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Percutaneous vertebroplasty for osteoporotic vertebral compression fracture (Review)

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[Intervention Review]

Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

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ABSTRACT

Background

Percutaneous vertebroplasty remains widely used to treat osteoporotic vertebral fractures although our 2015 Cochrane review did not support its role in routine practice.

Objectives

To update the available evidence of the benefits and harms of vertebroplasty for treatment of osteoporotic vertebral fractures.

Search methods

We updated the search of CENTRAL, MEDLINE and Embase and trial registries to 15 November 2017.

Selection criteria

We included randomised and quasi-randomised controlled trials (RCTs) of adults with painful osteoporotic vertebral fractures, comparing vertebroplasty with placebo (sham), usual care, or another intervention. As it is least prone to bias, vertebroplasty compared with placebo was the primary comparison. Major outcomes were mean overall pain, disability, disease-specific and overall health-related quality of life, patient-reported treatment success, new symptomatic vertebral fractures and number of other serious adverse events.

Data collection and analysis

We used standard methodologic procedures expected by Cochrane.

Main results

Twenty-one trials were included: five compared vertebroplasty with placebo (541 randomised participants), eight with usual care (1136 randomised participants), seven with kyphoplasty (968 randomised participants) and one compared vertebroplasty with facet joint glucocorticoid injection (217 randomised participants). Trial size varied from 46 to 404 participants, most participants were female, mean age ranged between 62.6 and 81 years, and mean symptom duration varied from a week to more than six months.

Three placebo-controlled trials were at low risk of bias and two were possibly susceptible to performance and detection bias. Other trials were at risk of bias for several criteria, most notably due to lack of participant and personnel blinding.

Compared with placebo, high- to moderate-quality evidence from five trials (one with incomplete data reported) indicates that vertebroplasty provides no clinically important benefits with respect to pain, disability, disease-specific or overall quality of life or treatment success at one month. Evidence for quality of life and treatment success was downgraded due to possible imprecision. Evidence was not downgraded for potential publication bias as only one placebo-controlled trial remains unreported. Mean pain (on a scale zero to 10, higher scores indicate more pain) was five points with placebo and 0.6 points better (0.2 better to 1 better) with vertebroplasty, an absolute pain reduction of 6% (2% better to 10% better, minimal clinical important difference is 15%) and relative reduction of 9% (3% better to14% better) (five trials, 535 participants). Mean disability measured by the Roland-Morris Disability Questionnaire (scale range zero to 23, higher scores indicate worse disability) was 14.2 points in the placebo group and 1.7 points better (0.3 better to 3.1 better) in the vertebroplasty group, absolute improvement 7% (1% to 14% better), relative improvement 10% better (3% to 18% better) (three trials, 296 participants).

Disease-specific quality of life measured by the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) (scale zero to 100, higher scores indicating worse quality of life) was 62 points in the placebo group and 2.75 points (3.53 worse to 9.02 better) in the vertebroplasty group, absolute change: 3% better (4% worse to 9% better), relative change: 5% better (6% worse to 15% better (two trials, 175 participants). Overall quality of life (European Quality of Life (EQ5D), zero = death to 1 = perfect health, higher scores indicate greater quality of life) was 0.38 points in the placebo group and 0.05 points better (0.01 better to 0.09 better) in the vertebroplasty group, absolute improvement: 5% (1% to 9% better), relative improvement: 18% (4% to 32% better) (three trials, 285 participants). In one trial (78 participants), 9/40 (or 225 per 1000) people perceived that treatment was successful in the placebo group compared with 12/38 (or 315 per 1000; 95% CI 150 to 664) in the vertebroplasty group, RR 1.40 (95% CI 0.67 to 2.95), absolute difference: 9% more reported success (11% fewer to 29% more); relative change: 40% more reported success (33% fewer to 195% more).

Moderate-quality evidence (low number of events) from seven trials (four placebo, three usual care, 1020 participants), up to 24 months follow-up, indicates we are uncertain whether vertebroplasty increases the risk of new symptomatic vertebral fractures (70/509 (or 130 per 1000; range 60 to 247) observed in the vertebroplasty group compared with 59/511 (120 per 1000) in the control group; RR 1.08 (95% CI 0.62 to 1.87)).

Similarly, moderate-quality evidence (low number of events) from five trials (three placebo, two usual care, 821 participants), indicates uncertainty around the risk of other serious adverse events (18/408 or 76 per 1000, range 6 to 156) in the vertebroplasty group compared with 26/413 (or 106 per 1000) in the control group; RR 0.64 (95% CI 0.36 to 1.12). Notably, serious adverse events reported with vertebroplasty included osteomyelitis, cord compression, thecal sac injury and respiratory failure.

Our subgroup analyses indicate that the effects did not differ according to duration of pain $\leq$ 6 weeks versus ¿ 6 weeks. Including data from the eight trials that compared vertebroplasty with usual care in a sensitivity analyses altered the primary results, with all combined analyses displaying considerable heterogeneity.

Authors' conclusions

Based upon high- to moderate-quality evidence, our updated review does not support a role for vertebroplasty for treating acute or subacute osteoporotic vertebral fractures in routine practice. We found no demonstrable clinically important benefits compared with placebo (sham procedure) and subgroup analyses indicated that the results did not differ according to duration of pain $\leq$ 6 weeks versus ¿ 6 weeks.

Sensitivity analyses confirmed that open trials comparing vertebroplasty with usual care are likely to have overestimated any benefit of vertebroplasty. Correcting for these biases would likely drive any benefits observed with vertebroplasty towards the null, in keeping with findings from the placebo-controlled trials.

Numerous serious adverse events have been observed following vertebroplasty. However due to the small number of events, we cannot be certain about whether or not vertebroplasty results in a clinically important increased risk of new symptomatic vertebral fractures

and/or other serious adverse events. Patients should be informed about both the high- to moderate-quality evidence that shows no important benefit of vertebroplasty and its potential for harm.

PLAIN LANGUAGE SUMMARY

Vertebroplasty for treating spinal fractures due to osteoporosis

Background

Osteoporosis is characterised by thin, fragile bones and may result in minimal trauma fractures of the spine bones (vertebrae). They can cause severe pain and disability.

Vertebroplasty involves injecting medical-grade cement into a fractured vertebra, under light sedation or general anaesthesia. The cement hardens in the bone space to form an internal cast.

Study characteristics

This Cochrane review is current to November 2017. Studies compared vertebroplasty versus placebo (no cement injected) (five studies, 541 participants); usual care (eight studies, 1136 participants); kyphoplasty (similar, but before cement is injected a balloon is expanded in the fractured vertebra; seven studies, 968 participants) and facet joint steroid injection (one study, 217 participants). Trials were performed in hospitals in 15 countries, the majority of participants were female, mean age ranged between 63.3 and 80 years, and symptom duration ranged from a week to six months or more. Eight trials received at least some funding from medical device manufacturers and only two reported that they had no role in the trial.

Key results

Compared with a placebo (fake) procedure, vertebroplasty resulted in little benefit at one month:

Pain (lower scores mean less pain)

Improved by 6% (2% better to 10% better), or 0.6 points (0.2 better to 1.0 better) on a zero-0 to 10-point scale.

• People who had vertebroplasty rated their pain as 4.4 points.

• People who had placebo rated their pain as 5 points.

Disability (lower scores mean less disability)

Improved by 7% (1% better to 14% better), or 1.7 points (0.3 better to 3.1 better) on a zero to 23-point scale.

• People who had vertebroplasty rated their disability as 12.5 points.

• People who had placebo rated their disability as 14.2 points.

Vertebral fracture or osteoporosis-specific quality of life (lower scores mean better quality of life)

Better by 3% (4% worse to 9% better), or 2.75 points better (3.53 worse to 9.02 better) on a zero to 100-point scale.

.• People who had vertebroplasty rated their quality of life related to their fracture as 59.25 points.

• People who had placebo rated their quality of life related to their fracture as 62 points.

Overall quality of life (higher scores mean better quality of life)

Improved by 5% (1% better to 9% better), or 0.05 units (0.01 better to 0.09 better) on a zero = death to one = perfect health scale.

• People who had vertebroplasty rated their general quality of life as 0.43 points.

• People who had placebo rated their general quality of life as 0.38 points.

Treatment success (defined as pain moderately or a great deal better)

9% more people rated their treatment a success (11% fewer to 29% more), or nine more people out of 100.

• 32 out of 100 people reported treatment success with vertebroplasty.

• 23 out of 100 people reported treatment success with placebo.

Compared with a placebo or usual care:

New symptomatic vertebral fractures (at 12 to 24 months)

1% more new fractures with vertebroplasty (7% fewer to 9% more), or one more person out of 100.

• 13 out of 100 people had a new fracture with vertebroplasty.

• 12 out of 100 people had a new fracture with placebo or usual care.

Other serious adverse events:

1% fewer people (5% fewer to 3% more), had other serious adverse events with vertebroplasty; relative change 36% fewer (64% fewer to 12% more).

• eight out of 100 people reported other serious adverse events with vertebroplasty.

• 11 out of 100 people reported other serious adverse events with placebo.

Quality of the evidence

High-quality evidence shows that vertebroplasty does not provide more clinically important benefits than placebo. We are less certain of the risk of new vertebral fractures or other serious effects; quality was moderate due to the small number of events.

Serious adverse events that may occur include spinal cord or nerve root compression due to cement leaking out from the bone, cement leaking into the blood stream, rib fractures, infection in the bone, fat leaking into the bloodstream, damage to the covering of the spinal cord that could result in leakage of cerebrospinal fluid, anaesthetic complications and death.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Vertebroplasty for osteoporotic vertebral compression fracture

Patient or population: people with osteoporotic vertebral compression fracture
Settings: hospital, various countries including Australia, USA, UK, Canada, several European countries, Iran, China, Taiwan
Intervention: vertebroplasty versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo[1]	Vertebroplasty				
Pain Scale from: 0 to 10, 0 is no pain. Follow-up: 1 month	The mean pain in the control groups was **5 points**	The mean pain in the intervention groups was **0.6 points better** (0.2 better to 1.0 better)		535 (5 studies)	⊕⊕⊕⊕ **high**[2]	SMD -0.27 (-0.44 to -0.10) Absolute change 6% better (2% better to 10% better); relative change 9% better (3% better to 14% better)[3]
Disability (Roland-Morris Disability Questionnaire) Scale from: 0 to 23; 0 is no disability. Follow-up: 1 month	The mean disability in the control groups was **14.2 points**	The mean disability in the intervention groups was **1.7 points better** (0.3 better to 3.1 better)		296 (3 studies)	⊕⊕⊕⊕ **high**[2]	Absolute change 7% better (1% better to 14% better); relative change 10% better (3% better to 18% better)[3]
Disease-specific quality of Life (QUALEFFO) Scale from: 0 to 100; 0 is best. Follow-up: 1 month	The mean quality of life (QUALEFFO) in the control groups was **62 points**	The mean quality of life in the intervention groups was **2.75 points better** (3.53 worse to 9.02 better)		175 (2 studies)	⊕⊕⊕◯ **moderate**[4]	Absolute change 3% better (4% worse to 9% better); relative change 5% better (6% worse to 15% better)[3]

Overall quality of Life (EQ5D) Scale from: 0 to 1; 1 is best. Follow-up: 1 month	The mean quality of life (EQ-5D) in the control groups was **0.38 points**	The mean quality of life in the intervention groups was **0.05 points better** (0.01 better to 0.09 better)		285 (3 studies)	⊕⊕⊕◯ **moderate**[4]	Absolute change 5% better (1% better to 9% better); relative change 18% improvement (4% better to 32% better)[3]
Participant global assessment of success (People perceived their pain as better) Follow-up: 1 month	**225 per 1000**	**315 per 1000** (150 to 664)	**RR 1.40** (0.67 to 2.95)	78 (1 study)	⊕⊕⊕◯ **moderate**[4]	Absolute difference 9% more reported success (11% fewer to 29% more); relative change 40% more reported success (33% fewer to 195% more)
Incident symptomatic vertebral fractures Follow-up: 12 -24 months	**120 per 1000**	**130 per 1000** (68 to 247)	**RR 1.08** (0.62 to 1.87)	1020 (7 studies)[5]	⊕⊕⊕◯ **moderate**[4]	Absolute difference 1% more fractures with vertebroplasty (7% fewer to 9% more); relative difference 8% more (43% fewer to 106% more)
Other serious adverse events Follow-up: 12-24 months	**106 per 1000**	**76 per 1000** (6 to 156)	**RR 0.64** (0.36 to 1.12)	821 (5 studies)[5]	⊕⊕⊕◯ **moderate**[4]	Absolute difference 1% fewer events with vertebroplasty (5% fewer to 3% more); relative change 36% fewer (64% fewer to 12% more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% 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; **SMD:** Standardised mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] For incident vertebral fractures the comparison includes two placebo (sham)-controlled trials and three trials that compared vertebroplasty versus usual care.

[2] The internal validity of the five placebo-controlled trials that have full or some results available is high. Three trials have published their results in peer-reviewed journals (Buchbinder 2009; Clark 2016; Kallmes 2009) while a fourth trial (VOPE 2015), completed in April 2014, was published as a thesis (http://www.forskningsdatabasen.dk/en/catalog/2371744560), and reported at a conference. The fifth trial (VERTOS IV), completed in November 2014, had sufficient data available from a conference presentation. Therefore we did not downgrade the evidence due to suspected publication bias although the results of one additional placebo-controlled trial (VERTOS V) remain unpublished. This trial was previously reported as completed in June 2015, but its status has been changed to 'enrolling by invitation', at: https://clinicaltrials.gov/ct2/show/NCT01963039. While publication bias is possible, it is unlikely the conclusions will change when data from this trial become available.

[3] Relative changes calculated as absolute change (mean difference) divided by mean at baseline in the placebo group from Buchbinder 2009 (values were: 7.1 points on 0 to 10 point VAS pain; 17.3 points on 0 to 23 point Roland-Morris Disability questionnaire; 0.28 points on EQ-5D quality of life scale; 59.6 points on the QUALEFFO scale).

[4] Downgraded due to imprecision: the 95% confidence intervals do not exclude a clinically important change (defined as 1.5 points on the 0 to 10 pain scale; 2 to 3 points on the 0 to 23 point RMDQ scale; 0.074 on the 0 to 1 EQ-5D quality of life scale, and 10 points on the 0 to 100 QUALEFFO scale); or for dichotomous outcomes the total number of participants was small, or number of events was small (¡200); or data were from a single trial only

[5] Pooled both placebo and usual care comparisons in the safety analyses.

BACKGROUND

Description of the condition

Vertebral compression fractures are among the most common type of fracture in patients with osteoporosis (Ström 2011). The estimated incidence of osteoporotic vertebral compression fractures in individuals 50 years or older has been reported to be 307 per 100,000 year based upon a German study, with the rate in women aged between 85 and 89 years almost eight-fold higher that in women aged 60 to 64 years (Hernlund 2013). The same study estimated that the direct costs associated with a new osteoporotic vertebral fracture in the first year after its occurrence is about 6490 Euros, signifying that these fractures are costly. A Swedish study estimated that the lifetime risk for a symptomatic osteoporotic vertebral fracture for a person of the age of 45 is 15% for a woman and 8% for a man (Kanis 2000). In the USA, approximately 750,000 new osteoporotic vertebral fractures occur each year (Melton 1997).

A recent population-based study examining trends in fracture incidence over time in Olmstead County, Minnesota, observed a dramatic increase in the incidence of vertebral fractures, from 1989 to 1991 to 2009 to 2011, and this was associated with an apparent earlier onset of vertebral fracture over time (Amin 2014). The vast majority of these (83.4%) were considered osteoporotic, defined in the study as resulting from no more than moderate trauma (by convention, equivalent to a fall from standing height or less). While some of the observed increase could have been partially attributable to incidentally diagnosed vertebral fractures, the findings are in keeping with a Dutch study that observed a rise in the number of emergency department visits due to osteoporotic vertebral fractures between 1986 and 2008, due to an increase in falls among the most elderly (Oudshoorn 2012). The results are also consistent with a Canadian study that observed a decline in the rate of all low-trauma osteoporotic fractures over 20 years from 1986 to 2006 in the Province of Manitoba, except for vertebral fractures, which did not decline significantly in either sex (Leslie 2011).

Osteoporotic vertebral compression fractures are a common cause of both acute and chronic back pain in older populations, although only about a third of radiographic osteoporotic vertebral compression deformities present with acute pain. Both symptomatic and asymptomatic osteoporotic vertebral fractures can lead to substantial spinal deformity, functional limitation, pulmonary compromise and lowered quality of life. They are associated with an increased risk of further vertebral fractures and increased mortality (Lau 2008).

Management options for treating acutely painful osteoporotic vertebral fractures are limited and include provision of adequate analgesia, bed rest and physical therapy, as well as assessment and appropriate management of osteoporosis and risk factors for further fractures such as falls prevention. While most fractures generally heal within a few months, some people have persistent pain and disability, and require hospitalisation, long-term care, or both (Kanis 1999).

Description of the intervention

Percutaneous vertebroplasty was first described in 1987 as a treatment for vertebral angioma (Galibert 1987), and subsequently it has been used to treat both benign and malignant vertebral fractures. The procedure may be performed under intravenous sedation or general anaesthesia by interventional radiologists, neurosurgeons or orthopaedic surgeons. Under imaging guidance, most often fluoroscopy, a large calibre needle is inserted into the affected vertebral body usually via a transpedicular route and bone cement, usually polymethylmethacrylate (PMMA), is injected (Hide 2004).

Early open-label, and uncontrolled studies consistently reported dramatic immediate improvements in pain, and adverse events were reportedly uncommon (Hochmuth 2006). Despite the absence of evidence from high-quality randomised controlled trials (RCTs) confirming its benefits, over the last 20 years the procedure has become incorporated into standard care in many parts of the world, most commonly reserved for patients who fail a period of conservative therapy. In the USA, dramatic increases in the use of vertebroplasty have been observed over the last two decades (Gray 2007a; Lad 2009; Leake 2011).

Documented adverse events occurring either during or after the procedure have included cord compression due to extension of the cement outside of the vertebral body, cement pulmonary embolism, infection, rib fractures and new adjacent or non-adjacent vertebral fractures, osteolysis in the bone surrounding the injected material and death (Leake 2011).

How the intervention might work

The mechanism by which percutaneous vertebroplasty is purported to reduce pain is not known. At least three possible mechanisms have been proposed: (1) mechanical stabilisation of the fractured bone; (2) thermal destruction of nerve endings due to the high temperature reached during polymerisation of the injected cement; and (3) chemical destruction of the nerve endings due to the chemical composition of the cement (Belkoff 2001). The semisolid mixture of PMMA has been shown to restore strength and stiffness of vertebral bodies in post-mortem studies (Belkoff 2001).

Why it is important to do this review

Percutaneous vertebroplasty has been widely adopted into clinical practice to treat painful osteoporotic vertebral compression fractures prior to supporting evidence of its efficacy and safety

from high-quality RCTs. The first RCT of vertebroplasty compared with usual care was published in 2007 (Voormolen 2007), while the first two placebo-controlled trials were published in 2009 (Buchbinder 2009; Kallmes 2009).

Numerous systematic reviews and/or meta-analyses of vertebroplasty for osteoporotic spinal fractures have been published (Anderson 2013; Bliemel 2012; Eck 2008; Gill 2007; Han 2011; Hochmuth 2006; Hulme 2006; Lee 2009; Liu 2013; Ma 2012; McGirt 2009; Papanastassiou 2012; Ploeg 2006; Robinson 2012; Shi 2012; Stevenson 2014; Taylor 2006; Trout 2006; Wang 2012; Xing 2013; Zhang 2013; Zou 2012). These have varied in inclusion criteria and methodologic rigour, and have reported conflicting results.

In 2015, we published a Cochrane systematic review that synthesised the best available evidence for the efficacy and safety of this procedure including 11 RCTs and one quasi-RCT (1320 participants) (Buchbinder 2015). Based upon moderate-quality evidence, our review did not support a role for vertebroplasty for treating osteoporotic vertebral fractures in routine practice. Since then the results of further trials have been published and/or presented including two additional placebo-controlled trials. It is important to determine whether or not incorporation of the findings of the additional trials in an updated review alters our previous conclusions.

OBJECTIVES

To assess the benefits and harms of percutaneous vertebroplasty for treating patients with osteoporotic vertebral compression fractures.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of any design (e.g. parallel, cross-over, factorial) and controlled clinical trials using a quasi-randomised method of allocation, such as by alternation or date of birth. Reports of trials were eligible regardless of the language or date of publication. Only trials published as full articles or available as a full trial report were considered for inclusion.

Types of participants

We included trials that enrolled adults with a diagnosis of osteoporotic vertebral compression fracture/s of any duration. The diagnosis of osteoporosis could have been based upon bone mineral densitometry or explicit clinical diagnostic criteria as defined by the studies. Trials enrolling participants with vertebral fractures due to another cause such as major trauma and malignancy were excluded.

Types of interventions

We included trials that evaluated percutaneous vertebroplasty, defined as percutaneous injection of bone cement (usually polymethylmethacrylate (PMMA)) or similar substances into a vertebral body under imaging guidance.

Comparators could be any of the following.

- Placebo or sham procedure
- Usual care (best supportive care)
- Balloon kyphoplasty (similar to a percutaneous vertebroplasty, but prior to injection of bone cement a balloon is inserted into the vertebral body and expanded), or other similar procedures
- Pharmacologic treatment (e.g. calcitonin, bisphosphonates, complementary medicine)
- Non-pharmacologic interventions (e.g. bracing, physical therapy or surgery)

Types of outcome measures

Major outcomes

The following outcomes were selected as the most important.

- Mean overall pain measured on a visual analogue scale (VAS) or numerical rating scale (NRS)
- Disability measured by the Roland-Morris Disability Questionnaire (RMDQ) or other back-specific disability measure
- Vertebral fracture and/or osteoporosis-specific health-related quality of life, e.g. the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO)
- Overall health-related quality of life, e.g. European Quality of Life with 5 Dimensions (EQ-5D) or Assessment of Quality of Life (AQoL) questionnaire
- Treatment success measured by a participant-reported global impression of clinical change (much or very much improved), or similar measure
- New (incident) symptomatic vertebral fractures (the denominator was the number of participants, but the numerator could include more than one new fracture per participant)
- Number of serious other adverse events judged to be due to the procedure (e.g. infection, clinical complications arising from cement leakage)

Minor outcomes

- Proportion of participants with pain improved by a clinically relevant amount, for example improvement of at least 2.5 units or 30% on a zero or one to 10 scale
- New (incident) radiographic vertebral fractures (the denominator was the number of participants, but the numerator could include more than one new fracture per participant)
- Other adverse events

Timing of outcome assessment

We extracted outcome measures that assessed benefits of treatment (e.g. pain or function) at the following time points:

- one to two weeks;
- one month;
- two to three months;
- six months;
- 12 months;
- 24 months.

If data were available in a trial at multiple time points within each of the above periods (e.g. at one and two weeks), we only extracted data at the latest possible time point of each period. We extracted new vertebral fractures at 12 and 24 months, where available. We extracted other adverse events at all time points.

We collated the main results of the review into a 'Summary of findings' table which provides key information concerning the quality of evidence and the magnitude and precision of the effect of the interventions. We included the major outcomes (see above) in the 'Summary of findings' table at one month for outcomes assessing potential benefits of treatment (pain, disability, vertebral fracture and/or osteoporosis and overall quality of life and treatment success), 12 months for new symptomatic vertebral fractures (the most data available), and one month for serious other adverse events (judged to be related to the procedure).

Search methods for identification of studies

Electronic searches

We searched the following databases on 15 November 2017; updated from the search in the earlier version of this review, which was conducted on 12 November 2014.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochane Library to Issue 11 of 12, 2017)
- MEDLINE (via Ovid from January 2014 to 15 November 2017)
- Embase (via Ovid from January 2014 to 15 November 2017)

The search strategies are shown in Appendix 1; Appendix 2; Appendix 3).

We also searched for ongoing trials and protocols of published trials in the clinical trials register that is maintained by the US National Institute of Health (http://clinicaltrials.gov) and the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://www.who.int/ictrp/en/) on 18 November 2017 (see Appendix 4).

No language restrictions were applied.

Searching other resources

We also reviewed the reference lists of the included trials and any relevant review articles retrieved from the electronic searches, to identify any other potentially relevant trials.

Data collection and analysis

Selection of studies

Two review authors (SD and RO (for previous version of the review) or RB and RJ or KR and RJ) independently selected trials for possible inclusion against a predetermined checklist of inclusion criteria (see Criteria for considering studies for this review). We screened titles and abstracts and initially categorised studies into the following groups:

- possibly relevant - studies that met the inclusion criteria and studies from which it was not possible to determine whether they met the criteria either from their title or abstract;
- excluded - those clearly not meeting the inclusion criteria.

If a title or abstract suggested that the study was eligible for inclusion, or we could not tell, we obtained a full-text version of the article and two review authors independently assessed it to determine whether it met the inclusion criteria. The review authors resolved discrepancies through discussion or adjudication by a third author.

Data extraction and management

At least two review authors in various combinations (JH, AJ, RJ, KR) independently extracted data using a standard data extraction form developed for this review. The authors resolved any discrepancies through discussion or adjudication by a third author (RB). For each included study we recorded the following:

- trial characteristics, including type (e.g. parallel or crossover), country, source of funding, and trial registration status (with registration number recorded if available);
- participant characteristics, including age, sex, duration of symptoms, and inclusion/exclusion criteria;
- intervention characteristics for each treatment group, and use of co-interventions;
- outcomes reported, including the measurement instrument used and timing of outcome assessment.

Five review authors (JH, AJ, RB, RJ and KR) in various combinations independently extracted all outcome data.

For a particular systematic review outcome there may be a multiplicity of results available in the trial reports (e.g. multiple scales, time points and analyses). To prevent selective inclusion of data based on the results, we used the following *a priori* defined decision rules to select data from trials.

- Where trialists reported both final values and change from baseline values for the same outcome, we extracted final values.
- Where trialists reported both unadjusted and adjusted values for the same outcome, we extracted unadjusted values.
- Where trialists reported data analysed based on the intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as-treated), we extracted ITT-analysed data.
- For cross-over RCTs, we preferentially extracted data from the first period only.

Where trials did not include a measure of overall pain but included one or more other measures of pain, for the purpose of combining data for the primary analysis of overall pain, we planned to combine overall pain with other types of pain in the following hierarchy: unspecified pain; pain with activity; or daytime pain. For trials that included more than one back-specific measure of disability we preferentially extracted data for the RMDQ if reported.

Review authors who were also authors of relevant trials had no involvement in determining whether or not their trials met the inclusion criteria for this review, and also had no involvement in data extraction or 'Risk of bias' assessment of their own trials.

Assessment of risk of bias in included studies

At least two review authors (JH, AJ, RJ, KR) in various combinations independently assessed the risk of selection, performance, detection, attrition and reporting biases for all included RCTs by evaluating the following domains: random sequence generation, allocation concealment, blinding of participants, care provider, and outcome assessor for each outcome measure, incomplete outcome data and other biases, conforming to the methods recommended by Cochrane (Higgins 2011).

Each criterion was rated as low risk of bias, high risk of bias or unclear risk (either lack of information or uncertainty over the potential for bias). Disagreements among the review authors were discussed and resolved.

Measures of treatment effect

We used Cochrane's statistical software, Review Manager 5.3, to perform data analysis. We expressed dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous outcomes as mean differences (MDs) with 95% CIs if different trials used the same measurement instrument to measure the same outcome. Alternatively, we analysed continuous outcomes using the standardised mean difference (SMD) when trials measured the same outcome but employed different measurement instruments to measure the same conceptual outcome (e.g. disability).

To enhance interpretability of continuous outcomes, pooled SMDs of overall pain and disability were back-transformed to an original zero to 10 mm VAS for pain and the zero to 23 scale RMDQ respectively, by multiplying the SMD and 95% CIs by a representative pooled standard deviation (SD) at baseline of the trial with the highest weight in the meta-analysis and the least susceptibility to bias (Schünemann 2011b).

For studies comparing vertebroplasty with placebo, we used SD 2.3 for pain and SD 2.9 for RMDQ (Buchbinder 2009).

For analyses comparing vertebroplasty with usual care that included Farrokhi 2011, we used SMD for pain as (Farrokhi 2011 used a one to 10 pain scale in comparison to all other trials that used a zero to 10 pain scale), but back-transformed the SMD to MD on a zero to 10 scale by multiplying the SMD and 95% CIs by the SD of pain at baseline from the control group of the Klazen 2010 trial (SD 1.6). For disability (vertebroplasty versus usual care), which included data for the RMDQ and Oswestry Disability Index (ODI), we back-transformed the SMD to MD on the RMDQ (zero to 23 scale) by multiplying the SMD and 95% CIs by the SD of disability at baseline also from the control group of the Klazen 2010 trial (SD 4.2).

For analyses comparing vertebroplasty with kyphoplasty that included Evans 2015, we used SMD for disability (as Evans 2015 used the RMDQ compared to all other trials that used ODI), but back-transformed the SMD to MD on the RMDQ (zero to 23 scale) by multiplying the SMD and 95% CIs by the standard deviation (SD) of pain at baseline from the control group of the Evans 2015 trial (SD 6.6).

Unit of analysis issues

The unit of analysis was the participant, rather than the number of fractures treated. For studies containing more than two intervention groups, making multiple pair-wise comparisons between all possible pairs of intervention groups possible, we planned to include the same group of participants only once in the meta-analysis.

Dealing with missing data

Where important data were missing or incomplete, we sought further information from the trial authors.

In cases where individuals were missing from the reported results, we assumed the missing values to have a poor outcome. For dichotomous outcomes that measured serious and other adverse events (e.g. incident fractures), we calculated the adverse event rate using the number of patients that received treatment as the denominator (worst-case analysis). For dichotomous outcomes that measured benefits (e.g. proportion of participants reporting pain relief of 30% or greater), we calculated the worst-case analysis using the number of randomised participants as the denominator.

For continuous outcomes (e.g. pain), we calculated the MD or SMD based on the number of patients analysed at that time point. If the number of patients analysed was not presented for each time point, we used the number of randomised patients in each group at baseline.

For continuous outcomes with no SD reported, we calculated SDs from standard errors (SEs), 95% CIs or P values. If no measures of variation were reported and SDs could not be calculated, we planned to impute SDs from other trials in the same meta-analysis, using the median of the other SDs available (Ebrahim 2013). For continuous outcomes presented only graphically, we extracted the mean and 95% CIs from the graphs using plotdigitizer (http://plotdigitizer.sourceforge.net/). For dichotomous outcomes, we used percentages to estimate the number of events or the number of people assessed for an outcome.

Where data were imputed or calculated (e.g. SDs calculated from SEs, 95% CIs or P values, or imputed from graphs or from SDs in other trials), we reported this in the Characteristics of included studies tables.

Assessment of heterogeneity

We assessed clinical heterogeneity by determining whether the characteristics of participants, interventions, outcome measures and timing of outcome measurement were similar across trials.

We assessed statistical heterogeneity by visually assessing the scatter of effect estimates on the forest plots, and by using the Chi^2 statistic and the I^2 statistic (Higgins 2003). We interpreted the I^2 statistic using the following as an approximate guide:

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

(Deeks 2011).

In cases of considerable heterogeneity, we intended to explore the data further by comparing the characteristics of individual studies and any subgroup analyses.

Assessment of reporting biases

To assess publication bias, we planned to generate funnel plots if at least 10 trials examining the same intervention comparison were included in the review, and comment on whether any asymmetry in the funnel plot was due to publication bias, or methodological or clinical heterogeneity of the trials (Sterne 2011).

To assess for potential small-study effects in meta-analyses (i.e. the intervention effect is more beneficial in smaller studies), we planned to compare effect estimates derived from a random-effects model and a fixed-effect model of meta-analysis. In the presence of small-study effects, the random-effects model will give a more beneficial estimate of the intervention than the fixed-effect estimate (Sterne 2011). However, as no statistically significant results were found, and only two placebo-controlled trials could be pooled, we could not perform this analysis.

To assess outcome reporting bias, we compared the outcomes specified in trial protocols with the outcomes reported in the corresponding trial publications.

Data synthesis

Included studies were grouped based on whether percutaneous vertebroplasty was compared with a placebo or sham procedure, usual care or another active intervention.

For benefit, we considered the first comparison, vertebroplasty versus placebo, to be the least prone to bias and it was therefore the primary comparison for addressing the objectives of this review.

For safety (new vertebral fractures and other serious and other adverse events), as the results were similar for both placebo and usual care comparisons, to simplify the presentation we presented safety data in the same analyses.

We combined results of trials with similar characteristics (participants, interventions, outcome measures and timing of outcome measurement) to provide estimates of benefits and harms. To combine results we used a random-effects meta-analysis model based on the assumption that clinical and methodological heterogeneity was likely to exist and to have an impact on the results.

'Summary of findings' table

We presented the major outcomes for the primary comparison of vertebroplasty of the review in a 'Summary of findings' table (mean pain, disability, disease-specific quality of life, overall quality of life, treatment success, incident fractures, and total number of serious adverse events). This table reports the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data for each major outcome as recommended by Cochrane (Schünemann 2011a), and was produced using GRADEpro software. The overall quality of the evidence was graded for each of the major outcomes using the GRADE approach (Schünemann 2011b). We included evidence only from trials with adequate treatment allocation concealment and blinding of participants and outcome assessment.

In the comments column, we calculated the absolute percentage change and the relative percentage change. Relative changes were calculated as absolute change (MD) divided by mean at baseline in the placebo group from Buchbinder 2009 (values were: 7.1 points on zero- to 10-point VAS pain; 17.3 points on zero- to 23-point Roland-Morris Disability questionnaire; 0.28 points on EQ-5D quality of life scale; 59.6 points on the QUALEFFO scale). In interpreting results, we assumed a minimal clinically important difference of 1.5 points on a 10-point pain scale (Grotle 2004); two to three points on the zero- to 23-point RMDQ (Trout 2005), 10 points on the zero to 100 QUALEFFO scale (Lips 1999), and 0.074 points on the EQ-5D quality of life scale, zero = death to one = perfect health (Walters 2005).

Subgroup analysis and investigation of heterogeneity

Where sufficient data were available, the following subgroup analysis was performed.

- Duration of symptoms (≤ 6 weeks versus ¿ 6 weeks)

Sensitivity analysis

Sensitivity analyses were performed to investigate the robustness of the treatment effect (of main outcomes) by performing an analysis that included all trials combined, i.e. trials with placebo or usual care comparator groups, to see if inclusion of trials that did not blind participants changed the overall treatment effect.

RESULTS

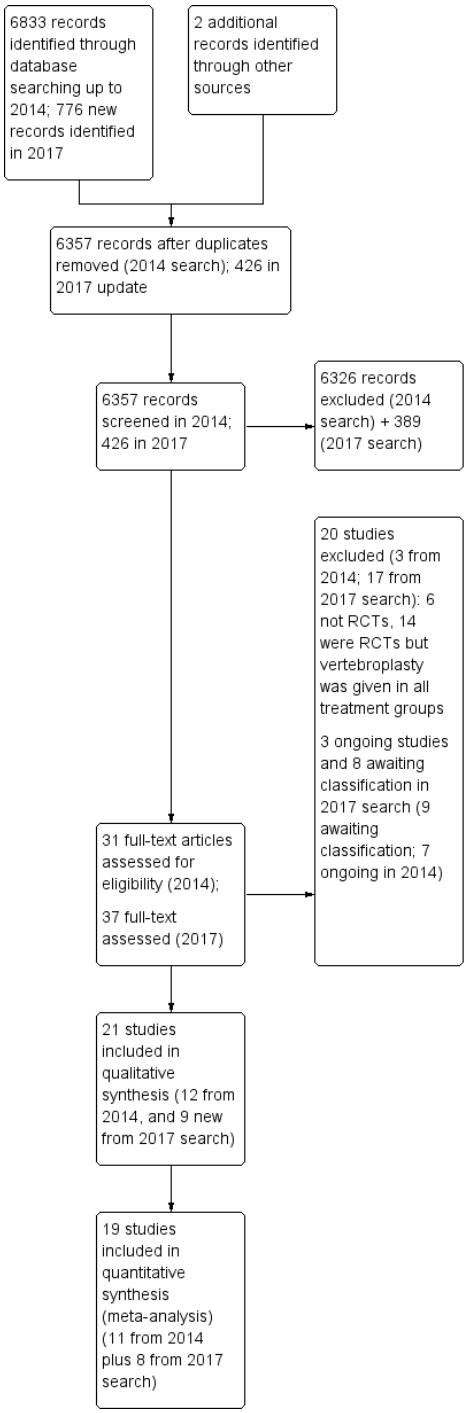
Description of studies

Results of the search

We updated the search for the current review on 15 November 2017, searching for studies published since 2014 (the date of the search in the first version of the review).

The results of the search are presented in Figure 1. The updated search strategy identified 776 new citations (426 after de-duplication). Of these, 37 were assessed in full text and nine new studies were included (Clark 2016; Evans 2015; Leali 2016; Sun 2016; VERTOS IV; VOPE 2015; Wang 2015; Wang 2016; Yang 2016). Five of these were identified as ongoing or completed studies in the 2015 version of this review and have since reported results (Clark 2016; Evans 2015; VOPE 2015; Wang 2015), or partially reported results (VERTOS IV), and are included in this review update. The partially reported results of VERTOS IV were presented at a conference but full results have not yet been published.

Figure 1. Study flow diagram.



Thus, in total in this update we included 21 trials (Blasco 2012; Buchbinder 2009; Chen 2014a; Clark 2016; Dohm 2014; Endres 2012; Evans 2015; Farrokhi 2011; Kallmes 2009; Klazen 2010; Leali 2016; Liu 2010; Rousing 2009; Sun 2016; VERTOS IV; Vogl 2013; Voormolen 2007; VOPE 2015; Wang 2015; Wang 2016; Yang 2016).

Ten randomised controlled trials (RCTs) were registered in a trial registry (Blasco 2012; Buchbinder 2009; Clark 2016; Dohm 2014; Evans 2015; Farrokhi 2011; Kallmes 2009; Klazen 2010; VERTOS IV; VOPE 2015), although one was registered retrospectively (Farrokhi 2011). One RCT reports that it is registered on clinicaltrials.gov (NCT00576546) (Vogl 2013), but this could not be verified. No trial registration was found for the other trials (Chen 2014a; Endres 2012; Leali 2016; Liu 2010; Rousing 2009; Sun 2016; Voormolen 2007; Wang 2015; Wang 2016; Yang 2016).

In total, 20 studies were excluded after full-text assessment (see table of Characteristics of excluded studies): 17 studies identified in the updated search were excluded (Cai 2015; Chen 2014b; Chun-lei 2015; Du 2014; Gu 2015; Li 2015a; Liu 2015; Min 2015; Son 2014; Xiao-nan 2014; Yang 2014; Yi 2016; Ying 2017; Yokoyama 2016; Zhang 2015a; Zhang 2015b; Zhang 2015c), in addition to the three studies excluded in the earlier version of this review (Gilula 2013; Huang 2014; Yi 2014).

Three trials are classified as ongoing, although it is unclear if the trials are completed. We could not find any trial registration details for one study (Longo 2010), while a second trial is registered at ClinicalTrials.gov with an expected completion date of December 2014 (Sun 2012), but the current recruitment status is unknown. The third trial (VERTOS V), was recorded as completed in June 2015 at clinicaltrials.gov, but the trialists subsequently altered the recruitment status in January 2017 to state that the study is now 'enrolling by invitation', with a new estimated completion date of July 2018 (see table of Characteristics of ongoing studies).

Based upon a search of trial registries, we identified an additional four registered RCTs that are reported to have been completed but we were unable to find results (Dolin 2003; Laredo (OSTEO-6); Laredo (STIC2); Sorensen 2005) (see table of Characteristics of studies awaiting classification). We also identified four completed RCTs that likely meet inclusion criteria of the review, but results are published in Chinese and we did not translate these prior to publication of this review update: two trials compare vertebroplasty with kyphoplasty (Tan 2016; Zhou 2015), another compared vertebroplasty with kyphoplasty and bone-filling mesh container (Li 2015b) and the third vertebroplasty with usual care (Chen 2015).

Since the last version of the review, we have removed three ongoing trials (Damaskinos 2015 NCT02489825; Nieuwenhuijse 2012 NTR3282); and Zhao 2014 ChiCTR-TRC-14004835), as percutaneous vertebroplasty was given to participants in both treatment arms and thus, when trial results become available, they will not be eligible for inclusion in this review. An additional trial that was reportedly suspended due to difficulty recruiting participants prior to completion and which was included as a study awaiting classification in the last version of the review (Nakstad 2008 NCT00635297) has also been removed from this current version of the review as if the trial had been completed it would not be eligible for inclusion.

Detailed descriptions of all unpublished trials that are either completed, suspended or ongoing are provided in either the table of Characteristics of studies awaiting classification or table of Characteristics of ongoing studies and a summary of all unpublished trials is provided in Table 1.

Included studies

A full description of all included trials is provided in the table of Characteristics of included studies and a summary of trial and participant characteristics is provided in Table 2.

Trial design, setting and characteristics

Five trials compared vertebroplasty with a placebo (a sham vertebroplasty procedure) (Buchbinder 2009; Clark 2016; Kallmes 2009; VERTOS IV; VOPE 2015), eight trials compared vertebroplasty with usual care/optimum pain management (Blasco 2012; Chen 2014a; Farrokhi 2011; Klazen 2010; Leali 2016; Rousing 2009; Voormolen 2007; Yang 2016), one trial compared vertebroplasty with injection of local anaesthetic and glucocorticosteroid into the facet joint of the fractured vertebra in the spine (facet joint injection) (Wang 2016), while seven trials compared vertebroplasty with different kyphoplasty techniques (Dohm 2014; Endres 2012; Evans 2015; Liu 2010; Sun 2016; Vogl 2013; Wang 2015).

Trials were conducted in 15 different countries including: Australia (Buchbinder 2009; Clark 2016), USA (Evans 2015), USA, Australia and UK (Kallmes 2009), the Netherlands (VERTOS IV; Voormolen 2007), the Netherlands and Belgium Klazen 2010), Denmark (Rousing 2009; VOPE 2015), Iran (Farrokhi 2011), Italy, France and Switzerland (Leali 2016), Spain (Blasco 2012), China (Chen 2014a; Sun 2016; Wang 2015; Wang 2016; Yang 2016), Taiwan (Liu 2010), Germany (Endres 2012), USA and Canada (Dohm 2014), and Germany and the USA (Vogl 2013).

Eight trials received at least some funding from medical device companies who manufacture vertebral augmentation systems (Buchbinder 2009; Clark 2016; Dohm 2014; Evans 2015; Farrokhi 2011; Klazen 2010; VERTOS IV; Vogl 2013); two clearly reported that they had no role in the trial (design, data collection, data analysis, preparation of the manuscript)(Buchbinder 2009; Clark 2016); while five trials did not report source of funding

(Chen 2014a; Leali 2016; Sun 2016; Voormolen 2007; Wang 2015).

Trial duration varied from two weeks (Voormolen 2007) to three years (Farrokhi 2011). Seven trials allowed cross-over: Kallmes 2009 allowed blinded cross-over to the alternate procedure at one month or later if adequate pain relief was not achieved; both Voormolen 2007 and Farrokhi 2011 allowed participants assigned to the control arm still in severe pain after two weeks to undergo vertebroplasty; Blasco 2012, Chen 2014a and Yang 2016 allowed participants in the conservative therapy group to be considered for vertebroplasty if there was no improvement in pain but the timing of this decision was not provided; and in VOPE 2015 cross-over between groups was allowed after three months although no details about who could cross over were not provided.

Trial participants

The 21 trials included 2852 randomised participants with trial sizes varying from 46 participants (Voormolen 2007) to 404 participants (Dohm 2014). In general, inclusion criteria for all trials were similar requiring a clinical history and imaging findings consistent with one or more acute osteoporotic vertebral fractures (see Characteristics of included studies table). Across all trials the majority of participants were female and Evans 2015 only included women (see Table 2). Mean age of participants ranged between 62.6 and 81 years.

Symptom duration varied across trials with mean duration ranging from around a week (Rousing 2009) to more than six months (Farrokhi 2011). For the placebo-controlled trials, mean duration of symptoms ranged from less than three weeks to 20 weeks across treatment groups in the individual trials (vertebroplasty and placebo: Buchbinder 2009 nine and 9.5 weeks; Clark 2016 2.8 and 2.4 weeks; Kallmes 2009 16 and 20 weeks; VERTOS IV 29.2 and 25.9 days; and VOPE 2015 did not report mean duration but trial inclusion specified a symptom duration of eight weeks or less).

Mean baseline pain and disability scores were similar across trials. Mean pain at baseline was greater than seven out of 10 (where 10 is the worst pain) in most trials, except the usual care group of Blasco 2012 (mean 6.3), both arms of Chen 2014a (means 6.5 and 6.4 in the vertebroplasty and usual care arms, respectively), the vertebroplasty arm of Kallmes 2009 (mean 6.9), and was low in Leali 2016 (mean 4.8 in vertebroplasty, not reported in usual care) and Leali 2016 (mean pain score 4.8 out of 25 and Oswestry Disability Index (ODI) 53.6% in the vertebroplasty group and not reported in the conservative care group). In VOPE 2015, the mean baseline pain was greater than 70 out of 100 for activity pain(74.68 in the vertebroplasty group and 76.08 in the placebo group), but not for rest pain (40.55 in the vertebroplasty group and 53.04 in the placebo group). Sun 2016 did not report baseline pain or disability scores.

Interventions

Details of interventions in each trial are presented in the Characteristics of included studies table. Vertebroplasty was performed by different specialists in the included trials: interventional radiologists in six trials (Blasco 2012; Buchbinder 2009; Clark 2016; Kallmes 2009; Klazen 2010; Voormolen 2007), orthopaedic surgeons in four trials (Chen 2014a; Endres 2012; Rousing 2009; VOPE 2015), neurosurgeons in one trial (Farrokhi 2011), spine surgeons in one trial (Wang 2016), a combination of interventional radiologists and neuroradiologists, orthopaedic surgeons and neurosurgeons in one trial (Dohm 2014), and the background of the interventionalist was not reported in eight trials (Evans 2015; Leali 2016; Liu 2010; Sun 2016; VERTOS IV; Vogl 2013; Wang 2015; Yang 2016).

Vertebroplasty appeared to have been performed in a similar way across all trials. However in Dohm 2014, the majority of participants in both treatment arms (75.1% in the vertebroplasty group and 80.6% in the kyphoplasty group) also had perioperative postural reduction in an attempt to correct vertebral deformity, and in Wang 2016 postural reduction was performed before surgery in both groups.

Mean vertebroplasty cement volume was not specified in four trials (Blasco 2012; Evans 2015; Rousing 2009; VOPE 2015) (see Characteristics of included studies table and Table 1). VOPE 2015 reported that up to 2 mL of cement was inserted but it was not clear if a uni- or bipedicular approach was used (which may mean that up to 4 mL was inserted). For the remaining trials, the mean cement volume ranged from 2.8 mL (Buchbinder 2009; Kallmes 2009) to 7.5 mL (Clark 2016). Mean (range) cement volume in the four placebo-controlled trials was 2.8 mL (1.2 ml to 5.5 mL) (Buchbinder 2009), 7.5 mL (4.7 mL to 10.3 mL) (Clark 2016), 2.8 mL (1 mL to 5.5 mL) (based upon a subset of 20 participants) (Kallmes 2009) and 5.11 mL (1 mL to 11 mL) (VERTOS IV).

There was diversity in the way that the sham vertebroplasty procedure was delivered in the five placebo-controlled trials. Buchbinder 2009 most closely simulated vertebroplasty using an identical procedure to that performed in the vertebroplasty group up to the insertion of the needle into the bone, at which point the vertebral body was gently tapped with a blunt stylet and bone cement was prepared to permeate the strong smell of the polymethylmethacrylate (PMMA) in the room. The sham procedure in the second placebo-controlled trial was similar except that the vertebral body was not tapped with a blunt stylet (Kallmes 2009). For Clark 2016, both the trial registry and protocol paper reported that the placebo involved a 4 mm skin incision and light tapping of the skin, while the results paper states that a short needle was passed into the skin incision but not as far as the periosteum and that manual skin pressure and regular tapping on the needle was performed. In VERTOS IV, verbal and physical cues (e.g. pressure on the back) and the methacrylate monomer was opened to simulate the odour of mixing the bone cement, but the needle was not placed and no cement was injected. In VOPE 2015, PMMA was also opened

for the odour but instead of cement, 2 mL of local anaesthetic (lidocaine) was injected into the fractured vertebrae.

Eight trials used variations on usual care as the comparator group (Blasco 2012; Chen 2014a; Farrokhi 2011; Klazen 2010; Leali 2016; Rousing 2009; Voormolen 2007; Yang 2016) (see Characteristics of included studies table). This included analgesics including acetaminophen, codeine, tramadol and/or opioids in all instances, and these could be adjusted as needed. Five trials specified the use of non-steroidal anti-inflammatory drugs (NSAIDs), which could have been in addition to analgesics, when simple analgesia was ineffective or for those intolerant to opioid derivatives (Farrokhi 2011; Klazen 2010; Leali 2016; Voormolen 2007; Yang 2016). Three trials also prescribed calcitonin (Blasco 2012; Farrokhi 2011; Yang 2016) and three also offered brace treatment (Chen 2014a; Rousing 2009; Yang 2016).

Seven trials compared vertebroplasty with kyphoplasty (Dohm 2014; Endres 2012; Evans 2015; Liu 2010; Sun 2016; Vogl 2013; Wang 2015). Dohm 2014, Endres 2012, Liu 2010 and Wang 2015 compared vertebroplasty with balloon kyphoplasty. Endres 2012 also compared vertebroplasty with a shield kyphoplasty which instead of a balloon, uses specialised instrumentation to create a central cavity in the vertebral body and inserts a self-expanding implant that controls the cement flow. Endres 2012 compared vertebroplasty with the same shield kyphoplasty. Evans 2015 compared vertebroplasty with kyphoplasty, however it did not report the kyphoplasty technique used. Sun 2016 compared high-viscosity cement vertebroplasty with low-viscosity cement kyphoplasty. A single trial injected a mixture of prednisolone (125 mg:5 mL) and lidocaine (100 mg:5 mL) under fluoroscopic monitoring into the facet joint of the fractured vertebra as the control intervention (Wang 2016).

Outcomes

Pain

All trials included at least one measure of pain, but its measurement varied across trials. Three trials specified pain over the preceding 24 hours (Clark 2016; Farrokhi 2011; Kallmes 2009), one trial specified pain over the course of the previous week (Buchbinder 2009), and 16 trials did not specify a time period (Blasco 2012; Chen 2014a; Dohm 2014; Endres 2012; Evans 2015; Klazen 2010; Leali 2016; Liu 2010; Rousing 2009; Sun 2016; VERTOS IV, Voormolen 2007; VOPE 2015; Wang 2015; Wang 2016; Yang 2016). Vogl 2013 only reported baseline pain in their published trial report but measurement of pain (and disability assessed by the Oswestry Disability Index (ODI)) was referred to in a congress abstract of the same trial published in German; whether or not a time period was specified is not known.

Buchbinder 2009 measured overall pain, pain at rest and pain in bed at night, while Kallmes 2009 measured average back pain intensity. Clark 2016 specified the measurement of pain at rest and pain with standing or activity in addition to average pain intensity but these results were not reported. Leali 2016 measured pain on a visual analogue scale (VAS) (zero - no pain to five - maximum pain) during walking, sitting and rising from a chair, bathing, dressing, and at rest, and summed all five scores to derive a total score out of 25. VOPE 2015 measured rest pain and pain during forward bending resembling a patient in activity (both on a zero to 100 VAS). All remaining trials referred to pain or mean pain unqualified by additional descriptors.

All but two trials, included a measure of pain using either a zero to 10 VAS or zero to 10 numerical rating scale, although the descriptor for a score of 10 differed across trials (e.g. maximum pain (Blasco 2012; Clark 2016), maximal imaginable pain (Buchbinder 2009), worst pain imaginable (Chen 2014a), worst possible (Dohm 2014), pain as bad as could be (Kallmes 2009), worst pain ever (Klazen 2010; VERTOS IV), worse pain possible (Rousing 2009), worst pain in the patient's life (Voormolen 2007), and no descriptors specified (Evans 2015; Liu 2010; Wang 2015; Yang 2016)). The pain scale investigated by Farrokhi 2011 measured pain on a one (no pain) to 10 (excruciating pain) VAS, while Endres 2012 did not specify the pain scale explicitly although it was likely to have been on a zero to 100-point scale (as mean baseline scores varied between 78.2 and 90). As described above, Leali 2016 used a zero to five VAS to measure pain during five activities and summed them for a score out of 25. Sun 2016 used a VAS to measure pain, but the scale range and descriptors (if any), were not reported. VOPE 2015 used a zero to 100 VAS and the descriptor (if any), were not reported.

Four trials also included a dichotomous measure of pain. Blasco 2012 measured the number of participants with moderate (pain $\geq$ 4) or severe (pain $\geq$ 7) pain at 12 months. Three trials included the proportion of participants with pain improved by a clinically relevant amount although the definitions varied. Buchbinder 2009 reported the proportion of people with improvement of overall pain, pain at rest and pain in bed at night of $\geq$ 2.5 units as post-hoc analyses performed at the request of the publishing journal (external reviewer request). Clark 2016 reported the proportion of participants achieving an NRS pain score of ¡4 out of 10 (from a baseline score of $\geq$ 7 out of 10). Kallmes 2009 measured the proportion of participants with clinically important improvement in pain defined as at least 30% improvement.

Four trials also included other measures of pain. Evans 2015 and Kallmes 2009 included the Pain Frequency and Pain Bothersomeness Indices (each measured on a zero to four-point scale, with higher scores indicating more severe pain). Klazen 2010 measured the number of pain-free days (defined as days with a VAS score of three or lower) and Rousing 2009 included the Dallas Pain Questionnaire (DPQ), a 16-item instrument that assesses four aspects of daily living affected by chronic back pain (day-to-day activities, work and leisure activities, anxiety and depression and social interest), measured as a percentage of pain interference in each of

the four aspects (0% is no pain and 100% is pain all the time).

Disability

All except four trials (Blasco 2012; Liu 2010; Rousing 2009; VOPE 2015), included a back-specific measure of disability or function and two trials included two back-specific measures (Chen 2014a; Wang 2016). Nine trials included the Roland-Morris Disability Questionnaire (RMDQ) (Buchbinder 2009; Chen 2014a; Clark 2016; Evans 2015; Kallmes 2009; Klazen 2010; VERTOS IV; Voormolen 2007; Wang 2016) and 10 trials included the ODI (Chen 2014a; Dohm 2014; Endres 2012; Farrokhi 2011; Leali 2016; Sun 2016; Vogl 2013; Wang 2015; Wang 2016; Yang 2016) (although no data were presented in Vogl 2013). In Dohm 2014, section eight, regarding sexual activity was removed from the ODI. Three trials also included the physical function dimension component of the SF-36 (Dohm 2014; Evans 2015; Kallmes 2009). Two trials only included the physical function dimension component of the SF-36 as a measure of disability (Rousing 2009; VOPE 2015) and two trials included no measures of disability (Blasco 2012; Liu 2010).

Evans 2015 and Kallmes 2009 also included the Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL) scale and Kallmes 2009 measured the proportion with clinically important improvement in disability (at least 30% improvement), while Rousing 2009 also included the Barthel Index and Farrokhi 2011 included ability to walk after one day.

