Chair's presentation

Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161)

2nd Appraisal Committee meeting

Committee B

Chair: Sanjeev Patel

Assessment Group: University of Sheffield - ScHARR

NICE technical team: Henry Edwards, Ahmed Elsada

23rd May 2017

For committee, projector & public

Preview of key issues for consideration

- Does the committee's consider the use of pooled efficacy estimates for bisphosphonates acceptable for decision making?
- Is committee satisfied that the approach to modelling residential and nursing care is appropriate?
- Should the cost effectiveness of oral and intravenous bisphosphonates be considered separately?
- Are the differences in risk thresholds between QFracture and FRAX important?
- Should consideration be given to which treatment has the highest incremental net benefit?
- Are there any equality issues that committee needs to consider?

Appraisal history

Events	Actions
Review of TA160, TA161 & TA204 (Feb 2014)	• Decision to have MTA
Submissions (Jan 2015)	• 29 companies invited, 2 (Rosemont and Actavis) submitted clinical evidence • Submissions also received from 6 consultees
Assessment group report (March 2015)	• Assessment group developed economic model and reported findings of clinical and cost effectiveness in the Assessment group report
ACM 1 (June 2015)	• Committee could not make a recommendation • No ACD released
Subcommittee	• Assessment group asked to examine areas of uncertainty
Assessment group addendum (Dec 2016)	• Assessment group addendum report and revised base case results
Consultation (Feb 2017)	• No comments received

Objective today

- To define patients in whom it would be cost effective to offer:
  - Oral bisphosphonates
    - (alendronate, ibandronate and risedronate)
  - IV bisphosphonates
    - (ibandronate and zoledronate)

- The committee is not defining:
  - In whom to determine fracture risk
  - How to determine fracture risk
  - Fracture risk thresholds for treatment

Summary technology appraisals
TA160 and TA161 (2008 and revised in 2011)

- Postmenopausal women without prior fracture (TA160) and women with a history of an osteoporotic fracture (TA 161)
- Fracture risk defined by combinations of clinical risk factors and BMD measurements

- Guidance - Bisphosphonates
  - Alendronate recommended 1st line:
  - Risedronate and etidronate recommended at higher fracture risk
  - (No guidance for ibandronate as not licenced at that time
- Guidance also given for non-bisphosphonate drugs (raloxifene, strontium ranelate and teriparatide)

Clinical Guideline *CG146*

Clinical Guideline - Osteoporosis: assessing the risk of fragility fracture (2012)

- Target risk assessment:
  - In all women aged ≥65 years and all men aged ≥ 75
  - In women aged <65 years and men aged <75 years in the presence of risk factors (e.g. previous fragility fracture, glucocorticoids, history of falls)
  - Do not routinely assess risk in people aged under 50 years unless they have major risk factors
- Estimate 'absolute' fracture risk
  - Use either of 2 risk calculators: FRAX (without BMD) or QFracture
  - If results in the "region of an intervention threshold …" recalculate absolute risk using FRAX with value for BMD
- Intervention thresholds
  - "It is out of the scope of this guideline to recommend intervention thresholds. Healthcare professionals should follow local protocols or other national guidelines for advice on intervention thresholds"

(N.B. BMD = bone mineral density)

Quality standard on Osteoporosis
(published 28th April 2017)

- Statement 1 Adults who have had a fragility fracture or use systemic glucocorticoids or have a history of falls have an assessment of their fracture risk (FRAX or QFracture) (*NB: not age stratified as in CG146*)
- Statement 2 Adults at high risk of fragility fracture are offered drug treatment to reduce fracture risk.
  - High risk of fracture and intervention thresholds defined for FRAX (*NB: No mention of QFracture*)

