Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

1.1 Definition of intervention

The intervention is opportunistic screening for low bone mineral density (BMD) for women aged 70 to 90 years who present to their GP for an unrelated purpose, and subsequent treatment of those who fall below the threshold for osteoporosis with raloxifene (a selective estrogen receptor modulator or SERM) 60 mg daily, and calcium 500 mg/day, for 5 years. In addition to preventing fractures, raloxifene also reduces the risk of breast cancer. Fig 1 shows the intervention pathway. Substantial uncertainty in various important parameters is examined in a sensitivity analysis. A similar exercise for alendronate has been reported on earlier. Residronate, the combination of calcium and vitamin D, and physical exercise will follow. All of these analyses will be replicated for men.

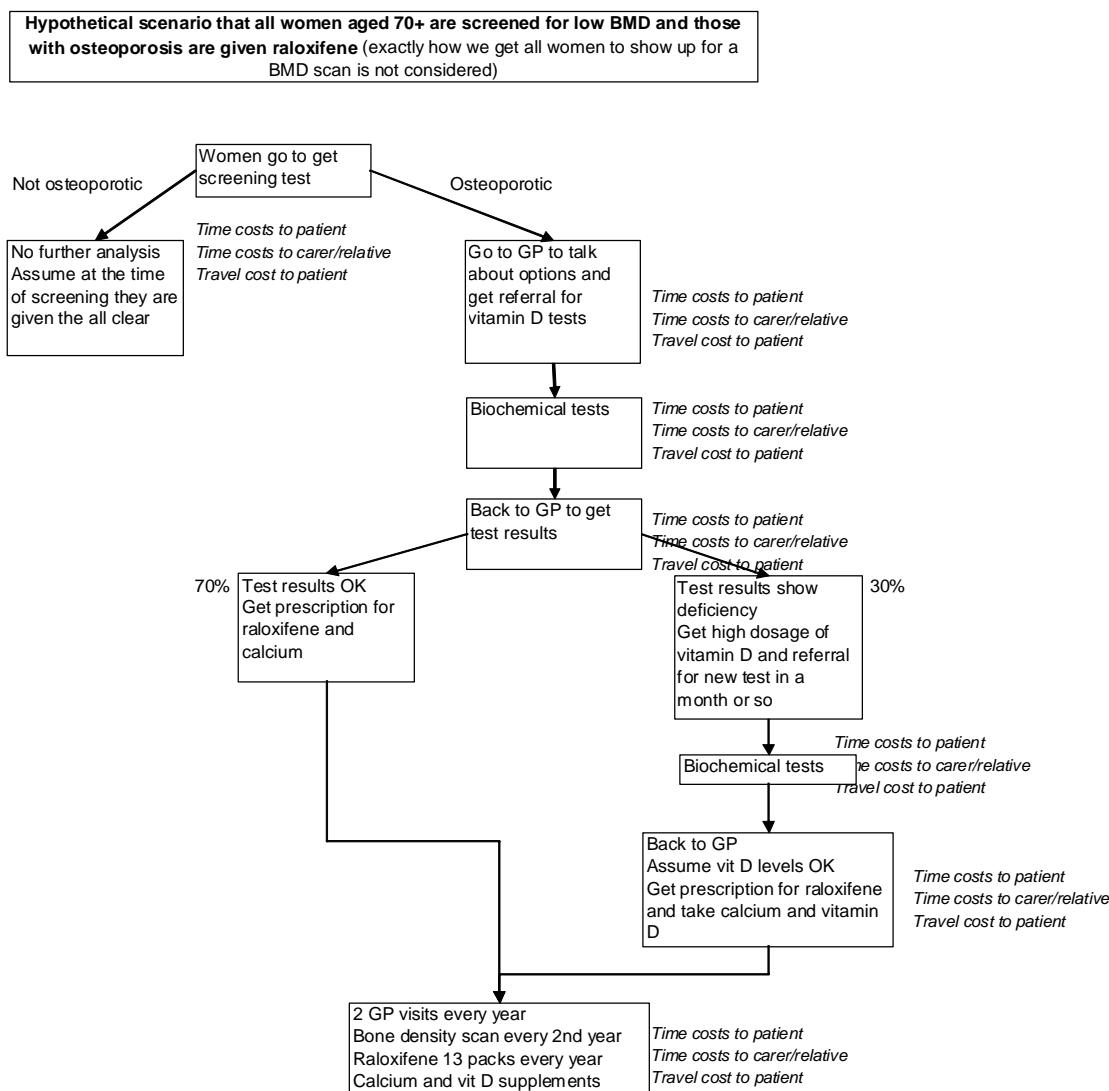## 1.2 Health states/risk factors affected by the intervention