Health-related quality of life

Eight trials did not include a measure of health-related quality of life (Chen 2014a; Endres 2012; Farrokhi 2011; Leali 2016; Liu 2010; Sun 2016; Vogl 2013; Wang 2015).

Seven trials included the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) (Blasco 2012; Buchbinder 2009; Clark 2016; Klazen 2010; VERTOS IV; Voormolen 2007; Yang 2016) as a vertebral fracture and/or osteoporosis-specific measure.

Six trials included an overall measure of health-related quality of life: five trials included the Mental Component Summary (MCS) subscale of the SF-36 (Evans 2015; Kallmes 2009; Rousing 2009; VOPE 2015; Wang 2016), eight trials included the European Quality of Life with 5 Dimensions (EQ-5D) (Buchbinder 2009; Clark 2016; Dohm 2014; Evans 2015; Kallmes 2009; Klazen 2010; Rousing 2009; VOPE 2015), one trial included the Assessment of Quality of Life (AQoL) (Buchbinder 2009), and one trial included the Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL6), Modified Deyo Patrick Pain Frequency and Bothersomeness Scale and the Osteoporotic Assessment Questionnaire (OPAQ) Body Image Scale (Evans 2015).

Treatment success

Two trials included a specific patient-reported measure of treatment success. Buchbinder 2009 defined treatment success as 'moderately better' or 'a great deal better' for pain, fatigue and overall health on seven-point ordinal scales, ranging from a 'great deal worse' to a 'great deal better'. Yang 2016 measured patient satisfaction as 'very satisfied' 'satisfied' or 'unsatisfied'.

As described above, three trials included one or more investigator-specified measures of treatment success as determined by the number of participants who achieved various thresholds of pain and/or disability improvement (Buchbinder 2009; Clark 2016; Kallmes 2009).

Incident symptomatic and/or radiographically apparent vertebral fractures

Most trials recorded the occurrence of new symptomatic and/or radiologically apparent vertebral fractures.

Three trials reported the occurrence of both (Blasco 2012 up to 12 months; Buchbinder 2009 up to 24 months; Dohm 2014 up to 24 months).

Four trials reported new symptomatic vertebral fractures (Chen 2014a up to one year; Farrokhi 2011 up to 24 months; Leali 2016 up to six months; Voormolen 2007 up to two weeks) and five trials only reported occurrence of incident radiographic vertebral fractures (Clark 2016 at six months; Klazen 2010 at one, three and 12 months; Rousing 2009 at three and 12 months; VOPE 2015 at 12 months; Wang 2016 at 12 months; Yang 2016 at one, three, six and 12 months).

Liu 2010 and Wang 2015 reported new vertebral fractures but did not specify if they were symptomatic or only detected on imaging, and Vogl 2013 reported radiographic refractures and adjacent level fractures up to 12 months and whether or not these were symptomatic. Endres 2012 only reported upon new adjacent fractures up to six months, while Evans 2015, Kallmes 2009 and Sun 2016 did not report occurrence of new vertebral fractures during the period of follow-up.

Other serious adverse events

Adverse events, other than reporting of new symptomatic or asymptomatic vertebral fractures were variably reported across trials. Ten trials made specific reference to presence/absence of other adverse events in both treated groups (Buchbinder 2009; Clark 2016; Dohm 2014; Endres 2012; Kallmes 2009; Leali 2016; Sun 2016; VERTOS IV; VOPE 2015; Yang 2016).

Blasco 2012, Chen 2014a, Wang 2015 and Yang 2016 reported on the presence/absence of clinical complications from cement leakage in the vertebroplasty-treated group but did not report whether or not other adverse events occurred in either group; Farrokhi 2011, Klazen 2010 and Voormolen 2007 reported adverse events that occurred in the vertebroplasty-treated group but did not report whether or not adverse events occurred in the usual care

group. Evans 2015, Liu 2010, Rousing 2009 and Wang 2016 did not report the presence or absence of other adverse events.

Excluded studies

One controlled trial was excluded because participants were not assigned treatment at random but rather the authors stated that a surgeon at the outpatient ward blindly chose one of three different treatment modalities (vertebroplasty, kyphoplasty or usual care) to ensure similar pre-treatment age, symptoms, grade and level of spinal diseases among the patients (Yi 2014). In addition, the vertebroplasty and kyphoplasty groups were combined in the data analysis and separate data for the vertebroplasty group were not provided. Another three studies were also excluded because participants were not assigned treatment at random (Du 2014; Yang 2014; Yokoyama 2016), and one study excluded was a retrospective study (Son 2014).

Other trials were excluded as vertebroplasty was administered to both treatment groups: with a different cement type in each group (Cai 2015; Chen 2014b; Gilula 2013; Gu 2015; Huang 2014; Li 2015a; Liu 2015; Min 2015; Xiao-nan 2014; Ying 2017; Zhang 2015a), or trials compared unipedicular vertebroplasty with bipedicular vertebroplasty (Chun-lei 2015; Zhang 2015b), or unilateral and bilateral vertebroplasty (Zhang 2015c).

Risk of bias in included studies

Risk of bias assessment for each study is reported in the Characteristics of included studies table and summarised in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

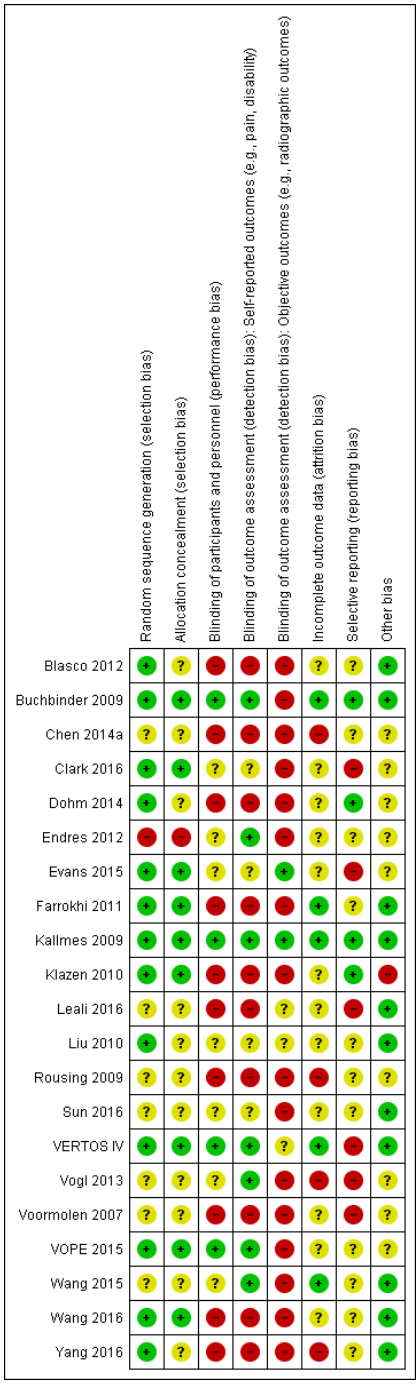
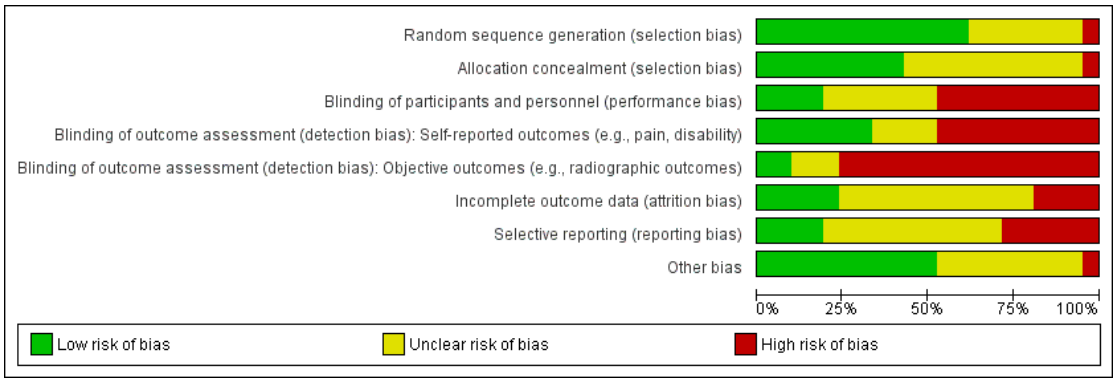


Figure 3. 'Risk of bias summary': review authors' judgements about the risk of bias of the available evidence presented as percentages across all included studies.



Allocation

Six trials described adequate sequence generation and allocation concealment and were assessed as being at low risk of selection bias (Buchbinder 2009; Clark 2016; Evans 2015; Kallmes 2009; VERTOS IV; Wang 2016). Dohm 2014 reported that randomisation was prepared by computer using a dynamic minimisation technique stratified by the number of prevalent vertebral fractures, aetiology and study centre, but treatment allocation was not concealed. Stratification by aetiology was unexplained as the selection criteria indicated that participants were included on the basis of osteoporotic fractures while fractures due to cancer and high-energy trauma were excluded.

Three additional trials were also assessed as being at low risk of selection bias even though randomisation or allocation concealment was not explicitly reported (Farrokhi 2011; Klazen 2010; VOPE 2015). Farrokhi 2011 reported that the treatment assignment was kept in sealed envelopes. It is not clearly reported who prepared and opened the envelopes, but it is likely that allocation was concealed as they reported that neither the neurosurgeon (performing vertebroplasty) nor the physician (administering usual care) knew about the other study group and had no role in allocation. Klazen 2010 reported that an independent telephone operator allocated participants by telephone, therefore the allocation was likely concealed from the investigators. VOPE 2015 reported block randomisation design using 52 envelopes but no further details were provided. However participants and the single outcome assessor, as well as the biostatistician who performed the analysis were reportedly blinded to treatment allocation.

Blasco 2012, Liu 2010 and Yang 2016 reported that they prepared a computer-generated random list but no information is provided regarding concealment of treatment allocation. In Chen 2014a, Leali 2016; Sun 2016; Vogl 2013 and Wang 2015, participants were "randomised" into treatment groups, however the trialists did not report the method of randomisation or whether concealment of treatment allocation was attempted. In Rousing 2009, sealed envelopes containing the treatment allocation were prepared beforehand by the investigating surgeon and 'sorted randomly' and type of treatment was unknown to the patient and the investigators until after the patient had provided written consent. In Voormolen 2007, the patients were randomised in two groups by an independent central operator but no further information is provided regarding concealment of treatment allocation. Endres 2012 was assessed as being at high risk of selection bias with respect to random sequence generation as participants were reported to have been distributed quasi-randomly into three groups and the method was not reported. It was judged to be at unclear risk of selection bias as the single investigator was not blinded to treatment allocation although participants were reported to be blinded and all procedures were performed under general anaesthesia.

Blinding

Two trials were judged to be at low risk of performance and detection bias for all clinical outcomes as they blinded participants and all study personnel other than the person performing the intervention, and success of participant blinding was assessed to be successful (Buchbinder 2009; Kallmes 2009). However, after the one-month follow-up, Kallmes 2009 was considered to be at

high risk of performance bias because more participants in the placebo group crossed over (27/63, 36%) compared with the vertebroplasty group (8/68, 12%) by the three-month follow-up. Buchbinder 2009 was judged to be at high risk of bias for the one- and two-year assessment of radiographically-apparent incident fractures as it was not possible to blind radiologists to treatment allocation due to the opacity of the cement. VERTOS IV was also judged to be at low risk of performance and detection bias for all clinical outcomes as they blinded participants although they did not explicitly report blinding of study personnel. Success of blinding was also assessed to be successful. In VERTOS IV it was not reported if incident fractures were detected clinically or radiographically. VOPE 2015 was also judged to be at low risk of performance and detection bias for all clinical outcomes as it appeared participants were blinded and the single assessor was blinded for all clinical outcomes, although blinding success was not evaluated. It was judged to be at high risk of bias for the assessment of radiographically-apparent incident fractures as it was not possible to blind radiologists to treatment allocation due to the opacity of the cement.

In Clark 2016, success of blinding was only reported for a subset of participants (35/55 (60%) and 35/57 (61.4%) in the vertebroplasty and placebo groups, respectively at 14 days, and not reported at three days. In those in whom this outcome was reported, results differed with 80% (28/35) of the of the vertebroplasty group correctly guessing that they had undergone vertebroplasty compared with 54% (19/35) of the control group correctly guessing that they had received a placebo. Thus, we judged this trial as having an unclear risk of performance bias and detection bias for participant-reported endpoints. Clark 2016 was judged to be at high risk of bias for radiographic outcomes as radiologists were not blinded due to the opacity of cement on imaging.

Ten trials were judged to be at high risk of performance and detection bias as participants and study personnel were likely aware of the treatment received (Blasco 2012; Chen 2014a; Dohm 2014; Farrokhi 2011; Klazen 2010; Leali 2016; Rousing 2009; Voormolen 2007; Wang 2016; Yang 2016). Evans 2015 did not report clearly if participants and personnel were blinded to treatment; the trial registry record reports the study was single-blinded, in that participants were masked, but the results paper reports that site co-ordinators and other personnel who collected trial participant data were unaware of treatment assignment. Two trials (Liu 2010; Sun 2016) were judged to be at unclear risk of detection bias for participant-reported endpoints as it was unclear whether or not participants were blinded to treatment allocation. Liu 2010 was judged to be at unclear risk of bias for radiographic outcomes of vertebral height and kyphotic angle as while these were measured by technicians who were blinded to treatment allocation, it was not clear how variability of assessment was 'controlled via inter- and intra-observer comparisons' (these outcomes were not reported in this review).

Vogl 2013 and Wang 2015 were judged to be at unclear risk of performance bias and low risk of detection bias for participant-reported outcomes as participants were blinded to treatment allocation. However both, Vogl 2013 and Wang 2015 were judged to be at high risk of detection bias for investigator-reported outcomes (In Vogl 2013, investigators were aware of treatment allocation and in Wang 2015, radiologists would have been able to tell the difference between vertebroplasty and kyphoplasty on imaging). Endres 2012 was assessed as being at unclear risk of performance bias as participants, but not the single investigator, were blinded to treatment allocation, low risk of bias for self-assessed outcomes as participants were blinded and another orthopaedic surgeon not involved in the primary surgery performed the final follow-up, and high risk of bias for investigator-reported outcomes as radiologic outcomes were analysed by the unblinded orthopaedic surgeon who performed all procedures as well as another radiologist (status of radiologist with respect to blinding not reported).

Incomplete outcome data

Five trials were assessed as at low risk for attrition bias (Buchbinder 2009; Farrokhi 2011; Kallmes 2009; VERTOS IV; Wang 2015), while the other trials were either considered to be at unclear (Blasco 2012; Clark 2016; Dohm 2014; Endres 2012; Evans 2015; Klazen 2010; Leali 2016; Liu 2010; Sun 2016; Voormolen 2007; Wang 2016) or high risk (Chen 2014a; Rousing 2009; Vogl 2013; Yang 2016).

Buchbinder 2009 had small and equal loss to follow-up across treatment groups for shorter-term benefit and safety outcomes although loss to follow-up was greater when considering longer-term outcomes. At two years, 29/38 (76%) and 28/40 (70%) had completed follow-up in the vertebroplasty and sham groups, respectively.

Kallmes 2009 had a small and balanced loss to follow-up across treatment groups up to one month.

Blasco 2012 was at unclear risk for attrition bias because while the proportion lost to follow-up at 12 months was similar between groups (17/64 (27%) from the vertebroplasty group and 13/61 (21%) from the usual care group), the authors reported that the losses may not have been random, but related to worse pain in the usual care group.

Chen 2014a was judged to be at high risk of attrition bias as they performed a completers' analysis and excluded 7/50 participants allocated to receive conservative care on the basis that four refused conservative treatment and decided to have vertebroplasty at the three-month follow-up and an additional three were lost to follow-up. However, while they stated that four participants in the vertebroplasty group were lost to follow-up, they appeared to include all 46 participants allocated to receive vertebroplasty in the analysis to 12 months.

Clark 2016 was at unclear risk for attrition bias because while the proportion lost to follow-up at three and six months was similar between groups (i.e. 8/61 (13.1%) from the vertebroplasty group

and 7/59 (11.9%) from the placebo group at three months, and 10/61 (16.7%) from the vertebroplasty group and 8/59 (13.6%) from the placebo group at six months), the proportion lost to follow-up at 14 days and one month were different (6/61 (9.8%) from the vertebroplasty group and 2/59 (3.4%) from the control group at both 14 days and one month). Reasons for withdrawal were also not reported. In addition, some data were missing for some outcomes reportedly due to inability to complete questionnaires by sick elderly participants. Most data were missing for the outcome of success of blinding at 14 days although the proportion missing was equal across treatment groups (data reported for 35/55 (60%) in the vertebroplasty group and 35/57 (61.4%) in the placebo group).

Dohm 2014 had small and equal loss to follow-up across treatment groups for shorter-term efficacy and safety outcomes. However, for the primary endpoints of new radiographic vertebral fracture at 12 and 24 months, loss to follow-up was much greater. At 12 months 130/190 (68%) and 143/191 (75%) had completed follow-up in the vertebroplasty and kyphoplasty groups, respectively, while at 24 months complete follow-up was 91/190 (48%) and 100/191 (52%) in the vertebroplasty and kyphoplasty groups, respectively. While the reasons for loss to follow-up were similar between groups, a higher proportion of those assigned to vertebroplasty (20/190; 11%) withdrew compared to the kyphoplasty group (11/191; 6%) and it is unclear if the reasons for withdrawal were systematically different.

In addition, seven participants who received vertebroplasty and four who received kyphoplasty underwent the alternate treatment for a subsequent vertebral fracture but the timing was not stated. An additional 70/88 (79.5%) participants with a new clinically recognised fracture underwent a subsequent vertebral augmentation during the trial - it is implied that these participants received the same type of procedure as they had received as part of the trial. In all instances of spinal augmentation for a new vertebral fracture, the last observation before surgery was carried forward to later visits.

Endres 2012 was judged to be at unclear risk of attrition bias as data were unavailable for seven participants (two deaths and five participants who refused follow-up although the treatment groups of these seven participants were not explicitly reported).

Evans 2015 was judged to be at unclear risk of attrition bias as a quarter of the participants did not complete follow-up (21.8% of vertebroplasty group, 29.3% of kyphoplasty group). The authors report that the pattern of loss to follow-up appeared to be missing at random.

Klazen 2010 was judged to be at unclear risk of attrition bias as a greater number of participants completed one-year follow-up in the vertebroplasty group (86/101, 85%) compared with 77/101 (76%) in the usual care group and 15 (15%) participants in the usual care group received vertebroplasty.

Leali 2016; Liu 2010; Sun 2016; Wang 2016 were judged to be at unclear risk for attrition bias because completeness of follow-up was not explicitly reported.

Rousing 2009 was judged to be at high risk of attrition bias for several irregularities including failure to report baseline and follow-up data for all participants.

Sun 2016 was judged to be at unclear risk of attrition bias as the numbers who were followed up were not reported.

In VERTOS IV, follow-up was nearly complete, with a small proportion lost in each group, for reasons that were likely unrelated to treatment.

Vogl 2013 was judged to be at high risk of attrition bias because of significant loss to follow-up in both treatment arms (follow-up complete at 12 months for 19 (68%) and 28 (57%) in the vertebroplasty and kyphoplasty groups, respectively), and the reasons for missing data were not reported.

Voormolen 2007 was judged to be at unclear risk of bias as the treatment group of four participants excluded from the analysis due to refusal to complete two-week follow-up was not reported.

VOPE 2015 was judged to be at unclear risk of bias because no data were presented for six participants who had been randomised. Two participants were excluded due to malignancy on biopsy and four were excluded due to receipt of further surgery during follow-up. The type of surgery was not specified and the treatment allocation of these exclusions was not reported.

Wang 2015 had small and similar loss to follow-up across treatment groups at three and 12 months.

Wang 2016 reported that 8/108 (7.4%) in the vertebroplasty group and 3/109 (2.7%) in the facet joint injection group were lost to follow-up.

Yang 2016 was judged to be at high risk of attrition bias as a greater number of participants were missing from the conservative treatment group compared with the vertebroplasty group (8/64 missing (13%) from vertebroplasty group and 15/66 missing (23%) from conservative treatment group). eight (12.1%) participants in the conservative treatment group received vertebroplasty, and two 2 (3%) had open surgery.

Selective reporting

Four trials were assessed as at low risk of reporting bias (Buchbinder 2009; Dohm 2014; Kallmes 2009; Klazen 2010), although Dohm 2014 included an additional outcome of time (in days) to new clinical vertebral fracture that was not pre-specified.

Six trials were judged to be at unclear risk of reporting bias because they did not appear to have been registered in a trial registry and did not publish a trial protocol (Chen 2014a; Endres 2012; Liu 2010; Rousing 2009; Sun 2016; Wang 2015; Wang 2016; Yang 2016). In addition Chen 2014a, only reported one-day outcomes for mean pain.

Blasco 2012 was judged to be at unclear risk of reporting bias because adverse events were only reported for the vertebroplasty group and mean pain and quality of life and confidence intervals were reported graphically only.

Leali 2016 was judged to be at high risk as the trialists did not report summary statistics for pain and function (only the P value to indicate if there were statistical differences between treatments). Further, the trial did not appear to have been registered and no protocol was published.

Farrokhi 2011 was judged to be at unclear risk of reporting bis as it was unclear if any additional outcomes were measured and not reported.

Clark 2016 was judged to be at high risk of reporting bias for several reasons. The primary outcome was inconsistently reported in the published protocol as both the proportion of patients whose numerical rating scale (NRS) pain score reduced from 7/10 (or more) to 4/10 (or less) at 14 days, and the proportion of patients achieving a 14-day pain score of less than four out of 10. The results paper states that the primary endpoint is the proportion of patients achieving an NRS pain score of less than four out of 10. In addition, several outcomes were pre-specified in the published protocol but not reported in the results paper and several outcomes reported in the results paper were not pre-specified.

Evans 2015 was judged to be at high risk of reported bias as adverse events were to be measured but were not reported.

Sun 2016 was judged to be at unclear risk of reporting bias as no registration or protocol were found although all outcomes reported in the methods were presented in the results.

VERTOS IV was judged to be at high risk of reporting bias as additional outcomes that were not pre-planned according to the trial protocol were reported at a conference (height loss, incident fractures, percentage with pain VAS score $\geq$ five at 12 months). Disability and quality of life were reported only in graphical format with no measures of variance. Adverse events were reported incompletely as they were not reported for the placebo group. This assessment may change when the results are published.

Vogl 2013 was judged to be at high risk of report bias because in a published congress abstract of the same trial it was reported that pain intensity on a visual analogue scale (VAS) and disability assessed by the Oswestry Disability Index (ODI) were measured, but only baseline pain was presented in the published paper. In addition, the trial registration information could not be located.

Voormolen 2007 was judged to be at high risk of bias because the number of participants with an incident clinical vertebral fracture was only reported for the vertebroplasty group and measures of variance were not reported for continuous outcomes.

VOPE 2015 was judged to be at unclear risk of bias because pain on a NRS and spirometry were not reported.

Other potential sources of bias

No other sources of bias were detected for 11 trials (Blasco 2012; Buchbinder 2009; Farrokhi 2011; Kallmes 2009; Leali 2016; Liu 2010; Sun 2016; VERTOS IV; Wang 2015; Wang 2016; Yang 2016).

Chen 2014a did not report on the number of 'prophylactic' vertebroplasties that were performed in the vertebroplasty group and did not specify a source of funding.

In Clark 2016, the description of the placebo procedure differed between the published protocol and results papers. The protocol states that a 4-mm skin incision will be made with light tapping on the skin. The results paper states that a short needle was passed into the skin incision but not as far as the periosteum and that manual skin pressure and regular tapping on the needle was done to mimic vertebroplasty needle advance.

Dohm 2014 was sponsored by a device company which also contributed to study design, data monitoring, statistical analysis and reporting of results including manuscript authorship, paid for independent core laboratory and data safety-monitoring board services, and terminated the study early.

Although Endres 2012 reported that there were no significant differences in baseline characteristics or planned vertebral treatment levels between treatment groups at baseline, participants in the vertebroplasty group appeared to be older on average than participants in the two other groups (71.3 versus 63.3 and 67.1 years in the balloon and shield vertebroplasty groups, respectively). In addition, participants in the kyphoplasty groups also appeared to have worse pain and disability scores at baseline compared to the vertebroplasty group (vertebroplasty: 78.2 and 68.2; balloon kyphoplasty: 90.0 and 77.0; and shield kyphoplasty 88.16 and 75.7, respectively). They also did not state whether BioMedEs had any role in the study other than funding translation and copy-editing.

In Evans 2015 the approach, device, and cement used for both the vertebroplasty and kyphoplasty procedures were at the operators' discretion.

Quality of life and disability were worse at baseline in the vertebroplasty group in Klazen 2010, which may have biased the results in favour of the vertebroplasty group.

In the trial by Rousing 2009, baseline pain was higher in the usual care group (8.8 versus 7.5) and it was only measured in 17/24 and 19/25 participants in the usual care and vertebroplasty-treated groups, respectively. In addition, participants receiving usual care were hospitalised for longer (11.7 days versus 7.6 days); it is unclear if more pain medication and physiotherapy was offered, and how this would affect outcomes.

Vogl 2013 reported that Soteira Inc. (Natick, MA) funded the trial and provided the Cement Directed Kyphoplasty Systems but whether or not it had any other role in the trial was not explicitly reported.

In Voormolen 2007, eight participants withdrew after randomisation as they were not assigned to their preferred treatment (two in the vertebroplasty group and six in the usual care group).

VOPE 2015 was completed in April 2014 and results have not been published in a peer-reviewed journal. Baseline pain at rest in the vertebroplasty group was lower than in the placebo group (40.55 (SE 4.55) compared with 53.04 (SE 4.35), P = 0.0476). This may have biased the results in favour of the placebo group.

Effects of interventions

See: **Summary of findings for the main comparison** Vertebroplasty for osteoporotic vertebral compression fracture

Benefits

1. Vertebroplasty versus placebo (sham)

We judged the five placebo-controlled trials to be clinically similar with respect to baseline participant characteristics of mean pain, disability and quality of life, facilitating pooling of data in a meta-analysis (see Table 2). Mean duration of symptoms ranged from less than three weeks to 20 weeks across treatment groups in the individual trials, however the influence of symptoms duration on treatment effect was investigated in a planned subgroup analysis (see below). The major outcomes for the primary comparison of vertebroplasty versus placebo (sham procedure) is shown in Summary of findings for the main comparison.

Statistical heterogeneity was moderate in the pooled analysis for pain at one to two weeks (I^2 = 32%), driven largely by the data from Clark 2016, the only placebo-controlled trial to have been judged as having unclear risk of performance bias and detection bias for participant-reported endpoints. Clark 2016 found a slight benefit in terms of pain relief with vertebroplasty, while the other studies found no evidence of an important difference with treatment. Heterogeneity was unimportant at the other time points.

There was no evidence of important differences between groups with respect to mean pain at one to two weeks (five studies, 539 participants) and a small, clinically unimportant improvement with vertebroplasty at one month (five studies, 535 participants), (standardised mean difference (SMD) -0.09 (95% confidence interval (CI) -0.30 to 0.12) at one to two weeks and SMD -0.27 (95% CI -0.44 to -0.10) at one month) (Analysis 1.1). This translates to a mean difference in pain of -0.20 (95% CI -0.69 to 0.28) at one to two weeks and -0.62 (95% CI -1.01 to -0.23 at one month on a zero to 10 VAS scale.

At one month, mean pain was five points on a zero to 10 scale with placebo and 0.6 points lower (0.2 lower to 1.0 lower) with vertebroplasty, an absolute pain reduction of 6% (2% better to 10% better) and relative reduction of 9% (3% better to 14% better) (Summary of findings for the main comparison).

Based upon four trials (Buchbinder 2009; Clark 2016; VERTOS IV; VOPE 2015), there was no evidence of important differences between groups in pain at three months (SMD -0.20, 95% CI -0.40 to -0.00, 394 participants), which translates to a mean reduction of 0.46 (-0.2 to 2.3) points (95% CI 0.92 to 0) on a 10-point VAS scale.

Based upon three trials (Buchbinder 2009; Clark 2016; VERTOS IV), there was no evidence of important differences between groups in pain at six months (SMD -0.21 (-0.42 to 0.01), 339 participants), which translates to a mean reduction of 0.48 points (95% CI -0.97 to 0.02) on a 10-point VAS scale. Based upon data from three trials (Buchbinder 2009; VERTOS IV; VOPE 2015), there was no evidence of important differences between groups in pain at 12 months (SMD -0.17 (-0.41 to 0.06, 269 participants), which translates to a mean reduction of 0.37 points (95% CI -0.94 to 0.14) on a 10-point VAS scale; and based on data from a single trial (Buchbinder 2009), no differences at 24 months were observed (MD -1.10 points on a zero to 10 VAS scale, 95% CI -2.68 to 0.48, 57 participants), although the lower limit of the 95% CI means that an important difference can neither be confirmed or excluded.

We combined data from three trials that included a measure of the proportion of participants whose pain improved from baseline by a 'clinically important' amount although the definitions varied by trial (¿ 2.5 units from baseline (Buchbinder 2009), 30% or more from baseline (Kallmes 2009), four or less out of 10 (Clark 2016)). Statistical heterogeneity was moderate to substantial at one to two weeks (I^2 = 51%), and one month (I^2 = 61%), but was unimportant at other time points that included combined data. Similar to the data for mean pain, this appeared to be driven by data from Clark 2016, which showed a benefit in terms of this outcome, while the other studies found no evidence of important differences with treatment. There was a benefit of vertebroplasty only at three and six months although the effect estimates were all greater than one: one to two weeks (data from two trials (Buchbinder 2009; Clark 2016): vertebroplasty: 38/99 versus placebo: 26/99, RR 1.43, 95% CI 0.78 to 2.60); one month (data from three trials (Buchbinder 2009; Clark 2016; Kallmes 2009): vertebroplasty: 89/166 versus placebo: 56/160, RR 1.53, 95% CI 0.99 to 2.36); three months (data from two trials (Buchbinder 2009; Clark 2016): vertebroplasty: 48/99 versus placebo: 30/99, RR 1.60, 95% CI 1.12 to 2.30); six months (data from two trials (Buchbinder 2009; Clark 2016): vertebroplasty: 54/99 versus placebo: 39/99, RR 1.38, 95% CI 1.02 to 1.87); 12 months (data from one trial (Buchbinder 2009): vertebroplasty: 15/38 versus placebo: 13/40, RR 1.21, 95% CI 0.67 to 2.20); and 24 months (data from one trial (Buchbinder 2009): vertebroplasty: 19/38 versus placebo: 14/40, RR 1.43, 95% CI 0.84 to 2.42)(Analysis 1.2). These results may be sensitive to different cut-off values (e.g. if Clark 2016 had utilised a cut-off pain score of four or less out of 10 for this outcome as also stated in their protocol, rather than ¡ 4 out of 10).

We could only combine data for up to three trials at any time point for back-related disability (Buchbinder 2009; Clark 2016; Kallmes 2009). Statistical heterogeneity for disability was moderate to substantial in the pooled analysis at one to two weeks (I^2 = 54%), and substantial to considerable at three months (I^2 = 79%) and six months (I^2 = 73%) but was zero at one month.

With respect to disability (measured with the RMDQ [zero to 23 scale]), there was a small, clinically unimportant improvement with vertebroplasty at one month (3 studies, 296 participants, MD -1.72, 95% CI -3.13 to -0.31). At one to two weeks (three studies,

299 participants), the MD was -0.02 points (95% CI -2.07 to 2.03); at three months (two studies, 162 participants) the MD was -0.87 points (95% CI -5.57 to 3.83); and at six months (two studies, 159 participants), the MD was -2.41 points (95% CI -6.23 to 1.41) (Analysis 1.3). While the lower 95% CIs in these analyses means that an important difference between groups can neither be confirmed or refuted, these results were largely driven by the data from Clark 2016, which had unclear risk of performance bias and detection bias for participant-reported endpoints.

There was no evidence of important between-group differences in RMDQ scores at 12 and 24 months based upon data from one trial (Buchbinder 2009; Analysis 1.3). One additional trial that measured RMDQ but not in a form that could be included in the pooled analysis, found no evidence of an important difference between groups in outcome for this measure up to 12 months (VERTOS IV). Data from the fifth trial did not measure disability by the RMDQ, but did report SF-36 physical function data for three and 12 months and also observed no important differences between groups (data not shown) (VOPE 2015).

At one month, the mean RMDQ was 14.2 points in the placebo group and 1.7 points lower (0.3 lower to 3.1 lower) in the vertebroplasty group, an absolute improvement in disability of 7% (1% better to 14% better) and relative improvement of 10% (2% better to 18% worse) (Summary of findings for the main comparison).

With respect to vertebral fracture and/or osteoporosis-specific health-related quality of life (measured by the QUALEFFO), there was a small clinically unimportant improvement with vertebroplasty at one to two weeks (2 studies, 176 participants, MD -4.76, 95% CI -7.83 to -1.68). At one month (two studies, 175 participants), the MD was -2.75 (95% CI -9.02 to 3.53); at three months (one study, 73 participants), the MD was -0.10 (95% CI -5.51 to 5.31); at six months (two studies, 165 participants), the MD was -3.34 (95% CI -10.50 to 3.81); at 12 months (one study, 67 participants), the MD was -2.10 (95% CI -8.21 to 4.01); and at 24 months (one study, 57 participants), the MD was 1.30 (95% CI -5.48 to 8.08) at (Analysis 1.4).

One trial found no evidence of important differences between groups in treatment success up to 24 months (Analysis 1.5).

There were no important differences between groups with respect to overall quality of life (measured with the EQ5D): MD 0.01 (95% CI -0.03 to 0.05) at one to two weeks (two studies, 164 participants); MD 0.05 (95% CI 0.01 to 0.09); at one month (three studies, 285 participants); MD 0.04 (95% CI -0.00 to 0.08); at three months (three studies, 203 participants); MD 0.06 (95% CI 0.01 to 0.10); at six months (two studies, 156 participants); MD -0.05 (95% CI -0.17 to 0.07); at 12 months (two studies, 93 participants); MD 0.00 (95% CI -0.24 to 0.24); at 24 months (one study, 44 participants) (Analysis 1.6).

2. Vertebroplasty versus usual care

The eight trials that compared vertebroplasty with usual care included participants with similar levels of baseline pain and disability and gender distribution was also similar across trials (see Table 2). Although one trial included younger participants (Chen 2014a), and the duration of symptoms varied from one week to six months, we judged that the trials were sufficiently clinically homogenous to allow data to be pooled. Data for pain and function from Leali 2016 could not be included in meta-analyses as means and variance were not reported. In instances where analyses within a single data plot required a mix of MD and SMD analyses, we have shown the SMD in the plots and present both the SMD and MD in the results. For clarity, we have indicated where the MD was back-transformed from the SMD to MD (either because Farrokhi 2011 was included together with other trials in the same meta-analysis for mean pain or because both RMDQ and ODI were included in the same meta-analysis for disability).

Based upon data from up to six trials, participants in the vertebroplasty group had greater improvement in mean pain compared with those in the usual care group at one to two weeks (six trials, 627 participants, SMD -1.33 (95% CI -2.26 to -0.39), back-transformed MD -2.13 (95% CI -3.62 to -0.62); one month (three trials, 384 participants), SMD -2.06 (95% CI -3.35 to -0.76), back-transformed MD -3.30 (95% CI -5.36 to -1.22); three months (six trials, 627 participants, SMD -1.18 (95% CI -1.95 to -0.40), back-transformed MD -1.89 (95% CI -3.12 to -0.64); six months (five trials, 573 participants, SMD -1.05 95% CI -1.82 to -0.28), back-transformed MD -1.68 (95% CI -2.91 to -0.45); and 12 months (six trials, 612 participants, SMD -1.02 (95% CI -1.74 to -0.30), back-transformed MD -1.63 (95% CI -2.78 to -0.48) (Analysis 2.1). However there was considerable statistical heterogeneity across all pooled pain analyses with the I^2 varying between 94% and 96%. Removing single trials from each analysis did not appreciably alter the results. At 24 months there was no evidence of important differences between groups in mean pain based upon one trial (77 participants, SMD -0.45 (95% CI -0.90 to 0.01) or MD -0.90 (95% CI -1.79 to -0.01).

There was no evidence of important differences between groups in the proportion of participants who reported moderate or severe residual pain at 12 months (vertebroplasty: 36% and 19%; usual care 34% and 18%, respectively) in one trial (Blasco 2012).

Based upon data from up to five trials, improvement in disability also favoured the vertebroplasty group at one to two weeks (five trials, 494 participants) SMD -2.06 (95% CI -3.28 to -0.83), back-transformed (0 to 23 RMDQ scale) MD -8.65 (95% CI -13.78 to -3.49); one month (three trials, 378 participants) SMD -1.52 (95% CI -3.00 to -0.04), back-transformed MD -6.38 (95% CI -12.60 to -0.17); three months (four trials, 460 participants) SMD -2.76 (95% CI -4.65 to -0.87), back-transformed MD -11.59 (95% CI -19.53 to -2.09); six months (four trials, 461 participants) SMD -1.84 (95% CI -3.37 to -0.30), back-transformed MD -7.73 (95% CI -14.15 to -1.26); 12 months (four trials, 455 participants) SMD -1.59 (95% CI -2.79 to -0.38), back transformed MD -6.68 (95% CI -11.72 to -0.91); and 24 months (one

trial, 77 participants) SMD -5.65 (95% CI -6.67 to -4.63) and MD -12.00 points on 0 to 100 ODI scale (95% CI -12.94 to -11.06) (Analysis 2.2). Considerable statistical heterogeneity was also present for all analyses (I^2 ranging from 97% to 98%). Data from the sixth trial did not measure disability by the RMDQ or ODI, but did report SF-36 physical function data for three and 12 months and observed no important differences between groups (data not shown) (Rousing 2009).

There was no significant between-group differences with respect to vertebral fracture or osteoporosis-specific quality of life at any time point measured by the QUALEFFO, based upon data from up to four trials (one to two weeks: four trials, 448 participants, MD -5.67 (95% CI -11.65 to 0.32); one month: two trials, 289 participants, MD -10.18 (95% CI -21.49 to 1.13); three months: three trials, 415 participants, MD -5.83 (95% CI -15.41 to 3.75); six months: three trials, 415 participants, (MD -5.14 (95% CI -15.02 to 4.74); and 12 months: three trials, 415 participants, MD -3.40 (95% CI -9.90 to 3.11)) (Analysis 2.3). Considerable statistical heterogeneity was also present for all analyses (I^2 varying between 83% and 95%).

Overall quality of life measured by the EQ-5D marginally favoured the vertebroplasty group at one to two weeks (one trial, 183 participants, MD 0.08 (95% CI 0.00 to 0.15)); one month (one trial, 183 participants, MD 0.09 (95% CI 0.01 to 0.16)); and three months (two trials, 215 participants, MD 0.10 (95% CI 0.00 to 0.20)), but not six months (one trial, 183 participants, MD 0.07 (95% CI -0.02 to 0.15)) or 12 months (two trials, 215 participants, MD 0.07 (95% CI -0.00 to 0.14))(Analysis 2.4). Statistical heterogeneity was unimportant for the pooled analyses (I^2 0% to 22%).

Treatment success was reported in one trial (Yang 2016) at 12 months (RR 1.43, 95% CI 1.03 to 1.98).

3. Vertebroplasty versus kyphoplasty

No efficacy data relevant to this review could be extracted from Vogl 2013. The aim of this trial was to compare leakage rates between treatment groups and only vertebral height and wedge angle were measured as efficacy outcomes. Only one of the four trials reported an *a priori* sample size calculation (Dohm 2014). However this trial was terminated after recruiting 404 of the planned sample size of 1234 participants.

Based upon data from up to four trials, there was no evidence of important differences between groups in pain at all time points: MD -0.06 (95% CI -0.37 to 0.25) at one to two weeks (two trials, 462 participants); MD -0.05 (95% CI -0.59 to 0.48) at one month (two trials, 441 participants); MD 0.14 (95% CI -0.11 to 0.39) at three months (two trials, 419 participants); MD -0.04 (95% CI -0.31 to 0.22) at six months (three trials, 230 participants); MD 0.16 (95% CI -0.07 to 0.40) at 12 months (four trials, 558 participants); MD -0.15 (95% CI -0.56 to 0.27) at 24 months (two trials, 320 participants) (Analysis 3.1). Statistical heterogeneity was unimportant for all analyses (I^2 varying between 0% and 7%).

Based upon data from up to four trials, there was no evidence of important differences between groups in degree of improvement in disability at all time points: one to two weeks (one trial, 98 participants) MD (0 to 100 ODI scale) 0.10 95% CI -2.12 to 2.32); one month (two trials, 425 participants) SMD -0.11 (95% CI -0.30 to 0.08), back-transformed to 0 to 23 RMDQ scale: MD -0.73 (95% CI -1.98 to 0.53); three months (two trials, 399 participants) MD 0.52 (95% CI -1.53 to 2.58); six months (one trial, 93 participants) SMD -0.06 (95% CI -0.46 to 0.35), back-transformed MD -0.40 (95% CI -3.03 to 2.31); 12 months (four trials, 542 participants) SMD 0.00 (95% CI -0.16 to 0.17), back-transformed MD 0.00 (95% CI -1.06 to 1.12); and 24 months (one trial, 201 participants) MD -1.30 (95% CI -6.45 to 3.85) (Analysis 3.2). Statistical heterogeneity was unimportant for all analyses (I^2 = 0%).

Based upon up to two trials, there was also no evidence of important differences between groups in degree of improvement in overall quality of life at one, three, six, 12 or 24 months (Analysis 3.3).

4. Vertebroplasty versus facet joint injection

Based upon one trial that compared vertebroplasty with facet joint injection with glucocorticosteroid and local anaesthetic, vertebroplasty was reported to be superior to facet joint injection with respect to improvement in pain on a zero- to 10-point scale (MD -1.61, 95% CI -1.84 to -1.38, 206 participants) and disability on the RMDQ 0 to 23-point scale (MD -3.42, 95%CI -3.72 to -3.12, 206 participants) at one week (Analysis 4.1; Analysis 4.2). There was no evidence of important differences between groups at other time points up to 12 months in pain or disability or quality of life (not reported at the one- to two-week time point).

Harms

1. Vertebroplasty versus placebo (sham) or usual care

New clinically apparent and new radiographic fractures

Based upon seven trials (control group was placebo for two trials and usual care for the other trials), there were slightly more new clinically apparent vertebral fractures at 12 months in the vertebroplasty group (70 fractures in 509 participants (14%)) in comparison with the control group (59 fractures in 511 participants (12%)), but this was not statistically significant (RR 1.08 (95% CI 0.62 to 1.87)) (Analysis 5.1). There was substantial statistical heterogeneity (I^2 49%), and clinical diversity: apart from different comparators, the trials also varied in terms of the age of participants (average age was younger in one trial) and symptom duration which varied from a mean of nine to 20 weeks.

There were no evidence of important differences between groups in the number of new radiographic vertebral fractures at 12 to 24 months based upon seven trials (vertebroplasty: 63 fractures in 327 participants (19.3%), control: 79 fractures in 335 participants (23.6%); RR 1.20 (95% CI 0.67 to 2.15) (control was placebo in three trials and usual care in four trials) (Analysis 5.2). However there was substantial statistical heterogeneity in the pooled analysis (I^2 68%). Similar to the above analyses, other than the comparators, participants in the individual trials differed mainly with respect to symptom duration (ranging from mean duration of less than a week to 20 weeks).

Other serious adverse events

Data from the three placebo-controlled trials (Buchbinder 2009; Clark 2016; Kallmes 2009) and two usual care-controlled trials (Leali 2016; Yang 2016) could be pooled. Based upon these trials, there were no significant between-group differences in the number of other serious adverse events (vertebroplasty: 18/408, placebo: 26/413; RR 0.64 (95% CI 0.36 to 1.12)(Analysis 5.3). However, several trials reported serious adverse events related to vertebroplasty.

Buchbinder 2009 reported that three participants reported new rib fractures (one in the vertebroplasty group and two in the placebo group) and one participant who received vertebroplasty developed an adjacent new fracture and osteomyelitis requiring surgical drainage and antibiotic therapy. Nine other adverse events were reported in the vertebroplasty group up to one month (chest pain (three participants), pain or burning in thigh or leg (three participants), tightness in the back or rib cage (one participant), stomach pain (one participant), increased pain or muscle cramping around puncture site (one participant)) compared to one in the placebo group (pain or burning in thigh or leg (one participant)).

Clark 2016 reported that one patient had a respiratory arrest after administration of sedation, before starting the procedure. The patient was resuscitated and underwent the trial procedure two days later without incident. Another patient sustained a supracondylar humerus fracture in a paretic arm during transfer onto the radiology table. The fracture healed with a plaster cast.

Kallmes 2009 reported that one participant in the vertebroplasty group had an injury to the thecal sac during the procedure requiring hospitalisation while one participant in the placebo group was also hospitalised overnight due to tachycardia and rigours of unknown cause.

Klazen 2010 reported that two participants required atropine because of pain-induced vasovagal reactions during the vertebroplasty procedure and a third participant developed an acute asthma exacerbation that led to stopping the procedure, although it was successfully completed one week later. These data could not be included in the pooled analysis as no adverse event data were reported for the usual care group. They also reported that asymptomatic cement leakage occurred in 97 of the 134 treated vertebrae (72%); most leakages were discal or into segmental veins and in one participant there was asymptomatic cement migration towards the lungs.

Voormolen 2007 reported that one participant in the usual care group who crossed over and received vertebroplasty after two weeks developed acute pain following the procedure due to an intrapedicular cement spur that broke upon manipulation by the bone biopsy needle causing a small cortical chip fracture at the medial border of the pedicle.

Farrokhi 2011 reported that one participant who received vertebroplasty developed severe right lower extremity pain and weakness due to epidural cement leakage which required immediate decompression through a bilateral laminectomy and evacuation of bone cement. After two months there was no radicular pain and the participant could walk unassisted. They reported that there were no instances of venous emboli or infection.

Blasco 2012 reported that asymptomatic cement leakage into the veins/discs during vertebroplasty occurred in 49% of procedures.

Chen 2014a reported that asymptomatic cement leakage occurred in 36 out of 69 (52%) treated vertebrae: intervertebral disc in eight participants (22%), puncture path in seven participants (19%), paravertebral space in nine participants (25%) and venous leakage in 12 participants (33%). There was asymptomatic cement migration into the venous system towards the lungs in two participants (2.9%).

2. Vertebroplasty versus kyphoplasty

New clinically apparent and radiographic fractures

Dohm 2014 reported 50/190 new clinically apparent vertebral fractures among participants who received vertebroplasty and 38/191 among those who received kyphoplasty over the course of the trial (RR 1.32 (95% CI 0.91 to 1.92)) (Analysis 6.1). Seventeen new clinical fractures were reported to have occurred within 30 days of vertebroplasty and nine within 30 days of kyphoplasty. One participant developed a new symptomatic vertebral fracture within two days of receiving vertebroplasty at the level below the procedure associated with inferior cement leakage, and it was considered to be possibly bone cement-related.

There was no evidence of important differences between groups in the number of new radiographic vertebral fractures at 12 months based upon two trials (vertebroplasty: 58 fractures in 181 participants (32.0%), control: 54 fractures in 191 participants (28.3%); RR 0.81 (95% CI 0.21 to 3.17)(Analysis 6.2). At 24 months, based upon data from one trial (Dohm 2014) there were reported to be 64/111 new radiographic vertebral fractures in the vertebroplasty group and 54/110 in the kyphoplasty group (RR 1.17 (95% CI 0.92 to 1.51)). The denominators reported in both these analyses differed from the numbers reported to have completed

12- and 24-month follow-up in both groups according to the flow diagram in the published reports.

Endres 2012 reported that there were no adjacent vertebral fractures in any of the three treatment groups (vertebroplasty, balloon or shield kyphoplasty) up to six months.

Vogl 2013 reported that one participant in the shield kyphoplasty group experienced a symptomatic refracture at the treated level (and was retreated with vertebroplasty), while there were no refractures in the vertebroplasty group up to 12 months. They also reported that three adjacent level fractures were detected in one participant in the vertebroplasty group (3/39 levels treated, 7.7%) compared with two adjacent fractures in two participants (2/65 levels treated, 3.1%) in the kyphoplasty group up to 12 months.

Other serious adverse events

Dohm 2014 reported device/procedure/anaesthesia-related (or possibly related) adverse events among 11 participants in the vertebroplasty group and 12 in the kyphoplasty group (RR 0.91, 95% CI 0.42 to 1.97, Analysis 6.3). Most of these occurred within 30 days of the procedures. Adverse events considered to be serious and related (or possibly related) to the anaesthesia included constipation (one kyphoplasty), procedural hypotension (one kyphoplasty), nausea/vomiting (one kyphoplasty), hypersensitivity (one vertebroplasty), postoperative change in mental status (one vertebroplasty), hallucination (one kyphoplasty), exacerbation chronic airways disease (one kyphoplasty), hypoxia (one vertebroplasty), and respiratory failure (one vertebroplasty). Adverse events considered serious and bone cement-related (or possibly related) included symptomatic cement embolism (one in each group). Three participants in each group had procedural pain considered to be device-related (or possible related) adverse events (4/4 and 2/3 were judged as serious events in the vertebroplasty and kyphoplasty groups, respectively). Other adverse events reported to be considered serious and device-related (or possible related) included spinal fracture (one kyphoplasty), symptomatic vertebral fracture (two vertebroplasty, one kyphoplasty) (the distinction between these two adverse events was not clear), back pain (three vertebroplasty, two kyphoplasty), arthralgia (one kyphoplasty) and muscle spasm (one kyphoplasty).

Additionally, one participant who received vertebroplasty developed implant site extravasation into the spinal canal considered non serious. A computed tomography (CT) scan demonstrated no significant canal stenosis and the participant required no medical intervention. One participant who received vertebroplasty also developed a haematoma, considered non serious and possibly related to the procedure as a result of lying prone on the operating table. No deaths were noted as device- or procedure-related.

Wang 2015 reported that there were no other serious adverse events in the vertebroplasty group but two in the kyphoplasty group (RR 0.20, 95% CI 0.01 to 4.14, Analysis 6.3). One patient experienced severe discogenic back pain related to a disk leak and finally underwent discectomy with posterior spinal fusion. Another patient experienced an asymptomatic cement emboli in the right lung related to venous leakage.

Endres 2012 reported that no clinically relevant adverse events were observed in any of the three treatment groups. No clinically relevant complications arose from cement leakage in any of the three treatment groups and there were no significant differences in cement leakage between groups (vertebroplasty: four lateral and four disc leakages; balloon kyphoplasty: three lateral and one disc; shield kyphoplasty: one disc).

Sun 2016 reported cement leakage in 9/54 (17%) vertebrae treated with vertebroplasty and 11/60 (18%) vertebrae treated with kyphoplasty.

Vogl 2013 reported that two participants treated with vertebroplasty and four treated with shield kyphoplasty died during the course of the trial from causes unrelated to the interventions. No clinically relevant complications (or symptoms) were reported to have arisen from cement leakage in either treatment group. Shield kyphoplasty was reported to have resulted in significantly fewer cement leaks overall (six levels had multiple leaks with 42 total leaks compared with 12 levels with multiple leaks, total 54 leaks in the vertebroplasty group, P value reported 0.0132) and cement leaks per level (data only showed graphically in percentages, P value 0.0012), compared with the vertebroplasty group.

4. Vertebroplasty versus facet joint injection

New fractures

One trial that evaluated vertebroplasty versus facet joint injection reported no difference in incident radiographic vertebral fractures at 12 months (13/100 in vertebroplasty group versus 11/106 in the facet joint injection group (RR 1.25; 95% CI 0.59 to 2.67; Analysis 7.1).

Subgroup Analysis

Data from the four placebo-controlled trials were available for subgroup analysis comparing participants with pain duration ≤ 6 weeks versus ¿ 6 weeks. Duration of pain did not influence outcome. In particular no differences were observed for pain duration ≤ 6 weeks versus ¿ 6 weeks with respect to pain at one to two weeks (Analysis 8.1) or one month (Analysis 8.2), disability at one to two weeks (Analysis 8.3) or one month (Analysis 8.4), or quality of life at one month (Analysis 8.5). These results are supported by the lack of between-group differences in pain, disability or quality of life outcomes in the fifth placebo-controlled trial which only included participants with pain up to eight weeks in duration (VOPE 2015).

Sensitivity Analyses

Including open trials comparing vertebroplasty with usual care altered the results, and the considerable statistical heterogeneity makes interpretation of these results difficult. In comparison to the lack of important between-group differences when only placebo-controlled trials were included in analyses, the addition of trials with a usual care control resulted in the analysis favouring vertebroplasty for all endpoints assessed in the sensitivity analysis with some differences possibly reaching clinically importance (pain at one to two weeks (11 trials, 1166 participants, SMD -0.76 (-1.30 to -0.22), back-transformed MD -1.75 (95% CI -2.99 to -0.51), I^2 95%); one month (eight trials, 919 participants, SMD -0.94 (-1.55 to -0.34), back-transformed MD -2.16 (95% CI -3.57 to -0.78), I^2 95%); and three months (10 trials, 1021 participants, SMD -0.78 (-1.28 to -0.29), back-transformed MD -1.79 (95% CI -2.94 to -0.67), I^2 93%); disability at one to two weeks (eight trials, 793 participants, SMD -1.25 (-2.06 to -0.43), back-transformed MD -3.63 (95% CI -5.97 to -1.25) and I^2 96%); one month (six trials, 674 participants, SMD -0.88 (-1.60 to -0.17), back-transformed MD -2.55 (95% CI -4.64 to 0.0.49), I^2 95%) and three months (six trials, 622 participants, SMD -1.85 (-3.08 to -0.61), back-transformed MD -5.37 (95% CI -8.93 to -1.77), I^2 98%).

DISCUSSION

Summary of main results

Vertebroplasty versus placebo (sham procedure)

Compared with placebo (sham vertebroplasty), high-quality evidence based upon five trials (541 randomised participants, one trial with incomplete data reported) indicates that vertebroplasty provides no clinically important benefits with respect to pain or disability, and moderate-quality evidence of no benefits in terms of quality of life or treatment success up to one month (Summary of findings for the main comparison).

We did consider downgrading the evidence for all outcomes due to potential publication bias, however there is only one additional placebo-controlled trial for which results are unavailable. We suspect that if the evidence from this trial becomes available, the conclusion is unlikely to change substantially. The evidence for quality of life and treatment success was downgraded from high to moderate due to imprecision but it is also unlikely that further data will alter our conclusions for these outcomes.

At one month, mean pain (on a scale zero to 10, higher scores indicate more pain) was five points with placebo and 0.6 points better (0.2 better to 1 better) with vertebroplasty, an absolute pain reduction of 6% (2% better to 10% better, minimal clinical important difference is 15%) and relative reduction of 8% (3% better to 14% better) (five trials, 535 participants). At one month, mean disability measured by the Roland-Morris Disability Questionnaire (RMDQ) (scale range zero to 23, higher scores indicate worse disability) was 14.2 points in the placebo group and 1.7 points better (0.3 better to 3.1 better) in the vertebroplasty group, absolute improvement in disability 7% (1% to 14% better), relative change 10% better (3% to 18% better) (three trials, 296 participants).

