



## EMAS position statement: The management of postmenopausal women with vertebral osteoporotic fracture



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### ABSTRACT

**Introduction:** Osteoporotic vertebral fractures are associated with significant morbidity, excess mortality as well as health and social service expenditure. Additionally, women with a prevalent osteoporotic vertebral fracture have a high risk of experiencing a further one within one year. It is therefore important for the physician to use a diagnostic and therapeutic algorithm for early detection and effective treatment of vertebral fractures.

**Aims:** The aim of this position statement is to provide and critically appraise evidence on the management of women with a vertebral osteoporotic fracture.

**Materials and methods:** Literature review and consensus of expert opinion.

**Results and conclusions:** The management of women with osteoporotic vertebral fractures includes measures to reduce pain providing early mobility, to support the affected spine ensuring fracture healing, as well as starting treatment for osteoporosis itself. Any other underlying pathology should be sought and treated. Early detection and treatment is essential as there is an increased risk of further fractures in patients with vertebral fractures. Treatment will depend on the underlying causes of bone loss, efficacy in any particular situation, cost and patient preference.

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## 1. Introduction

In osteoporotic women, the risk of spinal fragility fracture increases linearly after the age of 60. Vertebral osteoporotic fractures (VOFs) are associated with significant morbidity and mortality as well as with health and social service expenditure [1,2].

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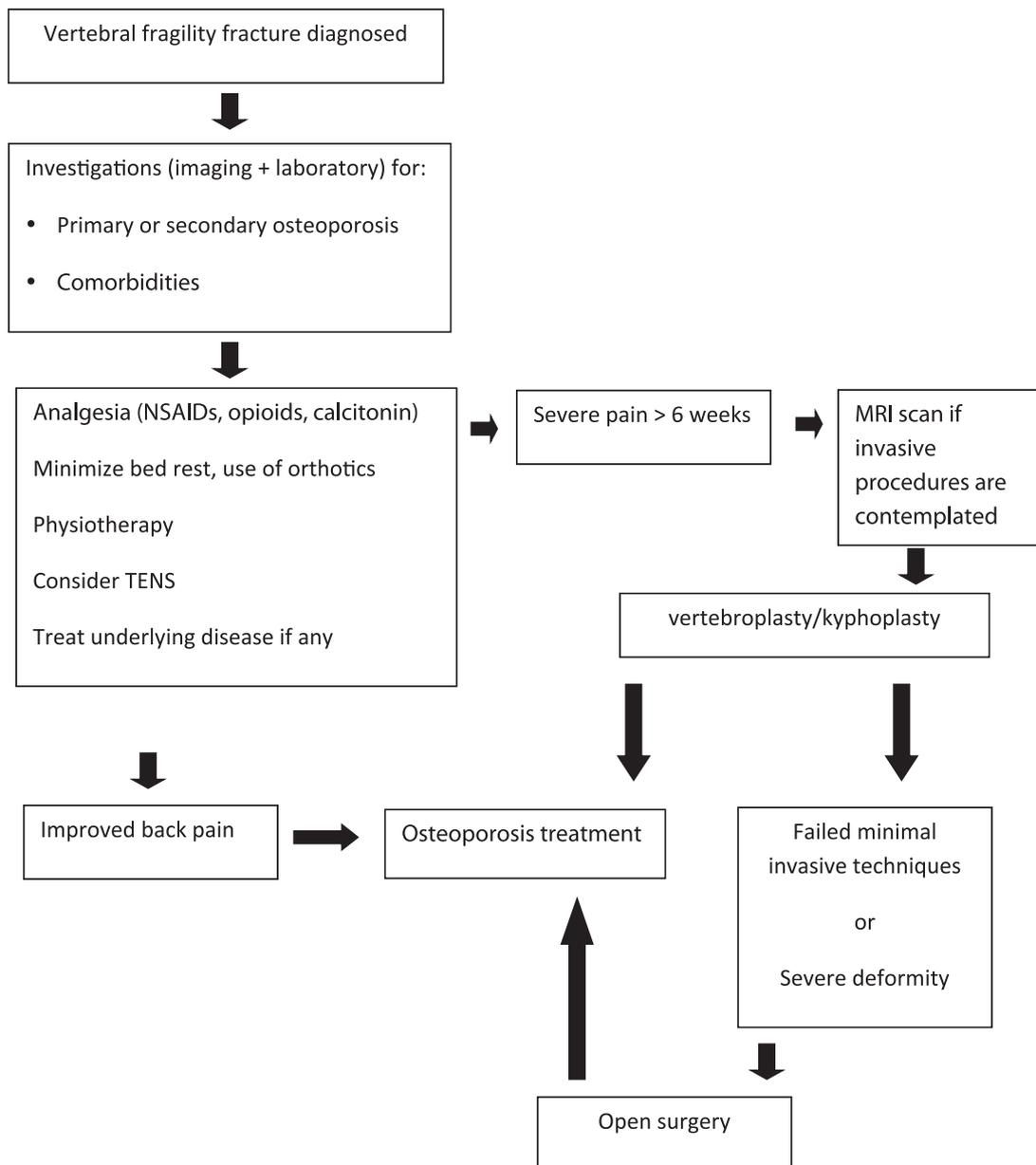


