Blood Pressure and Sickle Cell Disease:
A Systematic Review and Meta-Analysis, 2012

Prepared for the National Heart, Lung, and Blood Institute

Prepared by the Knowledge and Evaluation Research Unit, Mayo Clinic Rochester

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Included Studies

Table 1. Studies Reporting Baseline Blood Pressure in Sickle Cell Disease vs. Controls

Study	Objective of study	SCD: Description [age (yr), genotypes (%), other characteristics]	SCD: No.	SCD: DBP (mmHg) Mean (SD)	SCD: SBP (mmHg) Mean (SD)	Control: Description	Control: No.	Control: DBP (mmHg) Mean (SD)	Control: SBP (mmHg) Mean (SD)	Study conclusions about BP
Adams-Campbell, 1993[1]	To examine the relationship between sickle cell anemia (SCA) and blood pressure (BP) of subjects with hemoglobin genotypes HbSS, HbAS, and HbAA	Children with HbSS, recruited from the sickle cell clinics at the University of Benin Teaching Hospital Mean age: 10.3 (5.2)	39	60.6 (9.4)	107.3 (9.9)	Children with either HbAS or HbAA who were neighborhood-matched with the cases and also attended the general pediatric clinics Mean age HbAS: 11.6 (5.9) Mean age HbAA: 12.1 (6.2)	HbAS: 60 HbAA: 63	HbAS: 65 (9.7) HbAA: 63.2 (13.4)	HbAS: 106.3 (13.9) HbAA: 106 (13.9)	Systolic blood pressure (SBP) was similar in all groups, but the HbSS group had significantly lower diastolic blood pressures (DBP) than the HbAS and HbAA groups. Step-wise regression models controlling for genotype, body mass index (BMI), and sex revealed that age was the only significant independent correlate of BP explaining 58.5% of SBP variances and 43.5% of DBP variances among the offspring
Adebayo, 2002[2]	To examine the cardiovascular status of patients with steady-state SCA	Patients with steady-state HbSS Age: 15–37 Male: 42% HbSS: 100%	41	Before 6-min walk: 60.0 (9.4) After walk: 65.6 (9.1)	Before 6-min walk: 106.0 (8.94) After walk: 120 (11.9)	Age- and sex-matched controls with HbAA Age: 15–37 Male: 42% HbSS: 0%	41	Before 6-min walk: 67.1 (9.97) After walk: 74.2 (11.4)	Before 6-min walk: 108.98 (10.91) After walk: 124.4 (14.1)	Patients with HbSS had significantly lower DBP prior to a self-paced walking test, compared to HbAA controls (p<.01). After exercise, DBP was also significantly lower in patients than controls (p<.001). However, there was no significant difference in SBP or in the change in the SBP and DBP between patients and controls
Adeodu, 2001[3]	To determine if hepatic perfusion is poorer in HbSS children with chronic hepatomegaly (CH) compared to matched controls (both HbSS and HbAA) without CH	Children with steady-state SCA and routine followup at Obafemi Awolowo Hospital from July to Dec. 1998 Children with HbSS + CH HbSS: age- and sex-matched controls without CH Male: 50%	HbSS + CH: 14 HbSS: 14	HbSS + CH: 58.5 (5.1) HbSS: 60.1 (4.9)	HbSS + CH: 88.5 (6.5) HbSS: 90.1 (5.2)	Age- and sex-matched, healthy children with HbAA recruited from general clinic no less than 3 mo following recovery from acute illness Male: 50%	14	61.5 (5.5)	90.6 (4.2)	The mean SBP and DBP were not statistically different among the groups of patients and controls

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Aderibigbe, 1999[4]	To determine if SCA has any influence on the pattern of BP distribution in adult Nigerians	Patients ≥18 yr of age at the Adult Sickle Cell Clinic at the University of Illorin Hospital and crisis free for 2 mo Mean age: 22.1 Male: 58% HbSS: 100%	64	NR	Mean arterial pressure (MAP): 72.7 (7.3)	Adult Nigerians recruited from the hospital community Mean age: 27.2 Male: 53% HbAA: 100%	60	NR	MAP: 87.2 (9.9)	The MAP was significantly lower in those patients with SCA, compared to normal controls (p<.007). In a multiple regression analysis, neither weight, height, nor serum sodium correlated with the lower BP
Hatch, 1989[5]	To evaluate hormonal and hemodynamic parameters involved in BP control in normotensive patients with sickle cell disease (SCD) compared to controls without SCD	Patients with SCD Mean age: 27 (1.7) Male: 30% HbSS: 50% HbSC: 50%	10	73 (2.6)	117 (3.5)	Age-matched normal African American volunteers Mean age: 30 (1.9) Males: 9%	11	73 (2.9)	114 (3.8)	There was no significant difference between patients with SCD and normal controls
Homi, 1993[6]	To examine the role that factors such as weight and age may play in the low BP of patients with SCD	Children between 16 and 18 yr of age attended the Sickle Cell Clinic in Kingston, Jamaica, and were part of an SCD screening study at birth HbSS: Males=56% HbSC: Males=51%	HbSS: 51 HbSC: 41	HbSS: Males=59.4 (8.1) Females=61.3 (6.9) HbSC: Males=63.1 (9.2) Females=67.3 (8.1)	HbSS: Males=108.6 (11.5) Females=105.6 (8.3) HbSC: Males=108.5 (12.9) Females=110.6 (11.4)	The first 125 patients with SCD were matched with 2 control subjects of the same sex, born closest to the index case with HbAA Males: 49%	HbAA: 97	Men: 65.1 (8.9) Women: 64.2 (7.3)	Men: 118.4 (15.9) Women: 106.9 (8.9)	Crude analyses showed significantly lower systolic, diastolic, and MAP pressures in HbSS disease compared with control subjects with normal hemoglobin, but further analysis showed the systolic difference to be confined to males, and all differences disappeared after adjustment for weight. No differences occurred in HbSC disease
Jaja, 2000[7]	To examine whether there is a positive relationship between HbF, irreversibly sickled cells, and several lung function parameters	Patients at the adult Sickle Cell Clinic of Lagos Teaching Hospital Mean age: 21.7 Male: 100% HbSS: 100%	10	65 (50–80)	109 (100–120)	Students at the College of Medicine Lagos University Mean age: 21.0 Male: 100% HbAA: 100%	15	78.0 (70–80)	114 (110–120)	There was no difference in SBP; however, DBP is significantly lower in patients with SCA compared to normal controls (p<.001)