At one month, disease-specific quality of life measured by the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) (scale zero to 100, higher scores indicating worse quality of life) was 62 points in the placebo group and 2.75 points (3.53 worse to 9.02 better) in the vertebroplasty group, absolute change: 3% better (4% worse to 9% better), relative change 5% better (6% worse to 15% better (two trials, 175 participants). At one month, overall quality of life measured by the EQ5D (0 = death to 1 = perfect health, higher scores indicate greater quality of life at one month was 0.38 points in the placebo group and 0.05 points better (0.01 better to 0.09 better) in the vertebroplasty group, absolute improvement in quality of life 5% (1% to 9% better), relative change 18% better (4% to 32% better) (three trials, 285 participants). Based upon one trial (78 participants) at one month, 9/40 (or 225 per 1000) people perceived that treatment was successful in the placebo group compared with 12/38 (or 315 per 1000; 95% CI 150 to 664) in the vertebroplasty group, RR 1.40 (95% CI 0.67 to 2.95), absolute risk difference 9% more reported success (11% fewer to 29% more); relative change 40% more reported success (33% fewer to 195% more).

Based upon moderate-quality evidence from seven trials (four placebo, three usual care, 1020 participants), with up to 24 months follow-up, we are uncertain whether or not vertebroplasty increases the risk of new symptomatic vertebral fractures (70/509 (or 130 per 1000; range 60 to 247) observed in the vertebroplasty group compared with 59/511 (120 per 1000) in the control group; RR 1.08 (95% CI 0.62 to 1.87)). The evidence was downgraded due to imprecision.

Similarly, based upon moderate-quality evidence from five trials (three placebo, two usual care, 821 participants), the risk of other adverse events may not differ (18/408 (or 76 per 1000, range 6 to 156) were observed in the vertebroplasty group compared with 26/413 (or 106 per 1000) in the control group; RR 0.64 (95% CI 0.36 to 1.12)). The evidence was downgraded due to imprecision. Notably, serious adverse events reported with vertebroplasty included osteomyelitis, cord compression, thecal sac injury and respiratory failure.

Our subgroup analyses provided limited evidence that the effects did not differ according to duration of pain $\leq$ 6 weeks versus ¿ 6 weeks.

Including data from the eight trials that compared vertebroplasty with usual care in a sensitivity analyses altered the primary results

towards favouring vertebroplasty, with all combined analyses displaying considerable heterogeneity, largely driven by the variation in results amongst the studies with a usual care comparison. These data are explainable on the basis that trials that used a usual care comparator are likely to have provided a biased overestimate of the benefits of vertebroplasty due to the lack of participant blinding. At all analysed time points (one to two weeks, one and three months), sensitivity analyses indicated significant differences in outcome for pain and disability outcomes for trials that included a placebo group in comparison to a usual care control.

Vertebroplasty versus other comparators

Consistent with the sensitivity analysis, synthesis of the available data from up to six of the eight trials that compared vertebroplasty with usual care in an open design, generally favoured vertebroplasty with respect to pain and disability at all time points up to 24 months although there was considerable statistical heterogeneity across all pooled pain analyses with I^2 varying between 94% and 98%. There was no significant between-group differences with respect to vertebral fracture or osteoporosis-specific quality of life at any time point based upon data from up to four trials and these pooled data also displayed considerable statistical heterogeneity (I^2 varying between 83% and 95%). However, overall quality of life marginally favoured the vertebroplasty group up to three months but not six months and statistical heterogeneity was unimportant for these pooled analyses (I^2 0% to 22%).

Synthesis of the available data from up to three of the seven trials that compared vertebroplasty with kyphoplasty, indicate that there was no important differences between groups with respect to pain, disability or overall quality of life at any time point. Statistical heterogeneity was unimportant for all analyses (I^2 varying between 0% and 7%). There were also no detectable between-group differences with respect to incident radiographic or symptomatic vertebral fractures, adjacent fractures or other serious adverse events.

Based upon one trial that compared vertebroplasty with facet joint injection with glucocorticosteroid and local anaesthetic, vertebroplasty was reported to be superior to facet joint injection with respect to pain and disability at one week, and not superior for any outcomes at other time points up to 12 months. There was also no evidence of important differences between groups with respect to incident radiographic vertebral fractures at 12 months.

Overall completeness and applicability of evidence

This review included evidence provided from 20 randomised controlled trials (RCTs) and one quasi-RCT undertaken across 15 countries, to assess the effects of vertebroplasty compared with either placebo (sham) (five trials), usual care (eight trials), balloon or shield kyphoplasty (seven trials) and facet joint injection of glucocorticoid and local anaesthetic (one trial). Eight trials reported at least some funding from medical device companies who manufacture vertebral augmentation systems, and, of these, only two reported that they had no other role in the trial.

Data from one placebo-controlled trial has only been published as a thesis (VOPE 2015), while we could only include partial data from a second placebo-controlled trial based upon conference proceedings as it remains unpublished to date (VERTOS IV). A third placebo-controlled trial (VERTOS V), was recorded as completed in June 2015 at clinicaltrials.gov, but the trialists subsequently altered the recruitment status in January 2017 to state that the study is now 'enrolling by invitation', with a new estimated completion date of July 2018.

With respect to trials that have used comparators other than placebo, we classified two as ongoing, although it is unclear if the trials are completed; an additional four have been reported to have been completed but we were unable to find published results; and another four completed RCTs that likely meet inclusion criteria have only been published in Chinese and are awaiting assessment. Inclusion of the results of these trials may alter the conclusions of our second and third comparisons (vertebroplasty compared with usual care or kyphoplasty, respectively).

Vertebroplasties were performed by interventional radiologists or neuroradiologists, orthopaedic surgeons or neurosurgeons across the different trials, however the procedure itself appeared similar. Mean cement injected varied across the 17 trials that reported these data. The study populations in all included trials appeared to be representative of patients seen in routine care. The age and gender ratio were similar across all trials apart from Chen 2014a, who included a younger study population. However symptom duration did vary widely across trials reflecting different philosophies on when vertebroplasty should be implemented. Some authors have suggested that vertebroplasty only be offered to patients with recent onset of pain (¡ 6 weeks) (Bono 2010). Our subgroup analysis, as well as the result of an individual patient data meta-analysis from the same two trials (Staples 2011), suggests that treatment outcome is not influenced by duration of pain $\leq$ 6 weeks versus ¿ 6 weeks. This supports our decision to include all trials in pooled analyses irrespective of symptom duration.

Trials varied in how they measured pain with respect to the scale used (although most used a continuous measure), time period specified and descriptors used. Only four trials included a dichotomous measure of pain. All except two trials included a measure of disability or function, with the RMDQ used most commonly (9/21 trials). Seven trials included the QUALEFFO and six included an overall generic measure of quality of life. Only two trials included a measure of patient-reported treatment success although three trials did report the number who achieved various thresholds of pain and/or disability improvement. Most trials reported on the presence of new symptomatic and/or radiologically apparent vertebral fractures (although two trials only considered adjacent fractures (Endres 2012; Vogl 2013) and one of these also considered refracture of the treated vertebra (Vogl 2013). However other

adverse events were less well-reported across trials with three trials only reporting on adverse events that occurred in the vertebroplasty group.

The RCTs included in this review also varied in terms of duration of follow-up (from two weeks to three years). For one placebo-controlled trial we only included data up to one month, despite the availability of one-year data, because of an *a priori* decision that for cross-over RCTs, we would preferentially extract data only from period before cross-over. Comstock 2013 reported that after one month, significantly fewer participants in the vertebroplasty group crossed over into the alternate group (11 of 68 participants (16%)) compared with the placebo (sham) group (38 of 63 participants (60%), P = 0.001). At one year, difference in pain favoured the vertebroplasty group (MD 1.02 (95% CI: 0.04 to 2.01); P = 0.042), but there was no evidence of an important difference in disability (MD in RMDQ 1.37 points (95% CI: 3.62 to 20.88), P = .231). In the as-treated analyses, participants treated with vertebroplasty did not differ from the placebo (sham) group in terms of either mean pain (MD 0.85 (95% CI: 2.05 to 20.35), P = 0.166) or disability (RMDQ, MD 0.66 (95% CI: 3.30 to 21.98); P = 0.625). Therefore, including data from the one-year intention-to-treat (ITT) analysis from this trial would not have appreciably altered our results. Based upon (ITT) pooled data from the two trials, at 12 months, there was no significant between-group differences with respect to mean pain (MD 0.77 (95% CI -1.85 to 3.39) (data not shown).

While the lack of significant benefits of vertebroplasty in terms of pain and disability shown in the main analysis of this review would appear to indicate that any other clinical benefits are unlikely, some (Chen 2013; Edidin 2011; Lange 2014; Zampini 2010), but not all (McCullough 2013; McDonald 2011), population or clinic-based observational studies have reported a reduction in mortality associated with spinal augmentation (vertebroplasty or kyphoplasty), compared to those who were untreated. However McCullough 2013 demonstrated that the survival benefit observed with traditional covariate adjustments was no longer in evidence after using propensity score matching to better account for selection bias (McCullough 2013), suggesting that selection bias from unrecognised confounding explains the observed survival benefit of spinal augmentation seen in other studies. Using propensity score matching McCullough 2013 also reported that one-year major medical complications were similar between the groups, while rates of health-care utilisation, including hospital and intensive care unit admissions and discharges to skilled nursing facilities, were higher among those treated with spinal augmentation.

Although this review did not demonstrate an increased risk of incident vertebral fractures associated with vertebroplasty, a clinically important increased risk cannot be excluded based upon our review due to the small number of events. Data from the RCTs that compared risk with vertebroplasty compared with placebo or usual care were also inconsistent as evident by the substantial statistical heterogeneity observed in the pooled analyses.

Observational studies that have compared the incidence of new vertebral fractures following vertebroplasty to the incidence in a cohort who did not receive the procedure have also reported conflicting results (Álvarez 2006; Chosa 2011; Mundano 2009; Tang 2011). To conclusively establish whether or not there is an increased risk of further vertebral fracture, particularly adjacent fracture associated with vertebroplasty will require additional large randomised trials with extended follow-up and/or population-based studies analysed carefully to account for differences in patient selection as outlined by McCullough 2013.

Based upon the randomised controlled data that we reviewed, cement leakage occurs frequently. While in most cases it does not result in symptoms, serious sequelae may occur. In our review, one trial reported one instance of cement leakage into the epidural space requiring immediate decompression. It is not possible to determine the rate of significant sequelae arising from cement leakage or embolism from our review due to the small number of events. However numerous cases of local cement leakage requiring decompression have been reported, as have reports of cement emboli requiring surgical removal from the inferior vena cava (Baumann 2006; Seo 2005), right heart chambers (Caynak 2009; Kim 2014), and the right pulmonary artery (François 2003). Cement embolism has also been reported to cause transient respiratory symptoms and death (Monticelli 2005), and deaths from fatal fat embolism after vertebroplasty have also been reported (Syed 2006). In a post-hoc analysis of data from Buchbinder 2009, there was an increased odds of cement leakage with higher volumes of injected cement (Odds Ratio (OR) 2.8; 95% CI 1.3 to 6.1), but they found no relationship between cement leakage and efficacy outcome (Kroon 2014).

Complications from vertebroplasty reported in the included trials were osteomyelitis requiring surgical drainage, rib fractures, thecal sac injury requiring hospitalisation, pain-induced vasovagal reactions an acute asthma exacerbation, and fracture of a cement spur. However, as event rates were low in included trials, we cannot be certain if there are, or are not, any between-group differences for reported adverse events among the trials we reviewed. We also note that severe adverse events such as deaths due to pulmonary thromboembolism, fat embolism, extensive local cement leakage, infection and complications of anaesthesia and infection requiring surgery have all been reported in the literature (Al-Nakshabandi 2011).

Quality of the evidence

The overall quality of evidence for our primary comparison (vertebroplasty versus placebo) was high for the pain and disability outcomes according to the GRADE approach (Schünemann 2011b). According to the GRADE Working Group grades of evidence, a grading of high quality of evidence indicates that further research is unlikely to change the effect estimates substantially. For the remaining outcomes, the evidence was downgraded from high to

moderate due to either imprecision (i.e. 95% CIs do not exclude clinically important differences (defined as 0.074 on the 0 to 1 EQ-5D quality of life scale), or because the total number of events was small (for other outcomes). According to the GRADE Working Group grades of evidence, a grading of moderate quality of evidence indicates that further research may have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

While the available data from eight trials that compared vertebroplasty with usual care generally favoured vertebroplasty for some, but not all outcomes, they were all rated as having a high risk of performance and detection bias for self-reported outcomes due to lack of participant and personnel blinding. While recognising that blinding of participants and personnel is difficult to achieve in procedural trials, failure to blind studies of this nature is problematic as trials with unblinded assessment of subjective outcomes (such as pain and function) are estimated to exaggerate the treatment benefit by 22% on average (ratio of OR 0.78; 95% credible interval 0.65 to 0.92) (Savović 2012). Correcting for these biases would likely drive the improvements seen with vertebroplasty over usual care, towards the null, in keeping with the findings from the placebo-controlled trials.

Potential biases in the review process

We believe that we identified all relevant trials following a thorough search of all major databases with no language restrictions.

Six review authors independently assessed the trials for inclusion in the review, extracted data and assessed the risk of bias, and a third review author adjudicated whenever there was any discrepancy. Two of the review authors (RB and DK) are authors of three of the trials included in this review (Buchbinder 2009, and Kallmes 2009 and Evans 2015, respectively). To avoid any bias, these papers were assessed by an independent review author to assess whether they met the inclusion criteria for this review. Neither author was involved in the data extraction or 'Risk of bias' assessment of their own trials.

In view of the potential for bias of open studies when the main outcomes are self-reported, we chose vertebroplasty compared with placebo (sham) as our primary analysis. This decision was vindicated based upon the results of our sensitivity analyses that were performed to determine whether our primary results were robust to the inclusion of the open trials.

Agreements and disagreements with other studies or reviews

Numerous systematic reviews and/or meta-analyses investigating the effects of vertebroplasty for osteoporotic spinal fractures have been published, e.g. Anderson 2013; Bliemel 2012; Eck 2008; Gill 2007; Han 2011; Hochmuth 2006; Hulme 2006; Lee 2009; Liu 2013; Ma 2012; McGirt 2009; Papanastassiou 2012; Ploeg 2006; Robinson 2012; Shi 2012; Stevenson 2014; Taylor 2006; Trout 2006; Wang 2012; Zhang 2013; Zou 2012). These have differed in terms of focus.

Reviews that have synthesised the effectiveness of vertebroplasty have reported conflicting conclusions explainable on the basis of their inclusion criteria and/or methodological rigour (Anderson 2013; Hochmuth 2006; Hulme 2006; Liu 2013; McGirt 2009; Papanastassiou 2012; Ploeg 2006; Robinson 2012; Shi 2012; Stevenson 2014; Taylor 2006). Our results are consistent with systematic reviews that only included RCTs and performed separate analyses according to comparator (e.g. Liu 2013; Robinson 2012; Shi 2012; Stevenson 2014), while differing conclusions in other reviews are explainable on the basis that these reviews included pooled analyses combining placebo-controlled and usual care comparators, included non-randomised studies and/or combined vertebroplasty and kyphoplasty data (e.g. Anderson 2013; Papanastassiou 2012).

Four previous reviews that have focused upon the available evidence with respect to incident vertebral fractures (Bliemel 2012; Trout 2006; Zhang 2013; Zou 2012), have reported conclusions broadly consistent with ours that it is not possible to definitely establish whether or not there is an increased risk of further vertebral fracture associated with vertebroplasty. Trout 2006a has suggested that adjacent fractures may occur significantly sooner.

In contrast to our review, previous reviews that have evaluated the comparative efficacy and safety of vertebroplasty compared with kyphoplasty have all combined data from observational and experimental studies (Eck 2008; Gill 2007; Han 2011; Ma 2012), making comparison with our results problematic. More recent reviews (Han 2011; Ma 2012), included one of the four RCTs in our review (Liu 2010). In keeping with the findings of our review based upon only RCT data, previous reviews have generally concluded that the two treatments were of comparable longer-term effectiveness and safety.

Dohm 2014 considered average kyphosis correction as a secondary radiographic endpoint and reported no between-group difference in kyphotic angulation correction post-operatively or at three or 12 months. At 24 months, the authors reported a mean difference of 1.43 degrees (95% CI 0.10 to 2.74 degrees) favouring the kyphosis group although the clinical importance of this finding was not discussed. Some previous reviews have suggested that kyphoplasty may be superior with respect to improving kyphosis angle and vertebral height compared with vertebroplasty, but have acknowledged that this remains to be proven in rigorous RCTs (Ma 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Based upon the currently available high- to moderate-quality evidence, our review does not support a role of vertebroplasty for the treatment of acute or subacute osteoporotic vertebral fractures in routine clinical care. There were no demonstrable clinically important benefits compared with a placebo (sham procedure) and subgroup analyses indicated that results did not differ according to duration of pain $\leq$ 6 weeks versus ¿ 6 weeks. Sensitivity analyses confirmed that open trials that compared vertebroplasty with usual care are likely to have overestimated any benefit of vertebroplasty. Correcting for these biases would likely drive any observed improvements seen with vertebroplasty over usual care towards the null, in keeping with the findings from the placebo-controlled trials.

Although we did not demonstrate an increased risk of incident symptomatic vertebral fractures or other serious adverse events associated with vertebroplasty, a clinically important increased risk cannot be excluded based upon our review due to the small number of events. Furthermore, serious adverse events related to vertebroplasty were reported in several trials. Patients should be informed about the lack of high-quality evidence supporting benefits of vertebroplasty and its potential for harm.

Implications for research

Further high-quality research is unlikely to substantially change the conclusions of this review regarding the potential benefits of vertebroplasty but may resolve whether or not it increases the risk of further vertebral fracture and serious adverse events. Current literature does not support the likelihood of identifying subsets of patients who would benefit from vertebroplasty. It is questionable whether further trials testing the efficacy of vertebroplasty are necessary. Any future review updates will restrict inclusion to only placebo-controlled trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Blasco 2012

Methods	**Design:** single-centre parallel group, two-arm open-label randomised controlled trial **Setting:** patients recruited from primary care centres, Spain **Timing:** April 2006 to Jan 2010 **Intervention:** percutaneous vertebroplasty and usual care versus usual care alone **Sample size:** 64 patients required per group to have 80% power to detect a difference of at least 1.5 units on a 0-10 VAS between groups in primary pain endpoint; overall type-1 error rate was set at 5% **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • 219 patients screened for eligibility • 94 excluded (55 did not meet inclusion criteria, 14 declined participation and 25 had other reasons) • 125 randomised (64 to vertebroplasty and 61 to usual care) • Data for 110 (54 (84%) for vertebroplasty and 56 (92%) for usual care) available at the 2-month follow-up • Data for 95 (47 (73%) for vertebroplasty and 48 (79% for usual care) available at the final 12-month follow-up **Inclusion criteria** • Acute, painful osteoporotic vertebral fracture from T4 to L5 with clinical onset ¡ 12 months confirmed by spine radiograph and oedema present on MRI or positive bone scan if MRI contraindicated • Pain at least 4 on a 0-10 VAS where higher scores indicated worse pain **Exclusion criteria** • Untreatable coagulopathy • Active local or systemic infection • Current malignancy • Vertebral canal occupation by a fragment of the vertebral body • Non-osteoporotic vertebral fracture • Active associated disorders such as fibromyalgia or spondyloarthropathies • Other disorders (such as dementia) that affect quality of life or pain assessment **Baseline characteristics** *Vertebroplasty group (64 participants)*: Mean (SD) age: 71.33 (9.95); 47 female, 17 male Mean (SD) duration of back pain: 140.3 (96.09) days Number (%) participants with symptom onset ¡ 6 weeks: 2 (3%) Number (%) participants with symptom onset ¡ 4 months: 32 (50%) Mean (SD) number of vertebral fractures at baseline: 3.55 (2.82) Mean (SD) baseline pain score 7.21 (0.33) on a 0-10 VAS (higher score indicates worse pain) Mean (SD) QUALEFFO-41 score: 65.19 (2.23) on a 0 to 100 scale (higher score indicates worse quality of life) *Usual care group (61 participants):* Mean (SD) age: 75.27 (8.53); 50 female, 11 male

	Mean (SD) duration of back pain: 143.1 (130.33) days Number (%) participants with symptom onset ¡ 6 weeks: 4 (7%) Number (%) participants with symptom onset ¡ 4 months: 32 (52.5%) Mean (SD) number of vertebral fractures at baseline: 3.02 (2.14) Mean (SD) baseline pain score: 6.31 (0.35) Mean (SD) QUALEFFO-41 score: 59.17 (2.17)
Interventions	**Vertebroplasty group** Percutaneous vertebroplasty was performed by an experienced interventional neuroradiologist A 25-gauge needle was used to infiltrate the skin overlying the pedicle and to infiltrate the periosteum of the posterior lamina. Using a bilateral transpedicular approach a 10- or 13-gauge needle was inserted posterolaterally relative to the eye of the pedicle, and through gentle tapping the needle penetrated the pedicle into the anterior two-thirds of the fractured vertebrae and polymethylmethacrylate cement was injected. Following the procedure, participants were strictly rested in bed for 6 hours. Standardised analgesics were given as necessary and nasal calcitonin was given for the first month **Usual care group** All participants received analgesics with a standardised format and nasal calcitonin for the first month. In case of no improvement in pain, the participant was considered for vertebroplasty (timing of decision not specified) **Both groups** When treatment in either group was ineffective (defined as pain 7 or more out of 10) or there was an intolerance to drug therapy, participants were offered rescue therapy consisting of an intrathecal infusion of 25 μg fentanyl and 1.5 mg bupivacaine After one month, both treatment groups began or continued treatment with bisphosphonates (or teriparatide or strontium ranelate if there was an intolerance to bisphosphonates), prescribed by the attending physician
Outcomes	Participants were assessed at baseline, 2 weeks, and at 2, 6 and 12 months **Outcomes** • Pain measured on a 0 to 10 VAS (0 indicates no pain and 10 is maximum pain) • Number of participants with moderate (pain $\geq$ 4) or severe (pain $\geq$ 7) pain at 12 months • Quality of life questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41), scores range from 0 to 100, with lower scores indicating a better quality of life • Analgesic consumption (nil, minor analgesics and/or NSAIDs, minor opioid derivatives, major opioid derivatives) • Radiologically apparent incident vertebral fractures measured at 6 and 12 months, defined as a reduction of 20% or more in the anterior, middle or posterior height of the vertebral body compared with adjacent undeformed vertebrae • Clinically apparent incident vertebral fractures confirmed on MRI at any time during follow-up • Bone densitometry (dual X-ray absorptiometry [DXA] measured at baseline and 12 months • Number of participants who received rescue therapy (intrathecal infusion with 25 μg and 1.5 mg bupivacaine) • Height

	• Weight (not reported in the paper) • Cement leakage during procedure • Development of chronic back pain **Outcomes included in this review** • Pain • QUALEFFO • Incident vertebral fractures
Source of funding	Fundacio La Marato de TV3, the Spanish Society of Medical Radiology and the Catalan Society of Rheumatology
Notes	Trial registered on 13 Oct 2009 at ClinicalTrials.gov, registration number NCT00994032 We extracted pain and quality of life data at 2 weeks, 2 months (pooled with the 3-month outcome data from other trials), 6 and 12 months. These outcomes were reported in graphical format only; we extracted the mean and 95% confidence intervals from the graphs (http://plotdigitizer.sourceforge.net/) and converted 95% CI to SD. Adverse events were only reported for vertebroplasty. It is not reported if any adverse events occurred with usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Performed using a computer-generated random list.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor personnel were blinded.
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	Participants assessed their pain and quality of life and were not blinded
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Rheumatologists who assessed radiographs and MRIs were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The proportion lost to follow-up was similar between groups at the 12-month follow-up (17/64 or 27% from vertebroplasty and 13/61 or 21% from usual care), although the authors report that the losses may not have been random, but related to

Blasco 2012 (*Continued*)

		worse pain in the usual care group
Selective reporting (reporting bias)	Unclear risk	Adverse events reported for vertebroplasty group; it is unclear if any adverse events occurred in the usual care group; mean pain and quality of life and confidence intervals were reported graphically only
Other bias	Low risk	None apparent.

Buchbinder 2009

Methods	**Design:** multicentre (four sites), parallel group, two-arm double-blind randomised placebo-controlled trial **Setting:** Melbourne, Australia **Timing:** April 2004 to October 2010 **Interventions:** percutaneous vertebroplasty versus sham vertebroplasty (placebo) **Sample size:** 24 participants per group required to detect at least a 2.5-unit (SD 3) advantage of vertebroplasty over placebo in terms of pain (0 to 10 point scale), based on a two-sided type 1 error rate of 5% and power 80%. Additional sample size calculation of 82 participants per group needed to show an increase by a factor of three in the risk of further vertebral fractures at 24 months. Original sample size was increased to 200 to allow for potential dropout. Trial enrolment terminated before reaching planned sample size for long-term outcomes because it became evident that this sample size would not be achieved within an acceptable period of time and that the study's power was sufficient to address the primary aim. This decision was made without knowledge of any outcome results **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • 468 participants screened for eligibility • 390 excluded (248 did not meet inclusion criteria; 141 declined to participate; 1 died) • 78 randomised (38 to vertebroplasty and 40 to placebo) • Data for 71 (35 (92%) for vertebroplasty and 36 (90%) for placebo) available at 6-month follow-up • Data for 57 (29 (76%) for vertebroplasty and 28 (70% for placebo) available at the final 24-month follow-up **Inclusion criteria** • Back pain of no more than 12 months duration. • Presence of one or two recent vertebral fractures, defined as vertebral collapse of grade 1 or higher according to the grading system of Genant 1993 (in which vertebral collapse is graded on a scale of 0 to 3, with higher numbers indicating greater vertebral collapse). • Bone oedema, a fracture line, or both within the vertebral body on magnetic resonance imaging (MRI) or positive bone scan if MRI contraindicated. **Exclusion criteria** • Presence of more than two recent vertebral fractures.

	• Spinal cancer. • Neurologic complications. • Osteoporotic vertebral collapse of greater than 90%, fracture through or destruction of the posterior wall, retropulsed bony fragment or bony fragments impinging on the spinal cord. • Medical conditions that would make the patient ineligible for emergency decompressive surgery if needed. • Previous vertebroplasty. • Inability to give informed consent. • Likelihood of noncompliance with follow-up. **Baseline characteristics** *Vertebroplasty group:* Mean (SD) age: 74.2 (14.0) years; 31 female: 7 male Median (interquartile range (IQR)) duration of back pain: 9.0 (3.8 to 13.0) weeks Duration of back pain ¡ 6 weeks: N = 12 (32%) Mean (SD) baseline pain score: 7.4 (2.1) Mean (SD) baseline QUALEFFO score: 56.9 (13.4) Mean (SD) RMDQ: 17.3 (2.8) Any medication for osteoporosis: N = 35 (92%); bisphosphonates: N = 31 (82%) Previous vertebral fractures: 18 (47%) Opioid use at baseline: 30 (79%) T score for bone mineral density (BMD) 2.5 or less at lumbar spine: 21/34; at femoral neck: 13/34 *Placebo group:* Mean (SD) age: 78.9 (9.5) years; 31 female: 9 male Median (IQR) duration of back pain: 9.5 (3.0 to 17.0) weeks Duration of back pain ¡ 6 weeks: N = 13 (32%) Mean (SD) baseline pain score: 7.1 (2.3) Mean (SD) baseline QUALEFFO score: 59.6 (17.1) Mean (SD) RMDQ: 17.3 (2.9) Any medication for osteoporosis: N = 37 (92%); bisphosphonates: N = 32 (80%) Previous vertebral fractures: 21 (52%) Opioid use at baseline: 34 (85%)
Interventions	Percutaneous vertebroplasty or placebo (sham) procedure, performed by experienced interventional radiologists, who had formal training in vertebroplasty and appropriate certification **Vertebroplasty** The left pedicle of the fracture site was identified with the use of a metallic marker. A 25-gauge needle was used to infiltrate the skin overlying the pedicle and a 23-gauge needle was used to infiltrate the periosteum of the posterior lamina. An incision was made in the skin, and a 13-gauge needle was placed posterolaterally relative to the eye of the pedicle. Gentle tapping guided the needle through the pedicle into the anterior two thirds of the fractured vertebral body. Anterior-posterior and lateral images were recorded with the needle in the correct position. Prepared PMMA (approximately 3 mL) was slowly injected into the vertebral body, infiltration of the vertebral body was confirmed radiographically. A bipedicular approach was used only if there was inadequate instillation of cement with the unipedicular approach. Injection was stopped when substantial resistance was met or when the cement reached the posterior quarter of the vertebral body; injection was

	also stopped if cement leaked into extraosseous structures or veins. All participants in the vertebroplasty group received cephalothin, administered intravenously immediately after PMMA injection **Sham procedure (placebo)** The same procedures as those in the vertebroplasty group up to the insertion of the 13-gauge needle to rest on the lamina. The central sharp stylet was then replaced with a blunt stylet. To simulate vertebroplasty, the vertebral body was gently tapped, and PMMA was prepared so that its smell permeated the room **Follow-up care** After the intervention, all participants received usual care. Treatment decisions were made at the discretion of the treating physician, who received up-to-date guidelines on the management of osteoporosis. Analgesia was given according to standard practice, and its use was recorded
Outcomes	Outcomes were reported at 1 week, and 1, 3, 6, 12 and 24 months. Primary endpoint was 3 months **Primary outcome** • Mean overall pain over the course of the previous week (0 to 10, 0 is no pain and 10 is maximum pain) **Secondary outcomes** • Quality of life, measured using the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) (0 to 100 scale, with lower scores indicating a better quality of life) • Assessment of Quality of Life (AQoL) questionnaire, (0 to 1 scale, 1 indicates perfect health) • European Quality of Life-5 Dimensions (EQ-5D) scale (0 to 1 scale, 1 indicates perfect health) • Pain are rest (0 to 10 scale, 0 is no pain) • Pain in bed at night (0 to 10 scale, 0 is no pain) • Roland-Morris Disability Questionnaire (RMDQ), modified 23-item version (0 to 23 scale, higher scores indicate worse physical functioning) • Participant global assessment of pain, fatigue and overall health, measured on 7-point ordinal scales, ranging from a 'great deal worse' to a 'great deal better'; treatment success' defined as responses of "moderately better" or "a great deal better" were classified as successful outcomes. • Adverse events • Incident clinical fractures • Incident radiographic fractures (12 and 24 months) • Proportion with reduction in pain by ≥ 2.5 units (post-hoc analysis requested by journal) • Timed up-and-go test (baseline, 12 and 24 months) **Outcomes included in this review** • Mean overall pain • Disability as measured by the RMDQ • Osteoporotic fracture-specific Quality of Life as measured by the QUALEFFO EQ-5D scale • Adverse events • Proportion with incident clinical fractures

Buchbinder 2009 (*Continued*)

Source of funding	The study was supported by grants from the National Health and Medical Research Council of Australia (284354), Arthritis Australia, the Cabrini Education and Research Institute, and Cook Australia. Cook Australia had no role in the design of the trial, the collection or analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication
Notes	Trial registered at anzctr.org.au, number ACTRN012605000079640 on 5 August 2005

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocked randomisation (in permuted blocks of 4 and 6) were generated by computer-generated random numbers; stratified according to treatment centre, sex and duration of symptoms (¡ 6 weeks or ≥ 6 weeks)
Allocation concealment (selection bias)	Low risk	Quote: "To ensure concealment of the assigned intervention, the treating radiologist received the opaque, sealed envelope containing the assigned intervention just prior to the procedure."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and investigators, other than the treating radiologists, were unaware of treatment assignments. At 24 months 55 participants completed the assessment of blinding question. In the vertebroplasty group 16/29 believed they had received vertebroplasty, 2 believed they had received placebo and 11 were unsure; in the placebo group 8/26 believed they had received vertebroplasty, 7 believed they had received placebo and 11 were unsure. The Blinding Index was 0.59 (95% CI, 0.47-0.71), indicating adequate blinding at the end of the study
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Low risk	Participants (who assessed their pain, disability, quality of life and treatment success) were unaware of treatment assignment
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic	High risk	Assessment of the timed up-and-go test was performed by a blinded outcome assessor at 12 and 24 months. Radiologists

Buchbinder 2009 (*Continued*)

outcomes)		who assessed follow-up radiographs and MRIs after 24 months were aware of treatment assignment as vertebroplasty cement is opaque and will be detected on imaging
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was small and equal across treatment groups for shorter-term outcomes. There was complete follow-up at one month for 35/38 from the vertebroplasty group (3 did not return questionnaire) and 38/40 from the sham group (2 did not return questionnaire); at 6 months this was 35/38 from the vertebroplasty group (2 died for reasons considered unrelated to the trial and 1 did not return their questionnaire), and 36/40 from the sham group (2 died for reasons considered unrelated to the trial and 2 did not return their questionnaires). Loss to follow-up was greater for longer-term outcomes. At two years, 29/38 (76%) participants in the vertebroplasty group had completed follow-up (5 had died, 1 withdrew due to dementia and 3 did not return questionnaires), and 28/40 (70%) participants in the sham group completed follow-up (7 had died, 1 withdrew due to illness and 4 did not return questionnaires)
Selective reporting (reporting bias)	Low risk	All outcomes planned in the published protocol were reported
Other bias	Low risk	None apparent.

Chen 2014a

Methods	**Design:** single-centre parallel group, two-arm open-label randomised controlled trial **Setting:** Shanghai, China **Timing:** Jan 2007 to Dec 2012 **Interventions:** percutaneous vertebroplasty or usual care **Sample size:** *a priori* sample size calculation not reported **Analysis:** completers' analysis
Participants	**Number of participants** • Numbers screened for eligibility and number excluded or declined to participate is not stated. • 96 participants randomised (46 to vertebroplasty and 50 to usual care) • Data for 89 (46 (100%) for vertebroplasty and 43 (86%) for usual care) available

	at 12-month follow-up although it is stated that 3 (6.5%) participants assigned to vertebroplasty group were lost to follow-up. • Four participants who were assigned to conservative care refused treatment and received vertebroplasty at the 3-month follow-up and another 3 were lost to follow-up. These participants were excluded from the analysis. **Inclusion criteria** • Chronic osteoporotic compression spinal fractures on MRI (low signal on T1-weighted and high signal on T2-weighted scans) and persistent back pain for at least 3 months were enrolled. No other inclusion criteria were specified **Exclusion criteria** • No exclusion criteria were specified **Baseline characteristics** *Vertebroplasty group:* Mean (SD) age: 64.6 (9.1) years; 32 female:14 male Duration (SD) of back pain: 7.07 (3.00) months Mean (SD) number of vertebral fractures at baseline 2.28 (1.00) Mean (SD) baseline pain score: 6.5 (0.9) N (%) use of osteoporotic drugs: 12 (26%) Bone density T score (SD): -3.02 (0.80) *Usual care group:* Mean (SD) age: 66.5 (9.1) years; 30 female:13 male Duration (SD) of back pain: 6.81 (2.51) months Mean (SD) number of vertebral fractures at baseline 2.00 (0.09) Mean (SD) baseline pain score: 6.4 (0.9) N (%) use of osteoporotic drugs: 18 (42%) Bone density T score (SD): -3.00 (0.44)
Interventions	Percutaneous vertebroplasty performed by orthopaedic surgeons **Vertebroplasty** All procedures were performed under local anaesthesia and undertaken on a single plane angiography system under fluoroscopic guidance in the operating theatre. The patient was placed in a prone position on the operating table. After local anaesthesia, a small incision was made with a scalpel blade. Thereafter, a bone puncture needle (13 G, Cook Medical, Bloomington, IN, USA) was placed transpedicularly in the fractured vertebra. After removal of the inner needle, commercially available polymethyl methacrylate (PMMA) (Osteo-Firm, Cook Medical) was carefully injected into the fractured vertebra under continuous fluoroscopic monitoring via lateral and anteroposterior (AP) projections in order to ensure adequate lesion filling and to avoid PMMA leakage or migration into the venous system Injection was ceased when substantial resistance was met or when the cement reached the cortical edge of the fractured vertebral body; injection was also stopped if cement leaked into extraosseous structures or veins. In general, a total of 3 mL to 5 mL of PMMA was injected into the fractured vertebral body Post-procedural fluoroscopic evaluation was obtained to show optimal filling of the lesion with no evidence of PMMA extravasation Vertebroplasty was also performed with one or more procedures on other fractures seen on MRI at adjacent levels above and below the chronic osteoporotic compression fractures to prevent new fractures. After the procedure, a CT scan of the treated vertebral bodies was done with 2 mm slices to identify the distribution of cement in the lesion, cement leakage outside the vertebral body, or other local complications

Chen 2014a (*Continued*)

	Conservative care Participants in the conservative care group were hospitalised and offered brace treatment, analgesia, general mobilising physiotherapy and treatment for osteoporosis including calcitriol and alendronate
Outcomes	Outcomes were reported at 1 day, 1 week, and 1, 3, 6 and 12 months after treatment **Primary outcomes** • Pain relief on a 0 to (no pain) to 10 (the worst pain imaginable) cm VAS scale **Secondary outcomes** • Capacity for walking, standing and sleeping, as measured by the Oswestry Low Back Disability Index (ODI) [range of total score not reported but presumably was 0 to 100 scale (0 is no disability)] • Physical function measured by the physical function items of the RMDQ [range of total score not reported and trialists reported that this was a measure of quality of life] • Use of analgesia which was interpreted to mean 'incomplete pain relief' [no use of analgesia was interpreted to mean 'complete pain relief'] • Hospital stay • Outpatient visits • Medical aids • Incidence of new symptomatic vertebral fractures (at 24 months) • AP and lateral spine radiographs at 1, 6 and 12 months - reason not reported • Computed tomography scans 3 days after vertebroplasty to study cement distribution or extravasations • MRI at 3 and 12 months in all participants - reason not reported • New vertebral fractures • Cement leakage in the vertebroplasty group and any clinical sequelae **Outcomes included in this review** • Mean pain • RMDQ • Incidence of new symptomatic vertebral fractures (at 24 months)
Source of funding	Not reported.
Notes	There is no record of trial registration.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to receive either vertebroplasty or conservative treatment" However, the method of randomisation was not described.
Allocation concealment (selection bias)	Unclear risk	No information was provided about whether or not treatment allocation was concealed

Chen 2014a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators were aware of treatment allocation. It is not clear if participants in the percutaneous vertebroplasty group were offered treatment for osteoporosis
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	Participants assessed their pain and function and were not blinded
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	It is not stated who assessed the imaging outcomes. It is unlikely that they were blinded to treatment assignment as vertebroplasty cement is opaque and will be detected on imaging
Incomplete outcome data (attrition bias) All outcomes	High risk	No flow diagram is provided. Of the 50 participants allocated to receive conservative care, four refused conservative treatment and decided to have vertebroplasty at the 3-month follow-up and an additional three were lost to follow-up. Results are presented for only 43 participants. The authors state that of the 46 participants allocated to receive vertebroplasty, four were lost to follow-up but they appear to perform the analysis on all 46 participants to 12 months
Selective reporting (reporting bias)	Unclear risk	The one-day outcomes are only reported for mean pain. Hospital stay, outpatient visits and medical aids were not reported. The trial does not appear to have been registered and no trial protocol is published
Other bias	Unclear risk	It is not clear how many 'prophylactic' procedures were performed in the vertebroplasty group

Clark 2016

Methods	**Design**: multicentre (nine sites), parallel group, double-blind randomised placebo-controlled trial **Setting:** Sydney, Australia **Timing:** November 2011 to December 2014 **Interventions:** percutaneous vertebroplasty versus sham vertebroplasty (placebo) **Sample size:** 60 patients required per group to have greater than 80% power and 95% confidence to detect a difference in the proportion of patients achieving a 14-day pain score of less than 4 out of 10 (from a baseline score greater than or equal to 7 out of 10) from 35% in the control group to 65% in the active group (as stated in the results paper). The protocol paper presents different primary endpoints in different parts of the manuscript both consistent with the results paper as well as the proportion of patients whose pain score reduces to 4 or less out of 10 at 14 days **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • 302 patients screened for eligibility • 182 excluded (149 did not meet inclusion criteria; 34 declined to participate) • 120 randomised (61 to vertebroplasty and 59 to placebo) • Data for 112 (55 for vertebroplasty and 57 for placebo) available at 1-month assessment • Data for 102 (51 for vertebroplasty and 51 for placebo) available at 6-month assessment **Inclusion criteria** • Older than 60 years • Back pain of less than 6 weeks' duration • NRS pain score of 7 or more (out of 10) • MRI (or single-photon emission computed tomography if MRI contraindicated) confirming one or two recent fractures **Exclusion criteria** • Inability to provide informed consent • Chronic back pain requiring opiate use • Substantial fracture retropulsion • Acute infection • Spinal malignancy • Neurological complications • Presence of more than two vertebral fractures **Baseline characteristics** *Vertebroplasty group:* Mean (SD) age: 80 (7) years; 48 female: 13 male Hospital inpatient: 34 (56%) Previous osteoporotic fractures: 36 (62%) Medications for osteoporosis: • Any: 48 (79%) • Calcium or vitamin D: 41 (70%) • Biphosphonates: 29 (49%) Bone mineral density (T score) • Lumbar spine: -4.1 (1.1) • Femoral neck: -2.2 (0.7) Serum vitamin D (nmol/L): 70 (27)

	Duration of fracture: • Mean (SD; weeks): 2.8 (1.6) • 1-3 weeks: 47 (77%) • 4-6 weeks: 14 (23%) Spinal segment of fracture: • Thoracic (T4-T10): 19 (31%) • Thoracolumbar (T11-L2): 37 (61%) • Lumbar (L3-L5): 7 (12%) Vertebral body height loss (percentage points): 47 (15) Genant grade (standing) • Grade 1: 3 (5%) • Grade 2: 13 (21%) • Grade 3: 45 (74%) Number of vertebral bodies treated • 1: 51 (84%) • 2: 10 (16%) Opioids for pain: 53 (87%) Baseline measures • Pain intensity in previous 24 hours on NRS (0-10 scale): 8.6 (1.3) • Pain intensity in previous 24 hours on VAS (0-100 scale): 81 (18) • RMDQ score: 19.5 (3.5) • EQ-5D score: 0.60 (0.07) • QUALEFFO score: 65.4 (11.4) • Timed up-and-go score: 26 (14) *Placebo group*: Mean (SD) age: 81 (7) years; 40 female: 19 male Hospital inpatient: 34 (58%) Previous osteoporotic fractures: 32 (54%) Medications for osteoporosis: • Any: 51 (86%) • Calcium or vitamin D: 48 (81%) • Biphosphonates: 21 (36%) Bone mineral density (T score) • Lumbar spine: -4.5 (0.9) • Femoral neck: -2.2 (1.0) Serum vitamin D (nmol/L): 73 (22) Duration of fracture: • Mean (SD; weeks): 2.4 (1.4) • 1-3 weeks: 48 (81%) • 4-6 weeks: 11 (19%) Spinal segment of fracture: • Thoracic (T4-T10): 16 (27%) • Thoracolumbar (T11-L2): 36 (61%) • Lumbar (L3-L5): 10 (17%) Vertebral body height loss (percentage points): 46 (15) Genant grade (standing) • Grade 1: 8 (14%) • Grade 2: 12 (20%)

	• Grade 3: 39 (66%) Number of vertebral bodies treated • 1: 53 (90%) • 2: 6 (10%) Opioids for pain: 53 (90%) Baseline measures • Pain intensity in previous 24 hours on NRS (0-10 scale): 8.6 (1.2) • Pain intensity in previous 24 hours on VAS (0-100 scale): 82 (15) • RMDQ score: 19.8 (3.7) • EQ-5D score: 0.59 (0.06) • QUALEFFO score: 67.7 (11.2) • Timed up-and-go score: 29 (15)
Interventions	Percutaneous vertebroplasty or placebo (sham) procedure, performed by interventional radiologists who had undergone vertebroplasty training and were actively providing a vertebroplasty service **Vertebroplasty** Participants were positioned prone on the procedure table with oxygen mask applied. Pulse oximetry and rate were monitored continuously. IV midazolam and fentanyl were given to all patients before starting the procedure. Lidocaine was injected subcutaneously and a 4 mm skin incision was made. An 11-gauge or 13-gauge vertebroplasty needle was introduced into the vertebral body with either a unipedicular or bipedicular technique with fluoroscopic guidance. An AVAMAX kit (CafeFusion Corporation) according to the approved kit technique. The aim was to fill the vertebral body with sufficient PMMA to prevent future collapse - from superior to inferior endplate, mid-pedicle in frontal projection, and from anterior cortex to posterior third of vertebral body. Injection was ceased when these endpoints were reached or if PMMA extravasated outside the bone. PMMA volume and extravasation were recorded **Sham procedure (placebo)** The placebo procedure, designed to simulate vertebroplasty, included subcutaneous lidocaine but not periosteal numbing. It is unclear whether or not a needle was passed into the skin incision: the protocol states that a 4-mm skin incision will be made with light tapping on the skin; the results paper states that a short needle was passed into the skin incision but not as far as the periosteum and that manual skin pressure and regular tapping on the needle was done to mimic vertebroplasty needle advance. Conversation about PMMA mixing and injection suggested that vertebroplasty was being done. The results paper states "that the vertebroplasty kit used in the trial is virtually odourless, with a closed mixing and delivery system, and was not opened during placebo procedures-patients could not smell, hear, or see it." **Follow-up care** After the procedure, participants received the usual medical care directed by their attending physicians
Outcomes	Outcomes were measured at baseline, 3 days, 14 days, and 1, 3, and 6 months. Baseline, 14 day, and 6 month interviews were done in person by research staff. The remaining interviews (day 3, month 1 and 3) were done by telephone by the same, masked research staff. An exception to this will be inpatients that remain in hospital at day 3 who may be interviewed at bedside. Patients unable to visit the research office at day 14 and 6 months were interviewed by telephone. The following outcomes were extracted from

	the protocol paper **Primary outcome** • Proportion of patients who achieve a pain score of less than 4 out of 10 at 14 days (Note: In the protocol paper the primary outcome is also stated to be proportion of patients whose pain score reduces to 4 or less out of 10 at 14 days. This proportion was taken from a measurement of pain intensity during the preceding 24 hours rated on a numerical rating scale (0 indicating no pain and 10 maximum pain)(see below, mean pain on this scale was also an outcome) **Secondary outcomes** • Average back pain intensity during the preceding 24 hours on a numerical rating scale (0 indicating no pain and 10 maximum pain) • Average pain in preceding 24 hours at rest using the same NRS • Average pain in preceding 24 hours during standing or moving using the same NRS • Average back pain intensity during the preceding 24 hours on a 10cm VAS ('no pain' at left extreme and 'worst possible pain' at right extreme) (baseline, 2 weeks, 6 months) • Average pain in preceding 24 hours at rest using the VAS (baseline, 2 weeks, 6 months) • Average pain in preceding 24 hours during standing or moving using the VAS (baseline, 2 weeks, 6 months) • Outcome assessor's estimate of patient pain at the clinic visits (method not reported) • Roland-Morris Disability Questionnaire (RMDQ) consisting of 24 questions about dysfunctions in daily activities experienced by patients with back pain. (0 to 24, higher numbers indicating worse physical function) • Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) (0 to 100 scale, with lower scores indicating a better quality of life) • European Quality of Life - 5 Dimensions (EQ-5D), (0 to 1 scale, 1 indicates perfect health) • EQ-5D 0 to 100 VAS to assess general health • Analgesic consumption within the previous 24-hour period (dosage and classified as strong opioid (includes oxycodone, morphine, fentanyl, pethidine, hydromorphone, buprenorphine and tramadol), mild opioid (include medications containing codeine or dextropropoxyphene) or non-narcotic analgesics (paracetamol, NSAIDs). Within each category a score of 0 (not taking any medications in the category) or 1 or 2 (indicating taking one two medications in the category. A Morphine Equivalent Daily Dose also calculated. • Change in pain (day 3, 2 weeks) (method not reported) • Perception of treatment assignment (day 3, 2 weeks)(method not reported) • Timed up-and-go test (baseline, 2 weeks, 6 months) • Adverse events • Duration of hospitalisation (6 months) • Resource use and health care utilisation (6 months) • Vertebral height measured by erect thoracic and lumbar spine lateral radiographs (measured at the posterior margin, mid-point and anterior margin of the vertebral body) (2 radiologists by consensus)(baseline, 6 months) • Incident vertebral fractures (two radiologists by consensus) (baseline, 6 months)

	The results paper included additional outcomes of participant rating of their confidence in the guess regarding treatment allocation at 2 weeks as a percentage, and nomination of the main reason for their guess; outcome assessor also guessed treatment allocation at 2 weeks, their confidence in the guess and main reason based on observed changes in patient mobility and apparent pain since baseline. The results paper also reported that the investigators had made changes to some outcome measures after trial commencement including removal of a planned SF-36 Health Survey at all time points and QUALEFFO at 3 days and 3 months (SF-36 not pre-planned and QUALEFFO not planned to be measured at these time points according to the published protocol paper. They also stated that the questionnaire to assess masking efficacy was added after trial commencement (although success of blinding at 3 days and 14 days was pre-specified in the published protocol) and that incomplete data collection occurred due to some sick, elderly patients having difficulty completing the long questionnaires **Outcomes included in this review** • Average pain in preceding 24 hours (NRS) • Proportion with pain less than 4 out of 10 • Roland-Morris Disability Questionnaire (RMDQ) • Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) • European Quality of Life - 5 Dimensions (EQ-5D) • Adverse events • Incident vertebral fractures
Source of funding	The study was funded by an unrestricted educational grant from CareFusion Corporation (San Diego, CA, USA). Carefusion Corporation had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication Study sponsor: Optimus Clinical Research
Notes	Clinicaltrials.gov trial identifier: NCT01482793 registered on 28 November 2011. For success of blinding, results were only presented for a subset of participants (35/55 (60%) and 35/57 (61.4%) in the vertebroplasty and placebo groups respectively at 14 days, and not reported at 3 days.80% of the vertebroplasty group correctly guessed their treatment assignment (vertebroplasty), compared with 58% of the placebo group (sham procedure) measured at 2 weeks. Success of blinding at 3 days, a pre-specified outcome, was not reported Three patients in each group died from causes judged unrelated to the procedure. In the vertebroplasty group there were two serious adverse events related to the procedure. One patient had a respiratory arrest after administration of sedation, before starting the procedure. The patient was resuscitated and underwent the trial procedure two days later without incident. One patient sustained a supracondylar humerus fracture in a paretic arm during transfer onto the radiology table. The fracture healed with a plaster cast. In the control group there were two serious adverse events related to the fracture. Both patients developed spinal cord compression due to interval collapse and retropulsion of the fracture several weeks after enrolment. Neither had substantial fracture retropulsion at time of study enrolment. One patient underwent spinal decompressive surgery with resolution of the neurological deficit. The other patient, not considered a surgical candidate, became paraplegic

	A pre-specified sub-group analysis comparing outcomes for three different regions of the spine (thoracic (T4 to T10), thoraco-lumbar (T11 to L2) and lumbar (L3-L5).) excluding those with two acute fractures involving more than one of these regions, was reported in the results paper, comparing thoracic or lumbar fractures combined versus outcomes for thoraco-lumbar fractures. Their logistic regression model showed strong evidence (P = 0.0012) of different treatment outcomes between these spinal segments (i.e. benefit of vertebroplasty only for a thoraco-lumbar fracture) Another subgroup analysis reported to be pre-specified (but not reported in the protocol paper) found no significant difference (P = 0.12) in treatment outcomes between fracture age ≤ 3 weeks versus ¿ 3 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1) to receive either vertebroplasty or placebo by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre automated telephone service, which provided random computer-generated numbers
Allocation concealment (selection bias)	Low risk	The interventional radiologist called this system once participant was in the procedure room, immediately before the procedure
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The participants, investigators (other than the radiologists performing the procedure), and trial outcome assessors were masked to patient group assignments." Unclear whether participants were successfully blinded due to incomplete outcome reporting (data for only 35/55 (60%) in the vertebroplasty group and 35/57 (61.4%) in the placebo group were reported for this outcome) and in those in whom success of blinding was reported there was a difference in the proportion who correctly guessed their assigned treatment. 28/35 (80%) of the vertebroplasty group correctly guessed that they had undergone vertebroplasty compared with 19/35 (54%) of the control group correctly guessing that they had received a placebo at 14 days [this difference is statistically significant, Chi-square = 8.8112, P value ¡ 0.01 as calculated by review authors]

		Success of blinding was also not reported at the pre-specified time point of 3 days
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Unclear risk	Unclear whether participants were successfully blinded.
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Radiologists who assessed follow-up radiographs were aware of treatment assignment as vertebroplasty cement is opaque and will be detected on imaging
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A greater number of participants were missing at the 14-day follow-up in the vertebroplasty group (6/61, 9.8%) compared with 2/59 (3.4%) in the placebo group. Data were unavailable for 8 (13.1%) and 7 (11.9%) in vertebroplasty and placebo groups respectively at the 3-month follow-up. Reasons for withdrawal were not reported In addition, some data were missing for some outcomes reported to be due to inability to complete questionnaires by sick elderly participants. Most data were missing for the outcome of success of blinding at 14 days although the proportion missing was equal across treatment groups (data reported for 35/55 (60%) in the vertebroplasty group and 35/57 (61.4%) in the placebo group)
Selective reporting (reporting bias)	High risk	Primary outcome is inconsistently reported in the published protocol as both the proportion of patients whose NRS pain score reduces from 7/10 (or more) to 4/10 (or less) at 14 days, and the proportion of patients achieving a 14-day pain score of less than 4 out of 10. The results paper states that the primary endpoint is the proportion of patients achieving an NRS pain score of less than 4 out of 10 The following outcomes were pre-specified in the published protocol but not reported in the results paper: • Average pain in preceding 24 hours at rest on NRS • Average pain in preceding 24 hours during standing or moving on NRS

		• Average pain in preceding 24 hours at rest on VAS (baseline, 2 weeks, 6 months) • Average pain in preceding 24 hours during standing or moving on VAS (baseline, 2 weeks, 6 months) • Change in pain (day 3, 2 weeks) • Success of blinding at 3 days • Resource use and health care utilisation (6 months) The following outcomes were not pre-specified in the published protocol but reported in the results paper: • Participant rating of their confidence in their guess regarding treatment allocation at 2 weeks as a percentage • Nomination of the main reason for their guess • Outcome assessor nominated treatment allocation at 2 weeks, their confidence in the guess and main reason based on observed changes in patient mobility and apparent pain since baseline
Other bias	Unclear risk	Placebo procedure differs between published protocol and results paper. The protocol reports that a 4-mm skin incision will be made with light tapping on the skin. The results paper states that a short needle was passed into the skin incision but not as far as the periosteum and that manual skin pressure and regular tapping on the needle was done to mimic vertebroplasty needle advance

