Appendix 2: Benefits of pharmacologic treatments[1]

Outcome & Study approach	Studies; sample size; follow-up	Anticipated absolute effects (95% CI)			Relative OR (95% CI)	Certainty	Judgement
		Assumed population risk[*]	Risk with treatment	Absolute difference			
Bisphosphonates (alendronate, risedronate or zoledronic acid) vs placebo (postmenopausal females)							
Hip fractures Intention to treat	14 RCT; 21,038 Follow-up: 12-72 months (1–17)	Control event rate (study data)			0.73 (0.58 to 0.92)	Low[a,c]	May reduce
		11 in 1000	8.1 per 1,000 (6.4 to 10.1)	2.9 fewer in 1000 (4.6 fewer to 0.9 fewer)			
		General population risk* (females)					
		20 in 1000	14.7 per 1,000 (11.7 to 18.4)	5.3 fewer in 1000 (8.3 fewer to 1.6 fewer)			
Clinical fragility fractures Intention to treat or ≥1 dose	19 RCT; 22,482 Follow-up: 12-72 months (1,3,12,13,15–22,4,23–25,5–11)	Control event rate (study data)			0.80 (0.73 to 0.88)	Moderate[a,c]	Probably reduces
		58 in 1000	46.9 per 1,000 (43.0 to 51.4)	11.1 fewer in 1000 (15.0 fewer to 6.6 fewer)			
		General population risk* (females)					
		202 in 1000	168.4 per 1,000 (156.0 to 182.2)	33.6 fewer in 1000 (46.0 fewer to 19.8 fewer)			
Clinical vertebral fractures; Intention to treat or ≥1 dose	11 RCT; 8,921 Follow-up: 12-72 months (1,2,20,22,25,5–9,11,14,16)	Control event rate (study data)			0.52 (0.33, 0.81)	Low[a,b,d]	May reduce
		21 in 1000	11.0 per 1000 (7.0 to 17.1)	10.0 fewer in 1000 (14.0 fewer to 3.9 fewer)			
		General population risk* (females)					
		27 in 1000	14.2 per 1000 (9.1 to 22.0)	12.8 fewer in 1000 (17.9 fewer to 5.0 fewer)			
All-cause mortality Intention to treat or exposed to ≥1 dose	8 RCT; 8,542 Follow-up: 12-72 months (2,5,6,8,14,16,21,24,26,27)	Control event rate (study data)			0.81 (0.59 to 1.12)	Low[a-c]	May not reduce
		30 in 1000	24.0 per 1,000 (17.6 to 32.9)	5.5 fewer in 1000 (11.9 fewer to 3.4 more)			
		General population risk* (females)					
		57 in 1000	46.7 per 1,000 (34.4 to 63.4)	10.3 fewer in 1000 (22.6 fewer to 6.4 more)			
Alendronate vs placebo (post-menopausal females)							
Hip fractures Intention to treat	7 RCT; 9,226 Follow-up: 12-48 months (1,2,11–16)	Control event rate (study data)			0.73 (0.43, 1.24)	Low[b,c,d]	May not reduce
		8 in 1000	5.9 per 1000 (3.5 to 9.9)	2.1 fewer in 1000 (4.5 fewer to 1.9 more)			
		General population risk* (females)					
		20 in 1000	5.9 per 1000 (3.5 to 9.9)	5.3 fewer in 1000 (11.3 fewer to 4.7 more)			
	8 RCT; 8,854	Control event rate (study data)				Moderate[b,c]	Probably reduces

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[1] Vitamin D and calcium were usually given as part of treatment to both cases and controls

