TCD-screened but not randomized had stroke.	No
Bernaudin, 2000[34]	P, Obs	TCD	No	NR	TCD was considered abnormal when mean Vmax was >200 cm/s or the MCA was not seen in the presence of an adequate temporal window	143	2	12	12 patients had abnormal TCD, all of whom were HbSS. The incidence of abnormal TCD in HbSS patients in this study was 9.6% (α2 of 125). TCD was possibly abnormal (mean Vmax between 170 and 200 cm/s) in 13 of 143 patients (9%). Patients with abnormal TCD had a lower performance than patients with normal TCD. However, no significant difference was observed after exclusion of stroke patients	No	No
Bernaudin, 2001[35]	P, Obs	TCD	No	NR	Abnormal high velocities were defined as mean maximum velocities >200 cm/s	244	NR	23	Velocities evolution according to aging: the analysis of 577 TCD performed in the patients without proved vasculopathy and not treated with HU, not transfused and not transplanted showed that, whereas in HbSC patients median and mean velocities remained relatively constant during aging and always <110 cm/s, in HbSS and HbSβ^0 patients, median and mean velocities were >120 cm/s between the 3rd and 12th yr of life in both sides reaching a peak during the 7th and 8th yr of life. Abnormal high velocities were detected in 23 patients (7 with a stroke history). In 11 cases, abnormal TCD was detected at the 1st evaluation, whereas in the 11 other cases, TCD had been found normal 1 or several times before detected abnormal. Range age of abnormal detection was 1.5–12.5 yr. The prevalence of TCD >200 cm/s was significantly related to phenotype (all HbSS: 11.3%) and the absence of α-deletion. Absence of flow in spite of available window was detected in 5 patients (all had a stroke history and thrombosis)	No	No

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Brambilla, 2007[37]	P, Obs	TCD	No	NR	Abnormal velocities ≥ 200 cm/sec conditional velocities ≥170–199 cm/sec	812	0	232 abnormal velocities 282 conditional velocities	The intrasubject differences between TCD velocities at the 1st 2 examinations failed to fit a normal distribution (*P*≤.01) mainly because of 7 subjects, all from the STOP, who had large differences between the velocities at their first 2 interpretable examinations (range of absolute differences: 69–112 cm/s). Excluding these subjects improved the fit to a normal distribution (*p*=.073). The average of the velocities at the 2 examinations was normal in 242 (29.8%) subjects, conditional in 350 (43.1%), and abnormal in 220 (27.1%)	No	No
Cheung, 2001[38]	P, Obs	2-MHz pulsed Nicolet TCD, model EME TC2000, Madison, WI	No	No gold standard, comparative study	Normal (<170 cm/s time-averaged mean velocity (TAMV); conditional (≥170 cm/s and <200 cm/s); high or abnormal (>200 cm/s), and unmeasurable	18	0	Varying by parameter	High MCA velocity was found in 4 patients with SCD. The same 4 patients also showed significantly abnormal conjunctival blood flow velocities. 3 patients with SCD had conditional MCA velocities; 2 of the 3 showed abnormal conjunctival velocities, while the remaining 1 showed normal conjunctival velocity. 1 patient with SCD who had unmeasurable MCA velocity showed abnormal conjunctival velocity. Of the remaining 10 patients with SCD who had normal MCA velocities, 2 showed and 8 showed normal steady-state SCD conjunctival velocities. The MCA velocities correlated significantly with the bulbar conjunctival velocities in this study (*p*=.008, Fisher exact test). Conjunctival velocity demonstrated a positive predictive value of 75% and a negative predictive value of 80% for abnormal MCA velocity	Yes (None of the patients with high or conditional MCA velocities have experienced a stroke in the 3 yr following the study)	No
DeBaun, 1995[42]	P, Obs	2-MHz sector transducers with color Doppler capabilities (S219) on an Acuson 128 U, MRA	At a maximum velocity cutoff of 180 cm/s, the sensitivity and specificity of TCD were 20% and 67%, respectively. No maximum velocity on TCD produced both sensitivity and specificity >50%	Neurologic examination, psychometric evaluation, MRI	4 velocity cutoffs (60, 100, 140 and 180 cm/s) are reported	24	0	12 abnormal from MRI 13 abnormal from MRA	No threshold provided a combined sensitivity and specificity of >50%. The highest sensitivity was 70% with a corresponding specificity of 0% at cutoff of 60 cm/s	No	No

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Hankins, 2008[52]	P, Obs	TCD	NR	NR	Normal TAMV <170 cm/s); low conditional (TAMV 170–184 cm/s); high conditional (TAMV 185–199 cm/s); abnormal (TAMV ≥200 cm/s)	274	0	54 patients (20%) had conditional TAMV either on initial screening or a subsequent examination	At first examination, 14 (5.1%) patients had abnormal, 29 (10.6%) had conditional, and 231 (84.3%) had normal TCD velocities.	Among patients with normal TAMV values on first examination, followup testing was performed in 153 (66%) during the analyzed time interval; 25 (16%) converted to a conditional velocity on a subsequent examination and 4 (2.6%) converted directly from a normal to an abnormal velocity. The cumulative incidence of conversion from a normal to a conditional TCD velocity was 18% (95% CI: 10–26%) within 18 mo from the first examination	No
Hogan, 2006[53]	P, Obs	TCD, Bayley Infant Neuro-developmental Screener (BINS)	No	NR	NR	14 SCA infants and 14 controls	0	NC	At each age, SCA infants obtained BINS scores indicative of greater risk of neurodevelopmental delay compared with controls. The number of moderate–high BINS risk scores increased significantly between 3 and 9 mo. At 9 mo BINS raw scores correlated negatively with TCD velocity and positively with haemoglobin. TCD at 3 mo MCA velocity ranged from 50 to 112 cm/s (SCA: n=9, median 70; controls: n=6, median 58), and basilar artery velocity ranged from 29 to 80 cm/s (SCA: median 48.5; controls: median 37.5). By 9 mo, this range increased to 50–160 cm/s for the MCA (SCA: n=13, median 89; controls: n=6, median 75), and to 31–91 cm/s for the basilar (SCA: median 50; controls: median 40). Similar ranges to those obtained at 3 mo were found at 12 mo. At 12 mo, the MCA range was 51–120 cm/s (SCA: n=10, median 97) and the basilar range was 31– 91 cm/s (SCA: median 46.5)	No	Age- and ethnic-similar infants
Jones, 2001[55]	P, Obs	Transcranial color Doppler imaging (TCDI)	No	TCD	Abnormal (1 or both sides=200 cm/s); normal (<170 cm/s); conditional (>170, but <199 cm/s)	29	0	NA	TCDI velocities were generally lower than TCD velocities for the same segment, but the difference was reduced (from 15 to 10% for the MCA) by modifications to the TCDI protocol	No	No
Jones, 2005[56]	P, Obs	TCD	No	NR	NR	1937	0	NA	Peak systolic velocity (PSV) and end diastolic velocity (EDV) were highly correlated to the TAMM velocity (r=0.94). The multivariate model for prediction indicated that TAMM velocity was a better predictor than EDV, and PSV and TAMM were approximately equivalent. 1358 were normal, 373 were conditional, 206 were abnormal. The mean PSV of normal studies was 193 cm/s, from conditional studies it was 246 cm/s, and from abnormal studies it was 298 cm/s	No	No

