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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
Figure 1.	6
RESULTS	8
DISCUSSION	9
AUTHORS' CONCLUSIONS	10
ACKNOWLEDGEMENTS	10
REFERENCES	11
CHARACTERISTICS OF STUDIES	13
DATA AND ANALYSES	15
Analysis 1.1. Comparison 1 ACE inhibitors versus placebo, Outcome 1 Urinary protein or albumin excretion (per hour).	15
Analysis 1.2. Comparison 1 ACE inhibitors versus placebo, Outcome 2 Adverse effects.	15
APPENDICES	16
WHAT'S NEW	16
HISTORY	17
CONTRIBUTIONS OF AUTHORS	17
DECLARATIONS OF INTEREST	17
SOURCES OF SUPPORT	17
INDEX TERMS	17

[Intervention Review]

Angiotensin-converting enzyme (ACE) inhibitors for proteinuria and microalbuminuria in people with sickle cell disease

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ABSTRACT

Background

Sickle cell disease is a group of disorders characterized by deformation of erythrocytes. Renal damage is a frequent complication in sickle cell disease as a result of long-standing anemia and disturbed circulation through the renal medullary capillaries. Due to the improvement in life expectancy of people with sickle cell disease, there has been a corresponding significant increase in the incidence of renal complications. Microalbuminuria and proteinuria are noted to be a strong predictor of subsequent renal failure. There is extensive experience and evidence with angiotensin-converting enzyme (ACE) inhibitors over many years in a variety of clinical situations for patients who do not have sickle cell disease, but their effect in people with this disease is unknown. It is common practice to administer ACE inhibitors for sickle nephropathy due to their renoprotective properties; however, little is known about their effectiveness and safety in this setting. This is an update of a Cochrane Review first published in 2013.

Objectives

To determine the effectiveness of ACE inhibitor administration in people with sickle cell disease for decreasing intraglomerular pressure, microalbuminuria and proteinuria and to assess the safety of ACE inhibitors as pertains to their adverse effects.

Search methods

The authors searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Hemeoglobinopathies Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Date of the most recent search: 03 June 2015.

Selection criteria

Randomized or quasi-randomized controlled trials of ACE inhibitors designed to reduce microalbuminuria and proteinuria in people with sickle cell disease compared to either placebo or standard treatment regimen.

Data collection and analysis

Three authors independently applied the inclusion criteria in order to select studies for inclusion in the review. Two authors assessed the risk of bias of studies and extracted data and the third author verified these assessments.

Main results

Five studies were identified through the searches, only one met our inclusion criteria. The included study randomized 22 participants (seven males and 15 females) having proteinuria or microalbuminuria with sickle cell disease and treated the participants for six months (median length of follow up of three months) with captopril or placebo. The overall quality of the outcomes reported was high, since most aspects that may contribute to bias were regarded to be of low risk, although allocation concealment was not reported. At six months, the study reported no significant difference in urinary albumin excretion between the captopril group and the placebo group, although the mean urinary albumin excretion in the captopril group was lower by a mean difference of -49.00 (95% confidence interval -124.10 to 26.10) compared to that of placebo. However, our analysis on the absolute change score showed significant changes between the two groups by a mean difference of -63.00 (95% confidence interval -93.78 to -32.22). At six months albumin excretion in the captopril group was noted to decrease from baseline by a mean of 45 ± 23 mg/day and the placebo group was noted to increase by 18 ± 45 mg/day. Serum creatinine and potassium levels were reported constant throughout the study. The potential for inducing hypotension should be highlighted; the study reported a decrease of 8 mmHg in systolic pressure and 5 mmHg in diastolic and mean blood pressure.

Authors' conclusions

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 sickle cell disease, although a potential for this was seen. More long-term studies involving multiple centers and larger cohorts using a randomized-controlled design are warranted, especially among the pediatric age group. Detailed reporting of each outcome measure is necessary to allow a clear cut interpretation in a systematic review. One of the difficulties encountered in this review was the lack of detailed data reported in the included study.

PLAIN LANGUAGE SUMMARY

Drugs that aim to prevent the loss of protein or albumin through urine in people with sickle cell disease

Review question

We reviewed the evidence on the effect of drugs that aim to prevent loss of protein or albumin through urine in people with sickle cell disease.

Background

Sickle cell disease is a group of inherited disorders that often lead to kidney damage. High protein or albumin levels in urine is a strong predictor of subsequent kidney failure. It is common practice to give angiotensin-converting enzyme (ACE) inhibitors to reduce the level of protein or albumin in urine, thus protecting the kidneys from damage. However, little is known about how effective and safe these are in people with sickle cell disease.

Search date

The evidence is current to: 03 June 2015.

Study characteristics

One study (22 adult participants) was included in the review. The participants with sickle cell disease had proteinuria or microalbuminuria and were selected randomly to be treated for six months with either captopril (an angiotensin-converting enzyme inhibitor) or placebo (dummy drug with no active medication).

Key results

The results from this small study were not convincing, with minor analysis changes leading to very different study conclusions. This study did not show that angiotensin-converting enzyme (ACE) inhibitors could reduce the level of protein or albumin in the urine. The level of creatinine and potassium in the blood were reported constant throughout the study. No serious adverse events were noted, although the potential for causing low blood pressure should be highlighted. More long-term studies involving multiple centers and larger numbers of participants are needed.

