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Interventions for chronic kidney disease in people with sickle cell disease (Review)

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Interventions for chronic kidney disease in people with sickle cell disease.
Cochrane Database of Systematic Reviews 2023, Issue 8. Art. No.: CD012380.
DOI: 10.1002/14651858.CD012380.pub3.

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[Intervention Review]

Interventions for chronic kidney disease in people with sickle cell disease

Noemi BA Roy[1], Abigail Carpenter[2], Isabella Dale-Harris[3], Carolyn Dorée[4], Lise J Estcourt[5]

[1]Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. [2]Medical School, University of Nottingham, Nottingham, UK. [3]Medical School, University of Leeds, Leeds, UK. [4]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. [5]Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK

Contact: Lise J Estcourt, lise.estcourt@nhsbt.nhs.uk.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2023.

Citation: Roy NBA, Carpenter A, Dale-Harris I, Dorée C, Estcourt LJ. Interventions for chronic kidney disease in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2023, Issue 8. Art. No.: CD012380. DOI: 10.1002/14651858.CD012380.pub3.

ABSTRACT

Background

Sickle cell disease (SCD), one of the commonest severe monogenic disorders, is caused by the inheritance of two abnormal haemoglobin (beta-globin) genes. SCD can cause severe pain, significant end-organ damage, pulmonary complications, and premature death. Kidney disease is a frequent and potentially severe complication in people with SCD.

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for more than three months. Sickle cell nephropathy refers to the spectrum of kidney complications in SCD.

Glomerular damage is a cause of microalbuminuria and can develop at an early age in children with SCD, with increased prevalence in adulthood. In people with sickle cell nephropathy, outcomes are poor as a result of the progression to proteinuria and chronic kidney insufficiency. Up to 12% of people who develop sickle cell nephropathy will develop end-stage renal disease.

This is an update of a review first published in 2017.

Objectives

To assess the effectiveness of any intervention for preventing or reducing kidney complications or chronic kidney disease in people with sickle cell disease. Possible interventions include red blood cell transfusions, hydroxyurea, and angiotensin-converting enzyme inhibitors (ACEIs), either alone or in combination.

Search methods

We searched for relevant trials in the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register, CENTRAL, MEDLINE, Embase, seven other databases, and two other trials registers.

Selection criteria

Randomised controlled trials (RCTs) comparing interventions to prevent or reduce kidney complications or CKD in people with SCD. We applied no restrictions related to outcomes examined, language, or publication status.

Data collection and analysis

Two review authors independently assessed trial eligibility, extracted data, assessed the risk of bias, and assessed the certainty of the evidence (GRADE).

Main results

We included three RCTs with 385 participants.

We rated the certainty of the evidence as low to very low across different outcomes according to GRADE methodology, downgrading for risk of bias concerns, indirectness, and imprecision.

Hydroxyurea versus placebo

One RCT published in 2011 compared hydroxyurea to placebo in 193 children aged nine to 18 months. We are unsure if hydroxyurea compared to placebo reduces or prevents progression of kidney disease assessed by change in glomerular filtration rate (mean difference (MD) 0.58 mL/min /1.73 m^2, 95% confidence interval (CI) −14.60 to 15.76; 142 participants; very low certainty). Hydroxyurea compared to placebo may improve the ability to concentrate urine (MD 42.23 mOsm/kg, 95% CI 12.14 to 72.32; 178 participants; low certainty), and may make little or no difference to SCD-related serious adverse events, including acute chest syndrome (risk ratio (RR) 0.39, 99% CI 0.13 to 1.16; 193 participants; low certainty), painful crisis (RR 0.68, 99% CI 0.45 to 1.02; 193 participants; low certainty); and hospitalisations (RR 0.83, 99% CI 0.68 to 1.01; 193 participants; low certainty).

No deaths occurred in either trial arm and the RCT did not report quality of life.

Angiotensin-converting enzyme inhibitors versus placebo

One RCT published in 1998 compared an ACEI (captopril) to placebo in 22 adults with normal blood pressure and microalbuminuria. We are unsure if captopril compared to placebo reduces proteinuria (MD −49.00 mg/day, 95% CI −124.10 to 26.10; 22 participants; very low certainty). We are unsure if captopril reduces or prevents kidney disease as measured by creatinine clearance; the trial authors stated that creatinine clearance remained constant over six months in both groups, but provided no comparative data (very low certainty).

The RCT did not report serious adverse events, all-cause mortality, or quality of life.

Angiotensin-converting enzyme inhibitors versus vitamin C

One RCT published in 2020 compared an ACEI (lisinopril) with vitamin C in 170 children aged one to 18 years with normal blood pressure and microalbuminuria. It reported no data we could analyse. We are unsure if lisinopril compared to vitamin C reduces proteinuria in this population: the large drop in microalbuminuria in both arms of the trial after only one month on treatment may have been due to an overestimation of microalbuminuria at baseline rather than a true effect.

The RCT did not report serious adverse events, all-cause mortality, or quality of life.

Authors' conclusions

We are unsure if hydroxyurea improves glomerular filtration rate or reduces hyperfiltration in children aged nine to 18 months, but it may improve their ability to concentrate urine and may make little or no difference to the incidence of acute chest syndrome, painful crises, and hospitalisations.

We are unsure if ACEI compared to placebo has any effect on preventing or reducing kidney complications in adults with normal blood pressure and microalbuminuria.

We are unsure if ACEI compared to vitamin C has any effect on preventing or reducing kidney complications in children with normal blood pressure and microalbuminuria.

No RCTs assessed red blood cell transfusions or any combined interventions to prevent or reduce kidney complications.

Due to lack of evidence, we cannot comment on the management of children aged over 18 months or adults with any known genotype of SCD.

We have identified a lack of adequately designed and powered studies, although we found four ongoing trials since the last version of this review. Only one ongoing trial addresses renal function as a primary outcome in the short term, but such interventions have long-term effects. Trials of hydroxyurea, ACEIs or red blood cell transfusion in older children and adults are urgently needed to determine any effect on prevention or reduction of kidney complications in people with SCD.

PLAIN LANGUAGE SUMMARY

Interventions to prevent or reduce kidney complications in people with sickle cell disease

Review question

Are there any safe and effective interventions that prevent or reduce kidney complications in people with sickle cell disease (SCD)?

Background

SCD is a serious inherited blood disorder where the red blood cells, which carry oxygen around the body, develop abnormally. Normal red blood cells are flexible and disc-shaped, but sickled cells are rigid and crescent-shaped, and stickier than normal red blood cells. This can lead to blockage of blood vessels, resulting in tissue and organ damage and episodes of severe pain. The abnormal cells are fragile and break apart easily, which leads to a decreased number of red blood cells, known as anaemia.

Kidney complications can start at an early age in children with SCD and are common in adults with the condition. Kidney complications leading to kidney protein leak and chronic kidney disease can be severe, with serious effects on health. Severe complications include the need for dialysis (a procedure to remove waste products and excess fluid from the blood when the kidneys stop working properly) or a kidney transplant. Identifying therapies that can prevent or slow down the decline in kidney function in people with SCD is critical for improving health outcomes.

Search date

The evidence is current to 22 September 2022.

Study characteristics

We found three randomised controlled trials, which enroled a total of 385 people. One trial, published in 2011, compared the drug hydroxyurea (which helps to maintain the shape and flexibility of red blood cells), to placebo (dummy treatment) in 193 children aged nine to 18 months. The second trial, published in 1998, compared captopril (a drug used to treat high blood pressure) to placebo in 22 adults with normal blood pressure and microalbuminuria (high levels of protein in the urine). The third trial, published in 2020, compared lisinopril (a drug used to treat high blood pressure) to vitamin C in 170 children aged one to 18 years.

Two trials received government funding; it was unclear how the third trial was funded.

Key results

In children aged nine to 18 months, hydroxyurea may increase the ability to produce normal urine, but we are unsure if it has any effect on the glomerular filtration rate (network of filters in the kidney that filter waste from the blood). Hydroxyurea may make little or no difference to the occurrence of serious complications including acute chest syndrome (pain, cough, fever, low oxygen levels, and abnormal substances in the lungs), painful crises, and hospitalisations.

We are unsure if giving captopril to adults with SCD who have normal blood pressure and early signs of kidney damage (microalbuminuria) reduces progression of kidney damage.

We are unsure if giving lisinopril to children aged one to 18 years with SCD who have normal blood pressure and early signs of kidney damage (microalbuminuria) reduces progression of kidney damage.

No trials reported quality of life.

Limitations of the evidence

We have little or very little confidence in the evidence because we only found three trials, and they had specific populations (only children or only adults), few participants, and wide variations in results.

Summary of findings 1. Hydroxyurea compared to placebo for preventing or reducing kidney complications in people with sickle cell disease

Hydroxyurea compared to placebo for preventing or reducing kidney complications in people with sickle cell disease

Patient or population: people with sickle cell disease
Setting: multiple centres
Intervention: hydroxyurea
Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (99% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with hydroxyurea				
Reduction or prevention of kidney disease progression	**GFR** (mL/min/1.73 m^2), assessed with ^{99m}Tc-DTPA clearance Follow-up: 18 to 24 months	Mean GFR measured at 18 to 24 months was 146.64 mL/min/1.73 m^2 (SD 43.7).	**MD 0.58higher** (14.6 lower to 15.76 higher)	—	142 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—
	Ability to concentrate urine (mOsm/kg) Follow-up: 18 to 24 months	Mean improvement in ability to concentrate urine measured at 18 to 24 months was 494.57 mOsm/kg (SD 110.07).	**MD 42.23higher** (12.14 higher to 72.32 higher)	—	178 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
Serious adverse events	**Acute chest syndrome**	**Study population**		**RR 0.39** (0.13 to 1.16)	193 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
		186 per 1000	72 per 1000 (24 to 215)				
	Painful crisis	**Study population**		**RR 0.68** (0.45 to 1.02)	193 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
		567 per 1000	386 per 1000 (255 to 578)				
	Hospitalisations	**Study population**		**RR 0.83** (0.68 to 1.01)	193 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
		866 per 1000	719 per 1000 (589 to 875)				
All-cause mortality		No deaths reported in either group.		Not estimable	193	⊕⊕⊖⊖	—

			(1 RCT)	**Low**[b,d]	
Quality of life	Not reported.				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **DTPA:** diethylenetriaminepentaacetic acid; **GFR**: glomerular filtration rate; **MD**: mean difference; **RCT**: randomised controlled trial; **RR**: risk ratio; **SD:** standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to unclear risk of attrition bias.
[b] Downgraded one level for indirectness, as the results apply only to children aged nine to 18 months.
[c] Downgraded one level for imprecision, as CIs are compatible with clinically significant harm or benefit.
[d] Downgraded one level for imprecision (no deaths occurred).

Summary of findings 2. Angiotensin-converting enzyme inhibitors compared to placebo for preventing or reducing kidney complications in people with sickle cell disease

ACEIs compared to placebo for preventing or reducing kidney complications in people with sickle cell disease

Patient or population: people with sickle cell disease
Setting: hospital outpatient
Intervention: ACEI (captopril)
Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with ACEI				
Reduction or prevention of kidney disease progression	**Proteinuria** (mg/day) Follow-up: 6 months	Mean proteinuria was 76 mg/day (SD 45).	**MD 49.00 lower** (124.10 lower to 26.10 higher)	—	22 (1 RCT)	⊕⊝⊝⊝ **Very low**[a]	—
Serious adverse events		Not reported.		—	—	—	—

All-cause mortality	Not reported.	—	—	—	—
Quality of life	Not reported.	—	—	—	—

*The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ACEI: angiotensin-converting enzyme inhibitor; **CI**: confidence interval; **MD**: mean difference; **RCT:** randomised controlled trial; **SD:** standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels for unclear or high risk of bias in all domains, one level for indirectness (small sample population of adults with normal blood pressure and microalbuminuria), and one level for imprecision (very wide CIs including clinically significant harm and benefit).

Summary of findings 3. Angiotensin-converting enzyme inhibitors compared to vitamin C for preventing or reducing kidney complications in people with sickle cell disease

ACEI (lisinopril) compared to vitamin C for preventing or reducing kidney complications in people with sickle cell disease

Patient or population: children with sickle cell anaemia and microalbuminuria
Setting: outpatients
Intervention: ACEI (lisinopril)
Comparison: vitamin C

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with vitamin C	Risk with ACEI (lisinopril)				
Reduction or prevention of kidney disease progression	**Proteinuria (mg/g)** Follow-up: 3 months	There was a reduction in proteinuria in both groups, but it is unclear whether there was a difference between groups. In the ACEI group, mean microalbuminuria reduced from 134.2 mg/g (SD 72.5) at baseline to 7.6 mg/g (SD 1.6) at 1 month, 7.0 mg/g (SD 1.4) at 3 months, and 6.5 mg/g (SD 1.1) at 3 months; whereas in the vitamin C group, mean microalbuminuria reduced from 107.6 mg/g (SD 58.0) at baseline to 11.5 mg/g (SD 2.9) at 1 month, 8.0 mg/g (SD 2.1) at 2 months, and 7.9 mg/g (SD 1.1) at 3 months.		—	170 (1 RCT)	⊕⊖⊖⊖ **Very low**[a]	Data presented as absolute values at baseline, 1 month, 2 months, and 3 months; we were unable to include change from baseline in our analyses. The trial authors reported that the large drop from baseline to month 1 in both

			groups may be due to overestimation of microalbuminuria at baseline rather than a true effect.
Serious adverse events	Not reported.		—
Mortality due to any cause	Not reported.		—
Quality of life	Not reported.		—

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ACEI: angiotensin-converting enzyme inhibitor; **CI**: confidence interval; **RCT:** randomised controlled trial; **SD**: standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to unclear or high risk of bias in all domains, and one level for imprecision (trial authors stated that microalbuminuria dropped between baseline and 1 month in both groups, possibly due to overestimation of microalbuminuria at baseline rather than a true effect).

BACKGROUND

Appendix 1 provides definitions of some technical terms.

Description of the condition

Sickle cell disease (SCD) is an inherited anaemia that can lead to episodes of severe pain and life-threatening acute complications such as chest crises, strokes, and splenic sequestration (Pleasants 2014). It mainly affects people from Sub-Saharan Africa, Spanish-speaking regions in the Western Hemisphere (South America, the Caribbean, and Central America), the Middle East, India, and parts of the Mediterranean region. Reductions in infant and child mortality and increasing migration from countries with high prevalence have made SCD a worldwide problem (Piel 2012). It affects around 12,500 to 15,000 people in the UK and approximately 100,000 in the USA (NICE 2021; CDC 2022). A 2012 study estimated that approximately 305,800 babies were born with SCD worldwide in 2010 (two-thirds in Africa), and that this figure could increase by 25% to approximately 404,200 by 2050 (Piel 2012).

SCD refers to all genotypes that cause the clinical syndrome. There are three main types of SCD. The most common form, accounting for up to 70% of cases of SCD in people of African origin, is sickle cell anaemia (SCA), which is due to the inheritance of two beta-globin S (βS) alleles (haemoglobin (Hb)SS). The second most common genotype, accounting for up to 30% of SCD cases in people of African origin, is HbSC disease, which is due to the co-inheritance of the βS and βC alleles. It tends to be a more moderate form of the disease. The third major type of SCD occurs when βS is inherited with a β-thalassaemia allele, causing HbS/β-thalassaemia (Rees 2010). People who have inherited a thalassaemia null mutation (HbSβ^0) have a disease that is clinically indistinguishable from SCA, whereas people with HbSβ$^+$ thalassaemia have milder symptoms. In high-income countries, people with SCD are expected to live into their 40s, 50s, and beyond, whereas in low-income countries, including some African nations, it is estimated that between 50% and 90% of children born with HbSS die before their fifth birthday (Gravitz 2014Grosse 2011).

In SCD, under conditions of low oxygen levels, acidity, and cellular dehydration, the HbS molecules polymerise and begin to distort the red blood cells, which take on a sickled shape. The main determinant of disease severity is the rate and extent of this HbS polymerisation (Rees 2010). This is exemplified by the co-inheritance of genetic factors that affect the intracellular HbS or foetal haemoglobin (HbF) concentration; these include the protective effects of co-inherited alpha (α)-thalassaemia (Rumaney 2014; Steinberg 2012), or hereditary persistence of HbF (Akinsheye 2011; Steinberg 2012). Sickling of red blood cells results in both obstruction of blood flow, leading to organ and tissue ischaemia, and haemolytic anaemia (Sparkenbaugh 2013). Both processes are thought to lead to increased inflammation and an increased tendency to develop blood clots (Frenette 2007; Rees 2010). Reduced blood flow is mediated via a dynamic interaction between sticky HbS-containing red blood cells, the vessel wall, and white cells (Rees 2010). Owing to intravascular and extravascular haemolysis, sickle red blood cells have a shorter lifespan (10 to 12 days versus 120 days for normal red blood cells), which leads to anaemia (Kato 2006a). Chronic intravascular haemolysis leads to a reduced nitric oxide level within the blood; nitric oxide is sequestered by free Hb, and this process increases the risk of pulmonary hypertension and ischaemic strokes over time (Kato 2006a; Kato 2006b).

Kidney dysfunction

Mechanisms of kidney dysfunction in sickle cell disease

See Figure 1 and Figure 2.

Figure 1. Sickle cell nephropathy pathophysiology in sickle cell disease: Adapted from Okafor 2013 and Nath 2015. RBC: red blood cell; FSGS: focal segmental glomerulosclerosis; ESRD: end-stage renal disease