Dohm 2014

Methods	**Design:** multicentre, parallel group, two-arm open randomised controlled trial including 75 sites **Setting:** USA and Canada **Timing:** October 2006 to May 2011 **Interventions:** percutaneous vertebroplasty versus balloon kyphoplasty **Sample size:** 1234 participants required to detect an 8.7% difference in subsequent radiographic fracture (40% in vertebroplasty, 31.3% in kyphoplasty), 20% withdrawal, 80% power and 5% type I error rate **Analysis:** modified intention-to-treat analysis using all data available from the 381 participants randomised and treated (23 participants withdrew before receiving treatment, 15 assigned to vertebroplasty and 8 assigned to kyphoplasty)
Participants	**Number of participants** • 3554 participants screened for eligibility • 3150 excluded (2331 did not meet inclusion criteria; 412 declined to participate; 407 other reasons for being ineligible) • 404 randomised (205 to vertebroplasty and 199 to kyphoplasty) • 23 did not undergo treatment (15 vertebroplasty and 8 kyphoplasty) • Data for 273 (143 (75%) for vertebroplasty and 130 (68%) for kyphoplasty) available at 12-month follow-up • Data for 191 (100 (53%) for vertebroplasty and 91 (48% for kyphoplasty) available at the final 24-month follow-up **Inclusion criteria** • Over 21 years old • 1 to 3 acute painful vertebral fractures from T5 to L5 due to osteoporosis less than 6 months old • Oedema on MRI, uptake on radionuclide bone scans, or acute vertebral height loss within 6 months by CT, MRI, or X-ray. • Treatment of all target VCFs is technically feasible and clinically appropriate for both procedures (vertebroplasty and balloon kyphoplasty) • Pre-treatment back pain score by NRS is ¿ 4 (0-10 scale) • Pre-treatment ODI is ¿ 20 (0-100 scale) • Stated availability for all visits • Participant understands the risks and benefits of participating in the trial and provides written consent • Mental capacity to follow protocol for up to 2 years **Exclusion criteria** • Back pain not attributable to vertebral fracture (e.g. sacroiliac fracture, symptomatic degenerative disc disease, lumbar spinal stenosis) • Presence of more than three acute vertebral fractures • Vertebral fractures more than 6 months old • Fractures due to suspected or proven cancer or high-energy trauma • Requiring other procedures for fracture stabilisation • Irreversible coagulopathy, bleeding disorder or known allergies to bone cement or contrast • Local or systemic infection • Any objective evidence of neurologic compromise at baseline • Previous vertebroplasty or kyphoplasty • Significant clinical comorbidity that may potentially interfere with long-term data

	collection or follow-up (e,g. dementia, severe comorbid illness • Pregnant or wanting children within study period **Baseline characteristics** *Vertebroplasty group:* Mean (SD) age: 75.7 (10.5) years; 144 female: 46 male Duration of back pain: not stated Mean (SD) baseline pain score (from the trial registry website): 7.7 (1.8) out of 10 Mean (SD) baseline Oswestry Disability Index score (from the trial registry website): 57.8 (16) out of 100 Bisphosphonate use: N = 65 (34.2%) Opioid use at baseline: 126/169 (74.6%) T score for bone mineral density (BMD) less than -1: N = 133 (83.2%) *Kyphoplasty group:* Mean (SD) age: 75.5 (10.3) years; 151 female: 40 male Duration of back pain: not stated Mean (SD) baseline pain score (from the trial registry website): 7.8 (1.8) out of 10 Mean (SD) baseline Oswestry Disability Index score (from the trial registry website): 59 (17.5) out of 100 Bisphosphonate use: N = 75 (39.3%) Opioid use at baseline: 122/165 (73.9%) T score for bone mineral density (BMD) less than -1: N = 138 (83.6%)
Interventions	Specialist training of those performing the procedures was not reported. Investigator requirements were 50 lifetime procedures or 20 in the last year for each procedure. If an investigator only qualified for one of the procedures, they could participate as a team with an investigator qualified in the other technique. Tools and polymethylmethacrylate bone cement used were approved or cleared by the FDA for treating vertebral fractures by using kyphoplasty and vertebroplasty, respectively **Vertebroplasty** Procedures were performed according to local practices and was not standardised across centres **Balloon kyphoplasty** The procedure was performed by using a bilateral approach. Kyphon Osteo Introducer Systems, Inflatable Bone Tamps, HV-R Bone Cement, Bone Filler Devices, and other balloon kyphoplasty devices were manufactured by Medtronic Spine, Sunnyvale, California **Both treatment groups** In the results it is stated that investigators were to attempt vertebral deformity correction regardless of treatment; 142/189 (75.!%) participants in the vertebroplasty group and 154/191 (80.6%) participants in the kyphoplasty group had perioperative postural reduction
Outcomes	Outcomes were reported at 7 days, 1, 3, 12 and 24 months after treatment **Primary outcomes** • New radiographic vertebral fractures (including any new or worsening index fracture) according to the method of Genant 1993 at 12 and 24 months (Standing lateral spine radiographs baseline, post-operatively, 3, 12, 24 months) **Secondary outcomes** • Physical function and quality of life measured by the SF-36 Physical Component

	Summary • EuroQol-5-Domain (EQ-5D) questionnaire • Numeric rating scale for back pain (scale 0-10, 0 indicates no pain and 10 being worst pain ever) (also measured on day 7) • Back function measured by the modified Oswestry Disability Index (Section 8, regarding sexual activity was removed) (score ranges from 0-100. The best score is 0 (no disability) and worst is 100 (maximum disability) • Vertebral kyphotic angulation by quantitative morphometry (angle formed by lines drawn parallel to the caudal and cranial fractured vertebral body endplates determined the kyphotic angulation) • New clinical fractures (defined as subsequent painful vertebral fractures coming to clinical attention) • Post-procedure CT through treated levels was performed to determine cement volume and leakage • All adverse events systematically classified into preferred terms and system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA). • Serious adverse events (SAEs) included death, serious deterioration in health, life-threatening injury/illness, hospitalisation or prolonged hospitalisation, or requiring medical or surgical intervention. • Rate of procedure/device related or possibly related serious adverse events at 30 days • Amount of analgesic use **Outcomes included in this review** • Mean pain • Modified Oswestry Disability Index • EQ-5D • New radiographic vertebral fractures • New clinical vertebral fractures • Serious other adverse events thought to be device/procedure/anaesthesia-related
Source of funding	Medtronic Spine sponsored the study and contributed to study design, data monitoring, statistical analysis and reporting of results and paid for independent core laboratory and data safety-monitoring board services
Notes	Trial registered on 5 May 2006, registration number: NCT00323609. Known as 'KAVIAR' trial Due to higher than anticipated withdrawal rate (38%), low patient enrolment, and patient/investigator willingness for randomisation, the sponsor terminated the study before reaching the planned sample size after enrolling 404 participants. This decision was made without knowledge of any outcome results. Enrolled participants left the study without additional follow-up except that any not reaching the 1-month visit were followed to collect 30-day safety data Outcomes reported in the published report differ from planned outcomes according to trial registration. Outcomes not reported in the published paper include SF-36 Mental Component Summary, quality of life questionnaire (mini-OQLQ), ambulatory status, change in vertebral body height; change in sagittal vertical axis; vertebral fracture-related health care utilisation. Time to new clinical fracture reported in results but not listed as outcome in trial registration We extracted the reported denominators for number of participants with new radio-

	graphic fractures at 12 and 24 months in each treatment group, which differed from the number of participants with complete follow-up at these time points as reported in the flow diagram

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by computer using a dynamic minimisation technique stratified by the number of prevalent vertebral fractures, aetiology and study centre. It is not clear how participants were stratified by aetiology as the inclusion criteria specified that participants have osteoporotic fractures (and people with fractures due to cancer or high-energy trauma were excluded)
Allocation concealment (selection bias)	Unclear risk	It is not reported whether or not the random sequence was concealed from investigators prior to allocating a participant to treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was not concealed from participants or investigators
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	Participants were told of their treatment group immediately following randomisation, this way may have influenced their assessment of self-reported outcomes
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	It is not stated who assessed the imaging outcomes but it is unlikely that they were blinded to treatment assignment as both procedures will be detected on imaging. An independent radiologist determined cement volume and was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up was small and equal across treatment groups for short-term outcomes. Follow-up was completed at 1 month for 181/190 who underwent vertebroplasty (5 withdrew, 1 lost, 1 other medical reason, 1 logistical reasons, 1 died) and 180/191 who underwent kyphoplasty (4 withdrew, 1 lost, 1 other medical reason, 4 other reason, 1 died) However loss to follow-up was greater for

		the primary endpoints measured at 12 and 24 months. At 12 months there was complete follow-up for 130/190 (68%) in the vertebroplasty group (20 withdrew, 4 lost, 3 logistical reason, 2 other medical reason, 3 other reason, 1 due to unrelenting pain, 14 died, 13 sponsor terminated study) and 143/191 (75%) in the kyphoplasty group (11 withdrew, 4 lost, 3 other medical reason, 4 logistical reasons, 1 due to unrelenting pain, 5 other reason, 10 died, 10 sponsor terminated study). At 24 months, 91/190 (48%) participants in the vertebroplasty group had completed follow-up (23 withdrew, 10 lost, 5 logistical reason, 7 other medical reason, 3 other reason, 1 due to unrelenting pain, 21 died, 29 sponsor terminated study), and 100/191 (52%) participants in the kyphoplasty group completed follow-up (13 withdrew, 9 lost, 3 other medical reason, 9 logistical reasons, 1 due to unrelenting pain, 11 other reason, 16 died, 29 sponsor terminated study) Overall, the reasons for the losses were similar except a higher proportion who received their assigned treatment withdrew from the vertebroplasty group (20/190; 11%) compared to the kyphoplasty group (11/191; 6%). It is unclear if the reasons for withdrawal were systematically different In the methods it is stated that seven participants who received vertebroplasty and 4 who received kyphoplasty underwent the alternate treatment for a subsequent vertebral fracture but the timing was not stated. It is stated that for any participant having surgery for a new vertebral fracture, the last observation before surgery was carried forward to later visits. In the results it is stated that 70/88 (79.5%) participants with a new clinically recognised fracture underwent a subsequent vertebral augmentation but these data are not presented by treatment group and the timing of further vertebral augmentation is not specified
Selective reporting (reporting bias)	Low risk	All outcomes planned at trial registration were reported although on the trial registration site primary and secondary outcomes

Dohm 2014 (*Continued*)

		were modified after the trial was completed. Some outcomes not reported in the published paper (e.g. SF-36 Mental Component Summary, quality of life questionnaire (mini-OQLQ), ambulatory status, change in vertebral body height; change in sagittal vertical axis; vertebral fracture-related healthcare utilisation) were reported in the trial registration report but not the published paper Time to clinical fracture (in days) was reported but was not listed as an outcome in the trial registration
Other bias	Unclear risk	The trial was sponsored by a device company. The company also contributed to study design, data monitoring, statistical analysis and reporting of results including manuscript authorship, paid for independent core laboratory and data safety-monitoring board services, and terminated the study early

Endres 2012

Methods	**Design:** two-arm open-label single-centre quasi-randomised controlled trial **Setting:** Germany **Timing:** not stated **Interventions:** percutaneous vertebroplasty, balloon kyphoplasty or shield kyphoplasty **Sample size:** *a priori* sample size calculation not reported **Analysis:** completers' analysis
Participants	**Number of participants** • Numbers screened for eligibility and number excluded or declined to participate is not stated. • 66 participants quasi-randomised (22 to each of the three groups) • Data for 59 (21/22 (95%) for vertebroplasty, 20/22 (91%) for balloon kyphoplasty and 18/22 (82%) for shield kyphoplasty available at the 6-month follow-up. • Two participants were deceased at the time of follow-up and five refused to participate and these participants were excluded from the analysis. **Inclusion criteria** • Patients with osteoporosis proven on DXA scan • Fresh painful single-level vertebral fracture in middle and lower thoracic spin. • Symptom duration 6 weeks or less • Magnetic resonance imaging demonstrating oedema in the affected vertebral body • Conservative treatment (analgesics according to the WHO scheme, physiotherapy, physical therapy, orthotics adjustment) ineffective for at least 4 weeks

	• Provoked percussion pain in the spinous process agreed with the site of the radiologically proven compression fracture **Exclusion criteria** • No painful vertebral deformation or considerable degenerative damage • Vertebral deformation (e.g. vertebra plana) • Tumour and metastasis • Local or systemic infection • Untreated clotting disorder **Baseline characteristics** *Vertebroplasty group:* Mean (range) age: 71.3 (63-77) years; 12 female:8 male (gender of one participant not specified) Prevalent vertebral fractures at baseline: 1 Mean (SD) baseline pain score: 78.2 (9.36) Mean (SD) baseline Oswestry Disability Index: 68.2 (5.7) *Balloon kyphoplasty:* Mean (range) age: 63.3 (53-77) years; 14 female:6 male Prevalent vertebral fractures at baseline: 1.25 (range 1 - 3) Mean (SD) baseline pain score: 90.0 (7.07) Mean (SD) baseline Oswestry Disability Index: 77.0 (4.2) *Shield kyphoplasty:* Mean (range) age: 67.1 (47-79) years; 14 female:4 male Prevalent vertebral fractures at baseline: 1.14 (range 1-2) Mean (SD) baseline pain score: 88.16 (15.06) Mean (SD) baseline Oswestry Disability Index: 75.7 (9.1)
Interventions	All procedures were performed by the same orthopaedic surgeon under biplane fluoroscopy and general anaesthesia **Vertebroplasty** This was performed through a unipedicular transpedicular approach with one 13-gauge bone biopsy needle (Stryker) placed in the anterior third of the vertebral body. Once the needle was in place, liquid and powder PMMA (high viscosity SpinePlex, Stryker, Germany) were mixed to toothpaste consistency. Under biplane guidance, the cement was injected through the needle until the vertebral body was filled in the posterior 25% or until there was leakage. No postural manoeuvre was performed to retain alignment before or during the procedure **Balloon kyphoplasty** This was also performed through a unipedicular approach with a unilateral working cannula and standard kyphoplasty equipment (high viscosity KyphX HV-R, Medtronic, Germany). A drill passing through the cannula created a tract for the 20 mm balloon to be inserted in the centre of the vertebral body. Cement, mixed according to the manufacturer's recommendations, was injected as described for vertebroplasty. Injection was usually about 14 minutes after start of mixing **Shield kyphoplasty** The Soteira shield kyphoplasty is a percutaneous minimally invasive system that enables a fractured vertebral body to be accessed through a unipedicular approach. The implant site was prepared by manually creating a cavity, and bone cement (Soteira, high viscosity) was delivered via an implantable cement director, the Shield Implant. This is a hollow, self-expandable, coated implant that is marketed in a range of sizes and is attached to a

Endres 2012 (*Continued*)

	disposable delivery system **Follow-up** All participants were discharged 2 days after surgery. All participants received daily standard doses of oral aminobisphosphonate, 1000 mg calcium and 1000 IU vitamin D3. In addition, physiotherapy and pain medication was prescribed as required
Outcomes	Outcomes were reported immediately postoperatively and a mean of 5.8 months (range: 4 to 7 months) after treatment **Primary outcomes** • Mean pain, measured on a VAS scale (scale not specified but appeared to be on a 0 to 100 scale) • Mean disability, measured by the Oswestry Low Back Disability Index (ODI), 0 to 100 scale (0 is no disability) **Secondary outcomes** • Beck Index (assesses vertebral height) • Surgery and fluoroscopy times • Dose-area product (cGy x cm^2) • Cement leakage • Incidence of new adjacent vertebral fractures • Other adverse events **Outcomes included in this review** • Mean pain • Disability as measured by the ODI • Incidence of new vertebral fractures • Adverse events
Source of funding	BioMedEs funded translation and copyediting. It is not reported whether or not other funding was received
Notes	Trial registration: not found. The authors stated that there were no significant differences in baseline characteristics between groups but the review authors judged there to be significant pre-treatment group differences: there were significant differences between groups with respect to age (mean age of participants in the vertebroplasty group was greater than the other groups) and participants allocated to the kyphoplasty groups appeared to have worse scores for pain and ODI at baseline compared with the vertebroplasty group We extracted data from vertebroplasty and balloon kyphoplasty groups only We converted the 0 to 100 pain scale to a 0 to 10 pain scale for the purposes of pooling data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The included participants were distributed quasi-randomly into three groups."

Endres 2012 (*Continued*)

Allocation concealment (selection bias)	High risk	Quasi-random method of allocation likely precluded concealment of sequence to the single investigator who allocated the participants to treatment as it was predictable
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded to treatment allocation. A single investigator who performed all procedures was not blinded to treatment allocation
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Low risk	Pain and disability was self-assessed by participants who were unaware of their treatment allocation. Another orthopaedic surgeon not involved in the primary surgery performed the final follow-up
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Images were analysed by the (unblinded) orthopaedic surgeon who performed the procedures, as well as by a radiologist. It is not reported whether or not the radiologist was blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were unavailable for 7 participants (two deaths and five participants who refused follow-up: treatment group not specified, however data were not reported for 1 participant in the vertebroplasty, 2 in the balloon kyphoplasty group and 4 in the shield kyphoplasty group)
Selective reporting (reporting bias)	Unclear risk	Trial not registered and trial protocol was not published. All outcomes listed in the methods are reported
Other bias	Unclear risk	Participants in the vertebroplasty group were older on average than participants in other groups (71.3 versus 63.3 and 67.1 years in the balloon and shield vertebroplasty groups respectively) Participants in the kyphoplasty groups also appeared to have worse pain and disability scores at baseline compared to the vertebroplasty group (vertebroplasty: 78.2 and 68.2; balloon kyphoplasty: 90.0 and 77.0; and shield kyphoplasty 88.16 and 75.7, respectively) It is not clear if BioMedEs had any role in the study other than funding translation and copyediting

Evans 2015

Methods	**Design**: multicentre (nine sites) parallel group, two-arm randomised controlled trial **Setting:** USA **Timing:** unclear **Interventions:** percutaneous vertebroplasty versus kyphoplasty **Sample size:** total sample size of 96 participants would provide 80% power to detect a 'medium' effect size of 0.58; planned to recruit a total of 120 participants assuming up to 20% loss to follow-up at 12 months **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • Numbers screened for eligibility and number excluded or declined to participate is not stated. • 115 patients randomised (56 to vertebroplasty, 59 to kyphoplasty) • Data for 88 (70.7% of vertebroplasty group, 78.2% of kyphoplasty group) available at 12-month assessment **Inclusion criteria** • Older than 50 years of age • Pain that had occurred in the previous 12 months attributable to one or more compression fracture of the vertebrae in the areas T4-L5 confirmed with a physical examination and imaging • Fractures detected on plain radiography • Pain of at least 5 (on a scale of 0 to 10) • Candidates for minimally invasive surgery • Able to successfully complete a battery of health questionnaires • Available and willing to participate in follow-up **Exclusion criteria** • Neurological deficits related to the compression fracture or other contraindications to vertebral augmentation • History of surgery within last 60 days • History of open back surgery • Concomitant hip fracture, rib fracture, or sacral insufficiency fracture • Malignant tumour deposit (multiple myeloma), tumour mass, or tumour extension into the epidural space at the level of the fracture to be treated **Baseline characteristics** *Vertebroplasty group:* Mean (SD) age: 76.1 (10.0) years; 77.6% female: 22.4% male Mean (SD) Charlson score: 0.43 (0.90) Comorbidities: 57.9% Neurological deficit: 4.7% Prior fracture history · Vertebral: 17.9% · Non-vertebral: 3.6% · None listed: 78.6% Prior back surgery: 3.6% Osteoporosis: 45.0% Mean (SD) current fracture %: 25.2 (18.8) Current fracture level · L1 only: 12.5%

	· T11 only: 7.1% · T12 only 8.9% · Other locations: 50.0% · Not listed: 21.4% Narcotic medication at entry: 64.1% NSAID at entry: 22.2% Mean (SD) average pain (0 to 10): 7.9 (2.0) Mean (SD) SOF-6 ADL score: 17.4 (3.1) Mean (SD) Roland-Morris disability score: 16.3 (7.4) Mean (SD) EuroQOL score: 10.1 (1.6) Mean (SD) SF-36 aggregate physical health: 26.6 (7.6) Mean (SD) SF-36 aggregate mental health: 42.4 (12.7) Mean (SD) OPAQ body image score (1 to 5): 3.5 (1.4) *Kyphoplasty group:* Mean (SD) age: 75.1 (10.1) years; 64.8% female: 35.2% male Mean (SD) Charlson score: 0.49 (0.99) Comorbidities: 60.5% Neurological deficit: 8.7% Prior fracture history · Vertebral: 10.2% · Non-vertebral: 11.9% · None listed: 78.0% Prior back surgery: 10.2% Osteoporosis: 37.2% Mean (SD) current fracture %: 23.1 (17.5) Current fracture level · L1 only: 17.0% · T11 only: 10.2% · T12 only 15.2% · Other locations: 35.6% · Not listed: 22.0% Narcotic medication at entry: 57.1% NSAID at entry: 26.2% Mean (SD) average pain (0 to 10): 7.4 (1.9) Mean (SD) SOF-6 ADL score: 17.7 (4.0) Mean (SD) Roland-Morris disability score: 17.3 (6.6) Mean (SD) EuroQOL score: 10.4 (1.9) Mean (SD) SF-36 aggregate physical health: 26.1 (6.9) Mean (SD) SF-36 aggregate mental health: 45.4 (14.2) Mean (SD) OPAQ body image score (1 to 5): 3.5 (1.4)
Interventions	**Vertebroplasty** Vertebral augmentation was performed according to standard practice according to each practitioner's preference. The approach, device, and cement used for the procedure were at the operators' discretion **Kyphoplasty** Also performed according to standard practice according to each practitioner's preference. The approach, device, and cement used for the procedure were at the operators' discretion

Evans 2015 (*Continued*)

Outcomes	Outcomes were measured at baseline, 3 days, 1 month, 6 months, and 12 months after treatment (telephone follow up at day 3, 1 month and 6 months and in person at 1 year) **Primary outcome** 1. Mean pain on a 0 to 10 numerical verbal scale **Secondary outcomes** • Use of pain medications • Roland-Morris Low Back Pain and Disability Questionnaire (RMDQ) • Short-Form Health Survey Instrument (SF-36) • EuroQOL EQ-5 Health States Instrument • Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL6) • Modified Deyo Patrick Pain Frequency and Bothersomeness Scale • Osteoporotic Assessment Questionnaire (OPAQ) Body Image Scale • Adverse events **Outcomes included in this review** • Mean pain • Roland-Morris Disability Questionnaire (RMDQ) • European Quality of Life - 5 Dimensions (EQ-5D) • Adverse events
Source of funding	Supported by Carefusion, Johnson and Johnson/DePuy Synthes Spine, Cardinal Health and Stryker
Notes	Clinicaltrials.gov trial identifier: NCT00279877 SD for EuroQOL EQ-5 Health States Instrument imputed from baseline for both treatment groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial participants were randomly assigned to either the kyphoplasty intervention or the vertebroplasty intervention using a variable block randomisation scheme to ensure balance of assignment to both groups over time. The block sizes were randomly varied and of sufficient size to minimise the ability of any investigator or co-ordinator to guess the next assigned treatment
Allocation concealment (selection bias)	Low risk	The random treatment assignments were placed in sequentially numbered envelopes and distributed to the clinical sites
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study is reported as 'single-blind' in the clinical trial registry, but reports of who was blinded are contradictory: the site co-ordinators and other personnel who collected trial participant data and adminis-

Evans 2015 (*Continued*)

		tered the study questionnaires were blinded to the assigned treatment, according to the results report but participant blinding was reported in the trial registry
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Unclear risk	Unclear if the 'single-blinded' study refers to blinding of participants or not
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	Low risk	No objective outcomes were measured.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A quarter of the participants did not complete follow-up (21.8% of vertebroplasty group, 29.3% of kyphoplasty group). The authors report that the pattern of loss to follow-up appeared to be missing at random
Selective reporting (reporting bias)	High risk	Adverse events were to be measured but were not reported.
Other bias	Unclear risk	Quote: "Another limitation of our study is the lack of standardisation of the procedures. The approach, device, and cement used for the procedures were at the operators' discretion."

Farrokhi 2011

Methods	**Design:** two-arm open-label randomised controlled trial; control group allowed to crossover into vertebroplasty group from one month (cross-overs ¡ 2 months = 4, ¡ 6 months = 3, ¡12 months = 3, ¡ 36 months = 10) **Setting:** Iran **Timing:** Sept 2004 to Jan 2009 **Interventions:** percutaneous vertebroplasty or usual care **Sample size:** *a priori* sample size calculation not reported **Analysis:** reported an intention-to-treat analysis
Participants	**Number of participants** • 105 screened for eligibility • 23 excluded (20 did not meet inclusion criteria and 2 declined to participate) • 82 patients were randomised (40 to vertebroplasty and 42 to usual care) • Data for 82 (40 (100%) for vertebroplasty and 42 (100%) for usual care) available at 6-month follow-up but 3 (7%) participants assigned to usual care received vertebroplasty before the 6-month follow-up

	• Data for 76 (37 (93%) for vertebroplasty and 39 (93%) for usual care) available at the final 36-month follow-up but 10 (24%) participants assigned to usual care received vertebroplasty before the 36-month follow-up **Inclusion criteria** • Severe back pain refractory to analgesic medication (analgesics or NSAIDs) for at least 4 weeks and no longer than 1 year • Vertebral compression fracture with 10%-70% loss of vertebral body height on X-ray of the spine • Focal tenderness on physical examination at the level of vertebral fracture • Vacuum phenomenon or bone marrow oedema of the vertebral fracture on MRI • Osteoporosis (T-score less than -2.5) on bone densitometry **Exclusion criteria** • Uncorrected coagulopathy • Local or systemic infection • Secondary osteoporosis • Inability to give informed consent • Impaired cardio-pulmonary function • Dementia • Posterior wall defect of the vertebral body on CT imaging • Spinal cancer • Traumatic fracture • Neurological complications **Baseline characteristics** *Vertebroplasty group:* Mean (range) age: 72 (59 to 90) years; 30 female:10 male Duration (range) of back pain: 30 (6 to 54) weeks Previous vertebral fractures: 50 Mean (SD) baseline pain score: 7.2 (1.7) Initial pain medication- paracetamol (acetaminophen) and codeine: 30 (75%); NSAIDs: 20 (50%) *Usual care group:* Mean (range) age: 74 (55 to 87) years; 30 female:12 male Duration (range) of back pain: 27 (4 to 50) weeks Previous vertebral fractures: 56 Mean (SD) baseline pain score: 8.4 (1.6) Initial pain medication- paracetamol (acetaminophen) and codeine: 30 (71%); NSAIDs: 32 (76%)
Interventions	Percutaneous vertebroplasty performed by neurosurgeons; usual care ('optimal medical therapy') delivered by a physician **Vertebroplasty** Induction of conscious sedation (a combination of IV fentanyl and midazolam) in 10 (25%) participants and general anaesthesia in 30 (75%) participants. Patients were placed prone and single-plane C-arm equipment was used. Using sterile techniques, an 11-gauge needle was inserted into the vertebral body via a unilateral parapedicular approach in 35 (87.5%) patients and via a bilateral transpedicular approach in 5 (12.5%) patients. A bilateral transpedicular approach was used only if there was inadequate instillation of cement with the unilateral approach under fluoroscopy. A polymethylmethacrylate mixture was injected into the vertebral body. Following the procedure, the patient remained

	supine in bed. During cement injection, fluoroscopic monitoring with a C-arm unit was used in both planes. It is not stated whether or not participants in the vertebroplasty group could also receive analgesia and/or treatment of osteoporosis **Usual care** The usual care group was prescribed 250 mg acetaminophen with codeine twice daily, 400 mg ibuprofen twice a day, 1000 mg calcium daily, 400 IU vitamin D daily, 70 mg alendronate orally once weekly, and 200 IU calcitonin daily. Analgesia could be increased by the treating physician as needed. Cross-over to vertebroplasty was permitted after 1 month **Follow-up care** A change in lifestyle and physical treatment (undefined) was also suggested to participants in both groups
Outcomes	Outcomes were reported at 1 week, and 2, 6, 12, 24 and 36 months after treatment **Primary outcomes** • Mean pain in previous 24 hours, measured on a 1 to (no pain) to 10 (excruciating pain) VAS scale. • Mean disability, measured by the Oswestry Low Back Disability Index (ODI), 0 to 100 scale (0 is no disability) **Secondary outcomes** • Ability to walk after one day • Incidence of new symptomatic vertebral fractures (at 24 months) • Radiographic measurement of vertebral body height (VBH, mm); and correction of spinal deformity (sagittal index, degrees) at 2, 6, 12, 24 and 36 months. • Adverse events **Outcomes included in this review** • Mean pain • Disability as measured by the ODI • Incidence of new symptomatic vertebral fractures • Adverse events
Source of funding	The Vice-chancellor for research affairs of Shiraz University of Medical Sciences and Apadana Tajhizgostar Co. (distributor of medical devices) provided grant support
Notes	Trial registered retrospectively on 11 Oct 2009 at www.irct.ir, number IRCT138804252193N1 All participants in the control group were permitted to undergo vertebroplasty after 1 month; 4 crossed over before 2 months, 3 before 6 months, 3 before 12 months and 10 before 36 months (total cross-over 20/42 (47.6%)) We included the 2-month follow-up data in the 3-month analyses/meta-analyses The trialists report epidural cement leakage in one participant receiving vertebroplasty, and no cases of venous emboli or infection. It is not reported if any adverse events occurred with usual care

Risk of bias

Bias	Authors' judgement	Support for judgement

Farrokhi 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	Generated by computerised random number generator
Allocation concealment (selection bias)	Low risk	The treatment assignment was kept in sealed envelopes. It is not explicitly reported who prepared and opened the envelopes, but it is likely that allocation was concealed and the neurosurgeon (performing vertebroplasty) and the physician (administering usual care) had no role in allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were unblinded; the treating clinicians were unaware of the other treatment group
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	Participants self-assessed pain and disability and were unblinded
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	It is not stated who assessed the imaging outcomes. It is unlikely that they were blinded to treatment assignment as vertebroplasty cement is opaque and will be detected on imaging
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was small and equal across groups (3/40 participants in the vertebroplasty group and 3/42 participants in the usual care group at the final 36 month follow-up)
Selective reporting (reporting bias)	Unclear risk	Unclear if any additional outcomes were measured and not reported; e.g., incident fracture is not listed in the methods as an outcome but data are reported in the results for the 2-year (but not end of study) follow-up
Other bias	Low risk	None apparent

Kallmes 2009

Methods	**Design:** multicentre, two-arm, randomised placebo-controlled cross-over trial; cross-over to the other treatment group was allowed at 1 month or later if adequate pain relief was not achieved **Setting:** USA (5 centres), UK (5 centres) and Australia (1 centre) **Timing:** not reported **Interventions:** percutaneous vertebroplasty versus sham vertebroplasty (placebo) **Sample size:** initial sample size calculation of 250 participants was based upon an ability to detect a 2.5-point difference on the Roland-Morris Disability Questionnaire (RMDQ) and a 1-point difference on the 0- to 10-point pain intensity scale, with at least 80% power and a two-sided type 1 error of 0.05. After early difficulty in recruitment and a planned interim analysis of the first 90 participants, target enrolment was reduced to 130 participants based upon accrual rates and revised power calculations. With 130 participants, there was more than 80% power to detect a 3-point difference between groups on the RMDQ (assumed SD 6.7), and a 1.5-point difference on the pain rating (assumed SD 2.7) at 1 month **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • 1813 participants were screened for eligibility • 1682 excluded (1382 did not meet inclusion criteria; 300 declined to participate) • 131 randomised (68 to vertebroplasty and 63 to placebo) • Data for 128 (67 (99%) for vertebroplasty with 1 crossing over before 1 month, and 61 (97%) for placebo with 2 crossing over before 1 month) available at 1-month follow-up • Data for (64 (94%) for vertebroplasty with 8 (8/68, 12%) crossing over before 3 months, and 61 (97%) for placebo with 27 (27/63, 36%) crossing over before 3 months) available at the 3-month follow-up. **Inclusion criteria** • Age 50 years or older • One to three painful osteoporotic vertebral compression fractures between vertebral levels T4 and L5 • Inadequate pain relief with standard medical therapy • A current rating for pain intensity of at least 3 on a scale from 0 to 10 • Duration of pain less than one year • For fractures of uncertain age, bone oedema on MRI or increased vertebral-body uptake on bone scan was required **Exclusion criteria** • Neoplasm in the target vertebral body • Substantial retropulsion of bony fragments • Concomitant hip fracture • Active infection • Uncorrectable bleeding diatheses • Surgery within the previous 60 days • Lack of access to a telephone • Inability to communicate in English • Dementia **Baseline characteristics** *Vertebroplasty group:* Mean (SD) age: 73.4 (9.4) years; 53 female:15 male

	Mean (interquartile range; IQR) duration of back pain: 16 (10 to 36 weeks) Duration of back pain ¡14 weeks: 30 (44%) Mean (SD) baseline pain score: 6.9 (2.0) points Mean (SD) baseline RMDQ score: 16.6 (3.8) points Number with 1; 2; or 3 spinal levels treated: 48 (71%); 13 (19%); 7 (10%) Opioid use: 38 (56%) *Placebo group:* Mean (SD) age: 74.3 (9.6) years; 46 female:17 male Mean (interquartile range; IQR) duration of back pain: 20 (8 to 38 weeks) Duration of back pain ¡14 weeks: 24 (38%) Mean (SD) baseline pain score: 7.2 (1.8) points Mean (SD) baseline RMDQ score: 17.5 (4.1) points Number with 1; 2; or 3 spinal levels treated: 41 (65%); 14 (22%); 8 (13%) Opioid use: 40 (63%)
Interventions	Percutaneous vertebroplasty or the sham procedure was performed by highly experienced interventional radiologists having performed a mean of 250 procedures (range: 50 to 800). Procedures were performed in a fluoroscopy suite, under conscious sedation using sterile technique. Using fluoroscopic guidance, the practitioner infiltrated the skin and subcutaneous tissues overlying the pedicle of the target vertebra or vertebrae with 1% lidocaine and infiltrated the periosteum of the pedicles with 0.25% bupivacaine **Vertebroplasty** 11-gauge or 13-gauge needles were passed into the central aspect of the target vertebra or vertebrae. Barium opacified PMMA was prepared on the bench and infused under constant lateral fluoroscopy into the vertebral body. Infusion was stopped when the PMMA reached the posterior aspect of the vertebral body or entered an extraosseous space **Sham procedure** Verbal and physical cues, such as pressure on the patient's back, were given, and the methacrylate monomer was opened to simulate the odour associated with mixing of PMMA, but the needle was not placed and PMMA was not infused **Follow-up care** Both groups of patients were monitored in the supine position for 1 to 2 hours before discharge
Outcomes	Outcomes were reported 3 and 14 days, and 1 month (and 3 months for the primary outcomes) and at various times up to one year **Primary outcomes** • Modified Roland-Morris Disability Questionnaire (RMDQ) (23-item version, 0 to 23 scale, with higher scores indicating worse physical functioning • Average back pain intensity during the preceding 24 hours (0 to 10 scale, with higher scores indicating more severe pain) **Secondary outcomes** • Pain Frequency Index and the Pain Bothersomeness Index (0- to 4-point scale, higher scores indicating more severe pain) • Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL) scale (0- to 18-point scale, higher scores indicating more disability) • European Quality of Life-5 Dimensions (EQ-5D) scale (-0.1- to 1.0-point scale, higher scores indicating better quality of life)

	• Use of opioid medications • Physical Component Summary (PCS) and Mental Component Summary (MCS) subscales of the Medical Outcomes Study 36-Item Short- Form General Health Survey (SF-36), version 2 (0- to 100-point score, higher scores indicate better outcome) • Proportion with clinically important improvement in pain (at least 30% improvement) • Proportion with clinically important improvement in disability (at least 30% improvement) • Adverse events **Outcomes included in this review** • Mean pain • Disability as measured by the RMDQ • Quality of life as measured by the EQ-5D • Proportion with clinically important improvement in pain (at least 30% improvement) • Adverse events
Source of funding	Supported by a grant (R01-AR49373) from the National Institute of Arthritis and Musculoskeletal and Skin Diseases
Notes	Trial registered at ClinicalTrials.gov, number NCT00068822. For this review, we only extracted outcomes at 2 weeks and 1 month (i.e. before cross-over, and thus prior to the likely breaking of the randomisation schedule). After 1 month, significantly fewer participants in the vertebroplasty group crossed over into the alternate group (11 of 68 participants (16%)) compared with the placebo (sham) group (38 of 63 participants (60%), P = 0.001). At one year, difference in pain favoured the vertebroplasty group (MD 1.02 (95% CI 0.04 to 2.01); P = .042) but there was no evidence of an important difference in disability (MD in RMDQ 1.37 points (95% CI 3.62 to 20.88) , P = .231). In the as-treated analyses, participants treated with vertebroplasty did not differ from the placebo (sham) group in terms of either mean pain (MD 0.85 (95% CI 2.05 to 20.35), P = .166) or disability (RMDQ MD 0.66 (95% CI 3.30 to 21.98); P = .625)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocked randomisation (sizes ranging from 4 to 12 participants), stratified by study centre; sequences were generated by a random-number generator
Allocation concealment (selection bias)	Low risk	Allocation occurred just prior to the procedure using numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Group assignments were concealed from participants and study personnel. Before one month one participant in the vertebroplasty group and two participants in the

		sham group crossed over to the other treatment group. By three months more participants in the placebo group had crossed over (27/63, 36%) compared with the vertebroplasty group (8/68, 12%) and the reasons for the different cross-over rate is unknown - while it is possible that more participants in the control group had unsatisfactory pain outcomes, no difference in pain intensity was observed At 14 days, 63% of patients in the control group correctly guessed that they had undergone the control intervention, and 51% of patients in the vertebroplasty group correctly guessed that they had undergone vertebroplasty. Patients in both the vertebroplasty group and the control group expressed a moderate degree of confidence, on a scale of 0 (not certain) to 10 (extremely certain), in their treatment guess (mean scores, 4.0 and 4.1, respectively; P = 0.78) In the control group, 18 of 33 patients (55%) who did not cross over to vertebroplasty correctly guessed at 14 days that they had undergone the control intervention, as compared with 20 of 27 patients (74%) who eventually crossed over (P = 0.12). Among the eight patients in the vertebroplasty group who crossed over to the control group, six (75%) guessed incorrectly at 1 month that they had received the control intervention As we only considered outcomes to one month, we judged this trial to be at low risk of bias up until one-month follow-up
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Low risk	Participants were blinded to treatment assignment.
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	Low risk	No objective outcomes were assessed up to one-month follow-up
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was small and balanced across treatment groups

Selective reporting (reporting bias)	Low risk	All outcomes measured to 3 months planned in the published protocol were reported
Other bias	Low risk	None apparent.

Klazen 2010

Methods	**Design**: multicentre (6 centres), two-arm open-label randomised controlled trial; control group allowed to cross-over to vertebroplasty at one week post intervention **Setting:** the Netherlands and Belgium **Timing:** not reported **Interventions:** percutaneous vertebroplasty or usual care **Sample size:** *a priori* sample size calculation based on ability to detect a difference of 25% in significant pain relief with vertebroplasty compared with usual care based on a two-sided type 1 error rate of 5% and power 80% **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • 934 participants screened • 732 were excluded (226 did not meet inclusion criteria, 229 met inclusion initially but then a decrease in pain during screening rendering them ineligible, 232 declined participation and 45 requested vertebroplasty) • 202 patients were randomised (101 in percutaneous vertebroplasty, and 101 in conservative treatment) • Data were available for 188 (96 (95%) for vertebroplasty and 92 (91%) for usual care) at the 1-month follow-up • Data were available for 163 (86 (85%) for vertebroplasty and 77 (76%) for usual care) at the final 1-year follow-up **Inclusion criteria** • Acute back pain for 6 weeks or less • Pain on 0-10 VAS of 5 or more • Focal tenderness at fracture level, as assessed by an internist on physical examination • Vertebral compression fracture on spine radiograph (minimum 15% height loss) at T5 or lower • Bone oedema of vertebral fracture on MRI • Decreased bone density (T scores $\leq$ 1) **Exclusion criteria** • Severe cardio-pulmonary comorbidity • Untreatable coagulopathy • Systemic or local spine infection • Suspected underlying malignant disease • Radicular syndrome • Spinal-cord compression syndrome • Contraindication for MRI **Baseline characteristics**

	Vertebroplasty Group: Mean (SD) age: 75.2 (9.8) years; 70 female, 31 male Mean (SD) duration of back pain: 29.3 (17.1) days Number of VCFs at baseline: 2.4 (1.9) Mean (SD) pain at baseline: 7.8 (1.5) Mean (SD) RMDQ: 18.6 (3.6) Mean (SD) QUALEFFO: 58.7 (13.5) Bone density T score: -3.0 (1.17) *Usual care group* Mean (SD) age: 75.4 (8.4) years; 70 female, 31 male Mean (SD) duration of back pain: 26.8 (16.0) days Number of VCFs at baseline: 2.1 (1.5) Mean (SD) pain at baseline: 7.5 (1.6) Mean (SD) RMDQ: 17.2 (4.2) Mean (SD) QUALEFFO: 54.7 (14.4) Bone density T score: -3.0 (1.05)
Interventions	**Percutaneous vertebroplasty** Percutaneous vertebroplasty was performed using a single or biplane angiography system under fluoroscopic guidance. After local analgesia, two 11- or 13-gauge bone-biopsy needles were placed transpedicularly in the fractured vertebral body. Polymethylmetacrylate bone cement (Osteo-Firm, COOK Medical, Bloomington, IN, USA) was injected through bone-biopsy needles under continuous fluoroscopic monitoring to identify local cement leakage or migration into the venous system towards the lung. In patients who had more than one fracture with bone oedema on MRI, all vertebral bodies were treated in one or more procedures. After the procedure, a CT scan of the treated vertebral bodies was performed with 2 mm slices to identify cement leakage or other possible local complications **Usual care** 'Optimal Pain Management (OPM)' consisted of the use of analgesics in ascending order • Acetaminophen • Tramadol • Tramadol and acetaminophen • Morphine • Non-steroidal anti-inflammatory drugs (NSAIDs) for those already using or intolerant to opiate-derivatives Corrections in dose and classification of pain medication were made when necessary by the internist, and in most cases physiotherapy was prescribed **Follow-up care** All patients received osteoporosis medication, such as bisphosphonates together with supplemental calcium and vitamin D
Outcomes	Outcomes were reported at baseline, 1 week, and 1, 3, 6 and 12 months. Pain diary - pain VAS and use of analgesia recorded daily to 1 month **Primary outcome** • Mean pain on VAS ranging from 0 (no pain) to 10 (worst pain ever); clinically significant pain relief was defined as a decrease of 3 points or more in VAS score from baseline **Secondary outcomes**

	• Pain-free days were defined as days with a VAS score of 3 or lower • Cost-effectiveness as costs per QALYs at one month and one year • Quality of life measured with the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO)(scores range from 0 to 100, with lower scores indicating a better quality of life) • Physical function: Roland-Morris Disability Questionnaire (RMDQ) (modified 23-item version, scores range from 0 to 23, with higher scores indicating worse physical functioning) • Quality of life: European Quality of Life-5 Dimensions (EQ-5D) scale, with a score range of 0 to 1 (1 is best quality of life) • Use of analgesia • Incident radiographic vertebral fractures measured at 1, 3 and 12 months • Adverse events **Outcomes included in this review** • Mean pain (0 to 10 VAS; 0 is no pain) • Function RMDQ (0 to 23 scale; 0 is better function) • Quality of life measured with the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO, 0 to 100; 0 is better) • Quality of life (EQ-5D, scores range from 0 to 1, with 1 being best quality of life) • Proportion with incident radiographic vertebral fractures
Source of funding	The study was sponsored by ZonMw (Dutch organisation for health care research and innovation of care), project number 945-06-351 and an unrestricted grant from the COOK Medical (Bloomington, IN, USA)
Notes	Trial registered at ClinicalTrials.gov. Registration number NCT00232466. "VERTOS II" Pre-treatment group differences: participants allocated to vertebroplasty had worse scores for EQ5-D; QUALEFFO and RMDQ at baseline RMDQ and QUALEFFO means only shown graphically in the trial report Dr Klazen provided mean (SD) data for the RMDQ, EQ5D and QUALEFFO at all time points to 12 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation codes with a block size of six
Allocation concealment (selection bias)	Low risk	As an independent telephone operator allocated participants by telephone, the allocation was likely concealed from the investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and study personnel were aware of treatment assignment

Klazen 2010 (*Continued*)

Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	Participants were not blinded to treatment assignment.
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Radiologists were not blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A greater number of participants completed one-year follow-up in the vertebroplasty group (86/101, 85%) compared with 77/101 (76%) in the usual care group. Fifteen (15%) participants in the usual care group received vertebroplasty
Selective reporting (reporting bias)	Low risk	The trial authors published the planned outcomes in a trial protocol and provided results for each planned outcome
Other bias	High risk	Quality of life and disability were worse at baseline in the vertebroplasty group which may have biased the results favouring the vertebroplasty group

Leali 2016

Methods	**Design**: multicentre (four centres) two-arm randomised controlled trial **Setting:** Italy, France, Switzerland **Timing:** not reported **Interventions:** percutaneous vertebroplasty or usual care **Sample size:** sample size calculation not reported **Analysis:** not explicitly reported
Participants	**Number of participants** • Number screened for eligibility not reported • 400 women were reported to have been randomised (200 in percutaneous vertebroplasty, and 200 in conservative treatment equally divided between 4 hospitals, each of which treated 50 with vertebroplasty and 50 with conservative care) • Data for 385 (185 (93%) for vertebroplasty and 200 (100%) for usual care) available at follow-up **Inclusion criteria** • Bone marrow oedema of the affected by VCF visible on MRI of the spine • VCF height of the visible loss of vertebral body in radiography • Acute pain from severe spinal fracture • Evidence of osteoporosis in bone densitometry • Evidence of an acute fracture in imaging

	Exclusion criteria • Pathological fracture due to myeloma/metastasis • Retropulsion mass of bone fragments in the spinal canal • Unstable cardiopulmonary conditions • Coagulopathy • Incurable, systemic infection in progress • Local infection spine (osteomyelitis, spondylodisciitis) • Radicular syndrome or spinal cord compression **Baseline characteristics:** characteristics were reportedly similar but as data were reported sparsely and not reported for both groups, this could not be verified *Overall:* age range: 56 to 82 years *Vertebroplasty group:* mean baseline pain score 0 to 10 VAS: 4.8, no measure of variance reported mean baseline ODI score: 53.6, no measure of variance reported *Usual care*: not reported
Interventions	**Vertebroplasty** Vertebroplasty was performed using transpedicular approach under local anaesthesia with mepivacaine 2% and naropin 10%. A mean volume of 4 ml of PMMA was injected into each fractured vertebral body with supervision of fluoroscopy. All the patients were subjected to analgesia after surgery, according to individual needs. According to increasing analgesic power, the patients were treated with acetaminophen, non-steroidal drugs (NSAIDs), or derivatives of morphine **Usual care** Conservative care consisting of pain medication, osteoporosis medication, physiotherapy or bracing
Outcomes	Outcomes were evaluated at 24 and 48 hours, 1 month later, 3 months, and 6 months **Study outcomes** • VAS pain score (0 - no pain to 5 - maximum pain) during walking, sitting and rising from a chair, bathing, dressing, and at rest; total score is the sum of all five scores (on a scale of 0 to 25). • Oswestry Disability Index (ODI), 0 to 100 scale (0 is no disability), measured at baseline and 6 months only • Proportion of participants with adverse events • Proportion of withdrawals • Proportion with incident clinical fractures • Death **Outcomes included in this review** • Adverse events • Incident clinical fractures
Source of funding	Not reported
Notes	No record of trial registration identified. Pain and disability could not be included in analyses: the trialists did not report summary statistics for each group. The trialists report that pain and disability were improved from

	baseline with vertebroplasty but not with usual care. Between-group analyses were not reported, except to say that clinical results were 'similar in both groups' at 6 weeks and 3 to 6 months **Adverse events:** vertebroplasty: death 'due to the fracture' (n = 1); fracture of a transverse process (n =2); bleeding of psoas muscles (n = 1); incident fractures (n = 3) Usual care: death 'due to the fracture' (n = 3), no incident fractures reported **Withdrawals**: n = 15 from vertebroplasty (7 for 'technical reasons', 8 could not maintain the prone position); none reported for usual care

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Process of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel unlikely due to the nature of the interventions
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	As participants were unblinded, there is a risk of bias in the measurement of pain and function, and adverse events
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	Unclear risk	Blinding of outcome assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on withdrawals or loss to follow-up given.
Selective reporting (reporting bias)	High risk	Pain and function could not be extracted as summary data for each treatment group were not reported. No trial registration and no published protocol
Other bias	Low risk	None apparent.

Liu 2010

Methods	**Design:** single-centre, two-arm, randomised controlled trial **Setting:** Taichung, Taiwan **Timing:** not stated **Interventions:** percutaneous vertebroplasty versus kyphoplasty **Sample size:** *a priori* sample size calculation not reported **Analysis:** not reported
Participants	**Number of participants** • Number screened not reported • 100 participants randomised (50 in each group) • Loss to follow-up not explicitly reported • Data may have been available for all participants at the final 6-month follow-up **Inclusion criteria** • Confirmed osteoporotic vertebral compression fracture at the thoraco-lumbar junction (T12-L1) **Exclusion criteria** • None reported **Baseline characteristics** *Vertebroplasty Group* Mean (SD) age: 74.3 (6.4) years; 38 female, 12 male Mean (SD) duration between 'injury' and treatment: 15.8 (6.7) days Location: 12 T12, 38 L1 Mean (SD) pain at baseline: 7.9 (0.7) *Kyphoplasty group* Mean (SD) age: 72.3 (7.6) years; 39 female, 11 male Mean (SD) duration between 'injury' and treatment: 17.0 (7.7) days Location: 11 T12, 39 L1 Mean (SD) pain at baseline: 8.0 (0.8)
Interventions	**Percutaneous vertebroplasty** The surgical procedures involved IV general anaesthesia (Propofol) and 2% xylocaine injected locally. A special bone biopsy needle (Angiotech, USA) was passed percutaneously and slowly through each side of the pedicle into the vertebral body. The bone filler PMMA (Zimmer) was prepared and mixed with both gentamicin, to reduce risk of infection, and powder containing barium, allowing X-ray visualisation. An optimal amount of bone filler was injected into the vertebral body via the needles on both sides. All procedures were performed under a mobile C-arm X-ray **Balloon kyphoplasty** The same anaesthesia was employed. Using image guidance, two small incisions were made, a probe was placed into the vertebral space at the fracture site. The bone was drilled and a balloon (VCF-X CentralMedical Tech., Taiwan), called a bone tamp, was inserted on each side. The balloons were then inflated with contrast medium (to facilitate image guidance X-rays) and expanded to the desired height and removed. The spaces created by the balloons were then filled with PMMA (prepared as for vertebroplasty) to bind the fracture **Follow-up** All participants undertook an orally administered treatment regimen to protect their bone density after surgery (details not reported)

Liu 2010 (*Continued*)

Outcomes	Outcomes were reported at baseline, 3 days, 6 months, 1, 2 and 5 years **Primary outcomes** • Measurement of vertebral body height • Measurement of kyphotic wedge angle (to evaluate kyphosis) • Pain, measured on a 10-point VAS **Outcomes included in this review** • Mean pain
Source of funding	Grant from Chung-Shan Medical University Hospital (CS08110).
Notes	Trial registration: not found. We extracted outcomes at 6 months, 1 and 2 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned according to permuted block randomisation which was likely to be adequate
Allocation concealment (selection bias)	Unclear risk	Whether or not treatment allocation was concealed is not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Whether or not participants and investigators were blinded to treatment allocation is not reported
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Unclear risk	Whether or not participants were blinded to treatment allocation is not reported
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	Unclear risk	Quote: "Radiographic measurement was made by technicians 'blind' to treatment group status, with variability controlled via inter- and intra-observer comparisons". No details of the inter- and intra-observer comparisons are reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completeness of follow-up was not explicitly reported.
Selective reporting (reporting bias)	Unclear risk	Trial not registered and trial protocol was not published. All outcomes listed in the methods are reported

Liu 2010 (*Continued*)

Other bias	Low risk	None apparent.