Fig. 1. Care pathway for the management of postmenopausal women with vertebral osteoporotic fracture.

Furthermore, in women with a VOF, there is an increased risk of further fragility fractures [3,4]. Prompt management is thus essential not only to deal with the current fracture but also to prevent subsequent ones. The aim of this position statement is to provide evidence-based advice and guidelines on the management of women with VOF (Fig. 1).

## 2. The burden of vertebral osteoporotic fracture

The incidence of VOF is underestimated as only about a third of people with the condition seek medical attention [5]. Those with acute back pain (*vertebral fracture type-1*) tend to present earlier than those who gradually lose height or become kyphotic (*vertebral fracture type-2*)

Up to 20% of women with an incident vertebral fracture will experience a second one within a year [6]. In addition low BMD and prevalent vertebral fractures are independently related to new

vertebral fractures over 15 years of follow-up [7]. Women with previous VOF also have a 3.8-fold increased risk of hip fracture, compared with the background female population [8,9]. It is therefore important that vertebral fractures are detected early, and treatment considered as soon as possible. Furthermore, the cause of osteoporosis and contributory factors must be understood to try and minimize damage. Diseases that also cause vertebral collapse such as myeloma, hyperparathyroidism or neoplastic metastases must be excluded [10].

VOFs have a high impact on patient's quality of life in terms of reduced mobility, pain, poor sleep and fear of future fractures [11]. In most patients with a VOF, back pain decreases significantly with conservative therapy, predominantly in the first 6 months [12]. However, almost 2 years after an acute VOF, a third of patients still have severe pain necessitating analgesia and physical therapy. Mortality is increased and is directly related to the number of fractures [1,2]. The mechanism of the increased fracture-associated mortality

remains uncertain: it may be related to co-morbid conditions (such as cardiovascular disease) or subsequent hip fracture and gender differences have been noted [13,14].

### 3. Assessment of a vertebral osteoporotic fracture

Initial assessment of VOFs is important to ensure that appropriate management is instigated. It has been estimated that underlying pathology is present in about one third of women with symptomatic VOFs [6]. A detailed medical history, physical examination and appropriate investigation are mandatory for all patients with non-traumatic vertebral fractures. Imaging [15] and laboratory tests [10] are the first line diagnostic tools.

#### 3.1. Imaging

The usual location of VOFs is the lower thoracic and upper lumbar spine and these can be seen on conventional chest X-rays. The international standard for the classification of vertebral osteoporotic fractures is the semiquantitative grading system was developed by Genant in 1993 [16]. According to this grading system, a vertebral deformity of T4–L4 with more than 20% height loss and a 10–20% area of height reduction is defined as a fracture. Four grades are differentiated: grade 0, no fracture; grade 1, mild fracture (reduction in vertebral height of 20–25%, compared with adjacent normal vertebrae); grade 2, moderate fracture (reduction in height of 25–40%); and grade 3, severe fracture (reduction in height of more than 40%). Wedge-shaped and biconcave fracture deformities are most common in osteoporosis, while posterior vertebral fractures are suggestive of neoplastic disease. Multidetector-CT can be used to diagnose incidental VOFs. The role of Dual-energy X-ray absorptiometry (DXA) measurement is of limited benefit as the diagnosis of osteoporosis can be assumed in the presence of a fracture especially in women aged over 75 [17]. However, DXA can be used to assess vertebral fracture [18]. Radionuclide bone scan and MRI scan are valuable diagnostic tools when there is suspicion of skeletal metastasis [19]. MRI with STIR sequencing can diagnose additional acute or chronic lesions not evident in plain X-rays. Therefore, it should be considered before cement augmentation procedures [20].

#### 3.2. Laboratory tests

Initial investigations should include full blood count, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), thyroid, renal and liver function tests; serum protein electrophoresis, calcium, albumin, phosphate and alkaline phosphatase [10]. Serum 25-hydroxyvitamin D (25OHD) and parathyroid hormone (PTH) measurements are useful for vitamin D deficiency and parathyroid disorders. Iron metabolism, as well as serum testosterone and SHBG should be also assessed in men. Finally, coeliac disease can be excluded with endomysial antibodies.

### 4. Initial management of vertebral osteoporotic fractures

There is no consensus as to the best management. A care pathway is detailed in Fig. 1. In general, initial management includes bed rest, analgesia, physiotherapy and bracing. According to the UK National Institute for Health and Care Excellence percutaneous vertebroplasty, and percutaneous balloon kyphoplasty without stenting, are recommended as options for treating osteoporotic vertebral compression fractures only in people who have severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management and in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging [21].

Finally, where neurological deficit or severe spinal instability has developed, spinal fusion may be considered.

#### 4.1. Physical support of the spine

After an initial short period of bed rest, mobilization should be encouraged with the use of physical supports. Corsets are no longer advocated, as they immobilize the spine and thus aggravate bone loss and muscle atrophy. Alternatively, a spinal orthosis such as a Jewett brace can be used (a) to stabilize the fracture area and therefore prevent further collapse or spinal deformity, (b) to provide stable positioning needed for faster bone healing, and (c) to allow immediate mobilization of the patient. Finally, walking aids will help compensate for loss of sagittal balance and impaired proprioception and reduce fall risk.

#### 4.2. Pain management

Analgesia should begin with simple pain-killers such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). If stronger analgesia is required, opiates or opioids such as oxycodone can be used in combination with paracetamol. If pain becomes chronic, tricyclic antidepressants may be useful. Finally, in severe pain, intercostal nerve blocks give satisfactory but short-term relief. Pain relief should be undertaken in consultation with a specialized pain management team and non-pharmaceutical options such as TENS should be considered [22,23].

Calcitonin appears to be effective in the management of acute pain associated with acute VOF by shortening time to mobilization [24]. Salmon calcitonin (not available in all countries) administered intramuscularly, intranasally or subcutaneously, for a period of two to four weeks, leads to a greater reduction in pain intensity compared to placebo [25]. However, there is no convincing evidence to support the use of calcitonin for chronic pain associated with older fractures of the same origin [26].

Intravenous bisphosphonates such as pamidronate or clodronate can also be used for the acute pain management of VOFs [27,28]. Furthermore zoledronic acid as a single annual 5 mg intravenous infusion significantly reduces the number of days with back pain compared to placebo [29]. Finally, subcutaneous daily teriparatide also significantly improves back pain due to osteoporotic fractures, although this medicine is not recommended for the sole purpose of analgesia and use varies between countries [30,31].

#### 4.3. Percutaneous vertebroplasty and kyphoplasty

Percutaneous vertebroplasty and kyphoplasty are used in patients with severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management, and in patients who develop significant deformity (e.g. >30% of kyphosis) [21,32].

Vertebroplasty involves the percutaneous injection of bone cement into the vertebral body under fluoroscopic guidance and can be performed as one-day or overnight procedure. Kyphoplasty is a similar technique, it involves, however, an additional step in which an inflatable tamp or balloon is first inserted percutaneously into the collapsed vertebral body under fluoroscopic guidance. The tamp is then inflated, compressing the cancellous bone and elevating the endplates. The fracture is then fixed by the injection of bone cement in a similar manner to vertebroplasty [33].

Both procedures seem to be equally effective but kyphoplasty seems to be safer than vertebroplasty [34]. In vertebroplasty and kyphoplasty, pain relief results from stabilization of the fracture, although thermal and chemical ablation of the nerve endings in the vertebral body may also contribute. In general, apart from pain

relief, these two techniques, when applied in carefully selected patients, offer significant functional recovery [35,36].

#### 4.4. Open surgery

Open surgical treatment of VOFs is challenging and tends to be reserved (1) for those cases where less-invasive approaches have not provided a satisfactory result in terms of relief of chronic pain and (2) as the initial surgical procedure for people with severe deformity, with or without vertebroplasty or kyphoplasty at the time of open surgery [33,35,36]. It is often difficult to achieve reliable fixation, and bone grafts frequently collapse into the weak osteoporotic bone. Careful patient selection is critical to achieve satisfactory results. Preoperative health status must be carefully evaluated when deciding whether open surgery is a reliable option. Anterior, posterior, or combined anterior and posterior approaches can be used, depending on the exact configuration of the fracture(s). The aim is to eliminate movement by enabling the fractured vertebra to fuse to the adjacent vertebrae by using a combination of bone graft, screws, and plates. Extension osteotomy of the spine may be considered to compensate for loss of sagittal balance. It is associated, however, with high complication rates.

### 5. Treatment of underlying osteoporosis

#### 5.1. General measures and advice

Women with a VOF should be advised on lifestyle measures to decrease bone loss. Such measures include eating a balanced diet rich in calcium, stopping smoking, avoiding excess alcohol consumption, maintaining regular physical activity and sunlight exposure [37]. Patients with limited sunlight exposure or low dietary calcium should be advised to take calcium and vitamin D supplementation [38]. Strategies for reducing falls should be instigated [39]. There is some evidence to support the use of individualized tailored exercise rehabilitation aimed at strengthening back muscles to maintain bone density and reduce further fracture incidence [40]. Of note, hip protectors seem to be an ineffective intervention for those living at home and their effectiveness in an institutional setting is uncertain [41]. Finally, underlying causes of secondary osteoporosis should be treated where possible.

The options discussed are calcium and vitamin D, menopausal hormone therapy, tibolone, selective estrogen receptor modulators, bisphosphonates and anabolic agents. While calcitonin is effective, its prolonged use has been associated with an increase in cancer rate. Thus, calcitonin is currently indicated only for the short term management of acute pain following a vertebral fracture in the European Union [42]. Strontium ranelate reduces the risk of vertebral fractures by 40%, an effect evident across multiple levels of risk, including women with VOF [43]. The European Medicines Agency concluded its review of strontium in February 2014 and recommended restricting its use to patients with no history of cardiovascular disease who cannot be treated with other medicines approved for osteoporosis. In addition these patients should continue to be evaluated regularly every 6–12 months by their doctor and treatment should be stopped if patients develop heart or circulatory problems, such as uncontrolled high blood pressure or angina [44].

#### 5.2. Calcium and vitamin D supplementation

Calcium and vitamin D play a key role in bone metabolism and correction of nutritional deficiencies is therefore advised as part of osteoporosis management [45,46]. However, caution has been expressed in using calcium supplements in women whose diet is replete. Excess calcium supplementation may be associated with

an increased risk of kidney stones and cardiovascular events. Thus it has been estimated that treatment of 1000 people with calcium supplements over a period of five years results in 26 fewer fractures, 14 more myocardial infarctions, 10 more strokes and 13 more deaths [47]. Therefore, it seems reasonable to encourage individuals of all ages to obtain their calcium needs from the diet and use supplements with caution.

Calcitriol or alfacalcidol, the active vitamin D metabolites can be used in glucocorticoid-induced osteoporosis [48]. These agents, however, have limited efficacy in decreasing vertebral fracture risk or the risk of a subsequent vertebral fracture [49]. Furthermore, the potential risk of hypercalcaemia and the need for regular monitoring of calcium and renal function limit the use of calcitriol in the management of osteoporosis.

Many housebound elderly are Vitamin D deficient. Vitamin D is essential for musculoskeletal health as it promotes calcium absorption from the diet, enables mineralization of newly formed bone and plays an important role in muscle function [38,50]. Vitamin D deficiency may result in bone loss and an increased risk of falls and fractures, whereas more severe deficiency leads to osteomalacia. In view of the key role of vitamin D, the UK National Osteoporosis Society produced a practical clinical guideline in 2013 on estimating vitamin D status, treatment (oral vitamin D3 being the preparation of choice), loading doses, maintenance therapy and monitoring [50]. The guidelines point out that serum calcium should be checked one month after loading to exclude the rare unmasking of primary hyperparathyroidism.

#### 5.3. Menopausal hormone therapy

Menopausal hormone therapy (MHT) is the treatment of choice for the management of bothersome menopausal symptoms and urogenital atrophy. According to the Women's Health Initiative (WHI) trial, MHT decreased the risk of vertebral fractures by 35% in women in their sixties receiving either estrogen or estrogen-progestin treatment [51,52]. The same effect was apparent in the observational Million Women Study [53]. Long-term estrogen-progestogen combined MHT is associated with a small but significant increase in the risk of breast cancer [51,53]. Thus a recent consensus concluded that 'MHT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause.' [54].

#### 5.4. Tibolone

Tibolone is a synthetic steroid with estrogenic, progestogenic and androgenic activity indicated for the management of menopausal symptoms and of urogenital atrophy in postmenopausal women. In the LIFT trial undertaken in women aged 60–85 years, tibolone (1.25 mg daily) decreased the occurrence of new vertebral fractures by 45% compared to placebo after 3 years of treatment. However tibolone increased the risk of stroke [55] and the study was discontinued prematurely. Thus in some, but not all, EU Member States tibolone is indicated for the prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products authorized for the prevention of osteoporosis.

#### 5.5. Selective estrogen receptor modulators (SERMs)

SERMs are compounds that act through the estrogen receptor, but depending on the tissue target they exert either estrogen-agonist activity (e.g. bone) or estrogen-antagonist activity (e.g. breast). In bone tissue they inhibit bone resorption and reduce bone turnover [56,57].

Raloxifene and bazedoxifene are two SERMs approved for the treatment of osteoporosis. Raloxifene is the first SERM approved for the treatment of postmenopausal osteoporosis. Raloxifene, taken orally on a daily basis, increases bone mineral density and reduces the incidence of vertebral fracture by 50% in women with no previous fracture and by 30% in women with prevalent fractures, as documented in its pivotal trial (MORE) [58]. There is no documented efficacy of raloxifene in non-vertebral or hip fractures. In addition it reduces the risk of breast cancer [59]. Raloxifene increases the risk of venous thromboembolism and hot flushes.

Bazedoxifene is a newer SERM approved for the treatment of postmenopausal women at risk of fracture. It is not available in all countries. It increases bone mineral density and decreases the risk of vertebral fracture by 35–40%. In primary analyses bazedoxifene was not shown to be effective in preventing non-vertebral or hip fractures. In subgroups of women at high risk of fracture, however, bazedoxifene also reduced the incidence of non-vertebral fractures. Like all other SERMS, it increases the risk of venous thromboembolism and hot flushes [60].

### 5.6. Bisphosphonates

Bisphosphonates are potent antiresorptive agents that are administered orally on a weekly (alendronate, risedronate) or monthly basis (risedronate, ibandronate) or intravenously every three months (ibandronate) or annually (zoledronic acid). Bisphosphonates reduce the risk of vertebral fractures by 40–70% in high risk populations including women with VOF [61]. Upper gastrointestinal irritation with oral agents and flu-like symptoms with the intravenous preparations are the most common side effects. Rare complications include osteonecrosis of the jaw and atypical femur fractures occurring at the shaft, the latter reported after prolonged treatment. Given their documented efficacy in patients with prevalent vertebral fractures, their favorable safety profile and their low cost, bisphosphonates should be considered as a first line option in women with VOF [10].

### 5.7. Denosumab

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL), a bone resorbing cytokine. It is administered as a subcutaneous injection every six months. Denosumab reduces the risk of all vertebral fractures by 68% and the risk of new clinical vertebral fractures by 69% after 3 years of use, an effect persistent after 5 years [62,63]. The effect of denosumab is particularly evident in high risk populations such as women with previous osteoporotic fractures [64]. Side effects are rare and include topical skin reactions and very rarely cellulitis. Although its cost may be an issue, denosumab is included among the first line options for women with prevalent VOF.

### 5.8. Anabolic agents

Teriparatide (recombinant human parathormone PTH 1–34) or the intact PTH molecule (1–84) increase bone density and decrease vertebral fracture incidence. Treatment of high risk postmenopausal women with teriparatide for a median of 20 months increased lumbar spine BMD by 9–13% than placebo group and reduced the risk of a new vertebral fracture by 65%. [65]. Intact PTH reduces vertebral fractures by 40% [66]. Teriparatide increase cortical bone formation, promoting thus bone strength [67].

The anti-fracture efficacy of teriparatide appears to be largely independent of age, initial BMD and the presence or absence of prevalent vertebral fractures [68]. In general, teriparatide is particularly useful in the management of women with severe osteoporosis who have a number of previous vertebral fractures or those

who failed to respond to anti-resorptive treatments. Furthermore, its use in the first 18 months after spondyloplasty or kyphoplasty reduces the risk of second fragility fractures in adjacent vertebral bodies (*domino effect*) [69].

## 6. Follow-up of patients with vertebral fractures

Patients with prevalent VOF should be closely monitored for subsequent VOF, as they are, as stated earlier, at particularly high risk. Relapse or new onset of back pain, height reduction or kyphosis should alert the physician toward a new VOF. Bone mineral density is useful to assess response to osteoporosis treatment and possibly to detect incident VOF, by the Vertebral Fracture Assessment (VFA) algorithm [69]. However biochemical markers of bone turnover levels respond rapidly to both anabolic and antiresorptive treatments [70].

## 7. Conclusions

Treatment of osteoporosis should be multidisciplinary dealing with the acute event, managing the underlying osteoporosis and endeavors to return to previous levels of activity. In postmenopausal women with a VOF, management starts with targeted analgesia, early mobilization of the patient and anti-osteoporotic treatment tailored to individual needs and medical problems. Underlying pathology such as multiple myeloma or metastatic disease should be sought and treated accordingly. Vertebroplasty and kyphoplasty may prove useful in selected patients unresponsive to conventional pain relief. Open surgical treatment is reserved for patients with severe spine deformity or when minimally invasive percutaneous cement augmentation techniques have failed. In addition the use of specific orthotic devices may help to reduce kyphosis, improve mobility and reduce pain.

## 8. Summary recommendations

- The management of postmenopausal women with a VOF includes measures to reduce pain and improve mobility as well as treatment of osteoporosis itself and the underlying disease in cases of secondary osteoporosis.
- It is essential to investigate and treat any non-osteoporotic vertebral pathology that could cause a fragility fracture such as metastatic disease or multiple myeloma.
- Medical treatment of osteoporosis with effective agents such as menopausal hormone therapy, SERMS, bisphosphonates or denosumab, depending on age and concomitant medical conditions, need to be started as soon as possible.
- The woman must be calcium and vitamin D replete.
- Sufficient pain relief, physiotherapy and falls assessments need to be in place to facilitate rehabilitation and return to normal activities.
- In most patients, non-operative interventions combined are sufficient. However, surgery such as vertebroplasty or kyphoplasty may be required.
- Treatment is best provided by a multidisciplinary team.

## Contributors

IT prepared the initial draft, which was circulated to EMAS board members for comment and approval, production was coordinated by MR, IL and IT.

## Competing interest

The authors have no conflicting interests to declare.

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