NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women

Response to the Guideline Development Group comments on the Appraisal Consultation Documents (ACD)

Guidelines Development Group	
Introduction The Osteoporosis guideline development group (GDG) welcomes the opportunity to respond to the ACDs for primary and secondary prevention of osteoporosis. The GDG comprises a group of eminent clinicians in the osteoporosis field, general practitioners, representatives from the National Osteoporosis Society, patients and researchers. Clinician members of the guideline group feel that their professional reputations and personal credibility amongst their peers are at stake if recommendations in the current ACDs mandate practice for the NHS and are forcibly included in the guideline. Patients and GPs, both from a personal and organisational perspective, have serious reservations about the recommendations, in particular, that those who merit treatment will not be treated if the ACD remains unchanged, and that those over 75 will be required to undergo scans that are unnecessary. The GDG members are united in their view that the ACDs, if they become mandatory recommendations, will have reversed the progress made in the field over the last 10 years, to the potential detriment of patients and the NHS alike. This GDG response document is important, as it provides a fair summary of the evidence, and gives constructive and pragmatic solutions in moving towards publication of both the technology appraisals and the guideline. This response has been produced by the National Collaborating Centre for Nursing and Supportive Care, on behalf of the GDG. The document was initiated at the GDG's recent meeting and has been through several iterations, with all GDG members contributing. The document is the united response of the GDG, and represents the views of all members. **Structure of the response:** This is in three main parts: A. It considers the current ACDs – which the GDG regards as misguided, incorrect and difficult to implement. B. It provides a synthesis of the evidence, with suggested revised recommendations that demonstrate a clear link between evidence and recommendations, providing the basis for NHS	Comment noted.

implementation. The GDG recognises that NHS resources are limited, but also wishes to indicate that osteoporosis is a common condition, the prevalence of which will increase in an ageing population - a fact that is currently ignored. C. Detailed evidence supporting the interpretation in section 2 is given in the Appendix.	
A) The ACDs – GDG reservations **1. The assumption that there is no efficacy of drugs for fracture risk that is not associated with low BMD, age or prior facture.** This issue challenges the whole basis for osteoporosis risk identification and ignores both home and international work in the field over the last decade. Although, seemingly, a pragmatic assumption designed to reduce NHS expenditure, it is illustrative of the limited clinical and scientific basis for the ACD recommendations. It is also in direct contrast to the precedent set in TA94 (Statins for the prevention of cardiovascular risk), in which, faced with similar evidence of the effect of treatment on the basis of risk factors, the Appraisal Committee assumed equal efficacies across risk levels. In this section, we explore the assumptions and consider whether there is evidence to support the approach taken.	At the Committee meeting to agree on the content of the ACD, the Committee concluded that there was insufficient evidence that the drugs under consideration would reduce fracture risks that was not associated with low BMD, age, or prior fracture (ACD Section 4.3.7). The Committee noted that the distribution of additional risk factors was similar across all BMD sub-groups in the large FIT trial. If there was an effect for all clinical risk factors a greater drug effect would have been expected in the higher (less severe) BMD sub-group than was observed. Following consultation on the ACD, the Committee decided that the assumption of no efficacy on fracture risk associated with risk factors other than low BMD, age, or prior fracture (0% efficacy assumption) was probably too extreme.,On balance, 50% efficacy for the fracture risk not associated with low BMD, age, or prior fracture was considered a reasonable, although necessarily approximate position. This position was taken as the Committee was still not persuaded that there was unequivocal evidence that the drugs alone would reduce the overall fracture risk for factors other than low BMD, age, or prior fracture. In addition, the Committee accepted an increased estimate for the RRs applied to the risk factors age, BMD, prior fracture to allow for this assumption.
1.1 Background Low bone mass is an important component of fracture risk and can predict fracture. However, the sensitivity for fracture prediction is relatively low such that the majority of fractures will occur in individuals who are categorised as not having osteoporosis. This means that identification of risk factors that are wholly or partially independent of BMD is important, since the detection rate (sensitivity) is	Comment noted.

enhanced without loss of specificity (Kanis 2002[1]). Over 90% of osteoporotic fractures result from a fall, predominately from low heights. The GDG has carried out a series of risk factor reviews, purposed to highlight the variety of factors linked to individual risk of sustaining an osteoporotic fracture. This framework allows for case-finding strategies to identify those individuals at high risk of fracture. The contribution of risk factors that are wholly or partially independent of BMD is not disputed by the secondary ACDs: • section 4.3.7, "*The Committee noted that the risk of fracture is clearly related to age, low BMD and previous fracture. The Committee accepted that other risk factors identified by the WHO study (see section 4.2.12[*]) were likely to be associated with an increased fracture risk*". • section 4.2.13, "*The clinical risk factors included (low) body mass index, previous fracture, ever use of corticosteroids, parental history of fracture, current smoking, alcohol intake of more than 2 units per day, and rheumatoid arthritis*". The primary prevention ACD also accepts that 'most' of the risk factors in the WHO model are associated with fracture, at least 'partially' independently of BMD. Inconsistency appears in the caveat about current smoking and alcohol consumption (4.3.6). The ACDs give no explanation to justify this.	The ACD Section 4.3.6 stated that "*The exceptions were the risk factors 'current smoking' and 'alcohol consumption of less than 4 units per day' because the Committee was not persuaded that the WHO data provided sufficient evidence for these two risk factors in women….*" Risk factors of current smoking and alcohol (less than 4 units) were not statistically significant. The Committee noted the further information provided by the GDG for these two risk factors, in particular the Siris 2001 study. This study did not provide evidence to contradict the committee's caution.
1.2 Assumptions Having acknowledged that additional clinical risk factors contribute to the fracture risk, the ACDs make two assumptions: • Risk of fracture is divided: that related to age, low BMD and prior fracture (which we shall call "type A" fracture risk), and that related to other clinical risk factors (type B fracture risk). • For type A, drugs are efficacious in reducing the risk of fracture, varying with the drug concerned, (up to 42% risk reduction), but for type B the drugs <u>have no effect at all.</u> The ACDs state that the basis for these assumptions is that, section 4.3.7 (primary and secondary) *"The Committee noted that there was an absence of evidence to demonstrate that treatment with any of the drugs under consideration would reduce fracture risk that was not associated with low BMD, age or prior facture".*	Comment noted.

[1] Kanis et al. J Bone Min Res 17:1237–44

[*] Presumably a misprint, should say section 4.2.13

This separation is not clinically intuitive: it is merely stratification according to what evidence the Appraisal Committee believes to be available.

The ACDs go on to state that, section 4.3.7, "*preventative drug therapy should be targeted to women whose absolute risk of fracture is driven by low BMD and that the recommendations should be made on the basis of BMD in the form of T-scores below which treatment is recommended*".

In practice, the health economic model calculates the cost effectiveness threshold in terms of the absolute risk of fracture as derived from age, BMD, and clinical risk factors. Then these are converted to T-score thresholds for each age band and for the number of clinical risk factors present.

1.3. Is the assumption of 0% efficacy justified from the evidence?

In this section, we show that this assumption is flawed and not consistent with the evidence.

1.3.1. Trial populations

The relative risk for any trial refers to the sample included in that trial. Clearly women meeting the inclusion criteria have a range of characteristics that will affect their fracture risk and their response to a drug. Whilst questioning the notion of an 'average' patient, trials do determine average treatment effects. There will always be patients who do not respond to drugs even when the results from randomised trials say the drugs are highly efficacious.

The studies included in the meta-analyses contained in the ACDs do not exclude patients with type B clinical risk factors. This is illustrated by examples given in table 1 on page 5. These trial data demonstrate that the populations have patients with different proportions of type A and type B risk factors.

Table 1

Study	Risk factor	Prevalence
Black 2000 (FIT) Fracture arm (n=2027)	Maternal history of fracture Current smoking History of falls	37% 11% 31%
Black 2000 (FIT) Non-fracture arm (n=1631)	Maternal history of fracture Current smoking History of falls	41% 13% 25%

See response to point 1.

