MINISTRY OF HEALTH
SINGAPORE

Osteoporosis

MOH CLINICAL PRACTICE GUIDELINES 3/2008

College of Family Physicians Singapore

Academy of Medicine, Singapore

Osteoporosis Society (Singapore)

Jan 2009

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2^{++}	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Osteoporosis

MOH Clinical Practice Guidelines 3/2008

Published by
Ministry of Health, Singapore
16 College Road,
College of Medicine Building
Singapore 169854

Printed by
National Photo Engravers

Copyright © 2008 by Ministry of Health, Singapore

ISBN 978-981-08-2173-9

Available on the MOH website: http://www.moh.gov.sg/cpg

Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

Foreword

Osteoporosis is a major public health problem worldwide, and it is of particular significance in an ageing society like Singapore. The clinical and public health importance of osteoporosis is related to the increased risk of fractures in patients with the disease. Fractures may require hospitalization and may cause further morbidity or mortality as a result of prolonged immobilization. In addition, many patients who sustain a fracture do not return to their previous functional status and may require long term institutional care. For example, in Singapore, at one year post hip fracture, 30% of survivors are semi- or fully dependent. Thus, the disease has significant medical, social and financial implications.

In order to prevent the many sequelae of osteoporosis, it is important to diagnose the condition early, to encourage modification of risk factors associated with osteoporosis such as smoking, heavy alcohol consumption and a sedentary lifestyle, and to treat with pharmacologic agents only when indicated. In addition, it is important to increase awareness of this condition amongst both healthcare professionals and the public.

This review of the Ministry of Health Clinical Practice Guidelines on Osteoporosis, first published in 2002, is a timely update that incorporates the best available evidence from the scientific literature and provides practical recommendations relevant to the local context. I hope these guidelines will assist all doctors in Singapore in the management of this disease.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Clinical risk evaluation

GPP Clinical evaluation should be directed at excluding modifiable causes of low bone mass, particularly clinical signs of medical conditions associated with secondary osteoporosis (such as Cushingoid appearance of chronic corticosteroid use or stigmata of alcoholic liver disease). Bone-mass-independent risk, including falls risks should be assessed and appropriately addressed (pg 17).

GPP

B All patients with prior fracture in adulthood with no other apparent causes should be considered for bone mineral density measurement, appropriate evaluation and treatment (pg 17).

Grade B, Level 2++

GPP Patient's concerns and expectations should be considered during the evaluation and treatment of osteoporosis (pg 17).

GPP

C Women identified as high risk using the Osteoporosis Self-Assessment Tool for Asians, should be recommended for bone mineral density measurement (see Table 3A and 3B). A case-finding approach should be employed for women falling into the moderate risk category and they should be evaluated for clinical risk factors (see Table 2), and have bone mineral density measured if clinical risk factors are present. The prevalence of osteoporosis is low enough in the low risk category for bone mineral density to be deferred, unless the woman has other identified clinical risk factors (pg 17).

Grade C, Level 2+

Diagnostic evaluation of osteoporosis

A Dual energy X-ray absorptiometry bone mineral density is widely available in Singapore. Hip and spine measurements are obtained and reported as T and Z scores. It should be the method of choice for the diagnosis of osteoporosis (pg 19).

Grade A, Level 1+

C As the diagnostic threshold has been best validated at the hip with dual energy X-ray absorptiometry, hip dual energy X-ray absorptiometry T-scores should be used for diagnosis of osteoporosis (pg 20).

Grade C, Level 2+

C Bone mineral density measurements using dual energy X-ray absorptiometry should be performed by trained dedicated staff, with appropriate quality control measures to ensure reliable results. Asian reference databases should be used for deriving T- scores (pg 20).

Grade C, Level 2+

GPP Quantitative ultrasound for screening in the community is not recommended because of the lack of validated threshold levels for diagnosis of osteoporosis in Asian populations, and further studies are required (pg 21).

GPP

C Measurements at other skeletal sites or using other methods are not well correlated with hip dual energy X-ray absorptiometry because of problems with measurement accuracy, variability in bone composition and differing rates of loss. T-scores therefore cannot be used interchangeably between sites and techniques. Currently, the use of methods other than hip dual energy X-ray absorptiometry to diagnose osteoporosis is not recommended (pg 21).

Grade C, Level 2+

GPP Individuals found to have osteoporosis should have relevant clinical, laboratory and radiological assessments to exclude diseases that mimic, cause or aggravate osteoporosis, so that appropriate managements may be implemented (pg 22).

GPP

Lifestyle management in osteoporosis

B Vitamin D supplementation (with calcium) should be considered in most individuals, particularly in the elderly and institutionalized. Vitamin D analogs should not be used as first line osteoporosis drugs. Care should be taken to avoid hypercalcemia when prescribing calcium and vitamin D in combination (pg 25).

Grade B, Level 1+

B Specific exercise training programs should be recommended for the management of osteoporosis as evidence shows that they can reverse or slow down bone loss as reflected by bone mineral density changes. The treatment effects were consistent for the lumbar spine and femoral neck in both pre and postmenopausal women (pg 25).

Grade B, Level 1+

C Both cigarette smoking and excessive alcohol consumption is associated with increase risk of osteoporotic fractures and should be avoided (pg 26).

Grade C, Level 2+

C Older people in the care of healthcare professionals should be asked routinely whether they have fallen in the last year and asked about the frequency, context, and characteristics of the fall (pg 26).

Grade C, Level 2+

C Older people who present for medical attention because of a fall, or report recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance should be offered a multifactorial falls assessment of risk (pg 26).

Grade C, Level 2+

A Following treatment for an **injurious fall**, older people should be offered an assessment to identify and address future risk and individualized intervention aimed at promoting independence and improving physical and psychological function (pg 26).

Grade A, Level 1+

A Older people who are assessed to have risk factors for falls or have recurrent falls should have targeted individualised multifactorial intervention. These interventions should include treatment of identified reversible medical problems, medication adjustments, home hazard assessment and modification, physical therapy and vision correction (pg 27).

Grade A, Level 1+

B Hip protectors may be used in people with a high predicted risk of hip fracture particularly nursing home residents (pg 27).

Grade B, Level 1+

Treatment of osteoporosis

GPP Before initiating therapy, secondary causes of osteoporosis should be considered and satisfactorily excluded (pg 28).

GPP

C Factors which can be taken into consideration in making a treatment decision include age, bone mineral density, and risk factors for fracture, falls or bone loss which are independent of bone mineral density (see Table 2 on page 16 and Table 5 on page 29) (pg 28).

Grade C, Level 2+

A Several therapies have been shown to be effective at reducing fractures in patients with either low bone mineral density (T-score ≤ -2.5 SD) or baseline fractures. The greatest fracture reductions were mostly achieved in women with lower bone mineral density. All individuals with osteoporosis (T-score ≤ -2.5) or previous fragility fracture, or high absolute risk of fractures (see section 7.1) should therefore be considered for, and offered appropriate intervention (pg 30).

Grade A, Level 1++, 1+

A Daily oral doses of the bisphosphonates, alendronate and risedronate, may be given to increase bone density and to reduce the risk of fractures, including vertebral and hip fractures in postmenopausal osteoporosis (pg 31).

Grade A, Level 1++

A Ibandonate, a newer bisphosphonate, in daily oral dosing may be used to reduce vertebral fracture risk in postmenopausal osteoporosis. A monthly oral regimen and a three monthly intravenous regimen of bisphosphonates may be used in comparison to the daily oral regimen as these regimens show better bone mineral density response and also improve patient compliance (pg 31).

Grade A, Level 1++, 1+

A IV Zoledronic acid once yearly may be used to reduce the risk of vertebral, non-vertebral and hip fractures (pg 31).

Grade A, Level 1++

A Strontium ranelate may be used to reduce the risk of vertebral fractures and non-vertebral fractures in postmenopausal women (pg 32).

Grade A, Level 1++

A Raloxifene is a selective estrogen receptor modulator (SERM) which may be used to prevent bone loss and reduce vertebral fracture risk but not non vertebral fracture risk (pg 32).

Grade A, Level 1++

A Daily subcutaneous injection of teriparatide (parathyroid hormone 1-34) is associated with a bone forming effect and may be used to reduce vertebral and non-vertebral fractures in women with prior vertebral fractures (pg 33).

Grade A, Level 1+

A Bisphosphonates and strontium ranelate can be used to decrease fracture risk in elderly 80-85 years old. In addition, calcium and oral vitamin D supplements (at 800 international units per day) should be given for optimal fracture prevention (pg 33).

Grade A, Level 1+

C The intervention strategies that may be used to improve management of osteoporosis and adherence to therapy include using more convenient drug dosing regimens, monitoring by a nurse, using educational materials, having education sessions, measuring dual energy X-ray absorptiometry and referral into a multidisciplinary program or to an osteoporosis clinic (pg 34).

Grade C, Level 2+

A The most important surrogate marker of therapeutic response is the follow-up bone density measurement in comparison with the baseline, usually at intervals in excess of one year, and is the recommended method of monitoring response to therapy. The lumbar spine measurement using the anteroposterior projection shows the most obvious changes with treatment, and is therefore the preferred site for monitoring treatment response. However, in the elderly, the hip measurement may be more reliable, as lumbar spine measurements may be spuriously elevated (pg 35).

Grade A, Level 1+

A An alternative method for monitoring therapeutic response is evaluating bone turnover markers at baseline and at 3-6 month intervals. The use of most effective osteoporosis drugs has been associated with reductions from baseline of between 20-40% for bone formation markers such as osteocalcin and bone alkaline phosphatase, and 30-60% for bone resorption markers such as N-telopeptide, C-

telopeptide and deoxypyridinoline. Because of significant biological variability, the timing and method of collection of blood or urine specimens should be consistent for serial measurements (second void for urine specimen and morning fasting for serum specimen) (pg 35).

Grade A, Level 1+

Osteoporosis in special circumstances

GPP There are no data on any established treatment for premenopausal women with osteoporosis. All such patients should be referred to specialist centres for investigation of possible underlying causes and advice on further management (pg 37).

GPP

C The absolute risk for fractures appears no different in men and women of the same age and bone mineral density so the diagnostic threshold for osteoporosis in women can be used in men (pg 37).

Grade C, Level 2+

C Secondary causes of osteoporosis are more commonly found among men. Evaluation for hypogonadism, high alcohol intake, corticosteroid therapy, idiopathic hypercalciuria and medical disorders associated with secondary osteoporosis and muscular instability should always be considered. Other risk factors for fractures in men include past fracture from age 50 years, physical inactivity, recent falls, sedative use, low body mass index and smoking (pg 37).

Grade C, Level 2+

GPP Referral of male patients with osteoporosis to specialist osteoporosis centres should be considered particularly in younger males with more severe disease, for assessment, investigation and monitoring of therapy (pg 38).

GPP

A **Alendronate** may be used to increase bone density and reduce vertebral fracture risk in men (pg 38).

Grade A, Level 1+

A **Risedronate** may be used to reduce the risk of hip fractures in men with stroke and concomitant osteoporosis, and to reduce the risk of vertebral fractures in men with idiopathic osteoporosis (pg 38).

GPP

A **Calcium and vitamin D** ssupplementation may be useful in preserving bone density and reducing non-vertebral fractures in men (pg 38).

Grade A, Level 1+

C Bone mineral density testing using dual energy X-ray absorptiometry is recommended for assessment of fracture risk in individuals who will be started on glucocorticoid for ≥ 3 months at ≥ 5 mg/day prednisolone or equivalent. Repeat bone mineral density should be done yearly while patients are on continuous glucocorticoid therapy (pg 39).

Grade C, Level 2+

GPP Measures to reduce glucocorticoid-induced bone loss include reduction or discontinuation of glucocorticoid, changing to alternative formulations or routes of administration and using alternative immunosuppressive agents. Lifestyle measures such as adequate calcium and vitamin D intake, appropriate weight-bearing exercises, smoking cessation, avoidance of excessive alcohol intake and prevention of falls are also recommended (pg 40).

GPP

C Primary prevention of glucocorticoid-induced osteoporosis should be considered in patients on long-term (>3 months) glucocorticoid (≥ 5 mg /day prednisolone or equivalent) with clinical risk factors for fracture. The dual energy X-ray absorptiometry bone mineral density T score for treatment of glucocorticoid-induced osteoporosis is -1.5 SD at the femoral neck and/or spine (pg 40).

