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Lewis SR, Butler AR, Brammar A, Nicholson A, Smith AF.
Perioperative fluid volume optimization following proximal femoral fracture.
Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD003004.
DOI: 10.1002/14651858.CD003004.pub4.

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[Intervention Review]

Perioperative fluid volume optimization following proximal femoral fracture

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Editorial group: Cochrane Anaesthesia, Critical and Emergency Care Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2016.
Review content assessed as up-to-date: 2 September 2015.

Citation: Lewis SR, Butler AR, Brammar A, Nicholson A, Smith AF. Perioperative fluid volume optimization following proximal femoral fracture. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD003004. DOI: 10.1002/14651858.CD003004.pub4.

ABSTRACT

Background

Proximal femoral fracture (PFF) is a common orthopaedic emergency that affects mainly elderly people at high risk of complications. Advanced methods for managing fluid therapy during treatment for PFF are available, but their role in reducing risk is unclear.

Objectives

To compare the safety and effectiveness of the following methods of perioperative fluid optimization in adult participants undergoing surgical repair of hip fracture: advanced invasive haemodynamic monitoring, such as transoesophageal Doppler and pulse contour analysis; a protocol using standard measures, such as blood pressure, urine output and central venous pressure; and usual care.

Comparisons of fluid types (e.g. crystalloid vs colloid) and other methods of optimizing oxygen delivery, such as blood product therapies and pharmacological treatment with inotropes and vasoactive drugs, are considered in other reviews.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 9*);* MEDLINE (October 2012 to September 2015); and EMBASE (October 2012 to September 2015) without language restrictions. We ran forward and backward citation searches on identified trials. We searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for unpublished trials. This is an updated version of a review published originally in 2004 and updated first in 2013 and again in 2015. Original searches were performed in October 2003 and October 2012.

Selection criteria

We included randomized controlled trials (RCTs) in adult participants undergoing surgical treatment for PFF that compared any two of advanced haemodynamic monitoring, protocols using standard measures or usual care, irrespective of blinding, language or publication status.

Data collection and analysis

Two review authors assessed the impact of fluid optimization interventions on outcomes of mortality, length of hospital stay, time to medical fitness, whether participants were able to return to pre-fracture accommodation at six months, participant mobility at six months and adverse events in-hospital. We pooled data using risk ratio (RR) or mean difference (MD) for dichotomous or continuous data, respectively, on the basis of random-effects models.

Main results

We included in this updated review five RCTs with a total of 403 participants, and we added two new trials identified during the 2015 search. One of the included studies was found to have a high risk of bias; no trial featured all pre-specified outcomes. We found two trials for which data are awaited for classification and one ongoing trial.

Three studies compared advanced haemodynamic monitoring with a protocol using standard measures; three compared advanced haemodynamic monitoring with usual care; and one compared a protocol using standard measures with usual care. Meta-analyses for the two advanced haemodynamic monitoring comparisons are consistent with both increased and decreased risk of mortality (RR Mantel-Haenszel (M-H) random-effects 0.41, 95% confidence interval (CI) 0.14 to 1.20; 280 participants; RR M-H random-effects 0.45, 95% CI 0.07 to 2.95; 213 participants, respectively). The study comparing a protocol with usual care found no difference between groups for this outcome.

Three studies comparing advanced haemodynamic monitoring with usual care reported data for length of stay and time to medical fitness. There was no statistically significant difference between groups for these outcomes in the two studies that we were able to combine (MD IV fixed 0.63, 95% CI -1.70 to 2.96); MD IV fixed 0.01, 95% CI -1.74 to 1.71, respectively) and no statistically significant difference in the third study. One study reported reduced time to medical fitness when comparing advanced haemodynamic monitoring with a protocol, and when comparing protocol monitoring with usual care.

The number of participants with one or more complications showed no statistically significant differences in each of the two advanced haemodynamic monitoring comparisons (RR M-H random-effects 0.83, 95% CI 0.59 to 1.17; 280 participants; RR M-H random-effects 0.72, 95% CI 0.40 to 1.31; 173 participants, respectively), nor any differences in the protocol and usual care comparison.

Only one study reported the number of participants able to return to normal accommodation after discharge with no statistically significant difference between groups.

There were few studies with a small number of participants, and by using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach, we judged the quality of the outcome evidence as low. We had included one study with a high risk of bias, but upon applying GRADE, we downgraded the quality of this outcome evidence to very low.

Authors' conclusions

Five studies including a total of 403 participants provided no evidence that fluid optimization strategies improve outcomes for participants undergoing surgery for PFF. Further research powered to test some of these outcomes is ongoing.

PLAIN LANGUAGE SUMMARY

Optimization of fluid levels in people suffering hip fractures

Background

Hip fractures are common among elderly people, who often have medical conditions that put them at risk of developing other problems whilst their fracture is treated. Treatment usually involves an operation to fix the break in the bone, and giving too much or too little fluid to a patient around this time may increase the risk of additional problems. Healthcare staff use many approaches to determine how much fluid a patient needs in this situation, but it is not clear whether some methods are better than others. For this Cochrane review, we looked at research on the effects of different methods of finding maximum effective fluid levels for adult men and women who undergo surgery for any type of hip fracture.

Study characteristics

Evidence is current to September 2015. We found five studies with 403 participants, each of which compared two or three methods of guiding fluid therapy. These methods include 'usual care' (whereby staff use changes in basic measurements, such as heart rate, to

decide for themselves how much fluid to give), 'protocols using standard measures' (whereby staff use changes in basic measurements when giving fluid according to a formal set of rules) and 'advanced haemodynamic monitoring' (whereby staff use invasive equipment, such as specialized blood pressure monitoring devices placed into arteries, to determine how much fluid to give).

Key results

These trials found no evidence to suggest that using one method instead of another reduces harm, including death, or decreases the number of complications. We found no evidence, when study results were combined, indicating that any method reduced length of hospital stay or time that participants were assessed as medically fit for discharge. Results also showed no difference in the number of participants able to return to normal accommodation after discharge.

Quality of evidence

We found few relevant studies with only a small number of participants. The time difference between the earliest study, published in 1985, and the latest study, published in 2014, suggests that standard practice for managing hip fracture may differ between these studies. We judged one study as having a high risk of bias, and we used the GRADE approach to assess evidence quality as low or very low. Results of the review are applicable only to countries in which the relevant studies were conducted, as 'usual care' may differ in other countries.

Conclusion

Current evidence is insufficient to show which method of finding maximum effective fluid levels in people undergoing hip fracture surgery is preferable.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Advanced haemodynamic monitoring compared with protocol using standard measures such as CVP for proximal femoral fracture

Patient or population: patients with proximal femoral fracture
Setting: hospital
Intervention: advanced haemodynamic monitoring
Comparison: protocol using standard measures such as CVP

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Protocol using standard measures such as CVP	Advanced haemodynamic monitoring				
All-cause mortality Advanced haemodynamic monitoring Follow-up: 30 days	**Study population**		**RR 0.41** (0.14 to 1.2)	280 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]	
	142 per 1000	**58 per 1000** (20 to 170)				
	Moderate					
Total length of hospital stay			Not estimable[d]	203 (2 studies)	⊕⊕◯◯ **Low**[c,d]	Data reported as median (range) in Bartha 2013 and as mean (95% confidence interval) in Venn 2002
Medically fit for discharge		Mean medically fit for discharge in the intervention groups was **7.7 higher** (5.9 to 0 higher)		90 (1 study)	⊕⊕◯◯ **Low**[e]	

Return to pre-fracture accommodation/ return to pre-fracture mobility			Not estimable	-	Not reported
Adverse outcomes - cardiopulmonary	**Study population**		Not estimable	0 (0)	
	Moderate				
Adverse outcomes - neurological			Not estimable	0 (0)	
Adverse outcomes - all	**Study population**		**RR 0.90** (0.37 to 2.18)	280 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]
	319 per 1000	**287 per 1000** (118 to 696)			
	Moderate				

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **CVP:** central venous pressure; **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.

[a] Concerns about randomization process in Schultz 1985; high risk of selection bias
[b] Confidence intervals cross no effect and are consistent with increased as well as decreased risk. Downgraded 1 level
[c] Estimate from few studies or from 1 study only. Downgraded 1 level

[d]Not possible to combine data. Wide confidence interval in Venn 2002 and wide range reported in Bartha 2013. Downgraded 1 level

[e]Data from 1 study only. Downgraded 2 levels

BACKGROUND

Description of the condition

Proximal femoral fractures (PFFs), or hip fractures, are fractures of the femur immediately distal to the articular surface of the hip joint to about 5 cm below the lesser trochanter. They can be subdivided into intracapsular and extracapsular fractures. Intracapsular (also termed *transcervical* or *subcapital*) fractures occur proximal to the trochanteric line, and extracapsular (also termed *pertrochanteric*, *subtrochanteric*, *trochanteric* or *intertrochanteric*) fractures occur distal to the trochanteric line, up to 5 cm below the lower border of the lesser trochanter.

These fractures occur most commonly in elderly people with osteoporosis after a simple mechanical fall. Approximately 1.5 million hip fractures are reported per year worldwide, and the number of hip fractures is projected to increase to 4.5 million by the year 2050 (Gullberg 1997; Sterling 2011). Incidence varies by country, from about 50 to 500 per 100,000, and is about two times higher among females than males, although this difference varies with race (Kanis 2012; Kannus 1996).

PFF is one of the most common orthopaedic emergencies, and most cases are managed by early surgical fixation to reduce complications from prolonged immobility associated with conservative treatment. Limited evidence has been obtained from randomized controlled trials (RCTs) to inform this practice, but other types of studies have shown increased risk of death when surgery is delayed; it would be difficult to conduct ethically sound trials that compare operative with conservative treatment (Bottle 2006; Handoll 2008). Generally, medically fit patients should undergo surgery within 24 hours.

Undisplaced intracapsular fractures usually are treated by internal fixation to preserve the femoral head, with screws or pins, with or without plates, fixed to the femur. Displaced intracapsular fractures may be reduced and internally fixated or may undergo replacement arthroplasty. Extracapsular fractures may be fixed with a screw passed up the femoral neck to the head,then attached to a plate on the side of the femur, or an intramedullary nail may be used with a side screw passed up into the femoral head.

Description of the intervention

Age-related co-morbidities and dehydration in people presenting with PFF put them at increased risk for peritraumatic and perioperative complications. Providing adequate fluid resuscitation is important in minimizing this risk. The adequacy of fluid therapy may be determined by simple, readily available clinical measures, such as tissue turgor, heart rate, blood pressure, urine output and central venous pressure (CVP). However, these are non-specific and poorly sensitive measures of fluid optimization (Marik 2008). Growing evidence suggests that predicting responsiveness to fluid therapy is more important (Funk 2009). The aim is to use goal-directed fluid therapy to optimize cardiac output, to avoid overloading the cardiovascular system and precipitating heart failure. This approach, along with adequate haemoglobin and inspired oxygen levels, optimizes delivery of oxygen to tissues and organs and may improve outcomes (Green 2010).

One way to assess fluid responsiveness is to use a protocol that combines several simple measures to determine the effect of a standardized fluid bolus and to decide whether additional fluid will provide benefit for the patient. Another method is to use advanced haemodynamic monitoring techniques to detect cardiovascular changes that occur with incremental fluid boluses, to predict responsiveness to increased fluid. Although some of these advanced techniques are in their infancy, several have become established in clinical practice. These approaches can be split into static measures of cardiac preload (load placed on the heart by blood returning to it) and dynamic measures of interactions between heart and lung. Static measures aim to determine cardiac preload but fail to estimate response to fluids in about one-half of patients, thus rendering them exposed to the hazards of unnecessary fluid therapy (Eyre 2010). Despite this, many of these measures are in clinical use. Right ventricular end-diastolic volume can be measured by a fast-response thermistor pulmonary artery catheter or by cardiac scintigraphy. Transoesophageal echocardiography (TOE) can measure left ventricular (LV) end-diastolic area, which correlates well with left ventricular end-diastolic volume - a measure of LV preload. Transpulmonary thermodilution measured by a commercially available device (PiCCO; Pulsion Medical Systems, Feldkirchen, Germany) assesses global end-diastolic volume (GEDV), the largest volume of blood contained within the four heart chambers, and intrathoracic blood volume; both measurements have been validated as indicators of cardiac preload (Bendjelid 2010; Muller 2008). Pulmonary artery (Swan-Ganz) catheters are inserted into the pulmonary artery to measure pulmonary artery occlusion pressure (PAOP); however, their use has been reduced over recent years, as PAOP has been shown to be a poor marker of left ventricular end-diastolic volume, and therefore of cardiac preload and cardiac output (Maus 2008).

Dynamic measures are generally superior to static measures in predicting fluid responsiveness, although this has been demonstrated mainly in sedated ventilated patients (Eyre 2010). Various technologies use these measures, which include stroke volume variation (SVV), systolic pressure variation (SPV), pulse pressure variation (PPV), aortic blood velocity (ABV), superior vena cava collapsibility index (SVCCI) and inferior vena cava distensibility index (IVCDI). The commercially available LiDCO device (Vigileo/FloTrac, Irvine, California, USA) analyses the waveform of the arterial blood pressure pulse for SVV, SPV and PPV; transthoracic echocardiography (TTE) measures IVCDI; oesophageal Doppler measures SVV and ABV; TOE can measure SVCCI and ABV; and PiCCO can measure SVV. LiDCO and TTE can be used with patients who are awake when undergoing regional anaesthesia, and

with those who are unconscious when undergoing general anaesthesia. Oesophageal Doppler and TOE can be used only with patients who are undergoing general anaesthesia.

