Washington State Health Care Authority

Vertebroplasty, Kyphoplasty, Sacroplasty

Assessing signals for update

December 9, 2016

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Vertebroplasty, Kyphoplasty, Sacroplasty: Assessing Signals for Update

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December 9, 2016

Contents

1. Introduction

A Health Technology Assessment titled: ***Vertebroplasty, Kyphoplasty, Sacroplasty***, was published on November 5, 2010 by the Health Care Authority. Findings and Coverage Decision was adopted on March 18, 2011. The Committee's Coverage Decision is summarized below.

HTCC Coverage Determination

Vertebroplasty, Kyphoplasty and Sacroplasty are not covered benefits.

HTCC Reimbursement Determination

Vertebroplasty, Kyphoplasty and Sacroplasty are not covered benefits.

Committee Findings

Having considered the evidence based technology assessment report and the written and oral comments, the committee identified the following key factors and health outcomes, and evidence related to those health outcomes and key factors:

1. Evidence availability and technology features

The committee concludes that the best available evidence on Vertebroplasty, Kyphoplasty and Sacroplasty has been collected and summarized. Summary of committee considerations follows.

- The evidence based technology assessment report indicates that vertebral compression fractures and sacral insufficiency fractures occur, commonly as part of the natural disease progression of osteoporosis or osteopenia. Some patients with fractures are asymptomatic but others experience acute pain, loss of function, and decreased quality of life thought to be caused by the fracture.
- Vertebroplasty (PV), kyphoplasty (KP) and sacroplasty are all cementoplasty techniques that aim to relieve pain thought to be caused by the fracture by stabilizing the fractured bone(s). Vertebroplasty and sacroplasty are considered minimally invasive procedures and are usually performed using only local anesthesia or with conscious sedation. General anesthesia may be used. Kyphoplasty almost always requires general anesthesia and at least one overnight stay in the hospital. The patient must lie prone during all three procedures. Multiple levels can be treated during the same session. Patients are usually selected based on failure of conservative treatment or incapacitating pain. Alternatives include conservative management and surgical fixation, though invasive surgery may be problematic due to common comorbidities in the elderly and female population most often considered for this treatment.
- Despite increasing use of these procedures (rates of kyphoplasty doubled between 2001 and 205), the evidence for the procedure remains low and the efficacy, safety and economic impact are not well understood. Patients are generally elderly women with osteopenic fractures and most included studies focused on this population.

- with conservative care which resolves pain in 4 to 6 weeks and is generally recommended first. However, patients with acute fractures (less than six weeks) may be more likely to experience pain relief and the rapid recovery from debilitating pain is a primary treatment aim. Fracture age is difficult to determine as patients may have difficulty pinpointing the onset of pain and whether a certain event may be associated with the onset.
- In addition to typical complications from invasive procedures, cementoplasty techniques include risk of possible increase of subsequent compression fractures near a cemented vertebra due to increased rigidity of the treated vertebrae and risk of cement leakage.
- Evidence included in the technology assessment review was obtained through systematic searches of the medical literature for systematic reviews including meta-analyses, randomized controlled trials, observational studies, and economic studies. 11 RCTs, 23 Observational studies, and 3 economic studies met inclusion criteria and were included in the review. Overall strength of evidence from these studies was low to very low or inconclusive. Two RCTs compared vertebroplasty with sham procedure; three RCTs compared vertebroplasty to conservative care; one RCT compared kyphoplasty to conservative care; and one RCT compared kyphoplasty and vertebroplasty.
    - The evidence based technology assessment report identified 4 clinical guidelines; there is no National Coverage decision on vertebroplasty, kyphoplasty or sacroplasty.
    - The committee also reviewed information provided by the state agencies, and public members; and heard comments from the evidence reviewer, clinical expert, HTA program, agency medical directors and the public.

2. Is it safe?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Key factors to the committee's conclusion include:

- The evidence based technology assessment report concluded that the overall strength of evidence for safety is low for vertebroplasty and kyphoplasty and very low for sacroplasty and evidence based estimate of effect are uncertain. While it appears that rates of serious complications are low for vertebroplasty and kyphoplasty, studies with long-term (> 5 year) follow-up are few and comparative studies, especially RCTs, may have too few patients to detect more rare but serious outcomes. Primary safety outcomes reported include rates of new fracture, cement leakage, pulmonary cement embolism, and mortality related to vertebroplasty and kyphoplasty.
- *New fractures (adjacent or non-adjacent)* – in comparative studies, rates of new fractures were up to 30% at 12 months, with no consistent pattern across studies of increased fracture rates for any one treatment (vertebroplasty, kyphoplasty, or conservative treatment). One RCT reported that the distribution of fracture location (adjacent or non-adjacent) was similar for vertebroplasty and non-surgical patients. Systematic reviews, incorporating information on longer-term follow-up with a large (pooled) number of patients in case series, suggest that rates of new fracture may be slightly higher in vertebroplasty (18-19% of patients, 16-21% of vertebral levels) than kyphoplasty (7-17% of

patients, 11-13% of levels). One systematic review concluded that the proportion of new fractures that were in adjacent vertebrae was higher for kyphoplasty (75%) than for vertebroplasty (52%).

- *Cement leakage* – in comparative studies, rates of cement leakage (largely asymptomatic) approached 80% for vertebroplasty and 50% for kyphoplasty, with some evidence that leakage is more common with vertebroplasty than with kyphoplasty. Systematic reviews also suggest that leakage is more common in vertebroplasty (19.7% - 79.0% of levels treated) than in kyphoplasty (0.51% - 11.2%), and that rates of symptomatic leakage are quite low (0.5%-1.6%of levels treated for vertebroplasty and 0% - 0.3% for kyphoplasty).
- *Pulmonary cement embolism* – as a result of differential surveillance in RCTs, nonrandomized studies, and case series, rates vary widely across studies. One RCT using computed tomography to detect emboli reported that 26% (15/54) of vertebroplasty patients had a cement embolism, all of which were asymptomatic. No incidents of symptomatic embolism were reported in comparative studies. A systematic review of cement embolism reported rates of 1.6% for asymptomatic PCE and 1.1% for symptomatic PCE (all but one of the case series included in the review were of vertebroplasty patients).
- *Mortality* – systematic reviews (based on case series) estimate mortality rates at 2.1% for vertebroplasty and 2.3%-3.2% for kyphoplasty; the timing of mortality was not reported. Perioperative mortality rate for kyphoplasty was .01% across 11 case series. Since the majority of patients receiving these procedures are elderly and/or have malignant disease, the extent to which mortality can be attributed to the procedures is unclear.
- *Sacroplasty* – the evidence based technology assessment report indicates that the overall strength of evidence about safety of sacroplasty is very low, and all data are from case series. Cement leakage was the only reported complication and occurred in 7 of 34 (20.6%) patients across four case series.

3. Is it effective?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Key factors to the committee's conclusion include:

- Vertebroplasty
    - *Pain Relief* – the evidence based technology assessment report concluded that the overall strength of evidence about effectiveness of vertebroplasty to reduce/relieve pain is *low*; any effect estimate is uncertain and may change with additional research. The low strength of evidence and lack of ability to estimate effect based on evidence is due to the limitations of the studies and that the studies reported differing outcomes (some studies showed benefit others did not). The RCTs were limited to patients with osteoporotic fractures and evaluated short-term effects (≤12 months). Two sham-controlled RCTs demonstrated no difference in pain relief (up to 1month in one study and 6 months in the other), though both studies were limited in power to detect differences in the proportion of patients with clinically meaningful improvement. Another RCT demonstrated statistically significant improvement in pain scores

sustained to the 12-month follow-up compared to conservative care and included more patients but was not blinded and did not include a placebo comparison. Two small RCTs reported no advantage for vertebroplasty over 2 weeks or 12 months. Four nonrandomized studies with follow-up up to one year found that vertebroplasty was more effective in reducing pain than conservative medical treatment at up to approximately six months, but no difference at one year.

- *Function and quality of life* – the evidence based technology assessment report concluded that the overall strength of evidence about effectiveness of vertebroplasty to improve patient function or quality of life is *low*; any effect estimate is uncertain and may change with additional research. One larger RCT demonstrated that PV was more effective than conservative treatment in improving functioning as measured by the QualEffo and RDQ, although it is possible that early differences in improvement diminish over time. Two small RCTs found comparable improvements in function over 2 weeks and 12 months for vertebroplasty and non-surgical patients. In 4 non-randomized studies, vertebroplasty showed superior effectiveness in improvements in functioning and quality of life in the first 3-6 months was followed by equivalence at one year.

- Kyphoplasty
  - *Pain Relief – the evidence based technology assessment report concluded that the overall strength of evidence about effectiveness of kyphoplasty to relieve/reduce pain is very low; any effect estimate is uncertain and may change with additional research.*
  - *Only one RCT compared kyphoplasty with conservative treatment, reporting that while pain was reduced more rapidly in kyphoplasty patients, this advantage over conservative treatment was diminished by the one-year follow-up. Because of the paucity of RCTs comparing kyphoplasty to conservative treatment, the overall strength of evidence is low and effect estimates may change with additional research. In two non-randomized studies, kyphoplasty reduced pain more than conservative medical treatment for periods up to 3 years.*
  - *Function and quality of life – the evidence based technology assessment report indicated that it is uncertain whether kyphoplasty improves patient functioning and quality of life. In these two studies, kyphoplasty improved a limited set of functional outcomes more than conservative medical treatment.*

- Sacroplasty
  - There is no evidence of efficacy for sacroplasty. Very limited data from 9 case series (N = 141 total patients) is available, the case series showed pain relief with sacroplasty; but the absence of comparative studies, small patient size do not permit an evidence based conclusion.

4. Is it cost-effective?

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows:

- The evidence based technology report summarized three economic studies, however, because the evidence about efficacy, effectiveness, and safety is low to very low and evidence based estimates

of effect are uncertain; conclusions about cost effectiveness are premature. No cost studies were conducted with U.S. data, the cost effectiveness of vertebroplasty, kyphoplasty or sacroplasty in a US setting is unknown.

