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Royal Australian College of General Practitioners



osteoporosis australia

*Osteoporosis prevention, diagnosis and management in
postmenopausal women and men over 50 years of age*
2nd edition



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The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002

Tel 03 8699 0414
Fax 03 8699 0400
www.racgp.org.au

Osteoporosis Australia
255 Broadway
Glebe, NSW 2037

Tel 02 9518 8140
Outside Australia + 61 2 9518 8140
Fax 02 9518 6306
www.osteoporosis.org.au

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We recognise the traditional custodians of the land and sea on which we work and live.

Executive summary

This guideline is an evidence update of *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men*, published in 2010 by The Royal Australian College of General Practitioners (RACGP).¹ The accumulation of high-quality evidence supporting changes to clinical practice over the last six years, the need for expert consensus in areas of conflicting evidence or variable practice, and new developments in the pharmacological management of osteoporosis were important factors in the decision to undertake this revision.

The publication of new data on the prevalence of osteoporosis in Australia and the health and economic impacts of this disease has also highlighted the need to clarify and re-enforce clinical guidance for health professionals at the front line of osteoporosis management. A burden of disease analysis recently published by Osteoporosis Australia estimates that in 2012, 4.74 million Australians older than 50 years of age (66%) had poor bone health, including more than one million with osteoporosis.² By 2022, it is estimated that 6.2 million Australians older than 50 years of age will have osteoporosis or osteopenia, a rise of 31% from 2012. A similar increase in the rate of fracture, from 140,882 in 2012 to 183,105 in 2022, is anticipated if action is not taken to improve the diagnosis and management of osteoporosis.²

In addition to its significant health and social burden, osteoporosis exerts considerable economic pressures on government. The total direct and indirect costs of osteoporosis and osteopenia in Australia were \$2.75 billion in 2012.² This total annual cost is predicted to reach \$3.84 billion by 2022. Hip fractures constitute the major burden, costing nearly \$800 million in 2012.² Evidence shows that timely diagnosis and appropriate pharmacological management reduces fracture rates. However, osteoporosis remains significantly underdiagnosed and inadequately managed in Australia. Less than 20% of patients presenting to healthcare services with minimal trauma fractures are investigated or treated for osteoporosis.^{3,4}

Purpose

This guideline is designed to provide clear, evidence-based recommendations to assist general practitioners and other health professionals in managing older patients with osteoporosis. The purpose of the guideline is to support clinical judgement, not to replace it.

Scope

A 12-member expert Working Group has developed 42 recommendations for this guideline, constituting Australian best practice in the identification, diagnosis, treatment and management of osteoporosis in the following populations:

- Postmenopausal women and men older than 50 years of age who may be at risk of minimal trauma fracture.
- Postmenopausal women and men older than 50 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 older than 50 years of age diagnosed with osteoporosis, defined as a T-score of -2.5 or less, but without evidence of a minimal trauma fracture.

The majority of the recommendations are based on critical analysis of the body of published, peer-reviewed evidence that has accumulated from September 2006 to February 2016, following a systematic review of the available evidence to support these recommendations. Where insufficient evidence is available, or where the quality of the evidence does not meet minimum requirements (as described in Appendix A), recommendations have been developed through Working Group consensus. Details on the guideline development process and Working Group membership can be found in Appendices A and B.

What's new?

Certain areas of osteoporosis management have developed significantly since the publication of the first guideline in 2010, and evidence has accumulated in other areas that supports change to clinical practice. Several new recommendations have been developed for the update to reflect this changing landscape. Recommendations on the use of denosumab, the only new medication approved since the publication of the 2010 guideline, have been added. Comprehensive information on the evaluation of absolute fracture risk and guidance on the use of fracture risk calculators is included, and new recommendations on exercise and the appropriate use of calcium and vitamin D supplements have been developed. A 'special issues' section makes several recommendations in the areas of osteoporosis management in the elderly, including minimising falls risk, as well as fracture risk reduction in patients undergoing androgen deprivation therapy for prostate cancer or aromatase inhibitor therapy for breast cancer.

Professor Peter R Ebeling AO MBBS MD FRACP
Chair, Osteoporosis Australia Guidelines Working Group

References

1. The Royal Australian College of General Practitioners. Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men. 1st edn. South Melbourne, Vic: RACGP, 2010.
2. Watts JJ, Abimanyi-Ochom J, Sanders K. Osteoporosis costing all Australians: A new burden of disease analysis – 2012 to 2022. Glebe, NSW: Osteoporosis Australia, 2013.
3. Elliot-Gibson V, Bogoch ER, Jamal SA, Beaton DE. Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: A systematic review. *Osteoporos Int* 2004;15:767–78.
4. Eisman J, Clapman S, Kehow L. Osteoporosis prevalence and levels of treatment in primary care: The Australian BoneCare Study. *J Bone Miner Res* 2004;19(12):1969–75.

Summary of recommendations

Risk factor assessment, diagnosis and referral			
Chapter	No.	Recommendation	Grade
Identifying patients to investigate for osteoporosis	1	All individuals over the age of 50 who sustain a fracture following minimal trauma (such as a fall from standing height or less) should be considered to have a presumptive diagnosis of osteoporosis.	A
	2	A presumptive diagnosis of osteoporosis can be made in a patient with a spinal compression fracture in whom there is no history of significant trauma and/or the patient is deemed to be at high risk of osteoporotic fracture. Caution regarding diagnosis and treatment should be exercised if only a single mild deformity is detected, especially in a patient under the age of 60.	B
	3	Conduct a clinical risk-factor assessment in postmenopausal women and men over the age of 50 with one or more major risk factors for minimal trauma fracture. Individual risk-factor profile should determine the need for assessment.	B
Diagnostic investigations	4	Measure bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) scanning on at least two skeletal sites, including the lumbar spine and hip, unless these sites are unsuitable (eg hip prosthesis).	A
	5	Diagnostic assessment for osteoporosis should consist of medical history, clinical examination and BMD measurement by DXA. If applicable, laboratory tests and radiographs of the thoracic and lumbar spine should also be performed.	D
Diagnostic investigations	6	Assessment of absolute fracture risk, using either the Garvan Fracture Risk Calculator (www.garvan.org.au/bone-fracture-risk) or the Fracture Risk Assessment Tool (www.shef.ac.uk/FRAX) may be useful in assessing the need for treatment in individuals who do not clearly fit established criteria.	D
Referral to a medical specialist	7	Refer postmenopausal women and older men to a specialist or a specialist bone centre according to individual need, or when there is restricted access to appropriate resources or required expertise.	D

General bone health maintenance and fracture prevention			
Chapter	No.	Recommendation	Grade
Diet and lifestyle	8	Promote the following important lifestyle choices for all postmenopausal women and men over 50 years of age: <ul style="list-style-type: none"> • Adequate calcium and protein intake • Adequate but safe exposure to sunlight as a source of vitamin D • Maintenance of a healthy weight and body mass index • Cessation of smoking • Avoidance of excessive alcohol consumption 	C
Education and psychosocial support	9	Provide postmenopausal women and men over 50 years of age at risk of or diagnosed with osteoporosis, access to education, psychosocial support and encouragement to seek support from appropriate sources according to individual needs.	D
Reducing the risk of falls	10	Conduct falls risk assessments and initiate targeted fall-prevention programs in older adults.	A

General bone health maintenance and fracture prevention			
Chapter	No.	Recommendation	Grade
Exercise	11	Individuals over 50 years of age without osteoporosis should participate regularly in progressive resistance training and balance training exercises. Resistance exercise should be regular (2–3 days per week), moderate–vigorous, progressive and varied to influence BMD and reduce fall and fracture risk.	A
	12	Prescribe high-intensity progressive resistance and balance training to older adults with osteoporosis to prevent further bone loss and/or improve BMD, improve function, treat sarcopenia, and decrease fall and fracture risk.	A
	13	Prescribe extended exercise therapy, including resistance and balance training, after hip fracture to improve mobility, strength and physical performance. Evidence for the benefits of exercise after vertebral and non-hip fractures is limited.	A
Calcium and vitamin D supplementation	14	Calcium and vitamin D supplements should not be used routinely in non-institutionalised elderly people. The absolute benefit of calcium and vitamin D supplements in terms of fracture reduction is low. There is evidence of significant benefit in people at risk of deficiency, particularly institutionalised individuals. Calcium and vitamin D supplements should be offered to people taking osteoporosis treatments if their dietary calcium intake is less than 1300 mg per day.	C

Pharmacologic approaches to prevention and treatment			
Chapter	No.	Recommendation	Grade
Bisphosphonates	15	Bisphosphonate therapy should be considered for the primary prevention of vertebral fractures in women with osteopenia who are at least 10 years postmenopause.	C
	16	Bisphosphonate therapy (alendronate, risedronate or zoledronic acid) is recommended for reducing the risk of vertebral and non-vertebral fractures in postmenopausal women and men over 50 years of age at high risk of fracture (those with osteoporosis by BMD criteria or a prior minimal trauma fracture).	A
	17	Reconsider the need to continue bisphosphonate therapy after 5–10 years in postmenopausal women and men over 50 years of age with osteoporosis who have responded well to treatment (T-score ≥ -2.5 and no recent fractures). If BMD remains low (T-score ≤ -2.5) and/or there are incident vertebral fractures, continue treatment. Treatment should be restarted if there is evidence of bone loss, especially at the hip, or if a further minimal trauma fracture is sustained.	D
Denosumab	18	Denosumab is recommended for the treatment of osteoporosis in postmenopausal women at increased risk of minimal trauma fracture.	A
	19	Denosumab should be considered as an alternative to bisphosphonates for the treatment of men at increased risk of minimal trauma fracture.	B
Hormone therapy	20	Consider oestrogen replacement therapy to reduce the risk of fractures in postmenopausal women. The increase in risk of adverse events associated with treatment should be weighed carefully against benefits. Long-term use is not recommended.	A
	21	Selective oestrogen receptor modulators (SERMs) should be considered as a treatment option for postmenopausal women with osteoporosis where vertebral fractures are considered to be the major osteoporosis risk (on the basis of low spine BMD and/or an existing vertebral fracture) and where other agents are poorly tolerated. SERMs may be particularly useful in younger postmenopausal women at risk of vertebral fracture and who have a prior or family history of breast cancer.	A

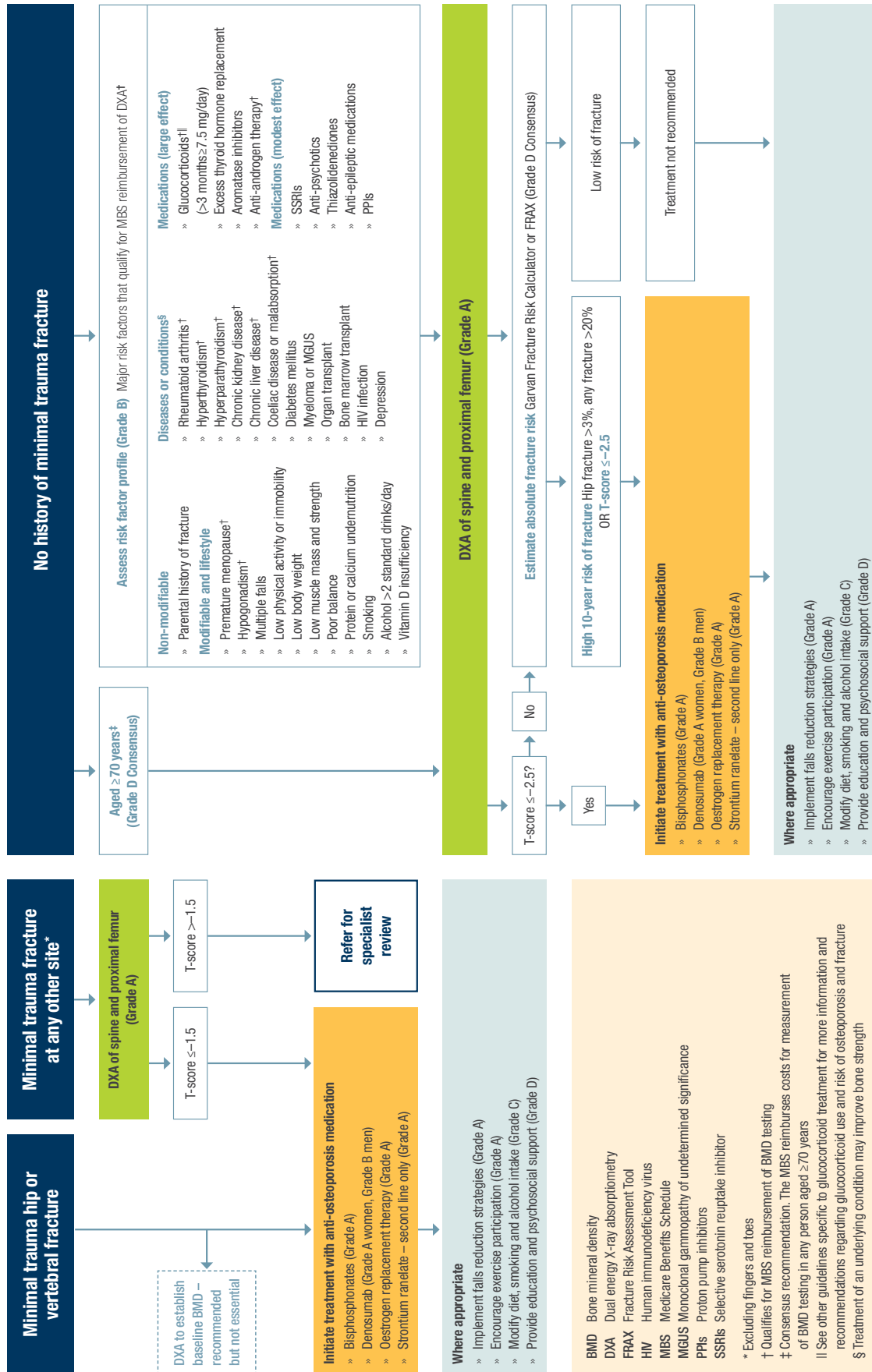
Pharmacologic approaches to prevention and treatment			
Chapter	No.	Recommendation	Grade
Parathyroid hormone	22	Teriparatide treatment is recommended to reduce fracture risk in postmenopausal women and men over 50 years of age with osteoporosis who have sustained a subsequent fracture while on anti-resorptive therapy, or in whom anti-resorptive therapy is contraindicated.	A
Strontium ranelate	23	Strontium ranelate at a dose of 2 g per day is an effective second-line option for reducing the risk of further osteoporotic fractures in postmenopausal women with prevalent fractures. Strontium ranelate should not be used in patients with previous or clinically active cardiovascular disease or uncontrolled hypertension and should only be used when other medications for the treatment of osteoporosis are unsuitable.	A

Ongoing monitoring			
Chapter	No.	Recommendation	Grade
	24	Regularly re-assess fracture risk and requirement for anti-osteoporotic therapy in patients who are not receiving therapy, but remain at increased risk of fracture.	B
	25	Review all patients 3–6 months after initiating a specific pharmacological intervention for osteoporosis, and annually thereafter. BMD testing at the 3–6 month review is not indicated.	B
	26	Biochemical markers of bone turnover should not be routinely used for the diagnosis of osteoporosis in general practice. Measurement of markers should be confined to specialist practice, and may be useful for the monitoring of adherence to treatment and in the evaluation of secondary causes of bone loss.	D

Special issues			
Chapter	No.	Recommendation	Grade
Management of osteoporosis in the elderly	27	Calcium and vitamin D supplementation is recommended for the prevention of fracture in the frail elderly and institutionalised elderly. Optimisation of calcium and vitamin D should be the standard of care for this group.	C
	28	Consider the use of hip protectors to reduce the risk of hip fracture in residential-care settings, but not in community settings.	C
	29	Anti-resorptive therapy is recommended for reduction of fracture risk in people over 75 years of age with osteoporosis.	A
	30	Anabolic therapy with teriparatide may be considered for reduction of vertebral fracture risk in people over 75 years of age with osteoporosis.	C
	31	Multifactorial assessment of falls risk, exercise programs and home-safety interventions are recommended to reduce the rate of falls in community-dwelling people over 75 years of age.	A
	32	Vitamin D supplementation of elderly people in care facilities is recommended to reduce the rate of falls. Vitamin D supplements given for falls prevention are normally combined with calcium to address the high rates of calcium deficiency also seen in this population.	A
	33	Evidence-based exercise modalities that progress in intensity as capacity improves are recommended for the maintenance of bone strength, muscle function and balance in people over the age of 75.	B
	34	Exercise programs for very frail elderly institutionalised people and those with vertebral fracture risk should be supervised, modified and tailored to minimise the potential to increase the risk of falls, injury and vertebral fractures.	C

Special issues			
Chapter	No.	Recommendation	Grade
Aromatase inhibitor and androgen deprivation therapy	35	All women undergoing aromatase inhibitor (AI) therapy should have a baseline assessment of fracture risk prior to commencing therapy.	A
	36	Women undergoing AI therapy who fall within one of the following two categories should commence anti-resorptive therapy unless contraindicated: 1. 70 years or over with a BMD T-score ≤ -2.5 2. 50 years or over with a minimal trauma fracture (including radiological vertebral fracture) or a high estimated 10-year risk of fracture. There is limited evidence specific to women receiving AI to guide firm recommendations outside these criteria, especially in premenopausal women.	A
	37	The duration of anti-resorptive treatment in women who are undergoing or have completed AI therapy should be individualised and based on absolute fracture risk.	D
	38	General measures to prevent bone loss should be implemented in all women commencing AI therapy.	C
	39	All men commencing androgen deprivation therapy (ADT) should have a baseline assessment of fracture risk. BMD by DXA should be measured in all patients at the time of commencement of ADT.	A
	40	All men receiving ADT who have a history of minimal trauma fracture should be commenced on anti-resorptive therapy, unless contraindicated.	A
	41	Management of bone health should be reviewed 1–2 yearly in men on continuous ADT.	C
	42	General measures to prevent bone loss should be implemented in all men commencing ADT.	C

Osteoporosis risk assessment, diagnosis and management flowchart



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Acronyms

25-OH D	25-hydroxyvitamin D	PINP	procollagen type 1 amino-terminal propeptide
AAOMS	American Association of Oral and Maxillofacial Surgeons	PPI	proton pump inhibitor
ADA	American Dental Association	PTH	parathyroid hormone
ADT	androgen deprivation therapy	QALY	quality-adjusted life year
AFF	atypical fracture of the femur	QCT	quantitative computed tomography
AI	aromatase inhibitor	QUS	quantitative ultrasound
ARR	absolute risk reduction	RACGP	The Royal Australian College of General Practitioners
BMD	bone mineral density	RANKL	receptor activator of nuclear factor kappa B ligand
BMI	body mass index	RaR	rate ratio
BP	blood pressure	RCT	randomised controlled trial
CEE	conjugated equine (o)estrogen	RDI	recommended dietary intake
CI	confidence interval	RR	relative risk
CTX	C-terminal telopeptide	SD	standard deviation
CV	cardiovascular	SERMs	selective oestrogen receptor modulators
DXA	dual energy X-ray absorptiometry	SFP	secondary fracture prevention
EMA	European Medicines Agency	SR	systematic review
ER	(o)estrogen receptor	SSRI	selective serotonin reuptake inhibitor
FN	femoral neck	TUG	timed up and go
FRAX	Fracture Risk Assessment Tool	WHI	Women's Health Initiative
GFRC	Garvan Fracture Risk Calculator	WHO	World Health Organization
GIT	gastrointestinal		
GnRH	gonadotropin-releasing hormone		
GP	general practitioner		
HIV	human immunodeficiency virus		
hPTH	human parathyroid hormone		
HR	hazard ratio		
HT	hormone therapy		
IV	intravenous		
MA	meta-analysis		
MI	myocardial infarction		
MRONJ	medication-related osteonecrosis of the jaw		
NHMRC	The National Health and Medical Research Council		
NNT	number need to treat		
OR	odds ratio		
PBS	Pharmaceutical Benefits Scheme		

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How to use the guideline

Recommendations

Each of the 42 recommendations has been graded from A to D according to the process described in [Appendix A](#). The grade reflects the degree of 'trust' that the clinician can place on the clinical application of the recommendation. The Working Group supports all recommendations and intends that they are used in conjunction with clinical judgement and patient preferences. They do not cover complex medical conditions and comorbidities.

Practical tips and precautions

The practical tips are pointers to effectively implement the recommendations. Unless otherwise referenced, the source of information presented in the practical tips is the Working Group.

Side effects and potential harms

Side effects and adverse events are summarised for each pharmacologic intervention. This guideline does not seek to provide full safety and usage information on medications. The Working Group recommends consulting the Therapeutic Guidelines (www.tg.org.au), NPS MedicineWise (www.nps.org.au) or the *Australian Medicines Handbook* (<https://shop.amh.net.au>) for detailed prescribing information.

Evidence statement

Each recommendation is supported by a critical appraisal of the evidence published in the peer-reviewed literature between 2006 and February 2016. [Appendix A](#) describes the processes used to review the evidence.

Resources and further information

Information to download

Osteoporosis Australia produces a range of publications for general practitioners (GPs) and other health professionals, available to download free of charge from the Osteoporosis Australia website: www.osteoporosis.org.au

- Osteoporosis Australia. *What you need to know about osteoporosis: Medical guide*. 3rd edn. Glebe, NSW: OA, 2014.
- Osteoporosis Australia. *Medical guides: Calcium, Vitamin D, Exercise, Medicine*. 2nd edn. Glebe, NSW: OA, 2014.
- Osteoporosis Australia. *Bone mineral density testing in general practice*. Glebe, NSW: OA, 2014.
- Osteoporosis Australia. *5 common myths de-boned for general practice*. Glebe, NSW: OA, 2015.
- GP *Osteoblast*, medical issue (quarterly).

Online resources

Fracture Risk Assessment Tool: www.shef.ac.uk/FRAX

Garvan Fracture Risk Calculator: www.garvan.org.au/bone-fracture-risk

Therapeutic guidelines: www.tg.org.au

NPS MedicineWise: www.nps.org.au

Useful websites

The Working Group takes no responsibility for the information provided on these sites or to any links to which they may connect. URL addresses were accurate at the time of publication.

Osteoporosis Australia: www.osteoporosis.org.au

National Osteoporosis Foundation (USA): www.nof.org

National Osteoporosis Society (UK): www.nos.org.uk

International Osteoporosis Foundation: www.iofbonehealth.org

The Royal Australian College of General Practitioners: www.racgp.org.au

Australian Rheumatology Association: www.rheumatology.org.au

Carers Australia: www.carersaustralia.com.au

Australian medicines handbook: <https://shop.amh.net.au>

General information

- Department of Health and Ageing and National Health and Medical Research Council. *Nutrient reference values for Australia and New Zealand: Executive summary*. Canberra: DoHA and NHMRC, 2006.
- Department of Health and Ageing and National Health and Medical Research Council. *Eat for health: Australian dietary guidelines. Summary*. Canberra: DoHA and NHMRC, 2013.
- The Royal Australian College of General Practitioners. *Smoking, nutrition, alcohol, physical activity (SNAP): A population health guide to behavioural risk factors in general practice*. 2nd edn. East Melbourne, Vic: RACGP, 2015.
- The Royal Australian College of General Practitioners. *Guidelines for preventive activities in general practice*. 9th edn. East Melbourne, Vic: RACGP, 2016.

Resources for patients

- The Osteoporosis Australia website (www.osteoporosis.org.au) provides comprehensive, consumer-friendly information for people who have been diagnosed with osteoporosis, are at risk of osteoporosis, or who wish to know more about bone health generally. A range of printable guides and factsheets translated into five languages are available to download from the website.
- 'Know your bones' (www.knowyourbones.org.au). A consumer-friendly, online bone-health assessment tool, based on the Garvan Fracture Risk Calculator.
- Healthy Bones Australia (www.healthybonesaustralia.org.au). Features an online calculator to help people of all ages track their daily calcium, vitamin D and activity levels towards a 'healthy bones score'.
- Osteoporosis Australia toll-free consumer helpline: 1800 242 141.

Background to osteoporosis

Definition

Osteoporosis is characterised by both low bone mineral density (BMD) and micro-architectural deterioration of bone tissue, leading to decreased bone strength, increased bone fragility and a consequent increase in fracture risk. Osteoporotic fractures usually result from falls from a standing height or less in individuals with decreased bone strength. BMD can be reliably measured by scanning of the axial skeleton by dual energy X-ray absorptiometry (DXA).

BMD is usually reported as a T-score, the number of standard deviations (SDs) of the BMD measurement above or below that of young healthy adults of the same sex. The World Health Organization (WHO) has defined osteoporosis and osteopenia on the basis of T-score (Table 1).¹ While Australia's Pharmaceutical Benefits Scheme (PBS) uses the WHO T-score range for osteoporosis to determine eligibility for subsidy on osteoporosis medications, it is important to note that BMD is only one of several factors that contribute to an individual's risk of fracture. Approximately 50% of first or subsequent minimal trauma fractures occur in people who have T-scores in the normal or osteopenic range.^{2,3}

Table 1. WHO definitions of osteoporosis and osteopenia¹

Normal BMD	T-score ≥ -1.0	BMD not more than 1.0 SD below young adult mean
Osteopenia	T-score between -1.0 and -2.5	BMD between 1.0 and 2.5 SDs below young adult mean
Osteoporosis	T-score ≤ -2.5	BMD 2.5 or more SDs below young adult mean

Clinical symptoms

Osteoporosis is known as a silent disease because the deterioration of skeletal tissue proceeds with no outward symptoms until a symptomatic fracture occurs, and thus the condition is under recognised and affected individuals are under treated.^{4,5} Vertebral 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 fractures 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.

Incidence and prevalence

Based on the WHO definition of osteoporosis and osteopenia, approximately 3% of men and 13% of women in Australia 50–69 years of age are osteoporotic, rising to 13% and 43% for men and women older than 70 years of age.⁶ Fifty-five per cent of men and 49% of women between 50 and 69 years of age are osteopenic, with similar prevalences in the over-70 years age group.⁶ It is estimated that by 2022 approximately 72% of women and 62% of men older than 50 years of age will have osteoporosis or osteopenia, according to WHO criteria.^{6,7}

Approximately 70% of minimal trauma fractures occur in women, with incidence increasing with age in both sexes.⁶ The residual lifetime risk of minimal trauma fracture is approximately 44% for women older than 60 years of age.⁸ The residual lifetime fracture risk among men is lower, but still substantial and higher than for many other chronic conditions, being around 25% for those older than 60 years of age.⁸

Between the ages of 50 and 69, non-hip, non-vertebral fractures (humerus, ankle, lower limb, rib, forearm, pelvis, forearm [not wrist], patella, foot and hand) are the most common minimal trauma fracture types in both men and

women.⁶ Wrist fractures are also common in women in this age group. The hip-fracture rate increases substantially with age, constituting only 4% of fragility fractures in women 50–69 years of age, but 26% of fractures in women older than 70 years of age.⁶ A similar trend with age is seen in men, although the overall incidence of hip fracture in men remains around one-third of that in women.⁶ The age-standardised hip-fracture incidence rate declined in Australia between 1997 and 2007, after a rise in the 1980s and stabilisation in the 1990s.⁹ However, the absolute number of hip fractures increased during this period.⁹ Any continued decline in incidence will be offset in the coming decades by the effects of an ageing population; the number of Australians older than 70 years of age is set to more than double from 2.2 million to almost five million by 2050.⁷

Vertebral fractures due to osteoporosis are associated with significant long-term disability due to pain and kyphosis. Vertebral fractures are usually defined on the basis of a 20% or more reduction in vertebral height on X-ray, and are often termed a 'vertebral deformity'. 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.¹⁰ In 2012, an estimated 25,502 vertebral fractures occurred in Australia.⁶ By 2022, incidence is expected to rise to over 35,000, an increase of 37%.⁶ The underdiagnosis of vertebral fractures is a major problem. Only around one-third of all radiographically observed vertebral deformities come to medical attention (ie are symptomatic with acute fracture-related pain).¹¹ The worldwide Improving Measurements of Persistence on Actonel Treatment (IMPACT) study reported that in Australia, approximately 30% of radiographically visible vertebral fractures in women with osteoporosis are not detected.¹²

Osteoporosis is a systemic condition. Almost all types of fracture are increased in patients with low BMD, and irrespective of fracture site, adults who sustain a minimal trauma fracture (and possibly even a high trauma fracture) are at subsequently greater (2–4-fold) risk of sustaining another fracture at a different site.^{6,13} Vertebral deformity is particularly associated with significantly higher risk of subsequent vertebral and non-vertebral fracture.¹⁴

Morbidity

Morbidity related to fractures can arise from pain, reduced mobility, loss of function and associated loss of quality of life.¹⁵ Many patients lose the ability to live independently following a hip fracture. Long-term morbidity is associated with almost all types of symptomatic osteoporotic fractures – only subjects with wrist, humerus or ankle fractures return to their pre-fracture health-related quality of life 18 months after a fracture.¹⁵

Mortality

Mortality in the first year after a major minimal trauma fracture in people older than 60 years of age is up to three times higher than in age-matched non-fracture populations for people with hip fracture and up to two times higher for other major fracture types.^{16–18} The mortality rate (per 100 person years) is higher in men than in women following any type of minimal trauma fracture; this effect is most pronounced in hip fracture.¹⁸ The risk of death is greatest in the first year after hip fracture: approximately 20% of women die within a year of fracturing a hip,¹⁸ with 10% dying during hospitalisation.¹⁹ Increased mortality during the immediate post-fracture period is associated with advanced age and male sex, and has been linked both to the presence of comorbid conditions such as congestive heart failure and liver disease,²⁰ and to the fracture event itself.²¹ Acute events such as post-operative infections and complications are also important.