Study	Objective of study	SCD: Description [age (yr), genotypes (%), other characteristics]	SCD: No.	SCD: DBP (mmHg) Mean (SD)	SCD: SBP (mmHg) Mean (SD)	Control: Description	Control: No.	Control: DBP (mmHg) Mean (SD)	Control: SBP (mmHg) Mean (SD)	Study conclusions about BP
Johnson, 1981[8]	To compare BP in patients with SCD with age- and sex-matched populations of African Americans	Patients with SCD admitted to hospital or seen at regular clinic visit at University of Southern California (USC) Medical Center and Martin Luther King (MLK) Hospital Mean age: 29 (range 18–67) HbSS: 69% HbSC: 22% HbSβ-thal: 8% Males: 42%	187	70	116	Age- and sex-matched African Americans included in the HES survey (1960–1962) and the NHANES survey, 1971–1974, including a subset of metropolitan-dwelling individuals (London Metropolitan Archives (LMA))	LMA: 383 NHANES: 765 HES: 514	No aggregate number provided but were significantly higher than SCD group	No aggregate number provided but were significantly higher than SCD group	The BPs in those with SCD were significantly lower than those in the control populations in all ages and did not demonstrate the expected rise with advancing age. In these patients, there was no difference between BP and sex, degree of anemia, or hemoglobin genotype. 4 patients had diastolic and 2 had systolic hypertension. The prevalence of hypertension was significantly less than that in the African American population
Martins, 1999[9]	To conduct an anatomical and functional assessment of the heart through Doppler and echocardiography in patients with SCA	Patients with SCA in ambulatory followup, pain or hemolytic crisis free for 4 weeks, and transfusion free for 3 mo Mean age: 26.6	25	62.0 (12.5)	NR	Healthy volunteers Mean age: 26.8	25	73.6 (7.3)	NR	Patients with SCD had significantly lower afterload DBP compared to healthy controls (p<.001)
Minniti, 2009[10]	To determine if elevated jet velocity affects 10% of pediatric patients, is associated with hemolysis and hypoxia, and has clinical correlates with acute chest syndrome (ACS), stroke, transfusion requirement, and abnormal 6-minute walk test	Patients with SCD presenting for routine outpatient care at 3 hospitals (2 in Washington, DC, and 1 in Ann Arbor, MI), aged 3–20	310	64 (range: 58–70)	112 (range: 103–120)	Controls were matched by age, sex, and ethnicity to every 6th patient. Could include family members and patients with sickle cell trait and HbC trait	54	67 (range: 61–73)	113 (range: 107–124)	No difference in BP among the 2 study groups

Study	Objective of study	SCD: Description [age (yr), genotypes (%), other characteristics]	SCD: No.	SCD: DBP (mmHg) Mean (SD)	SCD: SBP (mmHg) Mean (SD)	Control: Description	Control: No.	Control: DBP (mmHg) Mean (SD)	Control: SBP (mmHg) Mean (SD)	Study conclusions about BP
Mohan, 1995[11]	To establish how the resting levels of a range of cardiovascular variables might change in subjects with HbSS and controls during the working day	Males attending the West Indies Sickle Cell Clinic, who were normotensive, pain crisis free for 4 weeks, and transfusion free for 3 mo Mean age: 24.06 (5.9) Male: 100% HbSS: 100%	16	NR	MAP: 79.4 (10.2)	African American males who volunteered to act as controls Mean age: 19.53 (3.2) Male: 100% HbAA: 100%	17	NR	MAP: 85.9 (9.4)	Patients with HbSS had significantly lower resting MAP, as measured at 10 a.m. (p<.05). In both HbSS and HbAA, there were parallel increases in MAP from the morning MAP to the afternoon MAP (by 12% and 10%, respectively)
Oguanobi, 2010[12]	To compare the arterial BP in steady-state adult patients with SCD with those of age- and sex-matched, healthy controls	Adult patients with HbSS who were attending the adult sickle cell clinics of the University of Nigeria Teaching Hospital at Enugu and were in a steady state Mean age: 28.3 (5.6) Male: 50% HbSS: 100%	62	64.9 (8.9)	119.5 (11.7)	Age- and sex-matched healthy controls, including students, hospital workers, and community members Mean age: 28.4 (5.9) Male: 50% HbAA: 100%	62	76.9 (6.2)	121.2 (8.9)	The brachial SBP in patients with SCA from this study was not significantly different from that of the controls, but the DBP was found to be significantly lower in the patients than in the controls (p<.001)
Sullivan, 2010[13]	To determine the effect of oral arginine intake on exhaled nitric oxide levels in patients with SCD with and without history of ACS, and in healthy controls	African American, aged 6–21, nonsmokers	6 ACS 9 no ACS	67.7 (8.4) ACS 64.6 (7.6) no ACS	124.6 (11.7) ACS 117.5 (6.7) no ACS	Healthy controls	7	71.5 (5.5)	125 (11.5)	No significant difference in BP among the 3 study groups

Study	Objective of study	SCD: Description [age (yr), genotypes (%), other characteristics]	SCD: No.	SCD: DBP (mmHg) Mean (SD)	SCD: SBP (mmHg) Mean (SD)	Control: Description	Control: No.	Control: DBP (mmHg) Mean (SD)	Control: SBP (mmHg) Mean (SD)	Study conclusions about BP
Taylor, 2008[14]	To describe vascular complications and mortality in patients with chronic hyperhemolysis	2 cohort studies (NIH Pulmonary Hypertension (PH) and Cooperative Study of Sickle Cell Disease (CSSCD)) Mean age NIH: 36 Mean age CSSCD: 40 Male NIH: 48% Male CSSCD: 55%	350	High-lactate dehydrogenase (LDH) NIH: 65.8 (11.3) CSSCD: 68.7 (77.8) Low-LDH NIH: 65.4 (9.7) CSSCD: 68.5 (8.7)	High-LDH NIH: 121.5 (17.5) CSSCD: 113.5 (12.0) Low-LDH NIH: 115.2 (17.8) CSSCD: 110.8 (12.4)	NA	NA	NA	NA	Chronic hyperhemolysis subjects (top LDH quartile) had higher SBP
Thompson, 2007[15]	To examine the relationships between BP, renal hemodynamics, and urinary albumin excretion in subjects with HbSS and matched controls with a normal HbAA	Adults 18.5 yr or older, living in the Kingston, Jamaica area with HbSS Mean age: 20.8 Males: 51% HbSS: 100%	65	58 (range: 42–100)	103 (range: 85–153)	Matched by sex and time of birth, with an HbAA Mean age: 21.7 Men: 53%	15	84 (range: 70–102)	110 (range: 95–144)	Compared to controls, subjects with HbSS disease showed significantly lower DBP (p<.001) and slightly lower SBP (p=.09)

