INAHTA Joint Project

Bone Density Measurement and Treatments of Osteoporosis

Statement of findings

David Hailey, Laura Sampietro-Colom, Deborah Marshall, Rosa Rico, Alicia Granados, José Asua, Trevor Sheldon

September 1996
Acknowledgements

The authors and agencies involved in the preparation of this manuscript gratefully acknowledge and thank the following individuals, who reviewed this document in draft form and made many helpful comments and suggestions:

Ann Cranney, Beverly Shea, Peter Tugwell, University of Ottawa, Canada; Pierre Durieux, Assistance Publique Hôpitaux de Paris, France; David Feeny, McMaster University, Canada; Frederic Fleurette, Agence Nationale pour le Développement de l’Évaluation Médicale, France; Hellen Gelband, Robert McDonough, Office of Technology Assessment, USA; Line Gariépy, Guy Régnier, Conseil d’évaluation des technologies de la santé du Québec, Canada; Tom Holohan, Office of Health Technology Assessment, USA; Olof Johnell, Lund University, Sweden; Lawrence Joseph, McGill University, Canada; David Henry, The University of Newcastle, Australia; Albert Jovell, Catalan Agency for Health Technology Assessment, Spain; Sverker Ljunghall, Uppsala University, Sweden.

The authors are especially grateful for the assistance of Dr. David Henry and his colleagues at the University of Newcastle, Australia, who shared their unpublished work on HRT. Dr. Henry is also coordinating editor of the Cochrane Review Group that maintains systematic reviews on the prevention and treatment of osteoporosis.

They also acknowledge the valuable assistance of the following persons who participated in meetings to develop the draft statement and helped to develop the background documents:

David Banta, TNO Prevention and Health, The Netherlands; Renaldo Battista and Jean-Marie Lance, Conseil d’évaluation des technologies de la santé du Québec, Canada; Frederic Fleurette, Agence Nationale pour le Développement de l’Évaluation Médicale, France; Albert Jovell, Catalan Agency for Health Technology Assessment, Spain; Pedro Koch, Ufficio federale delle assicurazioni sociali, Switzerland; Robert McDonough, Office of Technology Assessment, USA; Devidas Menon, Canadian Coordinating Office for Health Technology Assessment; Penny Rogers, Australian Health Technology Advisory Committee; Robert Segar, Health Council of the Netherlands; Lars Werkö, The Swedish Council on Technology Assessment in Health Care.
This document is endorsed by the following organisations which are members of the International Network of Agencies for Health Technology Assessment (INAHTA):

Agencia de Evaluación de Tecnologías Sanitarias, Madrid (AETS)
Alberta Heritage Foundation for Medical Research, Edmonton (AHFMR)
Basque Office for Health Technology Assessment, Vitoria – Gasteiz (Osteba)
Catalan Agency for Health Technology Assessment, Barcelona (CAHTA)
Center for Health Care Technology, Agency for Health Care Policy and Research, Rockville (CHCT)
Danish Institute for Health Services Research and Development, Copenhagen (DSI)
NHS Centre for Reviews and Dissemination, York (UK NHS CRD)
Finnish Office for Health Care Technology Assessment, Helsinki (FinOHTA)
Swedish Council on Technology Assessment in Health Care, Stockholm (SBU)
TNO Prevention and Health, Leiden (TNO)
Contents

Summary ............................................................................................................................. 5
Introduction ....................................................................................................................... 6
Scope ................................................................................................................................... 6
Definitions and endpoints ................................................................................................. 6
Methods .............................................................................................................................. 6
Results ................................................................................................................................. 6
  1 Methods for bone density measurement................................................................... 6
  2 The use of bone density measurement to predict fractures in individuals.............. 7
  3 Effect of HRT in preventing fractures and preserving bone mass............................ 8
  4 Effect of intranasal salmon calcitonin in preventing fractures and preserving bone mass.................................................................................................................... 6
Discussion ........................................................................................................................ 5
  Table 1: Level of scientific evidence.............................................................................. 6
  Table 2: Characteristics of common methods for measuring bone density.................. 7
  Table 3: Relative risk of hip fracture according to age................................................... 8
  Table 4: Results of a meta-analysis of the effect of HRT on bone mass......................... 6
  Table 5: Potential impact of BDM screening and treatment with HRT in preventing hip fractures in a population of 20,000 menopausal women......................................... 7
References ........................................................................................................................ 6
Summary

**Objective:** To provide a summary of the available scientific evidence regarding the performance of bone density measurement (BDM) techniques and the effectiveness of BDM screening and related interventions (hormone replacement therapy (HRT) and intranasal salmon calcitonin SCT(N)) in menopausal women to prevent fractures in later life.

**Methods:** Synthesis of systematic reviews of evidence on BDM, HRT and SCT(N) undertaken previously by health technology assessment agencies, and other relevant systematic reviews. These sources were updated by adding primary studies identified through additional literature searches. The evidence was evaluated using an internationally accepted classification system incorporating study design and quality.

**Main Findings:** The analytical performance of BDM technologies in the routine clinical situation has not been adequately assessed. Fair evidence from prospective cohort studies suggests that BDM can predict the risk of fractures, but not with high accuracy. Although good evidence exists to support the efficacy of HRT and SCT(N) in preserving bone mass during treatment, there is also fair evidence that the effect wears off after cessation of therapy. Fair evidence, from low quality RCTs and observational studies, suggests that these therapies are efficacious in preventing fractures. However, when this evidence is used to evaluate the potential effectiveness of BDM screening of menopausal women in combination with these therapies it is estimated, using optimistic assumptions, that only 1-7% of hip fractures might be prevented.