Therapy aims to reduce fractures of the hip, spine (vertebrae), pelvis, clavicula/humerus (shoulder / upper arm), rib, wrist, hand, lower leg, foot. However, the effect of raloxifene has only been proven for vertebral fractures and this is the only fracture site included in this analysis. The model also includes a preventive effect on breast cancer but not the equally proven increase in thrombo-embolic events or any other effect on cardiovascular disease.

1.3 Current Practice

Recently about 15% of the women aged 70-90 years with osteoporosis received pharmaceutical treatment (Chiang, Jones et al. 2006). About 12% of these were prescribed raloxifene (PBS). Meta-analyses of trials with raloxifene are not yet available, so the effectiveness of the drug in preventing fractures for each fracture site is estimated based on a review.

ACE Prevention Briefing Paper no. X, July 2008

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

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Hypothetical scenario that all women aged 70+ are screened for low BMD and those with osteoporosis are given raloxifene (exactly how we get all women to show up for a BMD scan is not considered)

Women go to get screening test

Not osteoporotic

Osteoporotic

No further analysis
Assume at the time of screening they are given the all clear

Time costs to patient
Time costs to carer/relative
Travel cost to patient

Go to GP to talk about options and get referral for vitamin D tests

Time costs to patient
Time costs to carer/relative
Travel cost to patient

Biochemical tests

Time costs to patient
Time costs to carer/relative
Travel cost to patient

Back to GP to get test results

Time costs to patient
Time costs to carer/relative
Travel cost to patient

70% Test results OK
Get prescription for raloxifene and calcium

Test results show deficiency
Get high dosage of vitamin D and referral for new test in a month or so 30%

Biochemical tests

Time costs to patient
Time costs to carer/relative
Travel cost to patient

Back to GP
Assume vit D levels OK
Get prescription for raloxifene and take calcium and vitamin D

Time costs to patient
Time costs to carer/relative
Travel cost to patient

2 GP visits every year
Bone density scan every 2nd year
Raloxifene 13 packs every year
Calcium and vit D supplements

Time costs to patient
Time costs to carer/relative
Travel cost to patient

In vitamin D deficiency, supplementation with 3000–5000 IU ergocalciferol per day (Ostelin [Boots]; 3–5 capsules per day) for 6–12 weeks is recommended (MJA, 182(6)p.281)
The commonest form is 1000 IU of ergocalciferol (Ostelin; Boots Healthcare Australia). Loading doses of 3000–5000 IU per day are required to treat severe vitamin D deficiency Ebeling, P. R. (2005). Med J Aust 183(1): 4-5.
Assume 30% vitamin D deficient (Pasco, J. A., M. J. Henry, et al. (2001).Med J Aust 175(8): 401-5)
500mg Calcium supplements per day (value that most trials use)
Those who were initially deficient have large supplements initially then go onto 400IU daily thereafter (Nowson, C. A. and C. Margerison (2002). "Vitamin D intake and vitamin D status of Australians." Med J Aust 177(3): 149-52.)

Fig. 1. The intervention pathway.

1.4 Efficacy/Effectiveness of intervention/s

We used relative risks (RRs) from a recent review (Lee, Chao et al. 2008). Effectiveness has only been proven for vertebral fractures. The few available trials did not show an effect on hip or other non-vertebral fracture types. Raloxifene also more than halves the risk of breast cancer. We corrected the RRs for an average adherence in the trials of 92%, and

ACE Prevention Briefing Paper no. X, July 2008

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Researcher: Lennert Veerman

assumed 47% of those screened adhere to the drug (Sambrook 2006). Treatment is assumed to last for 5 years. There is no evidence on possible effects beyond the treatment period, so we cautiously assume no such effect exists. We arbitrarily assumed a random 33% of the target group participates in the screening programme. The participation rate has no influence on cost-effectiveness ratios but would affect estimates of total costs and health gains.

1.5 Modelling to health outcomes

The model mimics the 2003 Australian female population and compares extrapolations to future years (assuming no trends) with and without the screening programme.