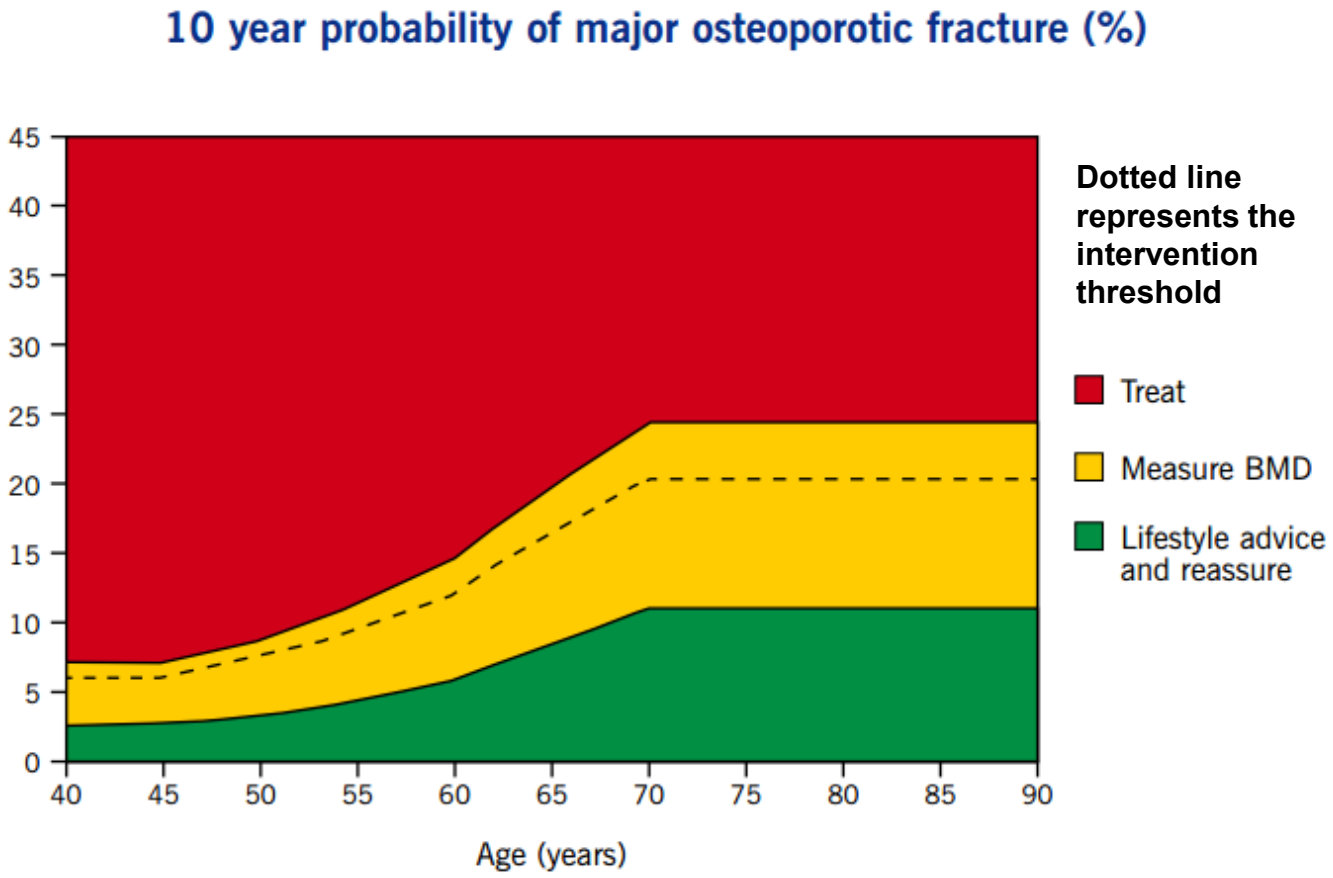
Age	40	45	50	55	60	65	≥70
10 year probability of a major osteoporotic fracture (%)	5.9	6.0	7.2	9.4	12	16	20

Source: Table 1, QS149 (based on National Osteoporosis Guideline Group)

Intervention thresholds

National osteoporosis guideline group assessment and intervention thresholds in the UK for major osteoporotic fracture probability

- NICE accredited
- Treatment threshold based on FRAX probability
- Intervention threshold <70 years old set at a risk equivalent to that associated with a prior fracture – rises with age
- Proportion of women eligible for treatment rises from around 30% to 50% with age - driven by prior fracture prevalence



Source: Figure 2, NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis

Review Proposal

Review of TA160, TA161 & TA204 (2015)

The review found that:

- the guidance is not aligned with the clinical guidelines
    - Need to link absolute fracture risk with intervention thresholds, based on cost effectiveness
- Need for clearer, less complex guidance
- The current guidance means that if a treatment is not tolerated, a patient may not be eligible for an alternative treatment until their fracture risk increases
- Guidance needed for men
- The guidance does not take account of the significant drop in the price of bisphosphonates since they are available as generics.