How the intervention might work

Major surgery and critical illness are associated with increased oxygen demand due to a systemic inflammatory response, the stress response and increased metabolic activity. Inadequate fluid resuscitation and cardiopulmonary disease may reduce the supply of adequate tissue blood flow and delivery of oxygen. This may result in cellular dysfunction, organ damage, organ failure and ultimately death. Fluid overload is also harmful, potentially causing cardiac performance to fall as the result of extreme right shift on the Starling myocardial performance curve, respiratory failure due to fluid accumulation in the lungs, gastric dysmotility and poor wound healing. Growing evidence indicates that standardized methods to optimize fluid and oxygen delivery to tissues may decrease morbidity and mortality in a variety of clinical settings, particularly among high-risk surgical patients and those with critical illness or sepsis (Lees 2009).

Why it is important to do this review

Protocols, or advanced methods of managing fluid therapy, may improve various outcomes in the large number of people who suffer from PFF each year. However, these methods may cause harm and may incur financial cost. A systematic evaluation of the current evidence is needed to assist clinicians who attempt to optimize fluid volume status in people undergoing surgery for PFF. We selected our included outcomes according to their frequency in studies of PFF and their usefulness in clinical decision making (Liem 2012).

This is the second update of a Cochrane review originally published in 2004 (Price 2004) and first updated in 2013 (Brammar 2013). New monitoring techniques and revised methods have been introduced within Cochrane; therefore, we have re-run the searches, including extra search terms, and have used different methods to assess study quality.

OBJECTIVES

To compare the safety and effectiveness of the following methods of perioperative fluid optimization in adult participants undergoing surgical repair of hip fracture: advanced invasive haemodynamic monitoring, such as transoesophageal Doppler and pulse contour analysis; a protocol using standard measures, such as blood pressure, urine output and central venous pressure; and usual care.

Comparisons of fluid types (e.g. crystalloid vs colloid) and other methods of optimizing oxygen delivery, such as blood product therapies and pharmacological treatment with inotropes and vasoactive drugs, are considered in other reviews.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs). If we could have obtained adequate method and results data, we would have considered for inclusion cluster-randomized trials, quasi-randomized trials (e.g. alternation) and trials in which treatment allocation was inadequately concealed, as well as unpublished studies and studies published only in abstract form. We did not expect to identify any cross-over trials for this condition.

Types of participants

We included studies on adults who underwent acute surgical treatment of any type for PFF while under regional or general anaesthesia.

Types of interventions

We included studies that compared use of any two of the following.

- Advanced invasive haemodynamic monitoring, such as transoesophageal Doppler and pulse contour analysis.
- A protocol using standard measures, such as blood pressure, urine output and central venous pressure.
- Usual care.

We undertook reviews of three different comparisons.

- Advanced haemodynamic monitoring versus a protocol using standard measures.
- Advanced haemodynamic monitoring versus usual care.
- A protocol using standard measures versus usual care.

Types of outcome measures

Primary outcomes

- All-cause mortality (within 30 days if reported, otherwise as reported in the trial).
- Length of hospital stay.
    - Total length of hospital stay.
    - Time to medical fitness for discharge.

- Return of participant to pre-fracture category of accommodation at six months.
- Return to pre-fracture mobility at six months.

Secondary outcomes

- Major adverse events in hospital.
    - Iatrogenic (related to intervention, e.g. pneumothorax, haemothorax, upper limb thrombosis, line sepsis, local haematoma).
    - Cardiopulmonary (e.g. myocardial infarction, cardiac or respiratory failure, thromboembolic event).
    - Neurological (e.g. delirium, postoperative cognitive dysfunction, cerebrovascular accident).

We also recorded any complications reported in the study, including minor events.
Outcomes did not form part of the study eligibility assessment. We included in the review studies that met design, participant and intervention criteria, even if they did not report relevant outcomes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 9; see Appendix 1); MEDLINE via Ovid SP (October 2012 to September 2015; see Appendix 2); and EMBASE via Ovid SP (October 2012 to September 2015; see Appendix 3) for relevant randomized trials published in any language. When searching MEDLINE, we combined our topic-specific keywords with the Cochrane highly sensitive search strategy for identifying RCTs (Higgins 2011). We modified this filter for use in EMBASE and used specific keywords to identify potential studies (see Appendix 1; Appendix 2; Appendix 3).
We performed original searches for the review in October 2003 (Price 2004) and October 2012 (Brammar 2013).
We searched for ongoing clinical trials and unpublished studies on the following Internet sites (July 2015).

- ClinicalTrials.gov trials registry (see Appendix 4).
- World Health Organization International Clinical Trials Registry Platform (see Appendix 5).

Searching other resources

We undertook backward and forward citation searching for key review articles identified through the initial searches (see Appendix 6). We used Google Scholar for forward citation searching. We read the reference lists of included articles for backward citations. We contacted investigators to ask for details of ongoing studies and to request unpublished data needed for our analyses.

Data collection and analysis

Selection of studies

Two review authors, Sharon R. Lewis (SRL) and Andrew R. Butler (ARB), independently screened all titles and abstracts identified by the searches for potentially eligible trials. We removed studies that were very unlikely to be eligible. If no abstract was available but the title was possibly relevant, we obtained the full text of the article. The same review authors then independently examined the full text of all remaining articles and made a joint decision at that time regarding inclusion.

Data extraction and management

Review authors SRL and ARB independently extracted and collected data using Covidence software (Covidence) based on the previously used data extraction form (see Appendix 7). No blinding of the study author, the institution or the publication source of the studies was performed. We resolved disagreements by discussion and consensus, and finally with involvement of a third review author (AFS).

Assessment of risk of bias in included studies

Review authors independently assessed risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011a). We assessed the following six domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting.
We considered blinding and incomplete outcome data separately for each outcome. Blinding of participants was of particular importance for patient-reported outcomes such as mobility. Blinding of assessors was particularly important for outcomes such as cognitive function that may be prone to detection bias.

Measures of treatment effect

For dichotomous outcomes (e.g. mortality, adverse outcomes), we entered numbers of events and total number within each randomization group into RevMan 5.3 (RevMan 5.3) and calculated risk ratios (RRs) with 95% confidence intervals (CIs) to express effect size. If data were presented in other forms, such as hazard or odds ratios, and if we were unable to obtain the required tabular data from study authors, we planned to enter these and to use the generic inverse variance option in RevMan 5.3. For continuous measures, such as length of stay, we calculated weighted mean differences when means and standard deviations were available. We calculated standard deviations from 95% CIs using the methods described in Higgins 2011 (Section 7.7.3.2).

Unit of analysis issues

In studies in which participants were randomly assigned to multiple intervention groups, we performed each pair-wise comparison separately. We did not combine multiple intervention groups in the same analysis.

Dealing with missing data

We attempted to contact the first author or the contact person for each trial with missing data before making a decision about trial eligibility.

Assessment of heterogeneity

Identified trials may not have been carried out according to common protocols, thus introducing differences in participant groups, clinical settings, concomitant care, etc. Important potential sources of heterogeneity include participant characteristics, differences in control or intervention protocols and duration of perioperative fluid optimization.
We described heterogeneity between studies on the basis of participant group, setting and type of intervention. We assessed this statistically when data allowed, using the Chi^2 test and the I^2 statistic. We investigated important heterogeneity (Chi^2 result with a P value < 0.1 and I^2 statistic > 50%), when possible, by conducting subgroup analyses and performing meta-regression.

Assessment of reporting biases

Reporting bias may occur within studies, with certain outcomes not reported. When a report or the original protocol suggested that data on an outcome were collected but were not reported in the paper, we would have contacted study authors to request the data.
If an adequate number of trials had been identified for inclusion, we would have constructed funnel plots and examined them visually to assess the presence of publication bias; we would have used Egger's test to look for asymmetry.

Data synthesis

We attempted meta-analysis for outcomes for which we had comparable effect measures from more than one study and when measures of heterogeneity indicated that pooling of results was appropriate. A value of I^2 statistic > 80% would argue against presentation of an overall estimate. When we had identified sufficient studies to allow combination of results, differences between studies related to duration and methods of fluid optimization and participant characteristics were likely to suggest that random-effects models would be the most suitable choice. We used Mantel-Haenszel models when possible for dichotomous outcomes.

Subgroup analysis and investigation of heterogeneity

If data were sufficient, we investigated the following subgroups, which may account for heterogeneity between studies.

- Duration of monitoring and protocol use.
- Timing of outcome measurement. If the timing of outcome measures varied between studies, we analysed the outcome only in a subgroup analysis.

We assessed any differences in effect size between subgroups in RevMan by using I^2 statistical estimates (Higgins 2011).

Sensitivity analysis

When possible, we performed the following sensitivity analyses.

- Re-analysis excluding studies with a high risk of bias.
- Re-analysis excluding unpublished studies.

'Summary of findings' table

We used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) (Guyatt 2008) to assess the quality of the body of evidence associated with the specific outcomes in our review.

- All-cause mortality.
- Length of hospital stay and time to medical fitness for discharge.
- Return to pre-fracture category of accommodation at six months.
- Return to pre-fracture mobility at six months.
- Major adverse events in hospital.

We constructed a 'Summary of findings' table by using GRADE software (gradepro.org). The GRADE approach appraises the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item assessed. The quality of a body of evidence is based on within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

RESULTS

Description of studies

Results of the search

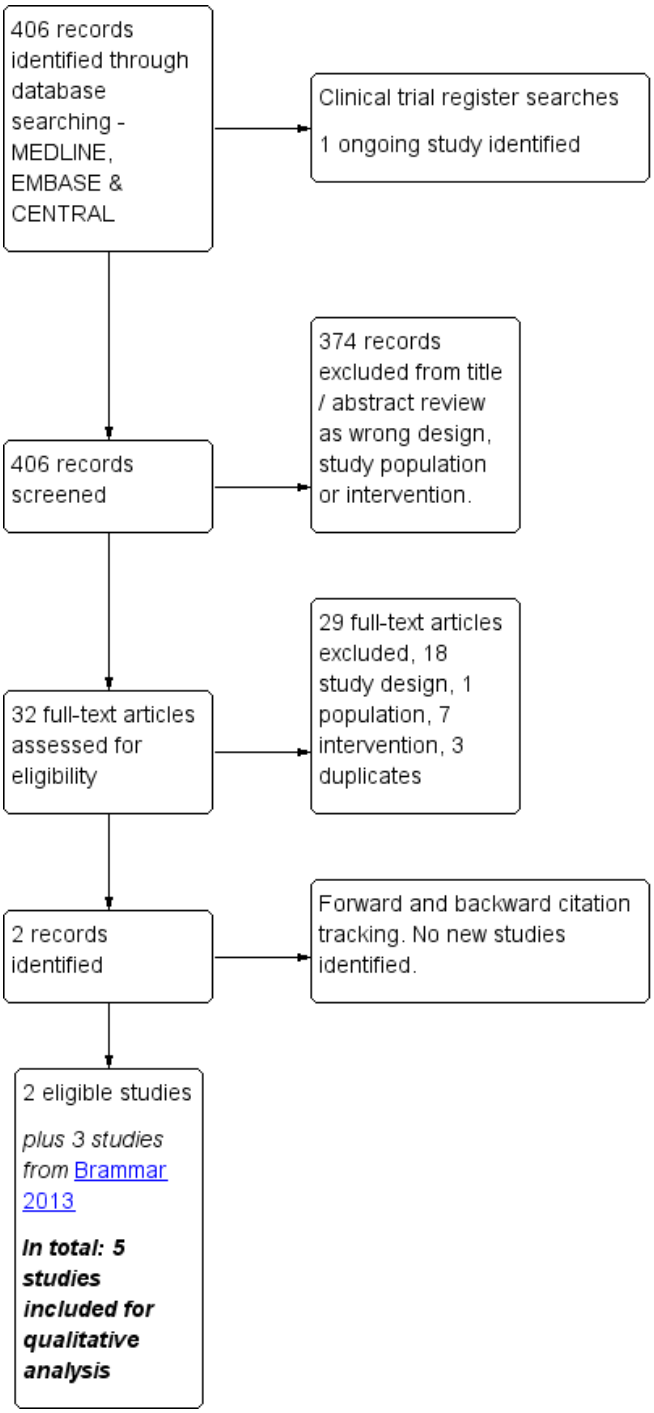
See Characteristics of included studies; Characteristics of ongoing studies; Characteristics of studies awaiting classification.
We identified 406 records through electronic database searches conducted for the 2015 update. Upon completion of these

searches, we included two new studies (Bartha 2013; Moppett 2014) in addition to the three studies included in the previous review update (Brammar 2013); (Schultz 1985; Sinclair 1997; Venn 2002).

We did not identify additional studies for backward citation searching during the 2015 search process. We completed backward citation searching and forward citation searching on the two new studies but identified no additional studies. We searched clinical trials databases using the strategies presented in Appendix 4 and Appendix 5.

See search flow results in Figure 1.

Figure 1. Study flow diagram. Updated search October 2012 to January 2015.



