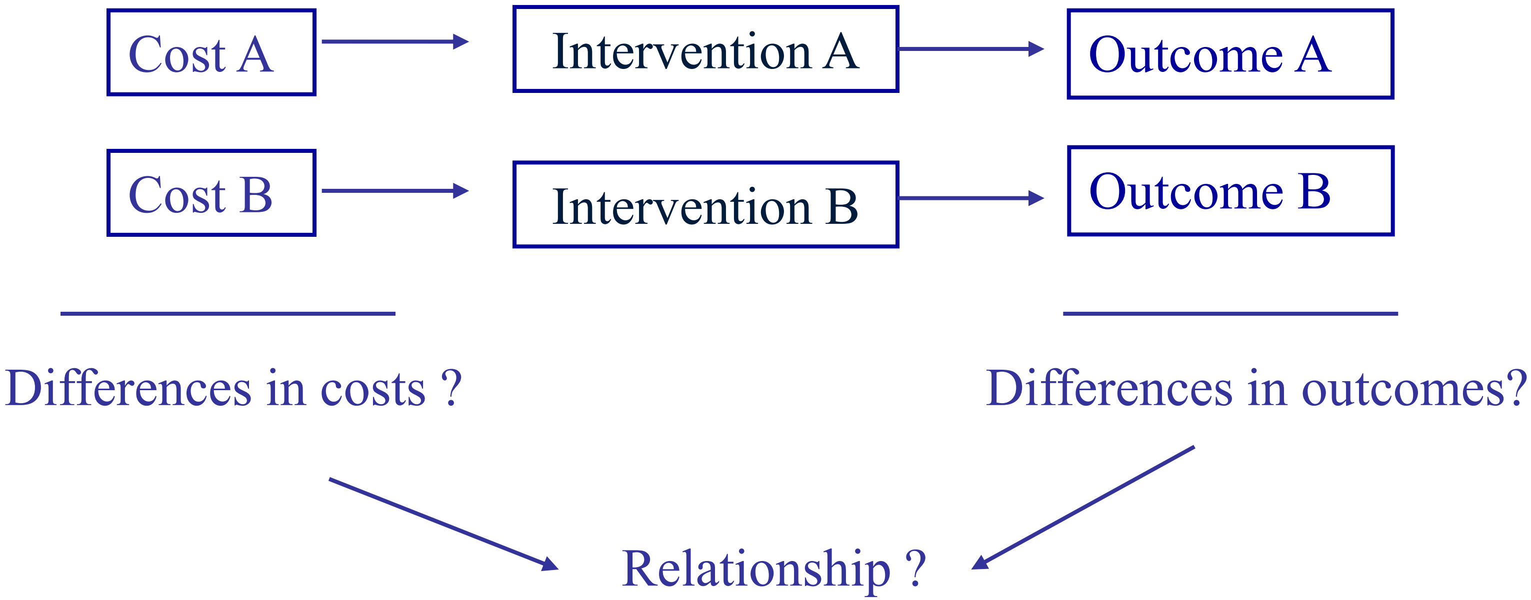
Modelling the cost-effectiveness of osteoporosis medications

Economic evaluation

« Comparative analysis between two or more health technologies in terms of costs and effects»



Full economic evaluation

Type of study	Costs	Outcomes
Cost-minimization	Euro’s	Identical in all relevant aspects
Cost-effectiveness	Euro’s	Natural unit (Clinical endpoints such as fracture events or life years)
Cost-utility	Euro’s	Quality-adjusted life years
Cost-benefit	Euro’s	Euro’s

