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# Vertebral fragility fractures – How to treat them?



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### A B S T R A C T

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Approximately 20% of men and women aged 50 years or older will present with a vertebral fragility fracture - a prevalence that steadily increases with age. The condition may be associated with severe pain and disability, significant reductions in overall quality of life, mobility, social participation, sleep quality and increased fear for the future. There is, however, no current consensus on what constitutes the best management of symptomatic vertebral fractures. Moreover, evidence supporting common treatment approaches is scarce and often of poor quality. The lack of adequate management of VFF and associated osteoporosis and the burden of this condition to patient and society are estimated to increase substantially in coming years as recurrent, disabling episodes are set to occur. This chapter will address these issues, including a discussion on existing care pathways for vertebral fragility fractures, and an overview of the evidence supporting recommendations of the main international clinical practice guidelines.

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## Vertebral fragility fractures

A vertebral fragility fracture (VFF) is said to be present if a radiographically evident abnormality has developed because of a minor injury (a force equivalent to a fall from a standing height or less) or in the absence of a recognised *cause*. For a VFF to be accepted as symptomatic, a credible association between

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the clinical symptoms and the radiological changes needs to be established. *Incident* fractures usually refer to those identified when the patient presents to care with a complaint, usually acute pain that is linked to a radiological finding suggestive of a recent fracture. When no prior imaging is available to determine whether the bony changes are new, additional imaging with modalities such as magnetic resonance imaging (MRI) can determine the recency by vascular activity. *Prevalent fractures* refer to those detected as part of regular screenings or as an incidental image finding ordered for another purpose (e.g., chest x-ray). Although most VFF will be associated with some level of pain and disability, incident fractures are usually the most severe manifestation, driving most care seeking behaviour [1]. Symptomatic vertebral fractures are associated with acute back pain, but chronic back pain may result from the associated bone deformity or tension on muscles and tendons [1].

VFF can also be classified in terms of duration of symptoms; with *acute* VFF used to define those episodes of recent (less than 6 weeks) onset, *sub-acute* VFF used to define episodes of lasting between 6 and 12 weeks and *chronic* VFF used to define episodes of at least 12-week duration. Management for each sub-classification of this condition may differ, although there seems to be no international consensus on clinical recommendations.

### Prevalence and global burden of VFF

The prevalence of VFF increases with advancing age and may vary greatly worldwide. A recently conducted systematic review of population-based studies has shown that the prevalence of morphometric VFF can be as high as 26% among Japanese and Scandinavian women, whilst up to 34% of women 50 years of age or older in the USA will be present with at least one VFF [2,3]. Both older men and older women are at risk of developing vertebral fragility fractures, although the risk increases slightly among women if compared to men at the same age [3]. Moreover, having previous vertebral fractures can increase the risk of sustaining a future fracture 5-fold [4]. A recent pooled analysis of 10 observational studies, with an average follow up of 5 years, has shown that the presence of one VFF will increase 4 times the risk of a subsequent VFF and over 2 times the risk of hip fractures [5]. In older adults, vertebral fragility fractures are known to be most commonly associated with osteoporosis, likely resulting from minimal trauma (e.g. falling or lifting). In Australia, it is estimated that more than 1.8 million people have been diagnosed with osteoporosis and would therefore be at risk of developing a vertebral fragility fracture. Because of its impact on quality of life of the older population as a result of on-going spinal pain [6,7], decreased mobility [6–8] and physical function [9], sleep loss [6] and even increased risk of age-adjusted mortality [10], vertebral fragility fractures have been recognized as a major global public health concern.

The pain associated with these fractures will also result in significant reductions in overall quality of life as a consequence of reduced physical and social participation and increased fear for the future, fear of isolation and concerns of dependency [9,11,12]. Patients with a VFF also consult their doctors 14 times more than matched controls in the year following the fracture diagnosis and are 5 times more likely to sustain a recurrent fracture. This represents an important economic burden reaching £12 million per year in the UK or \$113 million per year in Australia in direct medical costs.

