Original Article

# Risk of new vertebral compression fractures and serious adverse effects after vertebroplasty: a systematic, critical review and meta-analysis of randomized controlled trials

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**Background:** Osteoporotic vertebral fractures (OVFs) significantly impact morbidity, mortality, functionality, and quality of life. Vertebroplasty, a widely utilized treatment for OVFs, has its efficacy and safety debated due to varying outcomes reported across clinical trials and meta-analyses. This study aims to critically review and conduct a meta-analysis of randomized controlled trials (RCTs) focusing on the safety of vertebroplasty, specifically its association with serious adverse effects and the development of new vertebral fractures, while exploring potential confounders.

**Methods:** We conducted a systematic review and meta-analysis by searching PubMed, Web of Science, and EMBASE. The search was updated to February 23, 2024. We included published RCTs comparing vertebroplasty to conservative treatment (CT) or placebo/active control, focusing on new fractures and serious adverse effects. The primary outcomes were "incidence of new fractures" and "serious adverse effects". We applied the Dersimonian-Laird method with a random effects model to estimate risk ratios (RRs) of the primary outcomes, using the $I^2$ statistic to assess heterogeneity among studies. Sensitivity analyses were conducted when significant heterogeneity was detected. Subgroup analyses were performed based on the characteristics of the control groups, risk of bias based on The Cochrane Risk of Bias Tool 2, time from fracture onset, and multicentric versus single-center trials.

**Results:** In total, 14 RCTs encompassing 1,413 patients were analyzed. High and unclear risk of bias were observed in 15 and 25 items, respectively. No significant difference was observed in the incidence of new vertebral fractures between vertebroplasty and the control groups [RR =1.05, 95% confidence interval (CI): 0.71–1.56; $I^2$=55%; P<0.01]. However, vertebroplasty was associated with a significantly lower incidence of serious adverse effects (RR =0.53, 95% CI: 0.31–0.91; $I^2$=0%; P=0.93). Subgroup analyses revealed no significant differences based on control types, risk of bias, or number of institutions involved. Notably, early

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vertebroplasty (within 6 weeks of symptom onset) showed a protective effect against new vertebral fractures (RR =0.60, 95% CI: 0.38–0.92; $I^2$=0%; P=0.53). The sensitivity analysis showed that one study influenced the observed heterogeneity but did not significantly modify the pooled estimate.

**Conclusions:** Vertebroplasty is not associated with an increased risk of developing new vertebral fractures and may reduce the risk of serious adverse effects compared to placebo or CT. Early intervention post-fracture appears beneficial. However, the limited number and quality of RCTs call for further high-quality studies.

**Keywords:** Vertebroplasty; osteoporosis; vertebral fracture; randomized controlled trial (RCT); adverse effects

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## Introduction

Osteoporosis is the most prevalent metabolic disease worldwide (1). The main clinical consequence of this pathology is an increased risk of fragility fractures (2). Osteoporotic vertebral fractures (OVFs) are the most common type of osteoporotic fractures. Approximately 20–25% of white men and women over the age of 50 years exhibit a prevalent vertebral fracture (3). Although not all OVFs are clinically significant, the majority entail substantial morbidity in terms of pain, functionality, and quality of life, as well as a significant increase in mortality (3). Their detection directly leads to the diagnosis of osteoporosis and the subsequent initiation of treatment, which should initially be conservative, encompassing physical measures and pharmacological management (4).

Vertebroplasty is a technique widely used in clinical practice for the treatment of OVFs. Despite its widespread use, there is controversy over its efficacy and safety, stemming from contradictory outcomes in different clinical trials and meta-analyses (5-7). Generally considered safe, this technique is not without potential complications and serious adverse effects, such as nerve root compression due to cement leakage (8) or pulmonary embolism (9). Moreover, it is crucial to consider serious adverse effects with a less direct association with the procedure, such as deep vein thrombosis (DVT) or infections (10). Another clinically relevant aspect related to the safety of vertebroplasty is the incidence of new fractures. There are significant controversies regarding the safety and efficacy of vertebroplasty in this context, as some studies (11) have found an increased risk of new OVFs following vertebroplasty, while findings from other studies did not support such risk (12).

Although various meta-analyses on the efficacy and safety of vertebroplasty exist, few have specifically addressed these variables. Most of these meta-analyses include retrospective clinical studies with potential methodological biases that may be influenced by various confounding factors, limiting their generalizability (13,14). On the other hand, meta-analyses based on randomized clinical trials (RCTs) show contradictions (6,15,16). Factors such as methodological quality, characteristics of the control group, or time from fracture onset to treatment initiation have been proposed as potential confounders that could explain such discrepancies. In addition, other variables such as the number of institutions participating in the trials have not been explored in this setting. The recent publication of the VERTOS V clinical trial (17) could contribute to the quantitative synthesis of the available evidence to establish the efficacy and safety of vertebroplasty.

The aim of this work is to conduct a critical review and meta-analysis of the available evidence based on RCTs regarding the safety of vertebroplasty in terms of serious adverse effects and the development of metachronous vertebral fractures, exploring potential confounders and their significance in this scenario. We present this article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-396/rc).

## Methods

### *Eligibility criteria*

The design of the meta-analysis and the selection criteria were based on the PICO search strategy. The population was formed by patients with OVF susceptible of vertebroplasty or conservative treatment (CT); the

 

intervention was vertebroplasty; the comparators were CT or placebo/active control; and the primary outcomes were incidence of new fractures and serious adverse effects. The PRISMA (18) guidelines were followed in the design and writing of the study.

Accordingly, the inclusion criteria were the following: published RCTs on vertebroplasty versus CT or placebo/active control for OVFs which included quantitative results on at least one of the primary outcomes on both arms. The exclusion criteria were studies with non-OVFs, editorials, letters, abstracts, or conference proceedings.

### *Information sources and search strategy*

Two authors (A.J.L.R.B. and P.M.J.G.) searched the PubMed, Web of Science, and EMBASE databases. Different search strategies were carried out and a final consistent equation was constructed as follows: "Vertebroplasty AND osteopor* AND ("conservative treatment" OR "placebo") (Appendices 1-3). To increase the sensitivity of the search, references of all fully-read articles were also examined. No date or language restrictions were established. The search was updated to February 23, 2024.

All titles and abstracts of interest were screened and those which did not meet the eligibility criteria were excluded. Subsequently, the screened studies were fully read to assess whether they met all eligibility criteria. *Figure 1* shows the flow diagram of the study.

### *Measured variables*

The primary outcomes were the following:

(I) Development of new vertebral fractures on follow-up. The total number of adjacent or remote vertebral fractures reported in each RCT was obtained.

(II) Serious adverse effects on follow-up. These were defined as any event reported as such by the study authors or requiring medical hospitalization. Of note, complications not requiring additional measures such as non-symptomatic cement leaks were excluded.

### *Subgroup analyses*

When significant heterogeneity ($I^2$>40%) was present, we performed subgroup analyses for the following variables:

(I) Type of comparator used in the control group (placebo/active control *vs.* CT).

(II) Risk of bias according to the Risk of Bias Tool v. 2 (19) (see below). Studies were dichotomized into low *vs.* unclear/high-risk of bias. To be classified in the latter category, at least two items had to be classified as high-risk of bias, or at least 3 as unclear risk of bias items.

(III) Time from fracture onset to intervention. Studies were dichotomized into trials with OVFs ≤6 and >6 weeks before treatment initiation. This cut-off was chosen based on previous studies which found different outcomes between PVP and control groups for this time point (see discussion) (6).

(IV) Number of institutions involved in the RCT (single *vs.* multicentric).