- The economic impact of complications, reoperation, or revision following vertebroplasty, kyphoplasty, or sacroplasty is unknown.

- Washington state agency utilization and cost information indicates that the single agency that reimburses (UMP) for these procedures expended $868,543 in the last four years, with an average cost of $10,837; and both procedure volume and costs are rising annually.

5. Medicare Decision and Expert Treatment Guidelines

The committee deliberations included a discussion of National Medicare Decisions and expert treatment guidelines, and an understanding that the committee must find substantial evidence to support a decision that is contrary. RCW 70.14.110.

The Committee reviewed and discussed the expert guidelines as identified and reported in the technology assessment report. Overall, the clinical guidelines and Medicare coverage decisions included in the evidence report and the AAOS guideline published subsequent either do not cite evidence or rely on evidence assess as low or very low quality or consensus statements.

- Centers for Medicare and Medicaid Services (CMS) have no published National or Local coverage determinations for vertebroplasty, kyphoplasty or sacroplasty.

- The evidence based technology assessment report identified three guidelines on vertebroplasty, kyphoplasty and/or sacroplasty, although no guideline specifically addressed the procedures for osteoporosis or malignancy – the studied indications.
    - Two guidelines mentioned vertebroplasty and kyphoplasty as part of the assessment and management of spinal cord compression and chronic pain and indicate they may be considered.
        - Institute for Clinical Systems Improvement (ICSI), 2008
        - National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence (NICE), 2008
    - American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, American Association of Neurological Surgeons/Congress of Neurological Surgeons, and American Society of Spine Radiology -- A consensus statement on percutaneous vertebral augmentation was developed: “It is the position of the Societies that vertebral augmentation with vertebroplasty or kyphoplasty is a medically appropriate therapy for the treatment of painful vertebral compression fractures refractory to medical therapy when performed for the medical indications outlined in the published standards1-3.”
    - American Association of Orthopaedic Surgeons (AAOS) -- recommend against vertebroplasty for patients who present with an osteoporotic spinal compression fracture on imaging with correlating clinical signs and symptoms and who are neurologically intact. Strength of Recommendation: Strong. Kyphoplasty is an option for patients who present with an

osteoporotic spinal compression fracture on imaging with correlating clinical signs and symptoms and who are neurologically intact. Strength of Recommendation: Weak.

2. Purpose of Report

The purpose of this literature update is to determine whether or not there is sufficient evidence published after the original report to conduct a re-review of this technology based on the presence of preset signal criteria. The key questions included the following:

Key question 1

What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty or sacroplasty? Including consideration of:

a. Short-term and long-term outcomes
b. Impact on function, pain, quality of life
c. Other reported measures including: use of pain medications and opioids, return to work

Key Question 2

What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty? Including consideration of:

a. Adverse events type and frequency (mortality, major morbidity, other)
b. Revision/re-operation rates (if not addressed in efficacy)

Key Question 3

What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety issues in sub populations? Including consideration of:

- Gender
- Age
- Psychological or psychosocial co-morbidities
- Diagnosis or time elapsed from fracture
- Other patient characteristics or evidence based patient selection criteria
- Provider type, setting or other provider characteristics
- Payer/beneficiary type: including worker's compensation, Medicaid, state employees

Key Question 4

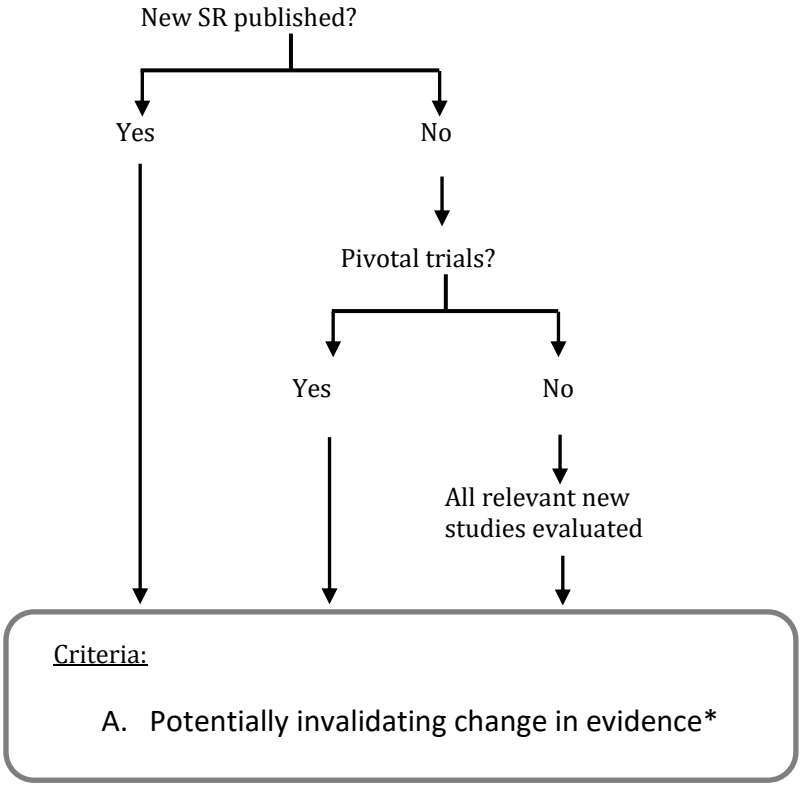
What is the evidence of cost implications and cost-effectiveness of vertebroplasty, kyphoplasty and sacroplasty? Including consideration of:

a. Costs (direct and indirect) in the short term and over expected duration of use
b. Revision/re-operation (if not addressed in efficacy)

3. Methods

To determine the need for systematic review update, the following algorithm was followed.

Figure 1. Algorithm of the modified Ottawa Method of Identifying Signals for SR



*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment

B-3. Clinically important caveat

B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

Updates

3.1 Literature Searches

We conducted a limited electronic literature of Medline for systematic reviews with meta-analysis during the period March 1, 2010 through November 26, 2016 using search terms used for the original report. Appendix A includes the search methodology for this topic. In addition, we searched the FDA website to determine if there was approval of new devices or indications for vertebroplasty, kyphoplasty or sacroplasty and for individual cost-effectiveness studies for KQ 4.

3.2 Study selection

We sought systematic reviews of randomized controlled trials (RCTs) of efficacy and safety with meta-analysis that included articles that met inclusion and exclusion criteria similar to the original report. In addition we sought systematic reviews reflecting updates or new advances for the technology. Secondary to the large number of citations returned, we focused on screening only systematic reviews and meta-analyses of RCTS published between 2011 and 2016. Although quality of systematic reviews was not formally evaluated for this report, we chose three systematic reviews that were the most comprehensive and of high quality based on the following: report of search strategies (two or more data bases and description of dates searched), number of included relevant RCTs, pre-stated inclusion and exclusion criteria, information on methodologies used for synthesis of data, inclusion of patient reported or safety outcomes and evaluation of the strength of the body of literature using GRADE or another analogous system. Only systematic reviews of RCTs were included. A summary of the three SRs is found in Appendix B.

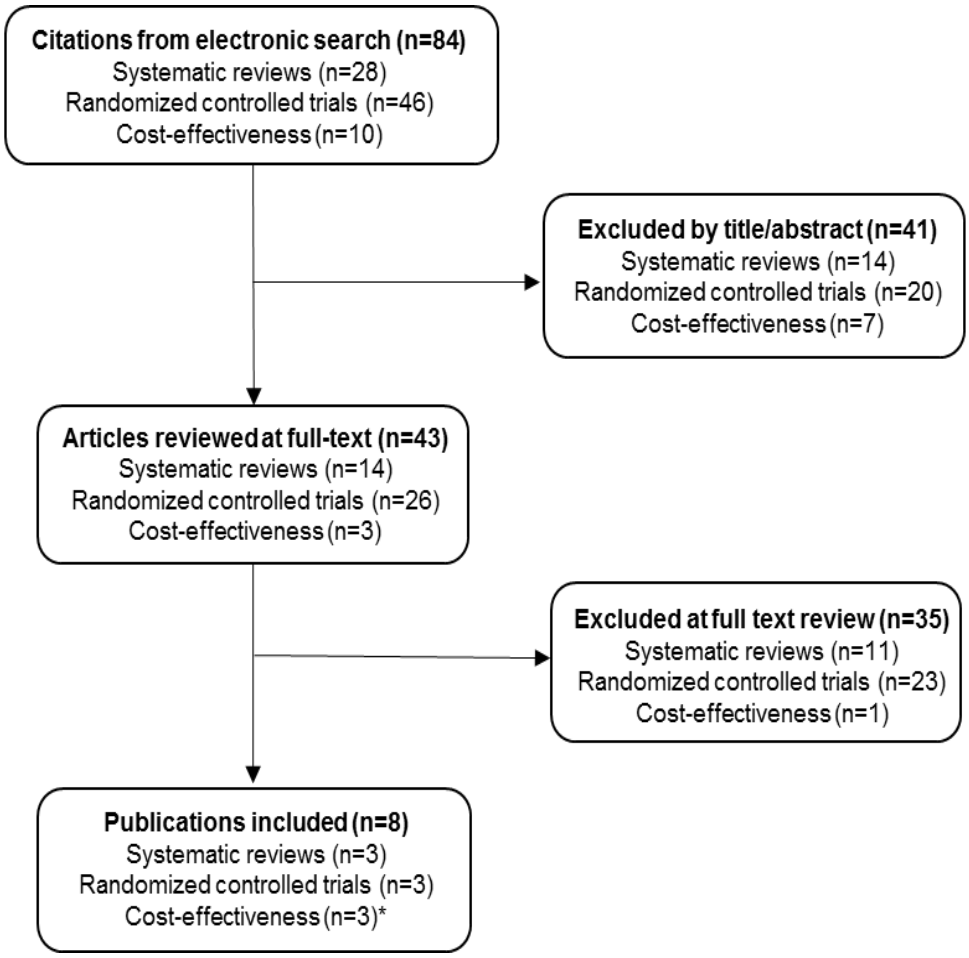
4. Results

4.1 Search

We identified 28 systematic reviews from the electronic search that addressed in part or in full key questions 1 and 2, Figure 2. We reviewed the full text of 14 systematic reviews that most closely met the inclusion criteria (see excluded studies and the reasons for exclusion in Appendix C). Two included systematic reviews provided analysis of differential efficacy (Key Question 3) and an additional three RCTs were identified that provided information on subpopulations not included in the systematic reviews. One of the new RCTs also provided data for key question 1. We found three new cost-effectiveness analyses (Key Question 4) one of which evaluated a subset of data from a study included in the previous HTA, two others were conducted as part of a systematic review.