Table 2. Studies Reporting Prognosis and Outcomes Related to Blood Pressure

Study	Objective of study	SCD: Description [age (yr), genotypes (%), other characteristics]	SCD: No.	SCD: DBP (mmHg) Mean (SD)	SCD: SBP (mmHg) Mean (SD)	Control: Description	Control: No.	Control: DBP (mmHg) Mean (SD)	Control: SBP (mmHg) Mean (SD)	Study conclusions about BP
Abo-Zenah, 2009[16]	To screen a population with sickle cell hematopathology (SCH) prospectively for surrogate markers of cardiorenal risk such as albuminuria and intima-media thickness(IMT)	Patients aged 15 yr or older with sickle cell hematopathology and Saudi nationality, receiving primary care at the King Abdulaziz Naval Base Mean age: 27.7 (7.5) Male: 19.5% HbAS: 73%	133	Normal albuminuria: 68.1 (9.8) Microalbuminuria: 71.9 (11.5) Macroalbuminuria: 72.3 (7.2)	Normal albuminuria: 115.9 (14.3) Microalbuminuria: 125.1 (13.2) Macroalbuminuria: 132.5 (8.1)	NA	NA	NA	NA	Patients with increased urinary albumin excretion had significantly higher SBP compared with those patients with normoalbuminuria. Markers of cardiorenal risk such as albuminuria and IMT are common findings in SCH patients of Arabic descent and could be useful screening tools to identify sicklers at risk for cardiovascular and renal events
Ataga, 2004[17]	To determine the prevalence of pulmonary hypertension (PHTN) in adult patients with SCD and to identify factors associated with this life-threatening complication	Participants at least 18 yr of age, followed in the Sickle Cell Clinic at the University of North Carolina Hospitals, and not in crisis Mean: 37 (12) Male: 47% HbSS: 80% HbSβ-thal: 10% HbSC: 10%	With PHTN: 18	Patients with PHTN: 64 (12)	Patients with PHTN: 119 (13)	Same group Participants at least 18 yr of age, followed in the Sickle Cell Clinic at the University of North Carolina Hospitals, and not in crisis Mean: 37 (12) Male: 47% HbSS: 80% HbSβ-thal: 10% HbSC: 10%	Without PHTN: 42	NA Patients without PHTN: 68 (13)	NA Patients without PHTN: 130 (16)	Patients with PHTN had significantly lower SBP (p=.01) than did those without PHTN. In a multivariate logistic model, lower SBP (OR per 10 mmHg decrease 1.8; 95% CI: 1.1 to 3.1) was associated independently with a greater risk of PHTN

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Ernst, 2000[18]	To compare the BP in African American patients with SCD-related crises and African American patients without SCD	All patients seen at an inner-city emergency department (ED) for SCD-pain crises over a 2-yr period Mean age: 28 Mean ED visits: 4.4 Male: 43% HbSS: 72% HbSC: 20% Hypertensive patients: 1%	106	72 (12)	119 (19)	African American patients without SCD Mean age: 35 Male: 54% HbAA: 100% Hypertensive patients: 20%	125	79 (13)	125 (17)	In patients without hypertension, both DBP (p<.01) and SBP (p<.01) were significantly lower in the SCD group compared to the patients without SCD
Gladwin, 2004[19]	To determine the prevalence and prognostic significance of PHTN in patients with SCD	Patients with SCD in community outpatient care who are stable (crisis free for at least 2 weeks, ACS free for 4 weeks) Mean age: 36 (12) Male: 42% HbSS: 69% HbSC: 28% HbSβ-thal: 12%	195	68 (12)	122 (18)	Age- and sex-matched HbAA African American participants Mean age: 37 (11) Male: 41%	41	77 (12)	133 (19)	Compared to controls, patients with SCD had significantly lower DBP (p<.001) and SBP (p=.002). Logistic-regression analysis of patients with SCD found that those patients with increased SBP were more likely to have PHTN (tricuspid jet velocity (TRJV) ≥2.5 m/s): OR=2.9 (95% confidence interval (CI) 1.6–5.3). TRJV ≥2.5 m/s was strongly associated with an increased risk of death (relative risk (RR): 10.1, 95% CI 2.2–47.0)

Study	Objective of study	SCD: Description [age (yr), genotypes (%), other characteristics]	SCD: No.	SCD: DBP (mmHg) Mean (SD)	SCD: SBP (mmHg) Mean (SD)	Control: Description	Control: No.	Control: DBP (mmHg) Mean (SD)	Control: SBP (mmHg) Mean (SD)	Study conclusions about BP
Gordeuk, 2008[20]	To determine if relative systemic hypertension (SBP 120–139 mmHg or DBP 70–89 mmHg) is associated with complications and adverse outcomes in SCD	Adults with HbSS or HbSβ-thal participating in the Sickle Cell Pulmonary Hypertension Screening Study HbSS: 97% HbSβ-thal: 3%	163	Group with DBP<70 Median: 59 (interquartile range: 54–64) Group with DBP 70–89 Median: 70 (interquartile range: 62–76) Group with DBP≥90 Median: 83 (interquartile range: 75–87)	Group with SBP<120: Median: 106 (interquartile range: 101–113) Group with SBP 120–139: Median: 127 (interquartile range: 121–131) Group with SBP≥140 Median: 148 (interquartile range: 144–155)	NA	NA	NA	NA	TRV was elevated (>2.5 m/s) in 27% of the patients with normal BP; in 37% with relative hypertension; and in 93% with hypertension (*P*<.0005 for trend). Serum creatinine was elevated (1.0 mg/dL or higher) in 7% of patients with normal BP; in 17% with relative hypertension; and 50% with hypertension (*P*<.0005 for trend). Over 2 yr of followup, there were trends for more frequent progression to elevated TRV (*P*=.073) or creatinine (*P*=.037) values in the higher systemic BP categories
Guasch, 2006[21]	To evaluate the role of anemia and other hematologic alterations in the pathogenesis of sickle cell glomerulopathy	Adult, active patients with SCA at Georgia Comprehensive Sickle Cell Center Median age: 32 (range 19–71) Male: 46% HbSS: 100%	184	Normoalbuminuria patients: 62 (1) Microalbuminuria patients: 63 (1) Macroalbuminuria patients: 69 (1)	Normoalbuminuria patients: 121 (2) Microalbuminuria patients: 124 (2) Macroalbuminuria patients: 127 (2)	Adult, active patients with HbSC, HbSD, or HbSβ-thal Median age: 36 (19–76) Male: 50% HbSS: 0%	116	Normoalbuminuria patients: 73 (2) Microalbuminuria patients: 75 (2) Macroalbuminuria patients: 86 (3)	Normoalbuminuria patients: 127 (2) Microalbuminuria patients 131 (3) Macroalbuminuria patients: 147 (6)	Patients with HbSS disease and macroalbuminuria had a much smaller increase in BP than patients with HbSS and normal urine albumin. The average increase in SBP and DBP was only 6 and 7 mmHg, respectively. (This increase occurred only in patients >40 yr.) Only individuals with advanced renal insufficiency (creatinine clearance <30 mL/min) had systemic BP levels higher than those of other patients with HbSS