Included studies

We included five studies with 403 randomized participants.
Three trials were conducted in the UK (Moppett 2014; Sinclair 1997; Venn 2002), one in the USA (Schultz 1985) and one in Sweden (Bartha 2013). All provided full-text publications in the English language. The interval between the first trial and the last trial was approximately 29 years.
All trials included solely adult participants who were undergoing surgery for PFF. Ages of participants ranged from 40 to 102 years. Participants in Bartha 2013 and Moppett 2014 underwent spinal anaesthesia, and those in Sinclair 1997 and Venn 2002 underwent general anaesthesia. Schultz 1985 did not explicitly state the type of anaesthesia, although from the year of this study, we assumed that the clinicians used general anaesthesia. Surgical techniques used to treat PFF included dynamic hip screw, arthroplasty and AO cannulated screws.
Each trial performed different comparisons: goal-directed haemodynamic treatment (with LiDCO monitor) versus routine fluid treatment based on a treatment algorithm (Bartha 2013); LiDCO monitor-guided fluid therapy versus standard care (Moppett 2014); Swan-Ganz monitoring versus CVP monitoring (Schultz 1985); oesophageal Doppler monitoring versus conventional fluid management (Sinclair 1997); and oesophageal Doppler monitoring versus CVP monitoring versus conventional fluid management (Venn 2002). These trial comparisons correspond to the following comparisons in our review: advanced haemodynamic monitoring (LiDCO, Swan-Ganz, oesophageal Doppler); a protocol using standard measures (CVP monitoring, routine fluid treatment with treatment algorithm); and usual care (standard care, conventional fluid management). Three trials studied only intraoperative fluid optimization (Moppett 2014; Sinclair 1997; Venn 2002); one trial studied intraoperative and postoperative fluid optimization (Bartha 2013); and one trial studied preoperative, intraoperative and postoperative fluid optimization (Schultz 1985).
All trials investigated mortality, although at different time points: at 30 days (Bartha 2013; Moppett 2014), undefined "postoperative" (Schultz 1985) and in-hospital (Sinclair 1997; Venn 2002). We excluded in-hospital deaths that occurred more than 30 days postoperatively (Sinclair 1997). On the basis of total hospital stays and ranges reported in Venn 2002, we assumed that all deaths and adverse events in this trial occurred within 30 days of operation. Four trials compared total length of hospital stay (Bartha 2013; Moppett 2014; Sinclair 1997; Venn 2002) and three compared time until medically fit for discharge (Moppett 2014; Sinclair 1997; Venn 2002). One study reported return to pre-fracture accommodation at six months (Moppett 2014). Across studies, a variety of adverse events were reported, including:

- cardiovascular (Bartha 2013; Moppett 2014);
- respiratory (Bartha 2013; Moppett 2014);
- cerebrovascular (Bartha 2013; Venn 2002);
- acute kidney failure (Bartha 2013; Moppett 2014);
- gastrointestinal bleeding (Bartha 2013; Moppett 2014);
- confusion/delirium (Bartha 2013; Moppett 2014);
- sepsis (Bartha 2013);
- deep vein thrombosis (Bartha 2013);
- wound infection (Bartha 2013; Schultz 1985; Venn 2002);
- decubitus (Bartha 2013; Schultz 1985);
- wound haematoma (Bartha 2013);
- abdominal complications (Moppett 2014);
- skin complications (Moppett 2014);
- pneumonia (Schultz 1985);
- dislocated prosthesis (Schultz 1985);
- pneumonitis (Schultz 1985);
- deep haemorrhage (Venn 2002);
- haematemesis (Venn 2002);
- chest infection (Venn 2002);
- urinary tract infection (Venn 2002);
- cellulitis (Venn 2002);
- pancreatitis (Venn 2002);
- pulmonary embolus (Venn 2002);
- myocardial infarction (Venn 2002);
- cardiac failure (Venn 2002);
- rapid atrial fibrillation (Venn 2002);
- hypotension (Venn 2002);
- impaired renal function (Venn 2002); and
- pseudo-obstruction (Venn 2002).

No studies reported return to pre-fracture mobility at six months.

Ongoing studies

We identified one ongoing study from clinical trial registers (NCT02382185). This study compares a non-invasive cardiac monitoring device with usual care and plans to enrol 250 participants. See Characteristics of ongoing studies.

Studies awaiting classification

Two studies are awaiting classification. One study includes a mixed high-risk surgical population; we have been unable to contact the study authors to request adequate data about participants within the orthopaedic group who were treated for PFF (Sandham 2003). One study appears to be eligible but provided only an abstract with insufficient data. We have not been able to make contact with study authors and await publication of the full report (Vanakas 2012). See Characteristics of studies awaiting classification.

Excluded studies

We excluded 28 full-text articles identified for further assessment in the 2015 update (see Figure 1). These articles provided the wrong intervention, included the wrong study population or were not RCTs. We have described in the Characteristics of excluded studies table three RCTs that were excluded in the 2015 update because of incorrect intervention or participant group, along with eight RCTs that were excluded in previous versions of this review.

Risk of bias in included studies

We have presented the various bias domains in the 'Risk of bias' graph and in a 'Risk of bias' summary figure. We evaluated risk of bias on the basis of major sources of bias (domains), as described above. For a more detailed description of individual trial qualities, see Characteristics of included studies (see Figure 2 and Figure 3).

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

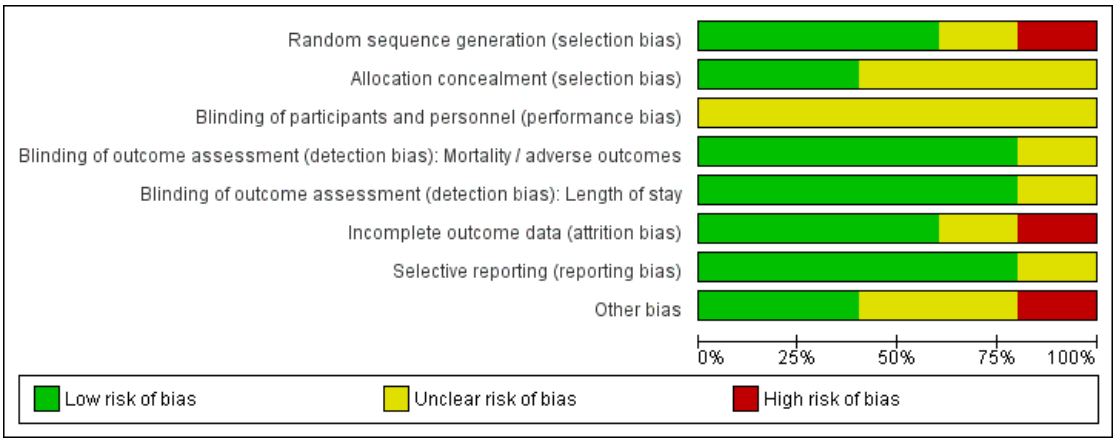


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Three studies adequately reported methods used for random sequence generation (Bartha 2013; Moppett 2014; Venn 2002), and two studies inadequately reported these methods (Schultz 1985; Sinclair 1997). We found baseline differences in Schultz 1985, which suggested that the randomization process may not have been adequate. Therefore, we judged this study to be at a high risk of bias. Bartha 2013 and Moppett 2014 adequately accounted for allocation concealment with the use of external allocation methods, but this information was not reported in Schultz 1985, Sinclair 1997 or Venn 2002.

Blinding

Defining adequate blinding in trials of fluid optimization was challenging. Given the different monitoring techniques described, it was not possible to effectively blind the anaesthetist/clinician. Three trials addressed this by ensuring that the anaesthetist was blinded to measurements from the Doppler and LiDCO monitors in the control groups (Bartha 2013; Moppett 2014; Sinclair 1997); however, anaesthetists remained aware of group allocation, and we were unclear about whether this may have affected their performance. Therefore, we judged all trials to be at unclear risk of performance bias.

Three studies had made adequate attempts to blind nursing personnel and/or those collecting outcome data to reduce risk of detection bias (Moppett 2014; Sinclair 1997; Venn 2002). Although data on the LiDCO monitor were coded, personnel collecting relevant outcome data for the review outcomes were not blinded in Bartha 2013, and we judged this study to be at a high risk of detection bias. Venn 2002 reported no details of data collection.

Incomplete outcome data

Two trials reported complete follow-up for mortality, morbidity, adverse events and length of stay (Sinclair 1997; Venn 2002). One trial provided no information about exclusions due to deviations from protocol (Schultz 1985) but reported no participants lost to follow-up. One study (Moppett 2014) reported a high number of losses (12%), and although study authors provided explanations, we considered this number of losses to have a potential influence on effect estimates. Bartha 2013 explained losses similarly but described fewer losses.Both Bartha 2013 and Venn 2002 performed intention-to-treat (ITT) analysis on lost data.

Selective reporting

Both Bartha 2013 and Moppett 2014 were registered with clinical trials registers, and we were able to compare protocols against published study reports. Moppett 2014 had also published a protocol in an open access journal (Wiles 2011). Bartha 2013 reported all outcomes relevant to this review, and we judged this study to be at low risk of bias; however, some long-term outcomes on health-related quality of life were reported in an interim publication but not in the full study publication. Similarly, we found that Moppett 2014 reported the outcomes relevant to this review, although study authors did not report data on cost of care nor on changes in the way the heart and blood vessels work with spinal anaesthesia. We judged both of these studies as having low risk of bias.

The remaining three trials were not registered, and we were unable to source any published protocols for them. Two of these trials reported all expected outcomes in their Methods section (Sinclair 1997; Venn 2002). One trial provided inadequate information about expected outcomes; therefore, we assessed the risk of selective reporting as unclear (Schultz 1985).

Some of our analyses were subject to limitations because length of stay data were published in graphical form without adequate corresponding numerical data. One trial did not provide details on length of follow-up in terms of mortality but provided sufficient data for analysis (Sinclair 1997); data regarding morbidity and adverse events were adequate in all studies.

Other potential sources of bias

Three studies received funding that appeared to be independent and unlikely to influence the results (Bartha 2013; Moppett 2014; Sinclair 1997). Four trials reported sample size calculations (Bartha 2013; Moppett 2014; Sinclair 1997; Venn 2002). One trial was stopped early because of difficulty in recruiting participants (Bartha 2013). Trials were too few to permit construction of funnel plots to facilitate assessment of publication bias, or to allow performance of Egger's test for asymmetry.

Analyses of the benefits of fluid optimization in this group of participants were limited by differences in study design. Three trials involved intraoperative optimization (Moppett 2014; Sinclair 1997; Venn 2002). One involved both intraoperative and postoperative optimization (Bartha 2013), and one involved preoperative, intraoperative and postoperative optimization (Schultz 1985). We noted differences between trials in outcome definitions, in time points for mortality and length of stay reporting and in types of adverse events reported. In addition, all trials involved relatively few participants.

Effects of interventions

See: **Summary of findings for the main comparison** Advanced haemodynamic monitoring compared with protocol using standard measures such as CVP for proximal femoral fracture; **Summary of findings 2** Advanced haemodynamic monitoring compared with usual care for perioperative fluid optimization;

Summary of findings 3 Protocol using standard measures such as CVP compared with usual care for perioperative fluid optimization
See also Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3.

Comparison 1. Advanced haemodynamic monitoring versus protocol using standard measures

All-cause mortality

Three trials reported mortality (Bartha 2013; Schultz 1985; Venn 2002). For one study, the follow-up period was unclear but was reported as "postoperative" (Schultz 1985). This trial showed a significant reduction in mortality (risk ratio (RR) 0.1, 95% confidence interval (CI) 0.01 to 0.74; 70 participants); however, we had serious concerns about its quality. In Venn 2002, the time frame for death was described as within hospital and results were consistent with both increased and decreased risk of mortality in the intervention group (RR 0.52, 95% CI 0.14 to 1.88; 61 participants). In Bartha 2013, the time frame for death was within 30 days, and again results were consistent with both increased and decreased risk of mortality in the intervention group (RR Mantel-Haenszel (M-H) random-effects 0.76, 95% CI 0.18 to 3.28; 149 participants). See Analysis 1.1 for pooled data that showed no statistically significant differences between groups (RR M-H random-effects 0.41, 95% CI 0.14 to 1.20; 280 participants). Using GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group), we downgraded the quality of this evidence to very low, as few studies were identified by which we could judge precision and we noted a high level of bias in Schultz 1985 and some inconsistency in the study results (see Summary of findings for the main comparison).

Length of hospital stay

Total length of hospital stay

Two trials reported length of hospital stay (Bartha 2013; Venn 2002) by providing data as median and interquartile range (Bartha 2013) and as mean and 95% CI (Venn 2002). Therefore, it was not possible for review authors to pool these data. Bartha 2013 (149 participants) reported median length of hospital stay as nine (range, three to 20) days in the advanced haemodynamic monitoring group and as 10 (range one to 38) days in the protocol group. Venn 2002 (61 participants) reported mean length of hospital stay as 13.5 (95% CI 10.9 to 17.5) days in the advanced haemodynamic monitoring group and as 13.3 (95% CI 10.3 to 19.2) days in the protocol group. Study authors did not report these data as statistically significant. Using GRADE, we downgraded the quality of this evidence to low, as studies were few and both studies reported a wide range and confidence interval (see Summary of findings for the main comparison).

Time to medical fitness for discharge

Venn 2002 also reported time to medical fitness as mean 7.8 (95% CI 5.9 to 12.3) days in the advanced haemodynamic monitoring group and 10.0 (95% CI 8.1 to 12.0) days in the protocol group. Study authors reported this finding as statistically significant (P value = 0.035). No other study reported this outcome. We also downgraded the quality of this evidence to low because data were available for only one study (see Summary of findings for the main comparison).

Return of participant to pre-fracture category of accommodation at six months; return to pre-fracture mobility at six months

No trial reported data for these outcomes.

Major adverse events in-hospital

Three trials investigated complications, reporting overall morbidity and cardiovascular or neurological outcomes; however, iatrogenic events were not reported clearly by intervention/control groups (Bartha 2013; Schultz 1985; Venn 2002), and cardiovascular and neurological events were reported in such a way that it was not clear whether participants had experienced more than one event. These results are presented in Table 1. We combined the numbers of participants with one or more complication in Analysis 1.2, which shows no statistically significant differences between the advanced haemodynamic monitoring group and those using a protocol (RR M-H random-effects 0.83, 95% CI 0.59 to 1.17; 280 participants). Using GRADE, we downgraded the quality of this evidence to very low, as again studies were too few to allow us to judge precision, level of bias in Schultz 1985 was high and results showed some inconsistency (see Summary of findings for the main comparison).