A table of new FDA approved devices is found in Appendix D. All were considered to be variations of existing devices versus new devices and were approved via the 510K process. In May 2015, Stryker received 510K approval to expand the indications for use of VertaPlex HV Radiopaque Bone Cement to pathological fractures of the sacral vertebral body. The FDA warning issued for bone cement has not changed since the previous report.
(http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062126.htm)

Figure 2. Electronic search results for systematic reviews



*One of the included systematic reviews also conducted a formal economic evaluation and so is included in the final count for both systematic reviews and cost-effectiveness studies. The systematic review for the other economic study did not meet inclusion criteria.

4.2 Identifying signals for re-review

Table 1 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the recommendations of Spectrum Research, Inc. (SRI) regarding the need for update.

Table 1. Vertebroplasty, Kyphoplasty, Sacroplasty Summary Table for Key Question 1.

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
Vertebroplasty (PV) vs. sham surgery ○ There is low evidence from two RCTs, PV was no more effective than sham surgery in reducing pain or improving function or quality of life at one month and three months. Pain improved in both groups by 2.6-3.0 points at follow-up, RDQ scores improved by 3.7-5.3, and EQ-5D improved by 0.1-0.2 points.	**Efficacy** *Systematic Review*: Buchbinder (2015, Cochrane Review)[3] (Updates to the two previously included RCTs; no new RCTs) *New RCT:* Clark (2016)[4] (not included in Buchbinder 2015) **Effectiveness** Not explored	**Efficacy**: • No between-group differences in outcome were observed for pain, RDMQ, QUALEFFO, EQ-5D at any time point in patients with osteoporotic fractures based on pooled analysis in the Buchbinder Cochrane review up to 24 months. • Clark RCT: PV was associated with reduction in pain and disability (RMDQ) at all time frames to 6 months; QUALEFFO scores were higher for PV at 0.5 and 6 months. • Preliminary pooled effect estimates combining Clark RCT data with data from the Buchbinder Cochran review (See Appendix C) suggests that: ○ Success, defined as with improvement in pain of 2.5 units (Buckbinder), or >30% or more from baseline (Kallmes) or pain less than 4 out of 10 (Clark) was more common following PV. Pooled RRs (95% CI) at 1 month were 1.6 (1.0, 2.5), at 3 months 1.6 (1.1, 2.3) and at 6 months 1.4 (1.1, 1.9)	• Short term (≤ 6months): Preliminary pooled analysis which includes the new RCT suggests an important change in the evidence for pain improvement success from no difference to difference favoring PV. (Criterion B1). • Short term: Pooled estimates for function do not provide a major change in the evidence (Criteria B1-4) • Longer term (>6 months to 24 months) Updated analyses from the systematic review do not change the conclusions of the previous report (criteria

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
		○ While there was statistically significant improvement in pain scores (VAS or NRS) at 1month (pooled MD -0.94,95% CI -1.59, -0.29) and 3 months (pooled MD -1.04, 95% CI 1.98, -0.09) it is likely not clinically meaningful; pooled mean difference in pain scores was similar between PV and sham at 1-2 weeks and at 6 months. ○ Reduction in disability (RMDQ) was similar between groups at 1-2 weeks, 3 and 6 months; a pooled MD of -1.72 (95%CI -3.13, -0.31) at 1 month was statistically significant but may not be clinically meaningful. ○ Pooled mean differences in EQ5D reached statistical significance at 1 and 6 months favoring PV., but mean differences were small, ranging from 0.01 to 0.06 across time frames.	A-1 or A3) nor provide major changes in the evidence (Criteria B1-4)
<u>Vertebroplasty (PV) vs. conservative treatment (CMT)</u> **Efficacy:** There is low evidence: • In a large RCT comparing PV with conservative treatment, PV was more	**Efficacy** *Systematic Reviews*: Buchbinder (2015, Cochrane)[3] (3 new RCTs in addition to	• Efficacy: • Buchbinder: VP was superior to CMT in pain and disability (RMDQ) improvement over 2 wks. to 12 mos. follow-up (for pain	• Findings from systematic reviews including new RCTs do not change the conclusions

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
effective than conservative treatment in reducing self-reported pain intensity for follow-up points of up to one year, with improvements of 6.6 points and 3.7 points respectively. • In this large RCT, improvement in RDQ scores was greater for PV patients than for CMT patients by 2-3 points over a year. PV patients also improved more than CMT patients on the QualEffo, but scores for the two groups were similar at 12 months. • In two small RCTs, PV and CMT patients showed comparable improvement in pain, with inconsistent findings for functional outcomes **Effectiveness:** There is low evidence • In four cohort studies (2 prospective, 2 retrospective): ○ PV was more effective than CMT in reducing pain (from 7.5-9 to 0.7-3.5) up to 6 months,	the 1 RCT included in previous report) Li (2015)[6] (2 of the 3 new RCTs included) 1 New RCT: Yang (2016)[8]; (patients >70 years old) **Effectiveness:** Not explored	only, no difference at 24 mos. in 1 RCT) and for EQ-5D from 2 weeks to 3 mos. follow-up (but no difference at 6 and 12 mos.). There was no difference between groups for QUALEFFO at any time point. Statistical heterogeneity varied from unimportant to considerable • Li: Evaluated pain only. Greater pain relief with PV than CMT at all time-points but only mid- and long-term were significant (p=0.003 and 0.000, respectively, vs. p=0.06 in the early-term) • Yang RCT: Early PV yielded faster, better pain relief and improved functional outcomes compared with conservative treatment, which were maintained for 1 year. Findings consistent with previous report.	from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
but pain levels were comparable for the two groups after one year. ○ For a very limited set of functional outcomes, PV led to earlier improvements than CMT, followed by equivalent levels of functioning after 6 months to a year.			
<u>Kyphoplasty (KP) vs. conservative treatment (CMT)</u> **Efficacy:** • There is low evidence from one RCT • KP was more effective than CMT by 0.9-2.2 points in reducing pain intensity for follow-up points up to one year. • Pain was reduced more rapidly in KP patients, and group differences were diminished by 12 months. • KP was more effective than CMT in improving functional outcomes (EQ-5D, RDQ, SF-36) over one year, but group differences were diminished at 12 months.	**Efficacy:** *Systematic Reviews*: Li (2015)[6] (3 Updates to previously included RCT) Stevenson (2014)[7] (2 updates to previously included RCT) **Effectiveness:** Not explored	**Efficacy:** • The Li systematic review evaluated pain only. KP provided greater pain relief than CMT at all time-points but only early (1 week) and mid-term (2-3 months) were significant (p=0.000 and 0.002, respectively, vs. p=0.08 in the long-term (1 year)) • The Stevenson systematic review (HTA) concluded that KP performs significantly better in unblinded trials than CMT in terms of improving quality of life and reducing disability.	• Analyses from the systematic reviews which include updated data from RCTs do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
Effectiveness: There is very low evidence from two cohort studies (1 prospective and 1 retrospective): • KP reduced pain more than CMT for periods up to 3 years. • KP improved a limited set of functional outcomes more than CMT			
<u>Vertebroplasty (VP) vs. kyphoplasty (KP)</u> • Efficacy: There is very low evidence from one poor-quality RCT that back pain scores improved equally (from 8.0 to 2.3-2.6) for PV and KP patients over 6 months • Effectiveness: There is low evidence from 12 cohort studies (6 prospective and 6 retrospective) that: • PV and KP led to comparable pain reduction (from 7.2-8.8 at baseline to 0.6-4.6) at follow-up periods up to 2 years in 8 of 10 studies. • PV and KP demonstrated	**Efficacy:** *Systematic Review*: Buchbinder (2015, Cochrane)[3] (3 new RCTs in addition to RCT included in previous report) **Effectiveness:** Not explored	**Efficacy**: No between-group differences in pain and disability (ODI), and QoL (EQ-5D) improvement over 1 mo. to 24 mos. follow-up observed in the systematic review;	• Updated analyses from the systematic review including new RCTs do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
comparable improvements (from 30.8-77 to 4.8-56) in the ODI at follow-up times up to 2 years in 4 of 5 studies			
Sacroplasty ○ No comparative studies identified. There is very low evidence across four case series that suggests improvement in pain following sacroplasty.	**Efficacy:** No comparative studies identified **Effectiveness:** Not explored	○ No new RCT evidence	No new evidence

*Pathologic fractures may include multiple myeloma, hemangioma or metastases

Table 2. Vertebroplasty, Kyphoplasty, Sacroplasty Summary Table for Key Question 2.