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Lemogoum, 2004[22]	To evaluate if lower BP and increased vasodilatation in patients with HbSS are translated by lower arterial stiffness determined by pulse wave velocity (PWV) and wave reflections assessed by augmentation index	Ambulatory patients with SCA, clinically stable and averaged 1 vaso-occlusive crisis (VOC) per yr Mean age: 24 (7) HbSS: 100% Male: 60%	20	Aortic DBP: 67 (9) Brachial DBP: 65 (8)	Aortic SBP: 96 (10) Brachial SBP: 113 (12) MAP: 80 (9)	Age-, gender-, height-, and BMI-matched healthy community controls Mean age: 24 (6) HbAA: 100% Male: 50%	20	Aortic DBP: 77 (8) Brachial DBP: 75 (8)	Aortic SBP: 105 (11) Brachial SBP: 117 (13) MAP: 90 (8)	Brachial SBP did not differ between patients with HbSS and HbAA (p=.35). Brachial DBP was significantly lower in patients with HbSS (p=.0004), and both aortic SBP (p=.009) and aortic DBP (p=.0006) were lower in patients with HbSS compared to patients with HbAA. Multivariate analysis restricted to HbSS indicated a positive association between carotid PWV and carotid radial PWV with age, but a negative association with MAP (R^2=0.57 and 0.51, respectively, both P<.001), whereas MAP and heart rate were independently associated with augmentation index (R^2=.65, P<.001)

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Nebor, 2010[23]	To identify possible risk factors for albuminuria as an early marker of SCD glomerulopathy	Adults, 18–75 yr, French Caribbean HbSS: 100%	189: 85 were normoalbu-minuric (50.3%), 53 microalbu-minuric (28%), and 41 macroalbu-minuric (21.7%)	Normoalbuminuria patients: 65 (range: 42–82) Microalbuminuria patients: 66 (range: 50–100) Macroalbuminuria patients: 66 (range: 45–92)	Normoalbuminuria patients: 118 (range: 82–157) Microalbuminuria patients:: 120 (range: 95–190) Macroalbuminuria patients: 128 (range: 100–180)	NA	NA	NA	NA	28% had microalbuminuria, and 22% had macroalbuminuria The occurrence of albuminuria increased with age and duration of disease. SBP increased with graded albuminuria, reaching statistical significance in patients who were macroalbuminuric compared to patients who were normoalbuminuric Albuminuria-free survival is longer in SCD with α-thal than without it
Ohene-Frempong, 1998[24]	To examine prevalence and incidence of cerebrovascular accident in the sickle cell population and the effects of age, genotype, and other risk factors	Patients enrolled in the Cooperative Study of Sickle Cell Disease from 1978 to 1988 Mean age: 14.1 HbSS: 68% HbSC: 22% HbSβ-thal: 10%	4,082	NR	NR	NA	NA	NA	NA	Elevated SBP was a risk factor for ischemic stroke: Relative Risk was 1.31 per 10 mmHg increase (95% CI 1.03, 1.67, *p*=.33)

Study	Objective of study	SCD: Description [age (yr), genotypes (%), other characteristics]	SCD: No.	SCD: DBP (mmHg) Mean (SD)	SCD: SBP (mmHg) Mean (SD)	Control: Description	Control: No.	Control: DBP (mmHg) Mean (SD)	Control: SBP (mmHg) Mean (SD)	Study conclusions about BP
Pegelow, 1997[25]	To determine whether and to what degree BP in individuals with SCD is lower than published normal values	Patients with SCD seen at 23 clinical centers participating in the CSSCD study Age range: 2–44 HbSS: 76% HbSC: 24%	3,317	Values were provided for each age strata for males and females Median, F 2–3 yr : 52 4–5 yr: 60 6–7 yr: 60 8–9 yr : 60 10–11 yr : 60 12–13 yr: 62 14–15 yr: 70 16–17 yr : 70 18–24 yr : 64 25–34 yr: 68 35–44 yr: 70 Median, M 2–3 yr : 54 4–5 yr: 60 6–7 yr: 60 8–9 yr: 60 10–11 yr : 60 12–13 yr: 64 14–15 yr: 64 16–17 yr : 70 18–24 yr : 68 25–34 yr: 70 35–44 yr: 70	Values were provided for each age stratum for males and females Median, F 2–3 yr : 90 4–5 yr: 95 6–7 yr: 96 8–9 yr : 96 10–11 yr : 104 12–13 yr: 106 14–15 yr: 110 16–17 yr : 110 18–24 yr : 110 25–34 yr: 110 35–44 yr: 110 Median, M 2–3 yr : 90 4–5 yr: 95 6–7 yr: 100 8–9 yr : 100 10–11 yr : 100 12–13 yr: 110 14–15 yr: 108 16–17 yr : 112 18–24 yr : 112 25–34 yr: 114 35–44 yr: 110	Race-, age-, and sex-matched data from the National Health and Examination Survey (NHANES) I and II Age range: 2–44	Unclear	NR	NR	BP was significantly lower in patients with HbSS than published norms for age, race, and sex, a difference that increased with age. It correlated with BMI, hemoglobin, measures of renal function, and age. The risk for occlusive stroke increased with SBP (p=.04) but not DBP. Mortality was related to elevated BP in males (P<.05) and to a lesser extent in females (P=.10). In patients with HbSC disease, BP deviated from normal but to a lesser degree