Although hip fracture has the highest mortality, followed by pelvic and vertebral fractures, a quarter of excess mortality due to minimal trauma fracture is attributable to non-hip, non-spine fractures, due to the high prevalence of these fractures.¹⁸ Excess mortality occurs mainly in the first five years after a minimal trauma fracture, but may continue up to 10 years following the fracture.²²

Osteoporosis treatment has been shown in randomised controlled trials (RCTs) to significantly reduce mortality risk after hip fracture in elderly men and women,^{23,24} and cohort studies suggest this may also be the case for other fracture types.²⁵ The mechanisms behind mortality reduction remain speculative. Bisphosphonates may regulate immune processes and/or ion channel activity, with consequent effects on risk of infection, as well as cardiovascular and cerebrovascular events. Potent suppression by bisphosphonates of bone turnover and bone loss is another potential mechanism; bone loss and high bone turnover are independent predictors of mortality.²⁵

Management

Pharmacological interventions prevent further bone loss and reduce fracture risk. Treatment decisions should be based on age, sex, medical history, severity of the condition and estimated absolute risk of fracture. Despite high-level evidence for efficacy, safety and cost-effectiveness, less than 30% of Australian women and 10% of Australian men with osteoporosis (even with minimal trauma fractures) report taking specific osteoporosis-targeted pharmaceuticals.²⁶ Most current osteoporosis medications are anti-resorptive, and reduce the natural but excessive process of bone loss. Other agents increase the formation of new bone; these are most appropriate for more severe osteoporosis, especially if a patient is unresponsive to anti-resorptive therapy.

Modifiable risk factors are important in both the treatment and prevention of osteoporosis. A routine approach to addressing modifiable risk factors in general practice includes encouragement and support to increase weight-bearing exercise and strength training, maintain a healthy diet, ensure safe levels of sun exposure and avoid smoking and excessive alcohol intake. Exercise can assist in relieving pain as part of the post-fracture rehabilitation process. Only about 20% of Australians with osteoporosis report exercising most days and 6% do strength training.²⁶ Specific osteoporosis self-management programs are conducted by various public hospital health-promotion units and community health centres. These 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.

References

1. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. Technical Report Series, no. 843. Geneva: WHO, 1994.
2. Schuit SC, van der Klift M, Weel AE, et al. Fracture incidence and association with bone mineral density in elderly men and women: The Rotterdam Study. *Bone* 2004;34(1):195–202.
3. Bliuc D, Alarkawi D, Nguyen TV, Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: The Dubbo Osteoporosis Epidemiology Study. *J Bone Miner Res* 2015;30(4):637–46.
4. Eisman J, Clapham S, Kehoe L. Osteoporosis prevalence and levels of treatment in primary care: The Australian Bone Care Study. *J Bone Miner Res* 2004;19(12):1969–75.
5. Parker D. An audit of osteoporotic patients in an Australian general practice. *Australian Family Physician* 2013;42(6):423–27.
6. Watts JJ, Abimanyi-Ochom J, Sanders K. Osteoporosis costing all Australians: A new burden of disease analysis – 2012 to 2022. Glebe, NSW: Osteoporosis Australia, 2013.
7. Australian Bureau of Statistics. Population projections, Australia, 2012 to 2101. ABS cat. no. 32220.02013. Belconnen, ACT: ABS, 2013.
8. Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV. Residual lifetime risk of fractures in women and men. *J Bone Miner Res* 2007;22(6):781–88.
9. Crisp A, Dixon T, Jones G, et al. Declining incidence of osteoporotic hip fracture in Australia. *Arch Osteoporos* 2012;7(1–2):179–85.
10. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA. The prevalence of vertebral deformity in European men and women: The European Vertebral Osteoporosis Study. *J Bone Miner Res* 1996;11(7):1010–18.
11. Huan C, Ross PD, Wasnich RD. Vertebral fracture and other predictors of physical impairment and health care utilization. *Arch Intern Med* 1996;156(21):2469–75.
12. Delmas PD, van de Langerijt L, Watts NB, et al. Underdiagnosis of vertebral fractures is a worldwide problem: The IMPACT Study. *J Bone Miner Res* 2005;20(4):557–63.
13. Mackey D, Li-Yung Lui L, Cawthon P, et al. High-trauma fractures and low bone mineral density in older women and men. *JAMA* 2007;298(20):2381–88.
14. Pongchaiyakul C, Nguyen ND, Jones G, Center JR, Eisman JA, Nguyen TV. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: A long-term prospective study. *J Bone Miner Res* 2005;20(8):1349–55.
15. Abimanyi-Ochom J, Watts JJ, Borgström F, et al. Changes in quality of life associated with fragility fractures: Australian arm of the International Cost and Utility Related to Osteoporotic Fractures Study (AusICUROS). *Osteoporos Int* 2015;26(6):1781–90.
16. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: An observational study. *Lancet* 1999;353(9156):878–82.
17. Bliuc D, Alarkawi D, Nguyen TD, Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone mineral density: The Dubbo Osteoporosis Epidemiology Study. *J Bone Miner Res* 2015;30(4):637–46.
18. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;301(5):513–21.
19. Frost SA, Nguyen ND, Black DA, Eisman JA, Nguyen TV. Risk factors for in-hospital post-hip fracture mortality. *Bone* 2011;49(3):553–58.
20. Vestergaard P, Rejnmark L, Mosekilde L. Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications. *Osteoporos Int* 2007;18(12):1583–93.
21. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: A systematic epidemiological review. *Osteoporos Int* 2009;20(10):1633–50.
22. Bliuc D, Nguyen ND, Nguyen TV, Eisman JA, Center JR. Compound risk of high mortality following osteoporotic fracture and refracture in elderly men and women. *J Bone Miner Res* 2013;28(11):2317–24.
23. Center JR, Bliuc D, Nguyen ND, Nguyen TV, Eisman JA. Osteoporosis medication and reduced mortality risk in elderly women and men. *J Clin Endocrinol Metab* 2011;96(4):1006–14.
24. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357(18):1799–1809.
25. Sambrook PN, Cameron ID, Chen JS, et al. Oral bisphosphonates are associated with reduced mortality in frail older people: A prospective five-year study. *Osteoporos Int* 2011;22(9):2551–56.
26. Australian Institute of Health and Welfare. A picture of osteoporosis in Australia. Arthritis series no. 6. Cat. no. PHE 99. Bruce, ACT: AIHW, 2008.

Osteoporosis in the Australian setting

The treatment gap in osteoporosis care in Australia

Any osteoporotic fracture predisposes an individual to at least a two-fold risk in further fractures,^{1–9} significant morbidity and premature death.^{10,11} In a 2012 report of New South Wales hospital admission data from the Agency for Clinical Innovation, 46% of patients with an osteoporotic fracture were re-admitted to hospital due to a further fracture.¹²

The timely diagnosis and optimal treatment of osteoporosis prevents further fractures by up to 30%, 50% and 70% in patients with non-vertebral, hip and vertebral fractures, respectively. Several safe and effective medications are available for those who have sustained a minimal trauma fracture.^{13–19} Internationally, however, 70–85% of patients presenting with a minimal trauma fracture to their general practitioner (GP) or hospital are neither assessed for osteoporosis, nor appropriately managed to prevent further fractures.^{20–26} Two large retrospective studies of primary care practice in Australia demonstrated less than one-third of patients presenting with a minimal trauma fracture receive specific osteoporosis pharmacotherapy.^{27,28} This treatment gap is also evident in hospitals and tertiary referral centres.²⁹

Systematic interventions to address the care gap in osteoporosis management

Fracture liaison services or secondary fracture prevention (SFP) programs are the most proven methods to address the care gap in osteoporosis. SFP programs identify patients with a minimal trauma fracture, assess them for osteoporosis, initiate treatment (as appropriate) within the program and communicate with primary care providers. SFP programs in Australia have demonstrated improved osteoporosis treatment initiation and reduced re-fracture rates, compared to standard care.

The objectives of an SFP program are encapsulated by the '3i's' – identify patients with osteoporosis, investigate and determine fracture risk (also incorporating falls risk) and initiate interventions to reduce fracture risk. A 2013 systematic review³⁰ divided interventions into four models of care, according to intervention intensity (Table 2). A key aspect of any Type A or Type B SFP program is the presence of a coordinator who oversees all aspects of the program – from the initial patient contact following minimal trauma fracture, osteoporosis and falls risk assessment, and follow-up once interventions have been initiated. Once patients are captured, most programs perform a full risk factor assessment, including clinical osteoporosis risk factors, falls risk assessment and bone mineral density (BMD) testing.

Type A (3i) and Type B (2i) SFP programs have been shown in randomised controlled trials (RCTs) to improve process outcome measures (BMD testing and treatment initiation rates) compared to less-intensive Type C (1i) and Type D (0i) programs,^{31,32} while also reducing re-fracture rate^{33–35} in a clinically and economically effective manner.^{33,36–39} The SFP program at Concord Hospital, Sydney, was deemed highly cost-effective with a cost of around \$17,000 per quality-adjusted life year (QALY) gained.³⁷ It must be noted that the data demonstrating re-fracture risk reduction used historical controls or concurrent controls of patients who did not attend the SFP program.

Table 2. Description of models of care for secondary fracture prevention according to intervention intensity³⁰

Model of care	Description
A	Identification, assessment (risk factors, bloods, BMD), treatment initiation and correspondence with GP
B	Identification, assessment and treatment recommendation only
C	Information given to GP and patient
D	Information given to patient only

The role of primary care physicians

A number of patients with a minimal trauma fracture may not present to a hospital, whereas almost all patients with a minimal trauma fracture will eventually see their primary care physician (although, it should be noted, not necessarily for a minimal trauma fracture). Therefore, the primary care physician is key to ensuring patients are appropriately managed after a minimal trauma fracture. Furthermore, SFP programs primarily capture patients with non-hip, non-vertebral fractures and thus will not capture all patients at high risk of fracture or re-fracture, such as those with vertebral body fracture, frail elderly, those in institutionalised care and those with hip fractures managed via orthopaedic pathways.⁴⁰ Ortho-geriatric services, which are now present in most Australian hospitals, are critical to addressing this deficit. Potentially more importantly, primary care physicians need to be adequately equipped to detect and manage osteoporosis. The latter is being achieved through initiatives such as SFP in primary care and HealthPathways.

A recent systematic review of ortho-geriatric models of care, covering 18 (mainly retrospective cohort) studies from 1992 to 2012⁴¹ demonstrated a reduction in in-patient and long-term (6–12 months post-fracture) mortality (relative risk [RR]: 0.60, 95% confidence interval [CI]: 0.43–0.84 and RR: 0.83, 95% CI: 0.74–0.94, respectively). Length of stay was reduced in the ortho-geriatric care model. A number of important outcome measures were not reported in many of these studies, such as delirium, functional status, post-discharge destination of patients, time to surgery, complications post-surgery, institution of falls risk assessment, measures to reduce falls risk, institution of measures aimed at secondary fracture prevention.

The treatment gap in osteoporosis care in Australia can be addressed through implementation of SFP programs and ortho-geriatric services in both the hospital and primary care setting. Supporting primary care physicians to manage osteoporosis in patients who do not have access to these programs is critical to ensuring that all patients with a minimal trauma fracture are evaluated and managed appropriately.

Management of osteoporosis in rural and remote areas

In general, there tends to be less utilisation of health services in rural and remote areas and poorer global health outcomes.⁴² People living in rural and remote areas are more likely to suffer from chronic diseases than those in major cities. However, diagnosis of osteoporosis is more prevalent in major cities than in most other areas of Australia.⁴²

Bone densitometry (DXA) claims to Medicare increased by overall 78% in the 10 years from 2006 to 2015. The largest increase was seen in the service specific to osteoporosis screening in people older than 70 years of age. Claims for densitometry in this group more than tripled, while the population of men and women older than 70 years of age grew by an estimated 28% over the same 10-year period. Despite this overall growth in awareness and activity surrounding bone health, bone densitometry utilisation rates are significantly lower in rural and remote areas when compared to regional and urban areas. One study of Medicare claims between 2001 and 2005 showed that men and women in capital cities are around three times more likely to undergo densitometry than those in remote areas.⁴³

There is a particular need to facilitate health service activity for the detection and management of osteoporosis in rural and remote areas. Important factors are likely to be the limited provision of both primary healthcare and bone densitometry services in rural areas.

Sex differences

Data from the most recent Australian epidemiological study indicates a female:male fracture incidence ratio of 2.5:1.⁴⁴ The ratio for bone densitometry (DXA) utilisation, based on Medicare claims for 2015, is approximately 4.3:1. This suggests significant underuse of bone densitometry in men. The sex difference is more pronounced in rural and remote areas.⁴³

Aboriginal and Torres Strait Islander populations

Research on differences in the burden of osteoporosis in the Aboriginal and Torres Strait Islander 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 Aboriginal and Torres Strait Islanders compared to the non-Indigenous population of that area, but with a pattern of older age at the time of fracture for Aboriginal and Torres Strait Islander women.⁴⁵ The 2004–05 National Aboriginal and Torres Strait Islander Health Survey showed that an estimated 0.9% of the Aboriginal and Torres Strait Islander population reported that they had been told by a doctor that they had osteoporosis.⁴⁶ Aboriginal and Torres Strait Islander females were 1.5 times more likely to report having osteoporosis than Aboriginal and Torres Strait Islander males.⁴⁶ Comparing age-standardised rates, Aboriginal and Torres Strait Islander males are almost twice as likely to report osteoporosis than non-Indigenous males.⁴⁷ This contrasts with Aboriginal and Torres Strait Islander females, who are half as likely to report osteoporosis than non-Indigenous females.⁴⁷ BMD data are lacking for Aboriginal and Torres Strait Islander peoples. Findings from a recent small study indicate higher femoral neck BMD in Aboriginal and Torres Strait Islander peoples than in Caucasian Australians.⁴⁸ It is unknown at this stage whether this apparent difference in BMD translates into differences in fracture rates.

Differing patterns of risk factors such as smoking, nutrition, exercise, underweight, and high alcohol consumption are likely to be important in Aboriginal and Torres Strait Islander populations. The interaction of these factors, lower life expectancy, higher comorbidity rates, widely variable access to health services and socio-economic factors, is difficult to estimate. Promotion of good nutrition and reduction of risk factors is very important for a wide range of health issues, not only osteoporosis. It is expected that Aboriginal and Torres Strait Islander women and men suffer at least the same, if not a greater, limitation to densitometry access as noted for other rural and remote living people.

Ethnic and minority groups

Osteoporosis is most common in Caucasian people, followed by Asians and African Americans.⁴⁹ Therefore, there is an advantage in using normal ranges derived from ethnicity appropriate BMD T-scores. Some ethnic groups in Australia are at greater risk of vitamin D insufficiency (Asians, people with darker skin, and people who cover their skin for cultural or religious reasons) and relatively low calcium intakes; both should be corrected before initiating anti-osteoporotic therapy.

References

1. Ahmed LA, Center JR, Bjornerem A, et al. Progressively increasing fracture risk with advancing age after initial incident fragility fracture: The Tromso Study. *J Bone Miner Res* 2013;28(10):2214–21.
2. Bliuc D, Nguyen TV, Eisman JA, Center JR. The impact of nonhip nonvertebral fractures in elderly women and men. *J Clin Endocrinol Metab* 2014;99(2):415–23.
3. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007;297(4):387–94.
4. Johnell O, Kanis JA, Oden A, et al. Fracture risk following an osteoporotic fracture. *Osteoporos Int* 2004;15(3):175–79.
5. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone* 2004;35(2):375–82.
6. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA III, Berger M. Patients with prior fractures have an increased risk of future fractures: A summary of the literature and statistical synthesis. *J Bone Miner Res* 2000;15(4):721–39.
7. Laurs-van Geel TA, Center JR, Geusens PP, Dinant GJ, Eisman JA. Clinical fractures cluster in time after initial fracture. *Maturitas* 2010;67(4):339–42.
8. Melton LJ, 3rd, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL. Vertebral fractures predict subsequent fractures. *Osteoporos Int* 1999;10(3):214–21.
9. van Staa TP, Leufkens HG, Cooper C. Does a fracture at one site predict later fractures at other sites? A British cohort study. *Osteoporos Int* 2002;13(8):624–29.
10. Bliuc D, Nguyen ND, Nguyen TV, Eisman JA, Center JR. Compound risk of high mortality following osteoporotic fracture and refracture in elderly women and men. *J Bone Miner Res* 2013;28(11):2317–24.
11. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: An observational study. *Lancet* 1999;353(9156):878–82.
12. Health Economics & Analysis Team CPDIP. System wide analysis – Osteoporotic refracture prevention Model of Care. Chatswood, NSW: NSW Agency for Clinical Innovation, 2012.
13. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809–22.
14. Cranney A, Papaioannou A, Zytaruk N, et al. Parathyroid hormone for the treatment of osteoporosis: A systematic review. *CMAJ* 2006;175(1):52–59.
15. Guyatt GH, Cranney A, Griffith L, et al. Summary of meta-analyses of therapies for postmenopausal osteoporosis and the relationship between bone mineral density and fractures. *Endo Metab Clin North Am* 2002;31(3):659–79.
16. O'Donnell S, Cranney A, Wells GA, Adachi J, Reginster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database System Rev* 2006;(4):CD005326.
17. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension. *J Bone Miner Res* 2012;27(3):694–701.
18. Stevenson M, Davis S, Lloyd-Jones M, Beverley C. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess* 2007;11(4):1–134.
19. Stevenson M, Lloyd-Jones M, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* 2005;9(22):1–160.
20. Andrade SE, Majumdar SR, Chan AK, et al. Low frequency of treatment of osteoporosis among postmenopausal women following a fracture. *Arch Intern Med* 2003;163(17):2052–57.
21. Elliot-Gibson V, Bogoch ER, Jamal SA, Beaton DE. Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: A systematic review. *Osteoporos Int* 2004;15(10):767–78.
22. Follin SL, Black BS, McDermott MT. Lack of diagnosis and treatment of osteoporosis in men and women after hip fracture. *Pharmacotherapy* 2003;23(2):190–98.
23. Giangregorio L, Papaioannou A, Cranney A, Zytaruk N, Adachi JD. Fragility fractures and the osteoporosis care gap: An international phenomenon. *Semin Arthritis Rheum* 2006;35(5):293–305.
24. Leslie WD, Giangregorio LM, Yogendran M, et al. A population-based analysis of the post-fracture care gap 1996–2008: The situation is not improving. *Osteoporos Int* 2012;23(5):1623–29.
25. Port L, Center J, Briffa NK, Nguyen T, Cumming R, Eisman J. Osteoporotic fracture: Missed opportunity for intervention. *Osteoporos Int* 2003;14(9):780–84.
26. Shibli-Rahhal A, Vaughan-Sarrazin MS, Richardson K, Cram P. Testing and treatment for osteoporosis following hip fracture in an integrated U.S. healthcare delivery system. *Osteoporos Int* 2011;22(12):2973–80.
27. Chen JS, Hogan C, Lyubomirsky G, Sambrook PN. Management of osteoporosis in primary care in Australia. *Osteoporos Int* 2009;20(3):491–96.
28. Eisman J, Clapham S, Kehoe L, Australian BoneCare Study. Osteoporosis prevalence and levels of treatment in primary care: The Australian BoneCare Study. *J Bone Miner Res* 2004;19(12):1969–75.
29. Teede HJ, Jayasuriya IA, Giifillan CP. Fracture prevention strategies in patients presenting to Australian hospitals with minimal-trauma fractures: A major treatment gap. *Intern Med J* 2007;37(10):674–79.

30. Ganda K, Puech M, Chen JS, et al. Models of care for the secondary prevention of osteoporotic fractures: A systematic review and meta-analysis. *Osteoporos Int* 2013;24(2):393–406.
31. Majumdar SR, Johnson JA, Bellerose D, et al. Nurse case-manager vs multifaceted intervention to improve quality of osteoporosis care after wrist fracture: Randomized controlled pilot study. *Osteoporos Int* 2011;22(1):223–30.
32. Bliuc D, Eisman JA, Center JR. A randomized study of two different information-based interventions on the management of osteoporosis in minimal and moderate trauma fractures. *Osteoporos Int* 2006;17(9):1309–17.
33. Dell R, Greene D, Schelkun SR, Williams K. Osteoporosis disease management: The role of the orthopaedic surgeon. *J Bone Joint Surg Am* 2008;90 Suppl 4:188–94.
34. Lih A, Nandapalan H, Kim M, et al. Targeted intervention reduces refracture rates in patients with incident non-vertebral osteoporotic fractures: A 4-year prospective controlled study. *Osteoporos Int* 2011;22(3):849–58.
35. Nakayama A, Major G, Holliday E, Attia J, Bogduk N. Evidence of effectiveness of a fracture liaison service to reduce the re-fracture rate. *Osteoporos Int* 2015;27(3):873–79.
36. Sander B, Elliot-Gibson V, Beaton DE, Bogoch ER, Maetzel A. A coordinator program in post-fracture osteoporosis management improves outcomes and saves costs. *J Bone Joint Surg Am* 2008;90(6):1197–205.
37. Cooper MS, Palmer AJ, Seibel MJ. Cost-effectiveness of the Concord Minimal Trauma Fracture Liaison service, a prospective, controlled fracture prevention study. *Osteoporos Int* 2012;23(1):97–107.
38. Marsh D, Akesson K, Beaton DE, et al. Coordinator-based systems for secondary prevention in fragility fracture patients. *Osteoporos Int* 2011;22(7):2051–65.
39. Vaile J, Sullivan L, Bennett C, Bleasel J. First Fracture Project: Addressing the osteoporosis care gap. *Intern Med J* 2007;37(10):717–20.
40. Eekman DA, Helden SH, Huisman AM, et al. Optimizing fracture prevention: The fracture liaison service, an observational study. *Osteoporos Int* 2014;25(2):701–09.
41. Grigoryan KV, Javedan H, Rudolph JL. Orthogeriatric care models and outcomes in hip fracture patients: a systematic review and meta-analysis. *J Orthop Trauma* 2014;28(3):e49–55.
42. Australian Institute of Health and Welfare. A snapshot of osteoporosis in Australia 2011. Arthritis Series no. 15. Cat. no. PHE 137. Bruce, ACT: AIHW, 2011.
43. 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. *Med J Aust* 2009;190(3):126–28.
44. Watts JJ, Abimanyi-Ochom J, Sanders K. Osteoporosis costing all Australians. A new burden of disease analysis – 2012 to 2022. Glebe, NSW: Osteoporosis Australia, 2013.
45. 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.
46. Australian Bureau of Statistics. National Aboriginal and Torres Strait Islander Health Survey, 2004–05. ABS cat. no. 4715.0. Belconnen, ACT: ABS, 2006.
47. Australian Institute of Health and Welfare. A snapshot of osteoporosis in Australia 2011. Arthritis series no. 15. Cat. no. PHE 137. Bruce, ACT: AIHW, 2011.
48. Maple-Brown LJ, Hughes J, Piers LS, et al. Increased bone mineral density in Aboriginal and Torres Strait Islander Australians: Impact of body composition differences. *Bone* 2012;51(1):123–30.
49. Finkelstein JS, Lee ML, Sowers M, et al. Ethnic variation in bone density in premenopausal and early perimenopausal women: Effects of anthropometric and lifestyle factors. *J Clin Endocrinol Metab* 2002;87:3057–67.

Recommendations

Risk factor assessment, diagnosis and referral

Identifying patients to investigate for osteoporosis

Recommendation 1	Grade
All individuals over the age of 50 who sustain a fracture following minimal trauma (such as a fall from standing height or less) should be considered to have a presumptive diagnosis of osteoporosis.	A
Recommendation 2	Grade
A presumptive diagnosis of osteoporosis can be made in a patient with a spinal compression fracture in whom there is no history of significant trauma and/or the patient is deemed to be at high risk of osteoporotic fracture. Caution regarding diagnosis and treatment should be exercised if only a single mild deformity is detected, especially in a patient under the age of 60.	B
Recommendation 3	Grade
Conduct a clinical risk-factor assessment in postmenopausal women and men over the age of 50 with one or more major risk factors for minimal trauma fracture. Individual risk-factor profile should determine the need for assessment.	B

International guidelines recommend fracture risk assessment in postmenopausal women and men older than 50 years of age.¹⁻⁴

Major risk factors

- History of minimal trauma fracture
- Height loss ≥ 3 cm and/or back pain suggestive of vertebral fracture
- Female
- Older than 70 years of age
- History of falls
- Parental history of hip fracture
- Premature menopause or hypogonadism
- Prolonged use of glucocorticoids (at least three months cumulative prednisone or equivalent ≥ 7.5 mg per day)
- Use of other medications that cause bone loss
- Conditions or diseases that lead to bone loss
- Low body weight
- Low muscle mass and strength
- Low physical activity or prolonged immobility
- Poor balance

Other risk factors

- Smoking
- High alcohol intake
- Energy, protein or calcium undernutrition
- Vitamin D insufficiency

Risk factors for osteoporotic fracture

Presence of existing minimal trauma fractures

The single most easily recognised risk factor for osteoporotic fracture is the presence of any spinal or non-spinal minimal trauma fracture (a fracture occurring as a result of a fall from standing height or less). This also applies to vertebral fractures that are coincidentally detected on radiographs. It should be noted that not all vertebral deformities result from minimal trauma. A review of trauma history may guide interpretation of vertebral deformities. Dual energy X-ray absorptiometry (DXA) may be useful to determine if the patient has reduced bone mineral density (BMD) with a higher likelihood of sustaining an osteoporotic vertebral fracture.

Low BMD

Relative fracture risk approximately doubles for each unit (standard deviation) decrease in T-score, as measured by DXA. Postmenopausal women and men older than 50 years of age with osteoporosis (T-score ≤ -2.5) are already at increased risk of minimal trauma fracture. Absolute fracture risk increases with both increasing age and decreasing BMD. The absolute risk for fracture is therefore high in postmenopausal women and men aged 70 years or older with a T-score ≤ -2.5 (without fracture) and even higher in those with T-score ≤ -3.0 .

Age

Fracture risk is strongly affected by age for both sexes. With each decade the risk of minimal trauma fracture approximately doubles. Age as a fracture risk is independent of both BMD and clinical risk factors, such as risk of falling, 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. Vitamin D deficiency is associated with a higher risk of falling as well as with a lower BMD. Routine screening of vitamin D levels should not be carried out. Testing should be restricted to those with suspected or proven osteoporosis, conditions or medications known to decrease vitamin D levels, deeply pigmented skin, or severe lack of sun exposure due to cultural, medical, occupational or residential reasons.

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 minimal trauma fracture. However, family history of other types of minimal trauma fracture should also be considered.

Sex

At each age group, men are at approximately 50% lower fracture risk than women: for every three fractures, two will occur in women and one in a man. However, once a man has experienced a fracture, his risk of a subsequent fracture is equivalent to that of a woman of comparable age who has also experienced a fracture.

Falls

A history of falls increases the risk of peripheral minimal trauma 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, body sway, vitamin D deficiency, medications, visual impairment and environmental hazards.

Smoking

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

Low levels of physical activity or prolonged 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. The inability of a patient to rise from a chair without using their arms (a marker of loss of lower extremity strength and power) is associated with increased risk of minimal trauma fracture.

Low body weight and weight loss

Low body weight (body mass index <20) doubles the relative risk of a hip fracture for both women and men. An increased risk has also been demonstrated for spine and peripheral fractures. Unintentional weight loss is also associated with an increased risk of minimal trauma fracture. Anorexia nervosa is associated with increased risk of developing osteoporosis.

Loss of height

Some loss of height is typical with advancing age and can be due to disc degeneration and/or scoliosis. Accurate measurement and recording of height is important; loss of 3 cm or more, as measured by stadiometer, requires exclusion of vertebral deformity or fractures by X-ray. The greater the height loss, in the absence of obvious scoliosis, the greater the likelihood of vertebral fractures.

High alcohol intake

In this context, high alcohol intake is considered to be greater than two standard drinks per day for both men and women. For more information, refer to the [evidence statement for Recommendation 8](#) on page 28.