Key Question 2: What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
Vertebroplasty (VP) and Kyphoplasty (KP) There is low evidence for the following outcomes: • New fractures: ○ In comparative studies, the rate of new fractures at any location following PV, KP, or CMT was up to 25% at 6 months post-surgery, and up to 30% at 12 months, with no consistent pattern across studies in different rates for PV, KP, and CMT. ○ In cohort studies, from 22% to 66% of new fractures occurred in adjacent vertebrae, however, these rates are based on very small numbers. A systematic review concluded that the proportion of new fractures that were adjacent was higher for KP (75%) than for PV (52%). ○ Systematic reviews of case series report slightly higher rates of new fractures at any location for PV (16-21%) than for KP (7-17%). • Cement leakage ○ Rates of asymptomatic cement leakage are up to	*Systematic Reviews:* Buchbinder (2015, Cochrane)[3] Li (2015)[6] Stevenson (2014)[7]	• New Fractures: ○ Buchbinder: VP vs. Sham or CMT: • At 12 months, clinically apparent vertebral fractures were more common in the PV group vs. control group but this was not statistically significant (19.6% vs. 13.8%; RR 1.47 [95% CI 0.39 to 5.50]); there was substantial statistical heterogeneity (I2 = 73%). No between-group differences in the number of new radiographic vertebral fractures at 12 or 24 months were reported. ○ Buchbinder: VP vs. KP • No between-group differences in the number of clinically apparent vertebral fractures [RR 1.32 (95% CI 0.91 to 1.92)] or new radiographic vertebral fractures at 12 or 24 months or adjacent level fractures at 6 months ○ Li; combined PV and KP vs. control • No between-group differences in risk of new or adjacent vertebral compression fractures • Cement Leakage ○ Stevenson • Cement leakage is common, particularly with PVP: pooled data from the RCTs indicate an incidence of 44% of treated	• New RCTs included in systematic reviews do not change the conclusions from the previous report (criteria A-2).

Key Question 2: What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
80% for vertebroplasty and 50% for kyphoplasty. ○ Comparative studies and systematic reviews (consisting largely of case series) suggest that cement leakage is greater in PV than in KP; however, symptomatic leaks are rare (up to 1.6% in PV and 0.3% in KP; data from reviews of case series) • Pulmonary cement embolism (PCE) ○ One RCT reported a PCE rate for PV of 26%, with all cases asymptomatic ○ Systematic reviews of case series report pooled PCE rates from 0.1% to 1.7%, with insufficient information to compare rates for PV and KP. • Mortality: Data from systematic reviews primarily of case series ○ Rates in prospective studies of 2.1% (22/1051) for PV and 0.6% (24/5629) for retrospective studies. ○ Overall mortality for kyphoplasty ranging from 2.3% (13/588) to 3.2 % (25/522) from 2 different reviews		vertebrae for PVP and 27% for BKP, while the case series indicate a range of 5 % to 72% for PVP and 9% to 18% for BKP; they do not report symptomatic and asymptomatic leakage separately. • Pulmonary Cement Embolism ○ Buchbinder: Reported that it was not possible to determine the rate of significant sequelae arising from cement leakage or embolism due to the small number of events. • Mortality ○ Li; combined PV and KP vs. control groups • No between-group differences in procedure-related or all-cause mortality ○ Buchbinder: • No deaths as a result of the procedure from the trials reviewed • Other adverse events: ○ Buchbinder: PV vs. sham or CMT • No between-group differences in the number of serious other adverse events for VP vs. Sham (3/106 vs. 3/103; RR 1.01 [0.21 to 4.85 ○ Buchbinder: PV vs. KP • No significant between-group differences in the number of serious other adverse events	

Key Question 2: What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
○ Perioperative mortality: 0.01% (1/406).			
Sacroplasty • There is very low evidence across four case series that the rate of cement leakage was 20.5% (7/34 patients)	No systematic reviews or RCTs identified	○ No new evidence	No new evidence

Table 3. Vertebroplasty, Kyphoplasty, Sacroplasty Summary Table for Key Questions 3 and 4.

Key Question 3: What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety in subpopulations?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
<u>Vertebroplasty (VP) vs. sham surgery or conservative treatment (CMT)</u> There is very low evidence regarding the following: • Fracture age ○ No studies were designed to directly compare efficacy or safety outcomes between patients with acute, subacute, and/or chronic fractures. ○ Two RCTs reported that improvements in pain and functional outcomes were not significantly different for patients with acute and chronic fractures; however, the studies may not have had adequate power for these post-hoc analyses. ○ One RCT of PV vs. CMT in patients with acute fractures reported greater improvement in pain and function for PV patients, but evidence for differential efficacy cannot be derived since there was no direct comparison with more chronic fractures in the same underlying population • Osteoporotic versus malignant fractures ○ Two retrospective cohort studies in patients with malignancy fractures cannot	*Systematic Reviews*: Buchbinder (2015, Cochrane)[3] Li (2015)[6] *RCTs: trials in special populations not included in SR* Yang (2016)[8] Clark (2016)[4]	Duration of pain: differential efficacy • Buchbinder: VP vs. Sham ○ No evidence of differential efficacy based on pre-procedural duration of pain ≤ 6 weeks vs. >6 weeks for pain reduction or disability at 1-2 weeks, 1 month or for quality of life at 1 month; Tests for interaction between subgroups were not statistically significant. Fracture Age: differential efficacy • Li; VP and KP combined vs. control ○ No apparent evidence of differential efficacy based on fracture age <3 months vs. >3 months for pain reduction early (1 week to 1 month) mid-term (2-3 months) or longer term (12 months), based on qualitative assessment of stratum specific effect size estimates and their confidence intervals ; however, no test for interaction was provided; Special populations: Studies were not designed to evaluate differential efficacy or safety • Yang (RCT); PV vs. CMT in patients age ≥70 years In aged patients with acute osteoporotic fractures and severe pain, early PV yielded faster,	Findings from the systematic reviews and new RCTs do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).

Key Question 3: What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety in subpopulations?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
provide information for differential efficacy based on fracture etiology.		better pain relief and improved functional outcomes, which were maintained for 1 year. The overall complication rate following PV was significantly lower (16%) compared with CMT (35%) • Clark (RCT) PV vs. sham/placebo: Subanalysis of fracture age(≤ 3weeks vs. >3 weeks) does not appear to modify treatment with respect to proportion of patients achieving NRS score below 4 based on observed overlap of 95% CI, however no test for interaction was done and confidence intervals are wide. Fracture age ≤ 3weeks RD 31 (95% CI 12, 50), >3 weeks RD -4 (95% CI -39, 31). • Clark (RCT): Spine region may impact proportion of patients achieving NRS score below 4, however no test for interaction was provided: RD for thoracolumbar region, 48(95 %CI 27, 68), RD for non-thoracolumbar region -15 (95% CI -40, 9).	
<u>Kyphoplasty (KP) vs. conservative treatment (CMT)</u> Very low evidence: No comparative studies were identified that assessed differential efficacy or safety according to patient, provider, or payer factors.	*New RCT:* Berenson (2011)[2]	• Berensen (RCT); KP vs. CMT in patients with metastatic (pathological) fractures only ○ At 1 month, KP was associated reduced pain, disability and use of medication; SF-36 PCS and MCS scores were improved following KP vs. CMT	New RCT does not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4). Findings are consistent with results in general population.

Key Question 3: What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety in subpopulations?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
Vertebroplasty (VP) vs. kyphoplasty (KP) Very low evidence: • No comparative studies were identified that assessed differential efficacy or safety issues • Two retrospective cohort studies compared PV with KP among patients with fractures due to malignancy; one study reported comparable outcomes for PV and KP, and the other reported that KP led to more improvement in pain than PV over one year	No new evidence	No new evidence	No new evidence
Sacroplasty • Very low evidence: No comparative studies were identified	No new evidence	No new evidence	No new evidence.

Key Question 4: What are the cost implications and cost effectiveness of vertebroplasty, kyphoplasty and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
Vertebroplasty (PV) vs. sham surgery or conservative treatment (CMT) Very low Evidence: • One RCT reported that PV was associated with significant increases in cost and Quality Adjusted Life Years (QALY) at one month, but that these increases were no longer statistically significant by one year. • One retrospective cohort study reported that cost per patient per one-point reduction in pain rating (0-10 scale) was not significantly different for PV patients and CMT patients	*HTA with cost utility analysis:* Stevenson (2014)[7]	• Stevenson: Authors report that no definitive conclusion on the cost-effectiveness of PVP or BKP can be provided given the uncertainty in the evidence base. Cost-effectiveness analyses were varied, with all of KP, PV and operative placebo with local anesthesia appearing the most cost-effective treatment dependent on the assumptions made regarding mortality effects, utility, hospitalization costs and operative placebo with local anesthesia costs	New cost-utility study does not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).
Kyphoplasty (KP) vs. conservative treatment (CMT) Very low evidence • Cost data from one RCT showed that KP was associated with increased cost and increased QALY compared with CMT.	*HTA with cost utility analysis:* Stevenson (2014)[7] *New analysis:* Fritzell (2011)5 (additional analysis of previously included study)	• Stevenson: Authors report that no definitive conclusion on the cost-effectiveness of PVP or BKP can be provided given the uncertainty in the evidence base. Cost-effectiveness analyses were varied, with all of KP, PV and appearing the most cost-effective treatment dependent on the assumptions made regarding mortality effects, utility, hospitalization costs and operative placebo with local anesthesia costs. • Fritzell: Swedish participants ONLY from the FREE trial; 24 month follow-up data available. Conclusion: it was not possible to demonstrate that KP was cost-effective compared with standard	New cost-utility studies do not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).