The objective of this MTA is to align the technology appraisal guidance with that of the clinical guideline and to provide guidance for men, whilst addressing additional concerns.

Committee conclusions at Appraisal

Committee Meeting in 2015

Clinical effectiveness of bisphosphonates

Issue	Conclusion
Clinical need	• Important to patients and clinicians
Clinical management	• Bisphosphonates prescribed to people with the highest risk of osteoporotic fracture
Fracture risk assessment tools	• FRAX v QFracture: Not possible to determine which provided a more accurate & comprehensive assessment • Guidance needs to account for the variation in practice and differences between the tools
Efficacy of bisphosphonates	• Bisphosphonates are all more clinically effective than placebo in reducing the risk of fractures • No substantial differences in effectiveness between the treatments - assuming a class effect is appropriate

Committee conclusions at Appraisal

Committee Meeting in 2015

Cost effectiveness of bisphosphonates

Issue	Conclusion
Bisphosphonate costs	• Lowest acquisition costs should be used
Nursing home and care home costs	• Should be modelled separately.
Adverse events	• Adverse event rate between 15% and 25% should be explored
Survival extrapolation	• Assessment group's approach is appropriate
Cost effectiveness	• Different tools (FRAX and QFracture) provided different levels of costs effectiveness at different levels of absolute fracture risk
Provisional recommendation	• No recommendation was made

Committee's request for further analyses

as defined by a subcommittee

- Requested additional analyses on:
  1. Pooling efficacy of IV and oral bisphosphonates
  2. Separate nursing home and residential care costs
  3. External validity and UK context of results
- Report received on December 2016
- Consultation in January and February 2017
  - No comments received from consultees and commentators
- Assessment group found error in one of the model parameters
- Assessment group corrected the model and provided an updated report (April 2017)

Technologies

Bisphosphonates – summary of generics

Treatment/Dosage	Price per pack	Cost per annum
Alendronate (oral tablets) 10mg	Not used in model	
Alendronate (oral tablets) 70mg (4/pack)	£0.87[a]	£11.34
Alendronate (oral solution) 70 mg/100 mL	Not used in model	
Ibandronate (oral tablet), 150mg (1/pack)	£1.32[a]	£15.84
Ibandronate (IV) 3mg / 3ml (1 vial)	£8.51[b]	£34.04
Risedronate (oral tablet) 35mg (4/pack)	£0.98[a]	£12.78
Risedronate (oral tablet), 5 mg	Not used in model	
Zoledronate (IV) 1 x 5mg / 100ml	£9.18[b]	£9.18

a, National Drug tariff (May 2016); **b** eMIT database (data from 12 month period to end June 2015)

