

**ASSESSING THE FEASIBILITY OF TRANSFORMING
THE RECOMMENDATIONS IN TA160, TA161 AND TA204
INTO ABSOLUTE 10-YEAR RISK OF FRACTURE**

A REPORT PRODUCED BY THE DECISION SUPPORT UNIT
IN THE CONTEXT OF THE REVIEW PROPOSAL FOR TA160/1 AND TA204

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1. INTRODUCTION

NICE has undertaken considerable work in producing guidance for when interventions can be used cost-effectively in the prevention of osteoporotic fractures. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate were appraised for postmenopausal women without a previous osteoporotic fracture in TA160, and for postmenopausal women with a prior osteoporotic fracture in TA161, in which teriparatide was also appraised. From henceforth, the use of an intervention in people without a prior fracture will be denoted 'primary prevention', whereas the use of an intervention in people with a prior fracture will be denoted 'secondary prevention'. In TA204 denosumab was appraised for both primary and secondary prevention.

In each of these published technology appraisals the guidance was based on the risk of fracture, comprised of patient characteristics such as age, T-Score and the presence and number of risk factors for fractures. Within the published appraisals these were: parental history of hip fracture; alcohol intake of 4 or more units per day; and rheumatoid arthritis. Additionally in TA160 and TA161 indicators of low bone mineral density (BMD) were defined as: low body mass index (BMI) defined as less than 22kg/m²; medical conditions such as ankylosing spondylitis and Crohn's disease that result in prolonged immobility; and untreated premature menopause. The intervention thresholds differed between treatments due to different acquisition costs and efficacies regarding fracture prevention.

NICE has published a clinical guideline on assessing the risk of fragility fractures in people with osteoporosis. (<http://guidance.nice.org.uk/CG146>) This guideline recommends the use of FRAX® or QFracture for the estimation of absolute fracture risk. The guideline recommendations refer to intervention thresholds, but without cross referring to the technology appraisals, as in the latter the recommendations are not presented as absolute fracture risk. The scope for the guideline includes all people with osteoporotic fragility and specifies that drugs to prevent fractures will not be covered as they will be covered within future guidance produced by the Institute.

With the publication of the short clinical guideline on risk assessment, recommending the assessment of absolute fracture risk, integrating all risk factors quantitatively, it is necessary for NICE to consider if the recommendations on treatment decisions can be aligned with the recommendations on risk assessment. For this, a feasibility study is needed that explores if a translation of the recommendations (treatment thresholds) into absolute risk, or a derivation of absolute risk for hip and other fractures, provides a sensible tool to achieve the alignment of the guideline and technology appraisal recommendations. This report shows the results from this feasibility study. It is noted that

comparisons were carried out using FRAX® only as QFracture does not include BMD as the input within the risk calculator.

The author of this report is also the first author on the independent academic reports that underpinned the development for TA160 and T161. In these reports, the independent academic group suggested that the use of absolute fracture risk alone did not accurately predict cost-effectiveness, and therefore would not provide a robust basis for the Committee's decision-making (TA160, 4.2.41). The Appraisal Committee was aware of the availability of the FRAX® internet-based tool, which can be used to calculate a ten-year absolute risk of fracture, developed under the auspices of the WHO. The Appraisal Committee was aware that the FRAX® tool was based on the same epidemiological data that were used in the Assessment Group's model. However, the Committee was not persuaded that recommendations about treatment should be based on absolute risk as calculated using FRAX®. Firstly, the Committee did not agree that all clinical risk factors included in the WHO algorithm were appropriate. Secondly, the Committee was aware that absolute fracture risk is not directly related to cost-effectiveness (TA160 4.3.47). Also, FRAX® had not been published during the development of TA160 and 161.

Constraints to using absolute fracture to predict the cost-effectiveness of interventions

- 1) An absolute fracture risk does not consider the implications of the fracture. Fractures of the hip have considerable more costs and mortality and morbidity consequences than other fracture types. Therefore the proportions of the different fracture types (hip and non-hip) that make up the absolute risk would also be required which are influenced by the T-Score of the woman and by a person's clinical risk factor profile.
- 2) A given absolute fracture risk would not reflect how age influences the cost-effectiveness, for example in: differing hip to non-hip fracture ratios; differences in the mortality rate following a hip fracture and in the probability of being consigned to a nursing home following a hip fracture.
- 3) The remit for both TA160 and TA161 was understood to be for postmenopausal women with osteoporosis, that is with a T-Score of $-2.5SD$ or lower. It was shown in the independent academic report that there were combinations of patient characteristics where treatment was considered to be below £30,000 per QALY with less severe T-Scores, for example a T-Score of $-2.0SD$. In these circumstances the requirement that the woman needed to be osteoporotic increases the absolute risk of fracture at which alendronate could be considered cost-effective.
- 4) Establishing a person's absolute fracture risk in primary prevention would incur costs of identifying patients at a risk and the costs of a BMD scan where it was considered cost-effective to assess the BMD of the woman. These identification costs could outweigh any benefits from treatment and make the entire 'find and treat' strategy not cost-effective, despite

a small number of women who could have received treatment cost-effectively when identification cost were excluded.

- 5) In TA160 and 161 the Appraisal Committee assumed a threshold for cost-effectiveness of £30,000 per QALY for secondary prevention and £20,000 per QALY for primary prevention. This meant that a higher risk of fracture was typically necessary for primary prevention to be cost-effective.
- 6) Due to different acquisition prices of the interventions and different assumed efficacies a single absolute fracture risk intervention threshold could not be determined, even if it were possible to develop a robust algorithm. In this circumstance a separate fracture risk would be required for each intervention.

2. ISSUES TO BE CONSIDERED

The Assessment Group Model

The mathematical model developed by the assessment group which formed part of the evidence in TA160 and TA161 used the fracture risk estimates produced by an algorithm that was developed by the WHO to evaluate fracture risks of patients. The algorithm was based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD). For brevity this algorithm will be denoted as ALGO 2005 in this report. ALGO 2005 was subsequently developed into FRAX®. (www.shef.ac.uk/FRAX). The mathematical model used by the assessment group synthesised the annual risk of fracture together with the acquisition cost of the intervention, the assumed efficacy of the intervention, the costs of fracture and the utility multiplier associated with fractures in order to calculate the cost per QALY of the intervention.

ALGO 2005 provided risks of fracture in two main categories, hip fracture and major fracture which was defined as hip, vertebral, wrist and proximal humerus. The fracture risks were affected by the following characteristics: Age of woman; T-Score; and the presence of the following clinical risk factors (CRF) (none; parental history of hip fracture; smoking; corticosteroid use; rheumatoid arthritis; BMI and alcohol consumption (>2 units per day)). The *annual* risk of fracture was provided to the Assessment Group for women with: no CRF; each of the individual risk factors; all ten combinations of two CRF; and two estimates for people with three risk factors which were differentiated by whether a woman had a parental history of hip fracture or not. Within ALGO 2005 it was assumed that if BMD was known then the fracture risk was independent of BMI.

In order to simplify the complex risk factor modelling, the Appraisal Committee asked the Assessment Group to present results grouped by the number of clinical risk factors making the simplifying assumption that the impacts of all risk factors were identical. Following this grouping the cost-effectiveness estimates were based on the median value of all possible combinations of risk factors.

The Assessment Group model incorporated fractures not considered in FRAX® but which nevertheless incur cost and disutilities. These fractures were pelvis and other femoral fractures which were subsumed into the hip category, rib, sternum, scapula, and clavicle fractures which were subsumed into the proximal humerus category, and tibia and fibula fractures which were subsumed into wrist fractures. For the purposes of this feasibility study these additional fractures were excluded within the analysis conducted for this report. This is because the online FRAX® algorithm (accessed August 2012) does not include these types of fractures.

The consistency between the criteria within the published guidance and ALGO 2005.

The clinical risk factors included in the recommendations of TA160 and 161 did not faithfully follow the risk factors in ALGO 2005. ALGO 2005 included, amongst others, smoking, alcohol consumption greater than two units per day, and corticosteroid use as risk factors. In the recommendations, smoking was not included as a risk factor, and the amount of alcohol consumption was increased to greater than four units per day, and due to the agreed scope of these appraisals corticosteroid use was excluded.

Additionally, for primary prevention TA160 states that alendronate was recommended in postmenopausal women younger than 65 years who have an independent clinical risk factor for fracture and at least one additional indicator of low BMD (both defined in the introduction). This was not reflective of the results in the economic modelling. The presence of indicators for low BMD were not recorded in FRAX®

The Assessment Group model could not be altered to exclude smoking or corticosteroid use as a clinical risk factor, nor could the ALGO 2005 algorithm be adjusted for the increased threshold of alcohol consumption, which remained at the risks associated with greater than two units of alcohol per day, nor could the ALGO 2005 algorithm be adjusted for the presence of indicators of low BMD.

Evolution of the FRAX® algorithm.

Since the first publication of TA160 and 161, it appears that FRAX® has been refined, presumably in the light of more mature data sets. The version of FRAX® accessed in August 2012 will henceforth be referred to as FRAX® 2012. In addition to updating coefficients within the algorithm two structural changes to FRAX® have been identified. Firstly, FRAX® 2012 will not provide an estimate of fracture risk unless height and weight values are supplied (to calculate BMI); this contrasts with ALGO 2005 in which BMI was assumed of no importance if BMD was known (that is, there were two algorithms, one with and one without knowledge of BMD). Secondly, FRAX® 2012 allows fracture risks at all combinations of CRFs to be evaluated; ALGO 2005 was limited to only three CRFs (in addition to prior fracture history) and subsumed this into two groups dependent on whether there was a parental history of hip fracture. As such, the absolute fracture risks estimated by FRAX® 2012 and ALGO 2005 are not expected to be identical.