#### Care pathway for vertebral fragility fracture

Only about one fourth to one third of all VFFs are presented to care, despite this being the most common osteoporotic manifestation [13]. For that reason, the clinical pathway of VFF is unclear and undefined at present. Patients with VFF may often seek primary care when they experience symptoms; usually back pain and fractures will subsequently be confirmed by spinal radiograph [13,14].

Recent data from the Bettering Evaluation and Care of Health (BEACH) program in Australia, collected from April 2005 to March 2015, showed that there are approximately 26,000 (95% CI: 22,000 to 29,000) general practice encounters to manage VFF every year in Australia [14]. Typically, the patient with VFF presenting to a general practitioner will be female, aged 65 years or older and have multi-morbidities, the most common being hypertension, metabolic syndrome and depression [14]. The most common reason for seeking care is not surprisingly back pain (48 per 100 encounters for VFF) but patients also tend to seek care if they have experienced a trauma or injury (6 per 100 encounters) or

have a past diagnosis of fracture (6 per 100 encounters). Patients also often report not being able to sleep as the reason for seeking primary care [14].

Prescription of analgesics, in particular opioids (47.1 per 100 VFF; 95% CI: 38.4 to 55.7), is the most common treatment approach for VFF at the primary care level. Non-pharmacological treatment (e.g. counselling, advice, education and rehabilitation) is provided at a much lower rate (22.4 per 100 VFF; 95% CI: 14.6 to 30.1).

In general, just over half of the general practice encounters are follow-up assessments for VFF (59.2%; 95% CI: 52.4 to 66.1), the remaining 41% (95% CI: 33.9 to 47.6) being encounters for new cases of VFF [14]. These data suggest that patients with VFF are not often followed up at primary care. However, patients with VFF consulting primary care do not seem to be referred to other specialist or health care professionals, either. For instance, according to the Australian BEACH data, in only 6 of every 100 encounters, patients were referred to specialist care, and in only 4 encounters, patients received a referral to allied health services [14]. Moreover, the management of osteoporosis for patients with VFF seems to be rare at the primary care level - anti-osteoporotic medication was prescribed in only 5.5 (95% CI: 0.7 to 10.3) per 100 new episodes and 15.2 (95% CI: 6.6 to 23.8) per 100 of chronic or follow-up cases [14]. Lack of response to secondary prevention of fragility fractures in primary care does not seem to be a problem observed only in Australia, though. Recent data from the USA confirm that less than 2% of post-menopausal women consulting primary care in the USA are screened for osteoporosis or VFF. In those with a confirmed diagnosis, only one third were prescribed appropriate management, most commonly bisphosphonates [15,16]. European data also suggest low rates of adequate treatment of osteoporosis and secondary fracture prevention in those with a VFF, with lowest rates observed for women [17].

An alternative care pathway for VFF includes hospital admission. A recent study has shown that VFF was the second most common (14%) reason for hospital admissions between 2010 and 2013, among all fragility fractures (more than 268,000 admissions) across 548 USA hospitals [18]. Hospital readmissions within 60 days were highest for VFF compared to all other types of fragility fractures [18]. Moreover, hospital-related mortality, ICU admission rates, costs of episode of care and length of hospital stay for VFF are second only to hip fractures [18]. Over half of patients with VFF admitted to hospital will be discharged to long-term care facilities, with one third being discharged to home, and 14% to a rehabilitation facility. The care continuity for patients discharged from hospital for a VFF is, however, less clear.

Whilst international data on the different care pathways for VFF are currently scarce [19], alternative solutions have been proposed for other types of fragility fracture. For instance, Heilmann et al. have shown that an integrated pharmacists-run osteoporosis clinic targeting women aged 65 years or older with a documented vertebral fracture, significantly increased initiation and 12-month adherence to osteoporotic medication and BMD testing [20] and at comparable costs [21] when compared with traditional (nurse-led) clinics. The new rates of adherence to osteoporosis management with the pharmacist-led initiative were above USA national averages [20]. Whilst the study is limited by its retrospective design, the use of clinical pharmacy services for secondary prevention of VFF is promising. Likewise, electronic referral systems could be developed from general practice and hospital fragility fracture databases, to automatically refer patients admitted with a VFF to osteoporosis services. This initiative was shown to significantly improve the management of osteoporosis in patients with hip fracture in the UK [22] and could be adopted for those with VFF. There is an urgent need for more expertise in the field. Future discussions should also incorporate insurance companies, and pathways should be defined in terms of public or private practices.