Revised network meta analysis results

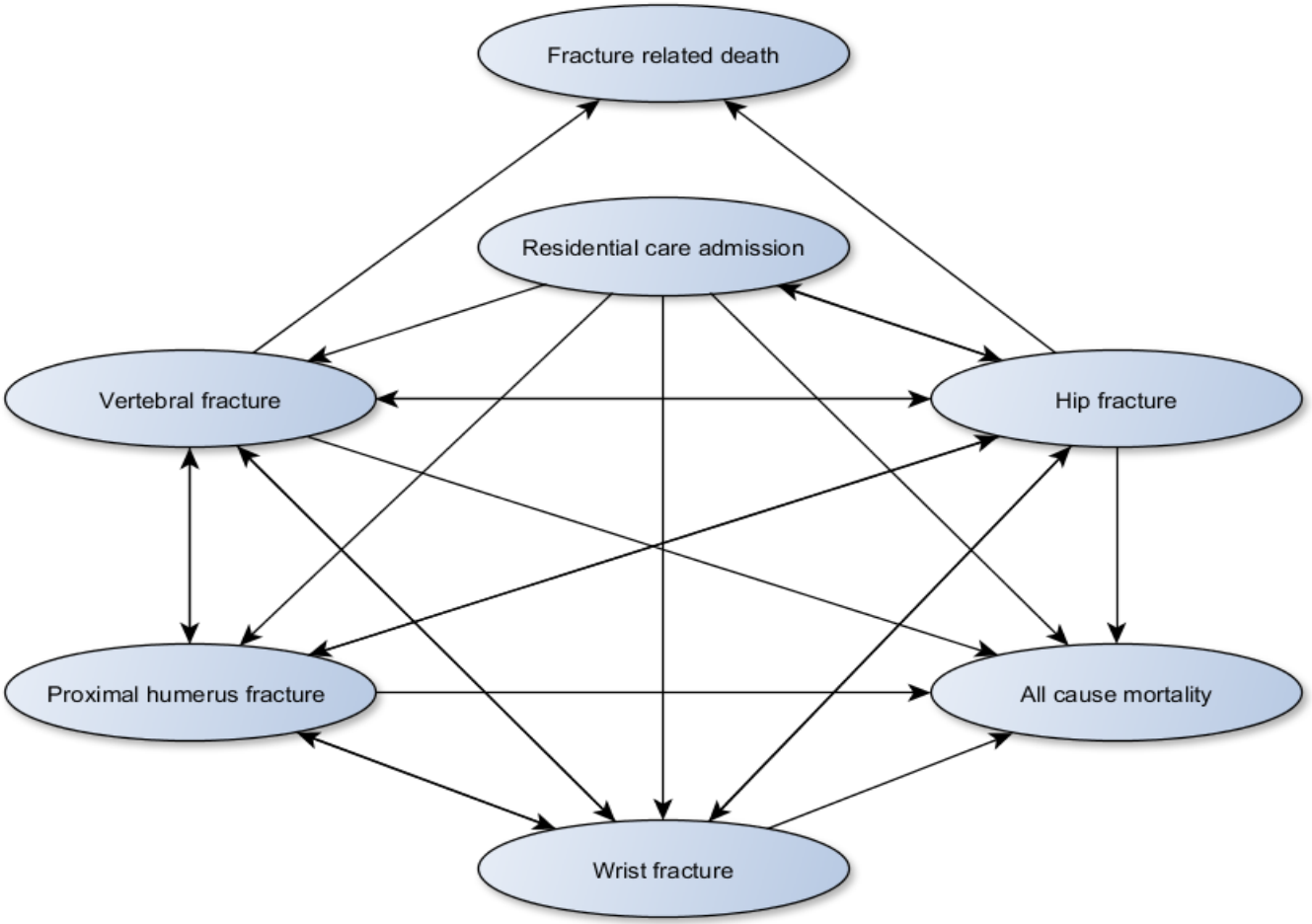
Results revised after Assessment group corrected input error

	Hip	Vertebral	Proximal humerus	Wrist
Hazard ratios (95% credible intervals)				
Alendronate	0.66 (0.41 – 1.05)	0.45 (0.25 – 0.79)	0.80 (0.54 – 1.07)	0.83 (0.34 - 1.86)
Risedronate	0.69 (0.44 – 1.10)	0.51 (0.27 – 0.84)	0.71 (0.49 – 1.02)	0.76 (0.32 – 1.78)
Ibandronate (oral)	0.68 (0.37 – 1.38)	0.45 (0.21 - 0.96)	0.80 (0.49 – 1.43)	0.83 (0.31 – 2.39)
Ibandronate (i.v.)	0.68 (0.37 – 1.38)	0.47 (0.25 - 0.86)	0.92 (0.59 – 1.43)	0.83 (0.31 – 2.39)
Zoledronate (i.v.)	0.65 (0.42 – 1.02)	0.41 (0.23 – 0.76)	0.75 (0.53 – 1.05)	0.81 (0.28 - 2.34)

Source: Table 2, Assessment report addendum

Model structure

Discrete event simulation model



- Shows the events that are possible and the paths patients can take between events