Based on population distributions of BMD, relative risks for fracture by BMD and age, and treatment as described above, the model estimates a change in the incidence of fractures due the screening program and subsequent drug treatment. The health impact of different fractures is estimated in a multi-state life table. All effects and costs are linked to the number of incident cases, by age, except for hip fractures, ischemic heart disease and stroke which also have long-term disability. (In the base case scenario, none of these diseases play a role.) Results are obtained separately for 5-year age groups and then added up.

The population distribution of BMD by age is fitted to data from the Geelong and Dubbo studies (Jones, Nguyen et al. 1994; Henry, Pasco et al. 2000). The threshold for osteoporosis has been defined on the same data, using the WHO definition (a BMD that is lower than 2.5 standard deviations below the mean for 25-year old women). In combination with age- and BMD level-specific fracture relative risks (Johnell, Kanis et al. 2005), this allows calculation of the average fracture risk for women with osteoporosis. This risk is lowered for the proportion of women at each age that use raloxifene. Before estimating the number of fractures that are prevented, the effect of current treatment (as described above) is removed by the same procedure in reverse, which leads to a slightly higher fracture incidence ("partial null scenario").

Incidence and mortality of vertebral fractures and breast cancer were estimated in the Australian Burden of Disease 2003. A vertebral fracture was associated with a loss of health-related quality of life of 26.6% in the first 51 days post-fracture. The average total disability that results from a case of breast cancer is modelled based on the Australian Burden of Disease 2003. This total loss of health per incident case over the years is the

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

equivalent of about 2.5 DALYs at younger ages and declines to 1 DALY in old age. The loss of life years and associated DALY loss due to breast cancer mortality is modelled separately. Again using the Burden of Disease data, for every age we estimated the proportion of incident cases that die of the disease, and the average age at death. Life table analysis then provided the number of life years and consequent DALYs lost.

The present analysis does not include the increased risk of thrombo-embolic events (deep venous thrombosis, pulmonary embolism and retinal vein thrombosis) that is associated with the use of raloxifene (Lee, Chao et al. 2008). This primarily has practical reasons; these particular thrombo-embolic events are not included in the Australian Burden of Disease study and their inclusion would not have altered the conclusions of this study.

1.6 Costs of interventions and offsets

Costs of the intervention were as per ACE economic protocol. It includes costs for bone density measurement, GP visits, drugs, and the women's time and travel. Costs of health care were based on the Medicare Benefit Schedule. Cost offsets in the first year post-fracture were based on the Dubbo study (Randell, Sambrook et al. 1995). Cost offsets for breast cancer are based on an AIHW report (Australian Institute of Health and Welfare (AIHW) 2004) and incidence data.

1.7 Uncertainty analysis

Parameter	Values	Uncertainty distribution	Source
Risk by level of BMD	Variable by age and BMD-level; see appendix.	Normal	Data (Johnell, Kanis et al. 2005) provided by prof. Kanis.
Efficacy spine	0.42 (0.35-0.52)	Normal around log	Review (Lee, Chao et al. 2008) (corrected for adherence)
Efficacy hip and other non-vertebral fractures	1.00	None	Review (Lee, Chao et al. 2008)
Proportion hospitalised	Varies by fracture site	Beta	Dubbo study (Randell, Sambrook et al. 1995)

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

Cost-offsets	Varies by fracture site. (Vertebra $4,410)	Gamma	Dubbo study (Randell, Sambrook et al. 1995)
Vit. D supplementation	4 (3,5) Caps/wk	Uniform	(Anonymous 2005)
Weeks of Vit. D	9 (6,12)	Uniform	(Anonymous 2005)
Raloxifene	$790 per year ($732 Gov't; $58 Pt)	None (None)	PBS, Nov. 2003
BMD screening	$85.05	None	MBS Nov. 2003
Test for vit D deficiency	$55.90	None	MBS Nov. 2003
Total costs scan Yr 1 (incl. pt. time & travel)	$109 ($64 Gov't; $45 Pt)	NA	(Several of the above)
Total Yr 1 excluding scan	$1,126 ($875 Gov't; $251 Pt)	NA	(Several of the above)
Total annual cost Yr 2-5	$932 ($793 Gov't; $138 Pt)	NA	(Several of the above)