Neer 2001 (Teraparitide) (n=1637)	current smoking	15-19%
MORE study (raloxifene) (n=593)	Family history (osteoporosis) Current smoking Alcohol use	27% 16% 17%

The relative risk (RR) in these studies is the ratio:

$$\frac{\text{risk of fracture for the randomised group of patients given the drug}}{\text{fracture risk for those given placebo}}$$

where, the risk of fracture is the number of patients that fracture divided by the total number.

Thus, the RR of fracture takes into account the fact that some patients in each group have a part (or all) of their fracture risk made up of type B clinical risk factors, which may be affected by drugs to a greater or lesser extent. In large trials (as these are) the distribution of type B clinical risk factors is comparable across randomised groups.

It is **incorrect** to assume that the relative risk recorded in a trial refers only to those patients who have type A risk factors. The relative risk refers to <u>all</u> patients in the trial. If it is really necessary to assume that only type A risk factors respond to drugs, then an increased efficacy would have to be estimated to allow for the (hypothetical) dilution imposed by type B. Estimation of this type would not be straightforward and may not be reliable.

It is **correct** to say that the efficacy estimate in the base case applies to the whole population under consideration.

The modelling included an upward adjustment for the RR for the risk factors age, previous fracture and low BMD, where a lower efficacy of the drugs for fracture risk associated with risk factors other than age, previous fracture and low BMD was modelled.

1.3.2 Direct evidence from trials that the 0% assumption is flawed

In sections 1.3.2 to 1.3.4 we present direct evidence to show the flawed nature of the assumption of 0% efficacy of drugs in type B fracture risk. Much of this evidence was submitted previously in the GDG's response to the assessment report, but has not been taken into account in the ACDs.

See response to point 1:

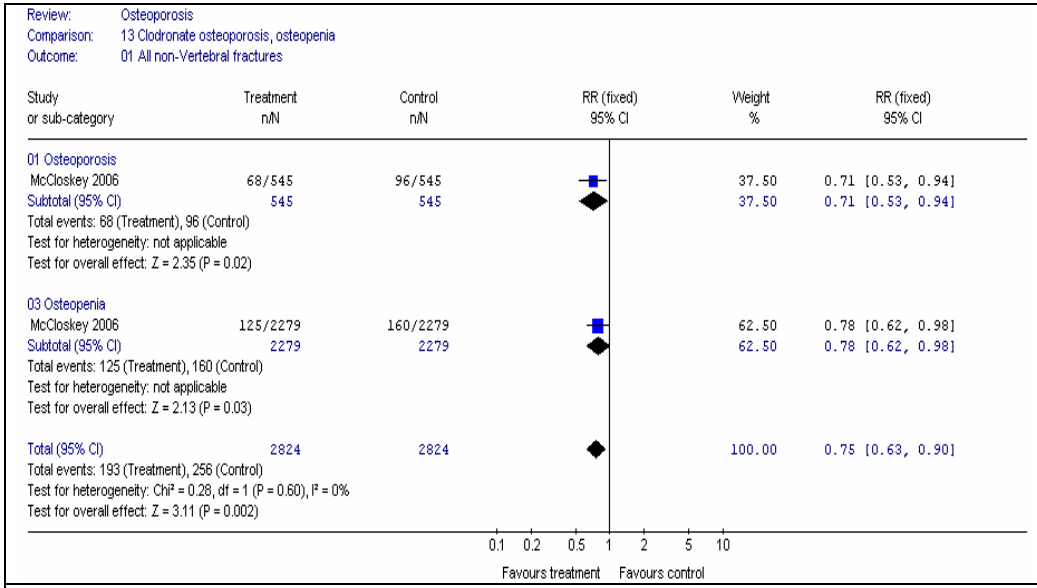
A published regression analysis of risedronate vs placebo data[2] shows that all treatment-by-non-BMD subgroup interactions were not significant ($p>0.2$) – these included BMI (above/below 26 kg/m^2) and smoking status (current/previous or none). Neither of these factors affected the efficacy of risedronate. In a similar study, Johnell et al 2004[3] examined the efficacy of raloxifene according to the presence of different risk factors. The authors found there were no significant interactions with the effect of raloxifene for subgroups based on height, age and family history of osteoporosis. This means that there was no significant difference in the relative risk for treatment with risedronate for patients with or without a family history of osteoporosis, for example. McCloskey 2004[4] showed there was no significant difference in clodronate efficacy for low body weight, smoking and prior fractures.	
1.3.3 Direct evidence in patients who have used glucocorticoids Women taking glucocorticoids have been excluded from the ACDs. There is no explanation for this omission, but reasons are necessary, given the prominent place of this risk factor in the health economic model. Fracture risk associated with glucocorticoid use fits into the type B group. The evidence is presented in Appendix A and shows there are three alendronate/risedronate studies, in men and women. Meta-analysis for all doses shows the effect to be statistically significant for vertebral fracture (RR=0.44 (95%CI 0.23, 0.84)), but not for non-vertebral fracture, although only a relatively small number of patients were included in the meta-analysis (figure 1).	The Committee accepts the importance of long-term systemic glucocorticoid therapy as an exceptional risk factor, which needs special consideration, a point which was brought up during earlier consultation exercises in this appraisal. The Committee understood from members of the GDG, that special recommendations for this patient group was best dealt with in the guideline. The Committee felt that medical conditions associated with low BMD (including premature menopause) should be listed in the technology appraisal guidance as risk factors to be included when assessing the need for a DXA scan. However, the Committee was not in a position to give separate, potentially more favourable, T-score thresholds for these groups of women, as they have not reviewed specific evidence for these groups of women. The Committee understands that the guideline will cover this.

[2] Kanis JA, Barton IP, Johnell O. Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. Osteoporosis International 2005; 16:475

[3] Johnell et al. J Bone Min Res 2004; 19:764

[4] McCloskey et al. J Bone Min Res 2004; 19:728

1.3.4 Direct evidence related to osteopenia / normal BMD patients Further support for the incorrectness of the 0% efficacy assumption comes from studies in patients with osteopenia or with normal BMD. If we assume it is reasonable to separate type A (low BMD, prior fracture and age related) risk factors from other clinical risk factors, and that these fracture risks are additive, it is likely that the trial populations will have similar prevalence of type B risk factors regardless of the BMD. (This assumption is an approximation because some of these risk factors are only partially independent of BMD). An illustration is provided by the FIT trial, in which the fracture and non-fracture arms have different BMD distributions, but similar prevalence of type B risk factors (see table 1). Despite a similar prevalence of type B risk factors in the trial populations, the proportion of overall fracture risk attributable to type B risk factors will be higher in osteopenic and normal BMD trials than in osteoporosis trials. If the drugs were ineffective at preventing fractures attributable to type B risk factors, then we would expect to find a lower treatment effect in the trials in women with osteopenia and normal BMD. Figures 2a -c in Appendix B show that, despite the decreasing number of fracture events as the BMD increases, with corresponding uncertainty in the point estimates, there is evidence supporting drug efficacy in populations with a high proportion of type B risk factors.	The Institute has decided that the technology appraisal will only consider osteoporosis (a T score of equal to or below -2.5 SD), and that osteopaenia (a T score between -2.5 and -1.0 SD) will be considered in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals al high risk'. It should be noted that weekly alendronate and risedronate, strontium ranelate and raloxifene have a marketing authorisation for the treatment of osteoporosis, and not osteopenia. This would have hindered the development of recommendations by the Appraisal Committee for the use of these drugs in osteopenia.
A further recent study of clodronate, McCloskey (in press), has examined the efficacy in osteopenic and osteoporosis populations. In 5592 women, 80% of whom were osteopenic, there is a statistically significant difference in non-vertebral fractures between clodronate and placebo, for both osteoporotic and osteopenic women. This is shown in figure 3, with little difference in the relative risk for the two patient groups. Figure 3.	Noted



1.4 Consequences of using the flawed 0% efficacy assumption

We have demonstrated that there is no validity in the assumption of 0% efficacy in treating type B fracture risk. Furthermore, mandatory use of the current ACD recommendations would bring several consequences.