Quality of the evidence

Overall, the study appeared to be well run, although the actual method used to assign participants to treatment groups was not reported, nor whether it was concealed which group they were assigned to.

BACKGROUND

For a glossary of terms used in this review please refer to the appendices ([Appendix 1](#)).

Description of the condition

Sickle cell disease (SCD) is a group of disorders characterized by the deformation of erythrocytes, due to a synthesis of an abnormal form of hemoglobin (HbS). Either a mutation in β -globin, where glutamic acid (GAG) is substituted into valine (GTG) in codon 6 of the gene (designated Glu6Val ([Driss 2009](#))) or a compound heterozygosity for Glu6Val and another β -globin mutation, causes the formation of HbS ([Steinberg 2006](#)). The erythrocytes have a markedly short life span, leading to hemolytic anemia and release of free hemoglobin into the circulatory system which binds to and inactivates nitric oxide (NO) with consequent vaso-occlusion. Reduced endothelial bioavailability of NO impairs its downstream homeostatic vascular functions which skews the vasoconstriction-vasodilation balance towards vasoconstriction, which in turn increases the possibility of sickle vaso-occlusion ([Kato 2007](#); [Kotiah 2009](#); [Pawloski 2005](#)).

Epidemiologically, SCD predominantly affects populations originating from Sub-Saharan Africa, the Mediterranean basin and Latin America. The disorder is most prevalent in African countries with approximately 200,000 babies born with sickle cell anemia every year ([Diallo 2002](#)). In the United Arab Emirates, the overall incidence of SCD among 22,200 screened neonates was one in 2500, while the incidence of sickle cell trait was 1.1% overall ([Al Hosani 2005](#)). In Latin America, a recent large population study involving more than 1.8 million Brazilian newborns revealed an incidence of one in 1300 live births ([Fernandes 2010](#)). SCD is the most common inherited blood disorder in the USA. It is responsible for approximately 113,000 hospitalizations and USD 488 million in hospitalization costs annually ([Steiner 2006](#)). Population estimates, with mortality adjusted by age and sickle-cell type, yielded an estimate for 2005 of 89,079 people with SCD in the USA, of which 80,151 were black and 8928 Hispanic ([Brousseau 2009](#)). In the UK there are approximately 12,500 people with the disease ([National Screening Committee for SC and Thal 2006](#)).

Disease manifestations in SCD can be roughly attributed to two phenomena: hemolysis (such as dilated cardiomyopathy, jaundice and pigmented gallstones); and vaso-occlusion (such as painful crisis, acute chest syndrome, renal dysfunction, and hyposplenism) ([Schnog 2004](#)). Although bone marrow transplantation may substantially reduce disease manifestations, choices of curative therapy are limited. Several factors determine the prognosis of affected individuals, including the frequency, severity, and nature of specific complications. The survival of young children with SCD has improved, especially those living in western industrialized countries. Most children with sickle cell anemia (93.9%) and nearly all children with milder forms of SCD (98.4%) now live to become adults ([Quinn 2010](#)).

Renal complications in SCD

Renal damage is a frequent complication in SCD as a result of long-standing anemia and disturbed circulation through the renal medullary capillaries ([Serjeant 1992](#)). Risk for the development of renal disease is influenced by genetic factors, severity of anemia, and overall disease severity, as well as the sickling process

and compensatory mechanisms such as prostaglandin-mediated increases in vascular flow and angiotensin-mediated glomerular hyperperfusion ([Powars 1991](#); [Scheinman 2009](#); [Schnog 2004](#)). Renal insufficiency is reported to affect 4% to 18% of adults with SCD ([Ataga 2000](#); [Pham 2000](#); [Powars 1991](#); [Steinberg 1999](#)). Renal complications in SCD are typically preceded by microalbuminuria or proteinuria ahead of renal failure. Microalbuminuria or proteinuria affects 16% to 28% of children with SCD ([Becton 2010](#)).

Proteinuria was noted to be a strong predictor of subsequent renal failure ([Powars 1991](#)). Increase of albumin and immunoglobulin G (IgG) excretion were noted to be the earliest clinically detectable features of glomerular injury in people with sickle cell anemia ([Guasch 1996](#)). Recent studies have also associated proteinuria and albuminuria with pulmonary hypertension in adults ([Ataga 2010](#)) and children ([Forrest 2012](#)). However, there are no long-term data to demonstrate that the reduction of proteinuria slows or prevents progression to chronic renal insufficiency and renal failure ([Lottenberg 2005](#)).

The underlying mechanisms of renal failure in SCD are thought to begin with hyperfiltration, or an increase in glomerular filtration rate (GFR) ([Etteldorf 1952](#); [Ware 2010](#); [Wigfall 2000](#)). This is followed by glomerular hypertension ([Falk 1992](#)), chronic hypoxia, renal medullary ischemias, and increased prostaglandin secretion that leads to glomerular hypertrophy ([Falk 1994](#)), increased glomerular permeability ([Guasch 1997](#)), and proteinuria ([Guasch 1999](#)). These events then progress to a decrease in GFR which eventually results in chronic renal failure. Furthermore, the hyperosmolar milieu of the medulla, a condition favouring HbS polymerisation and resulting in increased blood viscosity within the renal medullary capillaries, leads to loss of concentrating capacity, urinary acidification, and decreased potassium excretion ([Falk 1994](#); [Guasch 1997](#); [Guasch 1999](#); [Serjeant 1992](#)). In the American Cooperative Study of Sickle Cell Disease, almost 9% of people with SCD who died due to disease complications manifested overt renal failure, which was identified as the major cause of death in adults with SCD ([Platt 1994](#)).