#### *International clinical practice guidelines – is there a consensus?*

The lack of consensus on the care pathway of VFF could be a reflection of inconsistency in recommendations of international clinical guidelines underpinned by the lack of high quality clinical trials for existing or innovative interventions. A recent systematic review of 5 scientific databases and existing clinical guideline databases (i.e. National Guideline Clearinghouse) identified only four international guidelines selected among 442 possible titles [19]. Two guidelines were developed in the USA (American Academy of Orthopedic Surgeons and American College of Radiology): one from

the UK (National Institute for Health and Care Excellence Guidelines) and one from Canada (Canadian Association of Radiologists). In general, guidelines – all published between 2010 and 2013 – were of poor quality as measured by the Appraisal of Guidelines, Research & Evaluation (AGREE) II Instrument, main flaws being insufficient rigor of development, clarity of presentation and applicability [19].

Only two guidelines included any recommendation on diagnosis of VFF, both based on expert consensus, rather than scientific evidence. Three guidelines inconsistently recommended analgesics for pain control, all based on weak evidence. Whilst the American Academy of Orthopedic Surgeons recommended calcitonin for 4 weeks, followed by opioids, the American College of Radiology recommended a course of non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain associated with VFF. Recommendations on non-pharmacological treatments were equally inconsistent across guidelines based on weak evidence. Most commonly endorsed treatments included back braces and bed rest. Exercise and electrical stimulation were recommended only by the American Academy of Orthopedic Surgeons. Interestingly, the Canadian guidelines did not endorse any treatment for symptomatic VFF. Endorsement of interventional care (i.e. balloon kyphoplasty or vertebroplasty) also varied with the American Academy of Orthopedic Surgeons explicitly recommending against vertebroplasty, based on strong evidence of its inefficacy, whilst both the UK guidelines and the American College of Radiologist endorsing its use [19].

All guidelines, however, seemed to agree on the importance and strength of evidence of osteoporosis treatment for the secondary prevention of fractures in patients with VFF. Bisphosphonates and exercise were consistently endorsed by all but the American College of Radiologists, which did not include any recommendation [19].

These variations in endorsement of interventions across guidelines might be the result of the lack of a clear care pathway for VFF as patients will use multiple care entry points (e.g. emergency care versus rheumatologists, general or aged care physician) with distinct guidelines. There is an urgent need for an international and comprehensive mapping of care for VFF.

Another possible explanation is the scarce scientific evidence supporting most of these treatment approaches as well as the notion that one size fits all. There is a considerable paucity in evidence regarding allied health care for VFF for instance, including multidisciplinary pain management, hydrotherapy or use of braces (soft or semi-rigid). The next section will present the current evidence on conservative and interventional care for VFF.

### *Quality of the evidence supporting management of VCF*

#### *Analgesics*

Although most patients will experience a significant reduction in pain over the first 4 weeks [23,24], simple analgesics, NSAIDs and opiates are commonly used in practice [1,14] to facilitate mobility. There is, however, paucity in scientific evidence derived from randomised controlled trials in the field.

A systematic review published in 2015 identified only 5 randomised clinical trials assessing the treatment effects of first line, conservative care for pain relief associated with VFF [25]. In general, trials presented moderate risk of bias, most common flaws being lack of blinding of assessors, therapists or patients ( $n = 4$ ), and lack of concealment of group allocation ( $n = 3$ ). Although blinding of assessors and patients is nearly impossible in pragmatic, open trials, lack of blinding is known to be associated with over-estimation of treatment effects [26]. Moreover, when the allocation sequence of participants to treatment groups is not concealed, there is a higher risk of selection bias, also associated with over-inflated treatment effects [27].

The results suggest there is low quality evidence (i.e. lack of blinding and concealment of treatment allocation) from a small trial ( $n = 27$ ) that strong opioids (standardized mean difference (SMD): 1.66; 95% confidence interval (CI): 2.88 to 0.44) and NSAIDs (SMD: 1.58; 95% CI: 2.83 to 0.33) are superior to Chinese medicine (Xin Huang Pian) in reducing pain, at the one-month follow-up. However, when strong opioids are compared to placebo ( $n = 116$ ), the results show no difference in pain intensity between groups at the one-month follow-up for oxycodone (SMD: 0.09; 95% CI: -0.45 to 0.62) or tapentadol (SMD: 0.32; 95% CI: -0.23 to 0.87) [25]. No placebo-controlled randomised trials of NSAIDs have been identified. Likewise, no trials ascertaining the treatment effect of simple analgesics (e.g.

paracetamol) in this population have been conducted, and therefore, it is still uncertain whether these offer any benefit over placebo or no treatment for patients with VFF.

### *Lumbar braces*

Another commonly endorsed treatment approach for the acute phase of VFF is the use of lumbar belts or braces [19]. Two trials ( $n = 170$ ) compared the use of semi-rigid lumbar braces for 6 months, added to usual vs. usual care alone, and found the addition of braces significantly reduces pain (SMD:  $-1.47$ ; 95% CI:  $1.90$  to  $-1.01$ ) and disability (SMD:  $-1.73$ ; 95% CI:  $-2.09$  to  $-1.37$ ) associated with VFF. No blinding was possible in these trials, and it is possible, therefore, that treatment effects might have been overestimated [25].

### *Calcitonin*

Calcitonin has been suggested as an important pain relief option for patients with VFF and endorsed by international clinical practice guidelines [19]. A meta-analysis on the effectiveness of calcitonin to treat acute and chronic pain associated with VFF was conducted in 2011 [28]. The study included 11 placebo-controlled trials of moderate methodological quality. Most common methodological limitation was failing to conceal treatment allocation ( $n = 8$  studies). Blinding of patients was appropriate in all but one placebo-controlled trial. The results of the meta-analyses showed that, compared to placebo, calcitonin significantly reduces acute pain (i.e.  $<10$  days) at rest at all follow-ups, with pooled mean differences ranging from 3.4 (95%CI: 4 to 2.8; on a 11-point pain scale) at one week to 5 (95%CI: 5.7 to 4.3) at 3 weeks. Similarly, large effects were observed for acute pain during walking at one week (MD: 2.6; 95%CI: 4.1 to 1.1) and at four weeks post-treatment (MD: 6; 95%CI: 6.8 to 5.2), compared to placebo. No significant pain relief with calcitonin was observed for patients with chronic pain (i.e.  $>3$  months) at any follow-up (MD: 0.1; 95%CI:  $-0.13$  to 0.4) [28]. A total of 228 and 195 participants with acute and chronic, symptomatic VFFs, respectively, were included in the pooled analyses. A course of calcitonin, however, increases more than 3 times the risk of any side effect (RR: 3.1; 95%CI: 1.8 to 5.3), with main events being enteric disturbances (RR: 2.5; 95% CI: 1.1 to 6) and flushing (RR: 6.9; 95%CI: 2.5 to 19.4) [28]. The use of calcitonin has, however, been linked to an increased risk of cancer, based on poor quality evidence. A recent systematic review has concluded that current evidence may suggest the association with cancer; however, there is significant heterogeneity in trial methods, insufficient follow-up time to assess cancer outcomes and results seem to be derived by an excess of post-hoc analyses [29]. Until high-quality data are available to address the safety controversy of calcitonin use, we would caution its endorsement as a pain relief option for patients with VFF.

### *Interventional approaches*

When non-invasive, conservative care fails to improve patients' symptoms, interventional approaches, including balloon kyphoplasty or vertebroplasty, are often recommended [19]. To date, no randomised, blinded and placebo-controlled trials have been conducted for kyphoplasty, while the evidence for vertebroplasty remains inconclusive with high-quality sham-placebo controlled trials, showing no difference over placebo but a range of other studies suggesting short-term gains. Once again, we currently lack a sufficient body of scientific evidence to routinely support this practice.

The most recent Cochrane Systematic review on the efficacy of vertebroplasty for VFF was published in 2018 [30]. The review included eight randomised controlled trials comparing vertebroplasty to usual conservative care, five comparing vertebroplasty to placebo, seven comparing vertebroplasty to kyphoplasty and one comparing vertebroplasty to facet joint glucocorticoid injection. Data from 6 trials comparing vertebroplasty to usual care were pooled, and results showed a significant but small decrease in pain at 2 weeks ( $n = 627$ ; SMD: 1.3; 95%CI: 2.3 to 0.4; where values greater than 0.8 are considered clinically significant), one month ( $n = 384$ ; SMD 2.1; 95%CI 3.4 to 0.8), three months ( $n = 627$ ; SMD 1.2; 95%CI: 2 to 0.4) and 12 months ( $n = 612$ ; SMD: 1.0; 95%CI: 1.7 to 0.3), favouring vertebroplasty. In none of these trials were the patients or assessors blinded to treatment allocation, and it is possible that treatment effects were overestimated likely due to placebo effects associated with invasive interventions [31]. This phenomenon is common in open trials of invasive approaches [32] and will often result in high crossover rates across groups due to lack of equipoise between treatment comparisons.

The results of 5 ( $n = 539$ ) low risk-of-bias placebo-controlled trials of vertebroplasty have challenged the previous findings. Compared with placebo, there is moderate quality evidence that vertebroplasty provides no benefit on pain, disability or quality of life at any of the observed time points. Sub-group analyses showed that these results were consistent when surgery was performed before 6 weeks or after 6 weeks of pain duration.

A recently published randomised placebo-controlled trial of vertebroplasty has shown different results [33]. The trial included 120 patients with symptomatic VFF of moderate to severe intensity (i.e.  $>6$  on 0–10 NRS) and less than 6-week duration. The trial reports a between-group difference in proportion with improvement in pain of at least 3 points (or NRS pain score below 4, from a baseline of 7 or more) of 23% (95%CI: 6–39;  $p = 0.01$ ) at 2 weeks and 33% (95%CI: 17–50) at one month, favouring the vertebroplasty group. No between-group differences were observed for pain scores reported by patients at 2 weeks (MD: 10; 95%CI:  $-2$  to 22;  $p = 0.09$  on 0–100 VAS) or 6 months (MD: 11; 95%CI: 0 to 23;  $p = 0.05$ ). Significant, but small reductions for disability, favouring vertebroplasty, were observed at 1 (MD: 2.6; 95%CI: 0.42 to 4.78; on the 0–24 Roland Morris Disability Questionnaire) and 3 months (MD: 3.2; 95%CI: 0.36 to 6.04).

These treatment effects, however, are not large enough to change the conclusions derived from the Cochrane systematic review by Buchbinder et al. When the new results are pooled with previous evidence, no statistically significant differences on proportion improvement of pain, pain measured on a visual analogue scale or disability are observed between vertebroplasty and placebo [30].

Positive results have been observed favouring balloon kyphoplasty when compared to conservative care (i.e. analgesics, bed rest, back braces and physiotherapy) in 300 patients with VFF included in the FREE trial [34]. Small-to-moderate treatment effects were observed for pain reduction (MD: 2.2; 95%CI: 1.6 to 2.8 at 1 week; MD: 0.9; 95%CI: 0.3 to 1.5 at 1 year; 0-10-point scale) and disability reduction (MD: 4; 95%CI: 2.6 to 5.5 at 1 week; MD: 2.6; 95%CI: 1 to 4 at 1 year, 0–10 point scale) favouring balloon kyphoplasty. Two serious adverse events were observed in the balloon kyphoplasty group (haematoma and urinary tract infection), although there was no difference between groups in number or frequency of adverse events. Given this is an open trial, no blinding of participants, assessors or clinicians was possible. Moreover, there was a 10% crossover from the conservative care into the interventional approach given the lack of treatment equipoise and blinding [34]. To date, no placebo-controlled trials have been conducted to assess the efficacy of balloon kyphoplasty, and we should not rule out, therefore, the likely placebo effects associated with these results.

### Exercise

Patient with symptomatic VFF will often stop moving or engaging in physical activity due to fear of worsening of pain and fear of falls and future fractures [35]. Structured exercise and educational programs are, therefore, crucial in preserving mobility, bone and muscle health among patients with symptomatic VFF.

A total of 5 randomised controlled trials evaluating different types of exercise and educational programs to improve physical mobility have been included in a recent systematic review [36]. These studies suggest there is moderate quality evidence that exercise interventions that focus on improving balance and coordination significantly increase mobility (measured as walking speed and Time Up and Go test) at 3 months, compared to usual care. Treatment effects were small and of arguable clinical significance, however [36]. The effect of exercises on balance in this population, however, was inconsistent across studies, with one study showing a positive effect with a home-based exercise program (1 h/day, 3 times/week) at 6 and 12 months, and one study showing no difference between groups when exercises were compared to usual care. No adverse events associated with exercises were reported in the review.

The review has also shown that there is low quality evidence that exercise with or without education to improve coping strategies will reduce pain in patients with VFF. There is also moderate quality evidence that exercise will reduce fear of falling (measured with the Falls Efficacy Scale International – FES-I) in this population [36].

Although, in general, the evidence on the effectiveness of exercise for pain reduction and improved mobility is limited and of moderate quality; at best, there are no trials comparing exercise to placebo or no treatment, and we therefore lack evidence on its efficacy.

### Secondary fracture prevention

An important aspect of management of VFF is the prevention of future fractures. Clinical guidelines consistently recommend bisphosphonates for the prevention of future VFF based on strong evidence of its effectiveness compared to placebo [37]. Black et al. have shown that the 5-year risk of a new VFF in women treated with bisphosphonates is 3 times smaller than that with placebo. Among women with a prevalent VFF, the risk of a future fracture in the 5-year follow up is 6 times smaller with the bisphosphonate treatment.

In contrast, the benefit of vertebroplasty in preventing future fractures was rated as uncertain in the Cochrane systematic review by Buchbinder et al. The review provides moderate-quality evidence (3 trials or 281 participants) that vertebroplasty neither decreases nor increases the risk of future fractures (RR: 1.5; 95%CI: 0.4 to 5.5) [38].

### Summary

Although most international clinical practice guidelines are consistent in recommending conservative approaches as first-line care for symptomatic vertebral fragility fractures in the older person, no consensus has been reached on specific treatments, given the scientific paucity in the field. There seems to be moderate quality evidence supporting the use of calcitonin in the first weeks of a painful episode, although its safety profile is still uncertain, with prolonged use being linked to increased risk of cancer. The use of lumbar braces is promising as they offer moderate effects in the absence of serious adverse events. Likewise, there seems to be good evidence supporting bisphosphonates for the prevention of future VFF.

Moving forward, we need to acknowledge the important scientific gaps in this field, leading to unwarranted variations in care both across sectors and internationally. High quality, placebo-controlled randomised trials assessing the effectiveness and safety of pain relief medication for acute, symptomatic VFF need to be conducted. An optimised and evidence-based clinical pathway that includes primary care and is based on patient outcomes also needs to be established for symptomatic VFF.

#### Practice points

- Vertebral fragility fractures, also referred to as vertebral compression fractures, are common and steadily increase with age
- VFFs are associated with increased mortality and morbidity, pain and loss of quality of life compared to age- and gender-matched peers
- There is weak evidence supporting the use of braces for the acute management of vertebral fragility fractures
- There is inconclusive evidence supporting vertebroplasty with high-quality sham-placebo controlled trials showing no benefit over placebo, whilst some studies suggest short-term gains

#### Research agenda

- More high-quality, placebo-controlled trials are needed to identify the effectiveness and safety of pharmacological, non-pharmacological and interventional approaches for vertebral fragility fracture
- We currently also lack evidence-based care pathways for the management of vertebral fragility fractures

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## Conflicts of interest

None declared.

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