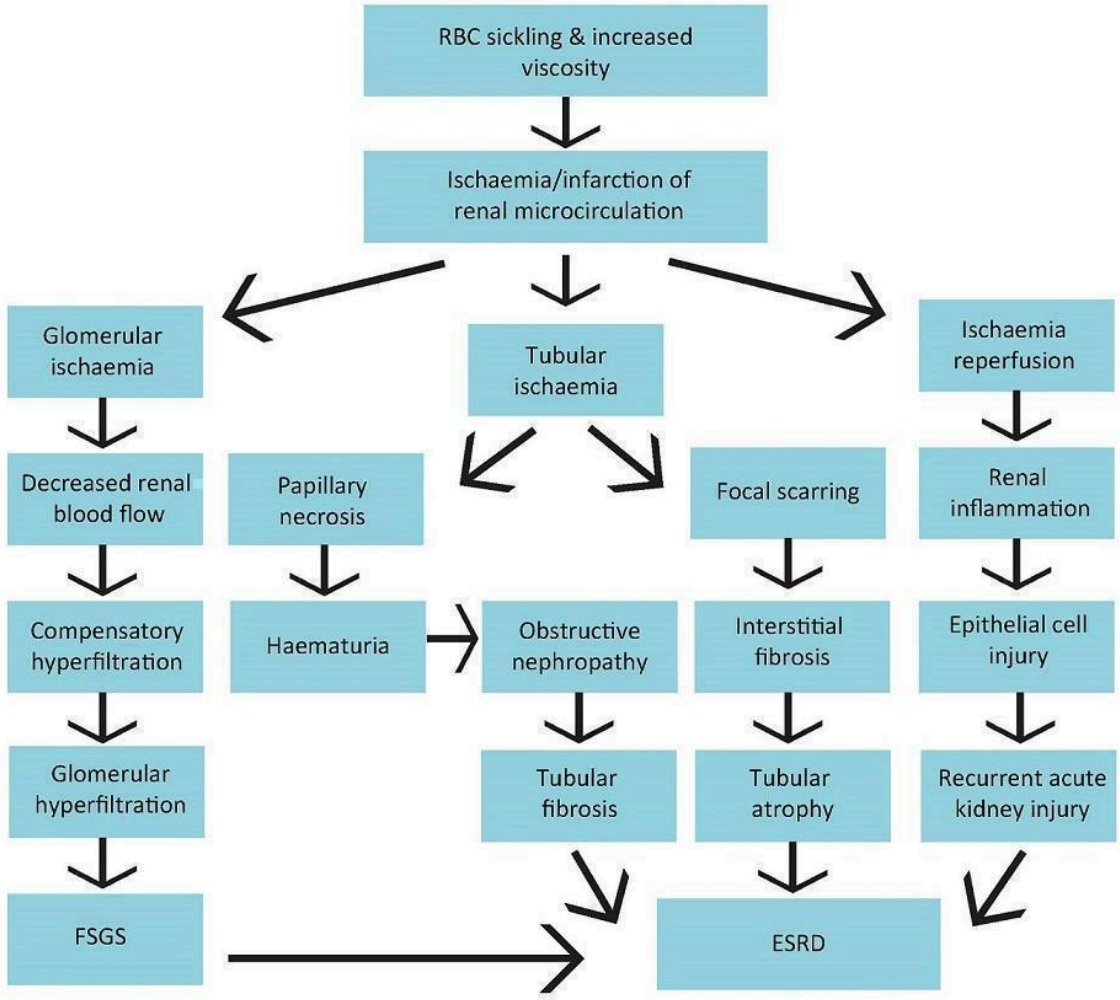
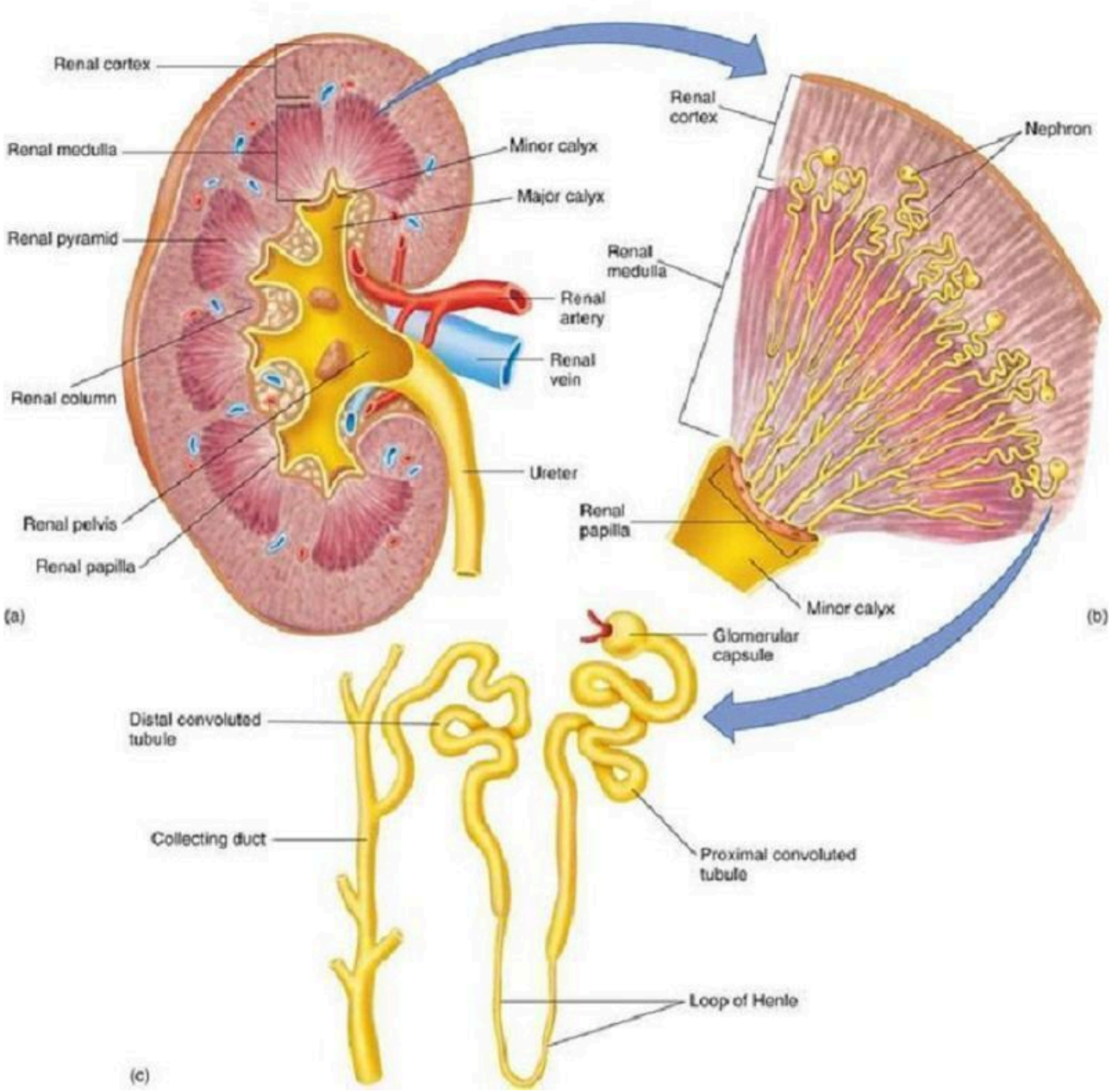


Figure 1. (Continued)

Figure 2. Structure of the kidney. From: Wikispaces. Human Physiology. 12. Urology.humanphysiology2011.wikispaces.com/12.+Urology



Kidney disease is a frequent and potentially severe complication of SCD. Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months, with implications for health (KDIGO 2012). It is more common in people with HbSS and HbSβ^0 than in people with HbSC or HbSβ$^+$; however, there is conflicting evidence relating to the relative prevalence of CKD in different SCD genotypes (Nath 2015, Yee 2011). CKD prevalence increases with age, reaching 50% in people with SCD aged over 40 years (Gosmanova 2014).

Sickle cell nephropathy refers to the spectrum of kidney complications in SCD (Figure 1). One hallmark of sickle cell nephropathy is hyperfiltration (a glomerular filtration rate (GFR) greater than 120 mL/min/1.73 m^2), which has been described in 51% of people with SCD, particularly younger individuals and people with higher levels of haemolysis (Haymann 2010). The inner kidney (medulla) is particularly prone to red blood cell sickling due to its acidotic and hypoxic environment (Figure 2). Damage is predominantly due to recurrent episodes of ischaemia and reperfusion injury or infarction leading to scarring (Hebbel 2014).

Glomerular damage (caused by hyperfiltration) leads to urinary protein leak. Renal tubule injury results in childhood enuresis and impaired ability to concentrate urine, with increased susceptibility to dehydration, which may precipitate a sickling crisis. Renal papillary necrosis due to infarction leads to haematuria, scarring, and further impairment of function. The combined effect of glomerular and tubulointerstitial scarring leads to progressive decline in kidney function (Nasr 2006; Sharpe 2014).

The risk of end-stage renal disease (ESRD), defined as requiring long-term dialysis or transplantation, is around 12% (Powars 2005). Risk factors for ESRD include proteinuria, anaemia, hypertension, and HbSS genotype (Ataga 2014).

Assessment of kidney function

The gold standard for assessing how well the kidneys are working is direct measurement of GFR. Generally, as kidney disease worsens, the GFR drops (see Table I below). In people with SCD, a GFR greater than 120 mL/min/1.73 m^2 is an additional indicator of abnormal kidney function. However, as direct measurement of GFR is invasive and time-consuming, GFR estimations based on serum creatinine are more common. Several equations exist, including the Modification of Diet in Renal Disease (MDRD), CKD Epidemiology Collaboration (CKD-EPI), and Cockcroft–Gault equations (Botev 2009; Levey 1999; Levey 2009). Two small studies evaluated different estimated GFR (eGFR) calculations versus measured GFR in people with HbSS from the Caribbean and sub-Saharan Africa, finding that the CKD-EPI equation gave the most accurate estimate (Arlet 2012; Asnani 2013). In individuals with SCD, increased proximal tubule secretion of creatinine compromises the accuracy of serum creatinine as a measure of GFR (Asnani 2015).

Table I: GFR categories in CKD (KDIGO 2012)

GFR category (CKD stage)	GFR (mL/min/1.73 m^2)	Terms
G1 (Stage 1)	≥ 90	Normal or high
G2 (Stage 2)	60 to 89	Mildly decreased*
G3a (Stage 3a)	45 to 59	Mildly to moderately decreased
G3b (Stage 3b)	30 to 44	Moderately to severely decreased
G4 (Stage 4)	15 to 29	Severely decreased
G5 (Stage 5)	< 15	Kidney failure

* Relative to young adult level

Proteinuria, an albumin-to-creatinine ratio (ACR) greater than 2.5 mg/mmol in men or 3.5 mg/mmol in women, or a protein-to-creatinine ratio (PCR) greater than 15 mg/mmol, are diagnostic indicators of CKD (see Table II below), and are independent risk factors for kidney and cardiovascular mortality in the general population (Astor 2011; de Zeeuw 2004). Proteinuria can be classified as microalbuminuria (3 mg/mmol to 30 mg/mmol creatinine) or macroalbuminuria (greater than 30 mg/mmol creatinine). ACR and PCR correlate well with 24-hour urinary protein excretion (Gaspari 2006).

Table II: Relationship amongst categories for albuminuria and proteinuria in CKD (KDIGO 2012)

Measure	Categories		
	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)

AER (mg/24 hours)	< 30	30 to 300	> 300
PER (mg/24 hours)	< 150	150 to 500	> 500
ACR	< 3	3 to 30	> 30
(mg/mmol)	< 30	30 to 300	> 300
(mg/g)			
PCR	< 15	15 to 50	> 50
(mg/mmol)	< 150	150 to 500	> 500
(mg/g)			

Abbreviations: A1–A3: albuminuria categories; ACR: albumin-to-creatinine ratio; AER: albumin excretion rate; PCR: protein-to-creatinine ratio; PER: protein excretion rate.

Relationships amongst measurement methods within a category are not exact. The relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g per day or 10 mmol per day. Creatinine excretion varies with age, sex, race, and diet; therefore, the relationship amongst these categories is approximate. The conversions are rounded for pragmatic reasons.

Prevalence

CKD stage 1 or 2 is present in 26.5% of children with SCD, and is defined as urinary structural or genetic abnormalities pointing to kidney disease or GFR below 90 mL/min/1.73 m^2 (Yee 2011). In a four-decade observational study of 1052 people with HbSS, 11.6% of participants developed ESRD, and 29.4% of participants who died had prior ESRD (Powars 2005). Furthermore, 16% to 18% of overall mortality in SCD is attributable to kidney disease (Hamideh 2013; Nath 2015).

An ACR that is repeatedly higher than 3 mg/mmol is present in up to 20% of children with SCD, and screening for microalbuminuria may be useful for identifying children with early sickle cell nephropathy (McKie 2007; Sharpe 2014). The prevalence of proteinuria increases with age and systolic blood pressure; it varies from 4.5% to 26% in people up to 21 years and from 26% to 68% in older people (Ataga 2014).

Description of the intervention

Recommended interventions for preventing kidney complications include avoiding dehydration and avoiding the chronic use of drugs that are harmful for the kidneys, such as nonsteroidal anti-inflammatory drugs (NSAIDs).

However, as kidney damage is initiated directly by the sickling of red blood cells in the kidneys, reducing sickling is expected to cut short the primary insult and, in the long term, slow the rate of progression of sickle cell nephropathy. This can be achieved through red blood cell transfusions, which directly reduce the percentage of HbS in the blood, or with drugs that increase HbF production, such as hydroxyurea (hydroxycarbamide).

Inhibition of the renin-angiotensin-aldosterone system (RAAS) by angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can reduce kidney damage by lowering intraglomerular pressure and reducing proteinuria. While there is a Cochrane Review on the use of ACEIs in SCD (Sasongko 2021), the mechanisms of action of blood transfusions, hydroxyurea, and ACEI may be synergistic. For this reason, we included ACEIs in this review, as trials may compare them with red blood cell transfusions or hydroxyurea, or use them in combination with these interventions.

Red blood cell transfusions

Red blood cell transfusion is not a specific treatment for acute kidney injury (AKI) in people with SCD unless it is required to treat other SCD complications such as acute chest syndrome (Yawn 2014). Chronic red blood cell transfusions, delivered as simple (top-up) or exchange transfusions, form part of the management of a number of SCD complications; for example, for the primary prevention of strokes in children with transcranial Doppler abnormalities (Adam 2008), and the prevention of further chest crises in people with recurrent episodes (Howard 2015).

Studies have suggested that red blood cell transfusions may help to prevent the progression of kidney disease in children (McKie 2007Marsenic 2008). One study of 120 children with sickle haemoglobinopathies found that chronic red blood cell transfusions before the age of nine years was protective against the onset of microalbuminuria (Alvarez 2006).

Red blood cell transfusions have reduced complications and improved the quality of life of people with SCD, but they are not without potentially serious complications. The benefits of transfusion therapy must be balanced against risks, including infections, iron overload, acute or delayed haemolytic transfusion reactions, and increased complexity of compatibility testing (Chou 2013a; Chou 2013b; Porter 2013; Scheunemann 2010; Ubesie 2012). Frequent blood transfusions in SCD can also lead to alloimmunisation (Yazdanbakhsh 2012).

Angiotensin-converting enzyme inhibitors

ACEIs prevent the formation of angiotensin II, a protein (peptide) that causes blood vessel narrowing (arteriolar vasoconstriction) and the release of the hormone aldosterone. This hormone causes the kidney tubules to retain more water, expanding circulating blood volume and increasing blood pressure.

Angiotensin II raises the pressure within the glomeruli (the first blood filters in the kidney). This increased pressure damages the filtration barrier and allows larger proteins to be lost in the urine (Macconi 2006). Angiotensin II is also a component in the progression of kidney fibrosis, which can lead to ESRD. ACEIs reduce intraglomerular pressure and proteinuria independently of their antihypertensive effect (Gansevoort 1995; Maki 1995). They were first shown to slow the decline in GFR in diabetic kidney disease (Lewis 1993).

Hypotension is a risk with ACEIs. However, these drugs are less effective for lowering blood pressure in people of African or Caribbean origin (Ventura 1985), the populations primarily affected by SCD. Therefore, people with SCD who do not normally have raised blood pressure and who are given ACEIs may be at a lower risk of hypotension.

Hydroxyurea

Physicians have prescribed hydroxyurea for SCD since the 1980s. Clinical trials have shown that it reduces vaso-occlusive crises and chest crises and improves survival in people with SCD (Field 2014). In one trial, children treated with hydroxyurea had better kidney function, assessed by the ability to concentrate urine, than those treated with placebo (Alvarez 2012). In one non-randomised study of children with SCD requiring hydroxyurea for standard indications, treatment for three years led to a mean decrease in GFR from 167 (standard deviation (SD) 46) mL/min/1.73 m^2 to 145 (SD 27) mL/min/1.73 m^2 (Aygun 2013), indicating an improvement in hyperfiltration.

How the intervention might work

Red blood cell transfusions

In its simplest form, blood transfusion proportionally reduces HbS, prevents direct sickling in the kidney, and prevents local vaso-occlusion, thereby reducing glomerular and tubular ischaemic damage to the kidney. However, a further mechanism by which transfusions could prevent kidney damage is by reducing sickling, thus decreasing haemolysis and with it, the sequestration of nitric oxide. Nitric oxide is known to have an important local vasodilatory effect, and nitric oxide sequestration by free Hb released during haemolysis is thought to contribute to the vasculopathy of sickle cell nephropathy (Potoka 2015). Finally, haemolysis directly leads to endothelial damage, inflammation, and dysfunction, a further mechanism of kidney disease that may play an important role in sickle cell nephropathy (Zafrani 2015).

Angiotensin-converting enzyme inhibitors

As described above, ACEIs reduce proteinuria and slow disease progression in other forms of CKD. It is plausible that this benefit would also apply in SCD, since angiotensin-converting enzyme inhibition decreases intraglomerular pressure, which is raised in all stages of SCD-related CKD. ACEIs also appear to increase the expression of the protein nephrin, helping to restore the kidney filtration barrier (Ziyadeh 2008). Furthermore, angiotensin-converting enzyme inhibition can reduce fibrogenesis and free radical-induced oxidative stress, which may be protective against endothelial damage induced by ischaemia-reperfusion injury (van der Meer 2010). However, in the context of medullary hypoperfusion or kidney ischaemia, this may lead to a fall in GFR, as is seen when ACEIs are continued during AKI. If sickle cell nephropathy is considered a form of recurrent ischaemic AKI, then ACEIs could theoretically be damaging, at least in the context of acute crises.

Hydroxyurea

Hydroxyurea is likely to reduce kidney damage through a variety of mechanisms, which are not entirely understood and probably reflect pleiotropic effects (a drug's actions, usually unexpected, that are not the main mechanism of action and may be beneficial or harmful). Hydroxyurea modestly increases HbF via a range of mechanisms, including epigenetic modifications (Pule 2015). The increase in HbF could diminish the primary kidney damage at both the glomerular and the tubular levels by reducing sickling and local ischaemia. Randomised controlled trials (RCTs) of hydroxyurea in SCD found that the drug increased total Hb and HbF levels and reduced vaso-occlusive crises; however, its benefit could not be solely attributed to the rise in HbF, with other likely mechanisms including the effects on platelet count, white blood cell count, and red blood cell adhesion to endothelia (Charache 1995; Wang 2011). Hydroxyurea also decreases intravascular haemolysis, which may ameliorate nitric oxide sequestration. Finally, a reduction in HbS erythrocyte adhesion by hydroxyurea (shown in vivo and in vitro) could lead to a reduction in kidney inflammation (Brun 2003; Hillery 2000; Styles 1997).

Why it is important to do this review

Glomerular damage is a cause of microalbuminuria that can develop at an early age in children with SCD and that becomes more frequent in adulthood. Outcomes are poor in people with SCD as a result of progression to proteinuria and chronic kidney insufficiency (Lebensburger 2011). Up to 12% of people who develop sickle cell nephropathy (i.e. microalbuminuria) will develop kidney failure (Powars 2005). ESRD and its treatment have a profound negative effect on people's quality of life and also have major resource implications.

The poor life expectancy of people with SCD in the past meant that relatively few people had long-term complications of SCD, such as kidney failure and pulmonary hypertension. However, life expectancy in this population has improved dramatically. In the 1970s, people born with SCD had a median survival of 14.3 years; in the 1990s, this increased to between 42 and 48 years; and it is now predicted that 50% of people with SCD born after 2000 will reach their fifth decade of life (Sandhu 2015; Boyle 2016). This means more people are surviving long enough to develop long-term complications, and the incidence of kidney failure requiring dialysis or kidney transplant (renal replacement therapy) is expected to rise.

Once CKD develops, it is associated with poor outcomes. Identifying therapies that can prevent or slow down the decline in kidney function in people with SCD will be critical for reducing the number requiring renal replacement therapy.

This is an update of a previously published review (Roy 2017).

OBJECTIVES

To assess the effectiveness of any intervention for preventing or reducing kidney complications or chronic kidney disease in people with sickle cell disease. Possible interventions include red blood cell transfusions, hydroxyurea, and angiotensin-converting enzyme inhibitors, either alone or in combination.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs. We excluded cross-over trials as they are inappropriate for long-term outcomes.

Types of participants

People with all types of SCD of any age and either sex.

Types of interventions

We included RCTs comparing all interventions, including red blood cell transfusions, hydroxyurea, and ACEIs (alone or in combination) compared to each other, placebo, or standard care.

Types of outcome measures

Primary outcomes

- Reduction or prevention of kidney disease progression
  - Incidence of ESRD measured as start of renal replacement therapy or death from kidney failure
  - Improvement or slower progression of GFR (including reduced hyperfiltration as evidenced by reduction of GFR to the normal range, measured by gold standard clearance methods, creatinine, or creatinine-based eGFR using the MDRD equation, Cockcroft-Gault, CKD-EPI, or modified versions of these calculations)
  - Reduction or slower progression of proteinuria (measured by random spot ACR, PCR, or 24-hour urinary collection)
  - New evidence of kidney disease (based on histological examination of kidney tissue)
  - Improvement in ability to concentrate urine (urine osmolality greater than 500 mOsm/kg H_2O after water deprivation)
- Serious adverse events (SAEs)
  - Transfusion complications (severe haemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO))
  - Drug treatments (e.g. neutropenic sepsis, hospital admission secondary to drug complications)
  - SCD complications (e.g. acute chest syndrome, stroke, painful crisis) up to 30 days post-transfusion or post-drug treatment
- All-cause mortality

Had we found sufficient data, we would have categorised kidney disease progression and all-cause mortality according to short-, medium-, and long-term outcomes. We would have reported the exact definition of these time frames over time periods that were common to as many trials as possible (e.g. 0 to 5 years, 6 to 10 years, over 10 years).

Secondary outcomes

- Other adverse events (AEs)
  - Transfusion-related AEs (alloimmunisation, infection from blood products, minor transfusion reactions, procedure-related)
  - Drug-related AEs (neutropenia, thrombocytopenia, hypotension, hyperkalaemia, infection, allergic reaction, skin ulcers up to 60 days after ingestion)
- Quality of life (measured on a validated scale)
- Number of units or volume (mL) of red blood cells infused (regardless of intervention)

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year, or publication status.

Electronic searches

We identified trials from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general)) AND nephro*.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference, the American Society of Hematology conference, the British Society for Haematology Annual Scientific Meeting, the Caribbean Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting), and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 22 September 2022.

In addition, we searched the following databases for RCTs on 30 August 2022.

- CENTRAL 2022, Issue 8 in the Cochrane Library (searched 30 August 2022)
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE; 1946 to 30 August 2022)
- Embase (OvidSP; 1974 to 30 August 2022)
- CINAHL (EBSCOHost; 1983 to 30 August 2022)
- PubMed (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, for recent records not yet added to MEDLINE; pubmed.ncbi.nlm.nih.gov/; 1966 to 30 August 2022)
- Transfusion Evidence Library (www.transfusionevidencelibrary.com; 1950 to 30 August 2022)
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to 30 August 2022)
- KoreaMed (koreamed.org; 1997 to 30 August 2022)
- PakMediNet (www.pakmedinet.com; 2001 to 30 August 2022)

- Web of Science (Conference Proceedings Citation Index-Science (CPCI-S); 1990 to 30 August 2022)

We searched the following trials registers for ongoing trials to 30 August 2022.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/)

We combined searches in MEDLINE and Embase with the recommended Cochrane RCT search filters (Lefebvre 2011), and we combined searches in CINAHL with an RCT filter based on the Scottish Intercollegiate Guidelines Network (SIGN) RCT filter (www.sign.ac.uk/methodology/filters.html). Appendix 2 presents the various search strategies.