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Kirkham, 2001[57]	P, Obs	TCD	No	NR	NR (used cutoff from previous sources)	95	0	NA	19 patients had CNS events (6 ischemic and 1 hemorrhagic stroke, 8 TIAs, and 4 seizures). Mean overnight oxygen saturation ((SaO_2 hazard ratio 0·82 per 1% in-crease (95% CI 0·71–0·93); *p*=.003) and higher internal-carotid or middle-cerebral artery velocity (1·02 for every increase of 1 cm/s (1·004–1·03); *p*=·009) were independently associated with time to CNS event. After accounting for mean SaO_2, artery velocity, and hemoglobinopathy, high Hb concentration was also associated with an in-creased risk of CNS event (1·7/g/dL, (1·18–2·43); *p*=.004). Dips suggestive of obstructive sleep apnea did not predict CNS events, and adenotonsillectomy seemed to have no effect, although the CI were wide and clinically important effects cannot be excluded	Yes	No
Kral, 2004[58]	P, Obs	TCD	No	NR	Normal: velocity mean (Vmean) <170 cm/s; conditional: Vmean between 170 and 200; abnormal: Vmean >200 cm/s	62	0	20 (17 were conditional)	The highest time-averaged TCD Vmean ranged from 92 to 276 cm/s (M=178.00, SD=41.18). Problem-solving flexibility and modulation of emotional responses in children with abnormal TCD values were not significantly different from children in the conditional group	No	No
Makani, 2009[64]	P, Obs	TCD	NR	NR	Cerebral blood flow velocity(CBFv) was classified as low (<50 cm/s), normal (50–149 cm/s), or high (≥150 cm/s)	105	0	7 patients had low, 18 high CBFv. 3 patients had conditional CBFv (170–199 cm/s)	7 (7%) patients with SCA had low, 80 (76%) normal and 18 (17%) high CBFv. Only 3 (3%) patients had conditional CBFv (170–199 cm/s) and none had abnormally high CBFv (>200 cm/s)	For the 95 children with available data none had suffered neurological complications but 11 (12%) had died. There was no significant difference in mortality between those with normal or low CBFv, compared to those with high CBFv (20 vs. 9%; *p*=.38)	No

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Malouf, 2001[65]	P, Obs	Duplex TCD-Elegra unit (Siemens, Issaquah, Wash) and 2.5-MHz pulsed Doppler probe	No	MRI/MRA	Abnormal: ≥200 cm/s; conditional: ≥170 cm/s; normal: <170; inadequate	125 and 8 controls	0%	10 (and 8 controls)	10 (8.0%) were classified as abnormal cases. 5 patients had abnormal findings on only 1 side, and 5 had abnormal findings on both sides. 16 (12.8%) patients were classified as having conditional studies; 91 (72.8%), normal studies; and 8 (6.4%), inadequate studies. At followup, 1 (0.8%) patient with a high normal velocity (167 cm/s) had a stroke 3 1⁄2 mo after his initial study; results of the repeat study performed at the time of the stroke revealed a velocity of 171 cm/s. No patients with conditional velocities had a stroke. 1 patient with abnormal velocities had a stroke between the time of TCD US and the initiation of transfusion therapy. The status of 2 patients with conditional velocities had progressed such that they had abnormal velocities at followup. 1 patient with 2 inadequate studies had a stroke 12 mo after his last TCD US study	No	Yes
McCarville, 2004[68]	P, Obs	TCD	No	This is a comparison study. None of the tests was labeled as the gold standard	Normal (TAMx<170 cm/s); conditional (TAMx ≥170 cm/s but <200 cm/s); or abnormal (TAMx ≥200 cm/s)	53	NR	Varying by parameter	TCD examinations placed 41 patients in the normal risk category, 12 in the conditional category, and 2 in the abnormal category. By the same (unadjusted) criteria, TCDI examinations placed 52 patients in the normal, 2 in the conditional, and 1 in the abnormal category (p=.01)	No	No
Neish, 2002[74]	P, Obs	Imaging and nonimaging technique TCD	No	This is a comparability study	Examination results were interpreted as normal if all Vmean values were <170 cm/s and if no Vmax was >170 cm/s in any artery	66	0	NC	The time-averaged maximum mean velocity measurements obtained with nonimaging and imaging techniques varied substantially for the bifurcation of the distal internal carotid artery, the posterior cerebral artery, and the basilar artery. Substantial differences were found in RIs for every vessel. Examination time was shorter with the nonimaging technique. Vmean measurements in the middle cerebral artery, distal internal carotid artery, and anterior cerebral artery did not vary substantially between nonimaging and imaging TCD US. RI data did not yield comparable measurements	No	No

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Pawlak, 2009[79]	P, Obs	TCD	No	NR	NR	56	0	NR	Reference ranges in centimeters per second for mean angle-corrected VMCA (velocity in the MCA) on the left and right sides were 62–198 and 69–153; those for velocity in the terminal portion in the internal carotid artery (VtICA) were 30–196 and 36–175; and those for velocity in the internal carotid artery (VICA) were 18–116 and 15–95, respectively. Reference ranges for mean angle-corrected VMCA /VICA ratio on the left and right sides were 1.2– 4.0 and 0.4–3.4 and those for VtICA /VICA ratio were 0.5–2.9 and 0.5–2.7, respectively. VMCA, VtICA, and VtICA /VICA ratio were not age dependent, contrary to VICA and VMCA /VICA ratio, after controlling for Hct and Hb	No	No
Silva, 2011[82]	P, Obs	TCD	NR	NR	CBFv <170 cm/s low risk, 170–184 low conditional risk, 185–199 high conditional risk, and >200, high risk	249	0	186 low risk; 19 low conditional; 7 high conditional; and 8 as high risk	The probability of ischemic stroke at 10 yr was 8.3% (standard error of the mean 2.3%); of stroke or high-risk TCD 15.6% (3.5%). Children with stroke or altered TCD (conditional and high risk) were compared to children with normal examinations. They were younger (p=.03), with lower Hb (p=.003), higher leukocytosis (p=.015), and higher reticulocytosis (P<.001)	Out of the 262 children studied, 13 (5%) suffered from ischemic stroke before starting the study. 1 (0.38%) had a hemorrhagic stroke with a normal examination of 2 mo before the event. 1 child had a TIA (0.38%) and presented an abnormal TCD and then a high conditional measurement when confirmation was carried out	No
Telfer, 2007[92]	P, Obs	TCD	NR	NR	High risk, conditional, standard risk, inadequate (did not mention specific cutoffs)	124	0	7 high risk, 11 conditional, 101 standard risk, 5 inadequate	The estimated risk of stroke was 0.7% (0.1–5.0%) at 5 yr; 2.7% (0.9–8.3%) at 10 yr; 4.3% (1.5–11.4%) at 15 yr; and 12.8% (4.8–31.3%) at 20 yr	NR	No
Verlhac, 1995[93]	P, Obs	Standard duplex (Ultramark 5, Advanced Technology Laboratories)	No	Either MRI, MRA, or conventional angiography	Velocity >1.70 m/s or when no flow could be recorded despite demonstration of an adequate temporal window	58 (and 16 controls)	NC	9	8/9 patients with abnormal TCD findings were found to have abnormal findings in MRI, MRA, or conventional angiography. The last 1 was found to have normal MRI with low Hct. Additionally, 2 patients with normal TCD were found to have abnormal MRI findings	No	Non-SCD subjects
Zafeiriou, 2004[95]	P, Obs	TCD	No	NR	The cutoff for the lower limit of normal for MCA mean velocity was defined as 50 cm/s	17	0	9	9 had abnormal TCD findings characterized by lowest to highest MCA ratio <0.5 (unilateral, n=3; bilateral, n=4) and/or asymmetry between MCA velocities >15% (n=4) and/or unilateral (n=3) mean MCA velocities <50 cm/s. Abnormal TCD was not significantly associated with abnormal MRI (Fisher's exact test, p=.15) or MRA (Fisher's exact test, p=.74)	No	No