### *Data extraction*

Two authors (A.J.L.R.B. and P.M.J.G.) independently extracted the data from the selected articles and the senior author (F.R.S.) reviewed the data and solved any discrepancies. If there were several publications on the same RCT that met these criteria, those with data covering the longest follow-up period were selected. All data were stored using a spreadsheet designed for such purpose.

### *Risk of bias and publication bias*

The Cochrane Risk of Bias Tool v. 2 (ROB2) (19) was used to systematically assess the existence of potential biases. For each RCT, two authors (L.B.C. and B.M.C.) classified the risk of bias as low, intermediate, or high. In case of discrepancy, the senior author (F.R.S.) was consulted to reach consensus. The publication bias was analyzed by means of funnel plots and Egger's test.

### *Statistical analysis*

We applied the Dersimonian-Laird method with a random effects model to estimate risk ratios (RRs) for the primary outcomes due to the anticipated heterogeneity among studies and to ensure a robust estimation of the overall effect size. We applied the $I^2$ statistic to assess heterogeneity among studies with non-relevant, moderate, and considerable cut-off values set at $I^2$<40%, 40%≤$I^2$≤75%, and $I^2$>75%, respectively (20). Sensitivity analyses were carried out in the cases of significant heterogeneity ($I^2$>40%) by consecutive elimination of each study in order to estimate

 

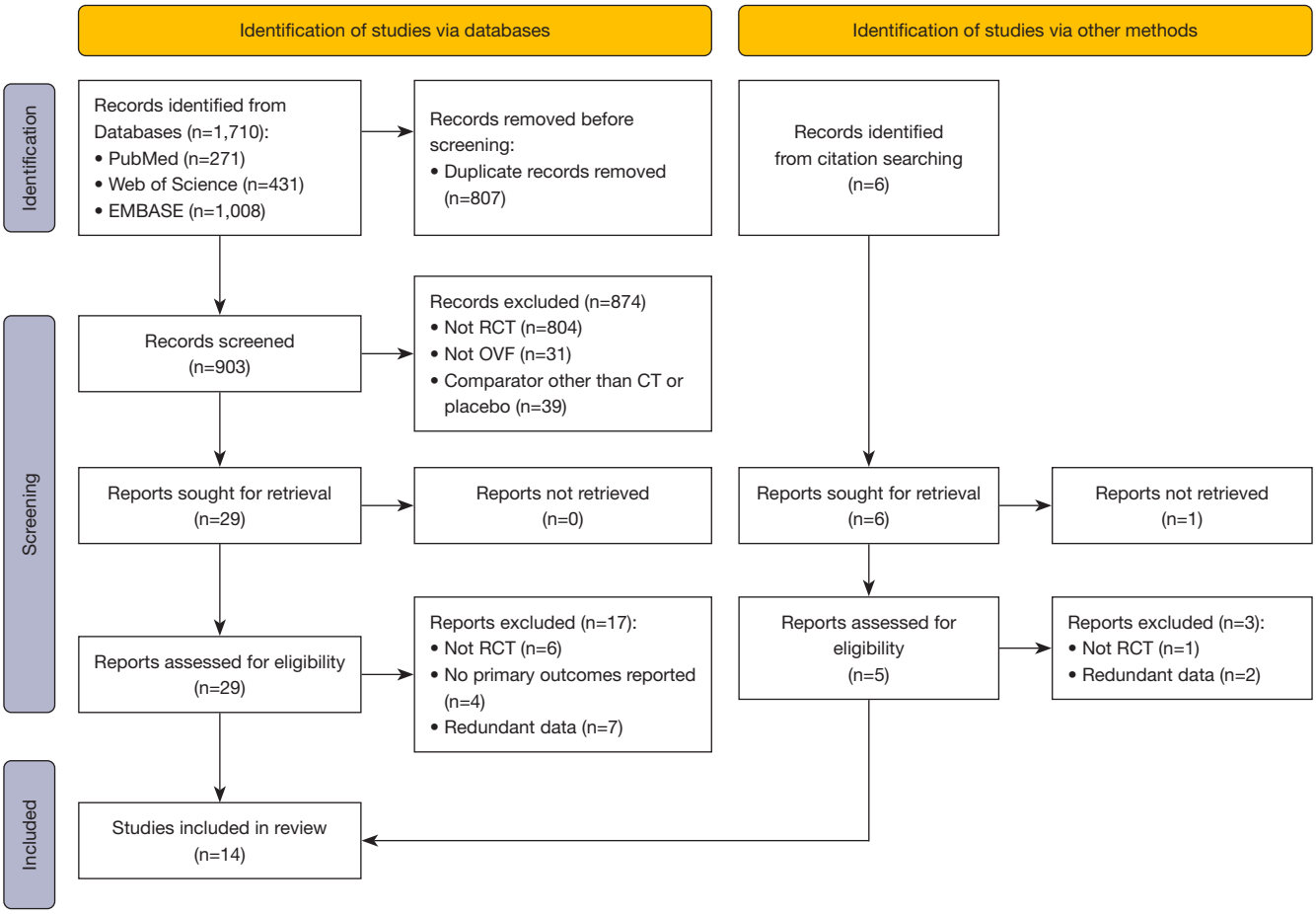


**Figure 1** Flow diagram of the meta-analysis. RCT, randomized control trial; OVF, osteoporotic vertebral fracture.

its contribution to the pooled estimates. To visually display the results, forest plots were generated, showing the effect sizes and 95% confidence intervals (CIs) for individual studies as well as the overall pooled estimate.

Two-tailed tests were performed with significant values set at P<0.05. All statistical analyses were carried out with software R (version 4.3.2 for Windows) (21) using the 'meta' package (22).

## Results

### *Baseline characteristics of patients*

A total of 14 RCTs were included in the meta-analysis (11,12,17,23-33). These RCTs encompassed data from 1,413 patients, of which 711 were in the vertebroplasty group and 702 in the control group (312 and 390 in the placebo/active control and CT groups, respectively). The RCT with a lowest sample size included 40 patients (27) and the largest one included 202 patients (24). Of the 14 RCTs, 8 compared vertebroplasty versus CT (24-30,33) and 6 compared vertebroplasty versus placebo (11,12,17,23,31,32). *Table 1* summarizes the baseline characteristics of participants in each study.

### *Incidence of new vertebral fractures*

A total of 13 RCTs reported outcomes on the incidence of new vertebral fractures on follow-up, including 595 patients in the experimental group and 579 patients in the control group. No significant between-group differences were observed (RR, 1.05; 95% CI: 0.71–1.56) and the heterogeneity was moderate ($I^2$=55%; P<0.01). *Figure 2* shows the forest plot of this analysis.