Rousing 2009

Methods	**Design**: single-centre, parallel group, two-arm open-label randomised controlled trial **Setting:** Denmark **Interventions:** percutaneous vertebroplasty or usual care **Timing:** not reported **Sample size:** *a priori* sample size of 16 participants per group was calculated, based on being able to detect a difference in pain of 2 points on a 0-10 VAS (SD set to 2 points) with 80% power and type 1 error rate of 0.05; increased to 20/group to allow for unpredictable patient exclusions and other unexpected events **Analysis:** completers' analysis used
Participants	**Number of participants** • Number of participants who were screened is not reported • 50 participants randomised (26 in percutaneous vertebroplasty and 24 in usual care) • Data were available for 24 (92%) in vertebroplasty group and 23 (96%) in usual care group at the 3-month follow-up • Data were available for (22 (85%) in vertebroplasty group and 22 (92%) in usual care group at the final 12-month follow-up **Inclusion criteria** • Intractable pain because of either acute (¡ 2 weeks, 40 participants) or subacute (between 2 and 8 weeks, 10 participants) osteoporotic vertebral fractures • Plain radiographs confirmed vertebral fracture • If there was only one vertebral fracture on plain radiograph and relevant acute/subacute pain, no further tests were performed. If there was more than one vertebral fracture, MRI scan or bone scan was performed to differentiate new from old fractures and fractures showing bone oedema on MRI or increased burn turnover on bone scan were accepted as new fractures **Exclusion Criteria** • Age under 65 years • Uncorrected therapeutic anticoagulation • Senile dementia, impaired cognitive function or other cerebral disease • Infection in the spine or the overlying skin • Malignant disease • Bone metabolic disease • Fracture of tubular bone • Allergy to radiopaque agents **Baseline characteristics** *Vertebroplasty Group* Mean (range) age: 80 (65 to 96) years; 19 female, 6 male Mean (95% CI) duration of fracture: 8.4 (3.7 to 13.0) days Mean (95% CI) pain at baseline: 7.5 (60.6 to 8.4) based upon 19 participants Mean (95% CI) physical function at baseline (SF-36 PCS): 36.7 (30.0 to 43.4) based upon 17 participants

	Mean (95%) CI) EQ-5D: 0.356 (0.196 to 0.516) based upon 17 participants *Usual care group (n = 24)* Mean (range) age: 80 (71 to 93) years; 21 female, 3 male Mean (95% CI) duration of fracture: 6.7 (21. to 11.4) days Mean (95% CI) pain at baseline: 8.8 (8.2 to 9.3) based upon 17 participants Mean (95% CI) physical function at baseline (SF-36 PCS): 33.4 (26.2 to 40.7) based upon 17 participants Mean (95%) CI) EQ-5D: 0.083 (-0.151 to 0.317) based upon 16 participants
Interventions	**Vertebroplasty** Percutaneous vertebroplasty was performed by orthopaedic surgeons specialised in spine surgery. Most patients were mildly sedated and all patients were prepared for general anaesthetic in case of complications. Under biplane fluoroscopic control and with the patients in a prone position 11- to 13-gauge needles were placed using a uni or bilateral transpedicular approach. Bone cement (PMMA) was injected under continuous fluoroscopy. In cases of extra vertebral cement leakage, the injection was terminated. Monitoring during the procedure included electrocardiogram, oxygen saturation, and blood pressure. After the procedure, the patients remained in a prone position for 30 minutes and then lay supine for a further 90 minutes **Usual care** Patients offered brace treatment in addition to pain medication and physiotherapy **Follow-up care** Both groups were hospitalised and offered pain medication and physiotherapy until discharge
Outcomes	Outcomes were reported at 3 and 12 months. **Outcomes** • Mean pain, measured on a 0 cm to 10 cm scale, where 0 is no pain and 10 is worst pain possible. • Quality of life, measured using the Short-Form health survey (SF-36), 0 to 100 scale, where a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. Only measured for participants with pain ¡ 2 weeks (40/50 participants). • Pain, measured using the Dallas Pain Questionnaire (DPQ), a 16-item instrument that assesses four aspects of daily living affected by chronic back pain (day-to-day activities, work and leisure activities, anxiety and depression and social interest), measured as a percentage of pain interference in each of the four aspects (0% is no pain and 100% is pain all the time). Only measured for participants with pain ¡ 2 weeks (40/50 participants). • Adverse events • Incident radiographic fractures at 3 months The following additional measures were added after commencement of the trial and only measured in 17 participants in each group • European Quality of Life-5 Dimensions (EQ-5D) scale, with a score range of 0 to 1, where 1 indicates perfect health • Activities of daily living measured using the Barthel Index, 0 to 20 score, higher score indicates more independence, or better daily function • Cognitive status, measured using the mini-mental status examination (MMSE), 30 questions, with 'impaired cognitive function' defined as a score less than 24/30

	correct answers • Physical tests: tandem test to measure time able to maintain balance; timed up-and-go (time taken to rise from chair, walk 3 metres and return); and the repeated chair test to assess muscle power (number of repeated chair stands in 30 seconds). These tests were only performed at 3 months **Outcomes included in this review** • Mean pain, measured on a 0 cm to 10 cm scale, where 0 is no pain and 10 is worst pain possible • Quality of life, measured using the SF-36, 0 to 100 scale, where a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability; only measured for participants with pain ¡ 2 weeks (40/50 participants). • Adverse events • Incident radiographic fractures at 3 months
Source of funding	Foundation and Danish government funds. The authors stated that no commercial party received benefits from the study
Notes	Trial registration: not found. Baseline pain score was higher in the usual care group (8.8 versus 7.5, P = 0.02) and mean stay in hospital was significantly longer in the usual care group (11.7 days vs 7.6 days, P = 0.01) We calculated the SD for pain, SF-36 Physical Function and EQ-5D outcomes from the reported 95% CIs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: sealed envelopes containing the treatment assignment "were prepared beforehand by the investigating surgeon and sorted randomly"
Allocation concealment (selection bias)	Unclear risk	It is not reported whether or not envelopes were opaque and whether steps were taken to ensure use of consecutive envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators were likely aware of treatment, given the nature of the interventions
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	Participants were aware of treatment assignment.
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic	High risk	Radiologists were aware of treatment assignment.

outcomes)		
Incomplete outcome data (attrition bias) All outcomes	High risk	Baseline data are not included for one participant in the vertebroplasty group as they did not contribute follow-up data (refused to attend for 3-month follow-up). An additional single participant in each group did not contribute outcome data as they died before the 3-month follow-up and an additional single participant in each group did not contribute 12-month outcome data as they died sometime after the 3-month follow-up. Additional outcomes were added after the trial started (EQ5D, Barthel, MMSE, three physical tests), and were not collected for all participants Baseline pain data were also either not collected and/or not reported for 6 (24%) participants in the vertebroplasty group and 7 (29%) participants in the usual care group and other baseline data were not collected and/or not reported for up to 13/25 participants in the vertebroplasty group and up to14/24 participants in the usual care group depending upon outcome Three-month follow-up outcome data were either not collected and/or not reported for up to 14/24 participants in the vertebroplasty-treated group and 9/23 participants in the usual care group depending upon outcome Twelve-month follow-up outcome data were either not collected and/or not reported for up to 10/22 participants in the vertebroplasty-treated group and 9/22 participants in the usual care group depending upon outcome
Selective reporting (reporting bias)	Unclear risk	Trial not registered and trial protocol was not published. All outcomes listed in the methods are reported
Other bias	Unclear risk	Baseline pain was higher in the usual care group (8.8 versus 7.5) (although it was only measured in 17/24 and 19/25 participants in the usual care and vertebroplasty-treated groups respectively Participants receiving usual care were hospitalised for longer (11.7 days versus 7.6

		days); it is unclear if more pain medication and physiotherapy was offered, and how this would affect outcomes

Sun 2016

Methods	**Design**: single-centre, parallel group, two-arm randomised controlled trial **Setting:** China **Interventions:** high-viscosity cement percutaneous vertebroplasty or low-viscosity cement percutaneous kyphoplasty **Timing:** June 2010 to August 2013 **Sample size:** sample size calculation not reported **Analysis:** completers' analysis
Participants	**Number of participants** • Number of participants who were screened is not reported • 98 participants randomised (46 in percutaneous vertebroplasty and 52 in percutaneous kyphoplasty) • There was no report of missing data or number of participants for the analysis **Inclusion criteria** • Acute back pain • No recent history of back trauma or spinal cord compression • MRI scanning showing bone oedema in the fractured vertebra **Exclusion criteria** None reported **Baseline characteristics** *Vertebroplasty Group* Mean (SD) age: 65.4 (2.6) years No. female/male: 34/12 Mean (SD) follow-up (months):22.7 (3.3) No. vertebra bodies: 54 Mean (SD) Injected cement volume (ml): 3.4(0.3) Mean (SD) operative time (min): 45.2 (4.7) Mean (SD) VAS: 8.5 (1.1) Mean (SD) ODI: 70.6 (8.6) *Kyphoplasty group (n = 24)* Mean (SD) age: 65.2 (3.3) years No. female/male: 38/14 Mean (SD) follow-up (months):21.7 (2.3) No. vertebra bodies: 60 Mean (SD) Injected cement volume (ml): 4.2 (0.2) Mean (SD) operative time (min): 64 (5) Mean (SD) VAS: 8.2 (0.9) Mean (SD) ODI: 71.7 (8.5)
Interventions	**High-viscosity cement percutaneous vertebroplasty** Patients were placed in a prone position and treated with local anaesthesia. The position of fractured vertebra was fixed by using C-arm fluoroscopy. A scalpel was used to make a 0.5 cm incision on the skin, after which the PVP needles were used to access the back

	muscle to reach the vertebral body. When the tip of the needle entered the posterior, middle and anterior of vertebral body, the frontal imaging displayed in C-arm fluoroscopy screen showed the position of the needle to be at the paries lateralis, middle line, and paries medialis of radix arcus vertebrae. When the tip of needle reached the anterior and middle 3/4 of the vertebral body, the position of the needle was adjusted to enable injection of the high-viscosity cement into the vertebral body. The volume of cement used was about 3 mLto 4 mL per vertebra. The entire surgery proceeding was guided by C-arm fluoroscopy **Low-viscosity cement percutaneous kyphoplasty** The anaesthesia and puncture techniques were the same as those of high-viscosity cement PVP. Through the working tunnel made by the needle, cannula, and drill, the balloon was inserted into the centre of the vertebral body and contrast medium was injected using a high pressure pump. Then the balloon was extracted and approximately 4 mL of cement was injected into each vertebral body
Outcomes	Outcomes were measured at 2 days and 12 months after surgery **Study outcomes** • Pain: Visual Analog Scale (VAS 0 to 10) measuring pain relief • Oswestry Disability Index (ODI 0 to 100) assessing functional activity • Radiological evaluation with plain digital radiography and CT scan to assess cement leakage, restoration of vertebral height, and the angle of kyphosis (day 2) **Outcomes used in this review** • Pain (VAS) • Disability (ODI)
Source of funding	Not reported
Notes	No trial registry record found **Adverse events** *Vertebroplasty:* serious adverse events: none reported; other adverse events: cement leakage 9/54 (16.7%) *Kyphoplasty: s*erious adverse events: none reported; other adverse events: cement leakage 11/60 (18.3%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear whether there was blinding of participants and study personnel

Sun 2016 (*Continued*)

Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Unclear risk	Since blinding of participants is not confirmed there could be a risk of bias in the measurement of self-reported outcomes of pain and functional activity
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Not reported but likely that radiologists would be able to tell the difference between vertebroplasty and kyphoplasty on a radiograph
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawals reported.
Selective reporting (reporting bias)	Unclear risk	Protocol not found. Trial not registered. The results of all outcomes specified in the methods are reported
Other bias	Low risk	No other bias apparent.

VERTOS IV

Methods	**Design:** multicentre (four sites), parallel group, two-arm randomised placebo-controlled trial **Setting:** the Netherlands **Timing:** January 2011 to January 2014 **Interventions:** percutaneous vertebroplasty versus sham vertebroplasty (placebo) **Sample size:** 90 participants per group required to detect at least a 1.5 point difference in pain relief on a 0 to 10 Visual Analogue Scale (VAS) between vertebroplasty and placebo, based on a two-sided type 1 error rate of 5% and a 20% withdrawal rate **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • 1280 participants screened for eligibility • 1100 excluded (872 did not meet inclusion criteria; 72 had decreased pain, 156 declined to participate) • 180 randomised (91 to vertebroplasty and 89 to placebo) • Data for 176 (90 (98%) for vertebroplasty and 86 (97%) for placebo) available at 1-month follow-up • Data for 170 (87 (95%) for vertebroplasty and 83 (93% for placebo) available at 3-month follow-up • Data for 166 (85 (93%) for vertebroplasty and 81 (91% for placebo) available at 6-month follow-up • Data for 156 (80 (88%) for vertebroplasty and 76 (85% for placebo) available at 12-month follow-up **Inclusion criteria** • Aged 50 years or older and referred for an X-ray of the thoracic or lumbar spine, or both. • Vertebral fracture on X-ray of the spine (minimal 15% loss of height)

VERTOS IV (*Continued*)

	• Level of vertebral fracture (Th5-L5) • Pain for 6 weeks or less at time of X-ray • Bone oedema on MRI of the fractured vertebral body • Focal tenderness on VCF level • Decreased bone density T-scores = -1 **Exclusion criteria** • Severe cardio-pulmonary condition • Untreatable coagulopathy • Systemic or local infection of the spine (osteomyelitis, spondylodisciitis) • Suspected alternative underlying disease (malignancy) • Radicular and/or cauda compression syndrome • Contra-indication for MRI **Baseline characteristics** *Vertebroplasty group:* Mean (SD) age: 74.7 (10.7) years; 67 female: 23 male Mean (SD) duration of back pain: 29.2 (16.3) days Mean (SD) baseline pain score: 7.7 (1.4) Mean (SD) RMDQ: 18.0 (4.5) Mean (SD) baseline QUALEFFO score: 68.4 (17.1) Number of vertebral compression fractures at baseline: 115 Medication for osteoporosis: n = 42 (47%) Number of vertebral fractures at baseline: 115 Opioid use at baseline: n = 42 (47%) Mean (SD) T score for bone mineral density (BMD): -2.4 (1.0) *Placebo group:* Mean (SD) age: 76.9 (8.1) years; 66 female: 20 male Mean (SD) duration of back pain: 25.9 (13.8) days Mean (SD) baseline pain score: 7.9 (1.6) Mean (SD) RMDQ: 17.8 (4.7) Mean (SD) baseline QUALEFFO score: 69.7 (17.9) Number of vertebral compression fractures at baseline: 108 Medication for osteoporosis: n = 49 (57%) Opioid use at baseline: n = 25 (29%) Mean (SD) T score for bone mineral density (BMD): -2.4 (1.0)
Interventions	Percutaneous vertebroplasty or placebo (sham) procedure. IV cefazolin (2g) one hour prior to procedure. Under fluoroscopic guidance, the practitioner infiltrates the skin and subcutaneous tissues overlying the pedicle of the target vertebra or vertebrae with 1% lidocaine and infiltrates the periosteum of the pedicles with 0.25% bupivacaine (Marcaine) **Vertebroplasty** 11-gauge or 13-gauge needles passed into the central aspect of the vertebrae, bone cement prepared on the bench and injected into the vertebral body under constant fluoroscopy, until the cement reaches the posterior aspect of the vertebral body or leaks into an extraosseal space **Sham procedure (placebo)** Verbal and physical cues (e.g. pressure on the back) and the methacrylate monomer is opened to simulate the odour of mixing the bone cement, but the needle is not placed and the no cement is injected)

VERTOS IV (*Continued*)

	Follow-up care Participants received osteoporosis medication and supplemental calcium and vitamin D. Pain medication (paracetamol, tramadol, tramadol and paracetamol, or morphine) dispensed as needed, according to participant demand, and their use recorded. NSAIDs were allowed only for participants intolerant of opiate-derived drugs, or if already used
Outcomes	Outcomes collected at 1-day, 1 week, and 1, 3, 6 and 12 months after the procedure **Primary outcome** • Mean pain: visual analogue scale (VAS), 0 (no pain) to 10 (worst pain ever) score **Secondary outcomes** • Roland-Morris Disability Questionnaire (RMDQ), modified 23-item version (0 to 23 scale, higher scores indicate worse physical functioning) • Quality of life, measured using the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) (0 to 100 scale, with lower scores indicating a better quality of life). • Pain medication use • Incident vertebral fractures (possibly post-hoc, not listed in protocol) • Adverse events (possibly post-hoc, not listed in protocol) • Height loss (possibly post-hoc, not listed in the protocol) • Percentage of patients with VAS score 5 or more at 12 months (conference proceedings indicates this to be a post-hoc analysis, not reported in protocol) **Outcomes included in this review** • Mean pain • Adverse events • Proportion with incident clinical fractures
Source of funding	Grant (S-I-013) from Stryker
Notes	Trial registration: NCT01200277 Sponsored by: St. Elisabeth Hospital, Tilburg, Netherlands Study completed as of 17 Nov 2014 at clinicaltrials.gov RMDQ and QUAlEFFO data could not be extracted - presented in graphical format with no measure of variance Adverse events are reported incompletely: there were 8 deaths in the vertebroplasty group and 5 in the placebo group (all reported as unrelated to the procedures by the trialists) ; cement leakage reported in 103/159 treated vertebral bodies in the vertebroplasty group (number of participants with an event not reported); in vertebroplasty, n=1 had respiratory insufficiency and n =1 a vasovagal response due to the procedure; adverse events not reported for the placebo group. Incident fractures: 15/91 participants (31 fractures) in vertebroplasty and 19/89 (28 fractures) in placebo Conference proceedings reported that 5 participants in the vertebroplasty group and 4 in the placebo group had 3 vertebral fractures and participants in the vertebroplasty group received vertebroplasty into all 3 levels

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

VERTOS IV (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer randomisation via a central independent telephone operator
Allocation concealment (selection bias)	Low risk	Protocol reports that randomisation occurs once the participant is prepped for surgery and sedated. It is probable that this process ensures the treatment group is concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	From the conference proceedings it is reported that 82.4% of participants in the vertebroplasty group correctly guessed their treatment assignment at one day while 81.2% of participants in the placebo group also believed they had received vertebroplasty; the remaining participants in both groups were unsure It is not reported whether or not other study investigators (aside from the unblinded treating radiologists) were blinded to intervention
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Low risk	A similar proportion of participants in both groups believed they had received vertebroplasty (82.4% and 81.2% in the vertebroplasty and placebo groups respectively) suggesting blinding was successful
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	Unclear risk	Not reported how incident vertebral fractures were assessed, or who assessed them, but if imaging was used, vertebroplasty cement is opaque and will be detected
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was nearly complete, with a small proportion lost in each group, for reasons that were likely unrelated to treatment. 35/38 in the vertebroplasty group completed follow up at 1 month (3 did not return questionnaires) versus 38/40 in the placebo group (2 did not return questionnaires); at 6 months, 35/38 from the vertebroplasty group (2 died for reasons considered unrelated to the trial and 1 did not return their questionnaire), and 36/40 from the placebo group (2 died for reasons considered unrelated to the trial and 2 did not return their questionnaires) completed follow up

VERTOS IV (*Continued*)

Selective reporting (reporting bias)	High risk	Additional outcomes that were not pre-planned according to the trial protocol were reported at a conference (height loss, incident fractures, percentage with pain VAS score ≥5 at 12 months). Disability and quality of life were reported only in graphical format with no measures of variance. Adverse events reported incompletely: not reported for placebo group
Other bias	Low risk	No other biases apparent.

Vogl 2013

Methods	**Design:** multicentre, two-arm, randomised controlled trial **Setting:** Germany (3 centres) USA (1 centre) **Timing:** March 2008 to Sept 2009 **Interventions:** percutaneous vertebroplasty versus kyphoplasty **Sample size:** *a priori* sample size calculation not reported **Analysis:** completers' analysis
Participants	**Number of participants** • Number of participants who were screened is not reported • 78 participants randomised 1:2 (28 (39 levels) in the percutaneous vertebroplasty and 49 (65 levels) in the cement directed kyphoplasty system groups respectively) • Data were available for 23 (82%) in vertebroplasty group and 37 (76%) in kyphoplasty group at the 3-month follow-up • Data were available for 19 (68%) in vertebroplasty group and 28 (57%) in the kyphoplasty group at the final 12-month follow-up **Inclusion criteria** • Up to three painful vertebral compression fractures between T4 and L5 unresponsive to at least 6 weeks of conservative treatment or were admitted to hospital for acute back pain • Confirmed diagnosis of osteoporosis or osteopenia **Exclusion criteria** • Burst fractures • Planar collapse • Vertebral bodies having inadequate space between endplates for cavity creation • Infection • Current cancer treatment at the affected level • Multiple myeloma • Prior cement at the affected level **Baseline characteristics** *Vertebroplasty* Mean (SD) age: 74 (11.5) years; 19 female, 9 male Mean (SD) pain at baseline: 8.49 (1.18) *Usual care*

	Mean (range) age: 80 (71 to 93) years; 21 female, 3 male Mean (SD) pain at baseline: 8.31 (1.12)
Interventions	**Percutaneous vertebroplasty** The procedure was performed using a bipedicular cement injection in accordance with each participating physician's standard technique. The same cement was used for both procedures (Spineplex, Stryker Instruments, Kalamazoo, MI) **Cement directed kyphoplasty system** The kyphoplasty system was provided by Soteira Inc, Natick, MA. The surgical procedure began with access gained through a unilateral intrapedicular or extrapedicular approach. The curved design of the cavity creation instrument allowed the physician to drill a curved path from one pedicle, crossing the sagittal midline and stopping with the contralateral anterior quadrant of the vertebral body. The drill converted to a cavity cutting reamer *in situ*, which created a 10-mm diameter cylindrical cavity. The cement directing implant consisted of a non load-bearing, hollow, passively self-expanding cylindrical device manufactured from a textile composite of nitinol wire, polyethylene teraphthalate fibre, and polycarbonate urethane. The implant was 10 mm in diameter and 15 mm, 20 mm or 25 mm long. The size of the implant was chosen to match the length of the cavity. The implant was designed to contain initially-injected cement then regulate and direct cement flow into surrounding cancellous bone. Because the cavity was created by cutting, in contrast to bone compaction as in a balloon kyphoplasty, cement was able to penetrate into the bone beyond the boundaries of the cavity. Cement injection into the implant and directed through openings in its wall created a cement mantle in the anterior vertebral body, which extended towards the endplates and stabilised the fracture by filling cracks and voids, interdigitating with viable cancellous bone. Device placement in a centrally-located cavity provided bilateral cement flow with the vertebral body, crossing both sides of the sagittal midline using a unipedicular approach. The nitinol-based implant is expanded prior to cement injection to create a barrier to limit posterior cement flow into the basivertebral vein and spinal canal, while still allowing cement to permeate the vertebral body
Outcomes	Patient follow-up occurred at 3 and 12 months. Plain radiographs and CT scans were taken within 24 hours of the procedure and at 3 months, and plain radiographs were also taken at 12 months **Outcomes** • Cement leakage rates based primarily on postoperative CT scans, supplemented by A/P and lateral radiographs • Cement leakage location using a newly developed leak location classification method (1. anterior, 2. lateral, 3. neuroforamen, 4 spinal canal or 5. superior or inferior endplate leaks). • Changes in vertebral height determined by comparing CT scans obtained postoperatively and at 3 months • Long-term stability of the cement mantle • Presence of new fractures at treated or adjacent level • Pain intensity on a visual analogue scale (VAS) (not reported in the published paper but referred to in a congress abstract of the same trial reported in German, no data available) • Disability assessed by the Oswestry Disability Index (ODI) was measured but these data are not presented in this paper (not reported in the published paper but

Vogl 2013 (*Continued*)

	referred to in a congress abstract of the same trial reported in German) **Outcomes included in this review** • Presence of new fractures at treated or adjacent level
Source of funding	Funding provided by Soteira Inc. (Natick, MA)
Notes	Trial reported to be registered with ClinicalTrials.gov with ID: NCT00576546 but this could not be verified No efficacy outcomes were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised into vertebroplasty or cement-directed kyphoplasty in a ratio of 1:2 but the method of generating the random sequence was not reported
Allocation concealment (selection bias)	Unclear risk	Whether or not treatment allocation was concealed is not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded but investigators were not blinded
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Low risk	Participants were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Cement leakage, changes in vertebral body height and the incidence of new fractures measured by investigators using radiographs were assessed by the investigators who were aware of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	A completers' analysis was performed. Data were available for 23 (82%) and 37 (76%) in vertebroplasty and kyphoplasty groups, respectively at the 3-month follow-up and 19 (68%) and 28 (57%) at the final 12-month follow-up. It is unclear it this is significantly different and the reasons for missing data are not reported
Selective reporting (reporting bias)	High risk	A Congress abstract of the same trial is reported in German (https://www.thieme-

Vogl 2013 (*Continued*)

		connect.com/products/ejournals/abstract/10.1055/s-0031-1279397), and indicates that pain intensity on a visual analogue scale (VAS) and disability assessed by the Oswestry Disability Index (ODI) were measured but these data are not presented in this paper
Other bias	Unclear risk	The role of Soteira Inc. (Natick, MA) in the trial, other than supply of the Cement Directed Kyphoplasty System, is not explicitly reported

Voormolen 2007

Methods	**Design:** multicentre (three hospitals), two-arm open-label randomised controlled trial; control group allowed to cross-over to vertebroplasty at two weeks **Setting:** the Netherlands and Belgium **Timing:** not reported **Interventions:** percutaneous vertebroplasty or usual care **Sample size:** *a priori* sample size calculation not reported **Analysis:** completers' analysis
Participants	**Number of participants** • Number of participants who were screened is not reported but it is stated that approximately one in four of those screened initially consented to participate • 46 participants randomised but 10 did not receive the assigned treatment (6 in the usual care group wanted to receive vertebroplasty and 2 in the vertebroplasty group wanted to be treated with usual care) • 38 received treatment (18 treated with vertebroplasty, 16 treated with usual care and 4 unknown) • Data were available for 34 participants at 2 weeks (18 for vertebroplasty and 16 for usual care) as 4 participants who were treated with unknown therapy did not complete 2-week follow-up and were excluded from the analysis **Inclusion criteria** • Patient age 50 years or older • Back pain due to vertebral fracture refractive to medical therapy for at least 6 weeks and no longer than 6 months • Focal tenderness on physical examination related to the level of the vertebral fracture • Height loss of the vertebral body of a minimum of 15% on plain radiograph of the spine • Bone density T-scores less than -2.0, 5 • Bone oedema of the affected vertebra on MRI **Exclusion criteria** • Poor cardio-pulmonary condition • Untreatable coagulopathy • Ongoing systemic infection or local infection of the spine (osteomyelitis,

	spondylodisciitis) • Radicular and/or cord compression syndrome • Indication of other underlying disease than osteoporosis • No informed consent **Baseline characteristics** *Vertebroplasty* Mean (range) age: 72 (59 to 84) years; 14 females, 4 males Mean (range) duration of back pain (units not reported, assumed as days): 85 (47 to 138) days Mean (range) number of pre-existing vertebral compression fractures: 3.3 (1 to 8) at T5 to L5 Mean (range) baseline pain: 7.1 (5 to 9) Mean (range) baseline disability, RMDQ: 15.7 (8 to 22) Mean (range) baseline quality of life, QUALEFFO: 60 (37 to 86) No pain medication: 2 (11%) Paracetamol: 4 (22%) NSAIDs: 6 (33%) Opioids: 6 (33%) *Usual care* Mean (range) age: 74 (55 to 88) years; 14 females, 2 males Mean (range) duration of back pain (units not reported, assumed as days): 76 (46 to 141) days Mean (range) number of pre-existing vertebral compression fractures: 3.1 (1 to 8) at T5 to L5 Mean (range) baseline pain: 7.6 (5 to 10) Mean (range) baseline disability,RMDQ: 17.8 (9 to 24) Mean (range) baseline quality of life, QUALEFFO: 67 (38 to 86) No pain medication: 1 (6%) Paracetamol: 7 (44%) NSAIDs: 3 (19%) Opioids: 5 (31%)
Interventions	**Vertebroplasty** Percutaneous vertebroplasty was performed under local anaesthesia on a biplane (in 2 hospital departments) or monoplane (in 1 hospital department) angiographic unit. In most cases, a bilateral transpedicular approach was used. Under continuous fluoroscopy, PMMA bone cement (Osteopal V; Biomet Merck, Ried B. Kerzers, Switzerland) was injected manually using 1 mL syringes and 11- or 13-gauge bone biopsy needles (Cook Europe Bjaeverskov, Denmark). Immediately after the percutaneous vertebroplasty, a CT scan with multiplanar reconstructions of the treated levels was performed to assess the cement deposition and to identify possible extra cement leakage or other local complications that might not have been noted under fluoroscopy **Usual care** Participants were treated with the following medications, in ascending order • Paracetamol (acetaminophen) • Non-steroidal anti-inflammatory drugs (NSAIDs) • Opioids The dose per day of prescribed analgesics was regulated, and the class of pain medication was adjusted as needed

Outcomes	Outcomes were reported at 1 day and 2 weeks **Outcomes** • Mean pain on a 0- to 10-point scale ranging from 0 (no pain) to 10 (worst pain in the patient's life) • Type of analgesic use (ordinal variable from 0 (no analgesic use) to 3 (use of opioids) • Disability: Roland-Morris Disability Questionnaire (RMDQ), 0 to 23-point scale, with higher scores indicating worse disability • Quality of life: Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO), scores range from 0 to 100, with lower scores indicating a better quality of life • Adverse events • Incident clinical vertebral fractures **Outcomes included in this review** • Mean pain • Disability measured by the RMDQ • Vertebral fracture-specific quality of life (QUALEFFO), scores range from 0 to 100, with lower scores indicating a better quality of life) at 2 weeks.
Source of funding	None reported.
Notes	Trial registration: not found. Standard deviations not reported for pain, disability or quality of life in the trial report but were provided by Dr Voormolen The trial authors report that the original protocol was to follow participants for up to 12 months with outcome assessments at 1 day, 2 weeks and 3, 6, and 12 months. Participants randomised to usual care who still had severe pain after two weeks could cross-over to receive vertebroplasty. As the majority of participants receiving usual care crossed over to vertebroplasty after two weeks, the authors stopped the study early, and did not collect outcome data beyond two weeks There were two adjacent incident vertebral fractures in the vertebroplasty group within the two-week follow-up period, but it is unclear if there were any incident fractures in the usual care group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of generating the random sequence was not reported
Allocation concealment (selection bias)	Unclear risk	An independent central operator allocated participants to treatment but whether or not treatment allocation was concealed is not reported

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators were not blinded to treatment assignment
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	Participants were not blinded to treatment assignment.
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Radiologists were not blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Four participants were excluded from the analysis (refused to complete 2-week follow-up). The treatment group of these participants is not reported
Selective reporting (reporting bias)	High risk	Trial protocol is not available. The number of participants with an incident clinical vertebral fracture is only reported for the vertebroplasty group. Measures of variance were not reported for continuous outcomes
Other bias	Unclear risk	Eight participants withdrew after randomisation as they were not assigned to their preferred treatment (2 in the vertebroplasty group and 6 in the usual care group) The source of funding is not reported.

VOPE 2015

Methods	**Design:** single centre two-arm double-blind randomised placebo-controlled trial **Setting:** Denmark **Timing:** May 2011 to April 2014 **Interventions:** percutaneous vertebroplasty versus sham vertebroplasty (placebo). The thesis stated that cross-over between groups was allowed after 3 months **Sample size:** *a priori* sample size calculation of 80 participants based upon requiring 26 participants per group to detect a difference of 20 units in improvement in pain on a 0 to 100 VAS (SD 25 units), based on a two-sided type 1 error rate of 5% and power 80% and allowing for dropouts. Sample size was reduced to 52 (26 per group) due to difficulties with recruitment (low willingness to participate). (NB unpublished manuscript in thesis differs to thesis text in sample size estimation. Unpublished manuscript indicates that sample size based upon requiring 23 participants per group to detect 20 units difference, SD 20 units) **Analysis:** completers' analysis (excluded 4 participants due to need for further spine surgery and 2 participants who were excluded prior to receipt of intervention due to malignant biopsies, treatment allocation not stated but based upon numbers four were from the vertebroplasty group and 2 were from the placebo group)
Participants	**Number of participants** • 342 participants screened for eligibility • 290 excluded (most due to unwillingness to participate in an RCT and symptom duration longer than 8 weeks) • 52 randomised (26 to vertebroplasty and 26 to placebo) • 46 participants (22 for vertebroplasty and 24 for placebo) 'eligible for statistical analysis' (2 excluded postoperatively due to malignant biopsies and 4 were excluded due to need for further spinal surgery during the first 3 months of follow-up) **Inclusion criteria (from trial registry)** • VCF on X-ray of the spine (minimal 15% loss of height) level of VCF Th6 or lower • Back pain $\leq$ 8 weeks at time of surgery • $\geq$ 50 years of age • Bone oedema on MRI of the fractured vertebral body • Focal tenderness on VCF level **Exclusion criteria (from trial registry)** • Severe cardio-pulmonary condition • Untreatable coagulopathy • Systemic or local infection of the spine (osteomyelitis, spondylodisciitis) • Suspected alternative underlying disease (malignancy) • Radicular and/or cauda compression syndrome • Contra-indication for MRI **Inclusion criteria (from thesis report)** • Vertebral fracture T6 to L5 • Back pain less than 8 weeks • Baseline pain at least 7 on a VAS score in either rest or activity • MRI that included a STIR with oedema present **Exclusion criteria (from thesis report)** • Previous malignant disease • Age below 50 years • Allergy of treatment substances

	• Dementia evaluated by MMSE test (0-30 points) with a cut-off of 24 • Fractures of other bones • Unable to consent to the study **Baseline characteristics** *Vertebroplasty group* Mean (range) age: 70.59 (54 to 90) years; 18 female: 4 male Mean (SE) baseline pain score at rest: 40.55 (4.55) Mean (SE) baseline pain score with activity: 74.68 (4.55) BMD T-score: -2.7 (0.25) Vertebral levels: T6 to L5, 27 levels treated *Placebo group* Mean (range) age: 69.33 (53 to 84) years; 22 female: 2 male Mean (SE) baseline pain score at rest: 53.04 (4.35) Mean (SE) baseline pain score with activity: 76.08 (4.35) BMD T-score: -2.2 (0.254) Vertebral levels: T7 to L5, 28 levels treated
Interventions	**Vertebroplasty** All procedures were performed by spinal surgeons in the operating room. All vertebroplasties were performed under local anaesthesia using the V-Max Mixing and Delivery System (DePuy Acromed, Leeds, England. Participants were placed prone on a Jackson table and lidocaine was used to anaesthetise the entry points. The 11-gauge needles (Jamshidi needles) were then inserted in the fractured vertebral body via the pedicles under fluoroscopic guidance and a biopsy specimen was taken (not specified if uni- or bilateral pedicular approach). The PMMA cement was mixed and 2 mL of cement was injected into the pedicle under constant fluoroscopic guidance. The injection was stopped if the cement reached the posterior border of the vertebrae, showed signs of disc infiltration or the patient complained of leg symptoms **Placebo (sham vertebroplasty)** The same procedure was performed for the placebo except that 2 mL of lidocaine (10 mg/mL) was injected into each Jamshidi needle (placed in the pedicle of the vertebral fracture as per the vertebroplasty group). The PMMA cement was mixed to create the odour similar to the vertebroplasty procedure **Both groups** At inclusion, after a DEXA scan, all participants were commenced on treatment for osteoporosis. Prior to injecting either lidocaine of the PMMA, a needle biopsy was obtained (standard procedure at this site). Through the procedure, the staff in the operation room communicated minimally to ensure patients were unaware of the procedure performed
Outcomes	Outcomes were reported at baseline, 6 hours, every week to 3 months, and 12 months The primary outcome was specified to be pain relief at 1 day, 1-12 weeks, and 12 months. Both VAS and NRS were specified in the clinical trial registry. The thesis specifies both pain at rest and pain with activity on a VAS but not which was the primary endpoint **Outcomes (from the published thesis)** • Mean pain at rest on a VAS score (0 to 100), in a pain diary • Mean pain during forward bending resembling a patient in activity on a VAS score (0 to 100), in a pain diary (not at 6 hours) • Use of pain medication (opioids and frequency during the day and week) • Danish version of SF-36 (baseline, 3 and 12 months)

	• Danish version of EQ-5D (baseline, 3 and 12 months) • Vertebral height of the fractured vertebrae from full standing spine radiographs, lateral view (baseline, 3 and 12 months) • Kyphosis of the fractured vertebrae (baseline, 3 and 12 months) • Number of new radiographic vertebral fractures (12 months) • Major complications Additional outcomes in the trial registration: Lung capacity (spirometer) at 3 and 12 months **Outcomes used in the review** • Mean pain during forward bending resembling a patient in activity (we used this outcome for the main comparison as overall pain was not measured and this outcome was specified in our a priori hierarchy of pain measures after unspecified pain) • Quality of life: EQ-5D • Number of new radiographic vertebral fractures as 12 months
Source of funding	The primary sponsor was Sygehus Lillebaelt, Denmark (Hospital). The secondary sponsor was Odense University Hospital
Notes	Trial registration: NCT01537770 and EUCTR2010-024050-10-DK Abstract (no numerical data reported): http://journals.sagepub.com/doi/abs/10.1055/s-0036-1582763, Global Spine J 2016; 06 - GO106 Thesis cited: http://www.forskningsdatabasen.dk/en/catalog/2371744560; full text copy of the thesis provided by the author No participants crossed over between treatment groups during this study As SF-36 physical function may be conceptually different to RMDQ and other back-specific disability measures we did not combine it with other disability measures in our meta-analysis. However no between-groups differences were reported for SF-36 at any time point. The amount and frequency of opioid use also did not differ between groups over time

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was a block randomisation design using 52 envelopes". No further details were reported
Allocation concealment (selection bias)	Low risk	The randomisation envelope was opened after the bone biopsy had been taken
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to treatment allocation. Throughout the procedure there was minimal communication with the participants and operating room staff. The primary investigator of the trial (EH) performed all screening procedures and follow-up examinations and was blinded to the participant's assigned treatment arm

VOPE 2015 (*Continued*)

		throughout the study period. Success of blinding was not assessed. The biostatistician was also blinded to treatment allocation when performing the analysis
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Low risk	Participants were unaware of treatment assignment.
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Radiologists who assessed follow-up radiographs at 3 and 12 months were aware of treatment assignment as vertebroplasty cement is opaque and will be detected on imaging
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Six of the 52 participants were not included in the analysis (4/26 (6.5%) in the vertebroplasty group and 2/26 (3.3%)in the placebo group. Of these, 2 were excluded due to malignant biopsies and 4 were excluded due to the need for further spinal surgery during the period of follow-up but their treatment allocation was not reported
Selective reporting (reporting bias)	Unclear risk	NRS pain data and spirometry were not reported. It is not clear whether pain at rest or with forward bending to resemble a patient in activity was the primary endpoint
Other bias	Unclear risk	Thesis published in 2015 and includes an unpublished manuscript Baseline pain at rest in the vertebroplasty group was lower than in the placebo group (40.55 (SE 4.55) compared with 53.04 (SE 4.35), P = 0.0476, although pain with activity was similar between groups (vertebroplasty 74.68 (SE 4.55), placebo 76.08 (SE 4.35))

Wang 2015

Methods	**Design**: single-centre, parallel-group, two-arm randomised controlled trial **Setting:** China **Timing:** 1 January 2012 to 12 February 2014 **Interventions:** high-viscosity cement vertebroplasty versus balloon kyphoplasty **Sample size:** *a priori* sample size calculation not reported **Analysis:** intention-to-treat analysis planned
Participants	**Number of participants** • 152 patients assessed for eligibility • 45 patients excluded (32 did not meet inclusion criteria, 13 refused to participate) • 107 enrolled and randomised (53 to vertebroplasty, 54 to balloon kyphoplasty) • Data for 105 (53 for vertebroplasty, 52 for kyphoplasty) available at 3-month assessment • Data for 101 (50 for vertebroplasty, 51 for kyphoplasty) available at 12-month assessment **Inclusion criteria** • Recent lumbar or thoracic vertebral compression fractures (proven by radiographs and MRI) • Unsatisfactory pain relief (VAS equal to or more than 5) after at least 4 weeks conventional therapy • Confirmed diagnosis of osteoporosis or osteopenia (proven by DEXA) **Exclusion criteria** • Burst fractures • Infection • Radicular syndrome • Primary bone tumours • Spinal metastases **Baseline characteristics** *Vertebroplasty group* Mean (SD) age: 69.43 (8.94) years; 77.4% female: 22.6% male Mean (SD) VAS pain score: 8.10 (1.23) Mean (SD) ODI score: 71.22 (10.56) Mean (SD) compression rate: 29.98 (18.12) *Balloon kyphoplasty group* Mean (SD) age: 68.63 (8.39) years; 74.1% female: 25.9% male Mean (SD) VAS pain score: 8.04 (1.13) Mean (SD) ODI score: 71.30 (10.22) Mean (SD) compression rate: 28.67 (19.31)
Interventions	A unipedicular approach was adopted in all patients in this study. Injected cement volume was recorded for patients in both treatment groups. The endpoint of cement injection for both techniques was the presence of radiologically-adequate filling, the start of leakage, and/or significantly increased pressure during injection **High-viscosity cement vertebroplasty** Vertebroplasty consists of injecting cement into a collapsed vertebra in order to reinforce the fractured vertebra and gain pain relief. The Confidence Spinal Cement System (DePuy Spine Inc, USA) was used **Balloon kyphoplasty** An inflatable balloon is inserted into a collapsed vertebral body. Once inflated, the balloon

	elevates the endplates and creates a cavity. Then the cement is injected at a low pressure into the cavity of the collapsed vertebral body. Injecting cement into a cavity under low pressure reduces the risk of cement leakage. The Kyphon system (USA) was used. A low-viscosity cement was used (OSTEOPAL V, Heraeus Medican GmbH, Germany) **Follow-up care** After the procedure all patients remained supine in bed for 24 hours, and were referred for treatment with calcium and vitamin D supplements, and anti-resorptive or anabolic agents
Outcomes	Outcomes were measured at baseline, 1 day, 3 months, and 1 year after treatment A primary outcome was not specified. Outcomes reported • VAS mean pain score (scale and time period not specified) • Oswestry Disability Index (ODI) • Assessment of cement leakage (based on radiographs, supplemented by postoperative CT scans) • Location of leakage (classified as disk space, epidural space, paravertebral areas, or peripheral veins) • Changes of the anterior vertebral body height • Compression rate (predicted height minus preoperative anterior height, divided by predicted height) • Height of restoration rate (post-operative fracture height minus preoperative fracture height divided by 100 minus preoperative fracture height) **Outcomes included in this review** • Mean pain • Oswestry Disability Index (ODI) • Adverse events • Incidence of new vertebral fractures
Source of funding	Funding source not stated.
Notes	Clinicaltrials.gov trial identifier: not reported. No published protocol found Triallists reported leakage in 9/68 vertebral joints in the vertebroplasty group and 22/72 joints in the kyphoplasty group, but did not report the number of participants with leakage

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were reportedly randomised into treatment groups, however randomisation method is not reported
Allocation concealment (selection bias)	Unclear risk	Whether or not treatment allocation was concealed is not reported

Wang 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients were blinded to which group they were assigned." Not reported whether personnel were blinded to treatment allocation
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	Low risk	Quote: "Patients were blinded to which group they were assigned."
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Not reported whether radiographers were aware of treatment. However, they would be able to tell the difference between vertebroplasty and balloon kyphoplasty on a radiograph. It is stated that blinded data about cement leakage and vertebral body height were collected by radiologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were unavailable for 0 (0%) and 2 (3.3%) participants in the vertebroplasty and balloon kyphoplasty groups respectively at the 3-month follow-up. Data were unavailable for 3 (5.7%) and 3 (5.6%) participants in the vertebroplasty and balloon kyphoplasty groups, respectively at the 12-month follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol found. Pain, ODI and vertebral body height data were excluded from participants who had a further vertebral fracture during follow-up
Other bias	Low risk	None apparent.

Wang 2016

Methods	**Design:** two-arm single-centre parallel-group randomised controlled trial **Setting:** China **Timing:** January 2009 to January 2013 **Interventions:** percutaneous vertebroplasty or facet joint injection with steroid and local anaesthetic **Sample size:** *a priori* sample size calculation not reported **Analysis:** intention-to-treat analysis
Participants	**Number of participants** • 384 screened for eligibility • 167 excluded (71 did not meet inclusion criteria, 42 declined to participate, 54 requested vertebroplasty)

	• 217 patients were randomised (108 to vertebroplasty and 109 to facet joint injection) • Data were available for 100 (92%) in vertebroplasty group and 106 (97%) in facet joint injection at 12-month follow-up **Inclusion criteria** Severe pain caused by acute (fracture occurred within 2 weeks) or subacute (fracture occurred within 2-8 weeks) osteoporotic vertebral fracture **Exclusion criteria** • Age ¡ 55 years • Posterior margin body or spinal cord damage • Long-term use of anti-coagulant drugs • Senile dementia • Cognitive damage or other cerebral disease • Malignant disease • Spinal infection or skin disease • Metabolic bone disease • Tubular bone fractures • Allergy to radiopaque agents **Baseline characteristics** *Percutaneous vertebroplasty* Mean (SD) age (years): 63.7 (5.7) No. male/female: 19/81 No. acute fractures: 87 No. Subacute fractures: 13 Mean (SD) Bone density T score: -3.06 (0.38) No. (%) use of osteoporotic drugs: 23 (23) No. (%) new fracture patients: 13 (13) *Facet joint injection* Mean (SD) age (years): 62.9 (5.3) No. male/female: 22/84 No. acute fractures: 90 No. Subacute fractures: 16 Mean (SD) Bone density T score: -3.03 (0.41) No. (%) use of osteoporotic drugs: 19 (18) No. (%) new fracture patients: 11 (10.4)
Interventions	Both vertebroplasty and facet joint injection were performed under local anaesthesia using a plane angiography system under fluoroscopic guidance by spine surgeons in the hospital. Postural reduction was performed before surgery **Percutaneous vertebroplasty** Vertebroplasty was performed using a bilateral or unilateral transpedicular approach. The patient was placed in the prone position on the table. After positioning of the fractured vertebrae and administration of local anaesthesia, an incision (approximately 5 mm long) was made using a scalpel. A bone puncture needle was then placed in the fractured vertebral body, transpedicularly. After removal of the inner needle, 3 mL to 9 mL of a poly methyl methacrylate (PMMA) bone cement was injected into the fractured vertebrae under continuous fluoroscopic visualization via lateral and antero-posterior projections in order to ensure adequate filling and to avoid cement extravasation posteriorly into the spinal canal or migration into the venous system to prevent pulmonary embolism,

	which is a significant complication. The injection was stopped when the surgeon met substantial resistance or when the cement reached the cortical edge of the fractured vertebral body; the injection was also stopped if cement was near the spinal canal or leaked into extraosseous structures **Facet joint injection** Injection was performed using a bilateral posterior approach with the participant in the prone position. After positioning of the fractured vertebral body and administration of local anaesthesia, a spinal needle was inserted into the facet joint capsule of the fractured vertebral body. Thereafter, a mixture of prednisolone (125 mg:5 mL) and lidocaine (100 mg:5 mL) was injected under fluoroscopic monitoring **Follow-up care** Participants in both groups wore a brace for 3 months after treatment
Outcomes	Outcomes were reported at 1 day, 1 week, 1, 3, 6, and 12 months after treatment A primary outcome was not specified. **Outcomes reported** • VAS scale measuring pain relief (scores range from 0 to 10, with 0 representing no pain and 10 representing the worst pain imaginable • Oswestry Disability Index (ODI) • Roland-Morris Disability Questionnaire (RMDQ) • SF-36 (measured only at 1, 3, 6 and 12 months) • Incident radiographic vertebral fractures detected on antero-posterior and lateral spinal radiograph examinations (3, 6, and 12 months) • Mean operation time • Postoperative hospitalisation time **Outcomes included in this review** • Pain (VAS) • Disability (RMDQ) • Quality of life (SF-36 MCS) • Incident radiographic vertebral fractures
Source of funding	The authors reported that no funds were received in support of this study
Notes	Clinicaltrials.gov trial identifier, or other trial registration record: none found. Protocol publication not found

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule.
Allocation concealment (selection bias)	Low risk	Not clearly reported, but as allocation was performed by an independent observer, bias may have been minimised

Wang 2016 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, appears unblinded.
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disability)	High risk	The article did not report blinding of participants. The primary and secondary outcomes were self-reported questionnaires, hence there is risk of bias in measurement of pain, physical functioning and quality of life
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	Outcome assessors were unblinded thus there is a risk of bias in the assessment of incident radiographic vertebral fractures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/108 (7.4%) in the vertebroplasty group and 3/109 (2.7%) in the facet joint injection group were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The results of all study outcomes were reported. Study protocol was not found
Other bias	Low risk	No other biases apparent.

Yang 2016

Methods	**Design**: single-centre, parallel-group, two-arm randomised controlled trial **Setting:** Shanghai, China **Timing:** January 2009 - December 2011 **Interventions:** high-viscosity cement vertebroplasty versus conservative treatment **Sample size:** sample of 48 participants per group would be required for 90% power to show at least a two-unit (on a 0 to 10 scale) advantage of vertebroplasty over conservative treatment in respect to pain with a SD of 3.0, based on a two-sided type 1 error of 5% **Analysis:** not reported
Participants	**Number of participants** • 158 patients enrolled • 23 patients excluded (18 declined to participate, 5 had other significant health problems) • 135 randomly assigned (66 to vertebroplasty, 69 to conservative treatment) • 5 excluded for metastases after randomisation (2 for vertebroplasty, 3 for conservative treatment) therefore 64 received vertebroplasty and 66 received conservative care • Data for 107 (56/64 (87.5%) for vertebroplasty, 51/66 (77.3%) for conservative treatment) available at 12-month assessment **Inclusion criteria** • Vertebral compression fracture after acute minor or mild trauma

	• Back pain 5 or more on a 0 to 10 cm VAS • Low signal on T1-weighted and high signal on T2-weighted in MRI • Level of fracture of T5 or lower • Independent living without use of wheelchair prior to trauma • Decreased bone mineral density (BMD) (T score less than or equal to -1) **Exclusion criteria** • Chronic back pain prior to trauma • Suspected underlying malignant disease • Spine infection retropulsion of bony fragments • Spinal cord compression syndrome • Concomitant hip fracture • Severe cardiopulmonary comorbidity • Major coagulopathy **Baseline characteristics** *Vertebroplasty group* Mean (SD) age: 77.1 (6.0) years; 64.3% female: 35.7% male Mean (SD) bone density T score: -3.3 (0.6) Mean (SD) VAS score: 7.5 (1.1) Mean (SD) ODI score: 80.2 (9.9) Mean (SD) QUALEFFO: 78.1 (8.1) *Usual care group* Mean (SD) age: 76.2 (5.6) years; 64.7% female: 35.3% male Mean (SD) bone density T score: -3.2 (0.7) Mean (SD) VAS score: 7.7 (1.1) Mean (SD) ODI score: 81.5 (9.7) Mean (SD) QUALEFFO: 77.5 (8.6)
Interventions	**Vertebroplasty** All vertebroplasties were performed by two experienced surgeons. The patient was placed in prone position on the operating table. After local infiltration anaesthesia, a bone puncture needle was placed transpedicularly in the fractured vertebral body under a C-arm fluoroscopic monitoring. Then, polymethylmethacrylate (PMMA) was carefully injected into the fractured vertebra with the fluoroscopic control. Injection ceased when cement reached the cortical edge of the vertebral body or leaked into the extraosseous structures or veins. If the cement did not reach the midline on the anterior-posterior fluoroscopic film, another side of injection was performed. In patients who had more than one fracture, all the fractured bodies were treated in a single procedure. After the treatment, a CT scan of the treated vertebral bodies was completed to identify cement distribution and leakage **Usual care** Patients were confined to horizontal bed rest for the initial 2 weeks after diagnosis. Then, they were encouraged to stand up and walk with brace and assistance. The bed rest time was extended if the back pain worsened when they stood up and walked. For pain medication, nonsteroidal anti-inflammatory drugs (NSAIDs) were prescribed for every patient. Additional analgesics, such as tramadol and morphine, would be added in case NSAIDs were not effective. Two weeks after diagnosis, physical therapy was started **Follow-up care** All patients in both groups were prescribed treatment for osteoporosis including bisphosphonates, calcium supplementation, and vitamin D

Outcomes	Outcomes were measured at 1 day, 1 week, 1, 3 and 6 months and 1 year **Primary outcome** • VAS mean pain score (0 to 10 cm) at one year **Secondary outcomes** • Oswestry Disability Index (ODI) • Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) • Patient satisfaction surveys (very satisfied, satisfied or not satisfied. Satisfaction rate reported as proportion very satisfied or satisfied) • Incidence of new vertebral fractures by anterior-posterior and lateral spine radiograph and MRI for confirmation if confirmation was required (1, 3, 6 months and 1 year) **Outcomes included in this review** • Mean pain • Oswestry Disability Index (ODI) • Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) • Incidence of new vertebral fractures
Source of funding	No commercial entity paid for any materials used in the study. Costs of the vertebroplasty procedure, medication and physical therapy were covered by insurance
Notes	Trial registration: not found. Not reported how many participants contributed data at 1 week, 1 month, 3 month and 6 month so we used number of participants for 12 months for all time points Cement leakage was seen in 22 out of the 65 treated vertebral bodies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Every patient was given a serial number according to the consecutive sequence of recruitment, and randomly assigned to PVP or conservative treatment group using computer-generated randomised codes, according to the serial number
Allocation concealment (selection bias)	Unclear risk	No information was provided about whether or not treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) Self-reported outcomes (e.g., pain, disabil-	High risk	Participants assessed their pain and function and were not blinded

Yang 2016 (*Continued*)

ity)		
Blinding of outcome assessment (detection bias) Objective outcomes (e.g., radiographic outcomes)	High risk	It is not stated who assessed the imaging outcomes. It is unlikely that they were blinded to treatment assignment as vertebroplasty cement is opaque and will be detected on imaging
Incomplete outcome data (attrition bias) All outcomes	High risk	A greater number of participants completed one-year follow-up in the vertebroplasty group (8/64 missing, 13%) compared with 15/66 missing (23%) in the conservative treatment group. 8 (12.1%) participants in the conservative treatment group received vertebroplasty, and 2 (3%) had open surgery
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol found.
Other bias	Low risk	No other biases apparent.

BMD: bone mineral density
CI: confidence interval
CT: computed tomography
IU: international unit
IV: intravenous
MD: mean difference
MMSE: Mini-Mental Status Examination
MRI: magnetic resonance imaging
NRS: numerical rating scale
NSAID: non-steroidal anti-inflammatory drugs
ODI: Oswestry Disability Index
PMMA: polymethyl methacrylate
QUALY:quality-adjusted life year
RCT: randomised controlled trial
RMDQ: Roland-Morris Disability Questionnaire
SD: standard deviation
SE: standard error
SF-36: Short form 36
VAS: visual analogue scale
VCF: vertebral compression fracture

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

Study	Reason for exclusion
Cai 2015	RCT comparing two different types of vertebroplasty.
Chen 2014b	RCT comparing two different types of vertebroplasty.
Chun-lei 2015	RCT comparing unipedicular vertebroplasty and bipedicular vertebroplasty, vertebroplasty given to both treatment groups
Du 2014	Treatment allocation not random, "Patients were divided according to the surgeon they had been referred to."
Gilula 2013	RCT comparing different cement types, vertebroplasty given to both treatment groups. Trial registration: NCT00290862
Gu 2015	RCT comparing screw fixation and vertebroplasty to vertebroplasty
Huang 2014	RCT comparing different cement types, vertebroplasty given to both treatment groups
Li 2015a	RCT comparing two different types of vertebroplasty.
Liu 2015	RCT comparing two different types of vertebroplasty.
Min 2015	RCT comparing vertebroplasty in both groups.
Son 2014	Not an RCT (retrospective cohort).
Xiao-nan 2014	RCT comparing different cement types, vertebroplasty given to both treatment groups
Yang 2014	Non-randomised study.
Yi 2014	Non-randomised study.
Yi 2016	Non-randomised study.
Ying 2017	RCT comparing low and high viscosity cement types, vertebroplasty given to both treatment groups
Yokoyama 2016	Non-randomised study.
Zhang 2015a	RCT comparing different cement types, vertebroplasty given to both treatment groups
Zhang 2015b	RCT comparing unipedicular vertebroplasty and bipedicular vertebroplasty, vertebroplasty given to both treatment groups
Zhang 2015c	RCT comparing unilateral and bilateral vertebroplasty, vertebroplasty given to both treatment groups

RCT: randomised controlled trial

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

Chen 2015

Methods	Two-arm randomised controlled trial.
Participants	Sample size = 84 **Inclusion criteria** • Elderly osteoporotic thoracolumbar compression fractures • Imaging diagnosis of osteoporotic thoracolumbar VCFs • Spinal cord or cauda equina nerve were not significantly compressed • Without systemic symptoms such as problems with urination • Can take care of themselves • No other systemic diseases, such as infectious diseases or haemorrhagic diseases **Exclusion criteria** • Patients with forced traction and spinal rotation injury • Spine burst fracture • Non-new osteoporotic compression fractures • Imaging examination showing more than 70% compression of the vertebral body
Interventions	• Vertebroplasty with bone cement injection • Bed rest and conservative treatment
Outcomes	Follow-up time was 3 months and at 12-54 months (average of 34.7 months for final follow-up) **Study outcomes** VAS score ODI and vertebral height
Study name	Bone cement injection as vertebral augmentation therapy for osteoporotic vertebral compression fractures. [Chinese]
Starting date	Jan 2010
Contact information	Chen Junping, Department of Orthopedics, the Fifth Affiliated Hospital of Zunyi Medical College, Zhuhai 519100, Guangdong Province, China
Notes	Trial not registered at clinical trials.gov website Published in Chinese, awaiting translation.

Dolin 2003

Methods	Randomised controlled trial, open-label. Sample size not specified.
Participants	**Inclusion criteria** • History of vertebral crush fractures proven on radiograph • Causes of crush fractures other than osteoporosis excluded • Persistent moderate/severe pain after 4 weeks conservative treatment • No more than four fractures

Dolin 2003 (*Continued*)

Interventions	• Vertebroplasty • Best medical treatment
Outcomes	Duration of follow-up and outcomes measured not specified.
Study name	A randomised controlled trial of vertebroplasty for the treatment of osteoporotic vertebral crush fractures
Starting date	November 2005.
Contact information	Principal Investigator: Simon Dolin
Notes	Trial Registration: ISRCTN14442024 (Also N0213112414); http://www.isrctn.com/ISRCTN14442024 Primary Sponsor: Record provided by the NHS Trusts Clinical Trials Register - Department of Health (UK) Completed, but no results available.