1. Many patients would not be treated even though they are at high risk of fracture, because their fracture risk derives from clinical risk factors other than age, low BMD and prior fracture (see below).
2. The ACDs would discriminate against younger people with several clinical risk factors. For example, 50-54 year olds with prior fracture and 2 other risk factors are treated under the 100% efficacy base case if their T score <-1.5 SD, but no-one under 60 is treated with the 0% efficacy assumption.
3. Clinical risk factors would be removed from the cost per QALY threshold tables, and equation of the T-scores with absolute risk of fracture is then meaningless.
4. The use of type B risk factors for case finding would be precluded.

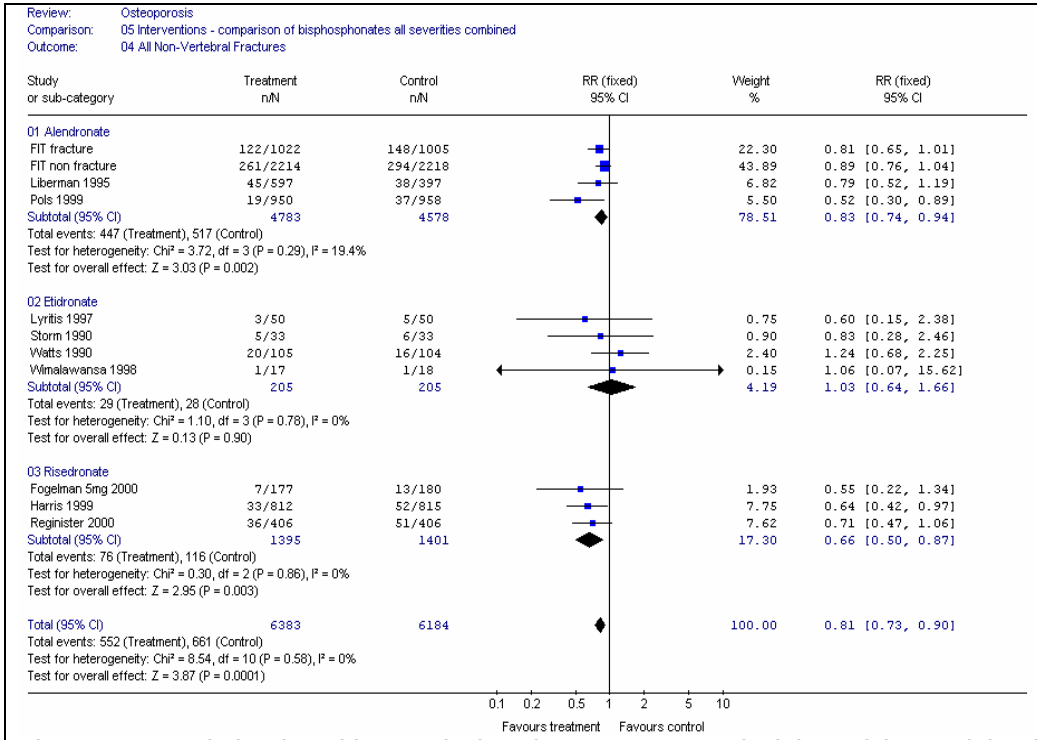
See response to point 1.

1.4.1. Why does this approach penalise women who are at high risk of fracture because of type B risk factors? Cost-effectiveness correlates with the reduction in absolute fracture risk. Within the 0% efficacy model, two patients with the same absolute risk, but different proportions of type A risk factors would be treated differently. For example, for a relative risk of 0.5 (treatment efficacy): • Patient 1: 4% fracture risk made up of 3% type A and 1% type B ⇨ reduction in risk 1.5%; post-treatment risk 2.5% • Patient 2: 4% fracture risk comprising 1% type A and 3% type B ⇨ reduction in risk 0.5%; post-treatment risk 3.5% Thus, women with the same risk are not treated equally, and depending on the cost effectiveness threshold, patient 1 may be treated and patient 2 not. A worse situation could arise in which patient 2 has an even higher contribution to the fracture risk from type B risk factors, and falls below the threshold for treatment of the type A risk. Thus patient 2 would not be treated, yet is at very high risk of fracture. In this way, perversely, the woman at higher risk is less likely to receive treatment.	Comment noted. The Committee noted the concept of absolute risk, but 1. The committee's view of CRF was that the combining of the epidemiological and trial evidence require the appropriate level of caution (see response to point 1.) 2. The committee is currently not in a position of endorse this because the WHO algorithm has not been validated and published. In due course the GDG may consider these issues and the viability of absolute risk within the guideline.
2. Neglect of all groups other than those with osteoporosis Both ACDs have eliminated patients with osteopenia. This is stated explicitly for primary prevention, section 4.3.5, "*The Committee noted that, for all the drugs, efficacy in reducing fracture-risk was less well established for osteopenic women (equivalent to a T-score between -2.5 and -1 SD) than for women with osteoporosis. The Committee was also aware that three of the drugs under consideration (weekly alendronate, weekly risedronate and strontium ranelate) have marketing authorisations only for the treatment of osteoporosis, implying a T-score of -2.5 SD or lower. The Committee therefore concluded that it was inappropriate for it to make recommendations about the use of the drugs in osteopenic women and suggested that this issue be explored by the Guideline Development Group in the forthcoming NICE guideline"*. In the secondary prevention ACD, the restriction to osteoporosis (T<-2.5 SD) appeared only in the recommendations, and was inconsistent with the assessment report results. No explanation was given for this truncation - an approach lacking in transparency. Comparison of the two sources demonstrates this: • Section 1.1 says, "*Alendronate is recommended for the secondary prevention of osteoporotic fragility fractures in women aged 65–74 years if a T-score of -2.5 SD or below is confirmed by DXA scanning*". • The assessment report (final page) using a MAICER of £30,000 and 0% efficacy for type B clinical risk factors has the following thresholds: 70-74 years - BMD and treat where T-score <-1.0 SD; 75+ years – BMD and treat where T-score <-0.5 SD. Even allowing for the effect of changing the vertebral disutility, the threshold will still be far from T<-2.5 in either case.	See response to point 1.3.4

2.1. The policy to target women whose absolute risk of fracture is driven by low BMD is unreliable and incorrect It is unclear why the ACDs have separated osteoporosis and osteopenia when: the BMD scale is continuous (see below), secondary prevention trials also include patients with osteopenia, women with osteopenia are at risk of fracture, partly on account of their type B clinical risk factors, and the relative risk for drug efficacy has been based on meta-analysis across all severities of osteoporosis, section 4.1.2, "*For this appraisal, reductions in RRs associated with treatment were pooled regardless of the baseline BMD and fracture status of the participants in the studies*". The osteoporosis literature has long recognised the need for risk assessment to determine those at risk of osteoporosis. An important question is how strong is the relationship between BMD and fracture risk (Ross 1989, Ross 1990[5]). A gradient of fracture risk exists over the BMD continuum because of progressive bone loss. The use of a BMD cut-off threshold ignores this gradient, which is also influenced by age and other factors such as prior fracture. The use of a multiple risk factors that are at least, in part, mutually independent serves to increase the sensitivity of risk assessment, without loss of specificity. The effect of imposing a cut-off of T<-2.5 is to preclude the treatment of patients with osteopenia, thus neglecting a large group for whom "*prevention of osteoporotic fracture*" is possible, and is clearly required by the Appraisal remit. Restricting the appraisals to osteoporosis only is inconsistent with the best available evidence and the Assessment Group's model results. It is also impractical to cover osteopenia only in the guideline. For example, one solution might be to add to the ACD recommendations wording such as, "if the patient has a T-score less negative than -2.5 SD (i.e. osteopenia), the osteoporosis guideline should be consulted". This would be unsatisfactory for clinicians and patients alike. On both counts, it is reasonable to expect that the appraisals cover the full spectrum of BMD values, and that recommendations also give absolute risks of fracture. A possible solution presented by the Appraisal Committee themselves in January 06.	See response to point 1.3.4
3. Etidronate Both ACDs have recommendations about etidronate that mirror those for alendronate, section 1.2, "*etidronate is recommended as an alternative treatment option under the circumstances specified in section 1.1*"., despite the lack of efficacy evidence supporting etidronate in preventing non-vertebral and hip fractures. The ACD reports the relative risk for hip fracture to be 0.50 (95% CI, 0.05 to 5.34, 2 RCTs, n = 180), and 1.04 (95% CI, 0.64 to 1.69; 4 RCTs, n = 410) for non-vertebral fractures (see	There are no updated cost effectiveness estimates for etidronate. The economic modelling carried out for the September Committee meeting uses an RR of 1 for the effect of etidronate on hip fracture (i.e. no effect on hip fracture risk reduction), but still the cost effectiveness was