Medications

Medications associated with increased risk of minimal trauma fracture include, but are not limited to, glucocorticoids, excessive thyroid hormone replacement, anti-androgen therapy, anti-oestrogen treatments (aromatase inhibitors), selective serotonin reuptake inhibitors, thiazolidinediones, proton pump inhibitors, certain anti-epileptic drugs and certain anti-psychotics. However, it is not always possible to distinguish the effects on bone health 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 an 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, male hypogonadism, coeliac disease or other malabsorption disorder, depression, organ or bone marrow transplantation, myeloma or monoclonal gammopathies, human immunodeficiency virus (HIV) infection and diabetes mellitus. These conditions are associated with an increase in the age-specific risk for osteoporosis and minimal trauma fractures. Multiple myeloma may also present with pathologic fractures.

Evidence statement

In patients who have sustained a recent minimal trauma fracture, there is a high prevalence of risk factors for osteoporosis that are independent of BMD.⁵ This suggests that all postmenopausal women and men older than 50 years of age should undergo an assessment of their risk factors for osteoporosis, and all patients who sustain a minimal trauma fracture should be screened for risk factors, regardless of BMD, so that action may be taken to reduce the risk of subsequent fractures.

There is strong multinational randomised controlled trial (RCT) evidence that mild (Grade 1: 20–25% vertebral height loss) vertebral fractures are a significant risk factor for future vertebral fractures.⁶ The risk of new vertebral fracture increases progressively with the grade of the initial vertebral fracture; a severe initial fracture is associated with a six-fold increase in the risk of new vertebral fractures in the following three years.⁶ A moderate increase in the risk of non-vertebral fractures is also seen following moderate to severe vertebral fracture, a finding that is independent of BMD.⁶ The Dubbo Osteoporosis Epidemiology Study found that all fracture types, except ankle and rib fractures, are associated with increased subsequent fracture risk, with even a minor initial fracture resulting in an increased risk of major or hip fracture.⁷ Approximately half of re-fractures occurred in the first two years, and the risk persists for up to 10 years.⁷

Practical tips and precautions

- Any postmenopausal woman or man older than 50 years of age should be considered to have osteoporosis if they suffer a fracture after minimal trauma, such as after a fall from standing height or less. Although bone densitometry is not always required, it can exclude non-fragility causes of fracture.
- Patients should be assessed for possible vertebral wedge or crush fractures if there is well-documented height loss of ≥ 3 cm (measured by stadiometer), kyphosis or unexplained episodes of back pain. A standard spine X-ray should be performed. If vertebral wedge or crush fractures are detected, bone densitometry should be performed to determine BMD at the hip and spine.

References

1. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2014;25(10):2359–81.
2. National Osteoporosis Guideline Group. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Sheffield, UK: NOGG, 2014.
3. Scottish Intercollegiate Guidelines Network. Management of osteoporosis and the prevention of fragility fractures. SIGN publication no. 142. Edinburgh, UK: SIGN, 2015.
4. Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2013;24(1):23–57.
5. Malgo F, Appelman-Dijkstra NM, Termaat MF, et al. High prevalence of secondary factors for bone fragility in patients with a recent fracture independently of BMD. *Arch Osteoporos* 2016;11;12. doi:10.1007/s11657-016-0258-3.
6. Johansson H, Odén A, McCloskey EV, Kanis JA. Mild morphometric vertebral fractures predict vertebral fractures but not non-vertebral fractures. *Osteoporos Int* 2014;25(1):235–41.
7. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007;297(4):387–94.

Diagnostic investigations

Recommendation 4	Grade
Measure bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) scanning on at least two skeletal sites, including the lumbar spine and hip, unless these sites are unsuitable (eg hip prosthesis).	A

The World Health Organization (WHO) international reference standard for osteoporosis diagnosis is a T-score of -2.5 or less at the femoral neck (FN). The reference standard from which the T-score is calculated is the female, white, age 20–29 years, Third National Health and Nutrition Examination Survey (NHANES III) database or equivalent. Osteoporosis may be diagnosed in postmenopausal women and in men aged 50 and older if the T-score of the lumbar spine, total hip or FN is -2.5 or less. In certain circumstances, the 33% radius (also called one-third radius) may be utilised.^{1,2} In premenopausal women and in men younger than 50 years of age, as well as in children, the WHO bone mineral density (BMD) diagnostic osteopenia and osteoporosis classifications should not be used. In these patient groups, the diagnosis of osteoporosis should not be made using dual energy X-ray absorptiometry (DXA) criteria alone.^{1,2}

Recommendation 5	Grade
Diagnostic assessment for osteoporosis should consist of medical history, clinical examination and BMD measurement by DXA. If applicable, laboratory tests and radiographs of the thoracic and lumbar spine should also be performed.	D – consensus

Practical tips and precautions

- Conventional radiographs should not be used for diagnosis or exclusion of osteoporosis.
- The evaluation of osteoporosis is based on the lower T-score of either the lumbar spine, FN or total hip.¹
- Repeat BMD measurements should only be performed to assess efficacy of treatment and residual fracture risk, or compliance.
- To reliably compare change in BMD it is recommended to perform repeat BMD tests using the same instrument or at least the same make of instrument (manufacturer and model type) to improve comparability of results in interpreting any change in BMD.¹
- Relevant blood and urine studies should be obtained prior to initiating therapy if the medical history and/or clinical examination is compatible with secondary osteoporosis, or the DXA Z-score is ≤ -2.0 .²

Dual energy X-ray absorptiometry

Dual energy X-ray absorptiometry (DXA) is the current gold standard for the diagnosis of osteoporosis. BMD of the lumbar spine and the proximal femur are the best sites to measure for prediction of future fracture risk. Both sites should be measured (Table 3). DXA 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, with 95% confidence that the change is real.

Each standard deviation (SD) reduction in FN 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 trauma 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). FN and total hip BMD appear to be the best overall predictors of fracture risk. The total hip is the better site for monitoring BMD as it has good precision (less affected by positioning) and is relatively unaffected by osteoarthritis, which can spuriously elevate spinal BMD values, as can vertebral fractures and arterial calcification.^{1,2}

Table 3. Recommendations for BMD assessment by DXA¹⁻³

Woman or man age (years)	Risk factor profile for which a diagnostic assessment is recommended
Younger than 50	Minimal trauma fracture as individual case decision Disease or condition associated with bone loss
50–60	Vertebral fracture (where there is no history of major trauma) Peripheral minimal trauma fracture as individual case decision Disease or condition associated with bone loss Medications increasing bone loss
60–70	Vertebral fracture (where there is no history of major trauma) Peripheral minimal trauma fracture Hip fracture in a parent Underweight Multiple falls Immobility Disease or condition associated with bone loss Medications increasing bone loss

BMD measurements and the initial assessment

BMD measurements in the initial assessment have the following aims:

- Determine the patient's BMD. Fracture risk is multifactorial and may be significantly elevated in individuals outside the osteoporotic range (T-score ≤ -2.5). The use of the osteoporotic T-score threshold is, however, the criterion by which healthcare funders define osteoporosis, as well as being consistent with studies in which the anti-fracture effects of anti-osteoporotic drugs have been demonstrated.
- Determine the precise extent of BMD reduction. This is important for the assessment of individual fracture risk and the extent of the recommended therapeutic measures. Absolute fracture risk algorithms (eg the Garvan Fracture Risk Calculator available at www.garvan.org.au/bone-fracture-risk or the Fracture Risk Assessment Tool [FRAX] available at www.shef.ac.uk/FRAX) may be useful in more accurately determining individual fracture risk and assisting the patient in making a treatment decision.⁴

As a reference for fracture risk calculation in women in Australia, 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 hip T-scores for men based on the US NHANES III normative data. There are no standardised reference ranges for spine BMD in men and the only option is the use of reference ranges provided by densitometer manufacturers. These may differ significantly.⁵

Practical tips and precautions

- For patients with ready access to a BMD measurement, a DXA measurement before commencing therapy is recommended, even in cases of typical minimal trauma fracture. A normal or near normal BMD, despite existing fractures, should always initiate a more extensive diagnostic work-up to exclude other potential causes of fracture. A normal BMD despite typical vertebral fractures also poses a problem with regard to the usefulness of anti-osteoporotic treatments that have not been tested in such a population. Such discrepant findings should be resolved on an individual basis. A past history of high-trauma falls resulting in vertebral fracture can leave evidence of vertebral deformities which may not indicate underlying osteoporosis. In such situations, consultation with a bone health expert (eg endocrinologist, rheumatologist) may be warranted.

- If radiographs reveal one or more vertebral fractures typical of osteoporosis, BMD measurement may not be essential before starting medical therapy, if this is appropriate to the overall clinical situation. There are a limited number of scenarios in which a meaningful evaluation of BMD is not possible despite fractures typical of osteoporosis (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 BMD 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 as well characterised as that in the spine and hip.

Repeat BMD testing

The use of repeat DXA scans at intervals of two years or longer is appropriate in settings where the efficacy of treatment, risk assessment or decision to change or interrupt treatment is being considered.^{6,7} Due to limitations in the precision of BMD testing, a minimum of two years may be needed to reliably measure a change in BMD. If BMD is stable and/or individual is at low risk of fracture (normal or mild osteopenia; T-score >-1.5), less-frequent monitoring, up to an interval of 5–15 years, can be considered. Shorter intervals between repeat DXA scans, at intervals of one year, may be appropriate in high-risk individuals (eg patients on corticosteroid therapy or induced hypogonadism). In all cases, the expected rate of change in BMD and fracture risk should guide repeat measurement.^{8,9}

Quantitative computed tomography BMD

Quantitative computed tomography (QCT) BMD measurement procedures can provide equivalent hip BMD to DXA scans and may be interpreted using the WHO T-score criteria.¹ Spinal QCT also provides information on fracture risk, but it is important to note that the WHO T-score osteoporotic criteria cannot be applied in this situation. Fracture risk in QCT of the spine is most commonly interpreted using the criteria of the American College of Radiology.¹⁰ There are no data demonstrating reduction of fracture risk by specific anti-osteoporotic treatment chosen on the basis of QCT measurements. However, given the equivalency of hip QCT to hip DXA, there is no reason to doubt the utility of hip QCT in guiding therapy.¹ The disadvantage of QCT remains the significantly higher radiation exposure compared to DXA,¹¹ particularly in the hip. DXA of the spine and hip remains the recommended measurement for diagnosis of osteoporosis and baseline BMD assessment. In some patients with moderate to severe osteoarthritic changes, spine QCT may have a particular advantage as it is less affected than DXA by osteoarthritic changes.

Quantitative ultrasound

Quantitative ultrasound (QUS) of the heel and other sites can provide information on fracture risk. However, QUS has not been demonstrated to provide information on absolute fracture risk and the reduction of fracture risk by a specific anti-osteoporotic treatment. QUS is not recommended as a diagnostic test for osteoporosis.

Biochemical markers of bone turnover

Increased biochemical markers 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. Bone turnover markers are useful markers of compliance and response to treatment and may help guide choice of treatments. However, variability in analysis and lack of standardisation reduce the utility of these assessments. The International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine recommend one serum bone formation marker (procollagen type I amino-terminal propeptide, or PINP) and one bone resorption marker (C-terminal telopeptide, or CTX) to be used as reference markers. These should be measured by standardised assays in observational and intervention studies in order to compare the performance of alternatives and to enlarge the international experience of the application of markers to clinical medicine.¹² Such standardised Australian reference intervals are now available for serum PINP and CTX in women and men.¹³

Evidence statement

Two major international guidelines recommend that the diagnostic assessment for osteoporosis consist of medical history, clinical examination, BMD measurement by DXA, and, if applicable, laboratory tests and radiographs of the thoracic and lumbar spine.^{2,3} The recommended standard procedure for BMD measurement is bone densitometry by DXA.¹⁻³

For some patients at risk, as indicated by history, clinical examination or Z-scores <-2.0 , laboratory findings can reveal unsuspected secondary osteoporosis or may influence some aspects of diagnostics and therapy. In patients in whom a specific secondary, treatable cause of osteoporosis is being considered, relevant blood and urine studies should be obtained prior to initiating therapy.²

References

1. The International Society for Clinical Densitometry. 2015 ISCD official positions – Adult. Middletown, CT: ISCD, 2015. Available at www.iscd.org/official-positions/2015-iscd-official-positions-adult [Accessed 31 January 2017].
2. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation, 2014.
3. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract* 2010;16 Suppl 3:1–37.
4. Johansson H, Kanis JA, Oden A, Johnell O, McCloskey E. BMD, clinical risk factors and their combination for hip fracture prevention. *Osteoporos Int* 2009;20(10):1675–82.
5. McMahon K, Kalnins S, Freund J, Pocock N. Discordance in lumbar spine T-scores and nonstandardization of standard deviations. *J Clin Densitom* 2003;6(1):1–6.
6. Leslie WD, Majumdar SR, Morin SN, Lix LM. Change in bone mineral density is an indicator of treatment-related antifracture effect in routine clinical practice: A registry-based cohort study. *Ann Intern Med* 2016;165(7):465–72. doi:10.7326/M15-2937.
7. Austin M, Yang YC, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res* 2012;27(3):687–93.
8. Berger C, Langsetmo L, Joseph L, et al. Association between change in BMD and fragility fracture in women and men. *J Bone Miner Res* 2009;24(2):361–70.
9. Nguyen TV, Center JR, Eisman JA. Femoral neck bone loss predicts fracture risk independent of baseline BMD. *J Bone Miner Res* 2005;20(7):1195–201.
10. American College of Radiology. ACR practice guideline for the performance of quantitative computed tomography (QCT) bone densitometry. Reston, VA: ACR, 2008.
11. Njeh CF, Fuerst T, Hans D, Blake GM, Genant HK. Radiation exposure in bone mineral density assessment. *Appl Radiat Isot* 1999;50(1):215–36.
12. Vasikaran S, Eastell R, Bruyère O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: A need for international reference standards. *Osteoporos Int* 2011;22(2):391–420.
13. Vasikaran SD, Chubb SP, Ebeling PR, et al. Harmonised Australian reference intervals for serum PINP and CTX in adults. *Clin Biochem Rev* 2014;35(4):237–42.

Assessment of absolute fracture risk

Recommendation 6	Grade
Assessment of absolute fracture risk, using either the Garvan Fracture Risk Calculator (www.garvan.org.au/bone-fracture-risk) or the Fracture Risk Assessment Tool (www.shef.ac.uk/FRAX) may be useful in assessing the need for treatment in individuals who do not clearly fit established criteria.	D

In addition to bone mineral density (BMD), there are other clinical factors associated with minimal trauma fracture risk. Two individuals with similar BMD measurements, but different clinical risk factors, will have different risk of fracture. Increasing age, prior minimal trauma fracture and propensity to fall are the clinical risk factors most strongly associated with increased fracture risk.¹ Fracture risk may be expressed as either relative risk or absolute risk. Absolute risk is the numerical risk of an event for an individual over a specified period of time. Absolute fracture risk is most commonly expressed as an individual's percentage chance of suffering a minimal trauma fracture over a given period of time, generally five or 10 years. Relative risk compares an individual's risk of an event (such as a fracture), to the risk of that event in a reference population, or to the baseline risk at a given point in time. An individual's relative risk will depend on the comparison group used. Assessing only the relative risk can lead to erroneous conclusions. For example, if the background absolute risk of a fracture at a given point of time is low (eg 0.2% five-year risk) then even after a doubling of that risk (relative risk increases to 2), the absolute risk remains low (0.4% five-year risk).

Practical tips and precautions

- Absolute fracture risk is not a qualifier for access to Pharmaceutical Benefits Scheme (PBS)-subsidised therapies.
- Estimation of absolute fracture risk using a fracture risk calculator does not take into account lumbar spine BMD, and such estimates should not disqualify therapeutic decisions made on the basis of a low lumbar spine T-score.
- Calculator-based estimations of fracture risk are estimates only, and should always be interpreted in the clinical, racial and cultural context of the patient.
- Absolute fracture risk is currently in use internationally as a basis for treatment decisions. Cost-effectiveness evaluation studies are underway.

Absolute fracture risk calculators

A number of absolute fracture risk calculators are now available. These aim to better estimate an individual's fracture risk by taking into account age and clinical risk factors as well as BMD, and have the potential to allow more effective targeting of therapy for osteoporosis. In Australia, the most common absolute fracture risk calculators in use are the following:

- Garvan Fracture Risk Calculator (GFRC). The GFRC was developed in Australia using data from the Dubbo Osteoporosis Epidemiology Study.^{2,3}
- Fracture Risk Assessment Tool (FRAX). FRAX uses data from nine epidemiological studies as well as the results of the placebo arms of clinical trials to estimate absolute fracture risk.^{4,5} Dual energy X-ray absorptiometry (DXA) scanners that incorporate specialised software have the ability to provide a FRAX estimate of absolute fracture risk.

While aiming to achieve the same outputs, FRAX and GFRC use different algorithms to estimate absolute fracture risk. The FRAX algorithm uses 13 risk factors, while GFRC uses five (Table 4). More variables however do not necessarily improve prediction, and fracture-risk calculators with five or fewer variables have been shown to perform as well as those with more variables.⁶ Both FRAX and GFRC can be used to calculate absolute fracture risk when BMD measurement is not available, because BMD is largely determined by age and weight. The different algorithms do result in different estimates of absolute fracture risk. FRAX was developed using multinational epidemiological data, and as such provides a country-specific fracture risk that takes into account different baseline fracture and

mortality rates. If a particular country is not available, FRAX recommends the use of the country most similar to the patient's background.

There are a number of other differences between FRAX and GFRC:

- FRAX predicts 'major osteoporotic fractures', categorised as clinical spine, hip, forearm or shoulder fracture. GFRC predicts any osteoporotic fracture.
- FRAX determines an individual's fracture risk over a 10-year period, while GFRC provides both five- and 10-year fracture predictions.
- FRAX links to a website that can adjust fracture risk estimate based on the patient's trabecular bone score.
- Both FRAX and GFRC are available online. FRAX is also available as part of the latest DXA software from all DXA scanner manufacturers and is therefore more readily accessible at the present time.

The FRAX and GFRC calculators both have limitations:

- Falls as a risk factor for fracture is not included in the FRAX calculator. Falls risk is, however, recognised as an independent risk factor for fracture. Falls and number of falls are included in the GFRC.
- The FRAX questionnaire provides a number of risk factors as binary variables (yes/no) and does not allow graduations in exposure to risk factors, including prior fractures, smoking, alcohol use and glucocorticoid use.
- FRAX calculates a 10-year fracture risk for hip fracture and the combined group of 'major osteoporotic' fractures. Many other fractures, including rib, other femur, tibia and fibular fractures, are excluded.
- GFRC uses fewer risk factors and does not include known variables which increase fracture risk (ie family history of fracture).
- GFRC was determined from a broad based Australian population of mixed ethnicity, predominantly Caucasian. Its applicability to other racial groups and to immigrants who have spent a significant period of their lives overseas is uncertain. GFRC has, however, been validated in a number of international populations, including Canada, the Netherlands and Poland.^{7,8}

Predictive accuracy

A number of studies have compared FRAX to GFRC in estimating fracture risk. The majority of these studies suggest that FRAX may underestimate fracture risk in men and women. GFRC possibly performs better than FRAX in men and at least as well in postmenopausal women,⁹ but overestimates fracture risk in patients in the highest quintile of risk. The impact of this overestimate on clinical practice is likely to be small, as osteoporosis treatment would generally be recommended in this group.¹⁰ Interestingly, some studies suggest that neither FRAX nor GFRC provide a better estimate of fracture risk than using age and BMD alone.^{11,12}

Fracture-risk intervention threshold

A potential important clinical application for fracture-risk calculators is to improve selection of individuals in whom to recommend treatment. Individuals who have not fractured but are in the osteoporotic BMD range, or middle-aged to elderly individuals with prior minimal trauma fracture, generally have high calculated absolute fracture risk, supporting a recommendation for treatment. Individuals with BMD values within the osteopenic range but without a prior history of fracture are more likely to benefit from fracture-risk algorithms. In this group, a high fracture risk estimate may change management and lead to therapy recommendation. Health economic modelling in the UK^{13,14} and USA¹⁵ has demonstrated that treatment is cost-effective when FRAX is used to identify at-risk patients. Based on a drug cost of \$US600 per year for five years (with 35% fracture reduction) and an average cost per quality-adjusted life year (QALY) designated at \$US60,000 or less, the US National Osteoporosis Foundation guidelines recommend treatment when the 10-year risk of hip fracture estimated by FRAX is 3% or higher, or the 10-year risk of major osteoporotic fracture is 20% or higher.¹⁶ Prospective studies to validate the clinical benefit and cost-effectiveness of this recommendation are not yet available.

Barriers to the implementation of fracture-risk calculators

The two major factors limiting widespread uptake of absolute fracture-risk calculators by clinicians are a general lack of awareness about how and when to use fracture risk calculators, and the requirement for significant general practitioner and specialist education. The PBS does not recognise absolute fracture risk as an indication for access to subsidised therapies to treat osteoporosis.

The main goal of treatment for osteoporosis is fracture prevention. Quantitative assessment of an individual's fracture risk has the potential to better guide decisions on pharmaceutical treatment.^{17–20} This could, for example, lead to high-risk osteopenic patients without fracture receiving effective therapy. Conversely, in situations of low absolute fracture risk where treatment can be safely delayed, the fracture-risk calculators may potentially limit unnecessary therapy, as well as the associated costs and side effects. The absolute fracture-risk estimates also provide medical practitioners with a tool to educate patients, potentially allowing them to better understand their own fracture risk. This would lead to more informed decisions on whether or not treatment is warranted.

Table 4. Clinical risk factors used in GFRC and FRAX	
FRAX	GFRC
Age	Age
Sex	Sex
Weight	Weight
Height	BMD
Femoral neck BMD	Prior fracture (and number)
Prior fracture	Number of falls in last 12 months
Rheumatoid arthritis	
Glucocorticoids	
Alcohol	
Smoking	
Trabecular bone score	
Parental hip fracture	
Secondary osteoporosis	

References

1. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002;359(9319):1761–67.
2. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. *Osteoporos Int* 2008;19(10):1431–44.
3. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. *Osteoporos Int* 2007;18(8):1109–17.
4. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;19(4):385–97.
5. Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007;18(8):1033–46.
6. Nelson HD, Haney EM, Dana T, Bougatsos C, Chou R. Screening for osteoporosis: An update for the US preventive services task force. *Ann Intern Med* 2010;153(2):99–111.
7. Pluskiewicz W, Adamczyk P, Franek E, et al. Ten-year probability of osteoporotic fracture in 2012 Polish women assessed by FRAX and nomogram by Nguyen et al. — Conformity between methods and their clinical utility. *Bone* 2010;46(6):1661–67.
8. Van Geel T, Geusens P, Dinant GJ, Huntjens K, Bours S, van den Bergh J. Comparing FRAX and Garvan fracture risk calculator in postmenopausal women: A prospective 5-year follow-up study. *Bone* 2011;48:S63.
9. Sandhu SK, Nguyen ND, Center JR, Pocock NA, Eisman JA, Nguyen TV. Prognosis of fracture: Evaluation of predictive accuracy of the FRAX™ algorithm and Garvan nomogram. *Osteoporos Int* 2010;21(5):863–71.
10. Langsetmo L, Nguyen TV, Nguyen ND, et al. Independent external validation of nomograms for predicting risk of low-trauma fracture and hip fracture. *CMAJ* 2011;183(2):E107–14.
11. Trémollières FA, Pouillès JM, Drewniak N, Laparra J, Ribot CA, Dargent-Molina P. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: Sensitivity of the WHO FRAX tool. *J Bone Miner Res* 2010;25(5):1002–09.
12. Bolland MJ, Siu AT, Mason BH, et al. Evaluation of the FRAX and Garvan fracture risk calculators in older women. *J Bone Miner Res* 2011;26(2):420–27.
13. McCloskey E, Kanis JA, Johansson H, et al. FRAX-based assessment and intervention thresholds – An exploration of thresholds in women aged 50 years and older in the UK. *Osteoporos Int* 2015;26(8):2091–99.
14. Kanis JA, McCloskey EV, Johansson H, et al. Case finding for the management of osteoporosis with FRAX – Assessment and intervention thresholds for the UK. *Osteoporos Int* 2008;19(10):1395–408.
15. Dawson-Hughes B, Tosteson AN, Melton LJ 3rd, et al. Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int* 2008;19(4):449–58.
16. Tosteson AN, Melton LJ, Dawson-Hughes B, et al. Cost-effective osteoporosis treatment thresholds: The United States perspective. *Osteoporos Int* 2008;19(4):437–47.
17. McCloskey EV, Johansson H, Oden A, et al. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. *J Bone Miner Res* 2012;27(7):1480–86.
18. Kaufman JM, Palacios S, Silverman S, Sutradhar S, Chines A. An evaluation of the Fracture Risk Assessment Tool (FRAX®) as an indicator of treatment efficacy: The effects of bazedoxifene and raloxifene on vertebral, nonvertebral, and all clinical fractures as a function of baseline fracture risk assessed by FRAX®. *Osteoporos Int* 2013;24(10):2561–69.
19. Harvey NC, Kanis JA, Oden A, et al. Efficacy of weekly teriparatide does not vary by baseline fracture probability calculated using FRAX. *Osteoporos Int* 2015;26(9):2347–53.
20. Harvey NC, Kanis JA, Oden A, et al. FRAX and the effect of teriparatide on vertebral and non-vertebral fracture. *Osteoporos Int* 2015;26(11):2677–84.

Referral to a medical specialist

Recommendation 7	Grade
Refer postmenopausal women and men over 50 years of age to a specialist or a specialist bone centre according to individual need, or when there is restricted access to appropriate resources or required expertise.	D – consensus

Practical tips and precautions

The following conditions might require a referral to a specialist or a specialist bone centre, depending on individual circumstances:

- Lack of access to appropriate bone densitometry service
- Osteoporosis is unexpectedly severe or has unusual features at the time of initial assessment
- Inadequate response to therapy, despite good adherence
- Contraindications to standard therapies
- Presence of other complex medical conditions
- Experiencing serious or unacceptable adverse effects with treatment
- Continuing to fracture despite normal bone mineral density (BMD)
- Secondary cause is identified or suspected (eg Z-score ≤ -2.0)

Evidence statement

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 general practitioner (GP) expertise and support. 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 men over 50 years of age:^{1,2}

- Osteoporosis is unexpectedly severe or has unusual features at the time of initial assessment
- Intolerance of first and second-line therapies, or experiencing problems beyond the scope of general practice
- Fracture or significant ongoing loss of BMD while on first-line therapy, despite good adherence
- Secondary causes that are outside the scope of general practice
- Initiation of teriparatide treatment
- Not having access to appropriate bone densitometry

References

1. National Osteoporosis Guideline Group. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 in the UK. Sheffield, UK: NOGG, 2014.
2. Papaioannou A, Morin S, Cheung AM, et al. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. *CMAJ* 2010;182(17):1864–73.

General bone-health maintenance and fracture prevention strategies

Prevention implies improvement in, and maintenance of, normal bone mineral density (BMD) and minimising the bone loss that is seen in postmenopausal women and ageing men, as well as prevention of minimal trauma fractures (which may occur in those with normal BMD or osteopenia as well). Fracture risk increases over the lifetime, due to declining BMD and strength, as well as to non-skeletal risk factors for falls, including sarcopenia, poor balance, neuropsychological impairment, polypharmacy, poor nutrition and chronic diseases. As such, there is a gradual transition from prevention to treatment paradigms with advancing age, with the emphasis on BMD from childhood to middle age broadening to other factors implicated in falls risk in later life.

Diet and lifestyle

Recommendation 8	Grade
<p>Promote the following important lifestyle choices for all postmenopausal women and men over 50 years of age:</p> <ul style="list-style-type: none"> • Adequate calcium and protein intake • Adequate but safe exposure to sunlight as a source of vitamin D • Maintenance of a healthy weight and body mass index • Cessation of smoking • Avoidance of excessive alcohol consumption 	C

Evidence statement

Osteoporosis is associated with a number of lifestyle factors, including nutritional intake, vitamin D status, physical activity, smoking and alcohol consumption. International guidelines recommend healthy lifestyle choices to reduce risks associated with osteoporosis.^{1,2}

Calcium

To help maintain optimum bone health, the Australian recommended dietary intake (RDI) is 1300 mg per day for women older than 50 years of age, 1000 mg per day for men 50–70 years of age, and 1300 mg per day for men older than 70 years of age.³ The Australian adult population does not meet RDIs for calcium. In 2011–2012, the average daily intake for people 51–70 years of age was 781 mg for males and 741 mg for females, with intakes lower in people older than 70 years of age.⁴ With ageing, absorption of calcium becomes less effective.^{5,6}

The richest sources of dietary calcium are dairy foods – milk, cheese and yoghurt. At least three serves of dairy food per day is recommended.³ High-fat soft cheeses should be avoided, and low-fat milks and yogurts chosen over regular varieties. Other calcium-rich foods include firm tofu (check label), almonds, sesame seeds, tinned fish, some green leafy vegetables, dried figs and calcium fortified soy milk.⁷ Patients who cannot achieve adequate calcium intake through diet alone may require supplementation.³ Guidelines for Australian recommended dietary intakes are listed in ‘[Resources and further information](#)’ earlier.