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Ausava-rungnirun, 2006[123]	Cross	TCD, TCDI	No	NR	NR	80	0	NA	For all intracranial arteries, there was no significant side-to-side difference for any dynamic vascular analysis parameter. Mean flow velocity, dynamic flow index (DFI), and (dynamic pressure index (DPI) were highest at the age of 6 to 9 yr, and declined with age, thereafter. In contrast, The DCI was the lowest at the age of 6 to 9 yr, and tended to increase thereafter. As compared to dynamic vascular analysis results from a healthy cohort of similar aged athletes, the 14–22-yr-olds with SCD, but no clinical stroke or TIA, showed higher DFI and DPI, with lower DCI, for the majority of the intracranial arteries. Most of the intracranial arteries in these patients with SCD had higher lnSA (natural log of systolic acceleration) and a little lower PI than the healthy athletes of similar age	No	Healthy young athletes, number unclear
Brass, 1991[135]	Cross	Model TC2-64, EME, Ueberlingen, FRG	No	MRI	NR	23	0	10	10 of the 23 patients had abnormal MRI (suggesting distal field infarction), 7 had a clinical history of stroke (all of these had abnormal MRI), and only 4 had clinical deficits (mild weakness) at the time of this study. 1 patient had clinical evidence for a new stroke within the month before her studies in this protocol	No	No
Bulas, 2000[136]	Cross	TCD and TCDI	No	NR	NR (STOP criteria were used)	22	NC	NA	All manually measured TCDI measurements were lower than the manually measured TCD measurements. The percentage difference varied, depending on which vessel was insonated. PSV, EDV, and mean velocities for each vessel demonstrated similar differences	No	No
Colombatti, 2009[143]	Cross	TCD	NR	NR	Low risk<170 cm/s, conditional ≥170–199 cm/s, or high ≥200 cm/s.	12 and 24 controls	0	3 (conditional velocities)	Time-average maximum velocities in the MCA and basilar artery (BA) were significantly higher in group A patients on TCD evaluation (p=.0001). African and Caucasian healthy controls had similar lower normal values	NR	2 groups of age-matched controls of Caucasian and African origin
de Melo, 2008[149]	Cross	TCD	No	NR	NR	34 (and 80 controls)	NR	NA	Patients with SCA had mean velocity (MV)=125.69 cm/s±23.40; PI=0.66±0.10. Controls had MV=79.44±15.54; PI=0.82±0.11. MV and PI differences were statistically significant between groups	No	Age- and gender-matched children
Deane, 2008[277]	Cross	TCD	No	NR	NR	48	NR	NR	The mean TAMMV (time-averaged mean of the maximum velocity) was 94 cm/s, with 98th percentile of 238 cm/s. This was found lower than published ranges for HbSS disease with a mean reading of 129 cm/s	1 child had a stroke at age 5 yr when her TAMMV was measured at 146 cm/s	No

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Kim, 2009[178]	Cross	TCD	No	NR	NR	18 (and 10 controls)	0	NA	MCA Vmean was higher (87±16 vs. 64±13 cm/s; *P*<.01) and cerebrovascular resistance lower (0.94±0.16 vs. 1.35±0.23 mm HG/cm*s; *P*<.01) in SCD. The postural decline in mean arterial pressure brain (-15%), MCA Vmean (-13% vs. -14%), and end-tidal CO_2 tension (-4% vs. -6%) was comparable. MAP low-frequency power was comparable for both groups, whereas MCA Vmean low-frequency power was higher in the SCD group (6.1 (4.6 to 7.0) vs. 4.2 (2.6 to 5.2) (cm/s) ^{2}*Hz^{-1}, *p*=.043	No	Age- and ethnicity-matched healthy subjects
Kral, 2003[185]	Cross	TCD	No	NR	Participants were assigned to the abnormal group when the highest Vmean exceeded 200 cm/s	60	0	20	The highest time-averaged TCD Vmean ranged from 92 to 276 cm/s (median: 175.00; SD: 41.85). 20 patients had abnormal results; 15 had conditional results. Children with abnormal TCD values performed more poorly than children with conditional TCD values on measures of verbal intelligence and executive function. Children with conditional TCD values performed more poorly than children with normal TCD values on measures of sustained attention/ concentration and executive function. TCD values also were a significant predictor of auditory working memory in exploratory analyses. Significantly more girls were in the conditional and abnormal TCD diagnostic groups, (x^2=6.24, *p*<.05)	No	No
Kral, 2006[186]	Cross	MRI, MRA, TCD	NR	NR	TCD velocities <170 cm/s were classified as normal, velocities between 170 and 200 cm/s were classified as conditional, and velocities exceeding 200 cm/s were classified as abnormal	27	NR	MRI: 5 abnormal; MRA: 8 abnormal; TCD: 9 conditional, 13 abnormal	Infarction, defined as an area of abnormally increased signal on the fluid-attenuated inversion recovery series and T2-weighted pulse sequences, was classified by size (small < 0.5 cm, medium = 0.5–1.5 cm, large > 1.5 cm) and anatomic location. MRI results were classified as normal (n = 22) versus abnormal (silent infarct; n = 5). Vascular stenosis was classified according to flow obstruction (i.e., normal, non–flow-limiting stenosis, flow-limiting stenosis, and occlusion) and anatomic location. Magnetic resonance angiographic results were classified as normal (n = 19) or abnormal (n = 8). Following the guidelines of the STOP, TCD of less than 170 cm/second were classified as normal (n = 5), velocities between 170 and 200 cm/second (n = 9) were classified as conditional, and velocities exceeding 200 cm/second (n = 13) were classified as abnormal	NR	No

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Nur, 2009[210]	Cross	TCD	No	NR	NR	23 patients with SCD and 16 controls	0	NA	The cerebrovascular CO_2 responsiveness determined with both TCD and near-infrared spectroscopy was lower in patients with SCD than in controls. During normocapnia, Vmean correlated to Ht (rs=-0.46, *p*=.004) When analyzed for the SCD and control groups separately, the correlations between normocapnic resting CBF velocity and Ht were rs=-0.40 (*p*=.68) and rs=-0.01 (*p*=.98), respectively	NR	Age-, gender- and ethnicity-matched healthy subjects
O'Driscoll, 2008[211]	Cross	TCD	No	NA	NR	115	0	NR	Correlation analysis was performed between LDH and the following time-averaged mean TCD measurements: maximum velocities in the proximal extracranial internal carotid arteries (mICA), the posterior cerebral arteries (mPCA), the anterior cerebral arteries (mACA) and the circulation of the middle cerebral arteries (distal internal carotid arteries (dICA), bifurcation and middle cerebral arteries) as defined in the STOP trial and referred to as the time-averaged mean of the maximum velocity (TAMMV). When all patients were studied, all 4 TCD readings correlated strongly with LDH. However, when the HbSC patients were removed there was only significant correlation with mACA and TAMMV; increased blood velocities in both these vessels have been linked to increased risk of stroke	No	No
Pavlakis, 2010[216]	Cross	Blood flow velocity in intracranial vessels	No	NR	Conditional 170–199 m/s, abnormal =or>200 m/s	199	3.5	4 patients had conditional velocity, 0 had abnormal velocity	No patient had an abnormal TCD as defined in the older child (time averaged maximum mean time-averaged maximum mean velocity (TAMMV) ≥ 200 cm/s) and only 4 subjects (2%) had velocities in the conditional range (170–199 cm/s). The average left middle cerebral artery (MCA) MCA TAMMV was 116.3±22.0 cm/s and that of the right MCA was 114.3±22.3 cm/s. 10% of subjects had TAMMVs ≥ 149 m/s and 20% ≥ 141 m/s. TCD velocities were inversely related to Hb concentration and directly related to increasing age	No	No
Quinn, 2009[219]	Cross	TCD	No	NR	NR	181	NR	NR	Daytime SpO_2 (measuring Hb saturation) was found to correlate significantly with TAMMV in the right and left MCA in the direction hypothesized. Lower Hb saturations were associated with higher TAMMVs. The same relationship was demonstrated in the anterior and posterior circulations. Age and Hct were also inversely correlated with SpO_2	No	No
Rees, 2008[222]	Cross	TCD	Sensitivity 100%, specificity (58%-73%)	NR	TAMMV >170 cm/s	96	NR	NR	The time-averaged mean of the maximum velocity (TAMMV) was 125 cm/s (78–215 cm/s) and correlated significantly with age, Hb, LDH, AST, WBC, and creatinine level	No	No