1.8 Results and Sensitivity Analysis

	Median	95% uncertainty interval
years of life saved	1,161	872 to 1,365
DALYs averted	1,504	1,131 to 1,766
cost intervention (million $)	272	271 to 274
Cost-offsets (million $)	7	6 to 9
net costs (million $)	265	262 to 267
ICER with cost-offsets	$176,000	150,000 to 236,000
ICER without cost-offsets	$181,000	154,000 to 241,000

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis
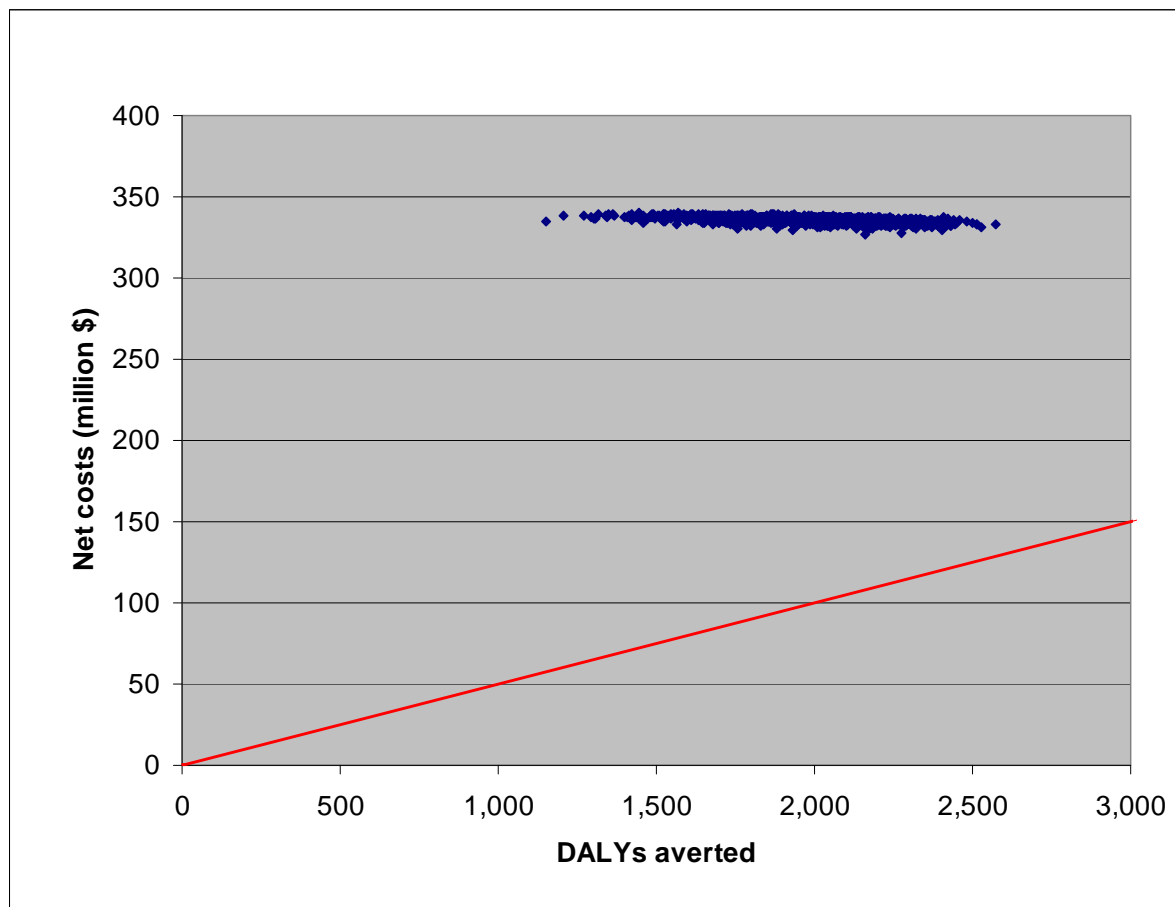
Researcher: Lennert Veerman

Fig. 2: Cost-effectiveness plane of base case scenario. The red diagonal line depicts the (arbitrary) $50,000 / DALY cut-off.

Figure 3 shows the probability that the intervention will turn out to be cost-effective for different levels of willingness to pay for one DALY. It also shows the effects of the most significant factors that introduce uncertainty in this analysis (fig. 3).