Incremental cost-effectiveness ratio

$$ICER = (C_A - C_B) / (E_A - E_B) = \Delta C/\Delta E$$

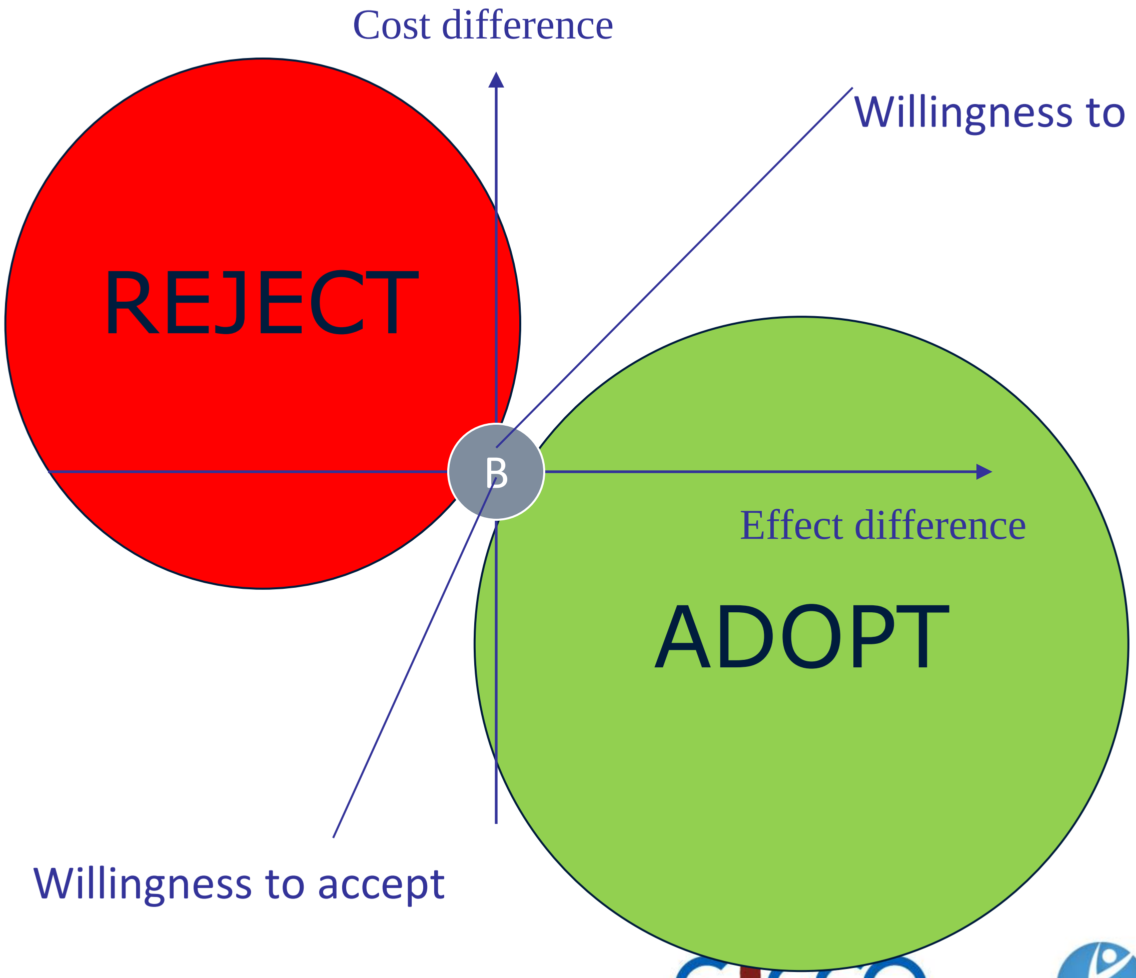
= *The additional cost per extra unit of effect from the comparator treatment*

Examples: additional cost per fracture prevented, additional cost per QALY gained etc.

The lower the ICER, the more cost-effective the intervention

Intervention adopted if **ICER < λ** (= willingness to pay per effectiveness unit)