Searching other resources

We handsearched the reference lists of the included trials to identify any further relevant trials. We contacted lead authors of the included trials to identify any unpublished material, missing data, or information regarding ongoing trials.

Data collection and analysis

Details of data collection and analysis are for the 2023 review update.

Selection of studies

To select trials, we followed the recommendations presented in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022). Two of three review authors (NR, AC, IDH) independently screened all electronically derived citations and abstracts of papers identified by the search strategy to exclude those that were clearly irrelevant. Two of three review authors (NR, AC, IDH) independently and formally assessed the full texts of all potentially relevant trials against our eligibility criteria. The two review authors discussed the results of trial selection and resolved any discrepancies between themselves. If this was not possible, we referred the decision of eligibility to a third review author (LE). We reported the results of trial selection using a PRISMA flow diagram (Page 2021). We would have sought further information from trial authors if the abstract or full report contained insufficient data to make a decision about eligibility. We used Covidence to assess relevance, which included ascertaining whether the participants had SCD, and whether the trial had red blood cell transfusion, ACEI, or hydroxyurea treatment arms (Covidence). We recorded the reasons for excluding trials at full-text review stage.

Data extraction and management

We piloted data extraction forms in Covidence (Covidence), and three review authors (NR, AC, IDH) independently extracted data from all the trials according to Cochrane guidelines (Li 2022). If they were unable to reach a consensus on any decision, they consulted another review author (LE).

Three review authors (NR, AC, IDH) independently extracted outcome data using templates modified to reflect the outcomes of this review. They were not blinded to the names of authors, institutions, journals, or the trial outcomes. We used Covidence and the available tables in the Review Manager 5 software (RevMan 5) to extract the following characteristics (Covidence; RevMan 2014).

- General information: review author's name, date of data extraction, trial ID, first author of trial, author's contact address (if available), citation of paper, objectives of the trial
- Trial details: trial design, location, setting, sample size, power calculation, treatment allocation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, statistical analysis, results, conclusion, funding
- Characteristics of participants: age, sex, total number of participants recruited, total number randomised, total number analysed, types of underlying disease, numbers lost to follow-up, dropouts (percentage in each arm) with reasons, protocol violations, previous treatments, current treatment, prognostic factors, HbS levels, kidney complications
- Interventions: experimental and control interventions, method of red blood cell transfusion (simple (top-up), partial, or full exchange transfusion), type of red blood cell transfusion (intermittent or chronic), or dose and duration of hydroxyurea or ACEI treatment
- Outcomes measured: reduction or prevention of kidney disease progression (including incidence of ESRD, improvement or slower progression of GFR, reduction or slower progression of proteinuria, evidence of kidney disease), mortality due to any cause, SAEs (related to transfusion complications, drug treatments), SCD complications, other transfusion-related AEs, other drug-related AEs, quality of life, number of units or volume (mL) of red blood cells infused.

We extracted data from full-text articles and abstracts. For publications reporting on multiple trials, we originally planned to use one data extraction form for each trial. For each trial with multiple publications, we extracted data using one form. We contacted authors and trial groups for additional details if the available publications did not provide sufficient information.

One review author entered information into RevMan 5 and a second review author checked this for accuracy (RevMan 2014).

Assessment of risk of bias in included studies

We assessed the risk of bias of all RCTs using the original Cochrane risk of bias tool (RoB 1), which covers the following domains (Higgins 2017).

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective reporting)
- Other bias

Three review authors (NR, AC, IDH) worked independently to assess each domain as high, low, or unclear risk of bias. We provided a brief justification of each judgement in the Characteristics of included studies table. To ensure consensus on each judgement, we compared the review authors' statements and consulted a third review author (LE) where necessary.

Measures of treatment effect

Where data allowed, we undertook quantitative assessments using RevMan 5 (RevMan 2014).

For continuous outcomes, we recorded the mean, SD, and total number of participants in the treatment and control groups. For continuous outcomes measured on the same scale, we performed analyses using mean differences (MDs) with 95% confidence intervals (CIs). For continuous outcomes measured on different scales, we planned to use standardised mean differences (SMDs).

For dichotomous outcomes, we recorded the number of events and the total number of participants in both the treatment and control groups. We reported the pooled risk ratio (RR) with a 95% CI. Where the number of observed events was small (less than 5% of sample per group), and where trials had balanced treatment groups, we reported the Peto odds ratio (OR) with 95% CI (Deeks 2022).

For mortality data, we planned to extract available data and report hazard ratios (HRs). We planned to estimate the HR as accurately as possible using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). However, we were unable to do this due to lack of data.

We reported secondary outcomes as groups of transfusion-related and drug-related AEs. If this was not possible due to duplicate counting of the same participant who may have experienced more than one AE of the same category (e.g. more than one transfusion-related AE), we reported subgroup categories of AEs separately and reported the 99% CI of the pooled RR to allow for multiple statistical testing.

Where appropriate, we planned to report the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) with CIs.

If we could not report the available data in any of the formats described above, we provided a narrative description of results and, if appropriate, presented the data in tables.

Unit of analysis issues

We did not expect to encounter unit of analysis issues, as we were unlikely to find eligible cluster-randomised trials or trials with multiple observations for the same outcome. Had we identified any trials with these characteristics, we would have followed the recommendations provided in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). If participants had been randomised more than once, we would have contacted the trial authors to request data on outcomes associated with the initial randomisation.

Dealing with missing data

We dealt with missing data according to the recommendations in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). We contacted the lead author of one trial for additional data on creatinine clearance and to confirm the number of participants included in the proteinuria analysis (Foucan 1998); at the time of review publication, we had received no response. We recorded the number of participants lost to follow-up for each trial if possible. We analysed data on an intention-to-treat (ITT) basis where possible, but if insufficient data were available, we presented per-protocol analyses (Deeks 2022).

Assessment of heterogeneity

If the clinical and methodological characteristics of included trials had been sufficiently homogeneous, we would have combined the data in meta-analyses. We would have assessed statistical heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. We would have used the I^2 statistic to quantify the degree of potential heterogeneity and classify it as moderate if the I^2 value was greater than 50%, or considerable if it was greater than 80%. We expected to identify at least moderate clinical and methodological heterogeneity between the included trials, so we planned to use the random-effects model throughout. If statistical heterogeneity was considerable, we would not have reported the overall summary statistic. We would have assessed potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2022).

Assessment of reporting biases

Had we identified at least 10 trials for inclusion in a meta-analyses, we would have explored potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test, considering $P < 0.1$ as significant (Page 2022).

Data synthesis

We presented the different comparisons separately. We performed analyses according to the recommendations in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using aggregated data (Deeks 2022). For statistical analysis, we entered data into RevMan 5 (RevMan 2014). One review author (NR) entered the data and a second (LE) checked for accuracy.

Had meta-analyses been feasible, we would have used the random-effects model for pooling the data. For dichotomous outcomes, we would have used the Mantel-Haenszel method or the Peto method as necessary, and for continuous outcomes, we would have used the inverse variance method (and SMDs as necessary). If we had identified considerable statistical heterogeneity ($I^2 > 80\%$), we would have presented results narratively and commented on any trends in the data within the Results section of the review.

Subgroup analysis and investigation of heterogeneity

Had there been sufficient data, we would have performed the following subgroup analyses according to Cochrane recommendations to assess the effect of different characteristics on heterogeneity (Deeks 2022).

- Age of participant (neonate, child (one to 15 years), adult (16 years and older))
- Genotype (homozygous SCD (SS), sickle beta thalassaemia ($S\beta^0$ and $S\beta^+$), and sickle haemoglobin C disease (SC))
- Severe SCD complications (strokes, acute chest syndrome, painful crisis, priapism)
- People with proteinuria (ACR > 3 mg/mmol or PCR > 5 mg/mmol) versus others
- Presence of CKD according to recognised classifications of kidney disease
- People with hyperfiltration (GFR > 120 mL/min/1.73 m^2) versus others

Sensitivity analysis

Had there been sufficient data, we would have assessed the robustness of our findings by performing the following sensitivity analyses according to Cochrane recommendations (Deeks 2022).

- Excluding trials with a high or unclear risk of selection bias
- Excluding trials with dropout rates of 20% or greater

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table for each comparison, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022a; Schünemann 2022b). We used the GRADE approach to rate the certainty of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations (risk of bias, inconsistency, indirectness, imprecision, publication bias).

We reported the following outcomes in each table.

- Reduction or prevention of kidney disease progression
- SAEs related to transfusion, drug treatments, or SCD complications
- All-cause mortality
- Quality of life

RESULTS

Description of studies

See the Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies tables.

Results of the search

See the PRISMA flow diagram (Figure 3).

Figure 3.

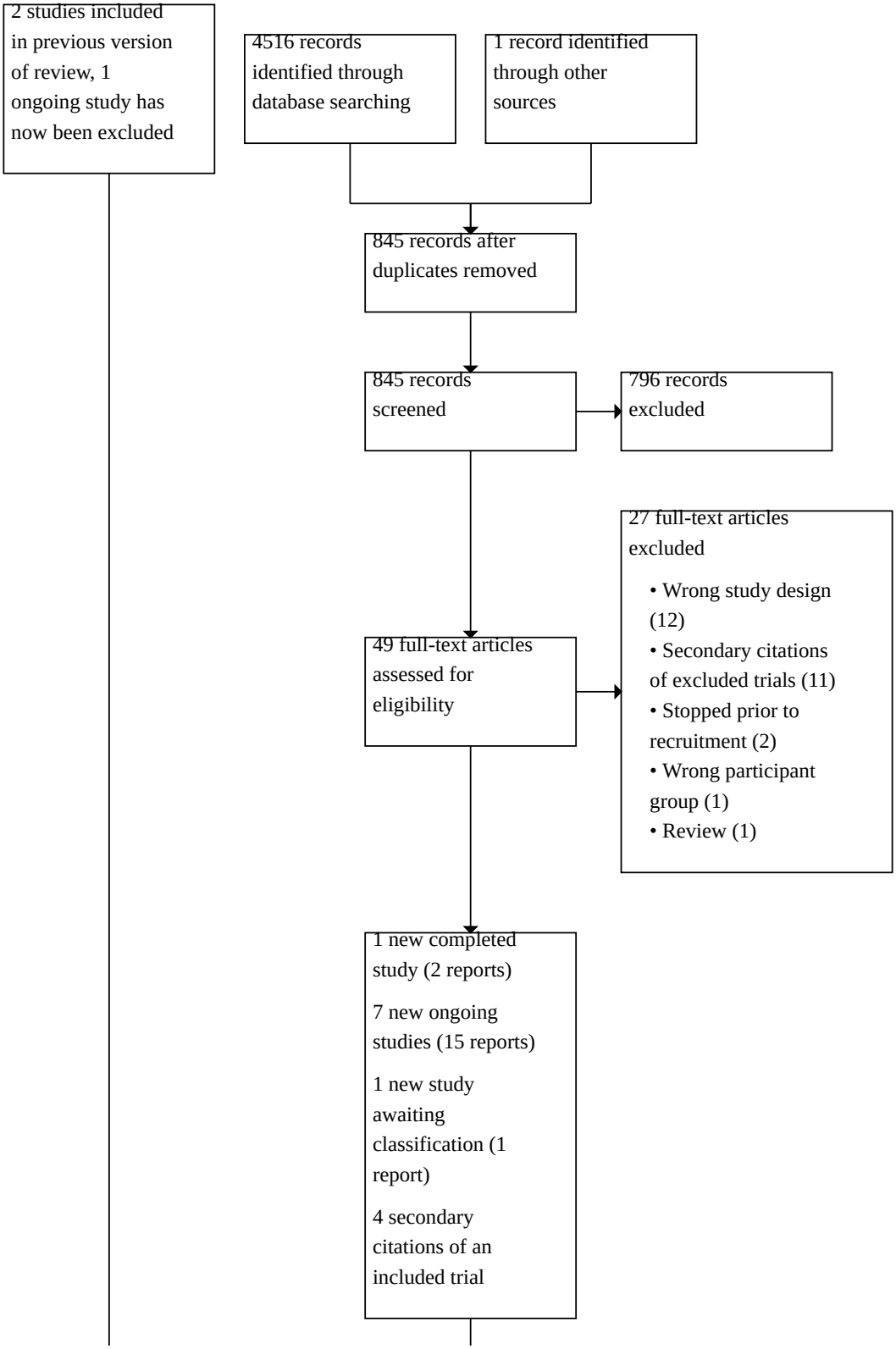
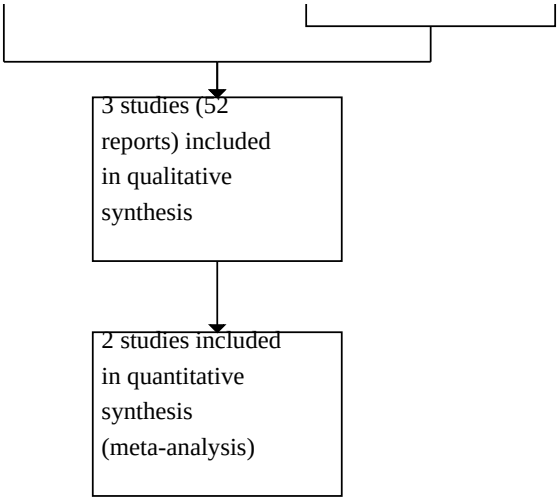


Figure 3. (Continued)



In the updated search, we identified a total of 4516 additional records (845 records after deduplication). Four review authors (NR, AC, IDH, LE) excluded 796 records during title and abstract screening, and three authors (NR, AC, IDH) then reviewed 49 full-text articles for relevance. We included one new trial (Aliu 2020), listed seven new trials (15 records) as ongoing (EUCTR2019-004471-39-GB; Kutlar 2019; NCT03806452 (SIKAMIC); NCT03814746 (STAND); Ataga 2019 (STEADFAST); NCT04084080 (SCD-CARRE); NCT04335721) and listed one trial (1 record) as awaiting classification (NCT05392894 (REDRESS)). We identified four secondary citations of two included trials (Aliu 2020; BABY HUG 2011).

In the original review, we identified two completed trials (BABY HUG 2011; Foucan 1998) and one ongoing trial (Ataga 2019 (ENDO)). In this update, we excluded the ongoing trial because it had the wrong design (cross-over trial).

Included studies

We identified three RCTs (385 participants) that met our predefined inclusion criteria (Aliu 2020; BABY HUG 2011; Foucan 1998).

Trial design and setting

Foucan 1998 was conducted in 1996 in an outpatient department in a university hospital centre in the French Caribbean Archipelago of Guadeloupe. BABY HUG 2011 was conducted in 13 centres in the USA between October 2003 and September 2009. Aliu 2020 was conducted in the paediatric department of a university hospital in Gombe, Nigeria.

Trial size

Foucan 1998 enroled 22 people and followed them for six months, BABY HUG 2011 enroled 196 children and followed them for two years, and Aliu 2020 enroled 170 children and followed them for three months.

Participants

Foucan 1998 enroled adults (aged 18 years of age or older) with HbSS disease, normal blood pressure, and persistent microalbuminuria. The exclusion criteria were hypertension; heart, kidney, liver, or systemic disease; pregnancy; and current use of anti-inflammatory or antihypertensive medications.

BABY HUG 2011 enroled children aged nine to 18 months with HbSS or HbSβ^0, irrespective of disease severity. The trial excluded children with transfusion within two months of enrolment or chronic transfusion therapy, abnormal transcranial Doppler (TCD) ultrasound velocity, severe developmental delay (e.g. cerebral palsy or other mental retardation, stroke with neurological deficit), surgical splenectomy, and previous or current treatment with hydroxyurea or another anti-sickling drug (see Characteristics of included studies for a complete list of exclusion criteria).

Aliu 2020 enroled children aged one to 18 years with SCA (genotype not specified) and microalbuminuria who had been stable for four weeks (no fever or veno-occlusive crisis). The trial excluded children with hypertension, diabetes mellitus, HIV, or a urinary tract infection.

Interventions

Foucan 1998 evaluated the ACEI captopril at 6.25 mg/day during the first month, 12.5 mg/day during the second and the third months, and 25 mg/day during months four to six versus a matching placebo. BABY HUG 2011 compared hydroxyurea 20 mg/kg/day to a matching placebo over 18 months. Aliu 2020 compared lisinopril 0.1 mg/kg/day to vitamin C 100 mg/day over three months.

Outcomes

Foucan 1998 measured the effects of captopril on the progression of albuminuria and blood pressure.

In BABY HUG 2011, a co-primary outcome was the effect of hydroxyurea on splenic and liver function, and secondary outcomes included growth and development, neurodevelopment assessment, complications of SCA, and any other SAEs.

Aliu 2020 measured the effect of lisinopril on microalbuminuria and GFR.

Source of funding

Foucan 1998 and BABY HUG 2011 received government funding, and Aliu 2020 did not specify any funding source.

Excluded studies

We excluded 19 studies. Sixteen trials had the wrong design: 11 were not randomised (Choi 2016; Laurin 2014; NCT01195818 (RAND); NCT01989078 (SCD-Losaratan); NCT02286154 (TREAT); NCT02373241; NCT02522104 (DARH); Quinn 2017; Silva Junior 2014; Steinberg 2003; Zahr 2019), four were not designed to assess renal outcomes (Ataga 2021 (HIBISCUS); George 2020; Jain 2012; Wood 2020 (PRAISE)), and one had a cross-over design (Ataga 2019 (ENDO)). Two trials were stopped prior to recruiting eligible participants (NCT01096121 (MADREPIEC); NCT01891292). One identified reference was a review (Estcourt 2016).

Ongoing studies

In the seven ongoing RCTs, planned duration ranges from 113 days (Kutlar 2019) to 12 months (Ataga 2019 (STEADFAST); EUCTR2019-004471-39-GB; NCT03806452 (SIKAMIC); NCT03814746 (STAND); NCT04084080 (SCD-CARRE)), and planned sample sizes range from 12 participants (NCT04335721) to 254 participants (NCT03814746 (STAND)). Six trials are randomising adults only (Ataga 2019 (STEADFAST); EUCTR2019-004471-39-GB; Kutlar 2019; NCT03806452 (SIKAMIC); NCT04084080 (SCD-CARRE); NCT04335721) and one trial is randomising older children and adults (NCT03814746 (STAND)). Five trials are multinational (Ataga 2019 (STEADFAST); EUCTR2019-004471-39-GB; NCT03806452 (SIKAMIC); NCT03814746 (STAND); NCT04084080 (SCD-CARRE)), and two are single-centre trials in the USA (Kutlar 2019; NCT04335721).

Two RCTs are placebo-controlled: Kutlar 2019 is evaluating ambrisentan versus placebo, and NCT03806452 (SIKAMIC) is evaluating hydroxyurea versus placebo. Two trials are comparing two active interventions: two different doses of IMR-687 in EUCTR2019-004471-39-GB, and two different doses of crizanlizumab in NCT03814746 (STAND). Three trials are comparing interventions to standard care: crizanlizumab versus standard care in Ataga 2019 (STEADFAST), blood transfusions versus standard care in NCT04084080 (SCD-CARRE), and voxelotor versus standard care in NCT04335721.

Change in albuminuria is the primary outcome of four trials (NCT03806452 (SIKAMIC); NCT03814746 (STAND); NCT04335721; Ataga 2019 (STEADFAST)); albuminuria, GFR, and CKD are secondary outcomes of one trial (NCT04084080 (SCD-CARRE)); renal function is a secondary outcome of one trial (Kutlar 2019); and renal function is an exploratory outcome of one trial (EUCTR2019-004471-39-GB).

Studies awaiting classification

One trial is awaiting classification (NCT05392894 (REDRESS)). This trial is being conducted at eight centres in the UK and is assessing the effect of haploidentical stem cell transplantation on SCD-related complications compared to standard medical care over two years.

Risk of bias in included studies

See Figure 4 and Figure 5 for visual representations of the risk of bias assessment across all trials and for each item in the included trials. See the risk of bias section in the Characteristics of included studies section for further information about the bias identified in each trial.