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis
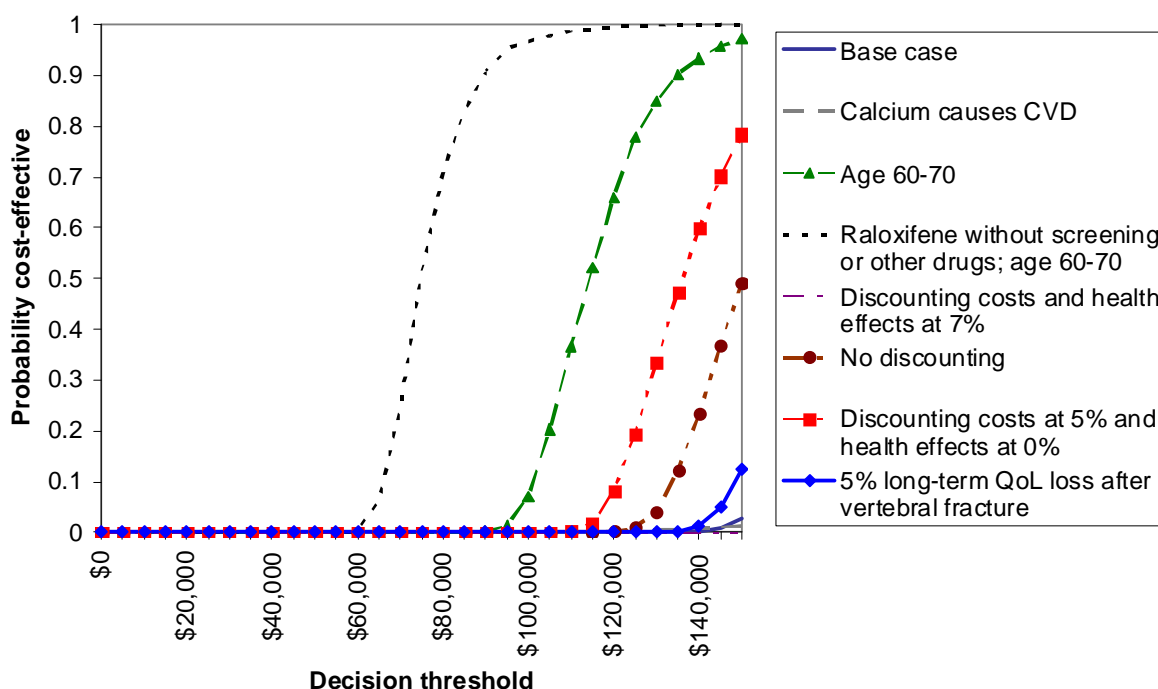
Researcher: Lennert Veerman

Fig. 3. Cost-effectiveness acceptability curve with results of the one-way sensitivity analysis.

The base case scenario is not cost-effective anywhere near the $50,000/DALY threshold (it just appears in the lower right corner of Figure 3). Adding the assumption that calcium which is provided with the raloxifene, increases the risk of coronary heart disease and stroke (Bolland, Barber et al. 2008) makes this even worse. Assuming a 5% loss of quality of life following vertebral fracture improves the cost-effectiveness only slightly. Targeting a younger age group (60 to 70 years old) makes the intervention more cost-effective because breast cancer is equally common at that age as at age 70 to 90 but the number of life years or DALYs gained per person is greater. Providing raloxifene to this age group without screening or calcium/vitamin D suppletion is the most favourable scenario with a median cost-effectiveness ratio of around $75,000/DALY. The improved cost-effectiveness results from avoiding of the costs of screening. Screening for low BMD is ineffective because it selects women at increased risk of vertebral fracture, but fractures have very limited effect on the health outcomes in this analysis. These outcomes are primarily determined by the risk of breast cancer. Varying the discounting rate does not alter the conclusions.

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

1.9 Discussion

Screening women aged 70 to 90 for low BMD and offering treatment with raloxifene is not cost-effective at the $50,000 per DALY level. None of the alternative scenarios in the sensitivity analysis are cost-effective at that level, either.

An important reason is that raloxifene does not prevent hip fractures, which are responsible for 80 to 90% of the loss of health and health care costs associated with osteoporotic fractures. Raloxifene does prevent breast cancer, and this has much more influence on health outcomes in our model than the prevention of fractures. However, this preventive effect on breast cancer is not strong enough to make the drug cost-effective at its current price level.