**Conclusion:** The currently available evidence does not support the use of BDM screening in combination with HRT or SCT(N) treatment.
Introduction

Bone fractures represent a serious health problem for older women. Osteoporosis - the natural loss of bone that occurs with age and especially within 3-6 years after the menopause - predisposes women to bone fractures that occur most commonly at the hip, wrist and spine.\(^1\)\(^2\) Hip fractures are of particular concern because of their high costs in terms of morbidity, mortality and their economic and social burden.\(^3\)\(^4\) They are estimated to increase worldwide from 1.66 million annually in 1990 to over 6 million by the year 2050.\(^5\)

Consequently, there is growing international interest in approaches to identify individuals at high risk for fractures and in interventions that might help to prevent these events.\(^6\) Various techniques to measure bone density have been developed for detecting those at high risk of having a fracture. These individuals are commonly prescribed treatments in the form of hormone replacement therapy (HRT), and in some Mediterranean countries, calcitonin (CT).

Scope

The objective of this review is to assess the available scientific evidence regarding the performance of bone density measurement (BDM) and its effectiveness in preventing fractures when used in conjunction with prophylactic treatments (HRT and intranasal salmon calcitonin) in menopausal women. The review has been produced through a collaboration between publicly-funded national and regional agencies from several countries, which undertake health technology assessment, to consolidate and critically evaluate the evidence on these topics. It is intended as a resource to those responsible for funding and using these technologies, which have been selected for review because:

- they are of interest to a number of national and regional health care systems and have been the subject of independent reports published by health technology assessment agencies in several countries;
- programmes to measure bone density in menopausal women to identify those at risk of fracture and who may benefit from treatment would have a considerable impact on health care systems if this were adopted as a widespread practice;
- HRT is prescribed widely in many countries and is the subject of current controversy regarding potential benefits in preventing fractures;
- calcitonin, especially in the form of intranasal salmon calcitonin (SCT(N)), is of particular interest in Mediterranean countries, where its use has increased substantially and the associated costs and effectiveness continue to be debated.

For the purposes of this analysis, it is assumed that the effectiveness of different types of HRT treatment is the same. This paper does not assess other approaches to identify individuals at high risk for fracture nor any alternative interventions such as exercise, hip protectors pads and vitamin D and bisphosphonates. These topics will require separate review. The impact of BDM and associated treatments is considered only in terms of their effects on the risk of fractures in women. Effects of HRT on other clinical conditions such as cardiovascular disease and breast cancer are not addressed, nor are resource implications discussed. Such important factors require consideration when addressing the clinical application of these technologies or formulating local policies on their use.

Definitions and endpoints

The diagnosis of osteoporosis is histologic.\(^7\) In practice, osteoporosis is commonly defined as a condition characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.\(^8\) More recently, it has been suggested in a report by a World Health Organization expert group that osteoporosis in an individual be defined solely on the basis of the level of bone density (as < 2.5 standard deviations (SD) below the young adult mean).\(^9\) The choice of this definition has profound effects on the proportion of women
in the population who are considered to be osteoporotic and thus potentially eligible for intervention.

Primary prevention with HRT or calcitonin is defined for the purposes of this paper as intervention in women with natural or surgical menopause with normal skeletal status and without a history of fracture. Secondary prevention is defined as intervention in women with natural or surgical menopause with one or more non-traumatic fractures or whose bone density is more than one or two standard deviations from young adult values or from age-matched controls, depending on the study.

Efficacy refers to the performance of a health technology under ideal clinical conditions of use in a defined population and effectiveness to its performance under average or routine conditions of use.

The main outcome measures used in this paper are bone density and fractures. Evaluations is in terms of the relative risk of fracture for a 1 SD decrease in bone mineral density below the age adjusted mean; the percentage of fractures potentially prevented by BDM screening linked to treatments; and the number of individuals who would need to be invited for screening in order to prevent one hip fracture.

Treatment effects of HRT and SCT(N) for preserving bone density are expressed as the number of SD units by which the average annual decline in bone mass in the control group exceeds that in the treatment group and as relative risks or odds ratios for fractures. An a level of 0.05 was used as the cut-off for statistical significance. The effects of SCT(N) for preserving bone density are expressed as the difference in the percent change between the treatment and control groups.

Methods

This paper is based primarily on systematic reviews of evidence undertaken by health technology assessment agencies and other systematic reviews that were relevant. These sources were updated by adding primary studies identified through additional literature searches.

For studies on bone densitometry, Medline, SweMed and EMBASE from September 1994 to May 1996 were searched. The main subject headings used in the searches were: 'bone and bones', 'bone density', 'densitometry', 'osteoporosis' and the names of the BDM technologies. Reference lists of review articles were also checked. Trials of screening programmes, prospective cohort studies examining the predictive value of BDM, case control studies of hip fractures (to September 1994) and studies evaluating or comparing methods of BDM in human subjects in English, French, German or Swedish were included for further review.

For studies on HRT, Medline was searched from 1993 to May 1996 using the main keywords 'osteoporosis', 'postmenopausal', 'postmenopause', 'bone and bones', 'bone density', 'fractures', 'estrogen replacement therapy'. In the case of calcitonin, both Medline and EMBASE were searched between 1990 up to 1994, and Medline only to May 1996 using the same keywords as for HRT, but with calcitonin as the therapy. Publications reporting randomised controlled trials, cohort studies and case control studies on SCT(N) in English, French, Italian and Spanish were selected for detailed review. Additional studies were obtained by checking reference lists from book chapters and review articles. Only original studies in human subjects were selected.

The conclusions in this paper are based on a classification system that considers the type of study design and conditions of scientific rigour, similar to that used by the Canadian Task Force on the Periodic Health Exam, the U.S. Preventive Services Task Force, and by Sackett (Table 1).

The search for relevant research was supplemented by two surveys of organisations that had produced reports addressing the issues of BDM and HRT. One survey included 24 organisations that had published reports on bone density measurement; the other included six health technology assessment agencies that had produced reports on the issue of HRT in primary and secondary prevention of osteoporosis. Both surveys asked questions about the process followed in preparing the report, its main purpose, and the conclusions made about the clinical applications of BDM and HRT.
Further details about the methodology are available in the background documents.