Comparison 2. Advanced haemodynamic monitoring versus usual care

All-cause mortality

Two trials reported in-hospital mortality (Sinclair 1997; Venn 2002), and one trial reported mortality at 30 days (Moppett 2014). We excluded two deaths from Sinclair 1997 - one each from the intervention and control groups - as they occurred more than 30 days postoperatively. Pooled results are consistent with both increased and decreased risks of mortality in participants who received advanced haemodynamic monitoring (RR M-H random-effects 0.45, 95% CI 0.07 to 2.95; 213 participants). See Analysis

2.1. Using GRADE, we downgraded the quality of this evidence to low, as studies were few (see Summary of findings 2).

Length of hospital stay

Total length of hospital stay

Three trials investigated total length of hospital stay (Moppett 2014; Sinclair 1997; Venn 2002). In Moppett 2014 (114 participants), the total mean length of stay was 15.3 (95% CI 13.8 to 17.2) days in the intervention group and 14.2 (95% CI 12.9 to 15.8) days in the usual care group.

For Venn 2002 (59 participants), we used the RevMan calculator to determine the mean difference between groups for length of hospital stay. We found no significant difference between the advanced haemodynamic monitoring group and the usual care group (4.00 days shorter, 95% CI 11.65 days shorter to 3.65 days longer). This result differs from previously reported in Brammar 2013 (see Differences between protocol and review).

We carried out meta-analysis on these two studies, using the RevMan calculator to calculate standard deviations. Results showed no difference between groups for overall length of hospital stay (MD IV fixed 0.63, 95% CI -1.70 to 2.96). See Analysis 2.2.

Sinclair 1997 (40 participants) provided data in the form of median and interquartile ranges, which were not suitable for inclusion in a meta-analysis, but reported a reduction of eight days in total hospital stay (from 20 to 12); study authors reported a significant difference at P value < 0.05 (Mann-Whitney U test). Using GRADE, we downgraded the quality of this evidence to low, as studies were few (see Summary of findings 2).

Time to medical fitness for discharge

Three trials investigated time to medical fitness for discharge (Moppett 2014; Sinclair 1997; Venn 2002). Moppett 2014 (114 participants) reported no difference between groups in time to medical fitness for discharge, with a mean of 13.1 (95% CI 11.9 to 14.5) days in the intervention group and 12.2 (95% CI 11.1 to 13.5) days in the usual care group. Venn 2002 (59 participants) described a reduction in time to medical fitness for discharge in the advanced haemodynamic group (6.20 days shorter, 95% CI 11.01 to 1.39 days shorter).

We carried out meta-analysis on these two studies, using the RevMan calculator to calculate standard deviations. Results showed no differences between groups in the number of days needed for participants to be medically fit for discharge (MD IV fixed 0.01, 95% CI -1.74 to 1.71). See Analysis 2.3. We noted a high level of statistical heterogeneity for this effect estimate (I^2 = 86%).

Sinclair 1997 (40 participants) provided data in the form of medians and interquartile ranges, which were not suitable for inclusion in a meta-analysis, but reported a reduction of five days in median time to fitness for discharge (from 15 days to 10 days); study authors reported a significant difference at P value < 0.05 (Mann-Whitney U test). Using GRADE, we downgraded the quality of this evidence to low, as studies were few (see Summary of findings 2).

Return of participant to pre-fracture category of accommodation at six months; return to pre-fracture mobility at six months

Moppett 2014 reported on the number of participants returning to their normal accommodation after discharge. They noted no statistically significant difference between groups, with 23 of 51 in the group monitored with LiDCO and 25 of 63 in the group receiving usual care. Using GRADE, we downgraded the quality of this evidence to low, as we identified only one study (see Summary of findings 2).

Major adverse events in hospital

Two trials (Moppett 2014; Venn 2002) reported these. Moppett 2014 reported two types of cardiopulmonary complications, and Venn 2002 reported three types. However, these results were not reported by participant; therefore, overall denominator figures were unclear. These results, along with all reported complications, are presented in Table 2. We combined neurological outcomes in Analysis 2.4, including the number of participants having acute delirium in Moppett 2014 and the number having a cerebrovascular accident in Venn 2002. The data for the number of participants developing one or more complications was combined in Analysis 2.4, noting no statistically significant differences between those receiving advanced haemodynamic monitoring and control groups (M-H RR random-effects 0.72, 95% CI 0.40 to 1.31; 173 participants). Using GRADE, we downgraded the quality of this evidence to low, as studies were few (see Summary of findings 2).

Comparison 3. Protocol using standard measures versus usual care

All-cause mortality

Only one trial reported on this outcome (Venn 2002) and found no difference in mortality between participants who received care according to the protocol and those given standard care (RR 2.81, 95% CI 0.61 to 12.81; 60 participants). See Table 3.

Length of hospital stay

Total length of hospital stay and Time to medical fitness for discharge

One trial reported a reduction in time to medical fitness (3.9 days shorter, 95% CI 7.05 to 0.75 days shorter; 60 participants) but not in total hospital stay (4.2 days shorter, 95% CI 11.0 days shorter to 2.60 days longer; 60 participants) (Venn 2002; see Table 3).

Return of participant to pre-fracture category of accommodation at six months; return to pre-fracture mobility at six months

No trial reported data for these outcomes.

Major adverse events in hospital

Only one trial reported these, and results were consistent with increased and decreased risk in participants who had received care according to a protocol for neurological events (RR 0.94, 95% CI 0.06 to 14.27; 60 participants) and for all complications (RR 0.53, 95% CI 0.26 to 1.08; 60 participants) (Venn 2002; see Table 3).

Subgroup and sensitivity analyses

No more than three studies were available for inclusion in any of the comparison groups, and it was not possible to perform meaningful subgroup analyses.

We were particularly concerned about the high risk of bias assessed for Schultz 1985. We removed this study from Analysis 1.1 and Analysis 1.2, with no effect on the results.

We obtained no unpublished data; therefore, it was not possible to carry out this sensitivity analysis.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Advanced haemodynamic monitoring compared with usual care for perioperative fluid optimization

Patient or population: patients with perioperative fluid optimization
Settings: hospital
Intervention: advanced haemodynamic monitoring
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Advanced haemodynamic monitoring				
All-cause mortality	Study population		RR 0.45 (0.07 to 2.95)	213 (3 studies)	⊕⊕◯◯ **Low**[a,b]	
	89 per 1000	40 per 1000 (6 to 263)				
	Moderate					
Total length of hospital stay	Mean total length of hospital stay in the control groups was **number of days**	Mean total length of hospital stay in the intervention groups was **0.63 higher** (1.7 lower to 2.96 higher)		175 (2 studies[c])	⊕⊕◯◯ **Low**[a,b]	
Medically fit for discharge	Mean medically fit for discharge in the control groups was **number of days**	Mean medically fit for discharge in the intervention groups was **0.01 higher** (1.74 lower to 1.71		175 (2 studies[d])	⊕⊕◯◯ **Low**[a,b]	

		higher)			
Return to pre-fracture accommodation/ return to pre-fracture mobility	**Study population**		Not estimable	114 (1 study)	⊕⊕◯◯ **Low**[b]
	397 per 1000	**0 per 1000** (0 to 0)			
	Moderate				
Adverse outcomes - cardiopulmonary	**Study population**		Not estimable	0 (0)	
	Moderate				
Adverse outcomes - neurological	**Study population**		**RR 1.10** (0.56 to 2.18)	173 (2 studies)	⊕⊕◯◯ **Low**[a,b]
	152 per 1000	**170 per 1000** (1000 to 336)			
	Moderate				
Adverse outcomes - all	**Study population**		**RR 0.78** (0.57 to 1.05)	173 (2 studies)	⊕⊕◯◯ **Low**[a,b]
	554 per 1000	**432 per 1000** (316 to 582)			
	Moderate				

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) 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

[a] Confidence intervals cross no effect and are consistent with increased as well as decreased risk. Downgraded 1 level
[b] Estimate from only 1 or a few studies. Downgraded 1 level
[c] Data for Sinclair 1997 not included in meta-analysis. Study authors report a reduction of 8 days in total hospital stay (from 20 to 12) in the advanced haemodynamic group (P value < 0.05)
[d] Data for Sinclair 1997 not included in meta-analysis. Study authors report a reduction of 5 days in median time to fitness for discharge (from 15 to 10 days)

Protocol using standard measures such as CVP compared with usual care for perioperative fluid optimization

Patient or population: patients with perioperative fluid optimization
Setting: hospital
Intervention: protocol using standard measures such as CVP
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Protocol using standard measures such as CVP				
All-cause mortality	Study population		RR 2.81 (0.61 to 12.81)	60 (1 study)	⊕⊕◯◯ **Low**[a,b]	
	69 per 1000	194 per 1000 (42 to 883)				
	Moderate					
Total length of hospital stay	Mean total length of hospital stay in the control groups was **4.2 days**	Mean total length of hospital stay in the intervention groups was **4.20 lower** (11.0 lower to 2.6 higher)		60 (1 study)	⊕⊕◯◯ **Low**[a,b]	
Medically fit for discharge		Mean medically fit for discharge in the intervention groups was **3.90 lower** (7.05 to 0.75 lower)		60 (1 study)	⊕⊕⊕◯ **Moderate**[b]	

Return to pre-fracture accommodation/ return to pre-fracture mobility			Not estimable	-		Not reported
Adverse outcomes - cardiopulmonary	**Study population**		Not estimable	0 (0)		Not reported
	Moderate					
Adverse outcomes - neurological	**Study population**		**RR 0.94** (0.06 to 14.27)	60 (1 study)	⊕⊕◯◯ **Low**	
	34 per 1000	**32 per 1000** (2 to 492)				
	Moderate					
Adverse outcomes - all	**Study population**		**RR 0.53** (0.26 to 1.08)	60 (1 study)	⊕⊕◯◯ **Low**[a,b]	
	483 per 1000	**256 per 1000** (126 to 521)				
	Moderate					

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **CVP:** central venous pressure; **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

[a] Based on 1 study with a small number of events. Wide confidence intervals consistent with increased as well as decreased risk. Downgraded by 1 level

[b] Based on 1 study with a small number of participants. Downgraded by 1 level

DISCUSSION

Summary of main results

We included in this review five studies with 403 participants.
The conclusions of this updated review remain the same as those of both the original review and the last update (Brammar 2013; Price 2004). We found no benefit for the use of fluid optimization strategies in participants undergoing surgery for proximal femoral fracture (PFF) in terms of rates of mortality or adverse events (Brammar 2013; Price 2004). In the previous review update, one study had presented data indicating a reduction in length of stay (Venn 2002). However, with the additional studies included in this update, we found no consistent evidence for this outcome. One study reported a reduction in time to medical fitness when advanced haemodynamic monitoring was compared with a protocol using standard monitoring, and when a protocol using standard monitoring was compared with usual care (Venn 2002).

Overall completeness and applicability of evidence

We conducted a thorough search for the 2015 update, carrying out both backward and forward citation tracking of included studies. We used the search strategies delineated in a previous version of this review (Brammar 2013). All five studies included here provided evidence applicable to participants with PFF, with appropriate comparisons of fluid optimization techniques.
Applicability may extend only to those countries in which included studies were conducted, as usual care, fluid management and perioperative care of patients with femoral fracture may differ considerably between countries. Management of this patient group may also differ within countries, with different institutions adopting different protocols; with such few included studies, it could be argued that applicability of the review is limited by institution.

Quality of the evidence

We noted differences in quality among our included studies. We were concerned about the robustness of the randomization process in one study and judged this study to have a high risk of bias (Schultz 1985). We included this study in our analysis but used GRADEpro software to downgrade the overall quality of evidence for relevant outcomes accordingly. Blinding of clinicians to group allocation was an inevitable challenge in this review. However, we were unable to make a decision about whether this had introduced performance bias to our review.
Our main concern was lack of data because we identified few studies with a small number of participants for each of our comparisons. It is arguable that any mortality reduction due to the interventions described in our review would be small because of the many other factors that put participants with PFF at relatively high risk of death. If in-hospital mortality of 6.6% is assumed (Moppett 2012), a study with 80% power to detect a 50% decrease in in-hospital mortality (from 6.6% to 3.3%) would require randomization of 678 participants into each group (α = 0.05). Therefore, much larger studies than the ones presented in this review are likely needed to show the benefit derived from these interventions. Similarly, to detect a 50% reduction in adverse event incidence (from 15% to 7.5%) (Lawrence 2002; Roche 2005), 278 participants would be required for each group. We used GRADEpro to downgrade the quality of most outcomes to low or very low, as the review could not offer precision for our objectives.

Potential biases in the review process

To the best of our knowledge, no potential biases arose from the review process.

Agreements and disagreements with other studies or reviews

The authors of the original version of this review stated that invasive methods of fluid optimization may shorten hospital stay, but their effects on other important, patient-centred, longer-term outcomes are uncertain. We would agree in general with this but urge caution in interpretation of hospital stay data that are limited in scale and in some cases are not adequate for detailed analysis. We are not aware of any other good quality studies or systematic reviews investigating perioperative fluid optimization after PFF.

AUTHORS' CONCLUSIONS

Implications for practice

Limited evidence of low quality is available to support or reject the hypothesis that fluid volume optimization improves mortality or reduces complication rates for patients with PFF, whether advanced haemodynamic monitoring or protocols based on standard measures are used.