**Table 1** Baseline characteristics of patients in each study included in the meta-analysis

| Authors (year) | Group | N | Age (years)* | M/F ratio | OVF duration** | F-U | New fractures, N (%) | Adverse effects, N (%) |
|---|---|---|---|---|---|---|---|---|
| Blasco *et al.* (2012) (26) | VP | 64 | 71.3 (10.0) | 17/47 | 140.3 (96.1) | 12 | 29 (45.3) | – |
| | CT | 61 | 75.3 (8.5) | 11/50 | 143.1 (130.3) | 12 | 8 (13.1) | – |
| Buchbinder *et al.* (2009) (11) | VP | 38 | 74.2 (14) | 7/31 | 9 W (IQR, 3.8–13) | 24 | 17 (44.7) | 2 (5.3) |
| | Placebo | 40 | 78.9 (9.5) | 9/31 | 9.5 W (IQR, 3–17) | 24 | 10 (25) | 2 (5.0) |
| Carli *et al.* (2023) (17) | VP | 40 | 69 (10.0) | 13/27 | >3 mo | 1 | 7 (17.5) | 0 (0) |
| | Placebo | 40 | 71 (10.0) | 13/27 | >3 mo | 1 | 6 (15.0) | 1 (2.5) |
| Chen *et al.* (2010) (27) | VP | 18 | 77.5 (0.8) | 4/14 | <6 W | 3 | 1 (5.6) | – |
| | CT | 22 | 76.3 (0.5) | 6/16 | <6 W | 3 | 0 (0) | – |
| Chen *et al.* (2014) (28) | VP | 46 | 64.6 (9.1) | 14/32 | 7.1 (3.0) | 12 | 4 (8.7) | – |
| | CT | 47 | 66.5 (9.1) | 13/30 | 6.8 (2.5) | 12 | 7 (14.9) | – |
| Chen *et al.* (2015) (33) | VP | 42 | 67 (8.4) | 18/24 | – | 34.7 | 4 (9.5) | 4 (9.5) |
| | CT | 42 | 66.1 (8.7) | 19/23 | – | 34.7 | 3 (7.1) | 8 (17.0) |
| Clark *et al.* (2016) (31) | VP | 61 | 80 (7.0) | 13/48 | 2.8 W (1.6) | 6 | 3 (4.9) | 2 |
| | Placebo | 59 | 81 (7.0) | 19/40 | 2.4 W (1.4) | 6 | 7 (11.9) | 2 |
| Farrokhi *et al.* (2011) (30) | VP | 40 | 72 (59–90) | 10/30 | 27 W (4–50) | 36 | 1 (2.5) | – |
| | CT | 42 | 74 (55–87) | 12/30 | 30 W (6–54) | 36 | 6 (14.3) | – |
| Firanescu *et al.* (2018) (12) | VP | 90 | 74.7 (10.7) | 23/67 | 43 (29–52) | 12 | 31 (34.4) | – |
| | Placebo | 86 | 76.9 (8.1) | 20/66 | 36 (24–51) | 12 | 28 (3.3) | – |
| Hansen *et al.* (2016) (32) | VP | 22 | 70.6 (54–90) | 4/18 | 74.7 (4.6) | 12 | 4 (18.2) | – |
| | Placebo | 24 | 69.3 (53–84) | 2/22 | 76.1 (4.4) | 12 | 5 (20.8) | – |
| Kallmes *et al.* (2009) (23) | VP | 68 | 73.4 (9.4) | 15/53 | 16 W (IQR, 10–36) | 1 | – | 1 (1.5) |
| | Placebo | 63 | 74.3 (9.6) | 17/46 | 20 W (IQR, 8–38) | 1 | – | 1 (1.6) |
| Klazen *et al.* (2010) (24) | VP | 101 | 75.2 (9.8) | 31/70 | 29.3 (17.1) | 12 | 18 (17.8) | – |
| | CT | 101 | 75.4 (8.4) | 31/70 | 26.8 (16.0) | 12 | 30 (29.7) | – |
| Rousing *et al.* (2009) (25) | VP | 25 | 80 (65–96) | 6/19 | 8.4 (3.7–13) | 12 | 3 (12.0) | – |
| | CT | 24 | 80 (71–93) | 3/21 | 6.7 (2.1–11.4) | 12 | 1 (4.2) | – |
| Yang *et al.* (2016) (29) | VP | 56 | 77.1 (6.0) | 20/36 | 5.5 (3.9) | 12 | 5 (8.9) | 9 (16.1) |
| | CT | 51 | 76.2 (5.6) | 18/33 | 5.6 (3.8) | 12 | 4 (7.8) | 18 (35.3) |

*, data are expressed as mean (standard deviation) or as mean (range), as provided in the original study; **, in days if not otherwise specified (i.e., weeks or months). M, male; F, female; OVF, osteoporotic vertebral fracture; F-U, maximum length of follow-up in months; VP, vertebroplasty; CT, conservative treatment; W, weeks; IQR, interquartile range; mo, months.

### *Serious adverse effects*

A total of 6 RCTs reported outcomes on serious adverse effects on follow-up, including 305 patients in the experimental group and 295 patients in the control group. Significant between-group differences were observed favoring the vertebroplasty group (RR, 0.53; 95% CI: 0.31–0.91) and the heterogeneity was null ($I^2$=0%; P=0.93). *Figure 3* shows the forest plot of this analysis.

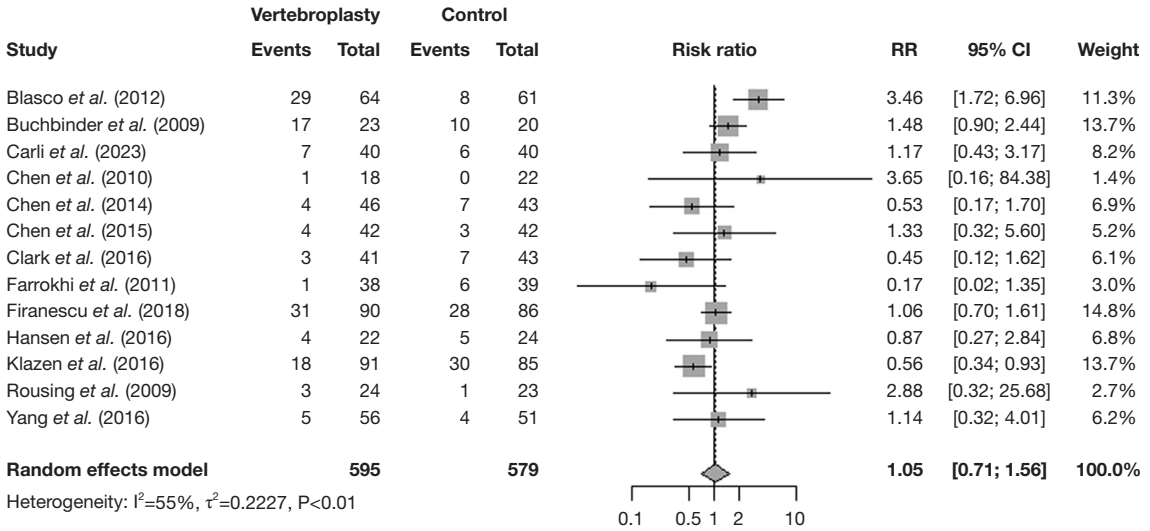


**Figure 2** Forest plot for the comparison of the risk of new incident vertebral fractures following vertebroplasty versus placebo/active control or conservative treatment. RR, relative risk; CI, confidence interval.

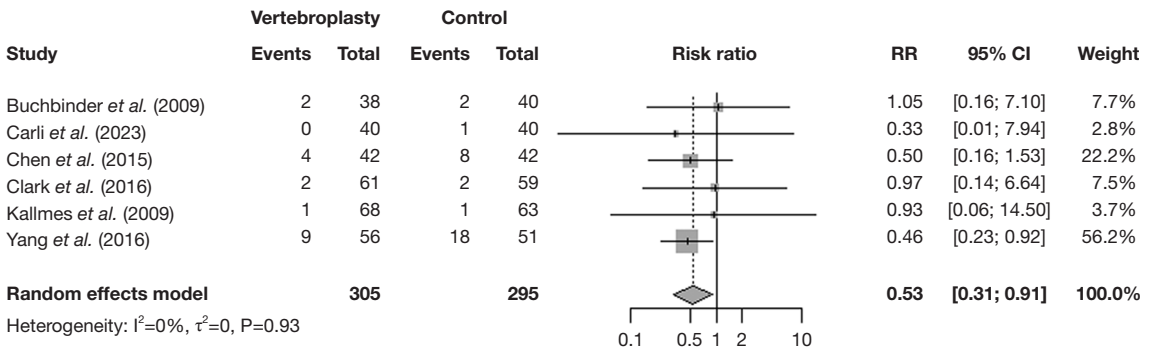


**Figure 3** Forest plot for the comparison of the risk of serious adverse effects following vertebroplasty versus placebo/active control or conservative treatment. RR, relative risk; CI, confidence interval.