Results

1 Methods for Bone Density Measurement

1.1 Various methods are currently used for measuring bone density, but x-ray based methods (dual x-ray absorptiometry (DXA) in particular) dominate the market. Ultrasound methods are gaining in popularity, but their analytical performance still requires validation.

1.2 The precision and accuracy of BDM technologies are measures of their performance as analytical methods. These measures are generally poorly defined in the routine clinical situation for all available methods.

Table 2 describes the performance characteristics of BDM methods in common use. Good precision means low random errors, so that there is small variation between results of measurements on the same sample. Good accuracy means that the systematic error is low, so that the average of a series of measurements on the same sample is close to the true value. Both precision and accuracy can be expressed as coefficients of variation (CV), and the total error associated with a BDM will be the sum of these errors. Variations in patient positioning, operator performance and machine characteristics will contribute to these errors.

Most available data are from measurements taken in a single centre over a short period by expert operators. Consequently, they tend to reflect the efficacy of the individual methods, and are likely to underestimate the error which will occur in routine clinical practice. Standards to define the levels of analytical performance required for different applications of BDM are essential.

1.3 The performance characteristics of BDM methods impose constraints on specific applications of these techniques.

Even with a precision error as low as 1% SD, serial measurements using BDM would require a minimum follow up interval of 1 to 1.5 years to detect a bone loss of 2-3% (the average loss per year for a normal woman at menopause) or nearly 5 years with a precision error of 5% SD. The interval needed would be much greater if BDM were used to monitor therapy or in other situations where the rate of bone loss is likely to be lower.

The usefulness of a single BDM, from a screening test for example, is affected by both accuracy and precision of the method. Given the performance levels of currently available methods, many individuals will be wrongly classified with regard to their risk of fracture, either as false positives or false negatives. This problem is compounded by systematic differences in ‘normal’ values in population (e.g. ethnic groups) from those used to set reference values for BDM equipment.

1.4 If bone density measurements are to be undertaken, it is essential that scrupulous quality control is followed.

Calibration and standardisation of bone densitometers is a complex undertaking that requires close attention since there is little agreement among manufacturers. Even with instruments calibrated according to manufacturer’s instructions, values obtained from imaging of spine phantoms by DPA or DXA have differed by as much as 16% because of differences as great as 8% in estimated values for both bone mass and bone area. Instrument performance also may vary over time.

Good quality control is essential and should include daily standardisation and calibration procedures, regular maintenance, careful attention to patient positioning and possible accreditation of units. There are currently no industry-wide, nor clinical standards for BDM technologies, although in Europe a spine phantom is now being used to calibrate equipment in various drug trials.
2.0  The use of bone density measurement to predict fractures in individuals

2.1 There are no randomised controlled trials which have evaluated the efficacy of using BDM to screen menopausal women and prevent fractures.

Ideally, there should be data available from controlled trials where menopausal women are randomised to a screening programme or no screening programme and subsequently followed for 20-30 years (at the age when most fractures occur) to determine the effect on the number of individuals in whom fractures are prevented. No data from studies with designs corresponding to Levels I-V (Table 1) are currently available, though a BDM screening programme is being piloted in the United Kingdom. 37

2.2 There is FAIR evidence that BDM can predict the risk of fracture in menopausal women. However, because of the considerable overlap between the distribution of bone mineral density for individuals who have and do not have fractures, BDM cannot reliably distinguish those who will have a fracture from those who will not.

BDM techniques are able to estimate, with various degrees of error, low bone mineral density which is a risk factor for future fracture. However, the main outcome measure of interest is fracture. A recent meta analysis of prospective cohort studies (Level VI), shows that there is an inverse association between bone density and the risk of future fractures.10 38 Eleven study populations, constituting about 90,000 person years of follow up time, were identified. The relative risk for all types of fractures at all sites of a decrease in bone density of 1 SD below the age adjusted mean was 1.5 (95% CI 1.4 to 1.6).

Some sites had a better predictive ability - measurement at the spine for predicting vertebral fractures (RR=2.3, 95% CI 1.9 to 2.8) and measurement at the hip for predicting hip fractures (RR=2.6, 95% CI 2.0 to 3.5). Using the relative risk value of 2.6 for hip fracture, derived from a meta-analysis 38, and assuming a Gaussian distribution of bone density values, the test characteristics can be determined for a theoretical cohort of women at the age of 50 years with a 15% lifetime risk of fracture 39. A cut-off value of 1 SD yields a sensitivity of 38%, a specificity of 88% and a positive predictive value of 36%.

However, most of these studies have a relatively short follow up time (weighted average 5.8 years), and the extent to which the results can be extrapolated to the prediction of fractures in individuals which will occur in 20 to 30 years in the future is not known. The ability of BDM to predict fracture risk will not be the same for all age groups because of the increased importance of other skeletal and extraskeletal risk factors with increasing age. 40 41

Two additional studies in menopausal women, published since this meta analysis, come to similar conclusions. For any fracture, RR=1.50; 95% CI 1.27 - 1.76 42; and OR =1.6; 95% CI, 1.16 - 2.34 43 for 1 SD reduction in bone mineral density at the spine; and, RR=1.41; 95% CI, 1.21 - 1.64 for 1 SD decrease in bone mineral density at the femoral neck. 42 However, these studies also had short follow up periods.

There are no threshold values of bone density below which fractures will necessarily occur, the relationship between risk and bone density being continuous. On the basis of data from case control studies (Level VII) of hip fracture, BDM does not accurately distinguish between patients with recent (non-traumatic) fractures and those without fractures.

A recent review of case control studies of hip fracture, using the same approach as that of Law et al. 44, determined the weighted average difference in bone mineral density between cases and controls to be 0.9 SD. 10 Error! Bookmark not defined. Using these figures, a 1 SD cut-off below the mean bone mineral density for those without a fracture would result in a 46% detection rate with a 16% false positive rate.

2.3 Low bone density is only one of a number of risk factors for fracture in menopausal women, some of which have similar estimates for risk association with fractures.