Model assumptions

- Population: All patients eligible for risk assessment under Clinical guideline146:
  - All women ≥ 65 years and all men ≥ 75 years
  - Women aged < 65 years and men < 75 years in the presence of risk factors (e.g. previous fragility fracture)
- Results presented in risk categories subdivided into deciles - each risk category contains one tenth of the population eligible for risk assessment.
- Uses estimates of cumulative risk over a defined time frame (10 years for FRAX and 1 to 10 years for QFracture)
- Fracture risk for each fracture site incorporated separately – age and gender included in fracture risk
- After each event occurred, risk of fracture increased, and after hip fractures, patients could move to a nursing home
- Fractures were limits by the total number of fractures on each site
- Adverse events included were GI symptoms (oral bisphosphonates) and flu-like symptoms (intravenous bisphosphonates)
- Risk of death captured by all-cause mortality and fracture-related deaths

Assessment report revised base case

From Assessment report addendum

- The Assessment group's revised base case included:
  - pooled efficacy estimates for bisphosphonates
  - separate unit costs for nursing homes and residential care homes
  - updated drug costs

Pooling of efficacy

For IV and oral bisphosphonates

- The efficacy estimates of oral and i.v. bisphosphonates were pooled for each fracture site but the costs and adverse effects are modelled separately for each bisphosphonate treatment strategy
  - If a technology had multiple prices the lowest was taken
  - Treatment duration and impact of adverse events were assumed to be equivalent for all oral bisphosphonates
  - Treatment duration was longer for intravenous compared to oral bisphosphonates
- Pooled mean hazard ratio for all bisphosphonate was taken from the network meta-analysis for each fracture site

Pooling of efficacy by fracture site

Revised estimates after input error corrected

	Hip	Vertebral	Proximal humerus	Wrist
Hazard ratio (predictive interval)				
Alendronate	0.66 (0.41 – 1.05)	0.45 (0.25 – 0.79)	0.80 (0.54 – 1.07)	0.83 (0.34 - 1.86)
Risedronate	0.69 (0.44 – 1.10)	0.51 (0.27 – 0.84)	0.71 (0.49 – 1.02)	0.76 (0.32 – 1.78)
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Hazard ratios applied in the updated analysis (credible intervals)				
All bisphosphonates	0.67 (0.48- 0.96)	0.45 (0.31 – 0.65)	0.79 (0.58 – 1.11)	0.81 (0.46 – 1.44)

Source: Table 2, Assessment report addendum

- *Has the committee seen anything that changes its view about using a pooled efficacy estimate for decision making?*

Nursing home and residential care
Model costs separately

- Original model: considered nursing home and residential care costs as identical
  - In practice costs are different dependent on care
- Revised approach: Assessment group adapted the model to allow for separate costs unit costs to be applied for long-term care provided in nursing home and residential care
- Annual cost of care following new admission to long-term care reduced from £36,500 to £23,500

Other model revisions

- Drug costs were updated to reflect latest unit costs (see slide13)

⊙ *Is committee satisfied that the approach to modelling residential and nursing care costs is appropriate?*