Implications for research

Broadening the scope of this review to include a greater number of clinical groups would increase the data set but would be clinically less useful to the reader who is interested in specific management of PFF. This approach would also further increase heterogeneity. Therefore, we suggest additional studies specifically for PFF that are adequately powered and methodologically robust to allow detection of differences in outcome measures.

It would be useful to assess the use of fluid optimization strategies within enhanced recovery programmes for PFF. These programmes comprise multi-factorial bundles of care that are becoming more widely used across a range of clinical conditions, although the quality of evidence of benefit is still low (Hoffman 2012). This assessment would provide the benefit of control of many of the confounding factors that limit studies comparing advanced monitoring or protocols against usual care.

ACKNOWLEDGEMENTS

We would like to thank Stephan Kettner (Content Editor), Cathal Walsh (Statistical Editor) and Sheila Page (Consumer Reviewer) for help and editorial advice provided during preparation of this updated systematic review.

We also would like to thank Dr Craig Goldsack, Dr Dominik Krzanicki and Dr Jonathan Pimm for their contributions in reshaping the original review to the new review format before it was updated (Brammar 2013), and we would like to thank previous Consumer Editor Robert Wylie.

We would like to acknowledge the work of Dr James Price, Dr John Sear and Dr Richard Venn, who authored the first review (Price 2004).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bartha 2013

Methods	Randomized controlled trial Parallel group
Participants	**Baseline characteristics** Advanced invasive haemodynamic monitoring goal directed • *Age*: 86 (71 to 101) years • *Gender (M/F)*: 71/29 • *BMI*: 23 (22 to 24) kg/m^2 • *ASA I - IV*: 1/19/43/7 Protocol using standard measures • *Age*: 85 (70 to 101) years • *Gender (M/F)*: 75/25 • *BMI*: 23 (22 to 24) kg/m^2 • *ASA I - IV*: 2/20/43/7 **Included criteria:** patients aged > 70 years weighing > 40 kg. Undergoing PFF surgery during regular operating hours **Excluded criteria:** patients who could be harmed by the treatment (ongoing myocardial infarction, chronic dialysis), concomitant medication with lithium, known allergy to lithium or medical device components, weight ≤ 40 kg, life expectancy < 6 months, pathological fractures and conditions, inability to give informed consent, anticipated difficulties obtaining data during the first postoperative year (as judged by a research team member), operations scheduled during hours when research team was unavailable. (Patients with pathological fractures had presumed survival < 12 months. Given the planned follow-up of 12 months, these patients were not included.) **Sponsorship source:** Stockholm county grant **Country:** Sweden **Setting:** hospital
Interventions	**Intervention characteristics** Advanced invasive haemodynamic monitoring goal directed • *Type of anaesthetic*: spinal 69, general 1 • *Type of fixation/surgery*: proximal femoral fracture • *Number randomized to group*: 74 • *Description of monitoring*: LiDCO monitor Protocol using standard measures • *Type of anaesthetic*: spinal 63, general 9 • *Type of fixation/surgery*: proximal femoral fracture • *Number randomized to group*: 75 • *Description of monitoring*: LiDCO monitor recorded data, but this was handled by attending personnel. Fluid was managed via a pre-established treatment algorithm
Outcomes	*Continuous* • Total length of hospital stay • Time to medical fitness for discharge

	Dichotomous • Mortality at 30 days *Adverse events* • Cardiovascular, respiratory, cerebrovascular, acute kidney failure, gastrointestinal bleeding, confusion, sepsis, deep vein thrombosis, wound infection, decubitus, wound haematoma, other complications
Notes	Number of participants: Tables showed discrepancy in the number of participants. Review authors have taken number of participants from the text, not from the tables Other: elderly patients. Poor recruitment to study led to early stop at 150 participants. Originally powered to include 460 participants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Low risk	Allocation obtained via telephone. Sequence not available to research team
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants, caregivers, anaesthetist not blinded. Unclear whether this could have affected performance of personnel
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Low risk	Personnel collecting data were not blinded, but assigned treatment was coded in the data set for primary and secondary outcome analyses. Therefore, attempts were made to blind data analysts
Blinding of outcome assessment (detection bias) Length of stay	Low risk	Personnel collecting data were not blinded, but assigned treatment was coded in the data set for primary and secondary outcome analyses. Therefore, attempts were made to blind data analysts
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of 7 participants after randomization. Reasons for loss given; analyses completed by study authors included ITT analyses
Selective reporting (reporting bias)	Low risk	ClinicalTrials. gov; ref NCT01141894. Protocol includes outcomes related to health-related quality of life and cost analysis, with plans for each participant to have 4 postoperative visits. This is not reported at all in full study pub-

Bartha 2013 (*Continued*)

		lication but is reported in interim report
Other bias	Unclear risk	Baseline characteristics well documented. Comparable, except for diabetes mellitus in twice as many participants in the GDHT group - unclear how this could affect results Wide exclusion criteria - this may indicate that the study favours patients who are healthier

Moppett 2014

Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Advanced invasive haemodynamic monitoring goal directed • *Age*: 85 (IQR 78 to 90; range 68 to 95) years • *Gender (M/F)*: 15/36 Protocol using standard measures • *Age*: 85 (IQR 80 to 88; range 63 to 95) years • *Gender (M/F)*: 22/41 **Included criteria:** patients admitted through the emergency department with primary fragility hip fracture, over 60 years of age and listed for surgical repair under spinal anaesthesia. Included patients unable to give consent on their own **Excluded criteria:** planned general anaesthetic for surgery repair, severe valvular heart disease (as this could affect the accuracy of the LiDCO device), taking therapeutic lithium (as this can affect the calibration of the LiDCO device), multiple injuries, revision hip surgery or requirement for total hip arthroplasty **Sponsorship source:** NIHR funding **Country:** UK **Setting:** hospital
Interventions	**Intervention characteristics** Advanced invasive haemodynamic monitoring goal directed • *Type of anaesthetic*: spinal • *Type of fixation/surgery*: DHS 22, ETS 20, TFN 2, AM 5, AO screws 2 • *Number randomized to group*: 62 allocated but 11 did not receive treatment. Therefore, 51 analysed • *Description of monitoring*: LiDCO monitor, arterial line (20 G) sited after local anaesthesia (lidocaine 1%) and before spinal anaesthesia Usual care • *Type of anaesthetic*: spinal • *Type of fixation/surgery*: DHS 25, ETS 29, AM 7, TFN 2 • *Number randomized to group*: 63 allocated but 5 did not receive treatment. Therefore, 63 analysed • *Description of monitoring*: LiDCO monitor, arterial line (20 G) sited after local anaesthesia (lidocaine 1%) and before spinal anaesthesia. Attending anaesthetist not allowed to view LiDCO monitor

Moppett 2014 (*Continued*)

Outcomes	*Continuous* • Total length of hospital stay • Time to medical fitness for discharge *Dichotomous* • Mortality up to 12 months after admission • Return to pre-fracture accommodation within 6 months *Adverse events* • Cardiovascular, respiratory, infectious, renal (RIFLE), abdominal, delirium, bleeding, skin
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated concealed tables with blocks of unequal size stratified according to gender and mortality risk
Allocation concealment (selection bias)	Low risk	"Patients were randomized...via a secure website"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Attending anaesthetist was aware of treatment allocation but was blinded from LiDCO monitor in control group. Unclear whether this could have affected performance of personnel
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Low risk	Data extracted from notes by staff unaware of treatment allocation Data analysis performed before unblinding of the trial
Blinding of outcome assessment (detection bias) Length of stay	Low risk	Data extracted from notes by staff unaware of treatment allocation Data analysis performed before unblinding of the trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss of 12% of data High number of losses in both groups after randomization. Explanations presented - several due to failure in anaesthetic/arterial lines. Study authors re-included lost participants for length of stay outcome and stated that this did not affect results. Inevitable losses due to participant group?

Moppett 2014 (*Continued*)

Selective reporting (reporting bias)	Low risk	Registered trial; ISRCTN88284896. Had not reported on cost of care or effects on heart and blood vessels, but not relevant to this review
Other bias	Unclear risk	Baseline characteristics comparable, although participants in intervention group transferred to theatre more quickly - unclear how this affected results

Schultz 1985

Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Advanced invasive haemodynamic monitoring goal directed • *Age*: 78 (range 40 to 95) years • *Gender (M/F)*: 10/25 Protocol using standard measures • *Age*: 67 (range 40 to 89) years • *Gender (M/F)*: 17/18 **Included criteria:** intracapsular and extracapsular hip fractures; specifics not described **Excluded criteria:** not described **Sponsorship source:** no details **Country:**: Westchester County Medical Centre, New York, USA **Setting**: single centre, hospital
Interventions	**Intervention characteristics** Advanced invasive haemodynamic monitoring goal directed • *Type of anaesthetic*: not stated, but assumed to be general • *Type of fixation/surgery*: Extracapsular fractures underwent open reduction and internal fixation with a sliding compression screw and a side plate; intracapsular fractures were treated by hemiarthroplasty • *Number randomized to group*: 70 • *Description of monitoring*: Swan-Ganz catheter was inserted, and systolic pressures in RA, RV and PA and PA wedge pressures were measured. Cardiac output was optimized with fluids; exact methods were unclear. Repeated until 1 to 2 days after surgery Protocol using standard measures • *Type of anaesthetic:* not stated, but assumed to be general • T*ype of fixation/surgery*: Extracapsular fractures underwent open reduction and internal fixation with a sliding compression screw and a side plate; intracapsular fractures were treated by hemiarthroplasty • *Number randomized to group*: 70 • *Description of monitoring*: CVP inserted; fluids as per protocol; exact management unclear

Schultz 1985 (*Continued*)

Outcomes	*Dichotomous* • Mortality - time point not defined *Adverse events* • Wound infection, pneumonia, dislocated prosthesis, pneumonitis, decubitus ulcer
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Paper states that participants were assigned on a random basis on admission to hospital. No details given. Large differences in groups at baseline
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about whether clinical staff in operating theatre or on ward were aware of participant allocation. Unclear whether knowledge of group allocation would have affected performance. Intervention not clearly defined
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Unclear risk	No information about how outcomes were assessed; no definitions
Blinding of outcome assessment (detection bias) Length of stay	Unclear risk	Outcome not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants included in analyses. No information about exclusions due to deviations from protocol
Selective reporting (reporting bias)	Unclear risk	Outcomes not fully described
Other bias	High risk	Serious baseline imbalances between monitored and non-monitored group raise questions about the randomization procedure; methods not fully clear; outcomes not fully defined

Sinclair 1997

Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Advanced invasive haemodynamic monitoring goal directed • *Age*: median 74 (IQR 70.5 to 82) years • *ASA status*: median I2 (IQR 2 to 3) Usual care • *Age*: median 75.57 (IQR 69 to 80) years • *ASA status*: median 2 (IQR 2 to 3) **Country:** London, UK **Setting**: single centre, teaching hospital **Included criteria:** adult patients with fractures of the femoral neck **Excluded criteria:** age < 55 years, fracture secondary to neoplasm, fractures occurring during hospitalization for acute illness, fracture through the site of a previous surgical correction or associated with instability of a previous prosthesis, planned regional anaesthesia (this would preclude the planned intervention)
Interventions	**Intervention characteristics** Advanced invasive haemodynamic monitoring goal directed • *Type of anaesthetic*: general anaesthetic • *Type of fixation/surgery*: dynamic hip screw (± plate) 8, AO cannulated screw 4, arthroplasty 8 • *Number randomized to group*: 20 • *Description of monitoring*: as for usual care plus protocol-guided colloid fluid challenges monitored by oesophageal Doppler ultrasonography to optimize cardiac stroke volume Usual care • *Type of anaesthetic:* not stated, but assumed to be general • *Type of fixation/surgery*: dynamic hip screw (± plate) 10, AO cannulated screw 3, arthroplasty 7 • *Number randomized to group*: 20 • *Description of monitoring*: GA plus conventional intraoperative fluid replacement. Oesophageal Doppler monitoring of fluid given and cardiovascular variables monitored
Outcomes	*Continuous* • Total length of hospital stay • Time until medically fit for discharge *Dichotomous* • Mortality at 30 days (also data for death at 36 days, 65 days) *Adverse events* • Pneumonia and congestive cardiac failure, bronchopneumonia (both given as causes for mortality in 2 participants). Adverse events not reported for all other participants • Change in intraoperative physiological parameters: stroke volume, corrected flow time, cardiac output, fluid per minute of surgery
Notes	

Sinclair 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomization process given
Allocation concealment (selection bias)	Unclear risk	Not clear whether sequentially numbered, opaque, sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Anaesthetist blinded to Doppler measurements but aware of fluid challenges and therefore likely to know the allocation - probably the surgeon as well. Unclear whether this could have affected performance of anaesthetist. Other medical and nursing staff unaware of randomization of participants
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Low risk	Medical and nursing staff unaware of randomization of participants
Blinding of outcome assessment (detection bias) Length of stay	Low risk	No discharge criteria given, but staff were blinded; therefore unlikely to bias results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers in each group included in Results unclear. No details about losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported, but length of stay reported in chart as median and IQR
Other bias	Low risk	Study groups similar at baseline

Venn 2002

Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Advanced invasive haemodynamic monitoring goal directed • *Age*: mean 82.0 (SD 8.7) years • *Gender (M/F)*: 6/24 • *ASA status*: median 3 (IQR 2.5 to 3) Protocol using standard measures