It is commented that FRAX appears to have been modified between August 2012 and May 2013, an evaluation of the changes that this would have has not been evaluated.

3. METHODS

The TA160 and 161 recommendations for alendronate are provided in

Table 1 for secondary prevention and Table 2 for primary prevention. The recommendations for risedronate are provided in Table 3 for secondary prevention and

Table 4 for primary prevention. Where cells are blank it indicates that identification and treatment was not recommended as this strategy was not considered cost-effective. In the analyses for secondary prevention the number of CRFs are in addition to the prior fracture, thus in secondary prevention a woman with one CRF would have an additional risk factor to the previous fracture.

It is commented that alendronate is recommended for primary prevention in women below 65 years although identification and treatment was not shown to be cost-effective in the analyses provided by the academic group; this was not the case for risedronate where treatment was not recommended in circumstances where the analyses did not demonstrate cost effectiveness.

TA160 and 161 also state that at ages above 75 years a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible and in the case of primary prevention the woman has two or more independent clinical risk factors for fracture or indicators of low BMD.

Table 1: T-Score threshold (SD) at which alendronate is recommended in secondary prevention

Number of CRFs	Age of woman (years)					
	50-54	55-59	60-64	65-69	70-74	75 and over
0	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5
1	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5
2 or more	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5

Table 2: T-Score threshold (SD) at which alendronate is recommended in primary prevention

Number of CRFs	Age of woman (years)					
	50-54	55-59	60-64	65-69	70-74	75 and over
0 *					-2.5	-2.5
1	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5
2 or more	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5

* and at least one indicator of low BMD

Table 3: T-Score threshold (SD) at which risedronate is recommended in secondary prevention

Number of CRFs	Age of woman (years)					
	50-54	55-59	60-64	65-69	70-74	75 and over
0		-3.0	-3.0	-3.0	-2.5	-2.5
1	-3.0	-3.0	-3.0	-2.5	-2.5	-2.5
2 or more	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5

Table 4: T-Score threshold (SD) at which risedronate is recommended in primary prevention

Number of CRFs	Age of woman (years)					
	50-54	55-59	60-64	65-69	70-74	75 and over
0					-3.5	-3.0
1				-3.5	-3.0	-3.0
2 or more				-3.0	-2.5	-2.5

The absolute risks of fractures corresponding to the recommendations in TA160 and 161 were estimated using two methods. The first method was to calculate the risks directly from FRAX® 2012. The second method was to construct a simple model using the ALGO 2005 data to estimate numbers of fractures. The simplified model was needed as the number of fractures was not recorded in the Assessment Group model used as part of the evidence base reviewed by the Appraisal Committee. As stated, the results presented to the Appraisal Committee used the median cost-effectiveness ratio from all combinations of possessing the specified number of CRFs. Therefore, if a woman had one CRF, the cost-effectiveness ratio was calculated for all five individual CRFs, were ranked and the third most cost-effective ratio presented in the results. For two CRFs, where there are ten potential combinations the average between the fifth and sixth ranked value was presented.

In the simplified model it was thus necessary to estimate the combination that would equate to the median cost-effectiveness. This cannot be conclusively determined by looking at fracture risks alone due to the different effect of hip and non-hip fractures. However, following a preliminary analysis the author has decided that assuming that if a woman had one CRF it was alcohol consumption, and if a woman had two risk factors it was smoking and corticosteroid use would be reasonable. It was deemed that any bias introduced by using these combinations would not be of importance within this feasibility study.

As the recommendations for alendronate were fairly broad and were in places more generous than the cost-effectiveness analyses suggested, a second intervention (risedronate) was selected so that a distinction could be made between the risks where a treatment was recommended, and the greatest T-Score at which treatment was not recommended. For example, if risedronate were recommended (for a given patient characteristic) at a T-Score of -3.5SD, it can be inferred that it was not recommended at a T-Score of -3.0SD, and the absolute risks associated with both values could be estimated. This was done to explore if there was an absolute risk threshold above which treatment was consistently recommended and below which it was not.

Estimating ten-year probability of fracture from FRAX® 2012.

The FRAX® algorithm for UK patients is available at

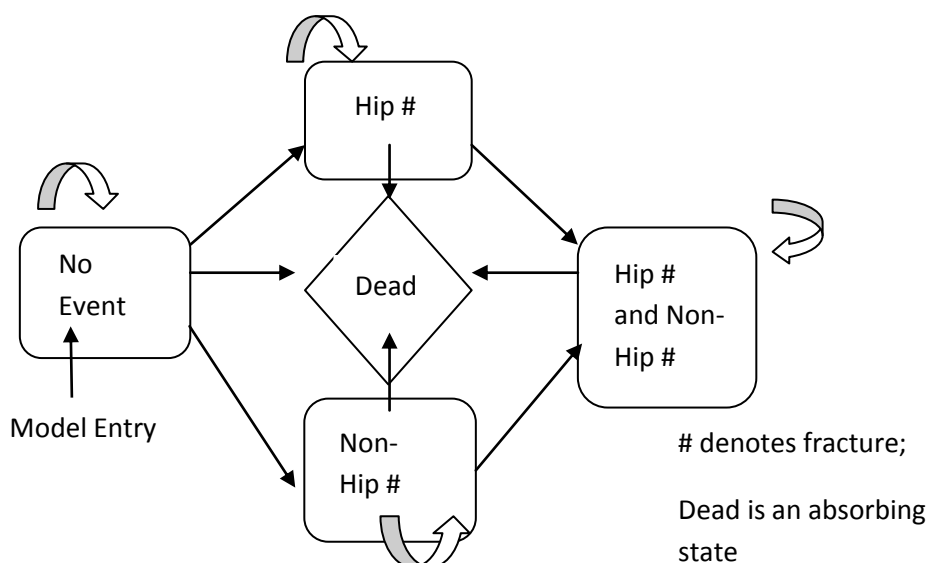
<http://www.shef.ac.uk/FRAX®/tool.jsp?country=1> and was accessed in August 2012. It was necessary to provide data on weight and height and an assumption was made that all women weighed 55kg and had a height of 160cm, which equates to a BMI of 21.5 kg/m². From a brief analysis of FRAX® 2012 and ALGO 2005 output it appeared that these height and weight values did not appear inappropriate, however this added additional uncertainty to the output.

Estimating the ten-year probability of fracture produced by the Assessment Group model.

Data from ALGO 2005 was used to estimate the assumed annual fracture risks for women with combinations of the following characteristics: Age (52.5, 57.5, 62.5, 67.5 and 72.5 years) T-Score (the values at which an intervention was recommended and not recommended) and number of clinical risk factors (0, 1 (assumed to be alcohol consumption) and two (assumed to be smoking and corticosteroid use). Data on underlying mortality risk, and the increased risks following hip fracture were taken from the model used by the Assessment Group. The simplified model used in this report did not consider mortality associated with vertebral fracture, which will cause an underestimation in the overall mortality rate. The conceptual model is displayed in

Figure 1.

Figure 1: The conceptual simplified model



The model employed a cohort-based state transition methodology with a time cycle of one year and a time horizon of ten years to align it with FRAX® 2012. As people moved through the model it was recorded whether they had a hip or non-hip fracture. FRAX® 2012 records solely the presence of a hip and the presence of a major fracture and not the predicted number of fractures, therefore a woman who had experienced both a hip and a non-hip fracture would be recorded as experiencing one hip and one major fracture, which leads to the same results as for a woman experiencing a hip fracture only. Due to the binary outcomes in FRAX® 2012 only one hip and one non-hip fracture was permitted. This limitation may underestimate the overall mortality rate as mortality due to second hip fractures would be excluded.

Comparison of ten-year absolute fracture risks estimated by FRAX® 2012 and estimated using the simplified model.

The results from each methodology were compared to assess their similarity. For brevity the comparison was made for both secondary and primary prevention at the midpoint of each age band (52.5, 57.5, 62.5, 67.5, 72.5 and 77.5 years), assuming a T-Score of -2.5SD and with zero, one and two CRFs. These have been presented as both absolute difference in fracture risks and as a linear regression. From this point onwards all risks of fracture are presented for a ten-year time horizon.

Exploring if a translation of the TA160 and TA161 recommendations into absolute risk, or a derivation of absolute risk for hip and other fractures, provides a sensible tool to achieve the alignment of the guideline and technology appraisal recommendations

Analyses were undertaken to assess whether a relatively simple algorithm was possible to develop that consistently generated absolute risk values that predicted if a treatment was recommended or not in TA160 and 161 (i.e. that had high sensitivity and specificity with respect to the NICE technology appraisals 160/101). This was operationalised by analysing the absolute fracture risks at which alendronate had been recommended and the absolute fracture risks at which risedronate had been recommended. Critically the absolute risks of fracture where risedronate was not recommended also need to be analysed. This will allow exploration of whether the risks differ between the circumstances where risedronate was recommended and where it was not. In circumstances where risedronate was recommended at a T-Score of $-2.5SD$ this was not possible (because no lower T-scores were considered in the appraisals), however where the T-Score threshold was higher (for example $-3.5SD$) then it can be inferred that risedronate was not recommended at a T-Score of $-3.0SD$. In scenarios where alendronate was not recommended it was assumed that this was due to the impact of identification costs and the data point was excluded from the analysis. Where there was no recommendation for risedronate but alendronate had been recommended then a value of $-3.5SD$ was assumed to be a representative T-Score at which risedronate had not been recommended.

A visual analysis was performed combining all data points regardless of whether risedronate had been recommended or not, and assessing whether it was possible to differentiate between the points associated with a positive and negative recommendation.