Scientific evidence of similar strength (Level VI) exists regarding many other risk factors in menopausal women that have similar independent predictive ability for fracture to that of bone mineral density.
For example, data from the Study of Osteoporotic Fractures \(^45\) identify a history of maternal hip fracture (RR=2.0; 95% CI, 1.4 - 2.9), previous fractures of any type after the age of 50 (RR=1.5; 95% CI, 1.1 - 2.0), self-rated health as fair to poor (RR=1.7; 95% CI, 1.3 - 2.2), and previous hyperthyroidism (RR=1.8; 95% CI, 1.2 - 2.6) as independent risk factors for hip fracture.

Other characteristics that are observable in a physical examination that were identified as risk factors included the inability to rise from a chair without using one’s arms (RR=2.1; 95% CI, 1.3 - 3.2), a faster resting pulse rate (RR=1.8; 95% CI, 1.3 - 2.5), and poorer depth perception (RR=1.5; 95% CI, 1.1 -2.0). The presence of five or more of the risk factors dramatically increased the incidence of fractures by about 18 times that for women with two or fewer risk factors.

In a study which involved over 25,000 younger women, body height (age-adjusted RR=3.2; 95% CI, 1.46 - 8.97) and history of diabetes mellitus (age-adjusted RR=5.81; 95% CI, 2.15 - 15.71) were also identified as risk factors for hip fracture. \(^46\)

In comparison with BDM, many of these other risk factors are easily and cheaply measured. A question here is the extent of any added value offered by BDM.

2.4 There appears to be no consensus about the appropriate applications of BDM between organisations that had published a report on this topic.

A survey (Level VIII) of reports on the applications of BDM technologies suggests that there is wide variation in the views taken on the appropriate use of BDM for clinical and screening purposes. Studies based on more systematic review methods tended to be more conservative in their conclusions about the potential uses of BDM.

3.0 Effect of HRT in preventing fractures and preserving bone mass

3.1 There is FAIR evidence that ever-use of HRT is associated with a decrease in fractures of all types.

Data from only one small RCT (Level III) are available, which show a reduction in new vertebral fractures with HRT used for secondary prevention. There were 8 new fractures in 7 women in the estrogen group compared to 20 fractures in 12 women in the placebo group, yielding a lower rate of vertebral fracture (61%) in the estrogen group (RR=0.39; 95% CI, 0.16 -0.95)). \(^47\)

However, the number of individuals who experienced a new vertebral fracture was reduced by a smaller amount (37%) and was not statistically significant. Data measuring treatment effects in terms of fractures must be interpreted cautiously - some studies use the number of fractures instead of the number of individuals with fractures as the endpoint which will overestimate the effectiveness of treatments. \(^48\) In the clinical context, the important result is whether or not an individual will have a fracture at all.

For all other types of fracture, data are available only from cohort and case control studies (Levels VI and VII). Pooled estimates from these observational studies show a tendency to a modest reduction in relative risk for hip fracture with any use of HRT. These estimates give RR=0.75; 95% CI, 0.68-0.84 for all observational studies; \(^49\) RR=0.85; 95% CI, 0.68-1.07 for cohort studies only (Level VI); and OR=0.57; 95% CI, 0.48-0.67 for case control studies only (Level VII) \(^18\). The results from the cohort studies are more reliable since they are less susceptible to bias than case control studies. The higher quality case control studies showed a trend to risk reduction similar to that for the cohort studies. \(^19\)

A similar protective effect was observed for forearm and wrist fractures (RR=0.70; 95% CI, 0.52-0.93 for cohort studies only and OR=0.60; 95% CI, 0.41-0.88 for case control studies only). \(^18\)

3.2 There is FAIR evidence that current long-term use of HRT has a protective effect for fractures.

A prospective cohort study \(^50\) (Level VI) analysed the risk of fracture for short-term (<10 years) and
long-term (>10 years) duration of use in women who were 65 at the time of entering the study and who were current and previous users of HRT. In current users, short-term duration of treatment was associated with a decrease of 30% (RR=0.67, 95% CI, 0.49-0.92) in the risk of all non-spinal fractures, whereas for long-term users this reduction was 40% (RR=0.60, 95% CI, 0.45-0.83). The decrease in risk of hip fractures in current users was 19% (RR=0.81, 95% CI, 0.40-1.65) and 73% (RR=0.27; 95% CI, 0.08-0.85) for short and long-term users respectively.

Woman over 75 years who were current users of estrogen therapy had a reduced risk of hip fracture (RR=0.18; 95% CI, 0.04-0.77). However, for women 75 years old or younger, who were also current users, there was no effect (RR=0.94; 95% CI, 0.51-1.69), both compared with women who had never used estrogens.

Pooling the results of four case control studies (Level VII) that examined the relationship between extended use of estrogen (>5 years) and never use, a trend to a 66% reduction in the relative risk of hip fracture (OR=0.34; 95% CI; 0.20-0.55) was found. When compared to a shorter term use (0-60 months) the estimated pooled relative risk reduction was 61% (OR=0.39; 95% CI, 0.25-0.62).

When the results from different cohort studies with a duration of use longer than 5 years were pooled, the risk reduction reported in wrist and forearm fracture was about 15% (estimated pooled RR=0.85; 95% CI, 0.73-0.99). This figure was not significantly different from that observed in never users.

A prospective cohort study found there was not a statistically significant difference in hip fracture risk between ever and never users of HRT regardless of the duration of therapy (less than 3 years, RR=1.19; 95% CI, 0.89-1.60; 4-14 years, RR=0.89; 95% CI, 0.63-1.23; >15 years, RR=0.88; 95% CI, 0.63-1.23).

3.3 There is FAIR evidence that there is no decrease in risk for hip fracture at older ages with ever use of HRT.

Three cohort studies and one case-control study reported a decrease in the potential protective effect for hip fracture with age and at older ages, when most hip fractures occur, there was no statistically significant difference in fracture risk between ever and never users of HRT (Table 3).