	• *Age*: mean 85.0 (SD 6.2) years • *Gender (M/F)*: 4/27 • *ASA status*: median 3 (IQR 3 to 4) Usual care • *Age*: mean 84.5 (SD 9.3) years • *Gender (M/F)*: 6/23 • *ASA status*: median 3 (IQR 3 to 4) **Included criteria:** adult patients undergoing repair of PFF under general anaesthesia **Excluded criteria:** age < 65 years, fracture secondary to neoplasm, oesophageal pathology, patients with central venous cannula in situ, planned regional anaesthesia (this would preclude 1 of the planned interventions) **Sponsorship source:** no details **Country:** London, UK **Setting:** single centre, teaching hospital
Interventions	**Intervention characteristics** Advanced invasive haemodynamic monitoring goal directed • *Type of anaesthetic:* general • *Type of fixation/surgery*: dynamic hip screw 13, arthroplasty 14, AO screw 3 • *Number randomized to group*: 30 • *Description of monitoring*: GA and conventional fluid management plus fluid challenges guided by oesophageal Doppler measurements, as per protocol Protocol using standard measures • *Type of anaesthetic*: general • *Type of fixation/surgery*: dynamic hip screw 21, arthroplasty 9, AO screw 0 • *Number randomized to group*: 31 • *Description of monitoring*: GA and conventional fluid management plus intraoperative fluid challenges guided by central venous pressure, as per protocol Usual care • *Type of anaesthetic*: general • *Type of fixation/surgery*: dynamic hip screw 11, arthroplasty 17, AO screw 1 • *Number randomized to group*: 29 • *Description of monitoring*: GA and conventional intraoperative fluid management
Outcomes	*Continuous* • Total length of hospital stay • Time to medical fitness for discharge *Dichotomous* • Mortality at 30 days *Adverse events* • Deep haemorrhage, haematemesis, chest infection, wound infection, urinary tract infection, cellulitis, pancreatitis, pulmonary embolus, cerebrovascular accident, myocardial infarction, cardiac failure, rapid atrial fibrillation, hypotension, impaired renal function, pseudo-obstruction • Difference in intraoperative CVP measurements (not including Doppler group)
Notes	
Risk of bias	

Venn 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not clear whether sequentially numbered, opaque, sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Anaesthetist (and surgeon) aware of fluid challenges and allocation of participants. Unclear whether this could have affected performance of personnel "Postoperative management was performed by orthopaedic medical team and nursing staff who were unaware of patient's randomization"
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Low risk	Medical and nursing staff unaware of randomization of participants
Blinding of outcome assessment (detection bias) Length of stay	Low risk	No discharge criteria given, but staff were blinded; therefore, unlikely to bias results
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in CVP group underwent intramedullary nailing but was included in ITT analyses. No losses to follow-up were reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Study groups similar at baseline

AM: Austin Moore uncemented hemiarthroplasty; AO: Association for the Study of Internal Fixation; ASA: American Society of Anesthesiologists (physical status classification system); BMI: body mass index; CVP: central venous pressure; DHS: dynamic hip screw; ETS: Exeter trauma stem-cemented hemiarthroplasty; F: female; GA: general anaesthesia; GDHT: goal-directed haemodynamic treatment; ITT: intention-to-treat; IQR: interquartile range; kg: kilograms; M: male; NIHR: National Institute for Health Research; PA: pulmonary artery; PFF: proximal femoral fracture; RA: right atrial; RIFLE: Risk/Injury/Failure/Loss/End-stage (classification system for acute kidney injury); RV: right ventricle; SD: standard deviation; TFN: trochanteric femoral nail

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

Study	Reason for exclusion
Carson 1998	Wrong intervention - Hb targeting, not fluid optimization
Carson 2006	Wrong intervention. Study concentrates on titration of Hb levels rather than on optimization of fluid status
Choong 2000	Wrong intervention
Eneroth 2005	Wrong intervention. Both groups had identical fluid regimen intraoperatively
Fathi 2013	Wrong intervention - designed to compare the effects of Ringer's lactate and hydroxyethyl starch 6% on haemodynamic parameters after spinal anaesthesia
Gan 2002	Wrong participants - elective surgery; no orthopaedic participants
Lopes 2007	Only 1 participant in study may have undergone PFF surgery (unclear) and was assigned to the control group. Would not be appropriate to include such a small sample
Messina 2013	Wrong intervention - comparison of spinal and general anaesthesia for participants with femoral fracture
Rowlands 2013	Wrong intervention - effect of iron infusions on postoperative transfusion requirements for participants with femoral fracture
Swanson 1998	Wrong intervention
Wilson 1999	No participants with PFF (all general/vascular/urological surgery)

Hb: haemoglobin; PFF: proximal femoral fracture

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

Sandham 2003

Methods	Publication type: full article Allocation random: by computer-generated sequence Allocation concealment: sequentially numbered opaque, sealed envelopes Baseline comparison: yes Baseline similarity: yes Blinding of caregivers: not considered feasible by investigators Additional features to blind fluid administered: not considered feasible Control of co-interventions: not described Completeness of follow up: yes - to hospital discharge Intention-to-treat analysis: yes
Participants	Location: Canada Centre: 19 centres Language: English Inclusion criteria: adults undergoing high-risk, urgent or elective major thoracic/abdominal/vascular/orthopaedic surgery, then ICU stay Exclusion criteria: nil specified Age: 60 years or older ASA grade: III to IV Surgery type: not specified
Interventions	PAC group: goal-directed fluid therapy, using PAC according to protocol to optimize oxygen delivery Control group: standard fluid therapy
Outcomes	In-hospital all-cause mortality 6-Month mortality 12-Month mortality Length of stay Iatrogenic complications: wound infections; problems due to line insertion Cardiopulmonary complications: myocardial infarction, left ventricular failure, arrhythmia, pneumonia, pulmonary embolism Other complications: renal/liver insufficiency, sepsis
Notes	To date, unable to contact study authors to obtain outcome data regarding hip fracture subgroup. If these data become available, this study will be included

Vanakas 2012

Methods	Randomized single-blind controlled trial Parallel design
Participants	Location: Greece Inclusion criteria: patients undergoing femoral fracture repair under spinal anaesthesia Number of participants: 20
Interventions	Advanced haemodynamic monitoring: goal-directed therapy, participants connected to Flo Trac/Vigileo haemodynamic monitoring system to measure cardiac output Control: standard monitoring

Vanakas 2012 (*Continued*)

Outcomes	Duration of hospital stay
Notes	Abstract only. Unable to contact study authors to obtain outcome data

ASA: American Society of Anesthesiologists (physical status classification system); PAC: pulmonary artery catheter

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

NCT02382185

Trial name or title	Non-invasive cardiac output monitoring to guide goal-directed fluid therapy in high-risk patients undergoing urgent surgical repair of proximal femoral fractures (ClearNOF)
Methods	Randomized single-blind controlled trial
Participants	Adults (50 years or older) due to undergo urgent or emergency repair of proximal femoral fracture
Interventions	Non-invasive cardiac monitoring device (Clearsight) vs usual care
Outcomes	Incidence of major and minor complications Morbidity at day 3, 5 and 10 Length of stay Time to drinking/eating/mobilization Change in perioperative haemodynamic variables (heart rate, blood pressure, stroke volume) Hypotension Total dose of vasopressor
Starting date	January 2015
Contact information	Simon Davies; York Teaching Hospitals NHS Foundation Trust
Notes	Estimated enrolment: 250

DATA AND ANALYSES

Comparison 1. Advanced haemodynamic monitoring versus protocol using standard measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	280	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.14, 1.20]
2 Adverse outcomes	3	280	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.17]
2.1 Any complications, including minor	3	280	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.17]

Comparison 2. Advanced haemodynamic monitoring versus usual care

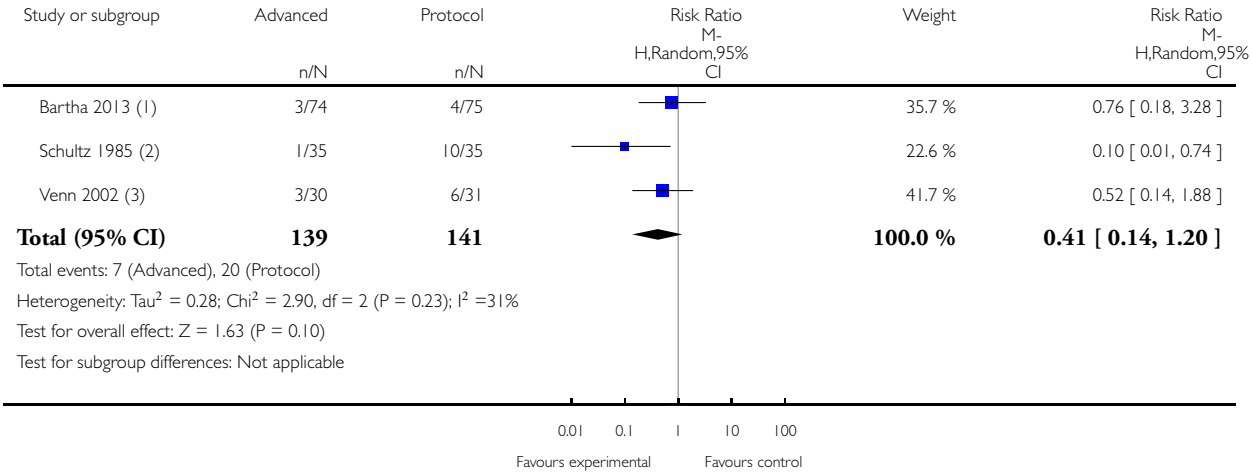
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	213	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.07, 2.95]
2 Total length of hospital stay	2	173	Mean Difference (IV, Fixed, 95% CI)	0.63 [-1.70, 2.96]
3 Days until medically fit for discharge	2	173	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-1.74, 1.71]
4 Adverse outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Neurological	2	173	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.56, 2.18]
4.2 Any complications, including minor	2	173	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.40, 1.31]

Analysis 1.1. Comparison 1 Advanced haemodynamic monitoring versus protocol using standard measures, Outcome 1 All-cause mortality.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 1 Advanced haemodynamic monitoring versus protocol using standard measures

Outcome: 1 All-cause mortality



(1) Within 30 days

(2) Mortality time point not defined

(3) In-hospital mortality

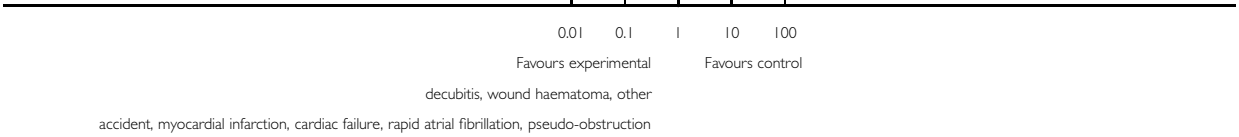
Analysis 1.2. Comparison 1 Advanced haemodynamic monitoring versus protocol using standard measures, Outcome 2 Adverse outcomes.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 1 Advanced haemodynamic monitoring versus protocol using standard measures

Outcome: 2 Adverse outcomes

Study or subgroup	Advanced n/N	Protocol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Any complications, including minor					
Bartha 2013 (1)	27/74	34/75		79.3 %	0.80 [0.54, 1.19]
Schultz 1985 (2)	3/35	3/35		5.2 %	1.00 [0.22, 4.62]
Venn 2002 (3)	7/30	8/31		15.5 %	0.90 [0.37, 2.18]
Total (95% CI)	**139**	**141**		**100.0 %**	**0.83 [0.59, 1.17]**
Total events: 37 (Advanced), 45 (Protocol)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.12$, df = 2 (P = 0.94); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.06 (P = 0.29)					
Test for subgroup differences: Not applicable					



(1) Number of patients with complications at hospital discharge: cardiovascular, respiratory, cerebrovascular, acute kidney failure, confusion, sepsis, wound infection, urinary tract infection,

(2) Postoperative complications: pneumonia, pneumonitis, decubitus ulcer, wound infection

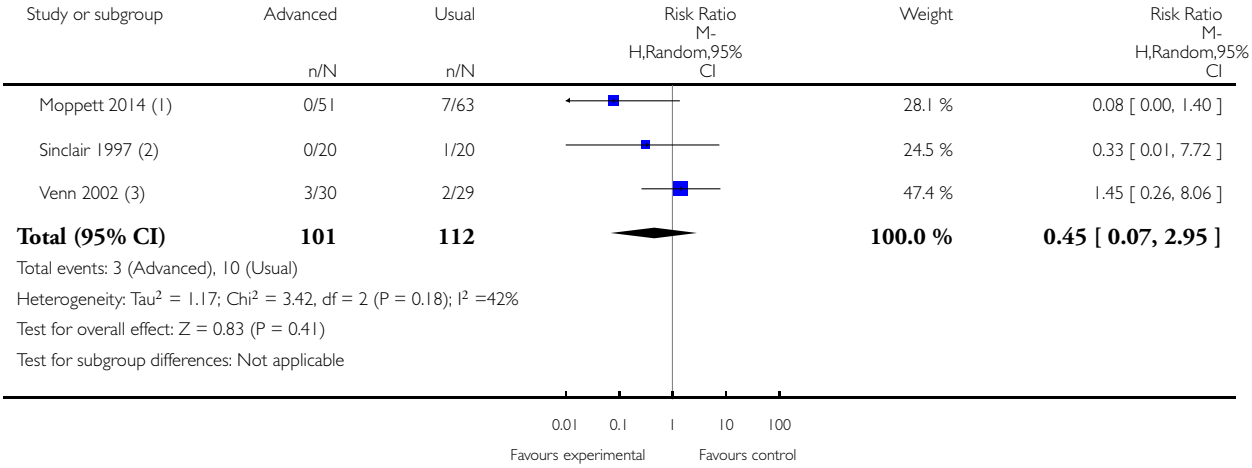
(3) Number of patients with any postoperative complication: deep haemorrhage, chest infection, wound infection, urinary tract infection, cellulitis, pancreatitis, pulmonary embolus, cerebrovascular

Analysis 2.1. Comparison 2 Advanced haemodynamic monitoring versus usual care, Outcome 1 All-cause mortality.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 2 Advanced haemodynamic monitoring versus usual care

Outcome: 1 All-cause mortality



(1) 30 day mortality

(2) 30 day mortality. Two patients who died after 30 days not included (one from each group).