Description of the intervention

As there is no proven treatment for sickle cell nephropathy, every attempt should be made to slow its rate of progression ([NIH-NHLBI 2002](#)). There is extensive experience and evidence with angiotensin-converting enzyme (ACE) inhibitors over many years in a variety of clinical situations for patients who do not have SCD. What is unknown is the effect of ACE inhibitors in people with SCD. Yet, administration of angiotensin-converting enzyme (ACE) inhibitors for such purpose has been commonly practiced due to their renoprotective properties ([Lerma 2010](#); [Saborio 1999](#); [Scheinman 2009](#)). Angiotensin blockade appears to effectively control proteinuria and stabilize kidney function in children with non-diabetic proteinuric kidney disease ([Chandar 2007](#)).

The ACE inhibitors competitively inhibit the activity of the angiotensin-converting enzyme to prevent the formation of the active octapeptide angiotensin II from its inactive precursor, angiotensin I. All ACE inhibitor drugs are bound to tissues and plasma proteins and this gives rise to a characteristic concentration-time profile whereby any free drug is relatively rapidly eliminated from the kidney, predominantly by glomerular filtration ([Reid 2006](#)). The ACE inhibitors are different from the angiotensin II receptor blockers (ARBs), which act specifically

to block the AT1 receptor in order to prevent its binding with angiotensin II.

Most ACE inhibitors are given as prodrugs, because the active forms are water soluble and poorly absorbed from the gut (Waller 2005). The initial dosage of ACE inhibitor therapy must be individualized, mainly due to the risk of hypotension (Reid 2006; Rxmed 1999). There are known interactions with various drugs such as diuretics, agents increasing serum potassium, allopurinol, alpha-blocking agents, iron, lithium, non-steroidal anti-inflammatory drugs (NSAIDs), and tetracycline (Rxmed 1999).

How the intervention might work

It has been suggested that destruction of the renal medulla results in the release of vasodilating substances which subsequently triggers glomerular hyperfiltration followed by glomerular hypertension. These events, which consequently lead to glomerulosclerosis, a decrease in GFR and subsequent proteinuria or microalbuminuria, are pathogenic factors in sickle cell nephropathy (Falk 1992; Guasch 1996; McKie 2007; Wesson 2002; Wigfall 2000). Proteinuria and microalbuminuria are mostly attributed to vaso-occlusive events (Schnog 2004), which happen as a result of a skewed vasoconstriction-vasodilation balance towards vasoconstriction (Kato 2007; Kotiah 2009; Pawloski 2005).

It has been observed that ACE inhibitors dilate the efferent glomerular arterioles, leading to a fall in the intra-glomerular pressure and a decrease in the glomerular permeability to albumin. These events lead to amelioration of pathological changes like perihilar focal segmental glomerulosclerosis with consequent decrease of urinary protein excretion (Anderson 1986; Powars 1991). In fact, experimental studies have shown that ACE inhibitors prevent the occurrence of albuminuria and glomerulosclerosis in diabetic rats (Zatz 1986).

For more than a decade ACE inhibitors and angiotensin II receptor blockers (ARB) are known to have pronounced antiproteinuric and renoprotective properties, independently from their primary antihypertensive effect. Several large studies confirmed the pronounced antiproteinuric and renoprotective effects of ACE inhibitors, which were associated with a major reduction of proteinuria, slower GFR decline and reduced risk of doubling serum creatinine or reduced rate of progression to end-stage renal disease (ESRD) (Appendix 1) (Kolesnyk 2010).

Why it is important to do this review

Due to the improvement in life expectancy of people with SCD (Quinn 2010), there is a corresponding significant increase in the incidence of renal complications. Previous studies have shown the potential clinical application of ACE inhibitors to reduce proteinuria in SCD (Lerma 2010; Powars 1991; Saborio 1999). As such, administration of ACE inhibitors has been commonly practised for the treatment of SCD-related proteinuria (Scheinman 2009). This review aims to bring together clinical trials in this area to establish the clinical value of this pharmaceutical approach. This is an update of a Cochrane review first published in 2013 (Sasongko 2013).

OBJECTIVES

To determine the effectiveness of ACE inhibitor administration in people with SCD for preserving renal function by decreasing

intraglomerular pressure and proteinuria thus maintaining current GFR or slowing the decline in GFR. A secondary objective is to assess the safety of ACE inhibitors as pertains to their side effects (hyperkalemia, hypotension, etc).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized trials. Trials in which quasi-randomized methods, such as alternation, are used will be included in future updates if there is sufficient evidence that the treatment and control groups were similar at baseline.