A prospective cohort study found not statistically significant decrease in risk of hip fracture for women over 65 years who were previous users of estrogens (RR = 1.03; 95% CI, 0.69-1.55). In comparison, the RR for all current users was 0.60 (95% CI, 0.36-1.02). For current users with a history of osteoporosis the RR was 0.86 (95% CI, 0.42-1.75), and for women with no history of the condition the RR was 0.45 (95% CI, 0.20-0.99).

3.4 There is FAIR evidence that the longer the period since cessation of therapy, the smaller the reduction in risk of fracture.

Pooling the results from two cohort studies not defined. (Level VI) gives an estimated protective effect on hip fracture between former and never users of RR=0.88 (95% CI, 0.67 - 1.15) when 2-14 years have elapsed since last estrogen use. When more than 15 years have lapsed, there is no evidence of any benefit (RR=1.07 (95% CI, 0.85-1.34)).

3.5 There is GOOD evidence that HRT, used alone or in combination with progestogens and/or calcium, for primary and secondary prevention, has a protective effect against bone mass loss, as measured by various BMD techniques at the forearm, spine and hip.

A meta analysis of RCTs (Level I) showed a trend towards a positive effect of HRT on bone mass both in primary and secondary prevention (Table 4). Effect sizes in the forearm and spine in studies of secondary prevention were larger than in studies of primary prevention and had wider confidence intervals.
3.6 The effect of HRT in reducing bone loss has mainly been studied in women shortly after menopause. However, there is GOOD evidence that age does not attenuate the short term response to treatment.

When the results of 43 RCTs examining skeletal response in women of various ages are examined, the protective effect of HRT appears to be the same for women who are under 60 years and those who are over 60 years old. Although results from different studies show that this effect may be greater in the lumbar spine than in the forearm or hip, the pooled effect size from these studies showed a tendency to be marginally greater for forearm than for the spine.

3.7 There is FAIR evidence that the protective effect of HRT on loss of bone mass may decline over time when therapy is started soon after the menopause, and that the protective effect wears off after cessation of treatment.

In a nested case control study, a statistically significant difference of 11.2% in bone mass averaged over all sites was found in women under 75 years with greater than 7 years of HRT therapy compared to those who had not received therapy. In women over 75 years with greater than 7 years of therapy compared to those with no therapy, a difference in bone mass of only 3.2% was found, which was only statistically significant at the radius shaft (8.5%, p<0.02).

Other studies indicate that the protective effect of HRT on bone loss is only maintained when currently used. The protective effect appears to disappear progressively after cessation of therapy, reaching a rate of bone loss equal to that in untreated or placebo treated women (2-3% per year) within a few years after withdrawal of treatment. This point is critically important since therapy with HRT is generally prescribed around or soon after the menopause and generally not for more than ten years, consequently leaving a period of 15-20 years between the cessation of treatment and the time when most fractures occur (> 75 years of age).

3.8 Long term compliance with HRT is likely to be less than 50% for menopausal women.

Data from different surveys suggest that long term compliance with HRT is low (approximately 30%). This is mainly because of the presence of various side effects (e.g. breast tenderness, bleeding, depression), fear of cancer, dislike of taking tablets and failure to continue treatment when climacteric symptoms disappear. Recent survey data of women in the United Kingdom who had a BMD in a population screening programme 1 year before, are somewhat more optimistic, suggesting short-term compliance rates of 48% for postmenopausal women and 59% for women with a simple hysterectomy. This is an important factor to take into account when considering the likely effectiveness of HRT, given the findings of reduced effect of HRT after cessation of therapy.

4.0 Effect of intranasal salmon calcitonin in preventing fractures and preserving bone mass

4.1 There is FAIR evidence to support the efficacy of intranasal salmon calcitonin in decreasing the risk of fractures.

Three RCTs (Levels II and III) on secondary prevention analysed the efficacy of SCT in decreasing the risk of fractures. Two of these concerned the effect of SCT (N) on vertebral fractures in women late after menopause with osteoporosis. One showed a decrease in the risk of patients with first vertebral fractures (RR=0.23;95% CI, 0.07-0.77) as well as in the rate of new fractures (RR=0.37; 95% CI, 0.14-0.95) in current users compared with non-users. The other RCT showed no statistically significant differences after three years of treatment.

Two case control studies (Level VII) and one meta analysis of RCTs (Level I) analysing the effect of all types of calcitonins on fracture rates were identified. Both case-control studies show evidence of reduced hip fracture risk comparing ever and never users of calcitonin.

Data from the Mediterranean Osteoporosis Study suggest a protective effect of about 30% (RR=0.71;
95% CI, 0.52-0.90, adjusted for previous estrogen intake). The other study found a 53% decrease in the risk of hip fracture (RR=0.47; 95% CI; 0.30-0.74) with previous use of calcitonin plus calcium. The meta analysis identified only two prospective trials and concluded that the protective effect of calcitonin still remains to be established.

4.2 There is GOOD evidence demonstrating the short term efficacy of intranasal salmon calcitonin (SCT(N)) in preserving bone mass in both primary and secondary prevention in postmenopausal women.

Several RCTs have shown that SCT(N) decreases bone loss and/or preserves bone mass in postmenopausal women. This is the case in both primary and secondary prevention, after both natural and surgical menopause. Only three of the RCT studies in primary prevention and four in secondary prevention in natural postmenopausal women were of good quality design. For primary prevention, one study showed an increase of 2.6% in vertebral bone mass (p<0.01 vs. baseline levels). Another study showed an increase of 2.9% at the forearm (first 6 months, 1.5%, p<0.005; last 6 months, 1.5%, p<0.002). One of the studies showed an increase in vertebral bone mass that was not statistically significant. For secondary prevention, statistically significant increases in bone mass were observed at vertebrae ranging from 3% to 8.6% depending on the dosage.

4.3 There is FAIR evidence demonstrating the long term preservation (5 year) of bone mass using SCT (N), but no data are available about the long term effect when treatment is started early after menopause.