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

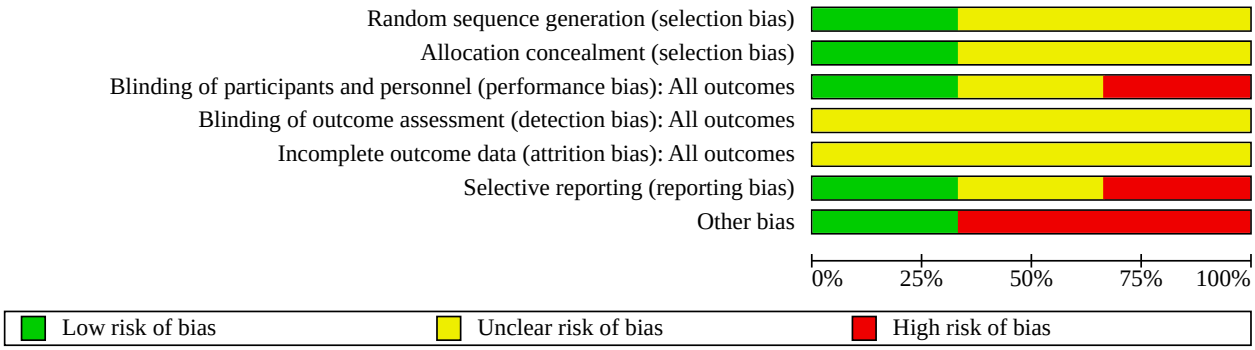
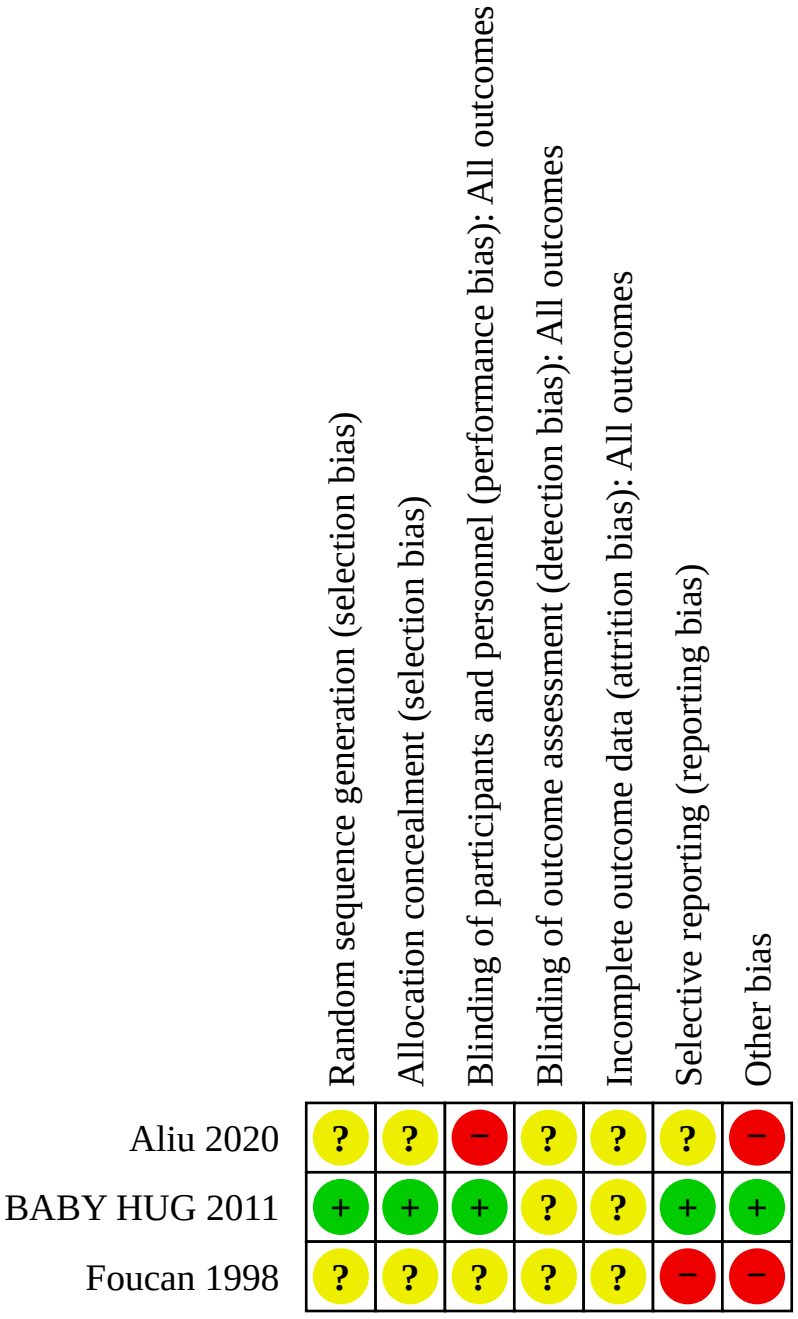


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation (selection bias)

We considered BABY HUG 2011 at low risk of bias related to random sequence generation, as the telephone randomisation schedule was developed by the medical co-ordinating centre. We considered Aliu 2020 and Foucan 1998 at unclear risk of selection bias for this domain, as they provided no description of the randomisation method.

Allocation concealment (selection bias)

We considered BABY HUG 2011 at low risk of bias for allocation concealment because the drug distribution centre allocated treatments centrally, and hydroxyurea and placebo had the same packaging, appearance, and taste. We considered Aliu 2020 and Foucan 1998 at unclear risk, as they provided no description of allocation concealment.

Blinding

Blinding of participants and personnel (performance bias)

We considered BABY HUG 2011 at low risk of performance bias, as participants, caregivers, and medical co-ordinating staff were masked to treatment. We considered Foucan 1998 at unclear risk because there was no description of blinding of personnel, and it was unclear if dosing schedules were similar in both groups. We considered Aliu 2020 at high risk of performance bias: the paper did not detail how the blinding was maintained; however, because the oral treatments of vitamin C and lisinopril are distinguishable, it is unlikely that personnel, parents, or children could remain blinded.

Blinding of outcome assessment (detection bias)

We considered all three trials at unclear risk of detection bias. In BABY HUG 2011, it was unclear if all assessors were blinded, and Aliu 2020 and Foucan 1998 provided no description of blinding of outcome assessment.

Incomplete outcome data

We judged all three trials at unclear risk of attrition bias. BABY HUG 2011 reported the co-primary endpoints only in participants with entry and exit values, resulting in a GFR analysis with missing values for approximately 25% of participants. In Foucan 1998, one participant from each group withdrew within the first month, one participant in the placebo group did not comply with treatment, and another participant in the placebo group developed proteinuria during the third month. It is unclear if these participants were included in the six-month analysis. In Aliu 2020, in the lisinopril arm (85 participants), six participants were lost to follow-up, and one participant discontinued the intervention due to dizziness. In the vitamin C arm (85 participants), five participants were lost to follow-up. The effect of these losses was unclear.

Selective reporting

We judged BABY HUG 2011 at low risk of reporting bias, as it reported all prespecified outcomes. We judged Foucan 1998 at high risk of bias for selective reporting because it provided no creatinine clearance data at six months, although this is an important marker of kidney disease progression. We considered Aliu 2020 at unclear risk because there was no protocol or prospective trial registration available to assess prespecified outcomes.

Other potential sources of bias

We considered Aliu 2020 and Foucan 1998 at high risk of other sources of bias. In Foucan 1998, the sample size was small and not powered to detect a difference between groups, and the follow-up period was too short to assess long-term benefits or harms. For Aliu 2020, we found four other potential sources of bias: first, participant age was imbalanced between the two groups; second, the follow-up was too short to assess long-term benefits or harms; third, the baseline microalbuminuria measurements were likely inaccurate, leading to a biologically implausible reduction in microalbuminuria after one month; and finally, the statistical analyses did not assess the change in measurements at baseline and at three months for each participant, but rather compared the means for all participants at the two time points.

We detected no other sources of bias in BABY HUG 2011.

Effects of interventions

See: **Summary of findings 1** Hydroxyurea compared to placebo for preventing or reducing kidney complications in people with sickle cell disease; **Summary of findings 2** Angiotensin-converting enzyme inhibitors compared to placebo for preventing or reducing kidney complications in people with sickle cell disease; **Summary of findings 3** Angiotensin-converting enzyme inhibitors compared to vitamin C for preventing or reducing kidney complications in people with sickle cell disease

Hydroxyurea versus placebo

One trial that enroled 193 young children aged nine to 18 months evaluated hydroxyurea versus placebo (BABY HUG 2011). See Table 1 for unadjusted HRs for SAEs and AEs reported in this trial. Summary of findings 1 shows the results of our analyses and GRADE judgements for the outcomes reduction or prevention of kidney disease progression, SAEs (except stroke), and all-cause mortality.

Reduction or prevention of kidney disease progression

We are unsure if hydroxyurea compared to placebo reduces or prevents kidney disease progression (assessed by change in GFR), or reduces hyperfiltration, in children aged nine to 18 months (MD 0.58 mL/min/1.73 m^2, 95% CI −14.60 to 15.76; 1 study, 142 participants; very low-certainty evidence; Analysis 1.1). We downgraded the certainty of evidence for risk of bias concerns (25% of participants were excluded from the analysis), imprecision (the estimate has a wide CI including clinically significant harm or benefit), and indirectness (results apply only to small children aged nine to 18 months).

Hydroxyurea compared to placebo may improve the ability to concentrate urine in children aged nine to 18 months (MD 42.23 mOsm/kg, 95% CI 12.14 to 72.32; 1 study, 178 participants; low-certainty evidence; Analysis 1.2). We downgraded the certainty of evidence for imprecision (one study with 178 participants) and indirectness (results only apply to small children aged nine to 18 months).

Serious adverse events

We could not report the overall effect of hydroxyurea on SCD-related SAEs. We reported subgroup categories of SAEs separately and reported the 99% CI of the pooled RR to allow for multiple statistical testing.

Acute chest syndrome

Hydroxyurea compared to placebo may have little or no effect on the incidence of acute chest syndrome in children aged nine to 18 months (RR 0.39, 99% CI 0.13 to 1.16; 1 study, 193 participants; low-certainty evidence; Analysis 1.3). We downgraded the certainty of evidence for imprecision (the estimate has a wide CI including a clinically significant benefit) and indirectness (results only apply to small children aged nine to 18 months).

Painful crisis

Hydroxyurea compared to placebo may have little or no effect on the incidence of painful crises in children aged nine to 18 months (RR 0.68, 99% CI 0.45 to 1.02; 1 study, 193 participants; low-certainty evidence; Analysis 1.4). We downgraded the certainty of evidence for imprecision (the estimate has a wide CI including a clinically significant benefit) and indirectness (results only apply to small children aged nine to 18 months).

Hospitalisations

Hydroxyurea compared to placebo may have little or no effect on hospitalisation in children aged nine to 18 months (RR 0.83, 99% CI 0.68 to 1.01; 1 study, 193 participants; low-certainty evidence; Analysis 1.5). We downgraded the certainty of evidence for imprecision (the estimate has a wide CI including a clinically significant benefit) and indirectness (results only apply to small children aged nine to 18 months).

Stroke

Hydroxyurea compared to placebo may have little or no effect on the incidence of stroke in children aged nine to 18 months (Peto OR 0.14, 99% CI 0.00 to 23.62; 1 study, 193 participants; Analysis 1.6).

All-cause mortality

No deaths were reported in either group (low-certainty evidence). We downgraded the certainty of evidence for indirectness (results only apply to small children aged nine to 18 months) and imprecision (no deaths occurred).

Secondary outcomes

Other adverse events

Neutropenia

Hydroxyurea compared to placebo may increase the risk of neutropenia in children aged nine to 18 months (RR 2.53, 99% CI 1.43 to 4.47; 1 study, 193 participants; Analysis 1.7).

Thrombocytopenia

Hydroxyurea compared to placebo may make little or no difference to the risk of thrombocytopenia in children aged nine to 18 months (RR 1.59, 99% CI 0.48 to 5.21; 1 study, 193 participants; Analysis 1.8).

Quality of life

BABY HUG 2011 did not report quality of life.

Number of units or volume (mL) of red blood cells infused

Number of participants transfused

Hydroxyurea compared to placebo may reduce the number of children aged nine to 18 months requiring a transfusion (RR 0.61, 95% CI 0.38 to 0.99; 1 study, 193 participants; Analysis 1.9).

Angiotensin-converting enzyme inhibitors versus placebo

One trial that enroled 22 adults with normal blood pressure and microalbuminuria evaluated an ACEI (captopril) versus placebo (Foucan 1998).

Primary outcomes

Reduction or prevention of kidney disease progression

We are unsure if captopril compared to placebo reduces proteinuria in adults with normal blood pressure and microalbuminuria (MD −49.00 mg/day, 95% CI −124.10 to 26.10; 1 study, 22 participants; very low-certainty evidence; Analysis 2.1). We downgraded the certainty of evidence for risk of bias concerns (high or unclear risk of bias in all domains), imprecision (the estimate has a very wide CI including clinically significant harm or benefit), and indirectness (small population of adults with normal blood pressure and albuminuria). See Summary of findings 2.

We are unsure if captopril compared to placebo reduces or prevents kidney disease as measured by creatinine clearance. Foucan 1998 states that creatinine clearance remained constant over six months in both groups, but provided no comparative data (very low-certainty evidence). We contacted the trial authors for data on creatinine clearance but received no response.

Serious adverse events

Foucan 1998 did not report SAEs.

All-cause mortality

Foucan 1998 did not report all-cause mortality.

Secondary outcomes

Other adverse events

Foucan 1998 reported one AE (dry cough) in the ACEI group (RR 2.54, 99% CI 0.04 to 148.91; 1 study, 22 participants; Analysis 2.2).

Quality of life

Foucan 1998 did not report quality of life.

Number of units or volume (mL) of red blood cells infused

Foucan 1998 did not report blood cell transfusions.

Angiotensin-converting enzyme inhibitors versus vitamin C

One trial that enroled 170 children aged one to 18 years with normal blood pressure and microalbuminuria evaluated an ACEI (lisinopril) versus vitamin C (Aliu 2020). We were unable to include any outcomes in an analysis.

Primary outcomes

Reduction or prevention of kidney disease progression

We are unsure if lisinopril compared to vitamin C reduces proteinuria in children with normal blood pressure and microalbuminuria. The investigators state that there is evidence of a reduction in proteinuria, with far fewer participants in both study arms having microalbuminuria, but they only present absolute data (mean (SD)) at baseline, one month, two months, and three months, and not the change from baseline at each time point. Therefore, we could not include the data in any analyses.

Time point	Microalbuminuria in mg/g, mean (SD)	P-value

	ACEI	Vitamin C	
Baseline	134.2 (72.5)	107.6 (58.0)	0.009
1 month	7.6 (1.6)	11.5 (2.9)	<0.001
2 months	7.0 (1.4)	8.0 (2.1)	0.176
3 months	6.5 (1.1)	7.9 (1.1)	0.001

The effects reported in the trial, as presented in the above table, were already apparent at one month after initiation of treatment, and follow-up lasted only three months. Clinically, a dramatic fall in microalbuminuria as reported here after one month is very unlikely, and the fact that this also occurred in the vitamin C arm suggests there may have been an overestimation of microalbuminuria in both groups at the beginning of the trial (e.g. due to a poor sampling technique that improved as the trial proceeded).

Similarly, the trial authors state that creatinine clearance was similar between the two groups at the end of the three-month study, but do not report the mean change from baseline. Data for baseline, one month, two months, and three months are presented in the table below. We are unsure if lisinopril compared to vitamin C reduces or prevents kidney disease progression as measured by creatinine clearance.

GFR (ml/min/1.73 m^2)	GFR in mL/min/1.73 m^2, mean (SD)		P-value
	ACEI	Vitamin C	
Baseline	122.0 (35.6)	121.0 (35.6)	0.789
1 month	117.8 (29.3)	117.5 (30.2)	0.822
2 months	121.0 (38.6)	114.2 (32.6)	0.829
3 months	115.4 (26.3)	117.0 (33.9)	0.055

Serious adverse events

Aliu 2020 did not report SAEs.

All-cause mortality

Aliu 2020 did not report all-cause mortality.

Secondary outcomes

Other adverse events

One child was excluded from the ACEI arm of Aliu 2020 due to dizziness. No other complications were reported.

Quality of life

Aliu 2020 did not report quality of life.

Number of units or volume (mL) of red blood cells infused

Aliu 2020 did not report red blood cell transfusions.

DISCUSSION

Summary of main results

Based on data from BABY HUG 2011, which enroled 93 children aged nine to 18 months, we are unsure if hydroxyurea compared to placebo improves GFR or reduces hyperfiltration, but it may improve the ability to concentrate urine. Hydroxyurea may have little or no effect on the incidence of acute chest syndrome, painful crises, and hospitalisations in this population. The trial reported no deaths and did not measure quality of life.

Based on data from Foucan 1998, which enroled 22 adults with normal blood pressure and microalbuminuria, we are unsure if ACEIs compared to placebo reduce proteinuria or reduce or prevent kidney disease as measured by creatinine clearance. The trial did not report SAEs, deaths, or quality of life.

Based on data from Aliu 2020, which enroled 170 children aged one to 18 years with normal blood pressure and microalbuminuria, we are unsure if ACEIs compared to vitamin C reduce proteinuria or maintain GFR. The trial reported no other outcomes of interest for this review.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the effectiveness and safety of interventions for preventing or reducing kidney complications in people with SCD.

The following considerations limit the applicability of our results.

- The findings for hydroxyurea treatment only apply to young children aged nine to 18 months.
- The findings for ACEI are based on a trial with few participants and a short follow-up.
- Due to lack of evidence, we cannot comment on management of children aged over 18 months with any known genotype of SCD other than HbSS, or adults with any known genotype of SCD.

Quality of the evidence

Overall, the certainty of the evidence was low or very low across different outcomes according to GRADE methodology (Summary of findings 1; Summary of findings 2; Summary of findings 3). We downgraded the certainty of evidence for risk of bias concerns, indirectness (e.g. because the sample populations were either only children or only adults), and imprecision (CIs were very wide and included clinically significant harm or benefit).

Potential biases in the review process

We conducted a comprehensive search of multiple databases and clinical trial registries to capture all relevant trials. This included the Haemoglobinopathy Trials Register and the Transfusion Evidence Library (Electronic searches); both registries perform handsearching of relevant journals to identify relevant trials within the grey literature. There were no restrictions on the language of publication. Two review authors independently assessed the relevance of each paper and extracted data in duplicate. We prespecified all outcomes and subgroups prior to analysis. There were insufficient numbers of included trials to conduct meta-analyses or assess publication bias.

Agreements and disagreements with other studies or reviews

One Cochrane Review on ACE inhibitors for proteinuria and microalbuminuria in people with SCD identified a single eligible study (Sasongko 2021), which was one of the three included in our review (Foucan 1998). The rationale for the overlap between the objectives of the two reviews was to identify any studies that compared ACEIs and blood transfusions as treatment modalities for preventing progression of kidney disease. Both reviews have similar conclusions: Sasongko 2021 concluded that "there is not enough evidence to show that the administration of ACE inhibitors is associated with a reduction of microalbuminuria and proteinuria in people with SCD, although a potential for this was seen", and one of our conclusions is that we are unsure if ACEIs have any effect on preventing or reducing kidney complications in adults with SCD and normal blood pressure and microalbuminuria.

No completed studies evaluated red blood cell transfusions for the prevention of CKD.

One uncontrolled study in 23 children with a mean age of 7.4 years (SD 3.5 years) showed a reduction in hyperfiltration after three years of treatment with hydroxyurea, although GFR remained elevated (Aygun 2013). The study authors suggested that escalating children to the maximum tolerated dose could have been a factor (amongst other variables) in GFR improvement, whereas in BABY HUG 2011, a 20 mg dose of hydroxyurea was administered with no dose escalation. However, the results reported by Aygun 2013 can only be confirmed by an adequately powered randomised dose-escalation trial.

AUTHORS' CONCLUSIONS

Implications for practice

Based on current evidence, we are unsure if hydroxyurea compared to placebo improves glomerular filtration rate (GFR) or reduces hyperfiltration in children aged nine to 18 months with sickle cell disease (SCD). The drug may improve their ability to concentrate urine and may make little or no difference to the incidence of acute chest syndrome, painful crises, and hospitalisations.

Based on current evidence, we are unsure if angiotensin-converting enzyme inhibitors (ACEIs) compared to placebo have any effect on preventing or reducing kidney complications in adults with normal blood pressure and microalbuminuria.

Based on current evidence, we are unsure if ACEIs compared to vitamin C reduce proteinuria in children with normal blood pressure and microalbuminuria.

This review identified no trials that investigated red blood cell transfusions or any other interventions to prevent or reduce kidney complications.

Due to lack of evidence, we cannot comment on management of children aged over 18 months or adults with SCD disease.

Implications for research

Using Sealed Envelope, we estimated that future trials would need an adjusted sample size of 2986 participants to have a 90% chance of detecting, as significant at the 5% level, a decrease in the incidence of proteinuria from 20% in the control group to 15% in the experimental group with 5% non-compliance or cross-over rate (McKie 2007; Sharpe 2014). We also estimated that future trials would need an adjusted sample size of 2356 participants to have a 90% chance of detecting, as significant at the 5% level, a decrease in the incidence of end-stage renal disease from 12% in the control group to 8% in the experimental group with a 10% non-compliance or cross-over rate (Powars 2005). This means that if the treatment is effective, we could detect its ability to prevent four people developing end-stage renal disease for every 100 people treated (a reduction of 33%).