Results of an economic evaluation



Cost-effectiveness plane

Methods of economic evaluation

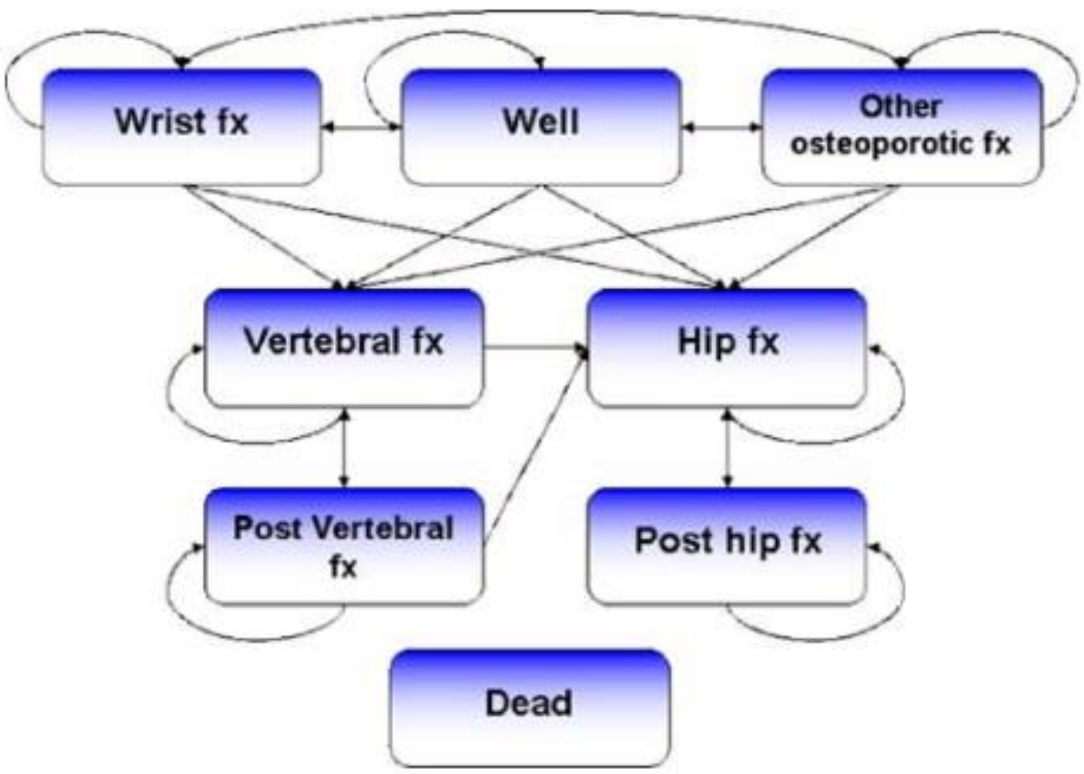
Trial-based economic evaluation

- Costs and outcomes alongside a RCT
- Cons: truncated time horizon, limited comparators

Decision-analytic modeling

- Mathematical models to synthetize all available information regarding health care process
- Pros: extending results from a single trial (lifetime); combining multiple sources of evidence to answer policy questions; extrapolation to final outcome (QALYs); modeling uncertainties in the knowledge base

Markov model



- Health states
- Patients progress through states over time
- At each cycle (length and number), transition probabilities
- Costs and health outcomes associated with time spent in states and/or transitions

Zethraeus, N., et al. Osteoporos Int, 2007. 18(1): p. 9-23.

Markov model

- Markov trace
- Expected values for a cohort of patients (= proportion of patients in each state, at each cycle multiplied by the corresponding costs/outcomes)

No Treatment								COSTS	QALYS
	No Fx	Hip	Post Hip	CV	Post CV	Death			
0	1000	0	0	0	0	0			
1	992	3	0	4	0	1		10000	975
2	981	5	3	5	3	3		20000	953
3	965	7	7	7	8	6		25000	925
Treatment								SUM	SUM
	No Fx	Hip	Post Hip	CV	Post CV	Death			
0	1000	0	0	0	0	0			
1	992	2	0	3	0	1			
2	988	3	2	3	2	2			
3	979	4	5	4	4	4			

Markov model

- Continuous risk over time
- Recurrence of events

Markov assumption of ‘no memory’: future transitions do not depend on previous ones

Bypassing this assumption of no memory:

- additional states (post-fracture states)
- microsimulation

Markov model

Cohort 'simulation'

- Based on applying the transition matrix directly

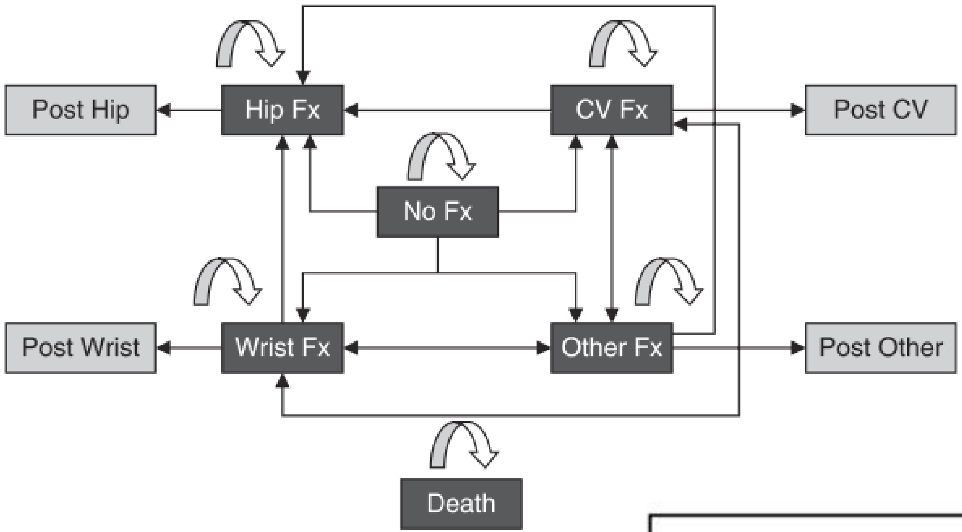
Monte Carlo simulation

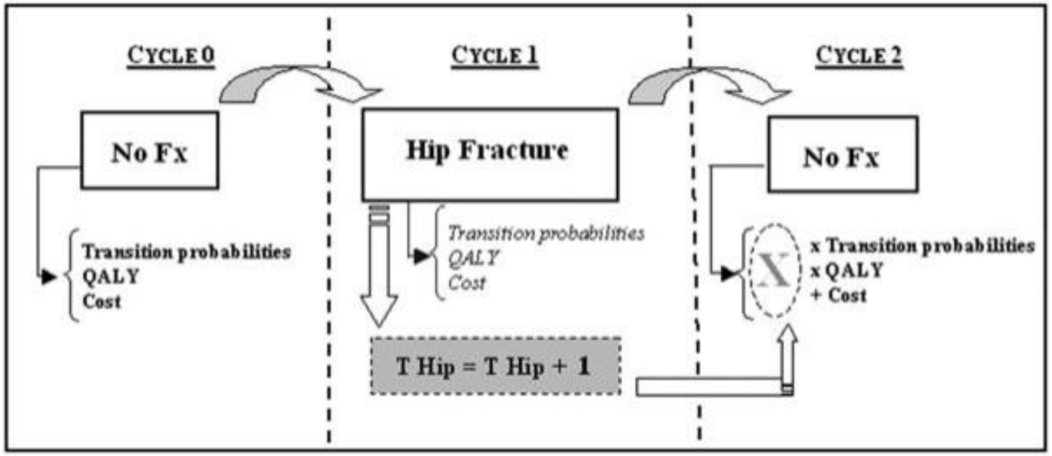
- A sample of individual patients is simulated in the Markov, one by one, and their progression is recorded
- Expected values are obtained by averaging

Cohort vs. Monte Carlo

- Monte Carlo allows relaxing some of the assumptions of cohort Models (eg. relax the assumption of lack of memory of Markov models)

Markov microsimulation





Hiligsmann et al. Value in Health 2009. 12(5): p. 687-96
Hiligsmann et al. Pharmacoeconomics, 2011. 29(10): p. 895-911

Questions to develop a CE model in osteoporosis

- Model structure

  model type; time horizon; health states; transitions and cycle length

- Transitions probabilities
- Treatment strategies
- Costs
- Outcomes
- Treatment characteristics
- Simulation and sensitivity analyses

Transitions probabilities

- Baseline fracture risk (fracture incidence)
- Target population: BMD; presence or absence of fracture; FRAX
- Effect of a fracture
- Presence or absence of therapy

- Fracture effects on mortality

Treatment strategies

- Comparator
- Indirect comparison?
- Sequential treatment

Costs

- Perspective: societal or healthcare (guidelines)
- Fracture costs
  - Short term costs (hospitalization)
  - Extra costs in the year following fractures
  - Long-term costs (admission to nursing home)
- Treatment costs

Outcomes

- QALY = *quantity of life X Utility*
- Effects of fracture on utility (e.g. ICUROS study)
  - Short term
  - Long term
  - Several fractures