Laredo (OSTEO-6)

Methods	Randomised controlled trial, open-label
Participants	N = 48 (planned sample size 300) **Inclusion criteria** • Patient is able to undergo the vertebroplasty or balloon kyphoplasty procedure • Patient must have signed the consent form (ZELEN randomisation protocol) • Male or female, 50 years or older • One or two non-traumatic vertebral fracture(s) between T5 and L5 • Of osteoporotic origin (low-speed trauma such as fall from his own height or less than 80 cm) • Fracture(s) of less than 6 weeks duration after the onset of pain related to the fracture and fracture(s) exhibit(s) high signal intensity on T2-weighted images and a benign appearance at MRI • The patient will be able to receive the selected protocol treatment within 6 weeks after onset of fracture-related symptoms and within 15 days after treatment randomisation • The benign nature of the vertebral fracture has to be confirmed by the results of the biopsy performed during vertebroplasty or balloon kyphoplasty or by one year follow-up in the conservative treatment group **Exclusion criteria** • Patient with a vertebral fracture of more than 6-week duration after onset of fracture-related symptoms • Neurological signs related to the vertebral fracture to treat • History of surgical or percutaneous spine treatment except simple discectomy at a single or multiple vertebral levels with no residual pain • More than two recent vertebral fractures • Current infection • Impossibility to perform the percutaneous approach of the vertebra to treat. • Reduction by more than 50% of the anteroposterior width of the bony spinal canal due to the vertebral fracture to treat. • Known allergy to a contrast media or to one of the cement components used for kyphoplasty • Vertebral fracture with loss of 90% or more of the vertebral body height • Neurological signs or symptoms related to the vertebral fracture • Malignant and traumatic vertebral fractures • Contraindication to MRI: Metallic implant (pace-maker, 'non movible auditive implant, metallic

Laredo (OSTEO-6) (*Continued*)

	vascular or cardiac device; metallic surgical clips; claustrophobia • Evolutive cardiac disease non reactive to medical treatment • Patient presenting a non correctable spontaneous or therapeutic coagulation disorder. • Presence of an unexplained biological inflammatory syndrome with NFS = 20 • Noncompliant patient: Impossibility to participate to the study and to be followed up for 1 year. • Pregnant or breast feeding women • Patient not affiliated to social security
Interventions	• Vertebroplasty • Kyphoplasty • Usual care with or without brace
Outcomes	Follow-up to one year **Primary outcome** • Change in Vertebral Kyphotic angle between preoperative and one-year follow-up measurements **Secondary outcomes** • Pain evaluation using a VAS • Analgesics intake according to the WHO classification (Classes 1, 2 and 3) • Changes in anterior, mid and posterior vertebral heights of the treated vertebral body • Changes in height of the intervertebral disc spaces adjacent to the treated vertebra • Cost evaluation in a sample of 10% of patients randomly selected including the following costs: intervention cost; medical treatment costs; consultation costs; hospitalisation cost; complication costs • EIFEL questionnaire for back pain evaluation • Follow-up of anterior, median and posterior height of the treated vertebral body, obtained by making an average of all measurements, on 3 cuts TDM on the sagittal level : lateral right, median and lateral left • Intensity of signal with T2 sequence • Number of new vertebral fractures occurring during the one-year follow-up period • Quality of life evaluation (QUALEFFO - SF 12). • Regional spine Kyphosis angle and global thoracic and lumbar Kyphosis angle
Study name	Prospective randomized comparative study of balloon kyphoplasty, vertebroplasty and conservative management in acute osteoporotic vertebral fractures of less than 6 weeks
Starting date	December 2007
Contact information	Principal Investigator: Jean-Denis Laredo
Notes	Trial Registration: NCT0749060 ('OSTEO-6') Primary sponsor: Assistance Publique - Hôpitaux de Paris; Secondary sponsor: Ministry of Health, France Completed June 2012.

Laredo (STIC2)

Methods	Randomised controlled trial, open-label
Participants	N = 97 (planned sample size 200) **Inclusion criteria** • Patient is able to undergo the vertebroplasty or balloon kyphoplasty procedure

Laredo (STIC2) (*Continued*)

	• Patient has read and signed informed consent • Male or female, 50 years or older • One or two non-traumatic vertebral fracture(s) between T5 and L5 • Of osteoporotic origin (low-speed trauma such as fall from his own height or less than 80 cm) • Fracture(s) older than 6 weeks duration after the onset of pain related to the fracture and fracture(s) exhibit(s) high signal intensity on T2-weighted images and a benign appearance at MRI • Persistent pain despite medical treatment according to VAS = 5 or a last resort to morphine treatment • The patient will be able to receive the selected protocol treatment within 15 days after treatment randomisation. • The benign nature of the vertebral fracture has to be confirmed by the results of the biopsy performed during vertebroplasty or balloon kyphoplasty. **Exclusion criteria** • Patient with a vertebral fracture of less than 6 weeks duration after onset of fracture-related symptoms. • Neurological signs related to the vertebral fracture to treat • History of surgical or percutaneous spine treatment except simple discectomy at a single or multiple vertebral levels with no residual pain • Patient with more than 2 fractures corresponding to the inclusion criteria (old fractures are not taken into account) • More than two recent vertebral fractures • Current infection • Impossibility to perform the percutaneous approach of the vertebra to treat. • Reduction by more than 50% of the anteroposterior width of the bony spinal canal due to the vertebral fracture to treat. • Known allergy to a contrast media or to one of the cement components used for kyphoplasty. • Vertebral fracture with loss of 90% or more of the vertebral body height • Neurological signs or symptoms related to the vertebral fracture • Malignant and traumatic vertebral fractures • Contraindication to MRI: Metallic implant (pace-maker, non AMOVIBLE auditive implant, metallic vascular or cardiac device; metallic surgical clips; claustrophobia • Evolutive cardiac disease non reactive to medical treatment • Patient presenting a non correctable spontaneous or therapeutic coagulation disorder. • Presence of an unexplained biological inflammatory syndrome with NFS = 20 • Noncompliant patient: Impossibility to participate to the study and to be followed up for 1 year. • Pregnant or breast feeding women • Patient not affiliated to social security
Interventions	• Vertebroplasty • Kyphoplasty
Outcomes	Follow-up to one year **Primary outcome** • Modification of the kyphotic angle of every treated vertebra (between the preoperative angle and measured after 1-year follow-up) **Secondary outcomes** • Analgesics intake according to the WHO classification (Classes 1, 2 and 3) • Evaluation of kyphotic angle and global thoracic and lumbar angulations • Evaluation of pain through the VAS • Evaluation of quality of life (QUALEFFO - SF 12) • Follow-up of anterior, median and posterior height of the treated vertebral body, obtained by making

Laredo (STIC2) (*Continued*)

	an average of all measurements, on 3 cuts CT-scan on the sagittal level : lateral right, median and lateral left • Functional scale (EIFEL) for lumbar pain • Intensity of signal with T2 sequence • Measurement of anterior, median and posterior height of the discs adjacent to the fracture • Measurement of disc angles adjacent to the fracture • Medico-economic follow-up on 10% of the randomly selected patients: cost of intervention; cost of prescribed medicines; cost of follow-up visits; cost of subsequent hospitalisation; cost of complications. • Number of new vertebral fractures documented radiologically
Study name	Prospective randomized study of balloon kyphoplasty and vertebroplasty in subacute (older than 6 weeks) osteoporotic vertebral fractures (STIC2)
Starting date	December 2007
Contact information	Principal Investigator: Jean-Denis Laredo
Notes	Trial Registration: NCT0749086 ('STIC2') Primary sponsor: Assistance Publique - Hôpitaux de Paris, France; Secondary sponsor: Ministry of Health, France Completed June 2012

Li 2015b

Methods	Three-arm randomised controlled trial
Participants	Sample size = 90 Inclusion and exclusion criteria not available
Interventions	• Bone filling mesh container • Percutaneous vertebroplasty • Percutaneous kyphoplasty
Outcomes	Duration of follow-up not given **Study outcomes** • Bone cement type • Vertebral uplift • Leakage rate • VAS score • ODI and Cobb's angle
Study name	Bone filling mesh container for treatment of vertebral compression fractures can reduce the leakage of bone cement
Starting date	Not given
Contact information	Not given

Li 2015b (*Continued*)

Notes	Trial not registered at clinicaltrials.gov website Publication in Chinese, awaiting translation

Sorensen 2005

Methods	Randomised controlled trial, open-label
Participants	N = 27 **Inclusion criteria** • New pain in spine (within 6 months) • X-ray verified low energy spinal fracture(s) **Exclusion criteria** • Less than 20% or more than 90% reduction of the vertebral height • Lack of pain at fracture level • No need for continuous analgesic treatment • Patient not able to communicate • General anaesthesia contraindicated • MRI not possible • Coagulopathy (not adjustable) • Spondylitis, disciitis or spinal metastasis
Interventions	• Vertebroplasty • Usual care
Outcomes	Follow-up to 12 months **Primary outcome** • Level of pain **Secondary outcomes** • Need for analgesics, • Number of days at hospital • Level of ADL
Study name	Percutaneous vertebroplasty versus conservative treatment of pain: a prospective, randomized controlled study of osteoporotic fractures in the spine
Starting date	March 2004
Contact information	Principal Investigator: Leif Sorensen
Notes	Trial Registration: NCT00203554 Primary sponsor: University of Aarhus, Denmark Completed January 2008, no results available

Tan 2016

Methods	Two-arm randomised controlled trial
Participants	Sample size = 106 53 randomised to percutaneous vertebroplasty group and 53 randomised to percutaneous kyphoplasty group Inclusion and exclusion criteria unable to read as the full text is in Chinese
Interventions	• Percutaneous kyphoplasty • Percutaneous vertebroplasty
Outcomes	Follow-up to 6 months **Study outcomes** • Vertebral compression deformation • Bone cement distribution • Midline vertebral bone cement condition • Vertebral height restoration • Bone cement leakage • Vertebral kyphosis • Progressive spinal collapse • Nerve damage • VAS scores • ODI scores
Study name	Percutaneous kyphoplasty versus percutaneous vertebroplasty for osteoporotic vertebral compression fractures: A randomized comparison. [Chinese]
Starting date	Not given
Contact information	Not available
Notes	Trial not registered in Clinicaltrials.gov website

Zhou 2015

Methods	Two-arm randomised controlled trial
Participants	Sample size = 80 Inclusion and exclusion criteria not provided
Interventions	• Percutaneous vertebroplasty with high viscosity bone cement • Percutaneous kyphoplasty with standard viscosity bone cement
Outcomes	Follow-up at 3 months **Study outcomes** • VAS measuring low back pain • ODI measuring functional status • Incidence rate of bone cement leakage • Adverse reactions after surgery

Zhou 2015 (*Continued*)

Study name	Percutaneous vertebroplasty with high-viscosity bone cement for treatment of severe osteoporotic thoracolumbar vertebral compression fractures. [Chinese]
Starting date	Not available
Contact information	Zhou Wei, Zhongxiang City, Hubei Province, 2005 Huazhong University of Science and Technology
Notes	Trial not registered in Clinical trials.gov website

ADL: activities of daily living
CT: computed tomography
MRI: magnetic resonance imaging
ODI: Oswestry disability index
TDM: tomodensitometry
VAS: visual analogue scale
VCF: vertebral compression fracture

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

Longo 2010

Trial name or title	The effectiveness and safety of vertebroplasty for osteoporotic vertebral compression fractures. A double blind, prospective, randomised, controlled study
Methods	Randomised controlled trial, participant blinded
Participants	Planned sample size = 164 **Inclusion criteria** • More than or equal to 50 years of age • Back pain (more than or equal to 4 on 0 to 10 scale) • 1 to 3 recent painful osteoporotic vertebral fractures (minimum 15% loss of height, oedema or fracture line within vertebral body) from T5 through L5 • Decreased bone density T-score less than or equal to -1. **Exclusion criteria** • More than 3 recent spine fractures, pedicle fracture, or previous vertebroplasty or kyphoplasty and neurological deficit, radicular pain, radicular and/or myelum compression syndrome or canal narrowing • More than 90% osteoporotic vertebral collapse, fracture through/destruction of posterior wall, retropulsed bony fragment or bone fragments impinging on spinal cord • Spinal or systemic infections • Vertebral fractures resulting from primary bone tumours osteoblastic metastases or current malignancy • Severe cardio-pulmonary condition • Dementia • Untreatable coagulopathy or uninterruptible anticoagulation therapy • Allergies to materials used in vertebroplasty or kyphoplasty materials and contraindications to MRI • Unable to give informed consent

Longo 2010 (*Continued*)

Interventions	• Vertebroplasty • Three weeks period of bed rest, wearing a rigid hyperextension suspension brace, with positive three-point suspension (sternal, suprapubic and thoracolumbar)
Outcomes	Duration of follow-up to 24 months **Primary outcome** 1. VAS score (10 cm scale - 0 (no pain) to 10 (worst pain ever) **Secondary outcomes** • RMDQ • ODI (version 2.0) • Assessment of Quality of life (AQoL) • Utility score (Health-related questionnaire) • Incidence of new fractures (plain film examination of the thoracic and lumbosacral spine at 1, 3, 6, 12 and 24 months)
Starting date	Not specified
Contact information	Principal Investigator: Umile Giuseppe Longo, MD, Italy Phone: +39 06 22 54 11 E-mail: g.longo@unicampus.it
Notes	Unclear if registered in a trial registry Primary sponsor: Not specified Status of trial unknown

Sun 2012

Trial name or title	Investigational percutaneous vertebroplasty efficacy and safety trial
Methods	Randomised controlled trial, open-label
Participants	Planned sample size = 140 **Inclusion criteria** • 50 Years and older • Have a confirmed diagnosis of osteoporosis or osteopenia. • Acute, painful OVCFs from T4-L5 • Clinical onset ¡ 6 weeks • VCF on spine radiograph (minimum 15% height loss) • VAS score = 4 for pain **Exclusion criteria** • Severe cardio-pulmonary condition • Untreatable coagulopathy • Active local or systemic infection • Current malignancy, or radicular or caudal compression syndrome
Interventions	• Vertebroplasty • Conservative therapy

Sun 2012 (*Continued*)

Outcomes	Follow-up duration 12 months **Primary outcome** • VAS score at 1 month **Secondary outcomes** • ED-5Q score • New vertebral fractures • QUALEFFO total score • RMDQ score • Total medical costs
Starting date	October 2012
Contact information	Principal Investigator: Gang Sun, The Jinan Military General Hospital
Notes	Trial registration: NCT01677806 Primary sponsor: Jinan Military General Hospital, China; Secondary sponsors: Beijing Friendship Hospital China Medical University; Shanghai 10th People's Hospital; Shanghai 6th People's Hospital; The Second Affiliated Hospital of Chongqing Medical University Recruitment status unknown at last date of verification (11 Sep 2014), although expected completion date was December 2014, as reported at clinicaltrials.gov (accessed 20 Dec 2017)

VERTOS V

Trial name or title	VERTOS V
Methods	Randomised controlled trial, participant blinded
Participants	Planned sample size = 94 **Inclusion criteria** 1. VCF on X-ray of the spine (minimal 15% loss of height) 2. Level of VCF Th5 or lower 3. Back pain ≥ 12 weeks at time of X-ray 4. Age 50 to 90 years 5. Bone oedema on MRI of the fractured vertebral body 6. Focal tenderness on VCF level 7. Decreased bone density T-scores ≤ -1 **Exclusion criteria** • Severe cardio-pulmonary condition • Untreatable coagulopathy • Systemic or local infection of the spine (osteomyelitis, spondylodisciitis) • Suspected alternative underlying disease (malignancy) • Radicular and/or cauda compression syndrome • Contra-indication for MRI
Interventions	• Vertebroplasty • Sham procedure (verbal and physical cues (e.g. pressure on the back) and the methacrylate monomer is opened to simulate the odour of mixing the bone cement, but the needle is not placed and the no cement is injected)

VERTOS V (*Continued*)

Outcomes	Duration of follow-up to 12 months **Primary outcome** • Pain score using VAS and questions relating to use of pain medication, pain location and type of pain (recorded daily for first month after randomisation) • Other medical treatment and visits to alternative medical specialists, GP's and physical therapists are recorded **Secondary outcomes** • Disability related to back pain with RMDQ questionnaire • Quality of life measured with QoLQ of European foundation for osteoporosis • Physical function measured with RMDQ questionnaire
Starting date	May 2013
Contact information	Dr Dennis Carli
Notes	Trial registration: NCT01963039 Primary sponsor: St. Elisabeth Hospital, Tilburg, the Netherlands Study completed June 2015 (as reported at clinicaltrials.gov in September 2016); no study results posted Status changed 12 January 2017: study now 'enrolling by invitation', with a new estimated completion date of July 2018

MRI: magnetic resonance imaging
ODI: Oswestry disability index
OVCF: osteoporotic vertebral compression fracture
RMDQ: Roland-Morris Disability Questionnaire
QUALEFFO: Quality of Life Questionnaire of the European Foundation for Osteoporosis
VAS: visual analogue scale
VCF: vertebral compression fracture

DATA AND ANALYSES

Comparison 1. Efficacy: Vertebroplasty versus placebo (sham)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 10 point scale)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 1 to 2 weeks	5	539	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.30, 0.12]
1.2 1 month	5	535	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.44, -0.10]
1.3 3 months	4	394	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.40, -0.00]
1.4 6 months	3	339	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.42, 0.01]
1.5 12 months	3	269	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.41, 0.06]
1.6 24 months	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.88, 0.17]
2 Proportion of participants with pain improved by a clinically relevant amount (¿2.5 units or 30% on a 0 or 1 to 10 scale from baseline or less than 4 out of 10	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 1 to 2 weeks	2	198	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.78, 2.60]
2.2 1 month	3	326	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.99, 2.36]
2.3 3 months	2	198	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.12, 2.30]
2.4 6 months	2	198	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.02, 1.87]
2.5 12 months	1	78	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.67, 2.20]
2.6 24 months	1	78	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.84, 2.42]
3 Disability (RMDQ)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 1 to 2 weeks	3	299	Mean Difference (IV, Random, 95% CI)	-0.02 [-2.07, 2.03]
3.2 1 month	3	296	Mean Difference (IV, Random, 95% CI)	-1.72 [-3.13, -0.31]
3.3 3 months	2	162	Mean Difference (IV, Random, 95% CI)	-0.87 [-5.57, 3.83]
3.4 6 months	2	159	Mean Difference (IV, Random, 95% CI)	-2.41 [-6.23, 1.41]
3.5 12 months	1	48	Mean Difference (IV, Random, 95% CI)	0.60 [-3.02, 4.22]
3.6 24 months	1	43	Mean Difference (IV, Random, 95% CI)	0.10 [-3.67, 3.87]
4 Quality of life (QUALEFFO) [0 to 100]	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 1 to 2 weeks	2	176	Mean Difference (IV, Random, 95% CI)	-4.76 [-7.83, -1.68]
4.2 1 month	2	175	Mean Difference (IV, Random, 95% CI)	-2.75 [-9.02, 3.53]
4.3 3 months	1	73	Mean Difference (IV, Random, 95% CI)	-0.10 [-5.51, 5.31]
4.4 6 months	2	165	Mean Difference (IV, Random, 95% CI)	-3.34 [-10.50, 3.81]
4.5 12 months	1	67	Mean Difference (IV, Random, 95% CI)	-2.10 [-8.21, 4.01]
4.6 24 months	1	57	Mean Difference (IV, Random, 95% CI)	1.30 [-5.48, 8.08]
5 Treatment success	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 1 week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 1 month	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.5 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.6 24 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Quality of Life (EQ5D)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 1 to 2 weeks	2	164	Mean Difference (IV, Random, 95% CI)	0.01 [-0.03, 0.05]

6.2 1 month	3	285	Mean Difference (IV, Random, 95% CI)	0.05 [0.01, 0.09]
6.3 3 months	3	203	Mean Difference (IV, Random, 95% CI)	0.04 [-0.00, 0.08]
6.4 6 months	2	156	Mean Difference (IV, Random, 95% CI)	0.06 [0.01, 0.10]
6.5 12 months	2	93	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.07]
6.6 24 months	1	44	Mean Difference (IV, Random, 95% CI)	0.0 [-0.24, 0.24]

Comparison 2. Efficacy: Vertebroplasty versus usual care (open label)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 or 1 to 10 point scale)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 1 to 2 weeks	6	627	Std. Mean Difference (IV, Random, 95% CI)	-1.33 [-2.26, -0.39]
1.2 1 month	3	384	Std. Mean Difference (IV, Random, 95% CI)	-2.06 [-3.35, -0.76]
1.3 2 to 3 months	6	627	Std. Mean Difference (IV, Random, 95% CI)	-1.18 [-1.95, -0.40]
1.4 6 months	5	573	Std. Mean Difference (IV, Random, 95% CI)	-1.05 [-1.82, -0.28]
1.5 12 months	6	612	Std. Mean Difference (IV, Random, 95% CI)	-1.02 [-1.74, -0.30]
1.6 24 months	1	77	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.90, 0.01]
2 Disability (RMDQ [0 to 24] or ODI [0 to 100])	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 1 to 2 weeks	5	494	Std. Mean Difference (IV, Random, 95% CI)	-2.06 [-3.28, -0.83]
2.2 1 month	3	378	Std. Mean Difference (IV, Random, 95% CI)	-1.52 [-3.00, -0.04]
2.3 3 months	4	460	Std. Mean Difference (IV, Random, 95% CI)	-2.76 [-4.65, -0.87]
2.4 6 months	4	461	Std. Mean Difference (IV, Random, 95% CI)	-1.84 [-3.37, -0.30]
2.5 12 months	4	455	Std. Mean Difference (IV, Random, 95% CI)	-1.59 [-2.79, -0.38]
2.6 24 months	1	77	Std. Mean Difference (IV, Random, 95% CI)	-5.65 [-6.67, -4.63]
3 Quality of Life (QUALEFFO)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 1 to 2 weeks	4	448	Mean Difference (IV, Random, 95% CI)	-5.67 [-11.65, 0.32]
3.2 1 month	2	289	Mean Difference (IV, Random, 95% CI)	-10.18 [-21.49, 1. 13]
3.3 2 to 3 months	3	415	Mean Difference (IV, Random, 95% CI)	-5.83 [-15.41, 3.75]
3.4 6 months	3	415	Mean Difference (IV, Random, 95% CI)	-5.14 [-15.02, 4.74]
3.5 12 months	3	415	Mean Difference (IV, Random, 95% CI)	-3.40 [-9.90, 3.11]
4 Quality of life (EQ5D)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 1 to 2 weeks	1	183	Mean Difference (IV, Random, 95% CI)	0.08 [0.00, 0.15]
4.2 1 month	1	183	Mean Difference (IV, Random, 95% CI)	0.09 [0.01, 0.16]
4.3 3 months	2	215	Mean Difference (IV, Random, 95% CI)	0.10 [0.00, 0.20]
4.4 6 months	1	183	Mean Difference (IV, Random, 95% CI)	0.07 [-0.02, 0.15]
4.5 12 months	2	215	Mean Difference (IV, Random, 95% CI)	0.07 [-0.00, 0.14]
5 Treatment success	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Efficacy: Vertebroplasty versus kyphoplasty (balloon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 10 point scale)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 1 to 2 weeks	2	462	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.37, 0.25]
1.2 1 month	2	441	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.59, 0.48]
1.3 3 months	2	419	Mean Difference (IV, Random, 95% CI)	0.14 [-0.11, 0.39]
1.4 6 months	3	230	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.31, 0.22]
1.5 12 months	4	558	Mean Difference (IV, Random, 95% CI)	0.16 [-0.07, 0.40]
1.6 24 months	2	320	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.56, 0.27]
2 Disability (ODI)	4	1758	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.12, 0.07]
2.1 1 to 2 weeks	1	98	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.38, 0.41]
2.2 1 month	2	425	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.30, 0.08]
2.3 3 months	2	399	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.16, 0.24]
2.4 6 months	1	93	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.46, 0.35]
2.5 12 months	4	542	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.16, 0.17]
2.6 24 months	1	201	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.35, 0.21]
3 Quality of Life (EQ5D)	2	1346	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.04, 0.17]
3.1 1 month	2	422	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.09, 0.29]
3.2 3 months	1	292	Std. Mean Difference (IV, Random, 95% CI)	0.0 [-0.23, 0.23]
3.3 6 months	1	88	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.39, 0.45]
3.4 12 months	2	342	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.15, 0.27]
3.5 24 months	1	202	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.18, 0.37]

Comparison 4. Efficacy: Vertebroplasty versus facet joint injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 10 point scale)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 1 to 2 weeks	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 1 month	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 3 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Disability (RMDQ)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 1 to 2 weeks	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 1 month	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 3 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Quality of Life (SF-36)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 1 month	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 3 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Safety: Vertebroplasty versus placebo (sham) or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New clinical vertebral fractures	7	1020	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.62, 1.87]
2 New radiographic vertebral fractures	7	662	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.67, 2.15]
3 Number of serious other adverse events	5	821	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.36, 1.12]

Comparison 6. Safety: Vertebroplasty versus kyphoplasty

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New clinical vertebral fractures	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 24 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 New radiographic vertebral fractures	2	593	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.97, 1.43]
2.1 12 months	2	372	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.21, 3.16]
2.2 24 months	1	221	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.92, 1.51]
3 Number of serious other adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 12 months	1	101	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.14]
3.2 24 months	1	221	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.42, 1.97]

Comparison 7. Safety: Vertebroplasty versus facet joint injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New radiographic vertebral fractures	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 8. Subgroup analysis: Duration pain ≤ 6 weeks versus ¿ 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at 1 to 2 weeks	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Duration pain ≤ 6 weeks	4	332	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.41, 0.25]
1.2 Duration pain ¿ 6 weeks	2	157	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.30, 0.33]
2 Pain at 1 month	4	489	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.43, -0.08]
2.1 Duration pain ≤ 6 weeks	4	332	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.46, -0.02]
2.2 Duration pain ¿ 6 weeks	2	157	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.61, 0.02]
3 Disability at 1 to 2 weeks	3	291	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.28, 0.18]
3.1 Duration pain ≤ 6 weeks	3	150	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.53, 0.11]
3.2 Duration pain ¿ 6 weeks	2	141	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.20, 0.46]
4 Disability at 1 month	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Duration pain ≤ 6 weeks	3	150	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.66, -0.02]
4.2 Duration pain ¿ 6 weeks	2	142	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.47, 0.19]
5 Quality of life (EQ-5D) at 1 month	3	281	Mean Difference (IV, Random, 95% CI)	0.05 [0.01, 0.08]
5.1 Duration pain ≤ 6 weeks	3	139	Mean Difference (IV, Random, 95% CI)	0.05 [0.01, 0.09]
5.2 Duration pain ¿ 6 weeks	2	142	Mean Difference (IV, Random, 95% CI)	0.04 [-0.02, 0.10]

Comparison 9. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at 1 to 2 weeks (0 or 1 to 10 point scale)	11	1166	Std. Mean Difference (IV, Random, 95% CI)	-0.76 [-1.30, -0.22]
1.1 Sham (placebo) control	5	539	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.30, 0.12]
1.2 Usual care (open label) control	6	627	Std. Mean Difference (IV, Random, 95% CI)	-1.33 [-2.26, -0.39]
2 Pain at 1 month (0 or 1 to 10 point scale)	8	919	Std. Mean Difference (IV, Random, 95% CI)	-0.94 [-1.55, -0.34]
2.1 Sham (placebo) control	5	535	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.44, -0.10]
2.2 Usual care (open label) control	3	384	Std. Mean Difference (IV, Random, 95% CI)	-2.06 [-3.35, -0.76]
3 Pain at 3 months (0 or 1 to 10 point scale)	10	1021	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-1.28, -0.29]
3.1 Sham (placebo) control	4	394	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.40, -0.00]
3.2 Usual care (open label) control	6	627	Std. Mean Difference (IV, Random, 95% CI)	-1.18 [-1.95, -0.40]
4 Disability at 1 to 2 weeks (RMDQ [0 to 24] or ODI [0 to 100]))	8	793	Std. Mean Difference (IV, Random, 95% CI)	-1.25 [-2.06, -0.43]
4.1 Sham (placebo) control	3	299	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.34, 0.34]
4.2 Usual care (open label) control	5	494	Std. Mean Difference (IV, Random, 95% CI)	-2.06 [-3.28, -0.83]

5 Disability at 1 month (RMDQ [0 to 24] or ODI [0 to 100])	6	674	Std. Mean Difference (IV, Random, 95% CI)	-0.88 [-1.60, -0.17]
5.1 Sham (placebo) control	3	296	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.50, -0.04]
5.2 Usual care (open label) control	3	378	Std. Mean Difference (IV, Random, 95% CI)	-1.52 [-3.00, -0.04]
6 Disability at 3 months (RMDQ [0 to 24] or ODI [0 to 100])	6	622	Std. Mean Difference (IV, Random, 95% CI)	-1.85 [-3.08, -0.61]
6.1 Sham (placebo) control	2	162	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.78, 0.55]
6.2 Usual care (open label) control	4	460	Std. Mean Difference (IV, Random, 95% CI)	-2.76 [-4.65, -0.87]

Analysis 1.1. Comparison 1 Efficacy: Vertebroplasty versus placebo (sham), Outcome 1 Pain (0 to 10 point scale).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 1 Efficacy: Vertebroplasty versus placebo (sham)

Outcome: 1 Pain (0 to 10 point scale)

Study or subgroup	Favours vertebro-plasty N	Mean(SD)[0 to 10]	Placebo N	Mean(SD)[0 to 10]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 1 to 2 weeks							
Buchbinder 2009	37	-1.5 (2.5)	37	-2.1 (2.8)		16.0 %	0.22 [-0.23, 0.68]
Clark 2016	55	-4.2 (2.7)	57	-3 (3)		21.2 %	-0.42 [-0.79, -0.04]
Kallmes 2009	68	4.3 (2.9)	63	4.5 (2.8)		23.7 %	-0.07 [-0.41, 0.27]
VERTOS IV	90	4.38 (2.5)	86	4.28 (2.84)		28.2 %	0.04 [-0.26, 0.33]
VOPE 2015	22	28.52 (21.8104)	24	34.83 (21.8005)		10.9 %	-0.28 [-0.87, 0.30]
Subtotal (95% CI)	**272**		**267**			**100.0 %**	**-0.09 [-0.30, 0.12]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.89, df = 4 (P = 0.21); I^2 =32%							
Test for overall effect: Z = 0.83 (P = 0.41)							
2 1 month							
Buchbinder 2009	35	-2.3 (2.6)	38	-1.7 (3.3)		13.7 %	-0.20 [-0.66, 0.26]
Clark 2016	55	-4.6 (3)	57	-3.2 (2.7)		20.6 %	-0.49 [-0.86, -0.11]
Kallmes 2009	67	3.9 (2.9)	61	4.6 (3)		24.0 %	-0.24 [-0.58, 0.11]
VERTOS IV	90	3.36 (2.63)	86	3.77 (2.91)		33.2 %	-0.15 [-0.44, 0.15]
VOPE 2015	22	17.33 (21.81)	24	26.27 (22.29)		8.5 %	-0.40 [-0.98, 0.19]
Subtotal (95% CI)	**269**		**266**			**100.0 %**	**-0.27 [-0.44, -0.10]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.26, df = 4 (P = 0.69); I^2 =0.0%							

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Study or subgroup	Favours vertebroplasty N	Mean(SD)[0 to 10]	Placebo N	Mean(SD)[0 to 10]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Test for overall effect: Z = 3.07 (P = 0.0021)							
3 3 months							
Buchbinder 2009	36	-2.6 (2.9)	37	-1.9 (3.3)		18.5 %	-0.22 [-0.68, 0.24]
Clark 2016	53	-5.4 (3.5)	52	-4.1 (3.1)		26.3 %	-0.39 [-0.78, 0.00]
VERTOS IV	87	2.79 (2.42)	83	3.05 (2.88)		43.4 %	-0.10 [-0.40, 0.20]
VOPE 2015	22	16.09 (21.34)	24	18.7 (21.8)		11.7 %	-0.12 [-0.70, 0.46]
Subtotal (95% CI)	**198**		**196**			**100.0 %**	**-0.20 [-0.40, 0.00]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.46, df = 3 (P = 0.69); I^2 =0.0%							
Test for overall effect: Z = 1.98 (P = 0.048)							
4 6 months							
Buchbinder 2009	35	-2.4 (3.3)	36	-2.1 (3.3)		21.1 %	-0.09 [-0.56, 0.38]
Clark 2016	51	-6.1 (3.3)	51	-4.8 (3.1)		29.7 %	-0.40 [-0.80, -0.01]
VERTOS IV	85	3.03 (2.61)	81	3.4 (2.59)		49.2 %	-0.14 [-0.45, 0.16]
Subtotal (95% CI)	**171**		**168**			**100.0 %**	**-0.21 [-0.42, 0.01]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.38, df = 2 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 1.91 (P = 0.056)							
5 12 months							
Buchbinder 2009	33	-2.4 (2.7)	34	-1.9 (2.8)		24.9 %	-0.18 [-0.66, 0.30]
VERTOS IV	80	2.85 (2.44)	76	3.38 (2.95)		58.0 %	-0.20 [-0.51, 0.12]
VOPE 2015	22	28.35 (24.2)	24	30.67 (22.78)		17.1 %	-0.10 [-0.68, 0.48]
Subtotal (95% CI)	**135**		**134**			**100.0 %**	**-0.17 [-0.41, 0.06]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 2 (P = 0.96); I^2 =0.0%							
Test for overall effect: Z = 1.43 (P = 0.15)							
6 24 months							
Buchbinder 2009	29	-3 (3.1)	28	-1.9 (3)		100.0 %	-0.36 [-0.88, 0.17]
Subtotal (95% CI)	**29**		**28**			**100.0 %**	**-0.36 [-0.88, 0.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.33 (P = 0.18)							
Test for subgroup differences: Chi^2 = 2.03, df = 5 (P = 0.85), I^2 =0.0%							

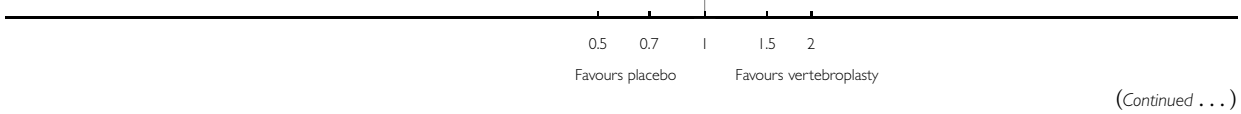
Analysis 1.2. Comparison 1 Efficacy: Vertebroplasty versus placebo (sham), Outcome 2 Proportion of participants with pain improved by a clinically relevant amount (¿2.5 units or 30% on a 0 or 1 to 10 scale from baseline or less than 4 out of 10.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 1 Efficacy: Vertebroplasty versus placebo (sham)

Outcome: 2 Proportion of participants with pain improved by a clinically relevant amount (>2.5 units or 30% on a 0 or 1 to 10 scale from baseline or less than 4 out of 10

Study or subgroup	Vertebroplasty n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 1 to 2 weeks					
Buchbinder 2009	14/38	14/40		50.0 %	1.05 [0.58, 1.90]
Clark 2016	24/61	12/59		50.0 %	1.93 [1.07, 3.50]
Subtotal (95% CI)	**99**	**99**		**100.0 %**	**1.43 [0.78, 2.60]**
Total events: 38 (Vertebroplasty), 26 (Placebo)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 2.04, df = 1 (P = 0.15); I^2 =51%					
Test for overall effect: Z = 1.16 (P = 0.24)					
2 1 month					
Buchbinder 2009	18/38	16/40		31.5 %	1.18 [0.71, 1.96]
Clark 2016	28/61	10/59		25.6 %	2.71 [1.45, 5.07]
Kallmes 2009	43/67	30/61		42.9 %	1.30 [0.96, 1.78]
Subtotal (95% CI)	**166**	**160**		**100.0 %**	**1.53 [0.99, 2.36]**
Total events: 89 (Vertebroplasty), 56 (Placebo)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 5.12, df = 2 (P = 0.08); I^2 =61%					
Test for overall effect: Z = 1.91 (P = 0.056)					
3 3 months					
Buchbinder 2009	19/38	13/40		43.4 %	1.54 [0.89, 2.66]
Clark 2016	29/61	17/59		56.6 %	1.65 [1.02, 2.67]
Subtotal (95% CI)	**99**	**99**		**100.0 %**	**1.60 [1.12, 2.30]**
Total events: 48 (Vertebroplasty), 30 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.04, df = 1 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 2.55 (P = 0.011)					
4 6 months					
Buchbinder 2009	19/38	15/40		35.2 %	1.33 [0.80, 2.22]
Clark 2016	35/61	24/59		64.8 %	1.41 [0.97, 2.06]
Subtotal (95% CI)	**99**	**99**		**100.0 %**	**1.38 [1.02, 1.87]**
Total events: 54 (Vertebroplasty), 39 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 2.10 (P = 0.036)					



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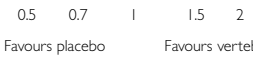
Study or subgroup	Vertebroplasty n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
5 12 months					
Buchbinder 2009	15/38	13/40		100.0 %	1.21 [0.67, 2.20]
Subtotal (95% CI)	**38**	**40**		**100.0 %**	**1.21 [0.67, 2.20]**
Total events: 15 (Vertebroplasty), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
6 24 months					
Buchbinder 2009	19/38	14/40		100.0 %	1.43 [0.84, 2.42]
Subtotal (95% CI)	**38**	**40**		**100.0 %**	**1.43 [0.84, 2.42]**
Total events: 19 (Vertebroplasty), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					



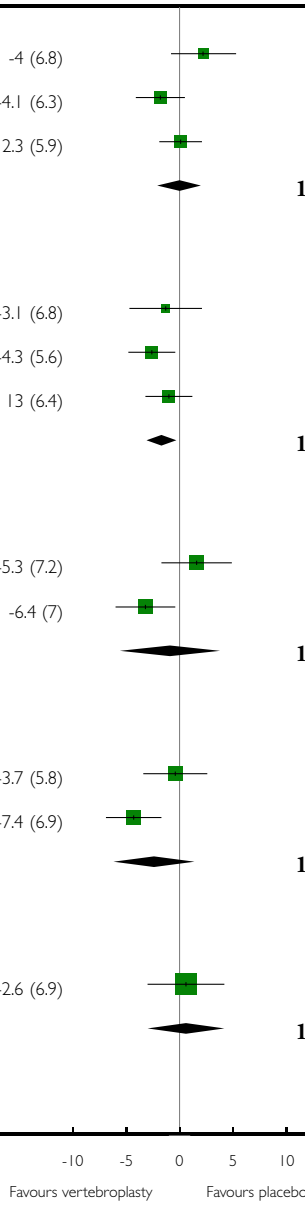
Analysis 1.3. Comparison 1 Efficacy: Vertebroplasty versus placebo (sham), Outcome 3 Disability (RMDQ).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 1 Efficacy: Vertebroplasty versus placebo (sham)

Outcome: 3 Disability (RMDQ)

Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 23]	Placebo N	Mean(SD)[0 to 23]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 1 to 2 weeks							
Buchbinder 2009	30	-1.8 (5)	29	-4 (6.8)		26.0 %	2.20 [-0.85, 5.25]
Clark 2016	53	-5.9 (5.8)	56	-4.1 (6.3)		35.1 %	-1.80 [-4.07, 0.47]
Kallmes 2009	68	12.4 (5.8)	63	12.3 (5.9)		38.8 %	0.10 [-1.91, 2.11]
Subtotal (95% CI)	**151**		**148**			**100.0 %**	**-0.02 [-2.07, 2.03]**
Heterogeneity: Tau² = 1.77; Chi² = 4.36, df = 2 (P = 0.11); I² =54%							
Test for overall effect: Z = 0.02 (P = 0.98)							
2 1 month							
Buchbinder 2009	30	-4.4 (6.6)	29	-3.1 (6.8)		17.0 %	-1.30 [-4.72, 2.12]
Clark 2016	55	-6.9 (6)	54	-4.3 (5.6)		42.0 %	-2.60 [-4.78, -0.42]
Kallmes 2009	67	12 (6.3)	61	13 (6.4)		41.0 %	-1.00 [-3.20, 1.20]
Subtotal (95% CI)	**152**		**144**			**100.0 %**	**-1.72 [-3.13, -0.31]**
Heterogeneity: Tau² = 0.0; Chi² = 1.09, df = 2 (P = 0.58); I² =0.0%							
Test for overall effect: Z = 2.39 (P = 0.017)							
3 3 months							
Buchbinder 2009	30	-3.7 (5.4)	29	-5.3 (7.2)		48.6 %	1.60 [-1.66, 4.86]
Clark 2016	53	-9.6 (7.7)	50	-6.4 (7)		51.4 %	-3.20 [-6.04, -0.36]
Subtotal (95% CI)	**83**		**79**			**100.0 %**	**-0.87 [-5.57, 3.83]**
Heterogeneity: Tau² = 9.09; Chi² = 4.74, df = 1 (P = 0.03); I² =79%							
Test for overall effect: Z = 0.36 (P = 0.72)							
4 6 months							
Buchbinder 2009	30	-4.1 (5.8)	29	-3.7 (5.8)		48.4 %	-0.40 [-3.36, 2.56]
Clark 2016	49	-11.7 (6.5)	51	-7.4 (6.9)		51.6 %	-4.30 [-6.93, -1.67]
Subtotal (95% CI)	**79**		**80**			**100.0 %**	**-2.41 [-6.23, 1.41]**
Heterogeneity: Tau² = 5.57; Chi² = 3.73, df = 1 (P = 0.05); I² =73%							
Test for overall effect: Z = 1.24 (P = 0.22)							
5 12 months							
Buchbinder 2009	26	-2 (5.7)	22	-2.6 (6.9)		100.0 %	0.60 [-3.02, 4.22]
Subtotal (95% CI)	**26**		**22**			**100.0 %**	**0.60 [-3.02, 4.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.32 (P = 0.75)							



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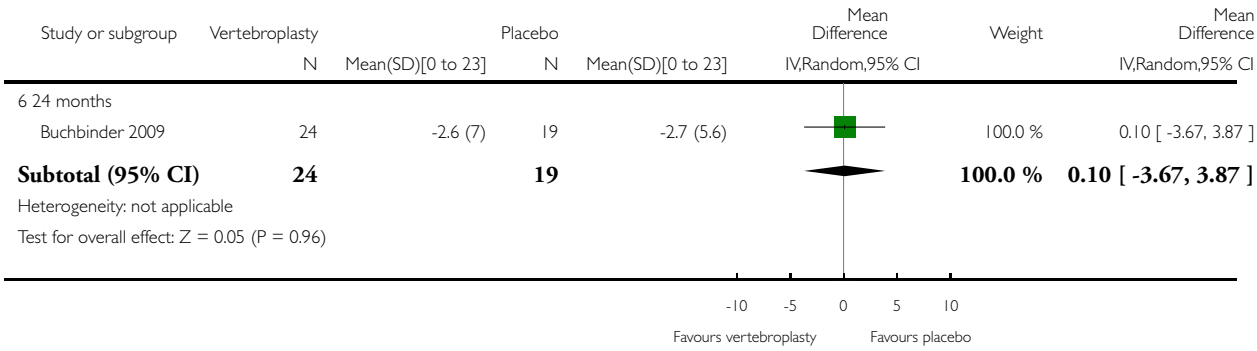
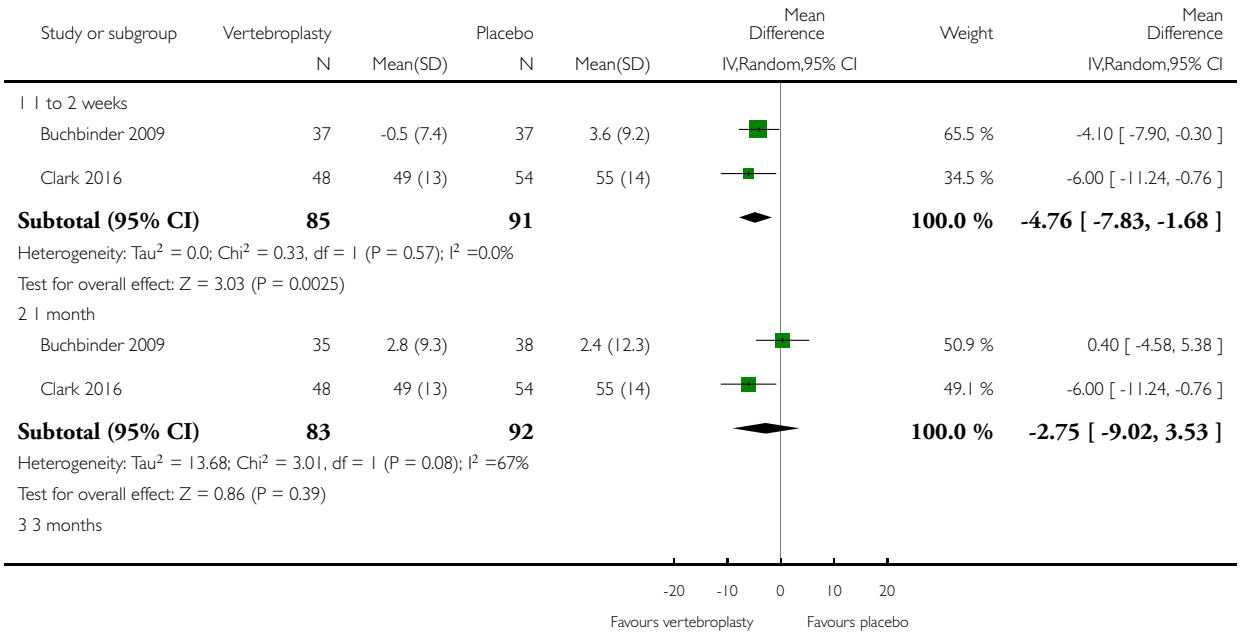


Analysis 1.4. Comparison 1 Efficacy: Vertebroplasty versus placebo (sham), Outcome 4 Quality of life (QUALEFFO) [0 to 100].

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 1 Efficacy: Vertebroplasty versus placebo (sham)

Outcome: 4 Quality of life (QUALEFFO) [0 to 100]



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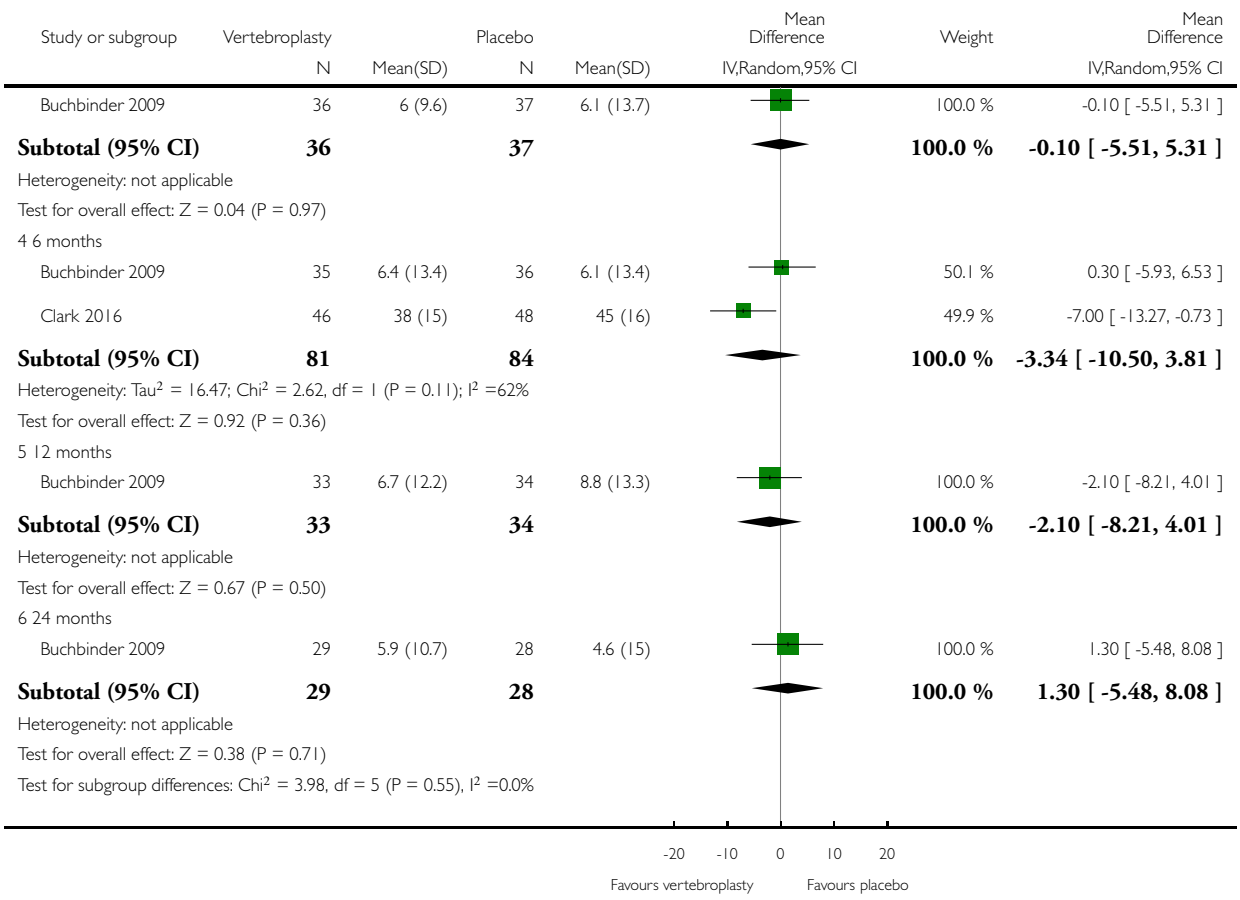


Analysis 1.5. Comparison 1 Efficacy: Vertebroplasty versus placebo (sham), Outcome 5 Treatment success.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 1 Efficacy: Vertebroplasty versus placebo (sham)

Outcome: 5 Treatment success

Study or subgroup	Vertebroplasty n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 1 week				
Buchbinder 2009	6/38	13/40		0.49 [0.21, 1.15]
2 1 month				
Buchbinder 2009	12/38	9/40		1.40 [0.67, 2.95]
3 3 months				
Buchbinder 2009	14/38	12/40		1.23 [0.65, 2.31]
4 6 months				
Buchbinder 2009	16/38	15/40		1.12 [0.65, 1.94]
5 12 months				
Buchbinder 2009	15/38	15/40		1.05 [0.60, 1.85]
6 24 months				
Buchbinder 2009	12/38	10/40		1.26 [0.62, 2.57]

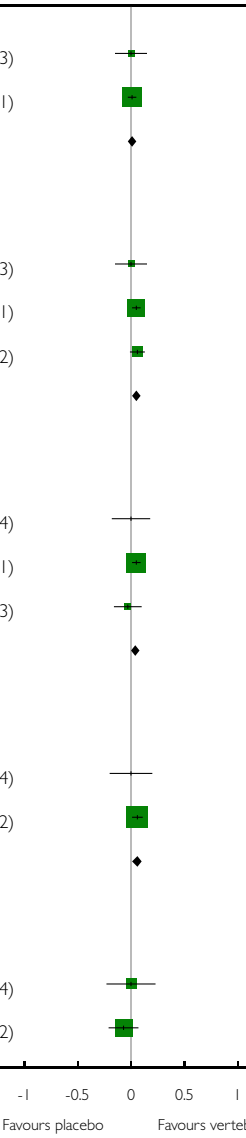
Analysis 1.6. Comparison 1 Efficacy: Vertebroplasty versus placebo (sham), Outcome 6 Quality of Life (EQ5D).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 1 Efficacy: Vertebroplasty versus placebo (sham)

Outcome: 6 Quality of Life (EQ5D)

Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 1]	Placebo N	Mean(SD)[0 to 1]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 1 to 2 weeks							
Buchbinder 2009	30	0.1 (0.3)	29	0.1 (0.3)		6.4 %	0.0 [-0.15, 0.15]
Clark 2016	49	0.69 (0.1)	56	0.68 (0.11)		93.6 %	0.01 [-0.03, 0.05]
Subtotal (95% CI)	**79**		**85**			**100.0 %**	**0.01 [-0.03, 0.05]**
Heterogeneity: Tau² = 0.0; Chi² = 0.02, df = 1 (P = 0.90); I² =0.0%							
Test for overall effect: Z = 0.47 (P = 0.64)							
2 1 month							
Buchbinder 2009	30	0.1 (0.3)	29	0.1 (0.3)		5.3 %	0.0 [-0.15, 0.15]
Clark 2016	47	0.75 (0.11)	51	0.7 (0.11)		66.0 %	0.05 [0.01, 0.09]
Kallmes 2009	67	0.7 (0.18)	61	0.64 (0.2)		28.7 %	0.06 [-0.01, 0.13]
Subtotal (95% CI)	**144**		**141**			**100.0 %**	**0.05 [0.01, 0.09]**
Heterogeneity: Tau² = 0.0; Chi² = 0.50, df = 2 (P = 0.78); I² =0.0%							
Test for overall effect: Z = 2.78 (P = 0.0055)							
3 3 months							
Buchbinder 2009	30	0.2 (0.3)	29	0.2 (0.4)		5.0 %	0.0 [-0.18, 0.18]
Clark 2016	47	0.75 (0.11)	51	0.7 (0.11)		85.8 %	0.05 [0.01, 0.09]
VOPE 2015	22	0.68 (0.23)	24	0.71 (0.23)		9.2 %	-0.03 [-0.16, 0.10]
Subtotal (95% CI)	**99**		**104**			**100.0 %**	**0.04 [0.00, 0.08]**
Heterogeneity: Tau² = 0.0; Chi² = 1.45, df = 2 (P = 0.48); I² =0.0%							
Test for overall effect: Z = 1.95 (P = 0.051)							
4 6 months							
Buchbinder 2009	30	0.2 (0.4)	29	0.2 (0.4)		4.8 %	0.0 [-0.20, 0.20]
Clark 2016	47	0.8 (0.11)	50	0.74 (0.12)		95.2 %	0.06 [0.01, 0.11]
Subtotal (95% CI)	**77**		**79**			**100.0 %**	**0.06 [0.01, 0.10]**
Heterogeneity: Tau² = 0.0; Chi² = 0.32, df = 1 (P = 0.57); I² =0.0%							
Test for overall effect: Z = 2.51 (P = 0.012)							
5 12 months							
Buchbinder 2009	26	0.2 (0.4)	21	0.2 (0.4)		27.9 %	0.0 [-0.23, 0.23]
VOPE 2015	22	0.67 (0.27)	24	0.74 (0.22)		72.1 %	-0.07 [-0.21, 0.07]