Grade C, Level 2+

A The following pharmacologic agents are recommended for prevention of bone loss in glucocorticoid-induced osteoporosis (pg 40):

1 Calcium and vitamin D supplementation (1000-1500 mg/day and 400-800 IU/day respectively) has been shown to reduce bone loss.
2. Intravenous pamidronate 30 mg every 3 months can be used for prevention or treatment, but there is no evidence on fracture prevention.
3. Testosterone replacement in men with glucocorticoid-induced hypogonadism.
4. Vitamin D analogues, such as alfacalcidol and calcitriol, are effective in both prevention and treatment of glucocorticoid-induced osteoporosis with improvement of bone mineral density.

5. Calcitonin: 200 IU/day can be used in acute pain due to fracture. It maybe considered if bisphosphonate is contraindicated or poorly tolerated. However, it has not been shown to reduce risk of fracture in glucocorticoid-induced osteoporosis.

Grade A, Level 1+

A The following pharmacologic agents are recommended for prevention of bone loss and fractures in glucocorticoid-induced osteoporosis (pg 41):

1. Bisphosphonate therapy: Alendronate 35 mg/week for prevention, 70 mg/week for treatment, risedronate 35 mg/week for prevention or treatment; cyclical etidronate 400 mg/day for 14 days followed by calcium every 3 months for prevention or treatment. These bisphosphonates have been shown to reduce vertebral fractures.
2. Parathyroid hormone is effective in the prevention and treatment of glucocorticoid-induced osteoporosis. It has also been shown to prevent vertebra fracture.

Grade A, Level 1+

Clinical quality improvement

A As the evidence for the effectiveness of osteoporosis therapies is strongest among patients with previous fragility fracture or osteoporosis as defined by bone mineral density, all such patients should be considered for, and started on osteoporosis treatment (pg 42).

Grade A, Level 1+

1 Introduction

1.1 Objectives

The guidelines are not to be viewed as a protocol, but provide a framework to:

- assist doctors in the diagnosis and management of osteoporosis without restricting the physician's individual judgment.
- provide a review of the therapeutic agents available for the treatment of osteoporosis, with the aim of reducing fracture rates.
- aid primary care physicians to decide when to refer patients with difficult problems to the relevant specialists.
- highlight some areas where further research may be pursued.

1.2 Target group

The target group of the guidelines are general practitioners, and specialist doctors who are involved in the management of osteoporosis.

1.3 Guideline development

These guidelines have been produced by a committee comprising of general practitioners, endocrinologists, geriatricians, a rheumatologist, physiotherapists, dieticians, a gynaecologist, orthopaedic surgeons and patient representatives appointed by the Ministry of Health. They were developed using the best available current evidence and expert opinion.

1.4 What's new in the revised guidelines

The following is a list of major revisions or additions to the guidelines:

(1) The inclusion of the National Institutes of Health (NIH) definition of osteoporosis in section 3.1
(2) Ultrasound measurement of bone in section 5.2
(3) Update on role of vitamin D, calcium and exercise in the prevention of osteoporosis in section 6.2 to 6.4

(4) The prevention of falls in section 6.6
(5) The concept of individual absolute fracture risk assessment before initiating therapy
(6) Update on therapies for osteoporosis in section 7.2 and 7.3
(7) New sections on treatment of women above eighty years old in section 7.4, the importance of adherence in section 7.5 and the role of hip protectors in section 6.7
(8) Update on male osteoporosis (section 9.2) and glucocorticoid induced osteoporosis (section 9.3).
(9) Cost-effectiveness issues are considered in section 11.

1.5 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supercede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Significance of osteoporosis

2.1 Epidemiology of osteoporosis

Based on the generally accepted World Health Organization (WHO) definition for osteoporosis using measurement of bone density[1] (see Section 5), the approximate worldwide prevalence of osteoporosis in women between 50-59 years of age is 4%. The incidence increases with age to 8% between 60 and 69 years, increases further to 25% between 70-79 years and up to 48% at 80 years and above.[2]

The incidence of forearm fracture rises shortly after the onset of menopause and plateaus at about 65 years of age. The true incidence of vertebral fractures is difficult to assess, but in women it increases after the menopause and continues to rise without reaching a plateau.[3,4] The incidence of hip fracture increases slowly with age until later life when it undergoes a steep, exponential rise.[3,5] The incidence of any type of fracture is higher in women than in men at any age.[3,4]

In Singapore as in the rest of Asia, osteoporosis will become an increasingly important public health problem. The prevalence of osteoporosis is likely to increase as the population ages.[6,7] In 2005, one in 12 residents was 65 years or older. In 2030, one in five residents will be 65 years or older.[8]

In Singapore the incidence of hip fracture has increased 1.5 times in men and 5 times in women since the 1960s.[5,9] This rise in incidence is consistent with secular trends seen in many countries. Age-adjusted rates among women over the age of 50 years are currently among the highest in Asia, and approaching those of the West.

2.2 Consequences of fractures

Data from Singapore show that the mortality rate one year post fragility hip fracture is approximately 20% to 27%.[10-12] Of the survivors, 20% become semi or fully dependent and 39% experience reduced mobility status.[10-12] Whilst only 8% are cared for by chronic health care facilities in 1994[11], the

figure has increased to 26% in 2002.[11] The acute care and rehabilitation of people with a hip fracture represent a significant cost to individuals and society.[10,13]

Vertebral fractures cause significant complications including chronic back pain, height loss, kyphosis and limitation of activity.[14,15] There is also an association with increased mortality.[4]

2.3 Natural history of osteoporosis

Bone density increases from birth, through childhood and adolescence before reaching a peak in both males and females in the mid-twenties to early thirties. Osteoporosis is likely to be polygenic, but hormonal, nutritional and other environmental factors also contribute to the attainment of peak bone mass. From the age of thirty to fifty years, bone density declines minimally. In men over 50 years, bone density continues to decline gradually at about 0.2%-0.5% per year. However, post menopausal women experience a period of accelerated bone loss in the order of 3%-5% per year due to estrogen withdrawal. This accelerated loss continues for approximately 5-8 years, after which it slows to a rate of 1-2% per year. Bone loss may increase again in some after the age of 70 years. Many factors contribute to bone loss including androgen or estrogen deficiency, illnesses, medications and lifestyle choices.[16]

3 Definition of osteoporosis

3.1 Definitions

WHO definition of osteoporosis

Osteoporosis is defined as a 'progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[17]

NIH definition of osteoporosis

National Institutes of Health (NIH), U.S.A. (2000) consensus conference modified this definition as follows: "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of 2 main features: bone density and bone quality".[18] In the absence of methods of measuring bone quality, the diagnosis of osteoporosis tends to be made on the basis of low bone density.

Fragility fracture

Clinically, a fragility fracture may be defined as one that occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma.

3.2 Implications of WHO and the NIH consensus definition

These definitions of osteoporosis are centred on the level of bone mass, usually measured as bone mineral density (BMD). Prospective studies have shown that the risk of fracture increases progressively with decreasing BMD. Using absorptiometric techniques, the risk of fracture increases approximately two-fold for each standard deviation decrease in BMD.[19] Measurements of BMD vary according to the site of measurement and the technique used.

Diagnostic thresholds based on the number of standard deviations (SD) above or below the peak bone mass of young adults (T-score), have been chosen to define categories of bone mass[1] (see Table 1). This categorization

provides a clinically useful standardized definition of osteoporosis[1] which is used to guide treatment. However, there are other factors that contribute to an individual's risk of fracture which should be considered when deciding on clinical management of individual cases (see section 7.1).

In addition to bone mineral density, most authorities would consider someone with a history of a fragility fracture to have osteoporosis, irrespective of the BMD measurement.[20]

Table 1 WHO definitions based on BMD

BMD T-score (S.D.)	Definition
≥ -1	Normal
< -1 to > -2.5	Low bone mass (osteopenia)
≤ -2.5	Osteoporosis
≤ -2.5 + fragility fracture	Severe or established osteoporosis

3.3 Other confusing terms

Confusion with similar appearing terms does occur:

Osteomalacia describes the failure of osteoid, the organic matrix of bone, to mineralize normally in adults. Common causes of this are vitamin D or phosphate deficiency and systemic acidosis. In this condition BMD is usually low and it should be considered in the work-up of osteoporosis.

Osteoarthritis refers to degenerative joint disease, which may involve the joints in the limbs as well as vertebral facet joints, resulting in back pain. The pathophysiology and management differs from that for osteoporosis.

4 Clinical risk evaluation

4.1 Approaches to the problem of osteoporosis

The problem of osteoporosis can be addressed using these approaches:

Population-based strategy
The population-based strategy involves addressing the lifestyle issues such as adequate nutrition, increased physical activities and weight bearing exercises, smoking cessation, avoidance of excessive alcohol consumption, through public education and other efforts such as environmental modifications.

High-risk strategy
The high-risk strategy identifies people at risk of osteoporosis for further evaluation, counseling and treatment. Those who meet set criteria can be further screened and evaluated (case-finding).

4.2 Risk evaluation

In several large epidemiological studies[21-23], including some from Asia[24,25], several risk factors have been found to be associated with osteoporosis and fractures (see Table 2A), and also for falls (see Table 2B).

Table 2 Risk factors for osteoporosis, falls and fracture

A. Risk factors for osteoporosis and fractures
Non-modifiable
• Personal history of previous fragility fracture as an adult • Height loss of more than 2 cm over 3 years • History of fracture in a first degree relative (especially maternal) • Low body weight (see Table 3A and 3B) • Elderly age group (see Table 3A and 3B) • Poor health or frailty
Potentially-modifiable
• Current cigarette smoking • Alcohol abuse (stronger data in men) • Low calcium intake (<500 mg/day among Asians) • Lack of regular physical activity • Prolonged immobilisation
Secondary Osteoporosis
• Drugs, e.g. corticosteroids (equivalent to prednisolone >7.5 mg/day for more than 6 months), excessive thyroxine, anticonvulsant. • Ongoing disease conditions, e.g. hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, chronic obstructive airways disease, liver disease, malabsorption, chronic renal failure, rheumatoid arthritis, organ transplantation and anorexia nervosa. • Early natural or surgical menopause before age 45 years, or prolonged premenopausal amenorrhea lasting >1 year.
B. Risk factors for falls and fracture
Patient factors • One or more previous falls in the past year • Impaired eyesight • Polypharmacy especially certain groups of drugs, e.g. sedatives, antihistamines, antihypertensives • Gait abnormality associated with medical conditions, e.g. stroke, parkinsonism, peripheral neuropathy, arthritis • Reduced muscle strength and impaired balance due to ageing and deconditioning • Cognitive impairment
Environmental factors (some examples are listed below) • Slippery floors • Obstacles on the floor, e.g. uneven carpet, wires. • Inadequate lighting • Inappropriate foot wear

It is not recommended to screen the general population at normal risk for BMD.[26] BMD screening should be employed selectively through a case-finding approach based on an individual's risk for low bone mass and/or bone-mass-independent risk.

GPP Clinical evaluation should be directed at excluding modifiable causes of low bone mass, particularly clinical signs of medical conditions associated with secondary osteoporosis (such as Cushingoid appearance of chronic corticosteroid use or stigmata of alcoholic liver disease). Bone-mass-independent risk, including falls risks should be assessed and appropriately addressed.

GPP

B All patients with prior fracture in adulthood with no other apparent causes should be considered for bone mineral density measurement, appropriate evaluation and treatment.[27,28]

Grade B, Level 2++

GPP Patient's concerns and expectations should be considered during the evaluation and treatment of osteoporosis.

GPP

4.3 Osteoporosis Self-Assessment Tool for Asians (OSTA)

The Osteoporosis Self-Assessment Tool for Asians (OSTA) is a simple tool based on age and weight which has been developed for the assessment of postmenopausal Asian women.[29] The index derived for the tool is able to categorize women into high, moderate and low risk of being diagnosed with osteoporosis on subsequent bone mineral density (BMD) measurement. In the validation study 61% of individuals in the high-risk category had osteoporosis as opposed to 15% in the moderate risk category and 3% in the low risk category.

C Women identified as high risk using the Osteoporosis Self-Assessment Tool for Asians[29], should be recommended for bone mineral density measurement (see Table 3A and 3B). A case-finding approach should be employed for women falling into the moderate risk category and they

should be evaluated for clinical risk factors (see Table 2), and have BMD measured if clinical risk factors are present. The prevalence of osteoporosis is low enough in the low risk category for bone mineral density to be deferred, unless the woman has other identified clinical risk factors.

Grade C, Level 2+

Table 3A Osteoporosis Self-Assessment Tool for Asians (OSTA)

Age (yr)	Weight (kg)							
	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
45-49								
50-54						Low Risk		
55-59								
60-64								
65-69			Moderate Risk					
70-74								
75-79	High Risk							
80-84								
85-89								

Copyright 2001, MSD, Whitehouse Station, NJ, USA. All rights reserved. Reproduced with permission.