4. RESULTS

Comparison of absolute fracture risks predicted by FRAX® 2012 and those estimated to have been produced by the simplified Assessment Group model.

Figure 2 shows the differences between the risks for hip fracture and for major fracture in secondary prevention estimated by the simplified Assessment Group model and those produced by FRAX® 2012.

Figure 3 provides the same comparison for primary prevention. In both figures a positive value denotes that the Assessment Group risks estimated from the simplified model are higher than from FRAX® 2012.

The patterns between Figure 2 and Figure 3 are similar. In ages below 65 years the discrepancy between the two methods was relatively small (typically less than 5%) with the simplified model always estimated the major fracture risk as higher than FRAX® 2012. A large discrepancy was observed at age 67.5 years and 77.5 years for major fractures and at age 67.5 years for hip fractures.

It is neither known for certain why these discrepancies exist, nor why it is particularly large in those aged 67.5 years. Plausible explanations include: that the refined algorithm used in FRAX® 2012 has downwardly revised the likely probability of fracture due to a more mature data set; and that the BMI value assumed by the author is associated with a lower risk of fracture than the values of BMI (unknown to the author of this report) that were used in the formulation of ALGO 2005.

Figure 2: Absolute difference between major fracture risks estimated from the simplified Assessment Group model and those produced by FRAX® 2012

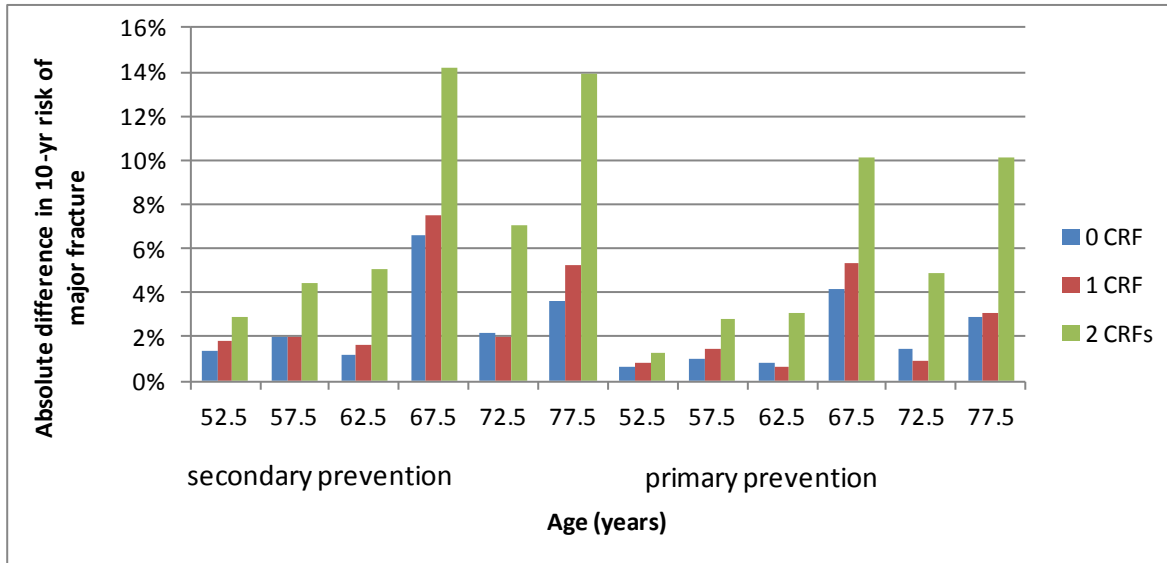
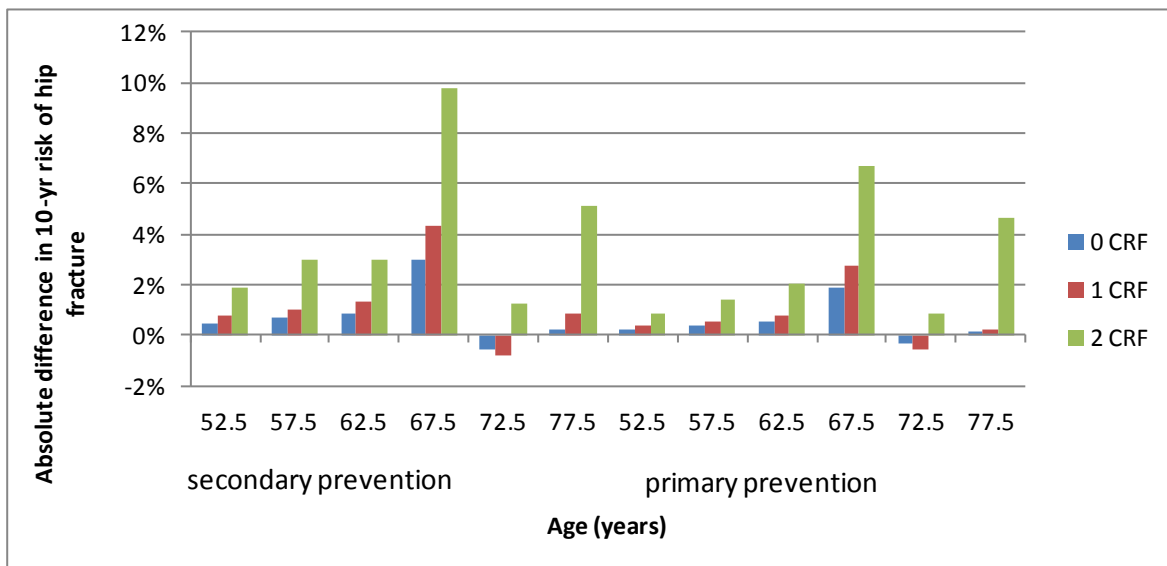


Figure 3 Absolute difference between hip fracture risks estimated from the simplified Assessment Group model and those produced by FRAX® 2012



These data have also been presented in terms of percentage difference between the two methods to take into consideration that the absolute risk is lower at younger ages. (

Figure 4 and Figure 5)

Figure 4 Percentage difference between fracture risks estimated by the simplified Assessment Group model and those produced by FRAX® 2012

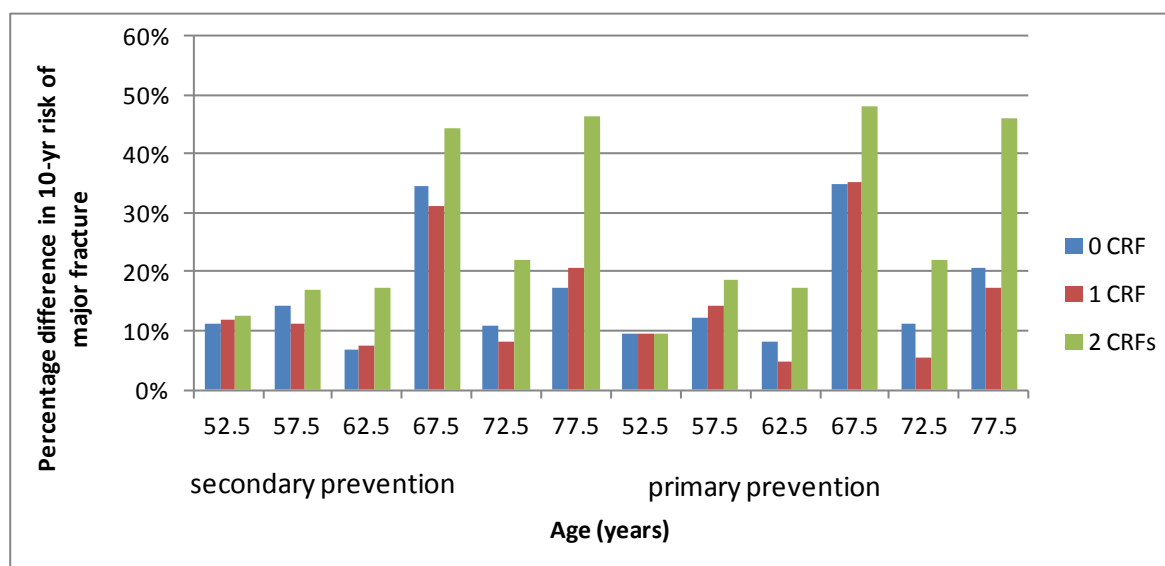
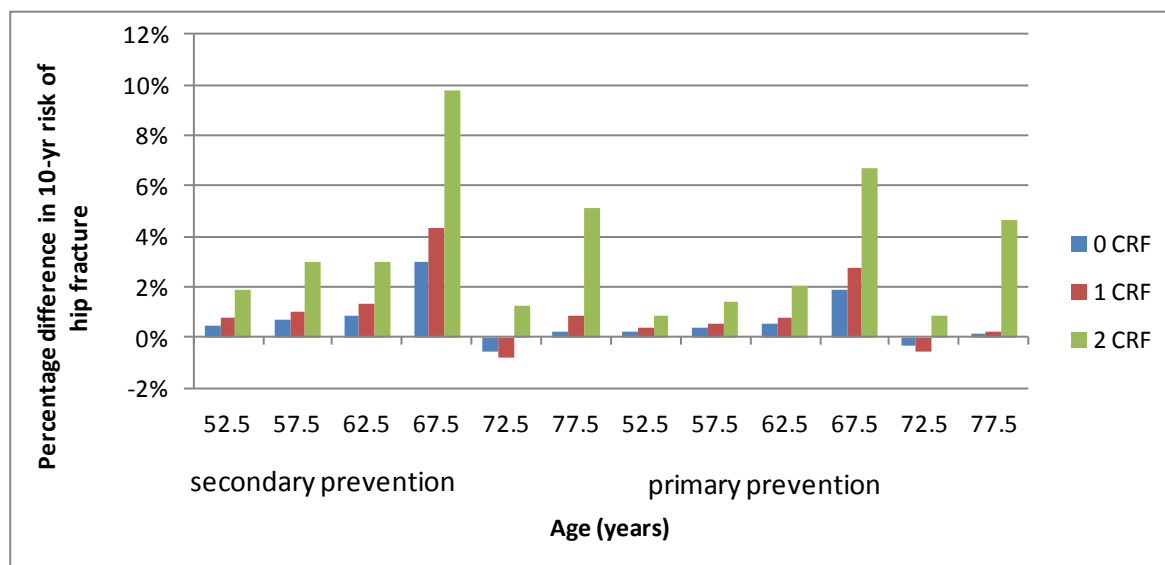


Figure 5 Percentage difference between hip fracture risks estimated by the simplified Assessment Group model and those produced by FRAX® 2012



The pattern is largely maintained, although the overestimation of fractures in women aged 77.5 is shown to be more consistent with other ages when presented in percentage terms.