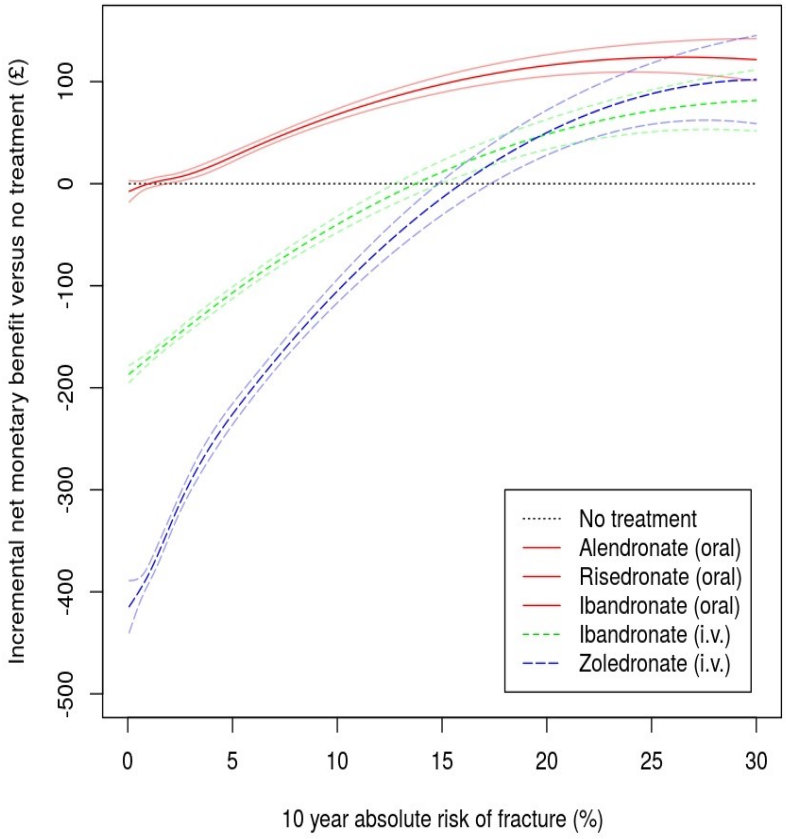
Results using Incremental Net Benefits

- Very small differences in costs and QALYs
- Assessment group examined threshold of risk for fracture at which bisphosphonates become cost effective
- Present results as incremental net benefits
  - QALYs are ‘monetised’ using an ‘exchange rate’ (ICER threshold)
  - This is the ‘Net Monetary Benefit”
  - Net Monetary Benefit of treatment minus Net Monetary Benefit of alternative is the Incremental Net Benefit
- A **positive** Incremental Net Benefit indicates a treatment could be considered cost effective at (for example) £20,000 per QALY, compared with no treatment.

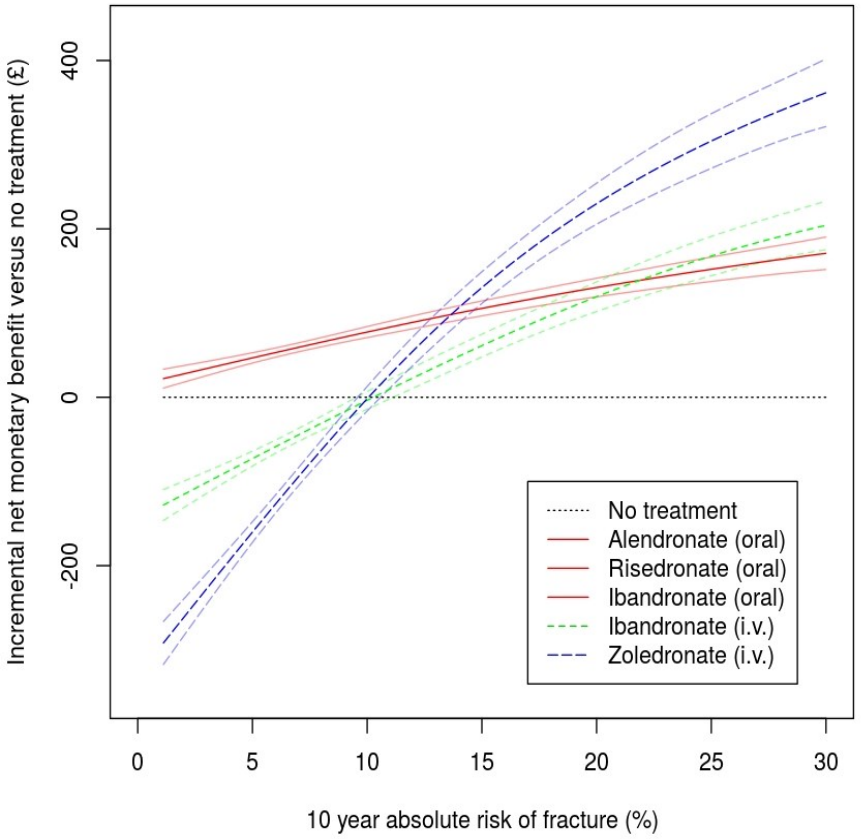
Revised base case regression for Incremental Net Benefit

compared with no treatment against 10 year fracture risk, valuing QALY at £20,000