Key Question 4: What are the cost implications and cost effectiveness of vertebroplasty, kyphoplasty and sacroplasty?			
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Findings**	**Conclusion from SRI**
		medical treatment in patients treated for an acute/subacute vertebral fracture due to osteoporosis.	
Cancer-related vertebral compression fractures • Vertebroplasty (PV) vs. non-surgical management • Kyphoplasty (KP) vs. non-surgical management **No evidence in 2010 report**	*New analysis:* Ontario HTA (2016)[1] on cancer-related VCF	• Ontario HTA: Systematic review clinical data are primarily from non-comparative studies of cancer-related VCF; only 1 of the included RCTs (Berenson described above) met our inclusion criteria. Conclusions are based on Markov models: Compared with nonsurgical management, PV and KP may be cost-effective at commonly accepted willingness to pay thresholds (ICERS of $17,870 and $33,471CAD respectively), however widespread use would increase healthcare costs to the system.	New economic study does not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1) given the absence of evidence on efficacy in those with cancer-related compression fractures. Evidence is primarily from non-randomized, non-comparative studies.
Vertebroplasty (VP) vs. kyphoplasty (KP) No Evidence	No new evidence	No new evidence	No new evidence
Sacroplasty No Evidence	No new evidence	No new evidence	No new evidence

5. Conclusions

Vertebroplasty (PV)

- There are several systematic reviews containing updates to previously included RCTs and new RCTs published subsequent to the 2010 HTA. Not included in the systematic reviews are new RCT comparing PV with sham in persons with fractures of ≤ 6 weeks duration and one comparing PV with conservative care in persons >70 years old that were identified.
- Pooled estimates including updated data from previous RCTs reported in systematic reviews and one new RCT comparing safety and efficacy of **PV with sham** surgery suggest that PV may improve pain success in the short term (≤ 6 months) and this section of the report may benefit from being updated. In the longer term (> 6 months) updated RCT data are consistent with the original HTA and does not need updating
- Synthesized results from new trials comparing the safety and efficacy of **PV with conservative treatment** are consistent with the findings in the original HTA. This section does not need updating.
- Systematic reviews did not identify modification of treatment by duration of symptoms and modification by fracture age is not evident based on informal examination in the new trial of **PV versus sham**. Findings from one new trial of **PV versus conservative** care in patients aged ≥70 years are consistent with those in the general population in the original HTA; no update is needed.
- New economic analysis in osteoporotic vertebral compression fractures reports that no definitive conclusion regarding cost-effectiveness of PV is possible given the uncertainty in the evidence base. This is consistent with the original HTA; no update is needed.
- New economic analysis in patients with cancer-related vertebral compression fractures suggests that PV may be cost-effective compared with non-surgical management, however, data on clinical efficacy/effectiveness are based primarily on non-comparative observational studies. In the absence of efficacy data, this section does not need updating.

Kyphoplasty (KP)

- There are several systematic reviews that include updates to the previously included RCT published subsequent to the 2010 HTA.
- Updated data on efficacy and safety from the RCT comparing KP with conservative treatment are consistent with findings in the original HTA. This section does not need updating.
- Findings from the one new trial comparing KP with conservative treatment in patients with metastatic fractures are consistent with findings in the general population. No update is needed.
- One economic analysis reports that no definitive conclusion regarding cost-effectiveness of PV is possible given the uncertainty in the evidence base, the other reported that KP was not cost-effective versus conservative treatment. Findings are consistent with those in the original HTA. This section does not need updating.
- One new economic analysis in patients with cancer-related vertebral compression fractures suggests that KP may be cost-effective compared with non-surgical management, however, data on clinical efficacy/effectiveness appear to be based on primarily on non-comparative observational studies. In the absence of efficacy data, this section does not need updating.

Vertebroplasty(PV) versus Kyphoplasty (KP)

- There are several systematic reviews comparing the safety and efficacy of PV with KP that included three new RCTs.
- Synthesized results that include the new trials are consistent with findings in the original HTA. No update of this section is needed.

Sacroplasty

- There is no new comparative evidence on sacroplasty; the sections of the previous report dealing with this application are still valid and do not need updating.

REFERENCES

1. Vertebral Augmentation Involving Vertebroplasty or Kyphoplasty for Cancer-Related Vertebral Compression Fractures: A Systematic Review. Ont Health Technol Assess Ser 2016;16:1-202.
2. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011;12:225-35.
3. Buchbinder R, Golmohammadi K, Johnston RV, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. Cochrane Database Syst Rev 2015;4:CD006349.
4. Clark W, Bird P, Gonski P, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1408-16.
5. Fritzell P, Ohlin A, Borgstrom F. Cost-effectiveness of balloon kyphoplasty versus standard medical treatment in patients with osteoporotic vertebral compression fracture: a Swedish multicenter randomized controlled trial with 2-year follow-up. Spine (Phila Pa 1976) 2011;36:2243-51.
6. Li L, Ren J, Liu J, et al. Results of Vertebral Augmentation Treatment for Patients of Painful Osteoporotic Vertebral Compression Fractures: A Meta-Analysis of Eight Randomized Controlled Trials. PLoS One 2015;10:e0138126.
7. Stevenson M, Gomersall T, Lloyd Jones M, et al. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. Health Technol Assess 2014;18:1-290.
8. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous Vertebroplasty Versus Conservative Treatment in Aged Patients with Acute Osteoporotic Vertebral Compression Fractures: A Prospective Randomized Controlled Clinical Study. Spine (Phila Pa 1976) 2016;41:653-60.

APPENDIX A. SEARCH STRATEGIES

Below is the search strategy for PubMed.

Search dates March 1, 2010 through November 26, 2016

General Search

	General Search
#1	Search **vertebroplast* OR kyphoplast* OR sacroplast* OR vesselplast* OR skyphoplast* OR vertebral augmentation** Filters: **Abstract; Publication date from 2016/03/01; English**
#2	Search **(#72)NOT cadaver* NOT sheep** Filters: **Abstract; Publication date from 2016/03/01; English**

Safety Search

	Safety Search
#1	Search **vertebroplast* OR kyphoplast* OR sacroplast* OR vesselplast* OR skyphoplast* OR vertebral augmentation**
#2	Search **(#1)NOT cadaver* NOT sheep**
#3	Search **(#2) AND (safety or complication or complications or adverse)**
#4	Search **(#2) AND (safety or complication or complications or adverse)** Filters: **Abstract; Publication date from 2016/03/01; English**
#5	Search **(#2) AND ("cement leakage" OR "cement leak")** Filters: **Abstract; Publication date from 2016/03/01; English**
#6	**(#2) AND (emboli*)** Filters: **Abstract; Publication date from 2016/03/01; English**
#8	Search **(#2) AND ("adjacent fracture" or "new fracture" or "subsequent fracture")** Filters: **Abstract; Publication date from 2016/03/01; English**

Cost-effectiveness search

	Cost effectiveness search
#1	Search **vertebroplast* OR kyphoplast* OR sacroplast* OR vesselplast* OR skyphoplast* OR vertebral augmentation OR percutaneous vertebral augmentation OR cement augmentation** Filters: **Abstract; Publication date from 2016/03/01; English**
#2	Search **(#1)NOT cadaver* NOT sheep** Filters: **Abstract; Publication date from 2016/03/01; English**
#3	**(#2) AND (economic OR cost OR cost-effectiveness OR cost-benefit OR cost-utility)** Filters: **Abstract; Publication date from 2016/03/01; English**

APPENDIX B. SUMMARY OF INCLUDED SYSTEMATIC REVIEWS.

Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
Buchbinder 2015 (Cochrane)	To synthesize the available evidence regarding the benefits and harms of vertebroplasty for treatment of osteoporotic vertebral fractures.	Osteoporotic vertebral fractures	VP vs. sham, CC, or KP	Pain, disability, disease-specific and overall health-related quality of life, patient-reported treatment success, new symptomatic vertebral fractures, serious adverse events	**VP vs. sham:** 2 RCTs (n=209) **VP vs. CC:** 6 RCTs (n=566) **VP vs. KP:** 3 RCTs, 1 quasi-RCT (n=545)	**VP vs. sham (efficacy):** No between-group differences in any efficacy outcome (pain, disability, quality of life) at any timepoint. **VP vs. CC (efficacy):** VP superior to CC in pain and disability improvement up to 12 months and for quality of life up improvement up to 3 months follow-up. **VP vs. sham or CC (safety)**: More new clinically apparent vertebral fractures at 12 months in the VP vs. the sham/ CC group but the difference was not statistically significant; no between-group differences in the number of new radiographic vertebral fractures at 12 or 24 months or in the number of other serious adverse events. **VP vs. KP:** No between-group differences in pain,

Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
						disability and quality of life improvement up to 24 months, or new clinical or radiographic vertebral fractures at 12 or 24 months, or adjacent level fractures at 6 months follow-up.
Li 2015	To compare clinical differences in pain relief, spinal functional outcomes, and overall quality of life between vertebral augmentation and control treatment for painful osteoporotic vertebral compression fractures	Osteoporotic vertebral fractures	VP or KP vs. sham or CC	Pain relief*	**VP vs. sham:** 2 RCTs (n=209) **VP vs. CC:** 5 RCTs (n=478) **KP vs. CC** 1 RCT (n=300)	**VP vs. sham (efficacy):** No differences between groups in early- and mid-term pain relief (no long-term data). **VP vs. CC (efficacy):** VP resulted in greater pain relief than CC at all time-points but only mid- and long-term were significant (p=0.003 and 0.000, respectively, vs. p=0.06 in the early-term). **KP vs. CC (efficacy):** KP resulted in greater pain relief than CC at all time-points but only early- and mid-term were significant (p=0.000 and 0.002, respectively, vs.