A limitation of this study is that it does not include proven effects on thrombo-embolic events. Their inclusion would have made the intervention even less cost-effective. Also, we do not assume quality of life loss to vertebral fractures after 1 year post-fracture and comparatively little during the first year. Including a 5% long-term loss of quality of life proved to have a negligible influence when tested. Thirdly, we study only the total population and do not distinguish by previous fractures, a family history of breast cancer or other individual indicators of risk other than bone mineral density. Targeting high-risk groups would improve cost-effectiveness, especially where it concerns the risk of breast cancer. However, to date the drug has not been listed as primary prevention for breast cancer anywhere in the world. This study is also limited by the current paucity of trial evidence on the effects and side-effects of raloxifene.

A CDC-funded study in the US that examined a very similar intervention with different methods comes to comparable conclusions (Mobley, Hoerger et al. 2006). Their median cost-effectiveness of $448,000 per QALY is higher than the one presented here, which is likely due to a (too) large effect via thrombo-embolic events. A Canadian study reports a C/E ratio of Can$114 070 per QALY, but this only seems to include the costs of raloxifene itself (Goeree, Blackhouse et al. 2006). An industry-funded UK study found a C/E ratio of around £26,000 per QALY (Kanis, Borgstrom et al. 2005). This is due to higher cost-offsets for breast cancer (double!), a lower price of raloxifene, not counting the costs of vitamin D and calcium, the use of high disability weights for vertebral fractures and a mortality effect of such fractures, a 5-year linear decrease in the effect on fractures after stopping medication and discount rates of 1.5% on effects and 6% on costs. On the other hand, they do include

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

thrombo-embolism. The same group found raloxifene similarly cost-effective for Sweden (Borgstrom, Johnell et al. 2004). A model from that group was also used in a study in the UK funded by NICE. This study gives a cost-effectiveness ratio of around £26,000 per QALY, but their methods and assumptions differ from ours on numerous points (Stevenson, Lloyd Jones et al. 2005). Differences that make their model less favourable for the drug compared to ours include (1) the model analyses a hypothetical cohort of individuals with a BMD at the threshold of osteoporosis, and (2) a negative association between BMD and breast cancer risk. Differences that make their analysis more favourable for the drug are (1) higher quality of life-loss is attributed to vertebral fractures; (2) less BMD measurements and GP visits were costed; (3) higher treatment costs for breast cancer; (4) discounting of costs at 6% and health outcomes at 1.5%. Mortality and disability are also calculated differently but it is not clear how this affects the results. As in our study, no effect on cardiovascular disease was included. In sum, the estimates of the cost per QALY for raloxifene vary widely but most studies not funded by the pharmaceutical industry suggest it is at least $100,000 for the general population.

1.10 References

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ACE Prevention Briefing Paper no. X, July 2008

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

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Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

1.11 Second stage filter analysis summary (appendix)

Table 1: Second stage filter summary

Cost per DALY	Strength of evidence	Equity	Acceptability	Feasibility	Sustainability	Relevance to indigenous population	'other effects' (not captured in modelling)
- cost offsets: $176,000 **+ cost offsets:** $181,000	Sufficient evidence of efficacy; weaker evidence on effect of calcium suppletion.	Potential to increase inequities due to differential uptake by socio-economic position, and because breast cancer is more prevalent among high SES women.	No issues expected as participation is voluntary and raloxifene seems to have few side-effects. Calcium suppletion might cause CVD.	Depends on capacity for BMD scans (including personnel)	Requires ongoing support.	Lower because lower life expectancy and less opportunity for screening in rural areas; higher because of smoking.	Positive: None identified. Negative: Medicalisation Increased risk (2 to 3-fold) of venous thrombosis and pulmonary embolism.
Decision point:	Additional data are unlikely to change conclusions.						

Policy Considerations: Unless new and convincing evidence emerges that it prevents hip fractures, raloxifene should not be considered in the prevention of osteoporotic fractures. It might be considered for the prevention of breast cancer, but this research suggests that it is unlikely to be cost-effective at the current price level.

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with raloxifene treatment for osteoporosis

Researcher: Lennert Veerman

APPENDIX: relative risks by BMD level

z-score of femoral neck

The same cohort as in the paper: Predictive value of BMD for hip and other fracture.