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Rodgers, 1993[26]	To compare the BP values in patients with SCA to patients with other congenital anemias of similar magnitude, and determine BP levels in patients with and without stroke	Patients with SCA admitted for routine followup at NIH from 1975 to 1984 African American: 100% Male: 59% HbSS: 100%	89	All patients: 69 (8)	All patients: 112 (11)	β-thal: Patients with β-thal admitted for routine followup at NIH from 1975 to 1984 Caucasian: 100% Male: 58%	β-thal:110	All β-thal: 65 (7)	All β-thal: 104 (10)	Patients with SCA had significantly higher DBP (p=.004) and SBP (p<.0001) compared to patients with β-thal when analyzed separately by logistic regression. With SBP in the regression equation, DBP was no longer significant. After age 17, patients with SCA had significantly lower SBP and DBP compared to normal age-matched controls. In patients with SCA, there was an association between stroke and elevated BP, even in a range of SBP and DBP that would be considered normal
Rogovik, 2009[27]	To identify factors associated with admission and a longer length of stay due to VOC in children with SCD	Children 18 yr and younger admitted to emergency room (ER) with painful VOC due to SCD Mean age: 10.6 (4.5) HbSS: 81.3% HbSA: 10.8% HbSβ-thal: 8% Male: 43.7%	428 visits (346 admissions and 82 discharges of 169 patients)	Admitted patients: 64 (12) Discharged patients: 61 (12)	Admitted patients: 112 (13) Discharged patients: 105 (17)	NA	NA	NA	NA	Increased SBP at triage was associated with admission to the hospital (odds ratio (OR), 1.04; P =.02)
Strouse, 2006[28]	To evaluate risk and prognostic factors for primary hemorrhagic stroke compared to ischemic stroke among children with SCD	Hospitalized children <19 yr, with SCD and intraparenchymal, subarachnoid, or intraventricular hemorrhage Mean age: 10.4 Male: 40% HbSS: 87% HbSβ-thal: 13%	15	74 (6)	130 (9)	Children with SCD and ischemic stroke, matched to cases by year of diagnosis Mean age: 5.2 yr Male: 45% HbSS: 97% HbSβ-thal: 3%	29	61 (2)	110 (2)	Children with hemorrhagic stroke had higher DBP (p<.05) and SBP (p<.01) at time of diagnosis compared to children with ischemic stroke. When compared with ischemic strokes, hemorrhagic strokes were associated with a history of hypertension (OR: not calculable; 95% CI: 1.7 to not calculable; P<.05)

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Strouse, 2008[29]	To characterize risk factors for re-admission and prolonged hospitalization after ACS	Patients <22 yr with SCD, hospitalized with ACS at Johns Hopkins from Jan. 1998 to Feb. 2004 Mean age: 125 HbSS: 86% episodes HbSC: 14% episodes Males: 65% episodes	129 admissions (65 patients, 58% with a single admission)	NR	NR	NA	NR	NR	NR	Risk of re-admission increased with higher diastolic BP (increase of 10 mg of Hg) 48 h after diagnosis (OR 1.8 (1.2–2.8) 95% CI, p<.01). A higher systolic BP (increase 10 mg of Hg) at diagnosis of ACS was also associated with increased risk of re-admission, but not significantly (OR 1.7 (.99–2.9) 95% CI, p=.06)

Table 3. Studies Reporting Treatment Outcomes of Hypertension

Study	Objective of study	Intervention 1: Description [age (yr), genotypes (%), other characteristics]	Intervention 1: No.	Intervention 1: DBP (mmHg) Mean (SD)	Intervention 1: SBP (mmHg) Mean (SD)	Intervention 2: Description	Intervention 2: No.	Intervention 2: DBP (mmHg) Mean (SD)	Intervention 2: SBP (mmHg) Mean (SD)	Study conclusions about BP (also describe in details the treatment of BP and how it affects outcomes)
Foucan, 1998[30]	To evaluate the effect of angiotensin-converting enzyme inhibition (captopril) on microalbuminuria in patients with SCA	Captopril Patients ≥18 yr, with SCA, who are taking captopril and have urinary albumin excretion between 30 and 300 mg per 24 h on 3 separate occasions during the 6-mo period preceding the study Patients received captopril 6.25 mg/d for 1 mo, 12.5 mg/d for 2 mo, and then 25 mg/d until the last 3 mo (6 mo total) Age: 30 Male: 42% HbSS: 100%	12	Before study starts 63 (7) End of study 58	Before study starts 121 (11) End of study 113	Placebo Patients ≥18, with SCA, who are taking placebo and have urinary albumin excretion of 30–300 mg per 24 h on 3 separate occasions during the 6-mo period preceding the study Patients received placebo daily Age: 28 Male: 20% HbSS: 100%	10	Before study 61 (6) End of study 64	Before study 118 (8) End of study No change	At 6 mo, in patients treated with captopril, there was a decline of 8 mmHg in SBP and of 5 mmHg in MAP and DBP. In placebo-treated patients, SBP did not change during the study, and DBP had increased by 3 mmHg by the end of the study. The change in BP was significantly different between the 2 groups only for DBP at 6 mo (*P*<.01). Captopril slightly decreases blood pressure in patients with SCA
Jaja, 2002[31]	To examine the effects of ascorbic acid (100 mg/d for 6 weeks) supplementation on BP, some hematological indices, and osmotic fragility in children suffering from SCA	Patients with SCA and regularly attending the pediatric outpatient clinic in Lagos, Nigeria Age range: 4–11 yr HbSS: 100%	15	Presupplement mean (range): 62.7 (50–70). Postsupplement mean (range): 55.5 (50–60).	Presupplement mean: 95.5 (range: 80–130). Postsupplement mean: 84.6 (range: 80–90)	NA	NA	NA	NA	6 weeks of supplementation of ascorbic acid (100 mg/d) significantly reduced SBP (*p*<.01) and DBP (*p*=<.01) in patients with SCA

Study	Objective of study	Intervention 1: Description [age (yr), genotypes (%), other characteristics]	Intervention 1: No.	Intervention 1: DBP (mmHg) Mean (SD)	Intervention 1: SBP (mmHg) Mean (SD)	Intervention 2: Description	Intervention 2: No.	Intervention 2: DBP (mmHg) Mean (SD)	Intervention 2: SBP (mmHg) Mean (SD)	Study conclusions about BP (also describe in details the treatment of BP and how it affects outcomes)
Uzun, 2010[32]	To determine the effectiveness of meperidine vs. tramadol in the management of vaso-occlusive crisis in patients with SCD	Patients with SCD presenting to the ER with pain crisis treated with meperidine (initial doses: 1 and 1.5 mg/kg, both as intravenous slow infusion in 20 min, respectively) Mean age: 24.9 yr HbSS: 97% HbSβ-thal: 3% Male: 76%	34	Baseline 71 (11) After 120 min 59 (7)	Baseline 121 (13) After 120 min 96 (10)	Patients with SCD presenting to the ER with pain crisis treated with tramadol (initial doses: 1 and 1.5 mg/kg, both intravenous slow infusion in 20 min, respectively) Mean age: 24.8 yr HbSS: 97% HbSβ-thal: 3% Male: 68%	34	Baseline 73 (10) After 120 min 59 (7)	Baseline 122 (17) After 120 min 114 (12)	At 2 h, there was a 25±3 mmHg decrease in SBP in patients receiving meperidine (p<.05); in the tramadol group, there was 8±5 mmHg decrease (p<.05). The greater reduction in the meperidine group began at 30 min onward (p<.05). A smaller decrease in DBP at 2 h was observed in both groups (p<.05), which was more pronounced within the meperidine group (12 mmHg). Both meperidine and tramadol administration resulted in a significant reduction in systolic and diastolic blood pressure after 2 hours (p<.05). Efficacy in pain relief between the analgesics was more rapid and better in the meperidine group, although the degree of relief was significantly improved compared to baseline levels in both groups (p<.05)

