WASHINGTON STATE HEALTH CARE AUTHORITY

Vertebroplasty, Kyphoplasty and Sacroplasty

Health Technology Assessment

Date: November 4, 2010

Health Technology Assessment Program
676 Woodland Square Loop SE
P.O. Box 42712
Olympia, WA 98504-2712

http://www.hta.hca.wa.gov

Provided by:

Spectrum Research, Inc.

Prepared by:

Barbara C. Leigh, PhD, MPH
Andrea C. Skelly, PhD, MPH
Nora B. Henrikson, PhD, MPH
Lisa Kercher, PhD, MPH,
Megan Skinner, BA, MPH

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

Table of contents

List of figures

List of tables

Executive Summary

Introduction

Vertebral compression fractures (VCFs) and sacral insufficiency fractures (SIF) often result in considerable pain, loss of function, and decreased quality of life. Patients with osteopenic vertebral or sacral fractures are at greater risk of morbidity and mortality, yet operative intervention (e.g. fusion with instrumentation) may be problematic in this elderly population making less invasive methods more attractive.

Vertebroplasty, kyphoplasty and sacroplasty (collectively, percutaneous vertebral and sacral surgery) are surgical procedures used to treat spinal pain believed to be caused by fractures in the vertebra or sacrum. These are all cementoplasty techniques that are thought to relieve pain by stabilizing the fractured bone(s), but the mechanism of pain relief is not clear. Osteoporosis, vertebral metastasis and multiple myeloma are the most frequently reported indications for these procedures.

Vertebroplasty involves injection of bone cement into a partially collapsed vertebral body under computed tomography (CT) or fluoroscopic guidance. Kyphoplasty is a modification of vertebroplasty that expands the partially collapsed vertebral body with an inflatable balloon before the injection of bone cement. Sacroplasty is an extension of vertebroplasty, involving the injection of bone cement into the sacrum to repair sacral insufficiency fractures.

These surgical procedures are less invasive than other spinal surgical procedures, but more invasive than conservative medical therapy. Although a number of non-randomized studies have reported improvements in pain and functioning following these procedures, significant questions remain about their safety, efficacy and effectiveness, and cost effectiveness.

Key questions

When used in patients with spinal pain *due to vertebral fracture*:

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

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

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)

Methods for evaluating comparative effectiveness

We selected articles to summarize based on the inclusion and exclusion criteria in the following table:

Study Component	Inclusion	Exclusion
Participants	Patients with spinal pain due to vertebral fracture secondary to • osteoporosis • malignancy	• Fractures due to high energy trauma
Intervention	• Vertebroplasty • Kyphoplasty • Sacroplasty	
Comparators	• Conservative care • Surgical procedures • Vertebroplasty vs. kyphoplasty	• Comparisons of different cement types • Comparisons of surgical approaches or techniques • Use of vertebroplasty, kyphoplasty or sacroplasty as an adjunct to other procedures (e.g. ablation)
Outcomes	• Functional outcomes (e.g. ODI) • Pain relief • Quality of life outcomes • Complications (e.g. procedure related, leakage, new fracture, medical complications, death. Revision/re-operation) • Return to work	
Study Design	• Comparative clinical studies (e.g. RCTs, cohort studies with concurrent controls) will be considered for questions 1, 3 and 4 • For question 2, safety, case series will be considered if adequate information not available from comparative studies • Formal economic studies will be sought for question 4	• Case reports • Case series with fewer than 5 patients (for sacroplasty)

Publication	• Full-length studies published in English in peer reviewed journals, published HTAs or publicly available FDA reports • Full formal economic analyses (e.g. cost-utility studies) published in English in HTAs or in a peer-reviewed journal published after those represented in previous HTAs.	• Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • Studies reporting on the technical aspects of these procedures • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

We conducted a formal, structured systematic search of the peer-reviewed literature across anumber of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments. Pertinent studies were critically appraised using our Level of Evidence (LoE) system, which evaluates the methodological quality based on study design as well as factors that may bias studies. An overall Strength of Evidence combines theLoE with consideration of the number of studies and the consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results

Key question 1: Efficacy

Vertebroplasty

- Pain relief: It is uncertain whether vertebroplasty is effective for the relief of pain due to VCF. All of the RCTs, which were limited to patients with osteoporotic fractures, evaluated relatively short-term effects (≤12 months). While two sham-controlled RCTs concluded that there was no benefit with regard to pain relief (up to 1month in one study and 6 months in the other), the studies did not have adequate power to detect differences in the proportion of patients with clinically meaningful improvement. While the largest RCT comparing vertebroplasty with conservative care in acute osteoporotic fractures demonstrated statistically significant improvement in pain scores that was sustained to the 12-month follow-up, the extent to which lack of patient blinding and possible placebo effect may contribute to the findings is not clear. Two small RCTs reported no advantage for vertebroplasty over 2 weeks or 12 months. The overall strength of evidence is low and effect estimates may change with additional research.
- Function and quality of life: It is uncertain whether vertebroplasty improves patient functioning and quality of life. In a large RCT, 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 largely comparable improvements in function over 2 weeks and 12 months for vertebroplasty and non-surgical patients. The overall strength of evidence is low and effect estimates may change with additional research.

Kyphoplasty

- Pain relief: It is uncertain whether kyphoplasty is effective for pain relief. 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.
- Function and quality of life: It is uncertain whether kyphoplasty improves patient functioning and quality of life. In the single RCT, kyphoplasty was more effective than conservative treatment in improving functioning as measured by the EQ-5d, RDQ, and SF-36 over most time periods. Following an early advantage for KP, group differences were diminished by 12 months as CMT patients improved over time. 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.

Vertebroplasty compared with kyphoplasty

- Pain relief: A single poor-quality RCT found that back pain scores improved equally for vertebroplasty and kyphoplasty patients over 6 months. The strength of evidence is very low.
- Function and quality of life: There is no evidence of efficacy for these outcomes, as the single RCT did not assess them.

Sacroplasty

- There is no evidence of efficacy for sacroplasty. The only data available are from case series.

Key question 1: Effectiveness

Vertebroplasty

- Pain relief: It is uncertain whether vertebroplasty is more effective than conservative medical treatment in reducing pain. Four nonrandomized studies with follow-up up to one year found that vertebroplasty was more effective in reducing pain than conservative medical treatment up to approximately six months. At one year, pain levels in both groups of patients were comparable. The strength of evidence is very low.
- Function and quality of life: A similar pattern was seen in these four studies in improvements in functioning and quality of life: superior effectiveness of vertebroplasty

in the first 3-6 months was followed by equivalent levels of functioning at one year. The strength of evidence is very low.

Kyphoplasty

- Pain relief: In two non-randomized studies, kyphoplasty reduced pain more than conservative medical treatment for periods up to 3 years.
- Function and quality of life: In these two studies, kyphoplasty improved a limited set of functional outcomes more than conservative medical treatment.

Vertebroplasty compared with kyphoplasty

- Pain relief: In 8 of 10 non-randomized studies, vertebroplasty and kyphoplasty led to comparable pain reduction up to 2 years.
- Function and quality of life: In 4 of 5 non-randomized studies, vertebroplasty and kyphoplasty patients demonstrated comparable improvements in ODI up to 2 years.

Sacroplasty

- Very limited data from9 case series (N = 141 total patients) suggests that patients experience pain relief following sacroplasty. In the absence of well-conducted comparative studies, no conclusions regarding effectiveness can be drawn and the strength of evidence is very low.

Key question 2: Safety

Overall, while it appears that rates of serious complications that have associated symptoms are low for vertebroplasty and kyphoplasty, studies with long-term (> 5 year) follow-up are few. Moreover, comparative studies, especially RCTs, may have too few patients to detect more rare but serious outcomes.

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. In other comparative studies, numbers of new fractures were too small to draw conclusions about fracture risk in adjacent versus non-adjacent vertebrae, due to the small number of patients in these studies.
    - 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%). Because systematic reviews include information on case series, the level of evidence is very low.

- Cement leakage
  - In comparative studies, rates of cement leakage 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, non-randomized 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. Peri-operative mortality rate for kyphoplasty was .01% across 11 case series.
  - Since the majority of patients receiving these procedures are either elderly and/or have malignant disease, the extent to which mortality can be attributed to the procedures is unclear.

Sacroplasty

- The overall strength of evidence 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.

Key question 3: Differential efficacy and safety for subpopulations

No studies were found that addressed differential efficacy or safety issues for subpopulations defined by gender, age, psychological or psychosocial co-morbidities, provider characteristics, or payer type.

Diagnosis (osteoporosis or tumor-related fractures)

- There are no studies that assessed differential outcomes of vertebroplasty or kyphoplasty by fracture etiology. The majority of studies were limited to patients with osteoporotic fractures. Only two retrospective cohort studies (both comparing vertebroplasty with kyphoplasty) studied patients with fractures due to malignancy, with one study reporting comparable outcomes both procedures and the other reporting that kyphoplasty led to more improvement in pain than vertebroplasty over one year.

Fracture age

The extent to which vertebroplasty may be more efficacious in patients with acute fractures, as compared to those with more chronic fractures, is uncertain based on available RCTs.

- No studies were designed to directly compare efficacy or safety outcomes between patients with acute, subacute, and/or chronic fractures. Two RCTs of vertebroplasty compared with sham surgery, which included patients with both acute and more chronic fractures, conducted post-hoc subgroup analysis indicating that pain outcomes did not differ significantly for more recent fractures compare to fractures of longer duration. However, these analyses were likely to have low power for detecting differential outcomes in patients of different fracture ages.
- The largest RCT comparing vertebroplasty with conservative care included only acute osteoporotic fractures (≤6 weeks pain duration), reporting that vertebroplasty was more effective in improving pain and functioning. However, it is difficult to establish differential effectiveness by fracture age without a direct comparison of patients who had more chronic fractures in the same underlying patient population. Thus, the findings from this study do not address the issue of differential efficacy.
- Across non-randomized cohort studies comparing vertebroplasty with conservative treatment, similar results were reported in studies of patients with acute fractures and with chronic fractures. The majority of these studies reported earlier pain reduction for vertebroplasty, with no significant group differences by one year after the procedure. Again, without direct comparison of outcomes, conclusions regarding differential efficacy are problematic.

Sacroplasty

- Among the published case series of sacroplasty, two included only patients with osteoporotic fractures, three were of patients primarily with multiple myeloma or other tumors, and four were of patients with SIF of undefined or mixed causes. Pain scores improved following sacroplasty for both osteoporotic and malignant fractures, from 8.1-9.1 pre-operatively to 0.8-3.8 at varying follow-up periods. The overall strength of evidence is very low.

Key question 4: Cost effectiveness

- Because the efficacy and effectiveness of these procedures is uncertain, their overall cost effectiveness is unclear. Because no cost studies were conducted with U.S. data, the cost effectiveness of vertebroplasty, kyphoplasty or sacroplasty in a US setting is unknown.
- Assuming benefit in quality of life (pain relief) at 12 months, balloon kyphoplasty may be associated with increased cost and a small increase in quality in adjusted life years at three years post-procedure.
- Percutaneous vertebroplasty was associated with early (<3 months) improvements in pain and function at comparable cost compared with medical therapy alone in two studies. At 12 months vertebroplasty and medical therapy were comparable on pain, function, and healthcare cost.
- The economic impact of complications, reoperation, or revision following vertebroplasty, kyphoplasty, or sacroplasty is unknown.

Summary by key question

Key Question 1: What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?

1. Vertebroplasty (PV) vs. sham surgery or conservative treatment (CMT)		
	Strength of evidence	**Conclusions/Comments**
Efficacy	**Low evidence**	• In two RTs, 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.
2. Vertebroplasty (PV) vs. conservative treatment (CMT)		
Efficacy	**Low evidence**	• In a large RCT comparing PV with conservative treatment, PV was more 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	**Low evidence**	• In four cohort studies (2 prospective and 2 retrospective): o PV was more effective than CMT in reducing pain (from 7.5-9 to 0.7-3.5) up to 6 months, but pain levels were comparable for the two groups after one year. o 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.
3. Kyphoplasty (KP) vs. conservative treatment		
	Strength of evidence	**Conclusions/Comments**
Efficacy	**Low evidence**	• In one RCT: o KP was more effective than CMT by 0.9-2.2 points in reducing pain intensity for follow-up points up to one year. o Pain was reduced more rapidly in KP patients, and group differences were diminished by 12 months. o 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.
Effectiveness	**Very low evidence**	• In two cohort studies (1 prospective and 1 retrospective): o KP reduced pain more than CMT for periods up to 3 years. o KP improved a limited set of functional outcomes more than CMT.
4. Vertebroplasty vs. kyphoplasty		
	Strength of evidence	**Conclusions/Comments**
Efficacy	**Very low evidence**	• One poor-quality RCT found that: o Back pain scores improved equally (from 8.0 to 2.3-2.6) for PV and KP patients over 6 months.
Effectiveness	**Low evidence**	• Evidence from 12 cohort studies (6 prospective and 6 retrospective) demonstrated that o 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. o PV and KP demonstrated 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.
5. Sacroplasty		
	Strength of evidence	**Conclusions/Comments**
Efficacy and effectiveness	**Very low evidence**	• No comparative studies identified; case series suggest improvement in pain following sacroplasty

Key Question 2:What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?

	Strength of evidence	Conclusions/Comments
Vertebroplasty and kyphoplasty	**Low evidence**	• New fractures: o 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. o 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%). o 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 o Rates of asymptomatic cement leakage are up to 80% for vertebroplasty and 50% for kyphoplasty. o 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) o One RCT reported a PCE rate for PV of 26%, with all cases asymptomatic o Systematic reviews of case series report pooled PCE rates from .1% to 1.7%, with insufficient information to compare rates for PV and KP. • Mortality o Data from systematic reviews primarily of case series o Rates in prospective studies of 2.1% (22/1051) for PV and 0.6% (24/5629) for retrospective studies. o Overall mortality for kyphoplasty ranging from 2.3% (13/588) to 3.2 % (25/522) from 2 different reviews o Perioperative mortality: 0.01% (1/406).
Sacroplasty	**Very low evidence**	• Across four case series, rate of cement leakage was 20.5% (7/34 patients)

Key Question 3: What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety issues in sub populations?

	Strength of evidence	Conclusions/Comments

1. Vertebroplasty vs. sham surgery or conservative treatment	**Very low evidence**	• Fracture age: o No studies were designed to directly compare efficacy or safety outcomes between patients with acute, subacute, and/or chronic fractures. o 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. o 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: o Two retrospective cohort studies in patients with malignancy fractures cannot provide information for differential efficacy based on fracture etiology.
2. Kyphoplasty vs. conservative treatment	**Very low evidence**	• No comparative studies were identified that assessed differential efficacy or safety according to patient, provider, or payer factors.
3. Vertebroplasty vs. kyphoplasty	**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.
4. Sacroplasty	**Very low evidence**	• No comparative studies were identified

Key Question 4: What is the evidence of cost implications and cost-effectiveness of vertebroplasty, kyphoplasty and sacroplasty?

	Strength of evidence	**Conclusions/Comments**
1. Vertebroplasty vs. sham surgery or conservative treatment	**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.
2. Kyphoplasty vs. conservative treatment	**Very low evidence**	• Cost data from one RCT showed that KP was associated with increased cost and increased QALY compared with CMT.
3. Vertebroplasty vs. kyphoplasty	**Very low evidence**	• No evidence
4. Sacroplasty	**Very low evidence**	• No evidence

Appraisal

Rationale

Fractures secondary to osteoporosis, vertebral metastasis and multiple myeloma are an important source of acute and chronic back pain as well as spinal deformity, reduced pulmonary function, decreased mobility and increased mortality. The majority of patients with osteoporotic fractures are older women. Patients with osteoporotic fracture are on average older than those with malignant fractures. Osteoporosis, vertebral metastasis and multiple myeloma are the most frequently reported indications for vertebroplasty and kyphoplasty. Sacroplasty is most frequently used to treat sacral insufficiency fractures (SIF), the majority of which are due to osteoporosis.

Patients with vertebral compression fracture (VCF) may or may not be symptomatic. Treatment of pain in VCF in the acute phase is not standardized. Chronic pain may be secondary to multiple fractures but the mechanism may be related more to muscle and ligament strain secondary to kyphosis. Such pain does not generally improve with analgesic use but may be addressed through exercise. While most patients are successfully treated with conservative therapy and pain relief occurs within a few weeks, persistent pain in a small percentage of patients leads to the consideration of operative treatment in this subset of patients. Vertebroplasty, kyphoplasty and sacroplasty are typically indicated for patients with painful insufficiency fracture due to osteoporosis or malignancy that is not responding to conservative treatment such as rest and analgesic use.

Vertebroplasty, kyphoplasty and sacroplasty are minimally invasive procedures which have purported benefits of relieving pain due to osteoporotic stress-related and tumor-related fractures and restoring function in patients whose bone maybe poor and/or who are poor candidates for more invasive surgical intervention. All involve the percutaneous injection of a cement (most commonly polymethylmethacrylate, PMMA) into the bone. These surgical procedures are less invasive than other spinal surgical procedures (e.g. fixation using screws), but more invasive than conservative medical therapy. Vertebroplasty, kyphoplasty and sacroplasty may relieve pain due to osteoporotic or malignant fracture by stabilizing the fracture and reducing pain from bone rubbing against bone. Another theory holds that the exothermic reaction of the cement as it hardens creates a thermal necrosis of intraosseous nerve fibers as a possible mechanism for pain relief. The precise mechanisms of pain relief are not well understood.

Despite increasing use of these procedures, the efficacy, safety and economic impact are not well understood.

Objective

The primary aim of this assessment is to systematically review, critically appraise and analyze research evidence comparing the efficacy, effectiveness and safety of vertebroplasty,

kyphoplasty and sacroplasty with other surgical and non-surgical treatment options. Available information on the economic impact of this will also be summarized and critically appraised.

Key questions

When used in patients with spinal pain *due to vertebral fracture*:

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
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)
3. What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety issues in sub populations? Including consideration of:
    a. Gender
    b. Age
    c. Psychological or psychosocial co-morbidities
    d. Diagnosis or time elapsed from fracture
    e. Other patient characteristics or evidence based patient selection criteria
    f. Provider type, setting or other provider characteristics
    g. Payer/beneficiary type: including worker's compensation, Medicaid, state employees
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)

Primary outcomes

Pain relief and restoration of function, as measured by validated outcomes instruments, were the primary, direct outcomes of interest for evaluating efficacy and effectiveness. Information on the following primary safety outcomes was sought: subsequent fractures (adjacent or non-adjacent to the treated vertebrae), symptomatic cement leakage, symptomatic pulmonary cement embolism, revision rates and mortality. Incremental cost-effectiveness of procedures was the main economic outcome of interest. Additional information on outcomes is presented later in the report.

Key considerations highlighted by clinical experts

Interventions

In patients whose bone quality is compromised, fracture fixation is a challenge and may not be feasible since screws and other devices may not hold. Vertebroplasty, kyphoplasty and sacroplasty provide an option for stabilizing fractures in patients whose bone is compromised by osteoporosis or tumor involvement that is less invasive than other surgical options.

Vertebroplasty and kyphoplasty have been demonstrated to relieve pain in clinical studies. The age of the fracture (and timing of intervention) is an important consideration. Patients with acute fractures (less than six weeks) may be more likely to experience pain relief compared with those whose fractures are more chronic.

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. If it is unclear, clinicians often order an MRI to assess for edema within the fractured level. If there is no edema, it is presumed to be a healed fracture and the procedures are unlikely to give relief. If there is edema that is suggestive of metabolic activity at the fracture site and the patient may get benefit from the procedure regardless of how long ago it actually fractured.

Overall, the risk of serious complications directly related to these procedures is generally considered to be low. While cement leakage is common with vertebroplasty, it is usually asymptomatic.

There is information on the short term complications and outcomes (peri-procedural to 1 year). The moderate term (2 to 5 year) and long-term (> 5 year) complications and outcomes of kyphoplasty and vertebroplasty are unknown. Very little is known about the safety and outcomes following sacroplasty.

Costs

Between 2001 and 2005, across the United States, vertebroplasty volumes and inflation-adjusted costs doubled, based on analysis of Medicare Part B fee for service claims.[1]Kyphoplasty is more expensive than vertebroplasty per treated level due to the increased length of procedure, cost of the balloon kit, anesthesia (usually), and at least one night stay in a hospital.[2]

Patient considerations

Patients presenting with either osteoporotic or tumor-related fractures may be in poor general health and have a number of co-morbid conditions that may make them poor surgical candidates.

Rapid pain relief and ability to perform activities of daily living may be the most important factors for patients. Patients with a greater degree of pain before the procedure may get more benefit out of the procedure. Deformity caused by multiple fractures may influence self-image

and, together with the pain, impact overall quality of life as well as ability to perform activities of daily living.

Professional considerations

PMMA residue is volatile and may cause headache or eye irritation in the operators. The PMMA package insert calls for double gloving when handling because there is inadequate information about the effect of PMMA resin on fertility, its teratogenic potential or its effect on fetuses.[3]

Provider experience may be an important factor. Among experienced interventional neuroradiologists with no prior vertebroplasty experience, cement volume utilization and postoperative rest pain both decreased as the operator became more experienced with vertebroplasty.[4]

Ethical considerations

Insufficiency fractures of the vertebrae or sacrum can take months to heal on their own. Patients may be in a great deal of pain and have significant difficulty in functioning. Is it more appropriate for patients to be treated immediately, or to undergo treatment later after conservative treatment has failed?[5]

Washington State utilization and cost data

Figure 1. UMP/PEP* Vertebral Augment (VA) Costs (+/- 3 day costs related by diagnosis)

Vertebral Augment Costs	2006	2007	2008	2009	Grand Total
Total Vertebral Augment Costs (3 day window of related charges)	$70,095	$156,750	$323,617	$318,081	$868,543*
Average Costs (UMP primary only)	$5,199	$11,516	$13,423	$10,837	$11,648
Minimum (UMP primary only)	$290	$722	$491	$1075	$290
Maximum	$11,815	$45,016	$42,130	$34,474	$45,016

**DSHS/DLI do not cover these procedures, and averaged 10 and 1 procedure(s)/year respectively.*

Figure 2. UMP/PEP VA Usage and Cost Trends

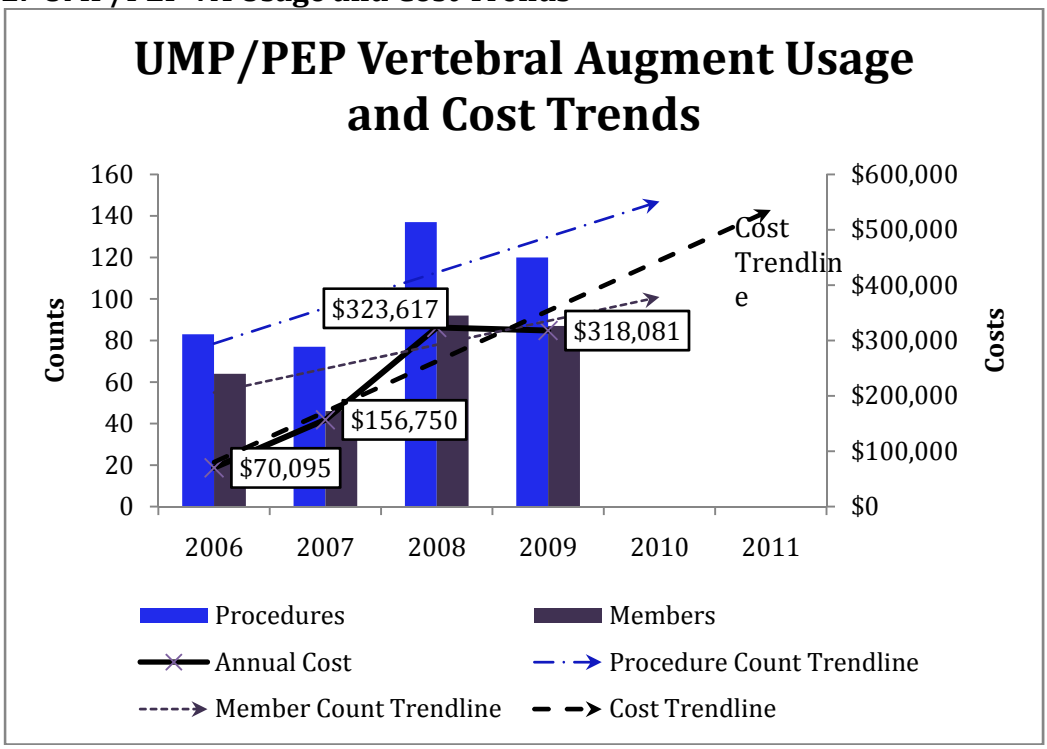


Figure 3: UMP/PEP Kyphoplasty/Vertebroplasty Comparison

Vertebral Augments	2006	2007	2008	2009	Overall
Vertebroplasty					
Procedures	25	31	53	55	164
Members	19	20	39	42	116
Total Costs	$16,590	$45,583	$99,705	$211,833	$373,711
Cost/Proc	$664	$1,470	$1,881	$3,852	$2,279*
Kyphoplasty					
Procedures	58	46	84	65	253
Members	45	26	53	45	170
Total Costs	$58,529	$121,275	$232,905	$273,983	$686,692
Cost/Proc	$1,009	$2,636	$2,773	$4,215	$2,714*
All Augments Summary					
Procedures	83	77	137	120	417
Members	64	46	92	87	286
Annual Cost	$70,095	$156,750	$323,617	$318,081	$868,543
Cost/Proc	$845	$2,036	$2,362	$2,651	$2,083

** Some patients had both types of procedures within the same hospital or outpatient encounter. In this case, related charges such as pre-surgery exams and imaging are included in both subsections, but are consolidated in the summary section.*

Figure 4: UMP/PEP Vertebral Augmentation Patients by Age and Gender, 2006-2009

Gender/Age	Counts by Age	Gender/ Totals	Average Age	SD	Max
Female					
43-65	19	82	75.7	11.6	96
66-80	33				
81+	30				
Male					
43-65	6	45	76.9	10.4	93
66-80	14				
81+	14				
Overall					
43-65	25	127	76.1	11.2	96
66-80	47				
81+	44				

Figure 5: UMP/PEP Repeat Procedures and Readmits within 30 days

Vertebral Augment Repeats	Repeat Procedure Count	% of total Procedures (417 total)	% of VA Patients (286)	Avg Days to Repeat/ Readmit	Max	Min
Readmits in 30 days	6	1.4%	2.1%	10	13	3
Repeated Procedures	58	13.9%	20.3%	194.7	1079	1

Related Medical Codes		
Codes	**Number**	**Description**
CPT Vertebroplasty	22520	Percutaneous vertebroplasty, one vertebral body, unilateral or bilateral injection, thoracic
	22521	Percutaneous vertebroplasty, one vertebral body, unilateral or bilateral injection, lumbar
	22522	Vertebroplasty: additional thoracic or lumbar vertebral body (list separately in addition to code for primary procedure)
CPT Kyphoplasty	22523	Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device, one vertebral body, unilateral or bilateral cannulation (e.g. kyphoplasty) thoracic
	22524	Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device, one vertebral body, unilateral or bilateral cannulation (e.g. kyphoplasty) lumbar

	22525	Kyphoplasty: Each additional thoracic or lumbar vertebral body (list separately in addition to code for primary procedure)
Radiologic support	72291	Radiological supervision and interpretation, percutaneous vertebroplasty or vertebral augmentation including cavity creation, per vertebral body, under fluoroscopic guidance
	72292	Radiological supervision and interpretation, percutaneous vertebroplasty or vertebral augmentation including cavity creation, per vertebral body, under CT guidance
CPT, Sacroplasty	0200T	Percutaneous sacral augmentation (sacroplasty), unilateral injections(s), including the use of a balloon or mechanical device (if utilized), one or more needles
	0201T	Percutaneous sacral augmentation (sacroplasty), bilateral injections(s), including the use of a balloon or mechanical device (if utilized), two or more needles
	72275	Epidurography, radiological supervision and interpretation
Deleted codes	76012	Expired on 12/31/2006 – Radiographic guidance for kyphoplasty and vertebroplasty, fluoroscopic
	76013	Expired on 12/31/2006 – Radiographic guidance for kyphoplasty and vertebroplasty, CT
	76499	Expired on 12/31/2005 – Radiographic guidance for kyphoplasty, fluoro or CT
	22899	Expired use on 12/31/2005 – kyphoplasty. Current data lists this as "Radiographic procedure"
Other Codes	S2360	Vertebroplasty, first level
	S2361	Vertebroplasty, additional levels
	S2362	Kyphoplasty, first level
	S2363	Kyphoplasty, additional levels
	20982	Tumor ablation – a procedure that can be done with KP/VP

Related Medical Codes cont.		
	20982	Unlisted musculoskeletal procedure- might be used for cervical vertebra – a procedure that can be done with KP/VP
DRGs		496,497,498,515,516,517
Related Diagnoses	733.00-733.09	Osteoporosis
Fractures	733.13	Osteoporotic fracture
	805.00-805.08	Other fractures
	805.2	Fx Dorsal vertebra-close
	805.4	Fx lumbar vertebra-close
	805.6	Fx Sacrum/coccyx –closed
	806.4	Cl Lumbar fx w cord Inj

	829	Fracture NOS-Closed
Related Cancer Diagnoses	198.5	Secondary Malig Neo Bone
	203	Mult Mye w/o Achv Rmson
	204.1	Ch lym leuk wo achv rmsn
Other Related Diagnoses	338.11	Acute pain due to trauma
	721.3	Spondylosis
	722.52	Disc degen
	723.4	Brachial Neuritis
	724.02	Spinal Stenosis-Lumbar
	724.1	Pain in thoracic spine
	724.2	Lumbago
	724.3	Sciatica
	724.4	Lumbo-sacral neuritis
	724.5	Backache NOS
	724.6	Disorders of sacrum
	724.79	Disorders of Coccyx NEC

1.Background

1.1 The condition

Vertebroplasty, kyphoplasty, and sacroplasty are surgical procedures in which bone cement is injected into a fractured vertebra in order to relieve pain from the fracture. While vertebroplasty and kyphoplasty are typically performed on the thoracic or lumber spine, sacroplasty is performed on fractures in the sacrum. The two primary indications for these procedures are osteoporotic or tumor-related fractures.

Osteoporotic fracture

Women are at greater risk of osteoporotic fractures than men. In general, the risk of osteoporotic fracture increases with age for both men and women.[6]Vertebral compression fractures (VCF) are the most frequent type of osteoporotic fracture. The prevalence of VCF is thought to be around 1.4 million out of 155 million people 50-79 years old.[7, 8]Patients may not always present with symptoms and only about one third of cases reach clinical diagnosis, making the precise prevalence difficult to estimate.[6, 9, 10] Patients with VCF can have height loss and severe back pain, which may inhibit the ability to perform normal activities.[11] Patients may also become depressed or have a negative self image.[11]

While most patients are successfully treated with conservative therapy and pain relief occurs within 4-6 weeks,[11] alternative treatments must be considered for the small percentage of patients with persistent pain. Patients who have had VCFs may subsequently have vertebral deformities that may influence clinical outcomes, and are at increased risk for recurrence of VCF[12]and other fractures.[13, 14]Patients with osteoporotic vertebral fractures are at greater risk of mortality[15] and morbidity due to respiratory complications,[16] kyphosis, and neurological complications.[17] Invasive operative intervention (e.g. fusion with instrumentation) may be problematic in the elderly because they are likely to have comorbidities that make invasive surgery difficult, and drilling or placing screws into cancellous bone may increase the chance of pedicle fracture. Thus, less invasive methods such as vertebroplasty, kyphoplasty and sacroplasty are more attractive in this population.

Sacral insufficiency fracture (SIF) is a type of stress fracture that occurs in the sacrum. The sacrum is located at the base of the spine and transmits the weight of the body to the pelvic girdle.SIF occurs when the sacral bone becomes too weak to handle the stress of weight bearing.[18] On either side at the top of the sacrum are two "wings" called the sacral ala. SIFs mostly present asvertical fractures in the sacral ala.[18, 19] Sometimes, a transverse fracture can occur that connects the vertical fractures on either side of the sacrum, forming an "H" pattern.[20, 21] Symptoms include severe pain in the buttock, back, hip, groin, and/or pelvis, limited range of motion, and tenderness in the lower back and/or pelvis. Walking becomes difficult, slow, and painful. Osteoporosis and osteopenia are the most common etiologies for SIF and because women are the majority of osteoporosis sufferers (80%), most SIFs occur in women. Less common etiologies for SIFs include rheumatoid arthritis, corticosteroid use, radiation therapy, renal osteodystrophy, osteomalacia, Paget's disease, hyperparathyroidism, joint arthroplasty and lumbosacral fusion.[22]Conventional treatment may consist of limited bed rest,[23, 24] early mobilization,[24, 25]corsets, and analgesic medications.[22, 23]Complete resolution of symptoms may not occur for up to 9 to 12 months even though initial clinical improvement may be more immediate.[26]Chronic pain and disability related to SIFs may be due to failure of the bone to heal, micromotion or resultant deformity.

Malignant/tumor related fracture

Patients with metastatic disease to the spine may present with pain, which can be caused by vertebral fracture, sacral fracture, and associated instability of the spine. Pain may also be due to intra- or extraosseous tumor, the latter potentially causing nerve root or cord compression resulting in neurological deficit. Radiation and/or chemotherapy may reduce pain due to metastasis but may not be effective in dealing with pain due to fracture. Surgical resection of the tumor and stabilization with fixation may be done, but the frailty of patients with metastatic disease makes these surgical options more risky.[27]Treatments may reduce pain only temporarily and a number of variables potentially influence the effectiveness of these pain relief options. Surgical procedures require lengthy recovery periods and have associated morbidity and mortality in patients who may have a short life expectancy.[28]

1.2 The technology and its comparator(s)

Technology

Vertebroplasty, kyphoplasty and sacroplasty are all cementoplasty techniques that aim to relieve pain due to osteoporotic or malignant vertebral or sacral fracture by stabilizing the fractured bone(s). Less frequent indications for these techniques include high-energy trauma and hemangioma. 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.[2]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.

Target population(s)

The ideal candidates for vertebroplasty, kyphoplasty, and sacroplasty are adults free of severe cardiovascular disease that have osteoporotic insufficiency fractures or metastatic disease resulting in severe back pain not easily resolved with conventional treatment. Patients are generally elderly women with low bone mineral density due to osteoporosis or osteopenia. The fragile nature of the patients' bones and potential co-morbidities makes them harder to treat safely. The aim of the described cementoplasty techniques is to reduce debilitating pain associated with insufficiency fractures of the vertebrae or sacrum, allowing patients to continue performing activities of daily living and enjoy improved quality of life.

Vertebroplasty

Vertebroplasty was introduced in the mid-1980s[29] and despite limited evidence on its effectiveness, rates of use more than doubled between the years 2001 and 2005.[1] It involves percutaneous injection of bone cement, usually polymethylmethacrylate (PMMA) via 11-13 gauge biopsy needles inserted into the ventral third of the cancellous bone of the vertebral body under computed tomography (CT) or fluoroscopic guidance. Calcium phosphate cements are also used. The liquid cement is injected under high pressure to fill the vertebral body and create an even distribution in the cancellous bone. When the cement hardens, it provides structure and strengthens the bone, decreasing the possibility of fracture and in theory, reduces pain from bone rubbing against bone. Another theory holds that the exothermic reaction of the PMMA as it hardens creates a thermal necrosis of intraosseous nerve fibers.[30]The precise mechanism of pain relief is not fully understood.[31]

A transpedicular approach is frequently used to inject the cement, and an extrapedicular approach may also be used. The transpedicular approach may be either bipedicular or unipedicular.[32] In the bipedicular approach, the tip of the bone trochar needle enters the pedicle inferolateral to the superior articulating facet. The needle is inserted until the tip is near the central aspect of the ipsilateral half of the vertebra or as far as the junction of the middle one-

third of the vertebral body. If the cement does not fill the space completely, then an injection on the other side is performed. In the unipedicular approach, the needle is inserted lateral to the superior articulating facet until it reaches the contralateral half of the vertebra. Bone cement is mixed directly prior to use and injected into the correctly placed bone trochar needle using a syringe.[33]

Kyphoplasty

Kyphoplasty, a minimally invasive procedure, is a modification of vertebroplasty initially developed and commercially marketed in the 1990s by Kyphon (Sunnyvale, CA) with the goal ofrestoring vertebral height and correcting spinal deformity.[34]Through two small incisions, transpedicular or extrapedicular channels are created through which a bone tamp with an inflatable balloon is inserted into the collapsed vertebral body. Inflation of the balloon expands the vertebral body to a more natural height and once the balloon is removed, bone cement is injected into the cavity using a lower pressure than that required for vertebroplasty.[35]The cement that is injected during the kyphoplasty procedure is thicker and thus less likely to enter the circulatory system.[37]Kyphoplasty is reportedly associated with less cement leakage than vertebroplasty, though cement leakage is typically considered clinically insignificant in either procedure.[35, 36] Kyphoplasty takes longer to perform than vertebroplasty and requires some additional equipment (an inflatable bone tamp kit).[2]

An extrapedicular or transpedicular entry point is identified using a guide pin and image guidance. A cannulated obturator is placed over the guide wire and then tapped into the bone over the guide wire. A working cannula is placed over the obturator and advanced until the tip of the cannula is seated in the posterior portion of the vertebral body. A corridor is drilled for the inflatable bone tamp to be passed through. The inflatable bone tamp is situated under the collapsed endplate on the lateral radiograph if possible. Inflation is slowly performed under image guidance and continued up to a maximum pressure of 220 psi or the maximum size dependent balloon volume is reached. Bone cement is mixed directly prior to use and the smaller cannulas, which fit inside the working cannula, are filled with cement. Cement is allowed to thicken slightly and then advanced through the working cannula to the anterior vertebral body wall, and cement is slowly extruded. Cement filling is stopped when the cement mantle reaches two thirds of the way back to the posterior vertebral body cortex on the lateral fluoroscopic images. The final volume of cement used is often larger than the size of the inflation volume because some of the cement interdigitates with the surrounding cancellous bone.[17]

Sacroplasty

Sacroplasty is a more recently reported procedure, being first described in 2000 for the treatment of metastatic disease.[38]It is an extension of vertebroplasty, involving the injection of synthetic bone cement (usually PMMA) into the fractured sacrum under CT or fluoroscopic guidance. The risks and benefits of sacroplasty have not been well defined and there is currently no agreement on the best technique.[23]

In the short axis approach, the bone trochar needles are inserted into the sacral ala post laterally along the short axis of the sacrum and cement is injected to fill both sides of the vertical fracture.[39] The long axis approach, first described in 2006, creates a vertical column of cement along the fracture line.[19] This adaptation was introduced to improve cement distribution and to prevent cement extravasation due to anterior cortex perforation. Rather than relying solely on imaging for guidance, it also uses the intramedullary space to guide the needle to the correct positioning.[19]

Contraindications for vertebroplasty, kyphoplasty, and sacroplasty

Contraindications for vertebroplasty, kyphoplasty, and sacroplasty include the following, as reported by the US Food and Drug Administration (FDA) and the American College of Radiology (ACR):

- Spinal canal or neural foramen compromise(FDA, ACR)
- Cortical disruption (FDA)
- Burst fractures (FDA)
- Pedicle fractures (FDA)
- Infection (FDA, ACR)
- Myelopathy (FDA, ACR)
- Coagulopathy (FDA, ACR)
- Allergy to device or material (FDA, ACR)
- Radiculopathy symptoms (ACR)
- Pregnancy (FDA)
- High energy trauma (FDA)
- Severe cardiopulmonary deficiencies (FDA)
- Active osteomyelitis of the target vertebra (ACR practice guideline)
- Asymptomatic vertebral body compression fracture or patient improving with medical therapy (ACR)
- Prophylaxis in osteoporotic patients (ACR)

Safety/FDA approval

PMMA has been approved for use in vertebroplasty and kyphoplasty procedures. In October 1999, PMMA was reclassified from class III to class II, which requires future 510(k) submissions to meet “special controls” instead of general controls in order to assure safety and effectiveness. The balloon tamp was approved for use in kyphoplasty by the FDA in 1998. A recall was issued in 2009 for a batch of KyphX Xpander inflatable bone tamps due to lack of sterility. There was also a recent report of the KyphX Xpander inflatable bone tamp not inflating

properly, though this caused no harm to the patient. Sacroplasty is an off-label use of PMMA. In 2002, the FDA posted a warning (updated in 2004) that serious complications can arise from the use of acrylic bone cements when treating compression fractures.

Potential complications

Patients who find it difficult to lie in the prone position on a firm table or who experience respiratory problems while lying prone may have to undergo general anesthesia or deep sedation for the vertebroplasty procedure.[3] Most of the patients are already taking opiate pain medication to relieve the pain of the fracture, so higher than normal doses of neuroleptics may be required.[3]

PMMA residue is volatile and may cause headache or eye irritation in the operators. The PMMA package insert calls for double gloving when handling because there is inadequate information about the effect of PMMA resin on fertility, its teratogenic potential or its effect on fetuses.[3]

Severe complications are rare for vertebroplasty, kyphoplasty, and sacroplasty; however, complications have been reported to the FDA's Manufacturer and User Facility Device Experience (MAUDE). Complications reported for kyphoplasty include death, canal intrusion with permanent paralysis, radiculopathy, paresthesia, loss of motor function, epidural hematoma causing permanent muscle weakness, canal intrusion/cord compression or epidural hematoma requiring decompression surgery, pulmonary cement embolism, ileus, infection (discitis/osteomyelitis), pneumothorax, drop in blood pressure, and equipment breakage. Complications reported for vertebroplasty include death, canal intrusion/cord compression leading to paralysis, cardiac arrest with no clinical sequelae, asymptomatic pulmonary cement embolism, anaphylaxis, blood pressure drop, and equipment breakage. [2] The most common complications for all procedures are described below.

Cement leakage

The most common complications of vertebroplasty, kyphoplasty, and sacroplasty stem from cement leakage, but for the most part, cement leakage does not produce symptoms.[40] Cement leakage can occur in the prevertebral soft tissue, spinal canal, foramen, intravertebral space, and intravenously.[41] Cement leakage most often occurs when too much pressure is applied while injecting or when PMMA is not viscous enough.[40, 42, 43]Neurologic deficit may occur if cement leaks into the spinal canal or neural foremen, and extravasation into the disc space may increase the likelihood of fracture at an adjacent level. Radiculopathy or spinal cord injury due to cement leakage is most common after treatment of fractures secondary to metastasis or myeloma.[35] Paraplegia due to spinal cord compression is very rare.[44]

Venous cement leakage is usually asymptomatic. However, pulmonary cement embolisms (PCE) may occur if cement is injected or leaks into paravertebral vessels,[43, 45] and risk of this complication ranges from 3.5 to 23% after vertebroplasty or kyphoplasty depending on the type of imaging used.[40] Symptomatic cases of PCE present with dyspnea/tachypnea, tachycardia, cyanosis, chest pain, coughing, hemoptysis, dizziness and/or sweating, and may result in death of

the patient.[40, 43, 46, 47] It is believed that many asymptomatic PCEs are not detected because proactive screening (with X-ray) exposes the patient to radiation.[40] It is difficult to draw a conclusion on the treatment of PCE due to the quality of evidence from previous studies, but it has been suggested that surgery only be performed to remove a central PCE[40] with bed rest and anticoagulant therapy for asymptomatic and non-centralized PCE.[40, 45]

There is debate over the importance of asymptomatic cement leakage, with some authors believing that asymptomatic leakage is a complication, while others claim that there are long term consequences of asymptomatic leakages.[36]

Dural tear, hematoma, new vertebral fracture, and other fractures

Dural tear, hematoma, spinal cord compression, and fractures of the rib or of the transverse spinal process are possible. One concern about the long-term effect of vertebroplasty with PMMA cement is the possible increase of subsequent compression fractures near a cemented vertebra due to increased rigidity of the treated vertebrae.[48, 49]The extent to which new fractures are due to these procedures or are a reflection of the natural progression of the disease process is difficult to determine in these patients whose bone quality is already compromised. Fracture etiology is multi-factorial, and new fractures often occur in the absence of cement augmentation. It has been noted that after kyphoplasty, adjacent level fractures are common within the first two months after procedure, but adjacent bone may eventually remodel to support additional stress from cemented vertebra (e).[49]Treatment of sacral insufficiency fractures with PMMA cement may also lead to other fractures in the surrounding bones. Rib fractures occur when there is too much pressure on the back and chest when the needle is being placed into a patient lying in the prone position.[3]

Alternative treatment

Conservative treatment

The standard conservative care for VCF and SIF is bed rest, bracing, and analgesics,[11, 50] with symptoms typically disappearing in 4-6 weeks.[11] External back bracing may be used for some patients. Most insufficiency fractures heal with this type of treatment and non-invasive measures are ideal for the elderly, but some sufferers do not heal using conservative treatment. Prolonged immobility can cause complications for sufferers of SIF and VCF due to reduced compression on the spine and bones in the lower extremities, reduced muscular force on all bones, loss of hydrostatic pressure in the vasculature below the heart, reduction in exercise, and socio-psychological changes.[25, 51, 52]Risk of mortality at one year has been estimated at 14.3% and half of patients do not return to normal activity following pelvic insufficiency fracture.[53]Immobility can also increase bone loss, which can lead to future insufficiency fractures.[11]

Vertebral fusion

Patients who require vertebral fusion have severe pain due to VCF that does not respond to conservative treatment. Involvement of the spinal cord is an indication for surgical

intervention.[54]Vertebral fusion is an invasive surgical procedure that involves placing a small piece of bone (a bone graft) between vertebrae. Pedicular screws are placed between the vertebrae to maintain alignment. As the patient heals, the grafted bone stimulates bone growth and fuses with the vertebrae on either side, resulting in one solid bone. Synthetic calcium/phosphate materials can also be used for the grafting material. Bone morphogenetic protein is a spinal fusion agent that has gained popularity since 2002 and is now used in 25% of spinal fusion procedures.[55] There are some complications that arise with vertebral fusion including blood clots, infection, pain, and nerve damage. It may take several months to heal from this procedure and patients must be kept immobilized. In patients with low bone mineral density, the possibility of failures of fixation such as screw pullout are of concern, and can lead to additional surgery. Because vertebral fusion is an invasive procedure, and most patients with insufficiency fractures of the vertebrae and sacrum have fragile bone and other co-morbidities, alternative treatments are more desirable.

1.3 Clinical guidelines

Sources, including the National Guideline Clearinghouse, major bibliographic databases, professional societies, and Medline were searched for guidelines related to vertebroplasty, kyphoplasty, and sacroplasty. Key word searches (and combinations of key word searches) performed were: "*vertebroplasty*," "*kyphoplasty*," "*sacroplasty*," "*cementoplasty*," "*spine fracture*," "*back pain*," "*osteoporosis*," and "*malignancy*." Eight documents were recovered that list vertebroplasty, kyphoplasty, or sacroplasty as a procedure for treatment of fractures caused by osteoporosis or malignancy. The four most relevant documents are summarized below.

National Guideline Clearinghouse (NGC)

No specific guidelines were found that addressed vertebroplasty, kyphoplasty, or sacroplasty for the treatment of vertebral compression fractures due to osteoporosis or malignancy. Two guidelines mentioned vertebroplasty and kyphoplasty as part of the assessment and management of spinal cord compression and chronic pain.

1. Assessment and management of chronic pain. 2008. *Institute for Clinical Systems Improvement (ICSI), Bloomington, MN*[56]

   > **"Level I Therapeutic Procedures**…Examples of commonly used Level I therapeutic procedures include facet joint injection, percutaneous radiofrequency neurotomy, intradiscal electrothermal therapy, epidural corticosteroid injections, **vertebroplasty and kyphoplasty**, and trigger point injections." No information was given about the conditions under which these procedures would be done.

2. Metastatic spinal cord compression. Diagnosis and management of adults at risk of and with metastatic spinal cord compression.2008. *National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence (NICE), clinical guideline no. 75.*[57]

"Consider vertebroplasty or kyphoplasty…. for patients who have vertebral metastases and no evidence of MSCC or spinal instability if they have:

- Mechanical pain resistant to conventional analgesia
- Vertebral body collapse

Vertebroplasty or kyphoplasty for spinal metastasis should only be performed after agreement between appropriate specialists (including an oncologist, interventional radiologist, and spinal surgeon), with full involvement of the patient and in facilities where there is good access to spinal surgery."

National Institute for Health and Clinical Excellence (NICE)

Interventional Procedure Guidance (IPG) for vertebroplasty and balloon kyphoplasty.[58] Vertebroplasty (IPG0012) and balloon kyphoplasty (IPG020):

- The procedure should only be undertaken when there are arrangements for good access to a spinal surgery service, and with prior discussion between a specialist multidisciplinary team that includes a radiologist and a spinal surgeon.
- Clinicians should receive training to reach an appropriate level of expertise before carrying out this procedure. In particular, they must follow the manufacturer's instructions for making the cement, to reduce the risk of embolisation.
- The procedure should be limited to patients whose pain is refractory to more conservative treatment.

Professional societies

A consensus statement on percutaneous vertebral augmentation was developed by the 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.[50]

Relevant statement (guideline not found on the NGC website):

"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 standards[1-3]."

1. Barr JD, Mathis JM, Barr MS, et al. Standard for the performance of percutaneous vertebroplasty. *In: American College of Radiology Standards 2000-2001*. Reston, VA: American College of Radiology; 2000:441-48.
2. McGraw JK, Cardella JC, Barr JD, et al. Quality improvement guidelines for percutaneous vertebroplasty. *J Vasc Interv Radiol* 2003;14:827-831.
3. Radvany MG, Murphy KJ, Millward SF, et al. Research reporting standards for percutaneous vertebral augmentation. *J Vas Interv Radiol* 2009;20:1279-1286.

The American Association of Orthopaedic Surgeons (AAOS) will release a guideline on vertebroplasty and kyphoplasty in the fall of 2010.

1.4 Previous systematic reviews/technology assessments

Previous technology assessments and systematic reviews have mixed conclusions about whether the use of vertebroplasty or kyphoplasty is significantly better than conventional methods for overall health outcomes of patients for treatment of vertebral compression fractures resulting from osteoporosis or malignancy. Some data suggests that both vertebroplasty and kyphoplasty can be effective in reducing pain and improving quality of life, especially in the immediate post-operative time period. However, no strong conclusions have been made about long-term, continued reduction of pain and functional outcomes, since most studies published are non-randomized comparisons or case series.

Two recent Health Technology Assessments (HTAs)[59, 60]cite two recent RCTs comparing vertebroplasty with sham controls. Although the patient numbers are small, the results indicate no difference in pain reduction or quality of life.

All of the reviews indicated that more multi-center, randomized controlled trials (RCTs) are necessary. However, authors note that the paucity of RCTs is due to the inherent difficulty in performing trials with surgical procedures. *Table 1* summarizes the previous technology assessments or related systematic reviews:

Table 1: Overview of previous systematic reviews/technology assessments of vertebroplasty, kyphoplasty, or sacroplasty for the treatment of fractures of the spine caused by osteoporosis or malignancy

Assessment (year)	Lit search dates	Procedure evaluated	Evidence base available*†	Critical Apprai -sal‡	Comments	Primary Conclusions
The California Technology Assessment Forum (CTAF)(2010) *Vertebroplasty as a treatment for osteoporotic compression fractures: A technology assessment (update to the 2008 evaluation)*	through 12/2009	Vertebroplasty	• 2 RCTs (%f/u >90 at 6 months); N = 209. Compared vertebroplasty to sham control • 11 case series (%f/u NR); N = NR	yes	• First two RCTs published (2009) comparing vertebroplasty with a sham control. • Report mentions kyphoplasty as a procedure that appears to have similar results to vertebroplasty. • Vertebroplasty **does not** meet 3 of the 5 CTAF criteria for safety, effectiveness and improvement in health outcomes for the treatment of osteoporotic vertebral compression fractures.	**Efficacy:** Both RCTs found no statistical or clinical difference in pain, quality of life, disability, or perceived recovery between the vertebroplasty and the sham groups (after 6 weeks), suggesting that vertebroplasty did not improve net health outcomes. For non-randomized comparative studies, it was concluded that both groups experienced significant and equal pain reduction. **Safety**: N/A **Economic**: N/A
California Technology Assessment Forum	Through April 2009	Kyphoplasty	• 1 RCT • 13 non-randomized	yes	Recommendations: • For osteoporotic vertebral	**Efficacy:** Based on one RCT, rapid and sustained

(CTAF) 2009 *Balloon Kyphoplasty as a Treatment for Vertebral Compression Fractures*			comparative studies • 49 case series Report focused on the RCT		compression fractures < 3months old kyphoplasty w/PMMA meets CTAF criteria 1-5 • For chronic (old) osteoporotic, traumatic or pathologic vertebral compression fractures CTAF criteria 3-5 are *not* met	improvement in pain and function seen for new (<3 month) confirmed osteoporotic fractures, however the same improvements are achieved after a year of usual back care **Safety:** Based on observational studies, cement leak can lead to neurological symptoms, may be increased rate of subsequent fractures (particularly adjacent). Pulmonary embolus remains a significant theoretical concern. **Economic**: N/A
			•		•	
BCBS Tec Assessment Program (2010) *Percutaneous vertebroplasty or kyphoplasty for vertebral fractures caused by osteoporosis.*	through 12/2009	Kyphoplasty: inflatable bone tamp: *KyphX*,(Kyphon, Inc). Polymethlyl methacrylate (PMMA) bone cement: *Vertaplex*, (Stryker); *KyphX HV-R bone cement*, (Kyphon, Inc.); *Vertebroplastic*, (DePuy Spine, Inc).	• 4 RCTs (%f/u NR); N = 543; compared vertebroplasty or kyphoplasty with sham controls or conservative medical management • 4 prospective case series with comparison group (%f/u NR); N = 226; patients that declined vertebroplasty or kyphoplasty used as comparison group • 15 case series (%f/u NR); N = 1,492.	yes	• Studies comparing vertebroplasty or kyphoplasty to sham controls, medical management (or to each other) and case series were sought. • Populations consisted of patients with vertebral fractures due to osteoporosis only. • Reported on relevant clinical outcomes of pain, functional status, or quality of life.	**Efficacy:** Two RCTs show vertebroplasty may not improve health outcomes when compared to a sham procedure. However, because both studies were underpowered, the interpretation of the data is unclear. In one RCT, it was not possible to determine the effect of kyphoplasty on the net health outcome of patients. Thus, the evidence is insufficient to determine if vertebroplasty or kyphoplasty improves the net health outcome or is as beneficial as any established alternatives, and therefore does not meet the TEC criteria. **Safety:** Adverse effects include localized bleeding, infection, and/or resultant pain or neurological symptoms following leakage of injected material.

						Economic: N/A
BCBS Tec Assessment Program (2008) *Percutaneous vertebroplasty or kyphoplasty for vertebral fractures caused by osteoporosis or malignancy.*	through 07/2008	Kyphoplasty: inflatable bone tamp: *KyphX*,(Kyphon, Inc). Polymethlyl methacrylate (PMMA) bone cement: *Vertaplex*, (Stryker); *KyphX HV-R bone cement*, (Kyphon, Inc.); *Vertebroplastic*, (DePuy Spine, Inc).	• 1 RCT (%f/u 100%); N = 34; compared vertebroplasty with conservative medical management • 4 prospective case series with comparison group (%f/u NR); N = 226; patients that declined vertebroplasty or kyphoplasty used as comparison group • 16 case series (%f/u NR); N = 2,214.	yes	• Studies comparing vertebroplasty or kyphoplasty to medical management (or to each other) and case series were sought. • Results are reported by procedure and for two indications: osteoporotic fractures and fractures to due malignancy. • Primary health outcomes included pain and the ability to function regarding daily living activities.	**Efficacy:** One RCT had a 2-week follow-up only, and no significant difference in VAS pain score between groups. Two of 3 nonrandomized studies show efficacy of the procedures. Case series studies show 4- to 5-point improvements in VAS pain ratings. Concluded a lack of rigorous comparative trials for either vertebroplasty or kyphoplasty and a lack of reliable evidence for efficacy of the procedures. **Safety:** Principal adverse event is leakage of cement out of the vertebral body. Other complications include localized bleeding, infection, and resultant pain or neurological symptoms (information from 2004 Tec assessment). **Economic:** N/A
Aggressive Research Intelligence Facility (ARIF) University of Birmingham *Vertebral balloon kyphoplasty/ vertebral compression fracture*	through 05/2008	N/A	• 4 SRs • 3 HTAs • 1 Medical Device Alert (MHRA) • 1 NICE guidance	no	• Brief report in response to a request for guidance; no data presented, no formal critical appraisal of studies done. • Only provides brief statements of findings for sources identified.	**Efficacy:** No good quality RCTs available, therefore no conclusion could be made about whether balloon kyphoplasty is more effective compared to conventional treatment. **Safety**: Cement leakage rate of 9% for balloon kyphoplasty. Other adverse events were new vertebral fractures (13%), pulmonary embolism (NR), and spinal cord compression nerve root pain (NR). **Economic**: N/A

Swedish Council on Technology Assessment in Health Care (2007) *Percutaneous vertebroplasty in severe back pain from vertebral compression fractures*	N/A	N/A	• 1 RCT (%f/u NR); N = 46 • 2 prospective, nonrandomized studies (%f/u NR); N = 269.	yes	• Brief report, no extensive literature search. • Additional studies available.	**Efficacy:** Limited evidence suggests vertebroplasty is superior to conventional treatment with regard to short-term pain relief in patients with osteoporotic vertebral compression fractures. **Safety**: Symptomatic complications were reported at a rate of 3% to 4%. **Economic**: N/A
KCE Reports vol. 39b (2006) *3. Balloon kyphoplasty and vertebroplasty*	through 2006	N/A	• 16 HTAs (both vertebroplasty and kyphoplasty) • 2 SRs (vertebroplasty) • 3 nonrandomized comparative studies (%f/u NR); N = NR	yes	• No RCTs found • Newer studies available	**Efficacy:** Efficacy of vertebroplasty is uncertain. Only one nonrandomized trial showed equivalence between vertebroplasty and conservative treatment. There is some evidence of the efficacy of balloon kyphoplasty for the treatment of vertebral compression fractures, which appears to reduce pain scores when compared to conventional therapy. **Safety**: Balloon kyphoplasty appears to be relatively safe; there are concerns about the increased rate of cement leakage from vertebroplasty. **Economic**: The general conclusion of an economic evaluation is that balloon kyphoplasty is 5-10 times more expensive than vertebroplasty.
CMS Technology Assessments (2005) *Percutaneous kyphoplasty for vertebral fractures caused by osteoporosis and malignancy*	through 04/2005	Inflatable bone tamp: *KyphX*,(Kyphon, Inc).	• 2 comparative studies (%f/u NR); N = 96; compared kyphoplasty to continued conservative management. • 11 case series	yes	• Published literature consists of mostly case series studies. • CMS uses the BCBS Technology Evaluation Center (TEC) criteria	**Efficacy:** No conclusive inference could be drawn on functional or other improved health outcomes regarding the effect of percutaneous kyphoplasty compared

			(%f/u NR); N = 437			with alternative treatments. **Safety**: Adverse effects include localized bleeding, infection, and/or resultant pain or neurological symptoms following leakage of the injected material. **Economic**: N/A
Medical Services Advisory Committee (MSAC) (2005) *Vertebroplasty and kyphoplasty for the treatment of vertebral compression fracture.*	1987-2004	*Ava-tex*™ single tray bone cement delivery system	• 57 case series or other nonrandomized comparative studies (%f/u NR); N = 4,114	yes	• Directly evaluated efficacy, safety, and cost-analysis of vertebroplasty and kyphoplasty compared to conservative medical management. • Additional comparative studies now available.	**Efficacy:** Results from one good-quality controlled trial indicate vertebroplasty is more effective than conservative medical management at relieving pain within 24 hours, however, there was no difference in the effectiveness of vertebroplasty at relieving pain in the longer term (6 weeks to 12 months). Concluded vertebroplasty appears to be more effective than conventional medical management in the short term, and as effective in the longer term. Only uncontrolled studies were available for kyphoplasty, suggesting it is more effective than conservative therapy for changes in quality of life and functioning, but not in comparison with conventional surgery. **Safety:** Among the 72 comparative and case series studies included for safety it appears that vertebroplasty is a safe procedure although there is insufficient evidence to determine if it is as safe or safer than medical management. Same conclusions are

						made for kyphoplasty, although no studies have directly compared kyphoplasty to alternative treatments. **Economic:** Based on several assumptions, there was a cost-saving estimate of $91,710 per 100 patients over 12 months for vertebroplasty. No data was available for kyphoplasty.
Ontario Health Technology Assessment Series (2004) *Balloon kyphoplasty*	01/2000 through 09/2004	Inflatable bone tamp: *KyphX*,(Kyphon, Inc).	• 11 case series (%f/u NR); N = 414	yes	• Objective of the assessment was to evaluate the safety and effectiveness of balloon kyphoplasty in the treatment of painful vertebral compression fractures. • Additional comparative studies now available.	**Efficacy:** Evidence from case series only suggests balloon kyphoplasty to treat pain is as effective as vertebroplasty. It also results in lower fracture rates in other vertebrae, and fewer leakage complications compared to vertebroplasty. **Safety**: Main complication is cement leakage, which can cause neurological complications, but the rate of leakage after kyphoplasty is lower compared to vertebroplasty. **Economic**: Report analyzed fees associated with procedures. Costs for balloon kyphoplasty are higher than for vertebroplasty because of anesthesia (required) and sizable device-cost add-on.
Centre for Clinical Effectiveness (CCE) (2002) *Safety and efficacy of percutaneous vertebroplasty in symptomatic osteoporotic vertebral compression*	through 2002	N/A	• 1 SR • 7 case series (%f/u NR); N = 351	yes	• Older study; only case series reports available. • Additional comparative studies now available.	**Efficacy:** Overall studies suggest a beneficial effect of percutaneous vertebroplasty on painful osteoporotic vertebral compression fractures with regards to pain relief and subsequent quality of life.

fractures.						**Safety**: Most frequent adverse events were cement leakage which occurred in 30-40% of patients. **Economic**: N/A

NR: Not Reported
N/A: Not Available
*Percent follow-ups were not given for all RCTs or case series
†N reflects numbers before loss to follow-up
‡Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.

As described in the Evidence section, a total of 24 publications indexed as systematic reviews or meta-analyses were found based on formal structured literature search. As noted above with most technology assessments, these reviews combined information from case series and other nonrandomized studies and did not contain more recently available comparative studies including randomized controlled trials. The most recent six of these reviews were judged to add information regarding safety and are summarized in the results section.

1.5Medicare and representative private insurer coverage policies

There are currently no national or local coverage determinations for vertebroplasty, kyphoplasty, or sacroplasty published from the Centers for Medicare and Medicaid Services (CMS). Coverage policies are consistent for these procedures for selected bellwether payers. The payers will provide coverage for vertebroplasty or kyphoplasty, as long as conventional medical treatment has failed and certain patient conditions are met. There is no coverage available for sacroplasty. Table 2 provides an overview of policy decisions.

- Medicare

  The Centers for Medicare and Medicaid Services have no published National (NCD) or Local coverage determinations (LCD) for vertebroplasty, kyphoplasty, or sacroplasty (or any other comparators; i.e., vertebral augmentation or cementoplasty).

  In February, 2010, CMS reviewed potential NCD topics, one of which was vertebroplasty and kyphoplasty. The relevant question asked was, "Typically, vertebroplasties are performed in an outpatient setting, while kyphoplasty typically requires hospital admission. Is the evidence adequate to demonstrate health benefits from pain reduction in selected patients?"

  A LCD for the region that includes Washington State related to vertebroplasty and kyphoplasty has been drafted and proposes non-coverage of the procedures. The formal commenting period for this draft ended in September of 2010.

- BCBS of Minnesota

Percutaneous vertebroplasty and kyphoplasty may be considered medically necessary for the following indications:

- Treatment of osteoporotic vertebral fractures that have failed to respond to conservative treatment (e.g., analgesics, physical therapy, and rest) for a period of at least six (6) weeks; and
- Treatment of severe pain due to osteolytic lesions of the spine related to multiple myeloma or metastatic malignancies.

Percutaneous vertebroplasty and percutaneous kyphoplasty are considered investigative and not medically necessary for all other indications.

Percutaneous sacroplasty is considered investigative and not medically necessary due to lack of evidence demonstrating an impact on improved health outcomes.

- BCBS of North Carolina

Percutaneous vertebroplasty or percutaneous kyphoplasty may be considered medically necessary for patients with vertebral collapse when the following criteria are met:

- For osteoporotic vertebral compression fractures with persistent debilitating pain, which has not responded to standard medical treatment including initial bed rest with progressive activity and narcotic or non-narcotic analgesics.

Persistent debilitating pain is defined as:

- Level of pain on a Visual Analog Scale (0-10) greater than 4 on a daily basis, or
- Pain on a daily basis that has a documented impact on at least two activities of daily living.

Up to six weeks of standard medical treatment is required unless the pain is not significantly relieved by rest, narcotic and non-narcotic pain medications (as appropriate), or the patient is unable to tolerate narcotic and non-narcotic pain medication.

- For treatment of severe pain in patients with osteolytic lesions of the spine related to multiple myeloma or metastatic malignancies.

Percutaneous vertebroplasty or percutaneous kyphoplasty are considered investigational for all indications that do not meet the medical necessity criteria listed above.

- CIGNA

CIGNA covers percutaneous vertebroplasty or percutaneous kyphoplasty as medically necessary when standard medical therapy has failed to alleviate symptoms and any of the following criteria are met:

- Osteoporotic, osteolytic, osteonecrotic (i.e., Kummel disease), or steroid-induced vertebral compression fracture with persistent, debilitating pain unresponsive to at least six weeks of conservative medical management;
- Severe back pain secondary to destruction of vertebral body due to osteolytic vertebral metastasis or multiple myeloma;
- Painful and/or aggressive hemangioma or eosinophilic granuloma of the spine.

CIGNA does not cover percutaneous sacroplasty because it is considered experimental, investigational, or unproven.

- AETNA

Aetna considers percutaneous polymethlymethacrylate vertebroplasty (PPV) or kyphoplasty medically necessary for members with persistent, debilitating pain in the cervical, thoracic or lumbar vertebral bodies resulting from any of the following:

- Primary malignant neoplasm of bone or bone marrow; *or*
- Secondary osteolytic metastasis, excluding sacrum and coccyx; *or*
- Multiple myeloma; *or*
- Painful and/or aggressive hemangiomas; *or*
- Painful, debilitating osteoporotic collapse/compression fractures (e.g., Kummell's disease); *or*
- Painful vertebral eosinophilic granuloma.

AND all of the following criteria have been met:

- Severe, debilitating pain or loss of mobility that cannot be relieved by optimal medical therapy (e.g., acetaminophen, NSAIDS, narcotic analgesics, braces, physical therapy, etc.); *and*
- Other causes of pain such as herniated intervertebral disk have been ruled out by computed tomography or magnetic resonance imaging; *and*
- The affected vertebra has not been extensively destroyed and is at least one-third of its original height.

Table 2: Overview of payer technology assessments and policies for vertebroplasty, kyphoplasty, and sacroplasty for the treatment of vertebral compression fractures caused by osteoarthritis or malignancy

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
Centers for Medicare and Medicaid Services (CMS)	N/A	N/A	• No NCD or LCDs for the region that includes Washington State. However, vertebroplasty and kyphoplasty are potential NCD topics.	• N/A
Regence (2010) *Percutaneous*	through 2010	• 2007 BCBS Tec Assessment • 1 prospective	Percutaneous vertebroplasty or kyphoplasty may be considered medically necessary for the	• Recent RCTs with short to mid-term follow-up have not shown improved

Vertebroplasty and Kyphoplasty (2010)		multicenter study • 1 meta-analysis	treatment of the following: • Symptomatic osteoporotic (compression) vertebral fractures of the thoracic or lumbar spine that have failed to respond to conservative treatment (e.g., analgesics, physical therapy and rest) for at least 6 weeks, or • Severe pain due to osteolytic lesions of the spine related to multiple myeloma, or primary or metastatic spinal malignancies Percutaneous vertebroplasty or kyphoplasty is considered investigational for all other indications, including but not limited to the following: • Vertebral hemangioma • Acute vertebral fractures due to osteoporosis or trauma • Stabilization of insufficiency fractures or lesions of the sacrum (sacroplasty) or coccyx (coccygeoplasty)	health outcomes with CAN.
BCBS of Minnesota (2010) *Percutaneous vertebroplasty, kyphoplasty, and sacroplasty*	N/A	N/A	Percutaneous vertebroplasty and kyphoplasty may be considered medically necessary for the following indications: • Treatment of osteoporotic vertebral fractures that have failed to respond to conservative treatment (e.g., analgesics, physical therapy, and rest) for a period of at least six (6) weeks; and • Treatment of severe pain due to osteolytic lesions of the spine related to multiple myeloma or metastatic malignancies. Percutaneous vertebroplasty and percutaneous kyphoplasty are considered investigative and not medically necessary for all other indications. Percutaneous sacroplasty is considered investigative and not medically necessary due to lack of evidence demonstrating	• No rationale for policy given • CPT codes if selection criteria is met: 22520, 22521, 22522, 22524, 22525, 72291, 72292.

			an impact on improved health outcomes.	
BCBS of North Carolina (2009) *Vertebroplasty and kyphoplasty_Percutaneous*	N/A	• BCBS Medical Policy reference manuals	Percutaneous vertebroplasty or percutaneous kyphoplasty may be considered medically necessary for patients with vertebral collapse when the following criteria are met: • For osteoporotic vertebral compression fractures with persistent debilitating pain, which has not responded to standard medical treatment including initial bed rest with progressive activity and narcotic or non-narcotic analgesics. Persistent debilitating pain is defined as: – Level of pain on a Visual Analog Scale greater than 4 on a daily basis, or – Pain on a daily basis that has a documented impact on activities of daily living (at least 2 ADL's or IADL's) Up to six weeks of standard medical treatment is required unless the pain is not significantly relieved by rest, narcotic and non-narcotic pain medications (as appropriate), or the patient is unable to tolerate narcotic and non-narcotic pain medication. • For treatment of severe pain in patients with osteolytic lesions of the spine related to multiple myeloma or metastatic malignancies. Percutaneous vertebroplasty or percutaneous kyphoplasty are considered investigational for all indications that do not meet the medical necessity criteria listed above.	•
CIGNA (2010) *Percutaneous Vertebroplasty, Kyphoplasty, and Sacroplasty*	through 2010	• 1 Meta-analysis • 1 HTA • 7 SRs • 3 RCTs • 10 Prospective case series	CIGNA covers percutaneous vertebroplasty or percutaneous kyphoplasty as medically necessary when standard medical therapy has failed to alleviate symptoms and any of the following criteria are met:	• Percutaneous vertebroplasty and kyphoplasty gained acceptance by practitioners as a safe and effective method to provide pain

			• Osteoporotic, osteolytic, osteonecrotic (i.e., Kummel disease), or steroid-induced vertebral compression fracture with persistent, debilitating pain unresponsive to at least six weeks of conservative medical management; • Severe back pain secondary to destruction of vertebral body due to osteolytic vertebral metastasis or multiple myeloma; • Painful and/or aggressive hemangioma or eosinophilic granuloma of the spine. CIGNA does not cover percutaneous sacroplasty because it is considered experimental, investigational, or unproven.	relief, increased mobility and improved quality of life for patients with painful osteolytic lesions and osteoporotic compression fractures refractory to conservative medical treatment. • Additional clinical trials are needed to determine the long-term safety and efficacy of percutaneous vertebroplasty and kyphoplasty. • There is insufficient evidence to demonstrate the safety, efficacy, and long-term outcomes of sacroplasty. • CPT codes if selection criteria is met: 22520, 22521, 22522, 22524, 22525.
Aetna (2010) *Clinical Policy Bulletin: Back Pain – Invasive Procedures*	through 2009	• Primary studies, systematic reviews, previous HTAs, and guidelines all cited (44 references).	Aetna considers percutaneous polymethlymethacrylate vertebroplasty (PPV) or kyphoplasty medically necessary for members with persistent, debilitating pain in the cervical, throracic or lumbar vertebral bodies resulting from any of the following: • Primary malignant neoplasm of bone or bone marrow; *or* • Secondary osteolytic metastasis, excluding sacrum and coccyx; *or* • Multiple myeloma; *or* • Painful and/or aggressive hemangiomas; *or* • Painful, debilitating osteoporotic collapse/compression fractures (e.g., Kummell's disease); *or* • Painful vertebral eosinophilic granuloma. AND all of the following criteria have been met: • Severe, debilitating pain or loss of mobility that cannot be relieved by optimal	• No rationale for policy given • CPT codes if selection criteria is met: 22520, 22521, 22522, 22524, 22525.

			medical therapy (e.g., acetaminophen, NSAIDS, narcotic analgesics, braces, physical therapy, etc.); *and* • Other causes of pain such as herniated intervertebral disk have been ruled out by computed tomography or magnetic resonance imaging; *and* • The affected vertebra has not been extensively destroyed and is at least one-third of its original height.	

N/A: Not Available
*Medicare does not report the current evidence available.

1.6 Other significant evidence

A number of clinical trials are being conducted on the use of vertebroplasty or kyphoplasty for vertebral fractures due to osteoporosis or malignancy. Currently active randomized controlled trials listed on clinicaltrials.gov are described below.

1.6.1 Vertebroplasty compared with sham surgical procedures

Vertebroplasty for the Treatment of Fractures Due to Osteoporosis (NCT00068822)

Investigational Vertebroplasty Efficacy and Safety Trial (INVEST)

This RCT is no longer recruiting patients. Discussion of publications from the study is included in the Evidence and Results sections of this report.[61]

A Trial of Vertebroplasty for Painful Acute Osteoporotic Vertebral Fractures (VertosIV) (NCT01200277)

A Randomised Sham Controlled Trial of Vertebroplasty for Painful Acute Osteoporotic Vertebral Fractures

This Phase III RCT, not yet open for recruitment; will compare vertebroplasty with a sham surgical procedure for osteoporotic fractures. The multicenter trial is based at St. Elizabeth Hospital, Tilburg, Netherlands. The primary outcome measure is pain relief at periods up to 12 months, with use of pain medication and health care utilization as secondary outcomes. Patients over 50 with osteoporotic fractures and back pain of 6 weeks duration or less are eligible. The trial is scheduled to begin recruiting patients in January, 2011, with completion in 2013.

1.6.2 Vertebroplasty compared with conservative medical treatment

VERTOS-II. Percutaneous Vertebroplasty Versus Conservative Therapy NCT00232466

VERTOS II. Percutaneous Vertebroplasty Versus Conservative Therapy in Patients With Osteoporotic Vertebral Fractures

This RCT is no longer recruiting patients. Discussion of publications from the study is included in the Evidence and Results sections of this report.[62-65]

Percutaneous Vertebroplasty Versus Conservative Treatment of Pain (NCT00203554)

Percutaneous Vertebroplasty Versus Conservative Treatment of Pain: A Prospective, Randomized Controlled Study of Osteoporotic Fractures in the Spine

A small (n=27) RCT from the University of Aarhus (Denmark) compared vertebroplasty with conservative medical treatment in the treatment of painful vertebral fractures in osteoporotic patients. Patients had spinal pain of less than 6 months' duration and low-energy spinal fracture verified by x-rays, and patients with spinal metastases were excluded. The primary outcome was reported pain, and secondary outcomes included analgesic use, number of days hospitalized, and Activities of Daily Living at several follow-up points up to 12 months. Data collection was completed in 2008. No publications from this study were found in a literature search.

Quality of Life After Vertebroplasty Versus Conservative Treatment in Patients With Painful Osteoporotic Vertebral Fractures (NCT00994032)

Analysis of the Impact in the Quality of Life of Patients With Pain Secondary to Osteoporotic Vertebral Fractures Receiving Conservative Treatment Versus Percutaneous Vertebroplasty

In this completed RCT, patients (estimated enrollment n=100) were randomized to receive vertebroplasty or conservative medical treatment, and were followed for 12 months. The trial took place at the Hospital Clinic of Barcelona (Spain), with support from the Sociedad Española de Radiologia Medica. Inclusion criteria were an osteoporotic vertebral fracture, pain of at least 4 on a 0-10 point scale, and pain duration of less than 1 year in duration. The primary outcome measure was score on the Qualeffo, with pain score as a secondary outcome. No publications from this study were found in a literature search.

Comparison of Balloon Kyphoplasty, Vertebroplasty and Conservative Management in Acute Osteoporotic Vertebral Fractures (OSTEO-6)(NCT00749060)

Prospective Randomized Comparative Study of Balloon Kyphoplasty,Vertebroplasty and Conservative Management in Acute Osteoporotic Vertebral Fractures of Less Than 6 Weeks

A trial that compares kyphoplasty, vertebroplasty, and conservative treatment for osteoporotic fractures is currently underway at the Assistance Publique - Hôpitaux de Paris (France), with support from the French Ministry of Health. To be included, patients must be 50 years old or older with osteoporotic fractures and pain of less than 6 weeks duration. Patients with more than two recent vertebral fractures, fractures with a loss of 90% or more of vertebral height, malignant fractures, or traumatic fractures are excluded. The primary outcome measure is the change in kyphotic angle at 12 months from pre-operative levels. Secondary outcome measures are pain, EIFEL questionnaire for back pain, Qualeffo,

analgesic use, changes in vertebral height and intervertebral disk spaces, new vertebral fractures, and cost. The study is expected to be completed in late 2012, with 300 patients.

1.6.3 Vertebroplasty compared with kyphoplasty

Cost Effectiveness and Efficacy of Kyphoplasty and Vertebroplasty Trial (NCT00279877)

This Phase III trial compares the cost effectiveness and efficacy of kyphoplasty and vertebroplasty for the treatment of osteoporotic vertebral compression fractures. The trial is sponsored by the Mayo Clinic, with industry support from Cardinal Health, ArthroCare Corporation, and Cook Medical. Primary outcome measures (measured at 12 months post-procedure) are Roland-Morris Disability (RDQ) scores and pain scores, with SF-36 as a secondary outcome measure. The study is estimated to be completed in May of 2011, with 112 patients enrolled. To be included, patients must be at least 50 years old with a painful compression fracture at T4-L5 within the previous 12 months. Patients with malignancy or previous back surgery are excluded.

KAVIAR Study - Kyphoplasty And Vertebroplasty In the Augmentation and Restoration of Vertebral Body Compression Fractures (NCT00323609)

A Multicenter, Randomized, Prospective Clinical Trial to Compare the Short- and Long-term Safety and Effectiveness of Balloon Kyphoplasty to Vertebroplasty in the Treatment of Painful, Acute Osteoporosis-related Vertebral Body Compression Fractures (VCFs).

A Phase IV multicenter RCT funded by Medtronic Spine LLC (Kyphon, Inc.) compares vertebroplasty with kyphoplasty for treatment of osteoporotic fractures. Patients are eligible if they are at least 21 years old with 1-3 osteoporotic vertebral fractures no more than 6 months old, back pain greater than 4 on a scale of 0-10, and a score of 20 or greater on the Oswestry Disability Index. Patients are excluded if they have fractures due to high-energy trauma or cancer, have had previous kyphoplasty or vertebroplasty, or have significant comorbidities. The primary outcome is the occurrence of new fractures at 12 and 24 months post-procedure, with secondary outcomes including back pain, quality of life, functioning, change in vertebral body height and angular deformity, and related health care utilization. The trial is scheduled to be completed in August, 2011, with 1234 patients.

Comparison of Balloon Kyphoplasty and Vertebroplasty in Subacute Osteoporotic Vertebral Fractures (OSTEO+6) (NCT00749086)

Prospective Randomized Comparative Study of Balloon Kyphoplasty,Vertebroplasty and Conservative Management in Acute Osteoporotic Vertebral Fractures of Less Than 6 Weeks

This RCT is underway at the Hôpital Lariboisière in Paris, with support from the Assistance Publique - Hôpitaux de Paris and the French Ministry of Health. Patients are randomized to receive vertebroplasty, kyphoplasty, or conservative medical treatment for osteoporotic fractures. Eligible patients are 50 years old or older with one or two non-traumatic vertebral

fractures of osteoporotic origin. Patients with fractures of less than 6 weeks old or with malignant fractures are excluded. The primary outcome measure is the modification of the kyphotic angle of every treated vertebra at 12 months post-procedure. Secondary outcome measures include pain, the EIFEL measure of functioning, Qualeffo, pain medication, vertebral height, and the occurrence of new vertebral fractures. The trial began in December 2007 and is scheduled for completion in late 2012 with 200 patients.

1.6.4 Kyphoplasty compared with conservative medical treatment

Vertebral Augmentation With Kyphoplasty vs. Nonsurgical Management for Vertebral Body Compression Fractures (NCT01175278)

A Pilot Study of Vertebral Augmentation with Kyphoplasty Versus Nonsurgical Management in Multiple Myeloma Patients With Mildly Symptomatic Vertebral Body Compression Fractures

This small single-center RCT is conducted at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, with support from Medtronic. The study compares kyphoplasty with non-surgical management for acute vertebral compression fractures in multiple myeloma patients. Patients are eligible if they are at least 21 years old with multiple myeloma and mild back pain related to a vertebral compression fracture ($\leq$ 4 on a 0-10 scale). The primary outcome measures are time to pain progression (severity of pain from the fracture rated greater than 4) and time to a vertebral event such as the end point of pain progression, hospitalization for pain, or subsequent surgery or therapy related to the fracture. Secondary outcome measures include the rate of hospitalization for pain related to the fracture, quality of life, changes in pulmonary function, and changes in kyphosis. The study is expected to be completed in 2013 with 30 patients.

CAFE Study - Cancer Patient Fracture Evaluation (NCT00211237)

A Multicenter, Prospective, Randomized, Controlled Study to Compare Balloon Kyphoplasty to Non-surgical Fracture Management in the Treatment of Painful, Acute Vertebral Body Compression Fractures in Cancer Patients

This multicenter Phase IV study, completed in late 2009 with 134 patients, was funded by Metronic. The trial compared kyphoplasty to nonsurgical treatment of vertebral fractures in patients with cancer. Eligible patients were at least 21 years old with one to three painful vertebral fractures (pain $\geq$4 on a scale of 0-10) and an RDQ scale greater than 10. Exclusion criteria included the presence of bone tumor or solitary plasmacytoma at site of the index fracture, significant comorbidities, and fracture morphology unsuitable for kyphoplasty. The primary outcome was improvement on RDQ scores at one month, and secondary outcomes included RDQ at 12 months, SF-36 up to 12 months, changes in back pain, and new fractures. No publications from this study were found in a literature search.

1.6.5 Vertebroplasty combined with radiotherapy compared to radiotherapy alone for malignant fractures

Potential Vertebroplasty Use in the Treatment of Vertebral Metastasis From Breast and Prostate Cancer (NCT00294151)

> *Challenging the Paradigm in Pain Relief for Advanced Breast and Prostate Cancer Patients With Vertebral Metastasis: Vertebral Augmentation With Cement Plus Radiotherapy Versus Radiotherapy. A Randomized, Prospective, Double Blind Pilot Study*
>
> This study conducted at McGill University Health Center (Montreal, Quebec, Canada) examines the effectiveness of adding vertebroplasty to radiotherapy among patients with breast or prostate cancer. The intervention group receives standard radiotherapy and vertebroplasty, and the control group receives radiotherapy and a simulated vertebroplasty procedure. The primary outcome is pain relief, with other outcomes assessed including pain medications, cost, survival, and the occurrence of new fractures. Eligibility criteria include age 35-75, breast or prostate cancer with spinal metastases, microfractures or compression fractures up to 40% of the original height of vertebral body, and pain of at least 5 on a scale of 0-10. Exclusion criteria include previous radiotherapy to the fracture area, and metastases without fracture. 30 patients are expected to be enrolled.

2. The evidence

2.1 Methods of systematic literature review

2.1.1 Inclusion/exclusion

Population. Studies of adults who underwent vertebroplasty, kyphoplasty, or sacroplasty for vertebral instability or fracture due to osteoporosis or malignancy were included. Studies in which more than 10% of fractures were caused by high-energy trauma were excluded.

Intervention. Studies that evaluated vertebroplasty, kyphoplasty, or sacroplasty.

Comparator. Studies that compared vertebroplasty, kyphoplasty, or sacroplasty with conservative medical treatment, sham treatment, or other surgical procedures. Studies that compared vertebroplasty with kyphoplasty. Studies that reported on procedural aspects of the surgery, such as comparisons of different cement types or of different surgical techniques, were excluded, as were studies in which vertebroplasty, kyphoplasty, or sacroplasty was performed as an adjunct to other procedures (e.g., ablation).

Outcomes. Eligible studies reported on at least one of the following outcomes: physical function/disability (e.g., ODI, RDQ), pain relief, quality of life outcomes, or complications (including procedure-related outcomes, cement leakage, new fractures).

Study design. Eligible studies compared vertebroplasty, kyphoplasty, or sacroplasty with a comparison group using a randomized controlled trial or cohort study design. In order to provide

additional context regarding key question 2, systematic reviews of non-randomized studies were considered for longer-term safety outcomes. Formal economic studies published in peer-reviewed journals were included for key question 4. Case reports were excluded, and case series with more than 5 patients were considered for sacroplasty.

Table 3: Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Participants	Patients with spinal pain due to vertebral fracture secondary to • osteoporosis • malignancy	• Fractures due to high energy trauma
Intervention	• Vertebroplasty • Kyphoplasty • Sacroplasty	
Comparators	• Conservative care • Surgical procedures • Vertebroplasty vs. kyphoplasty	• Comparisons of different cement types • Comparisons of surgical approaches or techniques • Use of vertebroplasty, kyphoplasty or sacroplasty as an adjunct to other procedures (e.g. ablation)
Outcomes	• Functional outcomes (e.g. ODI) • Pain relief • Quality of life outcomes • Complications (e.g. procedure related, leakage, new fracture, medical complications, death. Revision/re-operation) • Return to work	
Study Design	• Comparative clinical studies (e.g. RCTs, cohort studies with concurrent controls) will be considered for questions 1, 3 and 4 • For question 2, safety, case series will be considered if adequate information not available from comparative studies • Formal economic studies will be sought for question 4	• Case reports • Case series with fewer than 5 patients (for sacroplasty)
Publication	• Full-length studies published in English in peer reviewed journals, published HTAs or publicly available FDA reports • Full formal economic analyses (e.g. cost-utility studies) published in English in a HTA or in a peer-reviewed journal published after those represented in previous HTAs.	• Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • Studies reporting on the technical aspects of these procedures • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in

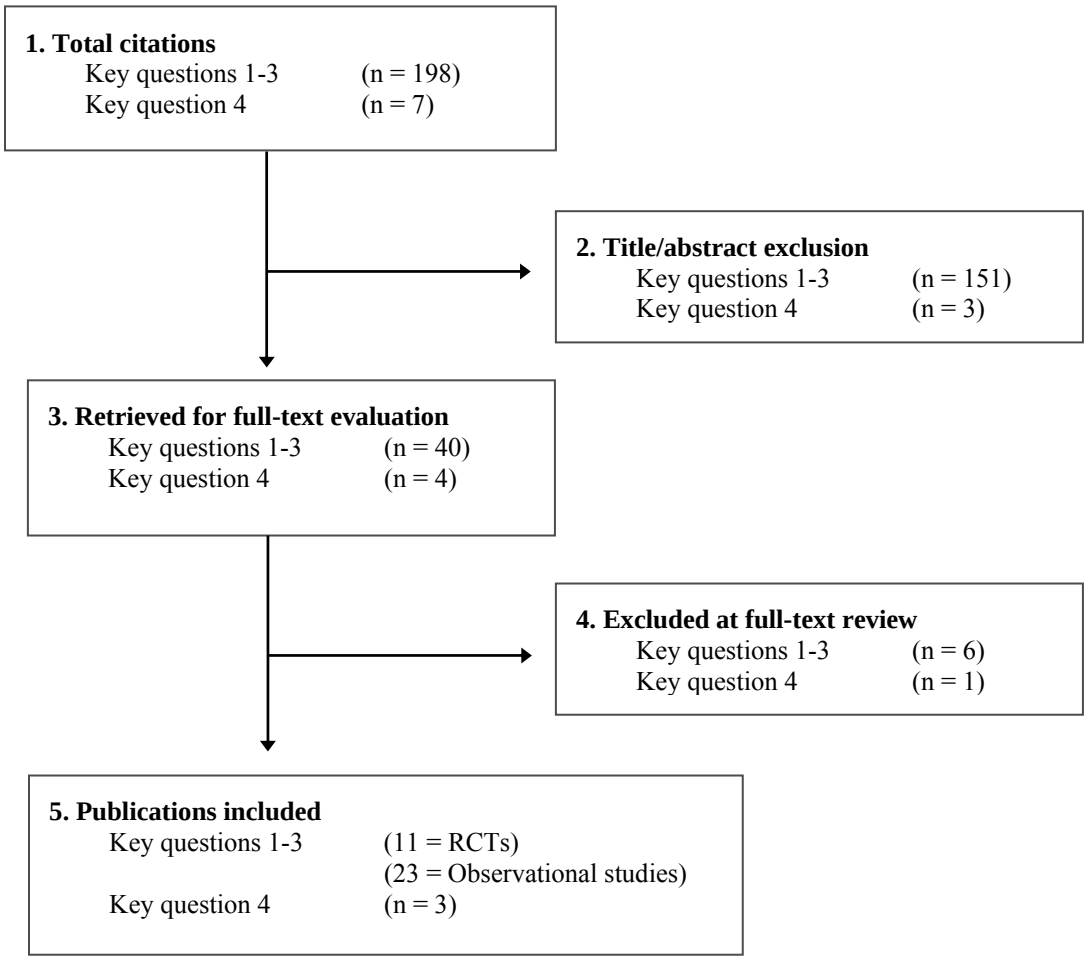
		later versions • Incomplete economic evaluations such as costing studies

2.1.2 Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any unresolved disagreement between screeners resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Electronic databases searched included PubMed, EMBASE, CINAHL, ClinicalTrials.gov, NIH Reporter, *The Cochrane Library*, EconLIT, PsychINFO, AHRQ, and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports. Reference lists of all eligible studies were also searched. The search strategies used for PubMed and EMBASEare shown in Appendix B. Figure 1 shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed in Appendix C.

Figure 1: Flow chart showing results of literature search



2.1.3 Data extraction

Reviewers extracted the following data from the included clinical studies: study population characteristics, study type, study period, patient demographics and preoperative diagnoses, study interventions, follow-up time, study outcomes (functional and clinical, motion, radiographic), adverse events (cement leakage, incident fractures, death), and other complications. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted.

2.1.4 Study quality assessment: Level of evidence (LoE) evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine,[66] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working

Group,[67] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[68]

Details of the Level of Evidence (LoE) methodology are found in Appendix D. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Appendix D. Standardized abstraction guidelines were used to determine the LoE for each study included in this assessment.

2.2 Quality of literature available

2.2.1 Quality of studies retained

We initially found 198 citations using the search strategy in Appendix B. For key questions 1, 2, and 3, we identified 34 publications that compared vertebroplasty or kyphoplasty with conservative treatment or other surgical procedures: 11 publications describing seven randomized controlled trials and 23 publications describing 20 cohort studies. The RCTs were all graded as LoE II, and cohort studies all received LoE grades of III.

For key question 2 on safety, we also summarized findings from systematic reviews, which provided information on longer-term follow-up with a large (pooled) number of patients, but included data from case series. Our search yielded 24 publications indexed as systematic reviews or meta-analyses. Only those reports which provided summary data for complications were selected. Reports that were published between 2007 and 2010 and whose search ending dates were 2006 or later were considered for inclusion, given that additional comparative studies have been published since 2007. A total of six systematic reviews that were judged to contribute to information on safety were included.[36, 40, 69-72] Reports which were primarily narrative reviews or listings of studies without summarization of data were excluded.

One 2004 publication described complications reported in the FDA's MAUDE database (Manufacturer and User Facility Device Experience).[2]This report was excluded sincethere is no denominator information available to provide rate information. Initiators of adverse event reports may include manufacturers, clinical users/providers, attorneys and patients, and it is unclear how many are unique reports. Two studies that analyzed administrative databases were excluded: one study[73] used claims data from Blue Cross/Blue Shield assess risk of new fractures, and one study[74] analyzed the Nationwide Inpatient Sample database for complications and post-hospital disposition. In general, administrative databases contain data that have been gathered as a by-product of some other process; the data may be collected and entered by hundreds of individuals at many locations; usually, there are few, if anyquality checks on the data; records may have different lengths andstructures within the same database; and missing data are common.[75, 76]Numeric coding systems (e.g., ICD-9-CM) are often used and these have their own peculiarities: There may not be a code for a particular hospital diagnosis and the level of detail in coding may vary or change over time. These characteristics of large databases lead to

controversy over their use in epidemiologic and health services research and point to the need to consider validity and reliability issues.[77, 78]

Level of Evidence tables for the comparative studies appear in Appendix E.

2.2.2 Critical appraisal

The comparative studies that we retrieved assessed a number of different outcomes over different follow-up periods. Both randomized controlled trials and non-randomized studies are limited by relatively short follow-up times: the longest follow-up is one year for the RCTs and three years for the non-randomized studies. Given the age of the majority of patients in these studies who undergo vertebral augmentation (in their 70s and older), follow-up times are likely to be relatively short, but these limited time frames make it difficult to draw conclusions about longer-term safety and functional outcomes.

Randomized controlled trials

Vertebroplasty compared with sham surgery

Two randomized controlled trials compared percutaneous vertebroplasty (PV) with sham surgery to assess short-term efficacy and safety.[61, 79] With the use of a sham procedure that closely mimics PV, these studies control for non-specific placebo effects, which can be of moderate size for invasive procedures (6-7 mm on a 100 mm scale).[80-83] One of the studies[61] included an injection of local anesthetic into the periosteum (in both vertebroplasty and control groups), which raises the question of whether the anesthesia itself could interrupt the pain cycle for these patients. However, no anesthetic injection was used in the second RCT,[79] which showed similar results.

Both studies had difficulty in recruiting participants and neither met their original recruitment goals. In both studies, large numbers of patients who were ineligible were screened, and 30-36% of eligible patients were enrolled, not uncommon for randomized trials of any intervention. Selection bias may have unknown effects on these studies, although patient characteristics were similar to those of participants in other studies of vertebroplasty. In one of these RCTs,[61] eligible patients who declined to enroll had similar levels of pain and disability as those who enrolled.[84]

Because the studies did not meet their original enrollment targets, the final sample sizes may not have allowed for power to test for differences in secondary outcomes and subgroup comparisons. One comparison of particular interest is of outcomes for patients with acute versus more chronic fractures, in part because VAS pain measurement may not be as responsive to changes in pain as other measures in those with chronic low back pain.[85]

Buchbinder (2009)

Buchbinder et al.[79] conducted a RCT in Australia, in which 78 patients were randomized to be treated with PV (38 patients) or with a simulated PV procedure (40 patients). All patients had vertebral fractures from osteoarthritis (fractures of other origin were excluded). Inclusion criteria

were the presence of one or two vertebral fractures with collapse of less than 90%, and back pain of no more than 12 months' duration. Mean patient age was 74.2 in the PV group and 78.9 in the sham group, with 82% and 78% female participants respectively. Demographic and clinical variables were similar at baseline, and statistical analysis was adjusted for baseline values.

Patients were randomly assigned to a treatment group using computer-generated random numbers, with the study assignment delivered in opaque envelopes to the treating radiologist just before the procedure was performed. In the sham surgical procedure, a needle was introduced and its sharp stylet replaced with a blunt stylet. The vertebral body was gently tapped to simulate vertebroplasty, and PMMA was prepared so that its smell would permeate the room. Participants, investigators, and outcome assessors were blinded to group assignments.

Follow-up assessments were conducted by mail at one week, one month, three months, and six months. A follow-up rate of 91% was achieved at the 6-month follow-up. Although the original target sample size was not achieved due to difficulty recruiting patients, the authors report that a statistical power analysis of the final sample size indicated sufficient power to detect a difference of 2.5 points on the 0-10 pain scale at 3 months, with 1.5 points considered a clinically significant pain reduction. Cook Australia, a manufacturer of medical devices, provided partial grant support. This study received a LoE grade of II.

Kallmes (2009)

Kallmes et al.[61] conducted a multicenter RCT with sites in the United States, the U.K., and Australia. 131 patients were randomized to be treated with PV (68 patients) or with sham surgery simulating PV (63 patients). Inclusion criteria were age 50 years or older, a diagnosis of one to three painful osteoporotic vertebral compression fractures (VCFs) no more than 12 months old (as indicated by duration of pain), inadequate pain relief with standard medical therapy, and a current pain rating 3 or above on a scale from 0 to 10. Crossover to the other arm of the study was offered if the patient had not improved by the one-month follow-up visit, and at 3 months 43% of the control group and 12% of the PV group had chosen to cross over. Because this crossover occurred after the primary outcome was measured, it did not affect the main results. Mean patient age was 73.4 in the PV group and 74.3 in the sham group, with 78% and 73% female participants respectively. Demographic and clinical variables were similar at baseline, and data analysis was adjusted for baseline values.

Patients were randomly assigned to a treatment group by a central data coordinating center, with the study assignment delivered in opaque, sealed envelopes. The group assignment was made after patients were sedated and after an injection of local anesthetic into the periosteum of the pedicle. The control intervention did not include needle insertion, but incorporated verbal and physical cues, including pressure on the patient's back and the odor of the cement. Group assignments were concealed from patients and study personnel who performed follow-up assessments.

Outcomes were reported at one month (the primary outcome measured) and also at 3 days, 2 weeks, and three months. A follow-up rate of 95.4% was achieved at the 1-month follow-up. The original target sample size was 250 patients, with sufficient power to detect differences of 2.5 points on the RDQ and one point on the pain rating. Difficulty in recruiting led to a reduction in target sample size to 130 patients, and revised power calculations estimated power of 80% to detect a 3-point difference between groups on the RDQ and a 1.5-point difference in pain rating. This study received a LoE grade of II.

Vertebroplasty compared with conservative medical treatment

Three RCTs compared PV with conservative medical treatment (CMT).[62, 86, 87] The primary limitations of these studies are the impossibility of blinded outcomes for patients and the potential for non-specific placebo effects. These studies share the potential for selection bias at entry: for example, in the largest of these RCTs,[62] 33% of patients who were eligible enrolled. In addition, two of the studies[86, 87] were quite small, and one of these[87] had only two weeks of follow-up for patients as randomized, due to a large number of patients crossing over from the CMT to PV arms.

Klazen (2010)

Klazen et al.[62] conducted this RCT at six hospitals in the Netherlands and Belgium. Inclusion criteria were age 50 years or older, presence of a VCF with a minimum of 15% height loss, back pain for 6 weeks or less, and a pain rating of at least 5 on a scale of 0-10. VCFs were verified radiographically and with the presence of bone edema on MRI. Patients with suspected underlying malignant disease were excluded, as were patients with contraindication for MRI or severe cardiopulmonary comorbidity. A total of 202 patients were randomized to be treated with PV (101 patients) or CMT (101 patients). Mean patient age was 75.2 in the PV group and 75.4 in the CMT group, with 69% female participants in both groups. Group differences in demographic and clinical variables were not reported, but analyses were adjusted for imbalances at baseline.

Patients were randomly assigned to a treatment group by an independent central operator. Patients could not be blinded to group assignment, but no attempts were made to mask treatment assignment for outcome assessors. Ten percent of patients in the CMT group crossed over to the PV arm, but no details are given whether or how patients were informed of a crossover option or when the crossover occurred.

Although surgery took place a mean of 5.6 weeks after onset of symptoms, this interval ranged up to 92 days. As a result, fracture age at the time of the intervention for some patients was longer than the 6 weeks specified in inclusion criteria. Of 431 patients eligible for the study and willing to enroll, 53% had spontaneous pain relief during assessment and were not randomized.

Pain and functional outcomes were assessed at 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months, and spine radiographs were done to identify new fractures at 1 month, 3 months, and 1 year. Follow-up was 81% at one year, with some differential follow-up (85% in the PV group

and 76% in the CMT group). The primary outcome was pain relief at 1 month and 1 year, with clinically significant pain relief defined as a decrease in VAS score from baseline of 3 points or more on the 0-10 scale. Statistical power was sufficient (80%) to detect a 25% group difference in significant pain relief.

Evaluation of the results of the study were made more difficult by several gaps in description of the analyses: a) statistical analyses incorporated imputation of missing data, but results without imputation were not provided for comparison; b) for several outcomes, only the results of statistical tests were provided, with no means, percentages, or description of variability of estimates; c) results of omnibus F tests for repeated measures ANOVA were given, but no tests for significant group differences at each follow-up point are described; d) many of the results were displayed in graphs without group mean values. Cook Medical provided partial grant support for the study. This study received a LoE grade of II.

Rousing (2010)

Rousing et al.[86] conducted a small RCT at the University Hospital of Odense, Denmark, with patients who were referred from other hospitals and practices in southern Denmark. Inclusion criteria were age 65 or older, intractable pain due to an osteoporotic fracture no more than 8 weeks old, and sufficient cognitive function to complete the study. Patients with malignant disease were excluded. 50 patients were randomized to be treated with PV (26 patients) or CMT (24 patients), with no information given on how patients were screened, the number who were eligible, or the number who refused participation. Mean patient age was 80 in both groups, with 76% female patients in the PV group and 87.5% in the CMT group. Potential group differences at baseline were not assessed or controlled with statistical adjustment.

Patients were assigned to conditions by opening a sealed envelope that was prepared and sorted randomly in advance and by the surgeon or a doctoral student. This lack of independent assignment to groups raises questions about potential bias in assignment. Patients and surgeons could not be blinded to group assignment, but no attempts were made to mask treatment assignment for outcome assessors.

Outcomes were assessed at time of inclusion and after three and 12 months. Several functional outcomes (including EuroQol and Barthel) were added to the study after it began, so that data are available for these outcomes for about 60% of the patients. Moreover, only 19/26 PV patients and 17/24 CMT patients were scored on VAS at baseline for reasons that are not described in the publication. Follow-up was 94% at three months and 90% at 12 months. Although a calculation of statistical power to detect a difference of 2 VAS units in pain is described, it is not clear how the methodology described for the power analysis led to determination of sample size. This study received a LoE grade of II.

Voormolen (2007)

A small study of patients from 3 hospitals in the Netherlands compared PV with optimal pain management.[87] Inclusion criteria were age 50 years or older, VCF with height loss of ≥ 15% of the vertebral body verified by x-ray, invalidating back pain refractive to medical therapy for at least 6 weeks and no longer than 6 months, focal tenderness at the site upon physical examination, and bone marrow edema of the VCF on MRI. Exclusion criteria were poor cardiopulmonary condition, ongoing infection, and indication of underlying disease other than osteoporosis. A total of 46 patients initially consented, and although the number who were eligible or who refused participation are not given, the authors state that approximately 1 in 4 potential study candidates were enrolled.

Patients were randomly assigned by an independent central operator to be treated with PV or by optimal pain management. However, six patients randomized for the control group left the study because they wanted to be treated by PV, two patients assigned to PV wanted conservative treatment, and four did not complete questionnaires at the 2-week follow-up, leaving 34 patients at two weeks (18 PV, 16 CMT, 74% follow-up rate). Mean age for the remaining patients was 72 in the PV group ad 74 in the CMT group, with 78% female participants in the PV group and 88% in the CMT group.

Patients could not be blinded to group assignment, but no attempt to mask treatment assignment for outcome assessors was mentioned. Patients in the control arm who still had severe pain 2 weeks after initiating treatment could cross over to the PV arm and undergo PV. The study was originally designed to follow patients for one year, but because of the large amount of crossover from the control group to the PV group (14/16 patients in the control arm requested PV), the study was stopped early. Consequently, follow-up data from 2 weeks after the start of treatment were not analyzed for group differences, limiting the conclusions that can be drawn to this very short post-procedure time period. No statistical power analysis or specification of expected effect size was described. This study received a LoE grade of II.

Kyphoplastycompared with conservative medical treatment

One RCT compared kyphoplasty (KP) with conservative medical treatment.[88] As mentioned earlier for trials of vertebroplasty, the potential for placebo effects and the inability to mask treatment from patients are the potential threats to validity.

Wardlaw (2009)

In an RCT funded by Medtronic, Wardlaw et al.[88] conducted an RCT at 21 sites in eight countries. Patients were eligible if they had one to three vertebral fractures from T5-L5 and back pain of ≥ 4 points on a 0-10 scale. At least one fracture needed to have edema assessed by MRI and at least one had to show a height loss of ≥ 15%. Patients were excluded if they were younger than 21; had fractures older than 3 months, pedicle fracture, or previous vertebroplasty; had contraindications to MRI; or had fractures from high-energy trauma. Patients with fractures

due to osteoporosis, myeloma, or osteolytic tumors were included, but patients with fractures from primary bone tumors or osteoblastic metastases were excluded. In the final sample of 300 (149 KP and 151 CMT), only four had non-osteoporotic fractures. 32% of eligible patients agreed to participate, but 10 patients in the KP group did not receive surgery, and 15 in the CMT group withdrew and underwent surgery. Mean patient age was 72.2 in the KP group and 74.1 in the CMT group, and 77% of both groups were female.

Pain and functional outcomes were assessed at 1 month, 3 months, 6 months, and 1 year, and spine radiographs were taken at 3 months and 1 year to identify new or worsening fractures. Patients and radiologists who scored x-rays could not be blinded to group assignment, but no attempt to mask treatment assignment for outcome assessors was mentioned. Follow-up at one month was 92.6% for the KP group and 84.7% for the CMT group, and these percentages at one year were 83% and 73.5% respectively. Of patients lost to follow-up at one year, 16 had died. All 300 patients were included in intention-to-treat analyses using mixed models for unbalanced data. The primary specified outcome was the difference in change from baseline to 1 month on the Physical Component (PCS) of the SF-36. Statistical power was calculated to be more than 80% for detecting a difference of 0.5 standard deviation in change scores between the groups.

Interpreting the results of this study is made somewhat difficult by the fact that the primary outcome was the difference between the groups in pre-post change. Results of selected comparisons at certain time points are presented in the text of the paper, with no group means shown. Graphs show the trajectory of improvement over the 12 months of follow-up, but the graphs do not include group means.

Vertebroplasty compared with kyphoplasty

Kyphoplasty relies on the same principle of vertebral stabilization as PV, and biomechanical data comparing the mechanical stabilization of these procedures show similar results.[89] Although KP is thought to lead to reduced cement leakage and to restore vertebral height, the relevance of these measures to patient functioning and safety is still in question. Although there are a number of nonrandomized studies that assess differential outcomes for vertebroplasty and kyphoplasty (KP), only one RCT was retrieved.

Liu (2010)

A RCT conducted in Taiwan[90] assessed pain, vertebral body height, kyphotic wedge angle in patients randomly assigned to undergo PV or KP. No inclusion or exclusion criteria were specified other than the presence of a confirmed osteoporotic VCF at the thoraco-lumbar junction (T2-L1). Mean age was 74.3 in the PV group and 72.3 in the KP group, with 76% female participants in the PV group and 78% in the KP group. The two groups were equivalent at baseline in age, gender, fracture age, or fracture location. No information was provided on how patients were recruited and screened, the number who were eligible, or the number who refused participation. Radiographic measurements were made by technicians blind to treatment status, but there is no mention of blinding of pain assessments. Minimum follow-up time was 6 months,

with no information on numbers of patients at follow-up. No statistical power analysis or specification of expected effect size was described, so it is unknown whether the number available for analysis was sufficient to detect important changes in the primary outcomes. Because it is an RCT, this study received a LoE grade of II despite the lack of information about procedures.

Cohort studies

Vertebroplasty compared with conservative medical treatment

All five cohort studies (2 prospective[91, 92] and 3 retrospective[54, 93, 94] were graded LoE III.

TREATMENT ASSIGNMENT

In four of the five studies,[54, 91, 92, 94] the CMT group comprised patients who met the criteria for vertebroplasty and agreed to be followed longitudinally, but chose not to undergo the surgery.

SAMPLE SIZE

Sample size for the five studies ranged from 60 to 375. All but one[94] of the studies had a total of 100 or more patients, and one study[93] had more than 100 patients in each group.

INDEPENDENT OR BLIND ASSESSMENT

None of the five studies reported the use of independent or blind assessment.

STATISTICAL ANALYSIS

All five studies delineated the descriptive and inferential statistics used, and three[91-93] stated an *a priori* alpha level of .05 for statistical significance. Three stated that they controlled for possible confounding factors via various statistical methods.[91, 92, 94]

FOLLOW-UP TIME AND PERCENT OF PATIENTS FOLLOWED

Follow-up periods ranged from one to two years across these studies, with one retrospective study[93] incorporating variable lengths of follow-up. In two of the studies, both retrospective,[93, 94] follow-up rates were not reported. Follow-up rates for the remaining three studies were 89%,[91] 76%,[92] and 92%.[54]

Kyphoplasty compared with conservative medical treatment or other spinal surgery

All three cohort studies (1 prospective[95] and 2 retrospective[96, 97]) were graded LoE III.

TREATMENT ASSIGNMENT

In one of the three studies,[95] the CMT group comprised patients who met the criteria for kyphoplasty and agreed to be followed longitudinally, but chose not to undergo the surgery. The method for assigning treatment in the other two studies was not described.

SAMPLE SIZE

Sample size for the three studies ranged from 58 to 86.

INDEPENDENT OR BLIND ASSESSMENT

None of the three studies reported the use of independent or blind assessment.

STATISTICAL ANALYSIS

All three studies delineated the descriptive and inferential statistics used, and one[97] stated an *a priori* alpha level of .05 for statistical significance. One stated that potential confounding was controlled with statistical methods.[95]

FOLLOW-UP TIME AND PERCENT OF PATIENTS FOLLOWED

Follow-up periods ranged from six months[97] to three years[95] across these studies. In two of the studies, both retrospective,[96, 97] follow-up rates were not reported. In the third study,[95] 80% of patients had radiographic outcomes at follow-up, and 92% had questionnaire data, with higher follow-rates in the KP group.

Vertebroplasty compared with kyphoplasty

All 12 cohort studies (6 prospective[98-103] and 6 retrospective[28, 41, 104-107]) were graded LoE III.

TREATMENT ASSIGNMENT BY INDICATION

Assignment of patients to PV or KP varied across these twelve studies. In four of the studies,[28, 100, 102, 106] patients were assigned a surgical procedure based on a treatment algorithm that took into account fracture age, fracture characteristics, and/or pain level. In these studies, therefore, group assignment is potentially confounded by treatment indication. In six studies,[98, 99, 101, 103-105] patients were not assigned to conditions based on their characteristics. For example, patients in three studies[101, 104, 105] were assigned consecutively to treatments, with the first consecutive series of patients receiving one procedure and the second series receiving the other procedure. In other studies, treatments were assigned based on the availability of equipment[99] or clinic site,[103] or "indifferently,"[98] while treatment assignment was not described in two studies[41, 107]

SAMPLE SIZE

Sample size for the 12 studies ranged from 20 to 154. Only two of the studies[100, 105] had a total of 100 or more patients (ns of 104 and 154).

INDEPENDENT OR BLIND ASSESSMENT

In one of the five studies,[99] although patients were not blinded, an independent assessor performed the follow-ups.

STATISTICAL ANALYSIS

All but one of the 12 studies[28] delineated the descriptive and inferential statistics used, and all but four[28, 99, 104, 106] stated an *a priori* alpha level of .05 for statistical significance. None of the studies stated that they controlled for possible confounding factors via various statistical

methods; however, five studies noted that baseline characteristics were similar for both groups.[99, 103-105, 107]

FOLLOW-UP TIME AND PERCENT OF PATIENTS FOLLOWED

Follow-up periods across these studies ranged from immediately post-operative[105, 107] to two years[99, 100]with one retrospective study[28] incorporating variable lengths of follow-up. A one-year follow-up was incorporated in four studies.[101-103, 106]

In five studies (three prospective[98, 99, 102] and two retrospective[104, 107], follow-up rates were not reported. In the other eight studies, follow-up rates ranged from 14% (in a 2-year follow-up of cancer patients[28] to 100% for an immediate post-operative assessment[105] with other rates from 85 to 94%.

Systematic reviews (KQ2)

Characteristics of the six systematic reviews are shown in Table 4.The reports summarized mostly retrospective studies, which consisted primarily of case series (LoE IV) of various sample sizes and lengths of follow-up. Some included available comparative studies.There is overlap in studies included across these reviews even though inclusion/exclusion criteria varied substantially across reviews.

Table 4: Overview of included systematic reviews of observational studies reporting complications from vertebroplasty and/or kyphoplasty

Author (pub year; search date*)	Number of studies, patients, follow-up	Interventions evaluated	Critical appraisal comments
Mixed indications‡			
Lee (2009; Dec 2006)	• PV N = 33 studies; N patients NR • BKP N = 82; N patients NR • Both N = 6 N patients NR • F/U = NR	PV and BKP	• Specifically selected studies (case series and comparative) addressing complications • No formal critical appraisal of included studies or evaluation of heterogeneity • 29 studies appeared to be prospective • Osteoporotic fractures N = 71 studies, pathologic N = 21 studies, mixed indications N = 35 studies • Study N ranged from 8-868 • Outcomes not for osteoporotic and tumor-related fractures separated except for cement leakage • Pooled estimates weighted by sample size • Separate analysis on prospective studies for most outcomes
Taylor (2007; April 2006)	• 7 non-randomized comparative studies; 5 were direct comparison (N = 313 patients, 481 levels)	BKP only	• Describes critical appraisal system based on estimated number of biases present; overall risk of bias (high, moderate, low) for comparative studies • Meta-analysis using random effects model

	• 35 case series (N = 2047 patients, 3302 levels) • F/U 4-43 months		• Separate analysis of comparative and non-comparative studies • Evaluation of heterogeneity and publication bias described
Krueger (2009; Oct 2008)	• PV N = 38 case series • BKP N = 1 case series • N = 5573 patients over all studies	PV and BKP	• Focused on cement pulmonary embolism as complication • No formal critical appraisal of included studies or evaluation of heterogeneity
Eck (2008; May 2006)	• PV N = 103 studies; N = 7,587 patients, 11,566 fractures • BKP N = 33; N = 1,963 patients, 3644 fractures • Both N = 1 study • F/U PV 1 day – 5 years; BKP 1 month-2 years	PV and BKP	• 1 RCT, 10 prospective comparative, 24 retrospective comparative, 99 case series were included • No formal critical appraisal of included studies or evaluation of heterogeneity • Primary focus on pain reduction (VAS) • Included case reports and case series; rates do not include case reports • Number of studies contributing to each outcome not reported
Pathologic fractures†			
Bouza (2009; Sept 2008)	• N = 7 studies (3 retrospective, 4 prospective) • N = 306 patients, 741 levels • F/U 3-24 months	BKP only	• Critical appraisal described • Meta-analysis using random effects • Evaluated sources of heterogeneity • Appears to have included 5 case series and 2 comparative studies
Mendel (2009; Sept 2008)	• PV N = 27, 877 patients, 1599 levels (5 prospective) • BKP N = 12; 333 patients, 481 levels (6 prospective)		• Prospective studies classified ad Level II, retrospective as Level III; no formal critical appraisal described. • Focus: studies of malignant fractures and included studies of tumor embolization • Reports summary data for prospective studies but cites heterogeneity concerns and no meta-analysis performed.

PV = percutaneous vertebroplasty, BKP = balloon kyphoplasty, NR = not reported
*First date is year of publication, second is last date reported for literature search
†Pathologic fractures may include multiple myeloma, hemangioma or metastases
‡Outcomes for osteoporotic and tumor-related fractures not separated

Sacroplasty

No studies comparing sacroplasty with other treatment options were found; therefore data from case series and a systematic review were summarized. One systematic review of sacroplasty for treatment of sacral insufficiency fractures caused by osteoporosis was retrieved[23] as well as nine

published case series with five or more patients (smaller series were excluded). All case series were LoE IV.

2.3 Description of study population

Randomized controlled trials of vertebroplasty and kyphoplasty included exclusively patients with painful vertebral compression fractures due to osteoporosis (in one RCT,[88] four out of 300 patients had fractures due to malignancy). Exclusion criteria varied across the studies, but in most cases patients with serious comorbidities were excluded (see Appendix F for details).

2.3.1 Vertebroplasty compared with sham surgery

Two moderate-sized RCTs compared outcomes in patients who underwent vertebroplasty with outcomes in patients who received sham surgery.[61, 79] In both studies, patients with osteoporotic fractures of 12 months duration or less were included. Duration of pain (an indicator of fracture age) was less than 13 weeks in 44%[61] to 75%[79] of patients. Patients had a mean age of 73-76 years, and the majority (75-80%) was female. In both studies, randomization resulted in groups that were equivalent in age, gender, duration of symptoms, and pain levels (see Table5).

Table5: Patient demographics and fracture characteristics for RCTs comparing vertebroplasty with sham procedure

	Buchbinder (2009)		Kallmes (2009)	
Variable	PVP (n = 38)	Sham (n = 40)	PVP (n = 68)	Sham (n = 63)
Patient demographics				
Gender				
No. males (%)	7 (18)	9 (22)	15 (22)	17 (27)
No. females (%)	31 (82)	31 (78)	53 (78)	46 (73)
Age, years; mean (± sd)	74.2 (± 14)	78.9 (± 9.5)	73.4 (± 9.4)	74.3 (± 9.6)
Follow-up, months (% followed)	6 (92)	6 (90)	1* (99)	1* (97)
Crossover to other intervention, n (%)				
At < 1 month	NR	NR	1 (1)	2 (3)
At < 3 months	NR	NR	8 (12)	27 (43)
Fracture type				
Osteoporotic	38 (100)	40 (100)	68 (100)	63 (100)
Pathologic	----	----	----	----
Fracture age, weeks†	median 9.0	median 9.5	mean 16	mean 20
Distribution of treated fractures	T1-L5‡	T1-L5‡	T4-L5	T4-L5
Number of fractures treated	45	47	95	93
Number of levels treated, n (%)				
One	31 (82)	33 (82)	48 (71)	41 (65)
Two	7 (18)	7 (18)	13 (19)	14 (22)
Three	----	----	7 (10)	8 (13)
Severity of fractures§, n (%)				
Mild	13 (29)	12 (26)	NR	NR
Moderate	21 (47)	24 (51)	NR	NR
Severe	11 (24)	11 (23)	NR	NR
Fracture shape, n (%)				
Wedge	35 (78)	33 (70)	NR	NR
Crush	6 (13)	10 (21)	NR	NR
Biconcave	4 (9)	4 (9)	NR	NR
Comorbidities/Characteristics, n (%)				
Smoking status				
Never	20 (53)	12 (33)	NR	NR

Former	14 (37)	24 (60)	NR	NR
Current	4 (10)	3 (7)	12 (18)	9 (14)
Alcohol use				
Never	8 (21)	12 (30)	NR	NR
Sometimes	17 (45)	18 (45)	NR	NR
Daily	13 (34)	10 (25)	NR	NR
Receiving worker's compensation	NR	NR	9 (13)	7 (11)
Comorbidity index**	NR	NR	1.9 ± 2.1	2.0 ± 1.9
Medication for osteoporosis				
Any	35 (92)	37 (92)	NR	NR
Calcium supplements	27 (71)	25 (62)	NR	NR
Vitamin D	14 (37)	18 (45)	NR	NR
Bisphosphonates	31 (82)	32 (80)	NR	NR
Initial VAS pain score††, mean (±sd)	7.4 ± 2.1	7.1 ± 2.3	6.9 ±2.0	7.2 ± 1.8
Opiods for pain	30 (79)	34 (85)	38 (56)	40 (63)

NR: not reported; PVP: percutaneous vertebroplasty
*The focus of the report was the primary outcomes at 1 month. Outcomes were also described at 3 days, 2 weeks, and 3 months. The percentage of patients with follow-up reported at 3 months was 94% for PVP and 97% for sham.
†Based on duration of back pain.
‡The study did not delineate the distribution of the spinal fractures but stated that the fractures were confined to the thoracic and lumbar spine.
§Severity assessed using the Genant assessment, a semiquantitative assessment that describes normal vertebra (grade 0) or mild (grade 1, 15%–25%), moderate (grade 2, 26%–40%), or severe (grade 3, >40%) deformity in any vertical direction.
**Scores on the comorbidity index range from 0 to 28, with higher scores indicating greater severity.
††Pain was assessed on a scale of 0 (no pain) to 10 (worst possible pain).

2.3.2 Vertebroplasty compared with conservative medical treatment

Three RCTs compared outcomes in patients who underwent vertebroplasty with outcomes in patients who received conservative medical treatment[62, 86, 87]. All three of these studies included only patients with osteoporotic fractures. Patients had a mean age of 72 to 80 years, and the majority (69-88%) was female. Fracture age varied across the studies. The largest RCT [62] included only patients with fracture ages (as indicated by duration of back pain) less than six weeks, with a mean fracture age of approximately one month at baseline. One small study included patients with pain duration from six weeks to six months (mean pain duration 10-12 weeks),[87] and the third study included patients with pain duration up to six weeks (mean pain duration 7-8 days).[86] Further details are shown in Table 6.

Table 6: Patient demographics and fracture characteristics for RCTs comparing vertebroplasty with conservative treatment

	Klazen (2010) [VERTOS II]		**Rousing (2010, 2009)**		**Voormolen (2007) [VERTOS]**	
Variable	PVP (n = 101)	Conservative (n = 101)	PVP (n = 25)	Conservative (n = 24)	PVP (n = 18)	Conservative (n = 16)
Patient demographics						
Gender						
No. males (%)	33 (31)	33 (31)	6 (24)	3 (12)	4 (22)	2 (12)
No. females (%)	68 (69)	68 (69)	19 (76)	21 (88)	14 (78)	14 (88)
Age, years; mean (± sd or range)	75.2 (± 9.8)	75.4 (± 8.4)	80 (65–96)	80 (71–93)	72 (59–84)	74 (55–88)
Follow-up (% followed)	1 year (85)	1 year (76)	1 year (92)	1 year (92)	2 weeks (100)*	2 weeks (100)*
Crossover intervention, n (%)	NR	NR	NR	NR	NR	14 (100)
Fracture type, n (%)						
Osteoporotic	101 (100)	101 (100)	25 (100)	24 (100)	18 (100)	16 (100)
Pathologic	----	----	----	----	----	----
Fracture age†, days (± sd)	29 (± 17)	27 (± 16)	8.4	6.7	85	76

Distribution of treated fractures	T5-L5	T5-L5	T7-L5	T7-L5	T6-L5	T6-L5
Number of fractures treated	136	120	31	32	28	21
Per patient, mean (± sd or range)	2.4 (± 1.9)	2.1 (± 1.5)	NR	NR	1.6 (1–3)	1.2 (1–2)
Number of levels treated, n (%)						
One	NR	NR	19 (76)	18 (75)	NR	NR
Two	NR	NR	6 (24)	4 (17)	NR	NR
Three	NR	NR	0 (0)	2 (8)	NR	NR
Severity of fractures‡, n (%)						
Mild	57 (42)	55 (46)	NR	NR	3 (11)	3 (14)
Moderate	58 (43)	45 (38)	NR	NR	6 (21)	5 (24)
Severe	21 (15)	20 (17)	NR	NR	19 (68)	13 (62)
Fracture shape, n (%)						
Wedge	90 (66)	97 (81)	NR	NR	25 (89)	13 (62)
Biconcave	46 (34)	23 (19)	NR	NR	3 (11)	8 (28)
Comorbidities/Characteristics, n (%)						
Any medication for osteoporosis	24 (24)	26 (26)	NR	NR	NR	NR
Initial pain score§, mean (±sd or range)	7.8 ± 1.5	7.5 ± 1.6	7.5**	8.8**	7.1 (5–9)	7.6 (5–10)

NR: not reported; PVP: percutaneous vertebroplasty
*All patients in the conservative treatment arm requested to be treated by PVP 2 weeks after start of therapy; thus follow-up after 2 weeks was not analyzed. The intention of the study was to follow the patients from both groups for 1 year at serial intervals of time.
†Based on duration of back pain.
‡Klazen 2010 defined fracture severity as follows: mild (10%–20% deformity), moderate (21%–40%), and severe (> 40%); andVoormolen 2007 determined fracture severity using the Genant assessment, a semi-quantitative assessment that describes normalvertebra (grade 0) or mild (grade 1, 15%–25%), moderate (grade 2, 26%–40%), or severe (grade 3, >40%) deformity in any vertical direction.
§Pain was assessed using a visual analog scale (VAS) where 0 = no pain and 10 = worst possible pain.
**Initial VAS pain scores were available for 19 (76%) and 17(71%) patients in the PVP and conservative treatment groups, respectively.

2.3.3 Kyphoplasty compared with vertebroplasty or conservative medical treatment

In an RCT comparing kyphoplasty with conservative treatment,[88] all but four of the 300 patients had osteoporotic fractures. The majority of patients (77%) were female, with a mean age of 72-74. Patients with pain duration of more than three months were excluded, and mean fracture age was 5-6 weeks.

One RCT compared kyphoplasty with vertebroplasty among patients with osteoporotic fractures.[90] All procedures were performed within 43 days of injury, with a mean of 16-17 days. Mean age of patients was 72-74, and 77% were female.

Further details of these two studies are shown in Table 7.

Table 7: Patient demographics and fracture characteristics for RCTs comparing kyphoplasty with either percutaneous vertebroplasty or conservative treatment

	Kyphoplasty vs. Vertebroplasty		**Kyphoplasty vs. Conservative**	
	Liu 2010		**Wardlaw (2009) [FREE]**	
Variable	KP (n = 50)	PVP (n = 50)	KP (n = 149)	Conservative (n = 151)
Patient demographics				
Gender				
No. males (%)	11 (22)	12 (24)	34 (23)	34 (23)
No. females (%)	39 (78)	38 (76)	115 (77)	117 (77)
Age, years; mean (± sd)	72.3 (± 7.6)	74.3 (± 6.4)	72.2 (± 9.3)	74.1 (± 9.4)
Follow-up (% followed)	6 months (NR)	6 months (NR)	1 year (83)	1 year (74)

Crossover to other intervention, n (%)	NR	NR	NR	NR*
Fracture type, n (%)				
Osteoporotic	50 (100)	50 (100)	147 (99)	149 (99)
Pathologic	----	----	2 (1)	2 (1)
Fracture age†, weeks (±sd)	NR	NR	5.6 (±4.4)	6.4 (±5.2)
Distribution of treated fractures				
T12	19 (38)	19 (38)	----	----
L1	31 (62)	31 (62)	----	----
T5-T9	----	----	49 (23)	41 (21)
T10-L2	----	----	127 (59)	130 (67)
L3-L5	----	----	38 (15)	24 (12)
Number of fractures treated	50	50	214	195
Number of levels treated, n (%)				
One	50 (100)	50 (100)	100 (67)	115 (76)
Two	----	----	34 (23)	28 (19)
Three	----	----	15 (10)	8 (5)
Severity of fractures‡, n (%)				
Moderate	NR	NR	113 (70)	123 (71)
Severe	NR	NR	49 (30)	50 (29)
Comorbidities/Characteristics, n (%)				
Medication for osteoporosis				
Calcium supplements	NR	NR	69 (46)	83 (55)
Vitamin D	NR	NR	60 (40)	77 (51)
Bisphosphonates	NR	NR	63 (42)	70 (46)
Initial VAS pain score§, mean (±sd)	8.0 ± 0.8	7.9 ± 0.7	NR	NR
Analgesics, n/N (%)	NR	NR	132/140 (94)	135/146 (92)

KP: kyphoplasty; NR: not reported; PVP: percutaneous vertebroplasty
*The authors stated that 14 patients assigned to the conservative group withdrew and underwent surgery (type not specified) at ≤ 1 month and one patient in the conservative under vertebroplasty because the investigator deemed kyphoplasty no longer feasible.
†Based on duration of back pain.
‡For Wardlaw (2009), at baseline, 338 index vertebra (162 KP; 173 conservative; 3 vertebra unaccounted for) were available for Genant assessment, a semiquantitative assessment that describes normal vertebra (grade 0) or mild (grade 1, 15%–25%), moderate (grade 2, 26%–40%), or severe (grade 3, >40%) deformity in any vertical direction.
§Initial VAS pain scores were available for 19 (76%) and 17(71%) patients in the PVP and conservative treatment groups, respectively

2.4 Description of study outcomes

2.4.1 Efficacy and effectiveness measures

Studies reported pain, functional and activity scores from generic quality of life, disease specific clinician-based or patient-reported outcomes. (see

Table 8).

Various quality of life measures were used, includingEuropean Quality of Life (EuroQoL)European Quality of Life–5 Dimensions (EQ-5D), Short form-36 health survey (SF-36, and Assessment of Quality of Life (AqoL.)[108]Domains assessed by the EQ-5D include patient mobility, self-care, usual activity, pain and anxiety/depression. SF-36 includes 8 subscales that assess physical function, role limitations due to physical health problems, pain, general health, vitality, limitations due to emotional problems, and mental health. The AqoL assesses illness, independent living, social relationships, physical senses, and psychological well-being.[109]

Patient-reported disease-specific outcomes measures were used, including Oswestry Disability Index (ODI)Roland-Morris Disability Questionnaire (RDQ), Quality of Life Questionnaire of the European Foundation for Osteoporosis (QualEffo), Study of Osteoporotic Fractures and Activities of Daily Living (SoF-ADL),[10]and European Vertebral Osteoporosis Study questionnaire(EVOS).[110] The ODI includes 10 subscales of function including pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and travelling. The RDQ includes 12 categories for function and general health, including pain intensity, self care, social life, walking, standing, sleeping, bending, stairs, appetite, general activity, and household chores. The QualEffo has seven subscales, including pain, ADL, jobs around the house, mobility, social function, general health perception, and mental function. The SoF-ADL questionnaire has six categories, including bending, lifting, reaching, putting on socks/stockings, getting into or out of a car, and standing for two hours. The EVOS questionnaire has seven domains, including pain, ADL, jobs around the house, mobility, leisure and social activities, general health perception, and mood.

The Barthel index, a clinician-reported outcome,includes five categories, feeding, self-care, walking, controlling bowels and bladder, and transfer.

Pain was assessed using a visual analog scale,[111]the Pain Bothersomeness Index, and the Pain Frequency Index.[112]

Table 8: Efficacy and effectiveness measures

Outcome measure	Clinician or patient reported	Instrument type	Components	Score range	Interpretation
Barthel index of activities of daily living	Clinician	Neurological	5 categories (10 items): feeding self care walking controlling bowels and bladder, transfer minimum score is 0 per item and variable maximum score of 5, 10, or 15	0-100 for total	Lower score = greater disability
Oswestry Disability Index (ODI)	Patient	Spine	10 subscales (10 items) pain intensity personal care lifting walking sitting standing sleeping sex life social life travelling	0-100	Higher score = greater disability

			each subscale score 0-5, with total score doubled and written as a percentage		
European Vertebral Osteoporosis Study questionnaire (EVOS)	Patient	Spine	7 domains: pain activities of daily living jobs around the house mobility leisure and social activities general health perception mood	0-100	Higher score = less disability
Short form-36 health survey (SF-36)	Patient	Generic	8 subscale (# items) Physical functioning (10) Role limitations due to physical health problems (4) Bodily pain (2) General health (5) Vitality (4) Social functioning (2) Role limitations due to emotional problems (3) Mental health (5)	0-100 for each subscale (total score not used)	Lower score = greater disability
Roland-Morris Disability Questionnaire (RDQ)	Patient	Spine	12 categories (24 items) Pain intensity (2) self care (3) social life (2) walking (2) sitting (2) standing (1) sleeping (2) bending (1) stairs (2) appetite (1) general activity (4) household chores (2)	0-24	Higher score = greater disability
European Quality of Life (EUROQoL)	Patient	Generic	6 categories Mobility Self-care Main activity Pain Mood Social relationships scored 1-3 for mobility, self-care and pain; and 1-2 for main activity, mood, and social relationships	0-1	Optimal health: 1 Death: 0
European Quality of Life – 5 Dimensions (EQ5D)	Patient	Generic	5 categories Mobility Self-care Usual activity Pain Anxiety/depression scored 1-3 for each category	0-1	Optimal health: 1 Death: 0

Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO)	Patient	Spine	7 subscales (41 items) pain activities of daily living jobs around house mobility social function general health perception mental function minimum score of 1 and variable maximum of 3-5; total normalized to 100	0-100	Higher score = greater disability
Study of Osteoporotic Fractures and Activities of Daily Living (SoF-ADL)	Patient	Spine	6 categories bending to pick up lightweight objects lifting a 10 pound object from the floor reaching for objects just over head putting on socks or stockings getting in and out of an automobile standing for two hours (each item scored 0-3)	0-18	Higher scores = greater disability
Assessment of Quality of Life (AQoL)	Patient	Generic	5 categories (15 items) Illness (3) Independent living (3) Social relationships (3) Physical senses (3) psychological well-being (3)	0-1	1 = perfect health 0 = worst health
Visual Analog Scale for Pain (VAS)	Patient	Generic	Pain	0-10	No pain: 0 Worst pain imaginable: 10
Pain Frequency Index	Patient	Generic	Pain frequency (4 items)	0-4	Higher scores = worse pain frequency
Pain Bothersomeness Index	Patient	Generic	Pain bothersomeness (4 items)	0-4	Higher scores = worse pain bothersomeness

EuroQoL: final score is a 6-digit descriptor that corresponds to the level of disability in each subcomponent and ranges from 111111-332232; each score is assigned a preferential weight to obtain a final score of 0 to 1.
EQ-5D: final score is a 5-digit descriptor that corresponds to the level of disability in each subcomponent and ranges from 11111-33333; each score is assigned a preferential weight (e.g., 21111 = 0.85) to obtain a final score of 0 to 1.

2.4.1.1 Clinically meaningful improvement

In general, self-reported ratings of pain and functional status are used to evaluate clinical change, with the magnitude of change assessed with statistical tests. However, a statistically significant difference in these outcomes may not represent a clinically meaningful change. The definition of a clinically meaningful improvement varies in the medical literature for different conditions, different outcomes, and different stakeholders. In the comparative studies of PV and KP

summarized in this report, assessment of clinically meaningful improvement is not common, and the definition of such improvement varies across studies.

Recent attempts to achieve consensus on the definition of clinically meaningful improvement include the work of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group, which is composed of 40 individuals from universities, governmental agencies, the pharmaceutical industry, and a patient organization. This group concluded that a 10–20% reduction in chronic pain appears to reflect a minimally important difference, while a ≥30% reduction reflects a moderate clinically important change and a ≥ 50% reduction reflects substantial improvement. They further recommend that the percentage of patients who respond with moderate (≥30%) and substantial (≥ 50%) reductions be reported in clinical trials of chronic pain treatments.[113]

A second report summarizes the recommendations of an expert panel that convened to recommend the most appropriate values for minimal important change (MIC) for several measures used in studies of low back pain, including three that are used in the studies summarized in this report (VAS pain rating, ODI, and RDQ). This panel proposed using MIC values of 2 for a 0-10 pain rating scale, 5 for the RDQ, and 10 for the ODI, or using a general guideline of 30% improvement from baseline.[114]

Both groups noted that these proposals are starting points for further research and an encouragement for more uniform reporting on pain and functional outcomes.

2.4.2 Safety outcomes

The safety outcomes assessed in comparative studies were of two general classes: occurrence of new vertebral fractures (adjacent or not adjacent to the treated fracture) and cement leakage (including pulmonary cement embolism). Although other isolated complications were reported in some of the studies, they were not systematically assessed.

Cement leakage occurs at the time of the procedure, and can be detected during fluoroscopy at the end of the procedure, or with post-procedural chest radiographs. Pulmonary cement embolism is a potential consequence of cement leakage if cement migrates toward the lungs. There is no clear diagnostic or treatment standard for PCE,[40] and the type of imaging and definition of PCE differs across studies. CT is more sensitive for detecting small cement deposits than either radiographs or fluoroscopy.[63]

New fractures may occur at any time post-procedure, as cement augmentation is thought to place additional stress on adjacent levels by augmenting the stiffness of the treated vertebra. However, new fractures may also result from inherent and spatial clustering of fractures or ongoing osteoporotic processes rather than cement augmentation. New fractures are diagnosed with spine radiographs, and are usually in terms of a specified decrease in vertebral height; however, the amount of height loss that represents a fracture is not defined consistently across studies. Fracture age is difficult to determine, as onset of pain and whether a certain event may be

associated with the onset may not be apparent.If it is unclear, clinicians often order an MRI to assess for edema within the fractured level. If there is no edema, it is presumed to be a healed fracture. If there is edema, that is suggestive of metabolic activity at the fracture site.

3. Results

For key questions 1-3, a total of 29 studies were identified, including seven randomized controlled trials. For three studies,[86, 92, 95]more than one published paper was found that reported results at different lengths of follow-up. For these studies, the most recent published paper or the paper describing the longest follow-up period was used. For key question 4, we identified three studies that incorporated cost utility or cost-effectiveness analysis.

In all of the RCTs of vertebroplasty, the sample was restricted to patients with osteoporotic fractures. Although the single RCT that compared kyphoplasty with conservative medical treatment[88] did not exclude patients with fractures due to malignancy, only 4 of 300 patients had such fractures. Two of the 20 cohort studies[28, 106] included only cancer patients with fractures due to malignancy, and the remainder were limited to patients with osteoporotic fractures.

3.1 Key question 1: What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, or sacroplasty?

Summarizing the results of RCTs (efficacy) and cohort studies (effectiveness) of these procedures is made difficult by the lack of a consistent measure of clinical success and little uniformity in the outcomes reported or in length of follow-up. The results of these studies are described in two major areas: pain reduction and improvements in functioning and quality of life. When available, radiographic outcomes (changes in vertebral height and kyphotic angle) are described, however, radiographic findings may not be consistently correlated with patient functioning.[83] Radiographic outcomes were considered indirect, secondary outcomes.

3.1.1. Efficacy of vertebroplasty and kyphoplasty

Vertebroplasty compared with sham surgery

Two randomized controlled trials compared percutaneous vertebroplasty (PV) with sham surgery to assess short-term efficacy and safety.[61, 79] As discussed earlier, a major advantage of these studies is the ability to control for non-specific placebo effects. The results of these studies showed that

- PV was no more effective than sham surgery in reducing self-reported pain intensity for follow-up points of up to six months.
- The percentage of patients who achieved a clinically meaningful improvement in pain was higher for PV than for sham surgery, but this difference did not achieve statistical significance in either study.

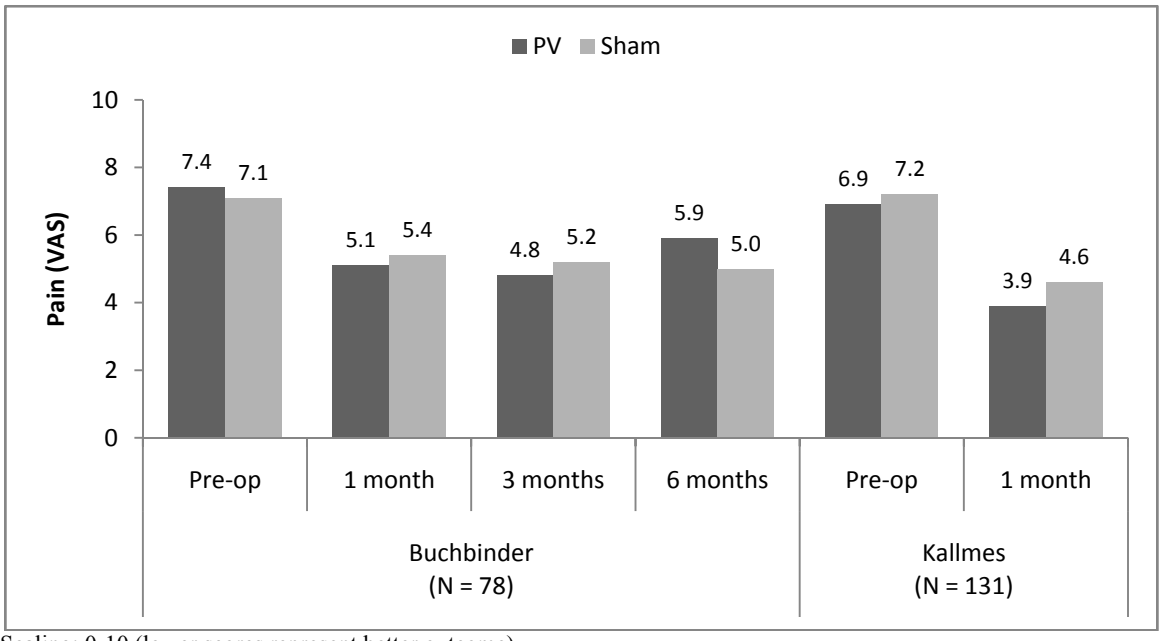
- PV was no more effective than sham surgery in improving scores on functional outcomes, including RDQ, SF-36, and EQ-5D for follow-up points of up to six months.

Pain reduction

Pain was measured with a 0-10 Visual Analog Scale (VAS) in both of the RCTs that compared vertebroplasty with sham surgery.[61, 79] In one of the studies, patients were asked to report on pain during the previous week,[79] and in the other, the time frame for reported pain was the previous 24 hours.[61]

In these two RCTs, pain scores (VAS) ranged from 6.9 to 7.4 at baseline and improved by 2.6-3.0 points at the longest follow-up. No statistically significant group differences in pain scores[61]or in improvement in pain scores[79]appeared at any follow-up points (Figure 2).

Figure 2: Mean pain (VAS) in studies comparing vertebroplasty with sham surgery



Scaling: 0-10 (lower scores represent better outcome)
No significant group differences
PV = percutaneous vertebroplasty
Sham = Sham surgery mimicking vertebroplasty

One of these studies[61] incorporated the Pain Frequency Index and the Pain Bothersomeness Index, and reported equivalent improvements in vertebroplasty and control groups of 0.8-1 points on a 4-point scale. One study[79]also assessed patients' perceived change in pain from baseline. At 1 week, 16% of the vertebroplasty group and 35% of the sham surgery group reported that their pain status was better (a risk difference (RD) of 19%). These percentages were 34% and 24% (RD 10%) at one month, 39% and 32% (RD 7%) at 3 months, and 46% and 42% (RD 4%) at 6 months, with no statistically significant group differences.

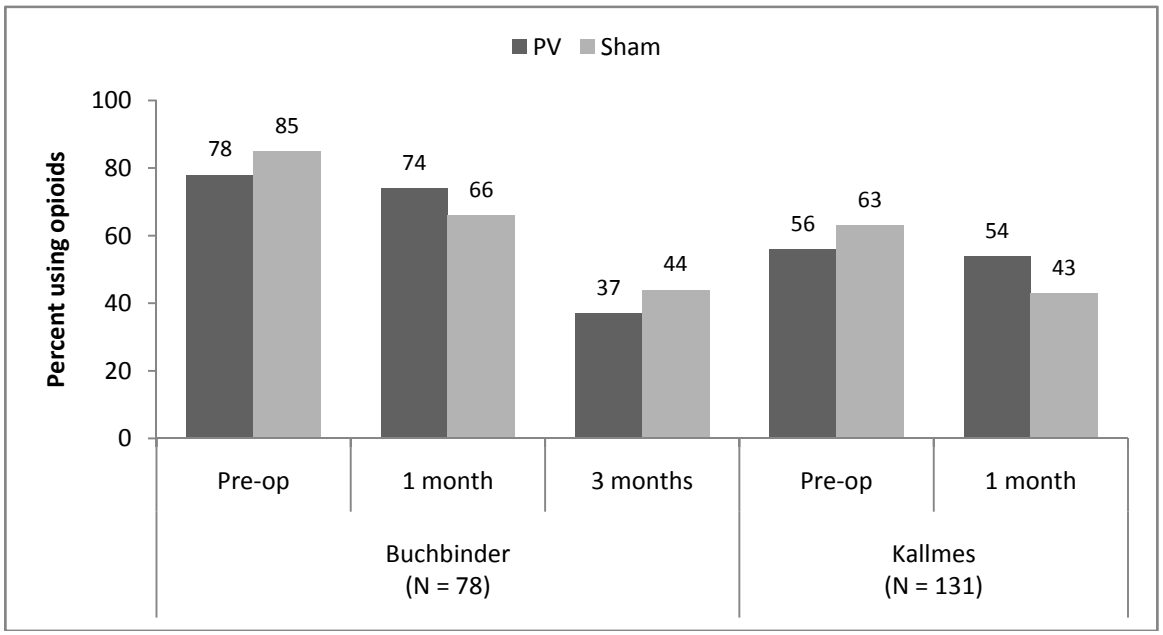
Both RCTs reported the percentage of patients who achieved what the authors defined as a clinically meaningful improvement in pain; however, the two studies used different definitions of

clinically meaningful improvement. As discussed earlier in section 2.5.1.1, although the definition of a clinically meaningful improvement varies in the medical literature, a 30% improvement in baseline may be considered a meaningful improvement.[113, 114] Buchbinder et al.[79]reported the percentage of patients with a change in pain of <2.5 units and ≥2.5 units on the 11-point scale. The percentage of patients reporting ≥2.5 units of improvement in pain (VAS) for the vertebroplasty and sham control groups was 51% and 42% (RD 9%) at one month, 53% and 35% (RD 18%) at 6 months, and 54% and 42% (12% RD) at 12 months. There were no statistically significant differences between groups; however, this study was not powered sufficiently to detect differences in these proportions (with 78 participants, power to detect a difference between 53% and 35% is 0.28). Kallmes et al.[61] reported the percentage of patients who achieved a 30% decrease in pain from baseline, and found a trend (p=.06) toward greater improvement in the vertebroplasty group (64%) compared with the sham control group (48%), a risk difference of 16%. This study was also not powered to detect a difference of this magnitude (power = 0.39).

In the Kallmes study, patients were asked to guess which intervention they had received. While patients in the vertebroplasty group guessed no better than chance (51%), a slightly higher percentage of the control group guessed correctly (63%). Any tendency for participants to become "unblinded" may have accounted for some portion of the trend toward clinically significant pain reduction in the vertebroplasty group.

Both of the RCTs reported patients' use of opiate pain medication. There were no statistically significant differences in medication use between groups over the follow-up period in either study (Figure 3).

Figure 3: Percent of patients using opiate medication in studies comparing vertebroplasty with sham surgery

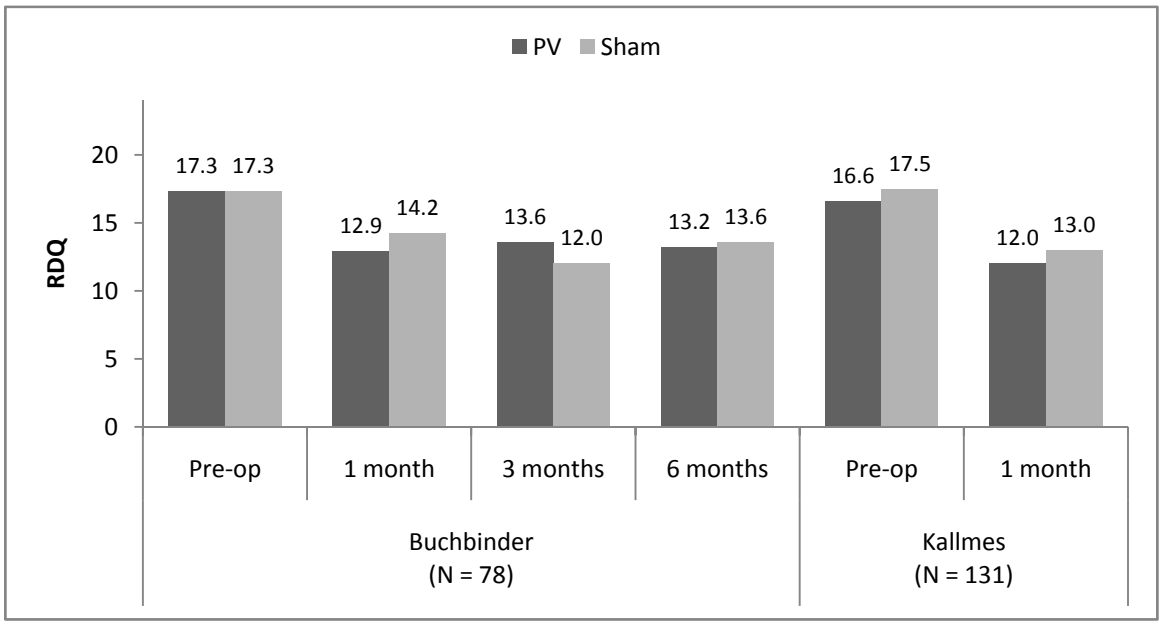


Scaling: 0-100% (lower scores represent better outcome)
PV = percutaneous vertebroplasty
Sham = Sham surgery mimicking vertebroplasty

Functional and Quality of Life outcomes

Roland-Morris Disability Questionnaire (RDQ): Improvements in RDQ scores did not vary significantly across vertebroplasty and sham control groups in either of the RCTs. Patients in both groups improved post-op by 3.7-5.3 points on the 23-point scale (Figure 4). In one study in which RDQ was a predefined primary outcome, equivalent proportions of patients in each group (40% and 41%) demonstrated a clinically meaningful improvement of 30% at one month.[61]

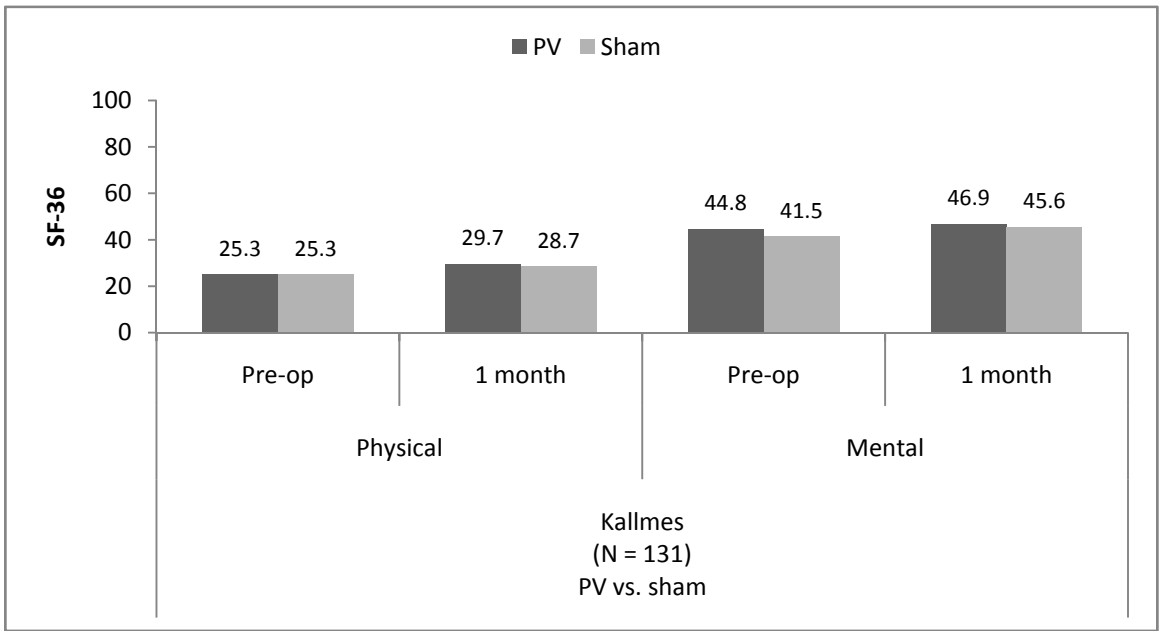
Figure 4: Mean Roland-Morris Disability Questionnaire in studies comparing vertebroplasty with sham surgery



Scaling: 0-23 (lower scores represent better outcome)
PV = percutaneous vertebroplasty
Sham = Sham surgery mimicking vertebroplasty

Short-form General Health Survey (SF-36): Kallmes et al.[61] reported no statistically significant differences between vertebroplasty and sham control groups in scores on the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36 (Figure 5).

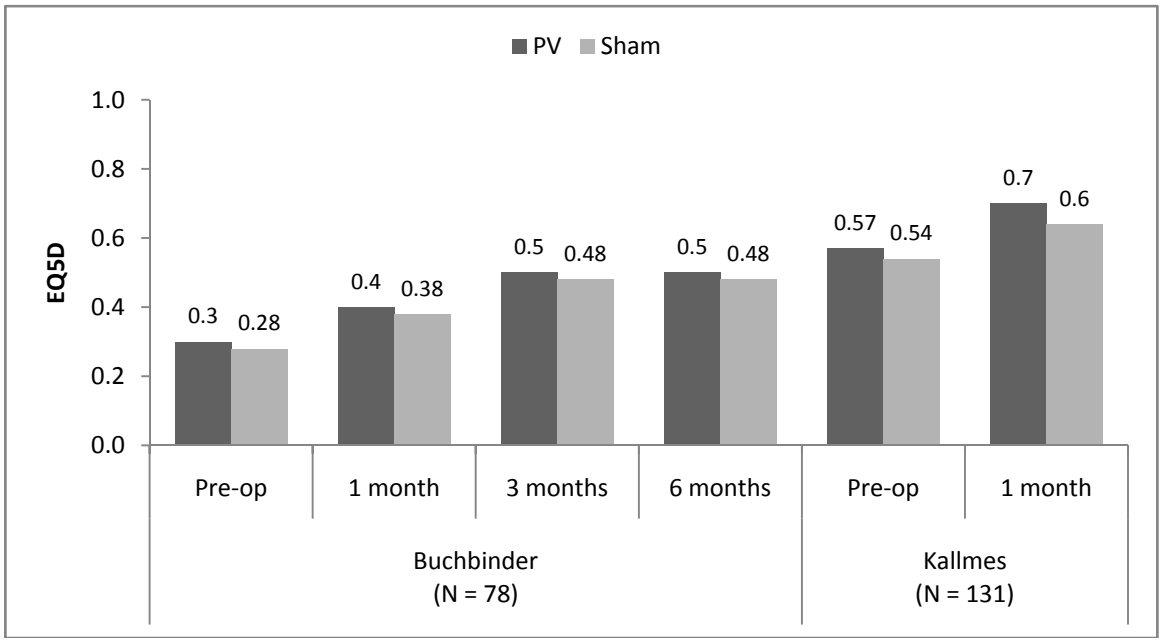
Figure 5: Mean SF-36 Physical and Mental Component Summariesin studies comparing vertebroplasty with sham surgery



Scaling: 0-100 (higher scores represent better outcome)
PV = percutaneous vertebroplasty
Sham = Sham surgery mimicking vertebroplasty

European Quality of Life – 5 Dimensions (EQ5D): No significant group differences in the mean EQ5D were reported in either of the two RCTs (Figure 6).

Figure 6: Mean EQ5din studies comparing vertebroplasty with sham surgery



Scaling: 0-1 (higher scores represent better outcome)
PV = percutaneous vertebroplasty

Sham = Sham surgery mimicking vertebroplasty

Other functional outcomes: The two RCTs found no significant group differences on the QualEffo,[79] the SoF-ADL,[61] or the AQoL.[79]

Vertebroplasty compared with conservative medical treatment

Three RCTs compared PV with conservative medical treatment (CMT).[62, 86, 87] The primary limitations of these studies are the impossibility of blinded outcomes assessment by patients and the potential for non-specific (placebo) effects. Moreover, two of the studies were quite small, with 34-50 total patients[86, 87]. The results of these studies showed that

- In the largest study (188 patients),[62]PV was more effective than conservative treatment in reducing self-reported pain intensity for follow-up points of up to one year. Two smaller studies showed equivalent improvement in pain intensity for patients treated with PV and conservatively-treated patients; however, the statistical power to detect group differences in these studies is low.
- In the same large study,[62] more PV patients than non-surgical patients achieved a clinically meaningful improvement in pain in a shorter period of time.
- 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.[62]

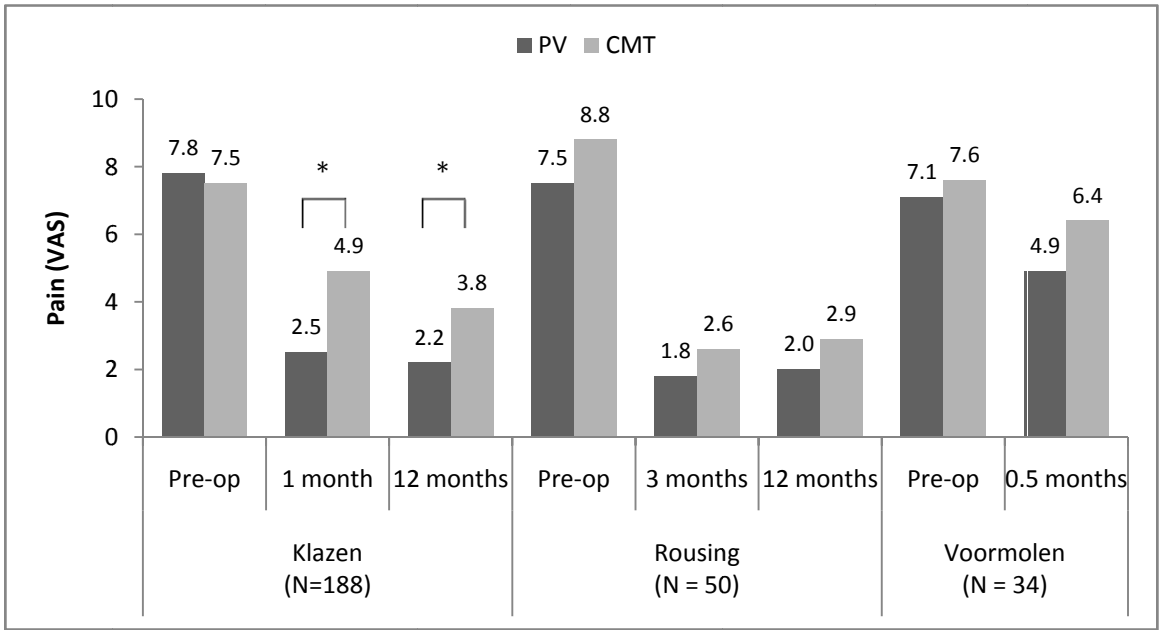
Pain reduction

Pain was measured with a 0-10 Visual Analog Scale (VAS) in all of the three RCTs that compared vertebroplasty with conservative medical treatment.[62, 86, 87] Two of the studies[86] did not define a clinically meaningful improvement in pain or assess the percentage of patients achieving such improvement. Klazen et al.[62] defined clinically significant pain relief as a decrease in pain scores of 3 points or more from baseline, but did not report the percentages of patients who achieved such relief. Follow-up times across these three RCTs varied from 2 weeks[87] to 12 months.[62, 86]In the Voormolen et al. study, patients with continuing pain were allowed to cross over to the other treatment arm after two weeks, and 14 of the 16 patients in the control arm requested vertebroplasty. Therefore, only 2-week outcomes for this study are reported in Figure 7.

Across these studies, pain scores (VAS) ranged from 7.1 to 8.8 at baseline and improved by 1.2-6.2 points at follow-up (Figure 7). The largest RCT that compared vertebroplasty with conservative medical treatment reported that vertebroplasty patients had significantly lower pain scores than conservatively-treated patients at all follow-up points (from 1 day to 1 year).[62] In the other two studies, no statistically significant group differences in pain scores[86]or in improvement in pain scores[87]appeared at any follow-up points longer than one day. Voormolen[87]reported that one day after vertebroplasty or initiation of optimal pain management, pain scores of vertebroplasty patients were significantly lower (by 2.4 points) than scores of patients treated

conservatively. At the 2-week follow-up in this study, however, pain scores were not significantly different between the groups.

Figure 7: Mean pain (VAS) in studies comparing vertebroplasty with conservative medical treatment

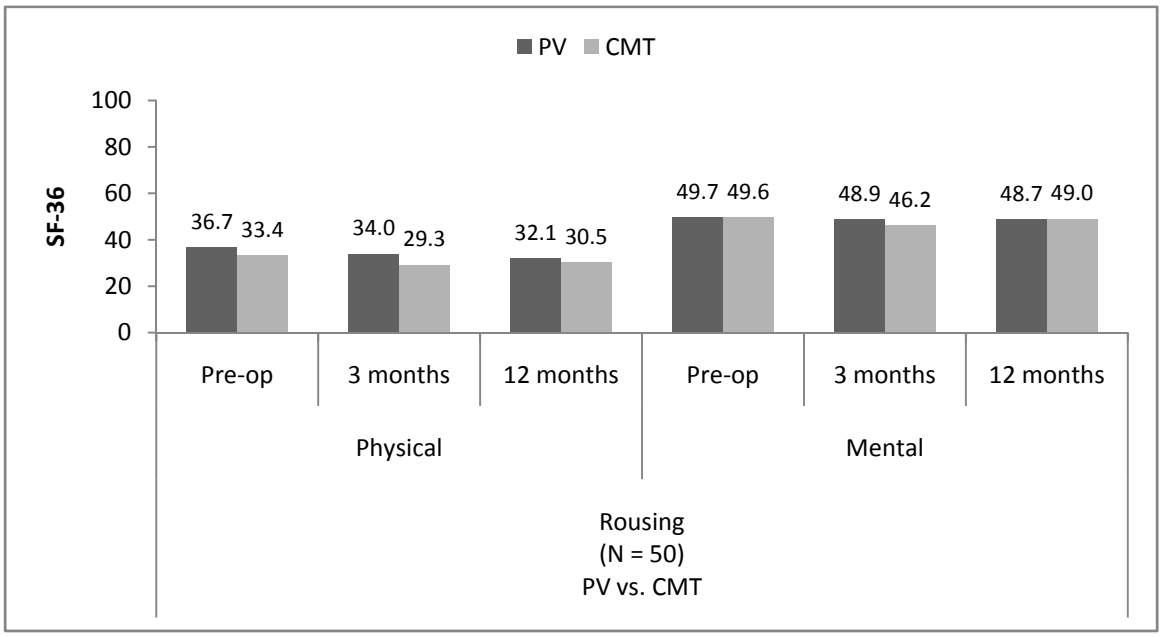


Scaling: 0-10 (lower scores represent better outcome)
Voormolen study allowed crossover after 2 weeks
Rousing study included baseline VAS for 19/25 in PV group and 17/24 in CMT group
* Statistically significant difference ($p<.05$) between PV and CMT groups
PV = percutaneous vertebroplasty
CMT = conservative medical treatment

Roland-Morris Disability Questionnaire (RDQ): In a small study comparing vertebroplasty with non-surgical management,[87] vertebroplasty patients had improved significantly more at two weeks (2.7 points) than control patients (-.02 points). A larger RCT reported that improvement over time was significantly greater for vertebroplasty patients than for conservatively-treated patients on the RDQ by approximately 2-3 points throughout the 1-year follow-up period (interpolated from study graphic; no mean values provided).[62]

Short-form General Health Survey (SF-36): In a study that assessed the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36,[86] nostatistically significant group differences were found (Figure 8).

Figure 8:Mean SF-36 Physical and Mental Component Summariesin studies comparing vertebroplasty with conservative medical treatment



Scaling: 0-100 (higher scores represent better outcome)
PV = percutaneous vertebroplasty
CMT = conservative medical treatment
Baseline SF-36 scores available for 17/25 in PV group and 17/24 in CMT group

European Quality of Life – 5 Dimensions (EQ5D): In one RCT that compared vertebroplasty with conservative treatment,[86] the vertebroplasty group had significantly better mean EQ5D scores than the control group at 3 months (0.73 versus 0.54), however, the patients differed at inclusion on this measure (0.36 versus 0.08) and thus the groups were not comparable. Adjusted outcomes were not reported. Klazen et al.[62] used EQ5d scores to calculate Quality-Adjusted Life Years (QALY), reporting higher QALY in vertebroplasty patients than in conservatively-treated patients (differences of .01 at one month and .108 at one year).

Other functional outcomes: In a small study comparing vertebroplasty with non-surgical management,[87] vertebroplasty patients had improved significantly more on the QualEffo at two weeks (6.8 points) than control patients (0.7 points). In a larger RCT, vertebroplasty patients improved significantly more overall than conservatively-treated patients on the QualEffo; however, scores for the two groups were similar at 12 months (interpolated from graphs; no mean values provided).[62]

Kyphoplasty compared with conservative treatment

One RCT compared kyphoplasty (KP) with conservative medical treatment.[88] As mentioned earlier for trials of vertebroplasty, the potential for placebo effects and the inability to mask treatment from patients are the major threats to validity. The primary outcome was the difference between the groups in pre-post change in pain and functioning. Because no group means are

provided in the published paper, no figures are included in this section. The results of this study showed that

- KP was more effective than conservative treatment in reducing self-reported pain intensity for follow-up points of 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 conservative treatment in improving functioning as measured by the EQ-5d, RDQ, and SF-36 over most time periods. Following an early advantage for KP, group differences were diminished by 12 months as CMT patients improved over time.

Pain reduction

Pain scores as rated on a scale from 0-10 decreased significantly more in kyphoplasty patients than in controls over the 12 months of follow-up. One week post-procedure, kyphoplasty patients had improved 2.2 points more than controls, and at 12 months, the differential improvement was 0.9 points. A significant interaction between treatment and follow-up time suggested early improvements in the kyphoplasty group followed by a slower rate of improvement over the 12 months.

At baseline, 74% of kyphoplasty patients and 68% of controls were using opioid pain medication (RD 6%). At the one-month follow-up, this proportion had decreased significantly more (to 46%) in the kyphoplasty group than in the control group (to 65%), a risk difference of 19%. By the 12-month follow-up, the two groups did not differ significantly in medication use, with 28% of kyphoplasty patients and 34% of controls using opioid medication (RD 6%).

Functional and Quality of Life outcomes

Improvements in EQ-5D, RDQ, and SF-36 PCS were significantly greater among kyphoplasty patients than among control patients at most time periods over the 12 months of follow-up. Improvement in the RDQ score was significantly greater in the kyphoplasty group at one month (4.0 points) and 12 months (2.6 points). Kyphoplasty patients improved significantly more than controls on EQ-5D scores at one month (0.18 points difference) and 12 months (0.12 points difference). Although SF-36 PCS improved significantly more in the kyphoplasty patients up to 6 months, by 12 months the gains were no longer statistically significant, with 1.5 points more improvement in the kyphoplasty group.

Significant interactions between treatment and follow-up time for the outcomes suggested early improvements in the kyphoplasty group followed by a subsequent slowing of improvement over the 12 months.

Vertebroplasty compared with kyphoplasty

Although there are a number of nonrandomized studies that assess differential outcomes for vertebroplasty and kyphoplasty (KP), only one RCT was retrieved.[90] The results of this study showed that

- Back pain scores improved equally for PV and KP patients over 6 months.
- Increases in vertebral body height and reductions in kyphotic wedge angle were larger for KP than for PV.

Pain reduction
Back pain scores improved significantly in both groups over 3 and 6 months of follow-up, with pain decreasing approximately 68% in both groups from baseline (from 8 to 2.3-2.6). No significant difference in pain between the two groups was found at any follow-up period.

Radiographic outcomes
Although both procedures significantly increased vertebral body height, the increase was significantly greater following kyphoplasty (1.13 cm pre-op to 2.04 cm immediately post-op) than vertebroplasty (1.01 cm to 1.32 cm). Similarly, reduction in kyphotic wedge angle was significantly greater following kyphoplasty (17.0º pre-op to 9.0º post-op) than vertebroplasty (15.5º pre-op to 12.2º post-op).

3.1.2. Effectiveness of vertebroplasty and kyphoplasty

Whereas randomized controlled trials provide information about the efficacy of a treatment, information about effectiveness is taken from non-randomized comparative studies. These cohort studies can describe how treatment works in practice, outside of RCTs with rigid controls and stringent inclusion criteria. Non-randomized studies, however, are more subject to bias and confounding.

Vertebroplasty compared with conservative treatment

Four cohort studies (2 prospective[91, 92] and 2 retrospective[54, 94] compared outcomes of PV and CMT patients for up to two years. These studies suggested that:

- Pain decreased over time in both PV and CMT patients
- PV patients experienced early decreases in pain compared to CMT patients, but pain levels are generally equivalent after 6 months to a year.
- Similar patterns were evident for functional outcomes, with early improvements in PV patients followed by equivalent level of functioning after 6 months to a year.

Pain reduction
In two prospective[91, 92] and two retrospective[54, 94] cohort studies, post-operative pain (measured by VAS) decreased significantly from pre-operative levels both for patients undergoing vertebroplasty and for those receiving conservative treatment. Pre-operative pain ranged from

7.5 to 9, with post-operative pain decreasing to 0.7-3.5 at one year. In three studies,[54, 91, 92] vertebroplasty patients reported significantly less pain than conservatively-managed patients during follow-up periods from 1 day to 6 months, but pain levels were comparable for the two groups after one year. One study[94] reported that vertebroplasty patients continued to report significantly less pain at one year (0.7 for PV patients versus 2.0 for CMT patients).

Functional and Quality of Life outcomes

In three cohort studies (two prospective[91, 92] and one retrospective[54]), patients treated by either vertebroplasty or conservative medical treatment improved on various functional measures over follow-up intervals of up to two years.

- Ambulation and daily activities: Patients in a retrospective cohort study[54] improved significantly in their ability to ambulate and perform daily activities by 2-2.5 points on a five-point scale over a year. Vertebroplasty patients reported significantly better functioning than conservatively-treated patients for the first 3 months of follow-up, and the groups were equivalent at one year.
- Barthel index of activities of daily living: In a prospective study, patients improved significantly from 14/20 pre-operatively to 19/20 at 6-12 months, with vertebroplasty patients reaching their maximum function in six weeks and CMT patients in 6-12 months. No significant group differences from 6 months to 2 years were reported.[92]
- Oswestry Disability Index: Vertebroplasty patients in a retrospective cohort study[91] improved from 34% pre-operatively to 17% by the one-year follow-up (lower scores indicate better function), with conservatively-managed patients improving from 28% to 11%. The vertebroplasty group was significantly more disabled at baseline and at the 6-month and 12-month follow-up measurements.

Radiographic outcomes

Nakano et al[94] described radiographic outcomes from a retrospective cohort, reporting that the mean recovery rate of the deformity index was significantly greater in the vertebroplasty group (+3.7% vs. -13.2%). Significant differences also were found in the mean recovery rate of kyphosis (+8.4% vs. -21%).

Kyphoplasty compared with conservative treatment

Kyphoplasty was compared with conservative treatment in one prospective[95] and one retrospective cohort study[96] (this latter study incorporated both a CMT control group and a group that received spinal fusion surgery). The results of these studies suggest that

- KP reduced pain more than CMT for periods up to 3 years.
- KP improved selected functional outcomes more than CMT, including EVOS and an assessment of mobility.

Pain reduction

In two cohort studies, patients who underwent kyphoplasty reported less pain over the follow-up periods than patients treated conservatively. In a prospective study with a three-year follow-up,[95] pain scores of kyphoplasty patients improved significantly, from 73.8 at baseline (scale 0-100) to 54-56 at 1-2 days post-procedure and throughout the follow-up period, while pain levels of patients managed conservatively showed no significant improvement (66 at baseline, 65.7 at one year, and 64 at 3 years). In this study, kyphoplasty patients reduced their use of opiate medication from 67.5% preoperatively to 55% at 6 months, significantly more than the CMT group (reduced from 70% to 65%). A retrospective study with two control groups (conservative treatment and posterior instrumentation and fusion)[96]reported that pain improved significantly more among kyphoplasty patients than among those treated conservatively: Pain scores in the kyphoplasty group decreased from 8.3 at baseline to 3.1 at 3 months and 3.2 at one year, while scores for the CMT group decreased from 7.9 at baseline to 4.8 at 3 months and 4.5 at one year.

Functional and Quality of Life outcomes

Two cohort studies reported significantly greater improvements in functional outcomes for kyphoplasty patients than for non-surgical patients.

- European Vertebral Osteoporosis Study questionnaire (EVOS): Kyphoplasty patients in a prospective cohort study[95] improved significantly from 43.8 at baseline to 54.2 within two days post-op on this 100-point scale of daily activities, while patients treated conservatively showed no significant improvement (39.8 to 43.6 over 3 years)
- Mobility: Patients in a retrospective cohort study[96] were assessed with an ordinal mobility scale, with options ranging from 0 (walking without assistance) to 4 (activity restricted to lying flat in bed). At baseline, all patients were rated grade 3 (sitting in bed) or 4. Kyphoplasty patients improved significantly more than CMT patients on this measure: All of the kyphoplasty patients and 36.5% of CMT patients reached grade 0 within a year, with the remainder of the CMT patients improving to grade 1 (walking with assistance, 54.5%) or grade 2 (wheelchair-bound, 9%).

Radiographic outcomes

In a prospective cohort study with a 3-year follow-up,[95] kyphoplasty and control patients differed significantly in loss of vertebral height over 3 years. While height was significantly improved over baseline in kyphoplasty patients (from 59.2% to 64.7%), patients treated conservatively continued to lose vertebral height (from 60.9% to 51.2%). The groups also differed significantly in improvement in kyphosis angle, with the angle decreasing in the kyphoplasty group (from 8.6 at baseline to 7.7 at 3 years) and increasing in the control group (from 8.0 at baseline to 11.1 at 3 years).

The retrospective study with two control groups (conservative treatment and posterior instrumentation and fusion)[96]reported that the kyphotic deformity angle improved significantly more for kyphoplasty patients (15.9º at baseline and 5.9º at final follow-up) than for patients

treated conservatively (5.2º at baseline and 14.8º at follow-up); however, the patients also differed substantially at baseline on kyphotic deformity angle.

Kyphoplasty compared withspinal fusion

In two retrospective cohort studies, kyphoplasty was compared with spinal fusion with instrumentation.[96, 97] These studies suggested that

- KP reduces pain more than spinal fusion immediately post-op, largely because of the noninvasiveness of kyphoplasty compared with open surgery.
- KP and spinal fusion result in similar improvements in pain and functioning over a year of follow-up.

Pain reduction

A retrospective study with two control groups (conservative treatment and posterior instrumentation and fusion)[96] reported no significant group difference in improvement in pain for kyphoplasty and instrumentation groups, with both improving from 8.3 at baseline to 3.1-3.2 over a year. Over the year of follow-up, all surgical patients improved functionally from activities restricted to sitting or lying in bed to walking without assistance. In the second study, pain decreased more for kyphoplasty patients (from 8.8 to 2.7 pre-op to one day post-op) than for patients with implanted pedicle screws (8.6 to 8.2), largely because of the noninvasiveness of kyphoplasty compared with open surgery.[97]

Radiographic outcomes

In a comparison of kyphoplasty with implantation of pedicle screws,[97] recovery of vertebral height did not differ significantly for the two groups (both groups improved from 18.3-18.4 mm to 23.3-23.4 mm). A comparison of kyphoplasty with posterior instrumentation and fusion[96] reported that kyphotic deformity angle improved somewhat more for kyphoplasty patients (15.9 at baseline and 5.9 at final follow-up) than for patients treated with posterior instrumentation and fusion (19.1 at baseline and 8.9 at follow-up). This group difference approached statistical significance (p=.081).

Vertebroplasty compared with kyphoplasty

Vertebroplasty was compared with kyphoplasty in 12 cohort studies (6 prospective[98-103] and 6 retrospective[28, 41, 104-107].As described in section 2, patients were assigned to treatment groups in different ways, some of which introduce bias if treatment assignment is confounded by indication. Although the results are somewhat mixed, the consensus of the findings suggests that

- PV and KP reduced pain by equivalent amounts at follow-up periods of up to 2 years.
- PV and KP both improved scores on the ODI, with no significant differences between groups.

Pain reduction

Of 12 nonrandomized studies that compared vertebroplasty with kyphoplasty, 10 included VAS measures of pain over follow-up periods of up to 2 years. Both prospective and retrospective cohort studies demonstrated improvements in pain following both procedures.

In six prospective cohort studies,[98-103] initial pain scores ranged from 7.2 to 8.8 on a 0-10 scale and decreased to .6 to 4.6 at the final follow-up. In these prospective studies, improvements in pain were statistically significant for both vertebroplasty and kyphoplasty patients, and five of the studies[98, 100-103] found no significant differences at follow-up between the two groups at the longest follow-up. In one study,[99] kyphoplasty and vertebroplasty patients experienced similar decreases in pain of 4.9 to 5.8 points one day after surgery. However, at 4 months, pain scores of vertebroplasty patients had increased from 3.0 to 5.7, while those of kyphoplasty patients continued to decrease. These group differences remained statistically significant at subsequent follow-up points up to 2 years.

In four retrospective cohort studies,[28, 104, 106, 107] initial pain scores ranged from 7.2 to 8.5, decreasing significantly to 1.3 to 2.0 over follow-up periods of one day[107]to 1 year.[28, 106] In three of these studies,[28, 104, 107]no significant differences in improvement were reported between the vertebroplasty and kyphoplasty groups, and the fourth study[106] reported that kyphoplasty patients showed more improvement at 6 months and 1 year.

Functional and Quality of Life outcomes

Five prospective cohort studies[98-102] reported scores on the Oswestry Disability Index (ODI) over follow-up periods up to 2 years. Mean pre-operative scores ranged from 30.8 to 77, with post-op scores from 4.8 to 56. Four of these studies[98, 100-102] reported that both vertebroplasty and kyphoplasty patients improved significantly post-surgery compared with baseline scores, with no significant differences in improvement between groups. Grohs et al.[99]found that vertebroplasty patients experienced no significant improvement in ODI at any point over 2 years of follow-up, while kyphoplasty patients showed significant improvement over baseline at four months and one year, but not at two years.

Radiographic outcomes

Radiographic findings of vertebral height were compared for vertebroplasty and kyphoplasty in 7 of the cohort studies.[99-103, 105, 107]Improvements in vertebral height following surgery ranged from less than 1 mm to increases of up to 5.4 mm. Three studies found that kyphoplasty was superior to vertebroplasty in improving vertebral height,[99, 100, 107] one study reported no improvements with either type of surgery,[102]one study found significant improvement in both groups with no group differences,[105] and one study[101] found that while vertebral height was significantly increased in the short term in both vertebroplasty and kyphoplasty patients, only kyphoplasty patients maintained improvements at one year.

Three cohort studies reported comparisons of improvements in kyphotic angle for vertebroplasty and kyphoplasty patients. Changes following surgery ranged from no improvement to decreases

of up to 6 degrees. In one study,[99] kyphotic angle was significantly improved only in kyphoplasty patients; in one study,[103] both groups improved, but with significantly larger improvement with kyphoplasty (5.4º versus 1.0º; and one study[105]reported significant improvement in both groups with no significant differences by type of surgery.

3.1.3 Sacroplasty

Effectiveness or efficacy of sacroplasty cannot be evaluated because of the lack of comparative studies. Information on sacroplasty from case series and literature reviews is summarized below.

Systematic review of sacroplasty
A systematic review of sacroplasty for the treatment of sacral insufficiency fractures (SIF) caused by osteoporosis[23] found 15 papers published between 2002 and 2008 that met the authors' inclusion criteria (published in English, SIFs not due to primary or secondary bone tumors). Seven of these were case series, three were case reports, and five were technical reports.

A total of 108 patients (range 1-52 per study) with a mean age of 75.5 years were included across all the studies in this review, with follow-up ranging from 24 hours to 42 months. Pain as measured by VAS was significantly improved in the 62 patients for whom it was measured, improving from 8.9 pre-operatively to 2.6 post-operatively. Very few adverse outcomes were reported (clinically insignificant cement leakage and S1 radiculopathy).

Case series of sacroplasty
We retrieved nine published case series (several of which were also included in the systematic review[23]) Only studies with five or more patients were considered for inclusion. Two studies[115, 116] were of patients with osteoporosis (N = 65 total patients), three[117-119] were of patients primarily with multiple myeloma or other tumors (N = 28 total patients), and four[120-123] were of patients with SIF of undefined or mixed causes (N = 48 total patients). Summarizing the results of these studies is made difficult by the lack of consistency in the outcomes reported or in length of follow-up.

Pain reduction
Six of the nine studies reported pain relief pre- and post-operatively in terms of VAS.[116-120, 122] Pain scores improved following sacroplasty for both osteoporotic and malignant fractures, from 8.1-9.1 pre-operatively to 0.8-3.8 at varying follow-up periods.

In two studies[115, 121] patients reported pain relief using a 4 point descriptive scale (complete, significant or moderate, some or slight, and none). Of the 19 patients in these two studies, 11 reported complete or significant pain relief at follow-up of approximately two weeks.

Medication use
Three studies reported decreases in the use of opioid pain medication following sacroplasty. Two series of patients with osteoporotic fractures[116, 122] reported reduced narcotic use following sacroplasty (71% to 21% and 58% to 10% respectively). In a series of eight patients with fractures due to malignancy,[117] all patients were using opioid medication before the procedure.

After the procedure, two patients were using no medication and six were using only nonsteroidal anti-inflammatory medications.

Functional outcomes

Two studies of patients with osteoporotic fractures reported on functional outcomes. In Kamel et al.,[122]patients reported a change in a 5-point mobility scale (1 = normal; 5 = bedridden) after sacroplasty from a mean of 4.3 ± 1 (range 3-5) at baseline to 2.3 ± 1.2 (range 1-5) post-procedure. Whitlow et al.[120]reported statistically significant improvements in all activities of daily living.

Patient satisfaction

In three studies (N = 79 total patients),[116, 122, 123] the majority of patients reported being satisfied with the procedure.

3.2 Key question 2: What is the evidence of safety of vertebroplasty, kyphoplasty, or sacroplasty?

To assess safety of these surgical procedures, we summarized 1) safety outcomes from the results of the comparative studies discussed previously, and 2) the findings of published systematic reviews of adverse events and complications. Although comparative studies, especially randomized controlled trials, may provide a more rigorous examination of outcomes, these studies are few and incorporate relatively short follow-up periods. In addition, such studies are most likely underpowered to detect statistically significant differences in rare events such as symptomatic pulmonary cement embolization and mortality. Systematic reviews provided information on longer-term follow-up with a large (pooled) number of patients, but included data from case series. Rates of serious complications, such as symptomatic pulmonary cement embolism, for these procedures appear to be fairly low.

3.2.1 Incident fractures

In research studies with ongoing assessment, new fractures can be detected with spine radiographs. As described previously, the presence of a new fracture may be attributed to the augmentation, but may also be due to other factors, such as the fragility of the bone secondary to osteoporosis or pathologic processes.

Findings from comparative studies and systematic reviews of case series suggest that

- In comparative studies, the rates of new fractures for PV, KP, and conservative treatment at 12 months were up to 30%, 41%, and 71% respectively, with wide variation among the studies. The differences in rates of fractures for vertebroplasty, kyphoplasty, and conservative treatment were generally less than 10%, with no consistent pattern across studies of increased risk for any one treatment.
- In most comparative studies, patient numbers were too small to draw conclusions about fracture risk in adjacent versus non-adjacent vertebrae, but one larger RCT concluded

that the distribution of adjacent to non-adjacent fractures was similar for vertebroplasty and conservative treatment.

- Information from systematic reviews of case series suggests that the proportion of new fractures that occur in adjacent vertebrae may be larger following kyphoplasty (74.8%) than vertebroplasty (51.6%).

Comparative studies

Rates of incident fractures were compared in seven RCTs, six prospective cohort studies, and five retrospective cohort studies, with follow-up periods up to three years. In these studies, rates of new fractures at 12 months ranged from 0 to 31% of procedures for vertebroplasty, 0 to 41% for kyphoplasty, and 0 to 71% for conservative medical treatment. Across the studies, the risk difference for these comparisons (PV/CMT, KP/CMT, PV/KP) ranged from 0 to 30%, and 11 of the 18 studies showed risk differences of less than 10% (Table 9- Table 11).

Across all randomized controlled trials, incidence of new fractures following PV ranged from 0 to 8.6% up to 6 months, and 16-30% at 12 months, compared with rates for CMT of 11-25% and for KP of 4 to 33%. No RCTs reported significant differences in rates of new fractures between any treatment groups.

Four of the RCTs reported data for both total new fractures and fractures that occurred in vertebrae adjacent to operated vertebrae. Rates of total new fractures are shown in Table 9. In a comparison of vertebroplasty with conservative treatment, Klazen et al.[65] reported that the distribution of fracture location was not significantly different between the two groups: Seven of the 18 new fractures found in 15 vertebroplasty patients were in adjacent vertebrae, and 11 of the 30 new fractures found in 21 conservatively-treated patients were in adjacent vertebrae. In two smaller studies of vertebroplasty compared with conservative treatment, the numbers of new fractures were quite small. In one study,[86] two of the seven new fractures in vertebroplasty patients and none of the four new fractures in conservatively-treated patients were in adjacent vertebrae. In the second study,[87] both of the two new fractures that occurred in the vertebroplasty group were in adjacent vertebrae. Finally, in a comparison of vertebroplasty with kyphoplasty,[90] both of the two new fractures occurring in the kyphoplasty group were in adjacent vertebrae.

Table 9: Rates of new vertebral fractures at longest follow-up in randomized controlled trials

	F/U (mo)	No. patients at F/U		Percent with new vertebral fracture		Risk difference
PV vs. sham surgery		PV	Sham	PV	Sham	PV-Sham
Buchbinder[79]	6	35	36	8.6	11.1	-2.5
Kallmes[61]	3	64	61	0	0	0
PV vs. CMT		PV	CMT	PV	CMT	PV-CMT
Rousing[86]	12	23	22	30.4	18.1	12.3

	F/U (mo)	No. patients at F/U		Percent with new vertebral fracture		Risk difference
Voormolen[87]	.5	18	16	11.1	0	11.1
Klazen[62, 65]	12	86	77	16.4	24.7	-8.3
KP vs. CMT		KP	CMT	KP	CMT	KP-CMT
Wardlaw[88§]	12	115	95	33.0	25.3	7.7
PV vs. KP		PV	KP	PV	KP	PV-KP
Liu[90]	6	50	50	0	4.0	-4.0

PV = percutaneous vertebroplasty; KP = kyphoplasty; CMT = conservative medical treatment
§Reported number of "new or worsening" fractures

Significant differences in rate of new fractures were found in two prospective cohort studies: while one study reported that vertebroplasty patients developed significantly more fractures over 12 months than non-surgical patients,[91] another reported significantly fewer incident fractures in kyphoplasty patients than in patients managed conservatively.[95] Four cohort studies reported rates of new adjacent fractures only,[99, 101, 103, 104] (see Table 10 and Table 11) and five reported numbers of both total and adjacent fractures.[54, 91, 92, 95, 100] In these studies, from 22% to 66% of new fractures occurred in adjacent vertebrae. However, in smaller studies the number of new fractures was small, and such percentages should be interpreted with caution.

Table 10: Rates of new vertebral fractures (any location) at longest follow-up in cohort studies: Denominator is number of patients

	Design	F/U (mo)	No. patients at F/U		Percent with new vertebral fracture		Risk difference
PV vs. CMT			PV	CMT	PV	CMT	PV-CMT
Alvarez[91]	Prospective	12	101	27	30.7	11.1	19.6[#]
Diamond[92]	Prospective	24	67	31	31.3	35.5	-4.2
Ehteshami Rad[93]	Retrospective	median 10-19	269	82	14.5	8.5	6
Masala[54]	Retrospective	12	54	86	3.7	4.7	-1.0
KP vs. CMT			KP	CMT	KP	CMT	KP-CMT
Kasperk[95]	Prospective	36	34	14	41.2	71.4	-30.2
PV vs. KP			PV	KP	PV	KP	PV-KP
Frankel[104†]	Retrospective	3	19	17	0	17.7	-17.7
Köse[106]	Retrospective	24	16	18	[§]	[§]	

	Design	F/U (mo)	No. patients at F/U		Percent with new vertebral fracture		Risk difference
Lovi[100]	Prospective	24	118	36	3.4	0	3.4
Schofer[103†]	Retrospective	mean 13.5	30	30	3.3	0	3.3

PV = percutaneous vertebroplasty; KP = kyphoplasty; CMT = conservative medical treatment
† Reports adjacent fractures only
§ Reports "no secondary collapse" at adjacent levels
# 95% confidence interval of risk difference excludes zero

Table 11: Rates of new vertebral fractures (any location) at longest follow-up in cohort studies: Denominator is number of vertebral bodies

	Design	F/U (mo)	No. patients at F/U		Percent with new vertebral fracture		Risk difference
			PV	KP	PV	KP	PV-KP
Röllinghoff[101†]	Prospective	12	51	53	7.8	13.2	-5.4
Grohs[99†]	Prospective	24	23	28	3.4	17.1	-13.7

PV = percutaneous vertebroplasty; KP = kyphoplasty; CMT = conservative medical treatment
† Reports adjacent fractures only

Systematic reviews

In clinical settings, the detection of a new fracture is influenced by whether or not it produces symptoms, is reported by the patient, and gets evaluated. Thus, results should be interpreted cautiously.

Systematic reviews that reported rates of new fractures included primarily case series, and therefore do not include patients who do not receive surgery. As previously described, there may be multiple factors (e.g. osteoporotic bone) contributing to risk of new fractures in both surgical and non-surgical patients. Across systematic reviews (see Table 12) it appears that

- Patients treated with vertebroplasty may have a slightly higher rate of new fracture than those treated with kyphoplasty.
- Among patients with new fractures, adjacent fractures (one level inferior or superior to the treated level) may be more common following kyphoplasty than vertebroplasty. One review[36] evaluated the distribution of new fractures, concluding that
    - When retrospective and prospective studies were combined, 51.6% (366/706) of new fractures were adjacent in patients who had vertebroplasty compared with 74.8% (116/155) in those who had kyphoplasty.

- Based on prospective studies, 45.5% (20/154) fractures were adjacent in patients who had vertebroplasty compared with 91.6% (11/12) of patients who received kyphoplasty.

- With regard to rates of adjacent fractures following kyphoplasty, one review[72] reported a rate of 13.8% (11.0, 17.4%) based on random-effects meta-analysis (110/871 patients) across indications (including patients with osteoporotic or pathologic fractures). One review of tumor-related fractures reported that no patients treated with vertebroplasty and 2.9% of patients treated with kyphoplasty (6/204) experienced adjacent level fracture.[71]

Table 12: Summary of pooled estimates for new fractures reported in systematic reviews of non-randomized studies (case series and cohort studies)

Author (year)	Number of studies	Any new fracture*	
		PV	KP
Mixed indications†			
Lee (2009)	•PV N = 28 (10 prospective) •KP N = 13 (2 prospective)	**All studies** •18.0% (490/2781 pts) •21% (830/3912 levels) **Prospective studies** •18.1% (122/672 pts) •16.3% (154/941 levels)	**All studies** •17.0% (123/727 pts) •13.0% (158/1192 levels) **Prospective studies** •16.1% (11/68 pts) •11.2% (12/107 levels)
Eck (2008; May 2006)	• PV N = 42§; 4266 pts; 6506 fractures • KP N = 10§; 957 patients 1600 fractures	•19.7% (565/3195 patients assumed)	•7.0% (134/947 patients assumed)
Taylor (2007)	• KP Only N = 10	NA	•13.6 % (9.0%, 20.7%)** 172/1151 patients
Pathologic fractures‡			
Bouza (2009)	•KP Only N = 4 studies	NA	•10.23% (2.8, 17.66%) ** (21/172 patients)
Mendel (2009)	•PV N = 5§ prospective •KP N = 6§ prospective	**Prospective studies** •NR	**Prospective studies** •NR

NA = not applicable, PV = percutaneous vertebroplasty, KP = balloon kyphoplasty
*Authors may report rate per number of patients (pts) or number of levels treated (level) or number of vertebrae as noted in the table
†Outcomes for osteoporotic and tumor-related fractures not separated
‡Pathologic fractures may include multiple myeloma, hemangioma or metastases
§Unclear if all studies contributed data to specific outcome(s)
**effect size and 95% confidence interval based on random effects model

3.2.2 Cement leakage

Cement leakage may be detected during fluoroscopy at the end of the procedure, or with post-procedural chest radiographs. Findings from comparative studies and systematic reviews of case series suggest that

- Asymptomatic cement leakage is quite common, with rates up to 87%.
- In comparative studies, there is some evidence that leakage is more likely with vertebroplasty (9-87%) than with kyphoplasty (0-49%), although only two studies with direct comparisons reported statistically significant differences in rates.
- Data from systematic reviews of non-randomized studies (including case series) suggest that leakage is more common in vertebroplasty (19.7% - 79.0% per level treated) than in kyphoplasty (0.51% - 11.2%).
- Systematic reviews conclude that symptomatic leakage is uncommon for both procedures, ranging from 0.5%-1.6% for vertebroplasty and 0% - 0.3% for kyphoplasty, per level treated.

Comparative studies

Rates of cement leakage were reported in three RCTs, with rates ranging from 27% for kyphoplasty[88] to 80% for vertebroplasty.[64] None of the RCTs reported any symptomatic cement leakage. Using CT, Venmans et al.[64] reported that most leaks were in perivertebral venous structures. In addition, comparisons of the post-procedural CT with follow-up CTs (mean 22 months post-operatively) showed no changes in the anatomical location of cement leakage, and no cement migration.

Rates of cement leakage of vertebroplasty and kyphoplasty were compared in 12 cohort studies with follow-up periods up to X years (Table 13 and Table 14). Three studies[41, 98, 103] reported significantly greater rates of cement leakage in vertebroplasty than kyphoplasty; however, none of these leaks were symptomatic. Of all the comparative studies, only two patients experienced symptomatic leaks in vertebroplasty procedures, which resulted in paraparesis that was treated and resolved within 3 months.[101]

Table 13: Rates of cement leakage from comparative studies of vertebroplasty and kyphoplasty: Denominator is number of patients

	Design	No. patients		Percent cement leakage		Risk difference
		PV	KP	PV	KP	PV-KP
De Negri[98]	Prospective cohort	10	11	50	0	50[#]
Köse[106]	Retrospective cohort	16	18	0	0	0

	Design	No. patients		Percent cement leakage		Risk difference
Lee[41]	Retrospective cohort	24	59	87.5	49.3	38.2[#]
Santiago[102]	Prospective cohort	30	30	46.7	30.0	16.7
Schofer[103]	Prospective cohort	30	30	33.3	6.7[*]	26.6[#]
Zhou[107]	Retrospective cohort	56	42	10.7	7.1	3.6

PV = percutaneous vertebroplasty; KP = kyphoplasty
[#] 95% confidence interval of risk difference excludes zero

Table 14: Rates of cement leakage from comparative studies of vertebroplasty and kyphoplasty: Denominator is number of vertebral bodies treated

	Design	No. patients or vertebral bodies		Percent cement leakage)		Risk difference
		PV	KP	PV	KP	PV-KP
Fourney[28]	Retrospective cohort	65	32	9.2	0	9.2
Frankel[104]	Retrospective cohort	26	30	11.5	10.0	1.5
Grohs[99]	Prospective cohort	29	35	27.6	22.9	4.7
Hiwatashi[105]	Retrospective cohort	124	57	50	24.6	25.4
Lovi[100]	Prospective cohort	118	36	15.3	16.7	-1.4
Röllinghoff[101]	Prospective cohort	51	53	25.5	22.6	2.9

PV = percutaneous vertebroplasty; KP = kyphoplasty

Systematic reviews

Differences in surveillance mechanisms and definitions of cement leakage across studies are highly likely and undoubtedly contribute to the wide range of rates for cement leakage. Authors may not consider asymptomatic leakage to be a complication.[36]

Data from systematic reviews of non-randomized studies were from a combination of case series (LoE IV) cohort studies and (LoE III) which were pooled to provide summary estimates. Data from included reviews is summarized in Table 15. Overall, it appears that

- Cement leakage across all indications is more common in vertebroplasty (19.7% - 79.0% per level treated) than in kyphoplasty (0.51% - 11.2%). Differences across studies in the extent of surveillance and reporting of leakage may influence the range of rates.

- Symptomatic leakage is uncommon for both procedures, ranging from 0.5%-1.6% for vertebroplasty and 0% - 0.3% for kyphoplasty, per level treated.
- Leakage may be more common in patients with pathologic fractures than in those with osteoporotic fractures treated with vertebroplasty, but this was not noted for those treated with kyphoplasty.
- Lower leakage rates were generally seen in studies with prospective data collection.[36]

Table 15:Summary of pooled estimates of cement leakage from systematic reviews of comparative studies and case series

Author (year)	Number of studies	Any leak*		Symptomatic*	
		PV	KP	PV	KP
Mixed indications†					
Lee (2009)	• PV N = 70 (16 prospective) • KP N = 33 (7 prospective)	**All studies** • 75.0% (3078/4097 pts) • 43.0% (3078/7184 levels) **Prospective studies** • 56.2% (401/713 pts) • 38.2% (401/1047 levels)	**All studies** • 14.0% (184/1297 pts) • 8.8%(184/2093 levels) **Prospective studies** • 13.6 (51/373 pts) • 8.1% (51/623 levels)	**All studies** • 1.48% (76/5067 pts) • 1.08% (76/7027 levels) **Prospective studies** • 0.8% (6/735 pts) • 0.5% (6/1078 levels)	**All studies** • 0.06% (1/1568 pts) • 0.04% (1/2794 levels) **Prospective studies** • 0.0% (0/631 pts) • 0.0% (0/1297 levels)
Eck (2008 May 2006)	• PV N = 103§ • KP N = 33§	• 19.7% (1838/9330 levels)	• 7.0% (213/3034 levels)	• 1.6% (65/4125 levels)	• 0.3% (3/963 levels)
Taylor (2007)	• KP Only • N = 28 for overall leakage; N = 8 for symptomatic	NA	• 9.0% (7.4%, 11.0%)** 193/2239 vertebrae	NA	• 0.2% (0%, 0.3%)** 1/678 vertebrae
Osteoporotic fractures					
Lee (2009)	• PV N = 38 (11 prospective) • KP N = 12 (4 prospective)	**All studies** • 20.79% (1094/5260 levels)	**All studies** • 6.89% (131/1901 levels)	**All studies** • 0.03% (21/5260 levels)	**All studies** • 0.05% (1/1901 levels)
Pathologic fractures‡					
Lee (2009)	• PV N = 13 (1 prospective) • KP N = 7 (2 prospective)	**All studies (per level)** • 79.07% (601/760 levels)	**All studies (per level)** • 6.07% (13/214 levels)	**All studies (per level)** • 0.26% (21/760 levels)	**All studies (per level)** • 0.0% (0/214 levels)
Bouza (2009)	• KP Only • N = 7 studies (4 prospective)	NA	**All studies** • 5.8% (1.96, 9.64%) ** (41 leaks, presume levels reported), **Prospective studies** • 11.2%** • **Retrospective studies** • 0.51%**	NA	• 0.0%

Mendel (2009)	• PV N = 5 prospective • KP N = 6 prospective	**Prospective studies** • 58.4% (59/101 levels)	**Prospective studies** • 12.1% 12/2391 levels)	**Prospective studies** • 3.1% (3/98 *patients*)	**Prospective studies** • 0%

NA = not applicable, PV = percutaneous vertebroplasty, KP = balloon kyphoplasty
*Authors may report rate per number of patients (pts) or number of levels treated (level) or number of vertebrae as note in the table
†Outcomes for osteoporotic and tumor-related fractures not separated
‡Pathologic fractures may include multiple myeloma, hemangioma or metastases
§Unclear if all studies contributed data to specific outcome(s)
**effect size and 95% confidence interval based on random effects model

3.2.3 Pulmonary cement embolism

Pulmonary cement embolism (PCE) is a potential consequence of cement leakage. Radiographic procedures may not routinely be performed following vertebroplasty or kyphoplasty and PCEs may not be detected, particularly if they are asymptomatic. There is no clear diagnostic or treatment standard for PCE,[40] and the type of imaging and definition of PCE differs across studies. Studies using chest radiographs may report higher rates than those evaluated during fluoroscopy.[63] The rates of PCE following vertebroplasty or kyphoplasty in the published literature vary widely, in part because of differential surveillance. With respect to symptomatic PCE in particular, sample sizes may have been inadequate to detect these events.

The largest RCT of vertebroplasty[63] reported a rate of PCE of 26% (16%-39%, 14/54 patients) using CT, all of which were asymptomatic. The authors report that no reactive pulmonary changes were seen adjacent to the PCE. Individuals available for follow-up (mean of 22 months) were invited to have a CT specifically to evaluate leakage and PCE, but follow-up CT was available in only 54 of the original 93 patients who received PV.

No incidents of embolism were reported across the non-randomized comparative studies, however, studies may not have had sufficient power to detect such events or to compare their occurrence across treatments. These studies may not have included imaging to identify potential emboli.

Rates of PCE were reported in three systematic reviews of non-randomized studies, one of which[40] focused specifically on this outcome (Table 16). As previously discussed, because the reviews combined information from case series and non-randomized comparative studies, the quality of evidence is low.

Overall, pooled estimates for PCE based on these systematic reviews ranged from 0.1% to 1.7%. There is insufficient information to formally compare rates for vertebroplasty and kyphoplasty, as only one review provided data for both procedures and was based on a heterogeneous collection of case series and comparative studies.[70]

- Pooled estimates in the Krueger systematic review[40] were 1.6% across case series reporting specifically on asymptomatic PCE, 1.1% for those reporting on symptomatic

PCE and 1.6% across those that did not provide information on symptoms. All but one study were of patients who had vertebroplasty. Rates ranged from 3.5% to 23% for individual studies. An additional 37 single case reports of PCE were described by the author, but without denominator information, it is not possible to determine how these may influence the overall rates.

- Two other reviews, one of kyphoplasty[72] and one of both vertebroplasty and kyphoplasty,[70] did not describe the outcomes with respect to the presence of symptoms.

Table 16: Pulmonary cement embolism rates from systematic reviews

Author (year)	Study characteristics	PCE rate/findings
Krueger (2009)	•Asymptomatic PCE: N = 25 case series; all vertebroplasty •Symptomatic PCE: N = 10 case series with denominators; 1 KP series •Symptoms not specified: N = 4 case series; all vertebroplasty	•Asymptomatic PCE: 1.6% (62/3774) •Symptomatic PCE: 1.1% (16/1431) •Symptoms unspecified: 1.6% (6/368)
Taylor (2007)	•Symptoms not specified: N = 7 studies, all kyphoplasty	•Symptoms unspecified: 0.10%* (1/377)
Eck (2008)	•Symptoms not specified; Number of studies for this outcome not given •Data from combination of comparative and non-comparative studies	•Symptoms unspecified: o Vertebroplasty: 0.9% (33/3601) o Kyphoplasty: 0.4% (2/565)

*based on random-effects model, 95% CI 0-0.17%

3.2.4 Procedure-related complications

In one review,[36] procedure-related complications were defined as those experienced as a direct effect of the procedure and not those related to any comorbid patient conditions, including cement embolism, neurological deficit, fracture (rib, transverse process, pedicle), discitis, dural tear, balloon rupture during kyphoplasty, infection, pain worse than before procedure, and subcutaneous hematoma.[36]

RCTs and cohort studies report infrequent and isolated procedural complications, but because these studies are relatively small and rates of complications are low, we focus on data from systematic reviews. Based on data from one systematic review, the overall procedure-related complication rates (per patient) ranged from 2.4% to 3.8% for vertebroplasty and from 0.4%-0.6% for kyphoplasty (Table 17).[36] Details for each of these were not presented and outcomes based on indication were not provided.

Table 17: Procedure-related complication rates from systematic reviews

		PV	KP
Lee MJ (2009)	•PV N = 71 (18 prospective) •KP N = 29 (6 prospective)	**All studies** •3.8% (215/5629 pts) •2.8% (215/7777 levels) **Prospective studies**	**All studies** •0.6% (9/1491 pts) •0.3% (9/2731 levels) **Prospective studies**

		•2.4% (29/1190 pts) •1.7% (29/1727 levels)	•0.4% (3/631 pts) •0.2% (3/1290) levels)

PV = percutaneous vertebroplasty, KP = balloon kyphoplasty

Two other reviews reported rates of specific complications, which in one review were from 0.1%-0.9% for vertebroplasty and 0.1% - 0.5% for kyphoplasty.[70] A second review[71] focused on unspecified neurological complications, finding a rate of 4.1% for vertebroplasty and 0% for kyphoplasty (Table 18).

Table 18: Specific perioperative complications from systematic reviews

	Complication	PV	KP
Eck (2008) *	•Hematoma •Rib fracture •Infection •BP or HR change	•0.3% (6/2396 pts) •0.9% (22/2442 pts) •0.1% (3/2192 pts) •0.2 % (6/2646 pts	•0.1% (1/603pts) •0.5% (2/422 pts) •0.3% (2/646 pts) •0.2% (1/434 pts)
Mendel (2009)	•Neurological (not specified) N = 11 prospective studies	•4.1% (4/98 pts)	•0%

BP = blood pressure, HR = heart rate, PV = percutaneous vertebroplasty, KP = balloon kyphoplasty
* Number of studies contributing to each outcome not provided

3.2.5 Medically-related complications

Medically–related complications, as defined in Lee's[36] systematic review, are those that were likely to be secondary to the patient's medical status. These include non-cement embolism, temporary respiratory insufficiency, stroke, cardiovascular complications, pneumonia, and fever.

Based on information from systematic reviews, the rates of medically-related complications appear to be low for both vertebroplasty and kyphoplasty (Table 19). Rates per patient for were higher for as reported in prospective studies were higher for both vertebroplasty (2.8%) and kyphoplasty (3.2%) compared with analyses which also included retrospective studies (0.05% - 0.4% for vertebroplasty and 0.5% -1.6% for kyphoplasty).

Table 19: Medically-related complications from systematic reviews

		PV	KP
Lee (2009) **Any medically-related complication**	•PV N = 71 (18 prospective) •KP N = 29 (6 prospective)	**All studies** •0.4% (22/5629 pts) •0.3% (22/7771 levels) **Prospective studies** •2.8% (29/1051 pts) •0.3% (5/1727 levels)	**All studies** •1.6% (24/1491 pts) •0.9% (24/2731 levels) **Prospective studies** •3.2% (18/558 pts) •0.7% (9/1290 levels)
Eck (2008) **•Myocardial infarction** **•Pneumonia, hypoxia**	•Number of studies for each outcome not stated	**Myocardial infarction** •0.05% (1/1938 pts) • **Pneumonia, hypoxia** •0.1% (3/2097 pts)	**Myocardial infarction** •0.5% (5/951 pts) • **Pneumonia, hypoxia** •0.5% (8/867 pts)

PV = percutaneous vertebroplasty, KP = balloon kyphoplasty
* Among patients with pathological fractures

3.2.6 Mortality

Two systematic reviews reported summary estimates for mortality.[36, 72] Taylor described perioperative mortality. Since the majority of patients receiving these procedures are either elderly and/or have malignant disease they may have a number of co-morbid conditions, thus, the extent to which mortality can be attributed to the procedures in unclear from the information presented in these reviews.

Lee[36] reports mortality rates among vertebroplasty patients at 2.1% (22/1051 patients) across prospective studies and 0.6% (24/5629) when retrospective studies are included. For kyphoplasty, the rates were 2.3% (13/588). Timing of mortality was not reported. Taylor[72] reports an overall mortality for kyphoplasty across 14 studies of 3.2% (0.7%, 5.6%) (25/552) and a perioperative mortality rate of 0.01% (0%, 0.64%) (1/406 patients)across 11 studies, with estimates and confidence intervals based on a random-effects model.

Sacroplasty

No major complications were reported in any of the case series of sacroplasty. Asymptomatic cement leakage was reported in 7 of 34 patients across four series.[118, 119, 121, 123] One patient developed radicular pain during cement injection, which was relieved 7 days later with an epidural steroid injection.[116] Two patients had radicular pain during the procedure from tumor extension into neural foramen, which was treated with selective nerve root block.[119]

3.3 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 (cancer or non-cancer) or time elapsed from fracture (acute, subacute, chronic)
- Other patient characteristics or evidence based patient selection criteria
- Provider type, setting or other provider characteristics
- Health care payer system type (worker's compensation, Medicaid, state employees)

3.3.1: Gender and age

To summarize findings with respect to gender and age:

- There are no comparative studies that assessed differential outcomes of PV and KP by gender and age, largely because patients with osteoporotic fractures were overwhelmingly elderly women.

There are two primary populations in which vertebroplasty, kyphoplasty and sacroplasty are thought to be of benefit, namely patients with osteoporotic or tumor-related fractures. As described in previous sections, osteoporotic fractures are most common among women, particularly white women over 50 years old.

The great majority of the comparative studies reviewed included only patients with osteoporotic fractures. Six of the seven RCTs excluded patients with non-osteoporotic fractures,[61, 62, 79, 86, 87, 90] and while in the seventh[88] only four of 300 patients had malignant fractures. The samples for these studies were in their 70s and 80s and 65-85% female, and none of the studies examined efficacy by gender or age.

Of non-randomized studies, 18 of 20 were limited to osteoporotic fractures, and thus the samples were primarily elderly women. None of the non-randomized studies examined effectiveness by gender or age.

3.3.1: Psychological or psychosocial co-morbidities

No comparative studies addressed differential efficacy or safety for patients with and without comorbidities. Although several comparative studies described various comorbid conditions among the patients, RCTs excluded patients with serious comorbidities.

3.3.2: Fracture etiology (osteoporotic or tumor-related)

As noted earlier, no RCTs included patients with fractures due to malignancy, and only two non-randomized studies (both of which compared vertebroplasty with kyphoplasty) studied patients with fractures due to malignancy.[106, 124]One of these studies reported comparable outcomes for PV and KP,[124] and the other reported that KP led to more improvement in pain than PV over one year.[106] No comparative studies separated outcomes for effectiveness or safety for patients with osteoporotic versus tumor-related fractures.

Although several systematic reviews (see Results section) summarized safety outcomes for these procedures, most of the reviews incorporated both osteoporotic and tumor-related fractures and reported results across both indications. One review of tumor-related fractures reported that no patients treated with vertebroplasty and 2.9% of patients treated with kyphoplasty (6/204) experienced adjacent level fracture.[71]

3.3.3: Age of fracture

It has been suggested that acute VCFs may be more amenable to treatment by PV or KP than fractures of longer duration.[125] However, acute fractures may also be those more likely to resolve without intervention, given that most symptomatic VCFs heal on their own within a month.[83]Moreover, the failure of conservative treatment is an indication for cementoplasty, so that many treated fractures are subacute. Patients with chronic pain often have had multiple compression fractures, and the source of the pain is believed to be primarily secondary to muscle

and ligament strain resulting from kyphosis as opposed to the vertebra itself.[60] Thus, there are biologically plausible reasons for considering the influence of fracture age.

To summarize outcomes with respect to fracture age:

- The extent to which vertebroplasty (or kyphoplasty) is more efficacious in patients with acute fractures versus chronic fractures is not clear
    - No studies were designed to directly compare efficacy or safety outcomes for patients with acute, subacute, and/or chronic fractures in the same underlying population.
    - Two RCTs comparing vertebroplasty to sham surgery[61, 79] conducted post-hoc subgroup analysis indicating that pain outcomes did not differ significantly for more recent fractures compared with fractures of longer duration. The use of a sham procedure is a major strength of the study design, and such subgroup analysis has the potential for considering differential efficacy by fracture age. However, analyses in these two studies were likely to have low power for detecting differences between groups defined by fracture age categories.
    - The largest RCT comparing vertebroplasty with conservative care included only acute osteoporotic fractures (≤6 weeks pain duration), reporting that vertebroplasty was more effective in improving pain and functioning.However, it is difficult to establish differential effectiveness by fracture age without a direct comparison of patients who had more chronic fractures in the same underlying patient population. Thus, the findings from this study do not address the issue of differential efficacy.
    - Information from cohort (LoE III) studies on PV is inconclusive and conflicting: While two studies[92, 94] in patients with acute fractures (≤6 weeks pain duration) reported that PV significantly reduced pain compared with CMT, two studies among patients with fractures up to 3 months[54] or 12 months old[91] also reported earlier improvement in pain with PV. Again, without sub-analysis or direct comparison of outcomes by fracture age, differential effectiveness is difficult to determine.
    - Differential outcomes by fracture age were not analyzed in any non-randomized studies comparing PV or KP with CMT.

Table 20 summarizes findings from RCTs with respect to fracture age.

Table 20: Summary of RCTs with respect to findings related to fracture age

Author (year)	Compari-son	Fracture ages included	Findings regarding fracture age	Comment
Buchbinder (2009)	PV vs. sham	• Inclusion criterion: fracture age ≤ 1 year old (based on	• Results appeared to be consistent regardless of duration of	• May be insufficient power to detect

	N = 78	duration of pain) • Duration of back pain (median): *PV*: 9.0 weeks *Sham*: 9.5 weeks • Duration of symptoms < 6 weeks: *PV*: 32% (n = 12) *Sham*: 32% (n = 13)	symptoms (<6 weeks vs. ≥ 6 weeks, or as a continuous measure; p >0.10 for assessments of interactions)	differences by fracture age • Patients were stratified by fracture age (<6 weeks, ≥ 6 weeks)
Kallmes (2009)	PV vs. sham N = 131	• Inclusion criterion: fracture age ≤ 1 year old (based on duration of pain) • Pain duration (mean): *PV*: 16 weeks *Sham*: 20 weeks • Pain duration < 13 weeks: *PV*: 44% (n = 30) *Sham*: 38% (n=24) • Pain duration 14-26 weeks: *PV*: 21% (n=14) *Sham*: 24% (n =15) • Pain duration 27-52 weeks: *PV*: 36% (n = 24) *Sham*: 38% (n = 24)	• No significant difference in treatment effect for pain across 3 categories of pain duration at baseline (p = 0.58 for assessment of interaction) • Treatment effects for patients: o with <13 weeks pain : 0.8 (95% CI -0.8, 2.4, p = 0.31) o 14-26 weeks pain: 1.3 (95% CI, -0.8, 3.4, p =0.23) o 27-52 weeks pain: 0.0 (95% CI, -1.7, 1. 6, p =0.96)	• Analyses by fracture age were specified post-hoc • May be insufficient power to detect differences by fracture age
Klazen (2010)	PV vs. CMT N = 202	• Inclusion criterion: fracture age ≤ 6 weeks (based on duration of back pain) • Pain duration (mean): *PV:* 29.3 days *CMT*: 26.8 days	• No analysis by fracture age • Main finding: PV reduced pain more than CMT across one year	• Although surgery took place a mean of 5.6 weeks after onset of symptoms, interval ranged up to 92 days; therefore fracture age at time of intervention may have been longer than the 6 weeks specified in inclusion criteria.
Rousing (2009, 2010)	PV vs. CMT N = 50	• Inclusion criterion: fracture age ≤ 8 weeks • Mean fracture age: *PV:* 8.4 days *CMT:* 6.7 days	• Although acute (<2 weeks) and subacute (2-8 weeks) fractures were included, no analysis by fracture age • Main finding: no significant differences in pain reduction for PV vs. CMT	
Voormolen (2007)	PV vs. CMT N = 34	• Inclusion criterion: fracture age 6 weeks to 6 months (based on duration of back pain) • Pain duration (median) *PV:* 12.14 weeks *CMT:* 10.86 weeks	• No analysis by fracture age • Main finding: no significant differences in pain reduction for PV vs. CMT	
Wardlaw (2009)	KP vs. CMT N = 300	• Inclusion criterion: fracture age ≤ 3 months • Fracture age (median): *KP*: 5.6 weeks *CMT*: 6.4 weeks	• No analysis by fracture age • Main finding: KP reduced pain more than CMT across one year	
Liu (2010)	PV vs. KP N = 100	• No inclusion criterion for fracture age specified	• No analysis by fracture age • Main finding: no significant	

		• Duration between injury and surgery (mean) *KP*: 17.0 days *PV*: 15.8 days • All procedures took place within 43 days of injury	differences in pain reduction for PV vs. KP	

PV = percutaneous vertebroplasty, KP = balloon kyphoplasty
CMT = conservative medical treatment

3.3.4: Other patient characteristics

No comparative studies were found that addressed differential outcomes by other patient characteristics.

3.3.5 Provider type or payer system type

No comparative studies were found that addressed differential outcomes by provider type or by payer system types.

3.4 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 short term and over expected duration of use

b. Reoperation or revision

3.4.1 Summary of findings

Seven (7) potential economic studies were identified from a systematic literature search as previously described. Four articles were selected for full text review [1, 54, 62, 126]. Of those four, three (3) articles met the inclusion criteria as full economic evaluations.[54, 62, 126] All of these studies evaluated populations in which osteoporotic fractures were the primary indication for the procedure, and no studies of these procedures in patients with tumor-related fractures were found. No studies were found that included reoperation or revision. None of the studies examined the cost effectiveness of either balloon kyphoplasty or vertebroplasty in a U.S. setting. No studies that examined the cost effectiveness of sacroplasty were found.

Relevant data from each peer-reviewed published study were abstracted and critically appraised using the Quality of Health Economic Studies (QHES), a quantitative method of assessing study design quality where 0 indicates low and 100 high quality. Qualitative assessment based on epidemiologic principles is also provided.

One reasonable quality,[126] one moderate quality,[62] and one poor quality study[54] were identified. All three were limited by lack of long-term data on effectiveness and safety and only one of the three[126] attempted to model results past one year. The other two used patient-level data for up to 12 months in European settings. These studies provide little information on the impact of various factors on overall cost effectiveness. Though there were methodological limitations with each

study, each found that vertebroplasty or kyphoplasty is associated with improved pain and/or function at increased or comparable cost. Economic models for a US setting that include new fractures, complications, mortality, and resource use over subsequent years are needed.

In summary, the strength of evidence for the economic evaluation of VKS is very low and subject to change as more clinical and cost evidence becomes available. However, the evidence from economic studies to date suggests that in the short term, vertebroplasty (two studies[54, 62]) and kyphoplasty (one study[126]) may be of at least comparable cost and may provide earlier pain relief compared with conventional treatment.

Table 21: Summary table of economic studies

First author, year (country)	Main findings	Study strengths	Limitations
Klazen 2010 (Netherlands, Belgium) Funding source: ZonMw; Cook Medical	Vertebroplasty associated with increased QALYs and increased costs compared to conventional treatment. Base case cost effectiveness ratio €22,685/QALY 70% of bootstrapping samples showed increased QALYs and increased costs at cost effectiveness ratios <€30,000 per QALY	Patient level data from RCT Use of cost utility methods, uncertainty analysis, use and choice of validated outcome measures	No modeling past 12 months Generalizability to U.S. unknown
Ström 2009 (UK) Funding source: Medtronic	Balloon kyphoplasty associated with increased quality adjusted life years and increased costs compared to conventional treatment. Cost effectiveness ratios remained <€30,000 per QALY gained under variations of age, quality of life, hospital length of stay.	Use of RCT data for outcome measure (FREE trial) Use of cost utility analysis methods Use of Markov modeling to allow transition in and out of health states over time	Data may not support modeling to age 100 Generalizability to US unknown Lack of societal perspective (patient resource use, recovery time not included)
Masala 2008 (Italy) Funding source not stated	Percutaneous vertebroplasty associated with earlier (one week and three months) sustained pain relief, function, and activities of daily living than conservative treatment. At 12 months comparable pain relief for vertebroplasty and conventional treatment. Difference in costs between vertebroplasty and conventional treatment approximate the cost of procedure.	Use of patient level data	Measure of cost effectiveness based on measure of unknown clinical significance (one-point reductions in pain, function, or activities of daily living) Possible confounding, since patients chose treatment No sensitivity analysis; no modeling Generalizability to US unknown

3.4.2 Details of included studies

Klazen et al. (2010)

This study reports on the cost utility of percutaneous vertebroplasty compared with conservative treatment, using data from the Vertos II randomized trial.[62] Pain-free days and utility measured via the EQ5D were study outcomes; medical costs were taken from the study and adjusted to 2008 Euros. Cost utility was estimated at one month and one year post-procedure. The authors report that vertebroplasty was associated with increased QALYs gained and increased cost at one month, both differences statistically significant at one month and no longer statistically significant by one year. The incremental cost effectiveness ratio (ICER) at one year was €22,685 per quality adjusted life year (QALY). Vertebroplasty was also associated with more pain-free days, with a cost of €20/pain-free day. Sensitivity analysis suggested that ~70% of bootstrapped samples resulted in both increased cost and QALYs gained. The cost effectiveness acceptability curve estimated that at a societal willingness to pay of €30,000/QALY—a cost effectiveness ratio "threshold" considered favorable by many decision-making bodies—vertebroplasty would be cost effective 70% of the time.

This analysis used patient-level data from a well-powered randomized trial, considered to be the best data source. It provides data about the effectiveness of vertebroplasty in improving pain at one year post-procedure compared with conservative treatment alone. As an economic evaluation, it received a moderate QHES quality score of 68/100, with point deductions for model presentation, time horizon, lack of stated perspective, and lack of discussion of limitations or bias. Although the use of trial data is a main strength, there was no modeling of costs, effects, relative impact of variables driving the results (sensitivity analysis), or adverse events past one year. This study does provide data on the early sustained benefit (to one year) in pain reduction associated with vertebroplasty compared with conservative medical treatment. Limitations of this RCT are described in previous sections and include lack of blinding for outcomes assessment and a potential that results may at least in part be due to placebo effect which may have influenced the differences in efficacy reported for the treatment arms. European cost data are of limited generalizability to the U.S., but the study did estimate that the difference in cost at one year for the two arms was roughly equal to the cost of the procedure. Overall, this study suggests that in the short term (1 year) vertebroplasty may be a cost effective intervention.

Ström et al. (2009)

In this cost utility analysis, the authors built a Markov model to estimate the cost utility of balloon kyphoplasty compared to non-surgical management.[126] Markov models allow for transitions between health states over time. The base-case population was a population of 70 year old UK patients with at least one vertebral fracture and a T-score of -2.5 (a clinical measure of bone density where -2.5 or lower indicates osteoporosis); health states of additional fracture or death were possible every 6 months until age 100 or death. The primary impact of kyphoplasty was assumed to be through improvements in quality of life, so the first 12 months of available

data from the FREE trial[88] were used. Limitations of this RCT are described in previous sections and include lack of blinding for outcomes assessment and a potential that results may at least in part be due to placebo effect. The base case assumed a 12-month benefit in quality of life and a 6 day improvement in hospital length of stay for kyphoplasty. Fracture incidence and mortality were modeled from UK and Swedish registry data; cost inputs were from published literature and U.K. National Health Service (NHS) data.

The base case analysis indicated increased cost (£1494) and increased quality-adjusted life years (QALY) (0.169) for balloon kyphoplasty compared with nonsurgical management, with an incremental cost-effectiveness ratio (ICER) of £8840 per QALY. Sensitivity analysis indicated that the ICER for kyphoplasty continued to be less than £30,000/QALY—widely considered a favorable cost effectiveness ratio—under variations of patient age (60-80 years), quality of life benefit (12 month-plus 1-, 2-, and 3- years post kyphoplasty, though there are no data beyond 12 months), and hospital length of stay benefit (0-11 days difference from non-surgical management). The authors conclude that kyphoplasty is a cost-effective intervention, but that this should be revisited as additional evidence becomes available.

This was a reasonably well-conducted economic evaluation, and received a QHES score of 88. The authors made use of RCT-level data, included a long-term time horizon (to age 100 years, likely ample time to model effects, though there is no trial data past 12 months), sensitivity analyses, and present the model and its inputs clearly. The main limitations are the lack of available long-term data on quality of life, effectiveness, or complications and mortality associated with balloon kyphoplasty. The use of 100 years of age for the time horizon may not be realistic. Also, the authors' unclear presentation of utility at less than 12 months and lack of presentation of sensitivity analysis of costs are limitations, especially for assessing generalizability to a US health care setting.

Masala et al. (2008)

This study presents cost and effectiveness data from a retrospective observational study (LoE III) of people with acute amyelic osteoporotic vertebral fracture at an Italian health system who chose percutaneous vertebroplasty or refused it and chose conservative medical therapy.[54] Patients were assessed at 1 week, 3 months, and 12 months for pain (visual analog scale), ambulation, and activities of daily living. Clinical data were obtained from retrospective medical record review. Hospital and outpatient costs were collected for study participants. Cost per patient per 1-point reduction in VAS, ambulation, or daily living at each time point was the measure of cost-effectiveness. The study reported an early benefit in pain reduction and increased function favoring vertebroplasty; however, at 12 months both groups reported significant and comparable improvements. Cost per patient per one-point improvement in pain or function was slightly lower for each of the three scales for vertebroplasty, but none of the differences were statistically significant between the two treatment groups.

This study presents patient-level data on the effect of percutaneous vertebroplasty compared with medical therapy, including hospital and outpatient costs from a LoE III retrospective cohort study. No information on potentially confounding factors or their control was provided so results related to effectiveness should be interpreted cautiously. Loss to follow-up was greater than 20%, creating a potential for selection bias which may influence the results on effectiveness. Although the authors describe which factors influenced costs, they do not present information on sensitivity analysis regarding factors that may have the greatest influence on cost effectiveness. Funding source for the study was not reported.

The measure of cost per patient per one-point improvement in pain or function is difficult to interpret the context of other economic evaluations. First, the authors do not discuss whether a one-point improvement (or other value) in VAS is a minimally important clinical difference. The endpoints of cost per one-point improvement in pain, ambulation, or ability to perform daily tasks are presented separately, limiting an overall assessment of value. Additionally, while the study was able to detect early, short-term difference (one week and three months) in pain reduction and increased function favoring vertebroplasty, these differences were no longer significant by 12 months. In a setting where subsequent fractures, mortality, and adverse events are relevant, 12 months would be considered a short term horizon.

In the absence of a model that integrates changes in pain, function, costs, and long-term (past one year) outcomes , this study is of limited usefulness for assessing the cost effectiveness of vertebroplasty compared with conservative medical treatment. The QHES assessment of study quality was 48/100, reflecting low study quality.

3.4.3 Conclusions

- Because the efficacy and effectiveness of these procedures is uncertain based on the data summarized in previous sections of this report, their overall cost effectiveness is unclear.
- The cost effectiveness of vertebroplasty, kyphoplasty or sacroplasty in a US setting is unknown.
- Percutaneous vertebroplasty was associated with early (<3 months) improvements in pain and function at comparable cost compared with medical therapy alone in two studies[54, 62]. At 12 months vertebroplasty and medical therapy were comparable on pain, function, and healthcare cost. These studies suggest that vertebroplasty and kyphoplasty may be associated with earlier pain relief than conventional treatment.
- The economic impact of complications, reoperation, or revision following vertebroplasty, kyphoplasty, or sacroplasty is unknown.
- Assuming benefit in quality of life (pain relief) at 12 months, balloon kyphoplasty may be associated with increased cost and a small increase in quality in adjusted life years at three years post-procedure, translating to favorable cost-effectiveness ratios

(<£30,000/QALY). Differences in provider and payer systems from the U.S. systems of care should be considered when interpreting these findings.

- No data are available to directly compare the cost effectiveness of balloon kyphoplasty with vertebroplasty. Such a comparison would assume that efficacy for both had been demonstrated.
- Data are needed on the cost and benefits of vertebroplasty and kyphoplasty in a US setting, as are long-term models based on larger sample sizes that include reoperation/revision rates, treatment of subsequent fractures, mortality and complications/adverse events.

5. Summary by key question

Key question 1: Efficacy

Vertebroplasty

- Pain relief: It is uncertain whether vertebroplasty is effective for the relief of pain due to VCF. All of the RCTs, which were limited to patients with osteoporotic fractures, evaluated relatively short-term effects (≤ 12 months). While two sham-controlled RCTs concluded that there was no benefit with regard to pain relief (up to 1 month in one study and 6 months in the other), the studies did not have adequate power to detect differences in the proportion of patients with clinically meaningful improvement. While the largest RCT comparing vertebroplasty with conservative care in acute osteoporotic fractures demonstrated statistically significant improvement in pain scores that was sustained to the 12-month follow-up, the extent to which lack of patient blinding and possible placebo effect may contribute to the findings is not clear. Two small RCTs reported no advantage for vertebroplasty over 2 weeks or 12 months. The overall strength of evidence is low and effect estimates may change with additional research.
- Function and quality of life: It is uncertain whether vertebroplasty improves patient functioning and quality of life. In a large RCT, 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 largely comparable improvements in function over 2 weeks and 12 months for vertebroplasty and non-surgical patients. The overall strength of evidence is low and effect estimates may change with additional research.

Kyphoplasty

- Pain relief: It is uncertain whether kyphoplasty is effective for pain relief. 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.

- Function and quality of life: It is uncertain whether kyphoplasty improves patient functioning and quality of life. In the single RCT, kyphoplasty was more effective than conservative treatment in improving functioning as measured by the EQ-5d, RDQ, and SF-36 over most time periods. Following an early advantage for KP, group differences were diminished by 12 months as CMT patients improved over time. 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.

Vertebroplasty compared with kyphoplasty

- Pain relief: A single poor-quality RCT found that back pain scores improved equally for vertebroplasty and kyphoplasty patients over 6 months. The strength of evidence is very low.
- Function and quality of life: There is no evidence of efficacy for these outcomes, as the single RCT did not assess them.

Sacroplasty

- There is no evidence of efficacy for sacroplasty. The only data available are from case series.

Key question 1: Effectiveness

Vertebroplasty

- Pain relief: It is uncertain whether vertebroplasty is more effective than conservative medical treatment in reducing pain. Four nonrandomized studies with follow-up up to one year found that vertebroplasty was more effective in reducing pain than conservative medical treatment up to approximately six months. At one year, pain levels in both groups of patients were comparable. The strength of evidence is very low.
- Function and quality of life: A similar pattern was seen in these four studies in improvements in functioning and quality of life: superior effectiveness of vertebroplasty in the first 3-6 months was followed by equivalent levels of functioning at one year. The strength of evidence is very low.

Kyphoplasty

- Pain relief: In two non-randomized studies, kyphoplasty reduced pain more than conservative medical treatment for periods up to 3 years.
- Function and quality of life: In these two studies, kyphoplasty improved a limited set of functional outcomes more than conservative medical treatment.

Vertebroplasty compared with kyphoplasty

- Pain relief: In 8 of 10 non-randomized studies, vertebroplasty and kyphoplasty led to comparable pain reduction up to 2 years.
- Function and quality of life: In 4 of 5 non-randomized studies, vertebroplasty and kyphoplasty patients demonstrated comparable improvements in ODI up to 2 years.

Sacroplasty

- Very limited data from 9 case series (N = 141 total patients) suggests that patients experience pain relief following sacroplasty. In the absence of well-conducted comparative studies, no conclusions regarding effectiveness can be drawn and the strength of evidence is very low.

Key question 2: Safety

Overall, while it appears that rates of serious complications that have associated symptoms are low for vertebroplasty and kyphoplasty, studies with long-term (> 5 year) follow-up are few. Moreover, comparative studies, especially RCTs, may have too few patients to detect more rare but serious outcomes.

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. In other comparative studies, numbers of new fractures were too small to draw conclusions about fracture risk in adjacent versus non-adjacent vertebrae, due to the small number of patients in these studies.
    - 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%). Because systematic reviews include information on case series, the level of evidence is very low.
- Cement leakage
    - In comparative studies, rates of cement leakage 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, non-randomized 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. Peri-operative mortality rate for kyphoplasty was .01% across 11 case series.
  - Since the majority of patients receiving these procedures are either elderly and/or have malignant disease, the extent to which mortality can be attributed to the procedures is unclear.

Sacroplasty

- The overall strength of evidence 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.

Key question 3: Differential efficacy and safety for subpopulations

No studies were found that addressed differential efficacy or safety issues for subpopulations defined by gender, age, psychological or psychosocial co-morbidities, provider characteristics, or payer type.

Diagnosis (osteoporosis or tumor-related fractures)

- There are no studies that assessed differential outcomes of vertebroplasty or kyphoplasty by fracture etiology. The majority of studies were limited to patients with osteoporotic fractures. Only two retrospective cohort studies (both comparing vertebroplasty with kyphoplasty) studied patients with fractures due to malignancy, with one study reporting comparable outcomes both procedures and the other reporting that kyphoplasty led to more improvement in pain than vertebroplasty over one year.

Fracture age

The extent to which vertebroplasty may be more efficacious in patients with acute fractures, as compared to those with more chronic fractures, is uncertain based on available RCTs.

- No studies were designed to directly compare efficacy or safety outcomes between patients with acute, subacute, and/or chronic fractures. Two RCTs of vertebroplasty compared with sham surgery,which included patients with both acute and more chronic fractures, conducted post-hoc subgroup analysis indicating that pain outcomes did not differ significantly for more recent fractures compare to fractures of longer duration. However, these analyses were likely to have low power for detecting differential outcomes in patients of different fracture ages.
- The largest RCT comparing vertebroplasty with conservative care included only acute osteoporotic fractures (≤6 weeks pain duration), reporting that vertebroplasty was more effective in improving pain and functioning. However, it is difficult to establish differential effectiveness by fracture age without a direct comparison of patients who had more chronic fractures in the same underlying patient population. Thus, the findings from this study do not address the issue of differential efficacy.
- Across non-randomized cohort studies comparing vertebroplasty with conservative treatment, similar results were reported in studies of patients with acute fractures and with chronic fractures. The majority of these studies reported earlier pain reduction for vertebroplasty, with no significant group differences by one year after the procedure. Again, without direct comparison of outcomes, conclusions regarding differential efficacy are problematic.

Sacroplasty

- Among the published case series of sacroplasty, two included only patients with osteoporotic fractures, three were of patients primarily with multiple myeloma or other tumors, and fourwere of patients with SIF of undefined or mixed causes. Pain scores improved following sacroplasty for both osteoporotic and malignant fractures, from 8.1-9.1 pre-operatively to 0.8-3.8 at varying follow-up periods. The overall strength of evidence is very low.

Key question 4: Cost effectiveness

- Because the efficacy and effectiveness of these procedures is uncertain, their overall cost effectiveness is unclear. Because no cost studies were conducted with U.S. data, the cost effectiveness of vertebroplasty, kyphoplasty or sacroplasty in a US setting is unknown.
- Assuming benefit in quality of life (pain relief) at 12 months, balloon kyphoplasty may be associated with increased cost and a small increase in quality in adjusted life years at three years post-procedure.

- Percutaneous vertebroplasty was associated with early (<3 months) improvements in pain and function at comparable cost compared with medical therapy alone in two studies. At 12 months vertebroplasty and medical therapy were comparable on pain, function, and healthcare cost.
- The economic impact of complications, reoperation, or revision following vertebroplasty, kyphoplasty, or sacroplasty is unknown.

Summary of evidence

Key Question 1: What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Vertebroplasty (PV) vs. sham surgery					
Efficacy	**Low evidence**	• In 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.	+	-	-
2. Vertebroplasty (PV) vs. conservative treatment (CMT)					
Efficacy	**Low evidence**	• In a large RCT comparing PV with conservative treatment, PV was more 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	**Low evidence**	• In four cohort studies (2 prospective and 2 retrospective): o PV was more effective than CMT in reducing pain (from 7.5-9 to 0.7-3.5) up to 6 months, but pain levels were comparable for the two groups after one year. o 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.	-	+	+

3. Kyphoplasty (KP) vs. conservative treatment					
Efficacy	**Low evidence**	• In one RCT: o KP was more effective than CMT by 0.9-2.2 points in reducing pain intensity for follow-up points up to one year. o Pain was reduced more rapidly in KP patients, and group differences were diminished by 12 months. o 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.	+	-	-
Effectiveness	**Very low evidence**	• In two cohort studies (1 prospective and 1 retrospective): o KP reduced pain more than CMT for periods up to 3 years. o KP improved a limited set of functional outcomes more than CMT.	-	-	+
4. Vertebroplasty vs. kyphoplasty					
Efficacy	**Very low evidence**	• One poor-quality RCT found that: o Back pain scores improved equally (from 8.0 to 2.3-2.6) for PV and KP patients over 6 months.	-	-	-
Effectiveness	**Low evidence**	• Evidence from 12 cohort studies (6 prospective and 6 retrospective) demonstrated that o 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. o PV and KP demonstrated 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.	-	+	+
5. Sacroplasty					
Efficacy and effectiveness	**Very low evidence**	• No comparative studies identified; case series suggest improvement in pain following sacroplasty	-	-	-

Key Question 2: What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
Vertebroplasty and kyphoplasty	**Low evidence**	• New fractures: o 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. o 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%). o 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 o Rates of asymptomatic cement leakage are up to 80% for vertebroplasty and 50% for kyphoplasty. o 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) o One RCT reported a PCE rate for PV of 26%, with all cases asymptomatic o Systematic reviews of case series report pooled PCE rates from .1% to 1.7%, with insufficient information to compare rates for PV and KP. • Mortality o Data from systematic reviews primarily of case series o Rates in prospective studies of 2.1% (22/1051) for PV and 0.6% (24/5629) for retrospective studies. o Overall mortality for kyphoplasty ranging from 2.3% (13/588) to 3.2 % (25/522) from 2 different reviews o Perioperative mortality: 0.01% (1/406).	-	+	+

Sacroplasty	**Very low evidence**	• Across four case series, rate of cement leakage was 20.5% (7/34 patients)	-	-	-

Key Question 3: What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety issues in sub populations?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Vertebroplasty vs. sham surgery or conservative treatment	**Very low evidence**	• Fracture age: o No studies were designed to directly compare efficacy or safety outcomes between patients with acute, subacute, and/or chronic fractures. o 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. o 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: o Two retrospective cohort studies in patients with malignancy fractures cannot provide information for differential efficacy based on fracture etiology.	-	-	-
2. Kyphoplasty vs. conservative treatment	**Very low evidence**	• No comparative studies were identified that assessed differential efficacy or safety according to patient, provider, or payer factors.	-	-	-
3. Vertebroplasty vs. kyphoplasty	**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.	-	-	-
4. Sacroplasty	**Very low evidence**	• No comparative studies were identified			

Key Question 4: What is the evidence of cost implications and cost-effectiveness of vertebroplasty, kyphoplasty and sacroplasty?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Vertebroplasty vs. sham surgery or conservative treatment	**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.	-	-	-
2. Kyphoplasty vs. conservative treatment	**Very low evidence**	• Cost data from one RCT showed that KP was associated with increased cost and increased QALY compared with CMT.	-	-	-
3. Vertebroplasty vs. kyphoplasty	**Very low evidence**	• No evidence	-	-	-
4. Sacroplasty	**Very low evidence**	• No evidence	-	-	-

References

1. Gray DT, Hollingworth W, Onwudiwe N, Jarvik JG. Costs and state-specific rates of thoracic and lumbar vertebroplasty, 2001-2005. Spine (Phila Pa 1976) 2008;33:1905-12.
2. Nussbaum DA, Gailloud P, Murphy K. A review of complications associated with vertebroplasty and kyphoplasty as reported to the Food and Drug Administration medical device related web site. J Vasc Interv Radiol 2004;15:1185-92.
3. Jensen ME, Evans AJ, Mathis JM, Kallmes DF, Cloft HJ, Dion JE. Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. AJNR Am J Neuroradiol 1997;18:1897-904.
4. McDonald RJ, Gray LA, Cloft HJ, Thielen KR, Kallmes DF. The effect of operator variability and experience in vertebroplasty outcomes. Radiology 2009;253:478-85.
5. Baerlocher MO, Munk PL, Liu DM, et al. Clinical utility of vertebroplasty: need for better evidence. Radiology 2010;255:669-74.
6. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ, 3rd. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. J Bone Miner Res 1992;7:221-7.
7. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17:1726-33.
8. EPOS group. Incidence of vertebral fracture in Europe: results from the European Prospective Osteoporosis Study (EPOS). J Bone Miner Res 2002;17:716–24.
9. Ross PD. Clinical consequences of vertebral fractures. Am J Med 1997;103:30S-42S; discussion S-3S.
10. Ettinger B, Black DM, Nevitt MC, et al. Contribution of vertebral deformities to chronic back pain and disability. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1992;7:449-56.
11. Silverman SL. The clinical consequences of vertebral compression fracture. Bone 1992;13 Suppl 2:S27-31.
12. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. Jama 2001;285:320-3.
13. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1999;14:821-8.
14. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 2000;15:721-39.
15. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int 2000;11:556-61.
16. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med 1999;159:1215-20.
17. Lieberman IH, Dudeney S, Reinhardt MK, Bell G. Initial outcome and efficacy of "kyphoplasty" in the treatment of painful osteoporotic vertebral compression fractures. Spine (Phila Pa 1976) 2001;26:1631-8.

18. Leroux JL, Denat B, Thomas E, Blotman F, Bonnel F. Sacral insufficiency fractures presenting as acute low-back pain. Biomechanical aspects. Spine (Phila Pa 1976) 1993;18:2502-6.
19. Smith DK, Dix JE. Percutaneous sacroplasty: long-axis injection technique. AJR Am J Roentgenol 2006;186:1252-5.
20. Binaghi S, Guntern D, Schnyder P, Theumann N. A new, easy, fast, and safe method for CT-guided sacroplasty. Eur Radiol 2006;16:2875-8.
21. Brook AL, Mirsky DM, Bello JA. Computerized tomography guided sacroplasty: a practical treatment for sacral insufficiency fracture: case report. Spine (Phila Pa 1976) 2005;30:E450-4.
22. Lin JT, Lane JM. Sacral stress fractures. J Womens Health (Larchmt) 2003;12:879-88.
23. Bayley E, Srinivas S, Boszczyk BM. Clinical outcomes of sacroplasty in sacral insufficiency fractures: a review of the literature. Eur Spine J 2009;18:1266-71.
24. Weber M, Hasler P, Gerber H. Insufficiency fractures of the sacrum. Twenty cases and review of the literature. Spine (Phila Pa 1976) 1993;18:2507-12.
25. Babayev M, Lachmann E, Nagler W. The controversy surrounding sacral insufficiency fractures: to ambulate or not to ambulate? Am J Phys Med Rehabil 2000;79:404-9.
26. Lin J, Lachmann E, Nagler W. Sacral insufficiency fractures: a report of two cases and a review of the literature. J Womens Health Gend Based Med 2001;10:699-705.
27. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. Support Care Cancer 2008;16:879-89.
28. Fourney DR, Schomer DF, Nader R, et al. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg 2003;98:21-30.
29. Galibert P, Deramond H, Rosat P, Le Gars D. [Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty]. Neurochirurgie 1987;33:166-8.
30. Amar AP, Larsen DW, Esnaashari N, Albuquerque FC, Lavine SD, Teitelbaum GP. Percutaneous transpedicular polymethylmethacrylate vertebroplasty for the treatment of spinal compression fractures. Neurosurgery 2001;49:1105-14; discussion 14-5.
31. Mark D. Percutaneous Vertebroplasty or Kyphoplasty for Vertebral Fractures Caused by Osteoporosis or Malignancy. In: BCBS Tec Assessment Program, ed.; 2008:1-38.
32. Martin JB, Wetzel SG, Seium Y, et al. Percutaneous vertebroplasty in metastatic disease: transpedicular access and treatment of lysed pedicles--initial experience. Radiology 2003;229:593-7.
33. Kim AK, Jensen ME, Dion JE, Schweickert PA, Kaufmann TJ, Kallmes DF. Unilateral transpedicular percutaneous vertebroplasty: initial experience. Radiology 2002;222:737-41.
34. Bouza C, Lopez T, Magro A, Navalpotro L, Amate JM. Efficacy and safety of balloon kyphoplasty in the treatment of vertebral compression fractures: a systematic review. Eur Spine J 2006;15:1050-67.
35. Garfin SR, Yuan HA, Reiley MA. New technologies in spine: kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. Spine (Phila Pa 1976) 2001;26:1511-5.
36. Lee MJ, Dumonski M, Cahill P, Stanley T, Park D, Singh K. Percutaneous treatment of vertebral compression fractures: a meta-analysis of complications. Spine (Phila Pa 1976) 2009;34:1228-32.

37. Lieberman IH, Phillips FM, Togawa D, et al. Vertebral augmentation and the limits of interpreting complications reported in the food and drug administration manufacturer and user facility device experience database. J Vasc Interv Radiol 2004;15:1193-6.
38. Dehdashti AR, Martin JB, Jean B, Rufenacht DA. PMMA cementoplasty in symptomatic metastatic lesions of the S1 vertebral body. Cardiovasc Intervent Radiol 2000;23:235-7.
39. Garant M. Sacroplasty: a new treatment for sacral insufficiency fracture. J Vasc Interv Radiol 2002;13:1265-7.
40. Krueger A, Bliemel C, Zettl R, Ruchholtz S. Management of pulmonary cement embolism after percutaneous vertebroplasty and kyphoplasty: a systematic review of the literature. Eur Spine J 2009;18:1257-65.
41. Lee IJ, Choi AL, Yie MY, et al. CT evaluation of local leakage of bone cement after percutaneous kyphoplasty and vertebroplasty. Acta Radiol 2010;51:649-54.
42. Bohner M, Gasser B, Baroud G, Heini P. Theoretical and experimental model to describe the injection of a polymethylmethacrylate cement into a porous structure. Biomaterials 2003;24:2721-30.
43. Padovani B, Kasriel O, Brunner P, Peretti-Viton P. Pulmonary embolism caused by acrylic cement: a rare complication of percutaneous vertebroplasty. AJNR Am J Neuroradiol 1999;20:375-7.
44. Laredo JD, Hamze B. Complications of percutaneous vertebroplasty and their prevention. Skeletal Radiol 2004;33:493-505.
45. Freitag M, Gottschalk A, Schuster M, Wenk W, Wiesner L, Standl TG. Pulmonary embolism caused by polymethylmethacrylate during percutaneous vertebroplasty in orthopaedic surgery. Acta Anaesthesiol Scand 2006;50:248-51.
46. Jang JS, Lee SH, Jung SK. Pulmonary embolism of polymethylmethacrylate after percutaneous vertebroplasty: a report of three cases. Spine (Phila Pa 1976) 2002;27:E416-8.
47. Tozzi P, Abdelmoumene Y, Corno AF, Gersbach PA, Hoogewoud HM, von Segesser LK. Management of pulmonary embolism during acrylic vertebroplasty. Ann Thorac Surg 2002;74:1706-8.
48. Tanigawa N, Komemushi A, Kariya S, et al. Relationship between cement distribution pattern and new compression fracture after percutaneous vertebroplasty. AJR Am J Roentgenol 2007;189:W348-52.
49. Fribourg D, Tang C, Sra P, Delamarter R, Bae H. Incidence of subsequent vertebral fracture after kyphoplasty. Spine (Phila Pa 1976) 2004;29:2270-6; discussion 7.
50. Jensen M, McGraw, JK, Cardella, JF, Hirsch, JA. Position Statement on Percutaneous Vertebral Augmentation: A Consensus Statement Developed by the 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. Am J Neuroradiol 2007;28:1439-43.
51. Uhthoff HK, Jaworski ZF. Bone loss in response to long-term immobilisation. J Bone Joint Surg Br 1978;60-B:420-9.
52. Convertino VA, Bloomfield SA, Greenleaf JE. An overview of the issues: physiological effects of bed rest and restricted physical activity. Med Sci Sports Exerc 1997;29:187-90.
53. Taillandier J, Langue F, Alemanni M, Taillandier-Heriche E. Mortality and functional outcomes of pelvic insufficiency fractures in older patients. Joint Bone Spine 2003;70:287-9.

54. Masala S, Ciarrapico AM, Konda D, Vinicola V, Mammucari M, Simonetti G. Cost-effectiveness of percutaneous vertebroplasty in osteoporotic vertebral fractures. Eur Spine J 2008;17:1242-50.
55. Cahill KS, Chi JH, Day A, Claus EB. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. JAMA 2009;302:58-66.
56. Institute for Clinical Systems Improvement (ICSI). Assessment and Management of Chronic Pain. In. Bloomington, MN: National Guideline Clearinghouse (NGC); 2008:84.
57. National Collaborating Centre for Cancer. Metastatic Spinal Cord Compression. Diagnosis and Management of Adults at Risk of and with Metastatic Spinal Cord Compression. In: (NICE) NIfHaCE, ed.; 2008:39.
58. Interventional Procedures Programme. Interventional Procedure Guidance (IPG) for Vertebroplasty and Balloon Kyphoplasty. In: National Institute for Health and Clinical Excellence; 2007.
59. California Technology Assessment Forum (CTAF). Vertebroplasty as a Treatment for Osteoporotic Compression Fractures. In; 2010:1-16.
60. Belinson S. Percutaneous Vertebroplasty or Kyphoplasty for Vertebral Fractures Caused by Osteoporosis: Kaiser Foundation Health Plan and Southern California Permanente Group; 2010 April, 2010.
61. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569-79.
62. Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet.
63. Venmans A, Klazen CA, Lohle PN, et al. Percutaneous Vertebroplasty and Pulmonary Cement Embolism: Results from VERTOS II. AJNR Am J Neuroradiol.
64. Venmans A, Klazen CA, van Rooij WJ, de Vries J, Mali WP, Lohle PN. Postprocedural CT for perivertebral cement leakage in percutaneous vertebroplasty is not necessary-results from VERTOS II. Neuroradiology 2010.
65. Klazen CA, Venmans A, de Vries J, et al. Percutaneous Vertebroplasty Is Not a Risk Factor for New Osteoporotic Compression Fractures: Results from VERTOS II. AJNR Am J Neuroradiol.
66. Oxford Centre for Evidence-based Medicine Levels of Evidence. 2009. (Accessed 9/27/10, at http://www.cebm.net/?o=1025.)
67. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
68. West S, King V, Carey TS, et al. Systems to Rate the Strength Of Scientific Evidence. Rockville, MD: Agency for Healthcare Research and Quality; 2002.
69. Bouza C, Lopez-Cuadrado T, Cediel P, Saz-Parkinson Z, Amate JM. Balloon kyphoplasty in malignant spinal fractures: a systematic review and meta-analysis. BMC Palliat Care 2009;8:12.
70. Eck JC, Nachtigall D, Humphreys SC, Hodges SD. Comparison of vertebroplasty and balloon kyphoplasty for treatment of vertebral compression fractures: a meta-analysis of the literature. Spine J 2008;8:488-97.
71. Mendel E, Bourekas E, Gerszten P, Golan JD. Percutaneous techniques in the treatment of spine tumors: what are the diagnostic and therapeutic indications and outcomes? Spine (Phila Pa 1976) 2009;34:S93-100.

72. Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. Eur Spine J 2007;16:1085-100.
73. Mudano AS, Bian J, Cope JU, et al. Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: a population-based cohort study. Osteoporos Int 2009;20:819-26.
74. Zampini JM, White AP, McGuire KJ. Comparison of 5766 Vertebral Compression Fractures Treated With or Without Kyphoplasty. Clin Orthop Relat Res 2010.
75. Lange LL, Jacox A. Using large data bases in nursing and health policy research. J Prof Nurs 1993
;9:204.
76. Baron JA, Weiderpass E. An introduction to epidemiological research with medical databases. Ann Epidemiol 2000;10:200-4.
77. Connell FA, Diehr P, Hart LG. The use of large data bases in health care studies. Annu Rev Public Health 1987;8:51-74.
78. Flood AB. Peaks and pits of using large data bases to measure quality of care. Int J Technol Assess Health Care 1990;6:253-62.
79. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557-68.
80. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 2001;344:1594-602.
81. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med 2004;256:91-100.
82. Vase L, Riley JL, 3rd, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. Pain 2002;99:443-52.
83. Jarvik JG, Deyo RA. Cementing the evidence: time for a randomized trial of vertebroplasty. AJNR Am J Neuroradiol 2000;21:1373-4.
84. Kallmes DF, Comstock BA, Gray LA, et al. Baseline pain and disability in the Investigational Vertebroplasty Efficacy and Safety Trial. AJNR Am J Neuroradiol 2009;30:1203-5.
85. Grotle M, Brox JI, Vollestad NK. Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back pain. Spine (Phila Pa 1976) 2004;29:E492-501.
86. Rousing R, Hansen KL, Andersen MO, Jespersen SM, Thomsen K, Lauritsen JM. Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: a clinical randomized study. Spine (Phila Pa 1976) 2010;35:478-82.
87. Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR Am J Neuroradiol 2007;28:555-60.
88. Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet 2009;373:1016-24.
89. Mathis JM, Ortiz AO, Zoarski GH. Vertebroplasty versus kyphoplasty: a comparison and contrast. AJNR Am J Neuroradiol 2004;25:840-5.

90. Liu JT, Liao WJ, Tan WC, et al. Balloon kyphoplasty versus vertebroplasty for treatment of osteoporotic vertebral compression fracture: a prospective, comparative, and randomized clinical study. Osteoporos Int 2010;21:359-64.
91. Alvarez L, Alcaraz M, Perez-Higueras A, et al. Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine (Phila Pa 1976) 2006;31:1113-8.
92. Diamond TH, Bryant C, Browne L, Clark WA. Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. Med J Aust 2006;184:113-7.
93. Ehteshami Rad A, Gray LA, Kallmes DF. Incident Vertebral Fractures in Patients not Undergoing Vertebroplasty. J Vasc Interv Radiol 2010.
94. Nakano M, Hirano N, Ishihara H, Kawaguchi Y, Watanabe H, Matsuura K. Calcium phosphate cement-based vertebroplasty compared with conservative treatment for osteoporotic compression fractures: a matched case-control study. J Neurosurg Spine 2006;4:110-7.
95. Kasperk C, Grafe IA, Schmitt S, et al. Three-year outcomes after kyphoplasty in patients with osteoporosis with painful vertebral fractures. J Vasc Interv Radiol 2010;21:701-9.
96. An KC, Kang S, Choi JS, Seo JH. The clinical and radiological availability of percutaneous balloon kyphoplasty as a treatment for osteoporotic burst fractures. Asian Spine J 2008;2:9-14.
97. Ming JH, Zhou JL, Zhou PH, Zhou JP. Comparison of therapeutic effect between percutaneous kyphoplasty and pedicle screw system on vertebral compression fracture. Chin J Traumatol 2007;10:40-3.
98. De Negri P, Tirri T, Paternoster G, Modano P. Treatment of painful osteoporotic or traumatic vertebral compression fractures by percutaneous vertebral augmentation procedures: a nonrandomized comparison between vertebroplasty and kyphoplasty. Clin J Pain 2007;23:425-30.
99. Grohs JG, Matzner M, Trieb K, Krepler P. Minimal invasive stabilization of osteoporotic vertebral fractures: a prospective nonrandomized comparison of vertebroplasty and balloon kyphoplasty. J Spinal Disord Tech 2005;18:238-42.
100. Lovi A, Teli M, Ortolina A, Costa F, Fornari M, Brayda-Bruno M. Vertebroplasty and kyphoplasty: complementary techniques for the treatment of painful osteoporotic vertebral compression fractures. A prospective non-randomised study on 154 patients. Eur Spine J 2009;18 Suppl 1:95-101.
101. Röllinghoff M, Siewe J, Zarghooni K, et al. Effectiveness, security and height restoration on fresh compression fractures--a comparative prospective study of vertebroplasty and kyphoplasty. Minim Invasive Neurosurg 2009;52:233-7.
102. Santiago FR, Abela AP, Alvarez LG, Osuna RM, Garcia MD. Pain and functional outcome after vertebroplasty and kyphoplasty. A comparative study. Eur J Radiol 2010.
103. Schofer MD, Efe T, Timmesfeld N, Kortmann HR, Quante M. Comparison of kyphoplasty and vertebroplasty in the treatment of fresh vertebral compression fractures. Arch Orthop Trauma Surg 2009;129:1391-9.
104. Frankel BM, Monroe T, Wang C. Percutaneous vertebral augmentation: an elevation in adjacent-level fracture risk in kyphoplasty as compared with vertebroplasty. Spine J 2007;7:575-82.
105. Hiwatashi A, Westesson PL, Yoshiura T, et al. Kyphoplasty and vertebroplasty produce the same degree of height restoration. AJNR Am J Neuroradiol 2009;30:669-73.

106.Köse KC, Cebesoy O, Akan B, Altinel L, Dincer D, Yazar T. Functional results of vertebral augmentation techniques in pathological vertebral fractures of myelomatous patients. J Natl Med Assoc 2006;98:1654-8.
107.Zhou JL, Liu SQ, Ming JH, Peng H, Qiu B. Comparison of therapeutic effect between percutaneous vertebroplasty and kyphoplasty on vertebral compression fracture. Chin J Traumatol 2008;11:42-4.
108.Chapman JR, Hanson BP, Dettori JR, Norvell DC. Spine outcomes measures and instruments. Dübendorf, Switzerland: AOSpine International; 2007.
109.Hawthorne G, Osborne R. Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. Aust N Z J Public Health 2005;29:136-42.
110.O'Neill TW, Cooper C, Cannata JB, et al. Reproducibility of a questionnaire on risk factors for osteoporosis in a multicentre prevalence survey: the European Vertebral Osteoporosis Study. Int J Epidemiol 1994;23:559-65.
111.Million R, Hall W, Nilsen KH, Baker RD, Jayson MI. Assessment of the progress of the back-pain patient 1981 Volvo Award in Clinical Science. Spine (Phila Pa 1976) 1982;7:204-12.
112.Patrick DL, Deyo RA, Atlas SJ, Singer DE, Chapin A, Keller RB. Assessing health-related quality of life in patients with sciatica. Spine (Phila Pa 1976) 1995;20:1899-908; discussion 909.
113.Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-21.
114.Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine (Phila Pa 1976) 2008;33:90-4.
115.Strub WM, Hoffmann M, Ernst RJ, Bulas RV. Sacroplasty by CT and fluoroscopic guidance: is the procedure right for your patient? AJNR Am J Neuroradiol 2007;28:38-41.
116.Frey ME, Depalma MJ, Cifu DX, Bhagia SM, Carne W, Daitch JS. Percutaneous sacroplasty for osteoporotic sacral insufficiency fractures: a prospective, multicenter, observational pilot study. Spine J 2008;8:367-73.
117.Anselmetti GC, Manca A, Ortega C, Grignani G, Debernardi F, Regge D. Treatment of extraspinal painful bone metastases with percutaneous cementoplasty: a prospective study of 50 patients. Cardiovasc Intervent Radiol 2008;31:1165-73.
118.Basile A, Tsetis D, Cavalli M, et al. Sacroplasty for Local or Massive Localization of Multiple Myeloma. Cardiovasc Intervent Radiol 2009.
119.Georgy BA. Interventional techniques in managing persistent pain after vertebral augmentation procedures: a retrospective evaluation. Pain Physician 2007;10:673-6.
120.Whitlow CT, Mussat-Whitlow BJ, Mattern CW, Baker MD, Morris PP. Sacroplasty versus vertebroplasty: comparable clinical outcomes for the treatment of fracture-related pain. AJNR Am J Neuroradiol 2007;28:1266-70.
121.Butler CL, Given CA, 2nd, Michel SJ, Tibbs PA. Percutaneous sacroplasty for the treatment of sacral insufficiency fractures. AJR Am J Roentgenol 2005;184:1956-9.
122.Kamel EM, Binaghi S, Guntern D, Mouhsine E, Schnyder P, Theumann N. Outcome of long-axis percutaneous sacroplasty for the treatment of sacral insufficiency fractures. Eur Radiol 2009.
123.Kang SE, Lee JW, Kim JH, Park KW, Yeom JS, Kang HS. Percutaneous sacroplasty with the use of C-arm flat-panel detector CT: technical feasibility and clinical outcome. Skeletal Radiol 2010.

124.Fourney DR. Vertebroplasty versus kyphoplasty in the cancer setting: rethinking the relative indications. Support Cancer Ther 2005;3:26-7.
125.Bono CM, Heggeness M, Mick C, Resnick D, Watters IWC. North American Spine Society. Newly released vertebroplasty randomized controlled trials: a tale of two trials. Spine Journal 2010;10:238-40.
126.Ström O, Leonard C, Marsh D, Cooper C. Cost-effectiveness of balloon kyphoplasty in patients with symptomatic vertebral compression fractures in a UK setting. Osteoporos Int 2009.