[5] Ross PD et al; J Bone Min Res 1989; 4:649; Ross et al; Bone 1990; 11:327

figure 4 below). The ACD also cites an observational study in support of the efficacy of etidronate at the hip. The secondary prevention ACD states, section 4.3.16, "*the Committee had concluded that the evidence base for etidronate was less robust than for the second generation bisphosphonates, particularly for hip and other non-vertebral fractures, and had noted that clinical experts and a number of consultees and commentators had indicated that etidronate was generally considered to be less clinically useful than alendronate or risedronate. The Committee therefore concluded that alendronate should be considered as the preferred treatment option.*" The conclusion reached is reasonable but does not extend to the recommendations, which allow either alendronate or etidronate to be prescribed. The evidence is less robust for etidronate, and the clinical efficacy is uncertain (the point estimate is close to one in a meta-analysis of four trials investigating the prevention of non-vertebral fracture risk; figure 4).	not considerably different from generic alendronate in the September modelling, and always more favourable than risedronate. Furthermore, the inclusion of the observational data for etidronate provides evidence of clinical effectiveness at the hip. The Committee does not feel in a position to totally ignore these cost-effectiveness data. However, the Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the FAD (Section 1.3) that etidronate is no longer a first line option. Instead it is an alternative (and not given preference over risedronate) when it is not appropriate to use alendronate (see FAD Section 1.2). It is not given preference over risedronate despite the fact that it could be argued to be more cost-effective. Furthermore, the Committee has included in the commentary in FAD section 1.3 that clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients (as in the published guidance on secondary prevention, TA 87).
Figure 4.	



The recommendation for etidronate is therefore contrary to principle 3 of the Social Value Judgements paper, "*NICE guidance should not support the use of interventions for which evidence of clinical effectiveness is either absent or too weak for reasonable conclusions to be reached* ". There is no justification for recommending etidronate as first line therapy simply based around cost.

4. Fracture utilities

The fracture utilities used in the base case are recommended. It is perfectly credible that the vertebral fracture value is lower than the hip fracture value: clinically-presenting vertebral fractures are very painful, and the pain persists for longer than for hip fracture. Furthermore, the hip and vertebral fracture data are sourced from the same study, which gives confidence in the results.

Within the assumption of equal utilities for hip and vertebral fractures, there is a further assumption – that the vertebral fracture utility should be *increased* to that for hip fracture. However, it would have been equally justifiable to *reduce* the hip fracture utility to the observed value for vertebral fractures. No reason is given for the arbitrary choice to increase the vertebral fracture utility, a decision which is, at best, arbitrary.

The Committee considered the utility multiplier for the first year after a vertebral fracture used in the base-case analysis and noted that it was considerably worse than that for a hip fracture. The Committee recognises that hip fracture is a major event and often argued to be a key goal for prevention of fractures. Although the Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that it was unlikely that this would so greatly outweigh the utility decrement associated with a hip fracture. Utility estimates are not

	immune from interrogation. They are dependent on the breadth of the patient group sampled. The Committee therefore considered it reasonable to assume that the disutility in the first year after a vertebral fracture was equivalent to the disutility in the first year after a hip fracture.
5. Treatment by age The GDG welcomes the statement for secondary prevention, that, section 4.3.17, "*At the age of 75 years and above, treatment should be started without the need for DXA scanning, because it was considered that at this age it is very likely that women who have sustained a fragility fracture will have a low BMD (T-score of -2.5 SD or below)*". We also recognise that it is even more likely that patients in this age group will have a T-score of -0.5 or below (see DSU last page) – the true threshold for cost-effective treatment. For primary prevention, the GDG is concerned that the removal of type B risk factors, coupled with the cut-off of T<-2.5 SD has distorted the identification of patients at risk of osteoporotic fracture. The GDG is concerned by the proposal that all patients over 75 with one or more clinical risk factors should be unable to receive treatment without the absolute requirement for a DXA scan to confirm their BMD status. This is not only counter-intuitive from a clinical perspective, but likely to be impossible to implement comprehensively because of clinical and logistic problems (such as mobility, frailty, transport, local availability) precluding the ready access of a subset especially of frail elderly women at high risk to DXA scans. It will also unnecessarily increase the additive costs to the NHS. The rational recommendation should be that patients at high risk of fracture, for whom access to DXA scanning is problematic for the reasons given, should be identified and treated on the basis of clinical risk factor assessment alone	Please note that the updated secondary prevention FAD has yet to be finalised. In previous consultation exercises for the appraisal of the drugs in secondary prevention, the Committee was criticised for not recommending a DXA scan confirmation in women over 65. However, the Committee concluded that women over 65 who have sustained a fracture are very likely to have a T-score of –2.5 or below and therefore did not recommend a confirmatory DXA scan in this group. The Committee concluded that this likelihood is lower in women who have not sustained a fracture. Therefore, for primary prevention, the Committee decided that all women over 70 will be required to have a DXA scan confirmation. The suggestion that a scan may not be needed may be attractive as regards savings on resourceing DXA facilities, but would in the Committee's view result in undesirable over-treatment.
6. Clinical risk factors for case finding **6.1. Primary prevention ACD: inconsistency of reinstating clinical risk factors for case finding** The reintroduction of clinical risk factors for case finding in primary prevention is completely inconsistent with the 0% efficacy assumptions made above, resulting in evidence blurring. The ACD introduces additional clinical risk factors (type B) in order to restrict the number of DXA scans, section 4.3.17, "*the Committee considered that this strategy needed added caution given that the adoption of such a strategy would result in many women (that is, all women aged over 75 visiting their GP for any reason) being referred for DXA scanning and that many of these women may be ostensibly well and asymptomatic and not at high risk of fracture. The Committee therefore agreed to exercise caution in formulating its recommendations, and to recommend DXA scanning only in women with at least one clinical risk factor, other than age, suggesting a low BMD*".	Firstly, the Committee considered that identifying women who are likely to be DXA-confirmed cases of osteoporosis using risk factors is not the same as ascribing benefit to women with risk factors independent of BMD. Secondly, the Committee have now explored the impact of clinical risk factors other than BMD, age and prior fracture on drug efficacy in the modelling (see response to point 1.) For long-term systemic glucocorticoid therapy, see response to point 1.3.3