Types of participants

People with known SCD (SS, SC, Sβ+ thal and Sβ° thal proven by electrophoresis and sickle solubility test, high performance liquid chromatography (HPLC), with family studies or DNA tests as appropriate) of all ages and both sexes, in any setting. Eligibility was defined as the presence of more than 30 mg of urinary albumin (for microalbuminuria) or more than 150 mg of urinary protein excretion (for proteinuria) in 24 hours detected on three separate occasions during six months preceding initiation of treatment. Participants were excluded if they were known to have hypertension, if there was evidence of organ failure (e.g. heart, kidney, liver), or systemic disease, if they were pregnant, or current user of NSAIDs (unless there is sufficient washout time period; i.e. five times half-life of the NSAIDs being used) or antihypertensive medications.

Types of interventions

Any ACE inhibitors designed to reduce proteinuria in people with SCD compared to either placebo or a standard treatment regimen.

Types of outcome measures

Primary outcomes

1. Urinary protein or albumin excretion (over 24 hours or first morning void (FMV))
2. Serum creatinine
3. Electrolyte levels

Secondary outcomes

1. Chromium-ethylenediaminetetraacetic acid (EDTA) GFR or estimated GFR (eGFR)
2. Blood pressure
3. Hemoglobin concentration
4. Comprehensive metabolic panel (CMP) excluding electrolytes and proteins parameters
5. Number of dialysis events
6. Occurrence of kidney transplantation
7. Any reported adverse effect or toxicity (e.g. hypotension, hyperkalemia, maculopapular rash, hematologic reactions, etc.)

Search methods for identification of studies

Electronic searches

The authors identified relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register

using the terms: sickle cell OR (haemoglobinopathies AND general)) AND (proteinuria OR microalbuminuria).

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 Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of the last search: 03 June 2015.

Please refer to a PRISMA diagram illustrating study selection ([Figure 1](#)).

Figure 1. Study flow diagram.

Searching other resources

The bibliographic references of all retrieved literature were reviewed for additional reports of studies. Experts will be contacted if the need arises for future updates.

Data collection and analysis

Selection of studies

Three authors independently applied the inclusion criteria in order to select studies for inclusion in the review. No disagreements

arose, but if for future updates any disagreements do arise on the suitability of a study for inclusion in the review, the authors will aim to reach consensus by discussion.

Data extraction and management

Two authors (THS and SN) independently extracted the data using the standard acquisition forms. One author (SKB) verified the data collection. No disagreements arose, but if for future updates any disagreements do arise on the suitability of a study for inclusion in the review, the authors will aim to reach consensus by discussion. The authors will contact study investigators whenever necessary. The eligible time period for endpoint analysis were at least one month after ACE inhibitor treatment. The authors excluded studies from analysis if the only time period reported is less than one month. Authors analysed data in three blocks of time: one to three months; over three months to six months; and longer than six months.

Assessment of risk of bias in included studies

Two authors (THS and SN) assessed the risk of bias of each study. One author (SKB) verified the assessment. Authors generated a risk of bias table as described in the *Cochrane Handbook of Systematic Reviews of Interventions* 5 (Higgins 2011). In particular, the authors examined details of the following components in each study:

1. sequence generation (e.g. whether randomization was adequate);
2. allocation concealment (e.g. whether the allocation was adequately concealed);
3. blinding of participants, personnel and outcome assessors (e.g. whether the participants, personnel and outcome assessors were blinded);
4. incomplete outcome data (e.g. whether attrition and exclusion were reported);
5. selective outcome reporting (e.g. whether the study was free from selective outcome reporting);
6. other sources of bias (will be specified during the assessment).

Authors assessed all components as having either a low risk of bias, an unclear risk of bias, or a high risk of bias.

Measures of treatment effect

The authors recorded continuous data such as urinary protein excretion and GFR or eGFR as either mean change from baseline for each group or mean post-treatment values and standard deviation (SD) for each group. The authors used the mean difference (MD) for the urinary protein excretion outcome, however, the standardized mean difference (SMD) may be used for future versions of the review if there are studies with data included which report on both 24-hour urinary excretion and first morning void (FMV). The 24-hour urinary protein excretion and FMV would be on the same scale with different mean and SD summaries, hence requiring standardization.

The authors recorded dichotomous outcomes, e.g. dialysis or no dialysis, as present or absent. For binary outcomes, the authors calculated the odds ratio (OR) based on the ratio of an outcome among treatment-allocated participants to that amongst controls. The authors aimed to calculate a pooled estimate of the treatment

effect for each outcome across studies by determining the OR or SMD.

Unit of analysis issues

The authors will only include cross-over studies in this review if they consider there to be a sufficient washout period between the treatment arms. The authors will analyze any data from such studies using paired analysis as described by Elbourne (Elbourne 2002). For cluster randomized studies, the authors will calculate the effective sample size and monitor and analyze them based on the method described by Donner (Donner 2002). The authors will analyze any such studies separately. The authors aim to address the risk of unit of analysis error caused by repeated observations on participants based on the information provided in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

For the 2015 update of the review, the review authors contacted the authors of the included study regarding outcomes where no exact value was indicated in the study manuscript and we await their reply (Foucan 1998). For any further studies included, the review authors will seek full reports from study investigators where studies have been published in abstract form, presented at meetings or reported to the authors. Where information is missing or unclear, the authors will contact the primary investigator. In order to allow an intention-to-treat analysis, the authors will group data by allocated treatment groups, irrespective of later exclusion (regardless of cause) or loss to follow up.