For completeness regression analyses were undertaken assessing the ability of the absolute fracture risks in the simplified model to predict those produced by FRAX® 2012. The R^2 statistics are seen to be good, although as highlighted in Figure 2 through to Figure 5 the linear regression may hide particularly high discrepancies at certain ages and also systematic overestimation of fracture rates.

Figure 6 A regression analysis comparing absolute rates of hip fractures produced by FRAX® 2012 and the simplified model in secondary prevention

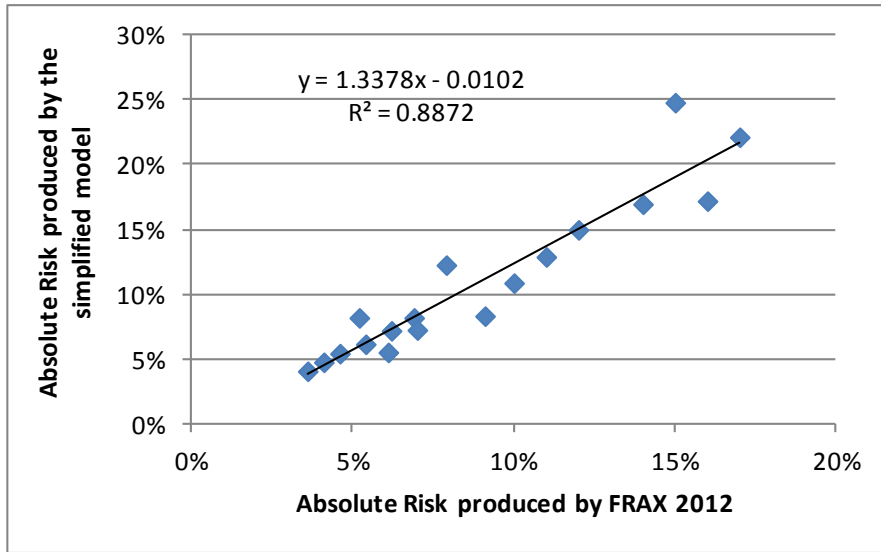


Figure 7 A regression analysis comparing absolute rates of major fractures produced by FRAX® 2012 and the simplified model in secondary prevention

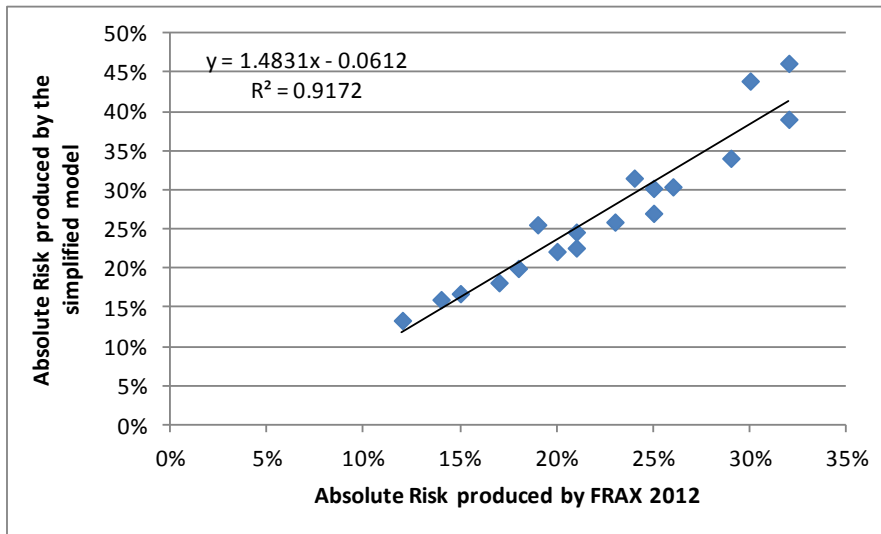


Figure 8 A regression analysis comparing absolute rates of hip fractures produced by FRAX® 2012 and the simplified model in primary prevention

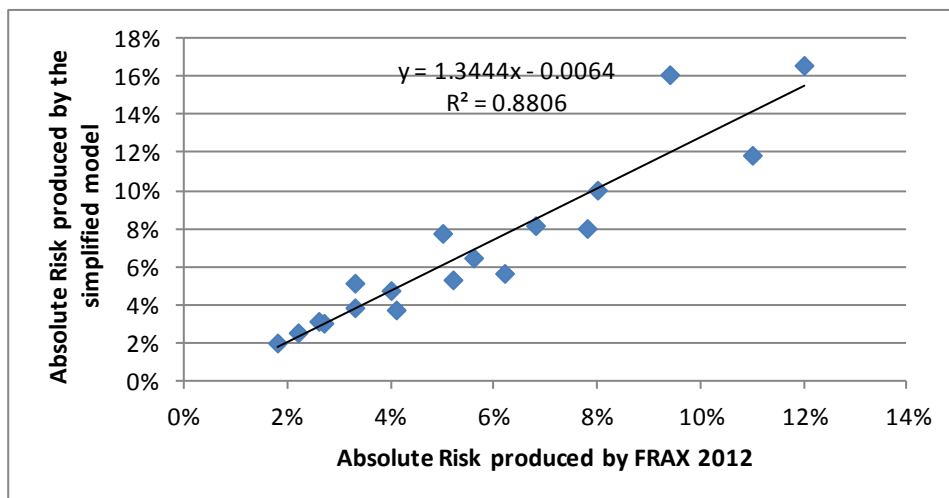
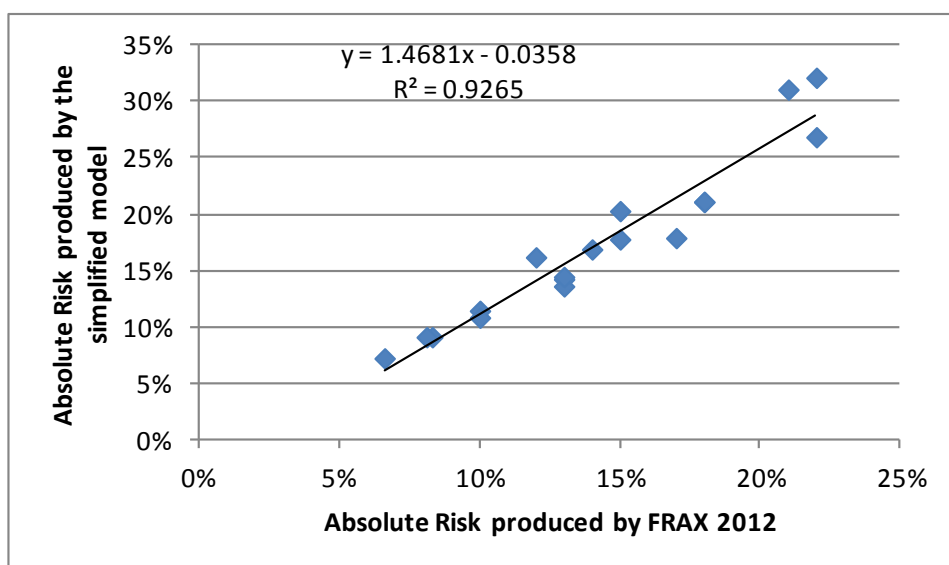


Figure 9 A regression analysis comparing absolute rates of major fractures produced by FRAX® 2012 and the simplified model in primary prevention



It can be concluded that the risks established by the two methods are reasonably similar, although the Assessment Group fracture risks estimated through the simplified model are higher than FRAX®2012, with this discrepancy increasing as the risk estimated by FRAX®2012 increases.

Exploring if a translation of the TA160 and TA161 recommendations into absolute risk, or a derivation of absolute risk for hip and other fractures, provides a sensible tool to achieve the alignment of the guideline and technology appraisal recommendations

Given that the clinical guideline (CG146) referred to FRAX® and that there was reasonable similarities between the risks produced by FRAX® 2012 and the results produced by the simplified model, it was decided to use FRAX® 2012 in assessing the absolute risks of fracture where alendronate and risedronate had been recommended or not recommended in TA160 and TA161. A further reason for using FRAX® 2012 was that this would have the most recent estimation of fracture risk.

The absolute risks of major fracture and hip fracture when alendronate was recommended are given in Figure 10 and

Figure 11, respectively. To make comparison easier the 18 scenarios for secondary prevention have been combined with the 18 scenarios for primary prevention to make 36 scenarios. The first three are for women aged 52.5 years with a prior fracture with zero, one and two CRFs, with scenarios 34, 35 and 36 representing women aged 77.5 years without a prior fracture and with zero, one and two CRFs respectively.