The evidence for the relationship between dietary calcium intake and fracture risk is contradictory; much is confounded by different methods of assessing calcium intake and the problems inherent in the self-reporting of calcium intake. A 19-year prospective cohort study of over 61,000 older Swedish women found that dietary intakes below 700 mg per day are associated with increased risk of fracture, including hip fracture, but higher

intakes of dietary calcium only marginally reduce fracture risk.⁸ The rate of self-reported fractures in a five-year prospective study of approximately 35,000 British men and women was substantially increased in women with a dietary calcium intake of less than 525 mg per day. Fracture rates decreased with each quintile of increasing calcium intake, up to at least 1200 mg per day.⁹ Several meta-analyses (MAs)^{10–12} have concluded that dietary calcium has no effect on fracture risk, and a recent systematic review of 44 cohort studies found no association between dietary calcium intake in people older than 50 years of age and risk of fracture.¹³ In general, the inadequate design and imprecision of studies into the effects of dietary calcium on fracture risk precludes the drawing of robust conclusions, and MAs have reported considerable heterogeneity.

The importance of adequate calcium intake throughout life for the building and maintenance of the skeleton is supported by Australian and New Zealand guidelines.¹⁴

Vitamin D

Vitamin D has an important role in maintaining bone health by promoting the absorption of calcium. Although some vitamin D can be acquired through diet (fatty fish, egg yolks, liver, irradiated mushrooms), the primary source for those residing in Australia is exposure to sunlight. Ultraviolet (UV) radiation from the sun has both beneficial and harmful effects on human health. A balance is required between excessive sun exposure, which increases the risk of skin cancer, and enough exposure to maintain adequate vitamin D levels. In Australia, the current recommendation for people with moderately fair skin is exposure of approximately 15% of the body (ie hands, face and arms) for 5–10 minutes, on most days of the week in summer before 10.00 am or after 3.00 pm (standard time).¹⁵ Exposure in winter should be 7–30 minutes, in the middle of the day. Exposure time depends on latitude and skin tone, with lower latitudes and darker skins requiring the longest exposures, as well as body fat level (obesity is associated with less synthesis of vitamin D).^{16,17} Clinicians should refer to recent national guidelines on seasonal sun exposure according to latitude and UV index.¹⁸

Additionally, after the age of 70, the skin is less efficient or incapable in some individuals of synthesising adequate amounts of vitamin D.¹⁹ Vitamin D supplements may be needed in order to maintain adequate levels.

Body weight

Low body mass index (BMI) is an established risk factor for fracture. An MA of almost 60,000 participants in 12 prospective population-based cohorts worldwide found that the risk of any type of fracture increased significantly with lower BMI, largely independent of age and sex.²⁰ When compared with a BMI of 25, a BMI of 20 was associated with a two-fold increased risk of hip fracture, independent of BMD. The association between high BMI and fracture risk is more complex. An MA of approximately 400,000 women from 25 prospective cohorts worldwide²¹ suggests that at a population level, high BMI (>35 kg/m²) is protective for all types of minimal trauma fracture, except humeral fracture. When adjusted for BMD however, obesity slightly increases the risk of all fractures. Weight fluctuation also appears to influence fracture risk. Post hoc analysis of data from over 120,000 women taking part in the Women's Health Initiative (WHI) observational study and clinical trials demonstrated that both weight gain and weight loss are associated with increased fracture incidence.²² Women who lost more than 5% of their baseline body weight over three years increased their risk of hip fracture by 65%, compared to those who maintained stable weight for three years. Significantly higher rates of spinal fracture were also seen in this group. A 5% weight gain over three years was associated with higher incidence of upper- and lower-limb fractures.²² The relationship between body weight and fracture risk is complex. Guidance related to weight control should balance an individual's current comorbidity status and/or comorbidity risk associated with overweight and obesity, such as type 2 diabetes and cardiovascular disease, with their risk of osteoporotic fracture. In particular, the increased risk of falls and fracture associated with frailty (of which weight loss is a component) in older individuals should be considered.

Smoking

Smoking is a well-recognised risk factor for osteoporosis. An MA of over 59,000 men and women in 10 prospective cohort studies found that current smoking is significantly associated with increased risk of any fracture, compared to non-smokers (relative risk [RR]: 1.25, 95% confidence interval [CI]: 1.15–1.36). The highest risk was seen for hip fracture.²³ A past history of smoking was also associated with significantly increased fracture risk in this analysis. The risk was lower than for current smoking, indicating that risk is

attenuated with cessation of smoking. Although smokers tend to be thinner than non-smokers, low BMD could only account for 23% of smoking-related hip fractures in this study, indicating a potential direct effect of cigarette smoke toxins on bone metabolism.²³

Alcohol

Excessive alcohol intake is also associated with increased fracture risk. A recent systematic review and MA of 22 observational studies suggests a significantly increased risk of fracture in men consuming alcohol daily or consuming more than 10 drinks per week (RR: 1.28, CI: 1.08–1.53).²⁴ An analysis of three prospective cohorts (approximately 6000 men and 11,000 women) also found a significant increase in hip-fracture risk with alcohol intake, although no increased risk was seen in men and women consuming two units or less daily.²⁵ Risk was only marginally lower in women compared to men. These observations were independent of BMD.²⁵ General practitioners should consult recent Royal Australian College of General Practitioners (RACGP) guidelines that outline preventive-health strategies and smoking-cessation interventions.^{26–28}

References

1. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation, 2014.
2. Scottish Intercollegiate Guidelines Network. Management of osteoporosis and the prevention of fragility fractures. Edinburgh: SIGN, 2015.
3. Department of Health and Ageing and National Health and Medical Research Council. Nutrient reference values for Australia and New Zealand. Canberra, ACT: DoHA and NHMRC, 2006.
4. Australian Bureau of Statistics. Australian health survey: Nutrition first results – Food and nutrients, 2011–2012. ABS cat. no. 4364.0.55.007. Belconnen, ACT: ABS, 2014. Available at www.abs.gov.au/ausstats/abs@.nsf/Lookup/4364.0.55.007main+features12011-12 [Accessed 1 February 2017].
5. Nordin BE, Need AG, Morris HA, O'Loughlin PD, Horowitz M. Effect of age on calcium absorption in postmenopausal women. *Am J Clin Nutr* 2004;80(4):998–1002.
6. Nordin BE, Morris HA. Recalculation of the calcium requirement of adult men. *Am J Clin Nutr* 2011;93(2):442–45.
7. Food Standards Australia New Zealand. Nutrient tables for use in Australia (NUTTAB) 2010. Barton, ACT: FSANZ, 2010. Available at www.foodstandards.gov.au/science/monitoringnutrients/nutrientables/pages/default.aspx [Accessed 1 February 2017].
8. Warensjo E, Byberg L, Melhu H, et al. Dietary calcium intake and risk of fracture and osteoporosis: Prospective longitudinal cohort study. *BMJ* 2011;342:d1473.
9. Key TJ, Appleby PN, Spencer EA, Roddam AW, Neale RE, Allen NE. Calcium, diet and fracture risk: A prospective study of 1898 incident fractures among 34,696 British women and men. *Public Health Nutr* 2007;10(11):1314–20.
10. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: A meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* 2007;86(6):1780–90.
11. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Milk intake and risk of hip fracture in men and women: A meta-analysis of prospective cohort studies. *J Bone Miner Res* 2011;26(4):833–39.
12. Xu L, McElduff P, D'Este C, Attia J. Does dietary calcium have a protective effect on bone fractures in women? A meta-analysis of observational studies. *Br J Nutr* 2004;91(4):625–34.
13. Bolland MJ, Leung W, Tai V, et al. Calcium intake and risk of fracture: Systematic review. *BMJ* 2015;351:h4580.
14. Ebeling PR, Daly RM, Kerr DA, Kimlin MG. Building healthy bones throughout life: An evidence-informed strategy to prevent osteoporosis in Australia. *Med J Aust* 2013;2 Suppl 1:1–10.
15. Nowson CA, McGrath JJ, Ebeling PR, et al. Vitamin D and health in adults in Australia and New Zealand: A position statement. *Med J Aust* 2012;196(11):686–87.
16. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;72(3):690–93.
17. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: A systematic review and meta-analysis. *Obes Rev* 2015;16(4):341–49.
18. Cancer Council Australia. Position statement – Sun exposure and vitamin D – Risks and benefits. Sydney: Cancer Council Australia, 2016. Available at http://wiki.cancer.org.au/policy/Position_statement_-_Risks_and_benefits_of_sun_exposure#_ga=1.231230879.1861465295.1485905775 [Accessed on 1 February 2017].
19. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* 1985;76(4):1536–38.
20. De Laet C, Kanis JA, Odén A, et al. Body mass index as a predictor of fracture risk: A meta-analysis. *Osteoporos Int* 2005;16(11):1330–38.
21. Johansson H, Kanis JA, Odén A, et al. A meta-analysis of the association of fracture risk and body mass index in women. *J Bone Miner Res* 2014;29(1):223–33.
22. Crandall CJ, Yildiz VO, Wactawski-Wende J, et al. Postmenopausal weight change and incidence of fracture: Post hoc findings from Women's Health Initiative Observational Study and Clinical Trials. *BMJ* 2015;350:h25.
23. Kanis JA, Johnell O, Odén A, et al. Smoking and fracture risk: A meta-analysis. *Osteoporos Int* 2005;16(2):155–62.
24. Drake MT, Murad MH, Mauck KF, et al. Risk factors for low bone mass-related fractures in men: A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2012;97(6):1861–70.
25. Kanis JA, Johansson H, Johnell O, et al. Alcohol intake as a risk factor for fracture. *Osteoporos Int* 2005;16(7):737–42.
26. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 8th edn. East Melbourne, Vic: RACGP, 2012.
27. The Royal Australian College of General Practitioners. Supporting smoking cessation: A guide for health professionals. East Melbourne, Vic: RACGP, 2011 [updated 2014].
28. The Royal Australian College of General Practitioners. Smoking, nutrition, alcohol, physical activity (SNAP): A population health guide to behavioural risk factors in general practice. 2nd edn. East Melbourne, Vic: RACGP, 2015.

Education and psychosocial support

Recommendation 9	Grade
Provide postmenopausal women and men over 50 years of age at risk of or diagnosed with osteoporosis, access to education, psychosocial support and encouragement to seek support from appropriate sources according to individual needs.	D – consensus

Osteoporosis is a chronic disease. Those at risk of developing osteoporosis may require access to education about disease prevention and strategies to encourage reduction in disease risk. Patients who have been diagnosed with osteoporosis may require ongoing education to improve medication adherence, as well as assistance with self-management strategies and 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, fear of falling).

Evidence statement

International guidelines recommend educational interventions for patients following a fragility fracture in order to increase the likelihood of adoption of bone-protective behaviours and to improve adherence to medication.^{1,2} High-quality trial or observational evidence concerning the value of education and psychosocial support for osteoporosis is lacking, particularly in the area of primary prevention. A systematic review of 13 cross-sectional studies investigating men's knowledge of osteoporosis found that men know very little about the disease, its risk factors, or prevention.³ Educational interventions were found to increase initiation of calcium supplementation and knowledge about osteoporosis prevention in this group. A two-year Australian randomised controlled trial of 470 healthy women aged 25–44 years found that individualised feedback on bone mineral density (BMD), combined with minimal education via leaflet or small groups is effective at increasing hip but not spine BMD in premenopausal women.⁴ Although any long-term benefits could not be ascertained by this study, the authors noted the potential for behavioural change in other disease risk areas using this approach.

Specific osteoporosis self-management programs are conducted by public hospital health-promotion units and community health centres. It is the consensus of the Working Group that general practitioners have an important role in delivering patient education, psychosocial support and referral to support groups where needed.

References

1. Scottish Intercollegiate Guidelines Network. Management of osteoporosis and the prevention of fragility fractures. Edinburgh: SIGN; 2015.
2. Papaioannou A, Morin S, Cheung AM, et al. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. *CMAJ* 2010;182(17):1864–73.
3. Gaines JM, Marx KA. Older men's knowledge about osteoporosis and educational interventions to increase osteoporosis knowledge in older men: A systematic review. *Maturitas* 2011;68(1):5–12.
4. Winzenberg T, Oldenburg B, Frendin S, De Wit L, Riley M, Jones G. The effect on behavior and bone mineral density of individualized bone mineral density feedback and educational interventions in premenopausal women: A randomized controlled trial. *BMC Public Health* 2006;6:12. doi:10.1186/1471-2458-6-12.

Reducing the risk of falls

Recommendation 10	Grade
Conduct falls risk assessments and initiate targeted fall-prevention programs in older adults.	A

Most people who sustain peripheral fractures do so after a fall. There is systematic review evidence that a range of interventions significantly reduce falls^{1,2} and that falls prevention exercise programs significantly reduce fall-related injuries including fractures.^{2,3} Therefore, assessing a person's risk of falling and implementing strategies to reduce this risk are also likely to reduce the risk of fractures.⁴

Screening and assessment for fall risk

A falls risk screen involves asking the following three questions:^{5,6}

1. Have you had two or more falls in the past 12 months?
2. Are you presenting following a fall?
3. Are you having difficulty with walking or balance?

If the answers to any of these are positive, a falls risk assessment is indicated.^{5,6} This comprises obtaining relevant medical history, completion of a physical examination, and cognitive and functional assessments to determine multifactorial fall risk:

- history of falls
- multiple medications, and specific medications (eg psychotropic medications and opiate-containing analgesic agents)
- impaired gait, balance and mobility
- impaired visual acuity, including cataracts
- issues with bifocal or multifocal spectacle use
- reduced visual fields
- other neurological impairment
- muscle weakness
- cardiac dysrhythmias
- postural hypotension
- foot pain and deformities and unsafe footwear
- home hazards
- vitamin D deficiency.

A quick screening tool is the timed up and go (TUG) test, which involves looking for unsteadiness as the older person gets up from a chair without using his or her arms, walks 3 m and returns.⁷ Simple alternatives to the TUG test are the repeated chair-standing test and the alternate-step test. The repeated chair-standing test measures how quickly an older person can rise from a chair five times without using his or her arms.⁸ A time of >12 seconds indicates an increased fall risk. The alternate-step test measures how quickly an older person can alternate steps (left, right, left, etc) onto an 18-cm-high step a total of eight times.⁸ A time >10 seconds indicates an increased fall risk.

Practical tips and precautions

To be successful, a falls prevention program needs to be tailored to the individual's needs and may include multiple strategies. A falls prevention program may include the following:^{5,6}

- Education on the risk of falling and prevention strategies.
- Prescription or referral for a home-based exercise program and/or encourage participation in a community-based exercise program. In either case, exercise for preventing falls needs to include medium-intensity to high-intensity balance training (ie exercises must be undertaken while standing and challenge balance), and be of long duration, preferably ongoing.⁹
- Medications reviews and discontinuation of centrally acting medications where appropriate.
- Prescribing of vitamin D for people with vitamin D levels <50 nmol/L for older people living in the community and prescription of vitamin D (unless contraindicated) for all older people living in residential aged care.¹⁰
- Referral of people with painful feet or foot deformities to podiatry for intervention.
- Provision of advice on the dangers of bifocal and multifocal glasses when walking outdoors (blurring of ground-level obstacles) and recommendation of the wearing of single lens glasses when outdoors.
- Identification of cataracts and referral for cataract extraction.
- Referral of people with a history of recent falls for an occupational therapy home assessment.
- Treatment of postural hypotension and cardiovascular disorders.

Evidence statement

A Cochrane review of 159 randomised controlled trials (RCTs) reported that multiple-component group exercise significantly reduces risk of falling (relative risk [RR]: 0.85, 95% confidence interval [CI]: 0.76–0.96, 22 trials, 5333 participants), as does multiple-component home-based exercise (RR: 0.78, 95% CI: 0.64–0.94, six trials, 714 participants).¹ Multifactorial interventions, which include individual risk assessment, were also found to reduce the rate of falls (Rate ratio [RaR]: 0.76, 95% CI: 0.67–0.86, 19 trials, 9503 participants).¹ Another systematic review of community-based falls prevention exercise programs found a significant reduction in the risk of fracture (RR: 0.39, 95% CI: 0.22–0.66, six trials).² A further recent meta-analysis indicates that exercise interventions prevent fall-related fractures in men and women 50 years of age and older (RR: 0.604, 95% CI: 0.453–0.840, $P = 0.003$, 15 studies, 3136 participants) and reduce risk factors for fall-related fractures (leg strength and balance).³ An RCT of home-based interventions teaching principles of balance and strength training and integrated selected activities into everyday routines (Lifestyle-integrated Functional Exercise [LIFE] program) was found to reduce the rate of falls by 31% (RaR: 0.69, 95% CI: 0.48–0.99).¹²

Overall, vitamin D supplements were not found to reduce risk of falling, but may do so in people with lower vitamin D levels before treatment.¹ Home-safety assessment and modification interventions were effective in reducing risk of falling (RR: 0.88, 95% CI: 0.80–0.96, seven trials, 4051 participants). These interventions were more effective in people at higher risk of falling, including those with severe visual impairment and implemented by an occupational therapist. An intervention to treat vision problems (616 participants) resulted in a significant increase in the risk of falling (RR: 1.54, 95% CI: 1.24–1.91). When regular wearers of multifocal glasses (597 participants) were given single-lens glasses, both inside and outside falls were significantly reduced in the sub-group that regularly took part in outside activities. Conversely, there was a significant increase in outside falls in intervention group participants who took part in little outside activity. Pacemakers reduced the rate of falls in people with carotid sinus hypersensitivity (RaR: 0.73, 95% CI: 0.57–0.93, three trials, 349 participants). First eye cataract surgery in women reduced the rate of falls (RaR: 0.66, 95% CI: 0.45–0.95, one trial, 306 participants), but second eye cataract surgery did not. Gradual withdrawal of psychotropic medication reduced the rate of falls (RaR: 0.34, 95% CI: 0.16–0.73, one trial, 93 participants), but not the risk of falling. A prescribing modification program for primary care physicians significantly reduced the risk of falling

(RR: 0.61, 95% CI: 0.41–0.91, one trial, 659 participants). One trial (305 participants) comparing multifaceted podiatry, including foot and ankle exercises, with standard podiatry in people with disabling foot pain significantly reduced the rate of falls (RaR: 0.64, 95% CI: 0.45–0.91) but not the risk of falling.¹

A complementary Cochrane review of falls prevention interventions for people residing in residential aged-care facilities included 43 trials (30,373 participants).¹¹ The results from 13 trials testing exercise interventions were inconsistent. Overall, there was no difference between the intervention and control groups in the risk of falling (RR: 1.07, 95% CI: 0.94–1.23, eight trials, 1887 participants). Post hoc sub-group analysis by level of care suggested that exercise might reduce falls in people in intermediate-level facilities, and increase falls in facilities providing high levels of nursing care. In care facilities, vitamin D supplementation reduced the rate of falls (RaR: 0.63, 95% CI: 0.46–0.86, five trials). For multifactorial interventions, the risk of falling (RR: 0.89, 95% CI: 0.77–1.02, seven trials, 2632 participants) suggested possible benefits.¹²

References

1. Gillespie L, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2012;(9):CD007146.
2. Franco MR, Pereira LS, Ferreira PH. Exercise interventions for preventing falls in older people living in the community. *Br J Sports Med* 2014;48(10):867–68.
3. El-Khoury F, Cassou B, Charles MA, Dargent-Molena P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013;347:f6234.
4. Benichou O, Lord SR. Rationale for strengthening muscle to prevent falls and fractures: A review of the evidence. *Calcif Tissue Int* 2016;98(6):531–45. doi: 10.1007/s00223-016-0107-9.
5. Panel on Prevention of Falls in Older Persons, American Geriatrics Society, British Geriatrics Society. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc* 2011;59(1):148–57.
6. Australian Commission on Safety and Quality in Health Care. Preventing falls and harm from falls in older people: Best practice guidelines for Australian hospitals, residential aged care facilities and community care. Darlinghurst, NSW: ACSQHC, 2009. Available at www.safetyandquality.gov.au/our-work/falls-prevention/ [Accessed 1 February 2017].
7. Podsiadlo D, Richardson S. The timed 'Up & Go': A test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142–48.
8. Tiedemann A, Shimada H, Sherrington C, Murray S, Lord S. The comparative ability of eight functional mobility tests for predicting falls in community-dwelling older people. *Age Ageing* 2008;37(4):430–35.
9. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: A systematic review and meta-analysis. *J Am Geriatr Soc* 2008;56(12):2234–43.
10. Nowson CA, McGrath JJ, Ebeling PR, et al. Vitamin D and health in adults in Australia and New Zealand: A position statement. *Med J Aust* 2012;196(11):686–87.
11. Clemson L, Fiatarone Singh MA, Bundy A, et al. Integration of balance and strength training into daily life activity to reduce rate of falls in older people (the LIFE study): Randomised parallel trial. *BMJ* 2012;345:e4547.
12. Cameron ID, Murray GR, Gillespie LD, et al. Interventions for preventing falls in older people in nursing care facilities and hospitals. *Cochrane Database Syst Rev* 2010;1:CD005465.

Exercise

Specific modalities of exercise have a preventive and therapeutic role to play in both skeletal and non-skeletal risk factors for osteoporosis and osteoporotic fracture. Resistance training (also known as strength training or weight lifting) is an exercise modality in which muscles are exposed to an uncustomary load, and in contracting to oppose this load grow in size and strength. This adaptation in muscle is associated with concomitant beneficial adaptations in bone structure, density and fracture resistance in skeletal sites attached to the trained muscle groups.

Balance training in isolation does not improve bone mineral density (BMD), although it reduces falls risk (see the section 'Reducing the risk of falls' earlier). Other kinds of exercise such as walking have minimal and inconsistent effects on BMD and no significant effects on falls risk in randomised controlled trials (RCTs), and may increase risk of fracture in those with poor balance and sarcopenia.

Recommendation 11	Grade
Individuals over 50 years of age without osteoporosis should participate regularly in progressive resistance training and balance training exercises. Resistance exercise should be regular (2–3 days per week), moderate–vigorous, progressive and varied to influence BMD and reduce fall and fracture risk.	A

Exercise for increasing bone mass

High-impact activities (jumping, skipping rope) and strength training are most effective for increasing BMD, and there is minimal evidence of benefit for low-impact weight-bearing aerobic exercises. High-velocity resistance training (power training) has been shown to provide further benefit when added to slow-velocity resistance training for BMD and muscle power. High-impact exercises such as jumping may be considered where the risk of fracture is thought to be low and there are no other contraindications (eg joint problems, severe balance impairment). Examples of weight-bearing aerobic exercises which are moderate-to-high impact that may benefit BMD and strength include jogging, tennis, volleyball, stair climbing and step aerobics.

Two short, intense exercise sessions separated by eight hours are better than one longer, less-intense session. The volume of exercise required is specific to the modality and intensity of the exercise chosen, and in general, is inversely proportional to the intensity of the exercise. Resistance training requires about three sets of eight repetitions at high intensity (approximately 80% of peak strength) for eight muscle groups for improvements in BMD (about 30 minutes per session, 2–3 days per week). Resistance training may be prescribed using machines or free weights that are increased over time as strength improves so that the desired intensity is maintained. High-impact exercise requires as little as 10 jumps, five days per week (1–2 minutes of exercise) alone or preferably integrated into other exercise regimens. In postmenopausal women, it is only effective when combined with resistance training and other activities.

Exercise to promote balance and prevent falls

Exercise for preventing falls needs to include medium-intensity to high-intensity balance training (ie exercises must be undertaken while standing and challenge balance), and be undertaken at a reasonable frequency and duration (ie for one hour, two times per week for six months).¹ Examples of medium-to-high-intensity balance exercises include standing with feet close together, standing on one leg, tandem walking, stepping exercises, backward walking, 'exer-games' and tai chi. Effective programs have been designed so that older people can undertake balance training safely unsupervised at home or in centre-based classes.

Recommendation 12	Grade
Prescribe high-intensity progressive resistance and balance training to older adults with osteoporosis to prevent further bone loss and/or improve BMD, improve function, treat sarcopenia and decrease fall and fracture risk.	A

Caution is advised regarding forward flexion and loading of the spine in those with spinal osteoporosis. Balance training should be undertaken in safe settings under supervision initially. Important muscle groups include back extensors, triceps, hip extensors, hip abductors, knee extensors, plantars and dorsiflexors.

Recommendation 13	Grade
Prescribe extended exercise therapy, including resistance and balance training, after hip fracture to improve mobility, strength and physical performance. Evidence for the benefits of exercise after vertebral and non-hip fractures is limited.	A

The goals of exercise in the treatment of osteoporotic hip fracture should be focused on the modifiable, non-skeletal contributors to weakness, frailty, falls and functional dependency, including muscle strength and power, balance, gait stability, poor appetite, depression, cognitive impairment, social isolation and polypharmacy (eg by substituting exercise for sedatives and antidepressants).

Practical tips and precautions

- The most important components of the exercise prescription are high-intensity resistance training and progressive balance training.
- Exercise programs should be individualised to the person'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 continuously progressive to reach target volumes and intensities as fitness improves. 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 of benefits.
- Avoidance of back-flexion exercises or flexed postures during daily activities and inclusion of back extension exercises may minimise the risk of vertebral fractures as well as exacerbation of pain from osteoarthritis in the spine. In the presence of existing spinal osteoporosis or vertebral fracture, avoid forward flexion and twisting movements involving the spine and stooped postures during sitting and activities of daily living (eg bowling, golf, gardening, vacuuming, picking up objects).
- Avoid flexion and internal rotation movements in those with a total hip replacement.
- Individuals with arthritis may need to modify exercises in terms of modality, intensity, range of motion, or extent of weight-bearing exercise to prevent exacerbation of joint symptoms. Seated resistance-training exercise is preferable to weight-bearing aerobic exercise or higher-impact activities for bone health in those with significant degenerative joint disease or instability, at least until joint and muscle health is improved or stabilised.
- To reduce falls risk, prescribe balance and resistance training prior to promotion of ambulation if gait and balance are impaired.
- Optimise lighting, visual and hearing aids, safety of exercise environment, climate conditions, and footwear in all exercise settings and exercise at times of day when sedation from medications or fatigue are at a minimum and cognition and mood are optimal.

Evidence statement

Specific kinds of exercise reduce bone loss associated with ageing and menopause. Exercise effects are modest and site-specific.² The most effective exercises include high-force, high-velocity, high-impact, intermittent stimuli, and novel directions of movement involving muscles that are attached to bones susceptible to fragility fracture (vertebrae, hip, femur, pelvic, ankle, wrist). Progressive resistance training alone or combined with high impact weight-bearing exercise generally provide the greatest benefit in older adults.^{3,4} Non-weight-bearing aerobic activities such as swimming and cycling may be associated with low BMD.⁵ Simple walking does not prevent osteoporosis or fracture. Walking alone has in fact been shown to increase upper extremity fracture incidence in one study of postmenopausal women.⁶ Low intensity resistance training also has no significant effect on BMD.⁴

Although fracture has been the primary outcome in only one RCT to date, there is evidence from three meta-analyses^{4,7,8} that exercise may reduce the risk of osteoporotic fracture if it includes resistance training or multimodal robust exercise regimens (lower-extremity strength training, high-impact exercises, and weight-bearing aerobic exercises).

No exercise regimens have yet been shown to reduce recurrent hip fracture. There is evidence that extended exercise therapy added to usual care is safe and effective after hip fracture, and results in improved mobility, strength and physical performance.^{9,10} Exercise may play a role in both the rehabilitation from the osteoporotic fracture itself as well as the prevention of additional fractures, and is often combined with other multidisciplinary care strategies.⁹ High-intensity progressive resistance training, in combination with other treatments for frailty and mobility impairment such as balance training, nutritional support, and treatment for depression, has resulted in reduced nursing home admission and overall mortality in a hip-fracture cohort,¹¹ as well as improved strength, nutritional status and depressive symptoms. By contrast, various hip-fracture rehabilitation strategies which included no exercise or only low-intensity exercise have had mixed or minimal impact on short- or long-term rehabilitative outcomes.^{12,13}

Robust data on exercise after vertebral fracture are very limited. One systematic review of nine trials has reported modest benefits of exercise for strength and balance without increases in pain, but no consistent or high-quality evidence for quality of life, BMD, recurrent fractures or other outcomes.¹⁴ Physiotherapy or exercises for upper-extremity fractures have shown little benefit for clinical outcomes such as pain, range of motion or strength,¹⁵ although few high-quality trials exist. A systematic review of 31 controlled trials of exercise after ankle fracture reported that commencing exercise after surgery in a removable brace or splint significantly improved activity limitation but also led to a higher rate of adverse events (relative risk [RR]: 2.61, 95% confidence interval [CI]: 1.72–3.97), while most other approaches were ineffective.¹⁶

In addition to the core prescription of resistance training and balance training, most consensus statements suggest that low-to-moderate impact weight-bearing activities such as stair climbing or stepping should replace jumping and other high-impact activities in those with pre-existing osteoporotic fracture, frailty, arthritis or very low BMD. Although data are limited, jumping by itself has not been shown to be effective for BMD in postmenopausal women with osteoporosis,³ although it may improve risk factors for fracture such as balance and muscle-power. Individual assessment of risk and adjustments of exercise regimens as capacity improves are essential features of exercise prescription for both prevention and treatment of osteoporotic fracture.