Table 2 EQ-5D HSUV, accumulated QoL loss, and QoL multiplier, for all time points by fracture type

	Hip fracture		Vertebral fracture		Distal forearm fracture	
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
EQ-5D HSUV						
Before fracture	0.77 (0.27)	0.75, 0.78	0.83 (0.23)	0.81, 0.85	0.89 (0.19)	0.88, 0.90
At enrollment	−0.11 (0.37)	−0.14, −0.10	0.17 (0.43)	0.13, 0.20	0.41 (0.34)	0.439, 0.43
4 months post	0.49 (0.38)	0.47, 0.51	0.60 (0.33)	0.57, 0.63	0.77 (0.25)	0.76, 0.79
12 months post	0.59 (0.37)	0.57, 0.61	0.70 (0.29)	0.67, 0.72	0.85 (0.21)	0.84, 0.86
18 months post	0.66 (0.34)	0.64, 0.68	0.70 (0.34)	0.67, 0.73	0.88 (0.20)	0.87, 0.89
HSUV decrement**						
At enrollment	−0.89 (0.40)	−0.91, −0.87	−0.67 (0.45)	−0.70, −0.63	−0.48 (0.34)	−0.50, −0.46
4 months post	−0.28 (0.40)	−0.30, −0.26	−0.23 (0.34)	−0.26, −0.20	−0.12 (0.26)	−0.13, −0.10
12 months post	−0.17 (0.38)	−0.19, −0.15	−0.13 (0.29)	−0.16, −0.11	−0.04 (0.22)	−0.05, −0.03
18 months post	−0.11 (0.37)	−0.12, −0.09	−0.13 (0.32)	−0.15, −0.10	−0.01 (0.22)	−0.02, 0.00
Accumulated QoL loss						
0–6 months	0.24 (0.17)	0.23, 0.25	0.19 (0.16)	0.17, 0.20	0.12 (0.12)	0.11, 0.12
7–12 months	0.11 (0.18)	0.10, 0.12	0.08 (0.14)	0.07, 0.10	0.03 (0.11)	0.03, 0.04
0–12 months	0.34 (0.34)	0.33, 0.36	0.27 (0.28)	0.24, 0.29	0.15 (0.22)	0.14, 0.16
13–18 months	0.07 (0.17)	0.06, 0.08	0.07 (0.14)	0.05, 0.08	0.01 (0.10)	0.01, 0.02
18–24 months	0.05 (0.18)	0.04, 0.06	0.06 (0.16)	0.05, 0.08	0.01 (0.11)	0.00, 0.01
12–24 months	0.12 (0.35)	0.10, 0.14	0.13 (0.30)	0.10, 0.15	0.02 (0.21)	0.01, 0.03
Subsequent years	0.11 (0.37)	0.09, 0.12	0.13 (0.32)	0.10, 0.15	0.01 (0.22)	0.00, 0.02
QoL multiplier*						
0–6 m	0.38	0.36, 0.40	0.56	0.53, 0.59	0.74	0.72, 0.75
7–12 m	0.72	0.70, 0.74	0.80	0.77, 0.82	0.92	0.91, 0.94
0–12 m	0.55	0.53, 0.57	0.68	0.65, 0.70	0.83	0.82, 0.84
13–18 m	0.82	0.80, 0.84	0.84	0.82, 0.87	0.97	0.96, 0.99
18–24 months	0.86	0.84, 0.89	0.85	0.81, 0.88	0.99	0.97, 1.00
12–24 months	0.84	0.82, 0.86	0.84	0.81, 0.88	0.98	0.97, 0.99
Subsequent years	0.86	0.84, 0.89	0.85	0.82, 0.87	0.99	0.97, 1.00

Svedbom et al. Osteoporosis International 2018
Epub Ahead of Print

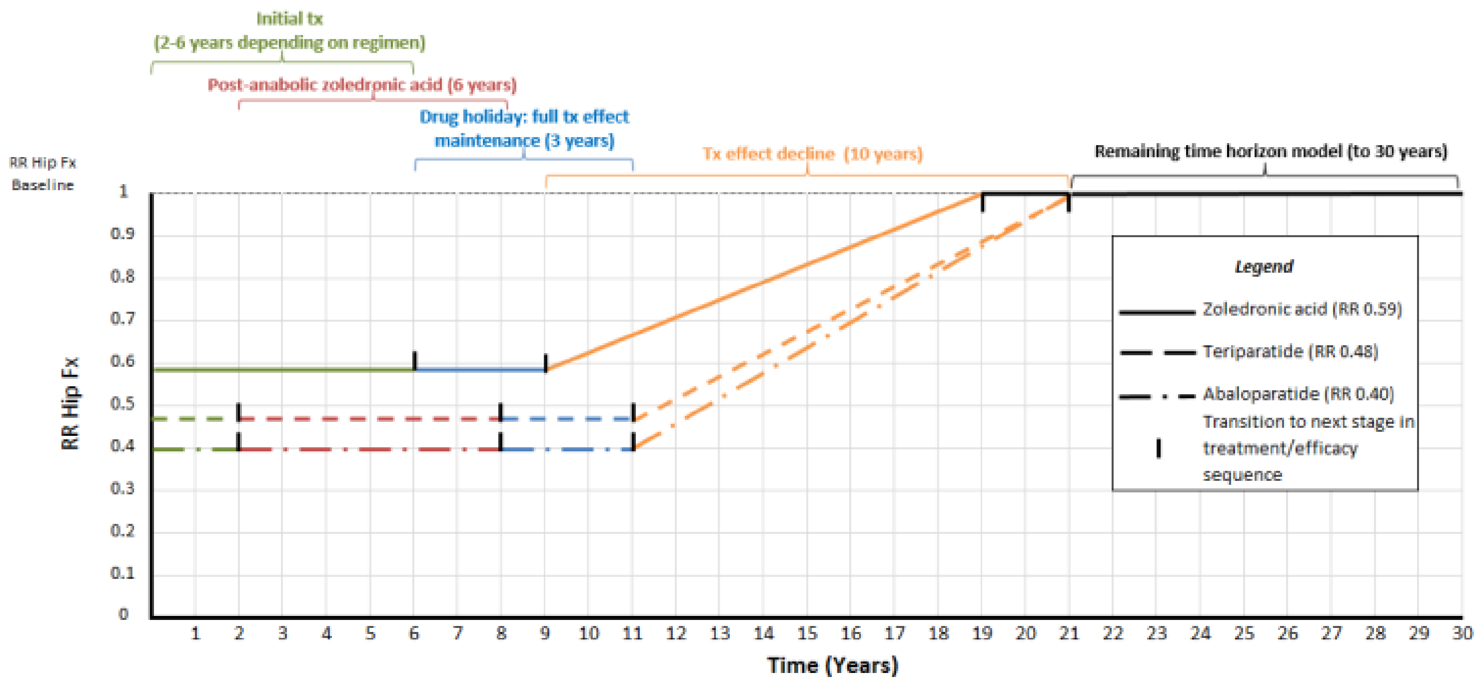
International Osteoporosis Foundation

Treatment - *efficacy*

- Treatment duration
- Anti-fracture efficacy during treatment and after discontinuation (offset time)
- Adherence effect

ESCEO International Osteoporosis Foundation

Figure 4. Treatment Sequencing and Effect Over Time for Hip Fractures



Note: Each treatment line is color-coded to match the X-axis labels at the top of the chart; vertical black lines indicate transitions to the next stage in sequence/efficacy. Line placement is not exact.
Fx: fracture, RR: relative risk, Tx: treatment

Treatment – *costs*

- Drug cost
- Monitoring cost (DXA, GP visit)
- Adverse events

Simulation and calculation

- ➢ Discounting (guideline)
- ➢ Incremental costs and effects
- ➢ ICER

Table 5: Cost-effectiveness results: base-case.

	Totals			Incremental			ICERs	
	Cost	LYs	QALYs	Cost	LYs	QALYs	Cost per LY saved	Cost per QALY gained
Generic alendronate	$31,456	7.9007	5.9866	—	—	—	*Ref.*	*Ref.*
Denosumab	$32,334	7.9339	6.0386	$878	0.0333	0.0520	$26,389	$16,888
Zoledronate	$35,138	7.9132	6.0037	$2,804	−0.0208	−0.0350	Dominated	Dominated
Risedronate	$35,232	7.8941	5.9760	$2,899	−0.0399	−0.0626	Dominated	Dominated
Ibandronate	$35,550	7.8867	5.9663	$3,216	−0.0472	−0.0723	Dominated	Dominated
Teriparatide	$48,828	7.9308	6.0279	$16,495	−0.0031	−0.0107	Dominated	Dominated

Numbers may not add up due to rounding.