Table 3B Suggested action based on Osteoporosis Risk from the OSTA

Osteoporosis Risk	Patient's Age (yr) minus Weight (kg)	Suggested Action
High	>20	Measure BMD
Moderate	0-20	Actively check for risk factors* or past history of fracture, and measure BMD if either is present
Low	<0	Can defer BMD unless patient is assessed to have high fracture risk

* Refer to Table 2 Section A

5 Diagnostic evaluation of osteoporosis

5.1 Introduction

Fracture risk is affected by several intrinsic bone factors such as bone mineral density, bone micro-architecture and elasticity. Bone mineral density (BMD) can be quantitatively measured using various techniques.

5.2 Bone mineral density (BMD) measurement

BMD is a measurement which gives an idea of fracture risk. BMD results are reported as T scores and Z score.

T Score

The values are measured using dual-energy X-ray absorptiometry (dual energy X-ray absorptiometry - see next section). T scores are derived by comparing the bone density of an individual with the mean bone density of young healthy adults of the same gender.[1,26] The result is expressed as the number of standard deviations (SD) from the mean. In the WHO report, T score is divided into 4 categories (See Table 1).[1]

Z Score

Z score compares the individual's BMD against the mean of persons of the same age and gender rather than young adults.[1,26] Whereas a T score predicts fracture risk, a low Z score may indicate a need for further investigation to rule out secondary causes of bone loss.

5.3 Methods used to measure BMD

5.3.1 Dual Energy X-Ray Absorptiometry (DXA) of hip and spine

A Dual energy X-ray absorptiometry bone mineral density is widely available in Singapore. Hip and spine measurements are obtained and reported as T and Z scores. It should be the method of choice for the diagnosis of osteoporosis.[20,26]

Grade A, Level 1+

C As the diagnostic threshold has been best validated at the hip with dual energy X-ray absorptiometry, hip dual energy X-ray absorptiometry T-scores should be used for diagnosis of osteoporosis.[20,26]

Grade C, Level 2+

Hip measurements at the femoral neck and of the total hip joint are the best predictors of hip fracture, and are also good predictors of other osteoporotic fractures. The risk of fracture increases more than 2 times for each SD decrease in hip BMD.[19]

Measurements are conventionally taken at the unfractured and non-dominant hip.

The lumbar spine (anteroposterior projection) is the preferred site for monitoring therapeutic response since in most trials, the largest changes in BMD with treatment have occurred at this site.[30-35]

However, in the elderly, lumbar spine measurements may be artificially increased by osteoarthritis, fractures and calcification of the aorta, in which case, the hip measurement could be used to monitor response.

C Bone mineral density measurements using dual energy X-ray absorptiometry should be performed by trained dedicated staff, with appropriate quality control measures to ensure reliable results. Asian reference databases should be used for deriving T- scores.[36,37]

Grade C, Level 2+

The development of ethnic group-specific databases would be ideal as ethnic differences in hip fracture rates have been demonstrated in Singapore.[5]

5.3.2 Ultrasound of the heel

Quantitative ultrasound has been proposed as an alternative method for osteoporosis assessment in postmenopausal women. A bone sonometer is a device that transmits ultrasound energy. By passing ultrasonic signal propagated through a bone, it is possible to estimate broadband ultrasonic

attenuation (BUA) and velocity of sound (VOS). BUA and VOS do not measure bone mass. The two acoustic parameters have been shown in prospective clinical trials to predict fracture incidence[38-40]

Currently there is no evidence for the use of quantitative ultrasound for the diagnosis of osteoporosis, the initiation or monitoring of treatment.[41]

GPP Quantitative ultrasound for screening in the community is not recommended because of the lack of validated threshold levels for diagnosis of osteoporosis in Asian populations, and further studies are required.

GPP

5.3.3 Quantitative CT scan

Quantitative CT (QCT) works on the principle that there is differential absorption of ionizing radiation by calcified tissue. The CT scans are compared with a standard reference to calculate the bone mineral density equivalents. The use of this technique is limited by increased radiation exposure and cost

5.3.4 Other methods

C Measurements at other skeletal sites or using other methods are not well correlated with hip dual energy X-ray absorptiometry because of problems with measurement accuracy, variability in bone composition and differing rates of loss.[3] T-scores therefore cannot be used interchangeably between sites and techniques. Currently, the use of methods other than hip dual energy X-ray absorptiometry to diagnose osteoporosis is not recommended.

Grade C, Level 2+

In the absence of dual energy X-ray absorptiometry, the use of these techniques might be reasonable, particularly if incorporated into a comprehensive risk assessment to decide on appropriate interventions for those at high risk.

Since almost all intervention trials on osteoporosis have reported exclusively on DXA as the sole technique for measuring BMD, there is limited data and experience in the use of other techniques for monitoring response to therapy.[30-35,42,43]

5.4 Bone turnover markers

There is currently no role for bone turnover markers in the diagnosis of osteoporosis. However, bone turnover markers do aid in fracture risk assessment, the prediction of rates of bone loss, as well as in monitoring response to treatment.[17,26]

5.5 Investigations for secondary osteoporosis

GPP Individuals found to have osteoporosis should have relevant clinical, laboratory and radiological assessments to exclude diseases that mimic, cause or aggravate osteoporosis, so that appropriate managements may be implemented.

GPP

Suggested routine investigations:

1. Relevant radiographs to document fractures.
2. Full blood count, ESR.
3. Creatinine, calcium, phosphate, albumin, AST, alkaline phosphatase.
4. Urinalysis to look for haematuria, proteinuria

Additional investigations to be considered:

1. Bone turnover markers, e.g. osteocalcin, C-telopeptide cross-links (CTX), N-telopeptide cross links (NTX).
2. Urinary calcium/creatinine ratio, or 24-hour urinary calcium
3. Testosterone levels in men.
4. Free T4, TSH, iPTH, 25-hydroxyvitamin D, FSH, LH, prolactin, urinary free cortisol, dexamethasone suppression tests.
5. Tumour markers, myeloma screen, bone marrow examination.
6. Scintigraphic bone studies.

6 Lifestyle management in osteoporosis

6.1 Population-based approach

A population-based approach to the management of osteoporosis would be through lifestyle and environmental modifications to improve the general health of the community. There is some evidence that bone mass can be modulated by changes in lifestyle habits in specific subsets of populations, such as calcium intake before the attainment of skeletal maturity.

6.2 Calcium intake

The current dietary recommendation for calcium intake in Singapore is 800 mg/day, based on the assumption that Asians require less calcium than Caucasians. According to the recent National Nutrition Survey in 2004, the average daily calcium intake of Singaporean is 627 mg.[44] Low calcium intake (<250-500 mg/day depending on the study) has been associated with lower bone density[45] and higher risk of fracture in Asian populations.[24,46] Milk supplementation appears to preserve bone density in Asian women who had low dietary calcium intake (<500 mg/day).[47] Higher dietary calcium intake appears to be associated with lower risk of fracture.[48] Calcium with vitamin D supplements decrease fracture risk, [48] particularly in women deficient in calcium and vitamin D,[49,50] although the benefits were less clear in those not deficient.[51] There is little data to support any benefit of calcium intake in excess of 2000 mg daily.

In the Women's Health Initiative (WHI) trial of calcium and vitamin D, a combination of 1000 mg calcium carbonate and 400 IU of vitamin D reduced the risk of hip fracture in women older than 60 years by 21% but had no effect on fracture at other sites.[52]

Although several guidelines on calcium intake exist, we recommend total daily calcium intakes consistent with the recommendations from the Health Promotion Board (Table 4).

Calcium intake includes contributions from the diet, dairy products and calcium supplements (see Annex A: Calcium content table).

A common lay misconception that requires correction is that having an

adequate daily calcium intake protects against osteoporosis. Patients with risk factors for osteoporosis still require evaluation and may require specific therapy over and above adequate calcium intake.

Table 4 Recommended dietary allowances for calcium and vitamin D

Category	Calcium	Vitamin D[53]
Adolescents 10-18 years old	1000 mg	400 IU
All adults 19-50 years old	800 mg	400 IU
All adults 51-70 years old	1000 mg	400 IU
All adults more than 70 years old	1000 mg	800 IU[54]
Breastfeeding/pregnancy	1000 mg	400 IU

6.3 Vitamin D and vitamin D analogs

A meta-analyses of vitamin D (native and analogs together) showed that vitamin D alone did not reduce hip, vertebral or any new fracture. Vitamin D with calcium marginally reduced hip and non-vertebral fractures, but not vertebral fractures, in those living in institutional care.[55] Another meta-analysis concluded that oral vitamin D supplementation between 700 to 800 IU/day reduced the risk of hip and non-vertebral fractures in institutionalized or ambulatory elderly persons, with the major effect in the institutionalized, whereas a dose of 400 IU/day was not sufficient for fracture prevention.[54] Another meta-analysis showed that vitamin D analogs (calcitriol and alphacalcidol) prevented bone loss and reduced vertebral and non-vertebral fractures compared to native vitamin D.[56]

A meta-analyses showed that vitamin D (native and analogs together) reduced the risk of falling in elderly individuals, with mean age >70 years.[57] Cholecalciferol 700 IU plus calcium 500 mg daily reduced the odds of falling in ambulatory women over 65 years old.[58] Alfacalcidol reduced the number of falls among a community-dwelling elderly population (>70 years old) with a minimum calcium intake of more than 500 mg daily.[59] Calcitriol reduced the rate of falls in an elderly population >65 years old.[60] Individual trials using vitamin D in various forms have produced inconsistent data and have shown only marginal benefits.

B Vitamin D supplementation (with calcium) should be considered in most individuals, particularly in the elderly and institutionalized. Vitamin D analogs should not be used as first line osteoporosis drugs. Care should be taken to avoid hypercalcemia when prescribing calcium and vitamin D in combination.

Grade B, Level 1+

6.4 Exercise

B Specific exercise training programs should be recommended for the management of osteoporosis as evidence shows that they can reverse or slow down bone loss as reflected by bone mineral density changes. The treatment effects were consistent for the lumbar spine and femoral neck in both pre[7] and postmenopausal women.[61-64]

Grade B, Level 1+

The benefits of exercise in women with osteoporosis are improved well-being, muscle strength[65], postural stability and reduced risk of further fractures.[62] Currently, there is little available evidence to support this statement in osteoporotic men.[66]

Weight bearing, high impact aerobic exercises as well as resistance training exercises have been shown to be effective in improving bone mineral density (BMD) in women. Different studies have used exercise programs of varying frequency and duration.

Exercises useful in the management of osteoporosis include the following[61,62,64,65,67]:

Resistance exercise uses free weights (dumbbells, weight belts, ankle weights) or weight machines at an intensity of 70%-80% maximum heart rate and 10-15 repetitions at low to moderate weight.

Weight bearing (impact) exercise are aerobics, step aerobics, brisk walking, jogging, jumping, stepping, stamping, hopping, skipping, dancing, ball games at intensity of 50%-70% of the maximal heart rate.

The frequency of exercise should be 2-3 times per week lasting about 50-60 minutes (including 10 minutes warm up, 20 minutes impact, 15 minutes resistance, 10 minutes cool down/stretching).

Precautions should be taken when recommending exercise *to* patients with established osteoporosis. Prior to the commencement of any exercise program, the health status of the individual should be assessed and taken into consideration.

Exercise in addition to hormone replacement therapy (HRT) and/or calcium supplements have been shown to be superior in improving BMD than exercise alone or HRT alone.[61,64]

6.5 Cigarette smoking and excessive alcohol consumption

C Both cigarette smoking and excessive alcohol consumption is associated with increase risk of osteoporotic fractures and should be avoided.[68,69]

Grade C, Level 2+

6.6 Prevention of falls

C Older people in the care of healthcare professionals should be asked routinely whether they have fallen in the last year and asked about the frequency, context, and characteristics of the fall.[70]

Grade C, Level 2+

C Older people who present for medical attention because of a fall, or report recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance should be offered a multifactorial falls assessment of risk.[70]

Grade C, Level 2+

A Following treatment for an **injurious fall**, older people should be offered an assessment to identify and address future risk and individualized intervention aimed at promoting independence and improving physical and psychological function.[70]

Grade A, Level 1+

A Older people who are assessed to have risk factors for falls or have recurrent falls should have targeted individualised multifactorial intervention. These interventions should include treatment of identified reversible medical problems, medication adjustments, home hazard assessment and modification, physical therapy and vision correction.[72,73]

Grade A, Level 1+

6.7 The use of hip protectors for the prevention of hip fractures in older people

B Hip protectors may be used in people with a high predicted risk of hip fracture, particularly nursing home residents.