One RCT (Level III) in primary prevention with a duration of 5 years shows a statistically significant increase in vertebral bone mass after 42 months of treatment compared with those women not treated (2.5%, p<0.001), but not at the end of the five years.

4.4 There are no prospective studies comparing the efficacy or the effectiveness of HRT and intranasal calcitonin.

Discussion

This paper has reviewed the current scientific evidence available regarding the ability of BDM to predict fractures, and the efficacy and effectiveness of some common associated treatments for low bone density. In summary, using the classification system for evidence outlined in Table 1, there is:

FAIR evidence from prospective cohort studies suggesting that BDM can assess the risk of future fracture occurrence in populations over the short term, but not with a high degree of accuracy;

FAIR evidence, from low quality RCTs and observational studies, showing the efficacy of HRT and SCT(N) in preventing fractures while therapy is continued;

GOOD evidence to support the efficacy of HRT and SCT (N) in preserving bone mass during therapy;

FAIR evidence that the protective effect of HRT diminishes and may eventually wear off after cessation of therapy.

Common limitations of the studies that have been undertaken are that sample sizes were often small and the follow up periods too short. These studies are subject to various errors and biases. Cohort studies are particularly subject to the effects of confounding and case-control studies to recall and observer bias, (and, when bone mass is measured after the fracture, to problems of interpreting the direction of causality). Because many of these summaries of the evidence are based only on observational studies, the degree to which they reflect a causal relationship is not certain. More research is needed to corroborate the results of these studies, given the methodological limitations.
Due to the relatively short follow up of these cohort studies, the accuracy with which BDM predicts fractures which occur many years after measurement is not known. Similarly, the long term positive and negative effects of HRT and SCT(N) are not accurately known. The follow-up period in most trials of these interventions is shorter than that recommended by the U.S. Food and Drug Administration or the European Foundation for Osteoporosis and Bone Diseases (2-3 years). These points are critical when considering BDM screening of menopausal women linked to subsequent treatment with HRT or SCT(N), since these interventions have not been shown to be beneficial at the ages when most fractures occur (>75 years).

While BDM has been proposed for a number of applications, there is particular interest in its potential use for population screening programmes and in opportunistic screening for women around the menopause who, for example, seek advice from medical practitioners on whether to take HRT. How should the individual components of evidence summarised above be interpreted in a broader context, in terms of health policy and for routine clinical practice?

In general, screening programmes must use a reliable diagnostic test and be offered in conjunction with treatment that has demonstrated effectiveness. There must be “conclusive evidence that screening can alter the natural history of the disease in a significant proportion of those screened.” When interventions are offered to patients who are not ill or who have not specifically sought assistance, the onus is on those offering the intervention to be certain that the patient will benefit. Current evidence is insufficient to reach conclusions about the value of BDM screening or HRT or SCT(N) therapy.

However, it is possible to get some indication of the potential population impact of BDM screening in preventing hip fractures. Table 5 presents a number of scenarios, using realistic assumptions, for a BDM screening program linked to treatment with HRT in a hypothetical cohort of 20,000 menopausal women. For the scenario with 50% screening uptake, 30% long term compliance with treatment and 30% reduction in life time fracture risk from HRT, one hip fracture would be avoided for every nine women identified through screening as being at risk, and who comply with therapy for 30 years. This apparently promising estimate represents the optimum benefit achievable, and has to be put in the context of the overall screening process.

Of the 20,000 women invited for screening, 10,000 are likely to attend for BDM. Of these, 1,600 will be identified as having a bone density of less than one SD below the population mean (assuming a Gaussian distribution) and will be offered HRT. Of those offered HRT, 576 will have been correctly identified (true positives) and 173 (30%) of them will comply with therapy, so preventing 52 fractures. There will, however, also be 1,024 false positives, so that almost two thirds of women advised to take HRT would be unnecessarily using this treatment since they would not have had a fracture, under the assumptions of the model used here.

A further summary measure of some interest is the number of false negative cases. Under this scenario, of 10,000 women who present for screening, 948 who will go on to have a hip fracture will be advised that they are not at high risk. Nearly two thirds of those who will sustain a fracture and who have a BDM will, therefore have been falsely reassured.

When this broader perspective is considered, 393 women would need to be invited for screening and 197 actually attend in order to avoid one fracture. Thus, the overall impact of the program would be to reduce the number of fractures over the remaining lifetime of the cohort of 20,000 women from 3,050 to 2,998, a reduction of 1.7%.

When all the scenarios presented in Table 5 are considered, a BDM screening program aimed at menopausal women might prevent between 1 and 7% of fractures. Taken together, these estimates of the effectiveness of such a program are not particularly encouraging from a public health perspective and are unlikely to represent good value for money. Similar indications might be expected to follow from scenarios in which SCT(N) was the available treatment.
For those formulating policy and considering offering such interventions to their patients, there are other potential effects to be considered. Current data suggest that HRT is associated with a 40-50% reduction in the risk of coronary heart disease among postmenopausal women\textsuperscript{109} and an increased risk of 30-70% for breast cancer, independent of levels of bone mass.\textsuperscript{110 111 112} Evaluation of incremental cost per health gain, taking account of these factors, is needed to further inform health policy makers of the worth of screening programs.

A number of important social and ethical concerns must also be addressed. At what point does a decrease in bone density with age become a medical problem requiring treatment? What are the implications of using a definition of disease (a BDM <2.5SD below the young adult mean proposed by the WHO\textsuperscript{9}) where, consequently, over 30% of women between 70 and 79 years of age could be considered in need of therapy because of a low bone mineral density.\textsuperscript{10}

Alternative approaches to preventing and treating osteoporosis also require further consideration. Other risk factors, observable in a clinical exam, might be used to identify high risk groups without using BDM.\textsuperscript{45} BDM and appropriate treatment might be better targeted to older women at ages when most fractures occur. Attention could also be given to alternative strategies to prevent fractures. These could include potentially more cost-effective prophylactic interventions such as annual Vitamin D injections or the prevention of accidents in older people.\textsuperscript{6}

Ongoing studies, such as the RCT of population screening being undertaken in the United Kingdom\textsuperscript{37.} and studies of alternative approaches to preventing osteoporosis, may provide better information upon which such decisions can be made in the future. The currently available evidence does not support BMD screening of menopausal women in combination with HRT or SCT(N) in the context of population or opportunistic screening for the prevention of fractures, and estimates based on what data are available are not encouraging about its potential effectiveness.
<table>
<thead>
<tr>
<th>Level</th>
<th>Strength of evidence</th>
<th>Type of study design</th>
<th>Conditions of scientific rigour*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest (I)</td>
<td>Good</td>
<td>Meta-analysis of randomised controlled trials</td>
<td>Analysis of patient individual data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Meta-regression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Different techniques of analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absence of heterogeneity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of the studies</td>
</tr>
<tr>
<td>Lowest (IX)</td>
<td></td>
<td>Large sample randomised controlled trials</td>
<td>Assessment of statistical power</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multicentre</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of the study</td>
</tr>
<tr>
<td>II</td>
<td>Good</td>
<td>Small sample randomised controlled trials</td>
<td>Assessment of statistical power</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of the study</td>
</tr>
<tr>
<td></td>
<td>to</td>
<td>Non-randomised controlled prospective trials</td>
<td>Concurrent controls</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td></td>
<td>Multicentre</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of the study</td>
</tr>
<tr>
<td>III</td>
<td>Good</td>
<td>Non-randomised controlled retrospective trials</td>
<td>Historical controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of the study</td>
</tr>
<tr>
<td>IV</td>
<td>Fair</td>
<td>Cohort studies</td>
<td>Concurrent controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multicentre</td>
</tr>
<tr>
<td></td>
<td>to</td>
<td>Case-control studies</td>
<td>Quality of the study</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td></td>
<td>Multicentre studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of the study</td>
</tr>
<tr>
<td>V</td>
<td></td>
<td>Non-controlled clinical series</td>
<td>Multicentre</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Descriptive studies: surveillance of disease, surveys,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>registers, data bases, prevalence studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expert committees, consensus conferences</td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td></td>
<td>Anecdotes or case reports</td>
<td></td>
</tr>
</tbody>
</table>

* Quality of the study assessed by specific protocols and conditions of scientific rigour.
Source: Adapted from reference 20.
### Table 2: Characteristics of common methods for measuring bone density

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy CV (%)</th>
<th>Precision CV (%)</th>
<th>Time of scan (minutes)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPA Single Photon Absorptiometry</td>
<td>2 - 8</td>
<td>2 - 5</td>
<td>5 - 15</td>
<td>Simple, relatively inexpensive, small radiation exposure. Decay of source affects performance</td>
</tr>
<tr>
<td>DPA Dual Photon Absorptiometry</td>
<td>3-10</td>
<td>2 - 6</td>
<td>20 - 45</td>
<td>Usually used for spine and hip measurements. Decay of source affects performance</td>
</tr>
<tr>
<td>SXA Single X-ray Absorptiometry</td>
<td>5</td>
<td>1</td>
<td>10 - 20</td>
<td>X-ray equivalent of SPA</td>
</tr>
<tr>
<td>DXA Dual X-ray Absorptiometry</td>
<td>3-6</td>
<td>1 - 3</td>
<td>3 - 10</td>
<td>Single X-ray source with two energies. Higher photon flux than radionuclide sources, improved detector configuration.</td>
</tr>
<tr>
<td>QCT Quantitative Computed Tomography</td>
<td>5 - 15</td>
<td>2 - 5</td>
<td>10 - 15</td>
<td>Able to measure bone structure. Need to measure calibration standards simultaneously with the patient.</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>20</td>
<td>2-4</td>
<td>5</td>
<td>Potential to measure bone structure</td>
</tr>
</tbody>
</table>

CV = Coefficient of variation

Source: References 9, 10, 12, 13, 16, 28, 31
### Table 3: Relative risk of hip fracture according to age

<table>
<thead>
<tr>
<th>Study</th>
<th>Age group</th>
<th>Relative risk (95% CI)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger</td>
<td>Older</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Pagnini-Hill, 1991</td>
<td>avg age=73</td>
<td>1.02</td>
<td>(0.81-1.27)</td>
<td></td>
</tr>
<tr>
<td>Naessén, 1990</td>
<td>&lt; 60 (trochanter)</td>
<td>&gt; 60 (trochanter)</td>
<td>0.37</td>
<td>(0.13-0.79)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 (cervical hip)</td>
<td>&gt; 60 (cervical hip)</td>
<td>0.58</td>
<td>(0.41-0.80)</td>
</tr>
<tr>
<td>Kiel, 1987</td>
<td>65-74</td>
<td>&gt; 75</td>
<td>0.37</td>
<td>(0.05-2.46)</td>
</tr>
<tr>
<td>Kanis, 1992</td>
<td>&lt; 80</td>
<td>&gt; 80</td>
<td>0.51</td>
<td>(0.31-0.84)</td>
</tr>
<tr>
<td>Cauley, 1995</td>
<td>≤75</td>
<td>&gt; 75</td>
<td>0.94</td>
<td>(0.52-1.69)</td>
</tr>
<tr>
<td>Cauley, 1995</td>
<td>&gt;65, current users</td>
<td>0.60</td>
<td>(0.36 - 1.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;65, previous users</td>
<td>1.03</td>
<td>(0.69 - 1.55)</td>
<td></td>
</tr>
</tbody>
</table>

*a* = age - adjusted RR  
*b* = recent estrogen use (< 2 years)  
*c* = adjusted by age, previous fractures, body mass index  
*d* = current users, multivariate-adjusted relative risk  
*e* = multivariate - adjusted, includes adjustment for history of osteoporosis (yes or no)
# Table 4: Results of a meta-analysis of the effect of HRT on bone mass