Table 4. Study Design and Quality*

Study	Design	Sampling	% Loss to followup	Baseline imbalances	BP measurement
Abo-Zenah, 2009[16]	Cross-sectional study	Unclear sampling (likely consecutive patients)	NR	NA	Clinical
Adams-Campbell, 1993[1]	Cross-sectional study	Unclear sampling	NR	Subjects with HbSS had lower weight and BMI compared to subjects with HbSA and HbAA	Clinical
Adebayo, 2002[2]	Prospective cohort	Unclear sampling (likely convenience sample)	NR	The mean packed cell volume was lower in patients with SCD compared with controls. There were significant differences in frequencies of displacement of apex beat, left parasternal heave, loud pulmonary component of the second heart sound, and the presence of cardiac murmurs	Clinical
Adeodu, 2001[3]	Cross-sectional study	Consecutive sample	27% of children with HbSS + CH were not enrolled in study	NA	Clinical
Aderibigbe, 1999[4]	Cross-sectional study	Random sample	NR	Controls were slightly older and weighed more than study subjects	Clinical
Ataga, 2004[17]	Cross-sectional study	Random for the first 45 patients, then consecutive patients	NR	NA	Clinical
Ernst, 2000[18]	Cross-sectional study	Consecutive sample	NR	Patients in control group were significantly older compared to patients with SCD	Clinical
Foucan, 1998[30]	RCT	Allocation concealment not reported Patients and caregivers blinded	2 (9%) patients withdrew	No	Clinical
Gladwin, 2004[19]	Prospective cohort	Consecutive sample	2.5%	Subjects with SCD had greater mean left and right atrial size, tricuspid regurgitant jet velocity, white cell platelet count, bilirubin, alanine and aspartate aminotransferase, lactate dehydrogenase, ferritin, and iron compared to control. They had low transferrin, hemoglobin, arginine, and arginine–ornithine ratio compared to control	Clinical
Gordeuk, 2008[20]	Prospective cohort	Convenience sample	NR, but 47% did not have 2-yr followup	NA	Clinical
Guasch, 2006[21]	Cross-sectional study	Unclear sampling (likely convenience sample)	NR	Patients with HbSS had worse anemia, a higher degree of ineffective erythropoiesis, and higher white blood cell and platelet counts. Body weight and BMI were significantly lower in patients with HbSS	Clinical
Hatch, 1989[5]	Prospective cohort, cross-sectional analysis	Unclear sampling, likely convenience sample	NR	NR	Clinical

* Quality assessment for randomized trials and comparative observational studies was based on selected items from the Cochrane Risk of Bias and Newcastle-Ottawa Scale.

Study	Design	Sampling	% Loss to followup	Baseline imbalances	BP measurement
Homi, 1993[6]	Prospective cohort, cross-sectional analysis	Unclear sampling	Only 39% of subjects had all 3 (BP, height, and weight) measurements to include	NR	Clinical
Jaja, 2000[7]	Cross-sectional study	Unclear sampling, likely convenience sample	NR	Mean height, weight, and body surface area were lower in SCA subjects	Clinical
Jaja, 2002[31]	Prospective cohort study	Unclear sampling, likely convenience sample	NR	NA	Clinical
Johnson, 1981[8]	Cross-sectional study	Unclear sampling	NR	NA	Clinical
Lemogoum, 2004[22]	Cross-sectional study	Unclear sampling	NR	No	Clinical
Martins, 1999[9]	Cross-sectional study	Unclear sampling	NR	No	Clinical
Minniti, 2009[10]	Prospective cohorts, cross-sectional analysis	Consecutive patients	NR	Differences in hemolysis measures, creatinine, hemoglobin O_2 saturation, walk-test results, and left ventricular internal diameter z-score	Clinical
Mohan, 1995[11]	Prospective cohort	Unclear sampling, likely convenience sample	NR	NR	Clinical
Nebor, 2010[23]	Prospective cohort, cross-sectional analysis	Unclear sampling	NR	NA	Clinical
Oguanobi, 2010[12]	Cross-sectional	Unclear sampling, likely convenience sample	NR	The study subjects had statistically significant lower mean height, weight, BMI, and body surface area compared to controls	Clinical
Ohene-Frempong, 1998[24]	Prospective cohort study	CSSCD study: Randomized sampling of patients seen at clinical centers over 2 yr	NR	NA	Clinical
Pegelow, 1997[25]	Prospective cohort	CSSCD Study: Randomized sampling of patients seen at clinical centers over 2 yr	NR	NA	Clinical
Rodgers, 1993[26]	Retrospective cohort	Consecutive sample	2% were excluded for renal insufficiency	NR	Clinical
Rogovik, 2009[27]	Retrospective cohort	Consecutive patients	NR	NA	Clinical
Strouse, 2006[28]	Retrospective case-control	Unclear sampling, likely consecutive sample	NR	Premorbid BP at well visits (systolic: 106±4 vs. 101±4 mmHg; diastolic: 61±4 mmHg vs. 57±2 mmHg) were higher in case than control subjects but were nearly identical after adjustment for age and gender	Clinical
Strouse, 2008[29]	Retrospective cohorts	Unclear sampling, likely consecutive sample	NR	Severity of ACS was greater in patients treated with corticosteroids and transfusions	Clinical
Sullivan, 2010[13]	Prospective cohort, cross-sectional analysis	Unclear sampling, likely convenience sample	0	Healthy controls had higher hemoglobin concentration and greater FEV1 and FVC values	Clinical

Study	Design	Sampling	% Loss to followup	Baseline imbalances	BP measurement
Taylor, 2008[14]	Prospective cohort, cross-sectional analysis	Unclear sampling of participants of the CSSCD and NIH PH studies	NR	Subjects with chronic hyperhemolysis had significantly higher levels of total bilirubin, AST, plasma hemoglobin concentration, and plasma vascular cell adhesion molecule-1. This group also had lower hemoglobin concentration, serum arginine, arginine to ornithine ratios, and HbF levels	Clinical
Thompson, 2007[15]	Prospective cohort, cross-sectional analysis	Convenience sample	0	Weight, body surface area, BMI, and age were lower in subjects with HbSS	Clinical
Uzun, 2010[32]	RCT	Consecutive patients, allocation concealment: NR No blinding	0	None	Clinical

Studies from Taylor[14], Ohene-Frempong[24], and Pegelow[25] used data from the Cooperative Study of Sickle Cell Disease (CSSCD) patient population.