Grade B, Level 1+

Hip protectors are externally worn protective devices designed to absorb the impact of a fall and prevent hip fracture. Hip protectors do not significantly decrease the incidence of hip fracture in community dwelling elderly, however evidence suggests that they may be effective in people with a high predicted risk of hip fracture, particularly nursing home residents. Poor compliance limits their efficiency.[74,75] Effectiveness may be improved by using them in association with multi-faceted falls risk education programmes and other interventions.[76]

7 Treatment of osteoporosis

7.1 Initiating therapy

GPP Before initiating therapy, secondary causes of osteoporosis should be considered and satisfactorily excluded.

GPP

The WHO diagnostic criteria for osteoporosis may serve as thresholds to guide decisions for instituting therapy (treatment thresholds) (see Table 1). Pharmacological intervention in osteoporosis has been directed at either the prevention (see Section 7.2) or the treatment (see Section 7.3) of osteoporosis.

Absolute risk

Although the diagnostic threshold is often used as the treatment threshold, epidemiological data has suggested that over half of women who fracture are not osteoporotic by bone mineral density (BMD) criteria.[77] There is a growing opinion that intervention thresholds for osteoporosis should be based on absolute risk of fracture, rather than solely on diagnostic thresholds based on BMD.[78] The inclusion of clinical risk factors enhances the performance of BMD in predicting fractures.[79] Several clinical risk scores have been published for estimating absolute fracture risk over a fixed time period, e.g. 5 or 10 years.[27,80,81] One useful tool is the WHO Fracture Risk Assessment (FRAX™) tool.[82] Decisions on the intervention threshold could then be based on morbidity burden[78] or economic considerations (e.g. health-related costs and cost effectiveness).[83]

Quantitative data on absolute fracture risk currently being established by the WHO may not be applicable to all countries, as there are international differences in fracture rates[84] and osteoporosis risk factors.[79] Validation studies using such scoring systems on our population would probably be required.

C Factors which can be taken into consideration in making a treatment decision include age, bone mineral density, and risk factors for fracture, falls or bone loss which are independent of bone mineral density (see Table 2 on page 16 and Table 5 on page 29).[79]

Grade C, Level 2+

Table 5 Factors to consider in decision to treat

Factors	Tend to treat if	Tend to defer if
Fracture risk	high	low
Past fracture	present	absent
Bone mineral density	lower (T-score <-2.5)	higher
Age	older (e.g. >65 years)	younger
Risk for bone loss	high	low
Risk for falls	high	low

7.2 Pharmacotherapy for the prevention of osteoporosis

The concept of prevention refers to instituting therapy in individuals with low bone density or osteopenia (T-score between -1 and -2.5 SD) and without fractures to delay or prevent the decrease of bone density below the osteoporotic threshold.[26,85] Several issues need to be taken into consideration in the approach to managing osteopenic patients who are usually younger. Firstly, although the proportion of women in this group is large, the risk of fracture among these women is relatively low. Secondly, the pattern of fracture differs from older women, with more wrist and other minor fractures, less vertebral and even less hip fractures. Thirdly, the most important measure of the effectiveness of any therapeutic measure is anti-fracture efficacy. Thus far, although most therapies initiated in osteopenic patients have resulted in increased bone mineral density, few have been shown to reduce fracture risk.[86-91] Although treating osteopenic individuals to improve bone density as the primary goal is possible, deferring intervention in those at low risk for fracture might be a reasonable option if fracture prevention is the primary goal.

The Women's Health Initiative hormone trials confirm the efficacy of hormone therapy in reducing the risk of hip, spine and all other nonvertebral fractures even in postmenopausal women with low risk of fracture.[92,93]

The use of hormone therapy for osteoporosis prevention should be evaluated based on an individual woman's history and risk factors, including the need for treatment for vasomotor symptoms.

Accumulating evidence suggests that the risk-benefit profile of hormone therapy may be different in women who initiate therapy soon after menopause. For example, recent data suggest that estrogen use in younger women close to menopause may be associated with a reduced risk of coronary heart disease and death. Still, the skeletal benefits of hormone therapy need to be balanced with the potential small increase in risk of breast cancer (with estrogen-progestin therapy), stroke and venous thromboembolism.[94,95]

Tibolone may be a suitable option for women with unacceptable side effects from HRT. It is effective in controlling hot flushes and preventing bone loss[96] and data have demonstrated a reduction in vertebral fracture. However there was an increased risk of stroke.[97]

Strontium Ranelate prevents bone loss and also vertebral fracture in patients who are osteopaenic.[98]

Raloxifene, a selective estrogen receptor modulator (SERM), prevents bone loss[91] and vertebral fracture in patients with osteopaenia but does not reduce, and may worsen menopausal symptoms.[42]

The alternatives for the prevention of osteoporosis such as the bisphosphonates, and calcitonin, do not impact on menopausal symptoms, and have not been demonstrated to reduce fractures when used in prevention, despite reducing bone loss.

7.3 Pharmacotherapy for the treatment of osteoporosis

A Several therapies have been shown to be effective at reducing fractures in patients with either low bone mineral density (T-score ≤ -2.5 SD) or baseline fractures.[30,32-35,42,43,99-101] The greatest fracture reductions were mostly achieved in women with lower bone mineral density. All individuals with osteoporosis (T-score ≤ -2.5) or previous fragility fracture, or high absolute risk of fractures (see section 7.1) should therefore be considered for, and offered appropriate intervention.

Grade A, Level 1++, 1+

The criteria for good quality intervention trials include randomised, placebo-controlled, double-blind design, large subject number, long duration, fracture risk reduction as the primary endpoint, computation of number of patients with fracture as opposed to number of fractures, low drop-out rates and intention-to-treat analysis.

Bisphosphonates

Cyclical etidronate increases bone density and decreases vertebral fracture risk.[102,103] The data on non-vertebral and hip fracture reduction is based on observational studies.[104]

A Daily oral doses of the bisphosphonates, alendronate and risedronate, may be given to increase bone density and to reduce the risk of fractures, including vertebral[30,31,33,34] and hip fractures[32,105] in postmenopausal osteoporosis.

Grade A, Level 1++

Weekly oral regimens of both bisphosphonates show an equivalent increase in bone density to daily dosing. Weekly regimens may be useful in improving patient compliance.[106]

A Ibandonate, a newer bisphosphonate, in daily oral dosing may be used to reduce vertebral fracture risk in postmenopausal osteoporosis.[107] A monthly oral regimen[108] and a three monthly intravenous regimen[109,110] of bisphosphonates may be used in comparison to the daily oral regimen as these regimens show better bone mineral density response and also improve patient compliance.

Grade A, Level 1++, 1+

A IV Zoledronic acid once yearly may be used to reduce the risk of vertebral, non-vertebral and hip fractures.[99]

Grade A, Level 1++

Due to the long half-lives of potent amino bisphosphonates in bone matrix, there have been concerns about the possibility of over suppression of bone turnover. There is a paucity of data, with some small studies showing severely suppressed bone formation.[111]

On the other hand, there are safety data for the use of alendronate and risedronate for up to 10 years and 7 years respectively.[112,113]

Osteonecrosis of the jaw (ONJ) is another potential complication, with the majority of cases seen with IV bisphosphonate therapy, typically given in high doses to cancer patients. Very few cases have been reported for oral bisphosphonates, and few patients with ONJ have a primary diagnosis of osteoporosis. Hence, the risk of ONJ in patients with osteoporosis treated with oral bisphosphonate is very low.[114-117]

Discontinuation of alendronate after 5 years of therapy does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.[112]

Strontium ranelate

A Strontium ranelate may be used to reduce the risk of vertebral fractures[118] and non-vertebral fractures in postmenopausal women.[119]

Grade A, Level 1++

It has also been shown to reduce the risk of hip fracture in a subgroup of women aged 74 years or older with low bone mineral density (T < -3.0).[119] Strontium ranelate was well tolerated apart from a low rate of gastrointestinal side-effects and an unexplained small increased risk of venous thrombosis.[118,119]

Raloxifene

A Raloxifene is a selective estrogen receptor modulator (SERM) which may be used to prevent bone loss and reduce vertebral fracture risk but not non vertebral fracture fracture risk.[42,120]

Grade A, Level 1++

It reduces the risk of breast cancer in women with osteoporosis[42] and is as effective as tamoxifen in preventing breast cancer in patients at high risk for this cancer. [121]

It neither increases nor decreases the risk of coronary events in patients with coronary heart disease (CHD) or multiple risk factors for CHD but it is associated with a slightly increased risk of fatal strokes in these patients.[122] Use of raloxifene carries an increased risk of venous thromboembolism.[122,123]

Calcitonin

Calcitonin prevents bone loss[124] and decreases vertebral fracture risk.[43] The data on non-vertebral[125] and hip fracture reduction is based on observational studies. Calcitonin also has analgesic properties in acute vertebral crush fractures.[126]

Teriparatide

A Daily subcutaneous injection of teriparatide (parathyroid hormone 1-34) is associated with a bone forming effect and may be used to reduce vertebral and non-vertebral fractures in women with prior vertebral fractures.[35]

Grade A, Level 1+

Animal studies show an increase in osteosarcoma after lifelong exposure.[127] In humans, the drug is only to be used for a maximum duration of 24 months. In addition, oral bisphosphonate[128], or raloxifene[129] used sequentially after parathyroid hormone treatment, may preserve the gains in bone density obtained from parathyroid hormone treatment.

Combination therapy

Combination therapy consisting of alendronate and alfacalcidol is superior to alendronate plus vitamin D in terms of the BMD increase after two years of treatment.[130]

7.4 Treatment of women above eighty years old

A Bisphosphonates[131] and strontium ranelate[132] can be used to decrease facture risk in elderly 80-85 years old. In addition, calcium and oral vitamin D supplements (at 800 international units per day)[54] should be given for optimal fracture prevention.

Grade A, Level 1+

7.5 Under-treatment and adherence

Several studies have shown that less than a third of patients who sustained fragility fractures were investigated for osteoporosis[133], and less than one fifth received osteoporosis therapy.[133,134] After bone mineral density measurements, between 40-70% of osteoporotic patients were prescribed osteoporosis drugs including HRT.[134]

For those prescribed osteoporosis drugs, about 50% failed to comply fully with or discontinued therapy within 1 year.[135] Poor compliance was associated with higher fracture rates, increased morbidity, mortality and cost, and smaller increments in bone mineral density.[135]

C The intervention strategies that may be used to improve management of osteoporosis and adherence to therapy include using more convenient drug dosing regimens, monitoring by a nurse, using educational materials, having education sessions, measuring dual energy X-ray absorptiometry and referral into a multidisciplinary program or to an osteoporosis clinic.[133-135]

Grade C, Level 2+

7.6 Choice of therapy

In choosing the most appropriate therapy for osteoporosis, the primary consideration is relative anti-fracture efficacy of each drug. In reality however, patients often have other concerns that impact on therapeutic decision-making. Factors that might be taken into consideration when choosing the most appropriate therapy for an individual patient are listed in Table 6. Non-skeletal benefits include breast cancer reduction.

Table 6 Factors to consider in decision to treat

Factors	Favourable	Less favourable
Anti-fracture efficacy	Good	Poor
Other non-skeletal benefits	Many	Few
Side effects	Few	Many
Drug cost	Low	High
Convenience of administration	Easy	Difficult
Patient contraindications	None	Present

7.7 Monitoring response to therapy

A The most important surrogate marker of therapeutic response is the follow-up bone density measurement in comparison with the baseline, usually at intervals in excess of one year, and is the recommended method of monitoring response to therapy.[136-138] The lumbar spine measurement using the anteroposterior projection shows the most obvious changes with treatment, and is therefore the preferred site for monitoring treatment response. However, in the elderly, the hip measurement may be more reliable, as lumbar spine measurements may be spuriously elevated.

Grade A, Level 1+

A An alternative method for monitoring therapeutic response is evaluating bone turnover markers at baseline and at 3-6 month intervals. The use of most effective osteoporosis drugs has been associated with reductions from baseline of between 20-40% for bone formation markers such as osteocalcin and bone alkaline phosphatase, and 30-60% for bone resorption markers such as N-telopeptide, C-telopeptide and deoxypyridinoline.[139] Because of significant biological variability, the timing and method of collection of blood or urine specimens should be consistent for serial measurements (second void for urine specimen and morning fasting for serum specimen).

Grade A, Level 1+

In patients who fail to respond, the following should be considered:

- non-compliance to therapy
- incorrect administration of drug, e.g. failure to follow specific instructions on how to take the drug, interactions with other drugs
- on-going, undiagnosed pathology which accelerates bone loss
- imprecision of the BMD measurement technique
- true treatment failure, in which case an alternative therapy might be considered.