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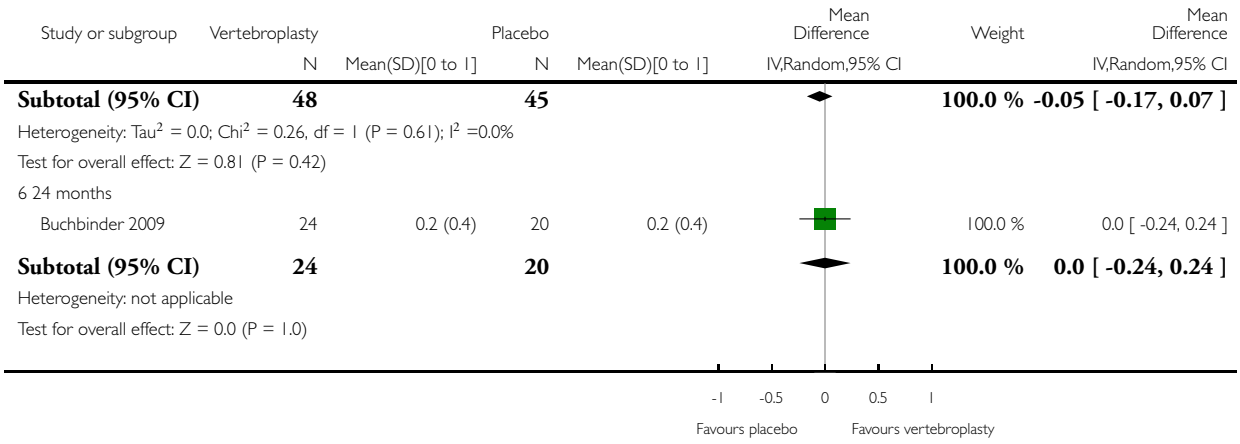
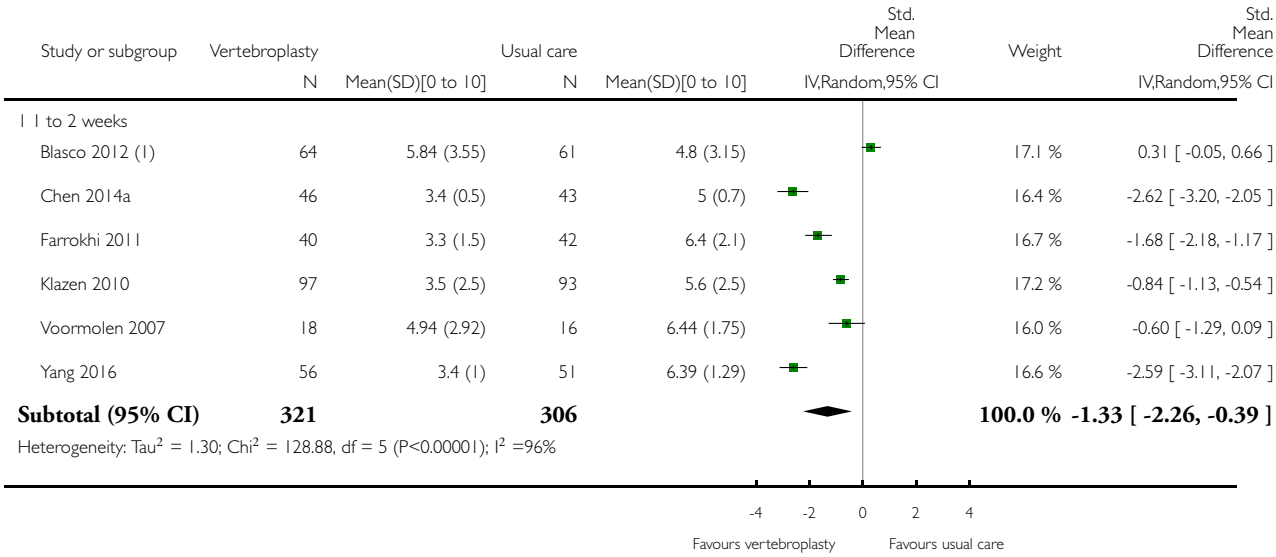


Analysis 2.1. Comparison 2 Efficacy: Vertebroplasty versus usual care (open label), Outcome 1 Pain (0 or 1 to 10 point scale).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 2 Efficacy: Vertebroplasty versus usual care (open label)

Outcome: 1 Pain (0 or 1 to 10 point scale)



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Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 10]	Usual care N	Mean(SD)[0 to 10]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Test for overall effect: Z = 2.78 (P = 0.0054)							
2 1 month							
Chen 2014a	46	2.8 (0.4)	43	4 (0.6)		32.9 %	-2.35 [-2.89, -1.80]
Klazen 2010	96	2.5 (2.5)	92	4.9 (2.6)		34.3 %	-0.94 [-1.24, -0.64]
Yang 2016	56	2.39 (0.7)	51	4.9 (0.99)		32.8 %	-2.93 [-3.48, -2.38]
Subtotal (95% CI)	**198**		**186**			**100.0 %**	**-2.06 [-3.35, -0.76]**
Heterogeneity: Tau^2 = 1.26; Chi^2 = 48.10, df = 2 (P<0.00001); I^2 =96%							
Test for overall effect: Z = 3.10 (P = 0.0019)							
3 2 to 3 months							
Blasco 2012 (2)	64	4.12 (3.37)	61	4.7 (3.11)		17.1 %	-0.18 [-0.53, 0.17]
Chen 2014a	46	2.5 (0.5)	43	3.9 (0.7)		16.3 %	-2.29 [-2.83, -1.75]
Farrokhi 2011	40	3.2 (2.2)	42	6.1 (2.1)		16.6 %	-1.34 [-1.82, -0.86]
Klazen 2010	92	2.5 (2.7)	86	3.9 (2.8)		17.3 %	-0.51 [-0.81, -0.21]
Rousing 2009	23	1.8 (2.45)	23	2.6 (3.43)		16.1 %	-0.26 [-0.84, 0.32]
Yang 2016	56	2.09 (0.59)	51	3.89 (0.81)		16.5 %	-2.54 [-3.05, -2.03]
Subtotal (95% CI)	**321**		**306**			**100.0 %**	**-1.18 [-1.95, -0.40]**
Heterogeneity: Tau^2 = 0.89; Chi^2 = 95.33, df = 5 (P<0.00001); I^2 =95%							
Test for overall effect: Z = 2.97 (P = 0.0030)							
4 6 months							
Blasco 2012 (3)	64	4.72 (2.86)	61	4.3 (2.97)		20.4 %	0.14 [-0.21, 0.49]
Chen 2014a	46	2.5 (0.6)	43	4 (0.8)		19.4 %	-2.11 [-2.64, -1.59]
Farrokhi 2011	40	2.2 (2.1)	42	4.1 (1.5)		19.8 %	-1.04 [-1.50, -0.57]
Klazen 2010	89	2.3 (2.7)	81	3.9 (2.9)		20.6 %	-0.57 [-0.88, -0.26]
Yang 2016	56	2.3 (0.65)	51	3.49 (0.7)		19.9 %	-1.75 [-2.20, -1.30]
Subtotal (95% CI)	**295**		**278**			**100.0 %**	**-1.05 [-1.82, -0.28]**
Heterogeneity: Tau^2 = 0.72; Chi^2 = 72.36, df = 4 (P<0.00001); I^2 =94%							
Test for overall effect: Z = 2.68 (P = 0.0075)							
5 12 months							
Blasco 2012	64	4.46 (2.96)	61	4.34 (2.91)		17.2 %	0.04 [-0.31, 0.39]
Chen 2014a	46	2.5 (0.5)	43	4.1 (0.8)		16.2 %	-2.40 [-2.95, -1.85]
Farrokhi 2011	38	2.2 (2.1)	39	4.1 (1.8)		16.6 %	-0.96 [-1.44, -0.49]
Klazen 2010	89	2.3 (2.7)	81	3.9 (2.9)		17.3 %	-0.57 [-0.88, -0.26]
Rousing 2009	22	2 (2.27)	22	2.9 (2.99)		16.0 %	-0.33 [-0.93, 0.26]
Yang 2016	56	1.9 (0.52)	51	3.1 (0.69)		16.7 %	-1.96 [-2.43, -1.50]
Subtotal (95% CI)	**315**		**297**			**100.0 %**	**-1.02 [-1.74, -0.30]**

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Favours vertebroplasty Favours usual care

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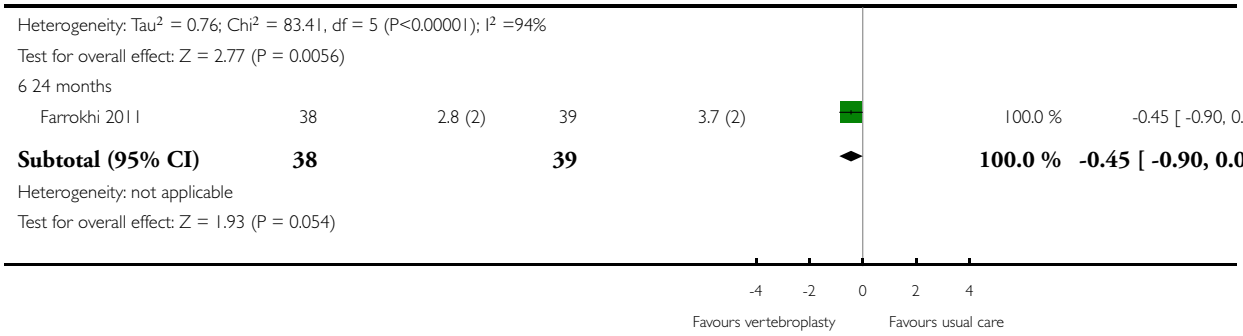
Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 10]	Usual care N	Mean(SD)[0 to 10]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Heterogeneity: $Tau^2 = 0.76$; $Chi^2 = 83.41$, df = 5 (P<0.00001); $I^2 = 94\%$							
Test for overall effect: Z = 2.77 (P = 0.0056)							
6 24 months							
Farrokhi 2011	38	2.8 (2)	39	3.7 (2)		100.0 %	-0.45 [-0.90, 0.01]
Subtotal (95% CI)	**38**		**39**			**100.0 %**	**-0.45 [-0.90, 0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.93 (P = 0.054)							



(1) 1 to 10 point scale

(2) 1 to 10 point scale

(3) 1 to 10 point scale

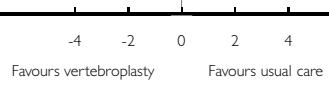
Analysis 2.2. Comparison 2 Efficacy: Vertebroplasty versus usual care (open label), Outcome 2 Disability (RMDQ [0 to 24] or ODI [0 to 100]).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 2 Efficacy: Vertebroplasty versus usual care (open label)

Outcome: 2 Disability (RMDQ [0 to 24] or ODI [0 to 100])

Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 23]	Control N	Mean(SD)[0 to 23]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 1 to 2 weeks							
Chen 2014a	46	13.2 (1.5)	43	15.7 (1.6)		20.4 %	-1.60 [-2.08, -1.12]
Farrokhi 2011	40	30.1 (3)	42	44 (2.5)		18.9 %	-5.00 [-5.89, -4.10]
Klazen 2010	93	13.68 (5.43)	89	15.71 (4.69)		20.8 %	-0.40 [-0.69, -0.10]
Voormolen 2007	18	12.69 (3.92)	16	18.17 (4.21)		19.5 %	-1.32 [-2.07, -0.57]
Yang 2016	56	62.29 (9.25)	51	80.01 (6.55)		20.4 %	-2.18 [-2.66, -1.70]
Subtotal (95% CI)	**253**		**241**			**100.0 %**	**-2.06 [-3.28, -0.83]**
Heterogeneity: Tau² = 1.86; Chi² = 115.92, df = 4 (P<0.00001); I² =97%							
Test for overall effect: Z = 3.29 (P = 0.0010)							
2 1 month							
Chen 2014a	46	11.7 (1)	43	13.8 (1.5)		33.2 %	-1.64 [-2.13, -1.16]
Klazen 2010	93	12.46 (6.32)	89	14 (5.73)		33.9 %	-0.25 [-0.55, 0.04]
Yang 2016	56	47.07 (9.83)	51	71.16 (7.61)		32.9 %	-2.70 [-3.23, -2.18]
Subtotal (95% CI)	**195**		**183**			**100.0 %**	**-1.52 [-3.00, -0.04]**
Heterogeneity: Tau² = 1.66; Chi² = 71.75, df = 2 (P<0.00001); I² =97%							
Test for overall effect: Z = 2.02 (P = 0.044)							
3 3 months							
Chen 2014a	46	9.9 (1.2)	43	12.5 (1)		25.2 %	-2.33 [-2.87, -1.78]
Farrokhi 2011	40	15 (2.2)	42	30 (3.1)		24.1 %	-5.51 [-6.47, -4.54]
Klazen 2010	93	10.45 (6.76)	89	12.94 (5.95)		25.6 %	-0.39 [-0.68, -0.10]
Yang 2016	56	30.42 (8.39)	51	56.15 (8.76)		25.2 %	-2.98 [-3.54, -2.43]
Subtotal (95% CI)	**235**		**225**			**100.0 %**	**-2.76 [-4.65, -0.87]**
Heterogeneity: Tau² = 3.60; Chi² = 157.03, df = 3 (P<0.00001); I² =98%							
Test for overall effect: Z = 2.87 (P = 0.0041)							
4 6 months							
Chen 2014a	46	9.3 (9)	43	11.1 (9)		25.4 %	-0.20 [-0.62, 0.22]
Farrokhi 2011	40	10 (2)	42	21 (2.5)		23.9 %	-4.80 [-5.67, -3.93]
Klazen 2010	93	9.97 (6.59)	90	11.65 (6.6)		25.6 %	-0.25 [-0.54, 0.04]



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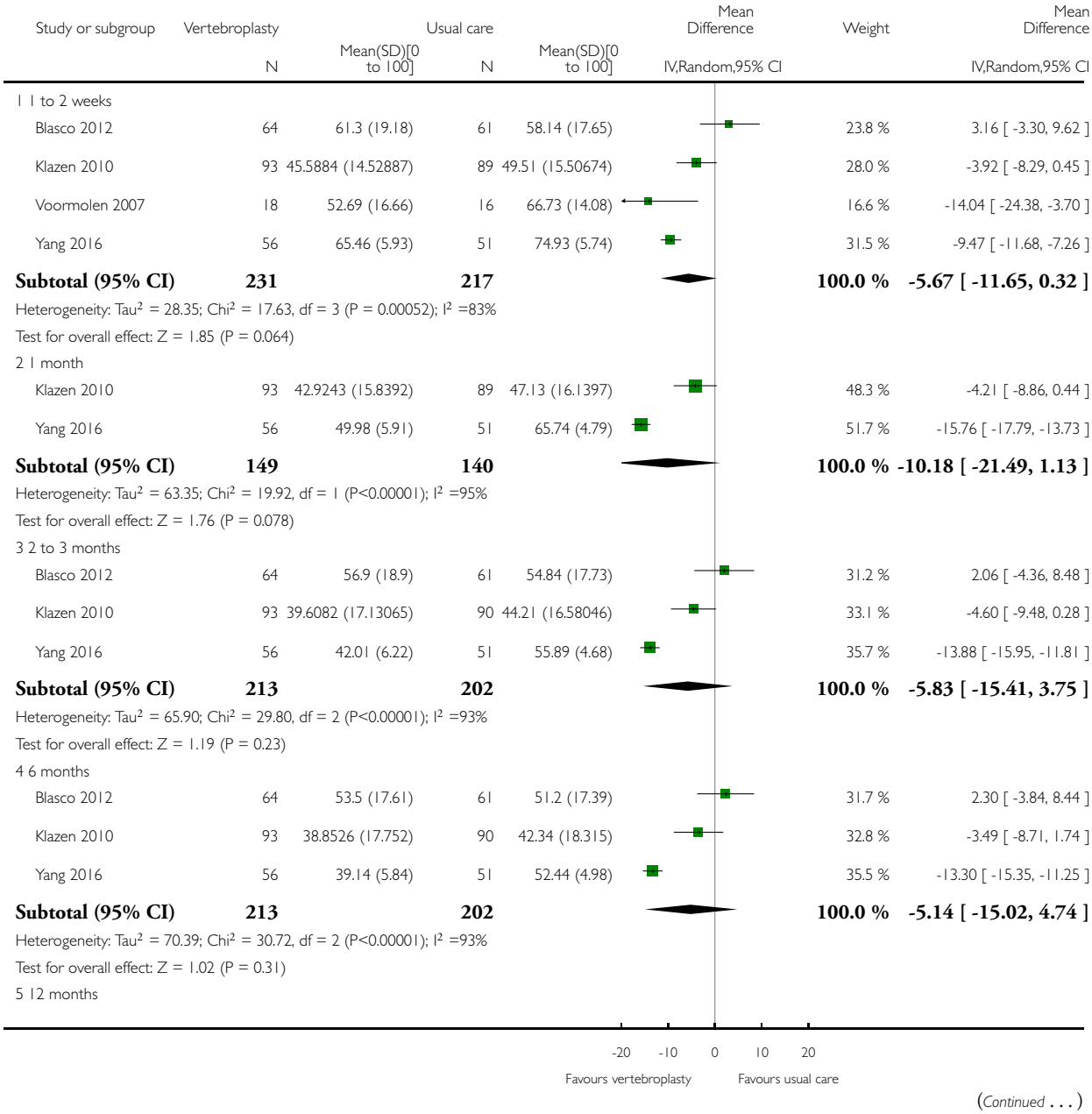
Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 23]	Control N	Mean(SD)[0 to 23]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Yang 2016	56	28.81 (7.61)	51	46.73 (8)		25.2 %	-2.28 [-2.77, -1.79]
Subtotal (95% CI)	**235**		**226**			**100.0 %**	**-1.84 [-3.37, -0.30]**
Heterogeneity: Tau^2 = 2.38; Chi^2 = 137.62, df = 3 (P<0.00001); I^2 =98%							
Test for overall effect: Z = 2.34 (P = 0.019)							
5 12 months							
Chen 2014a	46	8.1 (7)	43	10.7 (1.1)		25.5 %	-0.51 [-0.93, -0.08]
Farrokhi 2011	38	8 (3.2)	39	20 (1.7)		23.1 %	-4.65 [-5.53, -3.78]
Klazen 2010	92	9.6 (6.834)	90	11.53 (6.901)		25.9 %	-0.28 [-0.57, 0.01]
Yang 2016	56	29.64 (6.93)	51	38.4 (7.42)		25.5 %	-1.21 [-1.63, -0.80]
Subtotal (95% CI)	**232**		**223**			**100.0 %**	**-1.59 [-2.79, -0.38]**
Heterogeneity: Tau^2 = 1.44; Chi^2 = 92.05, df = 3 (P<0.00001); I^2 =97%							
Test for overall effect: Z = 2.58 (P = 0.010)							
6 24 months							
Farrokhi 2011	38	8 (2.2)	39	20 (2)		100.0 %	-5.65 [-6.67, -4.63]
Subtotal (95% CI)	**38**		**39**			**100.0 %**	**-5.65 [-6.67, -4.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 10.87 (P < 0.00001)							

Analysis 2.3. Comparison 2 Efficacy: Vertebroplasty versus usual care (open label), Outcome 3 Quality of Life (QUALEFFO).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 2 Efficacy: Vertebroplasty versus usual care (open label)

Outcome: 3 Quality of Life (QUALEFFO)



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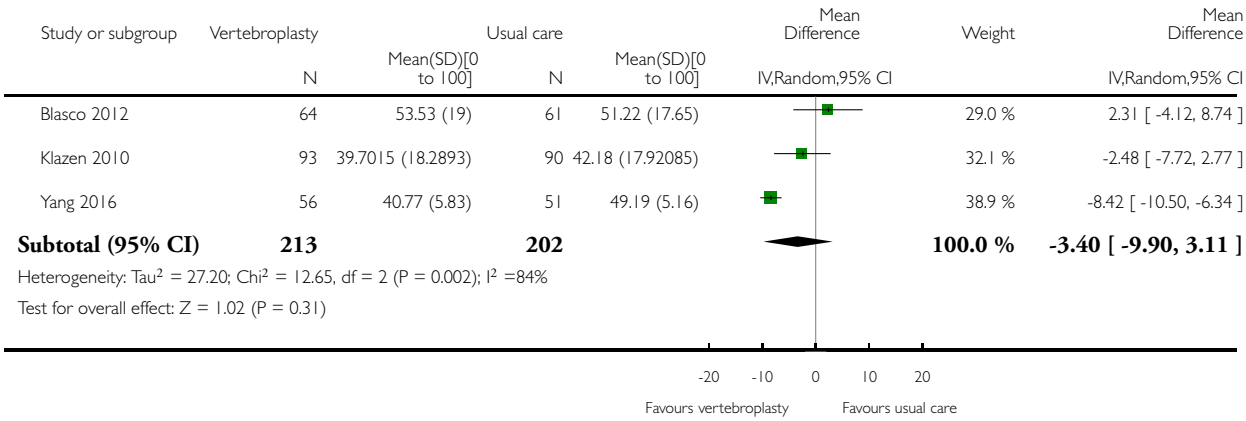
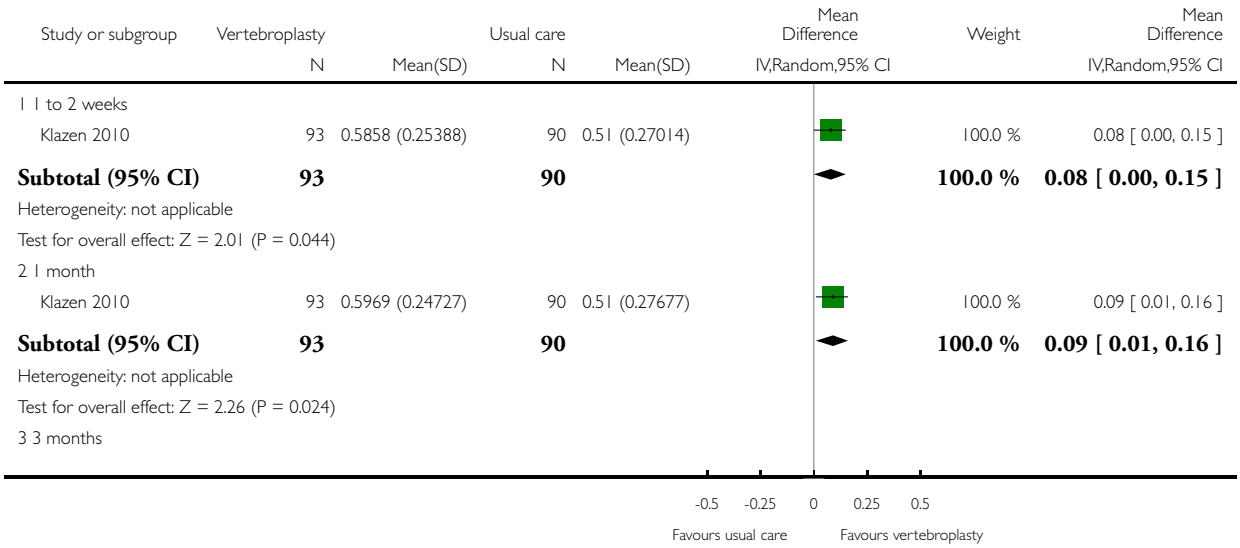


Analysis 2.4. Comparison 2 Efficacy: Vertebroplasty versus usual care (open label), Outcome 4 Quality of life (EQ5D).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 2 Efficacy: Vertebroplasty versus usual care (open label)

Outcome: 4 Quality of life (EQ5D)



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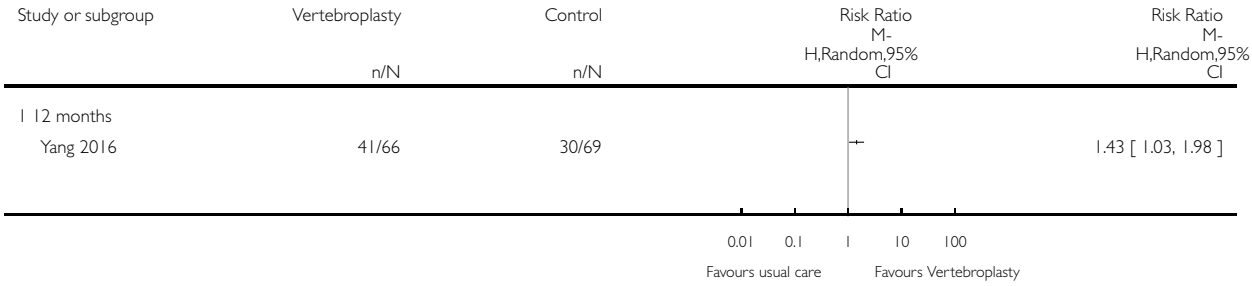
Study or subgroup	Vertebroplasty N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Klazen 2010	93	0.6459 (0.25629)	90	0.57 (0.29428)		73.7 %	0.07 [-0.01, 0.15]
Rousing 2009	15	0.731 (0.15)	17	0.54 (0.33)		26.3 %	0.19 [0.01, 0.36]
Subtotal (95% CI)	**108**		**107**			**100.0 %**	**0.10 [0.00, 0.20]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.38$, df = 1 (P = 0.24); $I^2 = 27\%$							
Test for overall effect: Z = 2.05 (P = 0.041)							
4 6 months							
Klazen 2010	93	0.6509 (0.27012)	90	0.58 (0.30254)		100.0 %	0.07 [-0.02, 0.15]
Subtotal (95% CI)	**93**		**90**			**100.0 %**	**0.07 [-0.02, 0.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.58 (P = 0.11)							
5 12 months							
Klazen 2010	93	0.6634 (0.26103)	90	0.6 (0.28551)		80.2 %	0.06 [-0.02, 0.14]
Rousing 2009	14	0.675 (0.19)	18	0.57 (0.27)		19.8 %	0.10 [-0.06, 0.26]
Subtotal (95% CI)	**107**		**108**			**100.0 %**	**0.07 [0.00, 0.14]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.24$, df = 1 (P = 0.63); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.89 (P = 0.058)							
Test for subgroup differences: $Chi^2 = 0.45$, df = 4 (P = 0.98), $I^2 = 0.0\%$							

Analysis 2.5. Comparison 2 Efficacy: Vertebroplasty versus usual care (open label), Outcome 5 Treatment success.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 2 Efficacy: Vertebroplasty versus usual care (open label)

Outcome: 5 Treatment success

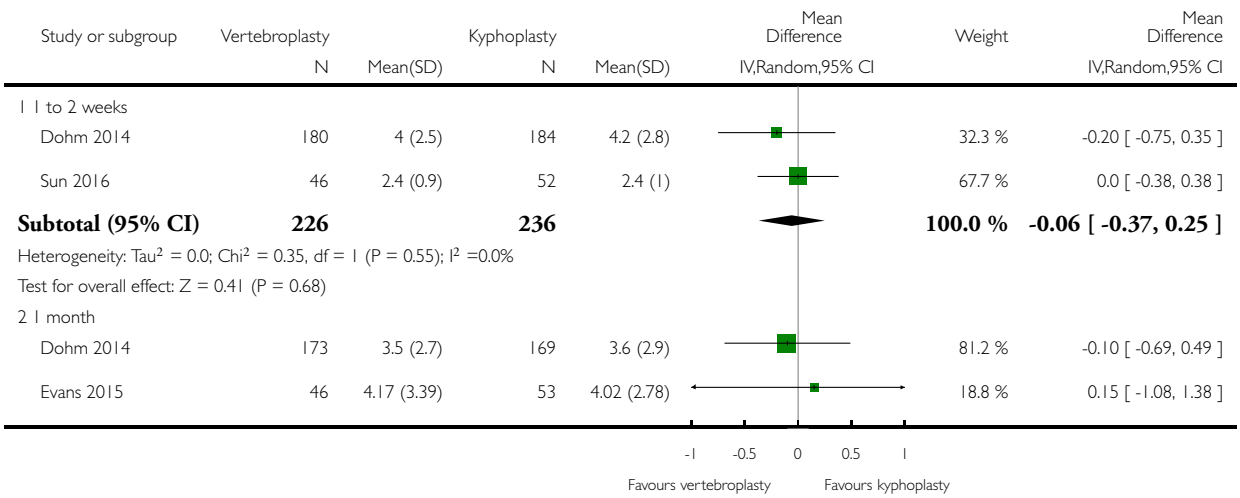


Analysis 3.1. Comparison 3 Efficacy: Vertebroplasty versus kyphoplasty (balloon), Outcome 1 Pain (0 to 10 point scale).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 3 Efficacy: Vertebroplasty versus kyphoplasty (balloon)

Outcome: 1 Pain (0 to 10 point scale)



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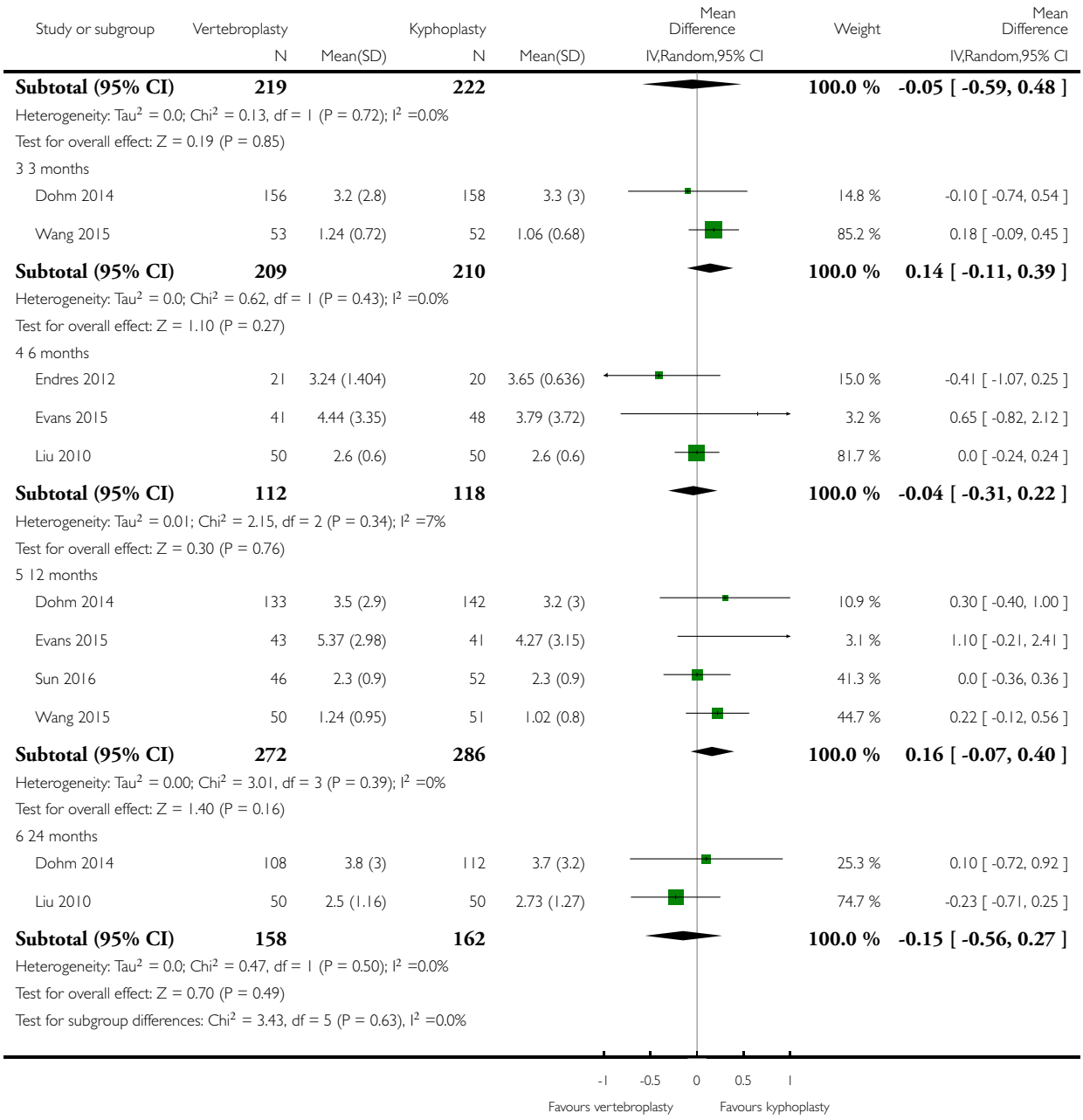
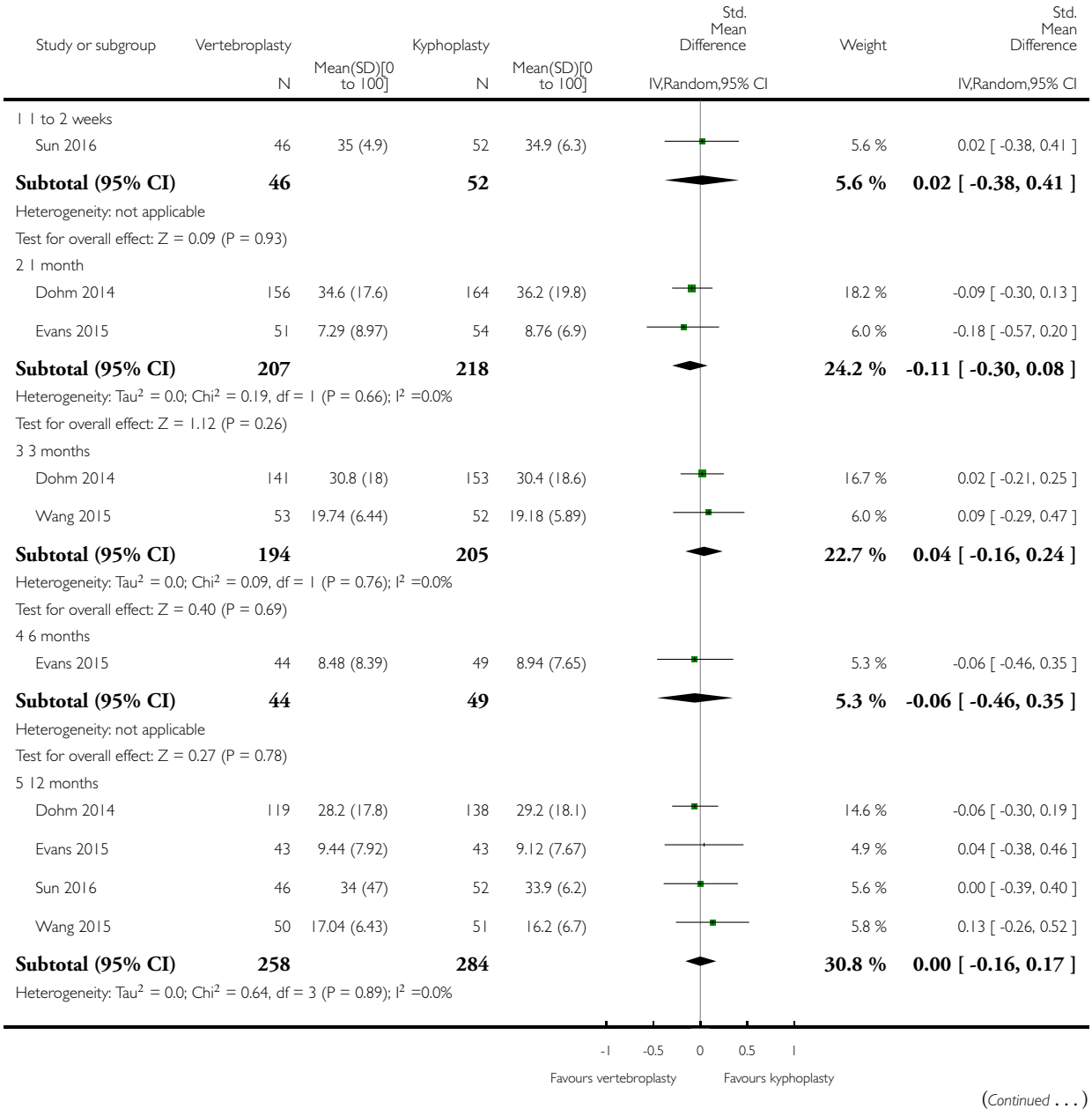


Analysis 3.2. Comparison 3 Efficacy: Vertebroplasty versus kyphoplasty (balloon), Outcome 2 Disability (ODI).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 3 Efficacy: Vertebroplasty versus kyphoplasty (balloon)

Outcome: 2 Disability (ODI)



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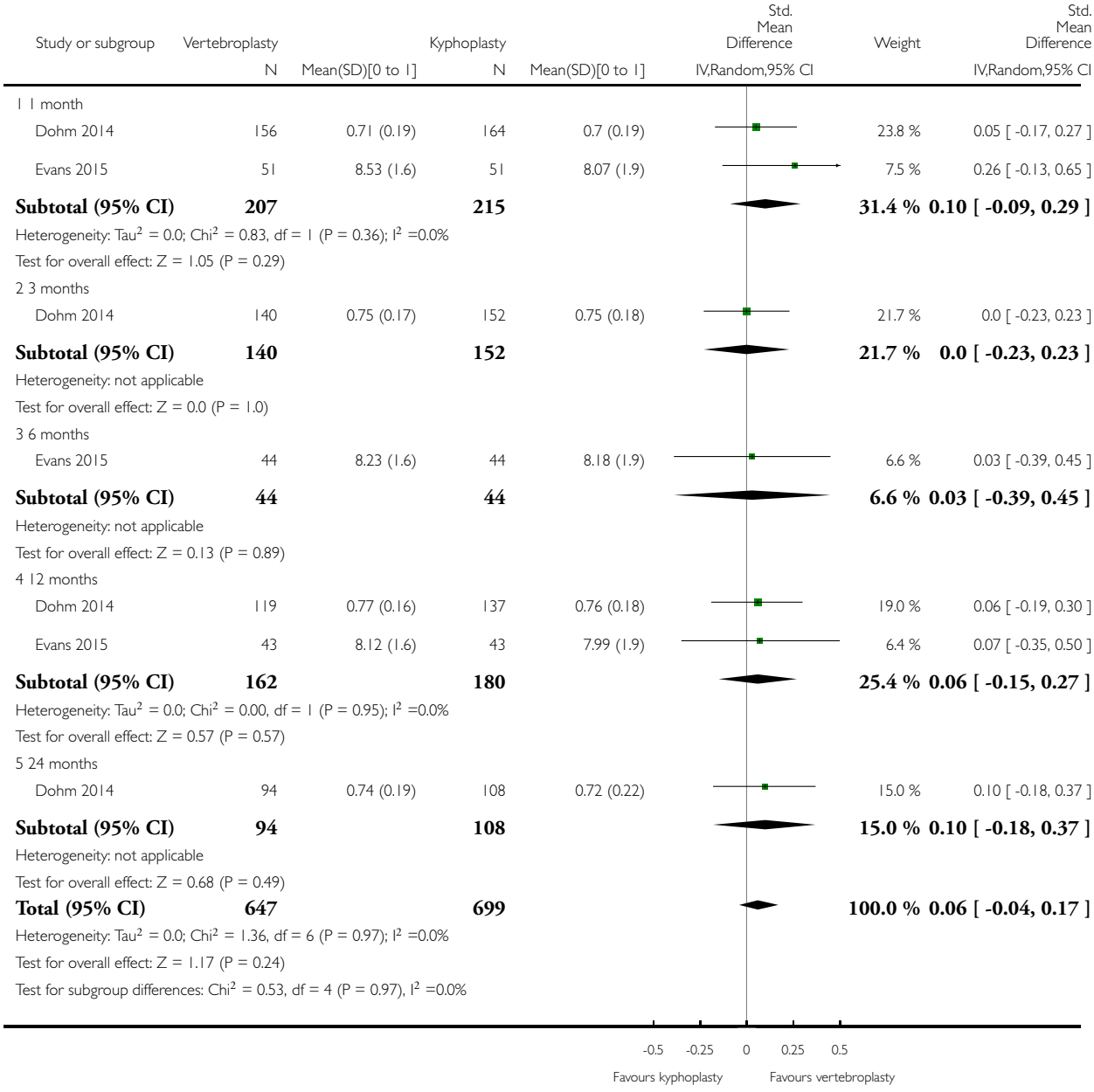
Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 100]	Kyphoplasty N	Mean(SD)[0 to 100]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Test for overall effect: Z = 0.05 (P = 0.96)							
6 24 months							
Dohm 2014	93	30.8 (17.8)	108	32.1 (19.4)		11.4 %	-0.07 [-0.35, 0.21]
Subtotal (95% CI)	**93**		**108**			**11.4 %**	**-0.07 [-0.35, 0.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.49 (P = 0.62)							
Total (95% CI)	**842**		**916**			**100.0 %**	**-0.03 [-0.12, 0.07]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.37, df = 10 (P = 0.99); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Test for subgroup differences: Chi^2 = 1.45, df = 5 (P = 0.92), I^2 =0.0%							

Analysis 3.3. Comparison 3 Efficacy: Vertebroplasty versus kyphoplasty (balloon), Outcome 3 Quality of Life (EQ5D).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 3 Efficacy: Vertebroplasty versus kyphoplasty (balloon)

Outcome: 3 Quality of Life (EQ5D)



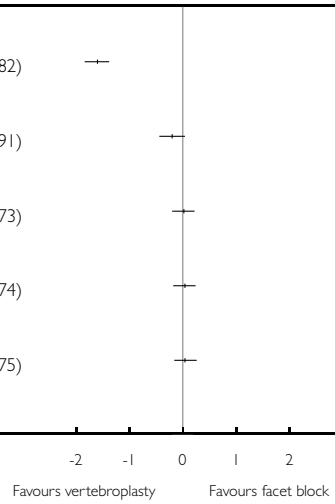
Analysis 4.1. Comparison 4 Efficacy: Vertebroplasty versus facet joint injection, Outcome 1 Pain (0 to 10 point scale).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 4 Efficacy: Vertebroplasty versus facet joint injection

Outcome: 1 Pain (0 to 10 point scale)

Study or subgroup	Vertebroplasty N	Mean(SD)	Facet block N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 1 to 2 weeks						
Wang 2016	100	1.62 (0.83)	106	3.23 (0.82)		-1.61 [-1.84, -1.38]
2 1 month						
Wang 2016	100	1.63 (0.88)	106	1.83 (0.91)		-0.20 [-0.44, 0.04]
3 3 months						
Wang 2016	100	1.45 (0.77)	106	1.44 (0.73)		0.01 [-0.20, 0.22]
4 6 months						
Wang 2016	100	1.31 (0.79)	106	1.28 (0.74)		0.03 [-0.18, 0.24]
5 12 months						
Wang 2016	100	1.19 (0.8)	106	1.15 (0.75)		0.04 [-0.17, 0.25]



Analysis 4.2. Comparison 4 Efficacy: Vertebroplasty versus facet joint injection, Outcome 2 Disability (RMDQ).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 4 Efficacy: Vertebroplasty versus facet joint injection

Outcome: 2 Disability (RMDQ)

Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 23]	Facet block N	Mean(SD)[0 to 23]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 1 to 2 weeks						
Wang 2016	100	12.52 (1.25)	106	15.94 (0.92)		-3.42 [-3.72, -3.12]
2 1 month						
Wang 2016	100	12.38 (1.25)	106	12.24 (1.21)		0.14 [-0.20, 0.48]
3 3 months						
Wang 2016	100	10.99 (1.14)	106	11.12 (1.19)		-0.13 [-0.45, 0.19]
4 6 months						
Wang 2016	100	10.49 (1.14)	106	10.48 (1.24)		0.01 [-0.32, 0.34]
5 12 months						
Wang 2016	100	9.42 (1.35)	106	9.58 (1.31)		-0.16 [-0.52, 0.20]

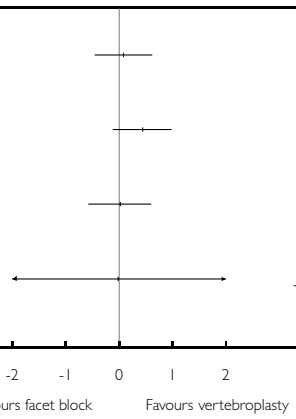
Analysis 4.3. Comparison 4 Efficacy: Vertebroplasty versus facet joint injection, Outcome 3 Quality of Life (SF-36).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 4 Efficacy: Vertebroplasty versus facet joint injection

Outcome: 3 Quality of Life (SF-36)

Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 100]	Facet block N	Mean(SD)[0 to 100]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 1 month						
Wang 2016	100	37.06 (1.64)	106	36.98 (2.28)		0.08 [-0.46, 0.62]
2 3 months						
Wang 2016	100	38.75 (1.79)	106	38.32 (2.23)		0.43 [-0.12, 0.98]
3 6 months						
Wang 2016	100	38.84 (2.14)	106	38.83 (2.2)		0.01 [-0.58, 0.60]
4 12 months						
Wang 2016	100	39.01 (12)	106	39.04 (2.29)		-0.03 [-2.42, 2.36]



Analysis 5.1. Comparison 5 Safety: Vertebroplasty versus placebo (sham) or usual care, Outcome 1 New clinical vertebral fractures.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 5 Safety: Vertebroplasty versus placebo (sham) or usual care

Outcome: 1 New clinical vertebral fractures

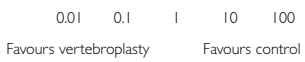
Study or subgroup	Vertebroplasty n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Blasco 2012	12/64	1/61		6.3 %	11.44 [1.53, 85.33]
Buchbinder 2009	14/29	13/28		27.2 %	1.04 [0.60, 1.80]
Chen 2014a	4/46	7/43		14.1 %	0.53 [0.17, 1.70]
Farrokhi 2011 (1)	1/38	6/39		6.0 %	0.17 [0.02, 1.35]
Leali 2016	3/185	0/200		3.2 %	7.56 [0.39, 145.47]
VERTOS IV (2)	31/91	28/89		30.5 %	1.08 [0.71, 1.65]
Yang 2016	5/56	4/51		12.7 %	1.14 [0.32, 4.01]
Total (95% CI)	**509**	**511**		**100.0 %**	**1.08 [0.62, 1.87]**

Total events: 70 (Vertebroplasty), 59 (Control)

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 11.73$, df = 6 (P = 0.07); $I^2 = 49\%$

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable



(1) Only includes new adjacent fractures

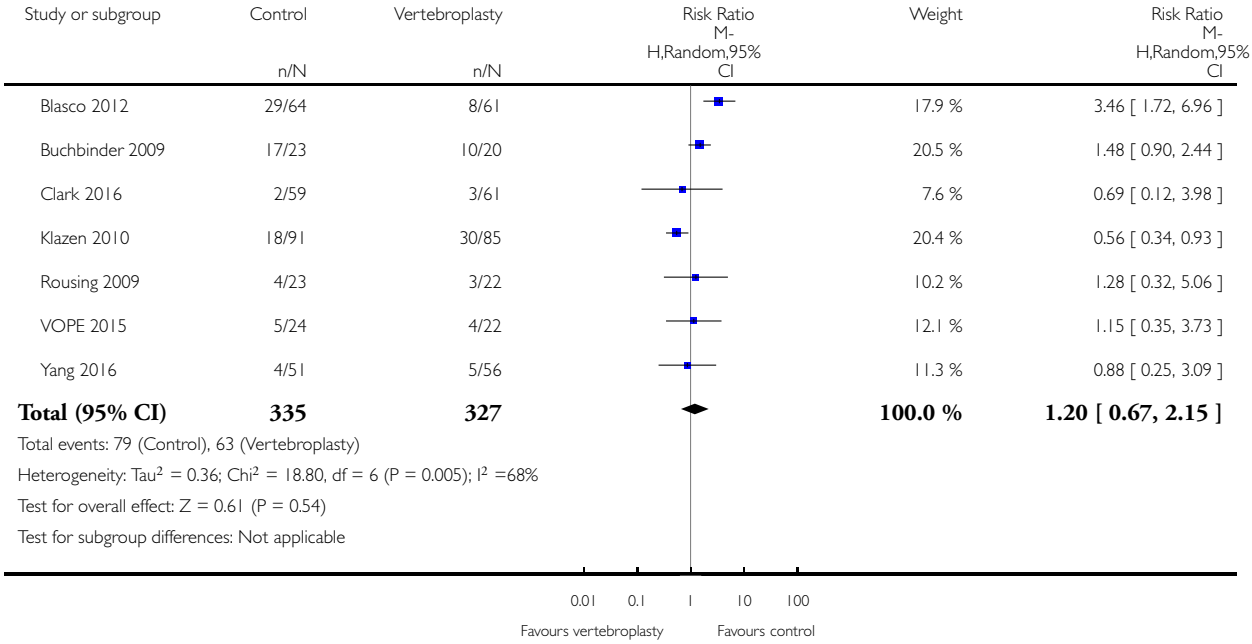
(2) Nor specified if these are clinical or radiographic fractures

Analysis 5.2. Comparison 5 Safety: Vertebroplasty versus placebo (sham) or usual care, Outcome 2 New radiographic vertebral fractures.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 5 Safety: Vertebroplasty versus placebo (sham) or usual care

Outcome: 2 New radiographic vertebral fractures



Analysis 5.3. Comparison 5 Safety: Vertebroplasty versus placebo (sham) or usual care, Outcome 3 Number of serious other adverse events.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 5 Safety: Vertebroplasty versus placebo (sham) or usual care

Outcome: 3 Number of serious other adverse events

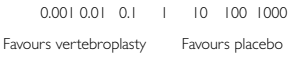
Study or subgroup	Vertebroplasty n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Buchbinder 2009	2/38	2/40		8.7 %	1.05 [0.16, 7.10]
Clark 2016	2/61	2/59		8.6 %	0.97 [0.14, 6.64]
Kallmes 2009	1/68	1/63		4.2 %	0.93 [0.06, 14.50]
Leali 2016	4/185	3/200		14.4 %	1.44 [0.33, 6.35]
Yang 2016	9/56	18/51		64.1 %	0.46 [0.23, 0.92]
Total (95% CI)	**408**	**413**		**100.0 %**	**0.64 [0.36, 1.12]**

Total events: 18 (Vertebroplasty), 26 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.57$, df = 4 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 1.57 (P = 0.12)

Test for subgroup differences: Not applicable



Analysis 6.1. Comparison 6 Safety: Vertebroplasty versus kyphoplasty, Outcome 1 New clinical vertebral fractures.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 6 Safety: Vertebroplasty versus kyphoplasty

Outcome: 1 New clinical vertebral fractures

Study or subgroup	Vertebroplasty n/N	Kyphoplasty n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 24 months				
Dohm 2014 (1)	50/190	38/191		1.32 [0.91, 1.92]

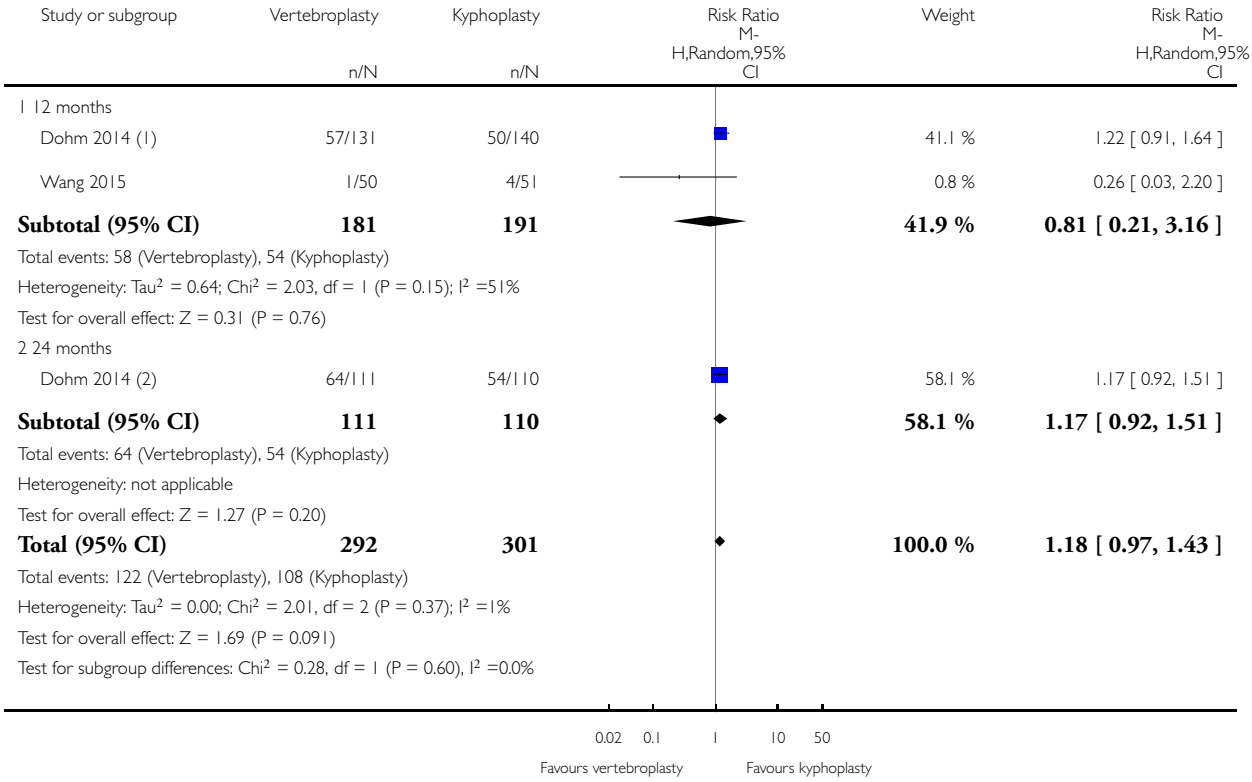
(1) For the denominator we have used the number of randomised participants in each group who received their allocated treatment..