The ACD then clarified which risk factors were meant, section 4.3.9, "*Having reviewed the evidence on risk factors and the views of the clinical experts, the Committee agreed that the appropriate clinical risk factors to be considered for case finding for the primary prevention should be: parental history of hip fracture; low body mass index (defined as less than 22 kg/m^2); alcohol intake of more than 3 units per day; and medical conditions associated with low BMD (as listed in section 2.11)"*. These are the same clinical risk factors for which the fracture risks are assumed to be unaffected by drugs. This is clearly an inequitable and inefficient strategy – with patients preferentially selected for drugs that have been assumed not to work for them. It also indicates that the T-score approach in the absence of type B clinical risk factors is unworkable for primary prevention. The obvious solution, and one that is the most clinically helpful, is a case finding approach using absolute risks of fracture. This is essentially the approach adopted for the DSU's base case model, and we also note that the WHO study is producing a risk calculator based on absolute fracture probabilities.	
6.2 Which risk factors should be used for case finding? The primary prevention ACD states that, section 4.3.6, "*The Committee accepted that most of the risk factors identified by the WHO study (see section 4.2.12) were likely to be associated with an increased fracture risk, which is partially independent of BMD. The exceptions were the risk factors 'current smoking' and 'alcohol consumption of less than 4 units per day' because the Committee was not persuaded that the WHO data provided sufficient evidence for these two risk factors in women*." It is not justified to eliminate current smoking and alcohol consumption (greater that two units per day). Firstly, there is an error here, as alcohol as a risk factor in the WHO study was 'consumption of more than 2 units per day' not 'less than 4 units per day'. Secondly, the exceptions in section 4.3.6, especially alcohol consumption of 4 units or more, is not supported by current evidence (see Appendix C). Meta-analysis of a number of cohort studies (not just the WHO study) shows both current smoking and alcohol consumption of 3 units or more have an effect on fracture risk. This neglect of alcohol and smoking is worrying, as there is no transparent link between the evidence and what is being recommended. It is also of concern that the GDG presented this evidence in its submission in response to the assessment report, and no reference has been made to this work.	As for the response to point 1.1:
7. Second line therapies In practice, it would be extremely difficult to implement the secondary prevention recommendations for patients who can not tolerate alendronate. 2nd line therapy using risedronate or strontium ranelate would mean that the clinician is unable to offer any alternative to the patient until their BMD had reduced even further (with no mention either of how often they should be re-sent for DXA scanning or the related costs).	The Committee is required to make recommendations based on clinical and cost effectiveness. The Committee has set its recommendations for the alternatives to alendronate at the point they become cost effective where treatment with alendronate is not possible.

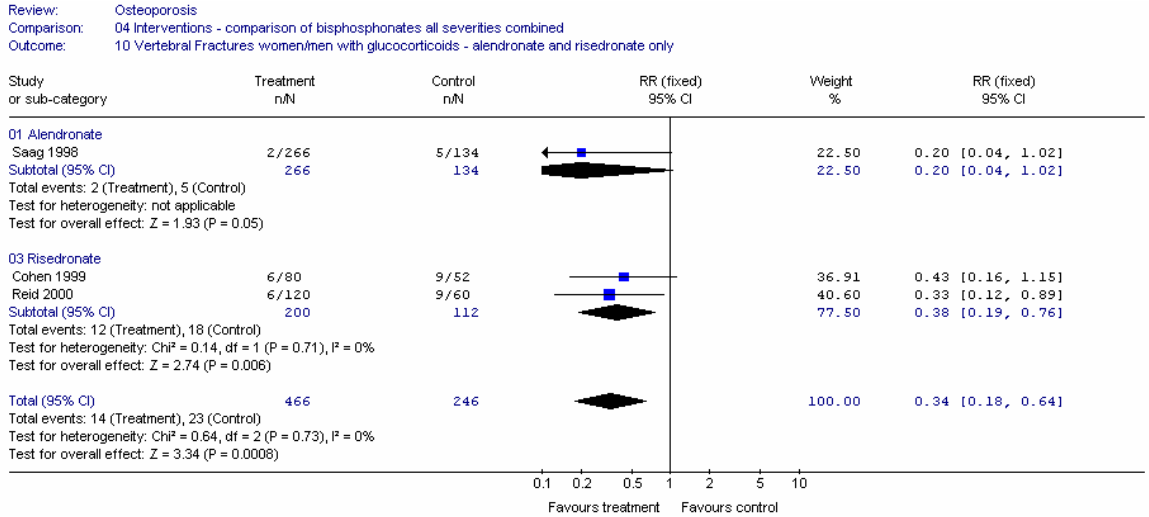
Interestingly, for teriparatide, a new risk factor (multiple fractures) specifically for this drug is introduced. Again, there is no transparent link between evidence and recommendation.	
B) GDG revised recommendations for prevention of osteoporotic fracture **1. Base case values to be used** • The same efficacies (treatment) should be used for all types of fracture risk. • The utility for vertebral fracture should be lower than for hip fracture in the first year. • The MAICER for secondary prevention should be £30,000 and £20,000 for primary prevention.	Noted.
2. Patients with osteopenia included A cut-off at T<-2.5 SD is not justified and patients with osteopenia should be included in the appraisals, allowing ready insertion of the appraisal recommendations into the guideline.	
3. Patients taking corticosteroids included Patients with conditions/ treatments resulting in low BMD should be excluded from the appraisals but dealt with in the osteoporosis guideline and clear reference to the guideline's recommendations should be made in the appraisals. There is a strong case to include patients taking corticosteroids because of the role that this risk factor plays in the WHO model (substantiated by other published evidence).	
4. Reporting of cost effectiveness thresholds The thresholds for cost-effective assessment and treatment should be reported both as absolute risks of fracture and by T-score, age and number of clinical risk factors, as agreed with the Appraisal Committee in January 2006.	
5. Clinical risk factors for case finding Clinical risk factors should be used for case finding, comprising prior fracture, low BMD, age, history of parental fracture, glucocorticoids, current smoking, alcohol consumption more than 2 units per day, low BMI in the absence of BMD	
6. No/fewer BMD scans for the over 75s For secondary prevention, BMD scans should not be given to the over 75s, as in the secondary prevention ACD. Treatment intervention in primary prevention should focus on clinical risk factors without the compulsory requirement for a BMD scan. One approach would be to determine two levels of fracture risk, either based on the number of risk factors or by using a risk calculator (existing tools have been reviewed in the guideline):	

• At moderate clinical absolute fracture risk, patients should, wherever possible, be sent for a BMD scan. Where access to DXA is problematic for clinical or logistic reasons, patients in the over 75 age group should be treated as at high risk. • At high clinical absolute fracture risk, patients in this age group should be offered treatment without the requirement for a BMD scan. Older people who have undergone comprehensive multifactorial falls risk assessment and intervention (NICE Guideline 21), and who in spite of this remain at high risk of recurrent falling should be eligible for primary preventative treatment if they have any other single clinical risk factor and/or a BMD in the osteopenic range or lower. This type of approach should allow the most effective use of resources by targeting patients at the highest absolute risk of fracture, thus giving an equitable approach to prevention.	
7. Etidronate and second line therapies Etidronate should not be recommended as a first or second line therapy. For patients who cannot tolerate bisphosphonates, strontium ranelate should be available as second line therapy without the need for further BMD scans.	
APPENDICES	Section comments noted

Appendix A: Effect of bisphosphonates in patients receiving oral corticosteroids

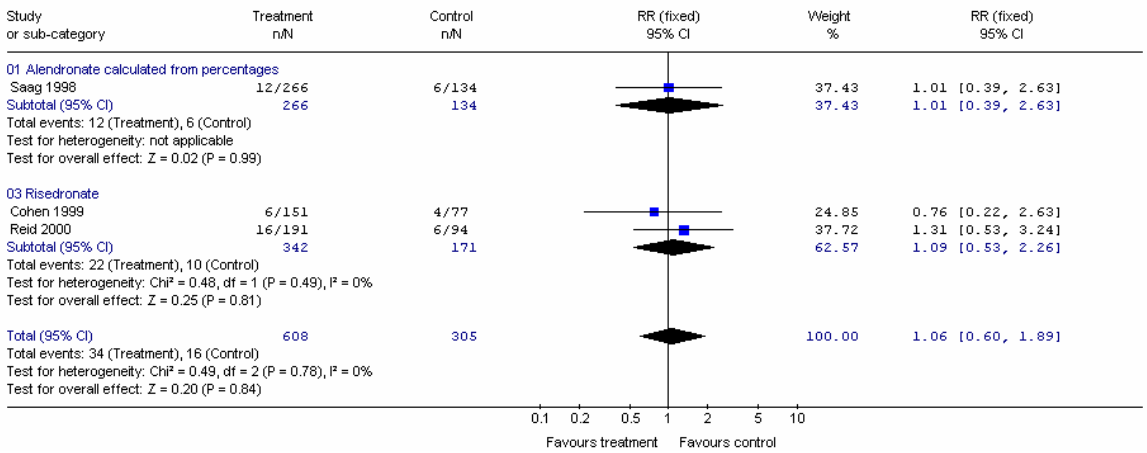
Figure 1: Alendronate or risedronate versus placebo for treatment of patients (women and men) receiving oral corticosteroids