The occurrence of a fracture however does not necessarily imply treatment failure, particularly if bone density has increased, and the osteoporosis drug should be continued.

8 Referral to specialist centres

8.1 Further evaluation

The following persons should be considered for referral to a specialist for further evaluation.

- Young female patients (premenopausal)
- Male patients
- Patients on long term steroids
- Patients with disproportionately low Z scores (which may indicate secondary causes of osteoporosis)
- Patients with endocrine diseases, e.g. hyperparathyroidism, hypogonadism, hypercortisolism and hyperthyroidism.
- Patients with metabolic bone disease
- Patients with structural or congenital bone conditions
- Patients with pathological fracture
- Patients suspected of having secondary osteoporosis

These patients may be referred to the following departments for further management based on the clinical indication.

1. Endocrinology
2. Rheumatology
3. Orthopedics

9 Osteoporosis in special circumstances

9.1 Premenopausal women

GPP There are no data on any established treatment for premenopausal women with osteoporosis. All such patients should be referred to specialist centres for investigation of possible underlying causes and advice on further management.

GPP

9.2 Male osteoporosis

Prevalence

Osteoporosis affecting men as well as women is often underappreciated. Worldwide, approximately 20% of symptomatic vertebral fractures and 30% of hip fractures occur in men[140], the latter figure being consistent in Singapore. In addition, hip fracture incidence rates among men in Singapore[5] and world-wide[141] have increased over time. Epidemiological data suggest that all major fractures are associated with increased mortality, especially in men.[4]

Diagnostic criterion

C The absolute risk for fractures appears no different in men and women of the same age and bone mineral density so the diagnostic threshold for osteoporosis in women can be used in men.[142]

Grade C, Level 2+

Bone mineral density (BMD) and fracture risk

The absolute risk for vertebral and hip fractures at any age appears to be similar in men and women with the same age and same BMD.[143,144-146]

Secondary causes

C Secondary causes of osteoporosis are more commonly found among men. Evaluation for hypogonadism, high alcohol intake, corticosteroid therapy, idiopathic hypercalciuria and medical disorders associated with secondary osteoporosis and muscular instability should always be considered. Other risk factors for fractures in men include past fracture from age 50 years,

physical inactivity, recent falls, sedative use, low body mass index and smoking.[24,140,147,148]

Grade C, Level 2+

GPP Referral of male patients with osteoporosis to specialist osteoporosis centres should be considered particularly in younger males with more severe disease, for assessment, investigation and monitoring of therapy.

GPP

Treatment

Established treatment options for osteoporosis in men are fewer than for women. There is a lack of data based on large randomized double blind placebo controlled trials using fractures as end point in men. Several smaller studies have been published recently using bisphosphonates and PTH in male osteoporosis.

A **Alendronate** may be used to increase bone density and reduce vertebral fracture risk in men.[149,150]

Grade A, Level 1+

A **Risedronate** may be used to reduce the risk of hip fractures in men with stroke and concomitant osteoporosis, and to reduce the risk of vertebral fractures in men with idiopathic osteoporosis.[151,152]

Grade A, Level 1+

Parathyroid hormone therapy in men suggests effects similar to those observed in women - a substantial increase in bone mineral density in men treated with PTH and decline following discontinuation although such decline is still higher than baseline bone mineral density. Use of anti-resorptives prevented the decline and tended to further increase bone mineral density. PTH is also effective in increasing bone mineral density in men with hypogonadism as it is in men with osteoporosis.[153-155]

A **Calcium and vitamin D** supplementation may be useful in preserving bone density and reducing non-vertebral fractures in men.[50,156]

Grade A, Level 1+

Other drugs which have been shown to be beneficial in preserving bone density, but without data on fracture reduction, include intermittent *cyclical etidronate therapy, calcitonin, and testosterone*.[157-160]

9.3 Glucocorticoid-induced osteoporosis (GIOP)

Oral glucocorticoid is associated with increased risks of hip and spine fractures.[161] The fracture risk, a result of increased bone resorption and decreased bone formation, increases within 3-6 months after glucocorticoid therapy and decreases after glucocorticoid is discontinued.[162,163] Both the average daily and cumulative glucocorticoid dose correlate with the degree of bone loss and fracture risk. The increased risk has been shown to occur at $\geq$ 5 mg/day prednisolone (or equivalent) for $\geq$ 3 months.[162,164] Bone loss has also been shown to occur in patients on alternate day oral glucocorticoid therapy.[165,166]

Increased bone loss has also been shown to occur with usage of high potency or prolonged low dose inhaled glucocorticoid but the bone loss is not as profound as that due to oral glucocorticoid.[167,168] There is a lack of study of the effect of inhaled glucocorticoid on fracture risk currently. Inhaled glucocorticoid below 400 mcg/day and usage of budesonide or fluticasone seemed to have minimal systemic effects compared to beclomethasone.[169-174] Use of spacer device significantly reduces the effect of inhaled glucocorticoid on bone formation.[175]

Other risk factors for osteoporosis besides glucocorticoid should be evaluated to assist therapeutic decision-making. These include advanced age (> 65 years old), BMI $\leq$ 20, Caucasian or Asian race, family history of fracture, hypogonadism, sedentary lifestyle, smoking, excessive alcohol intake (28-30 g/day) and increased propensity to fall (refer to Table 2).

C Bone mineral density testing using dual energy X-ray absorptiometry is recommended for assessment of fracture risk in individuals who will be started on glucocorticoid for $\geq$ 3 months at $\geq$ 5 mg/day prednisolone or equivalent.[176] Repeat bone mineral density should be done yearly while patients are on continuous glucocorticoid therapy.

Grade C, Level 2+

GPP Measures to reduce glucocorticoid-induced bone loss include reduction or discontinuation of glucocorticoid, changing to alternative formulations or routes of administration and using alternative immunosuppressive agents. Lifestyle measures such as adequate calcium and vitamin D intake, appropriate weight-bearing exercises, smoking cessation, avoidance of excessive alcohol intake and prevention of falls are also recommended.

GPP

C Primary prevention of glucocorticoid-induced osteoporosis should be considered in patients on long-term (≥3 months) glucocorticoid (≥ 5 mg /day prednisolone or equivalent) with clinical risk factors for fracture.[176,177] The dual energy X-ray absorptiometry bone mineral density T score for treatment of glucocorticoid-induced osteoporosis is -1.5 SD at the femoral neck and/or spine.[177]

Grade C, Level 2+

A The following pharmacologic agents are recommended for prevention of bone loss in glucocorticoid-induced osteoporosis:

1. Calcium and vitamin D supplementation (1000-1500 mg/day and 400-800 IU/day respectively)[178] has been shown to reduce bone loss.
2. Intravenous pamidronate 30 mg every 3 months can be used for prevention[179-181] or treatment, but there is no evidence on fracture prevention.
3. Testosterone replacement in men with glucocorticoid-induced hypogonadism.[182]
4. Vitamin D analogues, such as alfacalcidol and calcitriol, are effective in both prevention and treatment of glucocorticoid-induced osteoporosis[183-185] with improvement of bone mineral density.
5. Calcitonin: 200 IU/day can be used in acute pain due to fracture. It maybe considered if bisphosphonate is contraindicated or poorly tolerated. However, it has not been shown to reduce risk of fracture in glucocorticoid-induced osteoporosis.[183,186-188]

Grade A, Level 1+

A The following pharmacologic agents are recommended for prevention of bone loss and fractures in glucocorticoid-induced osteoporosis:

1. Bisphosphonate therapy: Alendronate 35 mg/week for prevention, 70 mg/week for treatment[189,190], risedronate 35 mg/week for prevention or treatment[191-194]; cyclical etidronate 400 mg/day for 14 days followed by calcium every 3 months for prevention or treatment.[195] These bisphosphonates have been shown to reduce vertebral fractures.
2. Parathyroid hormone is effective in the prevention and treatment of glucocorticoid-induced osteoporosis. It has also been shown to prevent vertebra fracture.[196,197]

Grade A, Level 1+

10 Clinical quality improvement

As fracture is the main clinically significant end-point, it is necessary to collect and study data on fracture incidence rates, and this is an important area for further research. Hip fractures have been the most reliably documented fracture as almost all cases have traditionally been admitted to hospitals. Changes in hip fracture incidence rates with time may reflect the effectiveness of current intervention strategies.

Research might be directed at attempts to record incident wrist, vertebral and other fractures as baselines for the evaluation of intervention strategies targeted at these problems. Research into the health care costs and effects of diagnostic and therapeutic strategies on fracture reduction would reveal the cost- effectiveness of such strategies.

A As the evidence for the effectiveness of osteoporosis therapies is strongest among patients with previous fragility fracture or osteoporosis as defined by bone mineral density, all such patients should be considered for, and started on osteoporosis treatment.[26]

Grade A, Level 1+

Research into the proportion of individuals with fragility fractures receiving treatment and data on osteoporosis awareness and prevalence in the community may reveal the effectiveness of the implementation of case finding strategies.

The following clinical quality improvement parameters, based on recommendations in these guidelines, are proposed:

Proportion of patients with prior fragility fracture in adulthood receiving the following:

a. appropriate evaluation for osteoporosis (pg 19)
b. bone mineral density measurement (pg 19)
c. appropriate treatment for osteoporosis (if diagnosed) (pg 28).

11 Cost-effectiveness issues

11.1 Cost effective prevention strategies

Beyond 50 years of life, the rate of bone loss inevitably increases with a corresponding decrease in bone mass. An effective prevention strategy will have to advocate building up sufficient bone reserves during the youthful years and making lifestyle adjustments to minimize bone loss. The general rules of healthy living that apply to chronic diseases in general are relevant to osteoporosis prevention as well. Smoking cessation and limiting alcohol intake are definitely cost saving and regular exercise with proper nutrition will likely be cost effective in the long term. Calcium and vitamin D supplementation in those with such deficiency is also easily achievable without incurring high cost. Improving awareness of osteoporosis amongst the public will be essential. The most at risk in the older population has the lowest awareness of osteoporosis in Singapore.[198] The challenge will be to design public strategies specifically targeted at these patients.

11.2 Cost effective treatment strategies

A summary of the factors for starting or delaying treatment, along with the factors that affect treatment cost effectiveness is shown in Tables 6 and 7.

Table 7 Factors that affect cost effectiveness of treatment

Treatment is more cost effective if:
- Absolute fracture risk of patient is high (based on estimated 10 year lifetime fracture risk)[1,27,78,81]
- Efficacy of therapy is high (based on relative risk reduction values in randomised controlled trials)
- Cost of medication is low
- Cost of treatment and rehabilitation of fracture is high

Among the factors influencing cost effectiveness, the most important is the individual's absolute fracture risk. The higher the fracture risk, the more cost effective it will be to treat the patient.[27,28]

The ten year absolute fracture risk assessment of the individual can be calculated using the WHO Fracture Risk Assessment (FRAX™).[82]

The following groups of patients are at high risk of recurrent fractures:

1. Patients who have previous osteoporotic vertebral fractures.
2. Patients who have previous osteoporotic non-vertebral fractures and a DXA BMD T score of less than -2.0.
3. Patients who are more than 75 years old and have a DXA BMD T score of less than -3.0.

In essence, a cost effective osteoporosis strategy will require a disease management, multi-disciplinary approach focusing on patients who are older, have low BMD and prior fracture history. Implementing an effective falls prevention plan and selection of therapeutic agents with proven effective fracture risk reduction for those at highest risk are the keys to ensuring maximal cost effectiveness.

Annex A Appropriate calcium content of some common foods

Food	Approximate Serving Size	Calcium (mg)
Full cream milk	1 glass (250ml)	280
Low fat milk	1 glass (250ml)	300
High calcium milk powder (skim/non-fat)	4 scoops (25g)	450
Low fat yoghurt (plain & fruit)	125–200g	160–220
Ice cream	1 scoop (50g)	65
Cheese (low fat)	1 slice (21–30g)	80–200
Creamer (non-dairy)	2 teaspoons (10g)	0
Ikan bilis (dried with bones)	2 tablespoons (40g)	240
Sardines (with bones)	1 fish (50g)	190
Pomfret (meat only)	1 fish (160g)	50
Oysters, raw	1	10
Beancurd, firm (tau kwa)	1 small cake (90g)	130
Beancurd, silken (tofu)	2 squares (170g)	50
Soya beans, cooked	1 cup (180g)	300
Soya bean drink (fortified)	1 glass (250ml)	200
Soya bean drink (hawker centre)	1 glass (250ml)	40
Soya bean curd with syrup (tau huay)	1 bowl (270g)	190
Spinach (bayam), cooked	¾ cup (100g)	145
Kai lan, cooked	¾ cup (100g)	160
Chye sim, cooked	¾ cup (100g)	135
Broccoli, cooked	¾ cup (100g)	45
Beans: long, french, cooked	¾ cup (100g)	45
Salad greens, raw (e.g. lettuce, romaine)	1 bowl (60g)	5–10
Yellow dahl	½ cup (95g)	160
Figs, dried	5 whole (95g)	135
Sesame seeds (white)	1 tablespoon (15g)	90
Bread (white/wholemeal)	2 slices (60g)	90
Egg	1 (50g)	30
Fried chicken wing	1 piece (50g)	5
Cooking oil	1 tablespoon (15g)	negligible

Source: Food Information and Nutrient Database, Health Promotion Board

References

1. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129.