Figure 10 The absolute risk of major fracture at which alendronate was recommended in TA160 and TA161 calculated from FRAX® 2012

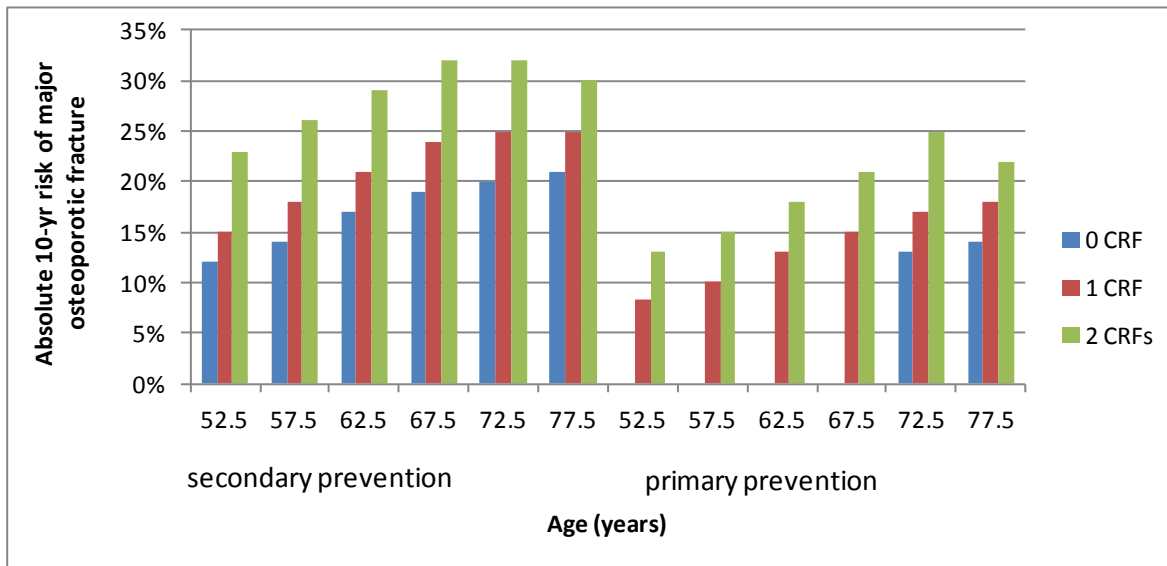
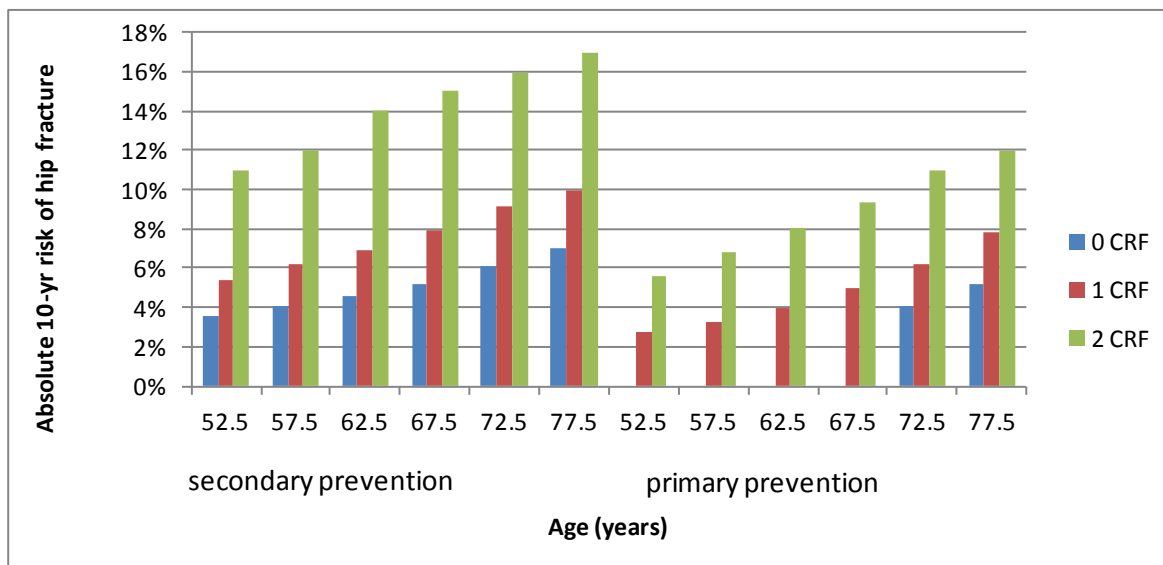


Figure 11 The absolute risk of hip fracture at which alendronate was recommended in TA160 and TA161 calculated from FRAX® 2012



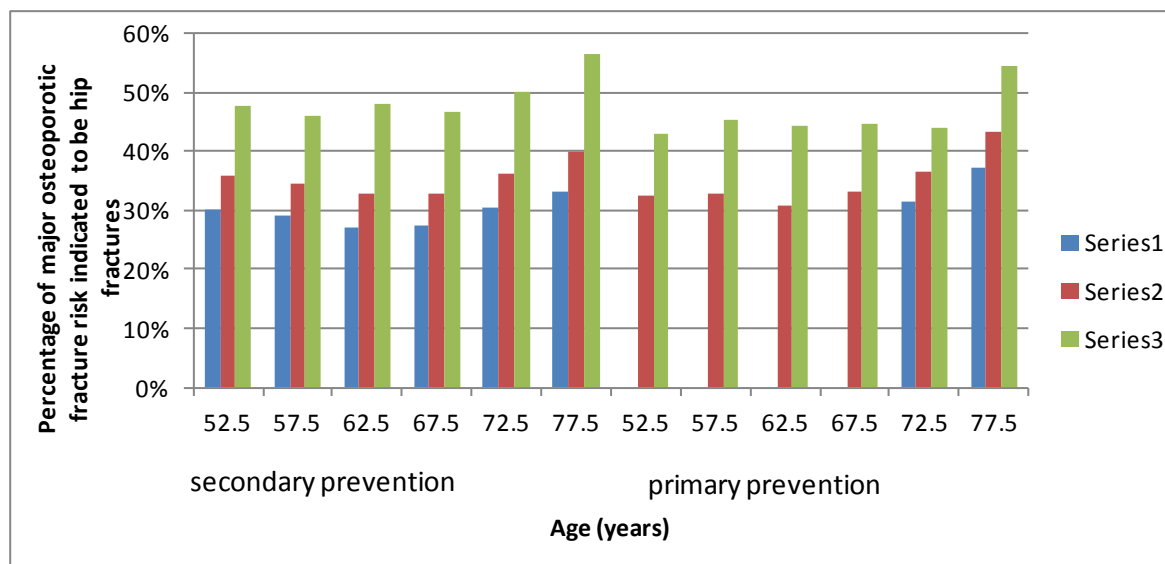
Broadly, alendronate was recommended at a T-Score of -2.5SD in all scenarios (see

Table 1 and Table 2). Where alendronate was not recommended, (primary prevention in women aged under 70 years with zero CRFs) this was not due to the cost-effectiveness of alendronate per se, but due to the high identification costs of identifying patients who could be effectively treated. This creates a difficulty for translating the recommendations from TA160 and 161 into an intervention threshold expressed as absolute risk of fracture.

In the circumstances where alendronate was recommended there is a discernible pattern which shows that the absolute risk of fracture intervention threshold increases as age increases and as the number of CRFs increases. Additionally the intervention threshold for a woman with a prior fracture is higher than those without a prior fracture. The lowest absolute risk of major fracture where alendronate was recommended was 8.30%, and the lowest absolute risk of hip fracture was 2.70%, both occurring in women without a previous fracture aged 52.5 years and with one CRF. (Figure 10)

An analysis on the proportion of major fractures that were hip fractures was undertaken. This was done to explore if the consideration of the proportion of fracture type leads to a measure more consistent with the TA160 and 161 recommendations across treatment groups (although this may be misleading as when a woman had both a hip and a non-hip fracture the non-hip fracture was excluded). These proportions are provided in Figure 12.

Figure 12 The proportion of major fractures indicated to be hip fractures when alendronate was recommended calculated from FRAX® 2012



A pattern can be seen that as the number of CRFs increases the proportions that are hip fractures also increase. This is due to the CRFs having a bigger effect on hip fractures than on non-hip fractures. The proportions were relatively constant across age, although there is an increase in the proportion of major fractures that are hip fractures when the absolute fracture risks are high, which may be accounted for by the fact that both hip and non-hip fractures have occurred, with the non-hip fracture excluded in the FRAX® 2012 output.

Data from alendronate alone is not sufficient to be able to provide an algorithm to ‘translate’ the current appraisal recommendations into absolute risk figures. This is because there are too few scenarios where alendronate was not recommended, and in these circumstances the guidance was driven by the identification costs. As such, data from risedronate was needed to be analysed using the same broad methodology as for alendronate. The two analyses are not entirely compatible, as the identification costs will have been borne when considering whether to prescribe alendronate which is not required for treatment with risedronate; however for the purposes of this paper we will assume the results are comparable.

The absolute risk of major fracture at which risedronate was recommended is given in Figure 13. There are fewer data points than for the corresponding alendronate figure (Figure 10) because risedronate, at its higher price, was not cost-effective for as many groups as was alendronate.

Figure 13 The absolute risk of major fracture at which risedronate was recommended in TA160 and TA161 calculated from FRAX® 2012

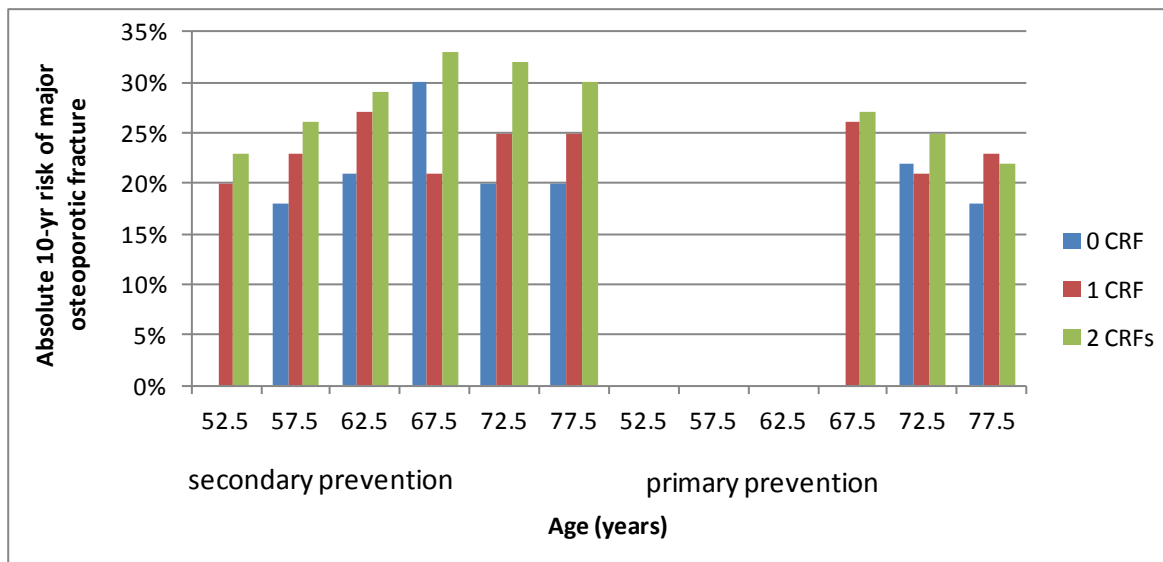
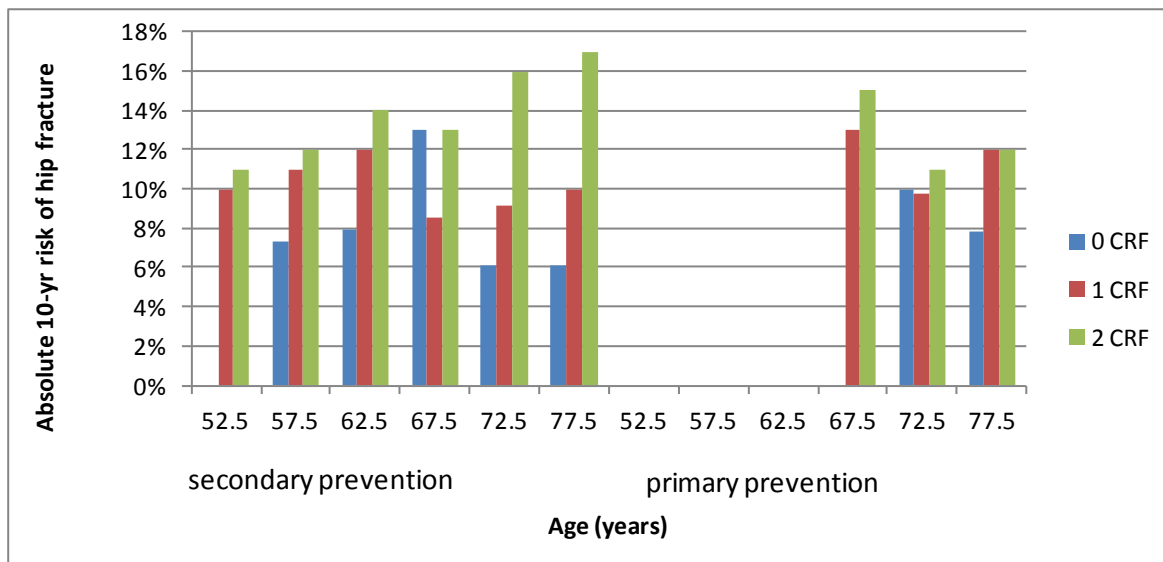


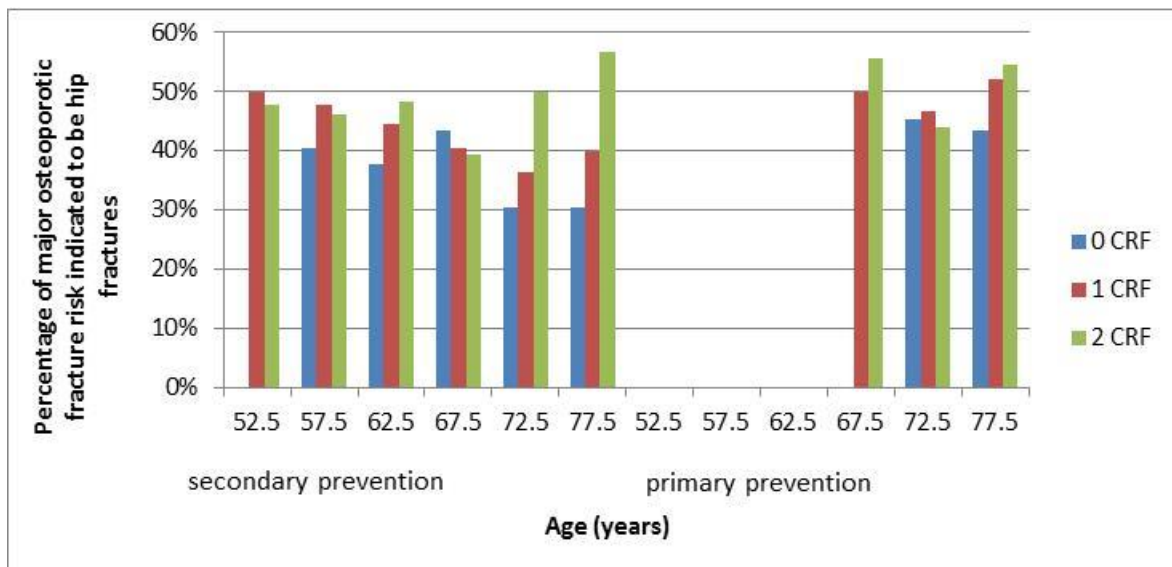
Figure 14 The absolute risk of hip fracture at which risedronate was recommended in TA160 and TA161 calculated from FRAX® 2012



There is less of a pattern in the risedronate data because the T-Score required for a positive recommendation is not always -2.5SD as it is for alendronate. For example in secondary prevention, aged 67.5 years with zero CRF, the T-Score needed was -3.0SD, when there was one CRF the T-Score required was -2.5SD, which resulted in the absolute risk of fracture being lower for patients with one CRF than for zero CRF. Similarly there is less of a pattern in the proportion of major fractures indicated to be hip fractures. (

Figure 15). The lowest absolute risk of major fracture where risedronate was recommended was 18.0%, and the lowest absolute risk of hip fracture was 6.10%, (Figure 13) although these were in different scenarios: age 57.5 years with fracture and with 0 CRFs and age 72.5 years with fracture and 0 CRFs respectively. The values were higher for risedronate than alendronate due to the increased acquisition cost of risedronate compared with alendronate.

Figure 15 The proportion of major fractures indicated to be hip fractures when risedronate was recommended calculated from FRAX® 2012



Further analyses were undertaken showing the absolute fracture risks at which risedronate was not recommended. These are provided in

Figure 16, Figure 17 and Figure 18.

Figure 16 The absolute risk of major fracture at which risedronate was not recommended in TA160 and TA161 calculated from FRAX® 2012