People with SCD are living longer and have an increased risk of developing chronic kidney disease during their lifetime. Both this Cochrane Review and the Cochrane Review on ACEIs for proteinuria and microalbuminuria in people with SCD have identified a striking lack of adequately designed and powered studies addressing this critical question (Sasongko 2021). Trials of hydroxyurea, ACEIs or red blood cell transfusions in older children and adults are urgently needed to determine any effect on prevention or reduction of kidney complications in people with SCD. Of the seven ongoing trials identified, only two have renal function or proteinuria as a primary outcome (NCT03806452 (SIKAMIC); NCT04335721). Of the remaining five, four are investigating renal function as a secondary outcome for which the studies are not powered, and one includes renal function as an exploratory outcome. In addition, these studies have a maximum follow-up of 12 months. Longer-term, adequately powered trials comparing hydroxyurea, ACEIs, or red blood cell transfusions with placebo or other interventions are urgently required, as renal failure develops over the course of many years, and it is important to find interventions that prevent this decline.

ACKNOWLEDGEMENTS

We thank the editorial base of the Cochrane Cystic Fibrosis and Genetic Disorders Group for their help and support.

We thank the UK Blood Services, who support the Systematic Review Initiative (NHS Blood and Transplant, Scottish National Blood Transfusion Service, Welsh Blood Service and Northern Ireland Blood Transfusion Service).

We thank Katherine Bull, Particia Fortin, Sally Hopewell, and Marialena Trivella, who were authors on the previous version of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aliu 2020

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group

Participants	**Inclusion criteria**
	
	• Age 1–18 years
	• SCA and microalbuminuria
	• Steady state (defined as absence of fever or crisis in the previous 4 weeks or more in a child who was not on any medication other than routine folic acid and prophylactic antimalarial drug)
	• Follow-up in the SCD clinic at the Federal Teaching Hospital, Gombe (FTHG)
	• Consent from caregivers
	
	Exclusion criteria
	
	• Known hypertension, diabetes mellitus, HIV, or urinary tract infection
	
	Baseline characteristics
	
	• Lisinopril Group
	  ◦ Number of participants: 85
	  ◦ Sex: 45 males (52.9%)
	  ◦ Age: mean 108.84 (SD 56.88) months
	  ◦ SCD genotype HbSS: NR
	  ◦ SCD genotype Hb Sβ^0thalassaemia: NR
	  ◦ Haemoglobin concentration: NR
	  ◦ % haemoglobin as foetal haemoglobin: NR
	  ◦ GFR: mean 122.0 (SD 35.6) mL/min/1.73 m^2
	  ◦ Splenic sequestration: NR
	  ◦ Hospitalisations: NR
	  ◦ Pain events: NR
	  ◦ Acute chest syndrome: NR
	  ◦ Transfusions: NR

Aliu 2020 *(Continued)*

- Serum creatinine: NR
- Urine osmolality: NR
- SBP: NR
- DBP: NR
- Microalbuminuria: NR

- Vitamin C Group
  - Number of participants: 85
  - Sex: 42 males (49.4%)
  - Age: mean 191.68 (SD 58.56) months
  - SCD genotype HbSS: NR
  - SCD genotype Hb Sβ^0thalassaemia: NR
  - Haemoglobin concentration: NR
  - % haemoglobin as foetal haemoglobin: NR
  - GFR: mean 121.0 (SD 35.6) mL/min/1.73 m^2
  - Splenic sequestration: NR
  - Hospitalisations: NR
  - Pain events: NR
  - Acute chest syndrome: NR
  - Transfusions: NR
  - Serum creatinine: NR
  - Urine osmolality: NR
  - SBP: NR
  - DBP: NR
  - Microalbuminuria: NR

Interventions	**Intervention:** oral lisinopril 0.1 mg/kg/day for 3 months. **Control:** oral vitamin C 100 mg/day for 3 months.
Outcomes	**Primary outcome** • Reduction of microalbuminuria (3 months) **Secondary outcome** • Progression of GFR (3 months)
Identification	**Source of funding:** NR **Country:** Nigeria **Setting:** 1 medical centre **Contact author:** Rasaki Aliu, Department of Pediatrics, Gombe State University and Federal Teaching Hospital, Gombe, Gombe State, Nigeria –aliu.abdurrazaq11@gmail.com
Notes	**Recruitment:** September 2016 to March 2017

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The weekly recruitment and randomization were done in such a way that each participant had a 50:50 chance of being randomized into the intervention or placebo group"

Aliu 2020 *(Continued)*

		The methods state that the probability of being put in each group is 50:50, but does not detail how this was achieved. The method of random sequence generation is not described.
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The participants and their parents were blinded in this study." "The use of vitamin C as a placebo in this study was a limitation. It would have been more appropriate to use a placebo indistinguishable from Lisinopril and that has no renal protective effect." By definition this is a single-blind study; however, the methods do not detail how the blinding was maintained. Vitamin C and lisinopril could be distinguished, so unclear how parents and children could remain blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of whether outcome assessors were blinded in this study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the lisinopril arm (85 participants), 6 participants were lost to follow-up and 1 participant discontinued the intervention due to dizziness. In the vitamin C arm (85 participants) 5 participants were lost to follow-up. The effect of this on outcomes was unclear.
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration or protocol. Trial registration was retrospective.
Other bias	High risk	There is an imbalance between the 2 arms of the trial in the mean age of the participants: 9.07 (SD 4.74) years in the lisinopril group and 7.64 (SD 4.88) years in the vitamin C group. Also, this trial is not placebo-controlled. Vitamin C can be differentiated from the intervention and is not inert.

BABY HUG 2011

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group
Participants	**Inclusion criteria** • Age 9–18 months • HbSS or Sβ^{0}thalassaemia, irrespective of clinical severity **Exclusion criteria** • Transfusion within 2 months • Height, weight, or head circumference < 5th percentile • MDI < 70 • Abnormal TCD velocity • Chronic transfusion therapy • Cancer

BABY HUG 2011 *(Continued)*

- Severe developmental delay (e.g. cerebral palsy or other mental retardation)
- Grade III/IV intraventricular haemorrhage
- Stroke with neurological deficit
- Surgical splenectomy
- Participation in other clinical intervention trials
- Probable or known diagnosis of haemoglobin S-hereditary persistence of foetal haemoglobin
- Known $HbS\beta^+$ thalassaemia (haemoglobin A present)
- Any condition or chronic illness that makes participation unadvised or unsafe in the opinion of the principal investigator
- Inability or unwillingness to complete baseline (pre-enrolment) studies, including blood or urine specimen collection, liver-spleen scan, abdominal sonogram, neurological examination, neuropsychological testing, or TCD (interpretable study not required, but confirmed velocity > 200 cm/second results in ineligibility)
- Previous or current treatment with hydroxyurea or another anti-sickling drug (additional exclusion criteria from trial registration NCT00006400).

Baseline characteristics

- Hydroxyurea group
  - Number of participants: 96
  - Sex: 44 males (46%)
  - Age: mean 13.6 (SD 2.7) months
  - SCD genotype HbSS: n = 94 (98%)
  - SCD genotype HbSβ^0 thalassaemia: n = 2 (2%)
  - Haemoglobin concentration: mean 90 (SD 13) g/L
  - % haemoglobin as foetal haemoglobin: mean 25.9% (SD 8.5%)
  - GFR: mean 126 (SD 39) mL/min/1.73 m^2
  - Splenic sequestration: n = 5 (5%)
  - Hospitalisations: n = 65 (68%)
  - Pain events: n = 25 (27%)
  - Acute chest syndrome: n = 3 (3%)
  - Transfusions: n = 10 (11%)
  - Serum creatinine: mean 0.25 (SD 0.09) mmol/L
  - Urine osmolality: mean 403.22 (SD 151.63) mOsm/kg
  - SBP: NR
  - DBP: NR
  - Microalbuminuria: NR
- Placebo group
  - Number of participants: 97
  - Sex: 40 males (41%)
  - Age: mean 13.5 (SD 2.8) months
  - SCD genotype HbSS: n = 93 (96%)
  - SCD genotype HbSβ^0 thalassaemia: n = 4 (4%)
  - Haemoglobin concentration: mean 92 (SD 13) g/L
  - % haemoglobin as foetal haemoglobin: mean 26.0% (SD 8.5%)
  - GFR: mean 124 (SD 30) mL/min/1.73 m^2
  - Splenic sequestration: n = 10 (11%)
  - Hospitalisations: n = 70 (73%)
  - Pain events: n = 26 (27%)
  - Acute chest syndrome: n = 5 (5%)
  - Transfusions: n = 17 (18%)
  - Serum creatinine: mean 0.23 (SD 0.07) mmol/L
  - Urine osmolality: mean 408.32 (SD 152.40) mOsm/kg

BABY HUG 2011 *(Continued)*

- SBP: NR
- DBP: NR
- Microalbuminuria: NR

Interventions	**Intervention:** hydroxyurea 20 mg/kg/day; local pharmacists reconstituted powder with syrup and water to a concentration of 100 mg/mL, and dispensed a 35-day supply. There was no dose escalation. **Control:** placebo. Hydroxyurea and placebo powders had the same appearance and packaging and the liquid formulations had the same appearance and taste. Hydroxyurea and placebo were distributed to clinical centres in encoded kits.
Outcomes	**Primary outcome** • splenic and liver function (as measured by GFR) **Secondary outcomes** • investigations of the brain, lungs, hepatobiliary system, and growth and development • Height, weight, and head circumference • Neurodevelopment assessment (Bayley Developmental and Vineland Adaptive Behavior Scales) • Adverse clinical events included known complications of sickle-cell anaemia, such as pain, dactylitis, acute chest syndrome, stroke, priapism, sepsis or bacteraemia, splenic sequestration, hospitalisation, and transfusion • SAEs
Identification	**Source of funding:** the US National Heart, Lung, and Blood Institute; and the National Institute of Child Health and Human Development **Country:** USA **Setting:** 13 medical centres **Contact author:** Prof. W C Wang MD, Hematology MS 800, Room R5036 St. Jude Children's Research Hospital 262 Danny Thomas Place Memphis, TN 38105-3678 – winfred.wang@stjude.org
Notes	**Recruitment:** October 2003 to September 2007 179 (93%) participants who completed ≥ 18 months of the trial and ≥ 1 exit assessment were analysed; 167 (86%) completed the full study. Hydroxyurea: 4 withdrawals: 3 lost to follow-up and 1 incorrect diagnosis; 91 analysed. Placebo: 9 withdrawals: 4 declined further participation, 2 moved, 2 lost to follow-up, and 1 placed on chronic transfusion; 88 analysed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation sequence was pre-decided by a randomisation schedule developed for each clinical site by the medical coordinating centre. Double-blind randomisation was done with an automated telephone response system and the use of a random three digit kit number for each enrolled participant."
Allocation concealment (selection bias)	Low risk	"The kit number, which was linked to the assignment sequence, was used by the drug distribution centre to ship the appropriate study drug to the clinical site pharmacy. Hydroxycarbamide and placebo powders had the same appearance and packaging and the liquid formulations had the same appear-

BABY HUG 2011 *(Continued)*

		ance and taste. Hydroxyurea and placebo were distributed to clinical centres in encoded kits."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Hydroxyurea and placebo were distributed to clinical centres in encoded kits. Local pharmacists reconstituted powder with syrup and water to a concentration of 100 mg/mL, and dispensed a 35-day supply. As in the HUSOFT trial, there was no dose escalation. Participants, caregivers, and medical coordinating centre staff were masked to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"An unmasked so-called primary endpoint person monitored laboratory values and assisted in clinical management. Masked readings of splenic uptake on ^{99} m Tc-sulphur colloid liver-spleen scans were categorised qualitatively as normal, decreased (but present), or absent." While the methods state "double blind randomisation", it is not clear whether this is at the level of the outcome assessors as well as at the level of the drug administration. The statement about an unmasked primary endpoint assessor monitoring laboratory values is suggestive of a risk of bias; however, they may have only monitored for safety, whereas the splenic readings were done by someone who was blinded to the study drug allocation. It is unclear whether the assessor of the GFR was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States that all participants randomly assigned to a treatment group were analysed for the co-primary endpoints, but also "Total number of participants assessed for each endpoint". N differs from the number reported in table one because only entry values that are paired with exit values from the same participants are included. Both co-primary endpoints are per protocol analysis and only include participants with paired entry and exit values. Approximately 25% of participants had no entry/exit GFR values. All other outcomes reported as intention-to-treat.
Selective reporting (reporting bias)	Low risk	All of the outcomes stated in the methods were reported in the results.
Other bias	Low risk	No other sources of bias were detected.

Foucan 1998

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group
Participants	**Inclusion criteria** • Homozygous for haemoglobin SS • Age ≥ 18 years • Diagnosis of SCA based on clinical and biological data including haemoglobin electrophoresis • Urinary albumin excretion 30–300 mg/24 hours on 3 separate occasions during the 6-month period preceding the trial **Exclusion criteria** • non-HbSS genotype • Hypertension (blood pressure > 140/90 mmHg) • Evidence of heart, kidney, liver, or systemic disease

Foucan 1998 *(Continued)*

- Pregnancy
- Anti-inflammatory or antihypertensive medications

Baseline characteristics

- ACEI (captopril) Group
  - Number of participants: 12
  - Sex: 5 males (41.7%)
  - Age: mean 30 (SD 8) years
  - SCD genotype HbSS: n = 12 (100%)
  - SCD genotype HbSβ^0 thalassaemia: n = 0 (0%)
  - Haemoglobin concentration: mean 80 (SD 10) g/L
  - % haemoglobin as foetal haemoglobin: mean 8% (SD 6%)
  - GFR: mean 113 (SD 24) mL/min/1.73 m^2
  - Splenic sequestration: NR
  - Hospitalisations: NR
  - Pain events: NR
  - Acute chest syndrome: NR
  - Transfusions: NR
  - Serum creatinine: mean 67 (SD 17) mg/dL
  - Urine osmolality: NR
  - SBP: mean 121 (SD 11) mmHg
  - DBP: mean 63 (SD 7) mmHg
  - Microalbuminuria: mean 121 (SD 66) mg/day
- Placebo Group
  - Number of participants: 11
  - Sex: 2 males (20%)
  - Age: mean 28 (SD 6) years
  - SCD genotype HbSS: n = 10 (100%)
  - SCD genotype HbSβ^0 thalassaemia: n = 0 (0%)
  - Haemoglobin concentration: mean 80 (SD 10) g/L
  - % haemoglobin as foetal haemoglobin: mean 11% (SD 4%)
  - GFR: mean 129 (SD 21) mL/min/1.73 m^2
  - Splenic sequestration: NR
  - Hospitalisations: NR
  - Pain events: NR
  - Acute chest syndrome: NR
  - Transfusions: NR
  - Serum creatinine: mean 58 (SD 10) mg/dL
  - Urine osmolality: NR
  - SBP: mean 118 (SD 8) mmHg
  - DBP: mean 61 (SD 6) mmHg
  - Microalbuminuria: mean 107 (SD 86) mg/day

Interventions	**Intervention:** ACEI (captopril) for 6 months. The initial dose was 6.25 mg/day (¼ of a tablet of 25 mg once a day) during the first month, 12.5 mg/day (¼ of a tablet twice a day) during the second and the third months, and 25 mg/day (½ of a tablet twice a day) after the third month. **Control:** indistinguishable placebo for 6 months
Outcomes	**Outcomes** • Progression of albuminuria

Foucan 1998 *(Continued)*

- Blood pressure, measured by the automated oscillometric method (Dynamap) after 5 minutes of rest in a half-sitting position. Systolic pressure, diastolic pressure, and mean arterial pressure were measured as the average of 3 measurements taken at 5-minute intervals.

Identification	**Source of funding:** supported by grants from the Programme Hospitalier de Recherche Clinique (PHRC), France **Country:** France (Guadeloupe) **Setting:** outpatients in one hospital (Centre Hospitalo Universitaire (CHU) of Pointe-à-Pitre in Guadeloupe in 1996) **Contact author:** Lydia Foucan, Departement d'Information Medicale et Sante Publique, Centre Hospitalier Universitaire de Pointe-a-Pitre 97159, Guadeloupe, French West Indies – lydia.foucan@chu-guadeloupe.fr
Notes	**Recruitment:** 1996 (months of recruitment not reported) We contacted the lead author for additional data on creatinine clearance and also to confirm the number of participants included in the proteinuria analysis. At the time of review publication, we had received no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomisation.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Patients were randomly assigned to two groups, and received captopril or an indistinguishable placebo". Participants may have been blinded to treatment, but not clear if dosing was done similarly in both arms. No description or statement regarding blinding of personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description if outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"All patients were included in an intention-to-treat analysis." 1 participant in the captopril group had an unusual pain in the shoulder and discontinued treatment on the 6th day, and 1 in the placebo group was unavailable for follow-up after the 1st month. These 2 participants were included in the results for as long as they participated. Does not appear that they were included in 6-month analysis though it was described as intention-to-treat. Very small sample size so all results should be included.
Selective reporting (reporting bias)	High risk	"Creatinine clearance was calculated by the modified Cockroft and Gault formula (10,11). All measurements were repeated at baseline and at 1, 3, and 6 months." "creatinine concentrations and creatinine clearance remained constant throughout the study in both groups (data not shown)." Creatinine clearance important marker of kidney progression but data not shown.

Foucan 1998 *(Continued)*

Other bias	High risk	This is a small sample size and likely not powered to detect any differences. Also follow-up is too short to assess longer-term AEs or actual effects on kidney disease progression.

ACEI: angiotensin-converting enzyme inhibitor; AEs: adverse events; DBP: diastolic blood pressure; GFR: glomerular filtration rate; MDI: mental developmental index; NR: not reported; RCT: randomised controlled trial; SAEs: serious adverse events; SBP: systolic blood pressure; SCA: sickle cell anaemia; SCD: sickle cell disease; SD: standard deviation; TCD: transcranial Doppler ultrasound.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ataga 2019 (ENDO)	Wrong study design: cross-over study.
Ataga 2021 (HIBISCUS)	Wrong study design: not designed to assess renal outcomes.
Choi 2016	Wrong study design: not randomised.
Estcourt 2016	Review, not a trial.
George 2020	Wrong study design: dose escalation study assessing maximum tolerated dose.
Jain 2012	Participants did not have chronic kidney disease.
Laurin 2014	Wrong study design: not randomised.
NCT01096121 (MADREPIEC)	Trial terminated prior to recruitment of eligible participants (only 5 recruited).
NCT01195818 (RAND)	Wrong study design: not randomised.
NCT01891292	No participants recruited. Trial withdrawn before recruitment.
NCT01989078 (SCD-Losaratan)	Wrong study design: not randomised.
NCT02286154 (TREAT)	Wrong study design: not randomised.
NCT02373241	Wrong study design: not randomised.
NCT02522104 (DARH)	Wrong study design: not randomised.
Quinn 2017	Wrong study design: not randomised.
Silva Junior 2014	Wrong study design: not randomised.
Steinberg 2003	Wrong study design: not randomised.
Wood 2020 (PRAISE)	Wrong study design: not designed to assess renal outcomes.
Zahr 2019	Wrong study design: not randomised.