Analysis 6.2. Comparison 6 Safety: Vertebroplasty versus kyphoplasty, Outcome 2 New radiographic vertebral fractures.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 6 Safety: Vertebroplasty versus kyphoplasty

Outcome: 2 New radiographic vertebral fractures



(1) We have reported the denominators for both groups as reported in the published paper although these differ from the number reported to have completed follow up at 12 months (130 participants in the vertebroplasty group and 143 in the kyphoplasty group)

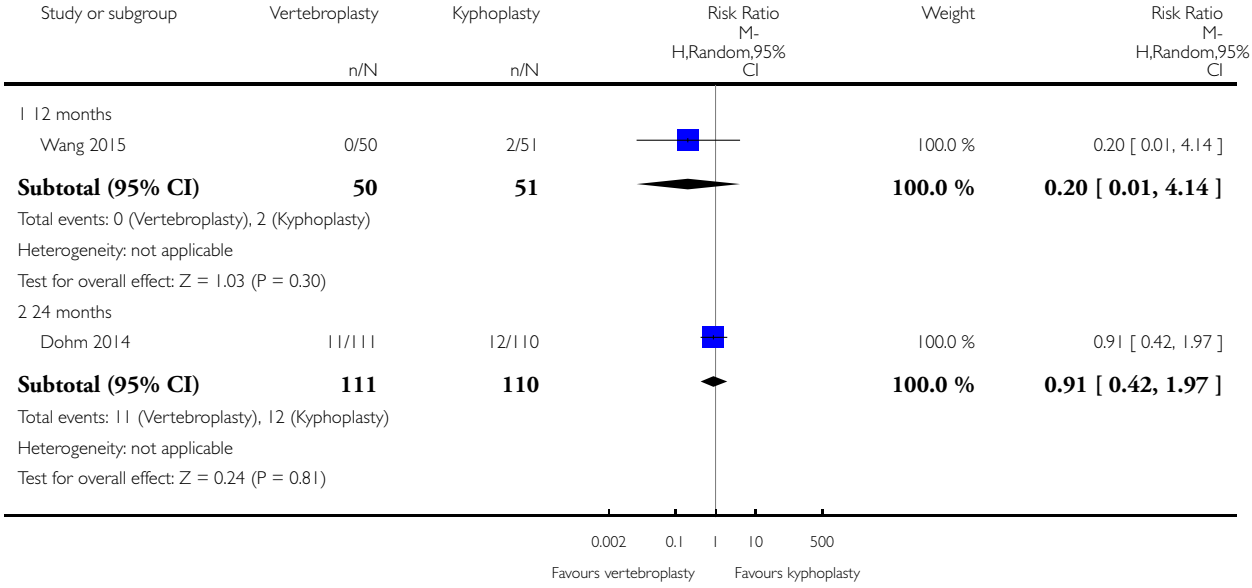
(2) We have reported the denominators for both groups as reported in the published paper although these differ from the number reported to have completed follow up at 12 months (91 participants in the vertebroplasty group and 100 in the kyphoplasty group)

Analysis 6.3. Comparison 6 Safety: Vertebroplasty versus kyphoplasty, Outcome 3 Number of serious other adverse events.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 6 Safety: Vertebroplasty versus kyphoplasty

Outcome: 3 Number of serious other adverse events



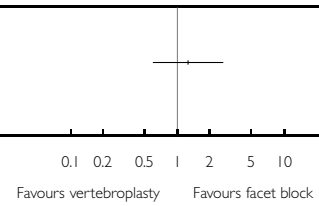
Analysis 7.1. Comparison 7 Safety: Vertebroplasty versus facet joint injection, Outcome 1 New radiographic vertebral fractures.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 7 Safety: Vertebroplasty versus facet joint injection

Outcome: 1 New radiographic vertebral fractures

Study or subgroup	Vertebroplasty n/N	Kyphoplasty n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 12 months				
Wang 2016	13/100	11/106		1.25 [0.59, 2.67]

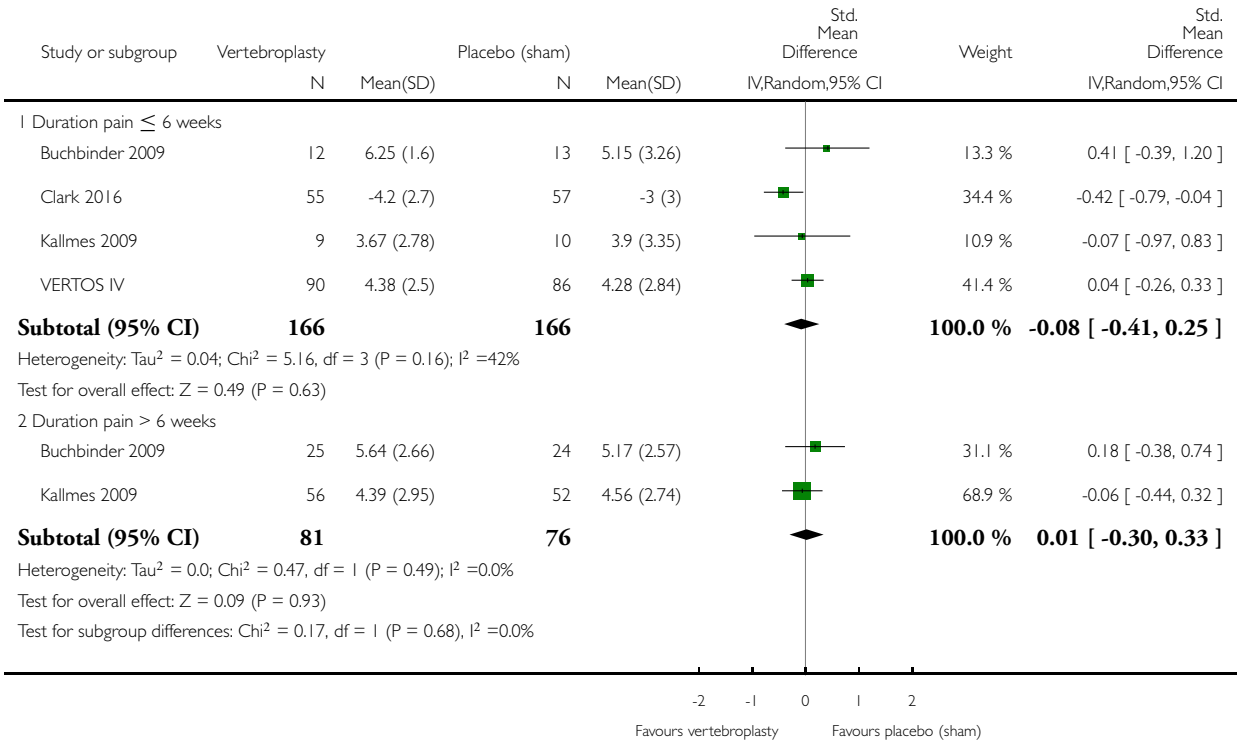


Analysis 8.1. Comparison 8 Subgroup analysis: Duration pain ≤ 6 weeks versus ¿ 6 weeks, Outcome 1 Pain at 1 to 2 weeks.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 8 Subgroup analysis: Duration pain ≤ 6 weeks versus > 6 weeks

Outcome: 1 Pain at 1 to 2 weeks



Analysis 8.2. Comparison 8 Subgroup analysis: Duration pain ≤ 6 weeks versus ¿ 6 weeks, Outcome 2 Pain at 1 month.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 8 Subgroup analysis: Duration pain ≤ 6 weeks versus > 6 weeks

Outcome: 2 Pain at 1 month

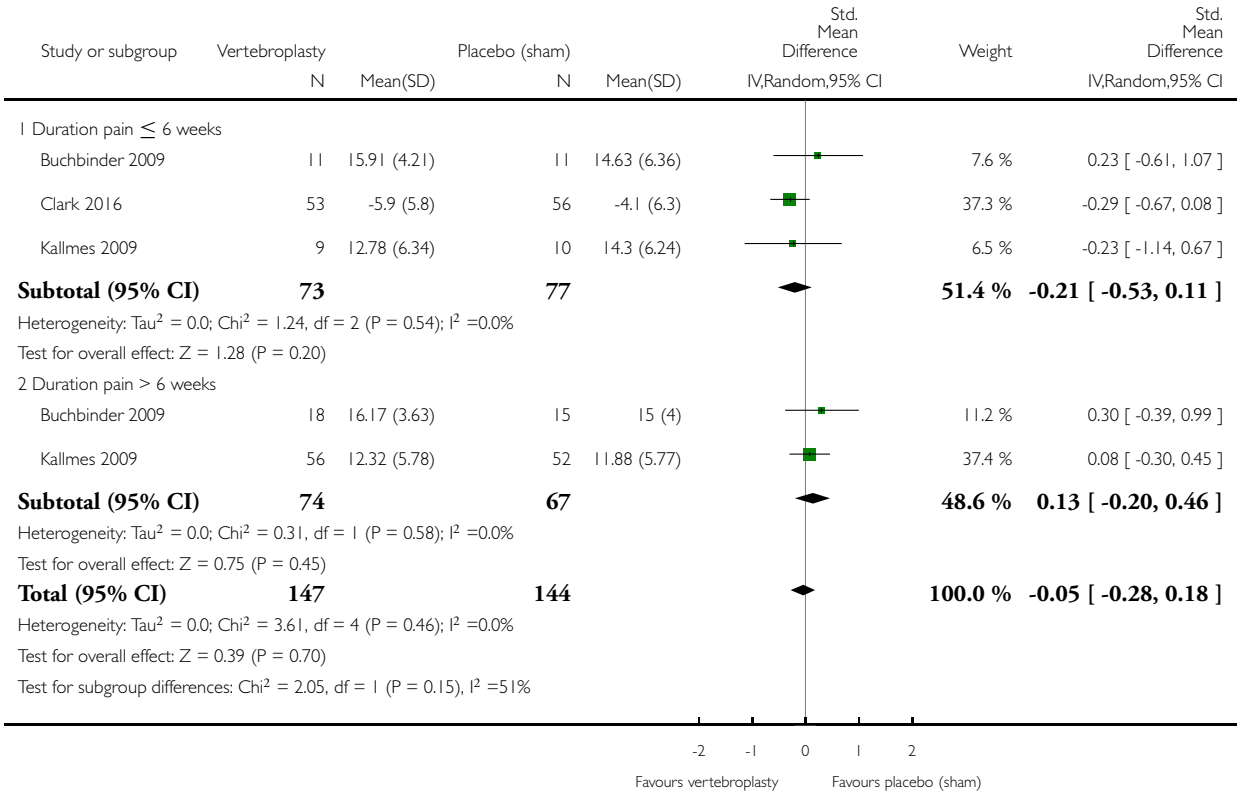
Study or subgroup	Vertebroplasty N	Mean(SD)	Placebo (sham) N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Duration pain ≤ 6 weeks							
Buchbinder 2009	12	5.08 (2.57)	13	5.08 (3.28)		5.2 %	0.0 [-0.78, 0.78]
Clark 2016	55	-4.6 (3)	57	-3.2 (2.7)		22.5 %	-0.49 [-0.86, -0.11]
Kallmes 2009	9	4 (3.04)	10	3.9 (3.7)		3.9 %	0.03 [-0.87, 0.93]
VERTOS IV	90	3.36 (2.63)	86	3.77 (2.91)		36.3 %	-0.15 [-0.44, 0.15]
Subtotal (95% CI)	**166**		**166**			**67.9 %**	**-0.24 [-0.46, -0.02]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.74, df = 3 (P = 0.43); I^2 =0.0%							
Test for overall effect: Z = 2.16 (P = 0.031)							
2 Duration pain > 6 weeks							
Buchbinder 2009	23	4.87 (2.1)	25	5.56 (3)		9.8 %	-0.26 [-0.83, 0.31]
Kallmes 2009	58	3.83 (2.91)	51	4.71 (2.83)		22.2 %	-0.30 [-0.68, 0.07]
Subtotal (95% CI)	**81**		**76**			**32.1 %**	**-0.29 [-0.61, 0.02]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%							
Test for overall effect: Z = 1.81 (P = 0.071)							
Total (95% CI)	**247**		**242**			**100.0 %**	**-0.26 [-0.43, -0.08]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.83, df = 5 (P = 0.73); I^2 =0.0%							
Test for overall effect: Z = 2.81 (P = 0.0050)							
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.79), I^2 =0.0%							

Analysis 8.3. Comparison 8 Subgroup analysis: Duration pain ≤ 6 weeks versus ¿ 6 weeks, Outcome 3 Disability at 1 to 2 weeks.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 8 Subgroup analysis: Duration pain ≤ 6 weeks versus > 6 weeks

Outcome: 3 Disability at 1 to 2 weeks

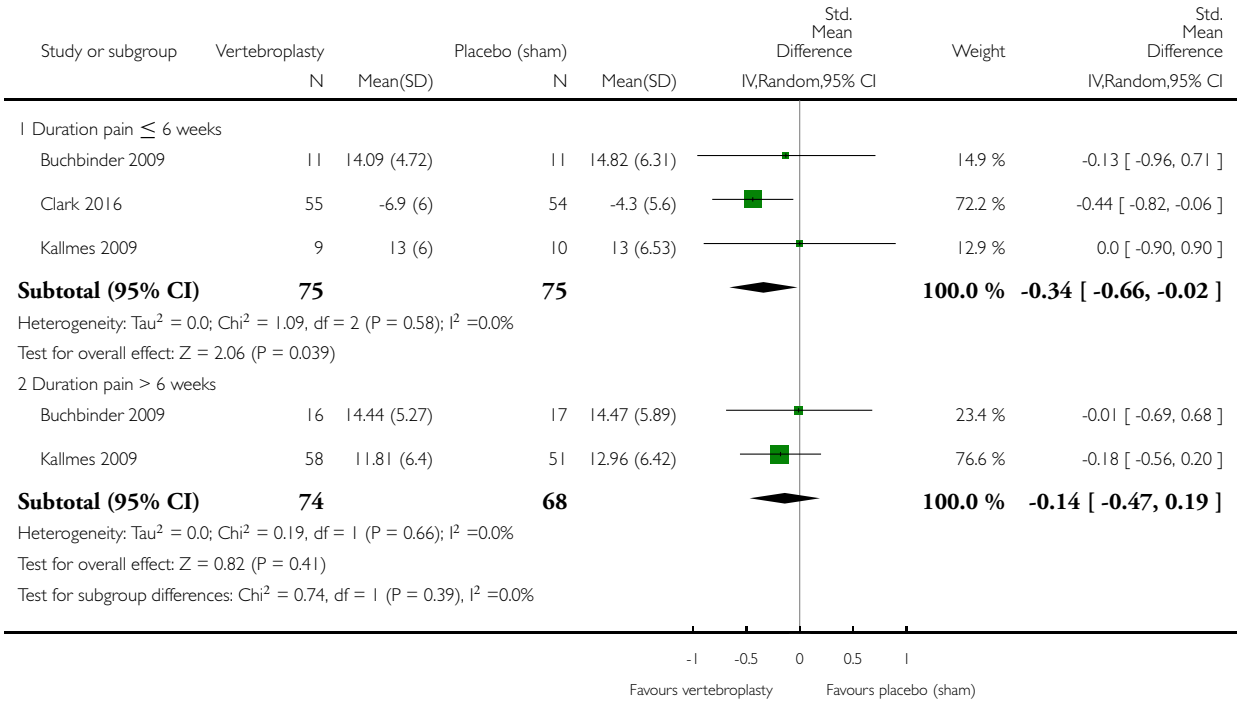


Analysis 8.4. Comparison 8 Subgroup analysis: Duration pain ≤ 6 weeks versus ¿ 6 weeks, Outcome 4 Disability at 1 month.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 8 Subgroup analysis: Duration pain ≤ 6 weeks versus > 6 weeks

Outcome: 4 Disability at 1 month

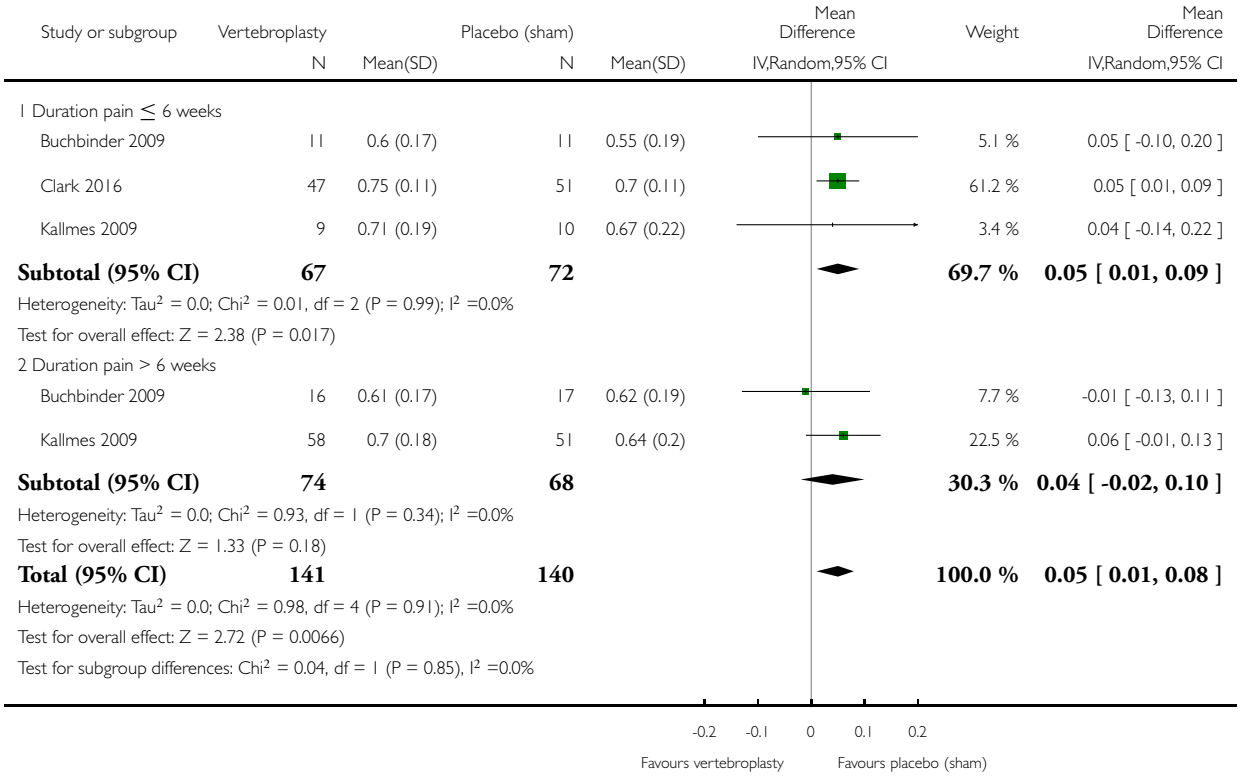


Analysis 8.5. Comparison 8 Subgroup analysis: Duration pain ≤ 6 weeks versus ¿ 6 weeks, Outcome 5 Quality of life (EQ-5D) at 1 month.

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 8 Subgroup analysis: Duration pain ≤ 6 weeks versus > 6 weeks

Outcome: 5 Quality of life (EQ-5D) at 1 month



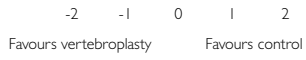
Analysis 9.1. Comparison 9 Sensitivity analysis, Outcome 1 Pain at 1 to 2 weeks (0 or 1 to 10 point scale).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 9 Sensitivity analysis

Outcome: 1 Pain at 1 to 2 weeks (0 or 1 to 10 point scale)

Study or subgroup	Vertebroplasty N	Mean(SD)[0 to 10]	Control N	Mean(SD)[0 to 10]	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Sham (placebo) control							
Buchbinder 2009	37	-1.5 (2.5)	37	-2.1 (2.8)		9.1 %	0.22 [-0.23, 0.68]
Clark 2016	55	-4.2 (2.7)	57	-3 (3)		9.3 %	-0.42 [-0.79, -0.04]
Kallmes 2009	68	4.3 (2.9)	63	4.5 (2.8)		9.4 %	-0.07 [-0.41, 0.27]
VERTOS IV	90	4.38 (2.5)	86	4.28 (2.84)		9.5 %	0.04 [-0.26, 0.33]
VOPE 2015	22	28.52 (21.8105)	24	34.83 (21.8005)		8.8 %	-0.28 [-0.87, 0.30]
Subtotal (95% CI)	**272**		**267**			**46.0 %**	**-0.09 [-0.30, 0.12]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.89$, df = 4 (P = 0.21); $I^2 = 32\%$							
Test for overall effect: Z = 0.83 (P = 0.41)							
2 Usual care (open label) control							
Blasco 2012	64	5.84 (3.55)	61	4.8 (3.15)		9.4 %	0.31 [-0.05, 0.66]
Chen 2014a	46	3.4 (0.5)	43	5 (0.7)		8.8 %	-2.62 [-3.20, -2.05]
Farrokhi 2011	40	3.3 (1.5)	42	6.4 (2.1)		9.0 %	-1.68 [-2.18, -1.17]
Klazen 2010	97	3.5 (2.5)	93	5.6 (2.5)		9.5 %	-0.84 [-1.13, -0.54]
Voormolen 2007	18	4.94 (2.92)	16	6.44 (1.75)		8.4 %	-0.60 [-1.29, 0.09]
Yang 2016	56	3.4 (1)	51	6.39 (1.29)		8.9 %	-2.59 [-3.11, -2.07]
Subtotal (95% CI)	**321**		**306**			**54.0 %**	**-1.33 [-2.26, -0.39]**
Heterogeneity: $Tau^2 = 1.30$; $Chi^2 = 128.88$, df = 5 (P<0.00001); $I^2 = 96\%$							
Test for overall effect: Z = 2.78 (P = 0.0054)							
Total (95% CI)	**593**		**573**			**100.0 %**	**-0.76 [-1.30, -0.22]**
Heterogeneity: $Tau^2 = 0.79$; $Chi^2 = 189.76$, df = 10 (P<0.00001); $I^2 = 95\%$							
Test for overall effect: Z = 2.74 (P = 0.0062)							
Test for subgroup differences: $Chi^2 = 6.40$, df = 1 (P = 0.01), $I^2 = 84\%$							



Analysis 9.2. Comparison 9 Sensitivity analysis, Outcome 2 Pain at 1 month (0 or 1 to 10 point scale).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 9 Sensitivity analysis

Outcome: 2 Pain at 1 month (0 or 1 to 10 point scale)

Study or subgroup	Vertebroplasty N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Sham (placebo) control							
Buchbinder 2009	35	-2.3 (2.6)	38	-1.7 (3.3)		12.4 %	-0.20 [-0.66, 0.26]
Clark 2016	55	-4.6 (3)	57	-3.2 (2.7)		12.7 %	-0.49 [-0.86, -0.11]
Kallmes 2009	67	3.9 (2.9)	61	4.6 (3)		12.8 %	-0.24 [-0.58, 0.11]
VERTOS IV	90	3.36 (2.63)	86	3.77 (2.91)		13.0 %	-0.15 [-0.44, 0.15]
VOPE 2015	22	17.33 (21.81)	24	26.27 (22.29)		11.9 %	-0.40 [-0.98, 0.19]
Subtotal (95% CI)	**269**		**266**			**62.9 %**	**-0.27 [-0.44, -0.10]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.26, df = 4 (P = 0.69); I^2 =0.0%							
Test for overall effect: Z = 3.07 (P = 0.0021)							
2 Usual care (open label) control							
Chen 2014a	46	2.8 (0.4)	43	4 (0.6)		12.1 %	-2.35 [-2.89, -1.80]
Klazen 2010	96	2.5 (2.5)	92	4.9 (2.6)		13.0 %	-0.94 [-1.24, -0.64]
Yang 2016	56	2.39 (0.7)	51	4.9 (0.99)		12.1 %	-2.93 [-3.48, -2.38]
Subtotal (95% CI)	**198**		**186**			**37.1 %**	**-2.06 [-3.35, -0.76]**
Heterogeneity: Tau^2 = 1.26; Chi^2 = 48.10, df = 2 (P<0.00001); I^2 =96%							
Test for overall effect: Z = 3.10 (P = 0.0019)							
Total (95% CI)	**467**		**452**			**100.0 %**	**-0.94 [-1.55, -0.34]**
Heterogeneity: Tau^2 = 0.71; Chi^2 = 127.34, df = 7 (P<0.00001); I^2 =95%							
Test for overall effect: Z = 3.05 (P = 0.0023)							
Test for subgroup differences: Chi^2 = 7.17, df = 1 (P = 0.01), I^2 =86%							

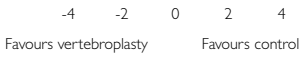
Analysis 9.3. Comparison 9 Sensitivity analysis, Outcome 3 Pain at 3 months (0 or 1 to 10 point scale).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 9 Sensitivity analysis

Outcome: 3 Pain at 3 months (0 or 1 to 10 point scale)

Study or subgroup	Vertebroplasty N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Sham (placebo) control							
Buchbinder 2009	36	-2.6 (2.9)	37	-1.9 (3.3)		10.0 %	-0.22 [-0.68, 0.24]
Clark 2016	53	-5.4 (3.5)	52	-4.1 (3.1)		10.2 %	-0.39 [-0.78, 0.00]
VERTOS IV	87	2.79 (2.42)	83	3.05 (2.88)		10.5 %	-0.10 [-0.40, 0.20]
VOPE 2015	22	16.09 (21.34)	24	18.7 (21.8)		9.5 %	-0.12 [-0.70, 0.46]
Subtotal (95% CI)	**198**		**196**			**40.3 %**	**-0.20 [-0.40, 0.00]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.46$, df = 3 (P = 0.69); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.98 (P = 0.048)							
2 Usual care (open label) control							
Blasco 2012	64	4.12 (3.37)	61	4.7 (3.11)		10.4 %	-0.18 [-0.53, 0.17]
Chen 2014a	46	2.5 (0.5)	43	3.9 (0.7)		9.7 %	-2.29 [-2.83, -1.75]
Farrokhi 2011	40	3.2 (2.2)	42	6.1 (2.1)		9.9 %	-1.34 [-1.82, -0.86]
Klazen 2010	92	2.5 (2.7)	86	3.9 (2.8)		10.5 %	-0.51 [-0.81, -0.21]
Rousing 2009	23	1.8 (2.45)	23	2.6 (3.43)		9.5 %	-0.26 [-0.84, 0.32]
Yang 2016	56	2.09 (0.59)	51	3.89 (0.81)		9.8 %	-2.54 [-3.05, -2.03]
Subtotal (95% CI)	**321**		**306**			**59.7 %**	**-1.18 [-1.95, -0.40]**
Heterogeneity: $Tau^2 = 0.89$; $Chi^2 = 95.33$, df = 5 (P<0.00001); $I^2 = 95\%$							
Test for overall effect: Z = 2.97 (P = 0.0030)							
Total (95% CI)	**519**		**502**			**100.0 %**	**-0.78 [-1.28, -0.29]**
Heterogeneity: $Tau^2 = 0.59$; $Chi^2 = 125.83$, df = 9 (P<0.00001); $I^2 = 93\%$							
Test for overall effect: Z = 3.09 (P = 0.0020)							
Test for subgroup differences: $Chi^2 = 5.69$, df = 1 (P = 0.02), $I^2 = 82\%$							

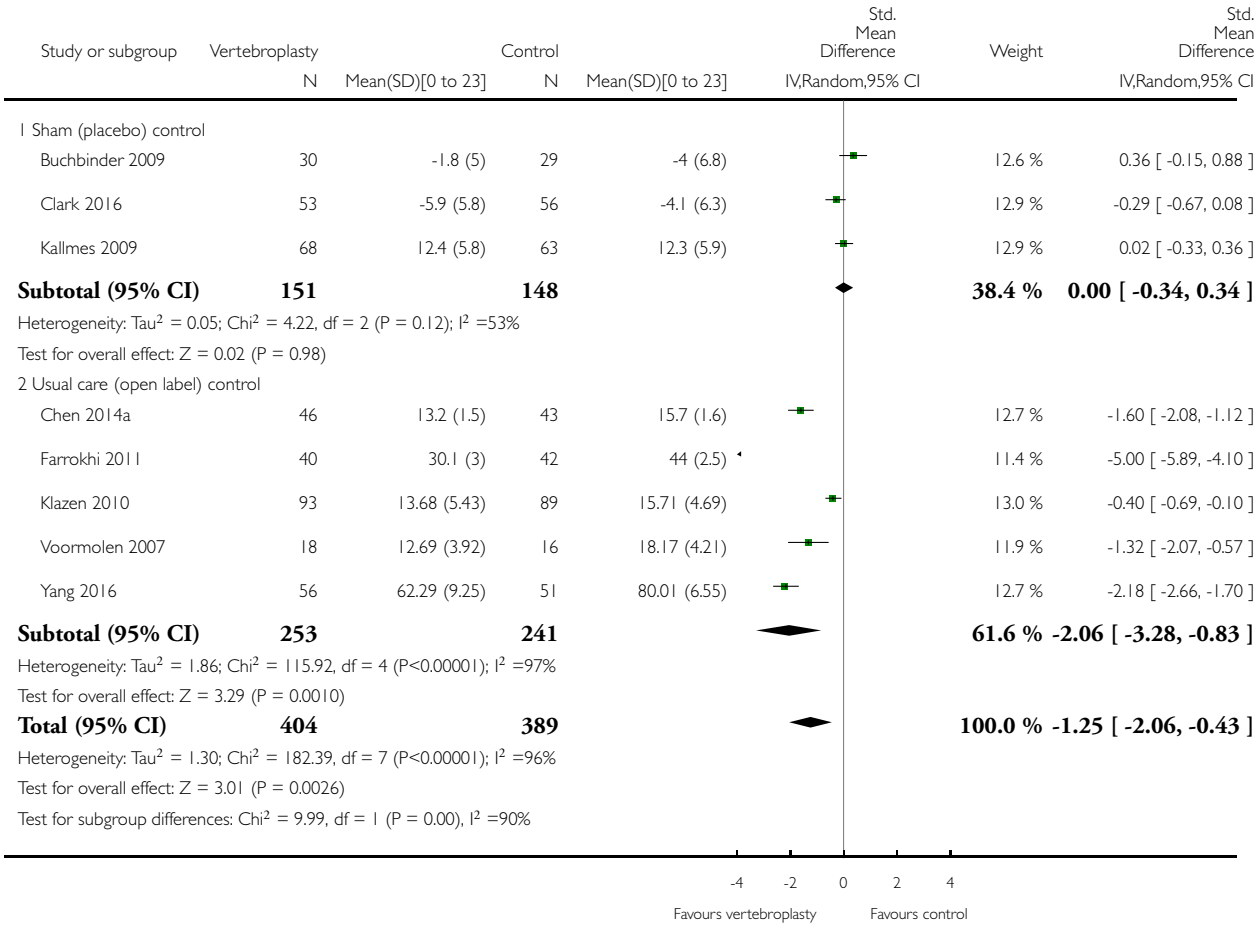


Analysis 9.4. Comparison 9 Sensitivity analysis, Outcome 4 Disability at 1 to 2 weeks (RMDQ [0 to 24] or ODI [0 to 100])).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 9 Sensitivity analysis

Outcome: 4 Disability at 1 to 2 weeks (RMDQ [0 to 24] or ODI [0 to 100]))

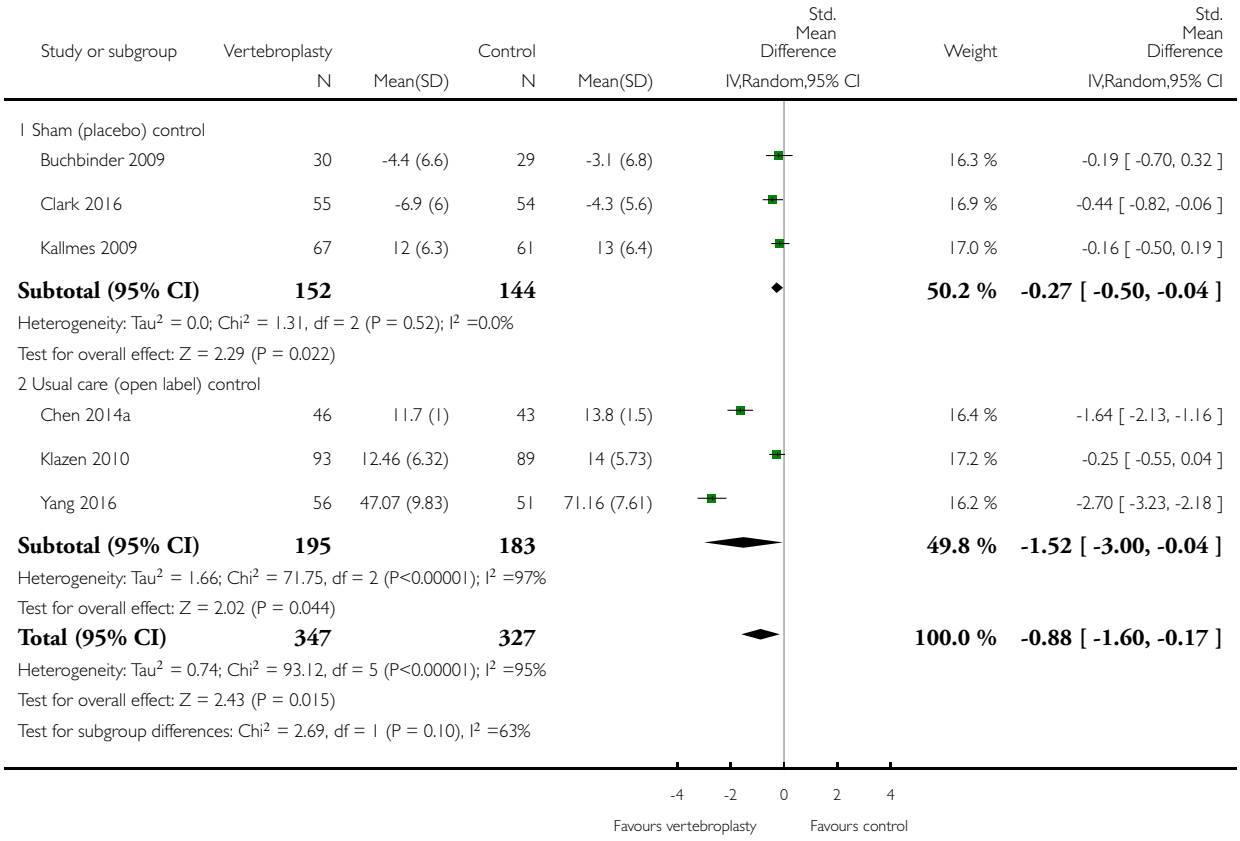


Analysis 9.5. Comparison 9 Sensitivity analysis, Outcome 5 Disability at 1 month (RMDQ [0 to 24] or ODI [0 to 100]).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 9 Sensitivity analysis

Outcome: 5 Disability at 1 month (RMDQ [0 to 24] or ODI [0 to 100])

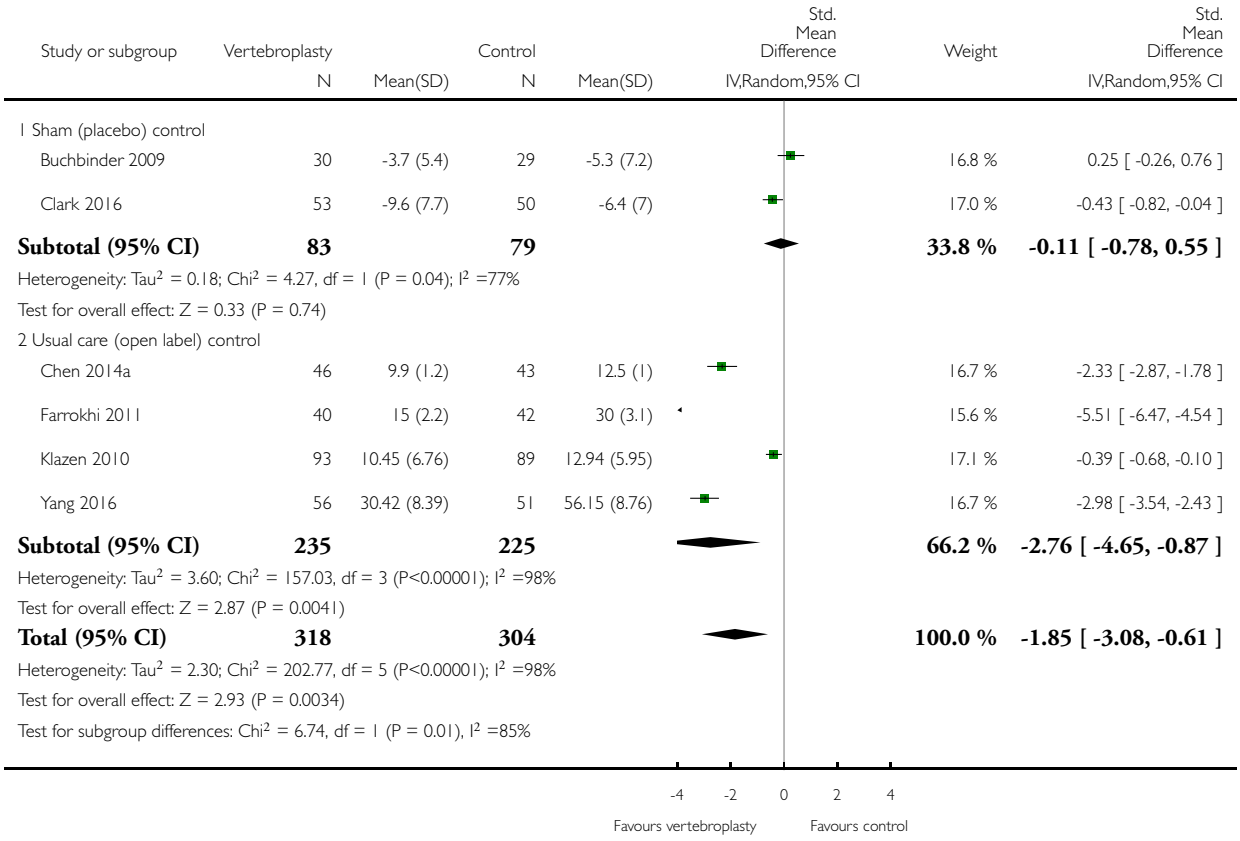


Analysis 9.6. Comparison 9 Sensitivity analysis, Outcome 6 Disability at 3 months (RMDQ [0 to 24] or ODI [0 to 100]).

Review: Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

Comparison: 9 Sensitivity analysis

Outcome: 6 Disability at 3 months (RMDQ [0 to 24] or ODI [0 to 100])



ADDITIONAL TABLES

Table 1. Study characteristics of unpublished, ongoing and suspended or terminated trials

Trial registration number	Principle Investigator/s and Country	Comparator/s	Main selection criteria	Registration date	Recruitment commenced	Status 8 January 2018	Planned sample size	Final sample size

Table 1. Study characteristics of unpublished, ongoing and suspended or terminated trials (*Continued*)

NCT0074900 'OSTEO-6'	Laredo JD France	Kyphoplasty; Usual care with or without brace	Age ≥ 50 years Fracture ¡ 6 weeks	8 Sept 2008	Dec 2007	Completed June 2012; results unpublished	300	48
NCT0074908 'STIC2'	Laredo JD France	Kyphoplasty	Age ≥ 50 years Fracture ¿ 6 weeks	8 Sept 2008	Dec 2007	Completed June 2012; results unpublished	200	97
NCT0020355	Sorensen L Denmark	Usual care	Fracture ¡ 6 months	16/09/2005	Mar 2004	Completed Jan 2008; results unpublished	27	27
IS-RCTN14442((Also N021311241	Dolin, S UK	Usual care	Fracture ¿ 4 weeks	12 Sep 2003	Nov 28 2005	Completed (last updated 6 Feb 2014) ; results unpublished	Not provided	Not provided
NCT0167780	Sun G China	Usual care	Age ≥ 50 years Fracture ¡ 6 weeks	23 Aug 2012	Oct 2012	Recruitment status unknown (last updated 11 Sep 2014)	114	-
Registration details not found.	Longo UG Italy	3 weeks bed rest, rigid hyperextension corset, followed by 2-3 months in a Cheneau brace (called 'double-blind)	Age ≥ 50 years	Trial registration not found	Unknown	Unknown (protocol published)	200	-
NCT0196303 'VERTOS V'	Carli D the Netherlands	Sham	Age ≥ 50 years Fracture ≥ 12 weeks	28 Aug 2013	May 2013	Previously reported as completed (Nov 2015) then recruiting again (Feb 2017)	94	-

Table 1. Study characteristics of unpublished, ongoing and suspended or terminated trials (*Continued*)

						(protocol published)		
Record of trial registration not found	Chen JP China	Usual care	Not available	Trial registration not found	Unknown	Completed; study awaiting translation	Unknown	84
Record of trial registration not found	Li DH China	Kyphoplasty Bone filling mesh container	Not available	Trial registration not found	Unknown	Completed; study awaiting translation	Unknown	90
Record of trial registration not found	Tan B China	Kyphoplasty	Not available	Trial registration not found	Unknown	Completed; study awaiting translation	Unknown	106
Record of trial registration not found	Zhou W China	Kyphoplasty	Not available	Trial registration not found	Unknown	Completed; study awaiting translation	Unknown	80

* Abstract reported that analysis favoured vertebroplasty at 1 day and 1 week for pain, and disability measured by RMDQ and ODI (data not provided), but no evidence of important differences between groups at 1, 3, 6, 12 months for pain, RMDQ, ODI and SF-36 function and SF-36 physical and mental component scores. After 12 months follow-up, there were 13 new fractures in the percutaneous vertebroplasty group and 11 new fractures in the facet joint block group. Abstract did not report method of randomisation, whether or not treatment allocation was concealed and whether or not participants and investigators were blinded to treatment allocation.

Table 2. Baseline demographic and clinical characteristics of the trial participants

Study	Country	Treatment Groups	Mean age, yrs	Mean symptom duration	Mean (SD) baseline pain (0-10 scale [$])	Mean (SD) baseline RMDQ[+] (0-24 scale[†])	Mean (SD) baseline QUALEFFO (0-100 scale)	Procedures performed by	Mean (range) volume cement injected (mL)	Follow-up
Blasco 2012	Spain	Vertebroplasty	71.3	140.3 days	7.2 (0.3)	-	65.2 (2.2)	Interventional radiologists	Not specified	2 weeks, 2, 6, 12 months
		Usual care	71.3	143.1 days	6.3 (0.4)	-	59.2 (2.2)			

Table 2. Baseline demographic and clinical characteristics of the trial participants (*Continued*)

Buchbinder 2009	Australia	Vertebroplasty	74.2	9 weeks^	7.4 (2.1)	17.3 (2.8)	56.9 (13.4)	Interventional radiologists	2.8 (1.2 - 5.5)	1 week, 1, 3, 6, 12, 24 months
		Placebo	78.9	9.5 weeks^	7.1 (2.3)	17.3 (2.9)	59.6 (17.1)			
Clark 2016	Australia	Vertebroplasty	80	2.8 weeks	8.1 (1.8)	19.5 (3.5)	65.4 (11.4)	Interventional radiologists	7.5 (4.7 - 10.3)	3 days, 14 days, 1, 3 and 6 months
		Placebo	81	2.4 weeks	8.2 (1.5)	19.8 (3.7)	67.7 (11.2)			
Chen 2014a	China	Vertebroplasty	64.6	31 weeks	6.5 (0.9) &	18.6 (1.8) #&	-	Orthopaedic surgeons	3.6 (3 - 6)	1 day, 1 week, 1, 3, 6, 12 months
		Usual care and brace	66.5	29.5 weeks	6.4 (0.9) &	16.7 (1.3) #&	-			
Dohm 2014	USA and Canada	Vertebroplasty	75.7	-¤	~7.6µ	-	-	Interventional radiologists and neuroradiologists, orthopaedic surgeons, neuroradiologists	4.0 (3.0 to 6.0)¢	7 days, 1, 3, 12 and 24 months
		Balloon kyphoplasty	75.5	-¤	~7.6µ	-	-	Not stated	4.6 (3.4 to 6.0)¢	
Endres 2012	Germany	Vertebroplasty	71.3	-§	7.8 (0.9)	-	-	Orthopaedic surgeon	3.1 (2 - 4)	Immediately, mean 5.8 months (range: 4 to 7)

Table 2. Baseline demographic and clinical characteristics of the trial participants (*Continued*)

		Balloon kyphoplasty	63.3	-[§]	9.0 (0.7)	-	-	Orthopaedic surgeon	3.9 (3 - 5)	
		Shield kyphoplasty	67.1	-[§]	8.8 (1.5)	-	-	Orthopaedic surgeon	4.6 (3 - 6)	
Evans 2015	USA	Vertebroplasty	76.1	-	7.9 (2.0)	16.3 (7.4)	-	Not reported	Not reported	3 days, 1, 6 and 12 months
		Kyphoplasty	75.1	-	7.4 (1.9)	17.3 (6.6)	-	Not reported	Not reported	
Farrokhi 2011	Iran	Vertebroplasty	72	27 weeks	8.4 (1.6)	-	-	Neurosurgeons	3.5 (1 - 5.5)	1 week, 2, 6, 12, 24, 36 months
		Usual care	74	30 weeks	7.2 (1.7)	-	-			
Kallmes 2009	US, UK, Australia	Vertebroplasty	73.4	16 weeks	6.9 (2.0)	16.6 (3.8)	-	Interventional radiologists	2.8 (1 - 5.5)*	3 days, 2 weeks, 1 month
		Placebo	73.3	20 weeks	7.2 (2.0)	17.5 (4.1)	-			
Klazen 2010	the Netherlands, Belgium	Vertebroplasty	75.2	29.3 days	7.8 (1.5)	18.6 (3.6)[#]	58.7 (13.5)	Interventional radiologists	4.1 (1 - 9)	1 day, 1 week, 1, 3, 6, 12 months
		Usual care	75.4	26.8 days	7.5 (1.6)	17.2 (4.2)[#]	54.7 (14.4)			
Leali 2016	Italy	Vertebroplasty	-	-[§]	4.8 (-)	53.6 (-)	-	Not reported	4 (-)	1 and 2 days, 6 weeks, 3 and 6 months
		Usual care	-	-[§]	-[§]	-	-	Not reported		
Liu 2010	Taiwan	Vertebroplasty	74.3	15.8 days	7.9 (0.7)	-	-	Not reported	4.9 (0.7)	3 days, 6 months,

Table 2. Baseline demographic and clinical characteristics of the trial participants (*Continued*)

										1, 3 and 5 years
		Balloon kypho-plasty	72.3	17.0 days	8.0 (0.8)	-	-	Not reported	5.6 (0.6)	
Rousing 2009	Denmark	Vertebro-plasty	80	8.4 days	7.5 (2.0)	-	-	Or-thopaedic surgeons	Not reported	3 months
		Usual care and brace	80	6.7 days	8.8 (1.2)	-	-			
Sun 2016	China	Vertebro-plasty	65.4	-	8.5 (1.1)	70.6 (8.6) ×	-	Not reported	3.4 (0.3)	2 days, 12 months
		Kypho-plasty	65.2	-	8.2 (0.9)	71.7(8.5) ×	-	Not reported	4.2 (0.2)	
VERTOS IV	the Nether-lands	Vertebro-plasty	74.7	29.2 days	7.7 (1.4)	18 (4.5)	68.4 (17. 1)	Not reported	5.11 (1 - 11)	1 day, 1 week, 1, 3, 6, 12 months
		Placebo	76.8	25.9 days	7.9 (1.6)	17.8 (4.7)	69.7 (17. 9)			
Vogl 2013	Germany and USA	Vertebro-plasty	74	-¥	8.5 (1.2)	-	-	Not reported	4.0 (1.1)	1 day, 3 and 12 months
		Shield kypho-plasty	80	-¥	8.3 (1.1)	-	-	Not reported	3.8 (0.7)	
Voor-molen 2007	the Nether-lands	Vertebro-plasty	72	85 days	7.1 (5 - 9) +	15.7 (8-24)	60.0 (37 to 86)	Interven-tional ra-diologists	3.2 (1.0 - 5.0)	2 weeks
		Usual care	74	76 days	7.6 (5-10)	17.8 (8-22)	60.7 (38 to 86)			
VOPE 2015	Denmark	Vertebro-plasty	70.6	-a	7.47 ()	-	-	Or-thopaedic surgeons	Not reported-	6 hours, weekly to 3 months,

Table 2. Baseline demographic and clinical characteristics of the trial participants (*Continued*)

										12 months
		Placebo (lidocaine injected)	69.3	-[a]	7.61 ()	-	-	Orthopaedic surgeons		
Wang 2015	China	Vertebroplasty	69.43	-	8.1 (1.2)	71.22 (10.56)[×]	-	Not reported	3.31 (0.77)	1 day, 3 and 12 months
		Balloon kyphoplasty	68.63	-	8.0 (1.1)	71.30 (10.22)[×]	-	Not reported	4.22 (1.29)	
Wang 2016	China	Vertebroplasty	63.7	-[a]	7.65 (1.11)	18.3 (1.0)	-	Spine surgeon	5.5 (3.0 - 9.0)	
		Facet joint injection	62.6	-[a]	7.76 (1.06)	18.45 (0.98)	-	Spine surgeon		
Yang 2016	China	Vertebroplasty	77.1	Not reported	7.5 (1.1)	80.2 (9.9)[×]	78.1 (8.1)	Not stated	4.5 (3-6.5)	1 week, 3, 6 and 12 months
		Usual care	76.2	Not reported	7.7 (1.1)	81.5 (9.7)[×]	77.5 (8.6)			

[$]1-10 point scale used by Farrokhi 2011, 0 to 100 scale used by VOPE 2015 and we report pain with forward bending for this trial as overall pain not reported and have converted SE to SD; [+]RMDQ: Roland-Morris Disability Questionnaire; [†]modified RMDQ (0-23 scale) used by Buchbinder 2009, Kallmes 2009 and VERTOS IV; [×]Oswestry Disability Index (0 to 100) used by Leali 2016, Wang 2015, Yang 2016; [^] median duration of symptoms; [¤]Not reported but symptom duration 6 months or less; [µ]Mean symptom duration reported graphically only; [¢]Median and interquartile range;[$]Not reported but symptom duration 6 weeks or less; [a]Not reported but symptom duration 8 weeks or less; [&]Data only included for the 42/46 in VP group and 43/50 in the usual care group who completed 12-month follow-up in groups assigned to at baseline; [#]Disability significantly higher in the vertebroplasty group; *from n = 20 treated at Mayo (personal communication); [¥]Not reported but at least 6 weeks of conservative treatment; [+]Only range provided; [~]up to 2 mL.

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials ¡November 2017¿

1 exp Spine/ (4032)
2 (spine or spinal or vertebra$).tw. (20306)
3 exp Fractures, Bone/ (3949)
4 fractur$.ti. (6791)
5 1 or 2 (21641)
6 3 or 4 (8007)
7 5 and 6 (1504)
8 exp Spinal Fractures/ (561)
9 7 or 8 (1528)
10 exp Bone Cements/ (769)
11 exp Methylmethacrylates/ (389)
12 methacrylate$.tw. (251)
13 bone cement$.tw. (201)
14 exp Fracture Fixation, Internal/ (1077)
15 exp Vertebroplasty/ (112)
16 vertebroplast$.tw. (202)
17 cementoplast$.tw. (10)
18 sacroplast$.tw. (2)
19 or/10-18 (2421)
20 9 and 19 (244)

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) ¡1946 to 15 Nov 2017¿

1 exp Spine/ (139498)
2 (spine or spinal or vertebra$).tw. (418563)
3 exp Fractures, Bone/ (178841)
4 fractur$.ti. (115672)
5 1 or 2 (468594)
6 3 or 4 (191239)
7 5 and 6 (26174)
8 exp Spinal Fractures/ (14540)
9 7 or 8 (27200)
10 exp Bone Cements/ (22211)
11 exp Methylmethacrylates/ (13907)
12 methacrylate$.tw. (14505)
13 bone cement$.tw. (5178)
14 exp Fracture Fixation, Internal/ (40925)
15 exp Vertebroplasty/ (2389)
16 vertebroplast$.tw. (2681)
17 cementoplast$.tw. (136)
18 sacroplast$.tw. (114)
19 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (80212)
20 9 and 19 (4910)
21 randomized controlled trial.pt. (504969)
22 controlled clinical trial.pt. (100398)
23 randomized.ab. (391361)
24 placebo.ab. (189112)

25 drug therapy.fs. (2146488)
26 randomly.ab. (265938)
27 trial.ab. (410806)
28 groups.ab. (1657653)
29 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (4140566)
30 exp animals/ not humans.sh. (4742004)
31 29 not 30 (3539516)
32 20 and 31 (999)

Appendix 3. Embase search strategy

Embase ¡1974 to 2017 November 13¿
1 exp Spine/ (167882)
2 (spine or spinal or vertebra$).tw. (539379)
3 exp Fracture/ (261382)
4 fractur$.tw. (268168)
5 1 or 2 (583524)
6 3 or 4 (343636)
7 5 and 6 (52536)
8 exp Spine Fracture/ (23056)
9 7 or 8 (57421)
10 exp Bone Cement/ (13553)
11 exp Methacrylic Acid Methyl Ester/ (6622)
12 methacrylate$.tw. (19209)
13 bone cement$.tw. (6639)
14 exp Fracture Fixation/ (80116)
15 exp percutaneous vertebroplasty/ (5942)
16 vertebroplast$.tw. (4173)
17 cementoplast$.tw. (264)
18 sacroplast$.tw. (166)
19 or/10-18 (119819)
20 9 and 19 (9183)
21 random$.tw. (1261919)
22 factorial$.tw. (31693)
23 crossover$.tw. (64719)
24 cross over.tw. (28196)
25 cross-over.tw. (28196)
26 placebo$.tw. (265608)
27 (doubl$ adj blind$).tw. (184923)
28 (singl$ adj blind$).tw. (20450)
29 assign$.tw. (329237)
30 allocat$.tw. (123296)
31 volunteer$.tw. (228042)
32 crossover procedure/ (54127)
33 double blind procedure/ (145236)
34 randomized controlled trial/ (482169)
35 single blind procedure/ (30196)
36 or/21-35 (1954138)
37 20 and 36 (905)

Appendix 4. Trial registries

ClinicalTrials.Gov
Intervention: Vertebroplasty
World Health Organization: International Clinical Trials Registry Platform Search Portal
Intervention: Vertebroplasty

WHAT'S NEW

Last assessed as up-to-date: 15 November 2017.

Date	Event	Description
30 April 2018	Amended	Minor correction in the plain language summary

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 4, 2015

Date	Event	Description
31 January 2018	New citation required but conclusions have not changed	Review updated, with nine new trials added; 21 trials included in total
15 November 2017	New search has been performed	Review updated and nine new trials included (Clark 2016; Evans 2015; Leali 2016; Sun 2016; VERTOS IV; VOPE 2015; Wang 2015; Wang 2016; Yang 2016) . Three of the new trials included a placebo control (Clark 2016; VERTOS IV; VOPE 2015). Full results of VERTOS IV are not yet published but this review includes results for pain, incident fractures and other adverse events from conference proceedings. One additional placebo-controlled trial (VERTOS V) remains unpublished.
24 April 2015	New citation required and conclusions have changed	Review published; 12 studies included.
16 October 2008	Amended	Converted to RM5. CMSG ID C142-P

CONTRIBUTIONS OF AUTHORS

For this review update: R Buchbinder, R Johnston and KJ Rischin drafted the review update. R Buchbinder, R Johnston, KJ Rischin, K Golmohammadi, A Jones, J Homik, and D Kallmes conducted the updated search and/or independently selected trials for inclusion and/or extracted the data, and/or performed a 'Risk of bias' assessment and/or assessed the quality of the body of evidence for the main outcomes using the GRADE approach and/or provided critical comment on the manuscript. All authors approved the final manuscript.

DECLARATIONS OF INTEREST

R Buchbinder was a principal investigator of Buchbinder 2009. D Kallmes was a principal investigator of Kallmes 2009 and Evans 2015.

D Kallmes participated in IDE trial for Benvenue Medical spinal augmentation device. He is a stockholder, Marblehead Medical, LLC, Development of spine augmentation devices. He holds a spinal fusion patent license, unrelated to spinal augmentation/vertebroplasty.

For all other authors there were no known declarations of interest.

SOURCES OF SUPPORT

Internal sources

- Monash Department of Clinical Epidemiology, Cabrini Institute and Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Australia.

External sources

- R Buchbinder is supported in part by an Australian National Health and Medical Research Council Practitioner Fellowship, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the original review the protocol was extensively updated to conform with updated conduct and reporting standards of systematic reviews as recommended by Cochrane and the MECIR project.

At the time that the protocol was developed, we had planned to include controlled before and after studies (CBAs) and interrupted time series (ITS) in our efficacy analysis if there were no published randomised controlled trials (CTs) or quasi-RCTs. Subsequent to the publication of the protocol, several RCTswere published and we therefore only included RCTs or quasi-RCTs in this review.

Subsequent to publication of the protocol, we clarified the possible comparators eligible for inclusion, i.e. that we would include randomised controlled trials of vertebroplasty compared with any comparator, including sham, conservative treatment or other surgical procedures such as kyphoplasty, but would exclude trials that compared vertebroplasty to another type of vertebroplasty.

Differences between first version of the review and current updated version

We removed four trials that were classed as ongoing trials or awaiting classification in the first version of this review (Damaskinos 2015 NCT02489825; Nakstad 2008 NCT00635297; Nieuwenhuijse 2012 NTR3282; Zhao 2014 ChiCTR-TRC-14004835), as we subsequently discovered that percutaneous vertebroplasty was given to participants in both treatment arms and thus, when trial results become available, they will not be eligible for inclusion in this review.

Calculating number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH), an additional person: we had planned to calculate these for outcomes that showed a statistically significant difference between groups. However, in light of any differences we found being small and clinically unimportant, we decided that such statistics were difficult to interpret.

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Cements [therapeutic use]; Fractures, Compression [*therapy]; Glucocorticoids [therapeutic use]; Osteoporotic Fractures [*therapy]; Pain Measurement; Pain, Postoperative; Quality of Life; Randomized Controlled Trials as Topic; Spinal Fractures [*therapy]; Vertebroplasty [adverse effects; *methods]

MeSH check words

Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged