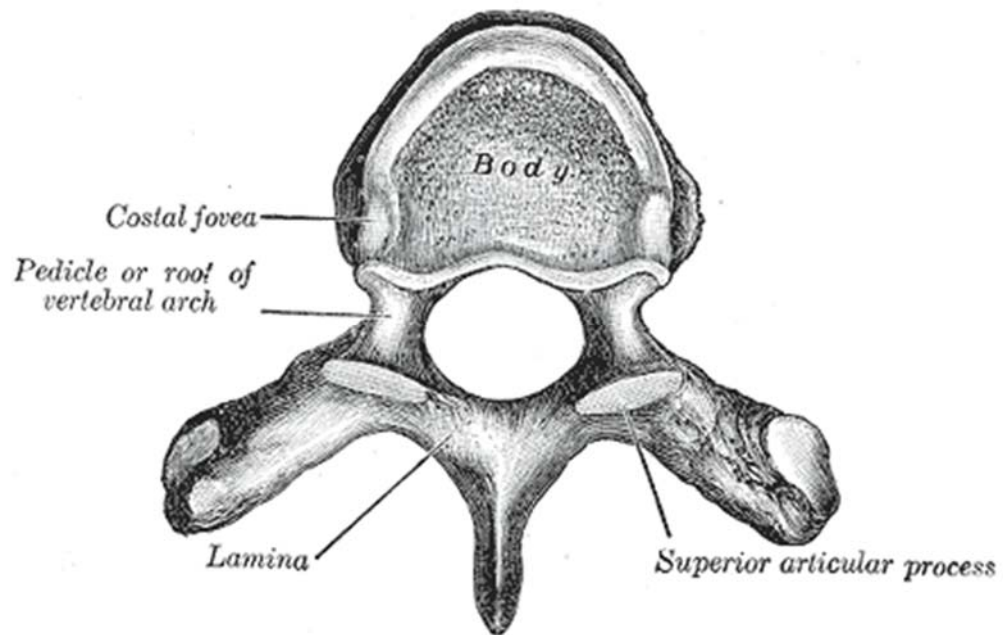


PERCUTANEOUS VERTEBROPLASTY AND BALLOON KYPHOPLASTY



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AQoL	Assessment of Quality of Life score
BKP	Balloon kyphoplasty
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMA	Cost-minimisation analysis
CRD	Centre for Review and Dissemination
CUA	Cost-utility analysis
DGSIE – ADSEI	Direction générale Statistique et Information économique – Algemene Directie Statistiek en Economische Informatie - Statistics Belgium
EQ-5D	EuroQol 5 dimensions
EUnetHTA	European Network on Health Technology Assessment
HCP	Health care payer
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
INAMI – RIZIV	Institut national d'assurance maladie-invalidité - Rijksinstituut voor ziekte en invaliditeits verzekering (Belgium)
IPD	Individual Patient Data (in the context of meta-analyses techniques)
LY	Life year
MCID	Minimal Clinically Important Difference
MMSE	Mini Mental State Examination
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence (UK)
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index



OPLA	Operative Placebo with Local Anaesthesia
OPM	Optimal Pain Management (or non-surgical optimal management of pain)
PICO	Patient/Intervention/Comparator/Outcomes questions
PVP	Percutaneous vertebroplasty
QALY	Quality-adjusted life year
QoL	Quality of Life
QUALEFFO	Quality of Life Questionnaire of the European Foundation for Osteoporosis
RCT	Randomised Controlled Trial
RDQ	Roland-Morris Disability Questionnaire
RHM – MZG	Résumé Hospitalier Minimum – Minimale Ziekenhuis Gegevens
RR	Relative Risk
SA	Sensitivity Analysis
ScHARR	School of Health And Related Research
SE	Standard Error
SF-36	Short Form questionnaire - 36 items
SF-36 MCS	SF-36 Mental Component Score
SF-36 PCS	SF-36 Physical Component Score
SOF-ADL	Study of Osteoporotic Fractures - Activities of Daily Living
SPF – FOD	Service Public Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement – Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu
UNAMEC	Federation of the Medical Technologies Industry (Belgium)
VAS	Visual Analogue Scale
VCF	Vertebral Compression Fractures



■ SCIENTIFIC REPORT

1 OBJECTIVE AND SCOPE

The aim of this rapid review is to give an overview of the current evidence on the effectiveness, safety and cost-effectiveness of two closely related treatment modalities for the management of serious vertebral compression fractures (VCF): percutaneous vertebroplasty and percutaneous balloon kyphoplasty.

Percutaneous vertebroplasty (PVP) and balloon kyphoplasty (BKP) are minimally invasive surgical techniques used in the management of vertebral compression fractures.

To improve readability these techniques will further be called in short *vertebroplasty* and *kyphoplasty*.

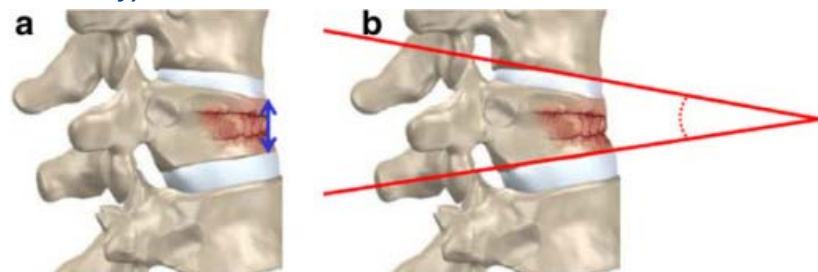
2 VERTEBRAL COMPRESSION FRACTURES (VCF)

2.1 Population and condition

Vertebral compression fractures (VCF) are an important source of acute back pain, chronic back pain and spinal deformity. Most frequently, those fractures are caused by osteoporosis, either postmenopausal or secondary such as corticoid-induced osteoporosis. Vertebral compression fractures associated with primary osteoporosis occur more frequently in women and incidence increases with age.¹

There are, however, other conditions that can cause vertebral compression fractures and vertebral instability such as vertebral metastases, myeloma, haemangioma, osteonecrosis and severe trauma.¹

Figure 1 – Diagram of a vertebral compression fracture (wedge deformity)



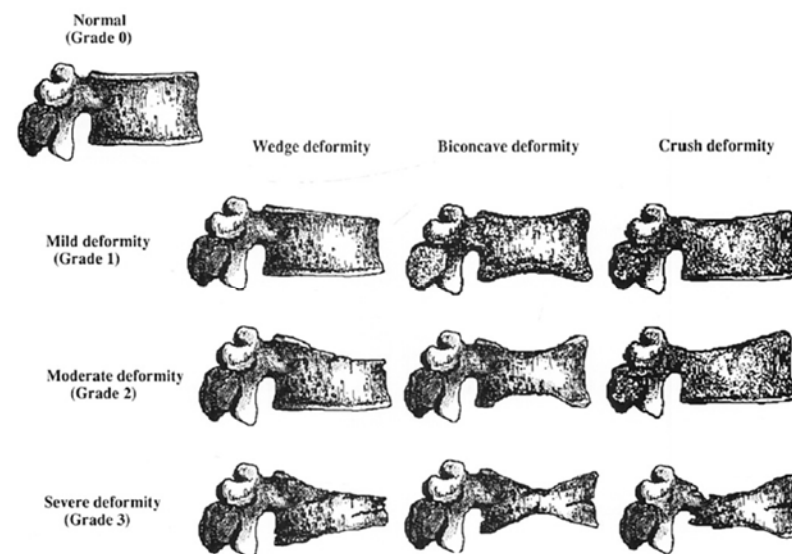
Source: U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894
<http://openi.nlm.nih.gov/gridquery.php?q=vertebroplasty&it=xg>.

The main complaint caused by VCF is pain. However, this is not always so and often VCF cause only minimal complaints limited in time. Therefore many of these fractures are chance findings detected through routine x-rays made for other reasons. The incidence of VCF is therefore difficult to assess. Prevalence can be assessed in population studies but are dependent upon the technology and definitions used to define a VCF. An often used definition was introduced by Genant et al. in 1993. It is a semi-quantitative assessment that describes normal vertebrae (grade 0) or mild (grade 1, 20–25%),

moderate (grade 2, 25–40%), or severe (grade 3, more than 40%) deformity in any vertebral vertical dimension (see Figure 2).²

Based on the extrapolation from Dutch longitudinal data where all participants had plain x-rays at baseline and at follow-up the total yearly incidence of VCF in the Belgian population was estimated at approximately 10 000 radiologically visible moderate or severe vertebral deformities (Genant classification). About 80% of these occur in women.^{3, 4} The proportion of VCF that spontaneously come to clinical attention because of complaints is unknown.

Figure 2 – Genant classification



Source: *Journal of Bone and Mineral Research*, Mary Ann Liebert, Inc., Publishers, Genant HK et al.²



2.2 Non-surgical management.

The complaints from VCF, mainly driven by pain, can often be managed by conservative (i.e. non-invasive) treatment such as bed rest, pain medication, osteoporosis medication and future fracture prevention, physical therapy, walking aids or external bracing. Further this will be called '*optimal pain management*' (OPM) or non-surgical management.

For the management of non-osteoporotic VCF additional specific radiotherapy, chemotherapy or cancer surgery can be indicated.

2.3 Vertebroplasty and kyphoplasty

In very severe cases of VCF vertebroplasty or kyphoplasty is sometimes considered. Vertebroplasty has originally been performed as an open procedure to secure pedicle screws and fill tumorous voids. However, this was a risky procedure which was the reason for the development of percutaneous vertebroplasty techniques.

The first percutaneous vertebroplasty was performed in 1984 at the University Hospital of Amiens (France), to fill a vertebral void left after the removal of a haemangioma. A report on this and six other patients was published in 1987.⁵ Later this technique was also applied to osteoporotic VCF and VCF caused by bone metastases. Kyphoplasty was first performed in the late nineties.⁶

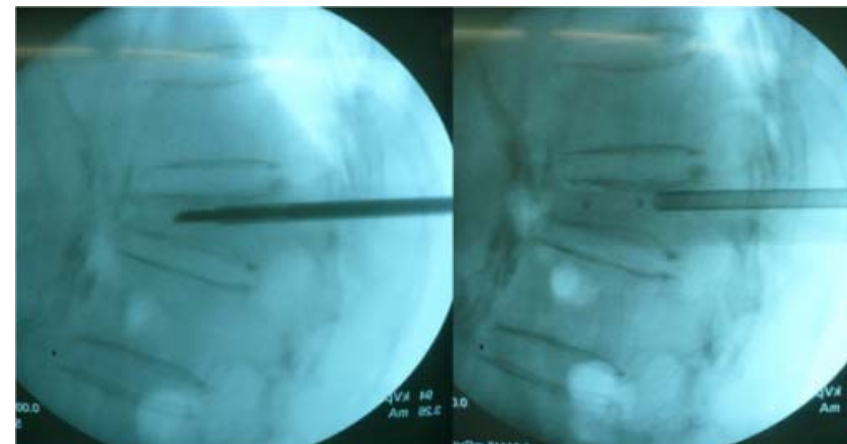
Vertebroplasty and kyphoplasty (both are also called '*vertebral augmentation techniques*') are relatively novel and minimally invasive treatments for VCF.⁷ Both techniques involve the percutaneous injection (through a small hole in the skin) of bone cement into a fractured vertebra with the goal of relieving the back pain caused by those fractures, restore the height of the vertebra and prevent further compression. The cement (originally polymethylmethacrylate - PMMA, although newer and high-viscosity cements are increasingly used) is injected with a biopsy needle under x-ray guidance. The cement quickly hardens and forms a support structure within the vertebra that provides stabilization and strength.¹

The techniques differ in the sense that in vertebroplasty only cement is injected to stabilize the vertebra, whereas in kyphoplasty restoration of vertebral height and kyphotic angle is additionally attempted by first inflating a balloon (tamp) inside the vertebra, creating a cavity and elevating the

endplates, prior to injecting the bone cement. This technique is also known as balloon assisted vertebroplasty.

The techniques can be performed bilaterally or unilaterally and the amount of cement depends upon patient and vertebra characteristics. Another variant is balloon kyphoplasty with stenting, where a metal stent surrounding the balloon is left in place while the cement is injected. Other variations of the technique are currently being used, but not included in this review due to a lack of data on the evidence on effectiveness.

Figure 3 – Radiographic image of kyphoplasty



Source: [U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894 http://openi.nlm.nih.gov/detailedresult.php?img=3922728_1471-2482-14-3-1&query=kyphoplasty&it=xg&req=4&npos=53](http://openi.nlm.nih.gov/detailedresult.php?img=3922728_1471-2482-14-3-1&query=kyphoplasty&it=xg&req=4&npos=53).

Vertebroplasty and kyphoplasty are minimally invasive procedures typically performed by a neurosurgeon, orthopaedic surgeon, anaesthetist or interventional radiologist. One or more vertebral levels can be treated during a single session. Patients can go home the same or the next day, although in Belgium they often stay in the hospital for several days (see section 3.2). Patients are given local anaesthesia and light sedation or total anaesthesia for the procedure although it can be performed using only local anaesthesia for patients with contraindications for sedatives.



3 BELGIAN SITUATION

3.1 Belgian regulation and reimbursement

Situation until March 31st, 2015

The kyphoplasty procedure and material were conditionally reimbursed for a maximum of two levels under the following billing codes^a (see Appendix for the complete French and Dutch labels):

- 589676 – 589680 Percutaneous balloon kyphoplasty for the treatment of vertebral compression fractures (per vertebral body) €305.35
- 162971 – 162982 Consumable material for balloon kyphoplasty, used for the procedure 589676 – 589680 €4257.64
- 162993 – 163004 Cement for balloon kyphoplasty used together with material 162971 – 162982, per level (max. 2 levels) €82.08

Reimbursement is limited to:

- A. Vertebral compression fractures caused by osteoporosis under specific conditions.
- B. Vertebral compression fractures caused by Kahler's myeloma under specific conditions.

This diagnosis for both indications must be made based on the three following examinations:

- an antero-posterior plain film radiography; and
- an MRI or a CT-scan when there is contraindication for MRI; and
- a bone scintigraphy without SPECT.

In case of an osteoporotic VCF an additional DEXA-scan is required.

The documents proving that the conditions are satisfied must be kept in a file and provided to the advisory physician if requested.

A maximum of 2 kyphoplasty interventions can be billed per two calendar years (exceptions were possible requiring the authorization of the College of Medical Directors).

Contrary to kyphoplasty covered since August 2008, vertebroplasty was not reimbursed in Belgium, neither the procedure nor the material (cement and injection kit). A kit of vertebroplasty currently amounts more or less to €500 per level treated. The INAMI – RIZIV explicitly forbids to assimilate the vertebroplasty to a kyphoplasty in order to get some reimbursement. Nevertheless, some of the experts accompanying the present report reported that some vertebroplasty interventions were probably improperly billed under the kyphoplasty medical fees code or under (a combination of) other billing codes. In the absence of reimbursement data, we will rely on other data sources to describe the current use of vertebroplasty in section 3.2.

Situation since April 1st, 2015

Due to budgetary constraints imposed by the Belgian authorities in the medical devices sector, the kyphoplasty material tariff (162971 – 162982) is €0 since April 1st, 2015. The cement coverage and the kyphoplasty medical fees are maintained. However the cement used during vertebroplasty is now reimbursed under the following codes, up to a same amount as the cement used in kyphoplasty:

- 171975 – 171986 Cement for vertebroplasty per level €82.08 (maximum 2 levels)

The INAMI – RIZIV implemented this decision immediately but this decision could be reconsidered later based on the conclusions of the present report.

^a Before the first of July 2014 and the new implant regulation, the kyphoplasty material and cement were billed under, respectively, the codes 683012 –

683023 and 683034 – 683045. These codes were used to analyze the Belgian data (see 3.2 Current Use in Belgium)



3.2 Current use in Belgium

3.2.1 Methods

To estimate the number of interventions performed in Belgium, we first used two different sources of data: one administrative database (RHM – MZG) for vertebroplasty and kyphoplasty and the input from the industry provided through UNAMEC. As kyphoplasty is reimbursed since 2008, the number and amounts reimbursed by the INAMI – RIZIV (Doc N) were used as a third source of data.

UNAMEC is the Belgian federation counting more than 200 firms in the medical technology field that covers 80% of the market. There are only a few firms that are not members of UNAMEC and sell a few vertebroplasty kits a year. This federation launched a survey in November 2014 asking their members to send us the number of vertebroplasty kits and kyphoplasty kits sold in the last two years. All UNAMEC members supplying kits for one of the two technologies participated to the survey and are listed in Table 1. In some cases, hospitals are free to buy elements from a kit separately.

Table 1 – Suppliers of kits available in Belgium included in the survey

Manufacturer	Distributor in Belgium	Vertebroplasty kit	Kyphoplasty kit
UNAMEC members (included in the survey)			
Medtronic	Medtronic	-	Kyphon Balloon Kyphoplasty
Seawon Meditech/Korea	Cormed	Spasy Kit	Spasy BCD Kit
Depuy Synthes	Depuy Synthes	VMAX	VBB SYNFLATE (vertebral Body Balloon system)
		VERTECEM	VBS Vertebral Body Stenting
CareFusion	HOSPITHERA	AVAmox	-
Ulrich	HOSPITHERA	UDURO	UDURO
Stryker	Stryker	No specific name	IVAS 1

Strictly speaking, only the balloon kyphoplasty might be reimbursed (source: INAMI – RIZIV), but it is not excluded that some similar technologies using another mechanism than a balloon to create a void prior to the cement injection got reimbursement. There was indeed no pre-control of the sickness funds on the hospital pharmacist invoice. Such systems include the VBS Vertebral Body Stenting using an expandable stent (Depuy Synthes), the Spinejack (Vexim, distributed by Medical Therapy Solutions b.v. and .be medical) using an expandable implant as a substructure under the cement. All types of vertebral augmentation system are included in the UNAMEC kyphoplasty sales.

Other manufacturers are potentially present on the Belgian market, both for vertebroplasty and kyphoplasty, like Joline, a German manufacturer whose kits and accessories are distributed by Eurox and .be medical, Globus Medical who also offers vertebroplasty or kyphoplasty solutions, or Zimmer with the vertebroplasty system VertoCure.

The second source is the Résumé Hospitalier Minimum – Minimale Ziekenhuisgegevens (RHM – MZG) managed by the Service Public Fédéral Santé Publique – Federale Overheidsdienst Volksgezondheid (SPF – FOD), ensuing from the mandatory registration of all hospitalisations in every Belgian general (non-psychiatric) hospital since 1991. Patient information data are recorded in this administrative database, such as year of birth, gender, residence as well as other information about the stay in the hospital such as length of stay, ICD-9-CM diagnostic codes of relevant diagnoses present on admission or appearing during hospitalisation and ICD-9-CM procedure codes for diagnostic and therapeutic procedures performed during the stay. After stripping direct patient-identifying information, records have to be sent twice a year to the SPF - FOD. As vertebroplasty and kyphoplasty are only performed in a hospital setting, we extracted the hospitalisations of patients discharged between 2008 and 2011 (last available year in November 2014) presenting an ICD-9-CM procedure code 81.65 *Percutaneous vertebroplasty* or 81.66 *Percutaneous vertebral augmentation* (kyphoplasty).

Finally the reimbursements (number and amounts) billed under the kyphoplasty nomenclature codes were retrieved from the Doc N INAMI – RIZIV database.

3.2.2 Number of vertebroplasties performed in Belgium

Table 2 – Number of vertebroplasties by data source

Source	Type of data	2008	2009	2010	2011	2012	2013
UNAMEC	Kits Sales	-	-	-	-	324	341
RHM MZG	Hospitalisations w/ vertebroplasty coded in ICD-9-CM and discharged in the year	550	527	506	550	-	-

Obviously, sales may differ from actually used vertebroplasty kits and there can be different time windows between procedures performed and procedures recorded in the hospital records. For example, a procedure performed in 2008 can be recorded in RHM – MZG 2009. Nevertheless, figures shown on Table 2 should be from the same order of magnitude. The experts accompanying the present study estimated that a same kit was never used in different patients and that hospital home-made kits were also no plausible explanation for the difference. Still, a few kits may have been provided by distributors that are not members of UNAMEC.

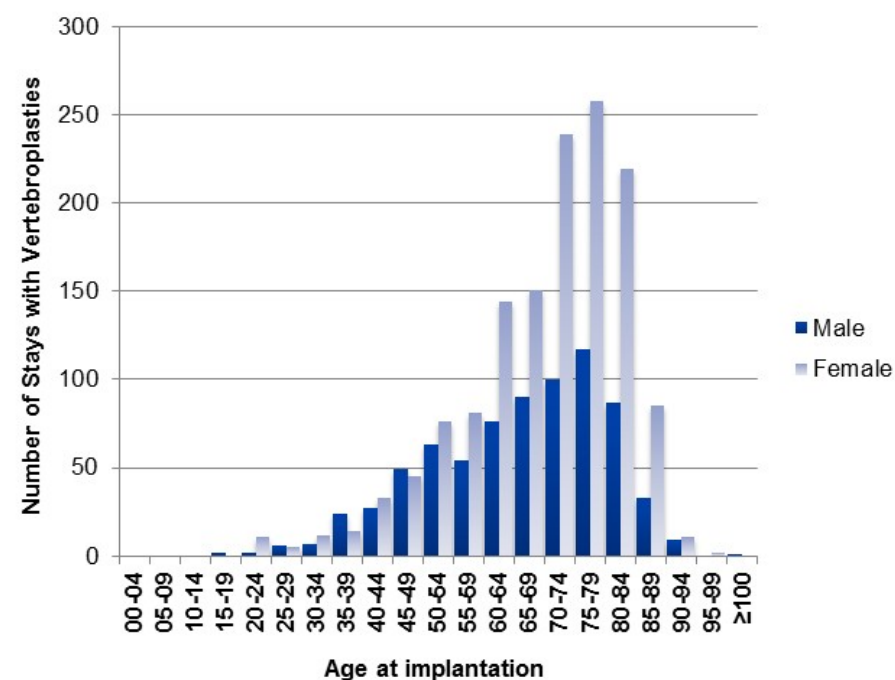
In the RHM – MZG, all hospitalisations during which at least one procedure was performed can be identified, but the number of times a procedure was performed, in the present matter the number of levels treated, is not a reliable variable and cannot be used. Hence, multi-level procedures are always counted once and this figure should have been in the same order of magnitude than the number of kits sold.

We roughly estimate the recent yearly number of vertebroplasties in Belgium at approximately five hundred.

3.2.3 Characteristics of patients undergoing a vertebroplasty

Based on the hospitalisations recorded in the RHM – MZG database for the period 2008-2011, 65% of the 2133 patients who underwent a vertebroplasty were female. On average, patients were 68 years old (SD: 13.8, median: 71, range: 15-100). Figure 4 shows the age distribution per 5-year category per gender.

Figure 4 – Vertebroplasties: Age distribution per gender



Source: RHM – MZG 2008-2011.

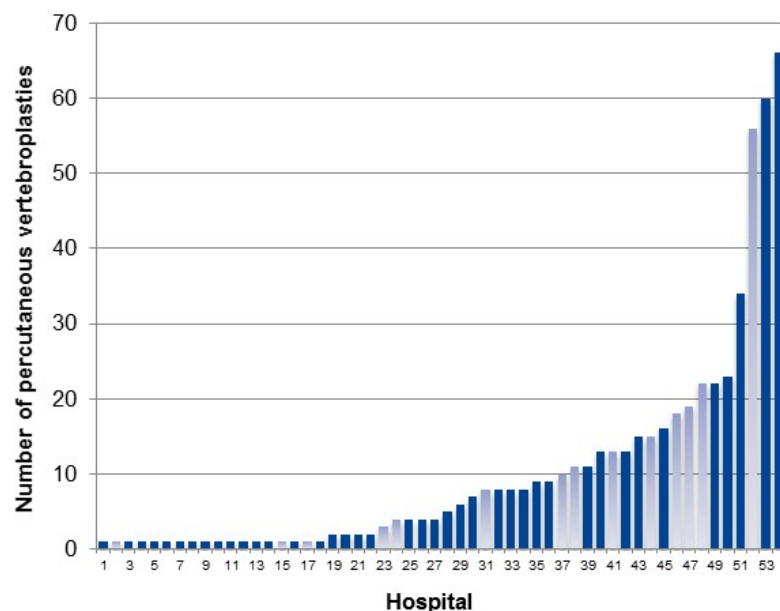
Most of the patients (91%) spent at least one night at the hospital. The mean length of stay amounted to 11.3 days (SD: 21.6, median: 4, range 0-326). Note that 24 patients (1.1%) died at the hospital (these patients were 70.4 years old on average, minimum 50 and maximum 93 years).



The most frequent principal diagnosis causing the admission was *Other disorders of bone and cartilage* (51.9% of the hospitalisations), followed by *Fracture of vertebral column without mention of spinal cord injury* (26.5%) or *Intervertebral disc disorder* (5.2%). Inside the first rather nonspecific category, most of the cases suffered from *Pathologic fracture of vertebrae* (49.1% of all hospitalisations). The top 10 of the principal diagnosis in 3-digit ICD-9-CM codes, as well as the details of the first code split into 5-digit codes can be found in appendix.

3.2.4 Geographic variation of vertebroplasties

Figure 5 – Number of vertebroplasties per hospital performing this technique in 2011



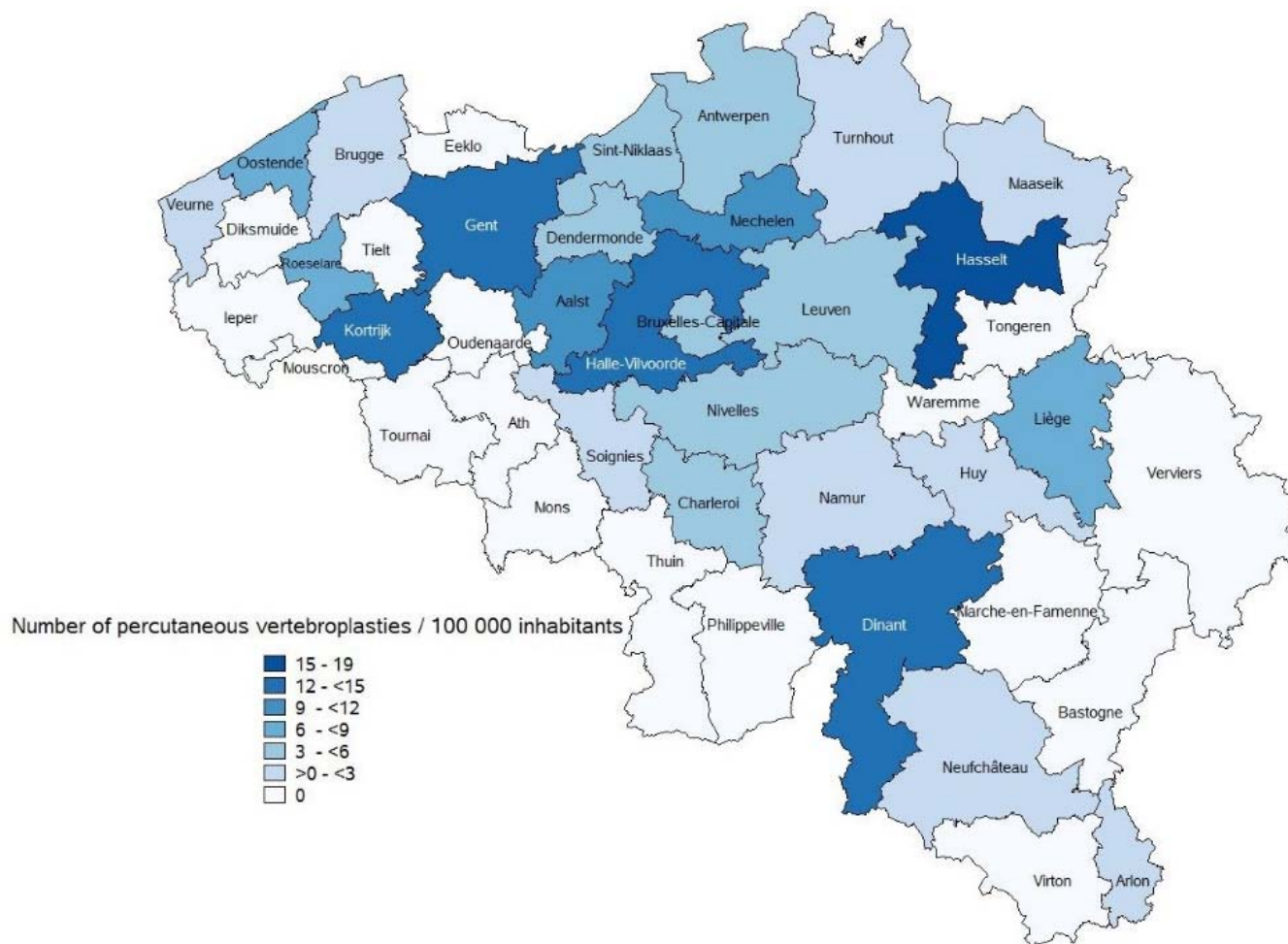
Source: RHM – MZG 2011 - Academic hospitals and hospitals with university beds are in light shade.

Fifty-four out of the 105 Belgian acute hospitals performed at least one of the 550 vertebroplasties recorded in 2011. As shown on the bar chart (Figure 5), the number of procedures performed ranged from 1 to 66, with a yearly median of 4.5 procedures. The mean number was 10.2 (SD: 14.4). Most hospitals (n=36, 67%) did not perform 10 procedures, and 18 amongst them (33.3%) performed only one procedure per year. Vertebroplasty is not concentrated in academic hospitals nor in hospitals with university beds that are shown in light shade in the bar chart.

The highest number of vertebroplasties performed in 2011 per district (76) took place in the district of Hasselt. The second highest number was found in the district of Halle-Vilvoorde.

Figure 6 presents the number of procedures performed in the hospitals of a district per 100 000 inhabitants. With 76 vertebroplasties and more than 400 000 inhabitants, Hasselt counted 18.5 procedures per 100 000 inhabitants. Fifteen vertebroplasties were performed in Dinant, which is not amongst the highest numbers but the district appears in dark on the map (14 procedures per 100 000), due to its low population density.

Figure 6 – Number of vertebroplasties performed in 2011 per hospital district ('arrondissement')



Source: RHM-MZG 2008-2011 - Population DGSIE – ADSEI 1 January 2011.



3.2.5 Number of kyphoplasties performed in Belgium

Table 3 – Number of kyphoplasties by data source

Source	Type of data	2008	2009	2010	2011	2012	2013
UNAMEC	Kits Sales	-	-	-	-	750	750
RHM – MZG	Hospitalisations with kyphoplasty coded in ICD-9-CM, discharged in the year	219	655	665	813	-	-
INAMI RIZIV	Reimbursed number						
	• Balloon kyphoplasty procedures*	196	792	829	1025	1034	-
	• Material kits	147	643	671	794	810	-
	• Cement units	164	723	702	903	950	-

*: level.

As for the vertebroplasty but to a lesser extent, the annual number of procedures recorded in the RHM – MZG is a bit higher than the annual number of sales, which can be explained by non UNAMEC distributors (Table 3).

Moreover, the number of hospitalisations with kyphoplasty in the RHM – MZG is similar to the number of kits reimbursed. This tends to validate the RHM – MZG registration for kyphoplasty. The number of procedures performed and reimbursed is obviously higher than the number of kits reimbursed as the procedure can be billed twice in case of multi-level procedures. In such cases, balloons used in a first level and still intact can be reused in a second level.

We roughly estimate the recent yearly number of kyphoplasties in Belgium at approximately eight hundred on 1000 levels.

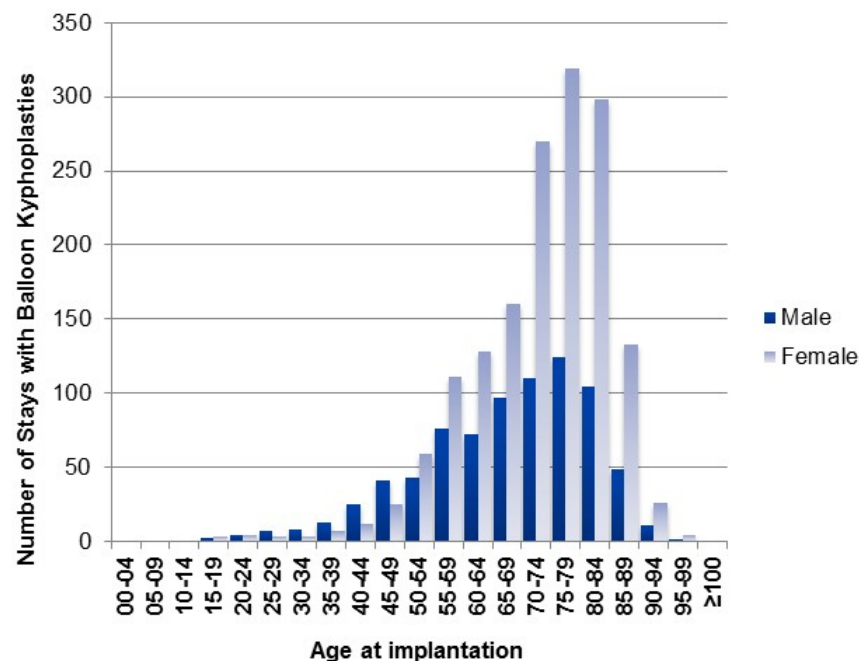
Table 4 – INAMI – RIZIV reimbursed amounts for kyphoplasties (€)

Type of data	2008	2009	2010	2011	2012
Balloon kyphoplasty procedures	55 967	237 976	252 340	312 477	308 770
Material kits	639 498	2 794 009	2 935 537	3 483 070	3 540 213
Cement kits	13 750	61 109	59 332	76 281	80 418
TOTAL	709 216	3 093 094	3 247 209	3 871 828	3 929 401

The reimbursements by the INAMI – RIZIV for kyphoplasty amounted to almost €4 million in 2012 (Table 4). Ninety percent of this amount pertained to the kyphoplasty kits. The reimbursement of these kits was stopped in April 2015.

3.2.6 Characteristics of patients undergoing a kyphoplasty

Based on the hospitalisations recorded in the RHM – MZG database for period 2008-2011, 66.5% of the 2352 patients who underwent a kyphoplasty were women. On average, patients were 70.6 years old (SD: 12.8, median: 73, range: 15-99). Figure 7 shows the age distribution per 5-year category per gender.⁸

**Figure 7 – Kyphoplasties: Age distribution per gender**

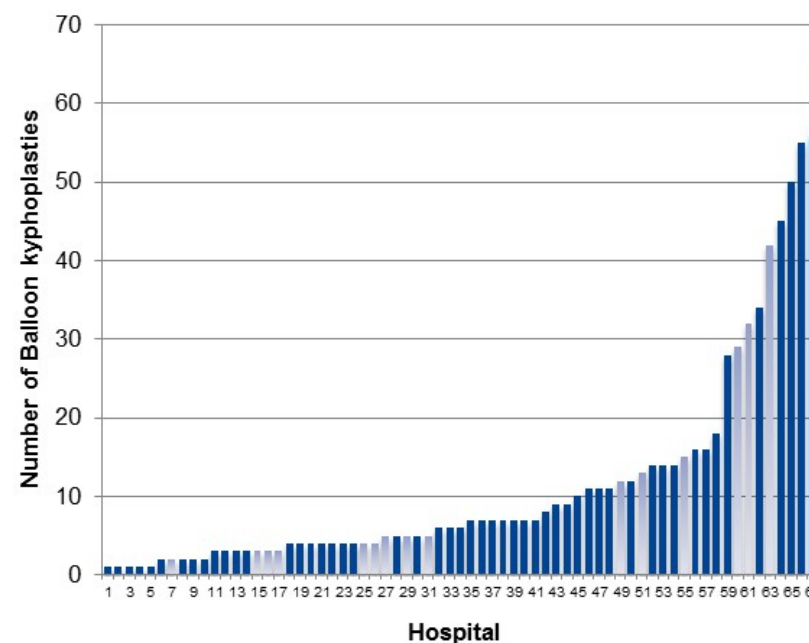
Source: RHM – MZG 2008-2011.

Most of the patients (95%) spent at least one night at the hospital. The mean length of stay amounted to 10.7 days (SD: 19.4, median: 3, range 0-279). Note that 24 patients (1%) died at the hospital (those patients were 80 years old on average, ranging from 48 to 93 year old).

The most frequent principal diagnosis causing the admission was *Other disorders of bone and cartilage* (64% of the hospitalisations), followed by *Fracture of vertebral column without mention of spinal cord injury* (25.9%) or *Multiple myeloma and immunoproliferative neoplasms* (1%). Inside the first rather nonspecific category, most of the cases suffered from *Pathologic fracture of vertebrae* (61.9 % of all hospitalisations). The top 10 of the principal diagnosis in 3-digit ICD-9-CM codes, as well as the details of the first code split into 5-digit codes can be found in appendix.

3.2.7 Geographic variation of kyphoplasties

Sixty-eight out of the 105 Belgian acute hospitals performed at least one of the 813 kyphoplasties recorded in 2011. As shown on the bar chart (Figure 8), the number of annual procedures performed ranged from 1 to 65, with a median of 6.5 procedures. The mean number was 12 (SD: 14.6). Most hospitals (n=44; 64.7%) did not perform 10 procedures, and 5 amongst them (7.4%) performed only one procedure that year. Kyphoplasty is not concentrated in academic hospitals and hospitals with university beds that are depicted in light shade in the bar chart.

Figure 8 – Number of kyphoplasties per hospital performing this technique in 2011

Source: RHM – MZG 2011 - Academic hospitals and hospitals with university beds are in light shade.

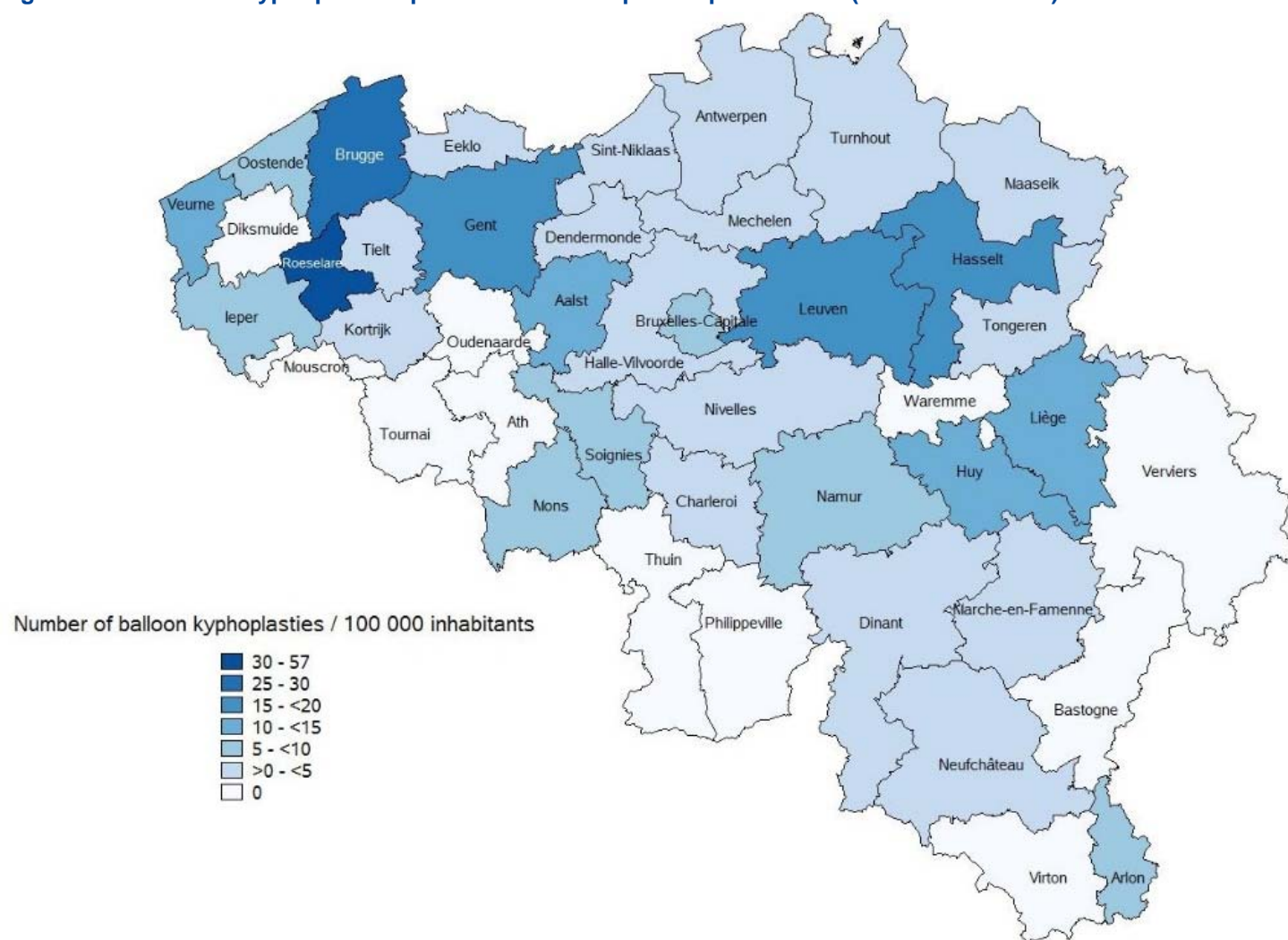


The highest number of kyphoplasty performed per district in 2011 (87) was in the district of Leuven. The second highest number was in the district of Roeselaere (82 kyphoplasties).

Figure 9 presents the number of procedures performed in the hospitals of a district per 100 000 inhabitants. With 82 kyphoplasties and only 146 000 inhabitants, the district of Roeselaere counted 56.2 procedures per 100 000 inhabitants. Seventy-six kyphoplasties were performed in Brugge, which is not amongst the highest numbers but the district appears in dark on the map (27.4 procedures per 100 000), due to its moderate population density.

3.3 Key points on the Belgian situation

- **Six manufacturers sell almost all vertebroplasty and/or kyphoplasty systems (mostly both) on the Belgian market.**
- **From April 1st 2015, the material for kyphoplasty, which costs approximatively €4000, is not reimbursed anymore for budgetary reasons. Cement is still reimbursed (€82) per level (maximum 2 levels). Medical fees for a kyphoplasty amount to €305. Only the cement can be billed (€82) in case of a vertebroplasty, a kit being sold at approximately €500.**
- **There are about 500 vertebroplasties and 800 kyphoplasties performed in Belgium each year, almost never in one-day hospitalisation. Patients undergoing these procedures are predominantly women (on average 65%) and with an average age of 70 years.**

**Figure 9 – Number of kyphoplasties performed in 2011 per hospital district ('arrondissement')**

Source: RHM-MZG 2008-2011 - Population DGSIE-ADSEI 1 January 2011.



4 METHODS FOR THE ASSESSMENT OF CLINICAL EFFECTIVENESS AND SAFETY

4.1 Introduction

This report is an update of a previous KCE report from 2006.⁹ At that moment the evidence base for both techniques was weak and no completed RCTs were available. For vertebroplasty the report concluded that the efficacy for treating VCF was uncertain at that time. Only one non-randomised controlled trial showed equivalence between vertebroplasty and conservative treatment. There were also some safety concerns about cement leakage after vertebroplasty.

For kyphoplasty there was low quality evidence on the efficacy for the treatment of non-traumatic vertebral compression fractures from non-randomised clinical trials and 1 month results from an ongoing RCT indicating that kyphoplasty reduced pain scores compared to conventional therapy. Long-term effectiveness was still uncertain. Based on a meta-analysis of case series, balloon kyphoplasty appeared to be relatively safe with apparently less cement leakage than vertebroplasty.

Information for the economic evaluation of both techniques was lacking at the time but it was reported that material for kyphoplasty was five to ten times more expensive than for vertebroplasty.

4.2 Methods

A systematic search for HTA reports, systematic reviews and randomised controlled trials on vertebral augmentation techniques vs. non-surgical management of VCF was carried out in the Medline, Embase and Cochrane databases (CDSR, DARE, HTA, Economic Evaluations and CENTRAL) on November 19th 2014. This search was limited to publications from 2006 and onwards. Additionally, we consulted the EUnetHTA POP^b and INAHTA databases and the ClinicalTrials.gov database (search words 'vertebroplasty' OR 'kyphoplasty'). Additional references were obtained

through grey literature or hand-searching through the references in selected publications.

Details on the Patient/Intervention/Comparator/Outcomes questions (PICO) and the search strategies are in the appendix.

4.3 Search results

From the search, and based on title and abstract, we retrieved and reviewed in detail fourteen recent (since 2010) systematic reviews.^{8, 10-22} Most reviews included evidence on osteoporotic VCF only but there was also one on VCF due to malignancies.¹¹

Thirteen original RCTs (seventeen publications) were retrieved and reviewed.²³⁻³⁹

From the same search we also retrieved and reviewed two recent meta-analyses.^{40, 41} While writing, additional full-text articles were retrieved when needed.

The search through the EUnetHTA POP database and the INAHTA database showed no current new projects but led to two finished projects with HTA reports published in 2014 (one unpublished at the moment of the search but the draft report was kindly obtained from the investigators; the report was officially published during our research).^{8, 42}

The additional retrieval of clinical trials through the clinicaltrials.gov in November 2014 yielded 31 additional ongoing trials within the scope of our research but none with data available so far. Thirteen trials were listed as completed but with no results available in the database or with no identified published results, while the others were either still recruiting, withdrawn or suspended. Unfortunately, this situation of unreported results from registered RCTs is not uncommon as was recently pointed out in a special article in the NEJM.⁴³

One specific blinded RCT comparing vertebroplasty to a sham intervention (VERTOS IV) was listed in clinicaltrials.gov as completed in November 2014. From the investigators (WJ van Rooij, personal communication) we understood that by November 2014 all patients were indeed included and

^b POP: Planned and Ongoing Projects Database of projects by EUnetHTA members



that 12 months follow-up and analysis can be anticipated by the end of 2015 at the earliest.^c

4.4 Sources for the evidence

4.4.1 Osteoporotic VCF

Systematic reviews and meta-analyses

After critical analysis of the selected systematic reviews we decided to base our description of the effectiveness and safety mainly on the results and conclusions of the most recent and most comprehensive systematic review from the School of Health and Related Research (SchHARR) by Stevenson et al. in 2014.⁸ This review includes nine RCTs on vertebroplasty and/or kyphoplasty and was the scientific basis for a NICE technology appraisal guidance 279, published in 2013.⁴⁵ Wherever possible, we performed additional meta-analyses to describe the overall effects.

The other systematic reviews are older and include either less RCTs,^{12-18, 20, 21, 41} and include non-randomised trials.^{10, 17, 19, 22, 42}

A very recent non-systematic review by Papanastassiou et al. includes 21 randomised and non-randomised studies,¹⁰ but includes only seven of the nine RCTs included in the SchHARR review excluding the RCTs from Blasco and Farrokhi^{26, 27} for unexplained reasons. Apart from the non-randomised studies this review includes two additional RCTs: one compares three different augmentation techniques (n=59),³⁸ while the other focuses on cement leak comparisons between vertebroplasty and kyphoplasty (n=77).³⁹ Both trials are informative for safety aspects only.

In 2013 a meta-analysis of six of the trials included in the SchHARR review was published by Anderson et al.⁴¹ However, for some outcomes where different measurement instruments were used this raises a problem. For example for HRQoL results obtained with EQ-5D and QUALEFFO were pooled using a standardised mean difference metric. Since these instruments are not intended to measure the same outcomes the results

should be interpreted with caution. However, we will mention these results where appropriate.

The SchHARR review

The SchHARR review we use includes nine RCTs on the treatment of osteoporotic VCF (also see Table 5):

- two blinded RCTs (n=78 and 131, total n=209) comparing vertebroplasty to a sham procedure (operative placebo with local anaesthesia, – OPLA) and optimal pain management;^{23, 25}
- five non-blinded RCTs (n= 82, 46, 202, 125 and 50, total n=505) comparing vertebroplasty with optimal pain management;²⁶⁻³¹
- one non-blinded RCT (n=300) comparing balloon kyphoplasty with optimal pain management;³²⁻³⁴
- one non-blinded RCT (n=100) comparing balloon kyphoplasty with vertebroplasty³⁵

Eight additional relevant but ongoing RCTs were identified in this SchHARR systematic review. In November 2014 we found published results for only one of these trials published in October 2014. This KAVIAR trial compares balloon kyphoplasty with vertebroplasty and was terminated early because of low recruitment and early withdrawals (n=381).³⁶ This trial is added to our description of the evidence on the clinical effectiveness.

4.4.2 VCF unrelated to osteoporosis

There is scarce literature on clinical effectiveness and safety regarding VCF that are not related to osteoporosis. Only one RCT was identified on kyphoplasty in cancer patients (CAFE trial).³⁷ A recent non-systematic review of this RCT and observational evidence was published by Papanastassiou et al.¹¹ We excluded the MSAC review from 2011 on VCF related to vertebral tumours because no RCTs were identified at that moment.¹⁴

^c VERTOS and VERTOS II are included in our selection, while VERTOS III was not a trial but an observational study on pain in conservatively treated patients with VCF.⁴⁴



Table 5 – Overview of clinical trials included or identified in recent systematic reviews

RCT	Year	Int/Control	Tech	Comp	SchARR 2014 ⁸	Pos Statm. 2014 ¹⁷	Anderson 2013 ⁴¹	IECS 2011 ¹⁵	Staples 2011 ⁴⁰	AAOS 2010 ¹⁹	Description
Vertebroplasty vs non-surgical management (blinded)											
Buchbinder ^{23, 24}	2009	38/40	PVP	OPLA (Sham)	Y	Y	Y	Y	Y	Y	Blinded RCT
INVEST ²⁵	2009	68/63	PVP	OPLA (Sham)	Y	Y	Y	Y	Y	Y	Blinded RCT
VERTOS IV		?/?	PVP	OPLA (Sham)	I						Blinded RCT Enrolment completed but no results available
Vertebroplasty vs non-surgical management (non-blinded)											
Diamond ⁴⁶	2006	88/38	PVP	OPM						Y	Non randomised
VERTOS ³¹	2007	18/16	PVP	OPM	Y		Y	Y		Y	RCT
Rousing ^{29, 30}	2009	25/24	PVP	OPM	Y	Y	excluded for missing baseline data	Y		Y	RCT
VERTOS II ²⁸	2010	101/101	PVP	OPM	Y	Y	Y				RCT
Farrokhi ²⁷	2011	40/42	PVP	OPM	Y	Y	Y				RCT
Blasco ²⁶	2012	64/61	PVP	OPM	Y						RCT
Kyphoplasty vs non-surgical management (non-blinded)											
Grafe ⁴⁷	2005	40/20	BKP	OPM						Y	Non randomised
FREE ^{32, 33}	2009/2011	149/151	BKP	OPM	Y	Y	Y			Y	RCT
Kyphoplasty vs. vertebroplasty (non-blinded)											
Grohs ⁴⁸	2005	28/23	BKP	PVP						Y	Non randomised
De Negri ⁴⁹	2007	11/10	BKP	PVP						Y	Non randomised
Liu ³⁵	2010	50/50	BKP	PVP	Y					Y	RCT
KAVIAR ³⁶	2014	191/190	BKP	PVP	I						RCT
Kyphoplasty in cancer related VCF (non-blinded)											
CAFE ³⁷	2011	70/64	BKP	OPM							RCT in Cancer Patients

Int: Intervention, Comp: Comparator, PVP: Vertebroplasty, BKP: Balloon Kyphoplasty, Stent: Stenting kyphoplasty, OPM: optimal pain management, Y: included, I: Identified
OPLA: Operative placebo with local anaesthesia.



4.5 Reported outcome measures in RCTs

Most RCTs measure several of these outcomes but often use different measurement instruments, with different scales. Therefore, these measurements are difficult to compare. Often used instruments are enumerated below (see also the abbreviations list for detail).

- Health-Related Quality of Life (HRQoL):
 - EuroQol 5 dimensions (EQ-5D);^d
 - QUALEFFO;
 - Short Form 36 (SF-36);^e
 - AQoL;
 - Dallas Pain Questionnaire (DPQ);
 - MMSE.
- Back-specific functional status/mobility:
 - Roland-Morris Disability Questionnaire (RDQ);^f
 - Barthel Index;
 - Oswestry Disability Index (ODI);
 - Study of Osteoporotic Fractures - Activities of Daily Living (SOF-ADL).
- Pain and analgesics use:
 - Bodily pain subscale of SF-36;^g
 - Visual Analogue Scale (VAS);^h
 - Numeric Rating Scale (NRS);
 - Analgesics use.
- Vertebral body height and angular deformity:
 - measured at different parts of the vertebra (posterior, middle, anterior);
 - absolute restoration in mm, per cent restoration relative to pre-operative height, per cent restoration relative to lost vertebral height (measured or estimated), per cent restoration relative to referent vertebral height;
 - angular deformity: kyphotic angle, sagittal index, sagittal balance.
- Incidence of vertebral fractures in follow-up:
 - progression of treated vertebra (loss of vertebral height);
 - symptomatic (clinical) or asymptomatic (morphometric);
 - adjacent or non adjacent vertebra.
- Mortality:
 - short-term;
 - medium-term.
- Safety:
 - complications related to insertion of a needle;
 - complications related to leakage of bone cement;

^d The estimated MCID for people with back pain is 0.08.⁸

^e Copay et al. have suggested a MCID of 4.9 points specifically for the PCS, while Angst et al.¹⁵⁶ have suggested a MCID for improvement of 2.0 in the PCS, 7.8 in the bodily pain subscale, and 3.3 in the physical function subscale. No MCID has been identified for the overall SF-36 utility score.⁸

^f The MCID for the RDQ varies according to the level of disability of the patients, from 1 to 2 points in patients with little disability to 7-8 points in patients reporting high levels of disability, and 5 points in uncategorised patients.⁸

^g An absolute cut-off value has been suggested for the MCID of 3 points overall or 2 points in populations attending hospital back pain clinics.⁸

^h Ostelo et al. have proposed an absolute cut-off value for the MCID of 15 on a 100-unit VAS, with a relative cut-off value of a 30% improvement from baseline. However, DeLoach et al. suggest that, because of the imprecision found in the immediate postoperative period, the MCID in that period should be 20 out of 100 units. Ostelo et al. also proposed that, when an 11-point numeric rating scale is used for low back pain, the absolute cut-off value for the MCID should be 2 points, again with a relative cut-off value of a 30% improvement from baseline. However, Copay et al. suggest a MCID of 1.2 points for back pain.⁸



- complications related to balloon rupture in kyphoplasty;
- complications related to systemic reactions to bone cement;
- complications related to procedure (positioning, anaesthesia...);
- hazards for health-care professionals (radiation, materials...).

A more detailed description of those outcome measures can be found in the SchHARR review.⁸

4.6 Follow-up time

In the SchHARR review outcomes are given as short-, medium- and long-term outcomes. Short-term outcomes in this review corresponds to outcomes measured at or before 3 weeks, medium-term outcomes are measured between 1 month and 6 months and long-term outcomes are measured at 12 months or later. In the description, tables and figures we use the same classification.

4.7 Additional meta-analyses

In addition to the data from the SchHARR review we perform additional meta-analyses where possible. For all meta-analyses a random effects model is used because of the large heterogeneity of the studies included.

4.8 Quality of the evidence

More details on the risk of bias assessment of individual RCTs and on the quality of the SchHARR systematic review can be found in the appendix.

No formal analysis of the quality of the evidence was made in this rapid review. Due to the non-blinded nature of most of the studies, the observed heterogeneity and the conflicting results (see chapter 5) we judged the quality of the body of evidence as low quality for the VCF related to osteoporosis and very low quality for the VCF related to malignancies. Consequently, we did not provide a GRADE score for each outcome separately. Besides, if there are very severe problems for any factor of the GRADE scoring tool, RCT evidence may fall by two levels due to that factor alone.⁵⁰

5 CLINICAL EFFECTIVENESS

5.1 Vertebroplasty compared to optimal pain management for osteoporotic VCF

5.1.1 Basic RCT characteristics

- Two blinded RCTs (with sham intervention and blinded for patients and study personnel performing the outcome assessment).²³⁻²⁵
- Five non-blinded RCTs.²⁶⁻³¹
- Inclusion criteria: one or more VCF. Three of the RCTs defined osteoporosis based on measured bone mineral density (BMD) while the other four assumed the presence of osteoporosis from the presence of VCF in the absence of other known aetiology.
- Other baseline characteristics of those trials can be found in tables 4 and 5 and in appendix 9 from the SchHARR report.⁸ Those other characteristics are only detailed when relevant for the results.

5.1.2 Health-Related Quality of Life

All included RCTs provide data on HRQoL using either EQ-5D or QUALEFFO, except the study by Farrokhi et al. that uses the functional ODI index as a proxy for HRQoL. Not the same outcome measures are used across studies and sometimes several measurement instruments are used in one study: three RCTs provide HRQoL outcome data based on the generic EQ-5D, four RCTs use the QUALEFFO disease specific HRQoL measure. Two studies use the SF-36 questionnaire, one the DPQ and one the AQoL.

Because of this heterogeneity of outcome measures no standard meta-analysis can be performed on all studies combined. However, Anderson et al.⁴¹ recently performed a meta-analysis using a random-effects model and the standardized mean difference technique (Hedges's g) on four of these vertebroplasty studies and mixing EQ-5D and QUALEFFO outcomes. Moreover, they also include the FREE study comparing kyphoplasty to non-surgical management.^{32, 33} They report, overall, a statistically significant HRQoL result in favour of vertebroplasty (standardized mean difference: 0.39, 95% CI: 0.16 to 0.62 at 2-12 weeks and 0.33, 95% CI: 0.16 to 0.51 at



26 weeks and more). However, these results should be interpreted with caution because the different outcome measures are intended to measure different things. Therefore, we perform separate meta-analyses for both outcomes and exclude the FREE study.

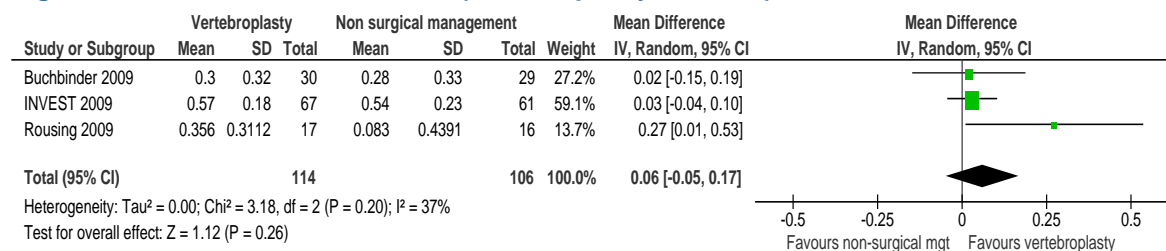
5.1.2.1 EQ-5D

Three of the RCTs report EQ-5D baseline and follow-up data. In two of them (Buchbinder and Rousing) relevant data were only collected for part of the participants.

The VERTOS II study only reports baseline EQ-5D data but no outcome assessment.

At baseline the EQ-5D scores for the two blinded studies (Buchbinder and INVEST) are balanced. In the Rousing study, however, the baseline score is in favour of the vertebroplasty group ($p=0.047$, own calculation, see Figure 10).

Figure 10 – Baseline EQ-5D scores (vertebroplasty vs. OPM)



In all studies EQ-5D improves over time in both groups (a higher EQ-5D score is an improvement). The two blinded RCTs (Buchbinder and INVEST) find no significant difference from baseline in the EQ-5D between vertebroplasty and OPM in terms of short- or medium-term outcomes. An important limitation is that the American trial (INVEST) reports outcomes only up to 1 month (after 1 month blinding was broken and cross-over allowed), while the Australian trial (Buchbinder) originally reports outcomes up to 6 months. Recently, and not included in the SchARR review, additional

12 and 24 months outcome data were published for this last trial, confirming this absence of a significant difference in the longer term.²⁴

A meta-analysis reanalysing the 1 month outcome data of these two blinded studies using individual patient data (IPD) shows a non-significant adjusted EQ-5D difference from baseline of 0.03 (95% CI: - 0.02 to + 0.08) in favour of vertebroplasty.⁴⁰ A subgroup analysis in this meta-analysis based on pain severity at baseline (less than 8 or 8 and more on a 10 point or 10 cm scale)



and duration of pain at baseline (up to 6 weeks or more than 6 weeks) show no different EQ-5D results for these subgroups.

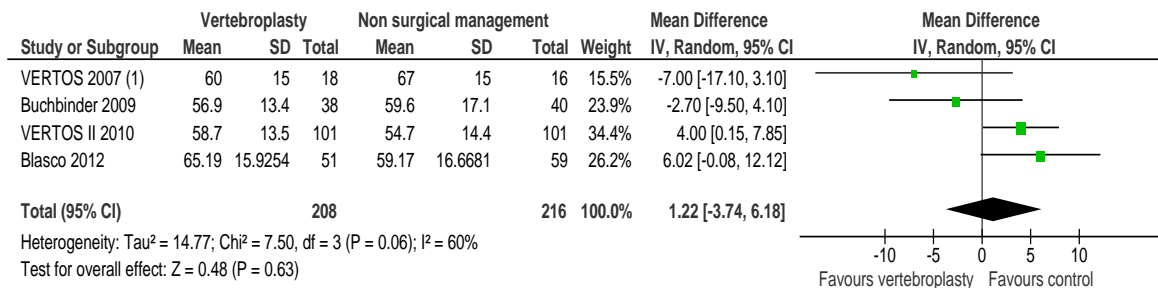
In the study by Rousing et al. the average EQ-5D at baseline, 3 and 12 months is always higher in the vertebroplasty group, but the difference existing at baseline decreases during follow-up in favour of the control group.^{29, 30} The authors warn that the groups are not comparable regarding EQ-5D because of the large difference at baseline.^{29, 30}

5.1.2.2 QUALEFFO

In all studies QUALEFFO improves over time in both groups (a lower QUALEFFO score is an improvement). Four studies assess HRQoL using QUALEFFO. At baseline there are no extreme imbalances, although in VERTOS II the baseline assessment only just favours controls ($p=0.04$, own calculation, see Figure 11). No MCID has been proposed for the QUALEFFO, therefore the clinical significance of the few observed differences is not clear.⁸

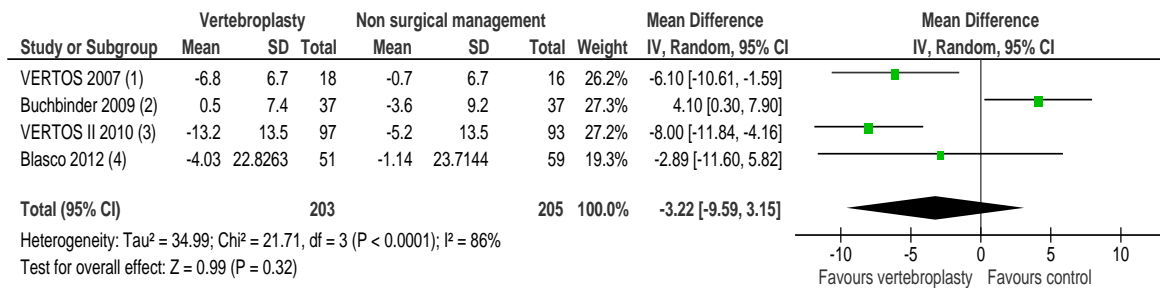
In the short term (1 or 2 weeks) the QUALEFFO change from baseline is statistically significant in favour of vertebroplasty in the two VERTOS studies but not in the two other studies. QUALEFFO difference from baseline at 6 and 12 months is only in favour of vertebroplasty in the VERTOS II study but the between group difference decreases over time since inclusion. The pooled estimate does not reach statistical significance at any of the time points.

Figure 11 – Baseline QUALEFFO scores (vertebroplasty vs. OPM)

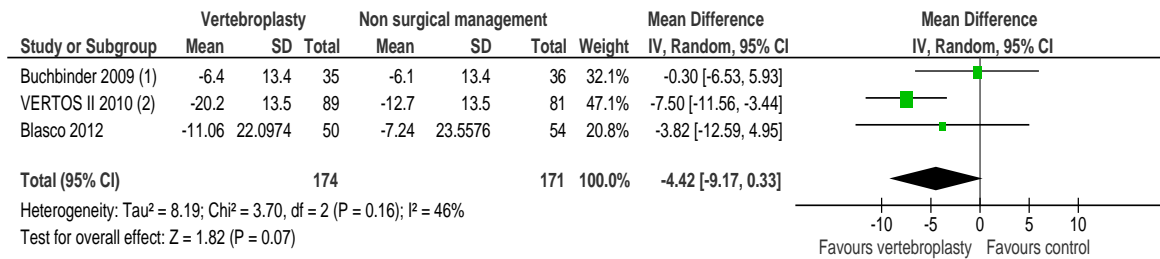


Footnotes

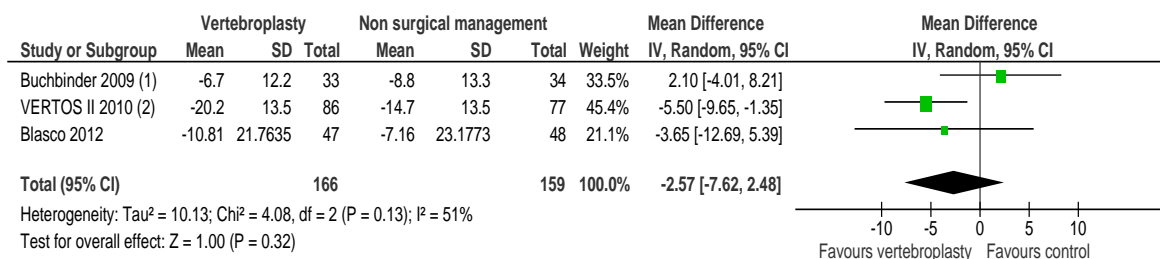
(1) SD estimated

**Figure 12 – Short-term QUALEFFO mean difference from baseline (vertebroplasty vs. OPM)**Footnotes

- (1) At 2 weeks (SD estimated)
- (2) At 1 week (signs inverted from article)
- (3) At 1 week (data estimated from figure, SD estimated)
- (4) At 2 weeks

Figure 13 – QUALEFFO mean difference from baseline at 6 months (vertebroplasty vs. OPM)Footnotes

- (1) Signs inverted from article
- (2) Estimated from figure, SD estimated

**Figure 14 – QUALEFFO mean difference from baseline at 12 months (vertebroplasty vs. OPM)****Footnotes**

(1) Signs inverted from article

(2) Estimated from figure, SD estimated

5.1.2.3 Other indicators for HRQoL

SF-36 (PCS and MCS scores) is measured in two studies (INVEST and Rousing). One study additionally uses the Dallas Pain Questionnaire (Rousing) and Buchbinder also uses the AQuoL. These indicators show no fundamental difference from previously reported results.

For further details the reader can consult the original SchARR report.⁸

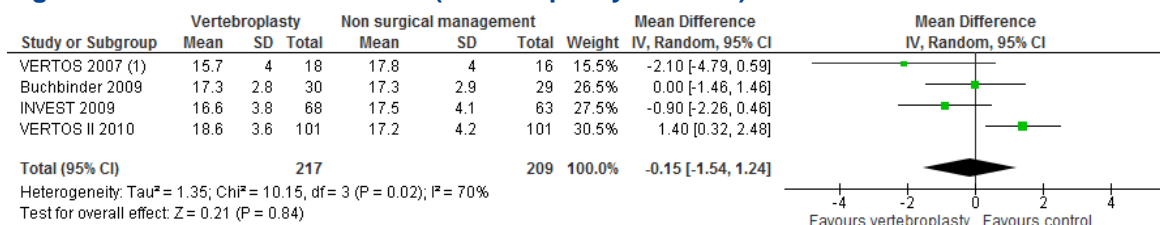
5.1.3 Back-specific functional status and mobility

All RCTs report some measure of back-specific functional status or mobility. However, here again they use different outcome measures. Four studies (Buchbinder, INVEST, VERTOS and VERTOS II) use Roland-Morris

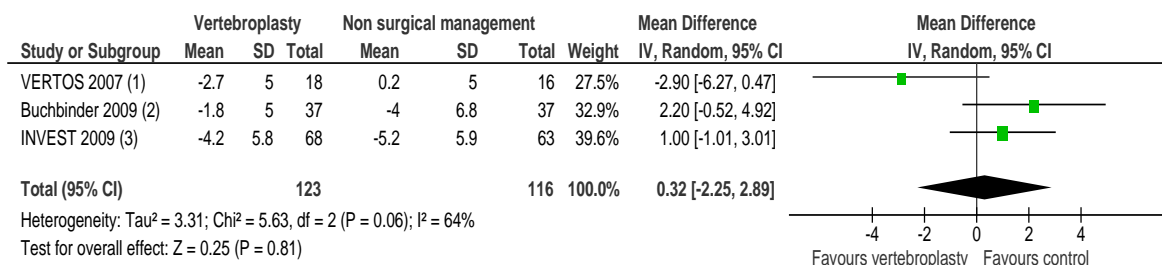
Disability Questionnaire (RDQ) but in different versions, making comparisons difficult. In most studies RDQ improves over time in both groups (a lower RDQ score is an improvement).

Apart from the VERTOS II study favouring control ($p=0.01$, own calculation, see Figure 15) there appear to be no major imbalances at baseline (higher numbers reflect more disability).

Three of those RCTs (Buchbinder, INVEST and VERTOS) report short-term outcomes at 1 or 2 weeks. In terms of between group differences from baseline no significant differences are reported. In the VERTOS II trial the graph in the manuscript indicates an outcome in favour of the vertebroplasty group but this is not quantified.

Figure 15 – Baseline RDQ scores (vertebroplasty vs. OPM)**Footnotes**

(1) SD estimated

**Figure 16 – Short-term RDQ mean difference from baseline (vertebroplasty vs. OPM)****Footnotes**

(1) At 2 weeks

(2) At 1 week (sign inversed)

(3) At 2 weeks

Medium- and long-term outcomes (1 month up to 24 months) also give mixed results. The two blinded RCTs report no significant between group differences and also the meta-analysis at 1 month indicates no significant differences.⁴⁰ The VERTOS II trial, however, reports a statistically significant difference at 12 months favouring vertebroplasty ($p < 0.0001$) but this is again not quantified and its clinical importance is unclear.

Other, non-blinded studies, use the ODI, the Barthel Index, the SOF-ADL and other indicators and report mixed results. A few RCTs report some statistically significant between groups differences favouring vertebroplasty at some specific moment of follow-up.^{27, 30}

For full details the reader should consult the original SchARR report.⁸

5.1.4 Pain and analgesic use

5.1.4.1 Visual Analogue Scale and Numeric Rating Scale (VAS and NRS)

All RCTs report pain measured on either a VAS (10 cm) or a NRS scale (0-10) with higher scores indicating more severe pain. Pain improves over time in both groups (a lower VAS or NRS score is an improvement).

It is not always clear from the manuscripts which of both scales was used although the majority of studies apparently used a NRS scale even when they call it VAS (for example when used over the telephone). We report all

pain scores on a 0-10 scale (either NRS or VAS). Since both scales are intended to measure the same outcome we added meta-analyses combining all the reported outcomes.

The periods covered by the questions are heterogeneous: average pain over the previous 24 hours, during the first month after the intervention, over the previous week or undefined. The data were collected at baseline and at various moments of follow-up.

In the pooled estimate pain scores are not significantly different at baseline. In two of the included studies, however, the scores at baseline were statistically significant different: 1.2 lower mean pain score in the control group in the Farrokhi study and 1.3 higher in the control group in the Rousing study (see Figure 17).

The two blinded studies (Buchbinder and INVEST) find no significant differences between treatment groups at any time point. Also the meta-analysis of the two blinded studies does not find a statistically significant difference in 1 month pain scores,⁴⁰ and the subgroup analysis (pain below or above 8 and pain duration below or above 6 weeks) does not show different results in those outcomes. The 12 and 24 months follow-up results of the Buchbinder trial also do not show statistically significant differences in pain scores.²⁴



In the short term, two out of four of the non-blinded studies (VERTOS II and Farokhi) report statistically significant different changes from baseline in favour of vertebroplasty (see Figure 18).

In the medium and long term statistically significant differences in favour of vertebroplasty are found in the same two studies but Rousing reports a difference in favour of the control group at 6 months. In the Blasco trial a statistically significant change from baseline is only reported at two months (data not shown) favouring vertebroplasty but not at 6 or 12 months.

Figure 18 to Figure 20 show an overall point estimate in favour of vertebroplasty. In general the difference between groups decreases over time.

The pooled difference becomes statistically significant only at 12 months with an estimated difference of -1.26 (-2.4 to -0.1). However, the Farrokhi study allowed for cross-over and at 12 months ten patients from the control

group did have a vertebroplasty, making these data less reliable. A sensitivity analysis eliminating the two studies with a significant imbalance at baseline shows a small reduction of this estimate to -1.1 that is still statistically significant (data not shown). The clinical relevance of this relatively small difference is unclear as there is considerable debate on how to define the Minimal Clinically Important Difference (MCID) as illustrated in section 4.5.

The longitudinal trends show that in most studies there is a steep initial decline in the pain scores in the vertebroplasty groups.⁸ In the two blinded studies the control groups show a similar pattern. In the non-blinded studies, however, there is a more gradual decline in the control groups.

Full results of these pain scores are described on pages 54-59 and in tables 124-126 and the figures in appendix 12 of the SchARR report.⁸

Figure 17 – Baseline pain scores (vertebroplasty vs. OPM)

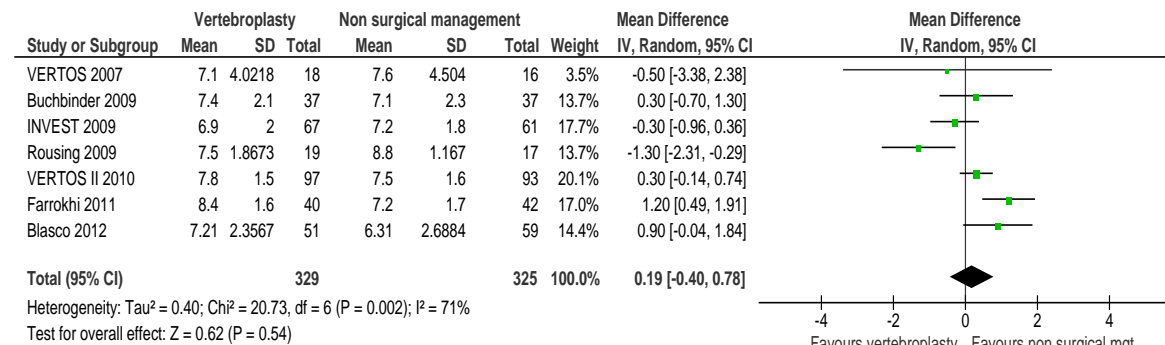
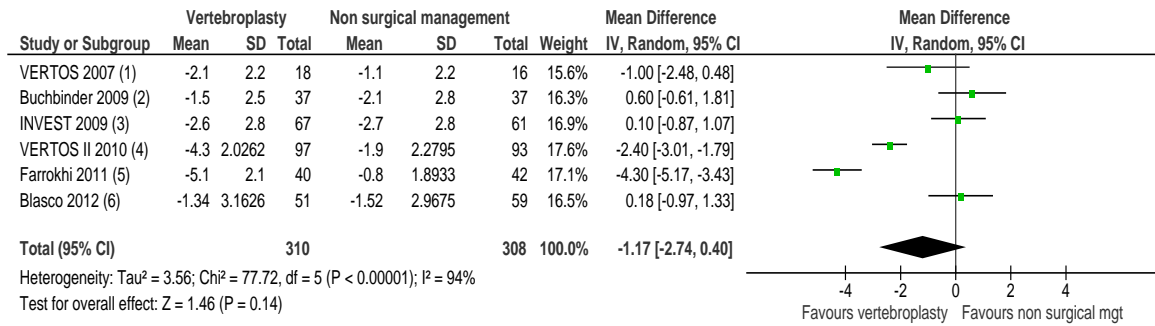




Figure 18 – Short-term pain mean difference from baseline (vertebroplasty vs. OPM)

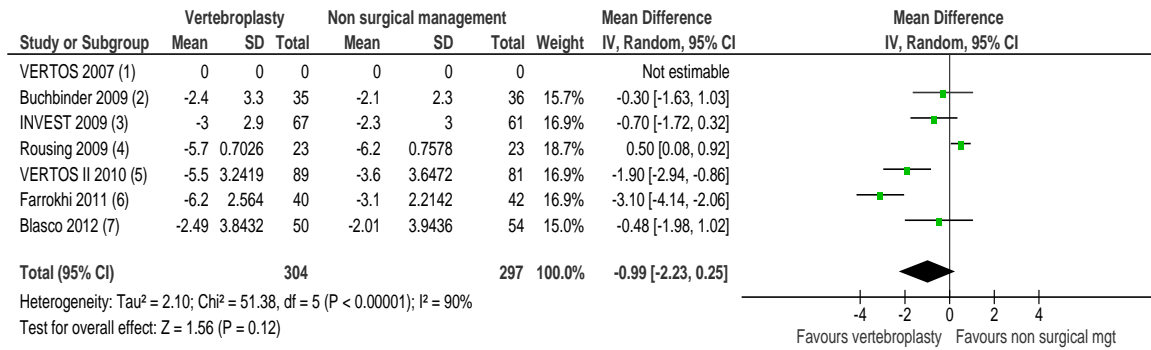


Footnotes

- (1) At 2 weeks (misreported sign corrected)
- (2) At 1 week
- (3) At 1 week
- (4) At 1 week
- (5) At 1 week
- (6) At 2 weeks



Figure 19 – Medium-term pain mean difference from baseline (vertebroplasty vs. OPM)



Footnotes

(1) Only short term data. Cross-over allowed after 2 weeks

(2) At 6 months

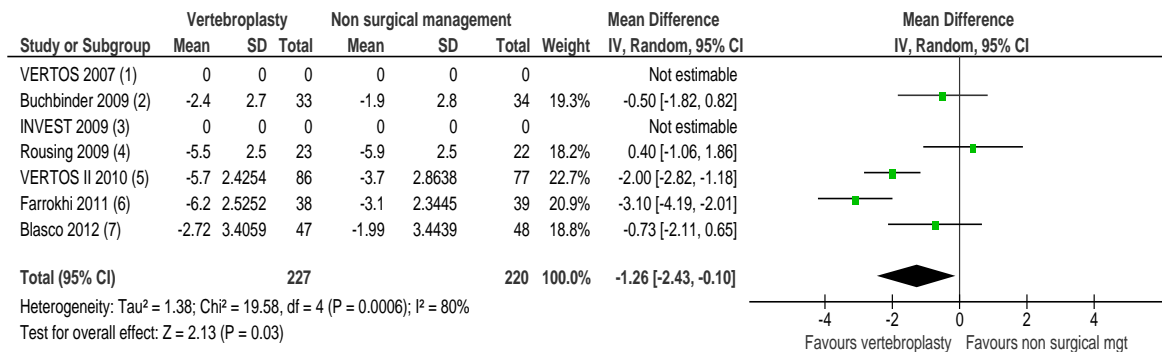
(3) At 1 month (corrected for reported adjustment)

(4) At 3 months

(5) At 6 months

(6) At 6 months, 7 cross overs

(7) At 6 months

**Figure 20 – Long-term mean difference from baseline at 12 months (vertebroplasty vs. OPM)**Footnotes

(1) Only short term data. Cross-over allowed after 2 weeks

(2) At 12 months (Kroon)

(3) No data beyond 1 month

(4) At 12 months (SD estimated)

(5) At 12 months

(6) 12 months, 10 cross-overs < 12 months Data are weird.

(7) At 12 months

5.1.4.2 Other pain scores

Some studies use additional pain scores such as the pain outcomes in terms of QUALEFFO, perceived pain, impact of pain on daily activities, pain frequency, etc. Those results, however, are not directly comparable to VAS or NRS scores but generally go in similar directions. Five of the studies (Blasco, Buchbinder, INVEST, VERTOS and VERTOS II) also report on analgesic use. However, due to the different classifications used those results are hardly comparable. More details can be found in the SchARR report.⁸

5.1.5 Vertebral body height and angular deformity

Two of the RCTs report changes in vertebral body height and/or angular deformity but using different methodologies. Blasco et al. find no significant difference between treatment groups in change in vertebral body height from baseline at 12 months. Farrokhi et al. on the contrary find a significant difference in change of vertebral body height from baseline at 12 months

(+0.9 cm, 95% CI: 0.04 to 1.76), and significantly different angular deformity from baseline at 12 months (mean difference: -13.0° , 95% CI: -13.47 to -12.53). Both differences favour the vertebroplasty group and are sustained through the 36 months of follow-up.

5.1.6 Progression of treated fractures

Only the VERTOS II trial reports that at the last follow-up examination (median 12 months), moderate or severe height loss (Genant classification²) was seen in eleven vertebrae in 12% of the patients in the vertebroplasty group, compared to 39 vertebra in 41% of patients in the control group. This difference is statistically significant.



5.1.7 Key points for vertebroplasty in osteoporotic VCF

- There is low quality evidence on the effectiveness of vertebroplasty compared to non-surgical pain management from two small blinded and five non-blinded RCTs.
 - Health Related Quality of Life (HRQoL):
 - HRQoL: improves both in the vertebroplasty and control groups after inclusion in the study.
 - EQ-5D score: none of the studies reports a statistically significant difference between the intervention and the control groups at any time point after inclusion in the study.
 - QUALEFFO score: at 1 or 2 weeks the difference is statistically significant in favour of vertebroplasty in two non-blinded studies out of four. At 6 and 12 months the score is statistically significant in favour of vertebroplasty in only one non-blinded study out of three, but in this single study the difference from baseline between groups decreases over time.
 - The pooled estimate of these studies is not statistically different between groups at any time point.
 - Back-specific functionality and mobility:
 - RDQ score improves in both the intervention and the control groups after inclusion in the study.
 - The blinded studies report no statistically significant RDQ difference.
 - One non-blinded study report outcomes in favour of vertebroplasty at 2 weeks and 12 months but without quantification.
 - Pain:
 - Pain score improves in both the intervention and control groups after inclusion in the study.
 - The two blinded studies show no statistically significant effect on pain scores at any time point.
- Two non-blinded studies out of four show significant pain reduction in the short term but the difference from baseline between groups diminishes after the short term.
 - The pooled estimate of pain reduction in favour of vertebroplasty is significant at 12 months only but not at earlier time points. The clinical relevance of this difference is unclear.
 - Vertebral body height of the treated vertebra and fracture progression:
 - Results on vertebral body height and angular deformity are conflicting and difficult to compare between the two non-blinded studies due to different methodologies used. One study finds better outcomes for vertebroplasty while the other finds no statistically significant differences.
 - One non-blinded trial reports a statistically significant difference in fracture progression of treated vertebrae in favour of the vertebroplasty group.



5.2 Kyphoplasty compared to optimal pain management for osteoporotic VCF

5.2.1 Basic RCT characteristics

- No blinded RCTs.
- One non-blinded RCT (FREE).³²⁻³⁴
- Inclusion criterion: one or more VCF.
- Other baseline characteristics of this trial can be found in tables 4 and 5 and in appendix 9 from the SchARR report.⁸ Those characteristics are only detailed here when relevant for the results.

5.2.2 Health-Related Quality of Life

5.2.2.1 EQ-5D

EQ-5D data are reported in the FREE trial with a follow-up up to 24 months.³²⁻³⁴ In both groups the HRQoL improves over time but with statistically significant differences favouring kyphoplasty over non-surgical management at different time points of follow-up.

Table 6 – Overview of EQ-5D baseline scores and mean changes from baseline in the FREE study

Time point	Kyphoplasty (SD or CI) Baseline and change from baseline	Control (SD or CI) Baseline and change from baseline	Between group mean difference (95% CI)
Baseline	0.17 (0.37)	0.19 (0.36)	–0.02 (–0.11 to 0.07 own calculation)
1 month	0.42	0.21	0.18 (0.08 to 0.28)*
3 months	0.45 (95% CI: 0.37 to 0.53)	0.34 (95% CI: 0.28 to 0.42)	0.11 (0.00 to 0.22)
6 months	0.46 (95% CI: 0.38 to 0.54)	0.34 (95% CI: 0.26 to 0.42)	0.12 (0.01 to 0.23)
12 months	0.47	0.35	0.12 (0.01 to 0.22)
24 months	0.46	0.37	0.12 (0.06 to 0.18)

Source of data Stevenson et al.⁸ SD: standard deviation; CI: confidence interval
*Adjusted for sex, aetiology, current treatment with corticosteroid, and any bisphosphonate treatment within 12 months before randomisation.

5.2.2.2 Other indicators for HRQoL

Also SF-36 (PCS and MCS scores) is reported in this study and shows similar results. The between group differences decrease steadily from 1 month onwards. At 12 and 24 months no statistically significant difference is observed between the groups.⁸

For full details the reader should consult the original report tables from the SchARR report.⁸

5.2.3 Back-specific functional status and mobility

The FREE study reports that kyphoplasty is associated with statistically significant better outcomes at 1 and 12 months, but not at 24 months. They also report on the use of walking aids, back braces, other aids and physiotherapy. Kyphoplasty is also associated with a statistically significant reduction in the risk of needing walking aids at 1 month but not at 12 months.

Table 7 – Overview of RDQ baseline scores and mean changes from baseline in the FREE study

Time point	Kyphoplasty (SD or CI) Baseline and change from baseline	Control (SD or CI) Baseline and change from baseline	Between group mean difference (95% CI)
Baseline	16.79 (4.95)	17.75 (3.96)	–0.96 (–2.03 to 0.11 own calculation)
1 month	–5.43	–1.43	–4.0 (–5.5 to –2.6)
12 months	–7.18	–5.68	–2.6 (–4.1 to –1.0)*
24 months	–7.00	–6.86	–1.43 (NS)

Source of data Stevenson et al.⁸ SD: standard deviation; CI: confidence interval; NS: Not statistically significant) *Adjusted for sex, aetiology, current treatment with corticosteroid, and any bisphosphonate treatment within 12 months before randomisation.



5.2.4 Pain and analgesic use

The FREE study reports pain on a 0-10 scale, reportedly a VAS scale. This study finds a statistically significant difference in favour of kyphoplasty between groups in short-, medium- and long-term changes from baseline. However, those between group differences decrease with follow-up time.

Table 8 – Overview of pain baseline scores and mean changes from baseline in the FREE study

Time point	Kyphoplasty (SD or CI) Baseline and change from baseline	Control (SD or CI) Baseline and change from baseline	Between group mean difference (95% CI)
Baseline	6.85 (1.57)	6.80 (1.53)	0.05 (-0.32 to 0.42 own calculation)
1 week	NR	NR	-2.2 (-1.6 to -2.8)
1 month	-3.42 (2.47)	-1.47	-1.9 (-2.5 to -1.3)
3 months	-3.97	-2.40	-1.57 (CI not calculable)
6 months	-4.17	-2.56	-1.61 (CI not calculable)
12 months	NR	NR	-0.9 (-1.5 to -0.3)
24 months	NR	NR	-0.80 (-1.4 to -0.20)

Source of data: Stevenson et al.⁸ SD: standard deviation; CI: confidence interval; NR: Not reported.

5.2.5 Vertebral body height and angular deformity

The FREE study reports the changes in vertebral body height and kyphotic angle.³⁴ Vertebral body height at 24 months is statistically significantly improved in the kyphoplasty group (6.7% and 5.9% for anterior and medial height respectively) while in the control group the anterior measurement improves with 1.1% but worsens with 1.9% in the medial measurement ($p=0.02$ and <0.001 respectively). No statistically significant difference is reported for posterior height.

At 24 months the angular deformity improves in both the intervention and control groups, but with a better improvement in the kyphoplasty group (mean difference -2.3° , $p=0.003$).

5.2.6 Progression of treated fractures

No data reported.

5.2.7 Key points for kyphoplasty in osteoporotic VCF

- There is low quality evidence on the effectiveness of kyphoplasty compared to non-surgical pain management from one non-blinded RCT.
- Health Related Quality of Life (HRQoL):
 - HRQoL: improves both in the kyphoplasty and control groups after inclusion in the study.
 - This study reports a statistically significant difference in EQ-5D outcomes in favour of kyphoplasty at several endpoints up to 24 months, but the difference is the highest at early time points.
 - This study also reports statistically significant differences in SF-36 PCS score in favour of kyphoplasty up to 6 months but not thereafter.
- Functional status and mobility (RDQ):
 - RDQ scores improve in both the intervention and control groups after inclusion in the study.
 - This RCT reports significantly better outcomes for functional status and mobility at 1 and 12 months but not at 24 months in favour of kyphoplasty.
 - RDQ differences decrease over time since inclusion in the study.
- Pain:
 - Pain scores improve in both the intervention and the control groups after inclusion in the study.
 - In this study pain scores improve more in the kyphoplasty group but the between group difference decreases with time since inclusion in the study.
- At 24 months this RCT reports significantly better improvement in the kyphoplasty group for angular deformity. Kyphoplasty compared to vertebroplasty in osteoporotic VCF.



5.3 Kyphoplasty compared to vertebroplasty for osteoporotic VCF

5.3.1 Basic RCT characteristics

- No double blinded RCTs.
- Non-blinded RCTs: 2.^{35, 36}
- Inclusion criterion: one or more VCF.
- Other baseline characteristics of the Liu trial, which is included in the SchARR systematic review, can be found in tables 4 and 5 and in appendix 9 from the SchARR report.⁸ This trial by Liu et al., the smallest of both RCTs (n=100), reports only on pain and radiographic outcomes.
- The KAVIAR RCT (n=381) was published after the SchARR report and includes patients with osteoporosis and one to three VCF. Analysed patients were randomised to either kyphoplasty (n=191) or vertebroplasty (n=190). The primary end points are 12 and 24-month new radiographic VCF incidence (including any new or worsening index fracture) using the method of Genant et al.² Secondary outcomes at 1, 3, 12 and 24 months include the SF-36 PCS, the EQ-5D, the NRS for back pain, and the Oswestry Disability Index (ODI). The characteristics and quality assessment of this trial are given in the appendix.

5.3.2 Health-Related Quality of Life

The Liu trial does not report on HRQoL. In the KAVIAR trial the kyphoplasty and vertebroplasty groups have similar baseline HRQoL as measured by EQ-5D and SF-36 PCS scores. For each outcome, statistically significant improvements from baseline are observed for both groups, but between group differences are not statistically significant.

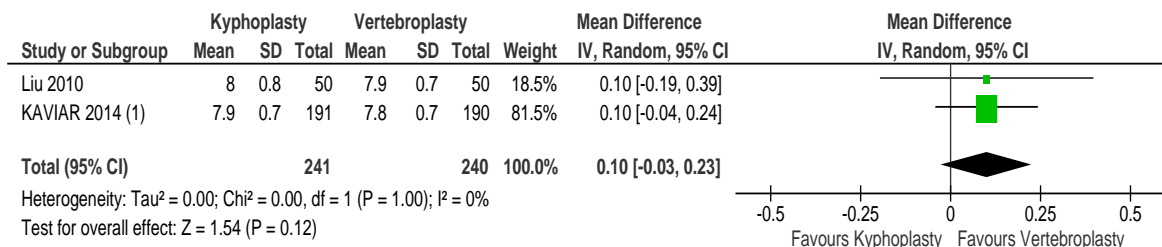
5.3.3 Back-specific functional status and mobility

The Liu trial does not report on this outcome. The KAVIAR trial uses the Oswestry Disability Index to assess this outcome. It shows similar functional improvements for both techniques but no statistically significant between group differences.

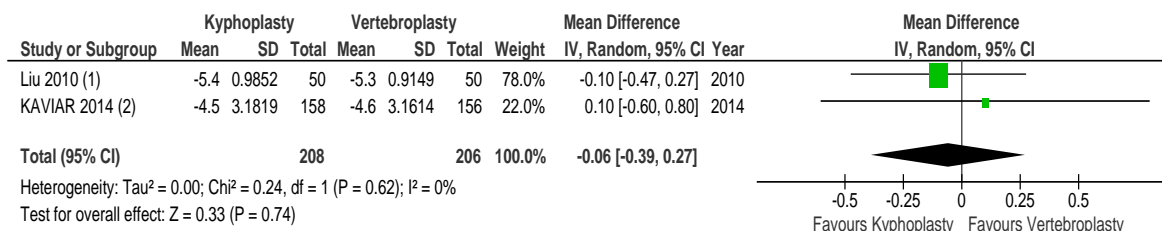
5.3.4 Pain and analgesic use

In the trial by Liu et al. pain is measured with the VAS at baseline, at 3 days and 6 months. Baseline scores are similar and the VAS scores do not differ significantly between both groups at both follow-up time points. In the KAVIAR trial the groups have similar baseline pain scores measured by NRS. Statistically significant improvements from baseline are observed for each group, but differences between treatment groups are not statistically significant. The results from the KAVIAR trial at 12 and 24 months equally do not show statistically significant differences (data not shown).

Use of opioid medications in the KAVIAR trial drops in both groups but without statistically significant between group differences.

**Figure 21 – Baseline pain scores (kyphoplasty vs. vertebroplasty)**Footnotes

(1) Estimated from graph

Figure 22 – Medium-term pain mean difference from baseline (kyphoplasty vs. vertebroplasty)Footnotes

(1) 6 months outcome

(2) 3 months outcome

5.3.5 Vertebral body height and angular deformity

The Liu study reports statistically significant postoperative improvement of vertebral body height in both groups but the mean difference in the improvement from baseline is 0.60 cm (95% CI: 0.43 to 0.77, own calculation) in favour of kyphoplasty. The KAVIAR trial does not explicitly report on vertebral body height.

Angular deformity is reported in both studies but results are difficult to compare. In the Liu trial the angular deformity improved in both groups but the mean difference in the improvement from baseline is -4.7° (95% CI: -

7.61 to -1.79 , own calculation) in favour of kyphoplasty. The KAVIAR trial, however, shows no immediate postoperative difference in angulation correction (-0.21° , 95% CI: -0.72 to 1.14), but a statistically significant difference at 24 months in favour of the kyphoplasty group (-1.42° , 95% CI: -2.74 to -0.10) due to a greater loss of correction in the vertebroplasty group.

5.3.6 Progression of treated fractures

No data reported.



5.3.7 *Keypoints for kyphoplasty compared to vertebroplasty in osteoporotic VCF*

- There is low quality evidence on the effectiveness of kyphoplasty compared to vertebroplasty from two non-blinded studies.
- **Health Related Quality of Life (HRQoL):**
 - Only one of the two studies reports on this outcome,
 - HRQoL improves in both the kyphoplasty and vertebroplasty groups after inclusion in the study.
 - There are no statistically significant differences between the groups at any end point.
- **Back-specific functionality and mobility:**
 - Only one of the studies reports on this outcome,
 - The KAVIAR trial shows similar functional improvements for both techniques but no statistically significant between group differences.
- **Pain:**
 - Pain scores improve in both the kyphoplasty and the vertebroplasty groups.
 - No statistically significant differences in pain scores at any time point of follow-up.
- **Vertebral body height of the treated vertebra and fracture progression:**
 - The Liu trial reports statistically significant improvement in favour of kyphoplasty in both postoperative vertebral body height and angular deformity.
 - The KAVIAR trial reports no immediate postoperative differences in angulation correction, but a statistically significant difference at 24 months in favour of the kyphoplasty group due to a greater loss of correction in the vertebroplasty group.
 - No trial reports data on vertebral fracture progression.

5.4 Kyphoplasty and vertebroplasty for VCF unrelated to osteoporosis

5.4.1 *Available information*

Most VCF are related to osteoporosis but these fractures can also be caused by severe acute trauma, haemangioma, malignancy or osteonecrosis. Evidence on the effectiveness of vertebral augmentation techniques for those patients is scarce and mainly based on case reports or small case series. An additional problem for the comparison is the heterogeneity of the patients and their condition leading to individual treatment decisions, small observational case series and almost no randomised interventional research.

The quality of the studies on the effectiveness and safety of vertebroplasty and kyphoplasty for the treatment of non-osteoporotic VCF is therefore very low. Studies are mainly not-randomised while the only RCT identified (CAFÉ) is small, allowed for cross-over and is industry sponsored. Obviously, setting up trials for those patients is even more time- and money intensive because there are fewer patients than for osteoporotic VCF.

5.4.2 *Results*

5.4.2.1 *Cancer related VCF*

For cancer patients some information on efficacy and safety is available. The skeletal system is the third most common site of metastases, after lung and liver, especially for breast, prostate, lung, bladder, and thyroid cancers.^{11, 51} When metastases occur in the spine these can lead to painful VCF, epidural cord compression or both.

A recent non-systematic review of both augmentation techniques in malignant VCF was published in 2014.⁵² It identifies fourteen observational studies and 1 non-blinded RCT (CAFÉ) on kyphoplasty vs. OPM.³⁷ The RCT is small and heterogeneous as different primary cancers are included (breast, multiple myeloma, lung, prostate and 'other').

This section is based on this review⁵² and on the single RCT.³⁷

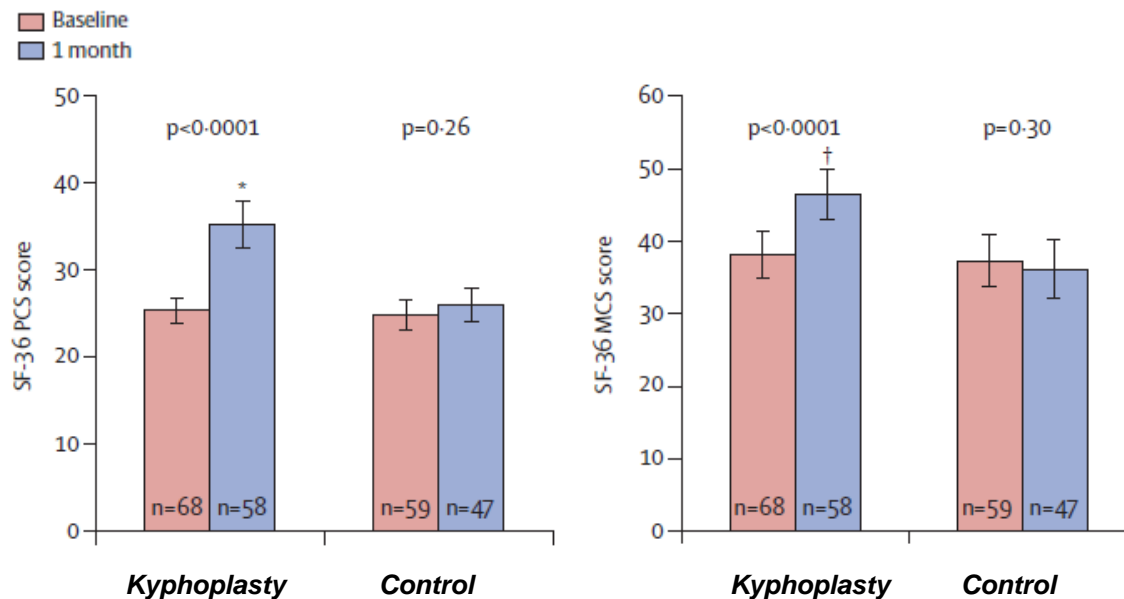


Deciding whether or not to intervene, and the choice of the technique (open surgery versus minimally invasive) is largely dependent on patient conditions and estimated survival rate. Open surgery is generally not recommended in patients with a life expectancy less than 6 months.⁵² However, kyphoplasty or vertebroplasty can at that moment be considered to improve HRQoL and manage pain.

Health-Related Quality of Life

HRQoL improves in several observational studies but results are heterogeneous and impossible to pool. In the RCT, a statistically significant difference in favour of kyphoplasty is shown at 1 month but patients in the control group were allowed to cross-over after 1 month. At 1 month the difference in SF-36 PCS (mean difference from baseline 8.4, 95% CI: 7.7 to 9.1) and SF-36 MCS (mean difference from baseline 11.1, 95% CI: 7.0 to 11.5) is statistically significant in favour of the kyphoplasty group. In the control group no statistically significant difference from baseline is observed at 1 month (see Figure 23).

Figure 23 – SF-36 scores (PCS on left and MCS on the right) at baseline and at 1 month (VCF related to cancer) in kyphoplasty group vs. control



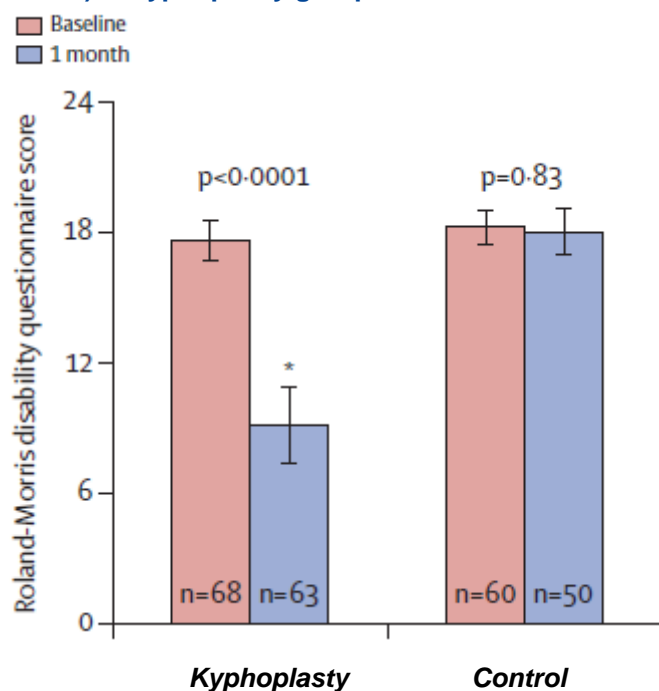
From Berenson et al.³⁷



Back-specific functional status

Mixed results are described in various observational studies but results are heterogeneous and impossible to pool. In the RCT back-specific functional status was the primary endpoint and assessed with the RDQ score (Roland Morris disability questionnaire). This study reports a 1 month treatment effect of -8.4 points RDQ (95% CI: -7.6 to -9.2) in favour of kyphoplasty.

Figure 24 – RDQ scores at baseline and at 1 month (VCF related to cancer) in kyphoplasty group vs. control

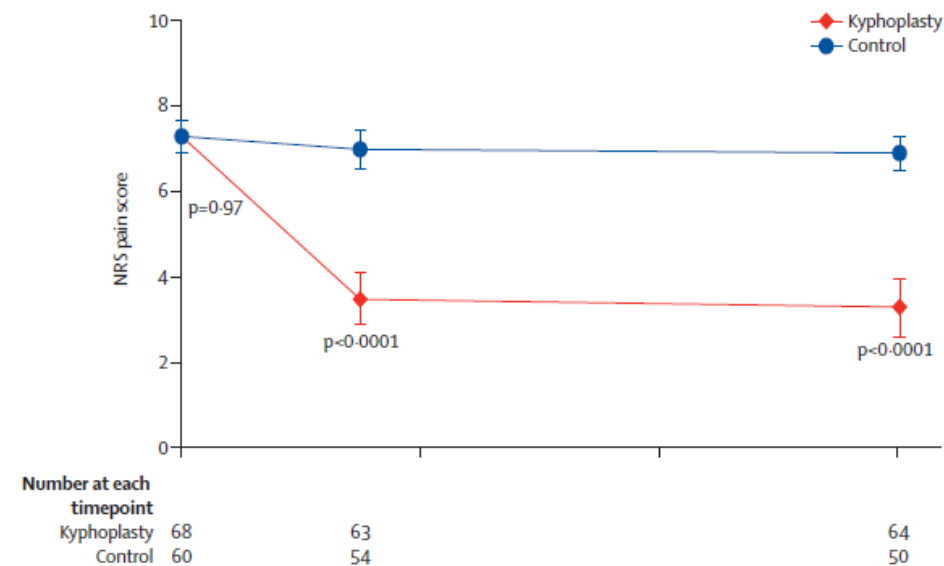


From Berenson et al.³⁷

Pain and analgesic use

Mixed results are reported but clinically significant pain relief of around four to five points (on a 10 point VAS) is reported in some observational studies, especially in patients with acute fractures and at early time points.⁵² In the RCT, statistically significant reduction of NRS pain scores is reported in the kyphoplasty group. Baseline NRS was 7.3 in both groups. At 7 days the mean difference in change from baseline was -3.5 (95% CI: -3.8 to -3.2) and -3.3 (95% CI: -3.6 to -3.0) at 1 month in favour of the kyphoplasty group (see Figure 25).

Figure 25 – Pain scores at baseline, at 8 days and 1 month (VCF related to cancer)



From Berenson et al.³⁷



Height restoration and angular deformity

Some observational studies report benefits in height restoration and angular deformity. The RCT does not report on this outcome.

Kyphoplasty vs. vertebroplasty

Within the setting of cancer patients one small study reports an advantage of kyphoplasty over vertebroplasty in pain control,⁵³ although both techniques are considered successful.

5.4.2.2 *Acute trauma VCF, osteonecrosis or vertebral haemangioma*

Several observational studies show mixed outcomes. Some report sustained reductions in pain scores for patients with acute trauma VCF, osteonecrosis or vertebral haemangioma in favour of both augmentation techniques, while other do not.⁵⁴⁻⁶¹

5.4.3 *Key points for kyphoplasty and vertebroplasty in VCF not-related to osteoporosis*

- **There is only very low quality evidence on the effectiveness of kyphoplasty or vertebroplasty in VCF unrelated to osteoporosis.**
- **The observational studies give mixed results but some report significant improvement in several outcomes in favour of both augmentation techniques.**
- **Only in cancer related VCF there is one small and heterogeneous RCT. This RCT reports statistically significant improvements in HRQoL, back-specific functional scores and pain in favour of kyphoplasty vs OPM.**

6 SAFETY

RCTs are not very efficient to study safety issues. Therefore, in this section, data from observational studies and registries are also included as described in the SchARR report.⁸

6.1 Mortality

6.1.1 *Procedure related mortality*

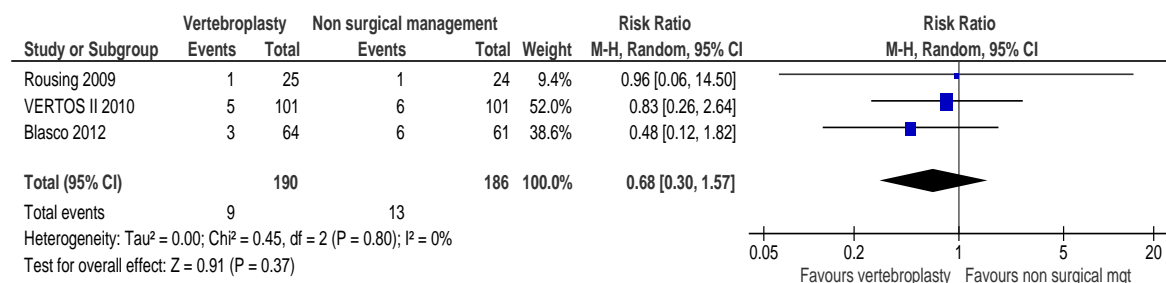
In the analysis of several large (n>200) observational case series, Stevenson et al. found one procedure-related death after kyphoplasty due to an infection in an immune-deprived patient.⁸ In individual case reports several deaths directly related to the procedure are reported. These are mainly related to cement leaks and related cement embolism (also see 6.2).

6.1.2 *Non-procedure related mortality*

In six of the RCTs included in the Stevenson review all-cause mortality is reported. None of the individual studies finds any statistically significant difference in overall mortality between groups, and no deaths in the studies appear to be directly related to the procedure. Three of the studies (Blasco, Rousing and VERTOS II) report 12 month mortality after vertebroplasty. The overall relative risk (RR) estimate is 0.68 (95% CI: 0.30 to 1.57) in favour of vertebroplasty, see Figure 26.



Figure 26 – Overall mortality at 12 months (vertebroplasty vs. OPM)



Medtronic provided registry data to the SchARR researchers (two from claims databases in the USA and two from Germany). These data suggest a decreased mortality risk with RR point estimates ranging from 0.56 - 0.93 after vertebroplasty or kyphoplasty compared to OPM.^{8, 62} The data also suggest a greater mortality benefit for kyphoplasty than for vertebroplasty. However, Stevenson et al. question the validity of the methods used, especially regarding the difficulty to define a valid control group. They conclude that

“In summary, it is possible that there is a causal difference in mortality between patients treated using OPM and patients receiving balloon kyphoplasty or percutaneous vertebroplasty given the size of the effect. Appropriately taking into account the potential endogeneity of the treatment would tend to reduce the point estimate of the effect size but may or may not eliminate it completely. It is not possible to say with certainty if there is a difference in mortality between patients undergoing kyphoplasty or vertebroplasty vs. OPM or for kyphoplasty vs. vertebroplasty as a result of the treatment based on the data presented in the studies included here. There is also considerable uncertainty, were kyphoplasty and vertebroplasty assumed to have a mortality benefit, regarding whether or not OPLA would also produce a mortality benefit, but no data are available on this.”¹⁸

6.2 Cement leakage

The most common risk associated with vertebral augmentation procedures is cement leakage outside the target vertebral body. The location of cement leakages has important implications for safety; intradiscal leakages are unlikely to lead to morbidity, but leakages into the epidural space or venous system have the potential to cause serious complications as witnessed by several case reports and observational studies.^{8, 63-66} The Stevenson review identifies 46 case reports on detected pulmonary cement embolism, 41 with vertebroplasty and five with kyphoplasty. Four deaths have been reported due to pulmonary embolism after vertebroplasty and none after kyphoplasty.

Most RCTs report cement leakage but using different definitions and imaging techniques. Because of the very different sensitivity of those different techniques the estimates vary widely. For vertebroplasty the proportion of reported leakages ranges from none to 72%. Pooled data suggest an incidence of 44% in vertebroplasty compared to 27% for kyphoplasty but there is much uncertainty about those estimates. All studies included in the Stevenson review apparently used PMMA cement and not one of the newer high-viscosity cements that are supposed to have a lower risk for cement leakage.



In the KAVIAR trial cement leakages are also more frequent in the vertebroplasty than in the kyphoplasty group. The difference, however, is only statistically significant for all leakages together (82% vs 73%, $p=0.047$). Leakage estimates by location are all in favour of kyphoplasty but not statistically significant.

From registry data and in terms of treated patients, leakage incidence ranges from 12% to 87% for vertebroplasty. Only one kyphoplasty study reports incidence in terms of treated patients, a rate of 19%. It is not clear why such wide variations in incidence are observed, but factors such as practitioner skills and experience, clinical setting, cement viscosity and thoroughness of follow-up may play a role.⁸

In general, epidural leaks appear to be common in vertebroplasty cohorts. This complication does not appear to be as common in kyphoplasty cohorts.⁸

Other reported adverse events which may be related to cement leakage include pulmonary embolism, radiculopathy, temporary radicular pain and temporary or permanent motor deficits or paraplegia of the legs.⁸

6.3 Intraoperative balloon rupture

This complication is not reported in the RCTs included in the Stevenson review and also the KAVIAR trial does not report on this adverse event. From observational studies it appears that intraoperative balloon rupture is a relatively rare complication of kyphoplasty. In the two studies that report on this event the incidence is 0.3% and 1.7%.^{65, 67} Neither of these studies discussed the clinical implications of balloon rupture although potential complications such as contrast leakage, procedural delay or gas embolism have been suggested.⁸

6.4 Other peri- and postoperative complications

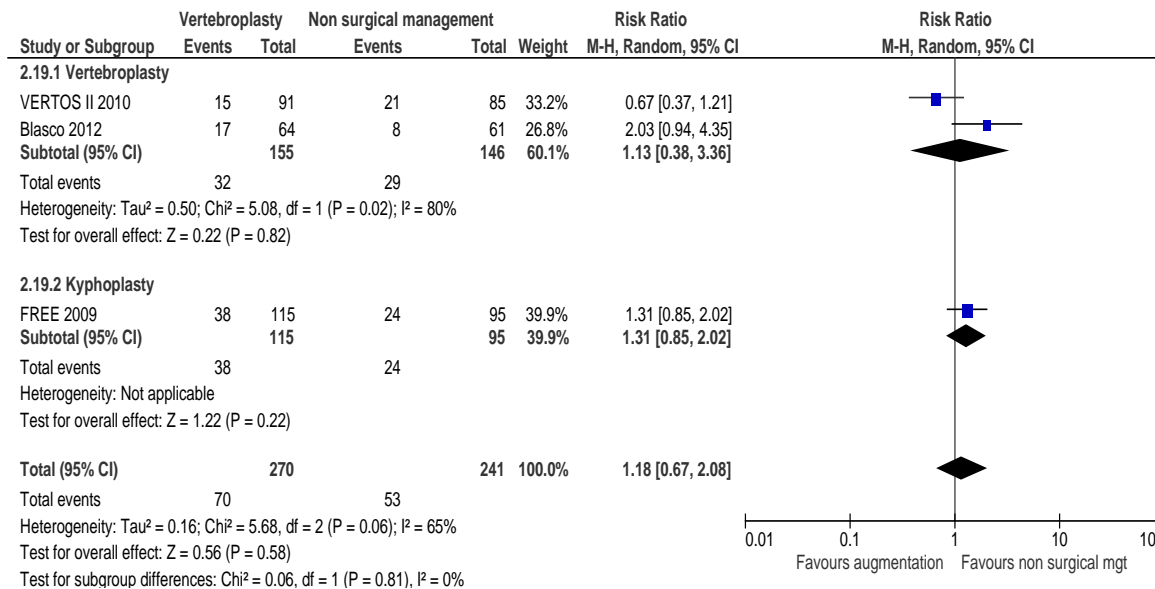
In the RCTs other peri- and postoperative complications are mainly anecdotal. In the observational studies these complications are also relatively rare and most of the medical complications relate to pre-existing disease. A few cases of surgery related infections are described.

6.5 Incidence of new vertebral fractures

It has been suggested in observational studies that augmentation techniques could potentially induce new vertebral fractures, especially in adjacent vertebrae.

6.5.1 Radiographic new vertebral fractures

In the RCTs the incidence of radiographic new vertebral fractures is reported in three RCTs (Blasco, FREE, VERTOS II). None of the RCTs finds statistically significant differences between groups and also the overall estimate is not significantly different (see Figure 27).

**Figure 27 – Patients with new radiographic incident VCF at 12 months (vertebroplasty vs. OPM)**

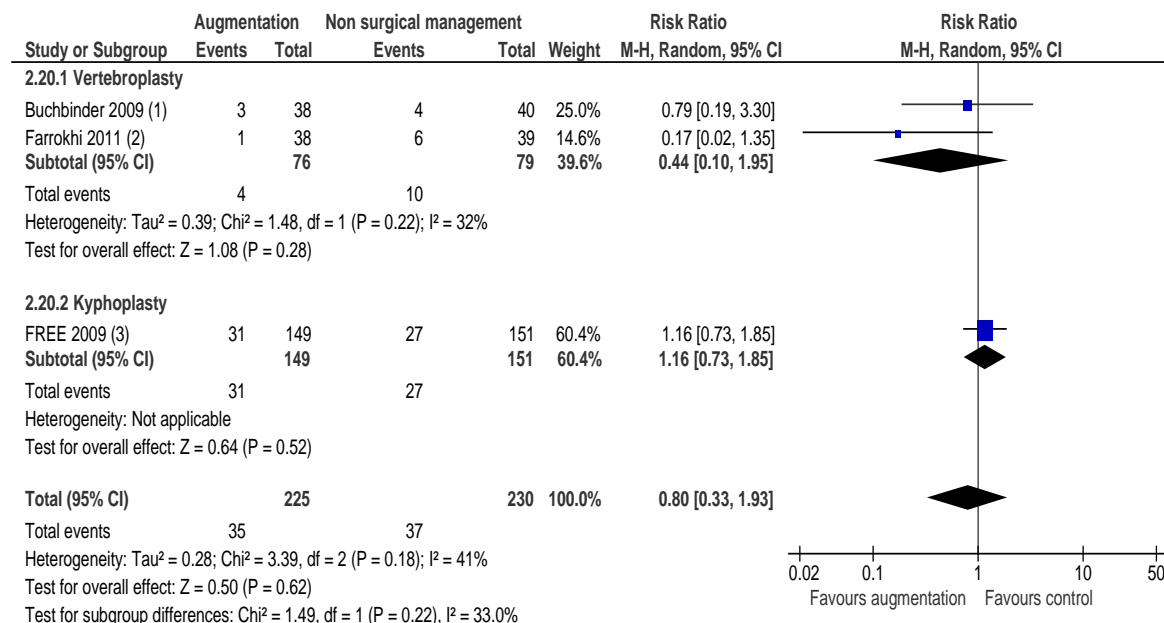
However, one of the studies reports that after vertebroplasty, 82% of new VCF occur in an adjacent vertebra compared with 27% in the control group.²⁶ In the FREE study 23.7% and 16.7% of patients suffer a new VCF in an adjacent vertebra in the kyphoplasty and control groups respectively.

The KAVIAR trial reports a not statistically significant trend towards a longer vertebral fracture free survival in the kyphoplasty group compared to the vertebroplasty group.

6.5.2 Clinical new vertebral fractures

The results for clinical new vertebral fractures are not very well reported. Five studies report the incidence of new clinical vertebral fractures but one of these (VERTOS) does this only for the vertebroplasty group. They also report on different timeframes. However, in none of the studies, nor overall, a statistically significant difference is found (see Figure 28).

Observational studies are of little help to study the incidence of new VCF since patients with osteoporosis have, by definition, an increased risk of new fractures and defining a control group is therefore difficult.

**Figure 28 – Patients with new clinical VCF (vertebroplasty or kyphoplasty vs. OPM)**Footnotes

(1) At 6 months

(2) At 24 months

(3) At 24 months

6.6 Other adverse events

Several other adverse events have been reported in RCTs and observational studies but those are mainly anecdotal and often probably not related to the intervention. There are also no clear differences between the groups.

In the observational studies a few rib fractures are described after vertebroplasty and none in the kyphoplasty case series. It has also been suggested that a treated vertebra may re-fracture but none of case series report this complication, so incidence is likely to be low.

Both procedures may be associated with a transitory increase in post-procedural pain but few case series report this complication. A number of case reports describe postoperative infectious complications, sometimes requiring further surgical intervention.

In a small proportion of patients repeat intervention is required. One study from 2008 reports that 1.3% of the patients needed revision intervention.⁶⁸



A number of case reports describe rare but serious cardiovascular complications related to air or cement embolism, including cardiac perforation, inferior vena cava syndrome, venous air embolism, vena cava thrombus, acute pericarditis, lumbar artery pseudo-aneurism and stroke.⁸ Other complications related to cement leakage, embolism, bleeding or injury have occasionally been reported. Although those complications are extremely rare they can have catastrophic consequences when they occur.

6.7 Key points for safety

- **Very low quality evidence from RCTs (vertebroplasty) and clinical registries (vertebroplasty and kyphoplasty) indicated that mortality after vertebral augmentation techniques might be lower.**
- **Vertebroplasty and kyphoplasty are relatively safe procedures.**
- **Cement leakage is the most common adverse event but often not clinically important.**
- **Some studies suggest that cement leakage is less frequent with kyphoplasty than with vertebroplasty.**
- **In some rare cases, however, complications can be very serious and even life-threatening.**

7 ECONOMIC EVALUATION

7.1 Introduction

The aim of this section is to provide a review of peer-reviewed full economic evaluations of vertebral augmentation techniques (vertebroplasty and kyphoplasty) versus each other or versus non-surgical optimal pain management (OPM) of adult patients with vertebral compression fractures (VCF) due to osteoporosis, malignancy, haemangioma, osteonecrosis or trauma.

7.2 Methods

7.2.1 Inclusion and exclusion criteria

The following criteria were developed:

- Inclusion and exclusion criteria describing the Population, the Intervention and the Comparator of interest are defined as in the methods chapter for the clinical effectiveness and safety assessment. They are described in appendix.
- Design: only full economic evaluations are considered, i.e. studies comparing at least two alternative treatments in terms of both costs and outcomes. Cost-minimization analyses (CMA), cost-utility analyses (CUA, with results expressed as incremental cost per quality-adjusted life year (QALY) gained), cost-effectiveness analyses (CEA, with results expressed as cost per life year gained) and cost-benefit analyses (CBA, with a monetary valuation of health outcomes) are eligible. Cost comparisons (not considering health outcomes), cost-outcome descriptions (not considering an alternative treatment) and cost-consequence analysesⁱ are not deemed relevant for inclusion. Both primary studies and reviews of full economic evaluations are considered relevant for inclusion; letters, news, conference proceedings and editorials were removed.

ⁱ In cost-consequence analyses, both costs and outcomes of different alternatives are described. In such studies however, an incremental cost-effectiveness ratio (ICER) is not calculated or the results are expressed in

disease-specific outcome (e.g. cost per patient reduction of one point in the Activities of Daily Living scale). Such studies are discarded as their results cannot be compared with those of other types of economic evaluations, mainly CEA and CUA.



- **Timing:** a previous KCE report published in 2006 performed a systematic literature review of full economic evaluations on the same interventions.⁹ That search was performed up to early 2006 but no original full economic evaluation was found. Building on the results of this report, the current search is limited to publications from 2006 up to April 2015.

7.2.2 Search strategy

Both electronic and manual searches were performed.

- **Electronic search:** the following databases were searched in April 2015: Medline(Ovid), Medline in-process and other non-indexed citations (Ovid), Embase, CRD (Centre for Review and Dissemination) HTA and CRD NHS EED (National Health Service Economic Evaluation Database). A combination of MeSH, Emtree and text word terms related to vertebroplasty, kyphoplasty and vertebral compression fractures were combined with those related to full economic evaluations (see appendix). The websites of the HTA institutes listed on the International Network of Agencies for Health Technology Assessment (INAHTA) were also consulted.
- **Manual search:** the reference lists of relevant review papers and full economic evaluations were also scrutinized for additional relevant articles.

7.2.3 Selection procedure

The selection was performed in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment if the title or the abstract or the keywords suggested relevant information or if no abstract was available. The flow chart of the selection processes can be found in appendix.

The search strategy yielded 170 unique, potentially relevant citations. After title and abstract review, 117 articles were excluded, the majority of which were not economic studies or did not assess the intervention or population of interest. Of the 53 full-text articles reviewed, 42 were excluded. The primary reason for exclusion was that most studies focused on efficacy/safety without reporting any economic result. Other reasons of exclusion were that the design of the studies was limited to a cost

comparison (6 studies^{13, 15, 21, 69-71}), a cost-consequence analysis (4 studies⁷²⁻⁷⁵) or a cost-outcome description (1 study⁷⁶).

A total of 11 articles were retained: 5 full economic evaluations,^{28, 77-80} 5 recent literature reviews^{14, 81-84} and 1 HTA report that contained both a literature review and a full economic evaluation.⁸

7.2.4 Coverage of the reviews

After critical analysis of the selected reviews, we decided to base our discussion on the very recent (2015) systematic review published by Borgström et al.⁸¹ This high-quality systematic review covers 5^{8, 28, 78-80} out of the 6 full economic evaluations identified. The study by Edidin et al.⁷⁷ was not included (but only briefly described) in the review by Borgström et al.⁸¹ as it did not comply with Borgström's inclusion criteria of being a cost-utility analysis. As a cost-effectiveness analysis relevant to our purpose, the study by Edidin et al.⁷⁷ was included in our description of the economic evidence and added as an update to the comparative tables produced by Borgström et al.⁸¹

The five other reviews were older (2011-2014),^{8, 14, 82-84} and covered fewer published economic evaluations. Three reviews^{14, 83, 84} included the study by Masala et al.⁷³ that, despite its title, was appraised here as being a cost-consequence analysis and therefore discarded. An overview of the studies covered by the six reviews identified is presented in Table 9.



Table 9 – Overview of the studies included in the identified economic literature reviews

Authors of the review	Borgström et al., 2015 ⁸¹	Stevenson et al., 2014 ⁸	Chandra et al., 2013 ⁸²	Montagu et al., 2012 ⁸³	Robinson et al., 2012 ⁸⁴	Doidge et al., 2011 ¹⁴
Time window	Up to March 2013 + 1 update in 2014	Up to November 2011	January 2000 to April 2013	1966 to July 2011	Not reported (2011?)	1987 to August 2010
Number of peer-reviewed studies included	5	1 ^b	3	2	3	3
Full economic evaluations						
Stevenson et al., 2014 ⁸	x					
Svedbom et al., 2013 ⁸⁰	x		x			
Edidin et al., 2012 ⁷⁷	(a)		x			
Fritzell et al., 2011 ⁷⁸	x		x		x	
Klazen et al., 2010 ²⁸	x			x		x
Ström et al., 2010 ⁷⁹	x	x			x	x
Cost-consequence analysis						
Masala et al., 2008 ⁷³				x	x	x

a: Article briefly described but not formally reviewed. b: It is not clear from the study why their systematic review covered only one economic evaluation. However, according to the authors, it may be due to the cut-off date of the review (Personal communication Pr. Stevenson, September 2015).

7.3 Narrative overview of the economic evaluations

Borgström et al.⁸¹ provided a summary of the methodology and the results of 5 full economic evaluations.^{8, 28, 78-80} The interested reader is referred to their article. Building further on Borgström et al.⁸¹ study, we provide here a summary of the 6th full economic evaluation⁷⁷ identified in our review and not covered by Borgström et al.

Borgström et al.⁸¹ converted the original costs reported in the studies into 2012 euro using 2012 exchange rates (1 EUR = 0.811 GBP = 8.705 SEK). For simplicity and consistency, the same conversion method was used and

applied to the US study by Edidin et al.⁷⁷ with the 2012 exchange rate 1 EUR = 1.321 USD.

Edidin et al., 2012⁷⁷

This study used real-world medical costs and life expectancies observed in a US Medicare administrative claims database to assess the cost-effectiveness of kyphoplasty and vertebroplasty versus OPM. Based on ICD-9-CM codes for newly diagnosed VCF and for kyphoplasty and vertebroplasty, a total of 858 978 vertebral fracture patients were identified between 2005-2008 in the US Medicare dataset, of which 119 253



underwent vertebroplasty and 63 693 underwent kyphoplasty, while the remaining 676 032 patients formed the non-operated cohort.⁶²

Using a parametric Weibull survival model for different age and gender combinations, extrapolated median life expectancy gains from 3 to 9.5 years and from 1 to 4.3 years were estimated for kyphoplasty and vertebroplasty, respectively, compared to OPM. Median life expectancy gains from 2 to 5.2 years were estimated for kyphoplasty compared with vertebroplasty. The difference in the cumulative median costs accruing over the observed 3-year observation time window (censored data) ranged from €6281 to €21 809 (\$US8300 to \$US28 820) for vertebroplasty and from €9520 to €14 000 (\$US12 580 to \$US18 500) for kyphoplasty, compared with OPM. The authors assumed that this costs difference would reduce to zero (so no difference in treatment costs) from the fourth year onwards.

The authors computed that, for different age and gender combinations, the median cost per life year gained for kyphoplasty and vertebroplasty ranged from €1410 to €5060 (\$US1863 to \$US6687) and from €1855 to €10 248 (\$US2452 to \$US13 543), respectively, compared with non-operated patients. Based on those results the authors concluded that VCF treatments with augmentation techniques are cost-effective in the Medicare population when compared with OPM.

The median cost per life year gained for kyphoplasty compared with vertebroplasty ranged from dominant to €2091 (\$US2763). The authors concluded that among patients for whom surgical treatment was indicated, kyphoplasty was cost-effective, and in some cases even dominant (i.e. not only more clinically effective, but also less costly), compared with vertebroplasty.

Except for the discount rate, no sensitivity analysis was performed.

One major drawback of this analysis is that it was based on observational data with no real control group and where treatment assignment is non-random. Such data can be subject to confounding factors that complicate the estimation of the treatment effect because of selection bias. As a consequence, it remains problematic to attribute a causal relationship between surgical treatment and improved patient survival based solely on the results of this study. Another drawback was the reporting of the results as median values, instead of the recommended mean values. A final major drawback of this study was the different time horizons considered for deriving costs and life expectancies. Costs were assessed over the 3-year observation period, whereas life expectancies and life year gained were extrapolated over the lifetime of the patients. In a full economic evaluation, all long-term consequences should be considered, both from the effectiveness as for the cost sides (e.g. long-term adverse events such as subsequent re-interventions). Ignoring the long-term costs while incorporating the full long-term clinical effects as done in this study may have affected the ICER downwards.

7.4 General characteristics and results of the economic evaluations

An overview of the characteristics of the six studies assessing the cost-effectiveness of PVP and BKP is presented in Table 10.

The results of the studies are presented in Table 11 and Table 12.


Table 10 – Base-case characteristics of the full economic evaluations of vertebroplasty and balloon kyphoplasty

	Ström et al., 2010 ⁷⁹	Svedbom et al., 2013 ⁸⁰	Fritzell et al., 2011 ⁷⁸	Klazen et al., 2010 ²⁸	Stevenson et al., 2014 ⁸	Edidin et al., 2012 ⁷⁷
Country	UK	UK	Sweden	The Netherlands	UK	USA
Funding source§	Industry support	Industry support	Industry support	Industry support	No industry support	Industry support
Design	CUA	CUA	CUA	CUA	CUA	CEA
Perspective	HCP	HCP	Societal (HCP‡)	HCP	HCP	HCP
Time horizon	Lifetime	Lifetime	2 years	1 year	Lifetime	Costs: 3 years Outcome: lifetime
Discount rate†	3.5%	3.5%	None	None	3.5%	3%
Costing year	2008	2009	2008	2008	2010-2011	2010
Analytic technique	Markov cohort model	Markov cohort model	Within-trial	Within-trial	Markov cohort model	Analysis of administrative data
Comparators	BKP, OPM	BKP, PVP, OPM	BKP, OPM	PVP, OPM	BKP, PVP, OPM, OPLA	BKP, PVP, OPM
Target patient group	70-year-old UK men and women with a T-score of -2.5, low bone mineral density and at least one VCF	70-year-old women with a T-score of -3.0 and a prevalent osteoporotic vertebral fracture	Similar to the Swedish patients included in FREE (72 years in the BKP arm and 75 years in the control arm)	Similar to patients in VERTOS II (75 years of age with prevalent VCF and back pain < 6 weeks)	70-year-old women with a T-score of -3 SD	Medicare population aged 65-year-old with ICD-9 codes suggesting VCF
Outcome	QALY	QALY	QALY	QALY	QALY	LY
Underlying instrument for QoL	EQ-5D (UK tariff)	EQ-5D (UK tariff)	EQ-5D (UK tariff)	EQ-5D (Dutch tariff)	Combination	Not applicable
Duration of QoL differential effect	1 year followed by 2 years linear decline to zero effect	2 years followed by 1 year linear decline to zero effect	2 years	1 year	Different scenarios	Not applicable
Source for QoL differential outcome	FREE ³² (1-year interim results)	FREE ³³ (2-year final results) VERTOS II ²⁸ (1-year final results)	FREE (subset of 67 Swedish patients, 2-year final results) ³³	VERTOS II ²⁸ (1-year final results)	Combination	Not applicable



	Ström et al., 2010 ⁷⁹	Svedbom et al., 2013 ⁸⁰	Fritzell et al., 2011 ⁷⁸	Klazen et al., 2010 ²⁸	Stevenson et al., 2014 ⁸	Edidin et al., 2012 ⁷⁷
Other differential effects	Reduced hospitalisation days with BKP	Reduced hospitalisation days with BKP and PVP Reduced mortality with BKP and PVP	No	No	Differing hospitalisation days, mortality and re-fracture rate	Reduced mortality with BKP and PVP
Source for other differential effects	Assumption	Assumption Published analysis of US Medicare claims data ⁶²	Not applicable	Not applicable	Combination	Published analysis of US Medicare claims data ⁶²
Adverse events considered	No	No	Yes	Yes	Yes	Unknown
Uncertainty analyses	Probabilistic SA One-way SA Scenario	Probabilistic SA One-way SA Scenario	Probabilistic SA One-way SA Scenario	Probabilistic SA	Probabilistic SA One-way SA Scenario	Scenario

Adapted from Borgström et al.⁸¹

CUA: cost-utility analysis, CEA: cost-effectiveness analysis, HCP: health care payer, BKP: kyphoplasty, PVP: vertebroplasty, OPM: non-surgical optimal pain management, OPLA: operative placebo with local anaesthesia, VCF: vertebral compression fracture, QALY: quality-adjusted life year, LY: life year, SA: sensitivity analysis.

§ Funding source was classified using three categories. Industry support: any explicit acknowledgment of support from private industry (generally manufacturers of medical devices). Unknown: no information about support provided. No industry support: explicit acknowledgment of support that did not include private industry (generally from either public sources or private foundations). An explicit statement of "funding source: none" was also included in this last category. † For both costs and effects. ‡ The base-case perspective of this study is societal with the inclusion of transport, informal care and productivity costs on top of direct medical costs. To comply with Belgian guidelines,⁸⁵ results from the HCP perspective (including only direct medical costs) were computed and added in the comparative tables.

7.4.1 Country and study design

Three studies were performed in the UK.^{8, 79, 80} The other three studies were performed in Sweden,⁷⁸ the Netherlands²⁸ and the USA.⁷⁷ All but one study⁷⁷ were cost-utility analyses, with outcomes expressed as quality-adjusted life years. Edidin et al.⁷⁷ used a cost-effectiveness design, with outcomes expressed as life years; thereby considering that improving life expectancy is the main objective of PVP and BKP.

7.4.2 Perspective

All but one study⁷⁸ adopted a health care payer perspective in their base-case, including direct medical and intervention costs only. In Fritzell et al.⁷⁸ a societal perspective is used, adding also transport costs, productivity costs due to work absenteeism from the patients and informal care costs due to relatives caring for a sick patient. This does not correspond to the recommendation by the recent Belgian guidelines on economic evaluations⁸⁵ to use a health care payer perspective in the base-case assessment of any intervention. As a consequence, results from Fritzell et



al.⁷⁸ were re-computed excluding the productivity and informal care costs and were added in our comparative tables.

7.4.3 Target population

Five of the six studies identified in the literature search assessed the cost-effectiveness of PVP and BKP for VCF due to osteoporosis, which is the majority of VCF. In Edidin et al.,⁷⁷ the cost-effectiveness of augmentation techniques for both traumatic and osteoporotic fractures is investigated, but the results are not reported separately by fracture type. Full economic evaluations focusing specifically on patients with non-osteoporotic VCF were not found.

7.4.4 Intervention and comparator

Most studies evaluated the use of PVP or BKP versus non-surgical optimal pain management (OPM). Only two studies compared PVP with BKP.^{77, 80} In the incremental analyses by Stevenson et al.,⁸ PVP, BKP, OPM and operative placebo with local anaesthesia (OPLA) are all compared according to the efficiency frontier approach (see Table 12 for an explanation of this approach).

7.4.5 Results of the economic evaluations

Reflecting the variability of their input parameters and assumptions, the results of the cost-effectiveness studies were quite different. This is illustrated in Table 11 and Table 12. As stated in the preceding paragraph, most studies performed predetermined pairwise comparisons of the interventions of interest (i.e. BKP versus OPM, PVP versus OPM, BKP versus PVP). In the presence of multiple interventions however, and as recommended by the Belgian guidelines on economic evaluations,⁸⁵ the appropriate comparator to an intervention should be identified according to the efficiency frontier approach. This has only been done in the Stevenson et al.⁸ study (where the interventions compared are BKP, PVP, OPM and OPLA). As both approaches are different, we present the results of the pairwise comparisons and of the incremental analyses by Stevenson et al.⁸ separately.

7.4.5.1 Balloon kyphoplasty versus non-surgical optimal management

In three studies BKP was found to be a cost-effective intervention compared to OPM.^{77, 79, 80} This contrasts with the study by Fritzell et al.⁷⁸ which resulted in an incremental cost of €101 626 (SEK884 682) per QALY gained from a societal perspective and which prompted the authors to state that it was not possible to conclude that kyphoplasty was cost-effective in a Swedish setting. In this study, the additional total costs of BKP versus OPM were also reported from a health care payer perspective and were estimated at €8152 (SEK70 966). This allowed us to compute an ICER of €95 907 (SEK834 894) per QALY gained from the health care payer perspective, which is rather similar to the ICER reported for the societal perspective. This is in line with the authors' conclusion stating that costs related to work absenteeism and informal care were irrelevant as almost all patients were retired and as almost no patient used help from the community.

In three studies⁷⁸⁻⁸⁰ uncertainty analyses showed that the results were most sensitive to assumptions about the persistence of QoL benefits, the avoided length of hospital stay and the mortality benefit with BKP. In Ström et al.,⁷⁹ if the QoL benefit was limited to the first year after surgery, as demonstrated at that time in the FREE trial, the ICER would increase to €17 880 (£14 500) per QALY gained. When no reduction in hospital length of stay was assumed, the ICER rose to over €38 000 (almost £25 000) per QALY gained. In Svedbom et al.⁸⁰ assuming no mortality benefit, the cost per QALY gained of BKP vs. OPM rose to €6988 (£5667). Assuming no mortality benefit and only 25% of the base-case health utility gain, the ICER increased to €28 360 (£23 000) per QALY gained. In Fritzell et al.⁷⁸ if the QALYs gained for BKP vs. OPM reported from the full FREE study population (0.21) was used instead of the QALYs gained from the Swedish patients in the FREE trial (0.085), the ICER would reduce to €41 256 (SEK359 146) per QALY gained, which could be considered cost-effective in Sweden. In Edidin et al.,⁷⁷ except for the discount rate, no sensitivity analysis was performed.



7.4.5.2 *Vertebroplasty versus non-surgical optimal management*

The studies comparing PVP to OPM all reported results in favour of PVP. In Klazen et al.²⁸ and in Edidin et al.⁷⁷ vertebroplasty was found to be a cost-effective intervention compared to OPM. Although their primary objective was not to compare PVP to OPM (but rather to compare BKP versus PVP and OPM), the results presented in Svedbom et al.⁸⁰ allowed us to conclude that PVP was dominant compared to OPM, i.e. PVP was more clinically effective and less costly than OPM.

In Klazen et al.²⁸ the probabilistic sensitivity analysis showed that PVP had a 70% probability of being cost-effective at an assumed €30 000 cost per QALY threshold. However, because the analysis did not detail the methods and assumptions used, it is not possible to make a comprehensive assessment of the strengths and limitations. In Edidin et al.⁷⁷ except for the discount rate, no sensitivity analysis was performed. As this was not their primary objective, no analysis exploring the uncertainty about PVP versus OPM was done in Svedbom et al.⁸⁰

7.4.5.3 *Balloon kyphoplasty versus vertebroplasty*

With a net 0.14 QALY gain and an incremental €2658 (£2156) cost, the incremental cost per QALY gained of BKP vs. PVP was estimated at €19 706 (£15 982) in Svedbom et al.⁸⁰ The authors concluded that BKP may be a cost-effective intervention compared to PVP. However, sensitivity analysis showed that results were especially sensitive to changes in the mortality benefit, and to a lesser extent in the QoL benefit. Assuming no mortality benefit, the cost per QALY gained of BKP vs. PVP rose to €259 171 (£210 188), which cannot be considered cost-effective. Assuming no mortality benefit and only 25% of the base-case health utility gain, the ICER of BKP vs. PVP increased to over €1 million (£826 858) per QALY gained. Taking into account the uncertainties around the estimates for health utilities and mortality and length of stay reduction, the probabilistic sensitivity analysis showed that in the base-case, BKP had a 60-75% probability of being the optimal intervention at conventional UK thresholds (£20 000 - £30 000 per QALY). However, assuming no mortality benefit, PVP had the highest probability of being the optimal intervention at conventional UK thresholds.

In Edidin et al.⁷⁷ the median cost per life year gained for BKP compared with PVP ranged from dominant to €2091 (\$US2763). The authors concluded that among patients for whom surgical treatment was indicated, BKP was cost-effective, and in some cases even dominant (i.e. not only more clinically effective, but also less costly), compared with PVP. Again, except for the discount rate, no sensitivity analysis was performed.

7.4.5.4 *PVP, BKP, OPM and OPLA compared according to the efficiency frontier approach*

In Stevenson et al.⁸ two “base-case” analyses (called “foundation analyses” by the authors) were modelled (see Table 12), which represented two of many plausible scenarios. The difference between both analyses was that one assumed a mortality benefit associated with BKP, PVP and OPLA while the other did not. The results from their incremental cost-effectiveness analyses varied, with either BKP, PVP or OPLA appearing to be the most cost-effective treatment dependent on the assumptions made regarding mortality effects, utility, hospitalisation costs and OPLA costs.

The authors concluded that the uncertainty in the underlying evidence means that no firm conclusion on the cost-effectiveness of PVP or BKP can be provided.



Table 11 – Results of the full economic evaluations of vertebral augmentation techniques

	Incremental cost (Euro 2012)	Incremental outcome	Incremental cost-effectiveness ratio	Authors' conclusion
Balloon kyphoplasty versus non-surgical optimal pain management (OPM)				
Ström et al., 2010 ⁷⁹	€1840	0.169 QALY gained	€10 900 per QALY gained	Kyphoplasty is cost-effective compared to OPM
Svedbom et al., 2013 ⁸⁰	€1657	0.500 QALY gained	€3337 per QALY gained	Kyphoplasty is cost-effective compared to OPM
Fritzell et al., 2011 ⁷⁸	Society: €8638 (95% CI: 1842 to 13 797)	0.085 QALY gained (95% CI: -0.132 to 0.306)	€101 626 per QALY gained	Kyphoplasty is <u>not</u> cost-effective compared to OPM
	HCP: €8152 † (95% CI: 1711 to 12 823)		€95 907 per QALY gained	Kyphoplasty is <u>not</u> cost-effective compared to OPM
Eddin et al., 2012 ⁷⁷ ‡	€9520 to €14 000	3 to 9.5 LY gained	€1410 to €5060 per LY gained	Kyphoplasty is cost-effective compared to OPM
Vertebroplasty versus non-surgical optimal management (OPM)				
Svedbom et al., 2013 ⁸⁰	-€1001 (savings)	0.360 QALY gained	Dominant	Vertebroplasty dominates OPM*
Klazen et al., 2010 ²⁸	€2450	0.108 QALY gained (95% CI: 0.040 to 0.177)	€22 685 per QALY gained	Vertebroplasty is cost-effective compared to OPM
Eddin et al., 2012 ⁷⁷ ‡	€6281 to €21 809	1 to 4.3 LY gained	€1855 to €10 248 per LY gained	Vertebroplasty is cost-effective compared to OPM
Balloon kyphoplasty versus vertebroplasty				
Svedbom et al., 2013 ⁸⁰	€2658	0.140 QALY gained	€19 706 per QALY gained	Kyphoplasty may be cost-effective compared to vertebroplasty
Eddin et al., 2012 ⁷⁷ ‡	-€7800 (savings) to €3240	2 to 5.2 LY gained	Dominant to €2091 per LY gained	Kyphoplasty is cost-effective compared to vertebroplasty

Adapted from Borgström et al.⁸¹

† The base-case perspective of this study is societal. To comply with Belgian guidelines,⁸⁵ results from the health care payer (HCP) perspective were computed and added in the comparative tables. ‡ Median values, instead of mean values, are reported. * This is not Svedbom et al.⁸⁰ conclusion but our own assessment, based on the figures reported in the study.

LY: life year, QALY: quality-adjusted life year, OPM: non-surgical optimal pain management. Exchange rates (2012): 1 EUR = 0.811 GBP = 8.705 SEK = 1.321 USD.



Table 12 – Results of two base-case analyses from Stevenson et al., 2014⁸ with different assumptions on mortality benefits

Intervention	Total cost	Total QALY	Incremental cost †	Incremental QALY †	ICER †	Net monetary benefit ‡
No mortality benefit for BKP, PVP or OPLA						
PVP	€7544	4.91	-	-	-	€4330
OPLA	€7544	4.83	€0	-0.08	Dominated by PVP	€2245
OPM	€7621	4.74	€78	-0.17	Dominated by PVP	-
BKP	€10 165	4.91	€2621	0	Dominated by PVP	€1700
Mortality benefit for BKP, PVP and OPLA						
OPLA	€7599	4.89	-	-	-	€3736
OPM	€7621	4.74	€22	-0.15	Dominated by OPLA	-
PVP	€7657	5.04	€58	0.15	€385	€7346
BKP	€10 490	5.27	€2832	0.23	€12 091	€10 291

BKP: kyphoplasty, PVP: vertebroplasty, OPM: non-surgical optimal pain management, OPLA: operative placebo with local anaesthesia, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio. Exchange rates (2012): 1 EUR = 0.811 GBP.

† In this study calculations of the ICERs follow the efficiency frontier approach. In this approach, interventions are ranked from the least to the most expensive one. Each intervention that is (extendedly) dominated by another intervention is then removed. An intervention is dominated when its effectiveness is lower and its cost higher than another intervention. ICER are only computed for the remaining interventions, by comparing each intervention with the previous less costly and less effective intervention.

‡ Net monetary benefit compared with OPM at a willingness to pay of €24 660 (£20 000) per QALY gained. The net monetary benefit is computed as follows: (Total QALY for a procedure – Total QALY OPM) * £20 000 – (Total cost for a procedure – Total cost OPM). Only procedures with a net monetary benefit > 0 are acceptable at the £20 000 threshold.



7.5 Main drivers of the results of the economic evaluations

The six published studies reviewed above differed widely in terms of study design, time horizon, assumptions and data used, yielding different results and conclusions regarding the cost-effectiveness of vertebral augmentation techniques. Further the studies' conclusions were rarely robust and were highly sensitive to alternative plausible assumptions. Borgström et al.⁸¹ identified the main factors that drove such variations in the cost-effectiveness between the studies: time horizon, effect of treatment, extrapolation of the treatment effect, reduced number of hospital days associated with PVP or BKP, mortality benefit with treatment and treatment associated adverse events. Their findings on each factor are summarized below.

7.5.1 Time horizon

A full economic evaluation should include all the significant consequences related to the interventions under consideration, no matter when they occur. To capture those long-term consequences, modelling beyond the limited time horizon of the RCTs is usually needed. In Edidin et al.,⁷⁷ Klazen et al.²⁸ and Fritzell et al.,⁷⁸ the time horizon of the analysis was 3 (for costs), 2 and 1 year, respectively. Thus, any (positive or negative) consequence beyond these time frames is not considered. Ström et al.,⁷⁹ Svedbom et al.⁸⁰ and Stevenson et al.⁸ used modelling to capture the long-term effects of the interventions, which seems to be most appropriate here.

The impact of a different time horizon on the cost-effectiveness results is clearly illustrated by Ström et al.⁷⁹ where derivation of the results over a 2-year time horizon instead of 1-year almost doubled the ICER for BKP over OPM, i.e. from €10 900 per QALY gained at 1 year to €17 880 at 2 years.

7.5.2 Treatment QoL effect

Four studies based the QoL impact of vertebral augmentation techniques compared to OPM directly from the EQ-5D results of either the FREE^{32, 33} and/or the VERTOS II²⁸ RCT(s). Ström et al.⁷⁹ and Svedbom et al.⁸⁰ used the full dataset from the FREE trial but at a different timing: the first study used the one-year interim results,³² whereas the latter used the two-year final results.³³ In Fritzell et al.,⁷⁸ the total QoL impact was based on a small Swedish subset of patients in the FREE trial, and was found to be markedly

lower (0.085) than the total QoL impact if the whole population was used (0.21). This highlights the sensitivity of the results to the treatment QoL effect, and the importance to use local data with the difficulty to transfer the results to other countries. Klazen et al.²⁸ used the final one-year VERTOS II QoL impact data. Further, valuation of the EQ-5D descriptions in those studies was performed using either the UK tariffs (FREE trial) or the Dutch tariffs (VERTOS II), which could also lead to different QALY outcomes.

In Stevenson et al.⁸ treatment effects were explored in two scenarios. One scenario combined the results of a number of studies and performed a network meta-analysis on stable VAS scores which were then converted into EQ-5D scores using the estimated statistical relationship. Another scenario used the EQ-5D data directly reported from the FREE,³² INVEST²⁵ and Buchbinder²³ trials.

7.5.3 Extrapolation of the treatment effect

The observed time periods in RCTs are often limited and modelling is thus required to extend the analysis beyond this time horizon. As the effect of an intervention beyond the timeframe of the clinical trial is unknown, assumptions have to be formulated on the plausible extent and duration of this effect.

In Ström et al.,⁷⁹ Svedbom et al.⁸⁰ and some scenarios in Stevenson et al.,⁸ a 3-year effect on QoL after vertebral augmentation techniques was modelled although evidence from the trials only covers up to two years of follow-up. Further, although a statistically significant difference in EQ-5D at 24 months is well documented for BKP versus OPM from the non-blinded FREE trial (section 5.2), this does not seem to be the case for PVP as none of the RCTs reported a significant difference (section 5.1). Thus while there is some low-quality evidence to support the assumption of a longer-term differential outcome for BKP, the same assumption is more uncertain for PVP.



Given the remaining uncertainty, the economic evaluations modelling results to longer time periods should explore the impact of their extrapolation assumptions by presenting different scenarios: a scenario modelling a residual treatment effect, and a more conservative scenario assuming that the treatment effect disappears immediately in the extrapolated phase. Such a conservative scenario was modelled in Stevenson et al.⁸ where it was assumed that all benefit disappear at 12 months.

7.5.4 Reduced number of hospital days associated with kyphoplasty and vertebroplasty

In Ström et al.,⁷⁹ Svedbom et al.⁸⁰ and Stevenson et al.,⁸ one of the input variables that exerted the largest effect on the cost-effectiveness was the number of reduced hospital days associated with vertebral augmentation techniques compared to OPM. In the base-case analyses in Ström et al.⁷⁹ and Svedbom et al.,⁸⁰ it was assumed that PVP and BKP resulted in six fewer hospital days than OPM (i.e. on average 15 days in hospital for OPM versus 9 days for BKP and PVP, as reported in the UK study by Svedbom et al.⁸⁰) In Stevenson et al.,⁸ UK estimates for mean hospital lengths of stay were lower with 9.5 days (standard error, SE, 0.20) for OPM, and 6.2 (SE 0.94) and 5.1 days (SE 1.01) for PVP and BKP, respectively. By contrast, as computed in section 3.2, mean lengths of stay for Belgium (11.3 days for PVP and 10.7 days for BKP) appear much higher than those reported for the UK.

In sensitivity analyses, using no difference in the number of hospital days led to a three-fold increase in the cost-effectiveness ratios of BKP vs. OPM in Ström et al.⁷⁹ (i.e. from €10 900 to €38 000) and in Svedbom et al.⁸⁰ (i.e. from €3337 to €10 000). The three other economic evaluations included in this review did not assume any difference in duration of hospitalisation between BKP, PVP and OPM. Fritzell et al.⁷⁸ justify this as Swedish patients in the FREE trial were not found to have a reduced hospital length of stay with BKP compared to OPM.

So far, the lower length of stay associated with patients receiving kyphoplasty and vertebroplasty is not a precise empirical estimate but an approximation based mainly on expert opinion. Further Stevenson et al.⁸ report that both the pivotal trials and clinical advice about current practice suggest that the length of stay is considerably shorter than past hospital database would suggest. For this reason, although a highly influential

parameter, there is currently considerable uncertainty regarding the mean length of stay associated with each intervention, such that it is difficult to assess the validity of the estimates.

7.5.5 Mortality benefit with treatment

Svedbom et al.⁸⁰ and Edidin et al.⁷⁷ assumed mortality benefits for BKP and PVP compared to OPM, as did Stevenson et al.⁸ in some of their scenario analyses. In the two first studies the mortality impact of vertebral augmentation techniques was derived from a published analysis of US observational Medicare claims data.⁶² Based on this analysis, in Svedbom et al.,⁸⁰ relative mortality risks after BKP and PVP compared to OPM in patients with an osteoporotic VCF were set at 0.56 (95% CI: 0.55 to 0.57) and 0.76 (95% CI: 0.75 to 0.77) the first 4 years after fracture. The reduced mortality with both procedures had a significant impact on the results of those studies.

As reported in section 6.1, there are indeed some indications from RCTs that mortality after vertebroplasty might be lower, although none of the studies report a statistically significant difference in overall mortality. Another source of evidence for this assumption are clinical registry studies (e.g. the US Medicare claims data analysis by Edidin et al.⁶²) whose results suggest a mortality difference between non-operated vertebral fracture patients, receiving only OPM, and operated patients (by BKP or PVP).^{62, 86, 87} One major drawback of such registry analyses however is that they are based on observational data with no real control group and where treatment assignment is non-random. Such data can be subject to confounding factors that complicate the estimation of the treatment effect because of selection bias. It is difficult therefore to attribute a causal relationship between the surgical procedures and improved survival based on these mortality studies as none was randomised and, even if correction techniques are used, it is difficult to correct for all factors that influence mortality and likelihood to be treated.

Besides, a formal analysis of observational mortality data was undertaken by Stevenson et al.⁸ who concluded that it was not possible to say with certainty if there is a difference in mortality between patients undergoing BKP and PVP compared with OPM.



Given the current weak and contradictory evidence, it cannot be inferred with certainty whether there is a difference in mortality between patients undergoing BKP and PVP compared to OPM. As the cost-effectiveness of VCF techniques highly depends on this crucial parameter, and as suggested by the authors of the Stevenson paper, studies of the mortality effect should receive the highest priority for future research.

7.5.6 Treatment associated adverse events

Neither Ström et al.⁷⁹ nor Svedbom et al.⁸⁰ incorporated adverse events in their cost-effectiveness assessment, the former stating adverse events to be negligible and the second stating data on adverse events were lacking. By contrast, although limited to a 2-year time frame, Fritzell et al.⁷⁸ incorporated the adverse events occurring during this period with, among others, two BKP patients with severe adverse events associated with high costs. In Klazen et al.²⁸ and in Stevenson et al.⁸ costs related to adverse events were included in the (sensitivity) analysis. In Edidin et al.⁷⁷ no details were provided on how adverse events were handled.

As reported in section 6 above on safety issues, PVP and BKP are relatively safe procedures. Cement leakage is the most common adverse event related to such techniques but is often not clinically important. In some rare cases however, serious and even life-threatening complications may arise, that can be associated with very high costs. Although rare, these complications may affect the ICER. Adverse events should therefore at least be considered in the sensitivity analyses of the economic evaluations.

7.6 Discussion

This review of the literature identified six full economic evaluations of vertebral augmentation procedures including vertebroplasty and kyphoplasty. Those evaluations were mostly related to vertebral compression fractures of osteoporotic origin; economic evidence for non-osteoporotic fractures alone (e.g. malignant VCF) was not found.

There was a large diversity in the results of the studies. Out of the four studies comparing kyphoplasty directly to OPM, three reported that kyphoplasty was a cost-effective intervention,^{77, 79, 80} whereas the opposite was reported in one study.⁷⁸ Vertebroplasty was found to be dominant (i.e. both more clinically effective and less costly) over OPM in one study⁸⁰ and cost-effective in two other studies.^{28, 77} Whether kyphoplasty is cost-effective

compared to vertebroplasty remains uncertain because the analyses were mainly based on indirect comparisons. In two studies, vertebroplasty was reported to be (potentially) more cost-effective than vertebroplasty.^{77, 80} In a third study, either vertebroplasty or kyphoplasty were the most cost-effective interventions, depending on different plausible assumptions on mortality benefits between the interventions.⁸

This review further highlighted that the baseline assumptions across the economic evaluations were extremely diverse, and that their results were highly sensitive to changes in those assumptions. This is illustrated by the numerous sensitivity and scenario analyses performed in Stevenson et al.⁸ where each treatment appeared to be the most cost-effective dependent on the assumptions (all plausible) modelled. The main drivers of the cost-effectiveness results were:

- **The mortality benefit accorded to vertebral augmentation techniques.** This reduced mortality had a significant impact on the results of the cost-effectiveness studies. If the mortality benefit observed in non-randomised studies is accounted for, kyphoplasty and vertebroplasty could be considered cost-effective compared to OPM. So far however it is not possible to say with certainty if there is a difference in mortality between patients undergoing kyphoplasty and vertebroplasty compared to OPM. Studies of the mortality effect should be high up on the coming research agenda.
- **The assumed difference in length of stay associated with patients receiving kyphoplasty and vertebroplasty versus OPM.** Studies assuming such a difference resulted in more favourable ICERs for vertebral augmentation procedures. However, the length of stay associated with patients receiving kyphoplasty, vertebroplasty and OPM is not known with certainty such that prospective studies to record such values would be beneficial.



- **The treatment effect.** There remains considerable uncertainty about the efficacy and the effectiveness of either technique. There is some evidence from short-term non-blinded RCTs and observational studies that vertebroplasty and kyphoplasty result in better QoL outcome than OPM. Results from blinded RCTs however report no statistically significant difference. There is also no convincing evidence of a different clinically meaningful outcome between kyphoplasty and vertebroplasty. Ongoing studies should provide further evidence.

Furthermore, as stated in section 5 above, the quality of the evidence on the clinical effectiveness for both augmentation techniques is low to very low due to small RCTs and to the non-blinded nature of most of them. Only two small RCTs are blinded^{23, 25} but they are against OPLA, not OPM. However, results from another blinded RCT on vertebroplasty (VERTOS IV) are expected towards the end of 2015 or early 2016, and may be highly influential in future policy.

Therefore, given the lack of current knowledge and awaiting confirmation of the crucial assumptions listed above, it is difficult to currently draw definite conclusions regarding the cost-effectiveness of kyphoplasty and vertebroplasty (versus OPM, sham intervention or each other).

None of the six economic evaluations was performed in Belgium, with costs and outcome data reflecting the Belgian health care system and organisation. Such between-country differences are clearly illustrated by the higher lengths of hospital stay derived for vertebroplasty (11.3 days) and kyphoplasty (10.7 days) for Belgium, as compared to the UK lengths of stays used in Svedbom et al.⁸⁰ (9 days for both procedures) and Stevenson et al.⁸ (6.2 days for vertebroplasty and 5.1 days for kyphoplasty). The results of those published economic evaluations are therefore not directly transferable to Belgium. Context-specific studies are always preferred and as such only the development of a model reflecting the Belgian situation and consequences could provide an assessment of the cost-effectiveness of the use of vertebroplasty and kyphoplasty in Belgium. However the literature review highlighted the great uncertainty surrounding some crucial baseline parameters determining the cost-effectiveness of vertebroplasty and kyphoplasty. Those uncertainties should first be addressed before providing further full economic evaluations on this topic.



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