QFracture

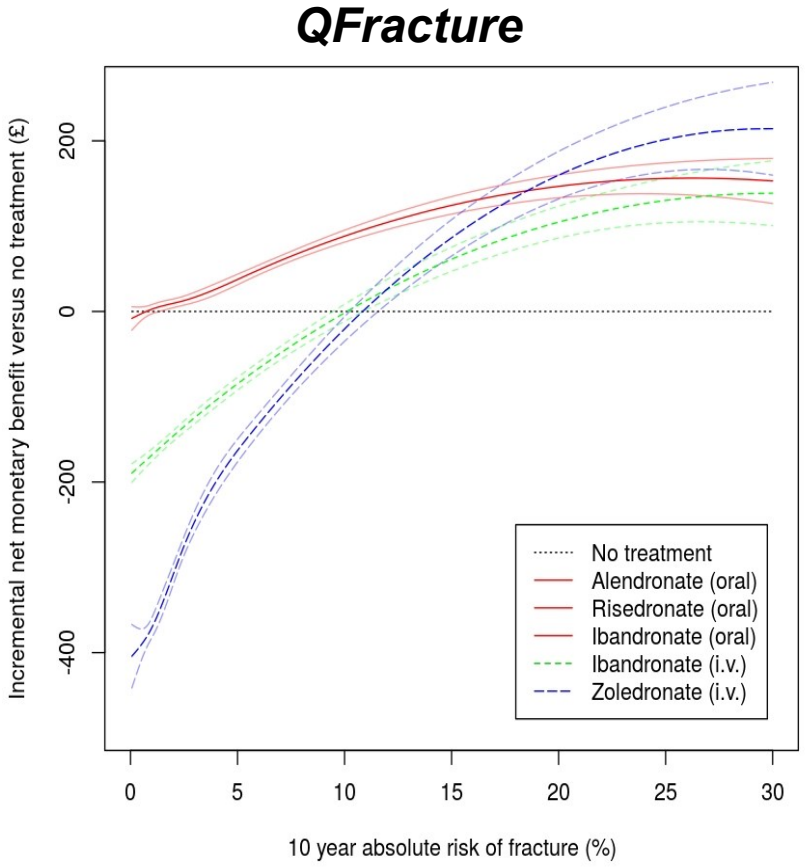


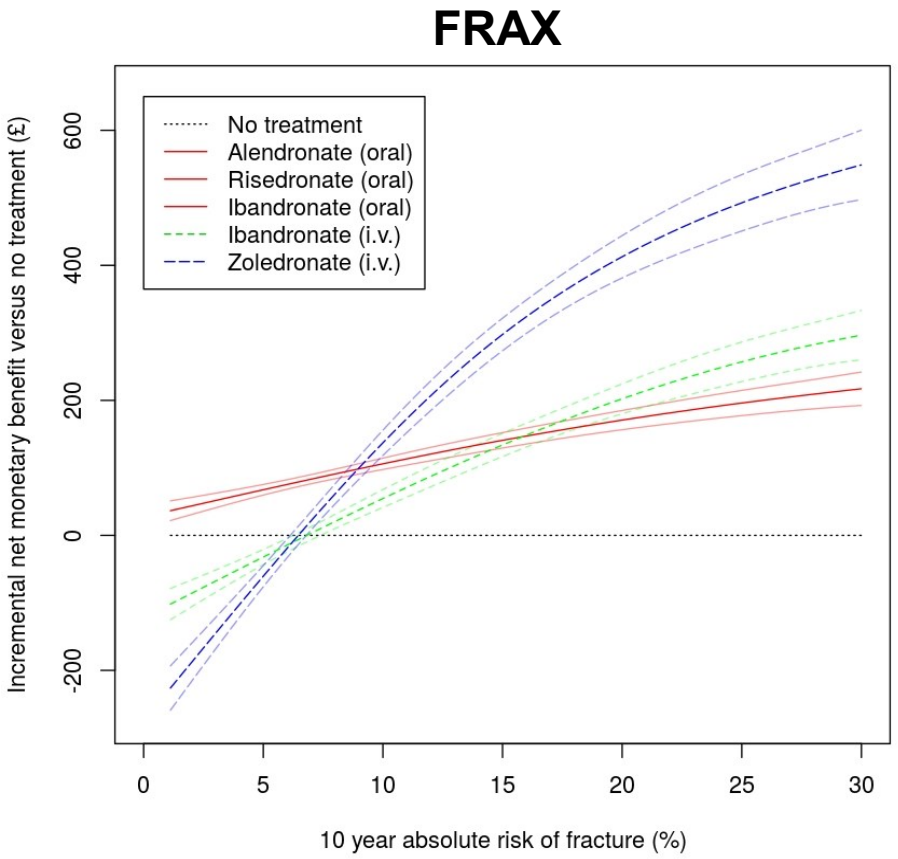
FRAX



Revised base case regression for Incremental Net Benefit

compared with no treatment against 10 year fracture risk, valuing QALY at £30,000