Poisson model: 1. constant, 2. current time, 3. current age, 4. BMD z-score, 5. age x BMD z-score, 6. BMD z-score x BMD z-score

RR (95% confidence interval)

Men+Women, Outcome: hip fracture

Age	-3	-2	-1	0	1	2	3
50	3.35(2.24, 5.00)	3.25(2.24, 4.73)	3.17(2.13, 4.70)	3.08(1.95, 4.88)	3.00(1.73, 5.20)	2.92(1.51, 5.65)	2.84(1.30, 6.18)
55	3.11(2.21, 4.38)	3.03(2.23, 4.12)	2.95(2.11, 4.11)	2.87(1.91, 4.31)	2.79(1.68, 4.64)	2.72(1.45, 5.07)	2.64(1.25, 5.59)
60	2.90(2.19, 3.84)	2.82(2.23, 3.58)	2.75(2.10, 3.59)	2.67(1.87, 3.82)	2.60(1.62, 4.16)	2.53(1.40, 4.58)	2.46(1.19, 5.07)
65	2.70(2.16, 3.37)	2.63(2.23, 3.09)	2.56(2.08, 3.15)	2.49(1.82, 3.40)	2.42(1.56, 3.75)	2.35(1.33, 4.16)	2.29(1.13, 4.62)
70	2.51(2.13, 2.97)	2.45(2.27, 2.64)	2.38(2.05, 2.76)	2.32(1.76, 3.05)	2.25(1.49, 3.40)	2.19(1.27, 3.80)	2.13(1.07, 4.24)
75	2.34(2.07, 2.64)	2.28(2.14, 2.34)	2.22(2.02, 2.43)	2.16(1.68, 2.77)	2.10(1.41, 3.12)	2.04(1.19, 3.49)	1.99(1.01, 3.91)
80	2.18(1.97, 2.41)	2.12(1.99, 2.26)	2.06(1.94, 2.20)	2.01(1.57, 2.56)	1.95(1.32, 2.89)	1.90(1.12, 3.24)	1.85(0.94, 3.63)
85	2.03(1.81, 2.28)	1.97(1.85, 2.10)	1.92(1.76, 2.10)	1.87(1.46, 2.40)	1.82(1.23, 2.70)	1.77(1.04, 3.02)	1.72(0.88, 3.39)

Men+Women, Outcome: osteoporotic fracture without hip fracture

Age	-3	-2	-1	0	1	2	3
50	1.37(1.09, 1.73)	1.30(1.08, 1.55)	1.23(1.07, 1.41)	1.16(1.03, 1.31)	1.10(0.95, 1.27)	1.04(0.86, 1.25)	0.98(0.78, 1.25)
55	1.41(1.13, 1.76)	1.33(1.13, 1.58)	1.26(1.12, 1.43)	1.20(1.08, 1.33)	1.13(1.00, 1.28)	1.07(0.90, 1.27)	1.01(0.81, 1.27)
60	1.45(1.17, 1.80)	1.37(1.18, 1.61)	1.30(1.17, 1.45)	1.23(1.13, 1.34)	1.16(1.04, 1.30)	1.10(0.94, 1.30)	1.04(0.83, 1.30)
65	1.49(1.21, 1.84)	1.41(1.22, 1.64)	1.34(1.21, 1.47)	1.27(1.17, 1.36)	1.20(1.08, 1.33)	1.13(0.97, 1.32)	1.07(0.86, 1.33)
70	1.54(1.25, 1.89)	1.45(1.25, 1.69)	1.38(1.25, 1.51)	1.30(1.21, 1.40)	1.23(1.12, 1.36)	1.17(1.00, 1.36)	1.10(0.89, 1.37)
75	1.58(1.28, 1.95)	1.50(1.29, 1.74)	1.42(1.28, 1.56)	1.34(1.24, 1.45)	1.27(1.14, 1.41)	1.20(1.03, 1.40)	1.14(0.91, 1.41)
80	1.63(1.31, 2.02)	1.54(1.32, 1.80)	1.46(1.31, 1.63)	1.38(1.26, 1.51)	1.30(1.16, 1.46)	1.23(1.05, 1.45)	1.17(0.93, 1.46)
85	1.67(1.34, 2.10)	1.58(1.34, 1.88)	1.50(1.32, 1.70)	1.42(1.27, 1.58)	1.34(1.18, 1.53)	1.27(1.07, 1.51)	1.20(0.95, 1.51)