### *Subgroup analyses*

Subgroup analyses were conducted for the primary outcome "incidence of new vertebral fractures", but not for the other primary outcome due to the low number of RCTs (n=6). Forest plot analysis for each subgroup revealed the following results:

(I) Subgroup analysis based on the characteristics of the control group (CT *vs.* placebo/active control, *Figure 4*):
  (i) Vertebroplasty versus CT: eight RCTs with 379 patients in the experimental group and 366 patients in the control group reported outcomes for this comparator. The results showed no significant between-group differences (RR, 1.07; 95% CI: 0.50–2.31) and the heterogeneity was moderate ($I^2$=69%; P<0.01).
  (ii) Vertebroplasty versus placebo: five RCTs with 216 patients in the experimental group and 213 patients in the control group reported outcomes in for this comparator. The results showed no significant between-group differences (RR, 1.13; 95% CI: 0.85–1.50) and the heterogeneity was not statistically significant ($I^2$=0%; P=0.90).

(II) Subgroup analysis based on the risk of bias of each

 

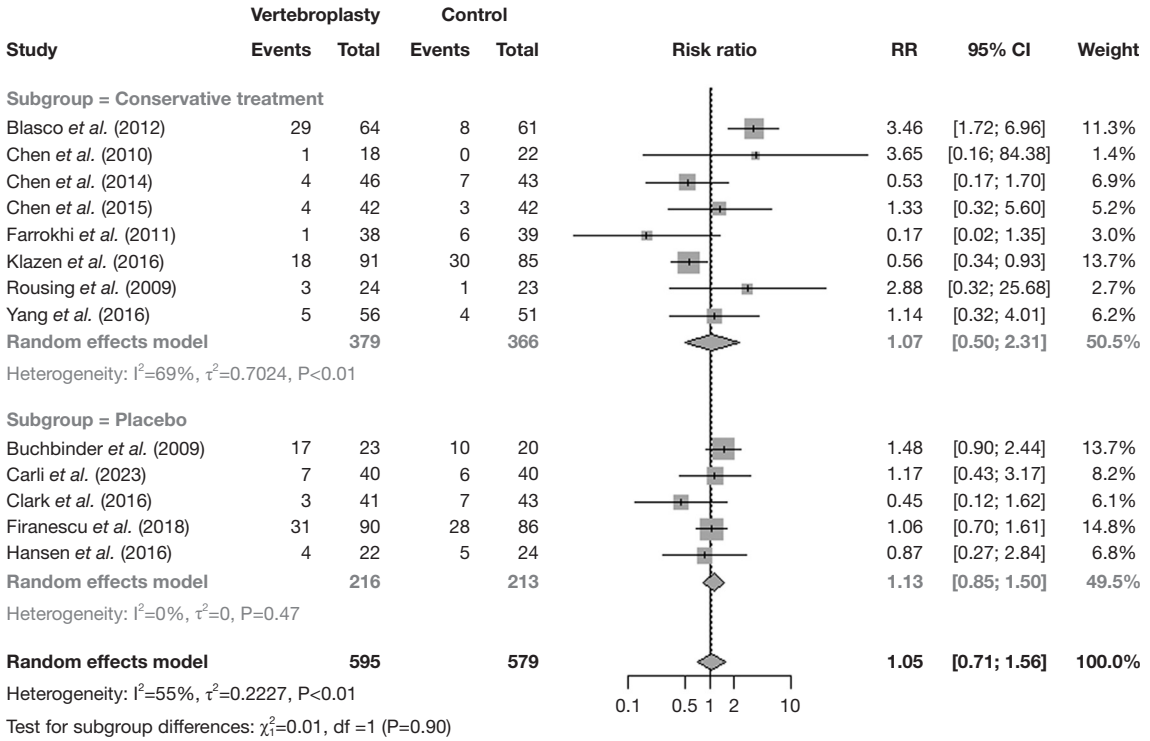


**Figure 4** Subgroup analysis. Forest plot for the comparison of the risk of new incident vertebral fractures according to the characteristics of the control group (placebo/active control *vs.* conservative treatment). RR, relative risk; CI, confidence interval.

RCT (unclear-high risk *vs.* low-risk, *Figure 5*):

(i) Unclear-high risk of bias: six RCTs with 250 patients in the experimental group and 242 patients in the control group were classified in this category and reported outcomes for this variable. The results showed no significant between-group differences (RR, 1.61; 95% CI: 0.78–3.34) and the heterogeneity was not statistically significant, although with a trend toward significance ($I^2$=42%; P=0.13).

(ii) Low risk of bias: seven RCTs with 345 patients in the experimental group and 337 patients in the control group were classified in this category and reported outcomes for this variable. The results showed no significant between-group differences (RR, 0.86; 95% CI: 0.57–1.30) and the heterogeneity was moderate with a trend toward significance ($I^2$=51%; P=0.06).

(III) Subgroup analysis based on the time from fracture onset (>6 *vs.* ≤6 weeks, *Figure 6*):

(i) Delayed intervention (>6 weeks): ten RCTs with 407 patients in the experimental group and 400 patients in the control group were classified in this category. The results showed no significant between-group differences (RR, 1.28; 95% CI: 0.84–1.93) and the heterogeneity was not statistically significant, although with a trend toward significance ($I^2$=44%; P=0.07).

(ii) Early intervention (≤6 weeks): three RCTs with 188 patients in the experimental group and 179 patients in the control group were classified in this category. The results showed significant between-group differences favoring the experimental group (RR, 0.60; 95% CI: 0.38–0.92) and the heterogeneity was not statistically significant ($I^2$=0%; P=0.53).

(IV) Subgroup analysis based on the number of institutions involved (single *vs.* multicentric, *Figure 7*):

(i) Single-center studies: nine RCTs with 350 patients in the experimental group and 345 patients in the control group were classified in this category. The results showed no significant between-group differences (RR,

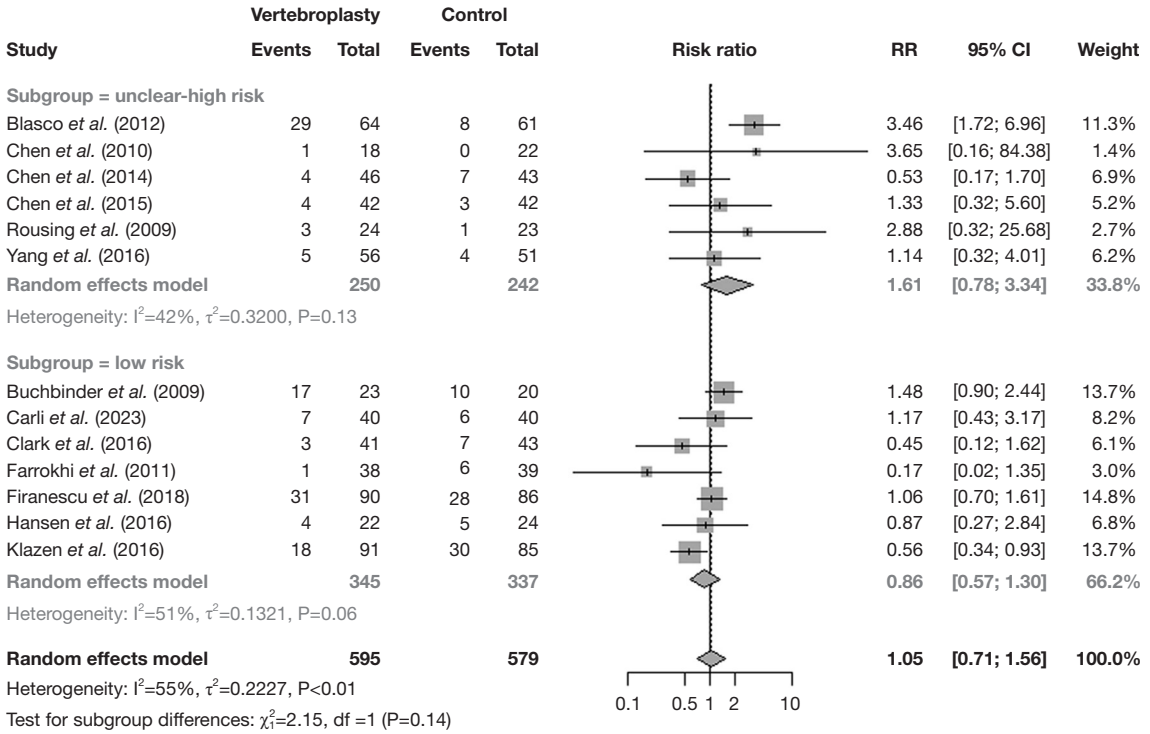


**Figure 5** Subgroup analysis. Forest plot for the comparison of the risk of new incident vertebral fractures according to the risk of bias of each RCT (unclear/high risk of bias *vs.* low risk of bias). RR, relative risk; CI, confidence interval; RCT, randomized controlled trial.

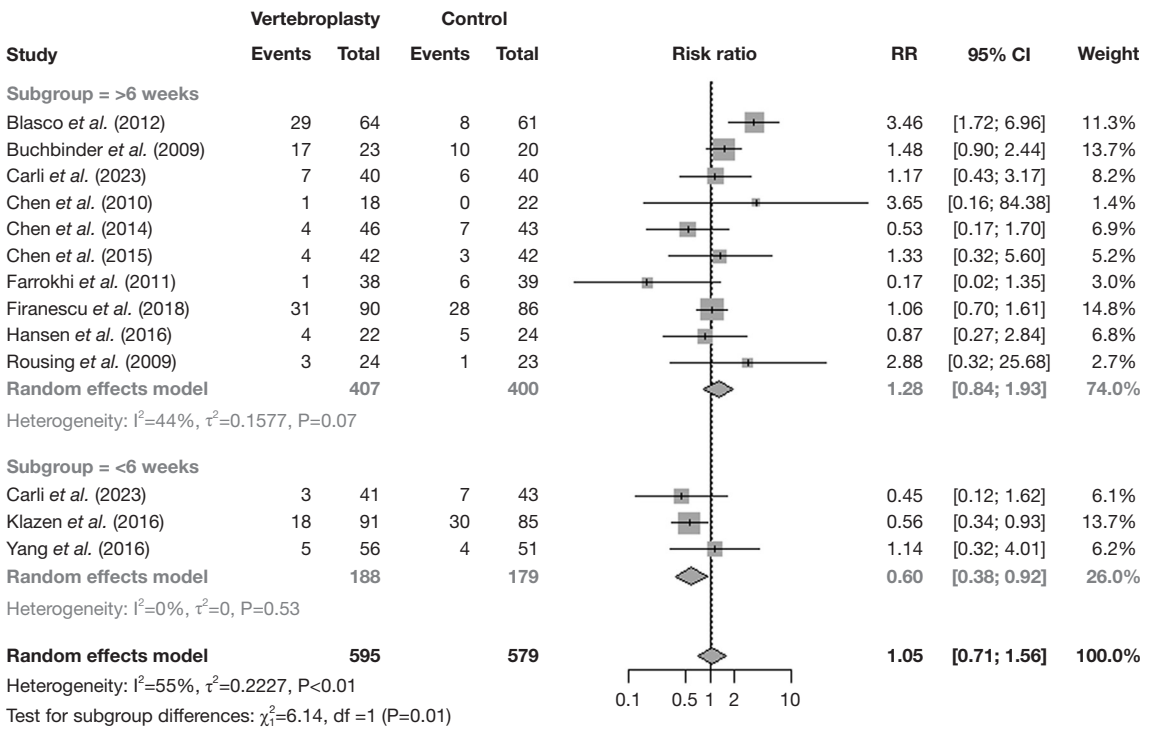


**Figure 6** Subgroup analysis. Forest plot for the comparison of the risk of new incident vertebral fractures according to the time from fracture onset to treatment administration (>6 *vs.* ≤6 weeks). RR, relative risk; CI, confidence interval.

 

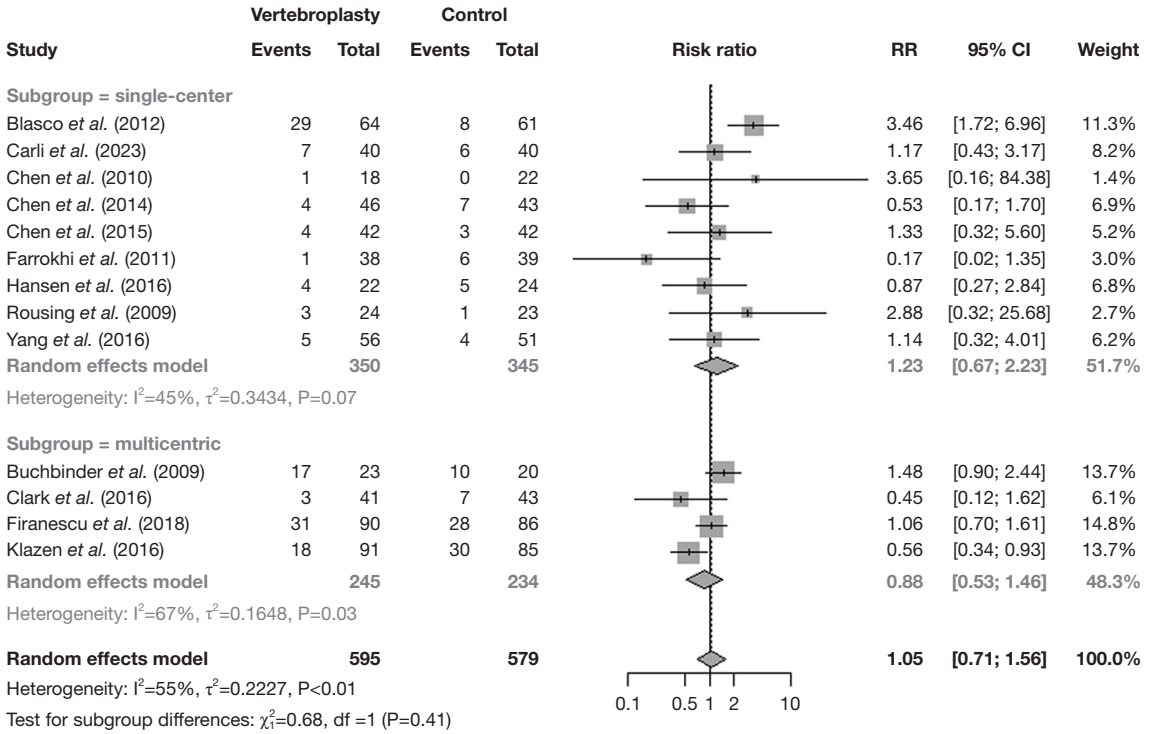


**Figure 7** Subgroup analysis. Forest plot for the comparison of the risk of new incident vertebral fractures according to the number of institutions involved (single-center *vs.* multicentric). RR, relative risk; CI, confidence interval.

1.23; 95% CI: 0.67–2.23) and the heterogeneity was not statistically significant, although with a trend toward significance ($I^2$=45%; P=0.07).

(ii) Multicentric studies: four RCTs with 595 patients in the experimental group and 579 patients in the control group were classified in this category. The results showed significant between-group differences favoring the experimental group (RR, 0.88; 95% CI: 0.53–1.46) and the heterogeneity was moderate ($I^2$=67%; P=0.03).

### *Risk of bias and publication bias*

High risk of bias was judged in different trials, specifically performance bias (n=6), detection bias (n=6), attrition bias (n=2), and other bias (n=1). In addition, several RCTs were judged to have an unclear risk of bias due to insufficient information on obtaining the sequence of randomization (n=2), allocation concealment (n=5), performance bias (n=1), attrition (n=7), reporting bias (n=9), or other bias (n=1). The remainder were judged to have low risk of bias. *Figure 8* summarizes the assessment of the risk of bias in the RCTs included in the meta-analysis.

Regarding publication bias, the shape of the funnel plot for the studies involved in the primary outcome "incidence of new fractures" indicated no significant biases (*Figure 9*), which was supported by the results of the Egger's test (t=0.14; P=0.898). No publication bias analysis was performed for the primary outcome 'adverse effects' due to the low number of studies involved.

### *Sensitivity analyses*

The sensitivity analysis for the primary outcome 'incidence of new fractures' showed that subtraction of the results of the study by Blasco *et al.* (2012) led to significantly decreased heterogeneity in the short-term ($I^2$ decreased from 54% to 26.1%), but no significant change in the pooled estimate was observed (RR, 0.919; 95% CI: 0.672–1.257). The rest of studies showed no significant modifications in $I^2$ values. No significant changes in the sensitivity analysis were observed for primary outcome "adverse effects" ($I^2$=0%) (Appendix 4).

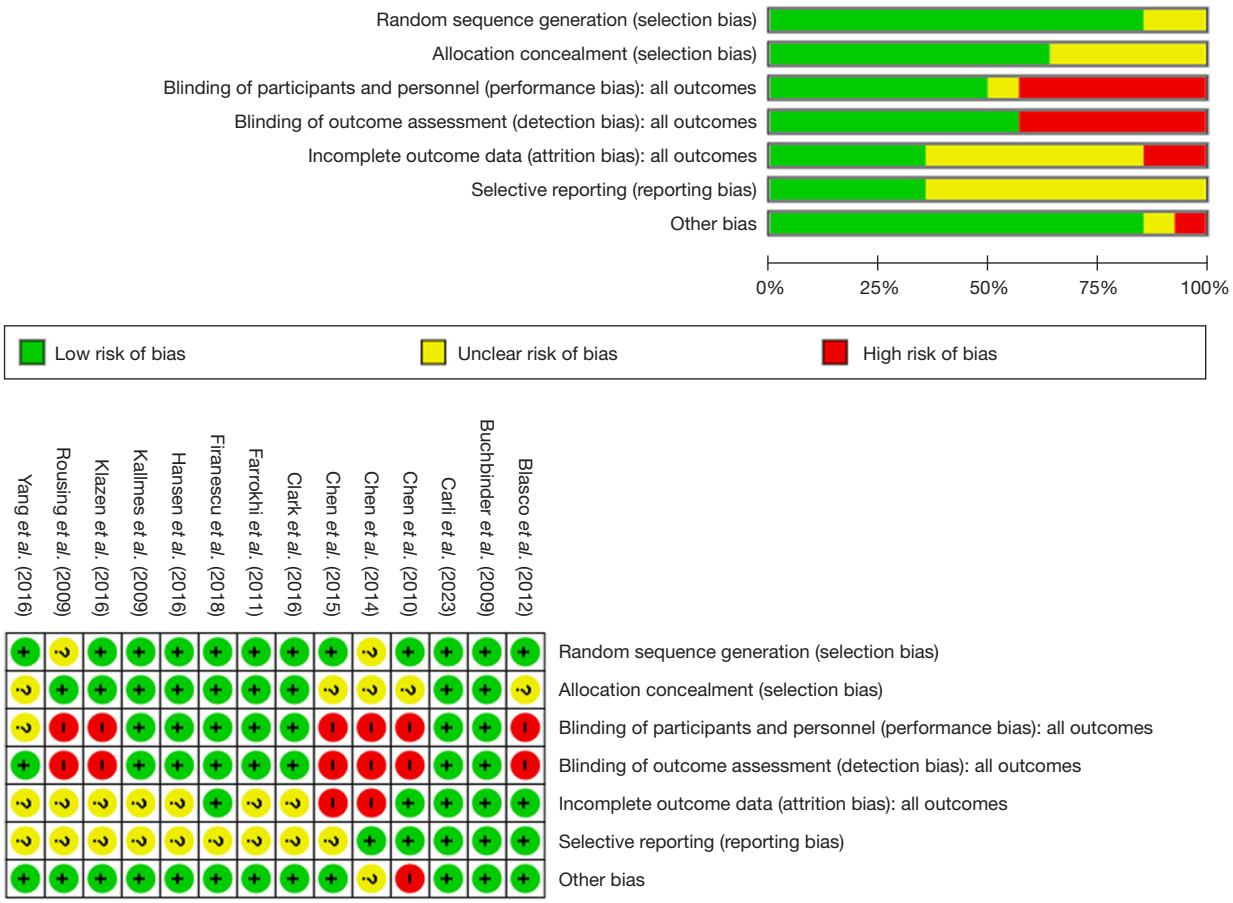


**Figure 8** Risk of bias of the studies included in the meta-analysis.

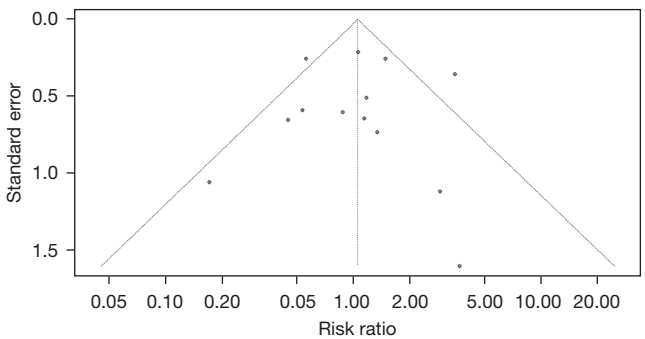


**Figure 9** Funnel plot of the studies reporting data on the primary outcome "incidence of new vertebral fractures".

## Discussion

Our meta-analysis included 14 studies encompassing over 1,400 patients, being the largest meta-analysis of RCTs on the safety of vertebroplasty to date. We found no statistically significant differences in the development of new incident OVFs between vertebroplasty and CT or placebo (13 RCTs, 1,179 patients). In addition, early (<6 weeks) vertebroplasty was shown to be associated with a lower risk of developing new incident OVFs. Other potential confounders (i.e., control group, risk of bias, number of institutions participating in the study) did not significantly modify this outcome. Moreover, a significantly lower risk of serious adverse effects was observed in vertebroplasty compared to CT/placebo. However, the limited number of studies (6 RCTs with 600 patients) precluded subgroup analyses for this outcome. Finally, we found a moderate-to-low quality of most RCTs, and no signs of publication bias were identified.

Previous studies have reported discordant results regarding the incidence of new fractures after vertebroplasty. The RCTs by Buchbinder *et al.* (11) and Farrokhi *et al.* (30) found that vertebroplasty is a risk

 

factor for this outcome, which was supported by a recent meta-analysis by Qiu *et al.* (34). However, other meta-analyses have found that vertebroplasty is not associated with an increased risk for new OVFs. For instance, the Cochrane meta-analysis by Buchbinder *et al.* (15) found that, although a slightly higher number of new incident OVFs were observed in patients treated with vertebroplasty, this difference was not statistically significant. This is in agreement with other studies, including several RCTs and meta-analyses (12,29,35-37). Our results showed that vertebroplasty is not associated with a higher risk of new incident vertebral fractures, and a potential confounder explaining discrepancies in previous results might lie in the time interval between fracture onset and treatment.

Regarding the development of adverse effects, previous meta-analyses have analyzed complications such as cement leaks (13). However, in most cases cement leaks are asymptomatic (38), thus our meta-analysis focused on serious adverse effects, which may affect the quality of life and increase mortality risk. The meta-analysis by Buchbinder *et al.* (15) found a lower number of serious adverse effects in patients treated with vertebroplasty compared to placebo/CT, but these differences did not reach statistical significance. On the basis of this conclusion, the Second ASBMR Task Force Report concluded that there is limited evidence to determine the risk of serious adverse effects (39). Conversely, our results clearly suggest that vertebroplasty is associated with a lower number of serious adverse effects compared to placebo or CT. We hypothesize that this may be explained by a faster patient recovery (i.e., lower pain and improved functionality). This leads to decreased hospitalization time and its associated morbidity, as well as faster patient mobilization, reducing complications such as DVT. One drawback of our findings is the low number of serious adverse effects reported across RCTs and the laxity to consider them as serious or not.

In relation to subgroup analyses, we found no significant differences in the incidence of new OVFs according to the type of control group (placebo *vs.* CT), risk of bias (unclear/high risk *vs.* low risk) or number of institutions involved (single *vs.* multicentric) (7). Interestingly, we found that the subgroup analysis based on the time from fracture onset revealed that when vertebroplasty was performed in the first 6 weeks, the experimental group showed a significantly lower risk of developing new vertebral fractures compared to placebo or CT. This finding suggests a time-dependent protective effect. Notably, early treatment with vertebroplasty has also been associated with better outcomes in terms of pain, functionality and quality of life (7,40,41), which reinforces the importance of patient selection according to fracture evolution. We hypothesize that vertebroplasty contributes to faster healing and fixing the fracture site, improving segmental stability and thus decreasing the risk of metachronous fractures, especially in adjacent levels.

Notably, there is no consensus on the cut-off point to define an 'early' OVF for treatment administration in the current literature. The VAPOUR trial used a 6-week cut-off to recruit patients for early vertebroplasty. This decision was grounded on clinical observations from early case series and on the histological changes proven in vertebral bone biopsies harvested from patients at the time of vertebroplasty (42). Similarly, the VERTOS 2 trial (24) and the RCT by Yang *et al.* (29) showed clear efficacy benefits favoring vertebroplasty performed before 6 weeks. Previous meta-analyses have also found differential benefits of vertebroplasty in terms of efficacy using this cut-off (6). Overall, this seemed sufficient rationale to establish this cut-off point in our meta-analysis. However, there are discrepancies with other RCTs and reviews. For instance, the cut-off to consider an OVF as 'chronic' in VERTOS V was 3 months, while subgroup analyses of the VAPOUR trial showed that improved benefits in efficacy could be obtained in patients treated before 3 weeks (43). Future studies should further investigate this issue to set the optimal moment for vertebroplasty treatment.

The main strengths of this meta-analysis are the specific inclusion of RCTs, which reduces potential biases compared to other trial modalities and study designs, providing reliable evidence, and the number of trials analyzed, which makes up the largest meta-analysis of RCTs comparing the incidence of vertebral fractures and serious adverse effects in vertebroplasty versus CT or placebo. Among the limitations of the study, it is worth noting the low number of studies evaluating the outcome "serious adverse effects" and the lack of homogeneity regarding its definition among RCTs, the need for establishing an optimal cut-off to define 'early' OVFs, the significant heterogeneity for the outcome "incidence of new fractures", and the moderate-to-low quality evidence of several of the included RCTs. Finally, the role of potential confounders such as the type of OVF or the degree of vertebral collapse (44) was not addressed and should be explored in future RCTs and meta-analyses.

## Conclusions

This meta-analysis found that vertebroplasty is not

associated with a higher risk of developing new vertebral fractures and is a protective factor against serious adverse effects compared to placebo or CT. In addition, the application of vertebroplasty during the first 6 weeks after symptoms onset is associated with a lower risk of developing new vertebral fractures, which reinforces the importance of early treatment application. However, there are some limitations regarding the number and quality of RCTs that need to be overcome in future studies.

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## References

1. Willers C, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, McCloskey EV, Borgström F, Kanis JA; SCOPE review panel of the IOF. Osteoporosis in Europe: a compendium of country-specific reports. Arch Osteoporos 2022;17:23.
2. Etxebarria-Foronda I, Caeiro-Rey JR, Larrainzar-Garijo R, Vaquero-Cervino E, Roca-Ruiz L, Mesa-Ramos M, Merino Pérez J, Carpintero-Benitez P, Fernández Cebrián A, Gil-Garay E. SECOT-GEIOS guidelines in osteoporosis and fragility fracture. An update. Rev Esp Cir Ortop Traumatol 2015;59:373-93.
3. Holroyd C, Cooper C, Dennison E. Epidemiology of osteoporosis. Best Pract Res Clin Endocrinol Metab 2008;22:671-85.
4. Hoyt D, Urits I, Orhurhu V, Orhurhu MS, Callan J, Powell J, Manchikanti L, Kaye AD, Kaye RJ, Viswanath O. Current Concepts in the Management of Vertebral Compression Fractures. Curr Pain Headache Rep 2020;24:16.
5. Zhu RS, Kan SL, Ning GZ, Chen LX, Cao ZG, Jiang ZH, Zhang XL, Hu W. Which is the best treatment of osteoporotic vertebral compression fractures: balloon kyphoplasty, percutaneous vertebroplasty, or non-surgical treatment? A Bayesian network meta-analysis. Osteoporos Int 2019;30:287-98.
6. Láinez Ramos-Bossini AJ, López Zúñiga D, Ruiz Santiago F. Percutaneous vertebroplasty versus conservative treatment and placebo in osteoporotic vertebral fractures: meta-analysis and critical review of the literature. Eur Radiol 2021;31:8542-53.
7. Hinde K, Maingard J, Hirsch JA, Phan K, Asadi H, Chandra RV. Mortality Outcomes of Vertebral Augmentation (Vertebroplasty and/or Balloon Kyphoplasty) for Osteoporotic Vertebral Compression Fractures: A Systematic Review and Meta-Analysis. Radiology 2020;295:96-103.
8. Kim DS, Jang SY, Kong MH, Song KY, Kang DS. Lumbar Nerve Root Compression due to Leakage of Bone Cement after Vertebroplasty. Korean J Neurotrauma 2014;10:155-8.
9. Satake K, Kanemura T, Yamaguchi H, Matsumoto A.

Pulmonary Embolism After Vertebroplasty with Use of Hydroxyapatite Blocks: A Case Report. JBJS Case Connect 2013;3:e132.
10. Chang M, Zhang C, Shi J, Liang J, Yuan X, Huang H, Li D, Yang B, Tang S. Comparison Between 7 Osteoporotic Vertebral Compression Fractures Treatments: Systematic Review and Network Meta-analysis. World Neurosurg 2021;145:462-70.e1.
11. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557-68.
12. Firanescu CE, de Vries J, Lodder P, Schoemaker MC, Smeets AJ, Donga E, Juttmann JR, Klazen CAH, Elgersma OEH, Jansen FH, van der Horst I, Blonk M, Venmans A, Lohle PNM. Percutaneous Vertebroplasty is no Risk Factor for New Vertebral Fractures and Protects Against Further Height Loss (VERTOS IV). Cardiovasc Intervent Radiol 2019;42:991-1000.
13. Sun Y, Zhang Y, Ma H, Tan M, Zhang Z. Therapeutic Efficacy and Safety of Percutaneous Curved Vertebroplasty in Osteoporotic Vertebral Compression Fractures: A Systematic Review and Meta-Analysis. Orthop Surg 2023;15:2492-504.
14. Tao XX, Li GF, Wu YL, Liu YS, Zhao Y, Shi YH, Zhuang MT, Hou TY, Zhao R, Liu FD, Wang XM, Shen Y, Cui GH, Su JJ, Chen W, Tang XM, Sun J, Liu JR. Relationship between intracranial internal carotid artery calcification and enlarged cerebral perivascular space. Neuroradiology 2017;59:577-86.
15. Buchbinder R, Johnston RV, Rischin KJ, Homik J, Jones CA, Golmohammadi K, Kallmes DF. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. Cochrane Database Syst Rev 2018;4:CD006349.
16. Xie L, Zhao ZG, Zhang SJ, Hu YB. Percutaneous vertebroplasty versus conservative treatment for osteoporotic vertebral compression fractures: An updated meta-analysis of prospective randomized controlled trials. Int J Surg 2017;47:25-32.
17. Carli D, Venmans A, Lodder P, Donga E, van Oudheusden T, Boukrab I, Schoemaker K, Smeets A, Schonenberg C, Hirsch J, de Vries J, Lohle P. Vertebroplasty versus Active Control Intervention for Chronic Osteoporotic Vertebral Compression Fractures: The VERTOS V Randomized Controlled Trial. Radiology 2023;308:e222535.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
19. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
20. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available online: www.training.cochrane.org/handbook
21. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, 2022. Available online: https://www.r-project.org/
22. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153-60.
23. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik JG. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569-79.
24. Klazen CA, Venmans A, de Vries J, van Rooij WJ, Jansen FH, Blonk MC, Lohle PN, Juttmann JR, Buskens E, van Everdingen KJ, Muller A, Fransen H, Elgersma OE, Mali WP, Verhaar HJ. Percutaneous vertebroplasty is not a risk factor for new osteoporotic compression fractures: results from VERTOS II. AJNR Am J Neuroradiol 2010;31:1447-50.
25. Rousing R, Andersen MO, Jespersen SM, Thomsen K, Lauritsen J. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: three-months follow-up in a clinical randomized study. Spine (Phila Pa 1976) 2009;34:1349-54.
26. Blasco J, Martinez-Ferrer A, Macho J, San Roman L, Pomés J, Carrasco J, Monegal A, Guañabens N, Peris P. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: a 12-month randomized follow-up, controlled trial. J Bone Miner Res 2012;27:1159-66.
27. Chen G, Zhang ST, Liu YC, Sun RZ, Zhao X, Luo D. Percutaneous vertebroplasty compared to conservative treatment in patients with osteoporotic vertebral compression fractures. J Cervicodynia Lumbodynia. 2010;31:323-6.
28. Chen D, An ZQ, Song S, Tang JF, Qin H. Percutaneous vertebroplasty compared with conservative treatment in

 

patients with chronic painful osteoporotic spinal fractures. J Clin Neurosci 2014;21:473-7.
29. Yang EZ, Xu JG, Huang GZ, Xiao WZ, Liu XK, Zeng BF, Lian XF. Percutaneous Vertebroplasty Versus Conservative Treatment in Aged Patients With Acute Osteoporotic Vertebral Compression Fractures: A Prospective Randomized Controlled Clinical Study. Spine (Phila Pa 1976) 2016;41:653-60.
30. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. J Neurosurg Spine 2011;14:561-9.
31. Clark W, Bird P, Gonski P, Diamond TH, Smerdely P, McNeil HP, Schlaphoff G, Bryant C, Barnes E, Gebski V. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1408-16.
32. Hansen EJ, Simony A, Carreon L, Andersen MO. Rate of Unsuspected Malignancy in Patients With Vertebral Compression Fracture Undergoing Percutaneous Vertebroplasty. Spine (Phila Pa 1976) 2016;41:549-52.
33. Chen JP, Qi XW, Li SJ, Kuang LP, Yuan XH, Wang GS, Tan WY. Bone Cement injection as vertebral augmentation therapy for osteoporotic vertebral compression fractures. Chinese Journal of Tissue Engineering Research 2015;19:3292-6
34. Qiu Z, Wang P, Chao Y, Yu Y. The risk of new vertebral fracture after percutaneous vertebral augmentation in patients suffering from single-level osteoporotic vertebral compression fractures: A meta-analysis and systematic review. Medicine (Baltimore) 2023;102:e35749.
35. Lou S, Shi X, Zhang X, Lyu H, Li Z, Wang Y. Percutaneous vertebroplasty versus non-operative treatment for osteoporotic vertebral compression fractures: a meta-analysis of randomized controlled trials. Osteoporos Int 2019;30:2369-80.
36. Anderson PA, Froyshteter AB, Tontz WL Jr. Meta-analysis of vertebral augmentation compared with conservative treatment for osteoporotic spinal fractures. J Bone Miner Res 2013;28:372-82.
37. Andreão FF, Borges P, Palavani LB, Machinski E, de Barros Oliveira L, Ferreira MY, Batista S, Semione G, Neto AR, Bertani R, Massella CR, Joaquim AF, Quadros DG. Percutaneous Vertebroplasty vs. Non-operative Treatment of Osteoporotic Vertebral Fractures: A meta-analysis of Randomized Controlled Trials. World Neurosurg 2024. doi: 10.1016/j.wneu.2024.07.127.
38. Venmans A, Klazen CA, van Rooij WJ, de Vries J, Mali WP, Lohle PN. Postprocedural CT for perivertebral cement leakage in percutaneous vertebroplasty is not necessary--results from VERTOS II. Neuroradiology 2011;53:19-22.
39. Ebeling PR, Akesson K, Bauer DC, Buchbinder R, Eastell R, Fink HA, Giangregorio L, Guanabens N, Kado D, Kallmes D, Katzman W, Rodriguez A, Wermers R, Wilson HA, Bouxsein ML. The Efficacy and Safety of Vertebral Augmentation: A Second ASBMR Task Force Report. J Bone Miner Res 2019;34:3-21.
40. Zuo XH, Zhu XP, Bao HG, Xu CJ, Chen H, Gao XZ, Zhang QX. Network meta-analysis of percutaneous vertebroplasty, percutaneous kyphoplasty, nerve block, and conservative treatment for nonsurgery options of acute/subacute and chronic osteoporotic vertebral compression fractures (OVCFs) in short-term and long-term effects. Medicine (Baltimore) 2018;97:e11544.
41. Clark W, Diamond T. Early Vertebroplasty for Severely Painful Acute Osteoporotic Compression Fractures: A Critical Review of the Literature. Cardiovasc Intervent Radiol 2023;46:1439-46.
42. Diamond TH, Clark WA, Kumar SV. Histomorphometric analysis of fracture healing cascade in acute osteoporotic vertebral body fractures. Bone 2007;40:775-80.
43. Diamond T, Clark W, Bird P, Gonski P, Barnes E, Gebski V. Early vertebroplasty within 3 weeks of fracture for acute painful vertebral osteoporotic fractures: subgroup analysis of the VAPOUR trial and review of the literature. Eur Spine J 2020;29:1606-13.
44. Ruiz Santiago F, Láinez Ramos-Bossini AJ, Moraleda-Cabrera B. Factors influencing vertebral collapse in osteoporotic vertebral fractures: a case-control study of symptomatic patients attended in the emergency department. Arch Osteoporos 2023;19:6.

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