Cochrane
Library

Cochrane Database of Systematic Reviews

Low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease (Review)

van Zuuren EJ, Fedorowicz Z

van Zuuren EJ, Fedorowicz Z.

Low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease.

Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD010155.

DOI: [10.1002/14651858.CD010155.pub3](https://doi.org/10.1002/14651858.CD010155.pub3).

www.cochranelibrary.com

Low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease (Review)

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	10
Figure 1.	11
Figure 2.	12
Figure 3.	13
DISCUSSION	15
AUTHORS' CONCLUSIONS	16
ACKNOWLEDGEMENTS	16
REFERENCES	17
CHARACTERISTICS OF STUDIES	19
DATA AND ANALYSES	23
Analysis 1.1. Comparison 1: Tinzaparin versus placebo, Outcome 1: Duration of the pain	23
Analysis 1.2. Comparison 1: Tinzaparin versus placebo, Outcome 2: Number of hospitalisations days	24
Analysis 1.3. Comparison 1: Tinzaparin versus placebo, Outcome 3: Number of adverse events	24
Analysis 2.1. Comparison 2: Dalteparin versus placebo, Outcome 1: Reduction of pain	24
ADDITIONAL TABLES	24
WHAT'S NEW	28
HISTORY	28
CONTRIBUTIONS OF AUTHORS	28
DECLARATIONS OF INTEREST	28
SOURCES OF SUPPORT	29
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	29
INDEX TERMS	29

[Intervention Review]

Low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease

Esther J van Zuuren¹, Zbys Fedorowicz²¹Department of Dermatology, Leiden University Medical Center, Leiden, Netherlands. ²Veritas Health Sciences Consultancy Ltd, London, UK**Contact:** Esther J van Zuuren, E.J.van_Zuuren@lumc.nl.**Editorial group:** Cochrane Cystic Fibrosis and Genetic Disorders Group.**Publication status and date:** Stable (no update expected for reasons given in 'What's new'), published in Issue 4, 2021.**Citation:** van Zuuren EJ, Fedorowicz Z. Low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD010155. DOI: [10.1002/14651858.CD010155.pub3](https://doi.org/10.1002/14651858.CD010155.pub3).

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Sickle cell disease is one of the most common and severe genetic disorders in the world. It can be broadly divided into two distinct clinical phenotypes characterized by either haemolysis or vaso-occlusion. Pain is the most prominent symptom of vaso-occlusion, and hypercoagulability is a well-established pathogenic phenomenon in people with sickle cell disease. Low-molecular-weight heparins might control this hypercoagulable state through their anticoagulant effect. This is an update of a previously published version of this review.

Objectives

To assess the effects of low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register comprising references identified from comprehensive electronic database searches. We also searched abstract books of conference proceedings and several online trials registries for ongoing trials.

Date of the last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register: 28 September 2015.

Selection criteria

Randomised controlled clinical trials and controlled clinical trials that assessed the effects of low-molecular-weight heparins in the management of vaso-occlusive crises in people with sickle cell disease.

Data collection and analysis

Study selection, data extraction, assessment of risk of bias and analyses were carried out independently by the two review authors.

Main results

Two studies comprising 287 participants were included. One study (with an overall unclear to high risk of bias) involved 253 participants and the quality of the evidence for most outcomes was very low. This study, reported that pain severity at day two and day three was lower in the tinzaparin group than in the placebo group ($P < 0.01$, analysis of variance (ANOVA)) and additionally at day 4 ($P < 0.05$ (ANOVA)). Thus tinzaparin resulted in more rapid resolution of pain, as measured with a numerical pain scale. The mean difference in duration of painful crises was statistically significant at -1.78 days in favour of the tinzaparin group (95% confidence interval -1.94 to -1.62). Participants treated with tinzaparin had statistically significantly fewer hospitalisation days than participants in the group treated with placebo, with a

mean difference of -4.98 days (95% confidence interval -5.48 to -4.48). Two minor bleeding events were reported as adverse events in the tinzaparin group, and none were reported in the placebo group. The second study (unclear risk of bias) including 34 participants and was a conference abstract with limited data and only addressed one of the predefined outcomes of the review; i.e. pain intensity. After one day pain intensity reduced more, as reported on a visual analogue scale, in the dalteparin group than in the placebo group, mean difference -1.30 (95% confidence interval -1.60 to -1.00), with the quality of evidence rated very low. The most important reasons for downgrading the quality of evidence were serious risk of bias and imprecision (due to low sample size or low occurrence of events).

Authors' conclusions

Based on the results of two studies, evidence is incomplete to support or refute the effectiveness of low-molecular-weight heparins in people with sickle cell disease. Vaso-occlusive crises are extremely debilitating for sufferers of sickle cell disease; therefore well-designed placebo-controlled studies with other types of low-molecular-weight heparins, and in participants with different genotypes of sickle cell disease, still need to be carried out to confirm or dismiss the results of this single study.

PLAIN LANGUAGE SUMMARY

Low-molecular-weight heparins for pain caused by obstruction of blood vessels in people with sickle cell disease

Review question

We reviewed the evidence about the effects of low-molecular-weight heparins in managing vaso-occlusive crises in people with sickle cell disease. This is an update of a previously published version of this review.

Background

Sickle cell disease is one of the most common and severe genetic blood disorders in the world. As the result of a change in the haemoglobin gene, red blood cells are transformed into cells with a sickle shape. This sickling of red blood cells results in various complications, amongst which are vaso-occlusive crises. In a vaso-occlusive crisis, the sickled red blood cells tend to clot together and block blood flow, which leads to pain in the organ involved. The pain can be very debilitating and often requires administration of morphine. Medication that prevents blood from clotting in the vessels might represent a useful contribution to existing treatment options for vaso-occlusive crises.

Search date

The evidence is current to: 28 September 2015.

Study characteristics

The review included two studies that lasted seven days with a total of 287 people. One study involved 253 people (aged approximately 22 years) with sickle cell disease and compared tinzaparin with placebo and people were selected for one treatment or the other randomly. The other study was smaller with 34 participants (aged approximately 27 years) and compared dalteparin versus placebo.

Key results

Tinzaparin reduced the number of days spent in hospital and reduced the pain (and the intensity of the pain) more rapidly. Two minor bleedings were reported in the tinzaparin group versus none in the placebo group. The data regarding the effectiveness of dalteparin were very limited and only addressed pain intensity, being more reduced by treatment with dalteparin than by placebo. These data are not sufficient to support the conclusion that low-molecular-weight heparins are effective in the treatment of vaso-occlusive crises in people with sickle cell disease. Additional studies with different types of low-molecular-weight heparin used in different forms of sickle cell disease, are necessary to confirm or dismiss the results of this single study. Vaso-occlusive crises can be extremely debilitating and can have a significant impact on quality of life; therefore it is important to know whether low-molecular-weight heparins might serve as a useful treatment option with few side effects.

Quality of the evidence

The quality of the evidence for the majority of outcomes was very low, this had mainly to do with risk of bias of the studies (e.g. method of blinding unclear) or with small sample size of the studies.

SUMMARY OF FINDINGS

Summary of findings 1. Tinzaparin compared to placebo for people with sickle cell disease

Tinzaparin compared to placebo for people with sickle cell disease

Patient or population: people with sickle cell disease

Settings: hospitals

Intervention: tinzaparin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tinzaparin				
Pain intensity Numeric pain scale Follow up: mean 7 days	See comment ¹	See comment ¹		253 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	The authors reported at D2 and D3, the pain severity score was lower in the tinzaparin group than in the placebo group (P < 0.01), to that at D4 (P < 0.05)
Pain duration Scale from: 1 to 7. Follow up: mean 7 days	The mean pain duration in the control group was 4.35 days	The mean pain duration in the intervention group was 1.78 lower (1.94 to 1.62 lower)		253 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	The duration of painful crises was almost 2 days shorter in the tinzaparin group
The requirement for opiate treatment Follow up: mean 7 days	See comment	See comment		253 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	This outcome was inadequately reported, only that during the study all participants received standard analgesia therapy consisting of morphine at 1 mg/h
Number of serious complications of SCD - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Number of other sickle-related events - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed

Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire either generic or SCD specific) - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Hospitalisation (number and duration) Scale from: 0 to 12. Follow up: mean 7 days	The mean hospitalisation (number and duration) in the control group was 12.06 days	The mean hospitalisation (number and duration) in the intervention group was 4.98 lower (5.48 to 4.48 lower)	253 (1 study)		⊕⊕⊕⊕ very low 2,3	Participants treated with tinzaparin had almost 5 hospitalisation days less compared with those in the group treated with placebo
Participant satisfaction with the medication assessed by any appropriate and validated questionnaire (either generic or SCD specific) - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Adverse events associated with the use of anticoagulants (e.g. bleeding) Follow-up: mean 7 days	See comment	See comment	RR 4.96 (0.24 to 102.31)	253 (1 study)	⊕⊕⊕⊕ low 4,5	Two minor bleeding events were reported in the tinzaparin group compared with none in the placebo group

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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).
CI: confidence interval; **RR:** risk ratio;

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ No precise data were reported.

² Downgraded two levels for very serious risk of bias. Sequence generation is unclear as well as allocation concealment and measurements to blind the investigators and participants. A potential conflict of interest cannot be excluded as one of the investigators is an employee of the manufacturer of tinzaparin. The NMS scale is not a validated tool for pain assessment.

³ Downgraded one level for serious imprecision. Total population size is less than 400

⁴ We did not downgrade for risk of bias for this outcome

⁵ Downgraded two levels for very serious imprecision due to very wide confidence intervals caused by low occurrence of events

Summary of findings 2. Dalteparin compared to placebo for people with sickle cell disease

Dalteparin compared to placebo for people with sickle cell disease

Patient or population: patients with people with sickle cell disease

Settings: hospital

Intervention: dalteparin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Dalteparin				
Pain intensity VAS 0-10. Scale from: 0 to 10. Follow-up: mean 7 days	The mean pain intensity in the control group was - 0.3	The mean pain intensity in the intervention group was 1.30 lower (1.60 to 1.00 lower)		35 (1 study)	⊕⊕⊕⊕ very low 1,2	Participants in the dalteparin group had less pain than the participants in the placebo group after one day. After 3 days there was a 41% loss to follow-up making data less usable
Pain duration - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
The requirement for opiate treatment - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Number of serious complications of SCD - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Number of other sickle-related events - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire either generic or SCD specific) - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed

Hospitalisation (number and duration) - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Participant satisfaction with the medication assessed by any appropriate and validated questionnaire (either generic or SCD specific) - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
Adverse events associated with the use of anti-coagulants (e.g. bleeding) - not measured	See comment	See comment	Not estimable	-	See comment	Not assessed
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. 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).</p> <p>CI: confidence interval;</p> <p>GRADE Working Group grades of evidence High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.</p>						

¹ Downgraded one level for serious risk of bias as almost all domains were judged as unclear

² Downgraded two levels for serious imprecision. Very small sample size

BACKGROUND

Please refer to an additional table for definitions of clinical terms (Table 1).

Description of the condition

Definition and clinical features

Sickle cell disease (SCD) is one of the most common and severe genetic disorders in the world. The term SCD covers several common genotypes (Rees 2010; Steinberg 2011).

- Sickle cell anaemia: homozygosity for the sickle haemoglobin gene (*HbS*). This is the most prevalent form of SCD and is caused by inheritance from both parents of an *HbS* gene.
- Sickle cell-haemoglobin C (*HbSC*) disease: compound heterozygosity for *HbS* and haemoglobin C (*HbC*) genes. This second most common type of SCD is caused by inheritance of one sickle cell gene from one parent and another abnormal haemoglobin gene (*HbC*) from the other.
- *HbS*- β -thalassaemia: compound heterozygosity for *HbS* and a β^0 - or β^+ -thalassaemia gene ($S\beta^0$, $S\beta^+$). The third major type of SCD, caused by inheritance of one sickle cell gene from one parent and one β^0 - or β^+ -thalassaemia gene from the other.
- Other double heterozygous conditions such as haemoglobin SD disease (*HbSD*), haemoglobin SE disease (*HbSE*), etc.

Homozygous sickle cell (SS) disease and sickle cell/ β^0 -thalassaemia are generally considered the more severe forms of the disease, whilst *HbSC* disease and sickle cell β^+ -thalassaemia tend to be milder (Al Hajeri 2008). Sickle cell trait (heterozygotes who carry one *HbS* allele and one normal adult haemoglobin (*HbA*) allele) is clinically benign and should not be considered a disease (Steinberg 2011). However, recent literature reports point to associations with serious conditions such as exercise-related sudden death, exertional rhabdomyolysis, venous thromboembolism and renal complications, suggesting that sickle cell trait is not as benign as it was previously considered to be (Austin 2007; Austin 2009; Goldsmith 2012; Key 2010).

Individual heterogeneity between people with SCD makes clinical manifestations of the diseases highly variable in frequency and severity, ranging from completely asymptomatic cases to very severe forms. However, most patients (about 70%) have a moderate phenotype (Inati 2009).

Sickle cell disease can be broadly divided into distinct clinical phenotypes characterised by either haemolysis or vaso-occlusion (Ballas 2010; Ballas 2012; Inati 2009). During haemolysis the red blood cells lyse prematurely and the content of the cells, that is, the haemoglobin, is released into the surrounding fluid; during vaso-occlusion the sickled red blood cells clump together, obstructing blood flow and damaging corresponding tissues and organs. Vaso-occlusion leads to both acute and chronic complications (Mousa 2010). Clinical manifestations of vaso-occlusion include acute episodes of severe pain (crises); acute chest syndrome (a life-threatening pneumonia-like illness); increased infections; joint necrosis; stroke; spontaneous abortion; and multi-organ failure (Ballas 2010; Ballas 2012; Ballas 2013; Inati 2009; Mousa 2010; Steinberg 1999). Chronic haemolysis manifests clinically as anaemia, cholelithiasis (presence of gall stones), pulmonary hypertension, priapism (painful persistent

erections), leg ulceration, sudden death, and possibly stroke (Gladwin 2012; Inati 2009b). However, the severity of the clinical manifestations depends on the degree of haemolysis, and those with less haemolysis are predicted to have pain crises, acute chest syndrome, and osteonecrosis (Bunn 2010). According to Bunn and colleagues, pulmonary hypertension is usually minor and is confounded by several co-morbid conditions including high cardiac output, pulmonary vascular inflammation and occlusion (thrombosis in situ, fat embolism), as well as left ventricular failure (Bunn 2010). A comprehensive overview of clinical signs and symptoms is provided in a article by Ballas 2010, in which clinical manifestations are divided into three groups; haemolytic anaemia and its sequelae, pain syndromes and related issues and complications in major organs and related co-morbidities. Morbidity and mortality in people with SCD mainly result from tissue infarction (tissue death due to oxygen shortage) secondary to obstruction of the small blood vessels by sickle cells (Davies 2012).

Symptoms

Pain is the hallmark of SCD (Ballas 2013; de Montalembert 2008; Steinberg 2011). It can be acute or chronic and most often is located in joints, extremities, back or chest, but pain can occur anywhere and can last several days or weeks, or longer (de Montalembert 2008; Steinberg 2011). The frequency and severity of painful episodes vary widely within and between individual patients (de Montalembert 2008; Steinberg 2011). Acute chest syndrome is characterised by fever, cough, sputum production, tachypnoea (rapid breathing) and dyspnoea (breathing difficulties) and is the second most common reason for hospitalisation in this group of patients after pain (Ballas 2010; Ballas 2013; de Montalembert 2008; Steinberg 2011).

Patients are more susceptible to infection; in children the most prevalent agent is *Streptococcus pneumoniae*, and in adults gram-negative organisms are more common (de Montalembert 2008; Steinberg 2011). Fatigue and shortness of breath are symptoms of pulmonary hypertension, which is another frequent complication. Strokes occur in approximately 10% of children and adults with sickle cell anaemia but are much less common in other genotypes of the disease (Inati 2009; Steinberg 2011) and can lead to cognitive impairment as a result of neurological changes.

Anaemia manifests as fatigue, dizziness, headache, and cold hands and feet. Other complications associated with SCD include priapism in men leading to painful erections; leg ulcers, which can be both painful and disabling; sight problems due to retinopathy; and renal failure. But in fact all organs can be affected, resulting in organ-specific symptoms and complications (Ballas 2010; Ballas 2012; Ballas 2013; de Montalembert 2008; Steinberg 2011).

Epidemiology and causes

With estimates of approximately 300,000 babies born each year with documented SCD, this is one of the most common genetic inherited diseases worldwide (de Montalembert 2008; Mousa 2010; Rees 2010; WHO 2006). Prevalence is highest among people whose ancestors come from sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries (Rees 2010; WHO 2006), but in our increasingly multi-ethnic world, the disease has become a global problem (de Montalembert 2008; Steinberg 2011; WHO 2006).

Sickle cell disease is caused by inheritance from both parents of a mutation in the beta-globin gene. As a result of this point mutation

in the sixth position of the β -globin chain, valine is substituted for glutamic acid, leading to the production of a defective form of haemoglobin (haemoglobin S (HbS)) (De Franceschi 2011; Inati 2009b; Mousa 2010). Upon deoxygenation, HbS polymerises to the sickle form with distorted, sickle-shaped dehydrated red blood cells (Inati 2009b). Sickie erythrocytes occlude blood vessels of all sizes (Steinberg 2011), causing a spectrum of clinical manifestations, in addition to haemolysis and anaemia (Mousa 2010). It can cause severe pain crises and progressive organ damage to virtually every organ system in the body, and it is associated with a reduced life expectancy (Mousa 2010; Rees 2010; WHO 2006).

Description of the intervention

Low-molecular-weight heparins (LMWHs) act through the antithrombin inhibition of Factor Xa more than Factor IIa (thrombin) and have greater bioavailability and longer duration of action than unfractionated heparin (Hoy 2010) (see Table 2 for the classes of anticoagulants). At a higher dose, LMWHs are used to treat active thrombotic diseases such as deep vein thromboses, pulmonary emboli, or both, and they are used at lower doses to prevent thrombosis. The LMWHs have a more predictable anticoagulant response than unfractionated heparin, allowing them to be administered in fixed, weight-based dosages without routine laboratory monitoring, thus facilitating outpatient therapy (Hoy 2010). Conducting a systematic review of the effectiveness and safety of LMWHs is warranted because hypercoagulability in SCD is a well-established pathogenic phenomenon (Ataga 2012). Several studies have suggested the use of tinzaparin (one of the commonly used LMWHs) to control the hypercoagulable state of SCD, but none have provided solid evidence to support or discourage the use of LMWHs (De Franceschi 2009; Hirani 2011; Mousa 2010; Qari 2007).

How the intervention might work

The pathophysiology of SCD has many facets, and no single treatment addresses all consequences of the disease. Hence, for treatment of patients with SCD, a combination of several interventions, depending on the expression of disease-specific features and complications, is necessary. In addition to standardised pain management (de Montalembert 2008; Mousa 2010; Rees 2010; Steinberg 2011), alternative approaches to therapy that have anti-adhesion, anti-inflammatory and anticoagulant effects have been proposed (Mousa 2010).

The LMWHs exert their major anticoagulant effect by binding to antithrombin via a pentasaccharide, consequently inactivating Factor Xa and Factor IIa (Hirsh 1992; Hirsh 2001; Mousa 2003). Furthermore, LMWHs have anti-inflammatory properties in addition to their anticoagulant properties (Carr 2007), in part caused by suppression of tumour necrosis factor- α , which is released during blood clotting, and in part because of binding to P-selectin to inhibit leukocyte migration. Vaso-occlusion also leads to an altered nitric oxide (vasodilator) metabolism and contributes to vascular dysfunction (Mousa 2010), whereas LMWHs increase nitric oxide production and enhance vasodilating effects.

Why it is important to do this review

Management of vaso-occlusive crises is complicated and may require multiple strategies and interventions. However, we are unaware of the existence of a current systematic review undertaken to examine available evidence for the benefits and harms of

LMWHs. This is an update of a previously published version of this review (van Zuuren 2013).

OBJECTIVES

To assess the effects of LMWHs in managing vaso-occlusive crises in patients with SCD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials (RCTs) and controlled clinical trials (CCTs).

Types of participants

People with SCD SS, HbSC, S β^0 , and S β^+ (confirmed by electrophoresis and sickle solubility test, with family studies or DNA tests as appropriate) of all ages and both sexes, in any setting.

Types of interventions

Any LMWH administered subcutaneously compared with placebo or standard care for a period of up to two years.

A *post hoc* change has been made to the protocol to include all LMWHs rather than just one (tinzaparin), as was previously included. This change is intended to provide a more comprehensive review of this treatment area.

Types of outcome measures

Primary outcomes

1. Pain
 - a. Intensity (expressed as scores obtained through any validated patient-reported outcomes instrument, either generic or SCD specific)
 - b. Duration
2. The requirement for opiate treatment
 - a. Dose
 - b. Type
 - c. Frequency

Secondary outcomes

1. Number of serious complications of SCD (e.g. stroke, acute chest syndrome, infection, acute splenic sequestration).
2. Number of other sickle-related events (e.g. priapism, leg ulceration).
3. Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire, either generic or SCD specific.
4. Hospitalisation (number and duration).
5. Participant satisfaction with the medication as assessed by any appropriate and validated questionnaire (either generic or SCD specific).
6. Adverse events associated with the use of anticoagulants (e.g. bleeding).

Search methods for identification of studies

Electronic searches

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 (bemiparin* OR certoparin* OR nadroparin* OR parnaparin* OR reviparin* OR ardeparin* OR danaparoid OR tinzaparin* OR dalteparin* OR enoxaparin* OR fondaparinux).

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 from 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 of the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 28 September 2015.

Searching other resources

The following additional resources were used:

1. the bibliographical references of identified studies for citations to additional studies (EvZ, 30 November 2015);
2. personal contact with corresponding authors of relevant trials or review authors and other experts (EvZ);
3. clinical trials registries: [ClinicalTrials.gov](#); [Current Controlled Trials](#) (across multiple registers) using the search terms (low-molecular-weight heparin OR sickle cell OR crises) AND trial (EvZ, 30 November 2015);
4. conference proceedings of the International Society of Thrombosis and Hemostasis (ISTH) and of the Scientific Subcommittee of the ISTH (EvZ, 30 November 2015).

Data collection and analysis

This is the first update of the original publication ([van Zuuren 2013](#)).

Selection of studies

Two review authors (EvZ and ZF) independently assessed the abstracts of trials resulting from the searches. They obtained full-text copies of all relevant and potentially relevant trials, those appearing to meet the inclusion criteria and those for which details in the title and in the abstract were insufficient to allow a clear decision. The two review authors then independently assessed the full-text articles. Any disagreements on the eligibility of trials were resolved through discussion and consensus. All irrelevant records were excluded, and details of the trials and the reasons for their exclusion were noted in the Characteristics of excluded studies in RevMan 5.1 ([Review Manager \(Revman\) 2014](#)).

Data extraction and management

Two review authors (EvZ, ZF) entered details for the included trials into the tables in the '[Characteristics of included studies](#)' in RevMan

5.1 ([Review Manager \(Revman\) 2014](#)) and collected outcome data using a pre-determined form designed for this purpose. Two review authors (EvZ, ZF) extracted data independently and in duplicate and included them if consensus was reached. Trial investigators were contacted and were asked to provide missing data or to clarify study details (see [Table 3](#)).

The review authors extracted the following details.

1. Trial methods
 - a. sequence generation
 - b. method of concealment of allocation
 - c. masking of participants, trialists and outcome assessors
 - d. exclusion of participants after randomisation and proportion and reasons for losses at follow up
2. Participants
 - a. country of origin and study setting
 - b. sample size
 - c. age
 - d. gender
 - e. inclusion and exclusion criteria
3. Intervention group
 - a. type of LMWH
 - b. dose and frequency
 - c. duration of intervention and follow up
4. Control group
 - a. dose and frequency
 - b. duration of intervention and follow up
5. Outcomes: primary and secondary outcomes mentioned in the '[Types of outcome measures](#)' section of this review and categorised and grouped accordingly: short-term data at three, six and 12 months and medium- to long-term data (beyond one year).

If stated in the trial reports, the review authors recorded the sources of funding of all included studies and used this information to help in assessment of the clinical heterogeneity and external validity of all included trials.

Assessment of risk of bias in included studies

Two review authors (EvZ, ZF) independently assessed the selected trials using a simple contingency form and in accordance with the domain-based evaluation described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1 ([Higgins 2011a](#)). The review authors compared evaluations and discussed and resolved any inconsistencies in these evaluations.

The review authors assessed the following domains as having low, unclear or high risk of bias:

1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data addressed;
5. free of selective outcome reporting;
6. free of other bias.

The review authors reported these assessments for each trial in the 'Characteristics of included studies' tables and in the 'Assessment of risk of bias in included studies' section of this review.

The authors categorised and reported the overall risk of bias of each of the included studies according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria met;
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria assessed as unclear; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria not met.

Measures of treatment effect

The review authors sought advice from the Cochrane Cystic Fibrosis and Genetic Diseases Group with regard to statistical analysis for data synthesis. They analysed the data using RevMan 5.1 and report the results according to Cochrane Collaboration criteria (Review Manager (Revman) 2014). The authors analysed binary data and report risk ratios (RRs) with corresponding 95% confidence intervals (CIs); they also analysed continuous outcomes and report mean differences (MDs) between treatment groups and their 95% CIs. For future updates, if different scales or different units are collected for continuous outcomes, the review authors will calculate and present the data using the standardised mean difference (SMD). In addition, for repeated observations for individual participants and for events that may recur, the authors will follow chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Unit of analysis issues

In future updates, if cluster-randomised or cross-over trials are included, they will be checked for unit of analysis errors based on the advice provided in chapters 16.3.4 and 16.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). For repeated observations per participant and for events that may recur, the review authors will follow guidance provided in chapters 9.3.4 and 9.3.5, respectively, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

Dealing with missing data

The review authors contacted principal investigators of included trials to request missing data and followed the advice provided in chapter 16.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d) (see Table 3).

Assessment of heterogeneity

The review authors will assess in future updates (when more studies are included) clinical diversity between trials by examining trial characteristics, similarities between types of participants, the interventions and the outcomes as specified in the inclusion criteria.

They will explore statistical heterogeneity using a Chi² test and the I² statistic, where I² values of 30% to 60% indicate moderate to high, 50% to 90% substantial, and 75% to 100% considerable heterogeneity. The review authors will consider heterogeneity to be significant when the P value is less than 0.10 for the Chi² test (Higgins 2003).

Assessment of reporting biases

In view of the low number of trials included, this assessment was not undertaken. In future updates, and if a sufficient number of trials (at least 10) assessing similar interventions are identified for inclusion in this review, the review authors plan to assess publication bias according to the recommendations on testing for funnel plot asymmetry as described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). If asymmetry is identified, the review authors will attempt to assess other possible causes, and these will be explored in the discussion section of the review if appropriate.

Data synthesis

Two review authors (ZF, EvZ) analysed the data in RevMan 5.1 (Review Manager (Revman) 2014) and reported them as specified in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1 (Higgins 2011c). They used a fixed-effect model to analyse data from studies, unless in future updates they plan to identify moderate or higher heterogeneity (see classifications above), in which case they will use a random-effects model to analyse data.

We applied the GRADE approach for the two comparisons to rate the quality of the evidence of each of the prespecified outcomes (Schünemann 2013).

Subgroup analysis and investigation of heterogeneity

In future updates, if a sufficient number of trials are included and if the authors identify moderate, substantial or considerable heterogeneity (see 'Assessment of heterogeneity'), they plan to carry out the following subgroup analyses based on:

- type of LMWH;
- type of SCD: sickle cell anaemia; haemoglobin SC disease; sickle cell β^0 -thalassaemia; sickle cell β^+ -thalassaemia;
- different dosing schedules.

Sensitivity analysis

The review authors will undertake sensitivity analyses in future updates if a larger number of trials are included, to assess the robustness of their review results by repeating the analysis with the following adjustments:

- exclusion of trials with an unclear or high risk of bias for allocation concealment;
- exclusion of trials with an unclear or high risk of bias for blinding of outcome assessment;
- exclusion of trials with an unclear or high risk of bias for completeness of follow up;
- exclusion of CCTs.

RESULTS

Description of studies

Results of the search

Study selection was carried out independently by both review authors (EvZ and ZF), who retrieved three studies, one of which was a duplicate. No ongoing trial was identified. For further details, see the 'Study Flow Diagram' (Figure 1).

Figure 1. Study flow diagram.

Included studies

Two studies comprising 287 participants were included. One study included 253 participants ([Qari 2007](#)). The second study, currently available as an abstract only, included 34 participants (see the 'Characteristics of included studies' tables of both studies).

Characteristics of the trial setting and methods

The Qari study was a randomised, double-blind, placebo-controlled trial conducted in three hospitals in Saudi Arabia ([Qari 2007](#)). The Shah study was a randomised, double-blind, placebo-controlled trial conducted in a university centre in the USA ([Shah 2013](#)).

Characteristics of the participants

A total of 253 participants (men and women) of approximately 22 years of age with homozygous SCD and with painful vaso-occlusive crises, severe enough to require narcotic analgesia, were included in the Qari trial ([Qari 2007](#)). In the Shah trial, 34 participants were randomised (both genders) with homozygous SCD, sickle cell-haemoglobin C disease, or sickle cell/ β^0 -thalassaemia that were admitted with a diagnosis of vaso-occlusive crisis ([Shah 2013](#)).

Characteristics of the interventions

Tinzaparin at 175 IU/kg given subcutaneously versus placebo was evaluated over seven days in the Qari study ([Qari 2007](#)).

All participants received standard analgesic therapy consisting of morphine at 1 mg/h given by intravenous infusion and rehydration with normal saline. In the Shah study, participants were given dalteparin 5000 units subcutaneously or placebo over seven days ([Shah 2013](#)). It was unclear if additional treatment was provided during these days.

Characteristics of the outcome measures

In the Qari study six outcome measures were assessed, including pain intensity and duration, as well as complications and adverse events of the therapy ([Qari 2007](#)), whilst in [Shah 2013](#) only one of our predefined outcomes; i.e. reduction in pain, was addressed (see 'Characteristics of included studies' for further details).

Excluded studies

No studies were excluded; just one study and a duplicate remained after assessment of the titles and abstracts resulting from the searches.

Risk of bias in included studies

The review authors assessed the included studies for risk of bias and reported the judgements for the individual domains in the risk of bias table associated with the study ([Characteristics of included studies](#)). The review authors have also presented these in the risk of bias graph in [Figure 2](#) and in a summary of the risk of bias in [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Qari 2007	?	?	?	?	+	+	-
Shah 2013	?	?	?	?	?	+	?

Allocation

Sequence generation

The method used to generate the allocation sequence was not described in either study, therefore, both studies were assessed as having an unclear risk of bias for this domain.

Allocation concealment

The method used to conceal the allocation sequence was not reported in either study, and a judgement of an unclear risk of bias was given for both studies for this domain.

Blinding

The reporting of the measures used to blind study participants and personnel from knowledge of which intervention a participant

received was inadequate, as was information on blinding of the outcome assessment. Therefore, a clear judgement could not be made for these domains for both studies.

Incomplete outcome data

No losses to follow up were reported in the Qari study, and this domain was therefore judged as having a low risk of bias (Qari 2007). However, five out of 34 participants (14.7%) were not included in the analyses in the Shah study and we judged this domain as at an unclear risk of bias for this (Shah 2013).

Selective reporting

Although the protocol was not available for the Qari study, all pre-specified outcomes appear to have been reported, and this domain was assessed as having a low risk of bias (Qari 2007). The protocol for the Shah study was available and there appeared to be no evidence of selective reporting based on the data provided (Shah 2013).

Other potential sources of bias

One of the investigators of the Qari study was employed by Leo Pharmaceutical Products (Athens, Greece), the manufacturer of tinzaparin, and a potential risk of bias cannot be excluded (Qari 2007). The same held true for the Shah study in that it was sponsored by Eisai Limited, the manufacturer of dalteparin (Shah 2013).

Effects of interventions

See: [Summary of findings 1](#) Tinzaparin compared to placebo for people with sickle cell disease; [Summary of findings 2](#) Dalteparin compared to placebo for people with sickle cell disease

Tinzaparin versus placebo

One single study (253 participants) with an overall unclear to high risk of bias provided data for this comparison (Qari 2007). See also [Summary of findings 1](#).

Primary outcomes

1. Pain

a. Intensity (expressed as scores obtained through any validated patient-reported outcomes instrument, either generic or SCD specific)

No precise data were reported; therefore, these were estimated from the graph-plot in the report. The authors indicated that at days two and three, the pain severity score was lower in the tinzaparin group than in the placebo group ($P < 0.01$ (ANOVA)), in addition to that at day 4 ($P < 0.05$ (ANOVA)), and thus that tinzaparin resulted in more rapid resolution of pain as measured by the numerical pain scale (NMS).

b. Duration

In the tinzaparin group, the duration of painful crises was 2.57 days (standard deviation (SD) 0.45) versus 4.35 days (0.78) for the placebo group; mean difference (MD) -1.78 days (95% CI -1.94 to -1.62; $P < 0.00001$), and this difference was statistically significant in favour of tinzaparin ([Analysis 1.1](#)).

2. The requirement for opiate treatment

This outcome was inadequately reported, only that during the study all participants received standard analgesia therapy

consisting of morphine at 1 mg/h given via intravenous infusion and rehydration with normal saline.

Secondary outcomes

1. Number of serious complications of SCD

Not assessed.

2. Number of other sickle-related events

Not assessed.

3. Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire, either generic or SCD specific

Not assessed.

4. Hospitalisation (number and duration)

Participants treated with tinzaparin had statistically significantly fewer hospitalisation days compared with those in the group treated with placebo. The number of days in the tinzaparin group was 7.08 (SD 1.8), and in the placebo group, the number was 12.06 (2.2), MD -4.98 days (95% CI -5.48 to -4.48; $P < 0.00001$) (see [Analysis 1.2](#)).

5. Participant satisfaction with the medication assessed by any appropriate and validated questionnaire (either generic or SCD specific)

Not assessed.

6. Adverse events associated with the use of anticoagulants (e.g. bleeding)

Two minor bleeding events were reported in the tinzaparin group compared with none in the placebo group, RR 4.96 (95% CI 0.24 to 102.31; $P = 0.30$). The difference was not statistically significant (see [Analysis 1.3](#)).

Dalteparin versus placebo

One study including 34 participants with an overall unclear risk of bias evaluated this comparison (Shah 2013). As data were summarized in a conference abstract, only limited data were available. See also [Summary of findings 2](#).

Primary outcomes

1. Pain

a. Intensity (expressed as scores obtained through any validated patient-reported outcomes instrument, either generic or SCD specific)

After one day, based on a visual analogue scale (VAS) score rated 0 to 10, pain was reduced by 1.6 (0.4) in the 16 participants on dalteparin versus a reduction of 0.3 (0.5) in the 13 participants on placebo with a MD -1.30 (95% CI -1.60 to -1.00; $P < 0.00001$), which favours dalteparin ([Analysis 2.1](#)). There was also a significant difference after three days in favour of dalteparin; the reductions were 2.4 (0.9) in nine participants on dalteparin and 0.9 (0.2) in 11 participants on placebo, MD -1.50 (95% CI -2.10 to -0.90) ($P < 0.00001$) ([Analysis 2.1](#)). However, we have no information on the 14 out of 34 (41%) participants that are not included in the analysis, making these data less usable.

b. Duration

Not assessed.

2. The requirement for opiate treatment

Not assessed.

Secondary outcomes

None of these outcomes were assessed.

DISCUSSION

Summary of main results

Two studies comprising 287 participants were included. One study (253 participants), at an unclear to high risk of bias, reported that tinzaparin reduced hospitalisation days and pain, as well as pain intensity, more rapidly when compared with placebo. The quality of the evidence was rated mainly very low for several outcomes. Another study (34 participants), at an unclear risk of bias, showed that dalteparin reduced pain intensity more than placebo after one day (quality of evidence very low), and probably as well after three days. However, it is unclear if a difference of 1.30 on a visual analogue scale (VAS) is a clinically important difference.

For further details, see [Summary of findings 1](#) and [Summary of findings 2](#).

Overall completeness and applicability of evidence

There is incomplete evidence to support or refute the effectiveness of low-molecular-weight heparins (LMWHs) for the management of vaso-occlusive crises in individuals with sickle cell disease (SCD). One of the two trials included in this review failed to address the majority of clinically relevant secondary outcomes, not least of all change in 'quality of life' and patient satisfaction; this somewhat limits the applicability of the evidence generated. However, the low number of adverse events reported appeared to illustrate the relative safety of the use of tinzaparin, albeit only over a short period of treatment time. The second study that was identified included a small (34) number of participants, provided even less information and reported mainly on pain intensity. There are still remaining gaps in the evidence for the effectiveness of LMWHs in managing vaso occlusive crises.

Quality of the evidence

Limitations in study design and implementation

Although the study design of the included studies appeared to have been at best adequate, our assessment of the risk of bias for several domains in this study revealed some of the limitations in its implementation, which have been reported in the '[Risk of bias in included studies](#)' section of this review. In particular, after unsuccessful attempts to contact the investigators in these studies, the methods used to generate the sequence and to conceal the allocation and the measures taken to blind investigators and participants remained unclear. Pain intensity and duration are key outcomes and require accurate assessment with the use of a valid and reliable tool. The numerical pain scale used in the Qari study did not appear to meet these criteria, making it difficult for the review authors to interpret the value of the reported outcomes and to further translate these into clinical practice ([Qari 2007](#)). Also, the minimal important difference of the VAS scale used in the Shah study for pain intensity has not yet been established ([Shah 2013](#)).

Indirectness of the evidence

Participants in the included studies, in general, constituted a clinically representative sample, matching the inclusion criteria; therefore, the review authors had no significant concerns about the appropriateness of including participants identified in the review.

Placebo-controlled, rather than head-to-head trials, are still required to evaluate whether LMWHs have any beneficial effect on vaso-occlusive crises. These trials should also consider evaluating other LMWHs.

The Shah study only addressed one of our predefined outcomes; i.e. pain intensity, whereas the Qari study addressed several of our predefined outcomes ([Qari 2007](#); [Shah 2013](#)). However, evidence was lacking on a requirement of opiates for pain relief and of participants' assessed outcomes (e.g. health-related quality of life (HRQOL) and participants' level of satisfaction). Patient-relevant outcomes are a pre-requisite for informing evidence-based clinical decision making, but the importance of patient-reported outcomes (PROs), specifically those used in evaluating the impact of the intervention on quality of life, appears to have been underestimated by the investigators in the included study.

Inconsistency of the results

As only two studies were included, assessment of inconsistency was not feasible. The results on reduction of pain intensity were in agreement for both studies.

Imprecision of the results

Low occurrence of events and small sample size were the most important reasons for downgrading the quality of evidence for imprecision for most outcomes.

Publication bias

Although our attempts to identify additional studies were unsuccessful, the possibility of unpublished research on this topic cannot be excluded. In future updates, and if further trials are identified for inclusion, we will assess publication bias as specified in the [Assessment of reporting biases](#) section of this review.

Potential biases in the review process

We made every attempt to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. The review authors' independent assessments of eligibility of studies for inclusion in this review minimised the potential for additional bias.

Agreements and disagreements with other studies or reviews

A number of literature reviews have described a range of management strategies for SCD-related vaso-occlusive crises; the most recent and relevant for our review is by Mousa, which referred to the Qari study identified in this systematic review and indicated that treatment with tinzaparin is "justified in the treatment of acute painful crisis in SCA based on that randomized controlled trial" ([Mousa 2010](#); [Qari 2007](#)). The report specifies tinzaparin as adjuvant therapy in its "evidence based recommendations for pain management" but provides no indication of any systematic search of the literature, nor a critical appraisal of the cited references, but

rather states that these recommendations are based on the "long term experience" of a panel of physicians and scientists.

Several studies have suggested the possible use of tinzaparin to control the hypercoagulable state occurring in SCD (De Franceschi 2009; Hirani 2011; Mousa 2010), but all were based on one study (Qari 2007). Whilst these investigators recognize its potential use in managing vaso-occlusive crises, they concur that it is still an experimental treatment option and provide no general recommendation as long as further studies have not been conducted.

AUTHORS' CONCLUSIONS

Implications for practice

Current recommendations and practices for the management of vaso-occlusive crises in people with SCD continue to be largely based on clinicians' judgement. However, the results of this review demonstrate that at present, there is very low quality evidence to support reliable clinical decision making regarding the use of LMWHs in patients with SCD.

Implications for research

This review highlights the need for further randomised placebo-controlled trials to evaluate the effects of LMWHs in the management of vaso-occlusive crises in people with SCD, which can ultimately provide reliable evidence to help inform clinical decision making.

Studies with other types of LMWHs, as well as in participants with different genotypes of SCD, still need to be carried out to confirm or dismiss the results reported by this single study.

Any future RCTs must be well designed, well conducted and adequately delivered with subsequent reporting, including high-quality descriptions of all aspects of methodology. Reporting should conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (<http://www.consort-statement.org/>), which will enable appraisal and interpretation of results, as well as accurate judgements to be made about the risk of bias and the overall quality of the evidence.

Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995).

For further research recommendations based on the EPICOT (evidence, population, intervention, comparison, outcomes and time) format (Brown 2006), see an additional table (Table 4).

ACKNOWLEDGEMENTS

The authors would like to thank Amani Al Hajeri, Moiz Bakhiet, Joel Beleno and Nilda Manansala for their contributions to the drafting of this protocol. The authors would also like to thank Tracey Remington and Nikki Jahnke of the Cochrane Cystic Fibrosis and Genetic Disorders Group for their support in developing this review.

REFERENCES

References to studies included in this review

Qari 2007 {published data only}

* Qari MH, Aljaouni SK, Alardawi MS, Fatani H, Alsayes FM, Zografos P, et al. Reduction of painful vaso-occlusive crisis of sickle cell anaemia by tinzaparin in a double-blind randomized trial. *Thrombosis and Haemostasis* 2007;**98**(2):392-6. [PMID: PMID: 17721622]

Qari MH, Mousa S, Alsaigh MA, Zografos P, Aljaouni SK, Fatani H, et al. Tinzaparin in the management of painful vaso-occlusive crisis of sickle cell anaemia. *Blood* 2005;**106**(11):Abstract no: 2340.

Shah 2013 {unpublished data only}

NCT01419977. Treatment of sickle cell patients hospitalized in pain crisis with prophylactic dose low-molecular-weight heparin (LMWH) versus placebo. www.clinicaltrials.gov/show/NCT01419977 (accessed 01 March 2013).

* Shah N, Willen S, Telen MJ, Ortel TL. Prophylactic dose low molecular weight heparin (dalteparin) for treatment of vaso-occlusive pain crisis in patients with sickle cell disease [abstract]. *Blood* 2013;**122**(21):2241. [CENTRAL: 983639]

Additional references

Al Hajeri 2008

Al Hajeri A, Serjeant GR, Fedorowicz Z. Inhaled nitric oxide for acute chest syndrome in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No: CD006957. [DOI: [10.1002/14651858.CD006957](https://doi.org/10.1002/14651858.CD006957)]

Ataga 2012

Ataga KI, Brittain JE, Desai P, May R, Jones S, Delaney J, et al. Association of coagulation activation with clinical complications in sickle cell disease. *Plos One* 2012;**7**(1):e29786. [PMID: PMID: 22253781]

Austin 2007

Austin H, Key NS, Benson JM, Lally C, Dowling NF, Whitsett C, et al. Sickle cell trait and the risk of venous thromboembolism among blacks. *Blood* 2007;**110**(3):908-12. [PMID: PMID: 17409269]

Austin 2009

Austin H, Lally C, Benson JM, Whitsett C, Hooper WC, Key NS. Hormonal contraception, sickle cell trait, and risk for venous thromboembolism among African American women. *American Journal of Obstetrics and Gynecology* 2009;**200**(6):620.e1-3. [PMID: PMID: 19306959]

Ballas 2010

Ballas SK, Lieff S, Benjamin LJ, Dampier CD, Heeney MM, Hoppe C, et al. Definitions of the phenotypic manifestations of sickle cell disease. *American Journal of Hematology* 2010;**85**(1):6-13. [PMID: PMID:19902523]

Ballas 2012

Ballas SK, Kesen MG, Goldberg MF, Luty GA, Dampier C, Osunkwo I, et al. Beyond the definitions of the phenotypic complications of sickle cell disease: An update on management. *The Scientific World Journal* 2012;**2012**:949535. [DOI: [10.1100/2012/949535](https://doi.org/10.1100/2012/949535)]

Ballas 2013

Ballas SK. Sickle cell anemia. <http://pier.acponline.org/physicians/diseases/d905/d905.html> (accessed 28 February 2013):1-93.

Brown 2006

Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. *BMJ* 2006;**333**(7572):804-6.

Bunn 2010

Bunn HF, Nathan DG, Dover GJ, Hebbel RP, Platt OS, Rosse WF, et al. Pulmonary hypertension and nitric oxide depletion in sickle cell disease. *Blood* 2010;**116**(5):687-92. [PMID: PMID:20395414]

Carr 2007

Carr JA, Cho JS. Low molecular weight heparin suppresses tumor necrosis factor expression from deep vein thrombosis. *Annals of Vascular Surgery* 2007;**21**(1):50-5. [PMID: PMID: 17349336]

Davies 2012

Davies EG, Hirst C, Lottenberg R, Dower N. Pneumococcal vaccines for sickle cell disease. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No: CD003885. [DOI: [10.1002/14651858.CD003885.pub2](https://doi.org/10.1002/14651858.CD003885.pub2)]

De Franceschi 2009

De Franceschi L. Pathophysiology of sickle cell disease and new drugs for the treatment. *Mediterranean Journal of Hematology and Infectious Diseases* 2009;**1**(1):e2009024. [PMID: PMID:21415994]

De Franceschi 2011

De Franceschi L, Cappellini MD, Olivieri O. Thrombosis and sickle cell disease. *Seminars in Thrombosis and Hemostasis* 2011;**37**(3):226-36. [PMID: PMID: 21455857]

de Montalembert 2008

de Montalembert M. Management of sickle cell disease. *BMJ* 2008;**337**:a1397. [PMID: PMID: 18779222]

Gladwin 2012

Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. *Journal of the American College of Cardiology* 2012;**59**(13):1123-33. [PMID: PMID:22440212]

Goldsmith 2012

Goldsmith JC, Bonham VL, Joiner CH, Kato GJ, Noonan AS, Steinberg MH. Framing the research agenda for sickle cell trait: building on the current understanding of clinical events and

their potential implications. *American Journal of Hematology* 2012;**87**(3):340-6. [PMID: PMID: 22307997]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011a

Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook of Systematic Reviews of Interventions*. Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Sterne JAC, Egger M, Moher D, on behalf of the Cochrane Bias Methods Group. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook of Systematic Reviews of Interventions*. Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook of Systematic Reviews of Interventions*. Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011d

Higgins JPT, Deeks JJ, Altman DG on behalf of the CSMG. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors). *Cochrane Handbook of Systematic Reviews of Interventions*. Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hirani 2011

Hirani A, Weibel S, Kane GC. Acute chest syndrome and other pulmonary manifestations of sickle cell disease. *Journal of Clinical Outcome Management* 2011;**18**(5):211-21.

Hirsh 1992

Hirsh J, Levine MN. Low molecular weight heparin. *Blood* 1992;**79**(1):1-17. [PMID: PMID: 1309422]

Hirsh 2001

Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001;**119** Suppl 1:64S-94S. [PMID: PMID: 11157643]

Hoy 2010

Hoy SM, Scott LJ, Plosker GL. Tinzaparin sodium: a review of its use in the prevention and treatment of deep vein thrombosis and pulmonary embolism, and in the prevention of clotting in the extracorporeal circuit during haemodialysis. *Drugs* 2010;**70**(10):1319-47. [PMID: PMID: 20568836]

Inati 2009

Inati A. Recent advances in improving the management of sickle cell disease. *Blood Reviews* 2009;**23** Suppl 1:S9-13. [PMID: PMID: 20116638]

Inati 2009b

Inati A, Chabtni L, Mounayar M, Taher A. Current understanding in the management of sickle cell disease. *Hemoglobin* 2009;**33** Suppl 1:S107-15. [PMID: PMID: 20001613]

Jaywant 2003

Jaywant S, Pai A. A comparative study of pain measurement scales in acute burn patients. *Indian Journal of Occupational Therapy* 2003;**35**(3):13-7.

Key 2010

Key NS, Derebail VK. Sickle-cell trait: novel clinical significance. *Hematology/ the Education Program of the American Society of Hematology* 2010;**2010**:418-22. [PMID: PMID: 21239829]

Mousa 2003

Mousa SA, Bozarth J, Barrett JS. Pharmacodynamic properties of the low molecular weight heparin, tinzaparin: effect of molecular weight distribution on plasma tissue factor pathway inhibitor in healthy human subjects. *Journal of Clinical Pharmacology* 2003;**43**(7):727-34. [PMID: PMID: 12856386]

Mousa 2010

Mousa SA, Al Momen A, Al Sayegh F, Al Jaouni S, Nasrullah Z, Al Saeed H, et al. Management of painful vaso-occlusive crisis of sickle-cell anemia: consensus opinion. *Clinical and Applied Thrombosis/Haemostasis* 2010;**16**(4):365-76. [PMID: PMID: 20530056]

Rees 2010

Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010;**376**(9757):2018-31. [PMID: PMID: 21131035]

Review Manager (Revman) 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editors. *GRADE handbook for grading quality of evidence and strength of recommendations*. Updated October 2013. Available from www.guidelinedevelopment.org/handbook, The GRADE Working Group, 2013.

Steinberg 1999

Steinberg MH. Management of sickle cell disease. *New England Journal of Medicine* 1999;**340**(13):1021-30. [PMID: PMID: 10099145]

Steinberg 2011

Steinberg MH. In the Clinic. Sickle cell disease. *Annals of Internal Medicine* 2011;**155**(5):ITC31-15. [PMID: 21893620]

WHO 2006

World Health Organization. Sickle-cell anaemia. Report A59/9. Provisional agenda item 11.4. 59th World Health Assembly. https://apps.who.int/gb/ebwha/pdf_files/WHA59/A59_9-en.pdf (accessed 13 March 2012).

References to other published versions of this review

van Zuuren 2013

van Zuuren EJ, Fedorowicz Z. Low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No: CD010155. [DOI: [10.1002/14651858.CD010155.pub2](https://doi.org/10.1002/14651858.CD010155.pub2)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Qari 2007

Study characteristics

Methods	<ul style="list-style-type: none"> Randomised, double-blind, placebo-controlled trial. <p>Setting</p> <ul style="list-style-type: none"> King Abdulaziz University Hospital, King Fahd General Hospital and King Abdulaziz Oncology Center; Jeddah, Saudi Arabia. <p>Date of study</p> <ul style="list-style-type: none"> Not reported. Duration of intervention: 7 days.
Participants	<ul style="list-style-type: none"> N = 253 (121 male/132 female). Mean age = 22.8 ± 4.5 years for tinzaparin group, 21.6 ± 3.8 years for control group. <p>Inclusion criteria of the study</p> <ul style="list-style-type: none"> Participants > 12 years with SCA with homozygous sickle cell (SS) disease. Admitted through the emergency room with painful vaso-occlusive crisis severe enough to require narcotic analgesia. <p>Exclusion criteria of the study</p> <ul style="list-style-type: none"> Presence of medical or surgical contraindication to LMWH. Pregnancy. Low platelet counts (< 100,000/dl) or impaired haemostasis on admission in the form of INR > 1.4 or prolonged APTT > 5 seconds of the hospital normal range. Complicated SCA. History of CVA. Current aplasia. Acute chest syndrome. Exchange transfusion. Sequestration. Anticoagulant therapy for other etiology. Painful crises within the month before this admission. Women on hormonal contraception. History of painful crisis within the preceding month. Other vascular complications of SCA (e.g. prior stroke, current aplasia, acute chest pain). <p>Randomised</p> <ul style="list-style-type: none"> N = 253.

Qari 2007 (Continued)

Withdrawals / losses to follow up

- No reported losses.

Baseline data

- Not reported.

Interventions	<u>Intervention</u> <ul style="list-style-type: none">• Tinzaparin once daily 175 IU/kg s.c. for 7 days (127). <u>Comparator</u> <ul style="list-style-type: none">• Placebo once daily s.c. for 7 days (126). <p>Standard analgesia therapy: morphine 1 mg/h intravenous infusion and rehydration with normal saline.</p>	
Outcomes	<u>Outcomes of the study</u> (as reported) <ul style="list-style-type: none">• Clinical improvement and pain reported by the patient as zero degree on the NMS#• Therapy discontinuation after seven days regardless of the outcome• Appearance of any complications including bleeding, heparin-induced thrombocytopenia or other complications• Total period of hospitalisation in days#• Number of days on which the patient experienced the highest intensity on the NMS (Jaywant 2003)#• Duration of painful crisis in days#• Adverse events# <p>Denotes outcomes pre-specified for this review.</p>	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote (page 393): "...Patients were randomized consecutively into either the study group.."</p> <p>Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.</p>
Allocation concealment (selection bias)	Unclear risk	<p>The method used to conceal the allocation sequence, that is, to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment was not reported.</p> <p>Comment: information was insufficient to permit a clear judgement.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Quote (page 393): "...double-blind.." and "All drug supplies were appropriately packaged, labeled, and kept in a locked, safe area under appropriate storage conditions with access limited to persons authorized by the investigator and those who [were] directly involved in the study."</p> <p>Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.</p>
Blinding of outcome assessment (detection bias)	Unclear risk	<p>Quote (page 393): "...double-blind.."</p>

Qari 2007 (Continued)

All outcomes		<p>Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel. It was unclear, therefore, whether the outcome measurement was likely to be influenced by the lack of blinding.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>No losses reported.</p> <p>Comment: we judged this as at low risk of bias.</p>
Selective reporting (reporting bias)	Low risk	<p>The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appear to have been reported.</p> <p>Comment: we judged this as at a low risk of bias.</p>
Other bias	High risk	<p>One of the investigators is employed by Leo Pharmaceutical Products, Athens, Greece, the manufacturer of tinzaparin.</p> <p>The NMS scale for assessing pain severity is not a validated tool for pain assessment.</p> <p>Comment: a potential risk of bias cannot be excluded.</p>

Shah 2013
Study characteristics

Methods	<ul style="list-style-type: none"> Randomised, double-blind, placebo-controlled trial. <p>Setting:</p> <ul style="list-style-type: none"> Duke University, Durham, North Carolina, US. <p>Date of study:</p> <ul style="list-style-type: none"> Started May 2011. Duration of intervention 7 days with follow up at 2 weeks.
Participants	<ul style="list-style-type: none"> N = 34 (18 males / 11 females / 5 gender unclear). Median 27 years, range 20 - 56 years. <p>Inclusion criteria of the trial</p> <ul style="list-style-type: none"> Documented HgbSS or HgbS-β^0-thalassaemia by previous haemoglobin electrophoresis. Age greater than 18 years. Admit diagnosis of vaso-occlusive crisis. <p>Exclusion criteria of the trial</p> <ul style="list-style-type: none"> End-stage renal disease (creatinine > 3.0 mg/dl). Use of antiplatelet or anticoagulation medication for an alternative indication. Use of steroids or immunosuppressive medications. Platelet count less than $100 \times 10^9/L$. History or development of heparin-induced thrombocytopenia. Packed red blood cell transfusion in the past month. Recent hospitalisation with discharge within the past 1 week. <p>Randomised</p> <ul style="list-style-type: none"> N = 34.

Shah 2013 (Continued)

Withdrawals / losses to follow up

- 5/34 (14.7%), unclear from which group
- 2 subjects withdrew prior to receiving study drug, 2 subjects were discharged and 1 subject received a transfusion prior to the blood draw on day 1.

Baseline data

- Not reported.

Interventions	<u>Intervention</u> <ul style="list-style-type: none">• Dalteparin 5000 units s.c. <u>Comparator</u> <ul style="list-style-type: none">• Placebo s.c.	
Outcomes	<u>Outcomes of the study</u> (as reported): <ul style="list-style-type: none">• Reduction in hypercoagulable markers.• Reduction in clinical pain scores (visual analog scale (VAS), with 0 = no pain and 10 = worst pain)#. Denotes outcomes pre-specified for this review.	
Notes	Only abstract, limited data were available.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2241): "...including 29 patients who were randomized .." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is, to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment was not reported. Comment: information was insufficient to permit a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 2241): "...double-blind.." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 2241): "...double-blind.." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel. It was unclear, therefore, whether the outcome measurement was likely to be influenced by the lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/34 (14.7%). Per-protocol analysis Comment: we judged this as at unclear risk of bias.

Shah 2013 (Continued)

Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov as NCT01419977, but the pre-specified outcomes and those mentioned in the methods section appear to have been reported. Comment: we judged this as at a low risk of bias.
Other bias	Unclear risk	Quote (page 2241): "Disclosures: Shah: Eisai: Research Funding. Telen: GlycoMimetics, Inc.: Research Funding; Dilaforette, NA: Research Funding; Pfizer, Inc.: Consultancy." Eisai is the manufacturer of dalteparin. Comment: we judged this as at an unclear risk of bias

APTT: activated partial thromboplastin time
CVA: cerebral vascular accident
INR: international normalized ratio
NMS: numerical pain scale
s.c.: subcutaneously
SCA: sickle cell anaemia

DATA AND ANALYSES

Comparison 1. Tinzaparin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Duration of the pain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Number of hospitalisations days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Number of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Tinzaparin versus placebo, Outcome 1: Duration of the pain

Study or Subgroup	Tinzaparin			Placebo			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Qari 2007	2.57	0.45	127	4.35	0.78	126	-1.78 [-1.94, -1.62]

Analysis 1.2. Comparison 1: Tinzaparin versus placebo, Outcome 2: Number of hospitalisations days

Analysis 1.3. Comparison 1: Tinzaparin versus placebo, Outcome 3: Number of adverse events

Comparison 2. Dalteparin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Reduction of pain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1.1 Reduction of pain after 1 day	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1.2 Reduction of pain after 3 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Dalteparin versus placebo, Outcome 1: Reduction of pain

ADDITIONAL TABLES

Table 1. Glossary of Terms

Term	Definition
Anticoagulant	A substance that prevents coagulation (clotting) of blood.
Genotype	The genotype of an individual is the set of inherited instructions carried within its genetic code. Not all organisms with the same genotype look or act the same way because appearance and behaviour are modified by environmental and developmental conditions.
Haemoglobin	The iron-containing oxygen-transport metalloprotein in the red blood cells. Haemoglobin in the blood carries oxygen from the respiratory organs (lungs) to the rest of the body.
Heterozygous	A cell is said to be heterozygous when it contains two different alleles of a gene.
Homozygosity	A cell is said to be homozygous for a particular gene when identical alleles of the gene are present on both homologous chromosomes. The individual is called a <i>homozygote</i> .
Lyse	To destroy or dissolve cells.
Necrosis	The premature death of cells in living tissue.
Phenotype	The composite of an individual's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties and behaviour.
P-selectin	A cell adhesion molecule (CAM) on the surfaces of activated endothelial cells (thin layer of cells that lines the interior surface of blood vessels), which line the inner surface of blood vessels, and activated platelets (thin layer of cells that lines the interior surface of blood vessels).
Polarize	Aggregate.
Tumour necrosis factor- α	A cytokine; cell-signalling (transmitting information between cells) protein involved in systemic inflammation; a member of a group of cytokines that stimulate the acute phase reaction.

Table 2. Classes of anticoagulants

Coumarins (vitamin K antagonists)	<ol style="list-style-type: none"> 1. Warfarin. 2. Acenocoumarol and phenprocoumon. 3. Atromentin. 4. Phenindione.
Heparins and derivative substances	<ol style="list-style-type: none"> 1. Unfractionated heparin. 2. Fractionated heparin or LMWHs such as dalteparin, enoxaparin, tinzaparin, nadroparin, bemi-parin, certoparin, parnaparin and reviparin.
Factor Xa inhibitors	<ol style="list-style-type: none"> 1. Synthetic pentasaccharide inhibitors of factor Xa such as fondaparinux and idraparinux. 2. Direct factor Xa inhibitors such as rivaroxaban and apixaban.
Direct thrombin inhibitors	Lepirudin, hirudin, bivalirudin, desirudin, argatroban, dabigatran

LMWH: low-molecular-weight heparin

Table 3. Contact with investigators

Study ID	Response	Additional	Comment
Qari 2007			<p>E-mail sent 6-1-2013</p> <p>mousas@acp.edu, shaker.mosua@acphs.edu</p> <p>Follow-up e-mail sent 15-1-2013</p> <p>mousas@acp.edu; shaker.mosua@acphs.edu; drqari@hotmail.com</p> <p>Both Mousa mail-addressed seem to be incorrect. Could not find more recent ones.</p>
Shah 2013			<p>E-mail sent 30-11-2015</p> <p>nirmish.shah@duke.edu</p> <p>Dear Dr Shah</p> <p>My colleagues and I are updating our Cochrane review (Low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease) and one of your studies have been identified as potentially eligible for inclusion (Prophylactic Dose Low Molecular Weight Heparin (dalteparin) For Treatment Of Vaso-Occlusive Pain Crisis In Patients With Sickle Cell Disease. Blood 2013;122 (21)</p> <p>To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details:</p> <ol style="list-style-type: none"> 1. the method used to <u>generate</u> the allocation sequence 2. the method used to <u>conceal</u> the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment i.e. participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 3. How were patients and investigators blinded? 4. In Clinicaltrials.gov it was stated that 34 participants were enrolled, but data are on 29. How many participants were initially randomised to each arm? We found the reasons for not including the five people, but unclear from which group

Table 4. Research recommendations based on a gap in the evidence of the effects of low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease

Core elements	Issues to consider	Status of research for this review
Evidence (E)	What is the current state of the evidence?	This systematic review identified one RCT, which provided insufficient high-level evidence of the efficacy and safety of LMWH for managing vaso-occlusive crises in people with SCD.
Population (P)	Diagnosis, disease stage, co-morbidity, risk factors, gender, age, ethnic group, specific	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants with sickle cell disease (all different genotypes). • Painful vaso-occlusive crisis severe enough to require narcotic analgesia.

Table 4. Research recommendations based on a gap in the evidence of the effects of low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease (Continued)

inclusion or exclusion criteria, clinical setting		Exclusion criteria
		<ul style="list-style-type: none"> • Contraindication to LMWH. • Pregnancy. • Low platelet counts (< 100,000/dl) or impaired haemostasis on admission in the form of INR > 1.4 or prolonged APTT > 5 seconds of the hospital normal range. • History of CVA. • Current aplasia. • Acute chest syndrome. • Exchange transfusion. • Sequestration. • Anticoagulant therapy for other etiology. • Patients with painful crises within the month before this admission. • Women on hormonal contraception. • History of painful crisis within the preceding month. • Other vascular complications of sickle cell disease (such as prior stroke, current aplasia, acute chest pain).
Intervention (I)	Type, frequency, dose, duration, prognostic factor	The study duration should be 1 - 2 weeks to assess a low-molecular-weight heparin. Concomitant pain medications allowed for ethical reasons but should be similarly available in both treatment arms.
Comparison (C)	Type, frequency, dose, duration, prognostic factor	No treatment or placebo treatment. Concomitant pain medications allowed for ethical reasons but should be similarly available in both treatment arms.
Outcome (O)	Which clinical or patient-related outcomes will the researcher need to measure, improve, influence, or accomplish? Which methods of measurement should be used?	<ul style="list-style-type: none"> • Pain: duration and intensity (assessed with a validated patient-reported outcomes instrument either generic or SCD specific). • Requirement for opiate treatment (dose, type and frequency). • Number of serious complications of SCD (e.g. stroke, acute chest syndrome, infection, acute splenic sequestration). • Number of other sickle-related events (e.g. priapism, leg ulceration). • Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire, either generic or SCD specific. • Hospitalisation (number and duration). • Participant satisfaction with the medication assessed by any appropriate and validated questionnaire (either generic or SCD specific). • Adverse events associated with the use of anticoagulants (e.g. bleeding).
Time stamp (T)	Date of literature search or recommendation	1 January 2013.
Study type	What is the most appropriate study design to address the proposed question?	<ul style="list-style-type: none"> • Randomised controlled trial (adequately powered / multi-centred). • Method: concealment of allocation sequence. • Blinding: blinding of participants, trialists and outcome assessors. • Setting: hospital / university.

APTT: activated partial thromboplastin time

CVA: cerebral vascular accident

INR: international normalized ratio

LMWH: low-molecular-weight heparins

RCT: randomised controlled trial

SCD: sickle cell disease

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Given this is no longer an active area of research, this review will no longer be regularly updated.

HISTORY

Protocol first published: Issue 10, 2012

Review first published: Issue 6, 2013

Date	Event	Description
26 November 2015	New citation required but conclusions have not changed	A new study has been added (Shah 2013). The plain language summary, abstract and main text of the review have been updated. An extra summary of findings table has been included.
26 November 2015	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register identified one new reference to a trial previously listed in 'Ongoing studies' (Shah 2013).
10 October 2012	Amended	A <i>post hoc</i> change has been made to the protocol to include all LMWHs rather than just one (tinzaparin) as previously included. This is to provide a more comprehensive review of this treatment area.

CONTRIBUTIONS OF AUTHORS

EvZ and ZF are responsible for the following:

- designing and co-ordinating the review (EVZ, ZF);
- co-ordinating the review (EvZ);
- organising the retrieval of papers (EvZ);
- writing to authors of papers for additional information (EvZ);
- screening search results (EvZ, ZF);
- screening retrieved papers against inclusion criteria (EvZ, ZF);
- appraising the quality of papers (EvZ, ZF);
- data collection for the review (EvZ, ZF);
- extracting data from papers (EvZ, ZF);
- obtaining and screening data on unpublished trials (EvZ);
- the analysis and interpretation of data (EvZ, ZF);

Both review authors contributed to development of the protocol.

ZF is the guarantor of the review.

DECLARATIONS OF INTEREST

No financial conflicts of interest have been reported, and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support, Bahrain
- No sources of support, Netherlands

External sources

- No sources of support, Netherlands
- No sources of support, Bahrain

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A *post hoc* change was made to the original protocol (before publication of the full review) to include all LMWHs rather than just one (tinzaparin), as was previously included. This was done in an effort to provide a more comprehensive review of this treatment area.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia, Sickle Cell [*complications]; Anticoagulants [*therapeutic use]; Dalteparin [*therapeutic use]; Heparin, Low-Molecular-Weight [*therapeutic use]; Pain Measurement; Peripheral Vascular Diseases [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Tinzaparin

MeSH check words

Humans