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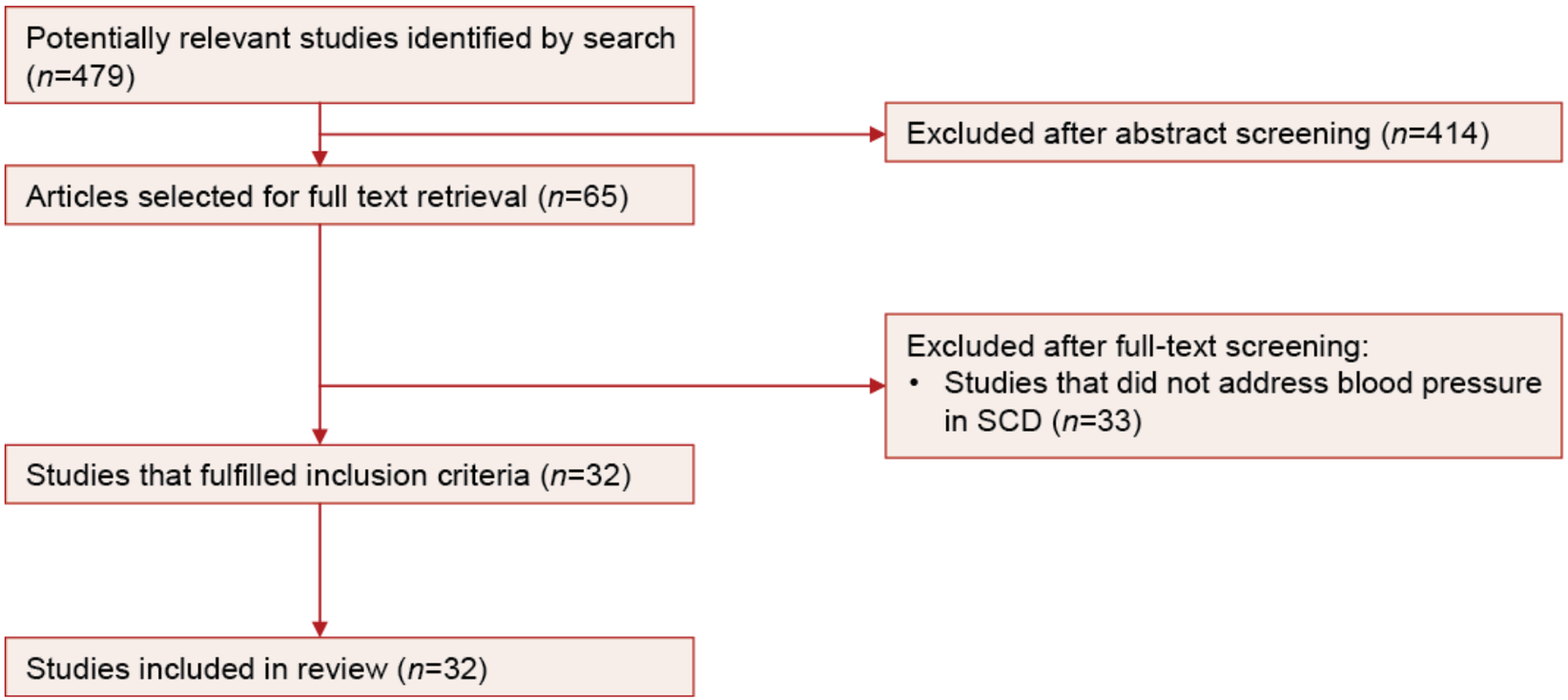
Appendix A: Study Selection Process



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 interviewer 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 Questions of the Systematic Review (PICOS)*

Question 1 (Observational studies have no intervention)

Patients/Exposure:

- Individuals with SCD

Comparison:

- Age- or sex-matched healthy controls or patients with confirmed AA genotype

Outcomes:

- Diastolic, systolic, and mean blood pressure
- Prognosis of hypertension

Study Design:

- Randomized or nonrandomized studies with original data

Question 2

Patients:

- Individuals with SCD and hypertension

Intervention:

- Treatment of hypertension (pharmacological or lifestyle-based)

Comparison:

- Alternative treatment approach of hypertension (pharmacological or lifestyle-based)

Outcomes:

- Cardiovascular and cerebrovascular outcomes
- Blood pressure control

Study Design:

- Randomized or nonrandomized studies with original data

* PICOS = patient/exposure, comparison, outcomes, and study design.

Appendix C: Data Sources and Search Strategies

A comprehensive search of several databases (from 1970 to January 2011, 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 sickle cell disease and blood pressure/hypertension as well as to limit to observational studies and randomized controlled trials. Additional references were identified by consulting with experts in the field.

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Database(s): EMBASE 1988 to 2011 Week 02, 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/	29,650
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.	34,025
3	1 or 2	34,026
4	exp Blood Pressure/	449,886
5	("blood pressure*" or "pulse pressure*" or "diastolic adj2 pressure*" or "systolic adj2 pressure*" or "blood tension" or "intravascular pressure*" or normotension or "vascular pressure*" or "arterial pressure*" or "capillary pressure*" or "atrium pressure*" or "ventricle pressure*" or "artery occlusion pressure*" or "venous pressure*").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	667,536
6	exp Hypertension/	467,216
7	(hypertension or hypertensive or "apparent mineralocorticoid excess syndrome" or "gordon syndrome liddle syndrome" or "ocular ischemic syndrome" or "posterior reversible encephalopathy syndrome").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	696,230
8	or/4-7	1,139,368
9	3 and 8	1,726
10	exp case study/	1,485,085
11	exp Cohort Studies/	1,221,521
12	exp longitudinal study/	816,106
13	exp retrospective study/	573,351
14	exp prospective study/	492,319
15	exp observational study/	17,629
16	((comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or followup or observational) adj (study or studies or survey or surveys or analysis or analyses)).mp.	3,658,969