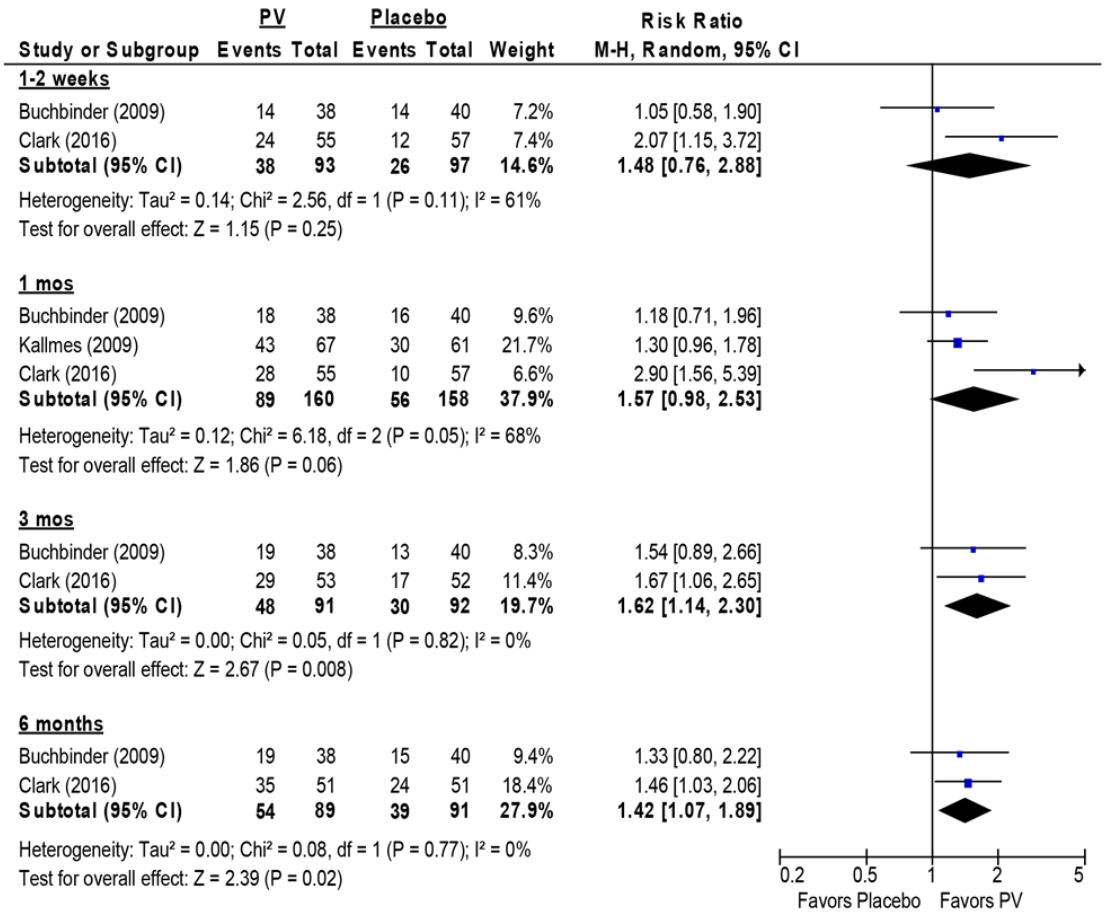
Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
						p=0.08 in the long-term) **VP/KP vs. sham/CC (safety):** No difference in risk of new or adjacent vertebral compression fractures or of procedure-related or all-cause mortality
Stevenson 2014	To systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of VP and percutaneous KP in reducing pain and disability in people with osteoporotic vertebral compression fractures in England and Wales	Osteoporotic vertebral fractures	VP or KP vs. sham or CC or each other	Health-related quality of life, back-specific functional status/ mobility, pain/analgesic use	**VP vs. sham:** 2 RCTs (n=209) **VP vs. CC:** 5 RCTs (n=505) **KP vs. CC** 1 RCT (n=300) **VP vs. KP** 1 RCT (n=100) **Cost-effectiveness** 1 study (hypo-thetical patient cohort); 2 models presented by industry (Johnson & Johnson, Medtronic)	**VP vs. sham:** There is as yet no convincing evidence that either VP performs better than sham. **VP vs. CC:** VP perform significantly better in unblinded trials than CC in terms of improving quality of life and reducing pain and disability **KP vs. CC:** KP perform significantly better than CC in terms of improving quality of life and reducing pain and disability **VP vs. KP:** No difference in pain between groups; function and quality of not assessed **Cost-effectiveness:** The uncertainty in the evidence base

Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
						means that no definitive conclusion on the cost-effectiveness of VP or KP can be provided.

CC: conservative care; KP: Kyphoplasty; RCTs: randomized controlled trials; VP: vertebroplasty.
*Only outcome for which results were reported stratified by comparison groups of interest (as opposed to the combined groups of VP/KP vs. sham/CC).

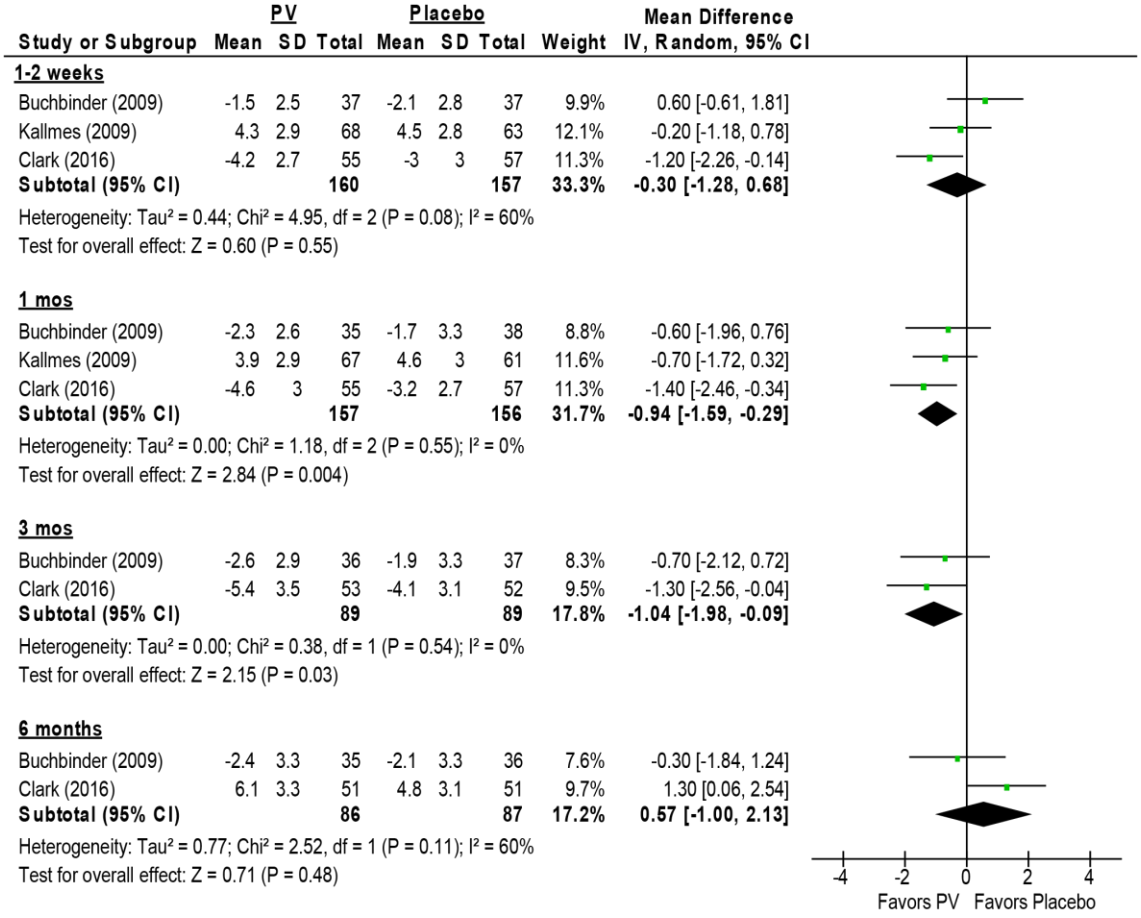
APPENDIX C. PRELIMINARY META-ANALYSES: PV vs. SHAM

Figure 1. Success: Proportion of patients with improvement in pain*



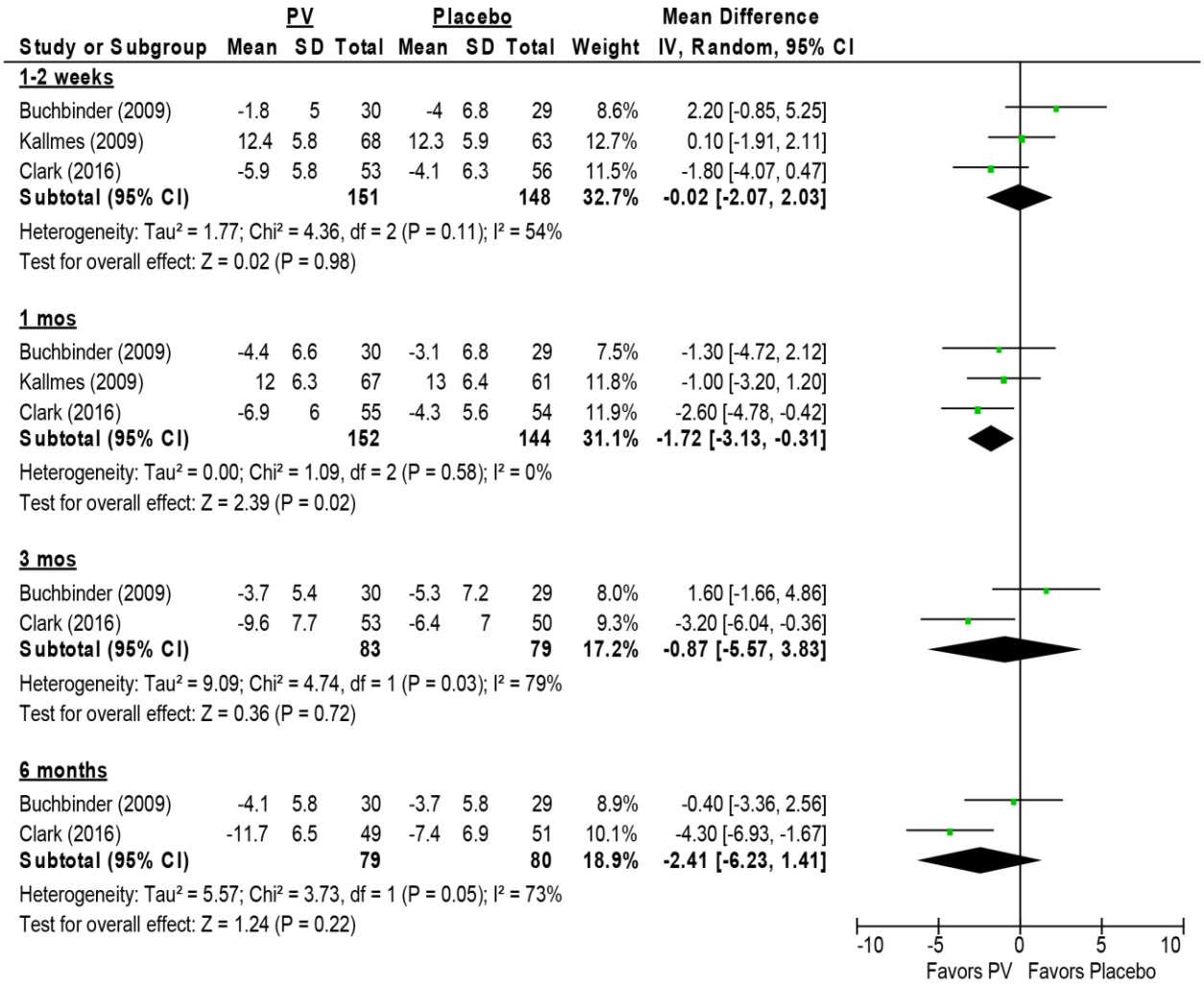
*Improvement in pain was defined variably across the three trials: 2.5 units (Buckbinder) or >30% or more from baseline (Kallmes) or pain less than 4 out of 10 (Clark)

Figure 2: Mean Difference in Pain Scores (VAS or NRS*)



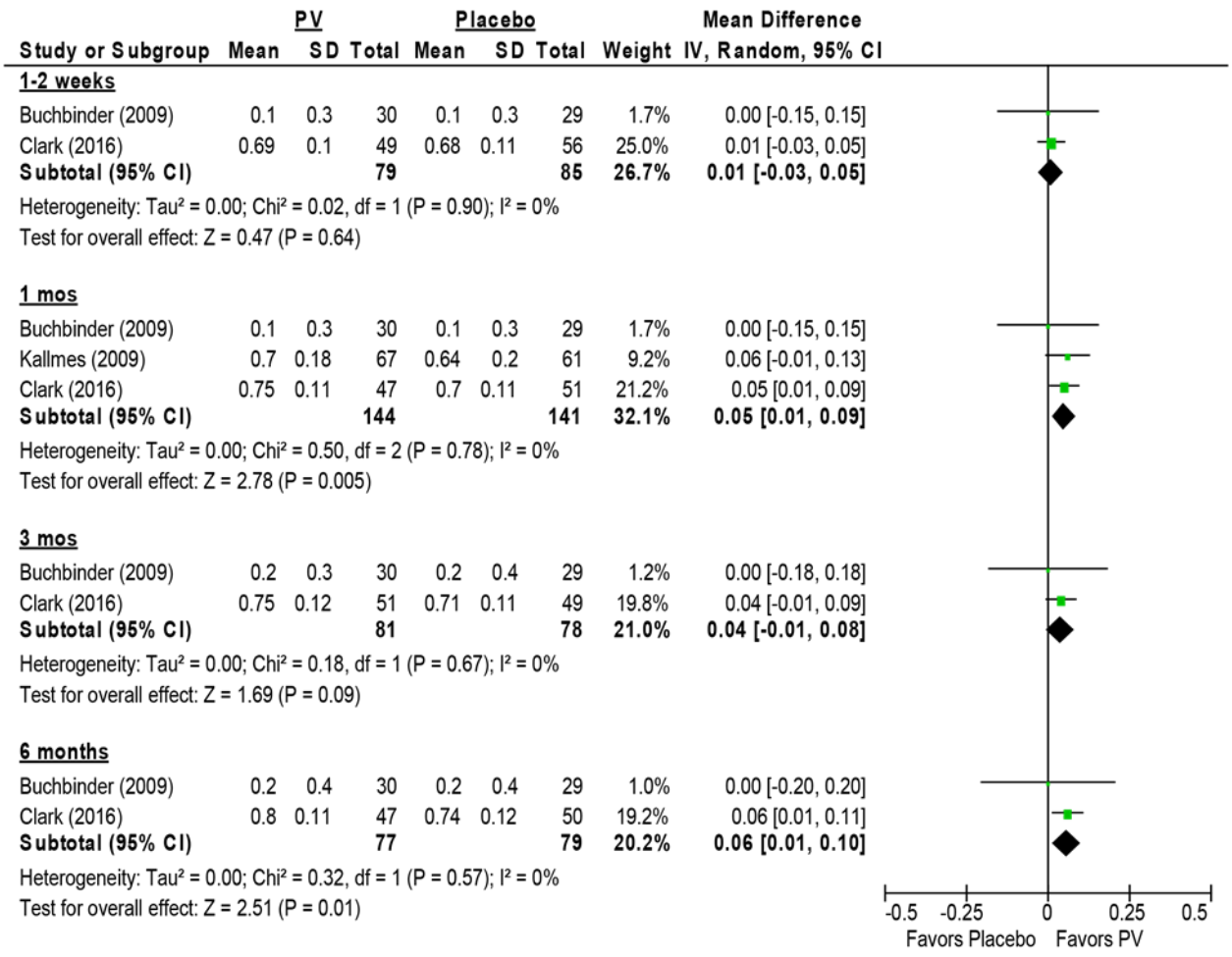
* O-10 point scale, 10 being worst pain; Buchbinder Cochrane review considered clinically important change to be 1.5 points

Figure 3: Mean Difference in Roland-Morris Disability Questionnaire (RMDQ) Scores*



*RMDQ range 0-23 points; higher score, worse disability. Buchbinder Cochrane review considered clinically important change to be 2-3 points

Figure 4: Mean difference in EQ5D*



Buchbinder Cochrane review considered clinically important change to be 0.074 on 0-1.0 EQ-5D

APPENDIX D. PUBLICATIONS EXCLUDED AT FULL TEXT REVIEW

Excluded systematic reviews

Citation	Reason for exclusion
Bouza C, Lopez-Cuadrado T, Almendro N, Amate JM. Safety of balloon kyphoplasty in the treatment of osteoporotic vertebral compression fractures in Europe: a meta-analysis of randomized controlled trials. Eur Spine J 2015;24:715-23.	Safety of kyphoplasty only; included trials of non-FDA approved devices
Chang X, Lv YF, Chen B, Li, HY, Han XB, Yang K, Zhang W, Zhou Y, Li CQ. Vertebroplasty versus kyphoplasty in osteoporotic vertebral compression fracture: a meta-analysis of prospective comparative studies. Int Orthop 2015;39:491-500.	Combined RCTs and observational studies
De la Garza-Ramos R, Benvenutti-Regato M, Caro-Osorio E. Vertebroplasty and kyphoplasty for cervical spine metastases: a systematic review and meta-analysis. Int J Spine Surg 2016;10:7.	Systematic review of case series only
Fan B, Wei Z, Zhou X, et al. Does vertebral augmentation lead to an increasing incidence of adjacent vertebral failure? A systematic review and meta-analysis. *Int J Surg.* 2016	Analysis of adjacent fractures only; Substantial overlap with Buchbinder SR with same conclusions; Poor documentation of included studies
Gu CN, Brinjikji W, Evans AJ, Murad MH, Kallmes DF. Outcomes of vertebroplasty compared with kyphoplasty: a systematic review and meta-analysis. J Neurointerv Surg 2015;11	Combined RCTs and observational studies
Han SL, Wan SL, Li QT, Xu DT, Zang HM, Chen NJ, Chen LY, Zhang WP, Luan C, Yang F, Xu ZW. Is vertebroplasty a risk factor for subsequent vertebral fracture, meta-analysis of published evidence? Osteoporos Int 2015;26:113-22.	Combined RCTs and observational studies
Liu J, Li X, Tang D, Ciu X, Li X, Yao M, Yu P, Qian X, Wang Y, Jiang H. Comparing pain reduction following vertebroplasty and conservative treatment for osteoporotic vertebral compression fractures: a meta-analysis of randomized controlled trials. Pain Physician 2013;16:455-64.	Not the most up to date systematic review identified (i.e., did not included all relevant RCTs published to date)
Mattie R, Laimi K, Yu S, Saltychev M. Comparing Percutaneous Vertebroplasty and Conservative Therapy for Treating Osteoporotic Compression Fractures in the Thoracic and Lumbar Spine: A Systematic Review and Meta-Analysis. J Bone Joint Surg Am. 2016;98(12):1041-1051	Includes same RCTs and data as Buchbinder SR with same conclusions
Vertebral Augmentation Involving Vertebroplasty or Kyphoplasty for Cancer-Related Vertebral Compression Fractures: A Systematic Review. Ont Health Technol Assess Ser. 2016;16(11):1-202.	Systematic review portion: primarily non-comparative studies of cancer-related VCF; 6 RCTs included, only 1 of which would meet inclusion criteria and is captured in the update report.
Yuan WH, Hsu HC, Lai KL. Vertebroplasty and balloon kyphoplasty versus conservative treatment for osteoporotic vertebral compression fractures: A meta-analysis. *Medicine (Baltimore).* 2016;95(31):e4491	Includes almost all the same RCTs as Buchbinder ,Li and Stevenson SRs; Buchbinder and Stevenson analyses higher quality, more thorough;
Zhao G, Liu X, Li F. Balloon kyphoplasty versus percutaneous vertebroplasty for treatment of osteoporotic vertebral compression fractures (OVCFs). Osteoporos Int. 2016;27(9):2823-2834.	Combines 1 RCT and 10 nonrandomized comparative studies;

Excluded randomized controlled trials

Citation	Reason for exclusion
Arabmotlagh M, Rickert M, Lukas A, Rauschmann M, Fleege C. Small cavity creation in the vertebral body reduces the rate of cement leakage during vertebroplasty. J Orthop Res 2016;26.	Comparison of techniques
Blasco J, Martinez-Ferrer A, Macho J, San Roman L, Pomes J, Carrasco J, Monegal A, Guanabens N, Peris P. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: a 12-month randomized follow-up, controlled trial. J Bone Miner Res 2012;27:1159-66.	Included in the systematic review by Buchbinder 2015
Boonen S, Van Meirhaeghe J, Bastian L, Cummings SR, Ranstam J, Tillman JB, Eastell R, Talmadge K, Wardlaw D. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. J Bone Miner Res 2011;26:1627-37.	Included in the systematic reviews by Li 2015 and Stevenson 2014
Chen D, An ZQ, Song S, Tang JF, Qin H. Percutaneous vertebroplasty compared with conservative treatment in patients with chronic painful osteoporotic spinal fractures. J Clin Neurosci 2014;21:473-7.	Included in the systematic review by Buchbinder 2015
Comstock BA, Sitlani CM, Jarvik JG, Heagerty PJ, Turner JA, Kallmes DF. Investigational vertebroplasty safety and efficacy trial (INVEST): patient-reported outcomes through 1 year. Radiology 2013;269:224-31.	Included in the systematic review by Buchbinder 2015
Dohm M, Black CM, Dacre A, Tillman JB, Fueredi G. A randomized trial comparing balloon kyphoplasty and vertebroplasty for vertebral compression fractures due to osteoporosis. AJNR Am J Neuroradiol 2014;35:2227-36.	Included in the systematic review by Buchbinder 2015
Endres S, Badura A. Shield kyphoplasty through a unipedicular approach compared to vertebroplasty and balloon kyphoplasty in osteoporotic thoracolumbar fracture: a prospective randomized study. Orthop Traumatol Surg Res 2012;98:334-40.	Included in the systematic review by Buchbinder 2015
Evans AJ, Kip KE, Brinjikji W, Layton KF, Jensen ML, Gaughen JR, Kallmes DF. Randomized controlled trial of vertebroplasty versus kyphoplasty in the treatment of vertebral compression fractures. J Neurointerv Surg 2015;24	Sufficient data from systematic reviews for this comparison (VP vs. conservative); single RCT not included (conclusions consistent with SRs) Epub version of citation below
Evans AJ, Kip KE, Brinjikji W, et al. Randomized controlled trial of vertebroplasty versus kyphoplasty in the treatment of vertebral compression fractures. J Neurointerv Surg. 2016;8(7):756-763.	Final citation for Evans study; Sufficient data from systematic reviews for this comparison (VP vs. conservative); single RCT not included (conclusions consistent with SRs)
Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. J Neurosurg Spine 2011;14:561-9.	Included in the systematic review by Buchbinder 2015
Korovessis P, Vardakastanis K, Vitsas V, Syrimpeis V. Is Kiva implant advantageous to balloon kyphoplasty in treating osteolytic metastasis to the spine? Comparison of 2 percutaneous minimal invasive spine techniques: a prospective randomized controlled short-term study. Spine (Phila Pa 2014;39:E231-9.	Comparison of techniques

Citation	Reason for exclusion
Korovessis P, Vardakastanis K, Repantis T, Vitsas V. Balloon kyphoplasty versus KIVA vertebral augmentation--comparison of 2 techniques for osteoporotic vertebral body fractures: a prospective randomized study. Spine (Phila Pa) 2013;38:292-9.	Comparison of techniques
Kroon F, Staples M, Ebeling PR, Ebeling PR, Wark JD, Osborne RH, Mitchell PJ, Wriedt CH, Buchbinder R. Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. J Bone Miner Res 2014;29:1346-55.	Included in the systematic review by Buchbinder 2015
Noriega DC, Ramajo RH, Lite IS, Toribio B, Corredera R, Ardura F, Kruger A. Safety and clinical performance of kyphoplasty and SpineJack procedures in the treatment of osteoporotic vertebral compression fractures: a pilot, monocentric, investigator-initiated study. Osteoporos Int 2016;8:8.	Comparator not FDA approved; Comparison of techniques
Peris P, Blasco J, Carrasco JL, Martinez-Ferrer A, Macho J, San Roman L, Monegal A, Guanabens N. Risk factors for the development of chronic back pain after percutaneous vertebroplasty versus conservative treatment. Calcif Tissue Int 2015;96:89-96.	Sufficient data from systematic reviews for fracture age and duration of symptoms; single RCT not included (conclusions consistent with SRs)
Petersen A, Hartwig E, Koch EM, Wollny M. Clinical comparison of postoperative results of balloon kyphoplasty (BKP) versus radiofrequency-targeted vertebral augmentation (RF-TVA): a prospective clinical study. Eur J Orthop Surg Traumatol 2016;26:67-75.	Comparison of techniques
Staples MP, Howe BM, Ringler MD, Mitchell P, Wriedt CH, Wark JD, Ebeling PR, Osborne RH, Kallmes DF, Buchbinder R. New vertebral fractures after vertebroplasty: 2-year results from a randomised controlled trial. Arch Osteoporos 2015;10:229.	Same population as an RCT included in the systematic review by Buchbinder 2015
Tutton SM, Pflugmacher R, Davidian M, Beall DP, Facchini FR, Garfin SR. KAST Study: The Kiva System As a Vertebral Augmentation Treatment-A Safety and Effectiveness Trial: A Randomized, Noninferiority Trial Comparing the Kiva System With Balloon Kyphoplasty in Treatment of Osteoporotic Vertebral Compression Fractures. Spine (Phila Pa 2015;40:865-75.	Comparison of techniques
Van Meirhaeghe J, Bastian L, Boonen S, Ranstam J, Tillman JB, Wardlaw D. A randomized trial of balloon kyphoplasty and nonsurgical management for treating acute vertebral compression fractures: vertebral body kyphosis correction and surgical parameters. Spine (Phila Pa 2013;38:971-83.	Included in the systematic review by Li 2015
Vogl TJ, Pflugmacher R, Hierholzer J, Stender G, Gounis M, Wakhloo A, Fiebig C, Hammerstingl R. Cement directed kyphoplasty reduces cement leakage as compared with vertebroplasty: results of a controlled, randomized trial. Spine (Phila Pa 2013;38:1730-6.	Included in the systematic review by Buchbinder 2015
Wang B, Guo H, Yuan L, Huang D, Zhang H, Hao D. A prospective randomized controlled study comparing the pain relief in patients with osteoporotic vertebral compression fractures with the use of vertebroplasty or facet blocking. Eur Spine J 2016;5:5.	Sufficient data from systematic reviews for this comparison (VP vs. conservative); single RCT not included (conclusions consistent with SRs)
Wang CH, Ma JZ, Zhang CC, Nie L. Comparison of high-viscosity cement vertebroplasty and balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures. Pain Physician 2015;18:E187-94.	Comparison of techniques

Citation	Reason for exclusion
Werner CM, Osterhoff G, Schlickeiser J, Jenni R, Wanner GA, Ossendorf C, Simmen HP. Vertebral body stenting versus kyphoplasty for the treatment of osteoporotic vertebral compression fractures: a randomized trial. J Bone Joint Surg Am 2013;95:577-84.	Comparator not FDA approved; Comparison of techniques
Yi X, Lu H, Tian F, Wang Y, Li C, Liu H, Liu X, Li H. Recompression in new levels after percutaneous vertebroplasty and kyphoplasty compared with conservative treatment. Arch Orthop Trauma Surg 2014;134:21-30.	Data combined for the vertebroplasty and kyphoplasty groups

Excluded economic studies

Citation	Reason for exclusion
Becker S, Pfeiffer KP, Ogon M. Comparison of inpatient treatment costs after balloon kyphoplasty and non-surgical treatment of vertebral body compression fractures. Eur Spine J 2011;20:1259-64.	Costing study; not a formal economic analysis
Takura T, Yoshimatsu M, Sugimori H, et al. Cost-Effectiveness Analysis of Percutaneous Vertebroplasty for Osteoporotic Compression Fractures. *Clin Spine Surg.* 2016	Single arm (PV only) study; evaluated change from baseline at 52 weeks; not comparative with other treatment

APPENDIX E. NEW FDA APPROVED DEVICES

Procedure/Device	Brief description	FDA Approval (Date)	Source
KIVA for VCF (Benvenue Medical, Santa Clara, CA)	A small coil-like flexible implant placed in the vertebral body that restores vertebral height and allows the direction of bone cement into the space surrounding the implant	FDA 510(k) clearance (January 2014)	http://benvenuemedical.com/products/ http://benvenuemedical.com/press-release/kiva-vcf-treatment-system-receives-fda-clearance-vertebral-compression-fractures/
Radiofrequency-targeted vertebral augmentation (RFTVA) (DFINE StabiliT San Jose, CA)	Targeted delivery of radiofrequency-activated warm, highly viscous bone cement PMMA using an articulating osteotome	510k approved (December 2009)	https://www.accessdata.fda.gov/cdrh_docs/pdf9/K090986.pdf
High-Viscosity cement vertebroplasty (HVCV) Confidence Spinal Cement System (DePuy Spine Inc, Raynham, MA, USA)	Modification of vertebroplasty designed to decrease cement leakage	FDA 510(k) clearance (December 2011)	https://www.accessdata.fda.gov/cdrh_docs/pdf11/K112907.pdf
Shield Kyphoplasty SOTEIRA, INC. 5 Whitcomb Avenue Ayer, MA 01432	includes a unilateral, steerable cavity creator and a self-expanding stent-like implant designed to direct PMMA cement flow for optimal placement during vertebral augmentation.	FDA 510(k) clearance (December 2011)	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K093477
Crosstrees PVA Pod System	Uses a soft woven fabric pod that allows the flow of bone cement to be controlled as it is injected into the vertebral body.	FDA 510(k) clearance (August 2013)	https://www.accessdata.fda.gov/cdrh_docs/pdf13/K130089.pdf http://xtreesmed.com/crosstrees-system-solution.php