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT05392894 (REDRESS)

Methods	**Study design:** RCT **Study grouping:** parallel assignment, open-label. **Location:** 8 centres in the UK

Participants	**Inclusion criteria**
	
	• Age ≥ 18 years
	• Confirmed haploidentical donor
	• Severe SCD phenotype at high risk for morbidity and mortality. Severe SCD is defined by ≥ 1 of the following.
	  ○ Clinically significant neurologic event (stroke) or deficit lasting > 24 hours
	  ○ History of ≥ 2 acute chest syndromes in a 2-year period preceding enrolment despite optimum treatment (e.g. with hydroxycarbamide)
	  ○ History of ≥ 3 severe pain crises per year in a 2-year period preceding enrolment despite the institution of supportive care measures (e.g. optimum treatment with hydroxycarbamide)
	  ○ Administration of regular transfusion therapy (8 packed red blood transfusions per year for 1 year to prevent vaso-occlusive complications)
	  ○ Requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion
	  ○ Requiring hydroxycarbamide/transfusion for treatment of SCD complications but intolerance to both therapies due to significant adverse reactions;
	  ○ Established end-organ damage relating to SCD, including, but not limited to, progressive sickle vasculopathy and hepatopathy. End-organ sufficient for entry to this trial shall be ratified at the UK NHP.
	• Fit to proceed to haploidentical stem cell transplant as defined below.
	  ○ Karnofsky score ≥ 60
	  ○ Cardiac function: LVEF ≥ 45% or shortening fraction ≥ 25%
	  ○ Lung function: FEV1, FVC and TLCO ≥ 50%
	  ○ Renal function: EDTA GFR ≥ 40 mL/min/1.73m^2
	  ○ Hepatic function: ALT < 3 × upper limit of normal and bilirubin < 2 × upper limit of normal
	  ○ No radiological evidence of cirrhosis
	
	Exclusion criteria
	
	• Fully matched sibling donor
	• Previous bone marrow transplant
	• Pregnancy or breastfeeding
	• In participants able to conceive a child, refusal to use effective contraception
	• Clinically significant donor-specific HLA antibodies
	• HIV infection or active hepatitis B or C
	• Uncontrolled infection including bacterial, fungal, and viral
	• Participation in another interventional trial in the last 3 months
	• Pre-existing condition deemed to significantly increase the risk of haploidentical stem cell transplant by the local principal investigator

Interventions	**Intervention:** stem cell transplant from bone marrow or peripheral blood from haploidentical donor using standard nationally approved transplant procedure **Control:** standard medical care, including any currently available therapies for people with SCD, which may or may not include regular elective transfusion therapy or medications such as hydroxycarbamide
Outcomes	**Primary outcomes**

NCT05392894 (REDRESS) *(Continued)*

- Treatment failure (defined as occurrence of vaso-occlusive crisis, or transfusion from 6 months post-randomisation)
- Mortality at 24 months post-randomisation

Secondary outcomes

- Health-related quality of life (EQ-5D-5L) at 3, 6, 9, 12, 15, 18, 21, and 24 months post-randomisation
- All-cause mortality at 24 months post-randomisation
- SCD-related mortality (excluding transplant related complications) at 24 months post-randomisation
- Sickle type haemoglobin percentage (HbS%) at 6, 12, and 24 months post-randomisation
- SCD-related complications at 24 months post-randomisation
- Haemoglobin levels, reticulocyte count, LDH, bilirubin at 6, 12, and 24 months post-randomisation
- Pulmonary function (FEV1 %, FEV1/FVC ratio, TLCO %) at 12 and 24 months post-randomisation
- Renal function at 6, 12, and 24 months post-randomisation
- Iron overload at 24 months post-randomisation
- Cardiac function and pulmonary hypertension at 12 and 24 months post-randomisation
- Cerebrovascular progression as measured by clinical stroke or evidence of progression on MRI/MRA at 24 months post-randomisation
- Evidence of hepatic progression as measured by liver function (ALT, AST, ALP, GGT, bilirubin) and FibroScan at 24 months post-randomisation
- Percentage of participants requiring opioid use for pain-related to vaso-occlusive SCD-related crisis at 12 and 24 months post-randomisation

Notes

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate aminotransferase; EDTA: ethylene diamine tetraacetic acid; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GFR: glomerular filtration rate; GGT: gamma-glutamyl transferase; HLA: human leukocyte antigen; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; MRA: magnetic resonance angiography; MRI; magnetic resonance imaging; RCT: randomised controlled trial; SCD: sickle cell disease; TLCO: transfer capacity of the lung.

Characteristics of ongoing studies *[ordered by study ID]*

Ataga 2019 (STEADFAST)

Study name	Study exploring the effect of crizanlizumab on kidney function in patients with chronic kidney disease caused by sickle cell disease (STEADFAST)
Methods	**Study design:** RCT **Study grouping:** parallel **Location:** Brazil, France, Greece, Ireland, Italy, Lebanon, Netherlands, Panama, Spain, Turkey, UK, USA
Participants	**Inclusion criteria** • Confirmed diagnosis of SCD (HbSS and HbSβ0-thal SCD genotypes are eligible) • eGFR 45–140 mL/min/1.73 m^2 based on CKD-EPI formula (if aged ≥ 18 years) or the creatinine-based 'Bedside Schwartz' equation (if aged < 18 years) • ACR 100–2000 mg/g (taken as an average of the 3 screening ACR values to determine eligibility) • Receiving ≥ 1 standard of care drug for SCD-related CKD; if receiving HU, the individual must have been receiving HU for ≥ 6 months and on a stable dose for 3 months, or an ACEI or ARB for 3 months and on a stable dose for those 3 months • Hb ≥ 4.0 g/dL, ANC ≥ 1.0 x 10^9/L, and platelet count ≥ 75 x 10^9/L • Adequate hepatic function as defined by:

Ataga 2019 (STEADFAST) *(Continued)*

	○ ALT < 3.0 x ULN; and ○ Direct (conjugated) bilirubin ≤ 3.0 x ULN **Exclusion criteria** • History of stem cell transplant • Evidence of AKI within 3 months of study entry (can decrease interval to within 6 weeks of study entry only if renal function has returned to pre-AKI values prior to study entry) • Blood pressure > 140/90 mmHg despite treatment • Current renal replacement therapy (i.e. haemodialysis, peritoneal dialysis, haemofiltration, and kidney transplantation) • Blood products within 30 days of Week 1 Day 1 • Participation in a chronic transfusion programme • History of kidney transplant • Hypoalbuminaemia • BMI ≥ 35 kg/m^2 • Voxelotor within 6 months of screening • Use of crizanlizumab or other selectin inhibitor, or intended use during the study
Interventions	**Intervention:** crizanlizumab plus standard of care **Control:** standard of care
Outcomes	**Primary outcome** • Percentage of participants with ≥ 30% decrease in albuminuria (ACR) at 12 months **Secondary outcomes** • Change from baseline in albuminuria (ACR) at 3, 6, 9, and 12 months • Percentage of participants with ≥ 30% decrease in albuminuria (ACR) at 6 months • Percentage of participants with PCR improvement at 12 months • Percentage of participants with a stable PCR at 12 months • Percentage change in eGFR • Slope of ACR decline • Slope of eGFR decline • Percentage of participants with progression of CKD at 12 months • Immunogenicity: change from baseline in levels of anti-drug antibodies to crizanlizumab (measured at select time points during follow-up period, assessed up to approximately 1 year and 4 months) • Annualised rate of visits to emergency room and hospitalisations (change from baseline measured at select time points during follow-up period, assessed up to approximately 1 year and 4 months) • Trough serum concentration of crizanlizumab (change from baseline measured at select time points during follow-up period, assessed up to approximately 1 year and 4 months)
Starting date	December 2019
Contact information	Novartis Pharmaceuticals
Notes	**Estimated study completion date:** 16 March 2023 **Actual recruitment:** 56 participants

EUCTR2019-004471-39-GB

Study name	A phase 2b study to evaluate the safety and efficacy of IMR-687 in subjects with sickle cell disease
Methods	**Study design:** RCT; triple-blinded trial (participant, care provider, investigator) **Study grouping:** 3-arm parallel assignment **Location:** Egypt, France, Ghana, Greece, Kenya, Lebanon, Morocco, Netherlands, Oman, Senegal, Tunisia, Uganda, UK, USA. No participants recruited in: Egypt, France, or Netherlands.

Participants	**Inclusion criteria**
	
	• Age 18–65 years
	• Confirmed diagnosis of SCD (HbSS, HbSB0 thalassaemia, or HbSB+ thalassaemia) in the medical record; if not available, the diagnosis must be confirmed at the site's local laboratory
	• 1–12 documented episodes of vaso-occlusive crises in the past 12 months (defined as a documented episode of an acute painful crisis (for which there was not an explanation other than VOC) that involved moderate to severe pain lasting ≥ 2 hours, and ≥ 1 of the following.
	  ○ Use of escalated analgesia (including healthcare professional-instructed use of an analgesic prescription)
	  ○ Hospital, emergency department, or clinic visit or healthcare telephone consultation at the time of occurrence
	  ○ Diagnosis of acute chest syndrome (defined as an acute illness characterised by fever or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray), hepatic sequestration, or splenic sequestration
	• Haemoglobin 55–105 g/L
	• Absolute reticulocyte count ≥ 80 × 10^9/L
	• Participants receiving HU must have received it continuously for ≥ 6 months, and must have been on a stable dose for at least 3 months, with no anticipated need for dose adjustments during the study
	
	Exclusion criteria
	
	• Hospital discharge for SCD crisis or other vaso-occlusive event within the 4 days prior to randomisation
	• Red blood cell transfusion within 60 days or on chronic transfusion therapy regimen
	• Hereditary persistence of HbF (i.e. HbF > 25% at screening)
	• Known active hepatitis A, hepatitis B, or hepatitis C, with active or acute event of malaria, or HIV
	• Pregnancy or breastfeeding, or possibility of becoming pregnant or impregnating partner during study
	• eGFR < 45 mL/min as calculated by the equation from the Modification of Diet in Renal Disease Study using creatinine, age, sex, and ethnicity
	• ALT or AST > 3 × ULN
	• BMI < 17.0 kg/m^2 and total body weight < 45 kg; or BMI > 35 kg/m^2
	• Current or history of malignancies (solid tumours and haematological malignancies), unless free of the disease (including completion of any active or adjuvant treatment for prior malignancy) for ≥ 5 years
	• History of a clinically significant allergic reaction or hypersensitivity to any drug or any component of the drug formulations used in the trial
	• History of unstable or deteriorating cardiac or pulmonary disease within previous 6 months
	• Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable)
	• On ECG testing at consent or randomisation, corrected QT interval, Fridericia's formula (QTcF) > 450 ms in men and > 470 ms in women, or the presence of clinically significant ECG abnormalities
	• History of major surgery within 4 weeks or minor surgery within 2 weeks of randomisation
	• Stroke requiring medical intervention within 24 weeks prior to randomisation

EUCTR2019-004471-39-GB *(Continued)*

	• Current use of direct acting oral anti-coagulants apixaban, dabigatran, rivaroxaban, edoxaban, or ticagrelor (due to the possibility of a cytochrome P450 (CYP)3A-mediated drug interaction), unless participant stopped the treatment ≥ 28 days prior to randomisation • Poorly controlled diabetes mellitus • Use of chronic systemic glucocorticoids within 12 weeks prior to randomisation (≥ 5 mg/day) • Any clinically significant bacterial, fungal, parasitic, or viral infection requiring antibiotic therapy should delay screening/randomisation until the course of antibiotic therapy has been completed
Interventions	**Intervention A:** IMR-687 200 mg **Intervention B:** IMR-687 100 mg **Control:** placebo
Outcomes	**Primary outcomes** • Increase of ≥ 3% in HbF from baseline to Week 24 • AEs, SAEs, clinically significant changes in laboratory tests, clinically significant changes in vital signs, and clinically significant changes in ECGs **Secondary efficacy outcomes** • Change in HbF from baseline to Week 24, Week 36, and Week 52 • Change in haemolysis markers (% and absolute reticulocytes) and related measures (unconjugated bilirubin and LDH) from baseline to Week 24, Week 36, and Week 52 • Change in soluble E-selectin, P-selectin, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and myeloperoxidase from baseline to Weeks 24, 36, and 52 • Change in the number of VOCs from baseline to Week 24, Week 36, and Week 52 • Change in each measured subdomain of the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me®) questionnaire from baseline to Week 24, Week 36, and Week 52 • Change in total preference score and individual domain scores of the Patient-Reported Outcomes Measurements Information System – Preference (PROMIS® 29 + 2 Profile v2.1 [PROPr]) questionnaire from baseline to Week 24, Week 36, and Week 52 • Change in overall score of the Sickle Cell Self-Efficacy Scale from baseline to Week 24, Week 36, and Week 52 **Pharmacokinetic endpoints** • Pharmacokinetic profile (concentration-time measurements) of IMR-687 and any major circulating metabolites **Exploratory efficacy endpoints** • Change in soluble transferrin receptor from baseline to Week 24, Week 36, and Week 52 • Change in RBC characteristics (e.g. mean corpuscular volume and total Hb) from baseline to Week 24, Week 36, and Week 52 • Change in renal function as measured by the urine protein-to-creatinine ratio from baseline to Week 24, Week 36, and Week 52 • Change related to index associated with cardiovascular pathophysiology and ischaemic stroke risk as measured by N-terminal prohormone of brain natriuretic peptide and high-sensitivity CRP levels from baseline to Week 24, Week 36, and Week 52
Starting date	13 August 2020
Contact information	Kevin B. Johnson, 116 Huntington Avenue 6th floor, MA 02116 Boston, USA – KJohnson@i-maratx.com
Notes	**Actual recruitment:** 115 participants; 16 completed trial; 99 did not complete trial

EUCTR2019-004471-39-GB *(Continued)*

Trial status: trial terminated early due to lack of efficacy. Stopped May 2022.

Kutlar 2019

Study name	The role of endothelin-1 in sickle cell disease
Methods	**Study design:** RCT, triple blind **Study grouping:** parallel **Location:** USA
Participants	**Inclusion criteria** • SS or Sβ^0-thalassaemia • Age 18–65 years • Microalbuminuria (24-hour albumin 150–300 mg) or macroalbuminuria (24-hour albumin > 300 mg) or random urine ACR ≥ 30 µg/mg creatinine • CKD stage 1, 2, or 3 • May be on hydroxyurea, ACE inhibitors, or ARBs for a period of 3 months or greater • Women of child-bearing potential must agree to use 2 forms of contraception with 1 being a barrier method; abstinence is an acceptable form of contraception **Exclusion criteria** • Other genotypes of SCD • History of renal transplant • CKD stage 4 or 5, including individuals on haemodialysis or peritoneal dialysis • Chronic transfusion therapy • Uncontrolled/poorly controlled hypertension or history of hypertension predating proteinuria • Known history of HIV, hepatitis C, or diabetes • Peripheral oedema • History of congestive heart failure or pulmonary oedema • Recent history of coronary artery disease • Pregnancy or breast feeding • ALT or AST > 3 × ULN • Albumin < 2.5 mg/dL • Haemoglobin < 60 g/L • History of non-compliance with medications and clinic visits • Inability to give informed consent • Deemed ineligible or unsuitable in the judgment of investigators
Interventions	**Intervention:** ambrisentan 5 mg oral tablet daily **Control:** inactive placebo oral tablet daily
Outcomes	**Primary outcome** • Safety and tolerability of ambrisentan in people with SCD measured by physical exam, vital signs, blood and urine testing, ECG (specified visits), concomitant medication review, adverse events review **Secondary outcomes** • Kidney function measured by blood testing at Day 1 (Baseline), Day 15, Day 29, Day 57, Day 85, and Day 113

Kutlar 2019 *(Continued)*

- TR velocity measured at Day 1 (Baseline) and at the end of the 12-week treatment period
- Inflammation measured from Day 1 (Baseline) through Day 113
- Micro-circulation measured at Day 1 (Baseline) and at the end of the 12-week treatment period
- Macro-circulation measured at Day 1 (Baseline) and at the end of the 12-week treatment period
- Nociception/pain measured at Day 1 (Baseline) and at the end of the 12-week treatment period
- Kidney function measured by urine testing for microalbuminuria/proteinuria at Day 1 (Baseline), Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and Day 113

Starting date	September 2015
Contact information	Abdullah Kutlar, Professor of Medicine, Augusta University, Augusta, GA
Notes	**Actual recruitment:** 26 participants No results available

NCT03806452 (SIKAMIC)

Study name	SIKAMIC (SIklos on Kidney Function and AlbuMInuria Clinical Trial)
Methods	**Study design:** RCT, triple blind **Study grouping:** parallel **Location:** Côte D'Ivoire, France, Guadeloupe, Mali, Martinique, Senegal
Participants	**Inclusion criteria** • Aged ≥ 18 years • HbSS or HbSβ^0 SCD • Albuminuria 3–100 mg/mmol, assessed by ACR and confirmed by 3 positive urine samples taken 1 day apart • Women of childbearing potential or postmenopausal female with last period < 12 months before screening must agree to use a highly effective form of contraception during the trial and for 3 months after HU discontinuation • Men with partners of childbearing potential must agree to use a highly effective contraception during the trial and for 3 months after HU discontinuation. Men with pregnant or lactating women must use a barrier method of contraception (condom) to prevent the foetus or breastfed infant from exposure to HU **Exclusion criteria** • Severe VOC requiring hospitalisation or acute chest syndrome within the last 4 weeks preceding screening visit • Treatment with HU for any reason within the previous 6 months • Chronic blood transfusion or transfusion in the last 3 months • History of hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) treated with antihypertensive agent belonging to pharmacological class of renin-angiotensin system inhibitor • Symptoms suggestive of urinary tract infection or gross haematuria • Concomitant primary kidney disease • Any systemic condition that could result in a glomerulopathy not related to SCD (e.g. diabetes mellitus, active hepatitis B or C infections, HIV infection, systemic lupus erythematosus, inflammatory arthropathies) • Stage 3, 4, or 5 CKD (eGFR < 60 mL/min/1.73 m^2)

NCT03806452 (SIKAMIC) *(Continued)*

- eGFR ≥ 140 mL/min/1.73 m^2 due to lack of information regarding the magnitude, direction, and significance of the trends in eGFR evolution that could be expected in this population
- Need for long-term treatment with potentially nephrotoxic drugs
- Need for ACEIs or ARBs within the 3 months before inclusion regardless of the indication
- Need for long-term treatment with nonsteroidal anti-inflammatory drugs
- Treatment that can modify kidney function (see non-exhaustive list) in the last 3 months
- Known HIV infection
- Pregnancy or lactation
- Unreliable participants, including non-compliant individuals, individuals with known alcoholism or drug abuse, or with a history of a serious psychiatric disorder, as well as those unwilling to give informed consent or to abide by the requirements of the protocol
- Simultaneous participation in other clinical trials on an investigational medicinal product or previous participation within 30 days before inclusion
- In detention by judicial or administrative decision
- Chronic conditions that may lead to a limited life expectancy, in the investigator's opinion

Interventions	**Intervention:** HU 15 mg/kg/day for 6–12 months **Control:** placebo

Outcomes	**Primary outcome**
	
	1. Proportion achieving ≥ 30% decrease in ACR baseline value at 6 months
	
	Secondary outcomes
	
	• Absolute mean changes in eGFR value at 6 months
	• Absolute mean changes in ACR value at 6 months
	• Proportion with a shift from macroalbuminuria to microalbuminuria at 6 months
	• Proportion with a shift from microalbuminuria to normoalbuminuria at 6 months
	• Proportion with a shift from macroalbuminuria to normoalbuminuria at 6 months
	• Proportion with a shift from microalbuminuria to macroalbuminuria at 6 months
	• Evolution curve of ACR at 6 months
	• Evolution curve of ACR from treatment initiation to month 12*
	• Evolution curve of eGFR at 6 months
	• Evolution curve of eGFR from treatment initiation to month 12*
	• Identification of clinical markers associated with response to treatment at 6 months (report of any SCD-related organopathy)
	• Identification of biological markers associated with response to treatment at 6 months
	  ◦ Haematology: RBC count and mean corpuscular volume, dense RBCs, reticulocytes, Hb, free Hb and HbF, mean corpuscular Hb and mean corpuscular Hb concentration, haematocrit, white blood cell counts, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet counts, endogenous erythropoietin and ferritin concentrations
	  ◦ Blood biochemistry: renal function: blood creatinine
	  ◦ Haemolysis biochemical markers: LDH, AST, ALT, BUN, conjugated and total bilirubin
	• Incidence of treatment-emergent AEs and SAEs to end of trial
	• Absolute mean changes of systolic and diastolic blood pressure at 6 months and 12 months*
	• Absolute mean changes of BMI at 6 months and 12 months*
	• Absolute mean changes of heart rate measured at 6 months and 12 months*
	• Absolute mean changes in WBC and platelet count at 6 months and 12 months*
	• Absolute mean changes in mean corpuscular volume and Hb concentration at 6 months and 12 months*
	• Absolute mean changes in HbF at 6 months and 12 months*
	• Absolute mean changes in free Hb at 6 months and 12 months*
	• Absolute mean changes in dense RBC percentage at 6 months and 12 months*

NCT03806452 (SIKAMIC) *(Continued)*

- Absolute mean changes in endogenous erythropoietin at 6 months and 12 months*
- Absolute mean changes in ferritin and LDH at 6 months and 12 months*
- Absolute mean changes in AST and ALT at 6 months and 12 months*
- Absolute mean changes in BUN at 6 months and 12 months*
- Absolute mean changes in conjugated bilirubin and total bilirubin at 6 months and 12 months*
- Absolute mean changes in reticulocytes at 6 months and 12 months*
- Rate of SCD-related clinical events at 6 months and 12 months*
- Biomarkers predictive of sickle cell nephropathy (only French participants) at 6 months and 12 months*

*12-month measurements for responder participants willing to continue the study after month 6.