Assessment of heterogeneity

In future updates of the review, when more studies are included, the authors plan to test for heterogeneity between studies using a standard χ^2 test and I^2 statistic (Higgins 2003). The χ^2 test is a statistical test for heterogeneity, whereas I^2 assesses the quantity of inconsistency across studies in the meta-analysis. The authors will use the following I^2 ranges to interpret heterogeneity:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

The authors compared the 'Methods' section of the full published paper to the 'Results' section to ensure that all outcomes which were measured, were reported. The authors could not obtain the protocol of the included study from trials registers. In future updates, the authors will try to obtain protocols from trials registers in order to identify any potential reporting bias.

Data synthesis

The authors employed a fixed-effect analysis in the review. In future updates of the review, when more studies are included, where the value of I^2 is up to 40%, the authors will continue to employ a fixed-effect analysis. However, if there is evidence of heterogeneity (I^2 is greater than 40%), the authors plan to use a random-effects analysis. In this case, for minimizing the imprecision (uncertainty) of the pooled effect estimate, the authors will employ inverse-variance method of calculating weights. In the random-effect analysis the authors will adjust the standard errors

of the study-specific estimates to incorporate a measure of the extent of heterogeneity.

Subgroup analysis and investigation of heterogeneity

For future updates, if the authors find heterogeneity between studies, examination of subgroups, such as: age of participants (0 years to 10 years, over 10 years to 20 years, over 20 years); type of SCD (SS, SC, Sβ+ thal and Sβ°); or ethnicity (Caucasian, Hispanic, African, Mediterranean, others), may help to explain the reasons for this. Where appropriate, the authors plan to perform subgroup analysis of different classes of ACE inhibitors to examine their relative benefits and risks.

Sensitivity analysis

If a range of studies are included in the review the authors plan to test the robustness of their results with the following sensitivity analyses:

- studies where quasi-randomisation methods are used;
- studies where there are variations among one or more inclusion criteria (such as different definitions for hypertension);
- studies of different designs (e.g. cross-over and cluster randomized studies).

In addition, the authors plan to undertake a sensitivity analysis to investigate the effects of combining endpoint analysis across all time-periods.

RESULTS

Description of studies

Results of the search

Five studies were identified from the searches. Four of them were non-randomized, observational studies and did not use any control groups (Aoki 1995; Falk 1992; Fitzhugh 2005; McKie 2007). These studies were therefore excluded from this review. One study was eligible for inclusion in the review (Foucan 1998).

Included studies

Study characteristics

The Foucan study was described as a double-blind, randomized, placebo-controlled trial. It was carried out in a single center in France. The participants were treated for six months with a median length of follow up of three months (Foucan 1998).

Participants

The Foucan study randomized 22 people (18 years or older, seven males and 15 females) having proteinuria or microalbuminuria with SCD. There were 12 participants in the treatment group and 10 in the placebo group (Foucan 1998).

Interventions

The Foucan study compared captopril and placebo. The captopril dose varied over time: 6.25 mg per day (¼ of a tablet of 25 mg once-a-day) during the first month; 12.5 mg per day (½ of a tablet twice-a-day) during the second and the third months; and 25 mg per day (½ of a tablet twice-a-day) after the third month (Foucan 1998).

Outcomes measured

The Foucan study reported the effect of captopril on albumin excretion, serum creatinine, potassium, blood pressure and hemoglobin concentration. Sodium level was not reported, although it was measured. Adverse effects were reported (Foucan 1998).

Excluded studies

Four studies were excluded from this review. None of these studies were randomized or used control groups (Aoki 1995; Falk 1992; Fitzhugh 2005; McKie 2007).

Risk of bias in included studies

Allocation

The Foucan study was judged to have an unclear risk of bias for the generation of allocation sequence (Foucan 1998). Although this study was described as using random assignment to generate allocation, the process was not described.

In addition, allocation concealment was not reported. Therefore, this study was judged to also have unclear risk of bias for this criterion (Foucan 1998).

Blinding

Participants, treating physicians and outcome assessors were blinded in the included study (Foucan 1998). Therefore, the authors judged this study to have low risk of bias for this criterion.

Incomplete outcome data

Two participants were withdrawn from the study: one in the ACE inhibitor group had an unusual pain in the shoulder and discontinued treatment on the sixth day; and one in the placebo group was unavailable for follow up after the first month. These participants were included in the intention-to-treat analysis (Foucan 1998). In this regard, this study was therefore judged to have a low risk of bias.

Selective reporting

Sodium level was not reported in the results section of the included study, although the methods section mentioned that it was measured (Foucan 1998). In addition, the exact serum creatinine level and hemoglobin concentration were not reported. The authors therefore judged there to be high risk of bias from selective reporting.

Other potential sources of bias

Baseline characteristics between the captopril group and placebo group in Foucan study were not systematically different. There was no significant difference in the mean age, body mass index, blood pressure, hemoglobin concentration, serum creatinine, urine albumin excretion and creatinine clearance (Foucan 1998). The authors therefore judged this study to have low risk for these potential sources of bias.