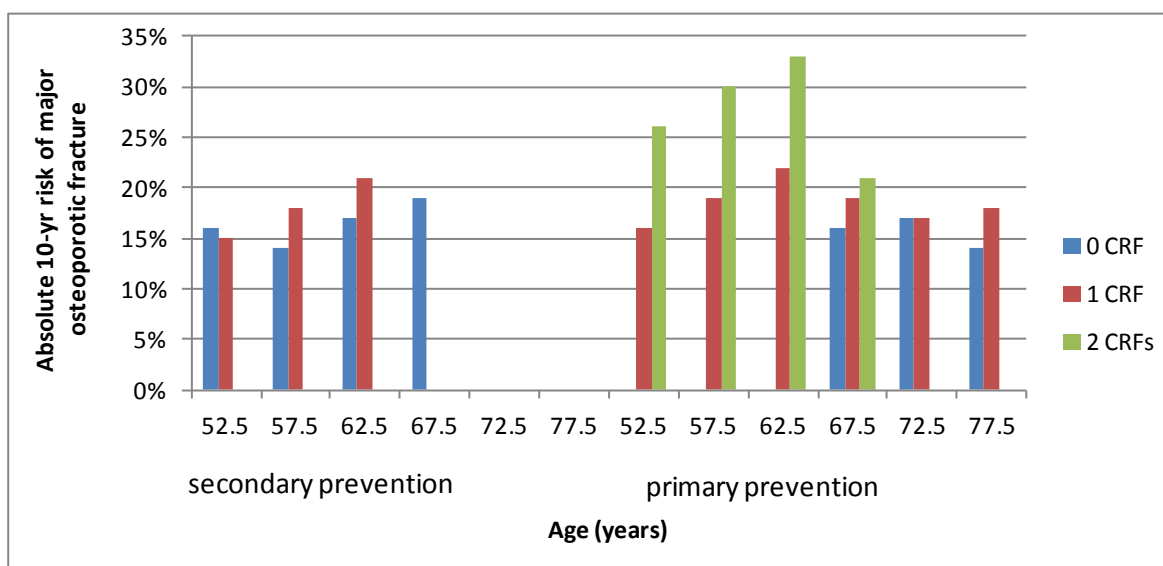
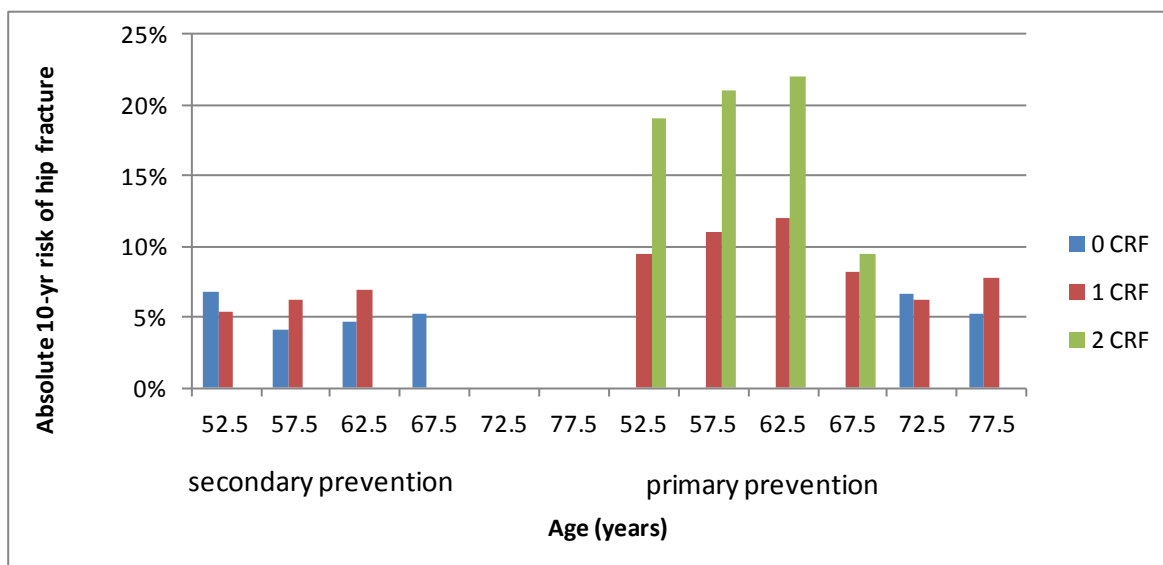
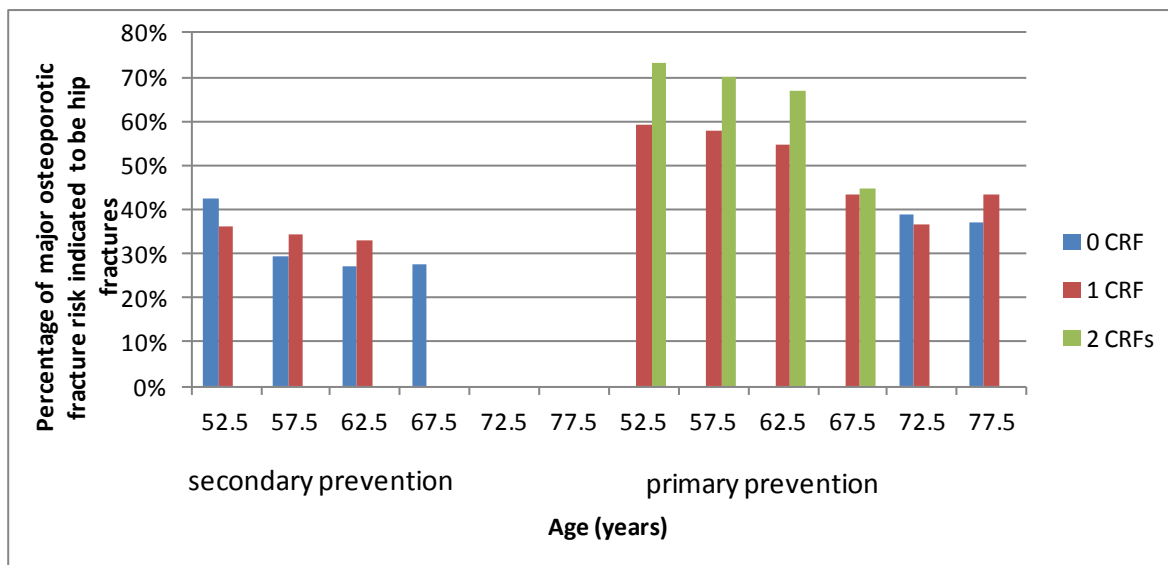


Figure 17 The absolute risk of hip fracture at which risedronate was not recommended in TA160 and TA161 calculated from FRAX® 2012



Similarly to the analyses where risedronate was recommended there is less of a pattern than in the alendronate data due to different T-Score threshold between scenarios. The highest absolute risk of major fracture where risedronate was not recommended was 33.0%, and the highest absolute risk of hip fracture was 22.1%, both for a 62.5 year old woman with two CRFs and an assumed T-Score of -3.5SD. These values contrast with the lowest absolute risk of major fracture where risedronate was recommended which was 18.0%, and the lowest absolute risk of hip fracture which was 6.10%

Figure 18 The proportion of major fractures indicated to be hip fractures when risedronate was not recommended calculated from FRAX® 2012



Data on the proportion of major fracture that were indicated to be hip fractures showed that this proportion could vary considerable, from below 30% in younger women with a prior fracture but without CRFs to approaching 80% in younger women without a prior fracture but with two CRFs.

Do absolute risk figures show a differentiation between circumstances where risedronate was recommended and where risedronate was not recommended?

A visual analysis of the absolute risks for risedronate regardless of recommendation decision was carried out.

Figure 19 provides information of the absolute risk of major fracture in which risedronate was recommended and not recommended.

Figure 20 details the absolute risk of hip fracture with

Figure 21 providing the percentage of major fracture indicated to be hip fracture. In all figures red indicating that risedronate was not recommended with blue indicating that risedronate was recommended. As some scenarios have two points, representing when risedronate was recommended and when it was not, a different presentational format has been adopted. There are 36 scenarios which align with the scenarios presented in the previous figures (for example Figure 10) with scenario one representing a 52.5 year old woman with a prior fracture and no further CRFs, with scenario 36 representing a 77.5 year old woman without a prior fracture and with two CRFs

Figure 19 The absolute risk of major fracture at which risedronate was recommended and not recommended in TA160 and TA161

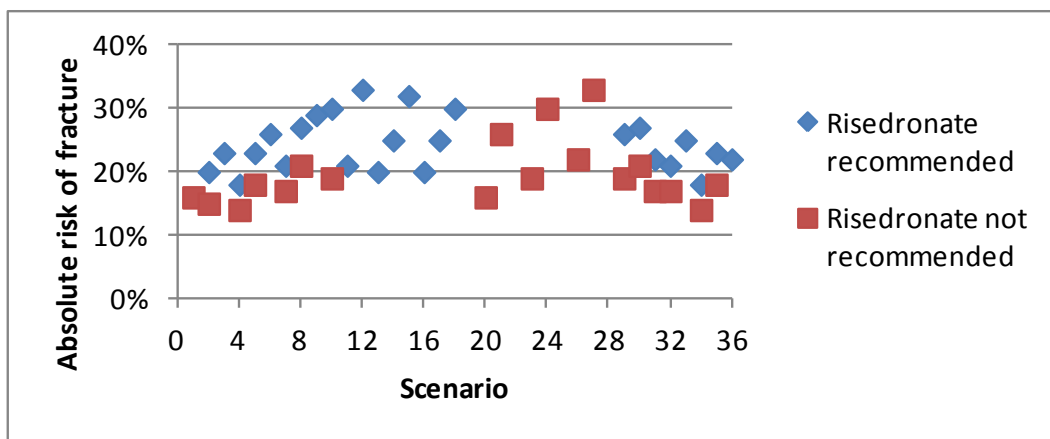


Figure 20 The absolute risk of hip fracture at which risedronate was recommended and not recommended in TA160 and TA161

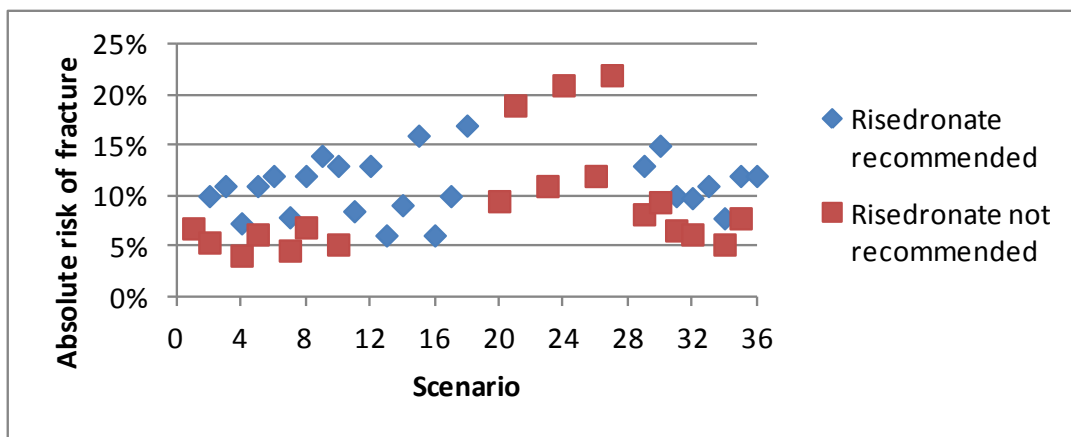
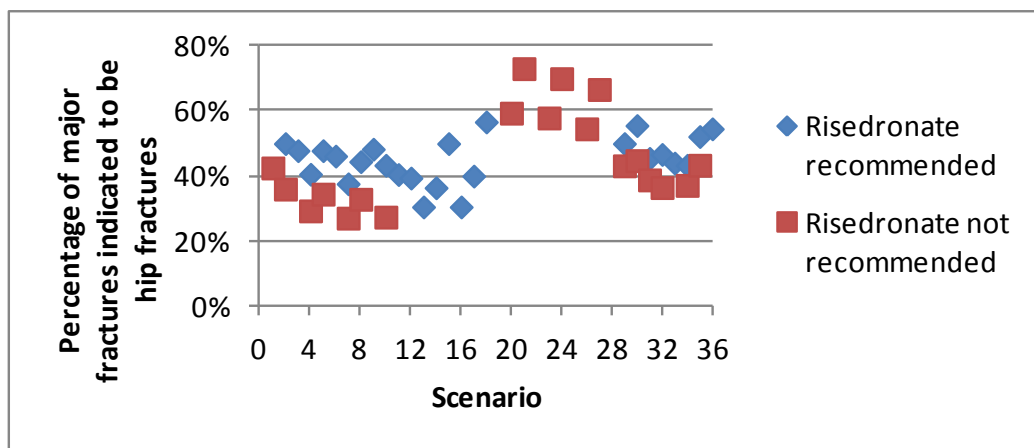


Figure 21 The percentage of major fracture indicated to be hip fracture where risedronate was recommended and not recommended in TA160 and TA161



These analyses appear to indicate that it would not be straightforward to develop an algorithm to translate the current intervention thresholds in in TA160 and TA161 into absolute risks of major fracture, hip fracture or percentage of major fractures. This is because of a number of anomalies which have been fully described within the introduction.

In order to address these anomalies, an alternative approach was undertaken. The minimum risks were calculated at which alendronate and risedronate were recommended, regardless of age, prior fracture status, probability of death from hip fracture.

The lowest absolute risk of major fracture where alendronate was recommended was 8.30%, and the lowest absolute risk of hip fracture was 2.70%, both occurring in women without a previous fracture aged 52.5 years and with one CRF. The lowest absolute risk of major fracture where risedronate was recommended was 18.0%, and the lowest absolute risk of hip fracture was 6.10%, although these were in different scenarios: age 57.5 years with fracture and with 0 CRFs and age 72.5 years with fracture and 0 CRFs respectively. The values were higher for risedronate than alendronate reflecting the increased acquisition cost of risedronate compared with alendronate.

An analysis was undertaken to assess the T-Score required for patients without prior fracture to have an estimated 10-year risk of major fracture in excess of 18.0%. These data are shown in Figures 22 and 23 for women with no CRFs and 1 CRF respectively. It is seen that in those women with 0 CRF the T-Score required at a younger age is -4.0 SD, which decreases to -3.0SD at older ages. A similar pattern is seen where a woman is assumed to have 1 CRF, although the required T-Score falls to -2.5SD at age 77.5 years.

Figure 22 The 10-year risk of absolute fracture in women without a prior fracture and with 0 CRF by T-Score and age

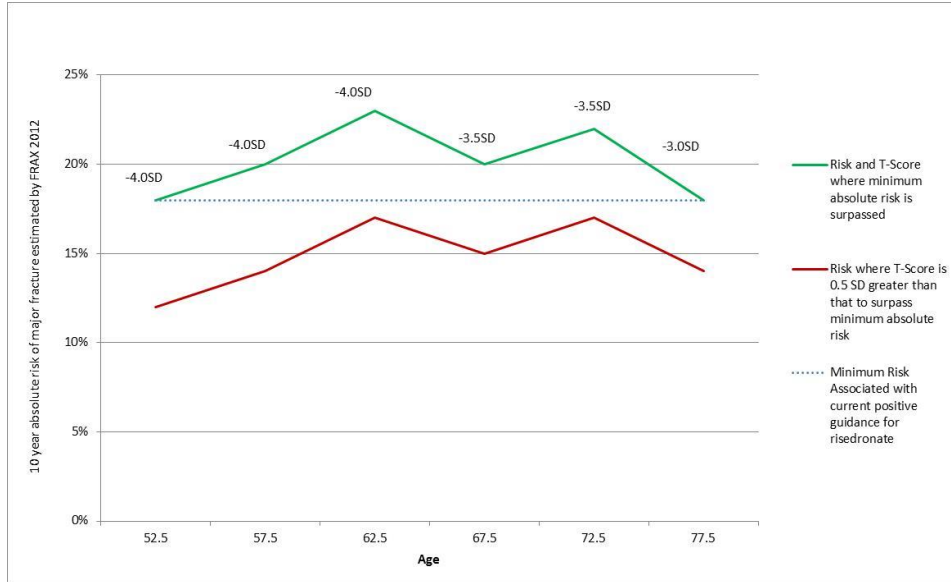
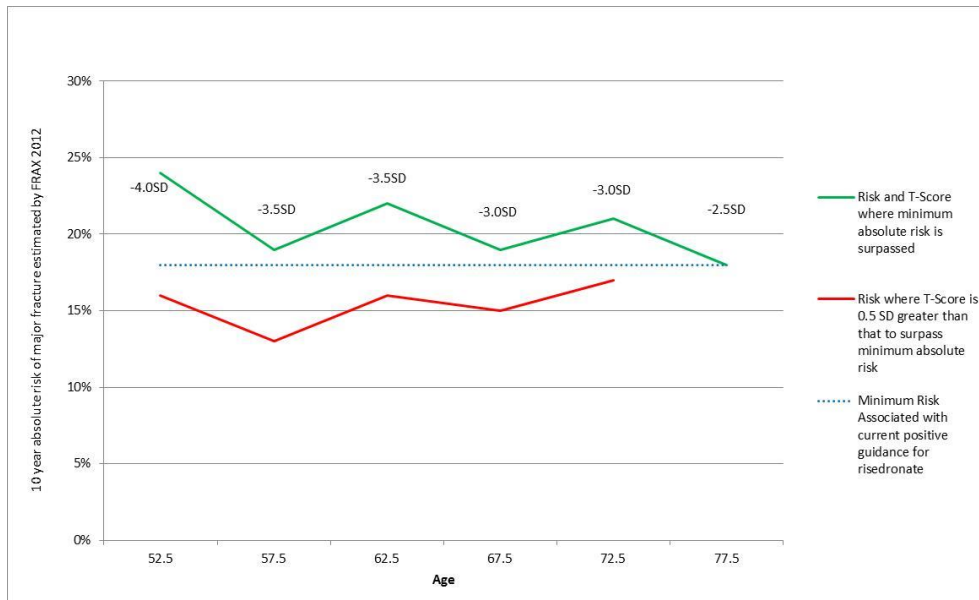


Figure 23 The 10-year risk of absolute fracture in women without a prior fracture and with 1 CRF by T-Score and age



It is uncertain whether the absolute fracture risks assumed for positive guidance in women with a previous fracture are appropriate to use in women without a prior fracture. This was encountered in TA160 and TA161 where a different willingness to pay for a QALY was assumed between the two groups signifying that treatment (and potential adverse events) in women who are asymptomatic was less desirable than in women who had already sustained a fracture.

In women with a prior fracture risedronate was recommended (with T-Score constraints) in TA161 for all excluding those aged 50-55 with 0 CRF. The T-Score required to reach an estimated 10-year risk of major fracture in excess of 18.0% was -3.5SD.

5. DISCUSSION

This report has attempted to address the following two key questions

- 1) What are the absolute risk values (hip and other major fractures as defined by FRAX® 2012) for the groups of people for whom alendronate is recommended in TA160 and TA161?

These values have been calculated from FRAX® 2012 and are given in Figure 10 and

Figure 11. These values are reasonably similar to the results from a simplified model replicating the Assessment Group model used in TA160 and TA161, although the simplified model regularly produces a larger value than FRAX® 2012. However, the algorithm underpinning FRAX has been updated since 2005 and so some inconsistency is not unexpected.

- 2) Is it possible to develop an algorithm that translates the recommendations from TA160 and TA161 in terms of ten-year absolute risk of fracture?

The difficulties in using absolute risk of fracture in developing the model submitted as evidence to the Appraisal Committee were documented in the introduction. These highlighted the potential disparity between isolated measures of fracture risk and the other parameters required for a formal economic evaluation, as well as the constraint of the scope considering only women with a T-Score of -2.5SD or lower. The analysis of the absolute fracture risks where treatment was, and was not, recommended according to TA160 and TA161 showed some inconsistencies. However, a practical way forward may be to use minimum fracture risk levels at which treatment can be recommended for the interventions included in the technology appraisals. This approach would require a discussion on the benefits of this simplified approach in relation to the potentially large numbers of treatments being provided which may not be cost-effective under the current recommendations. An example of this would be for a specific group where an absolute fracture risk of 14% was required for treatment to be cost-effective however the lowest value where positive guidance was produced was 12%. In this circumstance women within the specific group with a fracture risk between 12-14% would not have previously received treatment. The approach would also require a discussion on the generalisability of absolute fracture risks from a population with a prior fracture history to those without a prior fracture.

6. CONCLUSIONS

From the analyses undertaken within this report it does not appear straightforward to generate an algorithm based on absolute fracture risk (including ratio of hip to major fractures) that could robustly predict a positive recommendation in TA160 or TA161. However, a pragmatic way forward may be to assume a minimum fracture risk level. The acceptability of such an approach depends on weighing up the issues associated with a potentially very complex appraisal review with the advantages of combining already available recommendations in simplified form.