Starting date	May 2019
Contact information	corinne.duguet@addmedica.com
Notes	**Planned recruitment:** 120 participants **Estimated study completion date:** June 2023 **Primary study completion date:** June 2023

NCT03814746 (STAND)

Study name	Study of two doses of crizanlizumab versus placebo in adolescent and adult sickle cell disease patients (STAND)
Methods	**Study design:** RCT, phase 3 **Study grouping:** parallel **Location:** 60 locations across North America, South America, Europe, Africa, and Asia

Participants	**Inclusion criteria**
	• Written informed consent
	• Age ≥ 12 years on the day of signing informed consent
	• Confirmed diagnosis of SCD (all genotypes) by haemoglobin electrophoresis or high-performance liquid chromatography (performed locally)
	• ≥ 2 VOCs leading to healthcare visit within the 12 months prior to screening visit as determined by medical history. Prior VOC leading to healthcare visit must resolve ≥ 7 days prior to Week 1 Day 1 and must include:
	  ◦ pain crisis defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion
	  ◦ need for a visit to a medical facility or healthcare professional
	  ◦ receipt of oral/parenteral opioids or parenteral nonsteroidal anti-inflammatory drug analgesia, acute chest syndrome, priapism and hepatic or splenic sequestration will be considered VOC in this study
	• If receiving HU/HC or L-glutamine, must have been receiving the drug for ≥ 6 months and at a stable dose for ≥ 3 months prior to Screening visit and plan to continue taking it at the same dose and schedule until 1 year of study treatment. Those who have not been receiving these drugs must not have received it for ≥ 6 months prior to Screening visit to be included. Participants must have evidence of insufficient control of acute pain, such as at least 1 VOC leading to healthcare visit while on HU/HC or L-Glutamine treatment. If receiving erythropoietin stimulating agent, must have been receiving the drug for ≥ 6 months prior to Screening visit and plan to continue taking the treatment to maintain stable Hb levels at least until 1 year of study treatment

NCT03814746 (STAND) *(Continued)*

- Must meet the following central laboratory values prior to Week 1 Day 1.
  - Absolute neutrophil count ≥ 1.0 x 109/L
  - Platelet count ≥ 75 x 109/L
  - Hb ≥ 4.0 g/dL for adults and ≥ 5.5 g/dL for adolescents
  - GFR ≥ 45 mL/min/1.73 m^2 using CKD-EPI formula in adults, and Shwartz formula in adolescents
  - Direct (conjugated) bilirubin < 2.0 × ULN
  - ALT < 3.0 × ULN
- ECOG performance status ≤ 2.0 for adults and Karnofsky ≥ 50% for adolescents

Exclusion criteria

- History of stem cell transplant
- Participation in a chronic transfusion programme (preplanned series of transfusions for prophylactic purposes) or planned exchange transfusion during the study; episodic transfusion in response to worsened anaemia or VOC is permitted
- Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation. History of severe hypersensitivity reaction to other monoclonal antibodies, which in the opinion of the investigator, may pose an increased risk of serious infusion reaction
- Received active treatment on another investigational trial within 30 days (or 5 half-lives of that agent, whichever is greater) prior to Screening visit or plans to participate in another investigational drug trial
- Women of child-bearing potential, unless they are using highly effective methods of contraception during dosing and for 15 weeks after stopping treatment
- Concurrent severe or uncontrolled medical conditions which, in the opinion of the investigator, could cause unacceptable safety risks or compromise participation in the study
- History or current diagnosis of ECG abnormalities indicating significant risk of safety, such as:
  - concomitant clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), and clinically significant 2nd or 3rd degree heart block without a pacemaker; or
  - history of familial long QT syndrome or known family history of Torsades de Pointes
- Inability to understand and comply with study instructions and requirements
- Prior treatment with crizanlizumab or other selectin targeting agent

Interventions	**Intervention 1:** crizanlizumab 5.0 mg/kg IV **Intervention 2:** crizanlizumab 7.5 mg/kg IV **Control:** placebo
Outcomes	**Primary outcome** • Rate of VOC events leading to healthcare visit at 1 year **Secondary outcomes** • Rate of all VOCs leading to healthcare visits and treated at home at 1 year and 5 years (7.5 mg/kg dose versus placebo) • Duration of VOCs leading to healthcare visit at 1 year (5.0 mg/kg dose versus placebo) • Number free from VOCs leading to healthcare visit at 1 year (to assess the time to 1st and 2nd VOC leading to healthcare visit in each intervention group versus placebo) • Percentage free from VOCs leading to healthcare visit at 1 year (to assess the time to 1st and 2nd VOC leading to healthcare visit in each intervention group versus placebo) • Time to 1st and 2nd VOC leading to healthcare visit at 1 year (calculated as the time from date of randomisation until the 1st and 2nd VOC leading to healthcare visit) • Rate of visits to clinic, emergency department, and hospitalisations, both overall and VOC-related at 1 year • Evolution of albuminuria and ACR at 1 year (to assess SCD-related renal damage in each group)

NCT03814746 (STAND) *(Continued)*

- Pharmacokinetic profile of crizanlizumab after the 1st and 5th dose of both crizanlizumab 5.0 mg/kg and 7.5 mg/kg
  - AUC
  - C_{max}
  - T_{max}
  - Half-life
- Pharmacodynamic parameter (P-selectin inhibition) after the 1st and 5th dose of both crizanlizumab 5.0 mg/kg and 7.5 mg/kg
- Absolute change from baseline in Hb at 5 years
- Growth and sexual maturity assessment in 5 years (safety)
- Measurement of anti-drug antibodies to crizanlizumab at 5 years (immunogenicity)

Starting date	July 2019
Contact information	Novartis Pharmaceuticals
Notes	**Estimated study completion date:** 14 December 2026 **Primary study completion date:** 31 August 2022 **Actual recruitment:** 254 participants

NCT04084080 (SCD-CARRE)

Study name	Sickle Cell Disease and CardiovAscular Risk – Red Cell Exchange Trial (SCD-CARRE)
Methods	**Study design:** RCT, phase 3 **Study grouping:** parallel **Location:** 20 sites in USA and Europe

Participants	**Inclusion criteria**
	• Age ≥18 years
	• Diagnosis of SCD: homozygous SCD, HbSC, Sβ-thalassaemia, HbSO or HbSD
	• Not on a chronic exchange transfusion programme for ≥ 2 months
	• If on HU, glutamine, or selectin inhibitors, the doses must be stable for ≥ 2 months prior to randomisation
	• Any of the following vasculopathy biomarker clinical results measured in the 13 months before randomisation (indicative of high risk)
	  ◦ TR velocity 2.5–2.9 m/sec and NT-proBNP plasma level ≥ 160 pg/mL
	  ◦ TR velocity ≥ 3.0 m/sec
	  ◦ Pulmonary artery pressure by right heart catheterisation 20–24 mmHg and NT-proBNP plasma level ≥ 160 pg/mL
	  ◦ Mean pulmonary artery pressure by right heart catheterisation ≥ 25 mmHg
	  ◦ CKD due to SCD with macroalbuminuria (ACR > 300 mg/g) on 2 occasions, or proteinuria (protein creatinine ratio > 30 mg/mmol) on 2 occasions, or eGFR < 60 mL/min/1.73 m^2 calculated on 2 occasions
	• Written informed consent
	Exclusion criteria
	• RBC alloimmunization resulting in inability of blood bank to obtain compatible components for chronic exchange transfusions

NCT04084080 (SCD-CARRE) *(Continued)*

	• Previous history of hyperhaemolysis syndrome • Previous history of severe transfusion reaction resulting in renal failure or due to serious complications such as hypotension or respiratory distress • > 10 VOCs in the past 12 months requiring hospitalisation for treatment • Religious objection to receiving blood transfusion • Diagnosis of ischaemic stroke within the past 6 months • Clinical evidence of liver failure or advanced cirrhosis, or any co-existing medical condition that, in the investigator's opinion, will substantially increase the risk associated with participation in the trial • Women of childbearing potential who have a positive pregnancy test at baseline
Interventions	**Intervention:** standard of care and automated exchange blood transfusion every 3–6 weeks for 12 months **Control:** standard of care alone

Outcomes	**Primary outcome**
	
	• Episodes of clinical worsening (acute health care encounters (non-elective infusion centre/emergency department/hospital visits) or death) at 12 months
	
	Secondary outcomes
	
	• Acute healthcare event at 12 months (a 6-level prioritised rank-based outcome involving death and acute health care encounters with evidence of cor pulmonale, stroke, liver failure, AKI, or acute chest syndrome during the 12 months of treatment and follow-up
	  ◦ No death or SCD-related acute health care encounters within 12 months
	  ◦ SCD-related acute health care encounter but NO major complications (AKI, acute chest syndrome, cor pulmonale, stroke, liver failure) or death within 12 months
	  ◦ SCD-related acute health care encounter with 1 major complication (AKI, acute chest syndrome, cor pulmonale, stroke, or liver failure) but no death within 12 months
	  ◦ SCD-related acute health care encounter with 2 major complications (AKI, acute chest syndrome, cor pulmonale, stroke, or liver failure) but no death within 12 months
	  ◦ SCD-related acute health care encounter with 3 or more major complications (AKI, acute chest syndrome, cor pulmonale, stroke, or liver failure) but no death within 12 months
	  ◦ Death within 12 months
	• 12-month survival
	• Survival free of acute healthcare encounters at 12 months
	• Total number of acute healthcare encounters (visit to non-elective infusion centre/emergency department/hospital) with evidence of cor pulmonale (physical exam findings, NT-proBNP increase plus echocardiographic evidence of worsening right heart function) at 12 months
	• Measures of exercise capacity: 6-minute walk distance at 4, 8, and 12 months
	• Measures of exercise capacity: outpatient activity at 4, 8, and 12 months
	• Cardiovascular risk: NT-proBNP, QT prolongation, systemic pulse pressure, albuminuria, eGFR and CKD progression at 12 months
	• Development of new leg ulcers at 4, 8, and 12 months
	• Measures of exercise capacity: WHO Classification at 4, 8, and 12 months
	• Nocturnal desaturation (blood oxygen measured over 7 nights at home) at 4, 8, and 12 months
	• SCD-specific self-reported outcomes at 4, 8, and 12 months
	  ◦ Self-reported pain
	  ◦ Quality of Life modified PROMIS scale
	  ◦ Quality of Life modified ASCQ-Me scale
	• Cardiovascular function by echocardiography at 4, 8, and 12 months
	  ◦ TR jet velocity in m/s
	  ◦ ECG: diastolic left heart function: E/A ratio
	  ◦ ECG: diastolic left heart function: E/Em ratio

NCT04084080 (SCD-CARRE) *(Continued)*

- ECG: diastolic left heart function: deceleration time
- ECG: systolic right heart function:E/Em ratio
- ECG: systolic right heart function: ventricular contractility
- ECG: systolic right heart function: tricuspid annular plane systolic excursion

Starting date	February 2020
Contact information	jonassaintjc@upmc.edu
Notes	**Estimated study completion date:** 30 April 2026 **Planned recruitment:** 150 participants

NCT04335721

Study name	A voxelotor for sickle cell anemia patients at highest risk for progression of chronic kidney disease
Methods	**Study design:** pilot RCT, open-label **Study grouping:** parallel **Location:** single centre (Chicago, USA)
Participants	**Inclusion criteria** • Age ≥18 years • Documentation of SCA genotype (HbSS or HbSβ^0-thalassaemia) confirmed by laboratory testing during screening • Urine dipstick-defined haemoglobinuria (positive for blood (+1 or higher) and ≤ 2 RBCs per high power field) on 2 prior outpatient visits • Albuminuria (urine albumin ≥ 30 mg/g creatinine) and eGFR ≥ 60 mL/min/1.73 m^2 calculated using the CKD-EPI equation on 2 prior outpatient visits • Hb 5.5–10.0 g/dL during screening • For participants taking HU, the dose must be stable for ≥ 90 days prior to signing the consent form and with no anticipated need for dose adjustments or initiation during the study, in the opinion of the Investigator • Endari stable dose for 1 month • For participants taking an ACEI or ARB, the dose must be stable for ≥ 90 days prior to signing the consent form and with no anticipated need for dose adjustments or initiation during the study, in the opinion of the Investigator • Women of childbearing potential to be using highly effective methods of contraception from study start to 30 days after the last dose of study drug, and men willing to use barrier methods of contraception, from study start to 30 days after the last dose of study drug • Documented informed consent reviewed and signed by each participant **Exclusion Criteria** • Pregnancy or breastfeeding • Regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or RBC transfusion for any reason within 30 days of signing the consent form or at any time during the screening period • Hospitalisation for SCD crisis or other VOC event within 14 days prior to signing the consent form (i.e. a VOC cannot be within 14 days prior to signing form) • Hepatic dysfunction characterised by ALT > 4 × ULN • Clinically significant bacterial, fungal, parasitic, or viral infection which requires therapy

NCT04335721 *(Continued)*

	◦ People with acute bacterial infection requiring antibiotic use should delay screening/enrolment until the course of antibiotic therapy has been completed ◦ Known active hepatitis A, B, or C, or HIV • Severe renal dysfunction (eGFR at the screening visit, calculated by the central laboratory) < 60 mL/min/1.73m^2, chronic dialysis, or previous kidney transplantation • History of malignancy within the past 2 years prior to treatment Day 1 requiring chemotherapy or radiation (except local therapy for non-melanoma skin malignancy) • History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including but not limited to the following ◦ Unstable angina pectoris or myocardial infarction or elective coronary intervention ◦ Congestive heart failure requiring hospitalisation ◦ Uncontrolled clinically significant arrhythmias • Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable) • Participation in another clinical trial of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or current participation in another trial of an investigational agent (or medical device) • Inadequate venous access as determined by the investigator/site staff • Medical, psychological, or behavioural conditions that, in the opinion of the Investigator, may preclude safe participation, confound study interpretation, interfere with compliance, or preclude informed consent • Receipt of erythropoietin or other haematopoietic growth factors within 28 days of signing consent form or anticipated need for such agents during the study
Interventions	**Intervention:** voxelotor 1500 mg once daily **Control:** usual care
Outcomes	**Primary outcome** • Change in albuminuria at 48 weeks **Secondary outcomes** • Proportion of participants achieving a 25% decline in albuminuria at 48 weeks • Change in 24-hour: urine protein, urine eGFR, urine albumin concentration, urine retinol binding protein, urine β2 microglobulin at 48 weeks • Change in 24-hour: serum creatinine, serum cystatin C, serum BUN at 48 weeks • Change in CKD stage at 48 weeks • Change in plasma cell-free Hb at 48 weeks • Change in urine Hb, urine dipstick-defined haemoglobinuria, urine nephron, urine podocalyxin, urine KIM-1, urine neutrophil gelatinase-associated lipocalin at 48 weeks • Change in LDH, AST, indirect bilirubin, serum methylenedioxyamphetamine, serum 8-hydroxy-2'-deoxyguanosine at 48 weeks • Change in Hb concentration, reticulocyte % at 48 weeks
Starting date	16 March 2021
Contact information	Principal Investigator: Santosh L Saraf, University of Illinois at Chicago (ssaraf@uic.edu) Sponsors and Collaborators: University of Illinois at Chicago, Global Blood Therapeutics
Notes	**Estimated Study Completion Date:** August 2024 **Planned number of participants:** 12

ACEI: angiotensin-converting enzyme inhibitor; AKI: acute kidney injury; ACR: albumin-to-creatinine ratio; AE: adverse event; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; ARB: angiotensin blocker; AUC: area under the curve; BMI: body mass index; BUN: blood urea nitrogen; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; C_{max}: maximum drug concentration; CRP: C-reactive protein; DBP: diastolic blood pressure; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; GGT: gamma glutamyl transferase; Hb: haemoglobin; HbF: foetal haemoglobin; HU:hydroxyurea; HU/HC: hydroxyurea/hydroxycarbamide; INR: international normalised ratio; IV: intravenous; KIM-1: kidney injury molecule-1; LDH: lactate dehydrogenase; LDL: low-density lipoprotein; NT-proBNP: N-terminal pro B-type natriuretic peptide; PCR: protein-to-creatinine ratio; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cell; SAE: serious adverse event; SBP: systolic blood pressure; SCA: sickle cell anaemia; SCD: sickle cell disease; sFLT-1: soluble fms-like tyrosine kinase-1; TF: tissue factor; T_{max}: time to achieve maximum drug concentration; TR: tricuspid regurgitant; ULN: upper limit of normal; VEGF: vascular endothelial growth factor; VOC: vaso-occlusive crisis; WBC: while blood cell; WHO: World Health Organization.

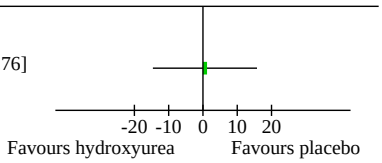
DATA AND ANALYSES

Comparison 1. Hydroxyurea versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 GFR (mL/min/1.73 m^2)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1.1 18 to 24 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2 Ability to concentrate urine (mOsm/kg)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.1 18 to 24 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3 Acute chest syndrome	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
1.4 Painful crisis	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
1.5 Hospitalisations	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
1.6 Stroke	1		Peto Odds Ratio (Peto, Fixed, 99% CI)	Totals not selected
1.7 Neutropenia	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
1.8 Thrombocytopenia	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
1.9 Number of participants transfused	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

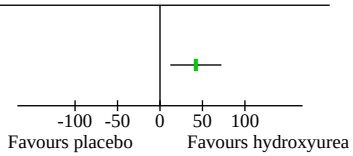
Analysis 1.1. Comparison 1: Hydroxyurea versus placebo, Outcome 1: GFR (mL/min/1.73 m^2)

Study or Subgroup	Hydroxyurea Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.1.1 18 to 24 months							
BABY HUG 2011	146.64	43.7	74	146.06	48.23	68	0.58 [-14.60 , 15.76]



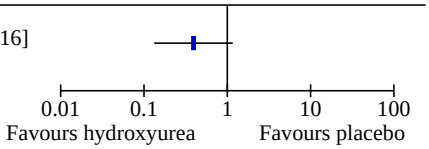
Analysis 1.2. Comparison 1: Hydroxyurea versus placebo, Outcome 2: Ability to concentrate urine (mOsm/kg)

Study or Subgroup	Hydroxyurea Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.2.1 18 to 24 months							
BABY HUG 2011	494.57	110.07	83	452.34	92.31	95	42.23 [12.14 , 72.32]



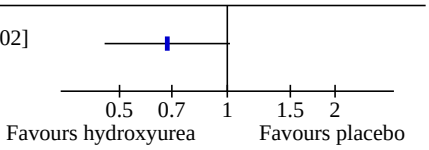
Analysis 1.3. Comparison 1: Hydroxyurea versus placebo, Outcome 3: Acute chest syndrome

Study or Subgroup	Hydroxyurea Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 99% CI
BABY HUG 2011	7	96	18	97	0.39 [0.13 , 1.16]



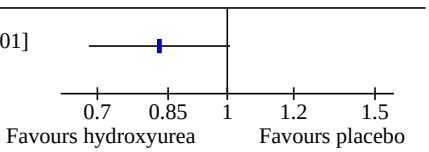
Analysis 1.4. Comparison 1: Hydroxyurea versus placebo, Outcome 4: Painful crisis

Study or Subgroup	Hydroxyurea Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 99% CI
BABY HUG 2011	37	96	55	97	0.68 [0.45 , 1.02]



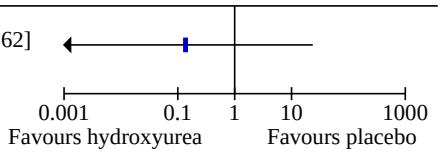
Analysis 1.5. Comparison 1: Hydroxyurea versus placebo, Outcome 5: Hospitalisations

Study or Subgroup	Hydroxyurea Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 99% CI
BABY HUG 2011	69	96	84	97	0.83 [0.68 , 1.01]



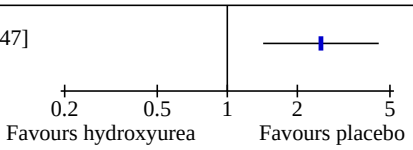
Analysis 1.6. Comparison 1: Hydroxyurea versus placebo, Outcome 6: Stroke

Study or Subgroup	Hydroxyurea Events	Hydroxyurea Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 99% CI
BABY HUG 2011	0	96	1	97	0.14 [0.00 , 23.62]



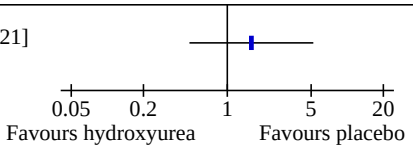
Analysis 1.7. Comparison 1: Hydroxyurea versus placebo, Outcome 7: Neutropenia

Study or Subgroup	Hydroxyurea Events	Hydroxyurea Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 99% CI
BABY HUG 2011	50	96	20	97	2.53 [1.43 , 4.47]



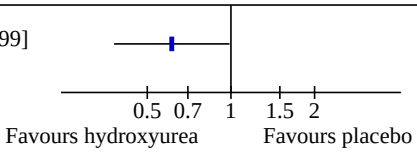
Analysis 1.8. Comparison 1: Hydroxyurea versus placebo, Outcome 8: Thrombocytopenia

Study or Subgroup	Hydroxyurea Events	Hydroxyurea Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 99% CI
BABY HUG 2011	11	96	7	97	1.59 [0.48 , 5.21]