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Forearm (SD, 95% CI)*</th>
<th>Spine (SD, 95% CI)*</th>
<th>Hip (SD, 95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral unopposed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>1.45 (1.12-1.78)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>0.95 (0.21-1.70)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oral unopposed + Calcium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>0.92 (0.33-1.51)</td>
<td>0.77 (0.33-1.51)*</td>
<td>-</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>-</td>
<td>2.27 (1.17-3.37)</td>
<td>-</td>
</tr>
<tr>
<td>Oral opposed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>1.33 (0.74-1.92)*</td>
<td>1.23 (0.75-1.72)*</td>
<td>-</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>-</td>
<td>1.18 (0.65-1.70)*</td>
<td>-</td>
</tr>
<tr>
<td>Oral opposed + Calcium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>1.52 (1.16-1.84)</td>
<td>0.94 (0.18-1.69)*</td>
<td>-</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>1.46 (0.95-1.97)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2.94 (-0.92-6.80)*</td>
<td>3.16 (1.83-4.49)*</td>
<td>-</td>
</tr>
<tr>
<td>Transdermal opposed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>1.10 (-0.09 to 2.29)*</td>
<td>1.02 (0.67-1.36)</td>
<td>-</td>
</tr>
<tr>
<td>Transdermal opposed + Calcium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>1.70 (1.09-2.31)</td>
<td>1.37 (0.45-2.30)</td>
<td>-</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>0.97 (0.46-1.48)</td>
<td>0.73 (0.24-1.21)</td>
<td>-</td>
</tr>
<tr>
<td>Overall Primary Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8 studies)</td>
<td>1.38 (0.93-1.84)*</td>
<td>1.17 (0.63-1.70)*</td>
<td>-</td>
</tr>
<tr>
<td>Overall Secondary Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2 studies)</td>
<td>2.90 (-0.99-6.79)*</td>
<td>2.23 (-0.81-5.28)*</td>
<td>-</td>
</tr>
<tr>
<td>Overall Secondary Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4 studies)</td>
<td>-</td>
<td>2.12 (0.89-3.34)*</td>
<td>0.92 (0.34-1.50)*</td>
</tr>
</tbody>
</table>

* SD = treatment effect size in terms of standard deviation units by which the average annual decline in bone mass in the control group exceeds that in the treatment group.

a Heterogeneity: p = 0.05;  b Heterogeneity: p< 0.05

c Standard dose (conjugated estrogens = 0.60-0.625 mg; estrone = 1.25 mg; estradiol = 2.0 mg)
d Low dose (conjugated estrogen = 0.30 mg; estrone = 0.625 mg; estradiol = 1.0 mg)

Source: References 18, 19.
### Table 5: Potential impact of BDM screening and treatment with HRT in preventing hip fractures in a population of 20,000 menopausal women (under realistic assumptions)\(^{a,b,c,d}\)

<table>
<thead>
<tr>
<th>Fracture risk reduction from HRT *</th>
<th>Compliance = 30%</th>
<th>Compliance = 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N hip fractures avoided</td>
<td>N hip fractures avoided</td>
</tr>
<tr>
<td></td>
<td>% hip fractures avoided</td>
<td>% hip fractures avoided</td>
</tr>
<tr>
<td></td>
<td>N needed to invite to screen per hip fracture avoided</td>
<td>N needed to invite to screen per hip fracture avoided</td>
</tr>
</tbody>
</table>

Screening uptake 50%: N false negatives = 948, N false positives = 1,024, N offered HRT = 1,600

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>27</td>
<td>44</td>
</tr>
<tr>
<td>(RR=0.85)</td>
<td>0.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>803</td>
<td>474</td>
</tr>
<tr>
<td>30%</td>
<td>53</td>
<td>87</td>
</tr>
<tr>
<td>(RR=0.70)</td>
<td>1.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td></td>
<td>393</td>
<td>234</td>
</tr>
<tr>
<td>50%</td>
<td>87</td>
<td>145</td>
</tr>
<tr>
<td>(RR=0.50)</td>
<td>2.9%</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>234</td>
<td>140</td>
</tr>
</tbody>
</table>

Screening uptake = 70%: N false negatives = 1,327, N false positives = 1,434, N offered HRT = 2,240

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>(RR=0.85)</td>
<td>1.2%</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>560</td>
<td>334</td>
</tr>
<tr>
<td>30%</td>
<td>74</td>
<td>122</td>
</tr>
<tr>
<td>(RR=0.70)</td>
<td>2.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>278</td>
<td>166</td>
</tr>
<tr>
<td>50%</td>
<td>122</td>
<td>203</td>
</tr>
<tr>
<td>(RR=0.50)</td>
<td>4.0%</td>
<td>6.7%</td>
</tr>
<tr>
<td></td>
<td>166</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 5 – Notes

These scenarios were calculated using the following assumptions:

A cohort of 20,000 menopausal women are invited to a BDM screening programme and those identified with a bone density < 1 SD below the healthy adult mean are treated with HRT.

Bone density values follow a Gaussian distribution in the population

The lifetime risk of hip fracture is 15.25% for women over 50 years

a Hip fracture RR=2.6 for 1 SD decrease in BMD below age adjusted mean

b For those who comply, compliance continues for their remaining lifetimes (about 30 years)

c There is no decrease in the protective effect of HRT over time

d No side effects are taken into account

e The reduced beneficial effect on those who would be treated because some women would already be taking HRT for other reasons is not taken into account.

f The range considered for fracture risk reduction is 15%-50%

The range considered for compliance is 30-50%

h The range for attendance to a screening programme is 50-70%
References

19. Henry D, Robertson J, O’Connell D, Gillespie W. *The skeletal effects of estrogen therapy in post-


81. Mazzuoli GF, Gennari C, Passeri M, Acca M, Camporeale A, Pioli G. Hip fracture in Italy:


100. Christiansen C. Use of nasally administered salmon calcitonin in preventing bone loss. *Calcif...