a) Vertebral fractures



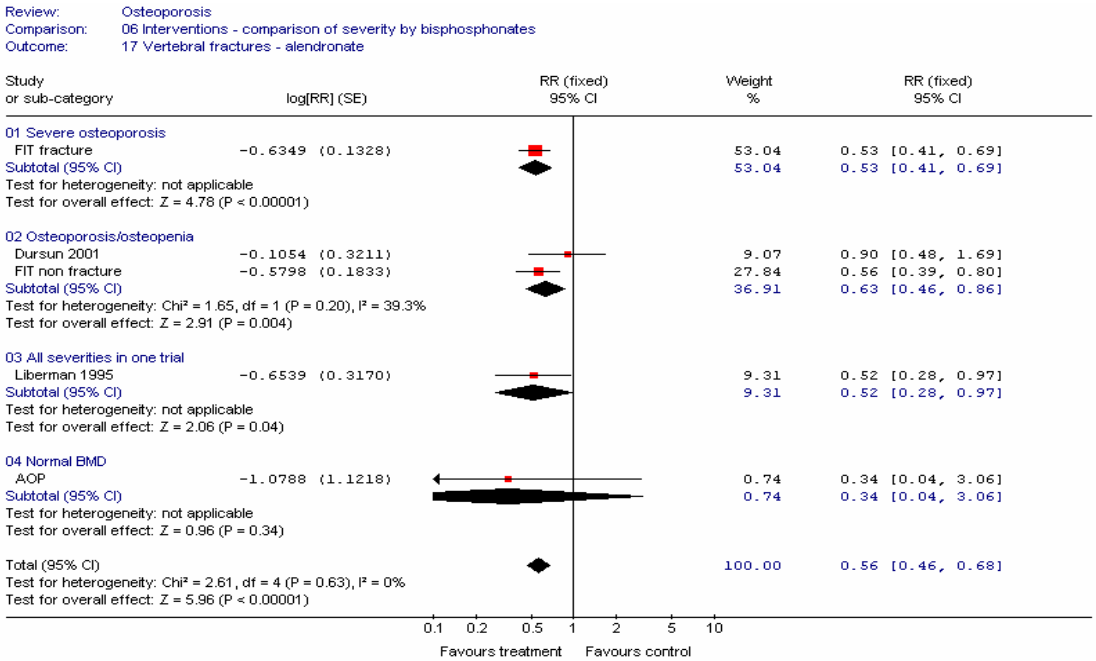
b) Non-vertebral fractures

Review: Osteoporosis
Comparison: 04 Interventions - comparison of bisphosphonates all severities combined
Outcome: 11 Non-Vertebral Fractures women/men with glucocorticoids - alendronate and risedronate only

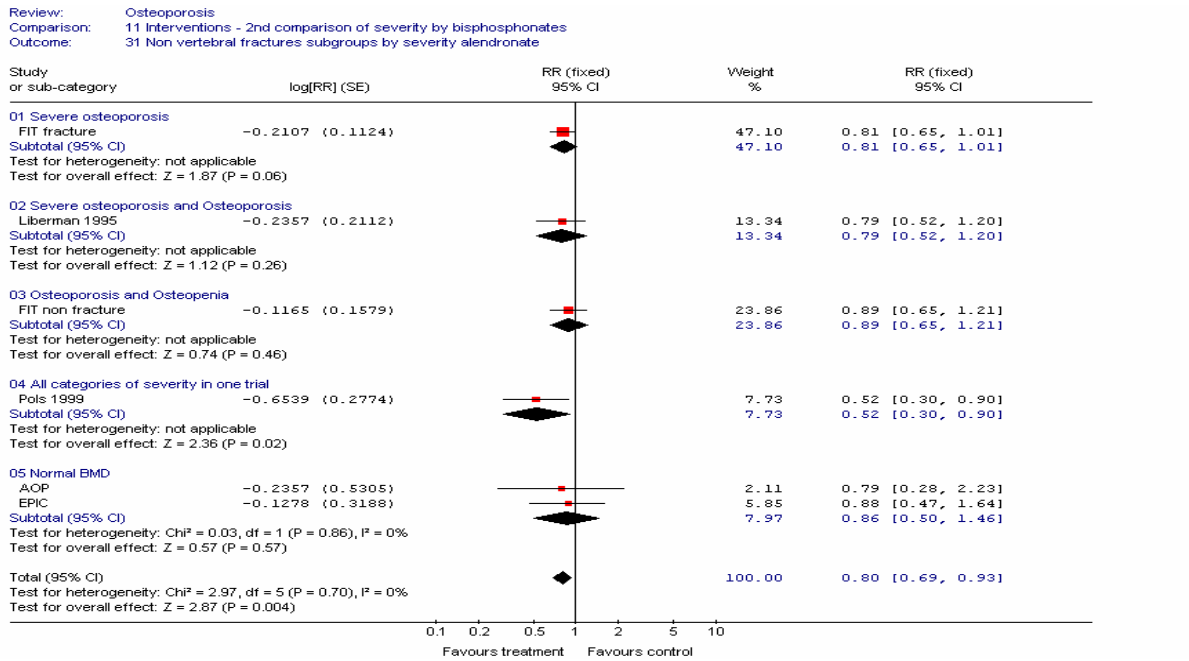


Appendix B: Effect of drugs for different BMD populations

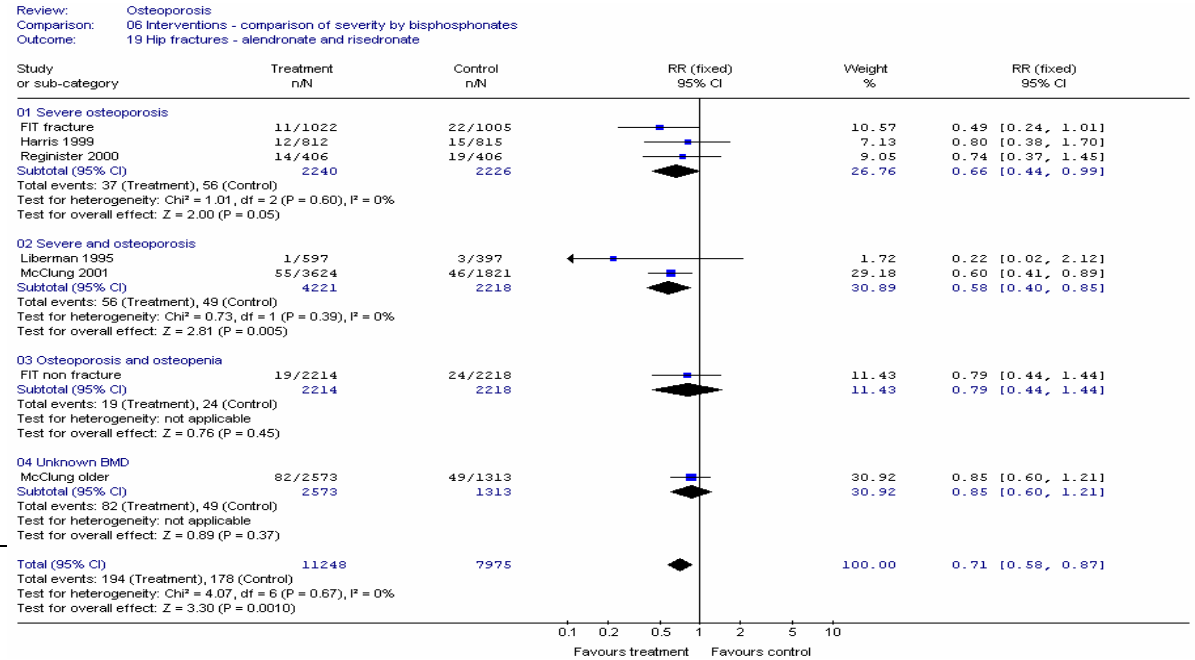
Figure 2: Effect of drugs for different BMD populations



b) Non-vertebral fracture alendronate



c) Hip fracture – alendronate and risedronate



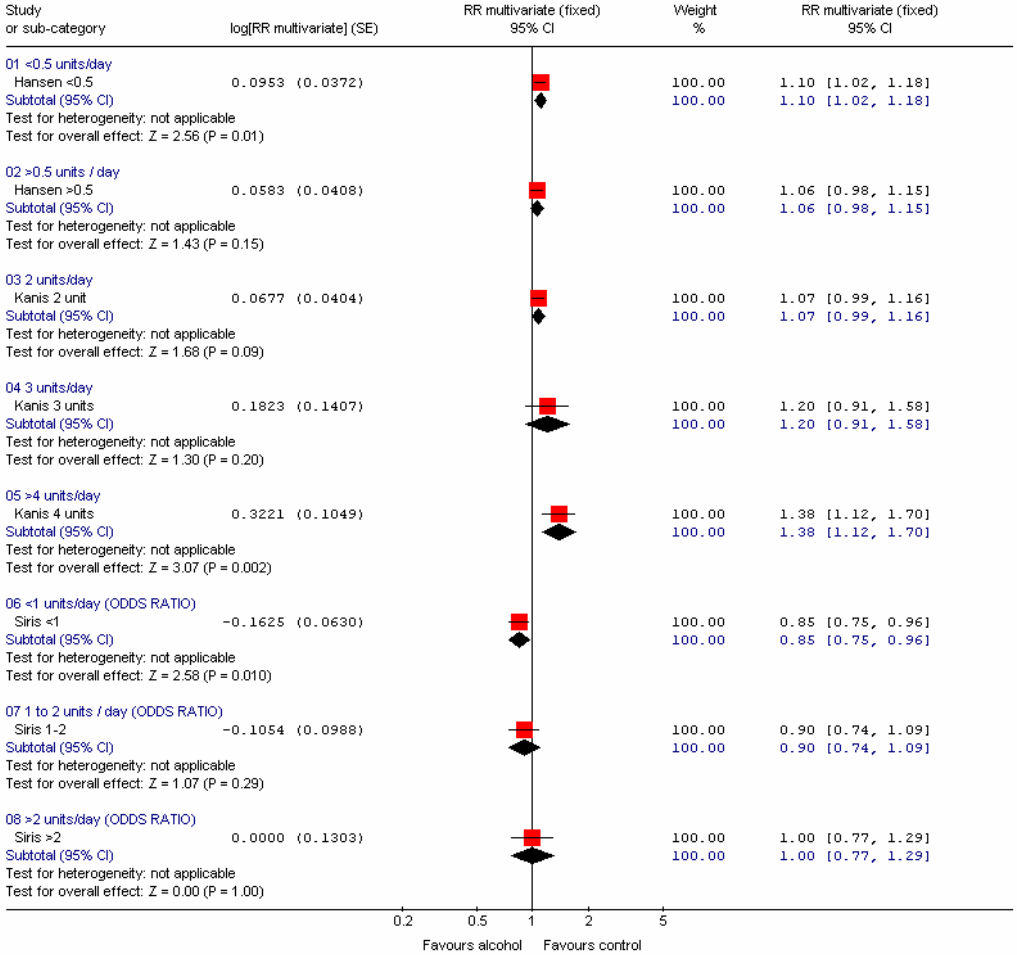
Appendix C: Risk factors smoking and alcohol

We present a brief meta-analysis of the relative risk of fracture from cohort studies that analysed their data with adjustment for multiple variables. The studies were exclusively or predominantly in post-menopausal women.

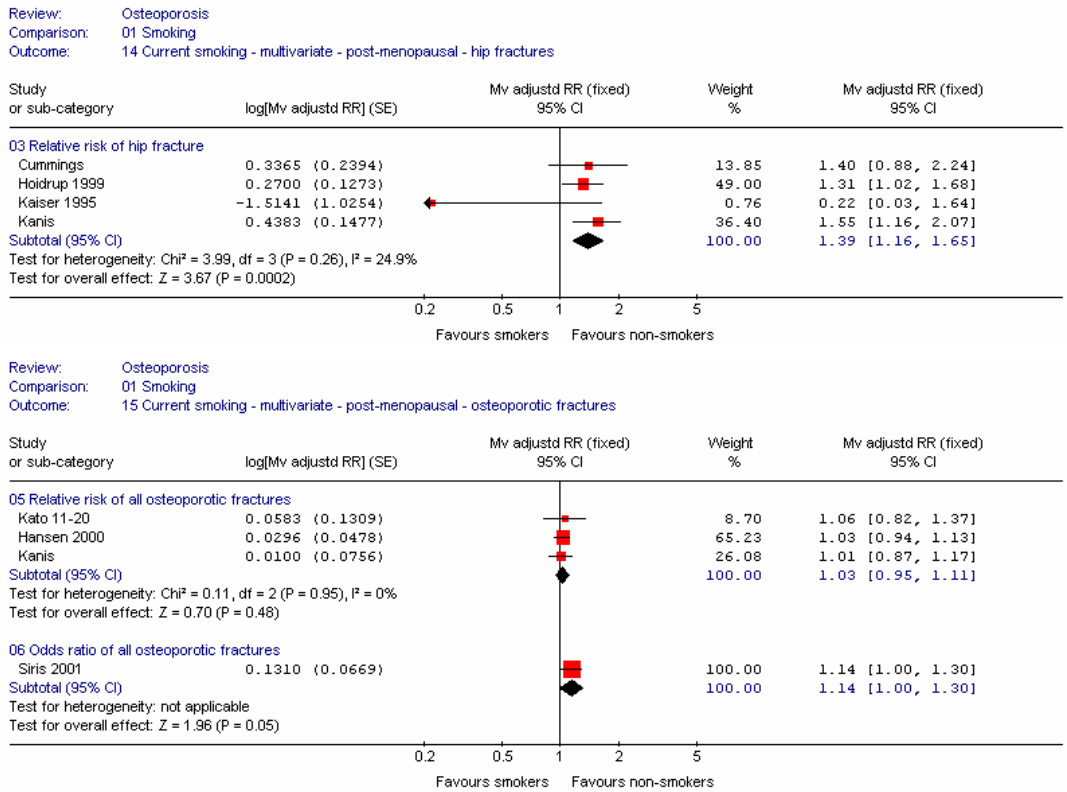
Smoking

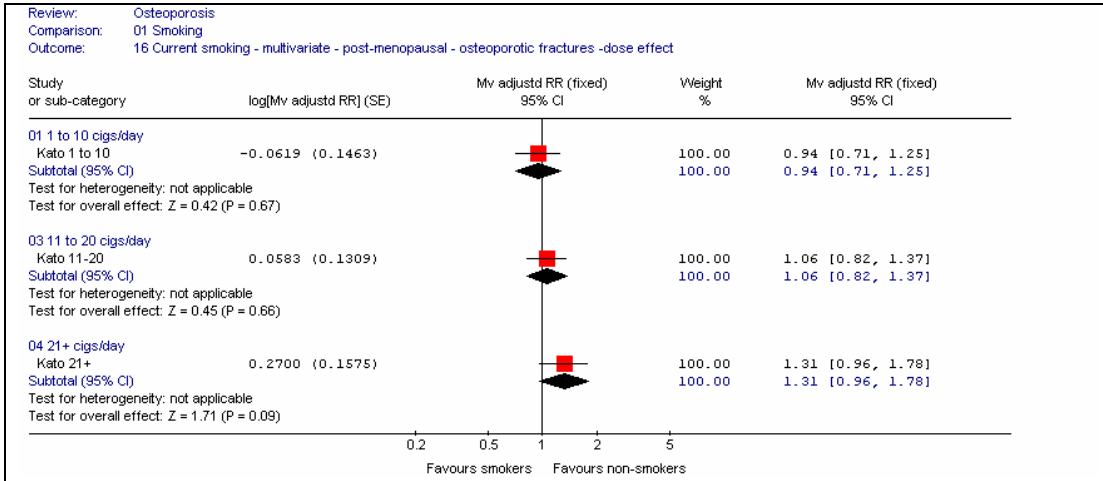
The two figures below show a statistically significant effect of smoking on the rate of hip fracture and little difference for all osteoporotic fractures (although the odds ratio in the large Siris study (200,000) was of borderline significance for the latter analysis). There is also a clear dose effect of smoking, illustrated in the third figure for all osteoporotic fractures.