Analysis 1.9. Comparison 1: Hydroxyurea versus placebo, Outcome 9: Number of participants transfused

Study or Subgroup	Hydroxyurea Events	Hydroxyurea Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
BABY HUG 2011	20	96	33	97	0.61 [0.38 , 0.99]

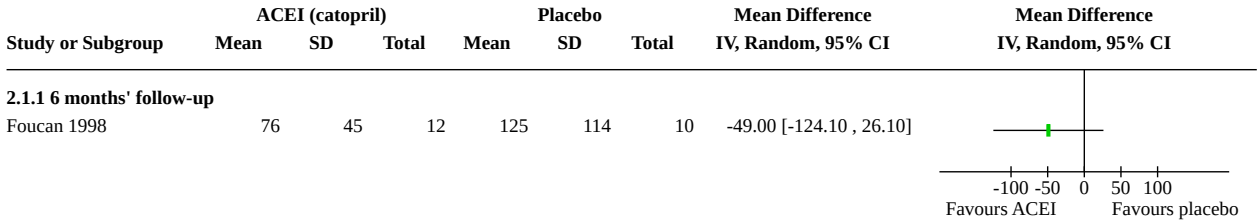


Comparison 2. ACEI (captopril) versus placebo

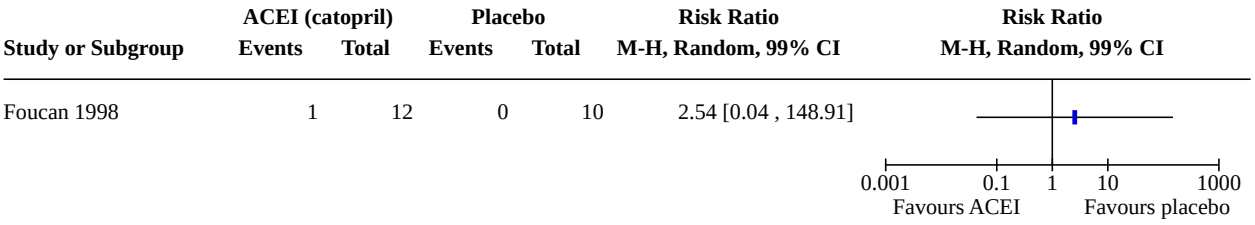
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Proteinuria (mg/day)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.1 6 months' follow-up	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2 Other drug-related adverse events (dry cough)	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected

Analysis 2.1. Comparison 2: ACEI (captopril) versus placebo, Outcome 1: Proteinuria (mg/day)



Analysis 2.2. Comparison 2: ACEI (captopril) versus placebo, Outcome 2: Other drug-related adverse events (dry cough)



ADDITIONAL TABLES

Table 1. Unadjusted hazard ratios for adverse events and serious adverse events reported in BABY HUG 2011

Unadjusted HRs reported in BABY HUG 2011		
Outcome	**HR**	**95% CI**
Acute chest syndrome	0.36	0.15 to 0.87
Painful crisis	0.54	0.36 to 0.83
Hospitalisations	0.73	0.53 to 1.00
Neutropenia	3.0	1.7 to 5.1
Thrombocytopenia	1.6	0.6 to 4.1
Transfusions	0.55	0.32 to 0.96

CI: confidence interval; HR: hazard ratio.

APPENDICES

Appendix 1. Glossary

Alloimmunisation
An immune response to foreign antigens as a result of exposure to donor blood transfusions

Enuresis
Inability to control urination, including bedwetting by children

Epigenetic
Traits that are not determined by the DNA code itself but rather by modifications of the DNA bases or of proteins associated with DNA

Extravascular
Outside the blood vessel or vascular system

Glomerular
Network of filters in the kidney that filter waste from the blood

Glomerulosclerosis
Scarring or hardening of the glomeruli, the tiny blood vessels in the kidney

Haematopoiesis
The production of red blood cells, white blood cells, and platelets from stem cells within the bone marrow

Hypoxia
Lack of oxygen reaching the cells of the kidney

Intravascular
Within the blood vessel or vascular system

Ischaemia
Restriction of blood supply to tissues

Nephropathy
Damage to or disease of the kidney

Renal papillary necrosis
This is a disorder of the kidneys in which all or part of the kidney papillae die. The kidney papillae are the areas where the openings of the collecting ducts enter the kidney, and where the urine flows into the ureters

Renal tubules
Small tube-shaped structures that remove salt, excess fluids, and waste products from the blood

Splenic sequestration
When large pools of sickled red blood cells are trapped in the spleen, resulting in damage to the spleen

Appendix 2. Search strategies

Database	Search strategy	Date last searched
CENTRAL (the Cochrane Library) (www.cochranelibrary.com/central)	#1 MeSH descriptor: [Anemia, Sickle Cell] explode all trees #2 MeSH descriptor: [Hemoglobin, Sickle] this term only #3 ("hemoglobin S" or "haemoglobin S" or "hemoglobin SC" or "haemoglobin SC" or "hemoglobin SE" or "haemoglobin SE" or "hemoglobin SS" or "haemoglobin SS" or "hemoglobin C disease" or "hemoglobin D disease" or "hemoglobin E disease" or "haemoglobin C disease" or "haemoglobin D disease" or "haemoglobin E disease" or "Hb SC" or HbSC or HbAS or HbSS or HbAC or "Hb	30 August 2022

(Continued)

	SE" or "Hb SS" or "Hb C disease" or "Hb D disease" or "Hb E disease" or "SC disease" or "SC diseases") #4 (sickle cell* or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*) #5 (sickle and SCD) #6 ((Hb S or HbS or sickle) near/3 (disease* or thalass?emi*)) #7 #1 or #2 or #3 or #4 or #5 or #6 #8 MeSH descriptor: [Kidney Diseases] explode all trees #9 MeSH descriptor: [Urologic Diseases] this term only #10 ((kidney or renal) near/5 (disease* or injur* or insufficienc* or function* or dysfunction* or abnormal* or damage* or failure* or complication* or manifestation*)) #11 ("end-stage renal" or "end-stage kidney" or "endstage renal" or "endstage kidney" or "chronic kidney" or "chronic renal") #12 (ESRF or ESKF or ESRD or ESKD or CKF or CKD or CRF or CRD or CAPD or CCPD or APD) #13 MeSH descriptor: [Hematuria] this term only #14 MeSH descriptor: [Proteinuria] explode all trees #15 (proteinuria* or hematuria* or haematuria* or hemoglobinuria* or haemoglobinuria* or erythrocyturia* or albuminuria* or microalbuminuria* or macroalbuminuria* or (albumin near/2 creatine)) #16 MeSH descriptor: [Renal Replacement Therapy] explode all trees #17 ((renal or kidney) near/3 (transplant* or replacement*)) #18 (predialysis or pre-dialysis or dialysis or hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration) #19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 #20 #7 and #19 #21 sickle cell nephropathy #22 #20 or #21	
MEDLINE (OvidSP) (ovidsp.ovid.com/)	1. exp Anemia, Sickle Cell/ 2. Hemoglobin, Sickle/ 3. (h?emoglobin S or h?emoglobin SC or h?emoglobin SE or h?emoglobin SS or h?emoglobin C disease or h?emoglobin D disease or h?emoglobin E disease or Hb SC or HbSC or HbAS or HbSS or HbAC or Hb SE or Hb SS or Hb C disease or Hb D disease or Hb E disease or SC disease*).tw,kf. 4. (sickle cell* or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw,kf. 5. (sickle and SCD).tw,kf. 6. ((Hb S or HbS or sickle) adj3 (disease* or thalass?emi*)).tw,kf. 7. or/1-6 8. exp Kidney Diseases/ 9. Urologic Diseases/ 10. ((kidney or renal) adj5 (disease* or injur* or insufficienc* or function* or dysfunction* or abnormal* or damage* or failure* or complication* or manifestation*)).tw,kf. 11. (end-stage renal or end-stage kidney or endstage renal or endstage kidney or chronic kidney or chronic renal).tw,kf. 12. (ESRF or ESKF or ESRD or ESKD or CKF or CKD or CRF or CRD or CAPD or CCPD or APD).tw,kf. 13. Hematuria/ 14. exp Proteinuria/ 15. (proteinuria* or h?ematuria* or h?emoglobinuria* or erythrocyturia* or albuminuria* or microalbuminuria* or macroalbuminuria* or (albumin adj2 creatine)).tw,kf. 16. exp Renal Replacement Therapy/ 17. ((renal or kidney) adj3 (transplant* or replacement*)).tw,kf.	30 August 2022

(Continued)

	18. (predialysis or pre-dialysis or dialysis or h?emodialysis or h?emofiltration or h?emodiafiltration).tw,kf. 19. or/8-18 20. 7 and 19 21. sickle cell nephropathy.tw,kf. 22. 20 or 21	
Embase (OvidSP) (www.wolterskluwer.com/en/solutions/ovid/embase-903)	1. exp Sickle Cell Anemia/ 2. Hemoglobin S/ 3. (h?emoglobin S or h?emoglobin SC or h?emoglobin SE or h?emoglobin SS or h?emoglobin C disease or h?emoglobin D disease or h?emoglobin E disease or Hb SC or HbSC or HbAS or HbSS or HbAC or Hb SE or Hb SS or Hb C disease or Hb D disease or Hb E disease or SC disease*).tw,kf. 4. (sickle cell* or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw,kf. 5. (sickle and SCD).tw,kf. 6. ((Hb S or HbS or sickle) adj3 (disease* or thalass?emi*)).tw,kf. 7. or/1-6 8. exp Kidney Disease/ 9. Urinary Tract Disease/ 10. ((kidney or renal) adj5 (disease* or injur* or insufficienc* or function* or dysfunction* or abnormal* or damage* or failure* or complication* or manifestation*)).tw,kf. 11. (end-stage renal or end-stage kidney or endstage renal or endstage kidney or chronic kidney or chronic renal).tw,kf. 12. (ESRF or ESKF or ESRD or ESKD or CKF or CKD or CRF or CRD or CAPD or CCPD or APD).tw,kf. 13. Hematuria/ 14. exp Proteinuria/ 15. (proteinuria* or h?ematuria* or h?emoglobinuria* or erythrocyturia* or albuminuria* or microalbuminuria* or macroalbuminuria* or (albumin adj2 creatine)).tw,kf. 16. exp Renal Replacement Therapy/ 17. ((renal or kidney) adj3 (transplant* or replacement*)).tw,kf. 18. (predialysis or pre-dialysis or dialysis or h?emodialysis or h?emofiltration or h?emodiafiltration).tw,kf. 19. or/8-18 20. 7 and 19 21. sickle cell nephropathy.tw,kf. 22. 20 or 21	30 August 2022
CINAHL (EBSCOHost) (www.ebsco.com/products/research-databases/cinahl-complete)	S1 (MH "Anemia, Sickle Cell+") S2 TX ("hemoglobin S" or "haemoglobin S" or "hemoglobin SC" or "haemoglobin SC" or "hemoglobin SE" or "haemoglobin SE" or "hemoglobin SS" or "haemoglobin SS" or "hemoglobin C disease" or "hemoglobin D disease" or "hemoglobin E disease" or "haemoglobin C disease" or "haemoglobin D disease" or "haemoglobin E disease" or "Hb SC" or HbSC or HbSS or HbAC or "Hb SE" or "Hb SS" or "Hb C disease" or "Hb D disease" or "Hb E disease" or "SC disease" or "SC diseases" OR sickle cell* or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*) S3 TX ((Hb S or HbS or sickle) N3 (disease* or thalass?emi*)) S4 S1 OR S2 OR S3 S5 (MH "Kidney Diseases+")	30 August 2022

(Continued)

S6 (MH "Urologic Diseases")

S7 ((kidney or renal) N5 (disease* or injur* or insufficienc* or function* or dysfunction* or abnormal* or damage* or failure* or complication* or manifestation*))

S8 ("end-stage renal" or "end-stage kidney" or "endstage renal" or "endstage kidney" or "chronic kidney" or "chronic renal")

S9 (ESRF or ESKF or ESRD or ESKD or CKF or CKD or CRF or CRD or CAPD or CCPD or APD)

S10 (MH "Hematuria")

S11 (MH "Proteinuria+")

S12 (proteinuria* or hematuria* or haematuria* or hemoglobinuria* or haemoglobinuria* or erythrocyturia* or albuminuria* or microalbuminuria* or macroalbuminuria* or (albumin N2 creatine))

S13 (MH "Renal Replacement Therapy+")

S14 ((renal or kidney) N3 (transplant* or replacement*))

S15 (predialysis or pre-dialysis or dialysis or hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration)

S16 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

S17 S4 AND S16

S18 sickle cell nephropathy

S19 S17 OR S18

S20 (MH Clinical Trials+)

S21 PT Clinical Trial

S22 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))

S23 TI ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*)) OR AB ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*))

S24 TI randomi* OR AB randomi*

S25 MH RANDOM ASSIGNMENT

S26 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))

S27 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*)))

S28 MH PLACEBOS

S29 MH META ANALYSIS

S30 MH SYSTEMATIC REVIEW

S31 TI ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*") OR AB ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*")

(Continued)

	S32 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*") S33 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) S34 TI placebo* OR AB placebo* S35 MH QUANTITATIVE STUDIES S36 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 S37 S19 AND S36	
PubMed (pubmed.ncbi.nlm.nih.gov/)	#1 ("hemoglobin S" OR "haemoglobin S" OR "hemoglobin SC" OR "haemoglobin SC" OR "hemoglobin SE" OR "haemoglobin SE" OR "hemoglobin SS" OR "haemoglobin SS" OR "hemoglobin C disease" OR "hemoglobin D disease" OR "hemoglobin E disease" OR "haemoglobin C disease" OR "haemoglobin D disease" OR "haemoglobin E disease" OR "Hb SC" OR HbSC OR HbAS OR HbSS OR HbAC OR "Hb SE" OR "Hb SS" OR "Hb C disease" OR "Hb D disease" OR "Hb E disease" OR "SC disease" OR "SC diseases" OR sickle* OR sickling OR meniscocyt* OR drepanocyt*) #2 (("Hb S" OR HbS) AND (disease* OR thalassemi* OR thalassaemia*)) #3 #1 OR #2 #4 ((kidney* OR renal) AND (disease OR diseases OR diseased OR injury OR injured OR insufficienc* OR function* OR dysfunction* OR abnormal* OR damage* OR failed OR failure* OR complication* OR manifestation* OR transplant OR transplants OR transplantation OR transplantations OR transplanted OR replacement*)) #5 ("end-stage renal" OR "end-stage kidney" OR "endstage renal" OR "end-stage kidney" OR "chronic kidney" OR "chronic renal" OR ESRF OR ESKF OR ESRD OR ESKD OR CKF OR CKD OR CRF OR CRD OR CAPD OR CCPD OR APD) #6 (proteinuria* OR hematuria* OR haematuria* OR hemoglobinuria* OR haemoglobinuria* OR erythrocyturia* OR albuminuria* OR microalbuminuria* OR macroalbuminuria* OR (albumin AND creatine)) #7 (predialys* OR pre-dialys* OR dialys* OR hemodialys* OR haemodialys* OR hemofiltrat* OR haemofiltrat* OR hemodiafiltrat* OR haemodiafiltrat*) #8 #4 OR #5 OR #6 OR #7 #9 #3 AND #8 #10 sickle cell nephropathy #11 #9 OR #10 #12 (random* OR blind* OR "control group" OR placebo* OR "controlled study" OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #13 #11 AND #12	30 August 2022
Transfusion Evidence Library	sickle AND (kidney OR renal OR dialysis OR hemodialysis OR haemodialysis OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR proteinuria OR hematuria OR haematuria OR hemoglobinuria OR	30 August 2022

(Continued)

(www.transfusionevidencelibrary.com/)	haemoglobinuria OR erythrocyturia OR albuminuria OR microalbuminuria OR macroalbuminuria OR nephropathy)	
LILACS (lilacs.bvsalud.org/en/)	tw:(sickle AND (kidney OR renal OR dialysis OR hemodialysis OR haemodialysis OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR proteinuria OR hematuria OR haematuria OR hemoglobinuria OR haemoglobinuria OR erythrocyturia OR albuminuria OR microalbuminuria OR macroalbuminuria OR nephropathy)) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))	30 August 2022
KoreaMed (koreamed.org/)	((sickle[All])) AND (randomized OR randomised OR randomly[All])	30 August 2022
PakMediNet (www.pakmedinet.com/)	((sickle[All])) AND (randomized OR randomised OR randomly[All])	30 August 2022
Web of Science CPCI-S (clarivate.com/webofsciencegroup/solutions/webofscience-cpci/)	TS=(sickle OR sicklemia OR sickled OR sickling) AND TS=(kidney OR renal OR dialysis OR hemodialysis OR haemodialysis OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR proteinuria OR hematuria OR haematuria OR hemoglobinuria OR haemoglobinuria OR erythrocyturia OR albuminuria OR microalbuminuria OR macroalbuminuria OR nephropathy) AND TS=(random* OR blind* OR control group OR placebo OR controlled study OR groups OR trial OR trials OR systematic review OR meta-analysis OR metaanalysis OR medline OR pubmed OR cochrane OR embase)	30 August 2022
ClinicalTrials.gov (www.clinicaltrials.gov/)	Search Terms: kidney OR renal OR dialysis OR hemodialysis OR hemofiltration OR hemodiafiltration OR proteinuria OR hematuria OR hemoglobinuria OR erythrocyturia OR albuminuria OR microalbuminuria OR macroalbuminuria OR nephropathy Condition: sickle cell anemia Study Type: Interventional Studies	30 August 2022
WHO International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/)	Title: kidney OR renal OR dialysis OR hemodialysis OR hemofiltration OR hemodiafiltration OR proteinuria OR hematuria OR hemoglobinuria OR erythrocyturia OR albuminuria OR microalbuminuria OR macroalbuminuria OR nephropathy Condition: sickle Recruitment Status: ALL OR sickle AND (kidney OR renal OR dialysis OR hemodialysis OR hemofiltration OR hemodiafiltration OR proteinuria OR hematuria OR hemoglobinuria OR erythrocyturia OR albuminuria OR microalbuminuria OR macroalbuminuria OR nephropathy)	30 August 2022

WHAT'S NEW

Date	Event	Description
4 August 2023	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register identified five references which were additional references to two already excluded studies (George 2020; Jain 2012). Additional searches were performed on 30 August 2022. We included one new trial (Aliu 2020), listed seven new trials (15 records) as ongoing (EUCTR2019-004471-39-GB; Kutlar 2019; NCT03806452 (SIKAMIC); NCT03814746 (STAND); Ataga 2019 (STEADFAST); NCT04084080 (SCD-CARRE); NCT04335721) and listed one trial (one record) as awaiting classification (NCT05392894 (REDRESS)). We identified four secondary citations to two included trials (Aliu 2020; BABY HUG 2011).
4 August 2023	New citation required but conclusions have not changed	Four authors have stepped down from the review team (PM Fortin, KR Bull, M Trivella, S Hopewell) and two new authors have joined the team (A Carpenter, I Dale-Harris). We identified one new trial that compared lisinopril against vitamin C (Aliu 2020). The review's conclusions have not changed, and we await the outcomes of the ongoing trials identified within this updated review.

HISTORY

Protocol first published: Issue 10, 2016
Review first published: Issue 7, 2017

CONTRIBUTIONS OF AUTHORS

NR: searching, selection of trials, eligibility assessment, content expert, and review content development
AC: screening and data extraction
IDH: screening and data extraction
CD: protocol development, search methods and strategies.
LE: review conception, review development, and content expert.

DECLARATIONS OF INTEREST

NR: none known
AC: none known
IDH: none known
CD: none known
LE: declares employment by NHS Blood and Transplant.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, UK

  To fund the work of the Systematic Review Initiative (SRI)

External sources

- National Institute of Health and Care Research (NIHR), UK

  This systematic review was supported by the National Institute for Health and Care Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.
- UK Forum (all the UK Blood Services), UK

To provide funding for the Systematic Review Initiative.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We adjusted the following statement for reporting 99% confidence intervals for serious adverse events and other adverse events (AEs) in the original protocol (Roy 2016): "We reported secondary outcomes as groups of transfusion-related and drug-related AEs. If this was not possible due to duplicate counting of the same participant who may have experienced more than one AE of the same category (e.g. more than one transfusion-related AE), we reported subgroup categories of AEs separately and reported the 99% CI of the pooled RR to allow for multiple statistical testing."

INDEX TERMS

Medical Subject Headings (MeSH)

Albuminuria [complications]; Anemia, Sickle Cell [*complications] [drug therapy]; Angiotensin-Converting Enzyme Inhibitors [*therapeutic use]; Antisickling Agents [*therapeutic use]; Creatinine [metabolism]; Glomerular Filtration Rate [drug effects]; Hospitalization [statistics & numerical data]; Hydroxyurea [*therapeutic use]; Kidney Failure, Chronic [drug therapy] [etiology] [*prevention & control]; Placebos; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans; Infant