References

1. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: A systematic review and meta-analysis. *J Am Geriatr Soc* 2008;56(12):2234–43.
2. Nikander R, Sievanen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: A systematic review and meta-analysis for optimising bone strength throughout life. *BMC Med* 2010;8:47.
3. Martyn-St James M, Carroll S. A meta-analysis of impact exercise on postmenopausal bone loss: The case for mixed loading exercise programmes. *Br J Sports Med* 2009;43(12):898–908.
4. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev* 2011;7:CD000333.
5. Nagle KB, Brooks MA. A systematic review of bone health in cyclists. *Sports Health* 2011;3(3):235–43.
6. Ebrahim S, Thompson P, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. *Age Ageing* 1997;26(4):253–60.
7. Kemmler W, Haberle L, von Stengel S. Effects of exercise on fracture reduction in older adults: A systematic review and meta-analysis. *Osteoporos Int* 2013;24(7):1937–50.
8. Zhao R, Feng F, Wang X. Exercise interventions and prevention of fall-related fractures in older people: A meta-analysis of randomized controlled trials. *Int J Epidemiol* 2016:1–13.
9. Auais MA, Eilayyan O, Mayo NE. Extended exercise rehabilitation after hip fracture improves patients' physical function: A systematic review and meta-analysis. *Phys Ther* 2012;92(11):1437–51.
10. Chudyk AM, Jutai JW, Petrella RJ, Speechley M. Systematic review of hip fracture rehabilitation practices in the elderly. *Arch Phys Med Rehabil* 2009;90(2):246–62.
11. Singh NA, Quine S, Clemson LM, et al. Effects of high-intensity progressive resistance training and targeted multidisciplinary treatment of frailty on mortality and nursing home admissions after hip fracture: A randomized controlled trial. *J Am Med Dir Assoc* 2012;13(1):24–30.
12. Rajashulakshana R, Haslinda B, Maria A, Nazri J, Nur Raudhah A. Does orthogeriatric model of care improve the outcome of patients with hip fractures? A systematic review. *Singhealth Proceedings* 2010;19 Suppl 2:S321.
13. Sherrington C, Tiedemann A, Cameron ID. Physical exercise after hip fracture: An evidence overview. *Eur J Phys Rehabil Med* 2011;47(2):297–307.
14. Dusdal K, Grundmanis J, Luttin K, et al. Effects of therapeutic exercise for persons with osteoporotic vertebral fractures: A systematic review. *Osteoporos Int* 2011;22(3):755–69.
15. Bruder A, Taylor N, Dodd KJ, Shields N. Physiotherapy for the rehabilitation of upper limb fractures in adults: A systematic review and meta-analysis. *Physiotherapy (United Kingdom)* 2011:eS163.
16. Lin CW, Moseley AM, Refshauge KM. Effects of rehabilitation after ankle fracture: A Cochrane systematic review. *Eur J Phys Rehabil Med* 2009;45(3):431–41.

Calcium and vitamin D supplementation

Recommendation 14	Grade
Calcium and vitamin D supplements should not be used routinely in non-institutionalised elderly people. The absolute benefit of calcium and vitamin D supplements in terms of fracture reduction is low. There is evidence of significant benefit in people at risk of deficiency, particularly institutionalised individuals. Calcium and vitamin D supplements should be offered to people taking osteoporosis treatments if their dietary calcium intake is less than 1300 mg per day.	C

Calcium and vitamin D supplements have been widely used in an attempt to prevent bone loss and prevent fractures in postmenopausal women and older men. However, evidence indicates that the absolute benefit of these treatments in terms of fracture prevention for non-institutionalised individuals is low and considerably less than that seen with licensed osteoporosis treatments. There could be benefit for those who may be deficient; particularly institutionalised individuals. The US Preventive Services Task Force has recommended against routine calcium and vitamin D supplementation in non-institutionalised elderly people.¹

The target calcium intake from dietary sources and supplements should be 1000 mg per day for adults, rising to 1300 mg per day for women older than 50 years of age and men older than 70 years of age. Vitamin D from sunlight exposure (avoiding periods of high ultraviolet-radiation intensity such as in the middle of the day) and supplements should ensure 25-hydroxyvitamin D (25-OH D) levels >50 nmol/L. If vitamin D supplements are required, a dose of 800–1000 IU per day is usually sufficient, although higher doses are needed in some people to achieve target levels. Dietary calcium intake is often suboptimal in the elderly, especially institutionalised individuals.

Calcium and vitamin D supplements work by reducing secondary hyperparathyroidism and reducing bone turnover. Bone mineral density (BMD) is also increased by calcium and vitamin D, but this effect appears to be modest. Calcium and vitamin D are not available on the Pharmaceutical Benefits Scheme (PBS) but are recommended for people likely to have insufficient intakes. This is particularly important for those taking other osteoporosis therapies.

Calcium supplements are available in two common forms: calcium carbonate and calcium citrate. Calcium tablets typically contain 250–600 mg of elemental calcium. The most commonly available type of vitamin D supplement is vitamin D3 or cholecalciferol. Vitamin D3 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 of vitamin D range from 400–1000 IU, available as capsules, tablets or liquid formulations.

Side effects and potential harms

Calcium supplements modestly increase the risk of renal calculi. Calcium supplements can also cause abdominal bloating and constipation. It has been reported that there could be an increased risk of myocardial infarction (MI) with calcium supplements, but not all studies support this conclusion. Calcium and vitamin D supplements do not increase the risk of death and some studies suggest a small reduction in the risk of death.

Clinical toxicity is uncommon with vitamin D, even in high doses. Single doses of up to 500,000 IU are tolerated without causing hypercalcaemia or hypercalciuria. However, the use of higher-dose formulations of vitamin D in elderly populations has been associated with an increased risk of falls.

Practical tips and precautions

- In otherwise healthy non-institutionalised individuals, the relative reduction in fracture risk with calcium and/or vitamin D supplementation alone is small and may be associated with some adverse events. As such, these should not be considered routinely in healthy people or as first-line treatments for people with osteoporosis.
- Target calcium intake should be 1000 mg per day in adults and 1300 mg per day in postmenopausal women and older men, ideally from dietary sources. Where this cannot be achieved, a supplement of 500–600 mg calcium is appropriate.

- Vitamin D from sunlight exposure (avoiding the middle of the day) and supplements should ensure that 25-OH D levels are above 50 nmol/L.
- 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. Calcium and vitamin D supplements may be taken at any time of the day.
- Calcium and vitamin D supplements are more likely to be effective in reducing fracture risk when given in combination to individuals who are deficient. The majority of studies demonstrating efficacy of other osteoporosis treatments have been conducted in the setting of concurrent calcium and vitamin D supplementation.

Evidence statement

There is mixed evidence for the impact of oral calcium and vitamin D supplementation on the reduction of fractures outside institutionalised settings. Overall, the reductions in fracture risk are small in absolute terms with relatively large numbers of people needed to be treated to prevent fractures.

A recent systematic review reported on the effect of calcium supplements (with or without vitamin D) in older adults.² Calcium supplementation (20 trials, 58,573 individuals) significantly reduced the risk of any fracture (relative risk [RR]: 0.89, confidence interval [CI]: 0.81–0.96). The risk of vertebral fracture was also reduced (RR: 0.74–1.00) but the risk of hip fracture was not. Only a small number of randomised controlled trials (RCTs) examined the effect of changes in dietary calcium intake on fracture risk and thus no conclusions could be drawn.

Another systematic review reported on the effect of vitamin D supplements (with or without calcium) in older adults.³ Vitamin D supplementation alone was not associated with a reduction in hip fractures (RR: 1.2, CI: 0.98–1.29), or any new fracture (RR: 1.03, CI: 0.96–1.11). Vitamin D plus calcium supplements resulted in a small reduction in hip fracture risk (RR: 0.84, CI: 0.74–0.96). In community-based individuals this translates into one fewer hip fracture per 1000 people treated per year, whereas for institutionalised individuals, supplementation would result in nine fewer hip fractures per 1000 people treated per year. Vitamin D plus calcium supplementation was associated with a small reduction in the risk of any fracture (RR: 0.95, CI: 0.90–0.99).

Safety

The safety of calcium and/or vitamin D supplements has been examined in several meta-analyses (MAs).^{3–5} In a recent Cochrane review, the risk of renal insufficiency or calculi was found to be increased by vitamin D and calcium supplements (RR: 1.17, CI: 1.03–1.34).³ There was also an increased risk of gastrointestinal symptoms (RR: 1.04, CI: 1.00–1.08). The risk of cardiac events has also been examined, but despite being based on datasets from the same RCTs, different MAs have drawn different conclusions. One MA found an increased risk of MI (RR: 1.24, CI: 1.07–1.45) and stroke (RR: 1.15, CI: 1.00–1.32) in people taking calcium supplements with or without vitamin D.⁵ Another MA found no association with MI (RR: 1.08, CI: 0.92–1.26) or coronary heart disease in general.⁴ MAs indicate that calcium supplements with or without vitamin D have no effect on overall mortality, and the combination of calcium and vitamin D has been found to reduce the risk of death in one MA.⁶

RCTs have evaluated the effectiveness of higher-dose vitamin D supplements to reduce the risk of falls in individuals at high risk of falling. The use of high-dose oral vitamin D increased the risk of falls rather than reduced it.^{7,8} One recent trial that compared the effect of 24,000 IU once per month to 60,000 IU once per month found that the higher dose was associated with a significantly increased incidence of falls.⁸

References

1. Moyer VA, US Preventative Services Task Force. Vitamin D and calcium supplementation to prevent fractures in adults: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013;158(8):691–96.
2. Bolland MJ, Leung W, Tai V, et al. Calcium intake and risk of fracture: Systematic review. *BMJ* 2015;351: h4580.
3. Avenell A, Mak Jenson CS, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev* 2014;(4):CD000227. doi: 10.1002/14651858.CD000227.pub4.
4. Lewis JR, Radavelli-Bagatini S, Rejnmark L, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: A collaborative meta-analysis of randomized controlled trials. *J Bone Miner Res* 2015;30(1):165–75.
5. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: Reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011;342:d2040. doi: <http://dx.doi.org/10.1136/bmj.d2040>.
6. Rejnmark L, Avenell A, Masud T, et al. Vitamin D with calcium reduces mortality: Patient level pooled analysis of 70,528 patients from eight major vitamin D trials. *J Clin Endocrinol Metab* 2012;97(8):2670–81.
7. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. *JAMA* 2010;303(18):1815–22.
8. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: A randomized clinical trial. *JAMA Intern Med* 2016;176(2):175–83.

Pharmacologic approaches to prevention and treatment

Bisphosphonates

Recommendation 15	Grade
Bisphosphonate therapy should be considered for the primary prevention of vertebral fractures in women with osteopenia who are at least 10 years postmenopause.	C

Recommendation 16	Grade
Bisphosphonate therapy (alendronate, risedronate or zoledronic acid) is recommended for reducing the risk of vertebral and non-vertebral fractures in postmenopausal women and men over the age of 50 at high risk of fracture (those with osteoporosis by bone mineral density [BMD] criteria or a prior minimal trauma fracture).	A

Recommendation 17	Grade
Reconsider the need to continue bisphosphonate therapy after 5–10 years in postmenopausal women and men over the age of 50 with osteoporosis who have responded well to treatment (T-score ≥ -2.5 and no recent fractures). If BMD remains low (T-score ≤ -2.5) and/or there are incident vertebral fractures, continue treatment. Treatment should be restarted if there is evidence of bone loss, especially at the hip, or if a further minimal trauma fracture is sustained.	D – consensus

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. As they are rapidly sequestered into bone (from where they are only slowly released) and eliminated by the kidney, exposure to soft tissues, including bone marrow, is transient.

Alendronate and risedronate are usually taken orally on a daily basis (alendronate 10 mg, risedronate 5 mg) or weekly (alendronate 70 mg, risedronate 35 mg). Intravenous bisphosphonates (once yearly 5 mg zoledronic acid) can be used as a first-line osteoporosis therapy but are often used in patients intolerant to oral preparations or likely to be non-adherent to oral medications.

Side effects and potential harms

Bisphosphonates used in the management of osteoporosis are usually well tolerated. In two separate systematic reviews of oral bisphosphonate therapy (alendronate and risedronate) there was no statistically significant difference in adverse events in the active versus placebo arm.^{1,2} The most commonly reported adverse effects from observational post-marketing data of oral bisphosphonate treatment are gastrointestinal (gastric irritation, oesophageal erosions, gastric ulcers, perforations and strictures). A causal link has not been established but is postulated to be related to incorrect administration.^{3,4} Oral bisphosphonate therapy may be associated with oesophageal cancer risk, according to one meta-analysis (MA),⁵ but this has not been found in two other MAs.^{6,7} Medication-related osteonecrosis of the jaw (MRONJ) is a rarely reported adverse effect. Incidence ranges between <1 case per 10,000 patients and 10 cases per 10,000 patients treated with oral bisphosphonates^{8,9} and 1.7 cases per 10,000 patients treated with zoledronic acid.¹⁰ Duration of therapy appears to be a risk factor for MRONJ in patients treated with oral bisphosphonates, with one study reporting 21 cases of MRONJ per 10,000 patients after four years of therapy,⁸ but six years of therapy with zoledronic acid has not been shown to increase risk.¹¹ There is a strong association between MRONJ and dental pathology and dental surgery such as extractions. Atypical fracture of the femur (AFF) also appears to be a rare adverse event, occurring at 3.2 to 50 cases per 100,000 person years of bisphosphonate treatment.¹² Long-term (over five years) bisphosphonate use may be associated with higher risk of AFF (100 per 100,000 person years), although there are few data in this area.

Practical tips and precautions

- Bisphosphonates approved in Australia for clinical use in osteoporosis are alendronate, risedronate, and zoledronic acid. Other bisphosphonates such as ibandronate, clodronate, etidronate and neridronate are in use outside Australia. Alendronate and risedronate (all available preparations) are supported under the Pharmaceutical Benefits Scheme (PBS) for women and men with evidence of osteoporotic fracture independent of age, bone mineral density (BMD) or other clinical risk factors. It is important to note that the PBS criteria for osteoporosis pharmacotherapy, 'established osteoporosis with fracture due to minimal trauma', means that an individual qualifies for subsidised treatment if a minimal trauma fracture has been sustained, regardless of T-score. Even a normal T-score in a patient with a minimal trauma fracture does not disqualify the patient from PBS subsidy. Assessment of absolute fracture risk and clinical judgement should guide individual decisions on osteoporosis pharmacotherapy.
- Active upper gastrointestinal (GIT) disorders (current strictures, Barrett's oesophagus and gastric, oesophageal or duodenal ulcers) are a contraindication to oral bisphosphonate use.
- Taking oral therapy after fasting for several hours (usually overnight) and then remaining upright and avoiding food for at least 30 minutes will maximise medication absorption. Enteric-coated risedronate can be taken with or without food.
- The incidence of GIT adverse events is low and may be minimised by taking the tablet with a large glass of water and remaining upright until after eating.
- Calcium and vitamin D intake appropriate for gender, age and menopause status is recommended alongside bisphosphonate therapy.
- Oral bisphosphonates should not be taken together with any other drug, particularly calcium, as it may affect bisphosphonate absorption. 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, as this increases the risk of hypocalcaemia, especially with parenteral bisphosphonates such as zoledronic acid.
- Intravenous (IV) zoledronic acid needs 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 per minute.
- 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 oral bisphosphonates, to reduce the risk of MRONJ.

Evidence statement

A number of good-quality systematic reviews (SRs) have found significant effects of bisphosphonates (alendronate, risedronate and zoledronic acid) in reducing fracture risk. Few studies have directly compared different agents or classes of agents used to treat osteoporosis and hence the data are insufficient to determine the relative efficacy or safety of these agents.

Primary prevention of osteoporotic fractures with bisphosphonates

A pivotal good quality SR² in 2002 included two randomised controlled trials (RCTs) (McClung et al and Hoskings et al, n = 1946)^{13,14} that reported the effect of alendronate 10–40 mg per day on fracture risk in postmenopausal women without osteoporosis. Alendronate was not associated with a reduction in the risk of vertebral fracture (relative risk [RR]: 0.45, 95% confidence interval [CI]: 0.06–3.15) or non-vertebral fractures (RR: 0.79, 95% CI: 0.28–2.24) compared to placebo. In the McClung trial,¹³ mean age was 51.8 years and T-score –1.8 and no patients had prevalent vertebral fractures, while in the Hosking trial,¹⁴ participant mean age was 53 years, mean T-score –1.8 and <10% had prevalent vertebral fractures. A Cochrane systematic review and MA in 2008¹⁵ reported a reduction in the risk of vertebral fractures (RR: 0.55, 95% CI: 0.38–0.80) but no reduction in non-vertebral fracture risk (RR: 0.89, 95% CI: 0.76–1.04) with alendronate therapy in one study (Cummings et al, n = 4432).¹⁶ The mean T-score was –1.9, mean age 67.6 years and no patients had prevalent vertebral fractures. The fact that patients in the latter study were older by 15 years is likely to have contributed to the positive findings.

An MA of RCTs of risedronate¹⁷ in postmenopausal women (n = 111 in one trial by Mortensen et al)¹⁹ conducted in 2002 did not demonstrate reductions in vertebral (RR: 2.44, 95% CI: 0.12–49.45) or non-vertebral (RR: 0.49, 95% CI: 0.12–2.03) fractures. A 2008 Cochrane review¹⁸ on the effectiveness of risedronate at doses of 2.5 mg per day and 5.0 mg per day for a duration of two years for primary prevention of osteoporosis fractures included two RCTs (Mortensen et al and Hooper et al)^{19,20} with 327 early postmenopausal women (mean age 52.6). Results were not significant compared to placebo for either vertebral (RR: 0.97, 95% CI: 0.42–2.25) or non-vertebral fracture risk (RR: 0.81, 95% CI: 0.25–2.58). In the Mortensen and Hooper trials, the mean ages were 51.2 years and 52.6 years, the mean T-scores were –1.0 and –0.4, and 0% and 18% of the subjects had prevalent fractures, respectively.^{19,20}

Treatment of postmenopausal women at high risk of osteoporotic fracture

A good-quality MA including six treatment trials showed a reduction in the risk of vertebral fracture for alendronate compared to placebo (RR: 0.53, 95% CI: 0.43–0.65), with no heterogeneity observed between trials.² This translated to a number needed to treat (NNT) of 72 (95% CI: 61–99) to prevent one vertebral fracture over two years of treatment in women considered to be at high risk of vertebral fracture. The patients included were at high fracture risk, as indicated by a weighted mean age of 67.8 years (range: 59.5 to 71 years), weighted mean femoral neck (FN) T-score of –2.6 (range: –3.3 to –2.3) and prevalent vertebral fractures weighted mean 29% (range: 0% to 100%). Among five treatment trials included in the MA of non-vertebral fracture risk, the weighted mean age was 63.0 years (range: 59.5 to 64 years), weighted mean FN T-score of –2.7 (range: –2.8 to –2.3) and prevalent vertebral fractures weighted mean 18% (range: 0% to 21%). The pooled RR for non-vertebral fracture was 0.49 (95% CI: 0.36–0.67), with no heterogeneity between trials. NNT to prevent one non-vertebral fracture over two years of treatment in women at high risk was 24 (95% CI: 19–37).²

A Cochrane review of RCTs in postmenopausal women compared risedronate 2.5 mg or 5.0 mg daily to placebo over 2–3 years.¹⁸ These trials were categorised as osteoporosis treatment (or secondary prevention) trials, based upon inclusion criteria of T-score ≤–2.0 or the presence of a prevalent vertebral fracture. Pooled data from three RCTs showed a 39% reduction in vertebral fractures (RR: 0.61, 95% CI: 0.50–0.76) for risedronate 5.0 mg per day with an estimated NNT of 48. The weighted mean age was 69.1 years (range: 64.7–71 years), weighted mean FN T-score of –2.7 (range: –2.9 to –2.4) and prevalent vertebral fractures weighted mean 79% (range: 30–100%). Pooled data from four RCTs showed a 20% reduction in non-vertebral fractures (RR: 0.80, 95% CI: 0.72–0.90), with an estimated NNT of 30. The weighted mean age was 76.9 years (range: 64.7–78 years), weighted mean FN T-score of –3.6 (range: –3.7 to –2.4) and prevalent vertebral fractures weighted mean 47% (range: 42% to 100%). For hip fractures, there was a 26% reduction in risk (three

RCTs, RR: 0.74, 95% CI: 0.59–0.94), with an estimated NNT of 202. The weighted mean age was 77.3 years (range: 69–78 years), weighted mean FN T-score of –3.6 (range: –3.7 to –2.4) and prevalent vertebral fractures weight mean 47% (range: 30–100%). The effect observed for 2.5 mg risedronate was not as large.¹⁸

The multi-centre international Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)–Pivotal Fracture Trial (PFT) has followed the safety and efficacy of zoledronic acid in a cohort of postmenopausal women with osteoporosis for nine years. In the initial trial, 7765 patients (mean age 73) were randomised to receive either placebo or a single infusion (5 g) of zoledronic acid at trial baseline, 12 months and 24 months. At 36 months from baseline, zoledronic acid treatment reduced the risk of morphometric vertebral fracture by 70%, compared to placebo (3.3% versus 10.9%, RR: 0.30, 95% CI: 0.24–0.38), and reduced the risk of hip fracture by 41% (1.4% versus 2.5%, hazard ratio [HR]: 0.59, 95% CI: 0.42–0.83).²¹ A post hoc analysis of the data from patients who received only one dose of zoledronic acid at baseline revealed a similar reduction in vertebral fracture risk (68%) at 18 months follow up, compared with placebo.²²

Treatment following hip fracture

An annual infusion of zoledronic acid within three months after a hip fracture was associated with a reduction in the rate of new clinical fractures and improved survival in women and men with an average age of 74.4 years, followed for a median of 1.9 years.²³ In this randomised, double-blind, placebo-controlled trial, the rates of any new clinical fracture were reduced by 35% ($P = 0.001$) from 13.9% in the placebo group to 8.6% in the zoledronic acid group. The respective rates of a new clinical vertebral fracture were 1.7% and 3.8% ($P = 0.02$), and the respective rates of new non-vertebral fractures were 7.6% and 10.7% ($P = 0.03$). There was also a reduction of 28% in deaths from any cause in the zoledronic acid group ($P = 0.01$). No adverse effects on the healing of fractures were noted. The rates of renal and cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the two groups.²³ On the basis of this trial, the US Endocrine Society *Practice guideline for osteoporosis in men* suggests treatment with IV zoledronic acid in men with a recent hip fracture.²⁴

Duration of therapy

The Fracture Intervention Trial Long-term Extension (FLEX) trial demonstrated a reduction in clinical (not morphometric) vertebral fractures among those who continued alendronate for 10 years, compared to those who discontinued after five years.²⁵ A post hoc analysis²⁶ revealed that among postmenopausal women without a vertebral fracture at FLEX baseline, an FN T-score of –2.5 or less at FLEX baseline were associated with non-vertebral fracture risk reduction (RR: 0.50, 95% CI: 0.26–0.96). A further post hoc analysis of the FLEX trial²⁷ showed that among women who discontinued alendronate after five years, the predictors of fracture were age (HR: 1.54 [95% CI: 1.26–1.85] per five-year increase) and FN T-score (lowest tertile of baseline FN DXA versus other two tertiles relative HR: 2.17, 95% CI: 1.38–3.41). Change in BMD after one year was not a predictor of further fracture.²⁷

In an extension of the HORIZON–PFT study, 1233 women who had received three annual doses of zoledronic acid in the original trial were randomised to receive either zoledronic acid for another three years under the same annual, three-dose regimen, or placebo.²⁸ At 36 months follow-up, the incidence of new vertebral fractures was lower in women who received six years of zoledronic acid, compared with those who had received the drug for only three years (14 versus 30, odds ratio [OR]: 0.51, $P = 0.035$), but there was no change in the fracture rate in the placebo group.²⁸ A further three-year extension of the trial did not show a significant difference in fracture rates between women taking zoledronic acid for a full nine years, compared with those who had taken the drug for six years followed by three years placebo.²⁹ These results indicate that maximum benefit of zoledronic acid may be achieved in some patients after six years of therapy (for reduction of vertebral fracture risk), and that for most patients, benefits are maintained for a further three years once therapy is stopped.

Treatment of osteoporosis in men

One RCT³⁰ found a significant reduction ($P = 0.02$) in the risk of vertebral fractures in older men with osteoporosis ($n = 241$) compared to placebo for alendronate 10 mg per day for two years. The effect on non-vertebral fractures was not significant. An RCT to assess the effectiveness of risedronate 5 mg daily

versus vitamin D/calcium in men with osteoporosis ($n = 316$) with a baseline mean lumbar spine T-score of -3.3 and a prevalent vertebral fracture rate of 50%,³¹ found a significant 60% RR reduction ($P = 0.028$) in new morphometric vertebral fractures and statistically significant increases in lumbar spine and hip BMD at one year of follow-up. A placebo-controlled RCT of risedronate involving 284 men over two years³² with a baseline mean lumbar spine T-score of -3.2 and 25% of subjects with prevalent vertebral fractures demonstrated improved lumbar spine and hip BMD with risedronate. However, there was no significant effect on vertebral or non-vertebral fractures, although the study was underpowered to detect differences in fracture rates.³²

Other data on the efficacy of zoledronic acid in reducing fracture risk in men are rare. In a multi-centre double-blinded trial of 1199 men with osteoporosis 50 to 85 years of age, randomised to receive either placebo or 5 mg zoledronic acid at baseline and at 12 months, zoledronic acid reduced the rate of morphometric vertebral fracture by 67% at 24 months follow-up (RR: 0.33, 95% CI: 0.16–0.70, $P = 0.002$).³³ The rate of non-vertebral fractures was also lower in the treatment group, but did not reach significance.³³

References

1. Dunstan CR, Felsenberg D, Seibel MJ. Therapy insight: The risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. *Nat Clin Pract Oncol* 2007;4(1):42–55.
2. 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. *Endocr Rev* 2002;23(4):508–16.
3. de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. *N Engl J Med* 1996;335(14):1016–21.
4. Papapetrou PD. Bisphosphonate-associated adverse events. *Hormones (Athens)* 2009;8(2):96–110.
5. Andrici J, Tio M, Eslick GD. Meta-analysis: Oral bisphosphonates and the risk of oesophageal cancer. *Aliment Pharmacol Ther* 2012;36(8):708–16.
6. Oh YH, Yoon C, Park SM. Bisphosphonate use and gastrointestinal tract cancer risk: Meta-analysis of observational studies. *World J Gastroenterol* 2012;18(40):5779–88.
7. Sun K, Liu JM, Sun HX, Lu N, Ning G. Bisphosphonate treatment and risk of esophageal cancer: A meta-analysis of observational studies. *Osteoporos Int* 2013;24(1):279–86.
8. Lo JC, O’Ryan FS, Gordon NP, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg* 2010;68(2):243–53.
9. Malden N, Lopes V. An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence. *J Bone Miner Metab* 2012;30(2):171.
10. Grbic JT, Black DM, Lyles KW, et al. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: Data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. *J Am Dent Assoc* 2010;141(11):1365–70.
11. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012;27(2):243–54.
12. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014;29(1):1–23.
13. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. *Ann Intern Med* 1998;128(4):253–61.
14. Hosking D, Chilvers CE, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med* 1998;338(8):485–92.
15. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008(1):CD001155.
16. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone mineral density but without vertebral fractures: Results from the Fracture Intervention Trial. *JAMA* 1998;280(24):2077–82.
17. Cranney A, Tugwell P, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev* 2002;23(4):517–23.
18. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008(1):CD004523.
19. Mortensen L, Charles P, Bekker PJ, Digenaro J, Johnstone CC Jr. Risedronate increases bone mass in an early postmenopausal population: Two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab* 1998;83(2):396–402.
20. Hooper MJ, Ebeling PR, Roberts AP, et al. Risedronate prevents bone loss in early postmenopausal women: A prospective randomized, placebo-controlled trial. *Climacteric* 2005;8(3):251–62.

21. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809–22.
22. Reid IR, Black DM, Eastell R, et al. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 milligrams. *J Clin Endocrinol Metab* 2013;98(2):557–63.
23. Lyles KW, Colón-Emeric CS, Magaziner JS, et al for the HORIZON Recurrent Fracture Trial. Zoledronic acid in reducing clinical fracture and mortality after hip fracture. *N Engl J Med* 2007;357:nihpa40967.
24. Watts NB, Adler RA, Bilezikian JP, et al; Endocrine Society. Osteoporosis in men: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97(6):1802–22.
25. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A randomized trial. *JAMA* 2006;296(24):2927–38.
26. Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: The FLEX trial. *J Bone Miner Res* 2010;25(5):976–82.
27. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: The FLEX study. *JAMA Intern Med* 2014;174(7):1126–34.
28. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012;27(2):243–54.
29. Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: A randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2015;30(5):934–44.
30. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000;343:604–10.
31. Ringe JD, Faber H, Farahmand P, Dorst A. Efficacy of risedronate in men with primary and secondary osteoporosis: Results of a 1-year study. *Rheumatol Int* 2006;26(5):427–31.
32. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD. Once-weekly risedronate in men with osteoporosis: Results of a 2-year, placebo-controlled, double-blind, multicenter study. *J Bone Miner Res* 2009;24(4):719–25.
33. Boonen S, Reginster JY, Kaufman JM, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *N Engl J Med* 2012;367(18):1714–23.

Denosumab

Recommendation 18	Grade
Denosumab is recommended for the treatment of osteoporosis in postmenopausal women at increased risk of minimal trauma fracture.	A

Recommendation 19	Grade
Denosumab should be considered as an alternative to bisphosphonates for the treatment of men at increased risk of minimal trauma fracture.	B

Denosumab is a fully human, high-specificity and high-affinity monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), an important regulator of osteoclast development and activity. Denosumab prevents RANKL binding to its receptor (RANK) on the osteoclast surface. As a consequence, osteoclast formation, function and survival is disrupted, resulting in decreased bone resorption and increased mass and strength of both cortical and trabecular bone. Denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures in postmenopausal women. At the time of writing, few data on fracture incidence in men treated with denosumab were available. However, the results of two recent trials in men with low bone mineral density (BMD) demonstrate similarly significant gains in BMD (8.0% lumbar spine, 3.4% total hip) after two years of denosumab treatment.^{1,2}

Denosumab has been registered for the treatment of osteoporosis in Australia since 2010, and is subsidised by the Pharmaceutical Benefits Scheme for men and women over the age of 70 years with a T-score -2.5 or less, and for men and women with a minimal trauma fracture. Denosumab is given as a subcutaneous injection of 60 mg every six months.

Side effects and potential harms

Denosumab used in the treatment of osteoporosis is generally well tolerated. Its subcutaneous mode of administration avoids the gastrointestinal side effects associated with oral bisphosphonate treatment. Randomised controlled trial (RCT) data to date indicate no significant increase in adverse events with long-term denosumab treatment, including infection, malignancy, pancreatitis, cardiovascular disease, peripheral vascular disease, medication-related osteonecrosis of the jaw (MRONJ) and atypical fractures of the femur (AFFs). Cellulitis has been more frequently reported with denosumab compared with placebo, although the incidence remains low (less than 0.2 events per 100 subject-years for long-term denosumab). Hypocalcaemia following denosumab administration is a significant risk in patients with severe renal impairment (chronic kidney disease stage 4 or 5) or in patients receiving dialysis.

Practical tips and precautions

- Hypocalcaemia is an identified risk of denosumab treatment, particularly in patients with severe renal impairment (creatinine clearance <30 mL per minute or receiving dialysis). Hypocalcaemia must be corrected prior to treatment initiation, and calcium levels monitored during treatment of such high-risk patients, especially in the first two weeks of initiating therapy.
- Dietary calcium intake and serum 25-OH D levels should be optimised, using supplements if required, prior to commencing denosumab therapy.
- Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
- Unlike bisphosphonates, which are sequestered in bone, the effects of denosumab on bone resorption do not persist after treatment has stopped. Therefore, regular six-monthly administration is required for continued reduction of fracture risk.

Evidence statement

The first randomised, placebo-controlled trial of denosumab with fracture as a primary outcome was the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months (FREEDOM) trial, published in 2009.³ Seven thousand six hundred and sixty-eight women aged 60 to 90 with a T-score at the hip or spine of -2.5 to -4.0 were randomised to receive either 60 mg denosumab or placebo subcutaneously every six months for 36 months. Relative to placebo, denosumab reduced the risk of new radiographic vertebral fractures by 68% (cumulative incidence in treatment and placebo groups 2.3% and 7.2%, respectively; relative risk [RR]: 0.32, 95% CI: 0.26–0.41, $P < 0.001$), hip fractures by 40% (cumulative incidence in treatment and placebo groups 0.7% and 1.2%, respectively; hazard ratio [HR]: 0.60, 95% CI: 0.37–0.97, $P = 0.04$) and non-vertebral, non-hip fractures by 20% (cumulative incidence in treatment and placebo groups 6.5% and 8.0%, respectively; HR: 0.80, 95% CI: 0.67–0.95, $P = 0.01$).³ The FREEDOM trial has been extended for a further seven years (total trial length 10 years), and outcomes of the first two,⁴ three,⁵ four and five⁶ years of the extension have been reported. The FREEDOM extension employs a crossover design. Women who completed three years of denosumab treatment in the original trial were eligible to continue denosumab treatment, while those in the placebo group ‘crossed over’ to receive denosumab for the duration of the extension. After five years of the extension (1542 long-term subjects completing eight years of denosumab treatment and 1462 subjects crossing over to receive five years of denosumab treatment), the annual incidence of new vertebral fractures in long-term subjects was 1.5%, 1.3% and 1.3% during extension years 4–5, 6 and 7–8 respectively, and the annual incidence in crossover subjects was 0.9%, 1.6% and 1.8%. The annual incidence of non-vertebral fractures also remained low in both the long-term and crossover groups during the extension years, varying between 0.7% and 1.8%, and 1.2% and 2.6%, respectively. The cumulative incidence of hip fractures over the five-year extension was 0.7% in the long-term group and 1.1% in the crossover group (mean age 79 years at year 8 of extension).⁶

The two-year Denosumab Fracture Intervention Randomised Placebo Controlled Trial (DIRECT)⁷ measured fracture incidence with denosumab treatment versus placebo in Japanese men and women older than 50 years of age with 1–4 prevalent fractures and mean T-scores of -2.8 at the lumbar spine and -2.0 at the hip. Over 24 months, the incidence of new or worsening vertebral fracture was 3.6% in the denosumab group versus 10.3% in the placebo group, a risk reduction of 65.7% ($P = 0.0001$). Sub-group analysis of female subjects showed that the risk of new or worsening vertebral fracture at 24 months was reduced by 63.2% in the denosumab group compared with placebo (HR: 0.368, 95% CI: 0.207–0.653, $P = 0.0004$). New vertebral fracture incidence was reduced by 74.0% ($P < 0.0001$). Sub-group analysis of male subjects showed a new or worsening vertebral fracture incidence at 24 months of 0% in denosumab treated men, compared with 12.5% in men treated with placebo. However, this difference did not reach statistical significance ($P = 0.07$) due to the small sample size (23 men in the denosumab arm and 24 in the placebo arm).⁷ A one-year crossover extension ($n = 775$) of the DIRECT trial⁸ showed maintenance of low-fracture rates, with no difference in annualised fracture incidence between two and three years of treatment in the long-term group. The rate ratio of new vertebral fractures in this group in year 2 compared with year 1 was 0.89 ($P = 0.83$), and year 3 compared with year 1 was 0.19 ($P = 0.13$). As expected, the incidence of new and worsening vertebral fractures was reduced in the crossover group after commencement of denosumab treatment; the rate ratios comparing years 2 and 1 and years 3 and 1 were 2.87 ($P = 0.003$) and 0.23 ($P = 0.0003$), respectively.⁸ These results suggest that the magnitude of effect on fracture risk reduction by denosumab depends on treatment duration. Results reported in the DIRECT extension were not stratified by sex. To date, no further denosumab trial data in men with fracture as an outcome measure have been published. However, in men with low BMD treated with denosumab, increases in BMD are similar to those seen in postmenopausal women.¹

Safety

The original three-year FREEDOM trial showed no significant increase in the incidence of cancer or infection compared with placebo.³ There was no increase in serious adverse events including coronary heart disease and stroke compared with placebo, but a significant increase in cellulitis requiring hospitalisation was reported (0.3% in the denosumab group compared with $< 0.1\%$ in the placebo group, $P = 0.002$). No cases of MRONJ or AFFs were reported.¹ In the five-year extension study, the yearly exposure-adjusted subject incidence for

all adverse events for the duration of the FREEDOM extension, including cellulitis and other serious infection, are similar to those in the denosumab group in the original FREEDOM trial, with no increases over time.⁶ A total of two cases of AFF occurred in years 3 (in the crossover group) and 7 (long-term group) of denosumab treatment, and a total of eight cases of MRONJ occurred in years 2 and 4 (in the crossover group), 6 and 7 (long-term group) of denosumab treatment. The cumulative incidence rates during the FREEDOM extension were 4.2 per 10,000 subject-years for MRONJ and 1.0 per 10,000 subject-years for AFF.⁴ Adverse-event rates were similarly low in the two-year DIRECT trial and one-year DIRECT extension, with no significant difference between treatment and placebo groups.^{7,8} One case of MRONJ occurred during the extension in a crossover subject (one year of denosumab treatment).^{7,8}

Although no head-to-head trials have been published, a systematic review of nine RCTs (n = 4890) comparing the safety and efficacy of denosumab with bisphosphonate treatment for up to two years found no statistical difference between groups in terms of fracture risk or adverse events.⁹

References

1. Orwoll E, Teglbjærg CS, Langdahl BL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. *J Clin Endocrinol Metab* 2012;97(9):3161–69.
2. Langdahl, BL, Teglbjærg CS, Ho PR, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: Results from the ADAMO trial. *J Clin Endocrinol Metab* 2015;100(4):1335–42.
3. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361(8):756–65.
4. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension. *J Bone Miner Res* 2012;27(3):694–701.
5. Bone HG, Chapurlat R, Brandi ML, et al. The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: Results from the FREEDOM extension. *J Clin Endocrinol Metab* 2013;98(11):4483–92.
6. Papapoulos S, Lippuner K, Roux C, et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: Results from the FREEDOM Extension study. *Osteoporos Int* 2015;26(12):2773–83.
7. Nakamura T, Matsumoto T, Sugimoto T, et al. Clinical Trials Express: Fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: Denosumab fracture intervention randomized placebo controlled trial (DIRECT). *J Clin Endocrinol Metab* 2014;99(7):2599–607.
8. Sugimoto T, Matsumoto T, Hosoi T, et al. Three-year denosumab treatment in postmenopausal Japanese women and men with osteoporosis: Results from a 1-year open-label extension of the Denosumab fracture intervention randomized placebo controlled trial (DIRECT). *Osteoporos Int* 2015;26(2):765–74.
9. Beaudoin C, Jean S, Bessette L, Ste-Marie LG, Brown JP. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: A systematic review and meta-analysis. *Osteoporos Int* 2016;27(9):2835–44. doi: 10.1007/s00198-016-3607-6.

Hormone therapy

Recommendation 20	Grade
Consider oestrogen replacement therapy to reduce the risk of fractures in postmenopausal women. The increase in risk of adverse events associated with treatment should be weighed carefully against benefits. Long-term use is not recommended.	A
Recommendation 21	Grade
Selective oestrogen receptor modulators (SERMs) should be considered as a treatment option for postmenopausal women with osteoporosis where vertebral fractures are considered to be the major osteoporosis risk (on the basis of low spine bone mineral density and/or an existing vertebral fracture) and where other agents are poorly tolerated. SERMs may be particularly useful in younger postmenopausal women at risk of vertebral fracture and who have a prior or family history of breast cancer.	A

Oestrogen

Oestrogen is available on the Pharmaceutical Benefits Scheme (PBS) for the prevention and treatment of osteoporosis in postmenopausal women. Oestrogen acts to decrease bone resorption. Oestrogen replacement therapy is effective in preventing loss of bone mineral density (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 osteoporosis.^{1,2-5} 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 two 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,⁶ but the beneficial effects of oestrogen therapy can be achieved by many routes of administration (including oral and transdermal). Patients who demonstrate ongoing bone loss with low-dose oestrogen replacement therapy may be considered for higher doses, with attention paid to calcium intake and vitamin D status, provided that the risk associated with oestrogen replacement therapy is not increased (eg clotting, cardiovascular [CV] disease or breast cancer).

Tibolone

Tibolone is a form of hormone therapy (HT) that has oestrogenic, progestogenic and androgenic effects and does not need to be given with a progestogen. It has similar efficacy to traditional HT in reducing fracture risk.

Raloxifene

Raloxifene is a selective oestrogen receptor modulator (SERM) and is available on the PBS for treatment of postmenopausal osteoporosis. SERMs have evidence of breast cancer prevention, so their use can be tailored to suit an individual's unique risk factor profile and may be particularly useful in the younger postmenopausal female with low spine BMD and a prior or family history of breast cancer.

While there is excellent evidence (Grade A) for raloxifene in reduction of vertebral fracture risk, there is minimal evidence for reduction in non-vertebral fractures. Therapy should be continuous and there is no need for concomitant progestogens.

Side effects and potential harms

The role of long-term postmenopausal HT in the prevention and management of osteoporosis remains controversial, following publication of the results of the Women's Health Initiative (WHI) study of combined oestrogen and progestin therapy⁴ and its study of oestrogen-alone therapy.² In the oestrogen-alone group, there was no increased risk of invasive breast cancer or CV disease, although the other outcomes were similar to the combined group. For the combined oestrogen/progesterone group, increased risk of invasive breast cancer has been reported, although the initial report of increased coronary heart disease was no longer significant in subsequent analyses.^{1,2-4,6} Increased risks of thromboembolic events and cerebrovascular accident are reported for both groups. Subsequent to the initial publication, there have been multiple reanalyses of the data, including by age of initiation of HT. The side effect profile is more favourable for those women starting HT within 10 years of the menopause (50–59 years) with low absolute risks of thromboembolic events and stroke.⁶

Tibolone has a different side effect profile from traditional HT. There is no randomised controlled trial (RCT) evidence for an increase in breast cancer, although there was a small increased risk in one large longitudinal study.⁷ However, tibolone does appear to increase breast cancer recurrence in those with treated breast cancer. There is no evidence for increased heart disease or thromboembolic events, but in older women there was an increased risk of stroke.⁷

Raloxifene may increase hot flushes and is likely to aggravate vasomotor symptoms. Like traditional HT, it is associated with increased thromboembolic events but has not been associated with heart disease or overall risk of stroke.⁸ In one study of women at high heart-disease risk it increased fatal but not overall stroke risk.⁹

Practical tips and precautions

- General practitioners should discuss with patients the long-term risks and benefits of HT, especially breast cancer, thromboembolic and CV effects. Side effects of traditional HT are minimised, with absolute risk low if given within 10 years of the menopause. The side effect profiles of traditional HT, tibolone and raloxifene are different.
- Individuals who require immobilisation for any period (eg hospitalisation or a long plane trip) should cease HT or raloxifene for a week before and afterward.
- Postmenopausal women taking HT should maintain adequate calcium intake (from dietary sources or supplements) and vitamin D status.
- Raloxifene should not be used in combination with oestrogen therapy.

Evidence statement

A good-quality systematic review (SR) pooled data from 47 RCTs investigating oestrogen alone and/or oestrogen with opposed progesterone compared to placebo for postmenopausal women.⁵ Treatment was associated with a significant improvement in BMD at the lumbar spine (weighted mean difference [WMD]: 4.86, 95% confidence interval [CI]: 3.70–6.02), forearm (WMD: 3.01, 95% CI: 2.29–3.74) and femoral neck (FN) (WMD: 2.25, 95% CI: 0.80–3.69) at 12 months, with the effect increasing at 24 months. Sub-analysis indicated that after two 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 FN BMD. A second good-quality SR presented evidence from five RCTs on the effectiveness of oestrogen in reducing vertebral, non-vertebral and/or hip fracture in postmenopausal women.¹ 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 (odds ratio [OR] not reported), as well as for groups at higher risk of fractures (relative risk [RR]: approximately 0.07).¹ In two clinical trials conducted by the WHI, conjugated oestrogen in combination with progestin in postmenopausal women ($n = 16,608$) or conjugated equine oestrogen (CEE) alone in women after hysterectomy ($n = 10,739$) were shown to reduce risk of osteoporotic fractures.^{2,4} Participants taking CEE 0.625 mg and medroxyprogesterone acetate 2.5 mg per day in a combined tablet (opposed oestrogen therapy) for an average of five years had a significant reduction in total fractures (hazard ratio [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, $P = 0.05$).⁴ Participants taking CEE 0.625 mg per day for an average of six years had a significant reduction in the 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, $P = 0.01$).²

In a good-quality RCT of Tibolone in 4500 women over three years, there was a decreased risk of vertebral fracture (HR: 0.55, 95% CI: 0.41–0.74) and non-vertebral fracture (HR: 0.74, 95% CI: 0.58–0.93).³

In a clinical trial of 7705 women randomised to two doses of raloxifene or placebo followed for up to four years there was a reduction of vertebral fractures (RR: 0.64, 95% CI: 0.53–0.76) for the approved dose of 60 mg.⁹ There was no significant reduction in non-vertebral fractures (RR: 0.93, 95% CI: 0.81–1.06). Similar results were found for another good-quality study of raloxifene in over 10,000 women at high risk of heart disease at baseline.⁸

Safety

Oestrogen

A good-quality SR 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.¹ 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).¹ These findings were consistent with those in the WHI trials, which were both ceased early due to the significant risk of serious side effects.^{2,4} In the moderate-quality oestrogen/progestin trial,⁴ HT was associated with an increased 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, $P = 0.05$). Subsequent analyses found that the initially reported increase in coronary artery disease was no longer statistically significant (HR: 1.18, 95% CI: 0.95–1.45). In the good-quality oestrogen alone trial,² HT was associated with an increased risk of stroke (HR: 1.39, 95% CI: 1.10–1.77) and venous thromboembolic disease (HR: 1.33, 95% CI: 0.99–1.79), 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). The increase in thromboembolic disease only reached borderline statistical significance for deep venous thrombosis (HR: 1.47, 95% CI: 1.04–2.08) but not pulmonary thromboembolism (HR: 1.34, 95% CI: 0.87–2.06). A small RCT of 1006 recently menopausal women (aged 45–58)¹⁰ of oestradiol plus 1 mg norethisterone acetate for 10 years versus placebo treated for 10 years reported a reduction in the primary composite outcome of death, admission to hospital for heart failure and myocardial infarction (HR: 0.48, 95% CI: 0.26–0.87, $P = 0.015$). There was no increased risk of cancer, venous thromboembolism or stroke. This is consistent with reanalyses of the WHI by 10-year age groups where the adverse effects of HT were less significant in those started on HT prior to 60 years of age.⁶

Tibolone

Another good-quality trial conducted in women older than 60 years of age reported a reduction in risk of invasive breast cancer (absolute risk reduction [ARR]: 1.9 per 1000 person years, 95% CI: 0.5–3.4, $P = 0.02$) and colon cancer (ARR: 1.3 per 1000 person years, 95% CI: 0.1–2.6, $P = 0.04$) associated with tibolone therapy.³ 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). There was no increased risk of heart disease or venous thromboembolic events.³ In a subsequent study of women already treated for breast cancer, tibolone was found to decrease vasomotor symptoms and maintain BMD, but there was an increased risk of breast cancer recurrence (HR: 1.40, 95% CI: 1.14–1.70).⁷ Similar to the above study, there was no increased risk of venous thromboembolic events or heart disease in this younger group.

Raloxifene

In the four-year follow-up of the pivotal raloxifene Multiple Outcomes of Raloxifene Evaluation (MORE) study,^{9,11} there was an increased risk of thromboembolic events, with an RR of 2.76 (95% CI: 1.30–5.86) for deep venous thrombosis and 2.76 (95% CI: 0.95–8.01) for pulmonary embolism. Unlike HT, there was a reduced risk of breast cancer (RR: 0.38, 95% CI: 0.24–0.58) and no increased risk of CV events.¹² In a subsequent RCT of raloxifene in over 10,000 women with either established heart disease or risk factors for heart disease, there was a similar reduction in breast cancer (primarily oestrogen receptor positive) and no increased risk of primary coronary events, overall risk of stroke or overall deaths.⁸ However, there was an increased risk of fatal strokes (HR: 1.49, 95% CI: 1.00–2.24) and venous thromboembolism (HR: 1.44, 95% CI: 1.06–1.95).⁸

References

1. MacLean C, Newberry S, Maglione M, et al. Systematic review: Comparative effectiveness of treatments to prevent fractures in men and women with low bone mineral density or osteoporosis. *Ann Intern Med* 2008;148(3):197–213.
2. 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. *JAMA* 2004;291(14):1701–12.
3. Cummings S, Ettinger B, Delmas P, et al. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008;359(7):697–708.
4. Rossouw J, Anderson G, Prentice R, et al. Risks and benefits of oestrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomised controlled trial. *JAMA* 2002;288(3):321–30.
5. 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. *Endocr Rev* 2002;23(4):529–39.
6. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomised trials. *JAMA* 2013;310(13):1353–68. doi:10.1001/jama.2013.278040.
7. Kenemans P, Bundred NJ, Foidart JM, et al. LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: A double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009;10(2):135–46.
8. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: Four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002;87(8):3609–17.
9. 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. *N Engl J Med* 2006;355(2):125–37.
10. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: Randomised trial. *BMJ*. 2012;345:e6409.
11. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomised clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282(7):637–45.
12. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: Four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomised trial. *JAMA*. 2002;287(7):847–57.

Parathyroid hormone

Recommendation 22	Grade
Teriparatide treatment is recommended to reduce fracture risk in postmenopausal women and men over the age of 50 with osteoporosis who have sustained a subsequent fracture while on anti-resorptive therapy, or in whom anti-resorptive therapy is contraindicated.	A

Parathyroid hormone (PTH) is approved in Australia in the form of hPTH(1-34), also known as teriparatide. PTH is also produced in the form of hPTH(1-84), not available in Australia. 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 are also increased.¹

Teriparatide increases lumbar spine and femoral neck (FN) bone mineral density (BMD) and decreases vertebral and non-vertebral fractures in postmenopausal osteoporosis with prior fracture. Hip-fracture risk has not been assessed.² Teriparatide has also been shown to improve new, worsening and moderate to severe back pain and reduce height loss in patients who have sustained one or more new vertebral fractures.³ Teriparatide increases BMD at the lumbar spine and FN in men with osteoporosis, but there are no data on fractures in this population.^{4,5}

Teriparatide is a costly medication with a recommended 18-month course duration. Teriparatide is now reimbursed by the Pharmaceutical Benefits Scheme for severe osteoporosis in patients with a very high risk of fracture who have:

- a BMD 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.

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. These are generally mild and do not require treatment discontinuation. Mild transient hypercalcaemia has been noted, but monitoring serum calcium is not a requirement of therapy.² Mild increases in uric acid without the development of acute gout and small increases in urinary calcium excretion without nephrolithiasis have been reported.⁶ Oncogenicity studies in rats treated with high doses of teriparatide of near lifetime duration resulted in an increased risk of osteogenic sarcoma.⁷ Surveillance of human osteosarcoma cases has found no relationship with teriparatide.⁸

Practical tips and precautions

- Teriparatide is given as a daily subcutaneous injection via a multi-dose pen device.
- Because of expense, teriparatide is generally restricted to patients at very high risk of fracture.
- Due to increased background risk of osteosarcoma, teriparatide is not recommended for patients with Paget disease, prior skeletal irradiation, bony metastases or prior skeletal malignancies, and for those with metabolic bone diseases (other than osteoporosis) or pre-existing hypercalcaemia.
- BMD decreases within 12 months of stopping teriparatide, unless followed by sequential treatment with an anti-resorptive drug.

Evidence statement

Treatment of osteoporosis in postmenopausal women

A good-quality systematic review (SR)² reported 10 moderate- and good-quality randomised controlled trials (RCTs) (including seven double-blind RCTs) investigating the effectiveness of hPTH(1-34). One trial³ in this SR reported fracture risk as a primary 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 per day (relative risk [RR]: 0.35, 95% confidence interval [CI]: 0.22–0.55). The absolute risk reduction (ARR) for vertebral fractures was 9% and ARR for non-vertebral fractures was 3% (RR: 0.47, 95% CI: 0.25–0.88) for hPTH(1-34) 20 µg per day. Six moderate to good quality RCTs reported in the SR² 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 per day had significant increases ranging from 9.7–10.3% in lumbar spine BMD and increases of 2.8–3.9% for FN BMD.

Treatment of osteoporosis in men

In a good-quality trial, men with idiopathic osteoporosis (n = 23) were randomly assigned to hPTH(1-34) 25 µg versus placebo.⁴ After 18 months, BMD had increased significantly by 13.5% and 2.9% at the lumbar spine and FN respectively. Total-hip BMD did not change significantly, but there was a significant decrease of 1.2% at the one-third distal radius. Another good-quality trial was conducted in men with low BMD who were predominantly hypogonadal (n = 437).⁵ Participants were treated with 20 µg or 40 µg of hPTH(1-34) versus placebo with calcium and vitamin D. After one year, lumbar spine BMD increased by 5.4% with 20 µg, compared with no change with placebo. There was no significant difference in the fracture rate with hPTH(1-34) compared with the placebo.⁵

Combination with anti-resorptive therapies in postmenopausal osteoporosis

There is strong evidence that combination therapy with alendronate and teriparatide may in fact blunt the anabolic effect of teriparatide on BMD.² There are no fracture data comparing the effect of the combination of teriparatide and alendronate with that of teriparatide alone.² A recent open-label RCT has compared the effect on BMD between teriparatide and denosumab alone, or in combination. At 24 months, combination treatment increased BMD at the lumbar spine and hip more than either treatment alone; the study was not powered to detect an effect on fracture rate.⁹

Safety

An increased risk of osteosarcoma was reported in a lifelong carcinogenicity study involving Fischer rats given high-dose hPTH(1-34) from infancy through senescence (eight weeks to two years of age).⁷ 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 conversely, after seven years of the Osteosarcoma Surveillance Study (an ongoing 15-year surveillance study initiated in 2003), there have been no osteosarcoma patients who have reported prior exposure to teriparatide.⁸ 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 post-dose 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.² 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%).

References

1. Dempster D, Cosman F, Parisien M, et al. Anabolic actions of parathyroid hormone on bone. *Endocr Rev* 1993;14(6):690–709.
2. Cranney A, Papaioannou A, Zytaruk N, et al. Parathyroid hormone for the treatment of osteoporosis: A systematic review. *CMAJ* 2006;175(1):52–9.
3. 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. *N Engl J Med* 2001;344(19):1434–41.
4. 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. *J Clin Endocrinol Metab* 2000;85(9):3069–76.
5. Orwoll E, Scheele W, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone mineral density in men with osteoporosis. *J Bone Miner Res* 2003;18(1):9–17.
6. Black D, Bilezikian J, Ensrud K, et al. One year of alendronate after one year of parathyroid hormone (1–84) for osteoporosis. *N Engl J Med* 2005; 353(6):555–65.
7. Barbehenn EK, Lurie P, Wolfe SM. Osteosarcoma risk in rats using PTH 1–34. *Trends Endocrinol Metab* 2001;12(9):383.
8. Andrews EB, Gilsenan AW, Midkiff K, et al. The US post-marketing surveillance study of adult osteosarcoma and teriparatide: Study design and findings from the first 7 years. *J Bone Miner Res* 2012;27(12):2429–37.
9. Leder BZ, Tsai JN, Uihlein AV, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): A randomised controlled trial. *J Clin Endocrinol Metab*. 2014;99(5):1694–700.

Strontium ranelate

Recommendation 23	Grade
Strontium ranelate at a dose of 2 g per day is an effective second-line option for reducing the risk of further osteoporotic fractures in postmenopausal women with prevalent fractures. Strontium ranelate should not be used in patients with previous or clinically active cardiovascular disease or uncontrolled hypertension and should only be used when other medications for the treatment of osteoporosis are unsuitable.	A

There is currently no evidence available for the effect of strontium ranelate in reducing fracture risk in men and early postmenopausal women. However, there is evidence to support the effectiveness of strontium ranelate 2 g per day for the prevention of bone mineral density (BMD) loss in early postmenopausal women, both Caucasian and Asian,^{1,2} and men.³ There is strong evidence to support the effectiveness of strontium ranelate 2 g per day for reducing the risk of further osteoporotic fractures in postmenopausal women with prevalent fractures.¹ Based on indirect comparisons, strontium ranelate appears to have similar efficacy to other therapies for spinal fractures apart from denosumab, where it is inferior.⁴ The effect of strontium may be partially blunted by prior bisphosphonates.⁵ Strontium may also be beneficial for fracture healing.⁶ Research suggests that strontium ranelate has a relatively greater effect on bone resorption than bone formation.⁷

Strontium ranelate was listed on the Pharmaceutical Benefits Scheme until 31 July 2016 for the treatment of women and men following a minimal trauma fracture and for the prevention of the first fracture in women 70 years of age or older with a T-score of ≤ -3.0 . Strontium ranelate is now available only on private prescription.

Side effects and potential harms

Strontium ranelate has been associated with an increased risk of venous thromboembolism in some randomised controlled trials (RCTs).¹ Recently, the European Medicines Agency (EMA) reviewed the risk benefit ratio based on the findings of an increase in the risk of cardiovascular (CV) disease in those with pre-existing CV disease and uncontrolled hypertension in the clinical trial program. While this effect has not been observed in observational studies,^{8,9} the EMA recommended suspension of strontium ranelate until more data become available.¹⁰ In Australia, a black box warning was added to the product information for strontium ranelate in 2014 after a review by the Therapeutic Goods Administration. Strontium ranelate should only be used when other options cannot be tolerated or are contraindicated, and where its use may be beneficial.¹¹

Practical tips and precautions

- Strontium ranelate is not recommended for patients with severe renal impairment.¹
- Do not use strontium ranelate in patients with current (or a history of) ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, venous thromboembolism or in patients with systolic blood pressure (BP) ≥ 160 mmHg or diastolic BP ≥ 90 mmHg.
- Calcium reduces absorption of strontium – administration of each should be separated by at least two hours.¹²
- 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 two hours.¹²
- The effect of strontium retention in bone and increased X-ray absorption of strontium compared to calcium leads to an amplification of BMD measurement by dual energy X-ray absorptiometry (DXA) that should be considered when using DXA to monitor treatment response.¹³ However, the greater increase in measured BMD is associated with greater efficacy for fracture-risk reduction, possibly because it reflects both compliance and the greater change in BMD seen in patients taking strontium ranelate.

Evidence statement

Treatment of osteoporosis

A Cochrane systematic review (SR)¹ reported on four RCTs (7093 participants) that compared the effectiveness of strontium ranelate daily to placebo for treating osteoporosis. 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. Women with osteoporosis who were treated with strontium ranelate 2 g per day showed a 37% reduction in vertebral fractures (two RCTs, $n = 5082$, relative risk [RR]: 0.63, 95% confidence interval [CI]: 0.56–0.71, number needed to treat [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 three years. Post hoc analyses suggested it was effective for hip fracture prevention in an older group with low hip BMD.

Safety

The same Cochrane SR¹ 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% versus 1.5%, odds ratio [OR]: 1.5, 95% CI: 1.1–2.1) and pulmonary embolism (0.8% versus 0.5%, OR: 1.7, 95% CI: 1.0–3.1). Strontium ranelate was associated with an increased risk of headache (3.9% versus 2.9%), seizures (0.3% versus 0.1%), memory loss (2.4% versus 1.9%) and disturbance in consciousness (2.5% versus 2.0%).

References

- O'Donnell S, Cranney A, Wells G, et al. Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database Syst Rev* 2006;4:CD005326. doi: 10.1002/14651858.CD005326.pub3.
- Liu JM, Wai-Chee Kung A, et al. Efficacy and safety of 2 g/day of strontium ranelate in Asian women with postmenopausal osteoporosis. *Bone* 2009;45(3):460–65.
- Kaufman JM, Audran M, Bianchi G, et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. *J Clin Endocrinol Metab* 2013;98(2):592–601.
- Freemantle N, Cooper C, Diez-Perez A, et al. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: A meta-analysis. *Osteoporos Int* 2013;24(1):209–17.
- Middleton ET, Steel SA, Aye M, Doherty SM. The effect of prior bisphosphonate therapy on the subsequent therapeutic effects of strontium ranelate over 2 years. *Osteoporos Int* 2012;23(1):295–303.
- Goldhahn J, Féron JM, Kanis J, et al. Implications for fracture healing of current and new osteoporosis treatments: An ESCEO consensus paper. *Calcif Tissue Int* 2012;90(5):343–53.
- Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350(5):459–68.
- Cooper C, Fox KM, Borer JS. Ischaemic cardiac events and use of strontium ranelate in postmenopausal osteoporosis: A nested case-control study in the CPRD. *Osteoporos Int* 2014; 25(2):737–45.
- Abrahamsen B, Grove EL, Vestergaard P. Nationwide registry-based analysis of cardiovascular risk factors and adverse outcomes in patients treated with strontium ranelate. *Osteoporos Int* 2014; 25(2):757–62.
- European Medicines Agency. PRAC recommends suspending use of Protelos/Osseor (strontium ranelate). London, UK: EMA, 2014. Available at www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/01/WC500159375.pdf [Accessed 17 February 2017].
- Carvalho NN, Voss LA, Almeida MO, et al. Atypical femoral fractures during prolonged use of bisphosphonates: Short-term responses to strontium ranelate and teriparatide. *J Clin Endocrinol Metab* 2011;96(9):2675–80.
- Rossi S, editor. *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd, 2006.
- 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.

Ongoing monitoring

Recommendation 24	Grade
Regularly re-assess fracture risk and requirement for anti-osteoporotic therapy in patients who are not receiving therapy, but remain at increased risk of fracture.	B

Frequency of re-assessment should be determined by the individual's overall fracture risk and occurrence of any new health events. Vigilance should be exercised for height loss and new episodes of back pain.

Recommendation 25	Grade
Review all patients 3–6 months after initiating a specific pharmacological intervention for osteoporosis, and annually thereafter. Bone mineral density testing at the 3–6 month review is not indicated.	B

Recommendation 26	Grade
Biochemical markers of bone turnover should not be routinely used for the diagnosis of osteoporosis in general practice. Measurement of markers should be confined to specialist practice, and may be useful for the monitoring of adherence to treatment and in the evaluation of secondary causes of bone loss.	D – consensus

At present, there are no validated criteria for the failure of medical therapy. However, therapeutic failure should be considered 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 (refer to [General bone-health maintenance and fracture prevention strategies](#) on page 26 for more information)
- there is a documented decrease in height of more than 3 cm since the last examination or acute back pain, which may be symptomatic of a new fracture – in these cases, a radiological examination is recommended.

Practical tips and precautions

- A decrease in bone mineral density (BMD) greater than measurement error is generally not seen before two years; hence, follow up bone densitometry is not recommended at intervals of less than two years.^{1,2}
- It is appropriate to recommend a repeat BMD test by dual energy X-ray absorptiometry (DXA) after two years for patients at risk of developing osteoporosis, to assist in re-evaluation of fracture risk.
- In patients with confirmed osteoporosis, a repeat BMD test is generally not required, but may be conducted before initiating a change in, or cessation of, anti-osteoporotic therapy.
- Wherever possible, perform repeat BMD 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.
- Changes of <5% at the lumbar spine or hip are within the precision error of most DXA machines and therefore should be regarded as representing no significant change.
- A radiographic assessment should be initiated if new fractures are suspected (eg height loss of 3 cm or more, new or acute pain).

Biochemical markers of bone turnover

Biochemical markers of bone turnover decrease rapidly (within three months) after initiation of anti-resorptive drugs such as oral or intravenous (IV) bisphosphonates, denosumab or raloxifene.³⁻⁵ They have also been shown to provide some prognostic information on the anti-fracture efficacy of these agents.⁶⁻⁸ Therefore, bone-turnover markers may be used at three and 12 months to assess the effect of alendronate, risedronate, zoledronic acid, denosumab or raloxifene on bone metabolism. Values of procollagen type I amino-terminal propeptide (PINP) increase soon after commencement of anabolic teriparatide therapy.⁹

Although the role of bone-turnover markers in monitoring osteoporosis treatments has not yet been fully investigated, measuring a bone resorption marker after three months of anti-resorptive treatment and finding a level in the lower half of the premenopausal range indicates compliance with therapy. However, in the absence of clear evidence of improved patient outcomes from their use, as well as cost-effectiveness data, their routine use in patient monitoring in general practice is not currently recommended.

Evidence statement

A failure to observe an increase in BMD during therapy with bisphosphonates, denosumab or raloxifene does not indicate decreased anti-fracture efficacy of the drug and is no indication to change treatment.¹⁰⁻¹⁵ A stable or increasing BMD during treatment with most agents currently approved for osteoporosis therapy should be considered as adequate response to therapy.¹⁰⁻¹⁵ In contrast, detectable loss of BMD 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.¹⁶⁻¹⁸

A decision to change treatment solely on the basis of a fracture occurring during treatment is not supported by randomised controlled trial 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 the type or route of administration of therapy on an individual basis. 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 the 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 osteoporosis therapy, it usually is low, even in patients with established fractures.^{19,20}

Follow-up visits, close contact between patient and health professionals, as well as repeat BMD and/or bone-marker measurements, may be used to improve medication adherence. 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 adherence to and persistence with medication.²¹ However, currently there is no consensus on the use of surrogate parameters to increase adherence. Three major international guidelines recommend follow-up to ensure that treatment is effective. Regular monitoring is an important component of any osteoporosis treatment plan.²²⁻²⁴ This applies to patients both with and without anti-osteoporotic drug treatment. Follow up BMD testing and physician check-ups are also recommended.^{22,23,25}

Patients with an increased risk of fracture 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 BMD below the measurement error before a time of two years is unlikely, follow-up examinations of BMD are usually not recommended at intervals of less than two years.²² The use of repeat DXA scans at intervals of two years or longer is appropriate in settings where the efficacy of treatment, risk assessment or decision to change or interrupt treatment is being considered.^{18,26} Repeat scans may also be useful for addressing patients' concerns in relation to treatment adherence.²³ If carried out less than two years after commencing treatment, the changes may be difficult to interpret unless the change is greater than 2.8 x precision (eg standard deviation or coefficient of variation of repeat measurements).

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.

References

1. Melton L, Atkinson E, O'Connor M, O'Fallon W, Riggs B. Determinants of bone loss from the femoral neck in women of different ages. *J Bone Miner Res* 2000;15(1):24–31.
2. Abrahamsen B, Nissen N, Hermann A, et al. When should densitometry be repeated in healthy peri- and postmenopausal women: The Danish Osteoporosis Prevention Study. *J Bone Miner Res* 2002;17(11):2061–67.
3. Naylor KE, Jacques RM, Paggiosi M, et al. Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: The TRIO study. *Osteoporos Int* 2016;27(1):21–31.
4. Brown JP, Roux C, Ho PR, et al. Denosumab significantly increases bone mineral density and reduces bone turnover compared with monthly oral ibandronate and risedronate in postmenopausal women who remained at higher risk for fracture despite previous suboptimal treatment with an oral bisphosphonate. *Osteoporos Int* 2014;25(7):1953–61.
5. Majima T, Shimatsu A, Satoh N, et al. Three-month changes in bone turnover markers and bone mineral density response to raloxifene in Japanese postmenopausal women with osteoporosis. *J Bone Miner Metab* 2008;26(2):178–84.
6. Sarkar S, Reginster J, Crans G, Diez-Perez A, Pinette K, Delmas P. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. *J Bone Miner Res* 2004;19(3):394–401.
7. 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.
8. 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. *J Clin Densitom* 2004;7(3):255–61.
9. Farahmand P, Marin F, Hawkins F, et al. Early changes in biochemical markers of bone formation during teriparatide therapy correlate with improvements in vertebral strength in men with glucocorticoid-induced osteoporosis. *Osteoporos Int* 2013;24(12):2971–81.
10. Cummings S, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry: Misleading changes and regression to the mean. Fracture Intervention Trial Research Group. *JAMA* 2000;283(10):1318–21.
11. Caro J, Ishak K, Huybrechts K, Raggio G, Naujoks C. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int* 2004;15(12):1003–08.
12. Cummings S, Karpf D, Harris F, et al. Improvement in spine bone mineral density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 2002;112(4):281–89.
13. 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.
14. Li Z, Chines A, Meredith M. Statistical validation of surrogate endpoints: Is bone mineral density a valid surrogate for fracture? *J Musculoskelet Neuronal Interact* 2004;4(1):64–74.
15. Sarkar S, Reginster J, Crans G, Diez-Perez A, Pinette K, Delmas P. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. *J Bone Miner Res* 2004;19(3):394–401.
16. Melton L, Atkinson E, O'Connor M, O'Fallon W, Riggs B. Determinants of bone loss from the femoral neck in women of different ages. *J Bone Miner Res* 2000;15(1):24–31.
17. Pouilles J, Tremollieres F, Ribot C. Variability of vertebral and femoral postmenopausal bone loss: A longitudinal study. *Osteoporos Int* 1996;6(4):320–24.
18. Leslie WD, Majumdar SR, Morin SN, Lix LM. Change in bone mineral density is an indicator of treatment-related antifracture effect in routine clinical practice: A registry-based cohort study. *Ann Intern Med* 2016;165(7):465–72. doi:10.7326/M15-2937.
19. Mayoux-Benhamou M, Roux C, Perraud A, Fermanian J, Rahali-Kachlouf H, Revel M. Predictors of compliance with a home-based exercise program added to usual medical care in preventing postmenopausal osteoporosis: An 18-month prospective study. *Osteoporos Int* 2005;16(3):325–31.
20. McCombs J, Thiebaud P, McLaughlin-Miley C, Shi J. Compliance with drug therapies for the treatment and prevention of osteoporosis. *Maturitas* 2004;48(3):271–87.
21. Clowes J, Peel N, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: A randomised controlled trial. *J Clin Endocrinol Metab* 2004;89(3):1117–23.
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. *Exp Clin Endocrinol Diabetes* 2006;114(10):611–22.

23. Scottish Intercollegiate Guidelines Network. Management of osteoporosis. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network, 2003.
24. 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 edn, updated 2003. *Endocrine Practice* 2003;9(6):544–64.
25. Cummings S, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry: Misleading changes and regression to the mean. Fracture Intervention Trial Research Group. *JAMA* 2000;283(10):1318–21.
26. Austin M, Yang Y-C, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res* 2012;27(3):687–93.

Special issues

Management of osteoporosis in the elderly

Practical tips and precautions

- Older people are at highest risk of minimal trauma fracture. It is essential to screen for osteoporosis by testing bone mineral density (BMD) in this population (BMD testing is Medicare subsidised for those with risk factors, those older than 70 years of age and those with fragility fracture). Primary prevention of fracture should be the objective.
- There is a paucity of evidence on strategies to reduce fragility fracture in the elderly.
- Older individuals have unique needs and differ quite significantly from younger populations in terms of their fragility fracture risk.
- It is important that clinicians apply a multifactorial and multidisciplinary approach to fracture reduction in elderly people.
- It is essential to address the triad of osteoporosis, falls risk and reducing the impact of falls in elderly people.
- Encourage safe mobility and exercise under appropriate supervision. 'If you don't use it, you lose it' applies.
- A safe environment (extrinsic) and minimising intrinsic factors (comorbidity, medications and polypharmacy) are critical to reducing falls risk.
- Optimise nutrition, calcium and vitamin D status. Older people are more likely to be deficient due to poor dietary intake, malabsorption or inadequate sun exposure (vitamin D). Supplementation should be considered for most elderly people unless their nutrition, calcium intake and vitamin D status are demonstrated to be sufficient.
- Choose anti-osteoporosis medications based on patient factors including compliance and persistence factors.
- Use of hip protectors should be judicious, as it is not possible to abolish the risk of falls and fracture in most elderly people. It should be noted that hip protectors do not work when not used. Compliance is crucial.

Supplementation of vitamin D and calcium with vitamin D in frail and residential-care-dwelling elderly

Recommendation 27	Grade
Calcium and vitamin D supplementation is recommended for the prevention of fracture in the frail elderly and institutionalised elderly. Optimisation of calcium and vitamin D should be the standard of care for this group.	C

The evidence and recommendations for the general population regarding calcium and vitamin D supplementation also apply to the elderly. However, the elderly are a special population due to higher osteoporosis and fracture risk and higher risk of calcium and vitamin D deficiency due to lifestyle factors and frailty. There is good evidence for high prevalence of vitamin D insufficiency in institutionalised and housebound older people and vitamin D supplementation is considered to be standard care in these populations. Calcium intake is often suboptimal, particularly in the elderly (especially institutionalised patients) who may have limitations to dietary intake, absorption and relatively limited sunlight exposure with low vitamin D. Calcium and vitamin D deficiency are especially important and should be optimised in patients with chronic kidney disease and patients on anti-resorptive therapy, with higher risk of hypocalcaemia and secondary hyperparathyroidism. Dietary calcium intake and serum 25-OH D levels should be checked before initiating anti-osteoporosis therapy, with appropriate supplementation to be recommended if calcium intake and/or vitamin D levels are inadequate.¹

Side effects and potential harms

Calcium supplements can increase the risk of renal calculi, particularly if given to individuals with adequate dietary calcium intake or calcium excess states. Calcium supplements can cause abdominal bloating and constipation. One randomised control trial (RCT)² reported an increase in cardiovascular adverse events with calcium in older postmenopausal women already having adequate dietary intake but not on anti-resorptive therapy. Further research is awaited to clarify this. Toxicity is uncommon with vitamin D, even in high doses. Single doses of up to 500 000 IU are tolerated without causing hypercalcaemia or hypercalciuria. However, higher doses may be associated with a higher risk of falls and fractures.³

Practical tips and precautions

- Serum 25-OH D levels should be checked, optimised and maintained during osteoporosis therapy.
- To optimise clinical efficacy, calcium at 500–600 mg per day should be taken in conjunction with vitamin D at 700–800 IU per day.^{4–6}
- Re-measure serum 25-OH D concentrations after three months of treatment to ensure levels 50–75 nmol/L.
- In patients with malabsorption or refractory vitamin D deficiency, parenteral vitamin D may be indicated (seek specialist advice).
- Vitamin D in combination with calcium rather than either alone appears most effective in fracture reduction.

Evidence statement

A Cochrane review of vitamin D in postmenopausal women and older men concluded that vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people.⁷ However, supplements of vitamin D with calcium may prevent hip or any type of fracture.⁷ A systematic review (SR) specifically assessing older and frailer populations analysed the benefit of vitamin D with and without calcium specifically in frailer residential and community-dwelling elderly.⁸ Two hundred and two abstracts were reviewed (44 studies fully reviewed). Thirteen publications met the specified eligibility criteria, with a further two studies meeting most eligibility criteria. There were eight studies with discrete residential-care populations. The average daily dosing of vitamin D in residential-care populations ranged from 400 IU to 1000 IU. In the residential-care populations, vitamin D significantly reduced non-vertebral fractures only when combined with calcium, with a relative risk reduction of 28% at three years in the Chapuy study ($P < 0.01$),⁹ while the other two studies recording non-vertebral fracture rates showed nonsignificant reduction in fractures.^{10,11} The percentage of patients sustaining non-vertebral fracture ranged from 12% in the active treatment group of the Meyer study to 27% in the placebo group of the Chapuy study. Hip fracture was significantly reduced in the Chapuy study ($P < 0.02$) and was nonsignificantly reduced in the Decalyos II study ($P = 0.07$).^{10,11} However, three other studies showed increases in hip fracture rates, although these failed to reach significance.^{11–13} The percentage of patients sustaining hip fracture in the placebo groups ranged from as low as 5–6% in the Lips and Lyons studies to as high as 16% in the placebo group of the Chapuy study.

References

1. Adami S, Giannini S, Bianchi G, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. *Osteoporos Int* 2009;20(2):239–44.
2. 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. *BMJ* 2008;336:262–66.
3. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: A randomised controlled trial. *JAMA* 2010;303(18):1815–22.
4. 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. *Am J Clin Nutr* 2007;86(6):1780–90.
5. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari H, Vanderschueren D, Haentjens P. 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. *J Clin Endocrinol Metab* 2007;92(4):1415–23.
6. 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. *Lancet* 2007;370:632–34.
7. Avenell A, Mak Jenson CS, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev* 2014 doi: 10.1002/14651858.CD000227.pub4.
8. Geddes JAA, Inderjeeth CA. Evidence for the treatment of osteoporosis with vitamin D in residential care and in the community dwelling elderly. *BioMed Res Int* 2013;2013:463589.
9. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994;308(6936):1081–82.
10. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: Confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: The Decalys II study. *Osteoporos Int* 2002;13(3):257–64.
11. Meyer HE, Smedshaug GB, Kvaavik E, et al. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomised controlled trial. *J Bone Miner Res* 2002;17(4):709–15.
12. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: A randomised, placebo-controlled clinical trial. *Ann Intern Med* 1996;124(4):400–06.
13. Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: A pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporos Int* 2007;18(6):811–18.

Hip protectors

Recommendation 28	Grade
Consider the use of hip protectors to reduce the risk of hip fracture in residential-care settings, but not in community settings.	C

Evidence statement

A Cochrane review¹ of pooled data from 14 studies (11,808 participants) conducted in nursing or residential-care settings found moderate-quality evidence for a small reduction in hip fracture risk (relative risk [RR]: 0.82, 95% confidence interval [CI]: 0.67–1.00); the absolute effect is 11 fewer people (95% CI, from fewer than 20 to 0) per 1000 having a hip fracture when provided with hip protectors. There is moderate-quality evidence when pooling data from five trials in the community (5614 participants) that shows little or no effect in hip fracture risk (RR: 1.15, 95% CI: 0.84–1.58).¹

Reference

1. Santesso N, Carrasco-Labra A, Brignardello-Petersen R. Hip protectors for preventing hip fractures in older people. *Cochrane Database Syst Rev* 2014.10.1002/14651858.CD001255.pub5.

Pharmacologic management in the elderly

Recommendation 29	Grade
Anti-resorptive therapy is recommended for reduction of fracture risk in people over 75 years of age with osteoporosis.	A

Recommendation 30	Grade
Anabolic therapy with teriparatide may be considered for reduction of vertebral fracture risk in people over 75 years of age with osteoporosis.	C

Evidence statement

Despite the high absolute fracture risk in the older adult population, there is a paucity of evidence-based literature, randomised controlled trials (RCTs) and head-to-head studies with fractures as an outcome in older patients. Elderly is defined as over 75 years for the purpose of this recommendation. This group is at the highest risk of fracture, with hip fracture the most common fracture type.^{1,2} Few studies include patients older than 75 years of age and, if they do, the numbers are often small and infrequently analysed as sub-groups. Most of the evidence is based on a systematic review.³ A review of the published literature on the clinical efficacy and safety of specific osteoporosis treatments in reducing fracture risk in women 75 years of age and older confirms the benefit of treatment.^{4,5-15} Denosumab and strontium ranelate are the only agents in which RCTs have been specifically designed and powered to demonstrate a benefit in reduction of the risk of hip fracture in females older than 75 years of age.^{4,12-14} Risedronate has been demonstrated to be beneficial in a mixed cohort of patients from the age of 70 to 100 years with demonstrated osteoporosis, but not in those over 80 years with risk factors only.⁶⁻⁸ For non-vertebral fracture, there is evidence for fracture risk reduction with the use of strontium ranelate^{12,13} and zoledronic acid¹¹ in the 75 years-plus cohort, and in the cohort of patients 70 to 79 years of age for risedronate.⁶ There are inadequate conclusive data for most other agents in terms of non-vertebral fracture risk reduction in older populations.^{4,15} All currently available agents (antiresorptives and teriparatide) are considered effective for vertebral fracture-risk reduction in older female populations.³⁻¹⁶ Only one study, which specifically included residents of a long-term-care facility treated with alendronate, reported an improvement in bone mineral density at two years.¹⁷ There is only one RCT sub-group analysis suggesting benefit of teriparatide in reducing vertebral fracture risk only in older cohorts.¹⁸

References

1. Sanders KM, Seeman E, Ugoni AM, et al. Age- and gender-specific rate of fractures in Australia: A population-based study. *Osteoporos Int* 1999;10(3):240–47.
2. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: The Dubbo Osteoporosis Epidemiology Study (DOES). *Osteoporos Int* 1994;4(5):277–82.
3. Inderjeeth CA, Foo AC, Lai MM, Glendenning P. Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: Review of the evidence. *Bone* 2009;44(5):744–51.
4. Inderjeeth CA, Poland KE. Management of osteoporosis in older people. *J Pharm Pract Res* 2010;40(3):226–31.
5. Ensrud KE, Black DM, Palermo L, et al. Treatment with alendronate prevents fractures in women at highest risk: Results from the Fracture Intervention Trial. *Arch Intern Med* 1997;157(22):2617–24.
6. Boonen S, McClung MR, Eastell R, El-Hajj Fuleihan G, Barton IP, Delmas P. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: Implications for the use of antiresorptive agents in the old and oldest old. *J Am Geriatr Soc* 2004;52(11):1832–39.
7. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001;344(5):333–40.
8. Masud T, McClung M, Geusens P. Reducing hip fracture risk with risedronate in elderly women with established osteoporosis. *Clin Interv Aging* 2009;4:445–49.
9. Boonen S, Black DM, Colon-Emeric CS, et al. Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. *J Am Geriatr Soc* 2010;58(2):292–99.
10. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809–22.
11. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357:1799–809.
12. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90(5):2816–22.
13. Seeman E, Vellas B, Benhamou C. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006;21(7):1113–20.
14. Boonen S, Adachi JD, Man Z, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. *J Clin Endocrinol Metab* 2011;96(6):1727–36.
15. McClung MR, Boonen S, Topping O, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. *J Bone Miner Res* 2012;27(1):211–18.
16. Boonen S, Marin F, Mellstrom D, et al. Safety and efficacy of teriparatide in elderly women with established osteoporosis: Bone anabolic therapy from a geriatric perspective. *J Am Geriatr Soc* 2006;54(5):782–89.
17. Greenspan SL, Schneider DL, McClung MR, et al. Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;136(10):742–46.
18. Inderjeeth CA, Chan K, Glendenning P. Teriparatide: Its use in the treatment of osteoporosis. *Clin Med Insights Ther* 2010;2:1–14.

Falls risk reduction in the elderly

Recommendation 31	Grade
Multifactorial assessment of falls risk, exercise programs and home-safety interventions are recommended to reduce the rate of falls in community-dwelling people over 75 years of age.	A

Recommendation 32	Grade
Vitamin D supplementation of elderly people in care facilities is recommended to reduce the rate of falls. Vitamin D supplements given for falls prevention are normally combined with calcium to address the high rates of calcium deficiency also seen in this population.	A

Evidence statement

Community-dwelling elderly people

Approximately 30% of community-dwelling elderly fall each year, with a high risk of injury including osteoporotic fracture, particularly hip fracture, the most common fracture in the very old. There is evidence in community-dwelling elderly¹ for group and home-based exercise programs and home-safety interventions for reducing the rate of falls and risk of falling. Multifactorial assessment and intervention programs appear effective in reducing the rate of falls, but not the risk of falling. Tai chi reduces the risk of falling. Overall, vitamin D supplementation does not appear to reduce falls in community-dwelling people, but may be effective in people who have lower vitamin D levels before treatment.

Residents of care facilities and hospitalised elderly

These are the frailest and highest risk population for falls and fracture risk, and the most challenging as falls and fracture risk in this group is usually multifactorial, and the potential to reverse these risks often limited. According to a Cochrane review² of studies conducted in care facilities, vitamin D supplementation is effective in reducing the rate of falls. Exercise in subacute hospital settings appears effective but its effectiveness in care facilities remains uncertain due to conflicting results, possibly associated with differences in interventions and levels of dependency. There is evidence that multifactorial interventions reduce falls in hospitals but the evidence for risk of falling was inconclusive. Evidence for multifactorial interventions in care facilities suggests possible benefits, but the evidence is also inconclusive.

References

1. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;12:CD007146.
2. Cameron ID, Gillespie LD, Robertson M, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev 2012;12:CD005465.

Exercise in the elderly

Recommendation 33	Grade
Evidence-based exercise modalities that progress in intensity as capacity improves are recommended for the maintenance of bone strength, muscle function and balance in people over the age of 75.	B

Recommendation 34	Grade
Exercise programs for very frail elderly institutionalised people and those with vertebral fracture risk should be supervised, modified and tailored to minimise the potential to increase the risk of falls, injury and vertebral fractures.	C

Evidence statement

The evidence presented in this guideline for the benefits of exercise applies (in general) to the elderly population. The strongest evidence for benefit is in those with mild to moderately impaired mobility. The frailest (eg highly dependent institutional populations), have limited potential for benefit and may be at higher risk of falls and fracture from exercise programs if left unsupervised. This may be due to either overestimation of ability following exercise (false sense of security) or a lag in improvement in balance, despite improvement in strength.¹⁻⁶

References

1. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev* 2011;7:CD000333.
2. Kemmler W, Haberle L, von Stengel S. Effects of exercise on fracture reduction in older adults: A systematic review and meta-analysis. *Osteoporos Int* 2013;24(7):1937-50.
3. Cameron ID, Gillespie LD, Robertson M, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev* 2012;12:CD005465.
4. El-Khoury F, Cassou B, Charles MA, Dargent-Molena P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013;347:f6234.
5. Martyn-St James M, Carroll S. A meta-analysis of impact exercise on postmenopausal bone loss: The case for mixed loading exercise programmes. *Br J Sports Med* 2009;43(12):898-908.
6. Dusdal K, Grundmanis J, Luttin K, et al. Effects of therapeutic exercise for persons with osteoporotic vertebral fractures: A systematic review. *Osteoporos Int* 2011;22(3):755-69.

Bone loss associated with aromatase inhibitor therapy for breast cancer and androgen deprivation therapy for prostate cancer

Most patients with a diagnosis of early oestrogen receptor (ER)-positive breast cancer or localised prostate cancer now have good prognosis, with 10-year survival greater than 90%. Survivorship issues such as unfavourable cancer treatment effects on bone health are of paramount importance. Endocrine treatments improve cancer-specific outcomes, but lead to severe hypogonadism and therefore accelerated bone loss.

Recommendation 35	Grade
All women undergoing aromatase inhibitor (AI) therapy should have a baseline assessment of fracture risk prior to commencing therapy.	A

Assessment includes review of clinical risk factors, basic laboratory testing (electrolytes, calcium, alkaline phosphatase and vitamin D), and hip and spine bone mineral density (BMD) measurement by dual energy X-ray absorptiometry (DXA). If reduced bone mass is present at baseline, individualised assessment is necessary to identify unrelated secondary causes of osteoporosis. In women with a T-score ≤ -1.0 , plain radiographs of the thoracolumbar spine should be performed to exclude subclinical vertebral fractures, defined by the Pharmaceutical Benefits Scheme (PBS) as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body. This is important, because evidence suggests that spinal fractures are often the first fracture to occur in osteoporosis, increase the risk of future fragility fractures, and are clinically silent in the majority.

While risk calculators such as the Garvan Fracture Risk Calculator or Fracture Risk Assessment Tool (FRAX) may be useful, they do not take aromatase inhibitor (AI) use into account and may substantially underestimate fracture risk. The utility of bone-remodelling markers or bone imaging other than DXA requires further evaluation.

Clinical risk factors for osteoporosis in cancer, including breast cancer

- High prevalence of vitamin D deficiency^{1,2}
- Decreased physical activity^{3,4}
- Increased risk of falls secondary to treatment-induced neuropathy⁵
- Chemotherapy-induced ovarian failure⁶
- AI therapy^{7,8}

Recommendation 36	Grade
<p>Women undergoing AI therapy who fall within one of the following two categories should commence anti-resorptive therapy unless contraindicated:</p> <ol style="list-style-type: none"> 1. 70 years or over with a BMD T-score ≤ -2.5 2. 50 years or over with a minimal trauma fracture (including radiological vertebral fracture) or a high estimated 10-year risk of fracture. <p>There is limited evidence specific to women receiving AI to guide firm recommendations outside these criteria, especially in premenopausal women.</p>	A

International consensus guidelines^{6,9} recommend that anti-resorptive therapy should be initiated in AI-treated women not fulfilling the above criteria if the lowest BMD T-score is ≤ -2.0 or if more than two fracture risk factors are present, and be considered where there is a >5–10% decrease in BMD in one year of AI treatment, or 10-year absolute risk of a major osteoporotic fracture of >20%, or of a hip fracture of >3%. However, this is outside current PBS of Australia subsidy criteria.

Premenopausal women commonly have normal baseline BMD with low short-term fracture risk, yet lose bone more rapidly than older postmenopausal women. Decisions regarding anti-resorptive treatment should be carefully individualised and discussed with the patient. Bisphosphonates can persist in the bone matrix for years after therapy is discontinued, potentially resulting in foetal exposure during pregnancy. Specialist referral may be appropriate.

Recommendation 37	Grade
The duration of anti-resorptive treatment in women who are undergoing or have completed AI therapy should be individualised and based on absolute fracture risk.	D

Bone loss in most untreated women is most marked in the 12–24 months post AI initiation, and limited data suggest partial BMD recovery after cessation of AI treatment. DXA should be repeated 12 months after commencement of AI therapy, with subsequent individualised monitoring frequency.

Recommendation 38	Grade
General measures to prevent bone loss should be implemented in all women commencing AI therapy.	C

- Regular moderate physical activity (weight-bearing exercises and resistance training)
- Smoking cessation
- Limitation of alcohol to <2 standard drinks per day
- Calcium intake of 1300 mg, preferably dietary
- Vitamin D supplementation to achieve and maintain 25-OH D levels >50 nmol/L

Recommendation 39	Grade
All men commencing androgen deprivation therapy (ADT) should have a baseline assessment of fracture risk. BMD by DXA should be measured in all patients at the time of commencement of ADT.	A

Key recommendations for the management of bone health in men receiving androgen deprivation therapy (ADT) are adapted from previously published management guidelines of the Endocrine Society of Australia, the Australian and New Zealand Bone and Mineral Society, and the Urological Society of Australia and New Zealand.¹⁰

Risk factors for osteoporosis should be ascertained, basic laboratory testing conducted (electrolytes, calcium, alkaline phosphatase and vitamin D), and hip and spine BMD measurement determined by DXA. Absolute baseline fracture risk may be estimated using mathematical tools such as the Garvan Fracture Risk Calculator or FRAX. However, neither of these algorithms is validated for men with prostate cancer receiving ADT, and they may underestimate true fracture risk. In men with a T-score ≤ -1.0 , thoracolumbar spine X-rays should be performed to exclude clinically silent vertebral fractures.¹⁰ DXA should be repeated 12 months after commencement of ADT, with subsequent individualised monitoring frequency.

Recommendation 40	Grade
All men receiving ADT who have a history of minimal trauma fracture should be commenced on anti-resorptive therapy, unless contraindicated.	A

There is currently insufficient evidence to make evidence-based recommendations regarding if and when bisphosphonate therapy for primary prevention should be commenced in men with prostate cancer who are receiving ADT. Consistent with the general recommendations in this guideline, all men older than 70 years of age with a T-score of ≤ -2.5 should commence anti-resorptive therapy, and therapy should be considered if there is an annual BMD loss of 5–10% or a 10-year absolute risk of a major osteoporotic fracture of $>20\%$, or of a hip fracture of $>3\%$.

Australian guidelines recommend that bisphosphonate therapy should be considered for primary prevention if the BMD T-score is ≤ -2.0 .¹¹ However, this recommendation is outside current PBS subsidy criteria. While bisphosphonates are recommended (and subsidised by the PBS) for primary fracture prevention in glucocorticoid-induced osteoporosis when the T-score is ≤ -1.5 , current evidence is insufficient to recommend the same or similar T-score cut-off for men receiving ADT.

Recommendation 41	Grade
Management of bone health should be reviewed 1–2 yearly in men on continuous ADT.	C

Management should also be re-evaluated after cessation of ADT, as the gonadal axis may recover in some men, with more rapid recovery reported in younger men (<65 years) or shorter (<24 – 30 months) duration of ADT.¹¹

Recommendation 42	Grade
General measures to prevent bone loss should be implemented in all men commencing ADT.	C

- Regular moderate physical activity (weight-bearing exercises and resistance training)
- Smoking cessation
- Limitation of alcohol to <2 standard drinks per day
- Calcium intake of 1000–1300 mg, preferably dietary
- 25-OH D supplementation to achieve and maintain levels >50 nmol/L

Evidence statement

AI therapy

Adjuvant endocrine therapy, either with selective ER modulators such as tamoxifen or AIs, is generally given for 5–10 years. Tamoxifen has partial ER-agonistic activity in bone and is protective in postmenopausal women but leads to accelerated bone loss in premenopausal women. AIs block oestradiol production, reducing circulating oestradiol by >98%. AIs inhibit the oestradiol-mediated negative feedback on gonadotropin production. They cannot be used in premenopausal women unless ovarian function is suppressed, typically by pharmacological or surgical means.

In postmenopausal women, AIs are preferred because of modest improvements in breast cancer outcomes, compared to tamoxifen.¹² While endocrine treatment in premenopausal women is evolving, the use of ovarian suppression plus AI is becoming more frequent, especially in younger (<35–40 year-old) women with high-risk breast cancer.¹³

In postmenopausal women, AIs are associated with a 2–3-fold accelerated BMD decline, and the magnitude of bone loss is greatest within the first two years. About 10% of untreated postmenopausal women will have a new clinical fracture within three years of AI treatment.¹⁴ In premenopausal women, bone loss is even higher; 7–9% in the first 12 months, and after five years of treatment, 13% with osteoporosis by DXA criteria.¹³ In randomised controlled trials (RCTs), bisphosphonates prevent AI-induced loss of bone loss, but studies are not powered for fracture endpoints. By contrast, a recent trial reported a 50% reduction in clinical fracture rates with denosumab (60 mg given six-monthly for three years) compared to placebo in postmenopausal women.¹⁴

ADT

While testosterone is important for bone health due to direct effects on the male skeleton, a large proportion of its bone-protective actions are indirect, via aromatisation to oestradiol. In addition, testosterone improves bone strength through its anabolic effects on muscle mass. Loss of muscle increases fracture risk due to higher propensity of falls.⁴ ADT usually involves depot preparations of gonadotropin-releasing hormone (GnRH) analogues and reduces sex steroids to castrate levels. Newer treatment modalities such as abiraterone also inhibit extra-testicular sex-steroid synthesis and lead to even more profound sex-steroid deprivation. Low BMD is highly prevalent among men even prior to commencement of ADT, and under recognised. A study among 236 Australian men (mean age 70 years) with prostate cancer, newly commencing ADT showed that, at baseline, 11% had osteoporosis and 40% osteopenia.¹⁵ Sixty-one per cent of the men with osteoporosis were unaware of the diagnosis. Even in the absence of ADT, bone health is a concern in older men with prostate cancer.

During the first year of ADT, BMD loss is accelerated by 2–7-fold relative to the 0.5–1% bone loss occurring in ageing men.¹¹ DXA may underestimate ADT-associated bone loss especially loss of cortical bone which can exceed 10%.¹⁶ BMD continues to decline with long-term ADT, albeit at a lower rate. Large registry studies have shown that ADT increases relative fracture risk by 30–60%.¹¹ In a cohort study of more than 50,000 men who survived for at least five years after prostate cancer diagnosis, fracture incidence approached 20%, and the number needed to harm for the occurrence of any fracture was 28 for GnRH agonist use and 16 for orchidectomy.¹⁷

Multiple RCTs have shown that bisphosphonate therapy prevents ADT-associated BMD loss, but they were too small to provide fracture outcomes.¹¹ By contrast, a large RCT in men receiving ADT showed that denosumab reduced the incidence of vertebral fractures (relative risk at three years 0.38 versus placebo, $P = 0.006$) in men receiving ADT with a median T-score of -1.5 at randomisation, with a number needed to treat to prevent a one-incident vertebral fracture of 42.¹⁸

References

1. Acevedo F, Pérez V, Pérez-Sepúlveda A, et al. High prevalence of vitamin D deficiency in women with breast cancer: The first Chilean study. *Breast* 2016;29:39–43.
2. Chen P, Li M, Gu X, et al. Higher blood 25(OH)D level may reduce the breast cancer risk: Evidence from a Chinese population based case-control study and meta-analysis of the observational studies. *PLoS ONE* 2013;8(1):e49312. doi: 10.1371/journal.pone.0049312.
3. Olsen CM, Wilson LF, Nagle CM, et al. Cancers in Australia in 2010 attributable to insufficient physical activity. *Aust NZ J Public Health* 2015;39(5):458–63.
4. Pizot C, Boniol M, Mullie P, et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. *Eur J Cancer* 2016;52:138–54.
5. Kolb NA, Smith AG, Singleton JR, et al. The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. *JAMA Neurol* 2016;73(7):860–66.
6. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force report: Bone health in cancer care. *J Natl Compr Canc Netw* 2009;11 Suppl 3:S1–S35.
7. Becker T, Lipscombe L, Narod S, Simmons C, Anderson GM, Rochon PA. Systematic review of bone health in older women treated with aromatase inhibitors for early-stage breast cancer. *J Am Geriatr Soc* 2012;60(9):1761–67.
8. Edwards BJ, Raisch DW, Shankaran V, et al. Cancer therapy associated bone loss: Implications for hip fractures in mid-life women with breast cancer. *Clin Cancer Res* 2011;17(3):560–68.
9. Rizzoli R, Body JJ, Brandi ML, et al. Cancer-associated bone disease. *Osteoporos Int* 2013;24(12):2929–53.
10. Grossmann M, Hamilton EJ, Gilfillan C, Bolton D, Joon DL, Zajac JD. Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. *Med J Aust* 2011;194(6):301–06.
11. Grossmann M, Zajac J. Management of side effects of androgen deprivation therapy. *Endocrinol Metab Clin North Am* 2011;40(3):655–71.
12. Dowsett M, Forbes JF, Bradley R, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: Patient-level meta-analysis of the randomised trials. *Lancet* 2015;386(10001):1341–52.
13. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371(2):107–18.
14. Gnant M, Pfeiler G, Dubsy PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386(9992):433–43.
15. Cheung AS, Pattison D, Bretherton I, et al. Cardiovascular risk and bone loss in men undergoing androgen deprivation therapy for non-metastatic prostate cancer: Implementation of standardized management guidelines. *Andrology* 2013;1(4):583–89.
16. Hamilton EJ, Ghasem-Zadeh A, Gianatti E, et al. Structural decay of bone microarchitecture in men with prostate cancer treated with androgen deprivation therapy. *J Clin Endocrinol Metab* 2010;95(12):E456–63.
17. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352(2):154–64.
18. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361(8):745–55.

Medication-related osteonecrosis of the jaw

Medication-related osteonecrosis of the jaw (MRONJ) is defined as an area of exposed bone in the maxillofacial region that has persisted for more than eight weeks, in a patient receiving bisphosphonates, denosumab or anti-angiogenic therapy for cancer, and where there is no history of radiation therapy to the jaws or obvious metastatic disease to the jaws.¹

A recently described condition with few prevalence studies published, MRONJ appears to occur more rarely in patients undergoing osteoporosis therapy than in patients with cancer being treated with anti-resorptives to prevent skeletal-related adverse events. The reported prevalence is between <1 and 10 cases per 10,000 in patients receiving oral bisphosphonate therapy for osteoporosis, marginally higher than the incidence in the general population.^{2,3} Duration of oral bisphosphonate therapy for osteoporosis is a risk factor for MRONJ, with one study reporting 21 cases per 10,000 after four years of therapy.² This time frame may be shortened if the patient is also being treated with long-term glucocorticoids or anti-angiogenic drugs.¹ A prevalence of 1.7 cases per 10,000 has been reported for patients undergoing annual intravenous zoledronic therapy for three years, with no change after six years therapy.^{4,5} For denosumab, the risk of MRONJ is reported to be four cases per 10,000.⁶ Compared with patients receiving higher doses of anti-resorptives (eg zoledronic acid or denosumab) for cancer treatment, the risk of MRONJ for patients with osteoporosis exposed to anti-resorptive medications is approximately 100 times smaller.¹

The aetiology of MRONJ is uncertain, but appears to be multifactorial and related to the dose and duration of exposure to the anti-resorptive agent, pre-existing oral disease profile, dentoalveolar oral surgery and genetic polymorphisms.⁷

Recent consensus recommendations from the American Association of Oral and Maxillofacial Surgeons (AAOMS)¹ and the International Task Force on Osteonecrosis of the Jaw⁷ state that elective dentoalveolar oral surgery does not appear to be contraindicated in patients undergoing anti-resorptive therapy for osteoporosis. However, identification and treatment of dental disease prior to the initiation of anti-resorptive therapy, if possible, is recommended.⁷ Patients should be adequately informed of the very small risk of MRONJ.

The AAOMS recommends that if systemic conditions permit, discontinuation of oral bisphosphonates for two months before and three months after elective invasive dental surgery may be considered in order to lower the risk of MRONJ.¹ This guidance contrasts with that of the American Dental Association (ADA), as well as the International Task Force on Osteonecrosis of the Jaw, both of which state that there is insufficient evidence to recommend a break from anti-resorptive drug therapy, or a waiting period before performing minor oral surgical treatment.^{7,9} However, the International Task Force on Osteonecrosis of the Jaw recommends that in those at high risk for the development of MRONJ, pausing anti-resorptive therapy following extensive oral surgery should be considered until the surgical site heals with mature mucosal coverage.⁷ Patients with established MRONJ should avoid elective dentoalveolar oral surgery, as this may result in additional areas of exposed necrotic bone.¹ Research also suggests an improved outcome of MRONJ if anti-resorptive therapy is ceased.⁸

Optimising oral hygiene prior to initiating anti-resorptive therapy may reduce the incidence of MRONJ.⁷ Good dental hygiene and care is therefore recommended for all patients undergoing anti-resorptive therapy for osteoporosis, particularly in those using long-term oral bisphosphonates. There is a strong association between periodontitis and MRONJ, due to the increased likelihood of extractions, the direct effects of bacterial infection and delayed healing due to inflammation.¹⁰ Improved dental awareness and prophylactic intervention have been shown to significantly reduce the incidence of MRONJ in patients receiving anti-resorptive therapy for cancer.¹¹

More research to understand the pathophysiology of MRONJ is required, and future recommendations may change to reflect improved knowledge of this condition. However, it is important to be aware of the proven benefits of anti-resorptive therapy in terms of reducing fracture risk, in comparison with the very small risk of serious adverse events such as MRONJ.

References

1. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg* 2014;72(10):1938–56.
2. Lo JC, O’Ryan FS, Gordon NP, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg* 2010;68(2):243–53.
3. Malden N, Lopes V. An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence. *J Bone Miner Metab* 2012;30(2):171–82.
4. Grbic JT, Black DM, Lyles KW, et al. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: Data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. *J Am Dent Assoc* 2010;141(11):1365–70.
5. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012;27(2):243–54.
6. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension. *J Bone Miner Res* 2012;27(3):694–701.
7. Khan AA, Morrison A, Hanley DA, et al, on behalf of the International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. *J Bone Miner Res* 2015;30(1):3–23.
8. Damm DD, Jones DM. Bisphosphonate-related osteonecrosis of the jaws: A potential alternative to drug holidays. *Gen Dent* 2013;61(5):33–38.
9. Hellstein JW, Adler RA, Edwards B, et al, American Dental Association Council on Scientific Affairs Expert Panel on Antiresorptive Agents. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: Executive summary of recommendations from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc* 2011;142(11):1243–51.
10. Tsao C, Darby I, Ebeling PR, et al. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. *J Oral Maxillofac Surg* 2013;71(8):1360–66.
11. Sim leW, Sanders KM, Borromeo GL, Seymour JF, Ebeling PR. Declining incidence of medication-related osteonecrosis of the jaw in patients with cancer. *J Clin Endocrinol Metab* 2015;100(10):3887–93.

Atypical fracture of the femur

Atypical fractures of the femur (AFFs) occur in the subtrochanteric region or femoral shaft. AFFs are associated with no trauma or minimal trauma; high trauma fractures are specifically excluded from this definition.¹ AFFs exhibit several different radiological and clinical features to ordinary osteoporotic femur fractures; in particular, a transverse orientation, lack of comminution or minimal comminution, and localised cortical thickening at the fracture site, which is characteristic of a stress fracture. Bilateral fractures occur in about 30% of cases, and prodromal pain in the groin or thigh is a distinguishing feature, occurring in more than 70% of individuals.¹

AFFs appear to be more common in patients on long-term bisphosphonate therapy, and have also been reported following denosumab therapy.² A recent systematic review of 11 studies³ found that bisphosphonate exposure is associated with an increased risk of AFF, with a relative risk of 11.78 (95% confidence interval [CI]: 0.39–359.69) although the wide confidence interval of this analysis indicates severe heterogeneity of the data, in part due to lack of agreement on the definition of AFF. While the relative risk of AFF with bisphosphonate therapy appears on this evidence to be high, the absolute risk remains very low, ranging from 3.2 to 50 cases per 100,000 person years.¹ However, long-term (over five years) bisphosphonate use may be associated with higher risk of AFF (100 per 100,000 person years), although there is a paucity of data in this area. Evidence also suggests that the risk of AFF may decline when bisphosphonate therapy is stopped.¹ Although there are case reports of healing of AFF with teriparatide therapy,⁴ subsequent case series show variable responses to treatment,⁵ and data from randomised controlled trials are lacking. Nevertheless, it is important to stop anti-resorptive therapy if an AFF is identified.

Although the epidemiological data are far from conclusive, AFFs are rare, both in the general population (7% occur in patients who have never received anti-resorptive therapy) and in patients undergoing bisphosphonate therapy for osteoporosis. The risk of AFF with bisphosphonate therapy must be considered against the far greater incidence of common osteoporotic fractures at all sites, and the proven effectiveness of bisphosphonates in reducing the incidence of such osteoporotic fractures.

References

1. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014;29(1):1–23.
2. Thompson RN, Armstrong CL, Heyburn G. Bilateral atypical femoral fractures in a patient prescribed denosumab – A case report. *Bone* 2014;61:44–47.
3. Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: A systematic review and meta-analysis. *J Bone Miner Res* 2013;28(8):1729–37.
4. Fukuda F, Kurinomaru N, Hijioka A. Weekly teriparatide for delayed unions of atypical subtrochanteric femur fractures. *Biol Ther* 2014;4(1–2):73–79.
5. Miller PD, McCarthy EF. Bisphosphonate-associated atypical sub-trochanteric femur fractures: Paired bone biopsy quantitative histomorphometry before and after teriparatide administration. *Semin Arthritis Rheum* 2015;44(5):477–82.

Appendix A. Process report

This guideline is an evidence update of *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men*, published in 2010 by The Royal Australian College of General Practitioners (RACGP) and approved by the National Health and Medical Research Council (NHMRC). The update process followed guideline development best practice but due to limited resourcing, some limitations were imposed.

The development of this guideline consisted of the following major phases:

- Formation of a multidisciplinary expert Working Group
- Working Group agreement on the scope of the guideline
- Formulation of literature-search strategies
- Systematic literature searches to identify primary evidence and syntheses of primary evidence
- Appraisal and selection of evidence
- Revision of existing or drafting of new evidence statements
- Revision of existing or formulation of new recommendations
- Full Working Group review of the draft guideline and agreement on recommendations
- Endorsement of the guideline by the RACGP

Identification, appraisal and synthesis of new evidence

The literature searches for this guideline were limited to studies published between 2006 and February 2016. However, some of the evidence used to support recommendations in the 2010 guideline has been included in this update if (in the opinion of the Working Group) these studies have retained their relevance and importance within the more recent body of evidence.

Published literature was searched systematically in three databases: Ovid Medline, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. Additional database searches were conducted for some topics. Filters were applied in Ovid Medline to identify randomised controlled trials (RCTs), systematic reviews (SRs) and meta-analyses (MAs).^{1,2} Other filters applied included men and women older than 45 years of age, and studies reporting outcomes of fracture and/or bone mineral density (BMD). As far as possible, evidence used to support recommendations covering pharmacologic and other interventions for osteoporosis prevention and treatment was restricted to studies with fracture as a primary outcome. However, for some interventions, evidence meeting this criterion is sparse or of variable quality, and high-quality studies with BMD as a primary outcome have been used if, in the opinion of the Working Group, the data can be used to support recommendations.

Evidence to support the recommendations was confined to papers complying with levels I (SR of level II studies) and II (RCT or prospective cohort study) of the NHMRC evidence hierarchy (Table 5). Evidence from cohort and observational studies was used to support some recommendations concerning diagnostic investigations, monitoring, diet and lifestyle, and to update epidemiological and background information.

Table 5. NHMRC evidence hierarchy³

Study type	Description
Level I	A systematic review of level II studies
Level II	An RCT or prospective cohort study
Level III	A pseudo-RCT, case-control study, retrospective cohort study, comparative study with concurrent controls or comparative study without concurrent controls
Level IV	Case series, study of diagnostic yield, cohort study of persons at different stages of disease or cross-sectional study

Adapted from National Health and Medical Research Council levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2009.

Rating of evidence

The body of evidence supporting each recommendation was rated according to the NHMRC body of evidence matrix (Table 6). This method is designed to allow for a mixture of components, taking into account the fact that although the body of evidence in any particular area may be small (therefore attracting a low evidence base component rating), a high clinical impact and applicability to the Australian population will merit a high overall rating.

Table 6. NHMRC body of evidence matrix³

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency	All studies consistent	Most studies consistent, and inconsistency 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 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 body of evidence differ from target population for guideline but it is clinically sensible to apply this evidence to target population	Population(s) studied in body of evidence differ from target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Adapted from National Health and Medical Research Council additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2009.

Grading of recommendations

Each recommendation was given a final grading according to the NHMRC grades of recommendation (Table 7). The grading represents the overall strength of the evidence, and reflects the confidence with which clinicians can apply a recommendation in a clinical situation. The final grades are based on a summation of individual components of the body of evidence assessment shown in Table 6. A recommendation cannot be graded A or B unless the volume and consistency of evidence components are both graded either A or B.

Table 7. NHMRC grades of recommendations³

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*

Adapted from National Health and Medical Research Council additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2009.

* The Working Group has also applied a Grade D to recommendations where there is expert consensus in the absence of a strong body of evidence.

Consultation and endorsement by the RACGP

Due to resources and time restrictions, the consultation period was focused on Osteoporosis Australia stakeholders and review by the main users of the guideline: general practitioners (GPs). The guideline was reviewed by GP subject matter experts and the RACGP's Expert Committee for Quality Care and endorsed by the RACGP Council.

Ongoing feedback on the guideline is encouraged and can be submitted via the online feedback tab.

References

1. White VJ, Glanville JM, Lefebvre C, Sheldon, TA. A statistical approach to designing search filters to find systematic reviews: Objectivity enhances accuracy. *J Inf Sci* 2001;27(6):357–70.
2. Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: Ten years on. *J Med Libr Assoc* 2006;94(2):130–36.
3. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2009. Available at www.nhmrc.gov.au/guidelines-publications/information-guideline-developers/resources-guideline-developers [Accessed 1 February 2017].

Appendix B. Working group

Name	Qualifications	Positions
Professor Peter Ebeling, AO (Chair)	MBBS, MD, FRACP	Head, Department of Medicine, School of Clinical Sciences, Monash University; Chair, Division of Medicine, Monash Health; Honorary Medical Director, Osteoporosis Australia; Past-President, Endocrine Society of Australia; Board Member, International Osteoporosis Foundation
Professor Jacqueline Center	MBBS, MS, PhD, FRACP	Head, Epidemiology and Clinical Research, Bone Biology Division, Garvan Institute of Medical Research; Deputy Director, Department of Endocrinology, St Vincent's Hospital; Professor of Medicine (Conjoint), University of NSW
Associate Professor Roderick Clifton-Bligh	MBBS, PhD, FRACP	Head, Department of Endocrinology, Royal North Shore Hospital, NSW; Associate Professor, Kolling Institute of Medical Research, Northern Clinical School, Sydney Medical School, University of Sydney, NSW
Professor Mark Cooper	BMBCh, PhD, FRCP (London), FRACP	Professor of Medicine, Concord Clinical School, University of Sydney; Consultant Endocrinologist, Concord Repatriation General Hospital, Concord, Sydney
Dr Dan Ewald	MPH&TM, MAppEpid, FAFPHM, FRACGP, FACTM, GAICD	Lead Clinical Advisor, North Coast Primary Health Network; Adjunct Associate Professor, Sydney Medical School, University of Sydney, NSW; General Practitioner
Professor Maria Fiatarone Singh	MD, FRACP	John Sutton Chair of Exercise and Sport Science, Faculty of Health Sciences, University of Sydney, NSW; Professor, Sydney Medical School, University of Sydney, NSW
Dr Kirtan Ganda	BSc (Med), MBBS, FRACP, PhD	Endocrinologist, Department of Endocrinology, Concord Repatriation General Hospital, NSW; Senior Lecturer, Concord Clinical School, University of Sydney, NSW
Associate Professor Mathis Grossmann	MD, PhD, FRACP	Associate Professor, Department of Medicine, The University of Melbourne, Austin Health, VIC
Professor Charles Inderjeeth	MBChB, MPH, FRACP	Clinical Professor, University of Western Australia; Consultant Physician (Geriatrician & Rheumatologist), NHMRC-NICS DVA Fellow and Clinical Epidemiologist, Sir Charles Gairdner Hospital, WA; Director of Clinical Training, Research and Programs, Osborne Park Hospital, WA
Professor Graeme Jones	MBBS (Hons 1), FRACP, FAFPHM, MD, MMedSci (Clin Epi)	Professor of Rheumatology and Epidemiology, University of Tasmania
Professor Stephen Lord	PhD, DSc	Senior Principal Research Fellow, NeuRA, NSW; Professor, School of Community Medicine and Public Health, University of NSW
Associate Professor Nicholas Pocock	MBBS, MD, FRACP	Visiting Scientist, Garvan Institute of Medical Research, NSW; Associate Professor of Medicine (Conjoint), University of New South Wales; Senior Staff Specialist in Nuclear Medicine, St Vincent's Hospital, NSW
Dr Morton Rawlin	BMed, MMedSci, DipPracDerm, DipFP, DipMedHyp, DipBusAdmin, FACRRM, FRACGP	RACGP representative; General Practitioner, Macedon Medical Centre, VIC; Chair, Victoria Faculty Board, RACGP; Adjunct Associate Professor, Department of General Practice, University of Sydney, NSW



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