Silverman S et al. J Osteoporos, 2015. 2015: p. 627-631

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Uncertainty

- Structural uncertainty (assumptions, methods)
- Parameters uncertainty (e.g. treatment effect)
- Heterogeneity (sex, age, subgroups)

Need to be addressed

⇒ Sensitivity analyses (univariate and probabilistic)

Univariate sensitivity analyses

Table 3 One-way sensitivity analyses on fracture risk and treatment cost on the cost in € per QALY gained of vitamin D and calcium supplementation compared with no treatment for women and men aged 60–80 years with a BMD *T*-score ≤−2.5 (95% CI are given in parentheses)

	60 years	70 years	80 years
Women			
Base-case analysis	40 578 (19 600; 61 556)	7912 (6216; 9608)	Cost-saving
Fracture risk −30%	50 582 (−35 280; 136 444)	24 897 (17 827; 31 968)	Cost-saving
Fracture risk +45%	20 017 (15 850; 24 184)	Cost-saving	Cost-saving
High treatment cost	52 394 (11 927; 92 860)	23 444 (20 431; 26 457)	Cost-saving
Men			
Base-case analysis	23 477 (19 277; 27 678)	10 250 (8910; 11 589)	Cost-saving
Fracture risk −45%	53 429 (−186 891; 293 748)	39 034 (23 778; 54 290)	15 352 (12 792; 17 913)
Fracture risk +45%	9355 (7250; 11 460)	Cost-saving	Cost-saving
High treatment cost	33 755 (−199; 67 708)	23 092 (18 600; 27 584)	3872 (2812; 4933)

Note: BMD, bone mineral density; CI, confidence interval; QALY, quality-adjusted life years.

Hiligsmann et al. Eur J Public Health 2015 25 (1), 20–25

Probabilistic sensitivity analyses

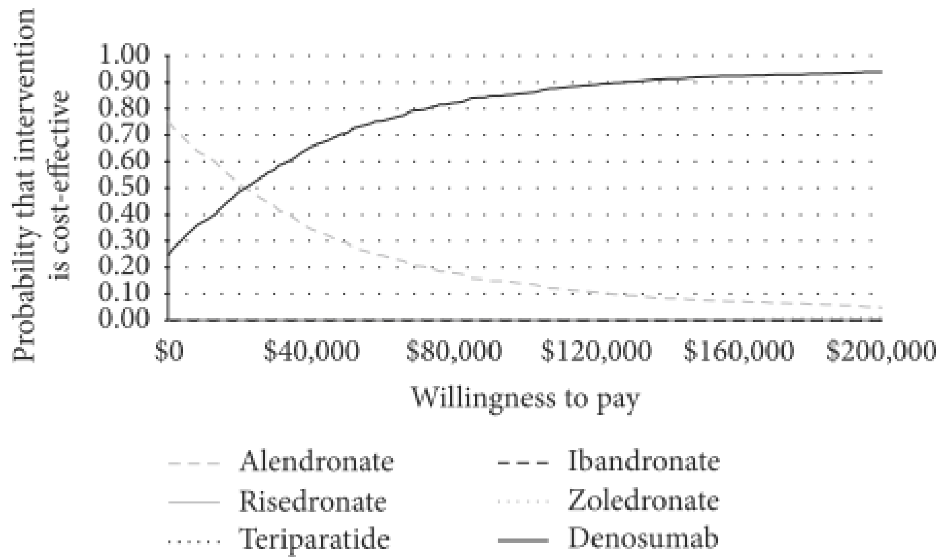

FIGURE 4: Base-case probabilistic sensitivity analysis. Note: CE curves for risedronate, ibandronate, and teriparatide do not appear in the figure, as they are not considered cost-effective at any threshold in this analysis.

Silverman S et al. J Osteoporos, 2015. 2015: p. 627-631