#	Searches	Results
17	exp comparative study/	2,095,838
18	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	138,131
19	or/10-18	5,292,824
20	exp controlled study/	3,447,907
21	exp evidence based medicine/	485,451
22	evidence-based.mp.	156,869
23	((controls or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	4,395,999
24	meta analysis/	78,413
25	meta-analyss.mp.	122,440
26	exp "systematic review"/	37,699
27	systematic reviews.mp.	84,000
28	exp Guideline/ or exp Practice Guideline/	256,636
29	guidelines.ti.	79,717
30	or/20-29	4,869,380
31	from 9 keep 1-1689	1,689
32	31 and (19 or 30)	660
33	from 9 keep 1058-1689	632
34	limit 33 to (comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial) [Limit not valid in EMBASE,CDSR; records were retained]	65
35	from 9 keep 1690-1726	37
36	32 or 34 or 35	697
37	remove duplicates from 36	527
38	limit 37 to English language [Limit not valid in CCTR,CDSR; records were retained]	502
39	limit 38 to yr="1970 -Current"	500
40	limit 39 to (book or book series or editorial or erratum or letter or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legislation or news or newspaper article 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]	35
41	39 not 40	465
42	from 41 keep 1-210	210
43	41 not 42	255
44	from 43 keep 1-250	250

#	Searches	Results
45	43 not 44	5
46	from 40 keep 17-35	19

Scopus

1. TITLE-ABS-KEY("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")
2. TITLE-ABS-KEY("blood pressure*" or "pulse pressure*" or (diastolic W/2 pressure*) or (systolic W/2 pressure*) or "blood tension" or "intravascular pressure*" or normotension or "vascular pressure*" or "arterial pressure*" or "capillary pressure*" or "atrium pressure*" or "ventricle pressure*" or "artery occlusion pressure*" or "venous pressure*")
3. TITLE-ABS-KEY(hypertension or hypertensive or "apparent mineralocorticoid excess syndrome" or "gordon syndrome" "liddle syndrome" or "ocular ischemic syndrome" or "posterior reversible encephalopathy syndrome")
4. 1 and (2 or 3)
5. TITLE-ABS-KEY("comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey")
6. TITLE-ABS-KEY("retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis")
7. TITLE-ABS-KEY("incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis")
8. TITLE-ABS-KEY("observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies")
9. TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analysis*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 study*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*))
10. 4 and (5 or 6 or 7 or 8 or 9)
11. PUBYEAR AFT 1969 AND LANGUAGE(English)
12. 10 and 11
13. 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*)
14. 12 and not 13
15. DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
16. 14 and not 15

Appendix D: Excluded Studies

Author	Yr	Title	Reason for Exclusion
Anyaegbunam	1988	The application of uterine and umbilical artery velocimetry to the antenatal supervision of pregnancies complicated by maternal sickle hemoglobinopathies	Does not include blood pressure outcomes
Aygun	2009	Glomerular hyperfiltration and microalbuminuria in children with sickle cell anemia	Does not include blood pressure outcomes
Braden	1996	Cardiovascular function during rest and exercise in patients with sickle-cell anemia and coexisting alpha thalassemia-2	Does not include blood pressure outcomes
Cabannes	1983	Acute painful sickle-cell crises in children. A double-blind, placebo-controlled evaluation of efficacy and safety of cetiedil	Does not include blood pressure outcomes
Christensen	1996	Transdermal fentanyl administration in children and adolescents with sickle cell pain crisis	Does not include blood pressure outcomes
De Castro	2008	Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes	Does not include blood pressure outcomes
Falk	1992	Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme	Does not include blood pressure outcomes
Fitzhugh	2005	Enalapril and hydroxyurea therapy for children with sickle nephropathy	Does not include blood pressure outcomes
Gordeuk	2009	Relationship of erythropoietin, fetal hemoglobin, and hydroxyurea treatment to tricuspid regurgitation velocity in children with sickle cell disease	Does not include blood pressure outcomes
Gurkan	2010	Lactate dehydrogenase as a predictor of kidney involvement in patients with sickle cell anemia	Does not include blood pressure outcomes
Hankins	2008	The natural history of conditional transcranial Doppler flow velocities in children with sickle cell anaemia	Does not include blood pressure outcomes
Hill	2006	Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function	Does not include blood pressure outcomes
Huynh	2009	Pulmonary embolism in sickle cell disease: a case-control study	Does not include blood pressure outcomes
Jaja	2008	Cardiac and autonomic responses to change in posture or vitamin C supplementation in sickle cell anemia subjects	Does not include blood pressure outcomes
Jyothi	2009	Prevalence and risk factors of microalbuminuria in children with sickle cell disease	Does not include blood pressure outcomes
Kabeya Kabenkana	1994	C.T. scan features in stroke in the urban black Africans	Does not include blood pressure outcomes
Kim	2009	Dynamic cerebral autoregulation in homozygous sickle cell disease	Does not include blood pressure outcomes
Kinney	1999	Silent cerebral infarcts in sickle cell anemia: a risk factor analysis	Does not include blood pressure outcomes
Larbpaiboonpong	2009	The early outcome of Birmingham hip resurfacing: an independent Thai surgeon experiences	Does not include blood pressure outcomes
Machado	2010	Evaluation of sildenafil therapy for patients with sickle cell disease and increased tricuspid regurgitant velocity: An independent Thai surgeon's experience(s)—preliminary results of the walk-PHaSST trial [Abstract]	Does not include blood pressure outcomes
Maduska	1975	Sickling dynamics of red blood cells and other physiologic studies during anesthesia	Does not include blood pressure outcomes

Author	Yr	Title	Reason for Exclusion
Mankad	1983	Clinical effects of intravenous cetiedil, a candidate anti-sickling agent	Does not include blood pressure outcomes
McKerrell	2004	The older sickle cell patient	Does not include blood pressure outcomes
Naoman	2010	Echocardiographic findings in patients with sickle cell disease	Does not include blood pressure outcomes
Nomura	2009	Low Apgar's score at first minute and maternal platelet count in pregnancies complicated by sickle cell disease	Does not include blood pressure outcomes
Powars	1991	Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality	Does not include blood pressure outcomes
Reid	1985	Haemorheological parameters in hypertensive Nigerians with and without sickle cell trait	Does not include blood pressure outcomes
Schein	2008	Magnetic resonance detection of kidney iron deposition in sickle cell disease: a marker of chronic hemolysis	Does not include blood pressure outcomes
Sellers	1978	Intermittent hypertension during sickle cell crisis	Does not include blood pressure outcomes
Strouse	2009	The excess burden of stroke in hospitalized adults with sickle cell disease	Does not include blood pressure outcomes
Weiner	2003	Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease [Erratum appears in JAMA. 2004 Aug 25;292(8):925.]	Does not include blood pressure outcomes
Yium	1994	Autosomal dominant polycystic kidney disease in blacks: clinical course and effects of sickle cell hemoglobin	Does not include blood pressure outcomes
Youssef	2008	Physiologic effects of pneumoperitoneum in adults with sickle cell disease undergoing laparoscopic cholecystectomy: a case control study	Does not include blood pressure outcomes

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