Revised base case

Absolute fracture risk thresholds at which incremental net benefit becomes positive (when valuing QALYs at £20,000 and £30,000)

	QFracture		FRAX	
Treatment	*£20,000/ QALY*	*£30,000/ QALY*	*£20,000/ QALY*	*£30,000/ QALY*
Alendronate	≥1.0%	≥0.7%	Whole range observed in modelled population	Whole range observed in modelled population
Risedronate	≥1.1%	≥0.8%		
Ibandronate (oral)	≥1.4%	≥1.0%		
Ibandronate (i.v.)	≥13.7%	≥10.1%	≥10.3%	≥6.8%
Zolendronate	≥15.9%	≥10.9%	≥10.1%	≥6.4%

- *Should oral and intravenous bisphosphonates be considered separately?*
- *Are the differences in risk thresholds between QFracture and FRAX important?*
- *Should consideration be given to which treatment has the highest INB?*

External validity
Using intervention thresholds

- A pragmatic review of literature identified 8 studies – 3 stated thresholds

Study	Intervention threshold
Borgstrom *et al*. 2010)	Estimated that treatment is cost-effective for a 10 year risk of fracture of 18.6% (at £20,000 per QALY)
Van Staa et al (2007)	Estimated that treatment is cost-effective for a 5 year risk of fracture of 9.3% (at £20,000 per QALY WTP)
Borgstrom (2006)	Threshold not consistent with the NICE reference case

Other sources	Intervention threshold
NOGG (2013)	Treatment was cost-effective across all age groups 10 year risk of fracture >7% (FRAX)
TA160 and TA161	Lowest level of fracture risk recommended for treatment was at a 10 year risk of fracture of 8.3% (FRAX) *Note: this single figure cannot be considered to accurately represent the treatment thresholds in TA160 and TA161*

External validity

Current pricing and additional criteria

- Differences in the prices used in the published studies and the current costs for generic bisphosphonates
- Interventional thresholds would be greatly reduced if current prices used
- AG's base case results are consistent with expectations based on published literature when taking into account the lower prices applied for generic bisphosphonates

Source	Average costs per annum
Borgstrom *et al*. (2010)	£265
Van Staa et al (2007)	£284
National osteoporosis guideline group (2013)	£95
TA160 and TA161	£54
Assessment group analysis (range)	£9.18 - £34.04

Potential equality issues

- Some groups may have difficulty adhering to the complex instructions for taking oral bisphosphonates and their benefit from these treatments may be compromised.
  - People with dementia, learning disabilities
  - Those unable to remain upright for the specified time period
  - People in whom oral bisphosphonates might be contraindicated, such as those with oesophageal stricture.
- Committee should consider those who are unable to comply with the recommended treatment in its decision making as done in NICE Technology Appraisals 160 and 161.

Equality considerations from previous TAs

TA160,161,204 recognised that some women have conditions where:

- Alendronate is contraindicated
- They cannot administer alendronate

At least some women in this patient group were likely to be disabled as defined by the Disability Discrimination Act 1995

Issue raised at appeal and judicial review (dismissed on both):

- Appeal panel and judge decided recommendation not discriminatory - because women who cannot take alendronate because of disability are treated the same as people who cannot take it for other reasons

Innovation

- How innovative are the technologies in their potential to make a significant and substantial impact on health-related benefits? Liquid formulation of alendronate?

- Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

Key considerations

- Does the committee's consider the use of pooled efficacy estimates for bisphosphonates acceptable for decision making?
- Is committee satisfied that the approach to modelling residential and nursing care is appropriate?
- Should the cost effectiveness of oral and intravenous bisphosphonates be considered separately?
- Are the differences in risk thresholds between QFracture and FRAX important?
- Should consideration be given to which treatment has the highest incremental net benefit?
- Are there any equality issues that committee needs to consider?