Review: Osteoporosis
Comparison: 02 Alcohol
Outcome: 08 Alcohol by dose - osteoporotic fracture - women (All)



The GDG recommends current smoking as a risk factor for osteoporosis.



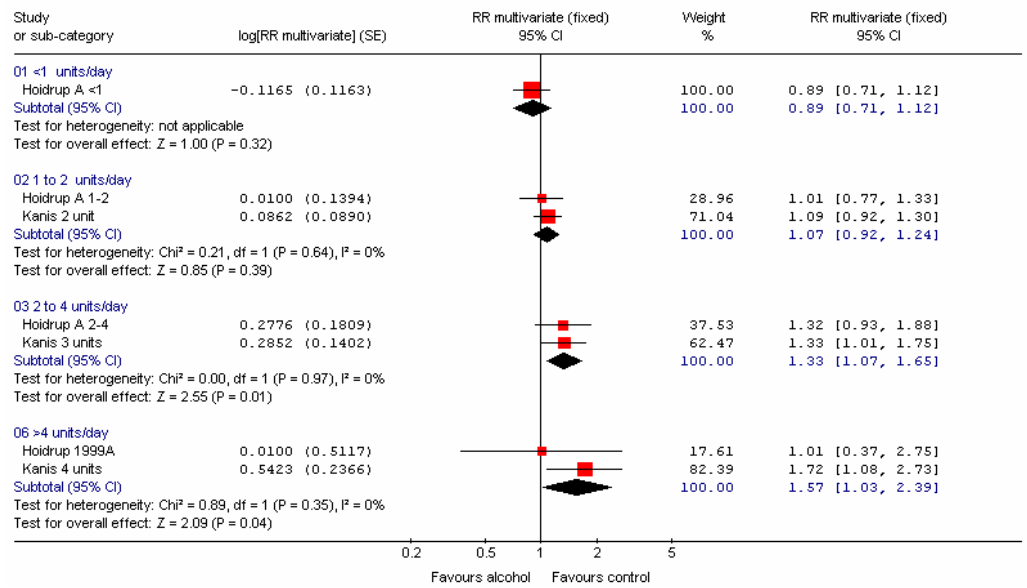


Alcohol

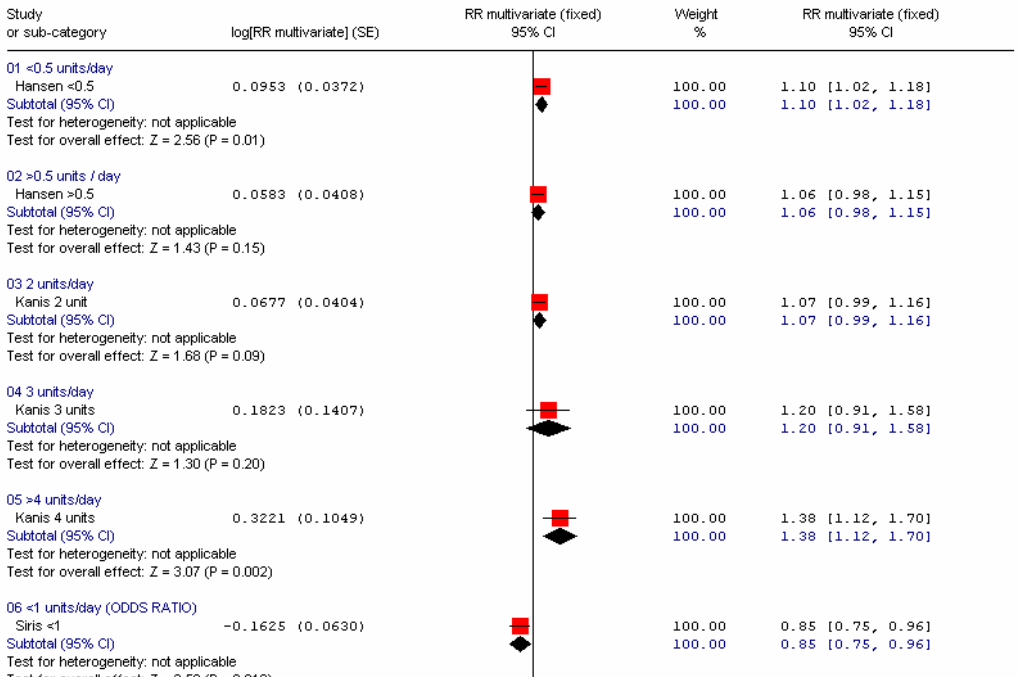
The Kanis meta-analysis and three studies (Hoidrup 1999A – Copenhagen; Hansen – Iowa Women's Health study; and Siris 2001 - NORA) looked at the effect of the amount of alcohol. The Hansen and Siris studies were in post-menopausal women only, and the other studies were mainly in post-menopausal women. The Kanis meta-analysis had a comparator cohort of 1 unit/day and the others had zero or <1 unit/week. Where doses were comparable, meta-analysis was carried out (despite the different comparators). The two figures below show the effects on hip fracture and any osteoporotic fracture.

There is evidently a dose effect of alcohol on the rate of fracture. On the grounds of hip fracture alone, **the GDG recommends alcohol as a risk factor for those who take 3 or more units per day of alcohol.**

Review: Osteoporosis
Comparison: 02 Alcohol
Outcome: 19 Alcohol by dose - hip fracture - mainly postmenopausal women



Review: Osteoporosis
Comparison: 02 Alcohol
Outcome: 08 Alcohol by dose - osteoporotic fracture - women (All)



Appendix D – explanation of direct evidence against 0% efficacy for type B fracture risk (refers to section 1.3.2 in main text)

$$RR = \frac{\text{risk of fracture for the randomised group of patients given the drug}}{\text{fracture risk for those given placebo}}$$

The Appraisal Committee assumes that there are two types of fracture risk, A and B, due respectively to low BMD/prior fracture/age and other (e.g. family history of fracture, excessive alcohol consumption, glucocorticoids), which we denote r_A and r_B respectively. These risks are assumed to be independent and are additive. Each type of fracture risk is affected by the drugs, with relative risks RR_A and RR_B. Thus,

$$RR = \frac{RR_A\, r_A + RR_B\, r_B}{r_A + r_B}$$

$$= \frac{RR_A\, r_A + RR_A\, r_B + (RR_B - RR_A)\, r_B}{r_A + r_B}$$

$$= RR_A + \frac{(RR_B - RR_A)\, r_B}{r_A + r_B}$$

If the drugs are less efficacious for the type B fracture risk, then $RR_B > RR_A$, so the overall RR will be greater than RR_A.

As RR_B tends to 1 (0% efficacy of type B assumption), RR (overall) → maximum

As RR_B tends to RR_A (100% efficacy, base case), RR (overall) → RR_A

The trials show that the relative risk (treatment) is the same for subgroups with and without particular risk factors, i.e., RR (overall) = RR_A . Therefore, $RR_A = RR_B$ and the 100% efficacy for type B fracture risk is demonstrated.