(3) In-hospital mortality

Analysis 2.2. Comparison 2 Advanced haemodynamic monitoring versus usual care, Outcome 2 Total length of hospital stay.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 2 Advanced haemodynamic monitoring versus usual care

Outcome: 2 Total length of hospital stay

Study or subgroup	Advanced N	Mean(SD)	Usual N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Moppett 2014	51	15.3 (6.8)	63	14.2 (6.4)		90.7 %	1.10 [-1.35, 3.55]
Venn 2002	30	13.5 (10.8)	29	17.5 (18.1398)		9.3 %	-4.00 [-11.65, 3.65]
Total (95% CI)	**81**		**92**			**100.0 %**	**0.63 [-1.70, 2.96]**

Heterogeneity: Chi^2 = 1.55, df = 1 (P = 0.21); I^2 =35%

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Advanced haemodynamic monitoring versus usual care, Outcome 3 Days until medically fit for discharge.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 2 Advanced haemodynamic monitoring versus usual care

Outcome: 3 Days until medically fit for discharge

Study or subgroup	Advanced N	Mean(SD)	Usual N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Moppett 2014	51	13.1 (5)	63	12.2 (5)		87.1 %	0.90 [-0.95, 2.75]
Venn 2002	30	7.7 (12.3)	29	13.9 (5.3)		12.9 %	-6.20 [-11.01, -1.39]
Total (95% CI)	**81**		**92**			**100.0 %**	**-0.01 [-1.74, 1.71]**

Heterogeneity: Chi^2 = 7.31, df = 1 (P = 0.01); I^2 =86%

Test for overall effect: Z = 0.01 (P = 0.99)

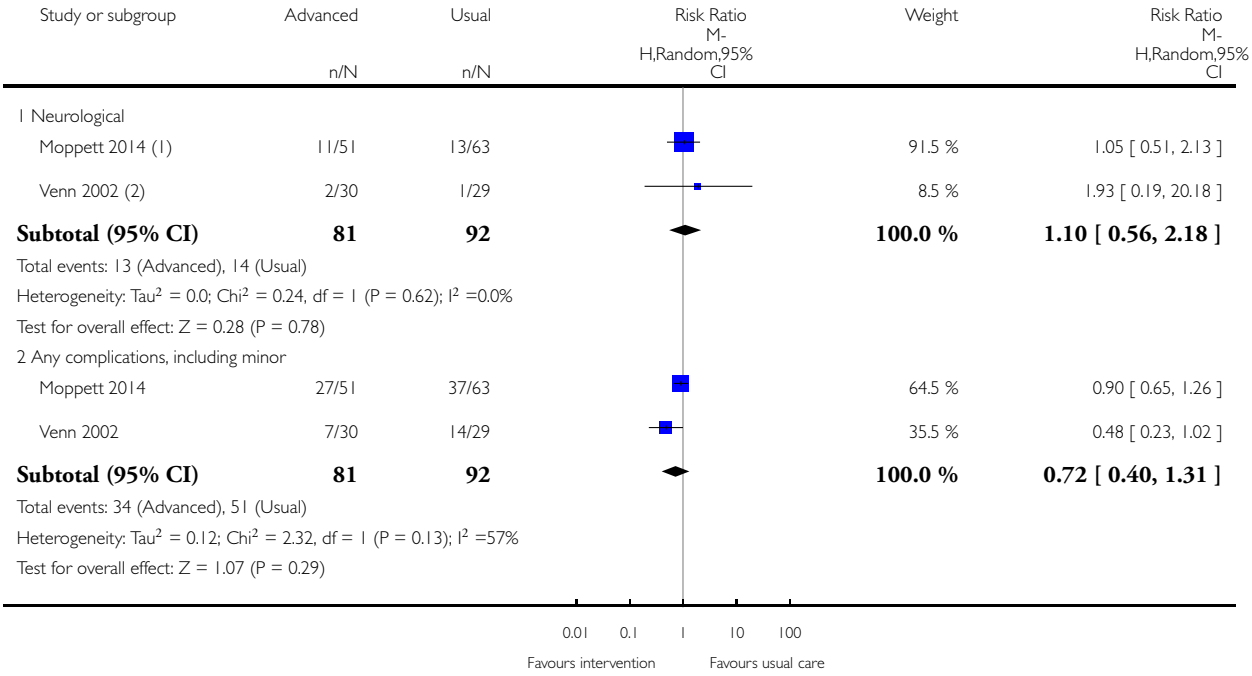
Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Advanced haemodynamic monitoring versus usual care, Outcome 4 Adverse outcomes.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 2 Advanced haemodynamic monitoring versus usual care

Outcome: 4 Adverse outcomes



(1) Delirium

(2) Cerebrovascular accident

ADDITIONAL TABLES

Table 1. Adverse events. Comparison 1. Advanced haemodynamic monitoring versus protocol using standard measures

Study ID	Adverse events	Advanced haemodynamic monitoring	Protocol using standard measures
Bartha 2013		**n = 74**	**n = 75**
	Cardiopulmonary	Cardiovascular 5 Respiratory 5	Cardiovascular 6 Respiratory 7
	Neurological	Cerebrovascular 0 Confusion 3	Cerebrovascular 2 Confusion 6
	Other	Acute kidney failure 1 Gastrointestinal bleeding 0 Sepsis 2 Deep vein thrombosis 0 Wound infection 2 Delayed healing 0 Urinary tract infection 16 Decubitus 6 Wound haematoma 0 Other 4	Acute kidney failure 1 Gastrointestinal bleeding 0 Sepsis 0 Deep vein thrombosis 0 Wound infection 1 Delayed healing 0 Urinary tract infection 12 Decubitus 1 Wound haematoma 1 Other 6
Schultz 1985		**n = 35**	**n = 35**
	Other	Pneumonia 1 Wound infection 1 Pneumonitis 1	Pneumonia 2 Decubitis ulcer 1
Venn 2002		**n = 30**	**n = 31**
	Cardiopulmonary	Chest infection 2 Pulmonary embolus 1 Myocardial infarction 0 Cardiac failure 0 Rapid atrial fibrillation 3 Hypotension 0	Chest infection 3 Pulmonary embolus 0 Myocardial infarction 1 Cardiac failure 1 Rapid atrial fibrillation 1 Hypotension 0
	Neurological	Cerebrovascular accident 2	Cerebrovascular accident 1
	Other	Deep haemorrhage 1 Haematemesis 0 Wound infection 0 Urinary tract infection 2 Cellulitis 0 Pancreatitis 0 Hypotension 0 Impaired renal function 0 Pseudo-obstruction 0	Deep haemorrhage 0 Haematemesis 0 Wound infection 0 Urinary tract infection 1 Cellulitis 1 Pancreatitis 0 Hypotension 0 Impaired renal function 0 Pseudo-obstruction 1

Table 2. Adverse events. Comparison 2. Advanced haemodynamic monitoring versus usual care

Study ID	Adverse events	Advanced haemodynamic monitoring	Usual care
Moppett 2014		**n = 51**	**n = 63**
	Cardiopulmonary	Cardiovascular 8 Respiratory 0	Cardiovascular 6 Respiratory 0
	Neurological	Acute delirium 11	Acute delirium 13
	Other	Infectious 21 Abdominal 2 Bleeding 0 Skin 0 Renal (RIFLE) 18* Other 3	Infectious 34 Abdominal 1 Bleeding 0 Skin 0 Renal (RIFLE) 32* Other 3
Venn 2002		**n = 30**	**n = 29**
	Cardiopulmonary	Chest infection 2 Pulmonary embolus 1 Myocardial infarction 0 Cardiac failure 0 Rapid atrial fibrillation 3 Hypotension 0	Chest infection 5 Pulmonary embolus 0 Myocardial infarction 0 Cardiac failure 0 Rapid atrial fibrillation 2 Hypotension 3
	Neurological	Cerebrovascular accident 2	Cerebrovascular accident 1
	Other	Deep haemorrhage 1 Haematemesis 0 Wound infection 0 Urinary tract infection 2 Cellulitis 0 Pancreatitis 0 Hypotension 0 Impaired renal function 0 Pseudo-obstruction 0	Deep haemorrhage 1 Haematemesis 1 Wound infection 2 Urinary tract infection 3 Cellulitis 0 Pancreatitis 1 Hypotension 3 Impaired renal function 2 Pseudo-obstruction 0

*RIFLE scores sum of patients at risk, injury or failure

Table 3. Comparison 3. Protocol using standard measures versus usual care (Venn 2002)

Outcomes reported in Venn 2002: comparison 3	**Protocol - CVP N = 31**		**Standard care N = 29**		**Effect estimate** (95% CI)
	Mean	SD	Mean	SD	Mean difference

Table 3. Comparison 3. Protocol using standard measures versus usual care (Venn 2002) (*Continued*)

Length of hospital stay (days)	13.3	12.1	17.5	13.8	-4.20 (-11.0 to 2.60)
Time to fitness to discharge	10	5.3	13.9	6.6	-3.90 (-7.05 to -0.75)
	Events		Events		MH relative risk
Mortality	6		2		2.81 (0.61 to 12.81)
Adverse events					
· Cardiopulmonary - episodes	6		7		N/A
· Neurological - participants	1		1		0.94 (0.06 to 14.27)
· Any, including minor - participants	8		14		0.53 (0.26 to 1.08)

APPENDICES

Appendix 1. CENTRAL search strategy

Search strategy used for databases

ID	Search run on CENTRAL 02/09/15
#1	MeSH descriptor Clinical Protocols explode all trees
#2	MeSH descriptor Water-Electrolyte Balance explode all trees
#3	MeSH descriptor Fluid Therapy explode all trees
#4	MeSH descriptor Infusions, Intravenous explode all trees
#5	MeSH descriptor Catheterization, Central Venous explode all trees

(*Continued*)

#6	MeSH descriptor Catheterization, Swan-Ganz explode all trees
#7	MeSH descriptor Axillary Vein explode all trees
#8	MeSH descriptor Echocardiography explode all trees
#9	MeSH descriptor Pulmonary Wedge Pressure explode all trees
#10	MeSH descriptor Critical Care, this term only
#11	MeSH descriptor Cardiac Output explode all trees
#12	MeSH descriptor Monitoring, Physiologic explode all trees
#13	(Hemodynamic* or Hemodynamic* or (critical near care) or (cardiac near output*) or (fluid near therap*) or (Electrolyte near Balance) or (infusion* near intravenous) or (fluid near volume)) or (fluid volume optimizat*) or (fluid volume optimisat*)
#14	(oesophageal or esophageal) near doppler
#15	(pulse contour analysis) or lidco or picco
#16	(Clinical Protocols) or (Water Electrolyte Balance) or (Fluid Therapy) or (Infusions Intravenous) or (Catheterization Central Venous) or (Catheterization Swan Ganz) or (Axillary Vein) or Echocardiography or (Pulmonary Wedge Pressure) or (Critical Care) or (Cardiac Output) or (Monitoring Physiologic) or (goal near directed near therapy)
#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18	MeSH descriptor Femoral Fractures explode all trees
#19	MeSH descriptor Femoral Neck Fractures explode all trees
#20	MeSH descriptor Hip Fractures explode all trees
#21	(fract* near (femor* or neck or hip))
#22	(#18 OR #19 OR #20 OR #21)
#23	(#17 AND #22)

Appendix 2. MEDLINE search strategy

	Search run on MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present **on 02/09/15**
1	exp Clinical Protocols/ or exp Water Electrolyte Balance/ or exp Fluid Therapy/ or exp Infusions Intravenous/ or exp Catheterization Central Venous/ or exp Catheterization Swan Ganz/ or exp Axillary Vein/ or exp Echocardiography/ or exp Pulmonary Wedge Pressure/ or Critical Care/ or exp Cardiac Output/ or exp Monitoring Physiologic/
2	(Hemodynamic* or haemodynamic* or (critical adj3 care) or (cardiac adj3 output*) or (fluid adj3 therap*) or (electrolyte adj3 balance) or (infusion* adj3 intravenous) or (fluid adj3 volume)).mp
3	(fluid volume optimizat* or fluid volume optimisat*) or (goal adj3 directed adj3 therapy).mp
4	((oesophageal or esophageal) adj3 doppler).mp.
5	(pulse contour analysis or lidco or picco).mp.
6	exp Femoral fractures/ or exp Hip Fractures/ or exp Femoral Neck Fractures/
8	(fract* adj6 (femor* or neck or hip)).mp.
9	or/1-5
10	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh
11	(Clinical Protocols or Water Electrolyte Balance or Fluid Therapy or Infusions Intravenous or Catheterization Central Venous or Catheterization Swan Ganz or Axillary Vein or Echocardiography or Pulmonary Wedge Pressure or Critical Care or Cardiac Output or Monitoring Physiologic).mp
12	11 or 9
14	12 and (8 or 6)
15	14 and 10

Appendix 3. EMBASE search strategy

	Search run in EMBASE on 02/09/15
1	exp Femoral fractures/ or exp Hip Fractures/ or exp Femoral Neck Fractures/
2	(fract* adj6 (femor* or neck or hip)).mp.

(*Continued*)

3	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab. or placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh
4	exp clinical protocol/
5	exp electrolyte balance/
6	exp fluid therapy/
7	exp intravenous drug administration/
8	exp central venous catheterization/
9	exp swan ganz catheter/
10	exp axillary vein/
11	exp echocardiography/
12	exp lung wedge pressure/
13	intensive care/
14	exp heart output/
15	exp monitoring/
17	(clinical protocol or electrolyte balance or fluid therapy or intravenous drug administration or central venous catheterization or swan ganz catheter or axillary vein or echocardiography or lung wedge pressure or intensive care or heart output or monitoring).mp
18	(Hemodynamic* or haemodynamic* or (critical adj3 care) or (cardiac adj3 output*) or (fluid adj3 therap*) or (electrolyte adj3 balance) or (infusion* adj3 intravenous) or (fluid adj3 volume)).mp
19	((fluid volume optimizat* or fluid volume optimisat*) or (goal adj3 directed adj3 therapy)).mp
20	((oesophageal or esophageal) adj3 doppler).mp.
21	(pulse contour analysis or lidco or picco).mp.
24	or/1-2
25	or /4-21
27	24 and 25 and 3

Appendix 4. ClinicalTrials.gov search strategy

Term	**Search run on:** clinicaltrials.gov 5 July 2015
1	Fluid optimisation
2	Esophageal Doppler
3	Femoral neck fracture
4	Lidco
5	Picco
6	1 or 2 or 3 or 4 or 5

Appendix 5. WHO International Clinical Trials Registry Platform

Term	**Search run on: WHO International Clinical Trials Registry:** www.apps.who.int/trialsearch July 2015
1	Fluid optimisation
2	Fluid optimization
3	Esophageal Doppler
4	Oesophageal Doppler
5	Femoral neck fracture
6	Lidco
7	Picco
8	1 or 2 or 3 or 4 or 5 or 6 or 7

Appendix 6. Articles used for forward and backward citation tracking

Titles used for backward citation in Brammar 2013

- Brienza, N., et al., *Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study.* Critical Care Medicine, 2009. **37**(6): p. 2079-2090.
- Bundgaard-Nielsen, M., et al., *Monitoring of peri-operative fluid administration by individualized goal-directed therapy.* Acta Anaesthesiologica Scandinavica, 2007. **51**(3): p. 331-340.
- Dalfino, L., et al., *Haemodynamic goal-directed therapy and postoperative infections: earlier is better. a systematic review and meta-analysis.* Critical Care, 2011. **15**(3).

• Giglio, M.T., et al., *Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials.* British Journal of Anaesthesia, 2009. **103**(5): p. 637-646.
• Grocott, M.P.W., M.G. Mythen, and T.J. Gan, *Perioperative fluid management and clinical outcomes in adults.* Anesthesia and Analgesia, 2005. **100**(4): p. 1093-1106.
• Guest, J.F., et al., *A cost analysis of a treatment policy of a deliberate perioperative increase in oxygen delivery in high risk surgical patients.* Intensive Care Medicine, 1997. **23**(1): p. 85-90.
• Hamilton, M.A., M. Cecconi, and A. Rhodes, *A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients.* Anesthesia and Analgesia, 2011. **112**(6): p. 1392-1402.
• Kern, J.W. and W.C. Shoemaker, *Meta-analysis of hemodynamic optimization in high-risk patients.* Critical Care Medicine, 2002. **30**(8): p. 1686-1692.
• Kirov, M.Y., V.V. Kuzkov, and Z. Molnar, *Perioperative haemodynamic therapy.* Current Opinion in Critical Care, 2010. **16**(4): p. 384-392.
• Mowatt, G., et al., *Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.* Health Technology Assessment, 2009. **13**(7): p. 1-+.
• Phan, T.D., et al., *Improving perioperative outcomes: fluid optimization with the esophageal Doppler monitor, a metaanalysis and review.* Journal of the American College of Surgeons, 2008. **207**(6): p. 935-41.
• Poeze, M., J.W.M. Greve, and G. Ramsay, *Meta-analysis of hemodynamic optimization: relationship to methodological quality.* Critical Care, 2005. **9**(6): p. R771-R779.
• Rhodes, A., et al., *Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study.* Intensive Care Medicine, 2010. **36**(8): p. 1327-1332.
• Spahn, D.R. and P.G. Chassot, *CON: Fluid restriction for cardiac patients during major noncardiac surgery should be replaced by goal-directed intravascular fluid administration.* Anesthesia and Analgesia, 2006. **102**(2): p. 344-6.

Titles used for forward citation in Brammar 2013

• Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture. BMJ 1997;315:909-12
• Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Rondomized controlled trial to investigate influence of fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. British Journal of Anaesthesia 2002;88:65-71.
• Gan T, Soppitt A, Maroof M, el-Moalem H, Robertosn K, Moretti E et al. Goal-directed intraoperative fluid administration reduces the length of hospital stay after major surgery. Anesthesiology 2002;97:820-6.
• Schultz R, Whitfield G, Lamura J, Raciti A, Krishnamurthy S. The role of physiologic monitoring in patients with fractures of the hip. Journal of Trauma 1985;25:309-16.

Appendix 7. Study eligibility and data extraction form

General information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Report title *(title of paper/abstract/report that data are extracted from)*	
Report ID *(ID for this paper/abstract/report)*	
Study ID *(surname of first author and year first full report of study was published, e.g. Smith 2001)*	
Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*	

Study eligibility

Study characteristics	Eligibility criteria *(insert eligibility criteria for each characteristic as defined in the protocol)*	Yes/No/Unclear	Details of outcomes and locations in text
Type of study	Randomized controlled trial		
	Controlled clinical trial *(quasi-randomized trial & cluster-randomized)*		
	Cross-over trial *(both interventions in patients - order randomized)*		
Participants	Adults with proximal femoral fracture who underwent surgical treatment of any type under regional or general anaesthesia		

(*Continued*)

Types of interventions and comparison	**Comparison of two or more of:** Advanced invasive haemodynamic monitoring such as transoesophageal Doppler, pulse contour analysis		
	Protocol using readily available parameters such as blood pressure, urine output, central venous pressure		
	Usual care		
Outcomes	Mortality		
	Complications		

Outcomes are not part of the eligibility criteria- so a study that meets design, participant and intervention criteria is included.

INCLUDE EXCLUDE UNCLEAR

Reason for exclusion:

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Population and setting

	Description	**Location in text**
Population description *(types of surgical procedures included)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		

(*Continued*)

Informed consent obtained		

Methods

	Descriptions as stated in report/paper	Location in text
Aim of study		
Design *(e.g. parallel, cross-over, cluster)*		
Unit of allocation *(by individuals, clusters/groups or body parts)*		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study		

Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text
Total no. randomized *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		

(*Continued*)

Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/Ethnicity		
Type and duration of surgery *(Method of fracture fixation)*		
Details of anaesthetic given *(GA or regional, sedation, neuromuscular blockade used, any specific details)*		
Seniority of anaesthetist		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		

Intervention groups

Intervention group- repeated as required

	Description as stated in report/paper	**Location in text**
Group name ***(advanced monitoring, protocol, or usual care)***	First or second generation SAD	
Specific monitoring used ***(Inc detail of protocols)***		

(*Continued*)

No. randomized to group		

Comparison group

	Description as stated in report/paper	Location in text
Group name ***(advanced monitoring, protocol, or usual care)***	Tracheal tube	
Specific monitoring used ***(Inc detail of protocols)***		
No. randomized to group		

Outcomes

For each outcome ticked, please complete a separate outcome form.

	Description as stated in report/paper	Location in text
Outcome name *(number of attempts, pain)*		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		

(*Continued*)

Unit of measurement *(if relevant)*		
Scales: levels, upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Power		
RESULTS	**Description as stated in report/paper**	**Location in text**
Comparison		
Outcome		
Subgroup		
Timepoint *(specify whether from start or end of intervention)*		
Postintervention or change from baseline?		
Results: Intervention*		
Results: Comparison*		
No. missing participants and reasons		
No. participants moved from other group and reasons		
Any other results reported		
Unit of analysis *(individuals, cluster/ groups or body parts)*		

(*Continued*)

Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*		
Reanalysis required? *(specify)*		
Re-analysed results		

*Results for continuous outcomes: mean: SD (or other variance): total number of participants
Results for dichotomous outcomes: numbers of participants with outcomes: total number of participants.

Risk of bias assessment

Domain	Risk of bias: high/low/unclear	Support for judgement	Location in text
Random sequence generation *(selection bias)*			
Allocation concealment *(selection bias)*			
Blinding of participants and personnel *(performance bias)*			
Blinding of outcome assessment *(detection bias)*			
Incomplete outcome data *(attrition bias)*			
Selective outcome reporting? *(reporting bias)*			
Other bias *(baseline characteristics for cluster-randomized, carryover for cross-over trials)*			

(*Continued*)

Applicability

	Yes/No/Unclear	Support for judgement
Have important populations been excluded from the study? *(consider disadvantaged populations and possible differences in the intervention effect)*		
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*		
Does the study directly address the review question? *(any issues of partial or indirect applicability)*		

Other information

	Description as stated in report/paper	Location in text
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		

WHAT'S NEW

Last assessed as up-to-date: 2 September 2015.

Date	Event	Description
16 February 2016	New citation required but conclusions have not changed	New review authors are Sharon Lewis and Andrew Butler. Marialena Trivella is no longer an author on the review. The review conclusions are unchanged
16 February 2016	New search has been performed	We re-ran searches in September 2015. We found 2 new eligible studies, 2 studies awaiting classification and 1 ongoing trial. We excluded 28 studies

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 1, 2002

Date	Event	Description
9 September 2013	New citation required but conclusions have not changed	The previous review authors (Price 2004) decided not to update this review. New review authors have prepared this updated version. We have made no changes to the conclusions
9 September 2013	New search has been performed	• We amended the search strategy and re-ran the search from inception of the databases to October 2012. We repeated title selection and full-text review in full • We moved 1 study from excluded to included studies (Schultz 1985). We added 1 study as awaiting classification pending contact with study authors (Sandham 2003) and added 2 ongoing studies (GDHT study; NOTTS study) • We included a 'Summary of findings' table for each comparison • We used the Cochrane 'Risk of bias' tool to assess the quality of studies. We did not exclude studies on the basis of low quality • We re-defined outcomes to separate length of stay into time to medical fitness and total stay. The all-cause mortality time frame was changed to include in-hospital, 30 days and undefined. We changed reduced return of function outcomes to time to the pre-fracture category of accommodation

(*Continued*)

		and mobility. We re-classified complications into major iatrogenic, cardiopulmonary, neurological and combined, including minor • We altered comparison groups so that protocol measures and advanced haemodynamic methods were not combined and were compared with each other
16 January 2008	Amended	We converted this review to the new review format
10 November 2003	New citation required and conclusions have changed	We made substantive amendments

CONTRIBUTIONS OF AUTHORS

Andrew F Smith (AFS) identified the need for the review update.

Sharon R Lewis (SRL) and Andrew R Butler (ARB) performed the initial searches, applied inclusion criteria and extracted study data.

SRL and ARB compiled the results.

SRL drafted the review.

All review authors reviewed and refined the final manuscript.

DECLARATIONS OF INTEREST

Andrew Brammar: none known.

Andrew F Smith: none known.

Sharon R Lewis: none known

Andrew R Butler: none known.

Amanda Nicholson (AN): From June 2015, AN has worked for Q Medical Technology Limited, a firm that markets and distributes a range of medical devices. AN made no substantial contribution to the review while working at Q Medical Technologies Limited. None of the company's products are directly relevant to the subject of this review. AN's husband has small direct holdings in several drug and biotech companies as part of a wider balanced share portfolio.

SOURCES OF SUPPORT

Internal sources

- Oxford Radcliffe Hospitals NHS Trust, UK.

External sources

- NIHR Cochrane Collaboration Programme Grant, UK.
- NIHR Cochrane Collaboration Programme Grant. Enhancing the safety, quality and productivity of perioperative care. Project Ref: 10/4001/04, UK. This grant funds the work of AN and AFS on this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Alterations made in earlier review (Brammar 2013)

We altered and re-ran the search strategy using updated key terms from inception of the databases to October 2012. In addition to CENTRAL, MEDLINE and EMBASE, we searched the International Clinical Trials Registry Platform and ClinicalTrials.gov websites for ongoing and unpublished studies (see Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5). We carried out backward and forward citation searching for key review articles identified during the initial searches (see Appendix 6). We repeated title selection and full-text review in full.

We moved one study from excluded to included studies (Schultz 1985). We added one study as awaiting classification pending contact with study authors (Sandham 2003). We added two ongoing studies (GDHT study; NOTTS study).

We used the Cochrane 'Risk of bias' tool to assess the quality of studies. We did not exclude studies on the basis of low quality.

We altered comparison groups so that protocol measures and advanced haemodynamic methods were compared with each other and were not combined.

We redefined outcomes to separate length of stay into time to medical fitness and total stay. The all-cause mortality time frame was changed to include in-hospital, 30 days and undefined. We changed reduced return of function outcomes to time to the pre-fracture category of accommodation and mobility. We re-classified complications into major iatrogenic, cardiopulmonary, neurological and combined, including minor.

We included 'Summary of findings' tables for all comparisons, using the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Femoral Fractures [therapy]; Fluid Therapy [*methods]; Hip Fractures [complications; *surgery]; Hypovolemia [complications; *therapy]; Length of Stay; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans