Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men

February 2010

Approved by NHMRC
on 5 February 2010

THE ROYAL AUSTRALIAN
COLLEGE OF
GENERAL PRACTITIONERS

The Royal Australian College of General Practitioners, 1 Palmerston Crescent, South Melbourne, Vic 3205 Australia
ACN 000 223 807, ABN 34 000 223 807

Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men

The National Health and Medical Research Council (NHMRC) is Australia's leading funding body for health and medical research. The NHMRC also provides the government, health professionals and the community with expert and independent advice on a range of issues that directly affect the health and wellbeing of all Australians.

The NHMRC provided support to this project through the Guidelines Assessment Register (GAR) process. The GAR consultant on this project was Karen Grimmer-Somers.

The guidelines were approved by the Chief Executive Officer of the NHMRC on 5 February 2010 under Section 14A of the National Health and Medical Research Council Act, 1992. Approval for the guidelines by NHMRC is granted for a period not exceeding 5 years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every 5 years.

This publication was supported by funding from the Australian Government. The publication reflects the views of the authors and does not necessarily reflect the views of the Australian Government.

Published by:
The Royal Australian College of General Practitioners
College House
1 Palmerston Crescent
South Melbourne, Victoria 3205
Australia
Tel 03 8699 0414
Fax 03 8699 0400
www.racgp.org.au

ISBN 978-0-86906-306-4

Published February 2010

© The Royal Australian College of General Practitioners. All rights reserved.

CONTENTS

INTRODUCTION

Chronic diseases have a major impact on Australian society, accounting for about two-thirds of health care expenditure (more than $35 billion) in 2000 and 2001.[1] An increasing proportion of the population has risk factors for, or at least one, chronic disease, leading to increasing public health costs. Health service policy and delivery must address not only acute conditions, but also effectively respond to the wide range of health and public services required by people with chronic illness.[1,2] Strong primary health care policy is an important foundation for a successful national health delivery system and long term management of public health. It is also linked to practical outcomes including lower mortality, decreased hospitalisation and improved health outcomes.[1] National strategic health policy has recently given increased recognition to the importance of chronic disease management, with Federal Government endorsement of a number of initiatives for the prevention or delay in onset, early detection, and evidence based management of chronic diseases, including osteoporosis (OP).[1]

Osteoporosis exerts a significant burden on both individuals and the community. In terms of cost, it was estimated in 2001 that the combined direct and indirect cost of OP in Australia was approximately $7 billion annually.[3] For further details refer to the *Evidence to support the National Plan for Osteoarthritis, Rheumatoid Arthritis and Osteoporosis: Opportunities to improve health-related quality of life and reduce the burden of disease and disability.*[4]

Expiry date for the recommendations

This guideline presents a comprehensive review of pharmacological management of OP within the Australian health care context, based on the best available evidence up to September 2006. Specific additional literature searches covering the intervention options were conducted and publications considered important were included up to submission of the document to the National Health and Medical Research Council (NHMRC) in May 2009.

The guideline was approved by the CEO of the NHMRC on 5 February 2010, under Section 14A of the *National Health and Medical Research Council Act*, 1992. Approval for the guidelines by the NHMRC is granted for a period not exceeding 5 years. It is expected that the guideline will be reviewed, and revised if necessary, no less than once every 5 years. Review should be more frequent in areas where clinical practice or research is known to be changing rapidly. Readers should check with The Royal Australian College of General Practitioners (RACGP) website for any reviews or updates of this guideline.

The role of general practitioners

General practice plays an important role within the Australian health care system in the prevention, early detection and management of chronic disease. The nature of general practice provides the opportunity for early screening for chronic disease and enables preventable risk factors to be addressed. General practitioners have an important role in monitoring disease progression and response to treatment, as well as managing comorbidities in conjunction with the treating specialist and other members of the multidisciplinary team. However, as seen across the health care system, OP is frequently under treated in general practice.[5] This guideline is designed to provide clear, evidence based recommendations to assist GPs in managing patients with OP. The purpose of this guideline is to support clinical judgment, not to replace it.

Acknowledgments

This project was supported by the RACGP and the Australian Government Department of Health and Ageing (DoHA). The following experts were involved in the development of the guideline as part of the RACGP Osteoporosis Working Group:

Professor John Eisman AO (Chair), MBBS, PhD, FRACP

Professor Peter Ebeling MBBS, MD, FRACP

Dr Dan Ewald MPH&TM, MAppEpid, FAFPHM, FRACGP

Professor Leon Flicker GDipEpid, PhD, FRACP

Ms Barbara Holborow OAM, SAB

Associate Professor Peter Nash MBBS(Hons), FRACP

Professor Philip Sambrook OAM MBBS, MD, LLB, FRACP

Professor Markus Seibel MD, PhD, FRACP

Ms Judy Stenmark BAppSc, MPH

Dr Tania Winzenberg MBBS, FRACGP, MMedSc(ClinEpid), PhD

Ms Julia Herjandono BA(Hons), MFIA

RACGP contributors and NHMRC adviser

Dr Morton Rawlin BMed, MMedSci, DipPracDerm, DipFP, DipMedHyp, DipBusAdmin, FACRRM, FRACGP

Professor Karen Grimmer-Somers PhD, MMedSc, BPhty, LMusA, CertHlthEc

Amy Jasper MBA, GDip(HumServRes), BAppSc(AdvNsg)

Dr Jiri Rada PhD, MSc, BPHE, BA, FRSH

Emily Haesler BN, PGradDipAdvNsg

Note: All website references were current at the time of publication.

Commonly used abbreviations

25-OH D	25-hydroxyvitamin D
ARR	absolute risk reduction
BMD	bone mineral density
CEE	conjugated equine (o)estrogen
CHD	coronary heart disease
CI	confidence interval
CV	cardiovascular
DXA	dual energy X-ray absorpitometry
GIT	gastrointestinal
GP	general practitioner
hPTH	human parathyroid hormone
HR	hazard ratio
HT	hormone therapy
ITT	intention to treat
MA	meta-analysis
MI	myocardial infarction
NHMRC	[The] National Health and Medical Research Council
NNH	number needed to harm
NNT	number need to treat
OP	osteoporosis
OR	odds ratio
QCT	quantitative computed tomography
QOL	quality of life
QUS	quantitative ultrasound
PBS	Pharmaceutical Benefits Scheme
PTH	parathyroid hormone
RACGP	[The] Royal Australian College of General Practitioners
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
SD	standard deviation
SERMs	selective oestrogen receptor modulators
SEM	standard error of the mean
SR	systematic review
TSH	thyroid stimulating hormone
WHO	World Health Organization
WMD	weighted means difference

BACKGROUND

Osteoporosis

Osteoporosis (OP) is defined as a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.[6] It is diagnosed by a bone density test that usually measures the density at the hip and spine. The result is called a 'T-score,' and will be in the range of normal, osteopenia, or OP.[7]

Osteoporotic fractures usually result from a combination of decreased bone strength and injurious falls. However intervention studies to reduce falls have not shown a reduced fracture risk. It is not clear whether this relates to inadequate study size or design or that falls resulting in fractures may not be prevented by these approaches. Vertebral (spinal) fractures are the hallmark fracture of OP and occur with a higher incidence and earlier in life than any other types of minimal trauma fracture. Only about a third of vertebral fractures are associated with falls[8] and most are precipitated by routine activities such as bending or lifting. In a cross sectional study, less than 25% of fractures had been recognised by the patient as a fracture.[9] Non-vertebral factures are more common than vertebral fractures and their incidence is generally less responsive to therapy. Fractures at these non-vertebral sites, including hip, distal forearm, humerus, shoulder, ankle, pelvis and tibia, are approximately twice as common in women as in men, and their incidence also rises with age.[10,11]

Incidence and prevalence of osteoporosis

Osteoporotic fractures are more likely with decreased bone strength and an increased frequency of injurious falls. Irrespective of fracture site, adults who sustain a fracture are at substantially greater risk (2–4 fold) of sustaining another fracture of a different type. Apart from the fracture event *per se*, the burden of osteoporotic fractures fall into three broad categories: worsened quality of life, substantial health care costs, and associated premature mortality. Ideally, decisions about intervention should be based upon estimates of absolute risk of fracture but this can only be crudely estimated from current data (see Absolute fracture risk nomograms).

The incidence of minimal trauma fractures in Australia is higher among women than men and increases with age in both genders. Australian studies show that the lifetime risk of minimal trauma fracture is approximately 43% for women over 50 years of age and 56% among women over 60 years of age. The lifetime fracture risk among men is lower, but still substantial and higher than for many other chronic conditions, being around 27% for those over 50 years of age and 29% for men over 60 years of age.[12–14] Recall data from questionnaires from a large number of postmenopausal women attending typical general practices in Australia suggests that the peak incidence of low trauma fractures is in the 60–75 years age group and hip fractures are a relatively small percentage of the total number of fractures recalled. In fact, they were less common than wrist, clinical spine, ankle and rib fractures, with a range of other unspecified low trauma fractures also being more common.[5]

The prevalence of OP can be measured indirectly though measures of bone mineral density. According to the World Health Organization (WHO) definition of OP and osteopenia,[6] approximately 11% of men and 27% of women aged 60 years or over are osteoporotic. Approximately 42% of men and 51% of women are osteopenic based on bone densitometry measurements carried out in the Dubbo Osteoporosis Epidemiology Study.[15] The Geelong Osteoporosis Study estimates that by the age of 79 years up to 87% of Australian women will have evidence of OP using the WHO criteria.[16] On the other hand, in the 2001 National Health Survey only 299 800 people (17% male, 83% female) self reported OP in Australia, which was equivalent to approximately 1.6% of the population.[17] Although this represented a 21% increase since the previous survey conducted in 1995 when 248 000 people self reported OP,[18] it is probable that this increase reflects increased awareness of the diagnosis rather than a change in prevalence. This possibility is also suggested by the gender ratio of self reported prevalence in contrast to the gender ratio found in the systematic Dubbo survey. Analysis of Medicare claims for bone mineral density (BMD) testing 2001–2005 shows testing rates four times higher for women than men.[19]

Fractures of the hip, vertebral body and distal forearm have long been regarded as 'typical' osteoporotic fractures. However, the effect on the skeleton is systemic and almost all types of fracture are increased in patients with low bone density and, irrespective of fracture site, adults who sustain a low trauma fracture (and possibly even a high trauma fracture)[20] are at substantially greater (2–4 fold) risk of sustaining another fracture of a different type.

Management of osteoporosis

Minimal trauma (ie. fragility fractures), particularly with low bone density, ie. T-scores below about -1.5, supports the use of pharmacological interventions to prevent further bone loss and reduce subsequent fracture risk. Treatment decisions need to be based on age, gender, previous medical history, how advanced the condition is and an estimate of absolute risk of fracture. Despite high level evidence for efficacy, safety and cost effectiveness, less than 30% of Australian women and even fewer Australian men with OP (even with fragility fractures) take specific OP targeted pharmaceuticals and/or use appropriate vitamin/mineral supplements. Most current OP medications are anti-resorptive and reduce the natural but excessive process of bone loss. Some new agents can increase the formation of new bone and these may be most appropriate for the more severe degrees of OP, especially those that appear unresponsive to more common anti-resorptive therapy.

In general, advice also needs to be provided to assist the individual address their modifiable risk factors, as part of both the treatment and prevention of OP. This routine health care approach includes encouragement and support to increase weight bearing physical activity, to maintain a healthy diet and to avoid smoking and excessive alcohol intake. Exercise can assist in relieving pain as part of the rehabilitation process. Only about 20% of Australians with OP report exercising most days and 6% do strength training.[21] Specific OP self management programs are conducted by the state offices of Osteoporosis Australia and various public hospital health promotion units and community health centres. They usually focus on education and awareness about the disease process, prevention of fractures, pain management, rehabilitation techniques and falls prevention. However, particularly in rural and remote settings, it is likely that patient education will need to be coordinated and/or undertaken by general practice with links to local allied health services.

Scope and focus of the guideline

The guideline focus is on prevention and treatment of OP in postmenopausal women and older men. Although many of the recommendations are relevant to other populations with OP, evidence related to other populations, eg. children, was not reviewed. The guideline outlines a best practice approach for Australian GPs in:

- identifying, diagnosing, treating and managing, in a timely and accurate manner, men and women who have been diagnosed with at least one minimal trauma fracture
- reducing the progression of such individuals to a second fracture
- optimising patient and carer access to information, understanding of the condition and involvement in its management in order to help patients improve their health status.

The guideline is based on a systematic review (SR) of the evidence and constitutes Australian best practice approach to identifying, diagnosing, treating and managing OP in the following target populations:

- Postmenopausal women and older men who may be at risk of developing OP
- Postmenopausal women and men over 60 years of age diagnosed as having at least one fracture following minimal trauma (equivalent to a fall from standing height or less)
- Postmenopausal women and men over 50 years of age who have been diagnosed with OP defined as a T-score of -2.5 or less but without evidence of a minimal trauma fracture. (The Australian Pharmaceutical Benefits Scheme [PBS] currently applies a threshold T-score of -3.0 for access to PBS subsidised therapies in this population.)

Except where guidance is provided within the recommendation itself, advice on pharmacological treatment should be sought from a specialist endocrinologist, rheumatologist, geriatrician or general physician. The RACGP Osteoporosis Working Group recommends consulting the Therapeutic Guidelines (www.tg.org.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information including adverse events.

Target audience

This guideline is intended primarily for use in primary care settings by GPs and their patients. Additionally, it is intended that through this guideline any health care professionals that patients elect to consult regarding OP are aware of the evidence regarding effective management. These include, but are not limited to, physiotherapists, nurses, occupational therapists, sports medicine personnel, podiatrists, dieticians, psychologists, pharmacists and community health workers. The guideline is applicable to primary care settings in metropolitan, regional, rural and remote areas of Australia.

Methods

The process used to develop the guideline is based on the May 2006 *German Societies for Bone and Mineral Disorders* (*DVO*) guideline[22,23] and supplemented with more recent papers. For interventions, only randomised, blinded, placebo controlled studies were included.

This process is outlined in full in the Process Report *(Appendix A).*

Membership of the RACGP Osteoporosis Working Group included a wide range of expertise including that from endocrinologists, rheumatologists, geriatricians, GPs, a consumer representative and an OP organisation representative.

The guideline

The guideline has been designed to provide clear information to assist the clinical decision making of GPs and to support optimal patient care. Where appropriate, the evidence has been interpreted with regard to the Australian context in which the guideline will be implemented. It is intended that the guideline be considered according to the limitations outlined below and used in conjunction with clinical judgment and patient preference. The guideline contains the following information.

Algorithm (flowchart)

The algorithm summarises the main recommendations of the guideline and provides an accessible desktop reference.

Fracture risk nomograms

These published nomograms, developed from studies of Australian men and women in the Dubbo Osteoporosis Epidemiology Study, allow estimation of absolute fracture risk over 5 and 10 years.[24,25] These may be helpful in discussing risk and interventions with patients. These algorithms are available at www.fracturerisk calculator.com.

Recommendations

Each of the 28 recommendations has been graded from A to D according to the process outlined in *Appendix A*. The grade reflects the degree of 'trust' that the clinician can place on the clinical application of the recommendation. Each recommendation is supported by a summary of the evidence. The Working Group supports all 28 recommendations and intends that they are used in conjunction with clinical judgment and patient preferences. They do not cover complex medical conditions and comorbidities.

Practical tips and precautions

Where appropriate the recommendations are followed by practical tips, precautions and dosing options. The practical tips are essential tips on how to effectively implement the recommendations. Unless otherwise referenced, the source of information presented in the practical tips is the RACGP Osteoporosis Working Group.

Resources

Useful references and supporting information are provided throughout the guideline. *Appendix B* contains additional resources, as well as contact details for organisations providing services and support to people with OP. The Working Group recommends consulting the Therapeutic Guidelines (www.tg.org.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information, including adverse effects.

Limitations of the guideline

Medication information

This guideline does not seek to provide full safety and usage information on pharmacological interventions and should not be applied without consideration to the patient's clinical profile. The Working Group recommends consulting the Therapeutic Guidelines (www.tg.org.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information.

Search date

The *DVO* guideline was based on the best evidence available up to September 2006. This data was supplemented by formal, focused literature searches to include relevant information up to September 2008. These were further supplemented with specific high level evidence published up to the time of the submission of this document to the NHMRC in May 2009. This data has been incorporated in the interest of providing recently available information on specific aspects of the guideline.

Population

The following populations are beyond the scope of the guideline:

- individuals receiving prolonged (more than 3 months) oral corticosteroid therapy
- individuals with secondary causes of OP, including but not limited to, coeliac disease, chronic liver disease, chronic renal failure, hyperparathyroidism, hypercortisolism, hyperthyroidism, and transplant recipients
- individuals with compromised physical function resulting from factors such as rheumatoid arthritis, neurological conditions, or spinal paralysis from various causes
- women with untreated hypogonadism, including postmenopause, primary hypogonadism, premature menopause, secondary amenorrhea (eg. following anorexia nervosa or associated with extreme levels of exercise or certain forms of oral contraceptives) and early hysterectomy
- men with primary or secondary hypogonadism.

These populations are recognised as important, and some of the recommendations may be considered relevant. However, due to the limited resources for this project, literature specifically related to these populations was excluded from critical appraisal.

Interventions included

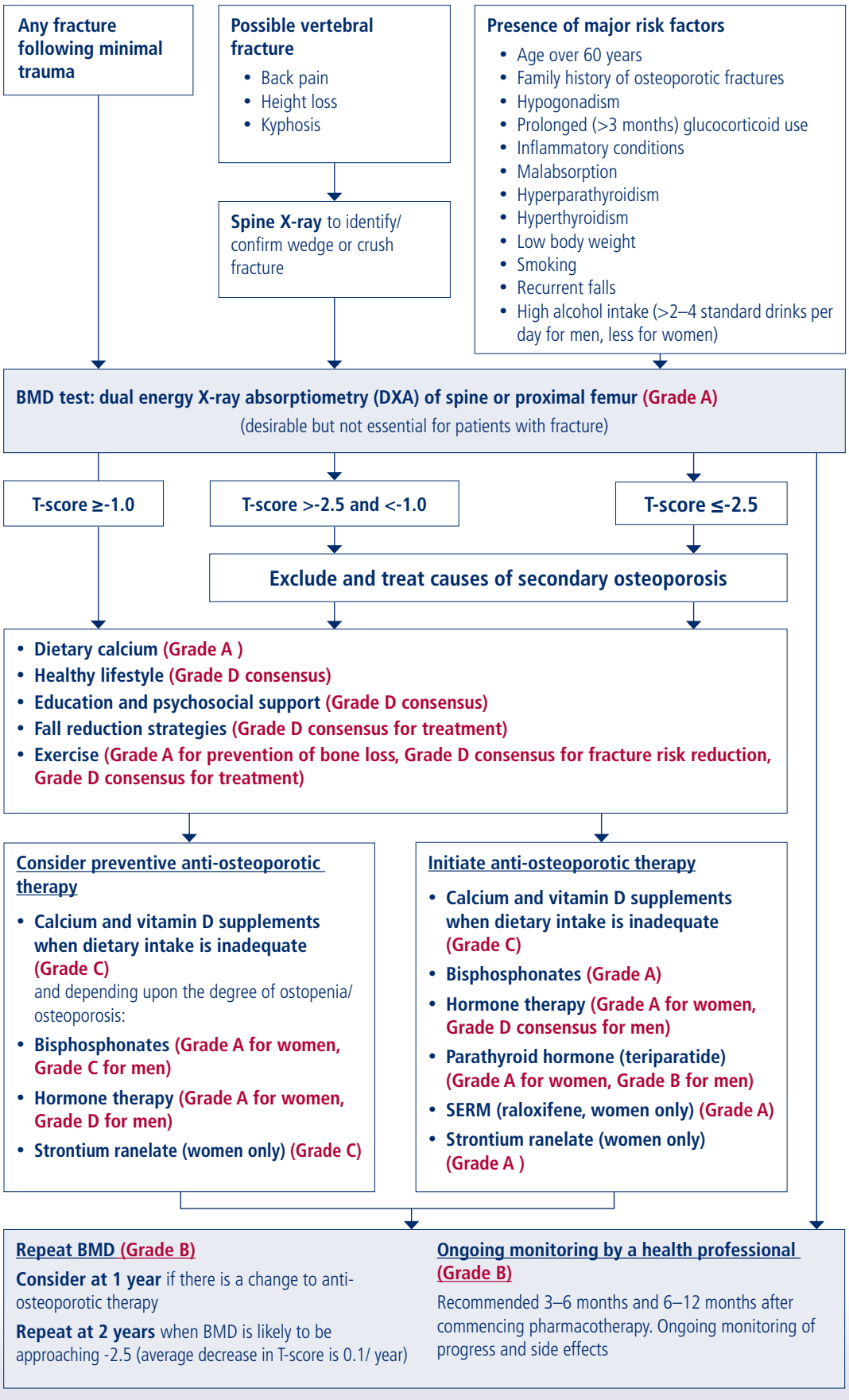
The search strategy was limited to papers graded as Level 1 or Level 2 evidence dealing with population of postmenopausal women or men over 50 years of age and reporting fractures or BMD outcome. The literature search focused on interventions with evidence for prevention and treatment of osteoporotic fractures. The search strategy for this guideline specifically considered interventions with fracture risk outcomes evaluated in randomised, placebo controlled trials. Data for all interventions was sourced from the primary base guideline, other international guidelines and supplemented, when possible, with more recent publications.

Studies that did not consider fracture outcomes were not included, with the exception of some studies addressing mechanism of action and complementing randomised, placebo controlled trials with fracture endpoints. Anecdotal reports or uncontrolled studies were not considered.

Cost effectiveness

As part of the project's brief, the guideline development process did not examine the cost effectiveness of any intervention. However, the pharmaceutical interventions recommended at the time of publication are supported by high level evidence of efficacy and safety and are approved by, and available under, the PBS. That approval formally includes full evaluation of efficacy, safety and cost effectiveness by the Pharmaceutical Benefits Advisory Committee.

OSTEOPOROSIS PREVENTION AND TREATMENT ALGORITHM



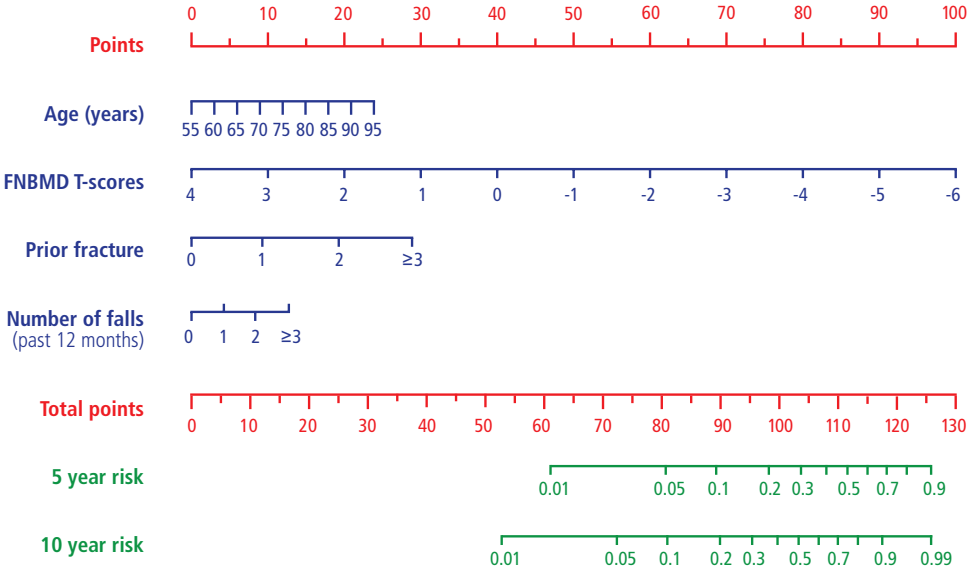
ABSOLUTE FRACTURE RISK NOMOGRAMS

These nomograms were developed from studies of Australian men and women, allowing estimation of absolute fracture risk over 5 and 10 years.[24,25] They may be helpful in discussing risk and interventions with patients. They are available at www.fracturerisk calculator.com.

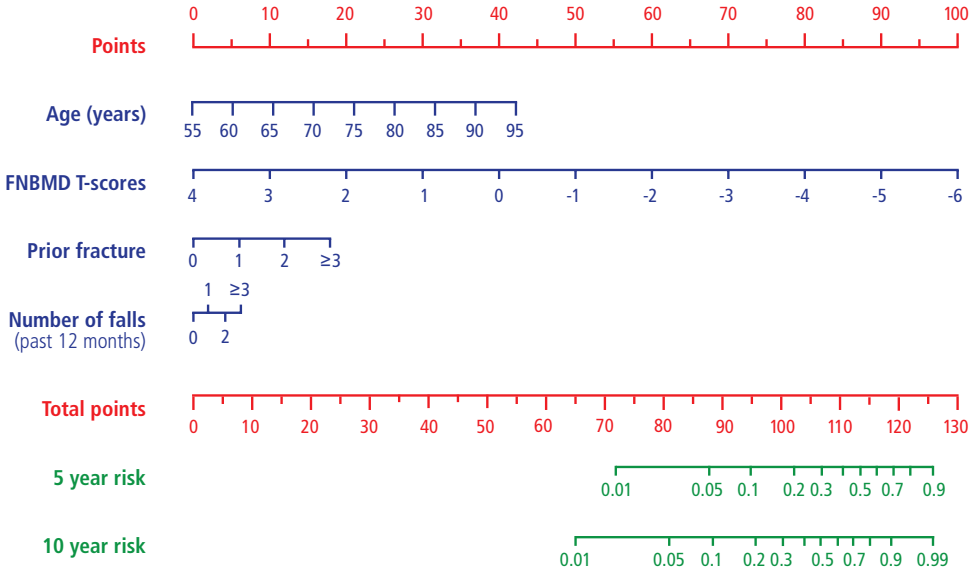
To use the nomograms for predicting 5 and 10 year absolute risk of hip and all fragility fractures for postmenopausal women and older men, read up vertically to the 'points' scale from the age of an individual on the 'age' axis and repeat for each additional risk factor.

Sum the points of the risk factors and then read down vertically from that final sum on the 'total points' axis to the 5 year or 10 year risk scales to find that individual's probability of sustaining a fracture within the next 5 or 10 years.

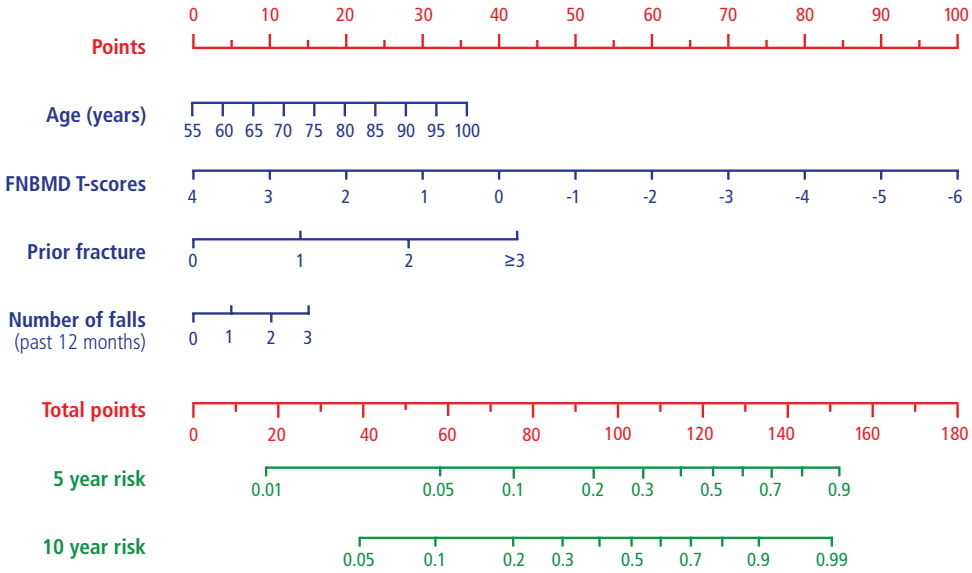
Hip fractures – women



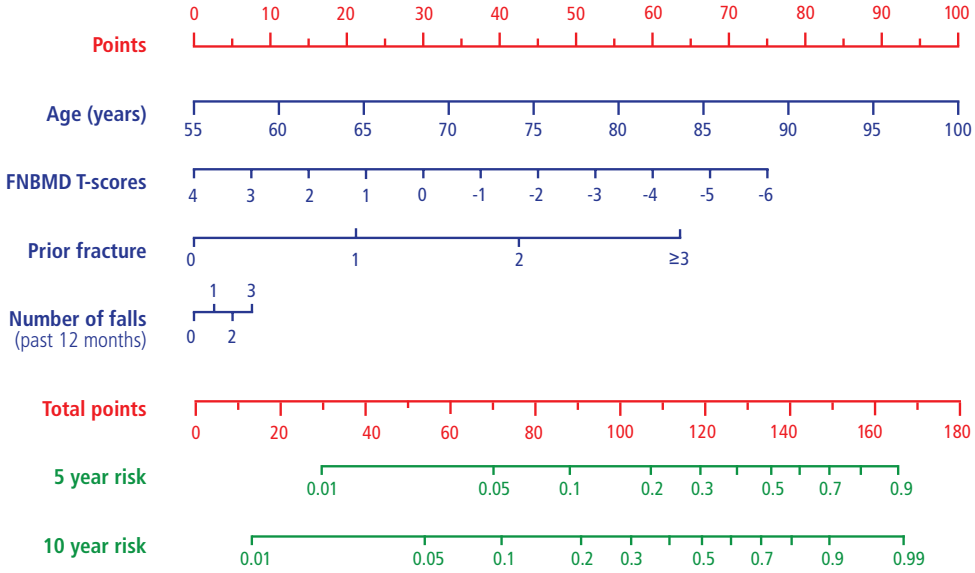
Hip fractures – men



All fragility fractures – women



All fragility fractures – men



SUMMARY OF RECOMMENDATIONS

Diagnosis and referral

RECOMMENDATION 1 – DIAGNOSIS OF OP – RISK FACTORS (Grade B)
There is good evidence to support GPs investigating any individual with risk factors for OP.

RECOMMENDATION 2 – DIAGNOSIS OF OP – LOW TRAUMA FRACTURE (Grade A)
There is excellent evidence to support GPs investigating patients with a fracture following low trauma.

RECOMMENDATION 3 – BMD MEASUREMENT (Grade A)
Bone mineral density should be measured by DXA scanning performed on two sites, preferably anteroposterior spine and hip.

RECOMMENDATION 4 – INVESTIGATIONS (Grade B)
Diagnostic assessment for OP should consist of medical history, clinical examination, a DXA bone density measurement and, if applicable, laboratory tests and radiographs of the thoracic and lumbar spine.

RECOMMENDATION 5 – REFERRAL (Grade B)
General practitioners should refer postmenopausal women and older men to a specialist or a specialist bone centre according to individual needs or when there is restricted access to appropriate resources or required expertise.

General recommendations

RECOMMENDATION 6 – DIETARY CALCIUM (Grade A)
General practitioners should recommend that postmenopausal women and older men maintain a diet high in calcium to meet the Australian recommended dietary intake.

RECOMMENDATION 7 – LIFESTYLE (Grade D consensus)
General practitioners should recommend the following important lifestyle choices for all postmenopausal women and older men:

- adequate but safe exposure to sunlight as a source of vitamin D
- maintenance of a healthy weight and body mass index (BMI)
- cessation of smoking
- avoidance of excessive alcohol consumption.

RECOMMENDATION 8 – EDUCATION AND PSYCHOSOCIAL SUPPORT (Grade D consensus)
General practitioners should provide postmenopausal women and older men at risk of, or diagnosed with OP, access to education, psychosocial support and encouragement to seek support from appropriate sources according to individual needs.

RECOMMENDATION 9 – REDUCING THE RISK OF FALLS (Grade D consensus)
There is good evidence to support GPs recommending an individually tailored, multifaceted fall reduction program to reduce the risk of falling in older adults. However, there is no evidence that such interventions reduce the risk of fractures, even in specialised settings.

Recommendations for prevention of osteoporosis

RECOMMENDATION 10a – EXERCISE and BONE LOSS (Grade A)
General practitioners should recommend regular, high intensity weight bearing exercise for preventing osteoporotic bone loss in postmenopausal women and older men.

RECOMMENDATION 10b – EXERCISE and FRACTURE RISK REDUCTION (Grade D consensus)

General practitioners could recommend sensible, moderate levels of physical activity throughout life as part of a healthy lifestyle. However, no studies have demonstrated any efficacy in fracture risk reduction and addressed side effects such as injuries.

RECOMMENDATION 11 – CALCIUM AND VITAMIN D SUPPLEMENTATION (Grade C)

There is mixed evidence on the effectiveness of calcium and vitamin D supplementation for prevention of bone loss and OP fractures in postmenopausal women and older men. There may be some benefit for those who have inadequate levels, particularly institutionalised patients.

RECOMMENDATION 12 – BISPHOSPHONATES (for postmenopausal women) (Grade A)

There is excellent evidence to support the effectiveness of alendronate in reducing the risk of vertebral fractures and increasing BMD in postmenopausal women at risk of OP.

RECOMMENDATION 13 – BISPHOSPHONATES (for older men) (Grade C)

There is evidence that bisphosphonates may reduce the risk of vertebral fractures and increase BMD in older men at risk of OP.

RECOMMENDATION 14 – HORMONE THERAPY (for postmenopausal women) (Grade A)

There is excellent evidence to support the effectiveness of hormone therapy in improving BMD and reducing the risk of fractures in postmenopausal women. The significant increase in risk of adverse events associated with treatment should be weighed carefully against benefits. Long term use is not recommended.

RECOMMENDATION 15 – HORMONE THERAPY (for older men) (Grade D consensus)

Hormone therapy used for men with hypogonadism is likely to prevent bone loss. The significant increase in risk of adverse events associated with treatment should be weighed carefully against benefits. Long term use is not recommended.

RECOMMENDATION 16 – STRONTIUM RANELATE (for postmenopausal women) (Grade C)

There is satisfactory evidence to support the effectiveness of strontium ranelate 2 g/day for prevention of BMD loss in early postmenopausal women.

Recommendations for treatment of osteoporosis

RECOMMENDATION 17 – EXERCISE (Grade D consensus)

There is evidence to support GPs recommending regular, weight bearing exercise for reducing osteoporotic bone loss in postmenopausal women and older men. However, there is no evidence of long term effects, side effects such as injuries, and any efficacy in fracture risk reduction.

RECOMMENDATION 18 – CALCIUM AND VITAMIN D SUPPLEMENTATION (Grade C)

There is good evidence for high prevalence of vitamin D insufficiency in institutionalised and home bound individuals and vitamin D supplementation is considered to be standard care in these populations. There may be some benefit for dietary change or calcium supplementation in postmenopausal women and older men with OP who have low dietary calcium intake.

RECOMMENDATION 19 – BISPHOSPHONATES (Grade A)

There is excellent evidence to support the effectiveness of bisphosphonates (alendronate, risedronate or zoledronic acid) in reducing the risk of vertebral and non-vertebral fractures and increasing BMD in postmenopausal women and older men with OP.

RECOMMENDATION 20 – DURATION OF BISPHOSPHONATE THERAPY (Grade D consensus)

General practitioners should reconsider bisphosphonate therapy after 5–10 years in postmenopausal women and older men with OP who have had a good response to treatment, determined through re-evaluation of BMD and fracture risk (ie. BMD above T-score -2.5 and no recent fractures). If BMD remains low (eg. T-score less than -2.5) continue treatment in view of the expected bone loss, especially at the hip, as soon as 1–2 years after stopping. Treatment should be restarted if there is evidence of bone loss (eg. lumbar spine BMD decrease of 5% or more) or with any additional fracture.

RECOMMENDATION 21 – HORMONE THERAPY (for postmenopausal women) (Grade A)

There is excellent evidence to support the effectiveness of hormone therapy (HT) in reducing the risk of fractures in postmenopausal women with OP. The significant increase in risk of adverse events associated with treatment should be weighed carefully against benefits, and long term use is not recommended.

RECOMMENDATION 22 – HORMONE THERAPY (for older men) (Grade D consensus)

Hormone therapy used for men with hypogonadism is likely to prevent bone loss. The increase in risk of adverse events associated with treatment should be weighed carefully against benefits in long term use.

RECOMMENDATION 23 – PARATHYROID HORMONE (for postmenopausal women) (Grade A)

There is excellent evidence to support the effectiveness of teriparatide in postmenopausal women with OP for reduction in fracture risk and improvement in BMD. Because of expense, teriparatide is generally recommended for patients at very high risk of fracture or in whom bisphosphonate therapy is contraindicated or has been ineffective.

RECOMMENDATION 24 – PARATHYROID HORMONE (for older men) (Grade B)

There is good evidence to support the effectiveness of teriparatide for improving BMD in older men with OP. Because of expense, teriparatide is restricted for patients at very high risk of fracture and after fracture has occurred while on anti-resorptive therapy.

RECOMMENDATION 25 – SELECTIVE OESTROGEN RECEPTOR MODULATORS (for postmenopausal women) (Grade A)

There is excellent evidence to support the effectiveness of selective oestrogen receptor modulators (SERMs) for postmenopausal women with OP where vertebral fractures, rather than non-vertebral fractures, are considered to be the major OP risk and where other agents are poorly tolerated.

RECOMMENDATION 26 – STRONTIUM RANELATE (for postmenopausal women) (Grade A)

There is excellent evidence to support the effectiveness of strontium ranelate 2 g/day for reducing the risk of further osteoporotic fractures in postmenopausal women with prevalent fractures.

Ongoing monitoring

RECOMMENDATION 27 – MONITORING INDIVIDUALS AT RISK (Grade B)

General practitioners should evaluate patients at increased risk for osteoporotic fractures who are not receiving specific preventive anti-osteoporotic therapy in regard to future fracture risk at intervals adequate to the risk in question. BMD measurement can identify some non-fragility causes of fracture, eg. T-score above -1.5. If a decision is made to not recommend specific preventive anti-osteoporotic therapy, this must be formally reviewed in relation to future fracture risk at intervals relevant to the risk in question. In most cases BMD testing is restricted to 2 year intervals.

RECOMMENDATION 28 – ONGOING MONITORING (Grade B)

General practitioners should provide regular monitoring and follow up of all patients with OP 3–6 months after initiating a specific pharmacological intervention and annually thereafter.

INTRODUCTION TO OSTEOPOROSIS

Clinical symptoms of osteoporosis

Osteoporosis is known as a silent disease because the deterioration of skeletal tissue proceeds with no outward symptom until a symptomatic fracture occurs, and thus the condition is under recognised and affected individuals are under treated.[26,27] Vertebral (spinal) fractures may cause no recognisable symptoms for the patient or may present with an acute self limiting episode of back pain. However, subclinical fractures are important predictors of future fracture risk. More commonly, vertebral factures are associated with gradual height loss with increasing thoracic kyphosis and back pain. Non-vertebral or peripheral fractures usually present with more obvious fracture symptoms following a fall, although stress fractures may present as acute regional musculoskeletal pain.

Vertebral fractures

Vertebral fractures are the hallmark fracture of OP and occur with a higher incidence and earlier in life than any other types of minimal trauma fracture. They are usually defined on the basis of a >20% reduction in vertebral height on X-ray and often termed a 'vertebral deformity'. Only around a third of all radiographically observed vertebral deformities come to medical attention (ie. are symptomatic with acute fracture related pain) and <10% result in hospitalisation.[28] Those identified medically are associated with significant long term disability through pain and kyphosis. Only about a third of vertebral fractures are associated with falls[8] and most are precipitated by routine activities such as bending or lifting light objects. The prevalence of radiologically identified vertebral deformities ranges from 5% in people aged 50–54 years to 50% in those over 80 years of age.[29] Data on a random sample of older Australian men and women suggests similar prevalence of vertebral deformity in men and women of the same age.[13] In men, occupation associated trauma has been suggested to account for this almost equal prevalence of radiographic deformity with women. The incidence of vertebral deformities is estimated to be 1% per year among women and 0.6% among men based on radiological evidence in men and women over 50–60 years of age.[11]

Hip and other non-vertebral fractures

Hip and other non-vertebral factures are more common than vertebral fractures and generally their incidence is less responsive to therapy. These fractures contribute a majority of the burden of osteoporotic fractures. The incidence of hip fractures increases exponentially with age. Most hip fractures occur after a fall with 60–80% occurring in women and 90% occurring among people over 50 years of age. In Australia it has been predicted that the annual incidence of hip fracture will increase from 15 000 in 1996 to 21 000 by 2010 and to 34 000 by 2026, nearly doubling again by 2051 when nearly one-quarter of Australia's population will be 65 years of age or older.[30] However, some data suggest that the increase in the incidence rate of hip fractures may be levelling off or declining in Australia and elsewhere.[31–33]

Minimal trauma fractures sustained at other sites are also projected to increase.[34] Wrist fractures show a different pattern of occurrence to that of hip and vertebral fracture.[10] The overall incidence of wrist fracture is 4–5 per 1000 person years in women and 1 per 1000 person years in men.[11] These incidence rates increase among caucasian women aged 45–60 years, followed by a plateau or more attenuated increase thereafter. Most wrist fractures occur in women, 50% of whom are aged over 65 years. The incidence in men is lower but also increases with ageing.

Consequences of osteoporosis

The adverse outcomes of osteoporotic fracture fall into three broad categories: premature mortality, morbidity, and cost. The effect of fractures on survival depends on fracture type. Hip fractures are the most devastating consequence of OP because they require hospitalisation, result in serious disability and are associated with an increase of 10–20% mortality over the first year following fracture.[35] The risk of death is greatest in the first 6 months immediately after the fracture and decreases over time. However, it is not clear that such deaths are directly attributable to the hip fracture. Some studies have suggested that 50% of the premature mortality is attributable to chronic illnesses. Acute events such as infections and postoperative complications are also important.

People with vertebral fractures have an increased mortality rate, which extends well beyond the first year. Again, reduced survival is difficult to attribute to direct effects of the fracture and premature mortality in some studies is attributed to comorbidities. Recent data indicate that all types of osteoporotic fractures are

associated with increased age specific mortality, that this effect lasts for at least 5 years after the fracture event, and that the impact is worse in men than in women.[35] A recent interventional randomised controlled trial (RCT) of intravenous bisphosphonate in men and women with prior hip fractures showed a reduction in subsequent fractures and a decrease in mortality.[36] This study and others studies showing mortality increases soon after fracture and declining toward the expected mortality rates, suggest that the fracture events may indeed have an impact on mortality. The latter data suggest that these effects are related to all types of low trauma/fragility fractures and not just to hip fractures.

Morbidity related to fractures can arise from pain, reduced mobility, loss of function and associated loss of quality of life. Many patients lose the ability to live independently following a hip fracture. Morbidity is associated with almost all types of symptomatic osteoporotic fractures.

Osteoporosis in the Australian setting

Barriers to diagnosis in Australia

Osteoporosis is both under diagnosed and under treated in Australia. It represents an example of a gap between evidence and clinical practice. Only 7–20% of patients who have sustained an osteoporotic fracture receive treatment for OP to prevent further fractures.[37] These rates are low in both tertiary[38] and primary care.[5] In the Australian Bone Care study of more than 8800 postmenopausal Australian women attending primary care physicians, 29% reported at least one low trauma fracture after menopause. However, only less than one-third of these women were on specific treatment for OP, and only 40% were ever told they had OP.[5]

The reasons for low rates of treatment and DXA screening are unclear. Many primary care and specialist physicians fail to recognise the patient's first fracture as osteoporotic and thus fail to initiate investigation or treatment for OP. In the tertiary setting, systematic approaches using either fracture protocols or a multidisciplinary approach including family doctor liaison have improved rates of treatment.[39,40] Qualitative data suggest that even the decision by GPs whether to screen a patient or not involves considerably more complex factors than simply being aware of clinical guidelines or of the importance of OP.[41] Given this complexity, it is likely that improvement in levels of both diagnosis and treatment of OP in multifaceted and systems based approaches are needed.[42] Contributing to this will be the development of a musculoskeletal curriculum at a national level for undergraduate and postgraduate medical education, which is currently underway.

One issue specific to densitometry screening may be poor accessibility of bone densitometry testing facilities. This is demonstrated by lower utilisation of densitometry services in rural and remote areas of Australia (particularly for men) compared with metropolitan areas.[19] Poor access may also be related to lack of Medicare reimbursement for bone densitometry for some patients, and gap fees.

Medicare reimbursement

The clinical risk factors for OP that qualify for Medicare payment for BMD measurement by DXA are:

- one or more pre-existing minimal trauma fracture(s)
- monitoring of low BMD proven by BMD at least 12 months previously
- age 70 years or more in women and men
- drugs such as prolonged glucocorticoid therapy, excessive thyroid hormone replacement
- rheumatoid arthritis, hyperparathyroidism, hyperthyroidism, chronic kidney disease, chronic liver disease, premature menopause of at least 6 months in women aged <45 years, hypogonadism in men and/or proven malabsorption.

DXA is also reimbursed for monitoring changes in BMD after 1 year in the case of a significant change in therapy, glucocorticoid excess, male or female hypogonadism; or 2 years in the case of minimal trauma fractures, low BMD or other associated medical conditions listed above. Computerised tomography (CT) is also reimbursed for densitometry but exposes individuals to a higher burden of ionising radiation and has lower reproducibility. Thus it is not recommended unless DXA is unavailable or uninterpretable, such as with gross degenerative changes in the spine and bilateral hip replacement and/or deformity.

DIAGNOSIS AND REFERRAL

Identifying patients to investigate for osteoporosis

RECOMMENDATION 1 (Grade B)

There is good evidence to support GPs investigating any individual with risk factors for OP.

RECOMMENDATION 2 (Grade A)

There is excellent evidence to support GPs investigating patients with a fracture following low trauma.

EVIDENCE STATEMENT

Investigating patients with risk factors

Three major international guidelines[3,4,7] identify the key risk factors for fractures as low BMD, past history of fracture, age, gender and multiple falls. Other risk factors include smoking, immobility, underweight and height.[3,4,7] All three guidelines recommend that all individuals with multiple risk factors for OP should undergo a diagnostic assessment.[3,4,7] The clinical practice guidelines of the American College of Physicians recommend that clinicians periodically perform individualised assessment of risk factors for OP in older men.[8]

Investigating patients with low trauma fracture

There is strong evidence from four large, 3 year OP treatment RCTs conducted at 373 study centers in North America, Europe, Australia and New Zealand showing that women who develop a vertebral fracture are at a substantial risk of sustaining an additional fracture within the next year.[9] Another large study showed there was a marked increase in subsequent incidence of hip and all fractures within the first year following hospitalisation for vertebral fracture in both men and women.[10] Other studies also indicate that fractures at any site are strong risk factors for subsequent fractures, among both older men and women.[4,11]

Two major international guidelines confirm that existing vertebral fractures significantly increase the risk of subsequent vertebral and hip fractures and strongly recommend investigating fractures following low trauma.[3,4] A diagnostic assessment is also recommended in patients with coincidently found vertebral fractures or any other minimal trauma fracture.[12]

Practical tips and precautions

Any adult woman or man should be considered to have OP if they suffer a fracture after minimal trauma, such as after a fall from standing height or less. All such individuals should have their management individualised by excluding causes of secondary OP, ensuring adequate calcium intake and high vitamin D status, by encouraging physical activity and implementing falls prevention strategies, modifying aggravating factors for bone loss, and by initiating long term specific anti-OP therapy. Although bone densitometry is not always required, it can exclude non-fragility causes of fractures. Particularly in younger men and women other causes need to be excluded, including greater force than reported. Bone densitometry can exclude some non-fragility causes of fractures.

Patients should be assessed for possible vertebral wedge or crush fractures, if there is any history suggestive of height loss, kyphosis and/or episodes of back pain. If the investigations are positive, investigate for OP. Similarly, standard spine X-rays should be performed to diagnose or exclude vertebral wedge or crush fractures.

Risk factors for osteoporotic fracture

Presence of existing fragility fractures

The single most easily recognised risk factor for osteoporotic fracture is the presence of any spinal or non-spinal minimal trauma fracture. This also applies to vertebral fractures that are coincidentally detected on radiographs. A single vertebral fracture is associated with a five-fold increase in subsequent vertebral fracture risk.[43] A minimal trauma fracture is defined as being due to a fall from standing height or less. The risk for further spinal fractures increases up to 11-fold if three or more fractures are present. The risk of hip fracture also increases after one or more spinal fractures. The risk of forearm fracture is higher if there has

been a previous forearm fracture. In patients who had had a distal forearm fracture, 46% of women and 30% of men suffered further fractures over the following 7 years. Moreover, in people suffering an incident fracture, the risk of a further fracture is increased by 30–40% within 3 years and this increase in risk persists for up to 10 years. Within this period 40% of women and 60% of men will experience a second fracture. Although almost all fracture types are associated with an increased risk of further fractures, men aged 60–69 years with hip or vertebral fractures have the highest risk relative to their non-fracture peers. Morbidity and mortality are also increased after both spinal and hip fractures.

Low bone mineral density

Fracture risk approximately doubles for each unit (standard deviation [SD]) decrease in T-score as measured by DXA. Postmenopausal women and men aged over 60 years with OP (T-score less than -2.5) are already at increased risk for minimal trauma fractures. The absolute fracture risk increases with both increasing age and decreasing bone density. The absolute risk for fracture is therefore high (10% or worse in 3 years) in postmenopausal women and men aged 70 years or over with a T-score less than -2.5 (without fracture) and even higher in those with a T-score -3.0 or less.

Age

Fracture risk is strongly affected by age for both genders. With each decade the fracture risk approximately doubles. Age as a fracture risk is independent of both bone density and clinical risk factors, such as immobilisation or multiple falls, which also increase with age and contribute to fracture risk.

Calcium and vitamin D status

Suboptimal dietary calcium intake and vitamin D deficiency are important public health problems in Australia and increase the risk of fragility fractures, particularly in women and men aged 70 years over. Vitamin D deficiency is associated with a higher risk of falling as well as with a lower bone density.

Paternal or maternal history of hip fractures

Paternal or maternal history of hip fractures is regarded as the most reliable indicator of genetic risk of osteoporotic fractures. However, family history of other types of osteoporotic/fragility fractures should also be considered.

Gender

At a comparable age and bone density T-score, using young reference ranges matched for gender, men have an approximately 50% lower risk of osteoporotic fractures than women. However, at comparable bone density values and age, male and female fracture risks are comparable.

Race

People from certain population groups may be more likely to suffer osteoporotic fractures. Part of this difference may relate to differences in bone mass and some may relate to bone macro-architecture, including bone size. Caucasian and Asian populations tend to have a lower average bone mass (and smaller bones) than black or Hispanic groups and a higher fracture incidence. However, this cannot be assumed to apply to Australian Aboriginal people or Torres Strait Islanders, as there is no data in these populations.

Falls

A history of multiple falls increases the risk of peripheral fractures for postmenopausal women and men of comparable age. This applies to falls without external cause that have occurred more than once in the past 12 months. Risk factors for falling include poor quadriceps strength and body sway, vitamin D deficiency, visual impairment, and environmental hazards.

Smoking

For both women and men smoking is an independent moderate risk factor for vertebral fractures and non-vertebral (including hip) fractures. The determination of a gradation of risk depending on the number of cigarettes is presently still inaccurate. However, smokers generally have a higher fracture risk than non-smokers.

Low levels of physical activity and immobility

Lack of physical activity is a risk factor for hip fractures and vertebral fractures. Immobility (ie. mobility limited to such a degree that the person cannot leave their home or cannot do any housework) may be associated with, and compounded by, low or no exposure to sunlight and subsequent vitamin D deficiency. Inability to rise from a chair without using the arms is associated with increased fragility fracture risk.[44,45]

Low body weight and weight loss

In cases of low body weight (BMI <20) the relative risk of a hip fracture is approximately doubled for both women and men. An increased risk is also probable for other fractures. Weight loss is also associated with an increased fracture risk. Anorexia nervosa is associated with a high risk for OP.

Loss of height

Some loss of height is typical with advancing age and can be due to disc degeneration and/or scoliosis. The greater the height loss, in the absence of obvious scoliosis, the greater the likelihood of vertebral fractures. Notwithstanding some lack of specificity, height loss of 3 cm or more requires exclusion of vertebral deformity or fractures.

High alcohol intake

In this context, high alcohol intake is considered to be greater than 2–4 standard drinks per day for men; less for women.

Drugs

Medications associated with increased fragility fracture risk include, but are not limited to, corticosteroids, excessive thyroid hormone replacement, anti-androgen and anti-oestrogen treatments (aromatase inhibitors), selective serotonin reuptake inhibitors (SSRIs), thiazolidenediones and certain anti-epileptic drugs. However, it is not always possible to distinguish the effect of the drug treatments from the effect of the underlying condition that required their use.

Medical conditions that increase fracture risk (secondary osteoporosis)

Medical conditions that increase bone loss or lead to lower BMD at earlier age include, but are not limited to, rheumatoid arthritis, Cushing syndrome (endogenous or exogenous), hyperparathyroidism, hyperthyroidism or thyroxine excess, chronic kidney disease, chronic liver disease, premature menopause in women, hypogonadism in men, malabsorption, depression, chronic obstructive pulmonary disease, and organ or bone marrow transplantation. They are therefore associated with an increase in the age specific risk for OP and fragility fractures. Multiple myeloma may also present with unexplained fragility fractures.

Diagnostic investigations

RECOMMENDATION 3 (Grade A)

Bone mineral density should be measured by DXA scanning performed on two sites, preferably anteroposterior spine and hip.

RECOMMENDATION 4 (Grade B)

Diagnostic assessment for OP should consist of medical history, clinical examination, a DXA bone density measurement and, if applicable, laboratory tests and radiographs of the thoracic and lumbar spine.

EVIDENCE STATEMENT

Two major international guidelines recommend that the diagnostic assessment for OP consist of medical history, clinical examination, a DXA bone density measurement and, if applicable, laboratory tests and radiographs of the thoracic and lumbar spine.[22,46] The recommended standard procedure for bone density measurement is bone densitometry by DXA.[22,46,47]

For some patients at risk, laboratory findings can reveal unsuspected secondary OP or may influence some aspects of diagnostics and therapy. Laboratory tests are used to exclude the most important forms of secondary OP and other potential bone diseases. It is crucial to exclude osteomalacia which is associated with low bone density values.[22]

Laboratory tests should follow the medical history, clinical examination and bone densitometry if:

- fractures after minimal trauma were the reason for the diagnostic assessment
- the medical history and/or clinical examination reveals or is compatible with secondary OP
- the Z-score is less than -2.0 measured by DXA.

Bone mineral density is the major criteria for the diagnosis and monitoring of OP. Because BMD differs between different body sites, a BMD of a specific site is the best predictor for fracture at that site.[46] The American College of Physicians recommends that clinicians obtain DXA bone density measurement for men and women who are at increased risk for OP and are candidates for drug therapy.[48]

Practical tips and precautions

- Conventional radiographs should not be used for diagnosis or exclusion of OP[46]
- The evaluation of OP is based on the lower T-score of either the lumbar spine or total hip
- Repeat BMD measurements should only be performed if they influence treatment[46] (see Recommendations for the treatment of osteoporosis)
- Wherever possible, perform repeat bone density tests on the same instrument or at least the same of instrument (manufacturer and model type) to improve comparability of results in interpreting any change in BMD[49]
- Increased biochemical parameters of bone turnover in the blood and/or urine have been shown in trials to be an independent risk factor for fractures in women and men. The lack of standardisation of these parameters under routine clinical conditions and the lack of evaluation in combination with other risk factors does not allow general recommendations for use as routine diagnostic tests at present.

DXA

Dual energy X-ray absorptiometry is the current gold standard for the diagnosis of OP. Bone mineral density of the lumbar spine and the proximal femur are the best current predictors of future fracture risk and both sites should be measured (*Table 1*). Dual energy X-ray absorptiometry is reliable, with a reported precision of about 1%, although in routine clinical practice this is closer to 2%. At this precision level, the least significant change at the lumbar spine would be 5.6% between measurements for 90% confidence that the change is real.

Each SD reduction in femoral neck BMD increases the age adjusted risk of hip fracture by a factor of approximately 2.5 (range 2.0–3.5) while the risk attributable to any minimal traumatic fracture is almost the same (range 1.7–2.4). Similarly, each SD reduction in lumbar spine BMD increases the risk of spinal fracture by a factor of approximately 2.3 (range 1.9–2.8). Total hip BMD appears to be the best overall predictor of fracture risk, particularly as it has good precision (less affected by positioning) and is unaffected by osteoarthritis, which can spuriously elevate spinal BMD values, as can vertebral fractures and arterial calcification.[50,51]

Table 1. Recommendations for bone density assessment by DXA[52]

Woman or man Age (years)	Risk factor profile for which a diagnostic assessment is recommended
50–60	Vertebral fracture Peripheral fracture as individual case decision
60–70	Vertebral fracture Peripheral fracture Hip fracture in a parent Underweight Smoking Multiple falls Immobility
Over 70	Age sufficient as risk

The role of bone turnover markers in the management of OP has not yet been fully investigated. In the absence of clear evidence of improved patient outcomes from their use and cost effectiveness data, routine use in patient monitoring in general practice is not currently recommended.

Bone density measurements and the initial assessment

The aims of bone density measurements in the initial assessment are to:

1. determine whether bone density is low (T-score <-2.5). This is the basis for the definition of OP, as well as identifying an individual's situation as consistent with the studies in which fracture reducing effects of anti-osteoporotic drugs have been demonstrated, and
2. determine the precise extent of bone density reduction. This is important for the assessment of the individual fracture risk and the extent of the recommended therapeutic measures.

In Australia as a reference for fracture risk calculation in women, the T-scores calculated from the Geelong Osteoporosis Study database are used for the lumbar spine and the proximal femur. Normative data in Australian men are not currently available. Most BMD assessments currently report T-scores for men based on the US National Health and Nutrition Examination Survey (NHANES) normative data or reference ranges provided by densitometer manufacturers.

For patients with ready access to a bone density measurement, a DXA measurement is recommended even in cases of typical vertebral fractures before starting a therapy. A normal bone density despite existing fractures should always initiate a more extensive diagnostic work up to exclude other potential causes of fracture. A normal bone density despite typical vertebral fractures also poses a problem with regard to the usefulness of anti-osteoporotic treatment. Such discrepant findings need to be resolved on an individual basis. High trauma falls that resulted in vertebral fracture in the past can leave evidence of vertebral deformity that may not indicate underlying OP. In such situations, consultation of a bone expert may be warranted.

If radiographs reveal one or more vertebral fractures typical of OP, bone density measurement may not be essential before starting a medical therapy, if this is appropriate to the overall clinical situation. There are also an increasing number of scenarios in which a meaningful evaluation of bone density is not possible despite fractures typical of OP (eg. in a combination of double sided hip replacements and several osteoporotic fractures in the lumbar spine region of BMD measurement). In such cases it should be assumed that bone density measurement would have been low and that therapy is likely to be beneficial. Forearm BMD may be useful, however its precise value has not been characterised as well as that in the spine and hip.

QUS and QCT bone density

Quantitative ultrasound (QUS) and quantitative CT (QCT) bone density measurement procedures can provide information on fracture risk. However, whereas the measurement of bone density by DXA gives information on the absolute fracture risk and the reduction of fracture risk by a specific anti-osteoporotic treatment, this has not as well been determined for ultrasound or QCT. In order to avoid an unnecessary double diagnostic test, the DXA measurement for diagnosis and base line bone density assessment is recommended.

Laboratory tests (including practical use of biochemical bone markers)

Table 2 shows the recommended laboratory tests and lists some of the most important bone disorders that commonly result in test abnormalities.

In the case of abnormal laboratory test results, an expert should be consulted for further diagnostic work up and therapy if necessary. Successful treatment of a secondary cause of OP may achieve sufficient improvement in BMD and reduction in fracture risk in order that other therapy may not be required. The following recommendations for therapy will not apply in many cases or may need to be modified for patients with secondary OP.

Table 2. Laboratory tests[22]

Test parameter	Associated diseases
Serum calcium	Primary hyperparathyroidism or other causes of hypercalcaemia Hypocalcaemia, eg. with secondary hyperparathyroidism potentially due to malabsorption
Serum 25-hydroxyvitamin D Serum phosphate	Vitamin D deficiency or insufficiency (<50 nmol/L) Secondary hyperparathyroidism Malabsorption
Serum alkaline phosphatase (AP)	Osteomalacia, metastatic bone disease, Paget disease increased with recent fracture
Gamma GT	Helpful in discriminating AP increases of skeletal origin from those of hepatic origin
Serum creatinine and eGFR	Renal osteodystrophy (eGFR <40)
ESR or C reactive protein	Differential diagnostics of inflammatory causes of spinal deformities
Full blood examination	Inflammatory disease, marrow infiltration
Serum protein electrophoresis	Multiple myeloma, monoclonal gammopathy of uncertain significance (MGUS)
Serum testosterone (with LH) in men (early morning collection)	Male hypogonadism
Serum TSH	<0.3 mU/L endogenous thyroxine excess or caused by excessive thyroxine treatment

What to do if BMD is not readily available

A diagnostic assessment by quantitative CT scan bone density measurement might be useful under the following exceptional circumstances:

- as part of the risk assessment for high risk patients in areas where no DXA equipment is available as a preliminary test preceding a DXA examination
- as part of the risk assessment for high risk patients with typical vertebral fractures in areas where no DXA equipment is available, in which it would make a difference to the recommendation for treatment.

However, the precision of QCT bone density measurements is not sufficient to allow for monitoring of responses to therapy and the T-scores of those measurement procedures are not transferable to T-scores of DXA measurements with regard to fracture risk assessment.

Most research into the effects of treatment for OP has used DXA derived BMD as an entry criteria. Consequently DXA derived BMD assessment allows the best alignment of a patient to the evidence.

Quantitative heel ultrasound has been found to be predictive of osteoporotic fracture in prospective studies. While DXA remains the gold standard for diagnosis of OP, and QUS has limitations compared to DXA, QUS may be a valid alternative to DXA where DXA is not accessible.[53]

Other diagnostic procedures

Computerised tomography, magnetic resonance imaging (MRI) and scintigraphic examinations are not part of the routine clinical assessment of OP. These methods are used in order to rule out other causes of vertebral deformities and for certain aspects of treatment. Radionuclide bone scans can be useful to exclude recent fracture as a cause of a non-specific vertebral deformity. In selected situations it may be appropriate to screen for coeliac disease (see www.coeliac.org.au for more information) and, rarely, mastocytosis.

Referral to a medical specialist

RECOMMENDATION 5 (Grade B)

General practitioners should refer postmenopausal women and older men to a specialist or a specialist bone centre according to individual needs, or when there is restricted access to appropriate resources or required expertise.

Practical tips and precautions

The following conditions might require a referral to a specialist or a specialist bone centre:

- lack of access to appropriate bone densitometry
- OP is unexpectedly severe or has unusual features at the time of initial assessment
- inadequate response to therapy
- having a suspected or known condition that may underlie OP
- contraindications to standard therapy
- presence of other complex medical conditions
- experiencing problems or side effects with treatment
- continuing to fracture despite normal bone density
- secondary cause is identified or suspected (eg. Z-score <2).

EVIDENCE STATEMENT

There is strong consensus that in specific situations GPs should refer patients to a specialist or a specialist bone centre. The following are strong indicators for referral in postmenopausal women and older men:[22,46,54]

- OP is unexpectedly severe or has unusual features at the time of initial assessment
- intolerance of approved therapies or experiencing problems
- failing to respond to treatment
- having fractures despite treatment or normal bone density
- not having access to appropriate bone densitometry.

Even though most experts agree that referral to specialists (eg. endocrinologist, rheumatologist) is important for specific conditions, there is no clear agreement as to what these conditions are. Circumstances depend on a combination of factors including severity of the condition, response to available treatment, availability of resources and GP expertise and support.

GENERAL INTERVENTIONS FOR PREVENTION OF OSTEOPOROSIS

Dietary calcium

RECOMMENDATION 6 (Grade A)

General practitioners should recommend that postmenopausal women and older men maintain a diet high in calcium in order to meet the Australian recommended dietary intake.

Calcium has a primary role in building and maintaining bone. With ageing, absorption of calcium is less effective and calcium replacement reduces, contributing to weak and thin bones.[55,56]
The main sources of dietary calcium are dairy milk, cheese (not soft) and yoghurt. Other foods that provide a moderate source of dietary calcium include white bread, sardines and calcium enriched soy milk.[46] Patients who cannot achieve an adequate calcium intake through diet alone may require additional supplementation. Relevant guidelines for Australian recommended dietary intakes are listed in the *Resources.*

EVIDENCE STATEMENT

Prevention and treatment of osteoporosis

An international guideline based on three good quality SRs reported that dietary calcium is as effective as supplements for adequate calcium balance. 1000 mg dietary calcium daily is associated with a 24% lower rate of hip fractures.[46] Other guidelines support the importance of dietary calcium in preventing and managing OP.[22,29,56]

To maintain optimum levels of calcium, the Australian recommended dietary intake is: 1300 mg/day for women aged over 50 years; 1000 mg/day for men aged 50–70 years; and 1300 mg/day for men aged over 70 years.[55,57]

Lifestyle

RECOMMENDATION 7 (Grade D consensus)

General practitioners should recommend the following important lifestyle choices for all postmenopausal women and older men:

- adequate but safe exposure to sunlight as a source of vitamin D
- maintenance of a healthy weight and BMI
- cessation of smoking
- avoidance of excessive alcohol consumption.

By addressing modifiable risk factors, a healthy lifestyle minimises the risk of developing OP. For patients who have been diagnosed with OP, a healthy lifestyle and diet will help prevent further bone loss and reduce the risk of secondary fractures.[21,46,58]

Relevant Australian guidelines aimed at assisting GPs in promoting a healthy lifestyle are listed in the *Resources.*

EVIDENCE STATEMENT

Prevention and treatment of osteoporosis

International guidelines recommend healthy lifestyle choices to reduce risks associated with OP, although few studies have been conducted on the efficacy of lifestyle change.[22,29,46,56]

Vitamin D has an important role in maintaining bones by promoting the absorption of calcium. Although some vitamin D is found in the diet (eg. fatty fish) the primary source is from exposure to sunlight. In Australia, the current recommended amount of sunlight required to produce optimum levels of vitamin D is exposure of approximately 15% of the body (ie. hands, face and arms) for 6–8 minutes, 4–6 times per week,

and before 10 am or after 2 pm (standard time) for moderately fair skinned people. Darker skinned ethnic groups require greater daily sunlight exposure.[21,59,60] General practitioners should refer to recent national guidelines on sun exposure.[60]

Maintenance of a healthy weight and BMI are important in reducing the risk of disease. Smoking cessation and moderate alcohol intake are important in maintaining an overall healthy lifestyle and for reducing risk factors for disease.[21,61] General practitioners should consult recent Australian guidelines that outline preventive health strategies[62] and smoking cessation interventions.[21,62,63]

Education and psychosocial support

RECOMMENDATION 8 (Grade D – consensus)

General practitioners should provide postmenopausal women and older men at risk of, or diagnosed with, OP, access to education, psychosocial support and encouragement to seek support from appropriate sources according to individual needs.

Osteoporosis is a chronic disease. Those at risk of developing OP may require access to education about disease prevention and national strategies to encourage reduction in disease risk. Patients who have been diagnosed with OP may require ongoing education on the disease process and self management strategies, as well as psychosocial support. A range of support agencies offer education material, programs and counselling. Self management programs usually focus on:

- education and awareness about the disease process
- promotion of a healthy lifestyle
- prevention of further fractures
- management and rehabilitation techniques
- pain management
- falls prevention techniques
- psychosocial welfare (dealing with depression, social isolation and fear of falling).

EVIDENCE STATEMENT

A full review of the literature relevant to this consensus recommendation was not undertaken.

Prevention and treatment of osteoporosis

Patients may require ongoing education regarding risk factors for disease and support in disease self management. Specific OP self management programs are conducted in some areas by Osteoporosis Australia, as well as various public hospital health promotion units and community health centres.[64]

It is the consensus of the Working Group that GPs have an important role in patient education, psychosocial support and referral to support groups where needed.

Reducing the risk of falls

RECOMMENDATION 9 (Grade D – consensus)

There is good evidence to support GPs recommending an individually tailored, multifaceted fall reduction program to reduce the risk of falling in older adults. However, there is no evidence that such interventions reduce the risk of fractures, even in specialised settings.

Most people who sustain peripheral fractures typically do so after a fall. Therefore assessing a person's risk of falling and implementing strategies to reduce this risk are highly likely to reduce the risk of sustaining a fracture.[65] However, it is the working group's consensus that there is no evidence that such interventions reduce the risk of fractures, even in specialised settings.

A comprehensive fall reduction intervention includes assessment of risk factors associated with falling and development of an individualised plan to address these factors. Factors that increase the risk of falls include (but are not limited to):[65]

- prior history of falls
- muscle weakness
- gait and balance deficits
- sensory impairment
- health conditions (eg. cognitive impairment, arthritis, depression, vitamin D deficiency)
- age >80 years
- a range of medications (eg. psychotropics, digoxin, anti-arrhythmic medication and diuretics)
- incontinence.

To be successful, a falls reduction program needs to be tailored to the individual's needs and include a range of strategies. A falls reduction program may include:[22,65,66]

- education on the risk of falling and prevention strategies
- medication review and modification
- exercise programs tailored to the individual's specific needs and abilities
- use of appropriate assistive devices
- treatment of postural hypotension and cardiovascular (CV) disorders
- reduction of environmental hazards.

Falls clinics are offered at most major public hospitals and many community health centres throughout Australia. Clinics can be located by contacting Osteoporosis Australia.

EVIDENCE STATEMENT

The literature search did not identify any relevant research reporting effectiveness of fall reduction interventions in reducing the rate of fractures.

Prevention and treatment of osteoporosis

A Cochrane review[66] presented evidence from 61 RCTs on the effectiveness of a wide range of interventions to reduce the incidence of falls in older adults living in the community or institutions. Mean age of participants exceeded 80 years in 17 studies, and approximately 70% of participants were female. Eleven studies (n=1480) reported on the effects of exercise interventions for community dwelling participants that were not individually prescribed. Pooled data from nine of the studies showed no significant effect in reduction of falls (pooled RR: 0.89; 95% CI: 0.78–1.01). Three studies (n=566) reported on the effect of individually prescribed exercise programs consisting of progressive muscle strengthening, balance retraining exercises and walking plans for community dwelling participants. Pooled results showed a significant reduction at 1 year in the risk of falling (pooled RR: 0.80; 95% CI: 0.66–0.98) as well as in the risk of sustaining injury from a fall (pooled RR: 0.67; 95% CI: 0.51–0.89). At 2 year follow up, the pooled relative hazard for risk of falling was 0.69 (95% CI: 0.47–0.97), and the pooled relative hazard for sustaining an injury from falling was 0.63 (95% CI: 0.42–0.95). Two RCTs reported a lack of effect of individually prescribed exercise regimens in reducing falls in frail and/or institutionalised participants. Data was pooled from five RCTs (n=1176) investigating the effectiveness of multidisciplinary, multifactorial, health and environmental risk factor screening interventions in reducing falls risks in community dwelling participants at high risk of falling. Compared to controls there was a small but significant reduction in the risk of falling associated with the intervention (RR: 0.86; 95% CI: 0.76–0.98). Five RCTs conducted in institutionalised settings found no effect of multidisciplinary care interventions in reducing falls risk.[66] A small reduction in risk of falls could be achieved, particularly in adults at higher risk of falling, through targeted, individualised interventions.[66]

A moderate quality, single blinded RCT[67] provided evidence on the efficacy of fall reduction interventions in an Australian setting. The study investigated the effectiveness of a cognitive behavioural program ('Stepping

On' program) in postmenopausal women and older men aged over 70 years (n=310, mean age 78 years, 74% female) living in the community. The intervention involved lower limb exercises and an education program. After 14 months there was a 31% reduction in risk of falls for participants in the intervention group (RR: 0.69; 95% CI: 0.50–0.96; *p*=0.025). The non-equivalent contact time with health professionals (2 vs. 15.5 hours) and disproportionate rate of previous hip fracture between study groups at baseline may have contributed to the findings.

A moderate quality Canadian study[68] (n=98) investigated whether reductions in fall risk attained during participation in exercise programs are maintained in older women with OP. Participants were randomised to one of two 25 week exercise programs (resistance training or agility training) or a sham stretching program. At 8 months all study groups achieved a decrease in falls risk measured using a validated tool and a decrease in rate of falls measured through self report by participants in monthly diaries, with no between group differences in either outcome measure. Twelve months after randomisation all three groups maintained a decrease in falls risk (*p*=0.001) and there was no difference in falls risk between the three exercise groups (*p*=0.23), nor in rate of falls (*p*=not reported). The results from this study demonstrated that older adults with OP can achieve a decrease in falls risk that is maintained for 12 months after participation in exercise programs.[68]

Hip protectors should be considered for patients who have significant risk factors for falling, although adherence to treatment is an issue. There was a reduction of femoral neck fractures by approximately 30% when hip protectors were used consistently; however, their efficacy is limited by the lack of acceptance and thus the lack of compliance.[69,70]

'Hip protectors, which consist of plastic shields or foam pads fitted in pockets within specially designed underwear, aim to reduce the impact of a fall on the hip, and thus the risk of a hip fracture. …in institutions with high rates of hip fracture, the use of hip protectors may help reduce the risk of hip fracture, but with new evidence the effect has become less certain. However, there was no evidence of any benefit from hip protectors for the majority of older people living in their own homes. Many people stop wearing hip protectors because they find them uncomfortable'.[71]

RECOMMENDATIONS FOR THE PREVENTION OF OSTEOPOROSIS

In this context, prevention implies improvement in, and maintenance of, healthy bone density and minimising the bone loss that is seen in postmenopausal women and, with ageing, in both men and women. There is a gradual transition from prevention to treatment paradigms with advancing age, falling bone density (ie. as fracture risk increases from both these declines and from other non-bone factors, eg. falls risk.)

Exercise

RECOMMENDATION 10a (Grade A)

General practitioners should recommend regular, high intensity weight bearing exercise for preventing osteoporotic bone loss in postmenopausal women and older men.

RECOMMENDATION 10b (Grade D – consensus)

General practitioners could recommend sensible, moderate levels of physical activity throughout life as part of a healthy lifestyle. However, no studies have demonstrated any efficacy in fracture risk reduction or addressed side effects, such as injuries.

Exercise may have additional benefits including weight control, reduction of blood pressure, pain relief and improvement in quality of life (QOL).[72] Exercise can also be beneficial for improving balance as part of a falls reduction program (see Recommendation 9). Particularly in patients diagnosed with OP, supervision by a physiotherapist, exercise physiologist or other appropriately trained and qualified health professional is recommended.[21,46,73]

Exercise helps to build and maintain strong bones. Regular weight bearing exercise and strength training can help reduce bone loss associated with ageing and menopause.[21,73,74]

Exercise should be appropriate to the patient's ability and preferences, but needs to be regular, vigorous and varied to influence bone density.[73] High impact activities, resistance training and aerobic exercise are effective for increasing bone mass.[74] High impact exercises may be considered where the risk of fracture is thought to be low and there are no other contraindications (eg. joint problems). Good weight bearing exercises include fast walking, jogging, dancing, tennis, volleyball and lifting weights.[73]

Individuals without OP should participate in exercise on a regular basis at least three times weekly for at least 1 year to achieve an effect on BMD. Most people should aim to exercise for 30–40 minutes per session, 4–6 times per week. Two short, intense exercise sessions separated by 8 hours are better than one longer, less intense session.[73,74]

No RCTs examined the direct effect of exercise on fracture risk. No evidence was available for effectiveness of exercise in preventing OP in older men; however, it seems likely that the effect would be equivalent to that observed in postmenopausal women. Also, no studies have addressed side effects, such as injuries.

Practical tips and precautions

- Exercise programs should be individualised to the patient's needs, abilities and interests
- Particularly when the individual has not undertaken recent physical activity, exercise programs should commence at a low level and be progressive in intensity
- Two short intense exercise sessions separated by 8 hours are more effective than one long training session
- Most people should aim to exercise for 30–40 minutes per session, 4–6 times per week
- A physiotherapist or exercise physiologist can assist in developing the most appropriate program, providing education on safe and effective training techniques, increasing motivation, and ongoing monitoring
- Individuals with OP should receive education about back care to reduce the chance of back injury.

EVIDENCE STATEMENT

Prevention of osteoporosis

A Cochrane SR[74] reported effectiveness of exercise in preventing bone loss in postmenopausal women aged 45–70 years. The SR included 18 RCTs (six of high quality) and controlled clinical trials. All studies used a regimen of exercise sessions 2–3 times weekly lasting 20–60 minutes for a minimum of 1 year, and compared the exercise intervention to a placebo group undertaking usual activity.[74]

Aerobic exercise programs (nine studies, n=375) consisted of upper and lower limbs exercises including a mixture of callisthenics, stretching, strengthening and walking exercises. Pooled results showed that aerobic exercise had a significant effect on lumbar spine BMD (seven studies; WMD: 0.83; 95% CI: 0.08–1.58; $p<0.05$) and wrist BMD (two studies; WMD: 1.22; 95% CI: 0.71–1.74; $p<0.05$). There was no significant effect of aerobic exercises on femoral neck BMD (five studies; WMD: -0.7; 95% CI: -1.18 to 1.03). Resistance exercise programs (four studies, n=156) included bench press, lateral pull down, biceps curl, knee extension and knee flexion, hip extension, back extension and abdominal flexion. Pooled results showed that resistance training had a significant effect on lumbar spine BMD (WMD: 2.50; 95% CI: 0.44–4.57; $p<0.05$) but not on femoral neck (WMD: 0.41; 95% CI: -8.5 to 1.67) or wrist (WMD: -0.28; 95% CI: -3.21 to 2.65) BMDs. Walking or exercise programs based around regular ADLs (three studies, n=156) had a significant effect on both lumbar spine BMD (WMD: 1.31; 95% CI: -0.03 to 2.65; $p<0.05$) and femoral neck BMD (WMD: 0.92; 95% CI: 0.21–1.64; $p<0.05$).[74] Combined WMD from pooled results of all aerobics and weight bearing programs for lumbar spine BMD was 1.79 (95% CI: 0.58–3.01). Adherence ranged from 39–100% but was higher in studies where the exercise most resembled ADLs (eg. fast pace walking).[74]

Calcium and vitamin D supplementation

RECOMMENDATION 11 (Grade C)

There is mixed evidence on the effectiveness of calcium and vitamin D supplementation for prevention of bone loss and OP fractures in postmenopausal women and older men. There may be some benefit for those who have inadequate levels, particularly institutionalised patients.

Total calcium intake from dietary sources and supplements should exceed 1200 mg/day. Vitamin D from sunlight exposure (avoiding the middle of the day) and supplements should ensure 25-hydroxyvitamin D (25-OH D) levels >60 nmol/L. If vitamin D supplements are required, doses of at least 800 IU/day are usually required. Calcium intake is often suboptimal, particularly in the elderly (especially institutionalised patients) who may have limitations to dietary intake and relatively limited sunlight exposure.

Calcium and vitamin D supplements work by reducing secondary hyperparathyroidism and reducing bone turnover. BMD is also increased by calcium and vitamin D, but their effects appear to be modest. With the exception of calcium in patients with chronic renal failure, calcium and vitamin D are not on the PBS.

Calcium supplements are available in two common forms: calcium carbonate and calcium citrate. The most commonly available type of vitamin D supplement is vitamin D3 or cholecalciferol. It elevates serum 25-OH D concentrations more than vitamin D2 or ergocalciferol, and is also more reliably measured by commercially available assays. Currently available doses range from 400–1000 IU, presented as either capsules or tablets.

Side effects and potential harms

Calcium supplements can uncommonly increase the risk of renal calculi, particularly if given to individuals with adequate dietary calcium intakes. Calcium supplements can cause abdominal bloating and constipation. One RCT[75] reported an increase in CV adverse events with calcium in older postmenopausal women, however further research is required.

Toxicity is extremely uncommon with vitamin D, even in high doses. Single doses of up to 500 000 IU are tolerated without causing hypercalcaemia or hypercalciuria.

Practical tips and precautions

- Total calcium intake from dietary sources and supplements should exceed 1200 mg/day.[76–78] Vitamin D from sunlight exposure (avoiding the middle of the day) and supplements should ensure 25-OH D levels are above 60 nmol/L
- To optimise clinical efficacy, calcium 1000–1200 mg/day should be taken in conjunction with vitamin D 700–800 IU/day[77–78]
- Calcium citrate does not need to be taken after meals like calcium carbonate, as it does not require an acid environment to be optimally absorbed
- There are some data suggesting that calcium supplements may be more effective if taken at night, eg. with the evening meal
- Vitamin D may be taken at any time of the day
- Recent research suggests that supplementation with calcium or vitamin D alone is not effective. They should be taken concurrently.

EVIDENCE STATEMENT

Prevention of osteoporosis

There is mixed evidence for the impact of oral calcium and vitamin D supplementation on reduction of fractures outside institutionalised settings.[76–79]

One good quality SR[78] (29 studies, 63 867 individuals, 92% female) reported on the effect of calcium supplementation (alone or in combination with vitamin D) in doses of 1000–1200 mg in adults aged over 50 years. Calcium supplementation was associated with a 12% reduction in risk of any fracture (RR: 0.88; 95% CI: 0.83–0.95; p=0.004), with similar reduction in risk of fractures in trials using calcium supplements alone (13% risk reduction) and those where calcium was administered in combination with vitamin D (10% reduction in risk). Pooled results from 24 trials showed calcium supplementation was associated with a reduction in bone loss at the hip (0.54% reduction, 95% CI: 0.35–0.73; p<0.0001) and at the spine (1.19% reduction, 95% CI: 0.76–1.61; p<0.0001). The estimated NNT to prevent one fracture over 3.5 years was 63 in the overall population. For individuals who were elderly, lived in institutions, had a low body weight, had a low calcium intake (<700 mg/day), or were at a higher baseline risk of fracture, the NNT to prevent one fracture over 3.5 years was 30.[78]

A good quality SR[76] (eight cohort trials, seven RCTs) reported on the effect of calcium intake on the risk of hip and non-vertebral fractures. Trials used calcium supplementation in doses between 800–1200 mg/day for a mean duration of 1.5–10.8 years compared to placebo or no treatment. Results from cohort trials showed no effect for calcium on hip fracture in postmenopausal women (RR: 1.01; 95% CI: 0.97–1.05) or men (RR: 0.92; 95% CI: 0.82–1.03). Results from four RCTs also showed no effect for calcium supplementation on risk of hip fracture in the overall trial populations (RR: 1.64; 95% CI: 1.02–2.64). Pooled results from five RCTs showed no effect of calcium supplementation on non-vertebral fracture risk in the overall trial populations (RR: 0.92; 95% CI: 0.81–1.05), women alone (RR: 0.92; 95% CI: 0.81–1.06) or men alone (RR: 0.94; 95% CI: 0.64–1.37). Subanalyses found no difference in results when pooling was limited to data for compliant participants.[76]

A good quality SR[77] (nine RCTs, n=53 260) investigated the need for calcium supplementation (500–1200 mg/day) in postmenopausal women and older men receiving vitamin D (cholecalciferol 700–800 IU/day [six RCTs] or 400 IU/day [three RCTs]) for prevention of fractures. Mean therapy duration was 20–84 months. Pooled results showed vitamin D alone was not associated with a reduction in risk of hip fracture (RR: 1.10; 95% CI: 0.89–1.36; p=0.38) or a reduction in risk of non-vertebral fractures (RR: 0.98; 95% CI: 0.83–1.16; p=0.79) compared to placebo. Results (six RCTs, n=45 509) of vitamin D in conjunction with calcium supplements compared to placebo or no treatment showed a significant reduction in risk of both hip fracture (RR: 0.82; 95% CI: 0.71–0.94; p=0.0005) and non-vertebral fracture (RR: 0.88; 95% CI: 0.78–0.99; p=0.036). NNT to prevent one hip fracture over 24–84 months was 276 and NNT to prevent one non-vertebral fracture was 72. An indirect comparison of trials investigating vitamin D with calcium compared to those investigating vitamin D alone showed a RR of 0.75 (95% CI: 0.58–0.96; p=0.021) for hip fracture.[77]

A Cochrane review[79] of 38 lower quality RCTs in postmenopausal women or older men aged over 65 years compared vitamin D supplements to placebo, no intervention, or calcium supplements. Medication regimens varied from calcium 1000–1200 mg and vitamin D3, 700–800 IU/day. Results from seven trials (10 376 participants) showed a significant reduction in incidence of new hip fracture (ES 0.81; 95% CI: 0.68–0.96) and non-vertebral fractures (RR: 0.87; 95% CI: 0.78–0.97) for vitamin D combined with calcium, however results for institutionalised older adults may have influenced the overall analysis as no significant effect was found for community dwelling individuals. There was also no evidence for effectiveness of vitamin D alone for prevention of fractures.[79]

Safety

One RCT[75] (n=1471) reported on CV adverse events associated with calcium supplements compared to placebo over 5 years in elderly postmenopausal women. There was no significant difference between groups in the risk of any CV event (angina, chest pain, myocardial infarction [MI] or sudden death), risk of stroke or risk of sudden death. Although risk of MI was not significant between groups for number of validated events (RR: 1.49; 95% CI: 0.86–2.57) the rate ratio approached significance (rate ratio 1.67, 95% CI: 0.98–2.87; *p*=0.058). NNT to cause one MI over 5 years of treatment with calcium was 44. For the primary endpoint (risk of MI, stroke or sudden death) there was no significant difference in number of validated events (RR: 1.21; 95% CI: 0.84–1.74), however the rate ratio showed a significant increase associated with calcium (rate ratio 1.43, 95% CI: 1.01–2.04; *p*=0.043). The trial was designed to assess the effect of calcium on BMD and the power to detect a clinical effect for CV outcome measures is not reported.[75]

Bisphosphonates

RECOMMENDATION 12 (Grade A)

There is excellent evidence to support the effectiveness of alendronate in reducing the risk of vertebral fractures and increasing BMD in postmenopausal women at risk of OP.

RECOMMENDATION 13 (Grade C)

There is evidence that bisphosphonates may reduce the risk of vertebral fractures and increase BMD in older men at risk of OP.

Currently, the only bisphosphonates approved in Australia for clinical use in OP are alendronate, etidronate, risedronate, and zoledronic acid. Other bisphosphonates such as ibandronate, clodronate and neridronate are in use outside Australia, or are currently under investigation for use for postmenopausal OP in Australia. The Therapeutic Goods Administration (TGA) approval for zoledronic acid restricts use to no more than three annual 5 mg doses due to the lack of clinical trial experience beyond 3 years for the treatment of OP. Alendronate and risedronate (all available preparations) are supported under the PBS for women and men with evidence of osteoporotic fractures independent of age, BMD or other clinical risk factors. This intervention depends on an individual's absolute risk of fracture (see Absolute fracture risk nomograms).

Alendronate and risedronate are also supported by the PBS in men and women 70 years or over, without prevalent fractures, but with a T-score of -3.0 or lower at the lumbar spine or femoral neck. Zoledronic acid is also available for women who meet these criteria.

Bisphosphonates are potent inhibitors of bone resorbing cells (osteoclasts). They work to inhibit bone resorption by interfering with normal osteoclast function and inducing osteoclast apoptosis. They are rapidly sequestered into bone (from where they are only slowly released) and eliminated by the kidney, therefore exposure to soft tissues, including bone marrow, is transient. Alendronate, one of the more commonly used bisphosphonates, has a half life of approximately 8 years.[80]

Alendronate and risedronate are usually taken orally on either a daily basis (alendronate 10 mg, risedronate 5 mg) or weekly (alendronate 70 mg, risedronate 35 mg). Intravenous bisphosphonates are often used in patients intolerant to oral preparations (eg. once yearly zoledronic acid) and this mode of delivery produces rapid anti-resorptive action in 24–48 hours.

There were no trials of alendronate or risedronate in older men and no trials on the effectiveness of zoledronic acid in preventive populations in the critically appraised studies. However, the Working Group found evidence in several studies[81–83] to support the notion that bisphosphonates have been shown to increase BMD and the risk of vertebral fractures in older men at risk of OP. These three studies have not been critically appraised.

Side effects and potential harms

Bisphosphonates used in the management of OP are usually well tolerated and the rate of adverse effects in every day clinical practice is low. The most frequent adverse effects observed with oral bisphosphonate treatment are gastrointestinal (GIT) symptoms (eg. gastric irritation, oesophageal erosions, gastric ulcers, perforations and strictures). Serious side effects have been observed when using very high doses (as in cancer indications) or when elimination is impaired.

Osteonecrosis of the jaw (ONJ) has recently been associated with long term and high dose bisphosphonate treatment. This is a very rare but potentially serious side effect seen mostly in patients with multiple myeloma or breast cancer bone metastases who receive frequent and high total doses of IV bisphosphonate treatment. While the aetiology is uncertain, a strong association with dental pathology and interventions highlights the need for close attention to dental health.[84,85]

Practical tips and precautions

- Active upper GIT disorders, including strictures, are a contraindication to oral bisphosphonate use
- Taking oral therapy after fasting for several hours (usually overnight) and then remaining upright and avoiding food or other medications for at least 30 minutes will maximise medication absorption
- The incidence of GIT adverse events is low and may be minimised by taking the tablet with a large glass of plain water and remaining upright until after eating
- Concurrent calcium and vitamin D supplementation is recommended alongside alendronate, risedronate or etidronate therapy
- To be absorbed properly, bisphosphonates should not be taken together with any other drug, particularly calcium. Calcium supplements should NOT be taken for at least 60 minutes after the administration of oral bisphosphonates
- Low serum levels of vitamin D should be corrected to a level above 50 nmol/L before commencing bisphosphonate therapy
- IV bisphosphonates need to be administered over at least 15–20 minutes as higher infusion rates can increase the risk of renal damage. Zoledronic acid is contraindicated in patients with a calculated creatinine clearance below 35 mL/min
- Combined use of bisphosphonates with other anti-resorptive (eg. raloxifene, hormone therapy) or anabolic drugs (teriparatide) is not recommended
- Good dental hygiene and care is recommended, particularly in those using long term IV bisphosphonates, to reduce the risk of ONJ. Treatment should be ceased in cases of confirmed ONJ. The dental practitioner should be made aware of bisphosphonate dosage and other risk factors, and extractions or other jaw bone surgery should be avoided. Where unavoidable, extractions should be performed under antibiotic prophylaxis with minimal trauma and suture socket.[85] The actual risk of ONJ with therapy for OP is considered to be very low.

EVIDENCE STATEMENT

Prevention of osteoporosis

A pivotal good quality SR[86,87] included two good quality trials (n=1946) that reported the magnitude of effect of **alendronate** 10–40 mg/day on vertebral fractures in postmenopausal women without OP. Alendronate was associated with a significant reduction in the risk of vertebral fracture (RR: 0.45; 95% CI: 0.06–3.15) and a non-significant reduction in the risk of non-vertebral fractures (RR: 0.79; 95% CI: 0.28–2.24) compared to placebo. There was also improvement in lumbar spine (WMD: 8.05; 95% CI: 7.06–9.05), total body and hip BMD. In comparing prevention and population trials, the review found no significant difference

in effect of therapy between postmenopausal women with or without confirmed OP, ie. similar relative risk reduction, albeit with different absolute risk reduction.[87]

A recent Cochrane review[88] on the effectiveness of **risedronate** at doses of 2.5 mg/day and 5.0 mg/day for a duration of 2 years for prevention of OP included one RCT with 381 early postmenopausal women (mean age 52.6 ± 3.3 years). Results were not significant compared to placebo for either vertebral (RR: 0.97; 95% CI: 0.42–2.25) or non-vertebral fracture (RR: 0.81; 95% CI: 0.25–2.58) risk.[88]

Results of these SRs were supported by an additional MA that combined preventive and treatment trials.[84] There are no trials of alendronate or risedronate in older men, and no trials on the effectiveness of zoledronic acid in preventive populations.

Duration of therapy

One moderate quality trial provided evidence that after 5 years of treatment with alendronate 10 mg the risk of fractures did not increase after 10 years, except in women with a high risk of fracture. Women who discontinued alendronate after 5 years therapy showed a small decline in BMD and a gradual rise in biochemical markers but no higher fracture risk, except for clinical vertebral fractures that did increase, compared with those who continued alendronate.[89] Given the lack of comparable evidence for duration of therapy for the other bisphosphonates used in Australia and the observed differences in return of bone turnover toward placebo after cessation with different bisphosphonates, the Working Group does NOT suggest that the concept could be applied to all bisphosphonates or even to all **oral** bisphosphonates.

Safety

A number of good quality SRs found no significant differences between alendronate, risedronate, or zoledronic acid compared to placebo for GIT effects[84,87,88] or for rate of discontinuing medication as a result of adverse effects.[87]

One trial reported an increased risk compared to placebo for serious atrial fibrillation with zoledronic acid (1.3 vs. 0.5%; $p<0.001$) but another large trial found no significant increase in risk (1.1 vs. 1.3%; $p<0.84$).[84]

A recent SR[84] reported that the only cases of ONJ have occurred in patients with cancer taking large IV doses of bisphosphonates. The reviewers noted that the American Society for Bone and Mineral Research had recently conducted a review and concluded that there appeared to be a low risk of ONJ in patients taking oral bisphosphonates, but suggested that the incidence may be higher than reflected in current literature.[84]

The United States Food and Drug Administration has recently concluded that there are no data indicative of increased risk of ONJ with oral bisphosphonate therapy for OP.

Hormone therapy

RECOMMENDATION 14 (Grade A)

There is excellent evidence to support the effectiveness of HT in improving BMD and reducing the risk of fractures in postmenopausal women. The significant increase in risk of adverse events associated with treatment should be weighed carefully against benefits. Long term use is not recommended.

RECOMMENDATION 15 (Grade D consensus)

Hormone therapy used for men with hypogonadism is likely to prevent bone loss. The significant increase in risk of adverse events associated with treatment should be weighed carefully against benefits. Long term use is not recommended.

Oestrogen (HT) is available on the PBS for the prevention and treatment of OP in postmenopausal women. Oestrogen acts to decrease bone resorption. Hormone therapy is effective in preventing loss of BMD and reducing the risk of fractures when given at, or near, menopause (and is also useful for control of menopausal symptoms) and has a role in reducing the risk of fractures in postmenopausal women with OP. [84,90–93]

Ideally, therapy should be continuous (ie. without a break in therapy). Adjuvant progestogens are necessary in women who still have a uterus to protect against endometrial cancer. They may be given cyclically for

10–14 days each month in perimenopausal women or as continuous therapy combined with oestrogen in postmenopausal women. The latter is more suitable for women more than 2 years postmenopause to avoid the initial irregular bleeding commonly seen with this regimen being unduly prolonged.

The minimum effective dose of oestrogen therapy on bone loss has yet to be clearly established,[93] but the beneficial effects of oestrogen therapy can be achieved by many routes of administration (including oral and transdermal) and lower doses can be used in combination with calcium supplements.

Follow up bone densitometry in individual patients may indicate the requirement for a higher dose and attention to calcium intake and vitamin D status, if there is a suboptimal response.

Prevention of osteoporosis in older men

With respect to the role of testosterone replacement in hypogonadal men, there are no data showing efficacy (or safety) in fracture reduction but there are data demonstrating that testosterone levels below the reference range are associated with increased fracture risk.[94] Hormone therapy may contribute to a reduction in fracture risk for this population.

Side effects and potential harms

The role of long term postmenopausal HT in the prevention and management of OP remains controversial following publication of the results of the Women's Health Initiative (WHI) study of combined oestrogen and progestin therapy[92] and its study of oestrogen alone therapy.[90] There was an increase in the risk of stroke in those aged 50–79 years, although the absolute risk was lower in those aged in their 50s.[90,92] Increased risks in CV disease, thromboembolic events, CV accident, and invasive breast cancer have been reported in good quality research.[84,90–92]

Practical tips and precautions

- GPs should discuss the long term risks and benefits of HT, especially breast cancer and CV effects
- Individuals who require immobilisation for any period (eg. hospitalisation or a long plane trip) should cease HT for a week before and afterward
- Individuals taking HT should maintain an adequate calcium intake (from dietary sources or supplements) and vitamin D status
- Raloxifene should not be used in combination with oestrogen therapy.

EVIDENCE STATEMENT

Prevention of osteoporosis in postmenopausal women

A good quality SR[93] pooled data from 47 RCTs investigating oestrogen alone and/or oestrogen with opposed progesterone compared to placebo for postmenopausal women. Treatment was associated with a significant improvement in BMD at lumbar spine (WMD: 4.86; 95% CI: 3.70–6.02), forearm (WMD: 3.01; 95% CI: 2.29–3.74) and femoral neck (WMD: 2.25; 95% CI: 0.80–3.69) at 12 months, with the effect increasing at 24 months. Subanalysis indicated that after 2 years treatment there was a larger effect on BMD at all sites of high dose therapy (equivalent to 0.9 mg Premarin) compared to low dose therapy (equivalent to 0.3 mg Premarin) but the difference was only significant for femoral neck BMD.

A second good quality SR[84] presented evidence from five RCTs on the effectiveness of oestrogen in reducing vertebral, non-vertebral and/or hip fracture in postmenopausal women. There was good evidence that compared to placebo, oestrogen is associated with decreased risk in vertebral, non-vertebral and hip fractures. This effect was observed in the analysis including all postmenopausal women (OR not reported), as well as for groups at higher risk of fractures (RR approximately 0.07).[84]

In two clinical trials conducted by the WHI,[90,92] conjugated oestrogen in combination with progestin in postmenopausal women (n=16 608) or conjugated oestrogen (CEE) alone in women after hysterectomy (n=10 739) were shown to reduce risk of osteoporotic fractures. Participants taking CEE 0.625 mg and medroxyprogesterone acetate 2.5 mg/day in a combined tablet (opposed oestrogen therapy) for an average of 5 years had significant reduction in total fractures (HR: 0.76; 95% CI: 0.69–0.85; p=0.05) as well as hip fractures (HR: 0.66; 95% CI: 0.45–0.98; p=0.05).[92] Participants taking CEE 0.625 mg/day for an average of 6 years had a significant reduction in rate of all osteoporotic fractures (HR: 0.70; 95% CI: 0.63–0.79; p=0.01) and rate of hip fractures (HR: 0.61; 95% CI: 0.41–0.91; p=0.01).[90]

Prevention of osteoporosis in older men

There was no evidence on the effectiveness of HT used in men. With respect to the role of testosterone replacement in hypogonadal men, there are no data showing efficacy (or safety) in fracture reduction; but there is data demonstrating that testosterone levels below the reference range are associated with increased fracture risk.[94]

It is the consensus of the Working Group that if HT is used for men with hypogonadism, it will reduce the risk of bone loss.

Safety

A good quality SR[84] reported an increase in risk compared to placebo of thromboembolic events (OR: 1.36; 95% CI: 1.01–1.86) and cardiovascular accident (OR: 1.34; 95% CI: 1.07–1.68) associated with oestrogen therapy. Although populations treated with oestrogen only had a lower risk compared to placebo for breast cancer (OR: 0.79; 95% CI: 0.66–0.93) the risk was significantly increased for women taking oestrogen/progestin combination therapy (OR: 1.28; 95% CI: 1.03–1.60).[84] These findings were consistent with those in the WHI trials, which were both ceased early due to the significant risk of serious side effects.[90,92] In the moderate quality oestrogen/progestin trial,[92] HT was associated with an increased the risk of coronary artery disease (HR: 1.29; 95% CI: 1.02–1.63; p=0.05), stroke (HR: 1.41; 95% CI: 1.07–1.85) and invasive breast cancer (HR: 1.26; 95% CI: 1.00–1.59; p=0.05). In the good quality oestrogen alone trial,[90] HT was associated with an increased the risk of stroke (HR: 1.39; 95% CI: 1.10–1.77; p=0.07) and pulmonary embolism (HR: 1.33; 95% CI: 0.87–2.06; p=0.007) but not coronary artery disease (HR: 0.91; 95% CI: 0.75–1.12) or breast cancer (HR: 0.77; 95% CI: 0.59–1.01).

Another good quality trial[91] conducted in women aged over 60 years, reported a reduction in risk of invasive breast cancer (p=0.02; ARR 1.9 per 1000 person years; 95% CI: 0.5–3.4) and colon cancer (p=0.04; ARR 1.3 per 1000 person years; 95% CI: 0.1–2.6) associated with tibolone therapy. However, relative hazard for stroke was 2.19 (95% CI: 1.14–4.23) and the absolute risk increase was 2.3 per 1000 person years (95% CI: 0.4–4.2), leading to early cessation of the trial. Absolute risk increased more in participants aged over 70 years (absolute risk increase 3.1 per 1000 person years). Women treated with tibolone had significant higher rates of vaginal bleeding (9.5 vs. 2.5%; p<0.001), vaginal discharge (9.8 vs. 1.8%; p<0.001), breast discomfort (9.05 vs. 2.9%; p<0.001), vaginal infection (8.3 vs. 2.5%; p<0.001) and pelvic pain (2.4 vs. 1.3%; p=0.007) compared to placebo.[91]

Strontium ranelate

RECOMMENDATION 16 (Grade C)

There is satisfactory evidence to support the effectiveness of strontium ranelate 2 g/day for the prevention of BMD loss in early postmenopausal women.

Research suggests that strontium ranelate simultaneously decreases bone resorption and stimulates bone formation both in vitro and in animal models.[95] In humans there is uncoupling of bone resorption and formation with increased serum levels of bone specific alkaline phosphatase (a marker of bone formation) and decreases in serum C-telopeptide cross links (a marker of bone resorption).[96]

In early menopausal women, strontium ranelate is associated with improvements in BMD.[97] While there is currently no evidence available for the effect of strontium ranelate in reducing fracture risk in these patients, findings in trials with postmenopausal women diagnosed with OP suggest that a satisfactory clinical impact is likely.[98]

Side effects and potential harms

Strontium ranelate has been associated with an increased risk of venous thromboembolism in some RCTs.[98]

Practical tips and precautions

- Strontium ranelate is not recommended for patients with severe renal impairment[98]
- In view of the increased risk of venous thromboembolism[98] take caution using strontium ranelate in patients with a history of, or at increased risk of, venous thromboembolism[99]

- Because calcium reduces absorption of strontium their administration should be separated by at least 2 hours[99]
- Strontium ranelate may form poorly soluble chelates with tetracyclines, reducing their absorption and anti-infective activity, so administration of these medications should be separated by at least 2 hours[99]
- The effect of strontium distribution in bone and increased X-ray absorption of strontium compared to calcium leads to an amplification of BMD measurement by DXA that should be considered when using DXA to monitor treatment response.[100] However, the greater increase in measured BMD is associated with efficacy in fracture risk reduction, possibly because it reflects compliance with therapy.

EVIDENCE STATEMENT

Prevention of osteoporosis

One moderate quality RCT[97] investigated strontium ranelate compared to placebo for prevention of OP. Participants were 140 women who had reached menopause before age 45 years (mean duration since menopause 36 months) without history of previous fracture. Participants received strontium ranelate in doses of 125 mg or 500 mg or 1 g/day or placebo. At 2 years, strontium ranelate 1 g significantly increased lumbar BMD compared to placebo (mean 1.41%; SD: 5.33%; $p<0.05$) for values adjusted for bone strontium content. The annual increase for adjusted lumbar spine BMD was 0.66% compared with a decline of 0.5% in the placebo group, with an overall beneficial effect after 2 years of about 2.4% with strontium ranelate 1 g relative to placebo. Femoral neck and total hip BMD measured without adjustment for strontium ranelate content were also significantly increased after 2 years with strontium ranelate 1 g/day compared to placebo (mean 2.46%, SD: 4.78% and mean 3.21%, SD: 4.68%, respectively; both $p<0.001$). Unadjusted values were not reported for these sites. Participants taking lower doses of strontium ranelate showed no significant difference in any outcome measure compared to placebo. The study did not investigate fracture risk.[97]

Another RCT[101] concluded that 'the minimum dose at which strontium ranelate is effective in preventing bone loss in early postmenopausal non-osteoporotic women is 1 g/day'. However, this study was not critically appraised.[101]

The Working Group recommends that until further research is available, 2 g/day is the most appropriate dose of strontium ranelate for prevention of OP. The RCT[97] investigating strontium ranelate for prevention of OP treatment was 2 years, thus there is currently no evidence to indicate the optimal duration of treatment. While there is currently no evidence available for the effect of strontium ranelate in reducing fracture risk used for prevention in early menopausal women, the finding of improvements in BMD with preventive strontium ranelate therapy in low doses,[97] and the reduction of fracture risk observed in populations with known OP treated with 2 g/day,[98] suggests that a satisfactory clinical impact is likely.

Safety

One Cochrane SR[98] reported safety data from four RCTs. There were no significant differences compared to placebo for rate of adverse events, rate of withdrawal related to an adverse event, or rate of serious adverse events. Participants treated with strontium ranelate showed an increase in diarrhoea (RR: 1.38; 95% CI: 1.02–1.87). Data from two RCTs (n=6669) showed an increased risk of vascular system disorders including venous thromboembolism (2.2 vs. 1.5%; OR: 1.5; 95% CI: 1.1–2.1) and pulmonary embolism (0.8 vs. 4.5%; OR: 1.7; 95% CI: 1.0–3.1). Strontium ranelate was associated with an increased risk of headaches (3.9 vs. 2.9%), seizures (0.3 vs. 0.1%), memory loss (2.4 vs. 1.9%) and disturbance in consciousness (2.5 vs. 2.0%).[98]

Exercise

RECOMMENDATION 17 (Grade D consensus)

There is evidence to support GPs recommending regular, weight bearing exercise for reducing osteoporotic bone loss in postmenopausal women and older men. However, there is no evidence of long term effects, side effects such as injuries, and any efficacy in fracture risk reduction.

Exercise may have additional benefits including weight control, reduction of blood pressure, pain relief and improvement in QOL.[72] Exercise can also be beneficial for improving balance as part of a falls reduction program (see Recommendation 9). Particularly in patients diagnosed with OP, supervision by a physiotherapist, exercise physiologist or other appropriately trained and qualified health professional is recommended.[21,46,73]

Exercise regimens should focus on low impact exercise and muscle strengthening. Because bones are brittle and there is higher risk of fracture, patients with OP should avoid high impact activities and abrupt, sudden and/or twisting movements (eg. running, sit ups, heavy lifting, swinging motions). Activities such as tai chi, hydrotherapy and walking may provide gentle strength training, muscle relaxation and pain relief.[21,46,73]

There were no reported RCTs examining the direct effect of exercise on fracture risk. Also, no studies have addressed side effects such as injuries and long term effects of exercise.

Practical tips and precautions

- The goal for exercising once the individual has established OP changes from high impact weight bearing exercise to improve BMD, to low impact exercise to improve balance and flexibility
- Exercise programs should be individualised to the patient's needs, abilities and interests
- Particularly when the individual has not undertaken recent physical activity, exercise programs should commence at a low level and be progressive in intensity
- A physiotherapist or exercise physiologist can assist in development of the most appropriate program, providing education on safe and effective training techniques, increasing motivation and ongoing monitoring
- Individuals with OP should receive education about back care to reduce the chance of back injury.

EVIDENCE STATEMENT

Treatment of osteoporosis

An international guideline[46] based on three good quality SRs and/or RCTs suggested that exercise programs may have an effect in maintaining BMD in postmenopausal women and older men, however it was not reported whether participants in these studies were diagnosed with OP. A moderate quality RCT[102] found no change in femoral neck and trochanter BMD in postmenopausal women participating in exercise compared to a significant decline in BMD in controls; however, between group differences were not significant. Although the study was not powered to study fracture events, the control group experienced significantly more fractures related to falls (p=0.019).[102] Another moderate quality RCT[103] showed that after 9 months, postmenopausal women and men aged over 78 years (mean 83 years, 30% participants had T-score <-2.5) had no changes in BMD (whole body, proximal femur and lumbar spine) after participating in either a supervised exercise program (intervention) or a low intensity home exercise program (control). A low quality trial[72] found no effect of exercise on BMD in a population with OP. Studies reporting other outcome measures (eg. quality of life, reduction in pain) for exercise were not reviewed. Exercise has also been shown to be effective in reducing the risk of falls for older adults when conducted as part of a comprehensive and multifaceted falls reduction program (see Recommendation 9).

An international guideline[46] and consensus report[73] suggest that once an individual has been diagnosed with OP, exercise should be undertaken with care due to increased risk of fracture. The goal for exercising once the individual has established OP changes from high impact weight bearing exercises to improve BMD to low impact exercises that will improve balance and flexibility. Exercise that places stress on the bones is not recommended and care should be taken to avoid jarring, twisting and sudden movements. Suggested exercises include tai chi, gentle weights, hydrotherapy and walking.[73]

Calcium and vitamin D supplementation

RECOMMENDATION 18 (Grade C)

There is good evidence for high prevalence of vitamin D insufficiency in institutionalised and home bound individuals and vitamin D supplementation is considered to be standard care in these populations. There may be some benefit for dietary change or calcium supplementation in postmenopausal women and older men with OP who have low dietary calcium intake.

Most specific anti-osteoporosis therapies (eg. SERMs, bisphosphonates, teriparatide) were evaluated in the context of adequate vitamin D stores and adequate calcium intake. Furthermore, there is evidence that the efficacy of alendronate is reduced in the presence of vitamin D deficiency.[104] Hence it is suggested that dietary calcium intake and serum 25-OH D levels are checked before initiating anti-osteoporosis therapy, with appropriate supplementation to be recommended if calcium intake and/or vitamin D levels are inadequate.

Total calcium intake from dietary sources and supplements should exceed 1200 mg/day. Vitamin D from sunlight exposure (avoiding the middle of the day) and supplements should ensure 25-OH D levels >60 nmol/L. If vitamin D supplements are required, doses of at least 800 IU/day are usually required. If the serum 25-OH D level is low, it would be useful to remeasure serum 25-OH D concentrations to ensure levels above 50–75 nmol/L after 3 months of treatment. Calcium intake is often suboptimal, particularly in the elderly (especially institutionalised patients) who may have limitations to dietary intake and relatively limited sunlight exposure.

Calcium and vitamin D supplements work by reducing secondary hyperparathyroidism and reducing bone turnover. Bone mineral density is also increased by calcium and vitamin D, but their effects appear to be modest. With the exception of calcium in patients with chronic renal failure, calcium and vitamin D are not on the PBS.

Vitamin D and calcium are available at no extra cost to the patient on the PBS with the non-generic versions of risedronate and alendronate. However, the dose of vitamin D (800 IU/day) may not be sufficient to treat vitamin D deficient individuals.

Calcium supplements are available in two common forms: calcium carbonate and calcium citrate. The most commonly available type of vitamin D supplement is vitamin D3 or cholecalciferol. It elevates serum 25-OH D concentrations more than vitamin D2 or ergocalciferol, and is also more reliably measured by commercially available assays. Currently available doses range from 400–1000 IU, presented as either capsules or tablets.

Side effects and potential harms

Calcium supplements can uncommonly increase the risk of renal calculi, particularly if given to individuals with adequate dietary calcium intakes. Calcium supplements can cause abdominal bloating and constipation. One RCT[75] reported an increase in CV adverse events with calcium in older postmenopausal women, however further research is required.

Toxicity is extremely uncommon with vitamin D, even in high doses. Single doses of up to 500 000 IU are tolerated without causing hypercalcaemia or hypercalciuria.

Practical tips and precautions

- Most specific anti-osteoporosis therapies (eg. SERMs, bisphosphonates, teriparatide) were evaluated in the context of adequate vitamin D stores and adequate calcium intake. Hence it is suggested that serum 25-OH D levels are checked before initiating therapy. Total calcium intake from dietary sources and supplements should exceed 1200 mg/day.[76–78] Vitamin D from sunlight exposure (avoiding the middle of the day) and supplements help ensure 25-OH D levels are above 60 nmol/L
- To optimise clinical efficacy calcium 1000–1200 mg/day should be taken in conjunction with vitamin D 700–800 IU/day[76–78]
- Calcium citrate, unlike calcium carbonate, does not need to be taken after meals as it does not require an acid environment to be optimally absorbed. There are some data suggesting that calcium supplements may be more effective if taken at night (eg. with the evening meal)
- If the 25-OH D level is low, it would be useful to remeasure serum 25-OH D concentrations to ensure levels above 50–75 nmol/L after 3 months of treatment
- Vitamin D may be taken at any time of the day
- Recent research suggests that supplementation with calcium or vitamin D alone is not effective.

EVIDENCE STATEMENT

Treatment of osteoporosis

One good quality RCT[105] (n=5292, 85% female) compared vitamin D and calcium for a minimum of 2 years in community dwelling adults aged over 70 years with a past history of osteoporotic fracture. Participants received 800 IU oral vitamin D3 supplements daily (n=1343), 1000 mg oral calcium supplements daily (n=1311), combination therapy (n=1306) or placebo (n=1332). There was no significant difference in incidence of new low trauma fractures (HR: 0.94; 95% CI: 0.81–1.09; *p*=NS) between the calcium (12.6%) and placebo group (13.7%). There was no significant difference (HR: 1.02; 95% CI: 0.88-1.19; *p*=NS) in the rate of fractures between those taking vitamin D (13.3%) and the placebo group (13.1%), nor in those taking combination therapy (12.6%) compared to placebo (13.4%). Subanalyses also showed no significant effect of treatment for patients aged over 80 years, those with lower body weight, lower calcium dietary intake, low sun exposure, lower vitamin D dietary intake, or compliant patients. Serious adverse effects including renal insufficiency, renal stones and hypercalcaemia were rare and did not differ between the groups.[105]

Bisphosphonates

RECOMMENDATION 19 (Grade A)

There is excellent evidence to support the effectiveness of bisphosphonates (alendronate, risedronate or zoledronic acid) in reducing the risk of vertebral and non-vertebral fractures and increasing BMD in postmenopausal women and older men with OP.

RECOMMENDATION 20 (Grade D – consensus)

General practitioners should reconsider bisphosphonate therapy after 5–10 years in postmenopausal women and older men with OP who have had a good response to treatment, determined through re-evaluation of BMD and fracture risk (ie. BMD above T-score -2.5 and no recent fractures). If BMD remains low (eg. T-score <-2.5) continue treatment in view of the expected bone loss, especially at the hip, as soon as 1–2 years after stopping. Treatment should be restarted if there is evidence of bone loss (eg. lumbar spine BMD decrease of 5% or more) or with any additional fracture.

Currently the only bisphosphonates approved in Australia for clinical use in OP are alendronate, etidronate, risedronate, and zoledronic acid. Other bisphosphonates such as ibandronate, clodronate and neridronate are in use outside Australia or are currently under investigation for the treatment of postmenopausal OP. Alendronate, etidronate and risedronate (all available preparations) are supported under the PBS for women and men with evidence of osteoporotic fractures, independent of age, BMD or other clinical risk factors. Furthermore, alendronate and risedronate are also supported in men and women aged 70 years or older, with no prevalent fragility fracture but a BMD T-score of -3.0 or less at the lumbar spine and/or hip. Zoledronic acid is supported under the PBS for women with postmenopausal OP and prevalent fragility fractures, and for men with a history of osteoporotic hip fracture. Zoledronic acid is also supported by the PBS in women aged 70 years or older, with no prevalent fragility fracture but a BMD T-score of -3.0 or less at the lumbar spine and/or hip. The TGA approval for zoledronic acid restricts use to no more than three annual 5 mg doses, due to the lack of clinical trial experience beyond 3 years for treatment of OP.

Bisphosphonates are potent inhibitors of bone resorbing cells (osteoclasts). They work to inhibit bone resorption by interfering with normal osteoclast function and inducing osteoclast apoptosis. They are rapidly sequestered into bone (from where they are only slowly released) and eliminated by the kidneys, therefore exposure to soft tissues, including bone marrow is transient. Alendronate, one of the more commonly used bisphosphonates, has a half life of approximately 8 years.[80]

Alendronate and risedronate are usually taken orally on either a daily basis (alendronate 10 mg, risedronate 5 mg) or weekly (alendronate 70 mg, risedronate 35 mg). Intravenous bisphosphonates are often used in patients intolerant to oral preparations (eg. once yearly zoledronic acid) and this mode of delivery produces rapid anti-resorptive action within 24–48 hours. In the prevention setting in early postmenopausal women, lower doses have been used and appear to prevent bone loss.

Side effects and potential harms

Bisphosphonates used in the management of OP are usually well tolerated and the rate of adverse effects in every day clinical practice is low. The most frequent adverse effects observed with oral bisphosphonate treatment are GI symptoms (eg. gastric irritation, oesophageal erosions, gastric ulcers, perforations and strictures). Serious side effects have been observed when using very high doses (as in cancer indications) or when elimination is impaired.

Osteonecrosis of the jaw has recently been associated with long term and high dose bisphosphonate treatment. This is a very rare but potentially serious side effect seen mostly in patients with multiple myeloma or breast cancer bone metastases who receive frequent and high total doses of IV bisphosphonate treatment. While the aetiology is uncertain, a strong association with dental pathology and interventions highlights the need for close attention to dental health.[84,85]

Practical tips and precautions

- Active upper GIT disorders, including strictures, are a contraindication to oral bisphosphonate use
- The incidence of GIT adverse events can be minimised by taking oral therapy after fasting for several hours (usually overnight) before drug ingestion and then remaining upright and avoiding food for at least 30 minutes
- Concurrent calcium and vitamin D supplementation is recommended alongside alendronate, risedronate or etidronate therapy
- To be absorbed properly, bisphosphonates should not be taken together with any other drug, particularly calcium. Calcium supplements should be taken at least 60 minutes after the administration of bisphosphonates
- Low serum levels of vitamin D should be corrected to a level above 50 nmol/L before commencing bisphosphonate therapy
- IV bisphosphonates need to be administered over at least 15–20 minutes, as higher infusion rates can increase the risk of renal damage. Zoledronic acid is contraindicated in patients with a calculated creatinine clearance below 35 mL/min
- Combined use of bisphosphonates with other anti-resorptive (eg. raloxifene, HT) or anabolic drugs (teriparatide) is not recommended
- Good dental hygiene and care is essential, particularly in those using long term bisphosphonates, to reduce the risk of ONJ. Treatment should be ceased in cases of confirmed ONJ. The dental practitioner should be made aware of bisphosphonate dosage and other risk factors and ensure the patient is dentally fit with a low chance of future extractions. Extractions or other jaw bone surgery should be avoided. Where unavoidable, extractions should be performed under antibiotic prophylaxis with minimal trauma and suture socket.[85]

EVIDENCE STATEMENT

A number of good quality SRs have found significant effects of bisphosphonates (alendronate, risedronate and zoledronic acid) in reducing fracture risk and increasing BMD.[84,87,88] Few studies have directly compared different agents or classes of agents used to treat OP and hence the data is insufficient to determine the relative efficacy or safety of these agents.

Treatment of osteoporosis in postmenopausal women

In a good quality MA,[87] pooled results from nine moderate and good quality RCTs showed a reduction in the risk of vertebral fracture for **alendronate** compared to placebo (RR: 0.52; 95% CI: 0.43–0.65) with no heterogeneity observed between trials. This translated to a NNT of 72 (95% CI: 61–99) to prevent one vertebral fracture over 2 years of treatment in women considered to be at high risk of vertebral fracture. Six trials presented data on non-vertebral fracture risk. Pooled RR was 0.49 (95% CI: 0.36–0.67) for non-vertebral fractures, with no heterogeneity between trials. NNT to prevent one non-vertebral fracture over 2 years of treatment in women at high risk was 24 (95% CI: 19–37). Alendronate also showed a significant effect on lumbar spine BMD compared to placebo (WMD: 7.36; 95% CI: 5.65–9.07). Alendronate 10 mg/day produced more significant outcomes than alendronate 5 mg/day.[87]

A Cochrane review[88] on **risedronate** in postmenopausal women included five RCTs (mean age of participants 51–78 years) comparing risedronate 2.5 mg or 5.0 mg daily to placebo over 2–3 years. Pooled data from three RCTs showed a significant 39% reduction in vertebral fractures (RR: 0.61; 95% CI: 0.50–0.76) for risedronate 5.0 mg/day. Pooled data from four RCTs showed a significant 20% reduction in non-vertebral fractures (RR:

0.80; 95% CI: 0.72–0.90) and for hip fractures there was a significant 26% reduction in risk (three RCTs, RR: 0.74; 95% CI: 0.59–0.94). The effect observed for 2.5 mg risedronate was not as large.[88]

Two RCTs[36,106] reported on **zoledronic acid** in preventing new clinical fractures in postmenopausal women and in older men. In one good quality trial,[106] 2127 participants received either annual IV infusion with 5 mg zoledronic acid (n=1065) or placebo infusion (n=1062). Zoledronic acid showed significant reduction in rate of both new vertebral fractures (HR: 0.54; 95% CI: 0.32–0.92; p=0.02) and new non-vertebral fractures (HR: 0.73; 95% CI: 0.55–0.98; p=0.03) compared to placebo. There was no significant difference between the groups for rate of new hip fractures (HR: 0.70; 95% CI: 0.41–1.19; p=0.18). Zoledronic acid showed significant increases in hip BMD (5.5%; p<0.001) and femoral neck BMD (3.6%; p<0.001) compared to decline in BMD for placebo.[106]

An excellent quality RCT[36] with 7765 women (mean age 73 years) compared zoledronic acid 5 mg via IV administration annually for 3 years to placebo infusion. Zoledronic acid showed significant increase compared to placebo in total hip BMD (6.02%; 95% CI: 5.77–6.28; p<0.001), lumbar spine BMD (6.71%; 95% CI: 5.69–7.74; p<0.001) and femoral neck BMD (5.06%; 95% CI: 4.76–5.36; p<0.001). The treatment group also had a 70% reduction in vertebral fracture (HR: 0.30; 95% CI: 0.24–0.38) and a 41% reduction in hip factures (HR: 0.59; 95% CI: 0.42–0.83) over 3 years.[36]

Another trial with 7765 women (mean age 73 years) compared zoledronic acid 5 mg via IV administration annually for 3 years to placebo infusion.[106] Zoledronic acid showed significant increase in total hip BMD compared to placebo (6.02%; 95% CI: 5.77–6.28; p<0.001), lumbar spine BMD (6.71%; 95% CI: 5.69–7.74; p<0.001) and femoral neck BMD (5.06%; 95% CI: 4.76–5.36; p<0.001). The treatment group also had a 70% reduction in vertebral fracture (HR: 0.30; 95% CI: 0.24–0.38) and a 41% reduction in hip factures (HR: 0.59; 95% CI: 0.42–0.83) over 3 years. In addition, there was a 28% reduction in mortality in the zoledronic acid treated group as compared to the placebo group.[106]

Etidronate may also prevent spinal fractures in postmenopausal women with OP, but problems in design, execution, and analysis of the existing studies make their results difficult to interpret.

Treatment of osteoporosis in men

One excellent quality trial[106] (reported above) of 5 mg **zoledronic acid** annual IV infusion compared to placebo was conducted in older men with prevalent fractures. Treatment was associated with a significant reduction in rate of both new vertebral fractures (HR: 0.54; 95% CI: 0.32–0.92; p=0.02) and new non-vertebral fractures (HR: 0.73; 95% CI: 0.55–0.98; p=0.03) and increases in BMD at the hip and femoral neck.[106]

Another good quality trial[36] (reported above) of 5 mg zoledronic acid annual IV infusion compared to placebo was conducted in older men with prevalent hip fractures. Treatment was associated with a significant reduction in rate of both new vertebral fractures (HR: 0.54; 95% CI: 0.32–0.92; p=0.02) and new non-vertebral fractures (HR: 0.73; 95% CI: 0.55–0.98; p=0.03), as well as increases in BMD at the hip and femoral neck.

One excellent quality RCT[107] found a significant reduction (p=0.02) in the risk of vertebral fractures in older men with OP (n=241) compared to placebo for **alendronate** 10 mg/day for 2 years. The effect on non-vertebral fractures was not significant. Men taking alendronate experienced a significant increase in lumbar spine BMD, with an absolute between group difference compared to placebo of 5.3% (95% CI: 4.3–6.3; p<0.001). Absolute differences between alendronate and placebo groups were also significant for trochanter, hip and total body BMD. Placebo groups had a reduction in BMD at the femoral neck compared to no significant change in the alendronate group (absolute difference 2.6%; 95% CI: 1.5–3.7%; p<0.001).[107]

Safety

A number of good quality SRs found no significant differences between alendronate, risedronate, or zoledronic acid compared to placebo for GIT effects[84,87,88] or rate of discontinuing medication as a result of adverse effects.[87] One trial reported an increased risk compared to placebo for serious atrial fibrillation with zoledronic acid (1.3 vs. 0.5%; p<0.001) but another large trial found no significant increase in risk (1.1 vs. 1.3%; p<0.84).[84]

A recent SR[84] reported that the only cases of ONJ have occurred in patients with cancer taking large IV doses of bisphosphonates. The reviewers noted that the American Society for Bone and Mineral Research had recently conducted a review and concluded that there appeared to be a low risk of ONJ in patients taking oral bisphosphonates but suggested that the incidence may be higher than reflected in current literature.[84]

Duration of therapy

One moderate quality trial provided evidence that after 5 years treatment with alendronate 10 mg, the risk of fractures did not increase after 10 years, except in women with high risk of fracture. Women who discontinued alendronate after 3–5 years therapy showed a small decline in BMD and a gradual rise in biochemical markers, but no higher fracture risk compared with those who continued alendronate. Women at high risk of fractures (eg. prevalent vertebral fracture and/or low baseline BMD) are considered likely to benefit by continuing therapy beyond 5 years.[89] Given the lack of comparable evidence for duration of therapy for the other bisphosphonates used in Australia, and the observed differences in return of bone turnover toward placebo after cessation with different bisphosphonates, the Working Group does NOT suggest this could be applied to all bisphosphonates or even to all oral bisphosphonates.

Hormone therapy

RECOMMENDATION 21 (Grade A)

There is excellent evidence to support the effectiveness of HT in reducing the risk of fractures in postmenopausal women with OP. The significant increase in risk of adverse events associated with treatment should be weighed carefully against benefits, and long term use is not recommended.

RECOMMENDATION 22 (Grade D – consensus)

Hormone therapy used for men with hypogonadism is likely to prevent bone loss. The increase in risk of adverse events associated with treatment should be weighed carefully against benefits in long term use.

Oestrogen (HT) is available on the PBS for the prevention and treatment of OP in postmenopausal women. Oestrogen acts to decrease bone resorption. Hormone therapy is effective in preventing loss of BMD and reducing the risk of fractures when given at, or near, menopause (as well as useful for control of menopausal symptoms) and also has a role in reducing the risk of fractures in postmenopausal women with OP.[84,90–93]

Ideally, therapy should be continuous (ie. without a break in therapy). Adjuvant progestogens are necessary in women who still have a uterus to protect against endometrial cancer. They may be given cyclically for 10–14 days each month in perimenopausal women or as continuous therapy combined with oestrogen in postmenopausal women. The latter is more suitable for women more than 2 years postmenopause to avoid the initial irregular bleeding commonely seen with this regimen being unduly prolonged.

The minimum effective dose of oestrogen therapy on bone loss has yet to be clearly established,[93] but the beneficial effects of oestrogen therapy can be achieved by many routes of administration (including oral and transdermal) and lower doses can be used in combination with calcium supplements.

Follow up bone densitometry in individual patients may indicate the requirement for a higher dose and attention to calcium intake and vitamin D status if there is a suboptimal response.

Treatment of osteoporosis in older men

With respect to the role of testosterone replacement in hypogonadal men, there are no data showing efficacy (or safety) in fracture reduction, but there are data demonstrating that testosterone levels below the reference range are associated with increased fracture risk.[94] Hormone therapy may contribute to a reduction in fracture risk for this population.

Side effects and potential harms

The role of long term postmenopausal HT in the prevention and management of OP remains controversial following publication of the results of the WHI study of combined oestrogen and progestin therapy[92] and its study of oestrogen alone therapy.[90] There was an increase in the risk of stroke in those aged 50–79 years, although the absolute risk was lower in women aged in their 50s.[90,92] Increased risks in CV disease, thromboembolic events, CV accident, and invasive breast cancer have been reported in good quality research.[84,90–92]

Practical tips and precautions

- GPs should discuss the long term risks and benefits of HT, especially breast cancer and CV effects
- Individuals who require immobilisation for any period (eg. hospitalisation or long plane trip) should cease HT for a week before and afterward

- Individuals taking HT should maintain an adequate calcium intake (from dietary sources or supplements) and vitamin D status
- Raloxifene should not be used in combination with oestrogen therapy.

EVIDENCE STATEMENT

Treatment of osteoporosis

A good quality SR[93] reported on HT used in the treatment of OP in postmenopausal women. Pooled data from moderate and good quality RCTs using either oestrogen alone or opposed showed a significant improvement in BMD at the lumbar spine (WMD: 7.70; 95% CI: 4.86–10.54), forearm (WMD: 3.27; 95% CI: 0.35–6.19) and femoral neck (WMD: 3.46; 95% CI: 0.74–6.19).[93]

A good quality RCT[91] (n=4568) investigated the effectiveness of tibolone, a modified oestrogen, on the risk of fractures in women aged 60–85 years who were diagnosed with OP. Tibolone 1.25 mg/day for a mean duration of 34 months reduced the risk of vertebral fractures (HR: 0.55; 95% CI: 0.41–0.74) which translated to an ARR of 8.6 per 1000 person years (95% CI: 4.4–12.9). There was also significant reduction in risk of non-vertebral fractures (HR: 0.74; 95% CI: 0.58–0.93) that translated to an ARR of 6.9 per 1000 person years (95% CI: 1.6–12.2).

Safety

A good quality SR[84] reported an increase in risk compared to placebo of thromboembolic events (OR: 1.36; 95% CI: 1.01–1.86) and CV accident (OR: 1.34; 95% CI: 1.07–1.68) associated with oestrogen therapy. Although populations treated with oestrogen only had a lower risk compared to placebo for breast cancer (OR: 0.79; 95% CI: 0.66–0.93) the risk was significantly increased for women taking oestrogen/progestin combination therapy (OR: 1.28; 95% CI: 1.03–1.60).[84] These findings were consistent with those in the WHI trials, which were both ceased early due to the significant risk of serious side effects.[90,92] In the moderate quality oestrogen/progestin trial,[92] HT was associated with an increased the risk of coronary artery disease (HR: 1.29; 95% CI: 1.02–1.63; p=0.05), stroke (HR: 1.41; 95% CI: 1.07–1.85) and invasive breast cancer (HR: 1.26; 95% CI: 1.00–1.59; p=0.05). In the good quality oestrogen alone trial,[90] HT was associated with an increased the risk of stroke (HR: 1.39; 95% CI: 1.10–1.77; p=0.07) and pulmonary embolism (HR: 1.33; 95% CI: 0.87–2.06; p=0.007) but not coronary artery disease (HR: 0.91; 95% CI: 0.75–1.12) or breast cancer (HR: 0.77; 95% CI: 0.59–1.01).

Another good quality trial[91] conducted in women aged over 60 years, reported a reduction in risk of invasive breast cancer (p=0.02; ARR 1.9 per 1000 person years; 95% CI: 0.5–3.4) and colon cancer (p=0.04; ARR 1.3 per 1000 person years; 95% CI: 0.1–2.6) associated with tibolone therapy. However, relative hazard for stroke was 2.19 (95% CI: 1.14–4.23) and the absolute risk increase was 2.3 per 1000 person years (95% CI: 0.4–4.2), leading to early cessation of the trial. Absolute risk increased more in participants aged over 70 years (absolute risk increase 3.1 per 1000 person years). Women treated with tibolone had significant higher rates of vaginal bleeding (9.5 vs. 2.5%; p<0.001), vaginal discharge (9.8 vs. 1.8%; p<0.001), breast discomfort (9.05 vs. 2.9%; p<0.001), vaginal infection (8.3 vs. 2.5%; p<0.001) and pelvic pain (2.4 vs. 1.3%; p=0.007) compared to placebo.[91]

Parathyroid hormone

RECOMMENDATION 23 (Grade A)

There is excellent evidence to support the effectiveness of teriparatide in postmenopausal women with OP for reduction in fracture risk and improvement in BMD. Because of expense, teriparatide is generally recommended for patients at very high risk of fracture or in whom bisphosphonate therapy is contraindicated or has been ineffective.

RECOMMENDATION 24 (Grade B)

There is good evidence to support the effectiveness of teriparatide for improving BMD in older men with OP. Because of expense, teriparatide is restricted for patients at very high risk of fracture and currently after fracture has occurred while on anti-resorptive therapy.

Parathyroid hormone is approved in Australia in the form of hPTH(1-34), also known as teriparatide. Parathyroid hormone is also produced in the form of hPTH(1-84), however this is not available in Australia and evidence on its effectiveness was not reviewed for this guideline.

Teriparatide acts predominantly on osteoblasts to increase new bone formation on trabecular and cortical surfaces by preferentially stimulating osteoblastic bone formation over osteoclastic bone resorption. Teriparatide acts to increase the lifespan of osteoblasts by reducing osteoblast apoptosis and by inducing recruitment and formation of new osteoblasts. The bone remodelling rate as well as the amount of bone deposited in each remodelling cycle is increased. Cancellous bone connectivity, trabecular thickness and cortical width are increased, as is periosteal bone formation, which is responsible for increasing cortical width and producing an increase in bone size. Skeletal mass and bone strength is also increased.[108]

Teriparatide increases lumbar spine and femoral neck BMD and decreases vertebral and non-vertebral fractures in postmenopausal OP with prior fracture. Hip fracture has not been assessed.[109] Teriparatide has also been shown to improve new, worsening and moderate to severe back pain (a major cause of suffering, disability and cost in OP) and reduce height loss in patients who have sustained one or more new vertebral fractures.[110] Teriparatide increases BMD at the lumbar spine and femoral neck in men with OP, but there are no data on fractures in this population.[111,112]

Teriparatide is a costly medication with a recommended 18 month course duration that is now reimbursed by the PBS for severe established OP in patients with a very high risk of fracture who have:

- a bone density T-score of -3.0 or less
- had two or more fractures due to minimal trauma
- experienced at least one symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses.

Because of expense, teriparatide is recommended for patients at very high risk of fracture by virtue of very low BMD with pre-existing fracture, or for patients who continue to sustain fractures despite adequate bisphosphonate therapy for an extended period, or in whom bisphosphonate therapy is contraindicated.[113]

Side effects and potential harms

Dizziness, leg cramps, nausea, injection reactions and headache are the most commonly described side effects, occurring in 5% or less of cases. They are generally mild and not requiring discontinuation. Mild transient hypercalcaemia has been noted, but monitoring serum calcium is not a requirement of therapy.[109] Mild increases in uric acid without the development of acute gout and small increases in urinary calcium excretion without nephrolithiasis have been reported.[114] Oncogenicity studies in rats treated with high doses of teriparatide of near lifetime duration resulted in an increased risk of osteogenic sarcoma. Three osteosarcomas have been described in patients with endogenous hyperparathyroidism.[109]

Practical tips and precautions

- Teriparatide is given as a daily subcutaneous injection via a multidose pen device
- Because of expense, teriparatide is generally restricted to specialist centres and is recommended for patients at very high risk of fracture
- Due to increased background risk of osteosarcoma, teriparatide is not recommended in patients with Paget disease, prior skeletal irradiation, bony metastases or prior skeletal malignancies, and in those with metabolic bone diseases other than OP or pre-existing hypercalcaemia.

EVIDENCE STATEMENT

Treatment of osteoporosis in postmenopausal women

A good quality SR[109] reported on 12 moderate and good quality RCTs (including seven double blind RCTs) investigating the effectiveness of hPTH(1-34).

One trial in the SR[109] reported fracture risk as an outcome measure. The trial compared hPTH(1-34) to calcium in postmenopausal women, reporting a reduction in risk of new vertebral fractures for hPTH(1-34) 20 µg/day (RR: 0.35; 95% CI: 0.22–0.55). The ARR for vertebral fractures was 9–10% and ARR for non-vertebral fractures was 3% (RR: 0.47; 95% CI: 0.25–0.88) for hPTH(1-34) 20 µg/day. One good quality trial included in the SR found a significant reduction (p=0.042) in non-vertebral fractures associated with hPTH(1-34) 20 µg/day compared to alendronate 10 mg/day.[109]

Six moderate to good quality RCTs reported in the SR[109] compared PTH to placebo or an active comparator and reported BMD as an outcome measure. Trials were for 1–3 years. Participants treated with hPTH(1-34) 20 µg/day had significant reduction ranging from 9.7–10.3% in lumbar spine BMD and reductions of 2.8–3.9% for femoral neck BMD. hPTH(1-34) 40 µg/day was associated with significant reductions of 13.7–14.3% in lumbar spine BMD, and reductions of 4.5–5.1% for femoral neck BMD. Two moderate quality RCTs reported in the SR showed that teriparatide produces greater BMD increases than alendronate. hPTH(1-34) 20 µg/day was associated with 10.3% greater improvement in lumbar spine BMD than alendronate 10 mg.[109]

Treatment of osteoporosis in men

In a good quality trial, men with idiopathic OP (n=23) were randomly assigned to hPTH(1-34) 25 µg versus placebo. After 18 months, BMD had increased significantly by 13.5% and 2.9% at the lumbar spine and femoral neck respectively. Total hip BMD did not change significantly, but there was a significant decrease of 1.2% at the one-third distal radius.[111] Another good quality trial was conducted in men with low BMD who were predominantly hypogonadal (n=437). Participants were treated with 20 µg or 40 µg of hPTH(1-34) versus placebo with calcium and vitamin D. After 1 year, lumbar spine BMD increased by 5.4% with 20 µg compared with no change with placebo. There was a non-significant decrease in non-vertebral fractures with hPTH(1-34) compared with placebo.[112]

Safety

An increased risk of osteosarcoma was reported in a life long carcinogenicity study involving Fischer rats given high dose hPTH(1-34) from infancy through senescence (8 weeks to 2 years of age). Osteosarcoma was found with all doses and, in the lower dose ranges, was first detected after about 20 months of therapy. There have been no reports of osteosarcoma in clinical trial subjects, and although there are isolated case reports of osteosarcoma in patients with long standing hyperparathyroidism, there is no evidence to suggest that osteosarcoma is of increased frequency in hyperparathyroidism. Nine trials investigating hPTH(1-34) reported postdose hypercalcaemia (serum calcium level above 2.6 mmol/L) that ranged from 3–11% among patients taking hPTH(1-34) 20 µg compared with 0–3% among those taking the comparator. These episodes were mild, with serum calcium levels usually returned to normal within 24 hours and no clinical sequelae. There were no reported increases in renal stones. hPTH(1-34) 20 µg was associated with a significant increase in the proportion of patients experiencing dizziness (3%) and leg cramps (range 2–8%).[109]

Selective oestrogen receptor modulators

RECOMMENDATION 25 (Grade A)

There is excellent evidence to support the effectiveness of selective oestrogen receptor modulators (SERMs) for postmenopausal women with OP where vertebral fractures (rather than non-vertebral fractures) are considered to be the major OP risk and where other agents are poorly tolerated.

Selective oestrogen receptor modulators are non-hormonal drugs that act to decrease bone resorption. Currently only one SERM, raloxifene (Evista), is approved for the treatment of OP in Australia. It is available on the PBS (Authority required) for established postmenopausal OP in patients with fracture due to minimal trauma.

Unlike oestrogens, which are uniformly oestrogen receptor agonist, SERMs exert selective agonist or antagonist effects in different oestrogen target tissues (eg. with raloxifene there is no stimulation of the breast or uterus, unlike with oestrogen). They are a chemically diverse set of compounds that lack the steroid structure of oestrogen, but possess a tertiary structure that allows binding to the oestrogen receptor. For example, raloxifene has a benzothiophene nucleus which differs substantially from the triphenylethylene structure of tamoxifen, another SERM available in Australia used in the treatment of breast cancer.

In postmenopausal women with established OP a reduction in risk of vertebral fractures is seen with raloxifene 60 mg/day, however the incidence of non-vertebral fractures has not been shown to be reduced.[84,115–119] Consequently, it is recommended that raloxifene be mainly used in postmenopausal women

with milder OP or in women with predominantly spinal OP. Unlike HT, raloxifene is not useful for control of menopausal symptoms, and may actually worsen menopausal symptoms, especially hot flushes.[116] In women further from the menopause, possible worsening of menopausal symptoms is less likely and the added protection from breast cancer associated with raloxifene[116,119] would be considered an advantage.

Although there is no clear evidence that short term use of raloxifene close to menopause would have a beneficial effect on fracture risk later in life, it could be considered as an alternative in women unable to take oestrogen for this indication.

Side effects and potential harms

An increased risk of venous thrombosis has been reported with raloxifene, similar to that associated with HT.[90,92,115] Leg cramps and hot flushes are a harmless but limiting side effect.[119]

Practical tips and precautions

- Raloxifene is taken as 60 mg/day. Fasting is not required
- Due to an increased risk of venous thrombosis, patients who require immobilisation for any period (eg. for hospitalisation or long plane trips) should cease raloxifene for a week before and afterward
- It is recommended that raloxifene users have an adequate calcium intake (from dietary sources or supplements) and vitamin D status
- There is no evidence for additional fracture reduction when used in combination with bisphosphonates, although an additional increase in BMD has been observed
- Raloxifene should not be used in combination with oestrogen therapy
- Patients can be monitored by bone densitometry every 2 years. There is no data on optimal duration of therapy.

EVIDENCE STATEMENT

Treatment of osteoporosis

One MA reported in the *DVO* international evidence based guideline for OP provided high grade evidence for the effectiveness of raloxifene compared to placebo for vertebral fracture prevention in postmenopausal women.[120] Another good quality MA supported the effect of raloxifene on reducing vertebral fractures in postmenopausal women with established OP.[84]

In one large (n=7705), good quality 4 year RCT,[115–118] raloxifene 60 mg/day was associated with a reduction in vertebral fractures compared to placebo (RR: 0.64; 95% CI: 0.53–0.76)[115] in postmenopausal women with OP. However, no effect was found on the overall risk of non-vertebral fractures (RR: 0.93; 95% CI: 0.81–1.06).[115] There was also good quality evidence from a subanalysis that in women at the highest risk of fracture (with at least one severity grade 3 vertebral fracture) raloxifene 60 mg/day decreased the rate of new vertebral fractures over 4 years (RR: 0.74; 95% CI: 0.54–0.99; p=0.048)[117] and over 8 years (HR: 0.78; 95% CI: 0.63–0.96; p=0.017).[118]

In another good quality, large (n=10 101) RCT of mean duration 5.6 years,[119] raloxifene 60 mg/day was associated with a reduction in clinical vertebral fractures (HR: 0.65; 95% CI: 0.47–0.89) compared to placebo. There was no significant effect on overall risk of non-vertebral fractures (HR: 0.96; 95% CI: 0.84–1.10).[119]

Safety

In the MORE trial, raloxifene was associated with a significant 76% reduction in risk of invasive breast cancer (RR: 0.24; 95% CI: 0.13–0.44; p<0.01; NNT 126).[116] In another good quality RCT there was also significant reduction in invasive breast cancer (HR: 0.56; 95% CI: 0.38–0.83; p=0.003) with an ARR of 1.2 per 1000 women treated for 1 year.[119]

A good quality SR[84] reported an increased risk with raloxifene compared to placebo for thromboembolic events (OR: 2.08; 95% CI: 1.47–3.02) pulmonary embolism (OR: 6.26; 95% CI: 1.55–54.80) and mild cardiac events such as chest pain, palpitations, tachycardia, and vasodilatation (OR: 1.53; 95% CI: 1.01–2.35).[84] In one study, raloxifene use was associated with increased risk of fatal stroke, but this was not associated with any increase in overall mortality.[115–118] In another study, raloxifene was associated with a 49% increase in risk of fatal stroke (HR: 1.49; 95% CI: 1.00–2.24; p=0.05; absolute risk increase: 0.7 per 1000 women treated for 1 year) but not overall mortality (HR: 0.92; 95% CI: 0.82–1.03; p=0.016).[119]

Strontium ranelate

RECOMMENDATION 26 (Grade A)

There is excellent evidence to support the effectiveness of strontium ranelate 2 g/day for reducing the risk of further osteoporotic fractures in postmenopausal women with prevalent fractures.

Research suggests that strontium ranelate simultaneously decreases bone resorption and stimulates bone formation both in vitro and in animal models.[95] In humans there is uncoupling of bone resorption and formation with increased serum levels of bone specific alkaline phosphatase (a marker of bone formation) and decreases in serum C-telopeptide cross links (a marker of bone resorption).[96]

Strontium ranelate is PBS listed for the treatment of women following a fragility or osteoporotic fracture and for the prevention of the first fracture in women aged 70 years or over with a T-score of <-3.0. In women with established OP, treatment with strontium ranelate is associated with improvements in BMD and reduction in risk of vertebral and non-vertebral fractures.[98]

Side effects and potential harms

Strontium ranelate has been associated with an increased risk of venous thromboembolism in some RCTs.[98]

Practical tips and precautions

- Strontium ranelate is not recommended for patients with severe renal impairment[98]
- In view of the increased risk of venous thromboembolism,[98] take caution using strontium ranelate in patients with a history of, or at increased risk of, venous thromboembolism[99]
- Because calcium supplements reduce absorption of strontium their administration should be separated by at least 2 hours[99]
- Strontium ranelate may form poorly soluble chelates with tetracyclines, reducing their absorption and anti-infective activity, so administration of these medications should be separated by at least 2 hours[99]
- The effect of strontium distribution in bone and increased X-ray absorption of strontium compared to calcium leads to an amplification of BMD measurement by DXA that should be considered when using DXA to monitor treatment response.[100] However, the greater increase in measured BMD is associated with efficacy in fracture risk reduction, possibly because it reflects compliance with therapy.

EVIDENCE STATEMENT

Treatment of osteoporosis

A Cochrane SR[98] reported on four RCTs (7093 participants) that compared effectiveness of strontium ranelate daily to placebo for treating OP. Participants were postmenopausal women with prevalent vertebral fractures and/or a lumbar spine BMD T-score of <-2.5. All RCTs investigated a daily dose of strontium ranelate 0.5–2.0 g concurrently with calcium and vitamin D supplementation for 2–5 years.[98]

Women with OP who were treated with strontium ranelate 2 g/day showed a 37% reduction in vertebral fractures (two RCTs, n=5082; RR: 0.63; 95% CI: 0.56–0.71; NNT 13) and a 14% reduction in non-vertebral fractures (two RCTs, n=6572; RR: 0.86; 95% CI: 0.75–0.98; NNT 10) over 3 years. Over 3 years strontium ranelate 2 g/day was associated with a significant increase in lumbar spine BMD (one RCT, n=1442; WMD: 8.09; 95% CI: 7.22–8.96), femoral neck BMD (two RCTs, n=4230; WMD: 8.25; 95% CI: 7.84–8.66; NNT 3), and total hip BMD (two RCTs, n=4230; WMD: 9.83; 95% CI: 9.39–10.26).[98]

Safety

The same Cochrane study[98] reported safety data from four RCTs. There were no significant differences compared to placebo for rate of adverse events, rate of withdrawal related to an adverse event, or rate of serious adverse events. Participants treated with strontium ranelate showed an increase in diarrhoea (RR: 1.38; 95% CI: 1.02–1.87). Data from two RCTs (n=6669) showed an increased risk of vascular system disorders including venous thromboembolism (2.2 vs. 1.5%; OR: 1.5; 95% CI: 1.1–2.1) and pulmonary embolism (0.8 vs. 4.5%; OR: 1.7; 95% CI: 1.0–3.1). Strontium ranelate was associated with an increased risk of headache (3.9 vs. 2.9%), seizures (0.3 vs. 0.1%), memory loss (2.4 vs. 1.9%) and disturbance in consciousness (2.5 vs. 2.0%).[98]

ONGOING MONITORING

RECOMMENDATION 27 (Grade B)

General practitioners should evaluate patients at increased risk for osteoporotic fractures who are not receiving specific preventive anti-osteoporotic therapy in regard to future fracture risk at intervals adequate to the risk in question. Bone mineral density measurement can identify some non-fragility causes of fracture (eg. T-score above -1.5). If a decision is made to not recommend specific preventive anti-osteoporotic therapy, this must be formally reviewed in relation to future fracture risk at intervals relevant to the risk in question. In most cases, BMD testing is restricted to 2 year intervals.

RECOMMENDATION 28 (Grade B)

General practitioners should provide regular monitoring and follow up of all patients with OP 3–6 months after initiating a specific pharmacological intervention and annually thereafter.

At present, there are no validated criteria for the failure of medical therapy. However, therapeutic failure may be assumed if:

- 'unexpected' fractures occur (usually more than one fracture event), in which case other non-pharmacological measures need to be implemented or reinforced as required
- a documented decrease in height of more than 2 cm since the last examination or acute back pain, which may be symptoms of a new fracture. In these cases a radiological examination is recommended.

Stable bone density (ie. a non-significant increase in bone density) during therapy with bisphosphonates or raloxifene, does not indicate decreased anti-fracture efficacy of the drug and is no indication to change treatment.[49,121–125] A stable or increasing BMD during treatment with most agents currently approved for OP therapy should be considered as adequate response to therapy.[49,121–125] In contrast, significant loss of BMD of more than 3–5% per year while on anti-resorptive treatment may be associated with negative clinical outcomes (increased fracture risk) and should prompt review of both diagnosis and treatment regimen.[126,127]

Biochemical markers of bone turnover decrease rapidly after initiation of anti-resorptive drugs such as bisphosphonates or raloxifene. They have also been shown to provide some prognostic information on the anti-fracture efficacy of these agents.[125,128–130] Therefore, bone turnover markers may be used at 3 and 12 months to assess the effect of alendronate, risedronate or raloxifene on bone metabolism.[125,128–130] Values of certain bone markers are expected to increase with teriparatide therapy, leading to some potential for confusion. However, the role of bone turnover markers in monitoring has not yet been fully investigated. In the absence of clear evidence of improved patient outcomes from their use and cost effectiveness data, their routine use in patient monitoring in general practice is not currently recommended.

Decisions about changing treatment are not supported by RCT data. As fractures will occur in some individuals even on effective therapy, fracture *per se* is not an indication to change. However, patient tolerance, compliance and side effect profile may suggest changing type or route of administration of therapy on an individual basis. Uncommonly, evidence of lack of response (eg. falling BMD or failure to achieve expected changes in bone turnover markers) could justify a change. However, compliance with, and correct mode of, taking medications should be evaluated first, as problems with one or other of these aspects is the most likely explanation.

Although long term compliance with non-pharmacological and pharmacological interventions is a principal goal of any OP therapy, it usually is low, even in patients with established fractures.[121,131,132]

Follow up visits, close contact between patient and health professionals as well as repeat BMD and/or bone marker measurements, may be used to reinforce compliance. In a British study, review of the results of serial BMD and/or bone marker measurements between nurse and patient, or doctor and patient, resulted in improved patient adherence and persistence.[133] However, currently there is no consensus on the use of surrogate parameters to increase patient compliance.

Practical tips and precautions

Usually a decrease in bone density greater than the measurement error is not seen before 2 years; hence, follow up bone densitometry is not recommended at intervals of less than 2 years[126,134]

- It is appropriate to recommend a repeat BMD by DXA after 2 years for patients at risk of developing OP, to assist in re-evaluation of fracture risk
- In patients with confirmed OP, repeat BMD is generally not required, however it may be conducted before initiating a change in, or cessation of, anti-osteoporotic therapy
- Wherever possible, perform repeat bone density tests on the same instrument or at least the same type (manufacturer and model type) of instrument, to improve comparability of results in interpreting any change in BMD[49]
- Changes of <3% at the lumbar spine and <1% at the hip are within the precision error of most DXA machines and therefore should be regarded as representing no significant change[49]
- A radiographic assessment should be initiated if new fractures are suspected (eg. if height loss of 2 cm or more, new or acute pain).

EVIDENCE STATEMENT

Three major international guidelines recommend follow up to ensure that treatment is effective. Regular monitoring is an important component of any OP treatment plan.[22,46,54] This applies to both patients with and without anti-osteoporotic drug treatment. Follow up bone density testing and physician check ups are also recommended.[22,46,49]

Patients with an increased risk in the initial examination should be re-evaluated in terms of the implementation of non-pharmacological measures, risk factors and the future development of fracture risk in intervals adequate to the risk in question. Because a decrease in bone density below the measurement error before a time of 2 years is unlikely, follow up examinations of bone density are usually not recommended in intervals of less than 2 years.[22] Repeated scans may be useful for addressing patients' concerns in relation to treatment adherence, but are more limited for monitoring response to treatment.[46] If carried out less than 2 years after commencing treatment the changes may be difficult to interpret unless the change is more than the 2.8 (coefficient of variation).

After initiating a specific pharmacological intervention clinical examinations are recommended after 3–6 months and after 6–12 months. This may include documenting pain, functionality, weight, and height.[22] Conduct ongoing monitoring of patients taking medication, particularly those taking bisphosphonates, to ensure compliance with administration instructions. Laboratory tests may be used to identify drug induced side effects or potentially treatable conditions contributing to the patient's skeletal disease.

SPECIAL ISSUES

Rural and remote issues

In general, there tends to be less utilisation of health services in rural and remote areas and poorer global health outcomes.[135] However, data specifically relating to the burden of OP in rural and remote areas compared to urban areas was not available.

The Working Group performed an analysis of bone densitometry claims processed by Medicare Australia between 2001 and 2005 for this guideline (*Table 3*). Age standardised densitometry claims have increased by 29% from 2001 to 2005, suggesting there is a growing awareness and activity for OP. A similar proportional increase is seen across urban, rural and remote areas; however the densitometry utilisation rates remain significantly lower in rural and remote areas. Women had BMD measurement seven times as often as men in 2001, decreasing to four times as often in 2005. This gender difference was more pronounced in rural and remote areas.[19] This analysis suggests there is a particular need to facilitate health service activity for the detection and management of OP in rural and remote areas. Important factors are likely to be access to primary health care (PHC) in rural areas, where PHC workforce issues are known to be a major issue,[136] as is access to densitometry services.

Table 3. Analysis of bone densitometry claims processed by Medicare Australia, 2001–2005

People aged 45+ years in 2005	Capital city	Other metropolitan centre	Large rural centre	Small rural centre	Other rural	Remote centre	Other remote
Men	7.6	7.0	6.9	6.1	4.6	1.8	2.3
Women	35.6	35.3	29.2	27.6	22.7	13.3	17.4
Ratio women/ men	4.5	5	4	4.5	5	7	7.5
Note: Tests per 1000 population per year. Direct age standardisation to 2001 gender specific population							

Gender

The analysis of bone densitometry utilisation also suggests there is relative underutilisation in men. Two Australian studies help to define the true gender difference in the prevalence of OP and the incidence of fragility fractures.[137,138] These studies suggest the true prevalence ratio F:M is around 2:1 compared to the range of ratios for densitometry utilisation of 4.5:1 to 7.5:1 seen in different settings in Australia in 2005 *(Table 3)*.

Aboriginal and Torres Strait Islander issues

Research on differences in the burden of OP in the indigenous population is very limited. A 2001 study from the Cairns Hospital in northern Queensland reported similar overall age standardised rates for fractured neck of femur in the indigenous compared to the non-indigenous population of that area, but with a pattern of older age at the time of fracture for indigenous women.[139]

Differing patterns of risk factors such as smoking, nutrition, exercise, underweight, and high alcohol consumption are likely to be important. The interaction of these factors, lower life expectancy, higher comorbidity rates, widely variable access to health services and socioeconomic factors, is hard to estimate.

Promotion of good nutrition and reduction of risk factors is very important for a wide range of health issues, not only OP.

It is anticipated that Aboriginal and Torres Strait Islander women and men will suffer at least the same, if not a greater, limitation to densitometry access as noted for other rural and remote living people. There is no reliable data on the incidence of osteoporotic fractures in Aboriginal people and Torres Strait Islanders. It is not known whether their recognised shorter life expectancy influences absolute fracture incidence.

Ethnic and minority groups

Osteoporosis is most common in caucasian people, followed by Asian and African Americans.[140] Therefore, there is an advantage in using normal ranges derived from ethnicity appropriate BMD T-scores. However, BMD data are lacking for Indigenous Australians. Some ethnic groups in Australia are at greater risk of vitamin D insufficiency (Asians, people with darker skin, and veiled women) and relatively low calcium intakes and both should be corrected before initiating anti-osteoporotic therapy.

Osteonecrosis of the jaw

Bisphosphonate associated ONJ is a relatively recently described entity. A confirmed case of bisphosphonate associated ONJ can be defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider and use of standard dental therapy, in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region.

The incidence of ONJ in patients receiving bisphosphonates for OP is not known, but appears to be relatively low.[141] Both USA pharmaceutical industry estimates of the worldwide, cumulative reporting rate and a recent German study of prevalence of ONJ are consistent at less than one in 100 000 patient treatment years. However, data from Australia and Israel suggest that the incidence could be up to 10-fold higher.[85] More information is needed on the true incidence of bisphosphonate associated ONJ as well as the major other risk factors for developing this complication, but poor dental hygiene, dental extraction and periodontal disease, as well as immunosuppressive therapy have been implicated.

Treatment is currently mainly supportive and involves local antibiotics to improve oral hygiene. Consideration should be given to avoiding invasive dental procedures such as dental extractions, and using more conservative techniques in patients on oral bisphosphonates and treating periodontal disease to minimise the risk of ONJ. The risk of ONJ is not great enough to recommend routine dental examinations in patients before commencing treatment with oral bisphosphonates for OP. However, there should be close communication between GPs and dentists when patients are receiving oral bisphosphonates.

References

1. Harris M, Harris E. Facing the challenges: general practice in 2020. Medical Journal of Australia 2006;185(2):122–25.
2. National Health Priority Action Council. National chronic disease strategy. Canberra: Australian Government Department of Health and Ageing, 2006.
3. Access Economics. The burden of brittle bones: costing osteoporosis in Australia. Canberra: Access Economics Pty Ltd, 2001.
4. National Arthritis and Musculoskeletal Conditions Advisory Group (NAMSCAG). Evidence to support the national action plan for osteoarthritis, rheumatoid arthritis and osteoporosis: Opportunities to improve health–related quality of life and reduce the burden of disease and disability. Canberra: Australian Government Department of Health and Ageing, 2004.
5. Eisman J, Clapham S, Kehoe L. Osteoporosis prevalence and levels of treatment in primary care: The Australian Bone Care Study. Journal of Bone and Mineral Research 2004;19(12):1969–75.
6. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO Study Group. Geneva: WHO, 1994 (Technical Report Series 843). Journal of the American Medical Association 2001;285:785–95.
7. Osteoporosis Australia. Osteoporosis – diagnosis. 2007 [updated 2007; cited 2009 Jan]. Available at www.osteoporosis.org.au/osteo_diagnosis.php.
8. Sambrook P, Cameron D, Chen J, et al. Influence of fall related factors and bone strength on fracture risk in the frail elderly. Osteoporosis International 2007;18(5):603–10.
9. Ismail AA, Cooper C, Felsenberg D, et al. Number and type of vertebral deformities: epidemiological characteristics and relation to back pain and height loss. Osteoporosis International 1999;9:206–13.
10. Nguyen T, Center J, Sambrook P, et al. Risk factors for proximal humerus, forearm and wrist fractures in elderly men and women: The Dubbo Osteoporosis Epidemiology Study. American Journal of Epidemiology 2001;153(6):587–95.
11. Woolf A, Pfleger B. Burden of major musculoskeletal conditions. Bulletin of the World Health Organisation 2003;81(9):646–56.
12. Cooley H, Jones G. A population–based study of fracture incidence in southern Tasmania: lifetime fracture risk and evidence for geographic variations within the same country. Osteoporosis International 2001;12(2):124–30.
13. Jones G, Nguyen T, Sambrook P, et al. Symptomatic fracture incidence in elderly men and women: The Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporosis International 1994;4(5):277–82.
14. Sanders K, Seeman E, Ugoni A, et al. Age- and gender-specific rate of fractures in Australia: a population-based study. Osteoporosis International 1999;10(3):240–47.
15. Nguyen T, Center J, Eisman J. Osteoporosis: underrated, underdiagnosed and undertreated. Medical Journal of Australia 2004;180(5 Suppl):S18–22.
16. Henry M, Pasco J, Nicholson G, et al. Prevalence of osteoporosis in Australian women: Geelong Osteoporosis Study. Journal of Clinical Densitometry 2000;3(3):261–68.
17. Australian Bureau of Statistics. National Health Survey 2001. Canberra: ABS, 2002. Report No.: ABS Cat. No. 4364.0.
18. Australian Bureau of Statistics. Occasional paper: long-term health conditions – a guide to time series comparability from the national health survey, Australia. Selected long-term health conditions – time series assessment: osteoporosis. Canberra: ABS, published online 4 June 2003.
19. Ewald DP, Eisman JA, Ewald BD, et al. Population rates of bone densitometry use in Australia, 2001–2005, by sex and rural versus urban location. Medical Journal of Australia 2009;190(3):126–8.
20. Mackey D, Li-Yung Lui L, Cawthon P, et al. High-trauma fractures and low bone mineral density in older women and men. Journal of the American Medical Association 2007;298(20):2381–88.
21. Australian Institute of Health and Welfare. A picture of osteoporosis in Australia. Arthritis series no. 6. Cat. No. PHE 99. Canberra: AIHW, 2008.
22. Pfeilschifter J. 2006 DVO-guideline for prevention, diagnosis, and therapy of osteoporosis for women after menopause, for men after age 60 executive summary guidelines. Experimental and Clinical Endocrinology and Diabetes 2006;114(10):611–20.
23. Pfeilschifter J. Dachverband der deutschsprachigen wissenschaftlichen Gesellschaften fur Osteologie (DVO) e.V. Evidenzbasierte Konsesus - Leitlinie zur Osteoporose. Prophylaxe, Diagnostik und Therapie bei Frauen ab der Menopause, bei Mannern ab dem 60. Lebensjahr. (In German). Stuttgart, Germany: DVO, 2006.
24. Nguyen ND, Frost SA, Center JR, et al. Development of a nomogram for individualising hip fracture risk in men and women. Osteoporosis International 2007;18(8):1109–17.
25. Nguyen ND, Frost SA, Center JR, et al. Development of prognostic nomograms for individualizing 5–year and 10–year fracture risks. Osteoporosis International 2008;19:1431–44.
26. Brecher L, Pomerantz S, Snyder B, et al. Osteoporosis prevention project: a model of multi-disciplinary educational intervention. Journal of the American Osteopathic Association 2002;102(6):327–35.
27. Diamond T, Lindenburg M. Osteoporosis detection in the community. Are patients adequately managed? Australian Family Physician 2002;31(8):751–52.
28. Cooper C, Melton L. Vertebral fractures, how large is the silent epidemic? British Medical Journal 1992;304:793–94.

29. O'Neill TW, Felsenberg D, Varlow J, et al. The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. Journal of Bone and Mineral Research 1996;11(7):1010–8.
30. Australian Government Department of Health and Ageing. Evidence to support the national action plan for osteoarthritis, rheumatoid arthritis and osteoporosis. Canberra: DoHA, 2004.
31. Chang K, Center J, Nguyen T, et al. Incidence of hip and other osteoporotic fractures in elderly men and women: Dubbo Osteoporosis Epidemiology Study. Journal of Bone and Mineral Research 2004;19(4):532–36.
32. Kannus P, Niemi S, Parkkari J, et al. Nationwide decline in incidence of hip fracture. Journal of Bone and Mineral Research 2006;21(12):1836–38.
33. Zingmond D, Melton L, Silverman S. Increasing hip fracture incidence in California Hispanics, 1983 to 2000. Osteoporosis International 2004;15(8):603–10.
34. Sambrook P, Cooper C. Osteoporosis. The Lancet 2006;367(9527):2010–18.
35. Center J, Nguyen T, Schneider D, et al. Mortality after all major types of osteoporotic fracture in men and women: an observational study. The Lancet 1999;353(9156):878–82.
36. Black D, Delmas P, Eastell R, et al. HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. New England Journal of Medicine 2007;356:1809–22.
37. National Institute of Clinical Studies (NICS). Evidence practice gaps report. Melbourne: NICS, 2005.
38. Wong P, Spencer D, McElduff P, et al. Secondary screening for osteoporosis in patients admitted with minimal-trauma fracture to a major teaching hospital. Internal Medicine Journal 2003;33(11):505–10.
39. Fisher A, Davis M, Budge M. The management of osteoporosis following hip fracture: how to improve our care. Osteoporosis International 2004;15(7):583–84.
40. Jones G, Warr S, Francis E, et al. The effect of a fracture protocol on hospital prescriptions after minimal trauma fractured neck of the femur: a retrospective audit. Osteoporosis International 2005;16(10):1277–80.
41. Richardson J, Hassell A, Thomas E, et al. GPs' perceptions of the role of DXA scanning: an exploratory study. Family Practice 2004;21(1):51–3.
42. Grol R, Baker R, Moss F. Quality improvement research: understanding the science of change in health care. London: BMJ Publishing Group, 2004.
43. Ross P, Davis J, Epstein R, et al. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Annals of Internal Medicine 1991;114(11):919–23.
44. Cummings S. Treatable and untreatable risk factors for hip fracture. Bone 1996;18(3 Suppl):165S–7S.
45. Cummings S, Nevitt M, Browner W, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. New England Journal of Medicine 1995;332(12):767–73.
46. Scottish Intercollegiate Guidelines Network. Management of osteoporosis. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network, 2003.
47. Brown J, Josse R. Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. Canadian Medical Association Journal 2002;167(10 Suppl):S1–34.
48. Qaseem A, Snow V, Shekelle P, et al. Screening for osteoporosis in men: a clinical practice guideline from the American College of Physicians. Annals of Internal Medicine 2008;148(9):680–701.
49. Cummings S, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry. Misleading changes and regression to the mean. Journal of the American Medical Association 2000;283(10):1318–21.
50. Leslie WD, Lix LM, Tsang JF, et al. Single-site vs multisite bone density measurement for fracture prediction. Archives Internal Medicine 2007;167:1641–7.
51. Maggio D, McCloskey EV, Camilli L, et al. Short-term reproducibility of proximal femur bone mineral density in the elderly. Calcified Tissue International 1998;63(4):296–9.
52. Pfeilschifter J. 2006 DVO-guideline for prevention, diagnosis, and therapy of osteoporosis for women after menopause, for men after age 60 executive summary guidelines. Table 1: recommendations for diagnostic assessment. Experimental and Clinical Endocrinology and Diabetes 2006;114(10):611–20.
53. Marin F, Gonzales-Macias J, Diez-Perez A, et al. Relationship between bone quantitative ultrasound and fractures: a meta-analysis. J Bone Miner Research 2006;21(7):1126–35.
54. American Association of Clinical Endocrinologists Osteoporosis Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocrine Practice 2003;9(6):544–64.
55. Osteoporosis Australia. Preventing osteoporosis – calcium. 2007 [updated 2007; cited 2009 Jan]. Available at www.osteoporosis.org.au/osteo_prevention_calcium.php.
56. National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Washington (DC): National Osteoporosis Foundation, 2003.
57. Australian Government Department of Health and Ageing and National Health and Medical Research Council. Nutrient reference values for Australia and New Zealand: Executive summary. Canberra: DoHA, 2006.
58. O'Neill S, Sambrook P, Diamond T, et al. Guidelines for the treatment of postmenopausal osteoporosis for general practitioners. Australian Family Physician 2002;31(10):1–8.

59. Osteoporosis Australia. Preventing osteoporosis – vitamin D. 2007 [updated 2007; cited 2009 Jan]. Available at www.osteoporosis.org.au/osteo_prevention_vitamind.php.

60. The Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, The Australasian College of Dermatologists, et al. Risks and benefits of sun exposure: Position statement. Canberra, 2007.

61. Osteoporosis Australia. Osteoporosis risk factors. 2007 [updated 2007; cited 2009 Jan]. Available at www.osteoporosis.org.au/osteo_riskfactors.php.

62. The Royal Australian College of General Practitioners National Standing Committee - Quality Care. Smoking, Nutrition, Alcohol and Physical activity (SNAP). A population health guide to behavioural risk factors in general practice. South Melbourne: The RACGP, 2004.

63. The Royal Australian College of General Practitioners. Putting prevention into practice. Guidelines for the implementation of prevention in the general practice setting. 2nd edn. South Melbourne: The RACGP, 2006.

64. Osteoporosis Australia. About Osteoporosis Australia. 2007 [updated 2007; cited 2009 Jun]. Available at www.osteoporosis.org.au/about_oa.php.

65. American Geriatric Society, British Geriatrics Society, American Academy of Orthopaedic Surgeons. Guideline for the prevention of falls in older persons. Journal of the American Geriatrics Society 2001;49(5):664–72.

66. Gillespie L, Gillespie W, Robertson M, et al. Interventions for preventing falls in elderly people. Cochrane Database of Systematic Reviews 2003; Issue 4:Art. No.: CD000340. DOI: 10.1002/14651858.CD000340.

67. Clemson L, Cumming R, Kendig H, et al. The effectiveness of a community-based program for reducing the incidence of falls in the elderly: a randomised trial. Journal of the American Geriatrics Society 2004;52(9):1487–94.

68. Liu-Ambrose T, Khan K, Eng J, et al. The beneficial effects of group-based exercises on fall risk profile and physical activity persist 1 year post-intervention in older women with low bone mass: follow-up after withdrawal of exercise. Journal of the American Geriatrics Society 2005;53(10):1767–73.

69. Pfeilschifter J, German Specialist Organisation for Osteology. 2006 DVO-guideline for prevention, diagnosis, and therapy of osteoporosis for women after menopause, for men after age 60 executive summary guidelines. Table 2: Laboratory tests. Experimental and Clinical Endocrinology and Diabetes 2006;114(10):611–22.

70. Birks Y, Porthouse J, Addie C, et al. Randomised controlled trial of hip protectors among women living in the community. Osteoporosis International 2004;15(9):701–06.

71. Parker M, Gillespie W, Gillespie L. Hip protectors for preventing hip fractures in older people. Cochrane Database of Systematic Reviews 2005; Issue 3. Art. No.: CD001255. DOI: 10.1002/14651858.CD001255.pub3.

72. Papaioannou A, Adachi J, Winegard K, et al. Efficacy of home-based exercise for improving quality of life among elderly women with symptomatic osteoporosis–related vertebral fractures. Osteoporosis International 2003;14(8):677–82.

73. Osteoporosis Australia. Preventing osteoporosis – exercise. 2007 [updated 2007; cited 2009 Jun]. Available at www.osteoporosis.org.au/osteo_prevention_exercise.php#weight.

74. Bonaiuti D, Shea B, Iovine R, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database of Systematic Reviews 2002; Issue 2:Art. No.: CD000333. DOI: 10.1002/14651858.CD000333.

75. Bolland M, Mason B, Horne A, et al. Calcium supplementation improves lipid profile but does not decrease the incidence of cardiovascular events in postmenopausal women. British Medical Journal 2008;336:262–66.

76. Bischoff-Ferrari H, Dawson-Hughes B, Baron J, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomised controlled trials. American Journal of Clinical Nutrition 2007;86(6):1780–90.

77. Boonen S, Lips P, Bouillon R, et al. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative meta-analysis of randomised controlled trials. Journal of Clinical Endocrinology and Metabolism 2007;92(4):1415–23.

78. Tang B, Eslick G, Nowson C, et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. The Lancet 2007;370(9588):632–34.

79. Avenell A, Gillespie W, Gillespie L, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database of Systematic Reviews 2006; Issue 4:Art. No.: CD000227. DOI: 10.1002/14651858.CD000227.pub2.

80. Dunstan C, Felsenberg D, Seibel M. Therapy insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. Nature Clinical Practice Oncology 2007;4(1):42–55.

81. Ringe JD, Farahmand P, Faber H, et al. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. Rheumatol Int 2009;29(3):311–5.

82. Reid DM, Devogelaer JP, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. The Lancet 2009;373(9671):1253–63.

83. Gonnelli S, Cepollaro C, Montagnani A, et al. Alendronate treatment in men with primary osteoporosis: a three-year longitudinal study. Calcif Tissue Int 2003;73(2):133–9.

84. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Annals of Internal Medicine 2008;148(3):197–213.

85. Sambrook P, Olver I, Goss A. Bisphosphonates and osteonecrosis of the jaw. Australian Family Physician 2006;35(10):801–03.

86. Cranney A, Guyatt G, Griffith L, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IX. Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocrine Reviews 2002;23(4):570–78.

87. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocrine Reviews 2002;23(4):508–16.

88. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008; Issue 1:Art. No.: CD004523. DOI: 10.1002/14651858.CD004523.pub3.

89. Black D, Schwartz A, Ensrud K, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomised trial. Journal of the American Medical Association 2006;296(24):2927–38.

90. Anderson G, Limacher M, Assaf A, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomised controlled trial. Journal of the American Medical Association 2004;291(14):1701–12.

91. Cummings S, Ettinger B, Delmas P, et al. The effects of tibolone in older postmenopausal women. New England Journal of Medicine 2008;359:697–708.

92. Rossouw J, Anderson G, Prentice R, et al. Risks and benefits of oestrogen plus progestin in healthy postmenopausal women. Journal of the American Medical Association 2002;288(3):321–30.

93. Wells G, Tugwell P, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocrine Reviews 2002;23(4):529–39.

94. Meier C, Nguyen T, Handelsman D, et al. Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. Archives of Internal Medicine 2008;168(1):47–54.

95. Marie P. Strontium ranelate: a dual mode of action rebalancing bone turnover in favour of bone formation. Current Opinion in Rheumatology 2006;18(Suppl 1):S11–5.

96. Meunier P, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. New England Journal of Medicine 2004;350:459–68.

97. Reginster J. Strontium ranelate in osteoporosis. Current Pharmaceutical Design 2002;8(21):1907–16.

98. O'Donnell S, Cranney A, Wells G, et al. Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database of Systematic Reviews 2006; Issue 4:Art. No.: CD005326. DOI: 10.1002/14651858.CD005326.pub3.

99. Rossi S, editor. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2006.

100. Ortolani S, Vai S. Strontium ranelate: an increased bone quality leading to vertebral antifracture efficacy at all stages. Bone 2006;38(2 Supp 1):19–22.

101. Reginster JY, Deroisy R, Dougados M, et al. Prevention of early postmenopausal bone loss by strontium ranelate: the randomized, two-year, double-masked, dose-ranging, placebo-controlled PREVOS trial. Osteoporosis International 2002;13(12):925–31.

102. Korpelainen R, Keinänen-Kiukaanniemi S, Heikkinen J, et al. Effect of impact exercise on bone mineral density in elderly women with low BMD: a population-based randomised controlled 30–month intervention. Osteoporosis International 2006;17(1):109–18.

103. Villareal D, Steger-May K, Schechtman K, et al. Effects of exercise training on bone mineral density in frail older women and men: a randomised controlled trial. Age and Ageing 2004;33(3):309–12.

104. Adami S, Giannini S, Bianchi G, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporosis International 2009;20(2):239–44.

105. Grant A, Avenell A, Campbell M, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. The Lancet 2005;365(9471):1621–28.

106. Lyles K, Colón-Emeric C, Magaziner J, et al. HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. New England Journal of Medicine 2007;357(18):1799–809.

107. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. New England Journal of Medicine 2000;343(9):604–10.

108. Dempster D, Cosman F, Parisien M, et al. Anabolic actions of parathyroid hormone on bone. Endocrine Reviews 1993;14(6):690–709.

109. Cranney A, Papaioannou A, Zytaruk N, et al. Parathyroid hormone for the treatment of osteoporosis: a systematic review. Canadian Medical Association Journal 2006;175(1):52–9.

110. Neer R, Arnaud C, Zanchetta J, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. New England Journal of Medicine 2001;344(19):1434–41.

111. Kurland E, Cosman F, McMahon D, et al. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. Journal of Clinical Epidemiology and Metabolism 2000;85(9):3069–76.

112. Orwoll E, Scheele W, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. Journal of Bone and Mineral Research 2003;18(1):9–17.

113. Miller P, Bilezikian J, Deal C, et al. Clinical use of teriparatide in the real world: initial insights. Endocrine Practice 2004;10(2):139–48.

114. Black D, Bilezikian J, Ensrud K, et al. One year of alendronate after one year of parathyroid hormone (1–84) for osteoporosis. New England Journal of Medicine 2005;353:555–65.

115. Delmas P, Ensrud K, Adachi J, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomised clinical trial. Journal of Clinical Endocrinology and Metabolism 2002;87(8):3609–17 reported in Pfeilschifter et al, 2006 (DVO).

116. Cummings S, Eckert S, Krueger K, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomised trial. Journal of the American Medical Association 1999;281(23):2189–97.

117. Delmas P, Genant H, Crans G, et al. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and non-vertebral fractures: results from the MORE trial. Bone 2003;33:522–32.

118. Siris E, Harris S, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. Journal of Bone and Mineral Research 2005;20(9):1514–24.

119. Barrett-Connor E, Mosca L, Collins P, et al. Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. New England Journal of Medicine 2006;355:125–37.

120. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocrine Reviews 2002;23(4):524–28 reported in Pfeilschifter et al, 2006 (DVO).

121. Caro J, Ishak K, Huybrechts K, et al. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporosis International 2004;15(12):1003–08.

122. Cummings S, Karpf D, Harris F, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. American Journal of Medicine 2002;112(4):281–89.

123. Delmas P, Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. Bone 2004;34(4):599–604.

124. Li Z, Chines A, Meredith M. Statistical validation of surrogate endpoints: is bone density a valid surrogate for fracture? Journal of Musculoskeletal and Neuronal Interactions 2004;4(1):64–74.

125. Sarkar S, Reginster J, Crans G, et al. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. Journal of Bone and Mineral Research 2004;19(3):394–401.

126. Melton L, Atkinson E, O'Connor M, et al. Determinants of bone loss from the femoral neck in women of different ages. Journal of Bone and Mineral Research 2000;15(1):24–31.

127. Pouilles J, Tremollieres F, Ribot C. Variability of vertebral and femoral postmenopausal bone loss: a longitudinal study. Osteoporosis International 1996;6(4):320–24.

128. Bjarnason N, Sarkar S, Duong T, et al. Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal women. Osteoporosis International 2001;12(11):922–30.

129. Reginster J, Sarkar S, Zegels B, et al. Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. Bone 2004;34(2):344–51.

130. Watts N, Cooper C, Lindsay R, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. Journal of Clinical Densitometry 2004;7(3):255–61.

131. Mayoux-Benhamou M, Roux C, Perraud A, et al. Predictors of compliance with a home-based exercise program added to usual medical care in preventing postmenopausal osteoporosis: an 18-month prospective study. Osteoporosis International 2005;16(3):325–31.

132. McCombs J, Thiebaud P, McLaughlin-Miley C, et al. Compliance with drug therapies for the treatment and prevention of osteoporosis. Maturitas 2004;48(3):271–87.

133. Clowes J, Peel N, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomised controlled trial. Journal of Clinical Epidemiology and Metabolism 2004;89(3):1117–23.

134. Abrahamsen B, Nissen N, Hermann A, et al. When should densitometry be repeated in healthy peri- and postmenopausal women: the Danish Osteoporosis Prevention Study. Journal of Bone and Mineral Research 2002;17(11):2061–67.

135. Australian Institute of Health and Welfare (AIHW). Rural, regional and remote health - indicators of health. Canberra: AIHW, 2005. Report No.: AIHW Catalogue Number PHE 59.

136. Australian Institute of Health and Welfare. Medical labour force 2004: National health labour force series number 38. Canberra: AIHW 2006. Report No.: Catalogue Number HWL 39.

137. Eisman J, Clapham S, Kehoe L. Osteoporosis prevalence and levels of treatment in primary care: the Australian Bone Care Study. Journal Bone Mineral Research 2004;19(12):1969–75.

138. Jones G, Nguyen T, Sambrook PN, et al. Symptomatic fracture incidence in elderly men and women: The Dubbo osteoporosis epidemiology study (DOES). Osteoporosis International 1994;4(5):277–82.

139. MacIntosh DJ, Pearson B. Fractures of the femoral neck in Australian Aboriginals and Torres Strait Islanders. Aust J Rural Health 2001;9(3):127–33.

140. Finkelstein J, Lee M, Sowers M, et al. Ethnic variation in bone density in premenopausal and early perimenopausal women: effects of anthropometric and lifestyle factors. Journal of Clinical Epidemiology and Metabolism 2002;87(7):3057–67.

141. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. Journal of Bone and Mineral Research 2007;22(10):1479–91.

142. AGREE Collaboration. Appraisal of guidelines for research & evaluation (AGREE) instrument. AGREE; 2001 [updated 2001; cited 2006 Nov]. Available at www.agreecollaboration.org.

143. International Osteoporosis Foundation. National & Regional Osteoporosis Guidelines. Unknown [updated unknown; cited 2008]. Available at www.iofbonehealth.org/health-professionals/national-regional-guidelines.html#agree_results.

144. Compston J. Prevention and treatment of osteoporosis. Clinical guidelines and new evidence. Journal of the Royal College of Physicians of London 2000;34(6):518–21.

145. Scottish Intercollegiate Guidelines Network (SIGN). A guideline developer's handbook. Edinburgh, Scotland: SIGN, 2006.

146. Oxford Centre for Evidence-based Medicine. Levels of evidence. Oxford, UK: Oxford Centre for Evidence-based Medicine, 2001.

147. Coleman K, Norris S, Weston A, et al. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2005.

148. Robinson K, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. International Journal of Epidemiology 2002;31:150–53.

APPENDIX A. PROCESS REPORT

This report outlines the process used for the development of the evidence based *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men.*

The project consisted of the following major phases:

- formation of a multidisciplinary expert working group
- development of a scoping document outlining the objectives of the project, including the process to be used in guideline development
- identification and appraisal of relevant existing clinical guidelines, leading to the selection of an existing guideline for use as a primary reference
- systematic literature searches to identify more recent evidence synthesis of new evidence and evidence from the primary reference guideline into graded clinical recommendations and algorithms
- peer review and appraisal through a public consultation process
- response to feedback and completion of final guideline.

Identification, appraisal and selection of existing clinical guidelines

In order to facilitate the most rapid preparation of the guideline due to time constraints (the Working Group was initially given 6 months for the project), the Working Group decided to use an existing guideline as a starting point. This was approved by the NHMRC GAR consultant before proceeding.

Relevant existing guidelines were identified by the Working Group in February 2006. These guidelines were most appropriate in terms of context and were also referred to in *Evidence to support the National Action Plan for Osteoarthritis, Rheumatoid Arthritis and Osteoporosis.*[30] Four guidelines were appraised using the Appraisal of Guidelines for Research and Evaluation (AGREE instrument).[142] The Scottish Intercollegiate Guidelines Network (SIGN 2003)[46] and *DVO*[22] percent scores were used from the International Osteoporosis Foundation website.[143]

Developers of the AGREE tool (www.agreecollaboration.org) propose its use to assess '…the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice'.[142] The AGREE tool includes 21 questions organised into six quality domains: scope and purpose; stakeholder involvement; rigour of development; clarity and presentation; applicability; and editorial independence. Each question is scored on a 4-point Likert scale (strongly agree, agree, disagree and strongly disagree) and the scores from multiple reviewers are used to calculate an overall quality percentage for each domain.

The six appraised guidelines are listed below. The results are presented in *Table 1*.

- Scottish Intercollegiate Guidelines Network (SIGN 2003)[46]
- Canadian Medical Association (2004)[47]
- Dachverband Osteologie (DVO)[22,23] – covering the relevant societies of Germany, Austria, Switzerland (original version January 2006 and the version published in May 2006)
- The Royal College of Physicians and Bone and Tooth Society of Great Britain (UK 2000)[144]
- National Osteoporosis Foundation (USA 2003)[56]
- Guidelines for the treatment of postmenopausal osteoporosis for general practitioners (the RACGP 2002).[58]

Table 1. AGREE scores for identified guidelines

(Shaded guideline was selected as a primary source)

AGREE domain	% rating of guidelines					
	SIGN	CMA	DVO	RCP	NOF	OP/ RACGP
Scope and purpose						
Overall objective(s) Clinical question(s) Target patient population	81	100	97	89	83	72
Stakeholder involvement						
Development group representative Patient views and preferences	58	63	69	58	69	29
Rigour of development						
Systematic evidence search Selection of evidence explicit Formulation of recommendations explicit Benefits, side effects, and risks described Explicit link between evidence and recommendations External review Procedure for updating guideline	57	79	90	67	68	17
Clarity and presentation						
Specific and unambiguous recommendations Different treatment options Key recommendations easily identified	56	80	98	92	69	54
Applicability						
End users of guideline stated Barriers to implementation are discussed Cost implications are discussed Tools for application Review/monitoring criteria defined Pilot testing	76	63	64	56	50	11
Editorial independence						
Editorial independence from funding body Conflicts of interest are stated	56	67	96	67	80	33

The guideline selected by the Working Group for use as the primary source of evidence was the *2006 German Dachverband Osteologie* (*DVO*) guideline.[23] This guideline presented a comprehensive review of pharmacological and non-pharmacological management of OP relevant to the Australian health care context; it was based on a systematic literature search until February 2005 and an interdisciplinary internal and external consensus process.[22] The DVO guideline was also the most recently published, having been released initially for peer review in January 2006 and then in final form in May 2006 (including an Executive Summary in English).[22]

Identification of the guideline focus

The Working Group reached consensus opinion on the primary focus of the guideline through discussion of areas considered most important for the primary audience (Australian GPs and their patients) and with consideration to the feasibility of completing the guideline within the prescribed timeframe and budget. Clinical questions relevant to the area of guideline focus were developed to focus the search for relevant literature.

Identification, appraisal and synthesis of new evidence

The evidence from the *DVO* guideline used two systems for the assignment of levels of evidence and deduction of the grades of recommendations (A to D). Treatment follows the SIGN criteria,[145] while the diagnostic assessment follows the Oxford criteria.[146]

The evidence from the *DVO* guideline was supplemented by several literature reviews. These reviews included areas not specifically addressed by the *DVO* guideline and with information from some additional key papers considered of special importance up to the finalisation of the guideline.

Using both the evidence contained in the *DVO* guidelines and from the subsequent literature reviews, the current guideline was constructed to address the specific Australian conditions and needs. The recommendations have been allocated a grading in accordance with the NHMRC's Pilot Program 2005–2006.[147] In areas where the 2004–2006 SR of RCTs or similar high quality evidence was not available, expert opinion was provided by the Working Group. This process ensured that the guidelines are based on the most up to date evidence available for Australia.

The group conducted three types of literature searches:

1. A Working Group member performed a 'personal search' yielding approximately 30 references. The search included literature published until June 2004.
2. A search (main search) was conducted for the period 1 June 2004 to 26 September 2006. This search was completed before the group finalising the full scope of the guideline. This has resulted in some areas of prevention in particular being based on ad hoc articles and/or group consensus.

   The initial search identified approximately 2500 papers which would potentially meet the review inclusion criteria. Working Group members independently reviewed the titles and abstracts and selected studies for retrieval and critical appraisal. After critical appraisal, 14 SRs and 20 RCTs were selected for inclusion in the literature review (*Table 2*). Main reasons for rejection were papers not directly relevant to the review, RCTs that were presented in SRs selected for inclusion, studies on interventions unavailable in Australia, and papers that did not add to the body of available evidence. Papers rejected for inclusion during the critical appraisal process are documented in Appendix 5 in *Osteoporosis: A literature review of recent evidence in postmenopausal women and older men.*
3. Ad hoc searches conducted by group members. These were specific searches to identify key references (sometimes outside the literature search timelines) and new papers on therapy (usually RCTs or MAs) of which members of the Working Group were aware. Some of these were sourced to deal with requests arising during the expert review process. The additional references are few in number but important, and were included to help keep the guideline current.

For the main search (June 2004 to September 2006), the following electronic bibliographical databases were searched: Ovid MEDLINE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, and NHS Economic Evaluation Database (Economic Evaluations).

Table 2. Number and type of studies included in literature review

Intervention	Systematic reviews	RCTs
Calcium and vitamin D	4	1
Hormone therapy	2	3
SERMs	1	4
Bisphosphonates	3	4
Parathyroid hormone	1	2
Strontium renelate	1	1
Exercise	1	3
Falls reduction	1	2
Total	14	20

Search strategy

For each intervention in the main search, a specific key word selection was used for the search strategy, as given in *Table 3*, combined with the following other search strategy components and limits:

- the revised Dickersin filter for RCTs[148] adapted to include SRs
- Osteoporo* [tw] OR bone density [mh] OR ('bone loss' [tw]) OR ('bone density' [tw]) OR ('bone mass' [tw]) OR bmd [tw] OR 'fractures, bone'[MeSH] OR fracture* [tw]
- limits of: middle aged + aged: 45+ years, English.

Table 3. Key word selection for search strategy

Intervention	Key words
Calcium and vitamin D and metabolites	'Calcium'[MeSH] OR 'calcium, dietary'[MeSH] OR calcium [tw] OR dairy [tw] OR milk [tw] OR dairy products [mh]OR dietary supplements [mh]
	Vitamin D [mh] OR ('vitamin D' [tw]) OR calcitriol [mh] OR calcitriol [tw] OR 1-hydroxycholecalciferol [substance name] OR alfacalcidol [tw] OR alphacalcidol [tw]
Physical activity	Exercise [mh] OR physical fitness [mh] OR sports [mh] OR exercise* [tw] OR ('physical activity' [tw]) OR ('physical activities' [tw]) OR exercise therapy [mh] OR exercis* [tw] OR ('physical fitness' [tw]) OR sport* [tw] OR ('physical education' [tw]) OR ('keep fit' [tw])
Falls prevention	Accidental falls [mh] OR ((fall OR falls OR faller* OR stumble* OR trip OR tripped OR trips OR slip*) [tw])
HT and SERMs	'Hormone replacement therapy'[MH] OR ('hormone replacement therapy' [tw]) OR hrt [tw] OR ('hormone therapy' [tw])
Bisphosphonates	raloxifene [mh] OR raloxifene [tw] OR selective estrogen receptor modulators [mh] OR ('selective estrogen receptor modulators' [tw]) OR SERM [tw]
Parathyroid hormone	'Diphosphonates'[MeSH]OR bisphosphonate* [tw] OR alendronate [mh] OR alendronat* [tw] OR risedronic acid [substance name] OR risedron* [tw] OR ibandronic acid [substance name] OR ibandron* [tw] OR etidronate [mh] OR etidron* [tw] OR zoledron* [tw] OR zoledronic acid [substance name]
Strontium ranelate	'Parathyroid hormone'[MeSH] OR ('parathyroid hormone' [tw]) OR ('teriparatide' [tw]) OR 'anabolic agents'[MeSH] OR ('anabolic therapies' [tw])
Total	'strontium ranelate'[substance name] OR strontium [tw] OR protelos [tw]

The above search strategy was not designed to specifically address the area of diagnosis of OR.

Inclusion/exclusion criteria

For each individual intervention, the references identified by the main search were assessed independently by two Working Group members against the following exclusion criteria:

- not RCT or SR
- not correct intervention
- not postmenopausal women or men aged over 50 years
- no fracture or BMD outcome
- concurrent condition affecting bone metabolism
- duplicate reference or data
- multiple reasons of the above (bisphosphonates).

Differences were resolved by consensus. The data in the included studies was then assessed by the Working Group members assigned to each intervention so that any relevant new data was used in drafting guideline recommendations for each intervention.

The above inclusion and exclusion criteria were not applied to the ad hoc searches or for personal searches.

Types of studies

Restricted to RCTs and SRs; however, some cohort trials and observational studies for diagnostic evidence have also been used to support the recommendations (*Table 4*).

Types of participants

The guideline is based on a SR of the evidence and constitutes Australian best practice approach to identifying, diagnosing, treating and managing OP in the following target populations:

- Postmenopausal women and older men who may be at risk of developing OP
- Postmenopausal women and men aged over 60 years diagnosed as having at least one fracture following minimal trauma (equivalent to a fall from standing height or less)
- Postmenopausal women and men aged over 50 years who have been diagnosed with OP defined as a T-score of -2.5 or less, but without evidence of a minimal trauma fracture. (The Australian Pharmaceutical Benefits Scheme currently applies a threshold of T-score of -3.0 for access to PBS subsidised therapies in this population.)

The following populations are beyond the scope of the guideline:

- individuals receiving prolonged (more than 3 months) oral corticosteroid therapy
- individuals with secondary causes of OP, including but not limited to, coeliac disease, chronic liver disease, chronic renal failure, hyperparathyroidism, hypercortisolism, hyperthyroidism, and transplant recipients
- individuals with compromised physical function resulting from factors such as rheumatoid arthritis, neurological conditions or spinal paralysis from various causes
- women with untreated hypogonadism, including postmenopause, primary hypogonadism, premature menopause, secondary amenorrhea (eg. following anorexia nervosa or associated with extreme levels of exercise or certain forms of oral contraceptives) and early hysterectomy
- men with primary or secondary hypogonadism.

These populations are recognised as important, and some of the recommendations may be considered relevant. However, due to the limited resources for this project, literature specifically related to these populations was excluded from critical appraisal.

Types of interventions

Interventions that were eligible for inclusion were:

- Calcium and vitamin D
- SERMs
- HT

- Bisphosphonates
- Parathyroid hormone
- Strontium ranelate
- Falls prevention
- Physical activity.

Table 4. NHMRC levels of evidence for intervention studies

Level of evidence	Description
I	Evidence obtained from a SR of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed RCT
III–1	Evidence obtained from well designed, pseudo randomised controlled trials (alternate allocation or some other method)
III–2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group
III–3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test

Critical appraisal

Originally a member of the Working Group reviewed each article, but documentation of the appraisal and scores achieved was not recorded in all cases. Later, one reviewer critically appraised all papers accepted by the Working Group for inclusion.

The following critical appraisal tools were used:

- SIGN appraisal tool for SRs (www.sign.ac.uk/guidelines/fulltext/50/checklist1.html)
- SIGN appraisal tool for RCTs (www.sign.ac.uk/guidelines/fulltext/50/checklist2.html).

Randomised controlled trials and SRs were graded as being of good, moderate or low quality based on the results of appraisal using the SIGN tools. Cochrane reviews and lower level evidence (eg. cohort studies) were not subject to critical appraisal.

Data extraction

One reviewer used the NHMRC RCT data extraction tool (www.nhmrc.gov.au) and the Joanna Briggs Institute (JBI) data extraction tool for SRs (available on request from JBI or NHMRC) to extract data from the included studies in a systematic manner. Data from included studies is presented in the literature review.

Special populations

People from certain population groups may be more likely to suffer osteoporotic fractures. Part of this difference may relate to differences in bone mass and some may relate to bone macro architecture, including bone size. Caucasian and Asian populations tend to have a lower average bone mass (and smaller bones) than black or Hispanic groups and higher fracture incidence. However, this cannot be assumed to apply to Australian Aboriginal people or Torres Strait Islanders.

The search strategy was designed to retrieve all available evidence meeting the inclusion criteria, including research specific to special populations identified by the Department of Health and Ageing (groups specified in the contract). Special interest groups included Indigenous Australians (Aboriginal people and Torres Strait Islanders), rural and remote communities, Muslim Australians, and Vietnamese Australians. The literature searches identified minimal or no evidence directly related to these populations, thus a broader search was conducted to identify any research that addressed management of OP in the special population groups.

The following search was conducted in MEDLINE, CINAHL, EMBASE and the Cochrane Library to identify relevant information:

1. Aboriginal.mp. OR Aborigine.mp. OR koori.mp. OR indigenous.mp. OR Torres Strait.mp. OR Vietnam/ OR Vietnamese.mp. OR rural health centers/ OR hospitals, rural/ OR rural health/ OR rural health services/ OR rural areas/ OR rural health nursing/ OR Muslim.mp. OR Islam/
2. Osteoporosis/ OR osteoporosis.mp
3. Both 2 and 3.

Ten papers were identified for retrieval. Five of these papers related to Australian Aborigines, three papers related to rural health and two focused on Muslim populations. All 10 papers were considered unhelpful as they did not directly relate to OP, or were historical health information.

Development and grading of the recommendations

Through group meetings, email circulation and feedback, the Working Group used the new evidence, together with evidence from the primary reference guideline and expert opinion, to develop recommendations relevant to general practice within Australia.

Evidence statements were developed that represented a summary of the most relevant evidence from the literature. A body of evidence assessment matrix developed by the NHMRC[147] (*Table 5*) was used to assess the volume and consistency of evidence supporting each recommendation, as well as the clinical impact, generalisability and applicability of the recommendation.

Table 5. NHMRC body of evidence assessment matrix[147]

Component	A Excellent	B Good	C Satisfactory	D Poor
Volume of evidence	At least one good quality SR that has at least two good quality RCTs	At least two good quality RCTs or a moderate quality SR that has at least two moderate or good quality RCTs; or SRs not specifically reporting quality of evidence included	At least one moderate quality RCT	Less than one moderate quality RCT or where full literature search was not conducted then consensus
Consistency	All studies consistent	Most studies consistent, and inconsistencies may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in the body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence different to the target population for the guideline but it is clinically sensible to apply this evidence to the target population	Population/s studied in the body of evidence different to the target population for the guideline and hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to the Australian health care context	Applicable to the Australian health care context with few caveats	Probably applicable to the Australian health care context with some caveats	Not applicable to the Australian health care context

Each recommendation was given a final grading (*Table 6*) representing its overall strength. The gradings reflect implementability in terms of confidence practitioners can use in a clinical situation. The overall grade of each recommendation was reached through consensus and is based on a summation of the grading of individual components of the body of evidence assessment.

Table 6. NHMRC grades of recommendations[147]

Grade	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Note: A recommendation cannot be graded A or B unless the volume and consistency of evidence components are both graded either A or B

Pre-consultation phase

At the end of 2007, before the public consultation took place, the OP guideline was sent to 14 experts for comments (both Australian and international). The comments were analysed by the Working Group and amendments made. Agreed changes were made to the guideline to provide greater clarity and, where appropriate, to add new information.

Public consultation

An interactive public survey was designed to collect comments from all potential stakeholders. The public consultation period was advertised in major national newspapers and over 200 known stakeholders (including members of RACGP musculoskeletal groups, consumer groups, academics and pharmaceutical companies) were sent personal invitations to review the material. The draft version of the *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men* was presented for public feedback via the RACGP website.

The recommendations with complete supporting evidence and the literature review for OP were not available for public consultation with the guideline as these aspects had not been completed. The NHMRC GAR consultant approved the posting of the guideline draft without the supporting documentation.

Post-consultation phase

Feedback collected from the survey and independent submissions was collated and presented to the Working Group Chair.

The Working Group Chair wrote a complete report on the responses to every comment and submission for both the pre-consultation and public consultation. The full report, as accepted by the Working Group, was submitted to the NHMRC along with a detailed consultation report.

Subsequent to the consultation phase, both the full recommendation evidence and the literature review documents have been compiled. A number of new articles have been identified by the Working Group in this process, resulting in rewording of the recommendations for clarity, improved comprehension and to maintain the most up to date evidence.

NHMRC peer review process

As part of the NHMRC approval process the guideline was reviewed by two external peer reviewers.

Feedback from the reviewer was incorporated into the final version of the guideline.

Dissemination

Final versions of the *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men,* together with supporting resources, are available to Australian GPs, and the public, on the RACGP website.

The RACGP has submitted to the Australian Government Department of Health and Ageing (DoHA) a detailed dissemination plan based on the NHMRC standards. The dissemination process is based upon four lines of deliberate action:

- specified target groups
- the most appropriate media
- resources allocated for the design, production and distribution of materials
- design, production and distribution process managed as a project, with appropriate evaluation and feedback.

APPENDIX B. RESOURCES

Useful publications

Australian Government Department of Health and Ageing and National Health and Medical Research Council. Nutrient reference values for Australia and New Zealand: Executive summary. Canberra: DoHA, 2006.

National Health and Medical Research Council. Making decisions about tests and treatments: Principles for better communication between healthcare consumers and healthcare professionals. Canberra: NHMRC, 2005.

National Prescribing Service Limited. 2006. Indicators of quality prescribing in Australian general practice. Sydney: National Prescribing Service Limited, 2006.

National Health and Medical Research Council. Dietary guidelines for Australian adults. Canberra: NHMRC, 2003.

The Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, The Australasian College Of Dermatologists, and The Cancer Council Australia. Risks and benefits of sun exposure: Position statement. Canberra, 2007.

The Royal Australian College of General Practitioners National Standing Committee – Quality Care, Smoking, Nutrition, Alcohol and Physical activity (SNAP). A population health guide to behavioural risk factors in general practice. South Melbourne: The RACGP, 2006.

The Royal Australian College of General Practitioners. Putting prevention into practice. Guidelines for the implementation of prevention in the general practice setting. 2nd edn. South Melbourne: The RACGP, 2006.

The RACGP Osteoporosis Working Group recommends consulting the Therapeutic Guidelines (www.tg.org.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information, including adverse effects.

Patient resources

Osteoporosis Australia provides a range of services for individuals at risk of, or diagnosed with, OP and their families. Services include classes and programs for people with OP and fractures such as self management programs, bone specific exercise classes, falls prevention programs and educational resources. Osteoporosis Australia has a range of handouts, leaflets and guidelines for patients and also provide a comprehensive website for patients and health professionals (www.osteoporosis.org.au).

1800 242 141 toll free

Osteoporosis Australia Information Hotline toll free number anywhere in Australia. Calls go directly to the state office of the state where the call originates.

Useful websites

The following websites have been found to be useful. However the Working Group takes no responsibility for the information provided on these sites or to any links to which they may connect.

Note: URL addresses were accurate at the time of publication.

Australian Rheumatology Association	www.rheumatology.org.au
Carers Australia	www.carersaustralia.com.au
The Royal Australian College of General Practitioners (RACGP)	www.racgp.org.au
International Osteoporosis Foundation	www.iofbonehealth.org
National Health and Medical Research Council (NHMRC)	www.nhmrc.gov.au
National Prescribing Service	www.nps.org.au
National Osteoporosis Foundation US	www.nof.org
National Osteoporosis Society UK	www.nos.org.uk
Osteoporosis Australia	www.osteoporosis.org.au
Therapeutic Guidelines	www.tg.org.au

APPENDIX C. MEMBERSHIP OF THE RACGP OSTEOPOROSIS WORKING GROUP

Aim of the Working Group

The aim of the Working Group was to undertake activities required to fulfil the aims of the project as outlined in the funding agreement, including:

- carrying out a review of literature as per the NHMRC requirements
- developing clinical practice guidelines for GPs based on the evidence obtained within the literature review.

Establishment of the Working Group

In accordance with the project contract, membership of the Working Group endeavoured to include:

- three or more experts in each field: medical (including one GP) and allied health
- one expert NAMSCAG member
- one consumer representative
- one departmental representative
- a consultant appointed by the NHMRC.
- In addition, the following groups were represented in accordance with the project contract:
- a nominee of the Australian Rheumatology Association or the Australian and New Zealand Bone and Mineral Society
- a nominee of the Endocrine Society of Australia and of the Faculty of Rehabilitation Medicine.

Membership of the RACGP Osteoporosis Working Group

Name	Qualifications	Position
Prof John Eisman AO (Chair)	MBBS, PhD, FRACP	Director, Bone and Mineral Research Program, Garvan Institute of Medical Research; Chair, NAMSCAG; Professor of Medicine (Conjoint), University of New South Wales; Staff Endocrinologist, St Vincent's Hospital, Sydney (NSW); Chair, National Arthritis and Musculoskeletal Conditions Advisory Group; Co-Chair, Better Arthritis and Osteoporosis Care Advisory Committee
Prof Peter Ebeling	MBBS, MD, FRACP	Chair, Department of Medicine (RMH/WH), University of Melbourne; Head of Endocrinology, Western Hospital, Footscray; Endocrine Society of Australia representative (Vic); Medical Director, Osteoporosis Australia
Dr Dan Ewald	MPH&TM, MAppEpid, FAFPHM, FRACGP	RACGP and rural general practice representative; Executive: Northern Rivers General Practice Network (NSW)
Prof Leon Flicker	PhD, GDipEpid, FRACP	Professor of Geriatric Medicine, University of Western Australia (WA); Director, Western Australian Centre for Health and Ageing; Geriatrician, Royal Perth Hospital
Ms Barbara Holborow OAM	SAB	Consumer Representative (NSW)
Dr Peter Nash	MBBS(Hons), FRACP	Director, Rheumatology Research Unit and Senior Lecturer, Department of Medicine, University of Queensland; Australian & New Zealand Bone & Mineral Society (ANZBMS) representative (Qld)

Prof Philip Sambrook OAM	MBBS, MD, LLB, FRACP	Professor of Rheumatology, University of Sydney (NSW); Director, Institute of Bone & Joint Research, Royal North Shore Hospital; President, Australian & New Zealand Bone & Mineral Society (ANZBMS)
Prof Markus Seibel	MD, PhD, FRACP	Professor and Chair of Endocrinology, Sydney University; Head, Department of Endocrinology & Metabolism, Concord General Hospital, Sydney; Director, Bone Research Program, ANZAC Research Institute, Concord (NSW)
Ms Judy Stenmark	BAppSc, MPH	Allied Health representative and CEO of Osteoporosis Australia (NSW)
Dr Tania Winzenberg	PhD, MMedSc(ClinEpi), FRACGP	RACGP (Tas); Research Fellow – General Practice, Menzies Research Institute
Ms Julia Herjandono	BA(Hons), MFIA	Project Officer; Managing Director, Duart Consultants Pty Ltd

RACGP contributors and NHMRC adviser

Dr Morton Rawlin	BMed, MMedSc, DipPracDerm, DipFP, DipMedHyp, DipBusAdmin, FACRRM, FRACGP	RACGP – Director of Educational Services Project Director
Prof Karen Grimmer-Somers	PhD, MMedSc, BPhty, LMusA, CertHlthEc	NHMRC Advisor
Dr Jiri Rada	PhD, MSc, BPHE, BA, FRSH	RACGP Project Officer
Emily Haesler	BN, PGradDipAdvNsg	RACGP Project Officer
Amy Jasper	MBA,GDip(HumServRes), BAppSci(AdvNsg)	RACGP Education Evaluation Manager Project Manager

NHMRC Evidence Translation Section project management staff

Vesna Cvjeticanin, Director

Cheryl Cooke, Assistant Director

Dr Stuart Barrow, Assistant Director

APPENDIX D. DECLARATION OF CONFLICTS OF INTEREST

In accordance with RACGP policy (included at the end of this appendix), all members of the Working Group involved in the development of *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men*, including external contractors and writers, completed a disclosure statement regarding any real or perceived dualities and conflicts of interest related to their participation in the guideline development. In addition, declaration of real or perceived dualities and conflicts of interest were declared as a standing item for all Working Group meetings.

Disclosure of interest statements are presented below in accordance with the NHMRC draft policy for declarations of interests and potential conflicts of interest for guideline developers introduced in October 2008.

Dualities and conflicts of interest summary

Working Group Chair – Prof John Eisman AO

Professor Eisman has received remuneration for consultancy and/or scientific advisory board service for Amgen, Merck Sharp & Dohme, Novartis, Sanofi-Aventis and Servier. He has received funding for research (in money or in kind) and participation in clinical trials from Amgen, Decode Genetics, Eli Lilly, Merck Sharp & Dohme, Novartis, Sanofi-Aventis and Servier. He has been involved in educational meetings and/or preparation of videos for GPs on osteoporosis for Eli Lilly, Merck Sharp & Dohme, Novartis, Sanofi-Aventis and Servier and has received support in part (including hospitality) from Amgen, Merck Sharp & Dohme, Novartis, Sanofi-Aventis and Servier during attendance at international or national scientific and educational meetings.

Members of the Working Group

Prof Peter Ebeling

Professor Ebeling has received research grant funding from Merck Sharp & Dohme, Amgen, Servier and Novartis and has served on advisory boards for Amgen, Merck Sharp & Dohme and Sanofi-Aventis.

Dr Dan Ewald

Dr Ewald undertakes the following roles that have potential to be viewed as a duality or conflict of interest:

- Director of General Practice NSW (Divisions SBO)
- Manager of Northern Rivers General Practice Network
- Member of Northern Rivers University Department of Rural Health Advisory Committee
- Supervisor Southern Cross University Exercise Physiology Honours Student
- Associate investigator in a beyondblue funder feasibility study of low intensity mental health services in Australia
- General practitioner in private practice
- Medical Educator for North Coast GP Training.

Prof Leon Flicker

Professor Flicker had no potential dualities or conflicts of interest to declare.

Ms Barbara Holborow OAM

Ms Holborow had no potential dualities or conflicts of interest to declare.

Dr Peter Nash

Dr Nash has received funding for clinical trials, research, travel to attend conferences or honoraria for lectures on behalf of, and for providing advice to Sanofi-Aventis, Merck Sharp & Dohme, Servier, Roche, Eli-Lily, Amgen, Novartis.

Prof Philip Sambrook OAM

Professor Sambrook has received grant support from Merck Sharp & Dohme, Sanofi-Aventis, Amgen & Servier for travel and accommodation to attend international scientific meetings. His department has conducted clinical trials on behalf of Novartis, Amgen and Servier and he has had membership on advisory groups for Merck, Sanofi-Aventis, Amgen, Servier, Novartis, Eli Lilly, Roche.

Prof Markus Seibel

Professor Seibel has served on advisory boards for, or has provided project specific advice to Sanofi-Aventis, Merck Sharp & Dohme, Amgen, Novartis, Wyeth, Roche, GlaxoSmithKline, Johnson & Johnson, Servier and Eli Lilly. He has received research support in the form of unrestricted grants from Sanofi-Aventis, Merck Sharp & Dohme, Amgen, Novartis, and Servier and been a paid speaker for Sanofi-Aventis, Merck Sharp & Dohme, Novartis, Eli Lilly and Servier.

Ms Judy Stenmark

Ms Stenmark was employed as CEO of Osteoporosis Australia during the development of the guideline. Merck Sharp & Dohme, Sanofi-Aventis, Roche, Fonterra Brands and Servier were general sponsors of Osteoporosis Australia. Eli Lilly and Fonterra Brands sponsored specific events for Osteoporosis Australia. Key Pharmaceuticals sponsored events for Osteoporosis Australia and supported research scholarships.

Dr Tania Winzenberg

Dr Winzenberg had no potential dualities or conflicts of interest to declare.

Ms Julia Herjandono

Ms Herjandono was appointed as a RACGP project officer.

Dr Morton Rawlin

Dr Rawlin was employed as the RACGP National Director of Educational Services from June 2006 until January 2009 and has been a member of the RACGP College Council since November 2008.

Prof Karen Grimmer-Somers

Ms Grimmer-Somers works for University of South Australia as a researcher and leads a research centre that brings in funds from research activity, consultancies and projects. All research support funds are handled by the university and activity is covered by the University of South Australia ethics and business management polices and structures. No money is received directly by Ms Grimmer-Somers.

Dr Jiri Rada

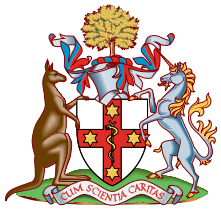
Dr Rada is a RACGP project officer.

Ms Emily Haesler

Ms Haesler was appointed as a RACGP consultant project officer on the guideline. During the period of the guideline's development she was providing consulting services to the RACGP's *gplearning* as a medical writer.

Ms Amy Jasper

Ms Jasper is employed by the RACGP. In 2008 Ms Jasper attended a presentation sponsored by a pharmaceutical company on the treatment of osteoporosis in order to gain the latest information in the field for the development of this guideline.



THE ROYAL AUSTRALIAN
COLLEGE OF
GENERAL PRACTITIONERS

I, ___*(insert name)*_____ acknowledge that my attention has been drawn to the Conflict of Interest Policy of The Royal Australian College of General Practitioners attached to this form, and I agree to abide by those principles.

Particulars of my pecuniary and non-pecuniary interests and those of my immediate family, of which I am aware, are set out below.

I undertake that I have advised/will advise the Chair of the appropriate RACGP Working Group of situations arising where an interest of mine or an interest of a member of my immediate family of which I am aware, whether pecuniary or otherwise, was or is in conflict, or has the potential to be in conflict, or may be perceived to be in conflict with duty as a representative of the RACGP.

I declare the following pecuniary and non-pecuniary interests for the time period:

_____ *1st January 2006*____ to _____ *1st June 2009*_____

Type of interest	Myself	Immediate family
Pecuniary interests#		
Shareholdings	No/Yes*	No/Yes*
Holdings in managed funds which have a particular focus on the field of the health, education and/or pharmaceutical industries	No/Yes*	No/Yes*
Indirect or beneficial interests in a company or organisation or in a trust which holds shares or investments in such a company or organisations	No/Yes*	No/Yes*
Directorships, board memberships or other offices	No/Yes*	No/Yes*
Paid employment or contracting work, including consultancies, commissions, presentations, and advising work, whether as an individual or on behalf of another organisation or person involved in postgraduate medical education	No/Yes*	No/Yes*
Funding for research or education purposes	No/Yes*	No/Yes*
Grants for travel or conference expenses	No/Yes*	No/Yes*
Hospitality of any kind	No/Yes*	No/Yes*
Other (please specify)	No/Yes*	No/Yes*
Non-pecuniary interests^		
Clinical trials	No/Yes*	No/Yes*
Research and development	No/Yes*	No/Yes*
Directorships/consultancies or advisory groups	No/Yes*	No/Yes*
Investigations or evaluations	No/Yes*	No/Yes*
Personal or religious beliefs about a therapeutic implication or education program or product under consideration by the RACGP	No/Yes*	No/Yes*
Direct relationships with a pharmaceutical/alcohol industry(s) or an education program or product being considered	No/Yes*	No/Yes*
Dualities or conflicts of interest in relation to work undertaken for the college where their primary employer has an interest	No/Yes*	No/Yes*
Dualities or conflicts of interest in relation to a non-RACGP panel or committee member where the work of the college is under consideration	No/Yes*	No/Yes*
Other (please specify)	No/Yes*	No/Yes*

* If you have answered 'yes', please give details, including the type of interest, the organisation and whether the interest is held by you or by your immediate family.

.....

.....

.....

.....

.....

.....

.....

.....

.....

Signature ..... Date .....

Pecuniary interests

List the names of any companies or other organisations involved in the development, manufacture or marketing and distribution and education around drugs and medicinal preparations, educational products or advisory bodies in relation to the pharmaceutical or alcohol industries or medical education (at undergraduate or postgraduate level) in which you have a pecuniary interest. List the names of any companies or other organisations that are known to you to be service providers to The Royal Australian College of General Practitioners or with which The Royal Australian College of General Practitioners has, a service/program contract in which you have a pecuniary interest.

A pecuniary interest may include any of the following:

- shareholdings;
- holdings in managed funds which have a particular focus on the field of the health, education and/or pharmaceutical industries;
- indirect or beneficial interests in a company or organisation or in a trust which holds shares or investments in such a company or organisation;
- directorships, board memberships or other offices;
- paid employment or contracting work, including consultancies, commissions, presentations, and advising work, whether as an individual or on behalf of another organisation or person involved in postgraduate medical education;
- funding for research or education;
- grants for travel or conference expenses;
- hospitality of any kind.

^ Non-pecuniary interests

List the names of any companies or other organisations involved in the development, manufacture or marketing and distribution and education around drugs and medicinal preparations, educational programs or products or advisory bodies in relation to the pharmaceutical or alcohol industries or medical education (at undergraduate or postgraduate level) in which you have a non-pecuniary interest. List the names of any companies or other organisations that are known to you as service providers to The Royal Australian College of General Practitioners or with which The Royal Australian College of General Practitioners has a service/program contract in which you have a non-pecuniary interest.

Non-pecuniary interests include any interests which may conflict, or give the appearance of being in conflict, with a member's obligations to RACGP. Examples of a non-pecuniary conflict of interest might be, but not limited to the following:

- where a member or his/her immediate family has direct relationships with the pharmaceutical or alcohol industries or an education program or product is being considered;
- where a member or his/her immediate family has strong personal or religious beliefs about a therapeutic implication or education program or product under consideration by the RACGP;
- where staff that are on secondment to the RACGP on a part-time basis and dualities or conflicts arise in relation to the work for the college and where their primary employer has an interest;
- where Fellows or staff are included on a non-RACGP panel or committee where the work of the college is under consideration;
- clinical trials;
- research and development;
- directorships/consultancies or advisory groups;
- investigations or evaluations; and/or
- other committees.

1. Policy title conflict of interest policy

1.1 Policy number: CO-O-029.0

1.2 Category: Organisational

1.3 Approval date: August 2009

1.4 Revision due date: August 2012

1.5 Unit responsible Office of the Chief Executive Officer

2. POLICY DECLARATION

This is the RACGP Conflict of Interest policy. It defines potential, perceived and actual conflicts of interest, and provides direction and procedures on disclosing and addressing potential, perceived and actual conflicts of interest, ensuring that risks associated with conflicts of interest are mitigated.

This policy is approved by Council and endorsed by the Chief Executive Officer.

3. BACKGROUND

3.1 Context

The RACGP places great importance on identifying and resolving any existing, perceived or potential conflicts of interest.

The College is committed to the highest levels of integrity. Councillors, committee members, staff members and other representatives of the College are expected to conduct their relationships with each other, the College, and outside organisations with objectivity and honesty.

In all interactions, Councillors, Fellows, other members and staff engaged by the College must observe high standards of ethical behaviour and avoid any activity or interest that might reflect unfavourably on the integrity of the RACGP. Councillors, Fellows, other members and staff engaged by the College have an obligation to avoid unacceptable ethical, legal, financial or other conflicts of interest and to ensure that their activities and interests do not conflict with their obligations to the RACGP. Ethical standards and conflicts of interest are covered in the College Constitution, and in the Commonwealth *Corporations Act*.

It is the responsibility of Councillors, Fellows, Members, and staff to identify any actual, potential or perceived conflicts of interest and to take action, as specified in this policy, to address situations in which a conflict of interest has arisen, or could perceivably arise, as soon as the conflict of interest is identified.

Existing or potential conflicts of interest can impair or might appear to impair an individual's independence in the discharge of their responsibilities to the College and injure the College's reputation if these matters are not addressed transparently.

Conflicts of interest include both pecuniary interests and non-pecuniary interests, and both categories are important to recognise and address. They include actual and perceived conflicts. Both have the capacity to adversely affect the College's reputation.

(i) Pecuniary interests A pecuniary interest is an interest that a person has in a matter because of the reasonable likelihood or expectation of appreciable financial gain or loss to the person or another person with whom the person is associated, including relatives, partners, colleagues and external employers.

(ii) Non-pecuniary interests

A non-pecuniary interest may include family relationships, friendships, positions in associations, professional relationships and other interests that do not involve financial gain or loss.

An important example of a potential conflict of interest in a professional relationship, that must be avoided, is a situation where a person providing peer review may stand to directly benefit in the event of providing either a favourable or non-favourable review or assessment.

3.2 Objectives

The objectives of this policy are to:

- Ensure policy and processes exist for identification of conflicts of interest
- Mitigate risks surrounding actual, perceived and/or potential conflicts of interest.

3.3 Specific aims

The specific aims of this policy are to:

- Define what a conflict of interest is, including actual, perceived or potential
- Provide procedures for reporting and recording conflicts of interest
- Provide a framework for resolving situations where conflicts of interest exist, or might be perceived to exist, or have occurred.

3.4 Related Policies, Documents, Legislation & Strategic Priorities

Some related RACGP documents are:

(i) Constitution

(ii) Code of Conduct for Committees

(iii) Council Code of Conduct

(iv) Certification in Respect of Conduct and Conflict of Interest form (Appendix 1 to this policy).

See also sections 191–193 and 195–196 of the *Corporations Act 2001* (Commonwealth) in relation to Councillors, meetings of Councillors, and material personal interests.

4. BODY OF POLICY

This policy cannot describe all conflict of interest situations that may arise involving the College. Therefore, Councillors, managerial staff and other College representatives must use good judgment to avoid any appearance of impropriety. Appropriate circumstances may also justify exceptions to the application of the policy.

If you have any questions about this policy or its application, please err on the side of caution and transparency and seek advice from the Chief Executive Officer prior to entering into such a transaction.

4.1 Definitions

A conflict of interest exists where there is a divergence between the interests of the individual and their professional obligation to the RACGP, to the extent that an independent observer might reasonably question whether the professional actions or decisions of the individual are influenced by their own interests, rather than by the interests of the College.

(i) Actual conflict of interest:
a direct conflict between current duties and responsibilities as a member of the College governance structure, and existing private interests, including both pecuniary and non-pecuniary interests.

(ii) Potential conflict of interest:
a situation where there is potential for private interests to interfere with official duties, including both pecuniary and non-pecuniary benefits.

(iii) Perceived conflict of interest:
a situation where it could be perceived, or appear, that private interests could improperly influence the performance of duties, whether or not this is in fact the case.

4.2 Conflicts of interest

There are many situations where affiliations and relationships may influence judgement or may give the impression that an individual might be influenced by personal interests.

The potential for actual, potential, and perceived conflicts of interest exists in many aspects of RACGP operations. Conflicts of interest can include, but are not limited to:

(i) Financial and commercial interests

(ii) External employer - employee relationships

(iii) Family connections and kinship

(iv) Receiving gifts or benefits

(v) Friendships

(vi) Membership of an association, society, company, union, or trusteeship

(vii) Professional relationships and collaborations

(viii) Domestic relationships

(ix) Intellectual property

(x) Use of College premises or facilities for personal gain.

4.3 Situations which are not a conflict of interest

The following situations are not usually considered to be an actual, potential or perceived conflict of interest:

(i) Membership of another organisation, association, society, company, union or trusteeship where there is no possible benefit or perception of benefit which might impact on the individual's motives, actions and/or decision making

(ii) College approved collaboration with another person or organisation.

4.4 Council members and Corporations Act

The *Corporations Act* contains specific provisions dealing with the potential conflict of interest applicable to Council members as directors of a company. These obligations also exist generally at law to directors to act in the best interests of the company - and not for personal interests or gain. Failure to comply may constitute a breach of directors' duties which carries heavy civil and criminal penalties.

Section 191 of the *Corporations Act* provides:

> "A director of a company who has a material personal interest in a matter that relates to the affairs of the company must give the other directors notice of the interest ..."

Failure to comply with that obligation is a strict liability offence which may result in a $1,100 fine, 3 months imprisonment, or both, and may also constitute a breach of directors' duties.

Where a director has a material personal interest in a matter, the director must leave the room, and not vote, when the matter is being considered (see section 195 – *Corporations Act*). Failure to comply with that obligation is a strict liability offence which may result in a $550 fine, and may also constitute a breach of directors' duties.

While the *Corporations Act* does not define "material personal interest", court cases have provided the following general guidance:

(i) material interests:

These are usually interests which are "substantial" or interests "seen to have a capacity to influence the vote of the particular director upon the decision to be made". For example, if the interest arises from a relationship, that relationship must be of "some substance" to the matter being considered.

(ii) personal interests:

An interest is unlikely to be personal if it applies to a director in the same way as an "ordinary customer of a bank or a shop". For example, a director who beneficially owns a property affected by a decision to be made usually has a personal interest.

The RACGP has considered that this policy is both intended to comply with these legislative requirements

– and extend the processes and procedures applicable to conflicts of interest to others in the College.

Council members must comply with these legislative provisions, notwithstanding anything to the contrary in this Policy.

4.5 Procedures for disclosing interests

4.5.1 Council members and disclosure of material personal interests

A Councillor who has a material personal interest in a matter before Council or any other meeting of Councillors, must disclose the material personal interest as required by section 191 of the *Corporations Act.* In summary:

- the Councillor must give notice of the material personal interest as soon as practicable after the Councillor becomes aware of his or her interest
- the Councillor must give that notice to Council and any other relevant meeting of Councillors
- the notice must provide details of the nature and extent of the interest, and how the interest relates to the affairs of the College
- details of the Councillor's interest must be recorded in the minutes of meeting
- the Councillor may also give or table a standing notice about an interest (including material personal interests) in a similar way. However, the standing notice ceases to have effect if a particular interest materially increases above that disclosed in the notice.

Section 191(2) of the *Corporations Act* provides limited exceptions to the requirement to disclose interests, for example in relation to directors' insurance contracts, or to the extent the Councillor's interest is as a member of the College in relation to membership matters.

4.5.2 Participation of Council members with material personal interests

If a Councillor has a material personal interest in a matter being considered by Council or a meeting of Councillors, the following procedures apply as required by section 195 of the *Corporations Act.*

- The Councillor must not be present (ie must leave the room).
- The Councillor must not vote on the matter.
- In addition to not voting and not being present, the Councillor may also be under an obligation to take positive steps to draw the attention of the remainder of Council to how harm arising from the conflict could be reduced or limited.

Section 195 of the *Corporations Act* provides limited exceptions which are intended for unusual and exceptional circumstances. Improper use of the exceptions may be a breach of directors' duties, which carries heavy civil and criminal penalties.

- The Councillors without any material personal interest in a matter (if quorum is met in the absence of the Councillors with material personal interests) may pass a resolution that they are satisfied that the interest should not disqualify the Councillor from voting or being present. The minutes must record full details of the Councillor and the material personal interest to which that resolution applies.
- A Councillor may ask the Australian Securities & Investments Commission to exempt them from being disqualified from voting or being present on the matter. An exemption is only granted if there is no quorum without that Councillor, and in urgent or compelling circumstances where it is not appropriate to call a general meeting of members.

4.5.3 Council members, Committee members, Fellows, and Members

A Councillor, Committee member, Fellow or Member who has an interest in a matter before Council, a Council committee, or the RACGP of which she or he is involved in, will disclose the interest to the relevant Chair or Executive staff member. If the matter relates to a material personal interest of a Councillor, the procedures below apply to the extent they are not inconsistent with 4.5.1 and 4.5.2.

The Chair, or Executive staff member, may determine that:

- the situation is innocuous, and take or require no further action
- the potential for risk to the College from a conflict of interest is remote, and requires no further action other than to record that the matter has been reviewed
- the Councillor's, Committee member's, Fellow's or Member's situation presents an actual, potential or perceived conflict of interest, which must be resolved. This may involve disclosure to the relevant committee/ working group for further action or, in the case of contract work, modified duties.

If the conflict of interest relates to a Council or Committee meeting, the conflict of interest must be disclosed to the Committee prior to discussion of the relevant agenda item. The Council or Committee will then decide whether the Councillor or Committee member should:

- leave the meeting
- address the meeting and then leave
- remain for the duration of the discussion.

If the Councillor or Committee member is in doubt regarding the potential, actual or perceived conflict of interest, the situation should be disclosed to the Chair prior to the meeting, whereby the Chair will consider the situation and determine whether the issue should be discussed at the Council or Committee meeting.

4.5.4 Staff members

A staff member who has an interest in a matter before the RACGP, of which she or he is involved in, will disclose the interest to their relevant manager.

If a staff member is in doubt, the potential, actual or perceived conflict of interest must be disclosed to their relevant manager at the earliest opportunity, whereby the manager will take appropriate action.

Managers may determine that:

- the situation is innocuous, and take no further action
- the potential for a conflict of interest is remote, and requires no further action other than to record that the matter has been reviewed
- the staff member's situation presents an actual, potential or perceived conflict of interest, which must be resolved
- the situation is of sufficient concern to refer the matter to the Chief Executive Officer, or the Chief Executive Officer's delegate, for advice, clarification and/or further action.

If it is determined that a conflict of interests exists, or there is a potential for a conflict of interest, the manager will either:

- authorise the staff member to continue their duties
- reorganise the duties of the staff member ensuring that the conflict of interest has been mitigated
- establish additional processes and/or safeguards to ensure the impartiality of the staff member in relation to the situation
- refer the matter to the matter to the Chief Executive Officer or their delegated authority.

4.5.5 Certification of agreement to abide by this policy

All Councillors and Committee Members, at the time of their appointment to Council or a College committee, will agree to sign a certification that they understand and will abide by this policy (see Appendix 1).

All Staff members, at the time of their appointment to employment of the College, will agree to sign a certification that they understand and will abide by this policy (see Appendix 1).

4.6 Procedures for dealing with undeclared conflicts of interests

4.6.1 Council members, Committee members, Fellows, and Members

If it becomes apparent that a decision may have been made by a committee member when a conflict of interest existed, the matter will first be properly investigated to determine the facts of the case.

In the event that it is found that a decision was made when an undeclared conflict of interest existed, disciplinary action may then be taken by the College in accordance with the College Constitution and relevant policies.

Disciplinary decisions may include:

(i) no penalty

(ii) a reprimand

(iii) a formal warning

(iv) direct the member to receive counselling

(iv) expel the member from College committees for a period of time

4.6.2 Voting

In relation to College Committees, if after a proper investigation to determine the facts of the case it is found that a decision was made by a committee member when a conflict of interest existed, the vote of that member will be discounted. If the vote was a deciding vote, then the motion or decision will not be carried. The issue may be reconsidered by the Committee.

4.6.3 Staff Members

In the event that it becomes apparent after proper investigation that a member of staff has acted or made decisions when an undeclared conflict of interest existed, Human Resources policies will be applied in relation to appropriate disciplinary action.

5. PROCEDURES

5.1 Access to published policy

Members, Staff, and the general public will have access to this policy.

5.2 Promulgation of published policy

Councillors, Committee members, RACGP staff, and other relevant Fellows and Members will be sent communications explaining the function and role of this policy.

Councillors, Committee members, RACGP staff, and other relevant Members and Fellows will at the time of their appointment be required to sign a certification that they understand and agree to abide by this policy (see Appendix 1).

All College committees will include in the standing orders for agenda papers the following declaration:

Declaration of Conflict of Interest

Any member of the committee who has a direct or indirect pecuniary or non-pecuniary interest in a matter being considered, or about to be considered by the committee shall, as soon as is practicable after the relevant facts come to the committee member's knowledge, disclose the nature of that interest to the committee Chair, or at a meeting of the relevant committee.

The Chair must cause this declaration to be recorded in the minutes of the meeting.

A member of the committee who has a conflict of interest in a matter must not be present during any deliberations by the Committee on the matter and is not entitled to vote on the matter.

5.3 Dealing with situations when decisions made involve conflicts of interest exist

If it becomes apparent following investigation that a committee decision was made, and one or more committee members had an undeclared conflict of interest, the decision of the Committee or Council will be reviewed.

If it is determined that the member(s) affected the overall decision of the committee or Council, including but not limited to the member casting the deciding vote and/or providing misleading information to the Committee or Council, then that decision of the Committee or Council will be overturned by Council. The issue may be reconsidered by the Committee.

If it is determined that the Committee or Council members' vote and/or input to discussion did not unduly affect the overall decision of the committee, then the decision of the committee will stand.

5.4 Review of this policy

This policy will have a review cycle of three years.