2. Kanis JA. Diagnosis of osteoporosis. Osteoporos Int. 1997;7 Suppl 3:S108-16.

3. Riggs BL, Melton LJ, 3rd. Involutional osteoporosis. N Engl J Med. 1986 Jun 26;314(26):1676-86.

4. 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 Mar 13;353(9156):878-82.

5. Koh LK, Saw SM, Lee JJ, Leong KH, Lee J. Hip fracture incidence rates in Singapore 1991-1998. Osteoporos Int. 2001;12(4):311-8.

6. Lau EM. Epidemiology of osteoporosis. Best Pract Res Clin Rheumatol. 2001 Jul;15(3):335-44.

7. Leong KH. Osteoporosis--the need for a paradigm shift. Ann Acad Med Singapore. 1998 Jan;27(1):100-4.

8. Committee on Ageing Issues: Report on Aging Population. 2006.

9. Wong PC. Fracture epidemiology in a mixed southeastern Asian community (Singapore). Clin Orthop Relat Res. 1966 Mar-Apr;45:55-61.

10. Wong MK, Arjandas, Ching LK, Lim SL, Lo NN. Osteoporotic hip fractures in Singapore--costs and patient's outcome. Ann Acad Med Singapore. 2002 Jan;31(1):3-7.

11. Mitra AK, Low CK, Chao AK, Tan SK. Social aspects in patients following proximal femoral fractures. Ann Acad Med Singapore. 1994 Nov;23(6):876-8.

12. Lee AY, Chua BS, Howe TS. One-year outcome of hip fracture patients admitted to a Singapore hospital: quality of life post-treatment. Singapore Med J. 2007 Nov;48(11):996-9.

13. Chen LT, Lee JA, Chua BS, Howe TS. Hip fractures in the elderly: the impact of comorbid illnesses on hospitalisation costs. Ann Acad Med Singapore. 2007 Sep;36(9):784-7.

14. Nevitt MC, Ross PD, Palermo L, Musliner T, Genant HK, Thompson DE. Association of prevalent vertebral fractures, bone density, and alendronate treatment with incident vertebral fractures: effect of number and spinal location of fractures. The Fracture Intervention Trial Research Group. Bone. 1999 Nov;25(5):613-9.

15. Ross PD. Clinical consequences of vertebral fractures. Am J Med. 1997 Aug 18;103(2A):30S-42S; discussion S-3S.

16. Who are candidates for prevention and treatment for osteoporosis? Osteoporos Int. 1997;7(1):1-6.

17. Consensus development conference: prophylaxis and treatment of osteoporosis. Am J Med. 1991 Jan;90(1):107-10.

18. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J. 2001 Jun;94(6):569-73.

19. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996 May 18;312(7041):1254-9.

20. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int. 2000;11(3):192-202.

21. Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, et al. Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. J Bone Miner Res. 1995 Nov;10(11):1802-15.

22. Bauer DC, Browner WS, Cauley JA, Orwoll ES, Scott JC, Black DM, et al. Factors associated with appendicular bone mass in older women. The Study of Osteoporotic Fractures Research Group. Ann Intern Med. 1993 May 1;118(9):657-65.

23. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995 Mar 23;332(12):767-73.

24. Lau EM, Suriwongpaisal P, Lee JK, Das De S, Festin MR, Saw SM, et al. Risk factors for hip fracture in Asian men and women: the Asian osteoporosis study. J Bone Miner Res. 2001 Mar;16(3):572-80.

25. Boonyaratavej N, Suriyawongpaisal P, Takkinsatien A, Wanvarie S, Rajatanavin R, Apiyasawat P. Physical activity and risk factors for hip fractures in Thai women. Osteoporos Int. 2001;12(3):244-8.

26. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Introduction. Osteoporos Int. 1998;8 Suppl 4:S7-80.

27. 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 Aug;18(8):1109-17.

28. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA. 2007 Jan 24;297(4):387-94.

29. Koh LK, Sedrine WB, Torralba TP, Kung A, Fujiwara S, Chan SP, et al. A simple tool to identify asian women at increased risk of osteoporosis. Osteoporos Int. 2001;12(8):699-705.

30. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996 Dec 7;348(9041):1535-41.

31. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998 Dec 23-30;280(24):2077-82.

32. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001 Feb 1;344(5):333-40.

33. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures

in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999 Oct 13;282(14):1344-52.

34. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11(1):83-91.

35. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001 May 10;344(19):1434-41.

36. Leong KH, Feng PH. Bone mineral density measurements using the Hologic QD2000 in 175 Singaporean women aged 20-80. Singapore Med J. 1997 Jan;38(1):25-6.

37. Ross PD, He Y, Yates AJ, Coupland C, Ravn P, McClung M, et al. Body size accounts for most differences in bone density between Asian and Caucasian women. The EPIC (Early Postmenopausal Interventional Cohort) Study Group. Calcif Tissue Int. 1996 Nov;59(5):339-43.

38. Hans D, Dargent-Molina P, Schott AM, Sebert JL, Cormier C, Kotzki PO, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. Lancet. 1996 Aug 24;348(9026):511-4.

39. Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1997 Mar 24;157(6):629-34.

40. Frost ML, Blake GM, Fogelman I. A comparison of fracture discrimination using calcaneal quantitative ultrasound and dual X-ray absorptiometry in women with a history of fracture at sites other than the spine and hip. Calcif Tissue Int. 2002 Sep;71(3):207-11.

41. Nayak S, Olkin I, Liu H, Grabe M, Gould MK, Allen IE, et al. Meta-analysis: accuracy of quantitative ultrasound for identifying patients with osteoporosis. Ann Intern Med. 2006 Jun 6;144(11):832-41.

42. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999 Aug 18;282(7):637-45.

43. Chesnut CH, 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med. 2000 Sep;109(4):267-76.

44. Health Promotion Board raspd. Report of National Nutrition Survey. 2004.

45. Ho SC, Leung PC, Swaminathan R, Chan C, Chan SS, Fan YK, et al. Determinants of bone mass in Chinese women aged 21-40 years. II. Pattern of dietary calcium intake and association with bone mineral density. Osteoporos Int. 1994 May;4(3):167-75.

46. Chan HH, Lau EM, Woo J, Lin F, Sham A, Leung PC. Dietary calcium intake, physical activity and the risk of vertebral fracture in Chinese. Osteoporos Int. 1996;6(3):228-32.

47. Lau EM, Woo J, Lam V, Hong A. Milk supplementation of the diet of postmenopausal Chinese women on a low calcium intake retards bone loss. J Bone Miner Res. 2001 Sep;16(9):1704-9.

48. Cumming RG, Nevitt MC. Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res. 1997 Sep;12(9):1321-9.

49. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992 Dec 3;327(23):1637-42.

50. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997 Sep 4;337(10):670-6.

51. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized,

placebo-controlled clinical trial. Ann Intern Med. 1996 Feb 15;124(4):400-6.

52. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006 Feb 16;354(7):669-83.

53. Institute of Medicine FaNB. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, DC: National Academy Press. 1997.

54. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005 May 11;293(18):2257-64.

55. Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2005(3): CD000227.

56. Richy F, Schacht E, Bruyere O, Ethgen O, Gourlay M, Reginster JY. Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. Calcif Tissue Int. 2005 Mar;76(3):176-86.

57. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA. 2004 Apr 28;291(16):1999-2006.

58. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Arch Intern Med. 2006 Feb 27;166(4):424-30.

59. Dukas L, Bischoff HA, Lindpaintner LS, Schacht E, Birkner-Binder D, Damm TN, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc. 2004 Feb;52(2):230-6.

60. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab. 2001 Aug;86(8):3618-28.

61. Bonaiuti D, Shea B, Iovine R, Negrini S, Robinson V, Kemper HC, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2002(3):CD000333.

62. Englund U, Littbrand H, Sondell A, Pettersson U, Bucht G. A 1-year combined weight-bearing training program is beneficial for bone mineral density and neuromuscular function in older women. Osteoporos Int. 2005 Sep;16(9):1117-23.

63. Judge JO, Kleppinger A, Kenny A, Smith JA, Biskup B, Marcella G. Home-based resistance training improves femoral bone mineral density in women on hormone therapy. Osteoporos Int. 2005 Sep;16(9):1096-108.

64. Milliken LA, Going SB, Houtkooper LB, Flint-Wagner HG, Figueroa A, Metcalfe LL, et al. Effects of exercise training on bone remodeling, insulin-like growth factors, and bone mineral density in postmenopausal women with and without hormone replacement therapy. Calcif Tissue Int. 2003 Apr;72(4):478-84.

65. Nichols DL, Sanborn CF, Love AM. Resistance training and bone mineral density in adolescent females. J Pediatr. 2001 Oct;139(4):494-500.

66. Huuskonen J, Vaisanen SB, Kroger H, Jurvelin JS, Alhava E, Rauramaa R. Regular physical exercise and bone mineral density: a four-year controlled randomized trial in middle-aged men. The DNASCO study. Osteoporos Int. 2001;12(5):349-55.

67. Vainionpaa A, Korpelainen R, Leppaluoto J, Jamsa T. Effects of high-impact exercise on bone mineral density: a randomized controlled trial in premenopausal women. Osteoporos Int. 2005 Feb;16(2):191-7.

68. Daniell HW. Osteoporosis of the slender smoker. Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. Arch Intern Med. 1976 Mar;136(3):298-304.

69. Hernandez-Avila M, Colditz GA, Stampfer MJ, Rosner B, Speizer FE, Willett WC. Caffeine, moderate alcohol intake, and risk of fractures of the hip and forearm in middle-aged women. Am J Clin Nutr. 1991 Jul;54(1):157-63.

70. National Collaborating Centre for Nursing and Supportive Care.

71. (NICE) NIfCE. Clinical practice guideline for the assessment and prevention of falls in older people.

72. Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH. Interventions for preventing falls in elderly people. Cochrane Database Syst Rev. 2003(4):CD000340.

73. Chang JT, Morton SC, Rubenstein LZ, Mojica WA, Maglione M, Suttorp MJ, et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. BMJ. 2004 Mar 20;328(7441):680.

74. Parker MJ, Gillespie WJ, Gillespie LD. Effectiveness of hip protectors for preventing hip fractures in elderly people: systematic review. BMJ. 2006 Mar 11;332(7541):571-4.

75. Sawka AM, Boulos P, Beattie K, Thabane L, Papaioannou A, Gafni A, et al. Do hip protectors decrease the risk of hip fracture in institutional and community-dwelling elderly? A systematic review and meta-analysis of randomized controlled trials. Osteoporos Int. 2005 Dec;16(12):1461-74.

76. Oliver D, Connelly JB, Victor CR, Shaw FE, Whitehead A, Genc Y, et al. Strategies to prevent falls and fractures in hospitals and care homes and effect of cognitive impairment: systematic review and meta-analyses. BMJ. 2007 Jan 13;334(7584):82.

77. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, et al. Hip fracture in women without osteoporosis. J Clin Endocrinol Metab. 2005 May;90(5):2787-93.

78. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int. 2005 Jun;16(6):581-9.

79. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, 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 Aug;18(8):1033-46.

80. van Staa TP, Geusens P, Kanis JA, Leufkens HG, Gehlbach S, Cooper C. A simple clinical score for estimating the long-term risk of fracture in post-menopausal women. QJM. 2006 Oct;99(10):673-82.

81. Kung AW, Lee KK, Ho AY, Tang G, Luk KD. Ten-year risk of osteoporotic fractures in postmenopausal Chinese women according to clinical risk

factors and BMD T-scores: a prospective study. J Bone Miner Res. 2007 Jul;22(7):1080-7.

82. www.shef.ac.uk/FRAX/.

83. Borgstrom F, Johnell O, Kanis JA, Jonsson B, Rehnberg C. At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. Osteoporos Int. 2006 Oct;17(10):1459-71.

84. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: implications for risk assessment. J Bone Miner Res. 2002 Jul;17(7):1237-44.

85. Kanis JA, Melton LJ, 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res. 1994 Aug;9(8):1137-41.

86. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. JAMA. 1996 Nov 6;276(17):1389-96.

87. Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, 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 Feb 19;338(8):485-92.

88. Pouilles JM, Tremollieres F, Roux C, Sebert JL, Alexandre C, Goldberg D, et al. Effects of cyclical etidronate therapy on bone loss in early postmenopausal women who are not undergoing hormonal replacement therapy. Osteoporos Int. 1997;7(3):213-8.

89. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston 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 Feb;83(2):396-402.

90. Reginster JY, Deroisy R, Lecart MP, Sarlet N, Zegels B, Jupsin I, et al. A double-blind, placebo-controlled, dose-finding trial of intermittent nasal salmon calcitonin for prevention of postmenopausal lumbar spine bone loss. Am J Med. 1995 May;98(5):452-8.

91. Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med. 1997 Dec 4;337(23):1641-7.

92. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003 Oct 1;290(13):1729-38.

93. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33.

94. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007 Apr 4;297(13):1465-77.

95. Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. Arch Intern Med. 2006 Feb 13;166(3):357-65.

96. Bjarnason NH, Bjarnason K, Haarbo J, Rosenquist C, Christiansen C. Tibolone: prevention of bone loss in late postmenopausal women. J Clin Endocrinol Metab. 1996 Jul;81(7):2419-22.

97. Cummings SR. LIFT study is discontinued. BMJ. 2006 Mar 18;332(7542):667.

98. Seeman E, Devogelaer JP, Lorenc R, Spector T, Brixen K, Balogh A, et al. Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. J Bone Miner Res. 2008 Mar;23(3):433-8.

99. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007 May 3;356(18):1809-22.

100. Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, Brandi ML, et al. Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum. 2008 Jun;58(6):1687-95.

101. Felsenberg D, Miller P, Armbrecht G, Wilson K, Schimmer RC, Papapoulos SE. Oral ibandronate significantly reduces the risk of vertebral fractures of greater severity after 1, 2, and 3 years in postmenopausal women with osteoporosis. Bone. 2005 Nov;37(5):651-4.

102. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med. 1990 Jul 12;323(2):73-9.

103. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med. 1990 May 3;322(18):1265-71.

104. van Staa TP, Abenhaim L, Cooper C. Use of cyclical etidronate and prevention of non-vertebral fractures. Br J Rheumatol. 1998 Jan;37(1):87-94.

105. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab. 2000 Nov;85(11):4118-24.

106. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int. 2007 Aug;18(8):1023-31.

107. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004 Aug;19(8):1241-9.

108. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis. 2006 May;65(5):654-61.

109. Adami S, Felsenberg D, Christiansen C, Robinson J, Lorenc RS, Mahoney P, et al. Efficacy and safety of ibandronate given by intravenous injection once every 3 months. Bone. 2004 May;34(5):881-9.

110. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol. 2008 Mar;35(3):488-97.

111. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005 Mar;90(3):1294-301.

112. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, 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 Dec 27;296(24):2927-38.

113. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004 Dec;75(6):462-8.

114. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Oct;102(4):433-41.

115. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007 Oct;22(10):1479-91.

116. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006 May 16;144(10):753-61.

117. Bilezikian JP. Osteonecrosis of the jaw--do bisphosphonates pose a risk? N Engl J Med. 2006 Nov 30;355(22):2278-81.

118. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med. 2004 Jan 29;350(5):459-68.

119. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, 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 May;90(5):2816-22.

120. Siris ES, Harris ST, Eastell R, Zanchetta JR, Goemaere S, Diez-Perez A, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005 Sep;20(9):1514-24.

121. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006 Jun 21;295(23):2727-41.

122. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006 Jul 13;355(2):125-37.

123. Grady D, Ettinger B, Moscarelli E, Plouffe L, Jr., Sarkar S, Ciaccia A, et al. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol. 2004 Oct;104(4):837-44.

124. Cardona JM, Pastor E. Calcitonin versus etidronate for the treatment of postmenopausal osteoporosis: a meta-analysis of published clinical trials. Osteoporos Int. 1997;7(3):165-74.

125. Kanis JA, McCloskey EV. Effect of calcitonin on vertebral and other fractures. QJM. 1999 Mar;92(3):143-9.

126. Lyritis GP, Tsakalakos N, Magiasis B, Karachalios T, Yiatzides A, Tsekoura M. Analgesic effect of salmon calcitonin in osteoporotic vertebral fractures:

a double-blind placebo-controlled clinical study. Calcif Tissue Int. 1991 Dec;49(6):369-72.

127. Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M. Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose. Toxicol Pathol. 2004 Jul-Aug;32(4):426-38.

128. Kurland ES, Heller SL, Diamond B, McMahon DJ, Cosman F, Bilezikian JP. The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide [human parathyroid hormone(1-34)]. Osteoporos Int. 2004 Dec;15(12):992-7.

129. Adami S, San Martin J, Munoz-Torres M, Econs MJ, Xie L, Dalsky GP, et al. Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis. Osteoporos Int. 2008 Jan;19(1):87-94.

130. Ringe JD, Farahmand P, Schacht E, Rozehnal A. Superiority of a combined treatment of Alendronate and Alfacalcidol compared to the combination of Alendronate and plain vitamin D or Alfacalcidol alone in established postmenopausal or male osteoporosis (AAC-Trial). Rheumatol Int. 2007 Mar;27(5):425-34.

131. 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 Nov;52(11):1832-9.

132. Seeman E, Vellas B, Benhamou C, Aquino JP, Semler J, Kaufman JM, et al. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. J Bone Miner Res. 2006 Jul;21(7):1113-20.

133. 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 Oct;15(10):767-78.

134. Solomon DH, Morris C, Cheng H, Cabral D, Katz JN, Finkelstein JS, et al. Medication use patterns for osteoporosis: an assessment of guidelines, treatment rates, and quality improvement interventions. Mayo Clin Proc. 2005 Feb;80(2):194-202.

135. Seeman E, Compston J, Adachi J, Brandi ML, Cooper C, Dawson-Hughes B, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. Osteoporos Int. 2007 Jun;18(6):711-9.

136. Leib ES, Lenchik L, Bilezikian JP, Maricic MJ, Watts NB. Position statements of the International Society for Clinical Densitometry: methodology. J Clin Densitom. 2002;5 Suppl:S5-10.

137. Lenchik L, Kiebzak GM, Blunt BA. What is the role of serial bone mineral density measurements in patient management? J Clin Densitom. 2002;5 Suppl:S29-38.

138. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab. 2000 Jan;85(1):231-6.

139. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int. 2000;11 Suppl 6:S2-17.

140. Eastell R, Boyle IT, Compston J, Cooper C, Fogelman I, Francis RM, et al. Management of male osteoporosis: report of the UK Consensus Group. QJM. 1998 Feb;91(2):71-92.

141. Melton LJ, 3rd, O'Fallon WM, Riggs BL. Secular trends in the incidence of hip fractures. Calcif Tissue Int. 1987 Aug;41(2):57-64.

142. Seeman E, Bianchi G, Khosla S, Kanis JA, Orwoll E. Bone fragility in men--where are we? Osteoporos Int. 2006;17(11):1577-83.

143. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int. 2001 Dec;12(12):989-95.

144. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12(5):417-27.

145. Kanis JA, Johnell O, Oden A, Borgstrom F, Johansson H, De Laet C, et al. Intervention thresholds for osteoporosis in men and women: a study based on data from Sweden. Osteoporos Int. 2005 Jan;16(1):6-14.

146. Kanis JA, Johnell O, Oden A, De Laet C, Oglesby A, Jonsson B. Intervention thresholds for osteoporosis. Bone. 2002 Jul;31(1):26-31.

147. Fitzpatrick LA. Secondary causes of osteoporosis. Mayo Clin Proc. 2002 May;77(5):453-68.

148. Poor G, Atkinson EJ, O'Fallon WM, Melton LJ, 3rd. Predictors of hip fractures in elderly men. J Bone Miner Res. 1995 Dec;10(12):1900-7.

149. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med. 2000 Aug 31;343(9):604-10.

150. Ringe JD, Dorst A, Faber H, Ibach K. Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. Rheumatol Int. 2004 Mar;24(2):110-3.

151. 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 Mar;26(5):427-31.

152. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Arch Intern Med. 2005 Aug 8-22;165(15):1743-8.

153. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab. 2000 Sep;85(9):3069-76.

154. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003 Jan;18(1):9-17.

155. Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int. 2005 May;16(5):510-6.

156. O'Brien KO. Combined calcium and vitamin D supplementation reduces bone loss and fracture incidence in older men and women. Nutr Rev. 1998 May;56(5 Pt 1):148-50.

157. Anderson FH, Francis RM, Bishop JC, Rawlings DJ. Effect of intermittent cyclical disodium etidronate therapy on bone mineral density in men with vertebral fractures. Age Ageing. 1997 Sep;26(5):359-65.

158. Erlacher L, Kettenbach J, Kiener H, Graninger W, Kainberger F, Pietschmann P. Salmon calcitonin and calcium in the treatment of male osteoporosis: the effect on bone mineral density. Wien Klin Wochenschr. 1997 Apr 25;109(8):270-4.

159. Anderson FH, Francis RM, Peaston RT, Wastell HJ. Androgen supplementation in eugonadal men with osteoporosis: effects of six months' treatment on markers of bone formation and resorption. J Bone Miner Res. 1997 Mar;12(3):472-8.

160. Bilezikian JP, Kurland ES. Therapy of male osteoporosis with parathyroid hormone. Calcif Tissue Int. 2001 Oct;69(4):248-51.

161. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res. 2004 Jun;19(6):893-9.

162. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002 Oct;13(10):777-87.

163. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res. 2000 Jun;15(6):993-1000.

164. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1995 Jun;22(6):1055-9.

165. Ruegsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography. Eur J Clin Pharmacol. 1983;25(5):615-20.

166. Gluck OS, Murphy WA, Hahn TJ, Hahn B. Bone loss in adults receiving alternate day glucocorticoid therapy. A comparison with daily therapy. Arthritis Rheum. 1981 Jul;24(7):892-8.

167. Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma.

Lancet. 2000 Apr 22;355(9213):1399-403.

168. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med. 1999 May 10;159(9):941-55.

169. Geddes DM. Inhaled corticosteroids: benefits and risks. Thorax. 1992 Jun;47(6):404-7.

170. Wolthers OD, Pedersen S. Growth of asthmatic children during treatment with budesonide: a double blind trial. BMJ. 1991 Jul 20;303(6795):163-5.

171. Ali NJ, Capewell S, Ward MJ. Bone turnover during high dose inhaled corticosteroid treatment. Thorax. 1991 Mar;46(3):160-4.

172. Volovitz B, Amir J, Malik H, Kauschansky A, Varsano I. Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. N Engl J Med. 1993 Dec 2;329(23):1703-8.

173. Yiallouros PK, Milner AD, Conway E, Honour JW. Adrenal function and high dose inhaled corticosteroids for asthma. Arch Dis Child. 1997 May;76(5):405-10.

174. Kemp JP, Osur S, Shrewsbury SB, Herje NE, Duke SP, Harding SM, et al. Potential effects of fluticasone propionate on bone mineral density in patients with asthma: a 2-year randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004 Apr;79(4):458-66.

175. Meeran K, Burrin JM, Noonan KA, Price CP, Ind PW. A large volume spacer significantly reduces the effect of inhaled steroids on bone formation. Postgrad Med J. 1995 Mar;71(833):156-9.

176. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. June, 2000. J Bone Miner Res. 2005 Aug;20(8):1487-94; discussion 6.

177. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum. 2001 Jul;44(7):1496-503.

178. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to

low-dose corticosteroids in patients with rheumatoid arthritis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1996 Dec 15;125(12):961-8.

179. Boutsen Y, Jamart J, Esselinckx W, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. J Bone Miner Res. 2001 Jan;16(1):104-12.

180. Krieg MA, Seydoux C, Sandini L, Goy JJ, Berguer DG, Thiebaud D, et al. Intravenous pamidronate as treatment for osteoporosis after heart transplantation: a prospective study. Osteoporos Int. 2001;12(2):112-6.

181. Gallacher SJ, Fenner JA, Anderson K, Bryden FM, Banham SW, Logue FC, et al. Intravenous pamidronate in the treatment of osteoporosis associated with corticosteroid dependent lung disease: an open pilot study. Thorax. 1992 Nov;47(11):932-6.

182. Reid IR, Wattie DJ, Evans MC, Stapleton JP. Testosterone therapy in glucocorticoid-treated men. Arch Intern Med. 1996 Jun 10;156(11):1173-7.

183. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. N Engl J Med. 1993 Jun 17;328(24):1747-52.

184. Ringe JD, Coster A, Meng T, Schacht E, Umbach R. Treatment of glucocorticoid-induced osteoporosis with alfacalcidol/calcium versus vitamin D/calcium. Calcif Tissue Int. 1999 Oct;65(4):337-40.

185. Reginster JY, de Froidmont C, Lecart MP, Sarlet N, Defraigne JO. Alphacalcidol in prevention of glucocorticoid-induced osteoporosis. Calcif Tissue Int. 1999 Oct;65(4):328-31.

186. Cranney A, Welch V, Adachi JD, Homik J, Shea B, Suarez-Almazor ME, et al. Calcitonin for the treatment and prevention of corticosteroid-induced osteoporosis. Cochrane Database Syst Rev. 2000(2):CD001983.

187. Luengo M, Pons F, Martinez de Osaba MJ, Picado C. Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy

for asthma: a two year follow up study. Thorax. 1994 Nov;49(11):1099-102.

188. Montemurro L, Schiraldi G, Fraioli P, Tosi G, Riboldi A, Rizzato G. Prevention of corticosteroid-induced osteoporosis with salmon calcitonin in sarcoid patients. Calcif Tissue Int. 1991 Aug;49(2):71-6.

189. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med. 1998 Jul 30;339(5):292-9.

190. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum. 2001 Jan;44(1):202-11.

191. Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 1999 Nov;42(11):2309-18.

192. Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int. 2000 Oct;67(4):277-85.

193. Reid DM, Adami S, Devogelaer JP, Chines AA. Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. Calcif Tissue Int. 2001 Oct;69(4):242-7.

194. Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res. 2000 Jun;15(6):1006-13.

195. Adachi JD, Roux C, Pitt PI, Cooper C, Moniz C, Dequeker J, et al. A pooled data analysis on the use of intermittent cyclical etidronate therapy for the

prevention and treatment of corticosteroid induced bone loss. J Rheumatol. 2000 Oct;27(10):2424-31.

196. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. J Clin Invest. 1998 Oct 15;102(8):1627-33.

197. Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007 Nov 15;357(20):2028-39.

198. Saw SM, Hong CY, Lee J, Wong ML, Chan MF, Cheng A, et al. Awareness and health beliefs of women towards osteoporosis. Osteoporos Int. 2003 Jul;14(7):595-601.

Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process and is not intended to "judge" your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

Instruction: Choose "True" or "False.

		True	False
1.	For patients who are on glucocorticoid		
	A) Increased fracture risk is associated with ≥ 5 mg/ day prednisolone for ≥ 3 months.	☐	☐
	B) Inhaled glucocorticoid therapy does not cause osteoporosis.	☐	☐
	C) Drug therapies can only prevent bone loss but cannot prevent vertebral fractures.	☐	☐
	D) One of the best ways to prevent glucocorticoid-induced osteoporosis is to use the minimal effective dose of glucocorticoid or to use alternative therapy if possible.	☐	☐
2.	For diagnosis and follow up of osteoporosis		
	A) Using dual-energy absorptiometry (DXA), a T score of "-1.7" measured at the hip suggests the diagnosis of osteoporosis, even if there is no past history of fragility fractures.	☐	☐
	B) The Z score, measured by DXA compares the bone density of the individual with the mean bone density of young health adults of the same gender.	☐	☐
	C) Based on current evidence, ultrasound of the heel *cannot* be used reliably as a tool to follow up patients on treatment for osteoporosis.	☐	☐
	D) In the elderly, lumbar spine measurements may be artificially increased by osteoarthritis, fractures and calcification of the aorta, in which case, the hip measurement could be used to monitor response.	☐	☐

		True	False
3.	With regard to male osteoporosis		
	A) Different diagnostic fracture thresholds for men and women are recommended routinely.	☐	☐
	B) Secondary causes of osteoporosis are more commonly found in men.	☐	☐
	C) Endocrine causes of osteoporosis include hyperparathyroidism, hypercortisolism and hypogonadism.	☐	☐
	D) All drugs used for treatment of osteoporosis in women have been shown to be as efficacious in men.	☐	☐
	E) Calcium and vitamin D are of no use in reducing vertebral fractures in men.	☐	☐
4.	With regard to dietary supplementation		
	A) There are few data to support any benefit of calcium intake in excess of 2000 mg daily.	☐	☐
	B) Patients with risk factors for osteoporosis still require evaluation and may require specific therapy over and above adequate calcium intake and exercise.	☐	☐
	C) In addition to drug therapy, calcium and oral vitamin D supplements (at 800 international units per day) should be given for optimal fracture prevention in the elderly.	☐	☐
	D) Vitamin D supplementation (with calcium) should be considered in most individuals, particularly in the elderly and institutionalized individuals, as commonly eaten foods do not contain enough vitamin D to fulfill the RDI.	☐	☐

		True	False
5.	For cost effectiveness of medical therapy:		
	A) The most important variable to consider for the individual patient is the 10 year estimated absolute risk of fracture.	☐	☐
	B) The higher the 10 year absolute risk of fracture, the more cost effective it will be to treat the patient.	☐	☐
	C) The higher the cost of the medication, the more cost effective it will be.	☐	☐
	D) The higher the cost of treatment for fracture, the more cost effective it will be to treat the patients.	☐	☐
	E) The more efficacious the medication in preventing fractures, the more cost effective it will be.	☐	☐
6.	With regard to osteoporosis medication:		
	A) An increase in BMD measurement alone in the trial results is sufficient evidence for the use of the medication.	☐	☐
	B) An ideal medication should have evidence showing reduction in both vertebral and non-vertebral fractures in randomised controlled trials.	☐	☐
	C) The side effects of the therapy should not be a consideration when prescribing medicine as long as it is effective.	☐	☐
	D) The more expensive the medicine, the more efficacious it is.	☐	☐
	E) Compliance with medication is important.	☐	☐
7 .	With regard to monitoring of treatment.		
	A) Bone mineral density should be done every year for most patients.	☐	☐
	B) Bone turnover markers can be a good surrogate marker for effectiveness of therapy.	☐	☐
	C) If there is no improvement in BMD after therapy, the most important measure is to change medication.	☐	☐
	D) Lack of improvement in BMD may be due to poor compliance or adherence, undiagnosed secondary osteoporosis or treatment failure.	☐	☐
	E) Ultrasound BMD can be used to monitor treatment.	☐	☐

		True	False
8.	With regard to falls prevention:		
	A) Falls in elderly are inevitable and it is a consequence of aging.	☐	☐
	B) Older people who are assessed to have risk factors for falls or have recurrent falls should have targeted individualised multifactorial intervention.	☐	☐
	C) Interventions for falls prevention should include treatment of identified reversible medical problems, medication adjustments, home hazard assessment and modification, physical therapy and vision correction.	☐	☐
	D) Hip protectors may be useful in preventing fractures during a fall.	☐	☐
9 .	With regard to fractures:		
	A) Anyone who has a history of fragility fractures should be evaluated for osteoporosis and falls risk assessment.	☐	☐
	B) Vertebral fractures are not life threatening and therefore should not be a concern for doctors.	☐	☐
	C) Patients with hip fractures tend to be very elderly and therefore need not be treated for osteoporosis.	☐	☐
	D) It is important to start anti-osteoporosis medicine in someone who has a fragility fracture to prevent a recurrent fracture.	☐	☐
	E) Anyone who has a history of fragility fractures, particularly for vertebral fractures, is at a much higher risk of fracturing again than someone who never had a fragility fracture before.	☐	☐
10.	The following persons should be considered for referral to a specialist for further evaluation.		
	A) Male patients.	☐	☐
	B) Patients on long term steroids.	☐	☐
	C) Patients with disproportionately low Z scores (which may indicate secondary causes of osteoporosis).	☐	☐
	D) Patients with endocrine diseases, e.g. hyperparathyroidism, hypogonadism, hypercortisolism and hyperthyroidism.	☐	☐
	E) Patients with pathological fracture.	☐	☐

This page has been intentionally left blank

Answer

1 A)	True	(pg 39)
1 B)	False	(pg 39)
1 C)	False	(pg 41)
1 D)	True	(pg 40)
2 A)	False	(pg 14)
2 B)	False	(pg 19)
2 C)	True	(pg 21)
2 D)	True	(pg 20)
3 A)	False	(pg 37)
3 B)	True	(pg 37)
3 C)	True	(pg 37)
3 D)	False	(pg 38)
3 E)	False	(pg 38)
4 A)	True	(pg 23)
4 B)	True	(pg 24)
4 C)	True	(pg 24)
4 D)	True	(pg 25)
5 A)	True	(pg 43)
5 B)	True	(pg 43)
5 C)	False	(pg 43)
5 D)	True	(pg 43)
5 E)	True	(pg 43)

6 A)	False	(pg 29)
6 B)	True	(pg 29)
6 C)	False	(pg 34)
6 D)	False	(pg 34)
6 E)	True	(pg 34)
7 A)	False	(pg 35)
7 B)	True	(pg 35)
7 C)	False	(pg 35)
7 D)	True	(pg 35)
7 E)	False	(pg 21)
8 A)	False	(pg 26)
8 B)	True	(pg 27)
8 C)	True	(pg 27)
8 D)	True	(pg 27)
9 A)	True	(pg 14)
9 B)	False	(pg 12)
9 C)	False	(pg 29)
9 D)	True	(pg 30)
9 E)	True	(pg 16)
10 A)	True	(pg 36)
10 B)	True	(pg 36)
10 C)	True	(pg 36)
10 D)	True	(pg 36)
10 E)	True	(pg 36)

Workgroup Members

The members of the workgroup, who were appointed in their personal professional capacity, are:

Chairperson

Dr Lau Tang Ching
Consultant
Department of Medicine
National University Hospital

Members

Dr Leonard Koh
Leonard Koh Diabetes, Thyroid & Hormone Practice
Gleneagles Medical Centre

Dr Leong Keng Hong
Leong Keng Hong Arthritis and Medical Clinic
Gleneagles Medical Centre

Dr Koh Ee Tzun
Senior Consultant,
Rheumatology, Allergy & Immunology Dept
Tan Tock Seng Hospital

Dr Chionh Siok Bee
Senior Consultant
Endocrinology Dept
National University Hospital

Dr Noor Hafizah Bte Ismail
Senior Consultant
Geriatrics Dept
Tan Tock Seng Hospital

A/Prof Rajasoorya C
Senior Consultant
Endocrinology Dept
Alexandra Hospital

Prof Das De Shamal
Senior Consultant
Orthopaedic Surgery Dept
National University Hospital

Dr Tay Boon Lin
Senior Consultant
Menopause Unit
KK Women's and Children's Hospital

Ms Louisa Zhang
Secretary of Osteoporosis Society (Singapore)

Dr Gilbert Tan
Deputy Director, Singhealth Polyclinics-Bukit Merah.

Dr Yee Jenn Jet Michael
Rapha Medical Centre

Dr Helen Thomas
Consultant
Dept of Geriatric Medicine
Changi General Hospital

Dr Lydia Au Shu Yi
Consultant, Geriatric Medicine
Alexandra Hospital

Members

Catherine Chua
Senior Physiotherapist
Rehabilitation Dept
KK Women's and
Children's Hospital

Max Lim Ming Xian
Physiotherapist
Rehabilitation Dept
Changi General Hospital

Mdm Koh Seow Ehian
Physiotherapist
Rehabilitation Dept
KK Women's and
Children's Hospital

Dr Yue Wai Mun
Consultant
Dept of Orthopeadic Surgery
Singapore General Hospital

Maggie Chan
Patient Representative

Nancy Chan
Patient Representative

Subsidiary editors:

Dr Pwee Keng Ho
Deputy Director (Health Technology Assessment)
Health Services Research & Evaluation Division
Ministry of Health

Dr Rajni Gupta
Assistant Manager (Health Technology Assessment)
Health Services Research & Evaluation Division
Ministry of Health

Acknowledgement:

The workgroup would like to thank the observers:
Yong Li Min, Karyn Tang and Megan Xi Wai Ming
Physiotherapists, Rehabilitation Dept, Changi General Hospital

Acknowledgement:

Dr Edwin Chan Shih-Yen
Head of Evidence-Based Medicine
and
Director of the Singapore Branch, Australasian Cochrane Centre
Clinical Trials & Epidemiology Research Unit

Dr Shi Luming
Senior Evidence-Based Medicine Analyst
and
Co-Director of the Singapore Branch, Australasian Cochrane Centre
Clinical Trials & Epidemiology Research Unit

Ministry of Health, Singapore
College of Medicine Building
16 College Road
Singapore 169854
TEL (65) 6325 9220
FAX (65) 6224 1677
WEB www.moh.gov.sg

ISBN 978-981-08-2173-9