Effects of interventions

Primary outcomes

1. Urinary protein or albumin excretion

In the Foucan study, urinary albumin excretion was examined at one month, three months and six months (Foucan 1998). At one month, it was reported that no significant changes were noted, although the report did not mention the exact level of excretion. At three months, it was reported that the urinary albumin excretion decreased from baseline in the treatment group and increased in the placebo group. The authors could not assess whether there was a statistically significant difference since exact levels of excretion were not reported. At six months, the study reported no significant difference in per-hour urinary albumin excretion between the captopril group and the placebo group, although the urinary albumin excretion in the captopril group was lower by a MD of -49.00 (95% CI -124.10 to 26.10) compared to placebo (Analysis 1.1). However, our analyses on the absolute change score showed significant changes between the two groups by a MD of -63.00 (95% CI -93.78 to -32.22) (Analysis 1.1). The captopril group was noted to decrease by a mean (SD) of 45 (23) mg/day and the placebo group was noted to increase by 18 (45) mg/day, when the albumin excretion was compared between that of the baseline and at six months.

Note: The authors planned to report on this outcome at over 24 hours or first morning void (FMV), however, only per hour data were available for the included study.

2. Serum creatinine

The Foucan study reported that serum creatinine was constant throughout the study within both the captopril and placebo groups (Foucan 1998). However, no statistical calculation could be made as the exact serum creatinine levels were not reported.

3. Electrolyte levels

Two electrolyte levels were examined in the Foucan study, sodium and potassium. However, only the potassium level was reported; this was constant throughout the study within each group. No statistical calculation can be carried out as the exact potassium level was not reported (Foucan 1998).

Secondary outcomes

1. Chromium-ethylenediaminetetraacetic acid (EDTA) GFR or estimated GFR (eGFR)

this outcome was not measured in the Foucan study (Foucan 1998).

2. Blood pressure

In general, the Foucan study recorded a decrease in blood pressure among participants within captopril group and constant blood pressure among participants within placebo group (Foucan 1998). A decrease of 5 mmHg was recorded for mean blood pressure and diastolic blood pressure. A decrease of 8 mmHg was recorded for systolic blood pressure.

3. Hemoglobin concentration

Hemoglobin concentration was reported to be constant throughout the study within each group (Foucan 1998). No statistical

calculation can be carried out as the exact concentration was not reported.

4. Comprehensive metabolic panel (CMP) excluding electrolytes and proteins parameters

This outcome was not measured in the Foucan study (Foucan 1998).

5. Number of dialysis events

No events were reported in the Foucan study (Foucan 1998).

6. Occurrence of kidney transplantation

No occurrences were reported in the Foucan study (Foucan 1998).

7. Any reported adverse effect or toxicity

No significant differences between groups were found for any adverse effect (Foucan 1998). The Foucan study reported dry cough at the end of the sixth month in one of the participants within the captopril group, RR 2.54 (95% CI 0.11 to 56.25) (Analysis 1.2). Another participant in the captopril group reported unusual pain in the shoulder and discontinued treatment on the sixth day, RR 2.54 (95% CI 0.11 to 56.25) (Analysis 1.2). One participant in the placebo group progressed to clinical proteinuria (urinary albumin excretion greater than 300 mg/day) during the third month, RR 0.28 (95% CI 0.01 to 6.25) (Analysis 1.2).

DISCUSSION

Summary of main results

In this review the authors could only identify one study which fulfilled the review criteria. The study included six-month urinary protein excretion as the primary outcome measure (Foucan 1998). Although other outcome measures were reported, none were detailed enough to allow statistical analysis.

The authors noted that the mean urinary albumin excretion was lower in the captopril group compared to the control group at six months of treatment. However, our systematic review found that different analyses resulted in different levels of significance. There was a non-significant difference in mean urinary albumin excretion between groups, MD -49.00 (95% CI -124.10 to 26.10); however, the change score for mean albumin excretion between groups was significant, MD -63.00 (95% CI -93.78 to 32.22). In the treatment group this decreased by 45 ± 23 mg/day and in the control group increased by 18 ± 45 mg/day. Under some circumstances, a change score can be more efficient because it can remove some between-person variability from the measurement. The confidence interval widths for the former and the latter analyses are 150.20 and 61.60, respectively. However, one could argue that the latter analysis is less efficient for difficult measurements that cannot be recorded precisely and perhaps more relevant for skewed distribution.

Serum creatinine and potassium levels were reported constant throughout the study. The potential for inducing hypotension should be highlighted; the study reported a decrease of 8 mmHg in systolic pressure and 5 mmHg in diastolic and mean blood pressure. Other reported events which were thought as due to the intervention were difficult to assess as there was no clear evidence of what they signify.

Overall completeness and applicability of evidence

Although reported only in very limited details, the authors admit that the included study has addressed the primary outcome measures in this review. However, there is no report of GFR, which could also indicate the level of glomerular damage. Relevant types of participants, interventions and outcomes were investigated in the study. Participants involved were all homozygous for hemoglobin SS, aged over 18 years and had urinary albumin excretion between 30 mg and 300 mg per 24 hours on three different occasions in the six months prior to the study. Captopril was used as an ACE inhibitor intervention and appropriately compared to placebo. Relevant primary and secondary outcome measures were reported, although not all that were proposed in this review.

Previous studies have mentioned the common practice of administering ACE inhibitors for the treatment of microalbuminuria and proteinuria in people with SCD (Lerma 2010; Saborio 1999; Scheinman 2009). Although there are no published guidelines on the administration of ACE inhibitors for proteinuria, it has been recommended that ACE inhibitors can be started once the urinary protein to creatinine ratio is persistently above 100 mg/umol (Sharpe 2011).

Quality of the evidence

While the only included study was small (22 participants), the overall quality of the outcomes reported was high, since most aspects that may contribute to bias were regarded to be of low risk (Risk of bias in included studies), although allocation concealment was not reported (Foucan 1998). There may be selective reporting on sodium level, but other electrolyte levels were reported. Nevertheless, the amount of data with detailed descriptions has allowed only limited analysis in this review.

Potential biases in the review process

No potential biases were identified in the current review process.

Agreements and disagreements with other studies or reviews

Four observational, non-randomized studies of enalapril (an ACE inhibitor) did not employ a control group (Aoki 1995; Falk 1992; Fitzhugh 2005; McKie 2007). The Falk study prospectively reported enalapril treatment in 10 participants, the length of treatment was only two weeks (Falk 1992). This study concluded that enalapril reduced the degree of proteinuria, since the rate of urinary protein excretion decreased in all 10 participants at the end of the two-week treatment period ($P < 0.001$), with a reduction of 57% from baseline.

The Aoki study included eight SCD participants with a urinary albumin excretion above 30 mg/day (Aoki 1995). In six of these urinary albumin excretion returned to normal after six months of treatment. One participant had a 70% reduction and another had a level beyond that observable. Electrolyte levels and creatinine clearance level did not change significantly throughout the study; but mean arterial pressure was significantly decreased by 8.1 mmHg ($P < 0.05$) (Aoki 1995).

The Fitzhugh study retrospectively reported on three participants, receiving enalapril alone followed by enalapril with hydroxyurea,

using their medical records as the main source of data (Fitzhugh 2005). Length of sole enalapril administration was 38.7 ± 15.3 months. All participants experience a reduction in urinary protein and creatinine ratio: before treatment 6.9 ± 3.7 ; and after treatment 2.2 ± 1.8 . Although the difference is not statistically significant, a substantial reduction of 4.7 in the urinary protein to creatinine ratio was noted. This study concluded that enalapril therapy for children with sickle nephropathy reduces urinary protein excretion.

The McKie study retrospectively reported on nine participants, using their medical records as the main source of data; for three of the participant in this study enalapril treatment was subsequently switched to a longer-acting lisinopril (McKie 2007). Length of treatment was 42 ± 19.2 months. In five of the participants proteinuria or microalbuminuria improved and the study summarized that these conditions may be amenable to ACE inhibitor treatment, although a further efficacy study is warranted.

None of the above studies have been reviewed systematically and presented different results, it is therefore difficult to determine agreement or disagreement among these four studies and the Foucan study. Although all studies showed reduction in urinary protein excretion, the statistical significance of the reduction was not noted in all of them.

AUTHORS' CONCLUSIONS

Implications for practice

There is not enough evidence that ACE inhibitors are associated with a reduction of microalbuminuria and proteinuria in people with SCD. This was observed through analyses on the effect of ACE inhibitors for decreasing urinary albumin excretion in people with SCD. There is also no evidence of other potential adverse effects on the administration of ACE inhibitor for people with sickle nephropathy. The use of ACE inhibitors for reducing proteinuria and microalbuminuria in people with SCD may not be indicated until further evidence is obtained, especially in light of a potential hypotensive effect.

Implications for research

The potential for ACE inhibitors to decrease microalbuminuria and proteinuria in people with SCD has been observed and randomized controlled studies are warranted. As microalbuminuria may develop during childhood (McKie 2007), randomized controlled studies in this group of participant should be conducted, with emphasis on investigating the long-term effectiveness and safety in preventing clinical proteinuria and chronic kidney disease. Longer-term studies involving larger cohorts from multiple centers should be carried out to investigate if the findings reported previously are sustained and consistent.

Detailed reporting of each outcome measure is necessary to allow a clear cut interpretation in a systematic review. One of the difficulties encountered in this review is lack of detailed data reported in the included study.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Foucan 1998

Methods	Double-blind, randomized, parallel, placebo-controlled trial.
Participants	22 participants were enrolled into the study, in which 12 were in the treatment group and 10 were in the placebo group. All were homozygous for hemoglobin SS. Ages >18 years. Urinary albumin excretion between 30 mg and 300 mg per 24 hours on 3 different occasions in the 6 months prior to the study.

Foucan 1998 (Continued)

Interventions	<p>Participants were randomized into either:</p> <ol style="list-style-type: none"> 1. captopril 6.25 mg/day for month 1, 12.5 mg/day for months 2 - 3 and 25 mg/day for months 3 onward; or 2. placebo.
Outcomes	<p>Primary outcomes include: urinary albumin (24 h), serum creatinine, sodium (results not stated), potassium</p> <p>Secondary outcomes include: hemoglobin concentration; blood pressure.</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random assignment. No process of generating allocation sequence was described.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was used. 2 participants were withdrawn from the study. Full reasons for withdrawal were given in the published paper.
Selective reporting (reporting bias)	High risk	Results for sodium level were not reported. Exact serum creatinine level and hemoglobin concentration were not reported.
Other bias	Low risk	No difference in baseline characteristics between the captopril group and placebo group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded. Treating physicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aoki 1995	Observational, not randomized, no control group.
Falk 1992	Interventional but not randomized, no control group.
Fitzhugh 2005	Observational, not randomized, no control group.
McKie 2007	Observational, not randomized, no control group.

DATA AND ANALYSES

Comparison 1. ACE inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary protein or albumin excretion (per hour)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Total albumin excretion at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Absoulte change in total albumin excretion at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Dry cough	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Pain in shoulder	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Clinical proteinuria	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 ACE inhibitors versus placebo, Outcome 1 Urinary protein or albumin excretion (per hour).

Study or subgroup	Favours ACE inhibitors		Placebo group		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.1.1 Total albumin excretion at 6 months						
Foucan 1998	12	76 (45)	10	125 (114)		-49[-124.1,26.1]
1.1.2 Absoulte change in total albumin excretion at 6 months						
Foucan 1998	12	-45 (23)	10	18 (45)		-63[-93.78,-32.22]
					Favours ACE inhibitors	Favours placebo

Analysis 1.2. Comparison 1 ACE inhibitors versus placebo, Outcome 2 Adverse effects.

Study or subgroup	ACE inhibitor group n/N	Placebo group n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Dry cough				
Foucan 1998	1/12	0/10		2.54[0.11,56.25]
1.2.2 Pain in shoulder				
Foucan 1998	1/12	0/10		2.54[0.11,56.25]
1.2.3 Clinical proteinuria				
Foucan 1998	0/12	1/10		0.28[0.01,6.25]
			Favours ACE inhibitors	Favours placebo

APPENDICES

Appendix 1. Glossary

Term	Definition
Angiotensin receptor blocker (ARB)	Medicines used to treat high blood pressure. They work by keeping the body from using angiotensin, hormone which raises blood pressure (American Kidney Fund 2008).
Comprehensive metabolic panel (CMP)	A group of blood tests involving 14 parameters that measure glucose level, protein level, electrolyte and fluid balance, kidney function and liver function (WebMD 2009).
Estimated GFR (eGFR)	Estimation of GFR using equation developed by the Modification of Diet in Renal Disease (MDRD) study. The equation takes into account serum creatinine level, age, gender and race (Xie 2008). Refer to GFR for comparison.
End stage renal disease (ESRD)	Complete or almost complete failure of the kidneys to function (MedlinePlus 2009). Refer to the definition of 'renal failure'.
Erythrocytes	Red blood cells.
Glomerular filtration rate (GFR)	Measure of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time using certain isotopic marker. GFR is often used to determine renal function (Xie 2008). Refer to eGFR for comparison.
Hemolysis	The breaking open of erythrocytes causing the release of hemoglobin into the surrounding fluid.
Heart failure	Defined based on Boston criteria (Shamsham 2000).
Hyposplenism	Diminished functioning of the spleen.
Hyperkalemia	Condition in which there is a higher than normal level of potassium in the blood.
Hypotension	Abnormally low blood pressure.
Liver failure	Defined based on King's College criteria (O'Grady 1989).
Microalbuminuria	Average urine albumin-to-creatinine ratio of 30 mg/g to 300 mg/g on two spot urine specimens obtained six months apart (Becton 2010).
Proteinuria	Average albumin-to-creatinine ratio > 300 mg/g on two spot urine specimens obtained six months apart (Becton 2010).
Renal/kidney failure	Glomerular filtration rate of less than 15 ml/min/1.73m ² (James 2010).
Vasoconstriction	Narrowing of the blood vessels resulting from contracting of the muscular wall of the vessels.
Vasodilation	Widening of the blood vessels resulting from the relaxation of the muscular wall of the vessels.

WHAT'S NEW

Date	Event	Description
26 January 2017	Amended	The 'Summary of findings' table has been removed, a corrected version will be included in the update to be published in 2017.

HISTORY

Protocol first published: Issue 7, 2011

Review first published: Issue 3, 2013

Date	Event	Description
3 June 2015	New citation required but conclusions have not changed	Minor changes have been made throughout the review. The review authors contacted the authors of the included study regarding outcomes where no exact value was indicated in the study manuscript and we await their reply (Foucan 1998).
3 June 2014	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register did not identify any new potentially eligible trials to be included in the review.

CONTRIBUTIONS OF AUTHORS

THS, SN and SKB independently applied the inclusion criteria for including studies into this review. THS and SN independently assessed the study quality and extracted data. SN verified the data. THS drafted the review text, SKB and SN provided reviews and suggestions to the draft.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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External sources

- National Institute for Health Research, UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

Albuminuria [*drug therapy]; Anemia, Sickle Cell [*complications] [urine]; Angiotensin-Converting Enzyme Inhibitors [*therapeutic use]; Captopril [*therapeutic use]; Creatinine [blood]; Potassium [blood]; Proteinuria [*drug therapy]; Randomized Controlled Trials as Topic; Renal Insufficiency [prevention & control]

MeSH check words

Female; Humans; Male