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Riebel, 2003[224]	Cross	TCD	TCD was false positive in 8/15 cases, i.e., MRA did not show any corresponding abnormalities	MRA	NR	47	0	16	16 patients (34%) showed 1 (*n*=3), 2 (*n*=8), or more abnormal Doppler findings. Maximum flow velocity in the MCA was increased above 200 cm/s or decreased below the levels in the posterior cerebral, vertebral, or basilar arteries, respectively, in 4 patients	No	No
Sampaio Silva, 2006[225]	Cross	TCD	No	NR	NR	56 (and 56 controls)	3.6	NA	The mean max FV was higher in patients with SCD (117.7±21.6 cm/s) (in children with HbSS, the MCA velocity is typically around 130 cm/s) than in healthy controls (72.45±11.48 cm/s) (*p*<.001). 7 patients (12.5%) had abnormally low FV (<70 cm/s)	No	Healthy volunteers
Sanchez, 2010[227]	Cross	Measures blood flow velocity in intracranial vessels	No	NR	TCD max velocity >170 cm/s	39	0	6	TCD Max values were correlated with the Syntactical Quotient and Phonological Processing Quotient (r=-.61, *p*<.01; r=-.42, *p*=.01, respectively), with poorer performance. Associated with higher CBFv. With respect to specific language subtests, TCD Max values were strongly associated with Grammatical Understanding (r=-.55, *p*<.01) and moderately associated with Sentence Imitation (r=-.51, *p*<.01). TCD Max velocities were also related to Phonemic Analysis (r=-.40, *p*=.01), but not to Word Discrimination (r=-.29, *p*=.08). TCD Max values were not related to Semantic Quotient (r=.20, *p*=.21) or to the other cognitive domains	5 of the 6 participants who exhibited elevated TCD velocities underwent a repeat TCD within a 6-mo period and elevated velocities persisted at the repeat exam for all	No
Siegel, 1995[235]	Cross	TCD	92% sensitivity and 83% specificity for cerebral infarction	MRI	Maximal flow velocity >200 cm/s or <100 cm/s	24	8.3 (2 patients)	9	TCD identified 9 of 12 patients with infarcts proved at MRI, with only 1 false-positive result (sensitivity, 75%; specificity 92%)	NR	No
Bernaudin, 2005[272]	Case series	TCD	No	MRI/MRA	Time-averaged mean of maximum velocities ≥200 cm/s in MCA, bifurcation or ICA	291	NR	35	35/291 had abnormal Dopplers. Of these 35 patients, 10 had normal MRI and MRA	No	No

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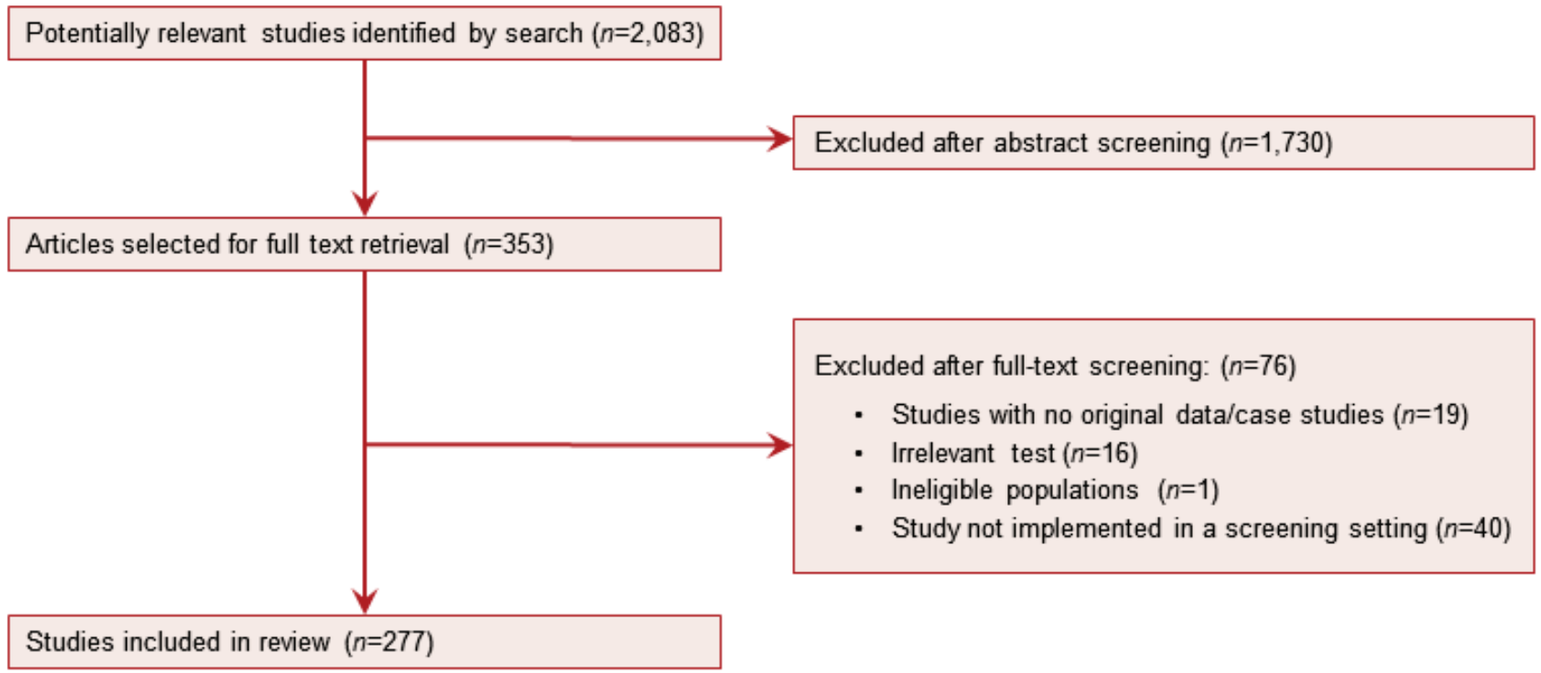
Appendix A: Study Selection Process



Evidence Selection

Study selection started by screening abstracts for eligibility followed by screening of full-text articles. Both steps followed an a priori established protocol. Study selection and data extraction were performed using piloted online reference management software (Distiller SR™). Abstracts were reviewed in duplicates until adequate inter-reviewer agreement was observed (kappa statistic ≥0.90). Data extraction was done by one reviewer and confirmed by a second reviewer. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was used to evaluate the quality of the evidence.

Appendix B: Methods

The Critical Question of the Systematic Review (PICOS)*

Patients:

Individuals with SCD

Intervention:

Screening strategies using the following tests (electrocardiogram, echocardiogram, pulmonary function testing, renal function testing, serial eye/retinal examination, brain imaging, and transcranial Doppler)

Comparison:

A control group in which no screening was provided

Alternate study type:

Studies that compare patients identified by screening in an asymptomatic state; then those with positive screening test were subjected to treatment vs. no treatment

Outcomes:

Development of acute and chronic complications

Study design:

Randomized or nonrandomized (including noncontrolled studies)

* PICOS = patients, intervention, comparison, alternate study type, outcomes, and study design.

Appendix C: Data Sources and Search Strategies

A comprehensive search of several databases (from 1970 to December 2010, English language, any population) was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the Guideline methodologist. Controlled vocabulary supplemented with keywords was used to search for the topic: screening for sickle cell disease complications. Additional references were identified by consulting with experts in the field.

OVID

Database(s): EMBASE 1988 to 2010 Week 52, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Central Register of Controlled Trials 4th Quarter 2010, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to December 2010

Search Strategy

#	Searches	Results
1	exp Anemia, Sickle Cell/	29614
2	(sickle cell or “hemoglobin s” or drepanocytemia or “drepanocytic anemia” or drepanocytosis or “hemoglobin ss” or meniscocytosis or “sickle anemia” or “ss disease” or “hemoglobin sc”).mp.	33985
3	1 or 2	33986
4	exp Anemia, Sickle Cell/co [Complications]	6858
5	(3 and complication*.mp.) or 4 [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	10018
6	exp Physical Examination/	966290
7	exp periodic medical examination/	1411
8	exp screening/	342861
9	exp Population Surveillance/	150067
10	exp DISEASE SURVEILLANCE/	3855
11	((periodic adj2 (examination* or checkup*)) or screening* or rescreening* or surveillance).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	869606
12	or/6-11	1909046
13	5 and 12	853
14	exp Electrocardiography/	224322
15	(electrocardiogra* or ecg or ekg or “body surface potential map*” or vectorcardiogra* or polarcardiogra* or cardiogram*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	322616
16	exp lung function test/	225085
17	exp Respiratory Function Tests/	225085

#	Searches	Results
18	(“lung function test*” or “respiratory function test*” or “pulmonary function test*” or “respiratory test*” or “pulmonary test*” or “ventilation test*” or “work of breathing” or bronchospirography or capnography or “exercise test*” or “hydrogen breath test*” or “nitrogen washout” or pneumography or pneumotachygraphy or “single breath nitrogen test*” or spirography or spirometry or “airway resistance” or “blood gas analys*” or “bronchial provocation test*” or “lung compliance” or “lung volume measurement*” or plethysmography or “pulmonary gas exchange” or “pulmonary ventilation” or “valsalva maneuver”).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	299979
19	exp Echocardiography/	208854
20	(echocardiogra* or “tissue doppler imaging” or “cardiac echography” or “cardiac scanning” or “cardial echography” or cardoechography or “echo cardiogra*” or “heart echo sounding” or “heart echogra*” or “heart scanning” or “myocardium scanning” or “ultrasound cardiogra*”).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	258526
21	exp eye examination/	4718
22	exp Vision Tests/	87199
23	((vision or eye or retinal or retina) adj (exam* or test*)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	25247
24	exp Kidney Function Tests/	60713
25	(“kidney function test*” or “renal function test*” or “blood urea nitrogen” or “glomerular filtration rate” or “radioisotope renography” or “kidney test*” or “renal test*” or “split function test*”).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	95617
26	exp creatinine blood level/	33136
27	exp Creatinine/bl [Blood]	25792
28	exp Proteinuria/	66559
29	exp protein urine level/	6288
30	(((blood or plasma or serum) adj creatinine) or proteinuria* or (protein adj (urine or urinary)) or uroprotein*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	120807
31	exp Ultrasonography, Doppler, Transcranial/	28021
32	exp Doppler echography/	22893
33	(transcranial adj (doppler or ultrasonogra* or echogra* or sonogra* or ultrasound)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	12937
34	exp Carotid Arteries/	76613
35	exp brain circulation/ or exp brain blood flow/ or exp brain blood vessel/	63473
36	exp Cerebral Arteries/	42850
37	exp Cerebrovascular Circulation/	52953
38	(“carotid arter*” or “carotid sinus” or cerebral or “circle of willis” or temporal or head or neck or cerebralvascula* or brain).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	2727022
39	(31 or 32 or 33) and (34 or 35 or 36 or 37 or 38)	18390
40	exp Magnetic Resonance Imaging/	582452
41	exp nuclear magnetic resonance imaging/	347253
42	(mri or mris or “magnetic resonance imaging” or “echo planar imaging” or “magnetic resonance angiography” or nmr or “chemical shift imaging” or tomography or “magnetization transfer contrast imaging” or zeugmatography or fmri or “magnetization transfer imaging” or “mr imaging” or “diffusion tensor imaging” or “diffusion weighted imaging” or “perfusion weighted imaging”).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	1474437
43	exp brain/	1428754

#	Searches	Results
44	(brain or cerebellum or diencephalon or “entopeduncular nucleus” or forebrain or “granule cell” or “interpeduncular nucleus” or “limbic system” or “mauthner cell” or “nucleus accumbens” or “optic disk cup” or “optic lobe” or pretectum or telencephalon).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	1792588
45	(40 or 41 or 42) and (43 or 44)	355817
46	or/14-30	1152317
47	39 or 45 or 46	1512726
48	exp Anemia, Sickle Cell/	29614
49	(sickle cell or “hemoblobin s” or drepanocytemia or “drepanocytic anemia” or drepanocytosis or “hemoglobin ss” or meniscocytosis or “sickle anemia” or “ss disease” or “hemoglobin sc”).mp.	33985
50	48 or 49	33986
51	47 and 50	2392
52	13 or 51	3078
53	remove duplicates from 52	2271
54	limit 53 to english language [Limit not valid in CCTR, CDSR; records were retained]	2103
55	limit 54 to yr=“1970 -Current”	2068
56	limit 55 to (book or book series or editorial or letter or note or addresses or autobiography or bibliography or biography or dictionary or directory or duplicate publication or historical article or interactive tutorial or interview or lectures or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or video-audio media or webcasts) [Limit not valid in EMBASE, Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process, CCTR, CDSR; records were retained]	153
57	55 not 56	1915

Scopus

1. TITLE-ABS-KEY(“sickle cell” OR “hemoblobin s” OR drepanocytemia OR “drepanocytic anemia” OR drepanocytosis OR “hemoglobin ss” OR meniscocytosis OR “sickle anemia” OR “ss disease” OR “hemoglobin sc”)

2. TITLE-ABS-KEY(electrocardiogra* or ecg or ekg or “body surface potential map*” or vectorcardiogra* or polarcardiogra* or cardiogram*)

3. TITLE-ABS-KEY(“lung function test*” or “respiratory function test*” or “pulmonary function test*” or “respiratory test*” or “pulmonary test*” or “ventilation test*” or “work of breathing” or bronchospirography or capnography or “exercise test*” or “hydrogen breath test*” or “nitrogen washout” or pneumography or pneumotachygraphy or “single breath nitrogen test*” or spirography or spirometry or “airway resistance” or “blood gas analys*” or “bronchial provocation test*” or “lung compliance” or “lung volume measurement*” or plethysmography or “pulmonary gas exchange” or “pulmonary ventilation” or “valsalva maneuver”)

4. TITLE-ABS-KEY(echocardiogra* or “tissue doppler imaging” or “cardiac echography” or “cardiac scanning” or “cardial echography” or cardoechography or “echo cardiogra*” or “heart echo sounding” or “heart echogra*” or “heart scanning” or “myocardium scanning” or “ultrasound cardiogra*”)

5. “vision exam*” or “vision test*” or “eye exam*” or “eye test*” or “retinal exam*” or “retinal test*” or “retina exam*” or “retina test*”

6. “kidney function test*” or “renal function test*” or “blood urea nitrogen” or “glomerular filtration rate” or “radioisotope renography” or “kidney test*” or “renal test*” or “split function test*”

7. “blood creatinine” or “plasma creatinine” or “serum creatinine” or proteinuria* or (protein W/3 urine) or (protein W/3 urinary) or uroprotein*

8. “transcranial doppler” or “transcranial ultrasonogra*” or “transcranial echogra*” or “transcranial sonogra*” or “transcranial ultrasound”

9. “carotid arter*” or “carotid sinus” or cerebral or “circle of willis” or temporal or head or neck or cerebralvascula* or brain

10. 8 and 9

11. mri or mris or “magnetic resonance imaging” or “echo planar imaging” or “magnetic resonance angiography” or nmr or “chemical shift imaging” or tomography or “magnetization transfer contrast imaging” or zeugmatography or fmri or “magnetization transfer imaging” or “mr imaging” or “diffusion tensor imaging” or “diffusion weighted imaging” or “perfusion weighted imaging”

12. brain or cerebellum or diencephalon or “entopeduncular nucleus” or forebrain or “granule cell” or “interpeduncular nucleus” or “limbic system” or “mauthner cell” or “nucleus accumbens” or “optic disk cup” or “optic lobe” or pretectum or telencephalon

13. 11 and 12

14. 1 and (2 or 3 or 4 or 5 or 6 or 7 or 10 or 13)

15. Complication*

16. (periodic W/2 examination*) or (periodic W/2 checkup*) or screening* or rescreening* or surveillance

17. 1 and 15 and 16

18. 14 or 17

19. PUBYEAR AFT 1969 AND LANGUAGE(english)

20. 18 and 19

21. PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)

22. 20 and not 21

23. DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

24. 22 and not 23

Appendix D: Excluded Studies

Author	Year	Title	Reason for exclusion
Akgul	2007	Pulmonary hypertension in sickle-cell disease: comorbidities and echocardiographic findings	Study not implemented in a screening setting
Adams	1989	Noninvasive detection of cerebral vasculopathy using transcranial Doppler and magnetic resonance imaging	Study with no original data or case study
Adams	2005	Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease	Study not implemented in a screening setting
Adams	1998	Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography	Study not implemented in a screening setting
Adams	1990	Cerebral vessel stenosis in sickle cell disease: Criteria for detection by transcranial Doppler	Study not implemented in a screening setting
Adams	1998	Stroke prevention in sickle cell disease (STOP): Results of transcranial doppler ultrasound screening stroke risk [abstract]	Study not implemented in a screening setting
Ahmed	2004	Echocardiographic abnormalities in sickle cell disease	Study not implemented in a screening setting
Al Hawsawi	1998	Stroke among sickle cell disease patients in Madina Maternity and Children's Hospital	Study not implemented in a screening setting
Al-Ali	2009	Assessment of pulmonary hypertension in patients with sickle cell disease with tricuspid regurgitant jet velocity of greater than or equal to 2.5 m/second on a routine echocardiogram	Study not implemented in a screening setting
Al-Harbi	1999	Renal reabsorption of phosphate in children with sickle cell anemia	Irrelevant test
Aquino	1994	Chronic pulmonary disorders in sickle cell disease: findings at thin-section CT	Study not implemented in a screening setting
Boga	2007	Assessment of corrected QT interval in sickle-cell disease patients who undergo erythroapheresis	Irrelevant test
Cetin	2009	Myocardial velocity and speed data in patients with hemolytic anemia	Study with no original data or case study
Chaudry	2009	Mild to moderate pulmonary hypertension in children with sickle cell disease is due to increased pulmonary blood flow secondary to anaemia rather than elevated pulmonary vascular resistance	Study with no original data or case study
Colombatti	2010	Pulmonary hypertension in young children with sickle cell disease: When does it start? Survey among immigrant patients in North-East Italy	Study with no original data or case study
Condon	1976	Ocular findings of elderly cases of homozygous sickle-cell disease in Jamaica	Study not implemented in a screening setting
d. Melo	2008	Transcranial doppler in sickle cell anaemia: evaluation of brain blood flow parameters in children of Aracaju, Northeast-Brazil	Study with no original data or case study
De Castro,	2008	Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes	Study not implemented in a screening setting
De Ceulaer	1981	Serum urate concentrations in homozygous sickle cell disease	Irrelevant test
Denenberg	1983	Cardiac function in sickle cell anemia	Study with no original data or case study
Dham	2010	Echocardiographic predictors of declining exercise performance in children with sickle cell disease	Irrelevant test
Dowling	2010	Prevalence of intracardiac shunting in children with sickle cell disease and stroke	Study not implemented in a screening setting
Emam	2009	Childhood stroke in Eastern Province, KSA: pattern, risk factors, diagnosis and outcome	Study not implemented in a screening setting

Author	Year	Title	Reason for exclusion
Emam	2009	Magnetic resonance spectroscopy of the brain in children with sickle cell disease	Irrelevant test
Emokpae	2010	Sex Dimorphism in Serum Lecithin: Cholesterol Acyltransferase and Lipoprotein Lipase Activities in Adult Sickle Cell Anaemia Patients with Proteinuria	Study not implemented in a screening setting
Fawibe	2010	Sickle cell chronic lung disease among young adult Nigerians	Irrelevant test
Gorman	2009	Submandibular TCD approach detects post-bulb ICA stenosis in children with sickle cell anemia	Study with no original data or case study
Hankins	2010	Ventricular diastolic dysfunction in sickle cell anemia is common but not associated with myocardial iron deposition	Study not implemented in a screening setting
Hankins	2008	Preservation of spleen and brain function in children with sickle cell anemia treated with hydroxyurea	Study not implemented in a screening setting
Hatch	1970	Renal circulatory studies in young adults with sickle cell anemia	Irrelevant test
Husain	1995	Prevalence of mitral valve prolapse in Saudi sickle cell disease patients in Dammam - A prospective-controlled echocardiographic study	Study not implemented in a screening setting
Husain	2000	Comparison of MRI and MRA findings in children with a variety of neurologic conditions	Study not implemented in a screening setting
Kirkham	2001	Perfusion magnetic resonance abnormalities in patients with sickle cell disease	Study not implemented in a screening setting
Knight-Madden	2010	The impact of recurrent acute chest syndrome on the lung function of young adults with sickle cell disease	Study not implemented in a screening setting
Koumbourlis	1997	Lung function in infants with sickle cell disease	Study not implemented in a screening setting
Kurt	2009	The evaluation of pulmonary functions in children with sickle cell anemia	Irrelevant test
Kwiatkowski	2010	Transcranial Doppler ultrasonography in infants with sickle cell disease-Is earlier identification of children at risk of stroke possible?	Study with no original data or case study
Kwiatkowski	2009	Changes in transcranial doppler (TCD) ultrasonography velocities on transfusion therapy - Extended analysis of stop II	Study not implemented in a screening setting
Kwiatkowski	2006	Elevated blood flow velocity in the anterior cerebral artery and stroke risk in sickle cell disease: Extended analysis from the STOP trial	Study not implemented in a screening setting
Leite	2009	Transcranial doppler (TCD) and neurological manifestations in Brazilian pediatric patients with SCD	Study with no original data or case study
Lonsdorfer	1983	Cardiorespiratory adjustments in chronic sickle cell anemia	Irrelevant test
Manno	1983	Biventricular function in sickle-cell anemia: radionuclide angiographic and thallium-201 scintigraphic evaluation	Study not implemented in a screening setting
Maunoury	2003	Myocardial perfusion in children with sickle cell disease	Study not implemented in a screening setting
McCarville	2009	Abdominal ultrasound findings in infants with sickle cell anemia: Baseline data from the BABY HUG trial	Irrelevant test
McMahon	2009	Transcranial Doppler (TCD) and magnetic resonance imaging to monitor cerebral vascular abnormalities in children with sickle cell disease	Study not implemented in a screening setting
Mercuri	1995	Neurological ‘soft’ signs may identify children with sickle cell disease who are at risk for stroke	Study not implemented in a screening setting
Metarugcheep	2008	Clinical silent cerebral infarct (SCI) in patients with thalassemia diseases assessed by magnetic resonance imaging (MRI)	Ineligible populations

Author	Year	Title	Reason for exclusion
Minniti	2009	Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation	Study with no original data or case study
Minniti	2004	Transcranial Doppler changes in children with sickle cell disease on transfusion therapy	Study not implemented in a screening setting
Minniti	2009	Sickle cell leg ulcers are associated with hyperuricemia, hemolysis, pulmonary hypertension and death	Study not implemented in a screening setting
Moran	1998	Sickle cell disease: Imaging of cerebrovascular complications	Study with no original data or case study
Morgan	2009	Neurological complications of paediatric sickle cell anaemia in Wessex	Study with no original data or case study
Niu	2009	Relationship of hemolysis, erythropoietin, other biologic mediators and hydroxyurea therapy to tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease	Study not implemented in a screening setting
Ozsahin	2008	MRI abnormalities in infants with sickle cell anemia-indication for pre-emptive therapy?	Study with no original data or case study
Pitcock	1970	Early renal changes in sickle cell anemia	Study with no original data or case study
Prohovnik	1989	Cerebral hyperemia, stroke, and transfusion in sickle cell disease	Irrelevant test
Rees	1978	Left ventricular performance in children with homozygous sickle cell anaemia	Study not implemented in a screening setting
Reyes	1985	Noninvasive assessment of left ventricular size and function in infants and young children with sickle cell anemia	Study with no original data or case study
Roberts	2009	Stroke prevention in the young child with sickle cell anaemia	Study with no original data or case study
Sangkatumvong	2010	Decrease in microvascular blood flow in sickle cell anemia triggered by autonomic responses to sighing	Study with no original data or case study
Sarnaik	2009	Elevated systolic blood pressure and low fetal hemoglobin are risk factors for silent cerebral infarcts in children with sickle cell anemia	Irrelevant test
Scarponi	2010	Microalbuminuria and Lactate Dehydrogenase (LDH) as predictors of kidney involvement in a pediatric Sickle Cell Disease (SCD) population	Study with no original data or case study
Seibert	1998	Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: An 8-year study	Study not implemented in a screening setting
Seliem	2002	Left ventricular diastolic dysfunction in congenital chronic anaemias during childhood as determined by comprehensive echocardiographic imaging including acoustic quantification	Study not implemented in a screening setting
Serjeant	2009	The changing face of homozygous sickle cell disease: 102 patients over 60 years	Irrelevant test
Suell	2005	Increased pulmonary artery pressures among adolescents with sickle cell disease	Study not implemented in a screening setting
Taher	2009	Silent brain abnormalities in thalassemia intermedia: Diagnostic contribution of positron emission tomography	Irrelevant test
Thornburg	2009	A pilot study of hydroxyurea to prevent chronic organ damage in young children with sickle cell anemia	Study not implemented in a screening setting
Uchida	1998	Effect of erythrocytapheresis on arterial oxygen saturation and hemoglobin oxygen affinity in patients with sickle cell disease	Irrelevant test
Vicari	2010	Absence of association between TNF-α polymorphism and cerebral large-vessel abnormalities in adults with sickle cell anemia	Study not implemented in a screening setting
Vichinsky	2001	Ischemic brain injury in neurologically normal adults with sickle cell disease	Study not implemented in a screening setting

Author	Year	Title	Reason for exclusion
Walker	1979	The diagnosis of pulmonary thromboembolism in sickle cell disease	Study not implemented in a screening setting
Watkins	1998	Cognitive deficits associated with frontal-lobe infarction in children with sickle cell disease	Study not implemented in a screening setting
Yazzie	1995	Decreased urinary excretion of beta-glucuronidase in sickle cell anemia in Nigeria	Irrelevant test
Young	1976	Lung function abnormalities occurring in sickle cell hemoglobinopathies: a preliminary report	Study with no original data or case study
Zimmerman	2007	Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia	Study not implemented in a screening setting

Appendix E: Acronyms and Abbreviations

Numbered

3TC	lamivudine
32P	radioactive phosphorous
51Cr-EDTA	chromium-51 labeled ethylenediaminetetraacetic acid; *see* Cr-EDTA
6MWD	6-minute walk distance

A

α	alpha, first letter of the Greek alphabet
α-thal	*See* α-thalassemia
α-thalassemia	alpha-thalassemia
AA	African American
AB	blood group AB
Ab	antibody
ABC	abacavir
ABG	arterial blood gas
A/C	albumin to creatinine ratio
ACE	angiotensin converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute chest syndrome
AE	adverse event
Æ	per each
AER	albumin excretion rate
AHR	airway hyperresponsiveness
AI	augmentation index
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ara-c	arabinosylcytosine (cytarabine)
ARV	antiretroviral
ASA	acetylsalicylic acid (aspirin)
ASPEN	Association of Sickle Cell Disease, Priapism, Exchange Transfusion and Neurological Events
ASSC	acute splenic sequestration crisis
AST	aspartate aminotransferase
atm	atmospheric
AUC	area under the curve
avL	automated volt left, EKG lead

B

β	beta, second letter of the Greek alphabet
β-thal	*See* β-thalassemia
β-thalassemia	beta-thalassemia
β^0-thal	beta zero-thalassemia
BABY HUG	Pediatric Hydroxyurea Phase III Clinical Trial
B cell	type of lymphocyte or immune mediator cell
beta	*See* β
b.i.d.	*bis in die,* twice a day
BM	Black male; bone marrow; bowel movement [see context]
BMI	Body Mass Index
BMT	bone marrow transplant
BP	blood pressure
B-TI	beta thalassemia intermedia
B-TM	beta thalassemia major

C

C	Celsius
Ca	calcium
CAD	coronary artery disease
CAR	Central African Republic haplotype
CBD	cortical bone density
CBFv	cerebral blood flow velocity
CBT	cognitive behavioral therapy
CCNU	1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)
CCT	clinically controlled trial
CH	chronic hepatomegaly
CI	confidence interval
cm	centimeter
cm^2	square centimeter
cm^3	cubic centimeter
CML	chronic myelogenous leukemia

cMRI	conventional magnetic resonance imaging
CMV	cytomegalovirus
CNS	central nervous system
cP	centipoise
CrCl	creatinine clearance
Cr-EDTA	chromium 51-labeled ethylenediaminetetraacetic acid; *see* 51Cr-EDTA
Cross	cross-sectional study
CRP	C reactive protein
CSSCD	Cooperative Study of Sickle Cell Disease
CT	computed tomography
CTA	computed tomographic angiography; concurrent treatment with an antisickling agent
CTX	chronic transfusion therapy
CUI	cumulative incidence
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
CXR	chest x ray

D

d	day
d4T	didehydrodeoxythymidine
DAT	direct antiglobulin test
DBP	diastolic blood pressure
ddI	didanosine, dideoxyinosine
DFO	deferoxamine
DH	day hospital
DHTR	delayed hemolytic transfusion reaction
DHTR/H	delayed hemolytic transfusion reaction/hyperhemolysis
dL	deciliter
DLCO	diffusing capacity of lung for carbon monoxide
DM	diabetes mellitus
DPI	dynamic pressure index
DTPA	diethylenetriamine pentaacetate
DW	dry weight
dyn	dyne
dx	diagnosis

E

E	E antigen; HbE/β-thalassemia [see context]
E wave	electromagnetic wave
E/A	Doppler ratio of early (E) to late atrial (A) transmitral flow velocity
ECG	electrocardiogram
ECHO	echocardiogram, echocardiographic, echocardiography
ECMO	extracorporeal membrane oxygenation
ED or ER	emergency department or emergency room
EDD	end diastolic diameter
EF	ejection fraction
EFV	efavirenz
EPO	erythropoietin
ESD	end systolic diameter
ESSm	end-systolic wall stress
ET	essential thrombocytopenia; exchange transfusion [see context]

F

F	female
F	Fahrenheit
f/u	follow up
FEF	forced expiratory flow
FEV1	forced expiratory volume at 1 second
fL	femtoliter
FS	fractional shortening
ft	feet
FVC	forced vital capacity

G

g	gram
G	gauge
GFR	glomerular filtration rate; mL/min/1.73 m^2
GI	gastrointestinal
GMP	granule membrane protein
Gp	group

H

h	hour
H1N1	respiratory virus, a variety of influenza A
H6CS	Harvard Six Cities Study
Hb	hemoglobin
HbA	hemoglobin A
HbAA	hemoglobin AA
HbAS	hemoglobin AS
HbF	hemoglobin F; fetal hemoglobin
HbH	hemoglobin H
HbI	hemoglobin I
HBM	health belief model
HbS	hemoglobin S; sickle cell hemoglobin
HbSα^+-thal	hemoglobin S alpha plus-thalassemia
HbSβ-thal	hemoglobin S beta-thalassemia
HbSβ^0-thal	sickle hemoglobin beta zero-thalassemia
HbSβ^+-thal	sickle hemoglobin beta positive-thalassemia
HbSC	hemoglobin SC disease; sickle hemoglobin C disease
HbSD	hemoglobin SD disease
HbSD^{LA}	hemoglobin SD disease, Los Angeles; also known as D-Punjab
HbS/O-Arab	hemoglobin SO-Arab
HbSS	homozygous sickle cell disease
Hct	hematocrit
HES	Health Examination Survey
Hg	mercury
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPRT	hypoxanthine phosphoribosyl transferase
HR	heart rate
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
HTN	hypertension
HTR	hemolytic transfusion reaction
HU	hydroxyurea
HUG KIDS	Phase I-II trial of the safety of HU in children by the Pediatric Hydroxyurea Group
HUSOFT	The Hydroxyurea Safety and Organ Toxicity trial
hx	history

I

IAT	indirect antiglobulin test
IDV	indinavir
IFN	interferon
i.m.	intramuscular
iNO or INO	inhaled nitric oxide
INR	international normalized ratio
IQR	interquartile range
IR	index of rigidity
IU	International unit
i.v. or IV	intravenous
IVIG	intravenous immunoglobulin
IVS	interventricular septal thickness

K

K	Kell
kg	kilogram
kJ	Kilojoule
kPa	kilo-Pascal

L

L	liter
LA	left atrium, left atrial
LACA	left anterior cerebral artery
LDH	lactate dehydrogenase
LFT	liver function test
LIC	liver iron content; liver iron concentration [see context]
LMCA	left main coronary artery
LOS	length of stay
Lp(a)	lipoprotein (a)
LPCA	left posterior cerebral artery
LQTS	long QT syndrome
LV	left ventricle; left ventricular
LVDD	left ventricular diastolic dimension
LVEDD	left ventricle end-diastolic dimension
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic dimension

LVH	left ventricular hypertrophy
LVPWD	left ventricular posterior wall dimension
LVPWT	left ventricular posterior wall thickness

M

μ	Greek letter mu; micro-
m	milli-; moles per liter [see context]
m	meter
m^2	square meter
MAP	mean arterial pressure
MCA	middle cerebral artery
MCT	methacholine challenge test
MCV	mean corpuscular volume; mean cell volume
MedAd	median study medication
MF	myelofibrosis
mg	milligram
MI	myocardial infarction
min	minute
mL	milliliter
mm	millimeter
mm^3	cubic millimeter
mmHg	millimeters of mercury
mmoL	millimolar
mo	month
mol	mole
mPAP	mean pulmonary artery pressure
MPD	myeloproliferative disorder; maximal permissible dose [see context]
MPI	myocardial performance index
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
ms	millisecond
MSH	Study of Hydroxyurea for Sickle Cell Anemia
MTD	maximum tolerated dose

N

n	nano
n	sample size
N	population size
NA or N/A	not applicable
NC	not clear
ng	nanogram
ng/mL	nanograms per milliliter
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
nmol	nanomole
NO or NOx	nitric oxide
NR	not reported
NR/NC	not reported/not clear
NS	not significant; normal saline [see context]
ns	nanosecond

O

Obs	observational
OCP	oral contraceptive pill
Od or o.d.	*omni die,* every day
Op	Operation; opioid [see context]
OR	odds ratio

P

p	probability
P, Obs	prospective observational
PAH	pulmonary arterial hypertension
PaO_2	symbol for partial pressure of oxygen in arterial blood
PASP	pulmonary artery systolic pressure
PCA	patient-controlled analgesia
pcMV	pressure-controlled mechanical ventilation
Pcr	plasma creatinine
PCV	packed cell volume
PCWP	pulmonary capillary wedge pressure
PEF	peak expiratory flow
PFT	pulmonary function test
pg	picogram
PH, PHT, PHTN	pulmonary hypertension
PICU	pediatric intensive care unit
PLC	propionyl-L-carnitine

plt	platelets
PMN	polymorphonuclear leukocytes
pmol	picomole
pO_2 or PO_2	partial oxygen pressure
POD	postoperative day
postop	postoperative
ppm	parts per million
PRBC	packed red blood cells
preop	preoperative
Prn	as needed
PSR	proliferative sickle retinopathy
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
PVR	pulmonary vascular resistance
PWV	pulse wave velocity

Q

Q	quality
Q wave	the initial downward deflection of the QRS complex
QID or q.i.d.	*quater in die*; 4 times a day
QOD	every other day
QTc	corrected QT interval

R

R wave	the initial upward deflection of the QRS complex
R, Obs	retrospective, observational
R-P, Obs	retrospective-prospective observational
RACA	right anterior cerebral artery
RAD	reactive airway disease
RBC	red blood cell
rCBF	regional cerebral blood flow
RCT	randomized controlled trial
RE	right extremity; right eye [see context]
retic	reticulocytes
Rev.	reviewer
RGD	arginyl-glycyl-aspartic acid (peptide)
RHC	right heart catheterization
RMCA	right middle cerebral artery
RPCA	right posterior cerebral artery
RR	relative risk
rTPA	recombinant tissue plasminogen activator
RV	right ventricle; right ventricular
RVEDD	right ventricular end-diastolic dimension
RVEF	right ventricular ejection fraction
RVESD	right ventricular end-systolic dimension
RVP	right ventricle pressure

S

s	seconds
S/O	hemoglobin SO Arab
S/O-Arab	hemoglobin SO-Arab
SA	substance abuse
SBP	systolic blood pressure
SCA	sickle cell anemia
SCD	sickle cell disease
SD	standard deviation
SEM	standard error of the mean
SF	serum ferritin
SLE	systemic lupus erythematosus
SPT	service perception test
STOP	Stroke Prevention Trial in Sickle Cell Anemia
sx	symptom

T

T wave	the first deflection in the electrocardiogram following the QRS complex
TACO	transfusion-associated circulatory overload
TAMMV	time-averaged mean of the maximum velocity
TCD	transcranial Doppler
TENS	transcutaneous electrical nerve stimulation
thal	thalassemia
TIA	transient ischemic attack
t.i.d.	*ter in die;* three times a day
TLC	total lung capacity
TNF-α	tumor necrosis factor alpha

TRF2	telomeric repeat-binding factor 2
TRV, TRJV	tricuspid regurgitant velocity, tricuspid regurgitant jet velocity
TScr	tubular secretion of creatinine
tx	therapy

U

U	unit
UAE	urinary albumin excretion
µg	microgram
µl	microliter
ULN	upper limit of normal
µm	micrometer
µmol	micromole
UNTH Enugu	University of Nigeria Teaching Hospital at Enugu
US	ultrasound; ultrasonography
UTI	urinary tract infection

V

V/Q	ventilation-perfusion scan
V_1, V_2, V_3, V_3–V_6	unipolar electrocardiogram lead (1–6)
VAS	visual analogue scale
VC	Vital capacity
VCFc	velocity of circumferential fiber shortening
VOC	vaso-occlusive crisis
Vrft	velocity of regurgitant flow of tricuspid
vs.	versus

W

walk-PHaSST	Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy
WBC	white blood cell; white blood cell count
wt	weight

Y

yr	year

Z

ZDV	zidovudine