Outcome & Study approach	Studies; sample size; follow-up	Anticipated absolute effects (95% CI)			Relative OR (95% CI)	Certainty	Judgement
		Assumed population risk[*]	Risk with treatment	Absolute difference			
Clinical fragility fractures Intention to treat	Follow-up: 12-48 months (1,10,21,11–13,15,16,18–20)	96 in 1000	79.3 per 1000 (69.5 to 91.4)	14.7 fewer in 1000 (24.5 fewer to 2.6 fewer)	0.83 (0.72, 0.97)		
		General population risk* (females)					
		202 in 1000	173.6 per 1000 (154.2 to 197.1)	28.4 fewer in 1000 (47.8 fewer to 4.9 fewer)			
Clinical vertebral fractures	5 RCTs; 6,324 Follow-up: 12-48 months (1,2,11,14,16,20)	The evidence from 5 RCTs was very uncertain				Very low[a,b,c,d]	Very uncertain
All-cause mortality	4 RCTs; 5,272 Follow-up: 12-48 months (2,14,16,21,26)	The evidence from 4 RCTs was very uncertain				Very low[a,b,c,d]	Very uncertain
Risedronate vs placebo (post-menopausal females)							
Hip fractures Intention to treat	4 RCT; 9,672 Follow-up: 12-36 months (3–5,17)	Control event rate (study data)			0.73 (0.56 to 0.95)	Low[b,c]	May reduce
		30 in 1000	22.1 per 1000 (17.0 to 28.5)	7.9 fewer in 1000 (13.0 fewer to 1.5 fewer)			
		General population risk* (females)					
		20 in 1000	14.7 per 1000 (11.3 to 19.0)	5.3 fewer in 1000 (8.7 fewer to 1.0 fewer)			
Clinical fragility fractures Intention to treat or ≥1 dose	7 RCT; 10,572 Follow-up: 12-36 months (3–5,17,19,22,23)	Control event rate (study data)			0.83 (0.73, 0.95)	Low[a-c]	May reduce
		48 in 1000	40.2 per 1000 (35.5 to 45.7)	7.8 fewer in 1000 (12.5 fewer to 2.3 fewer)			
		General population risk* (females)					
		202 in 1000	173.6 per 1000 (156.0 to 193.9)	28.4 fewer in 1000 (46.0 fewer to 8.1 fewer)			
Clinical vertebral fractures	2 RCT; 230 Follow-up: 12-36 months (5,22)	The evidence from 2 RCTs is very uncertain				Very low	Very uncertain
All-cause mortality	1 RCT; 170 Follow-up: 12 months (5)	The evidence from 1 RCT is very uncertain				Very low	Very uncertain
Zoledronic acid vs placebo (post-menopausal females)							
Hip fractures Intention to treat	3 RCT; 2,200 Follow-up: 12-72 months	Control event rate (study data)			0.69 (0.29 to 1.63)	Low[b,c]	May not reduce
		12 in 1000	8.3 per 1,000 (3.5 to 19.4)	3.7 fewer in 1000 (8.5 fewer to 7.4 more)			
		General population risk* (females)					

Outcome & Study approach	Studies; sample size; follow-up	Anticipated absolute effects (95% CI)			Relative OR (95% CI)	Certainty	Judgement
		Assumed population risk[*]	Risk with treatment	Absolute difference			
	(6–9)	20 in 1000	13.9 per 1,000 (5.9 to 32.2)	6.1 fewer in 1000 (14.1 fewer to 12.2 more)			
Clinical fragility fractures Intention to treat	5 RCT; 3,218 Follow-up: 12-72 months (6–9,24,25)	Control event rate (study data)			0.64 (0.51 to 0.82)	Moderate[b]	Probably reduces
		50 in 1000	37.9 per 1,000 (30.4 to 48.1)	20.1 fewer in 1000 (27.6 fewer to 9.9 fewer)			
		General population risk* (females)					
		202 in 1000	139.4 per 1,000 (114.3 to 171.9)	62.6 fewer in 1000 (87.7 fewer to 30.1 fewer)			
Clinical vertebral fractures Intention to treat	4 RCT; 2,367 Follow-up: 12-72 months (6–9,25)	Control event rate (study data)			0.44 (0.24 to 0.8)	Low[a,b,d]	May reduce
		34 in 1000	15.3 per 1,000 (8.4 to 27.4)	18.7 fewer in 1000 (25.6 fewer to 6.6 fewer)			
		General population risk* (females)					
		27 in 1000	12.1 per 1,000 (6.6 to 21.7)	14.9 fewer in 1000 (20.4 fewer to 5.3 fewer)			
All-cause mortality	3 RCT; 2,656: Follow-up: 12-72 months (6,8,24,27)	The evidence from 3 RCTs is very uncertain				Very low[a,b,c,d]	Very uncertain
Zoledronic acid vs placebo (males)							
Hip fractures Intention to treat	1 RCT; 1,199 Follow-up: 24 months (28)	Control event rate (study data)			2.08 (0.19 to 22.98)	Low[b,c]	May not reduce
		2 in 1000	4.2 per 1,000 (0.4 to 44.0)	2.2 more in 1000 (1.6 fewer to 42.0 more)			
		General population risk* (males)					
		16 in 1000	32.7 per 1,000 (3.1 to 272.0)	16.7 more in 1000 (12.9 fewer to 256.0 more)			
Clinical fragility fractures Intention to treat	1 RCT; 1,199 Follow-up: 24 months (28)	Control event rate (study data)			0.57 (0.21 to 1.54)	Low[b,d]	May not reduce
		18 in 1000	10.3 per 1,000 (3.8 to 27.5)	7.7 fewer in 1000 (14.2 fewer to 9.5 more)			
		General population risk* (males)					
		105 in 1000	62.7 per 1,000 (24.0 to 153.0)	42.3 fewer in 1000 (81.0 fewer to 48.0 more)			
All-cause mortality	1 RCT; 1,199: Follow-up 24 months (28)	The evidence from 1 RCT is very uncertain				Very low[a,b,d]	Very uncertain
Denosumab vs placebo (post-menopausal females)							
Hip fractures	3 RCT; 8,542	Control event rate (study data)				Low[b-d]	May not reduce

Outcome & Study approach	Studies; sample size; follow-up	Anticipated absolute effects (95% CI)			Relative OR (95% CI)	Certainty	Judgement
		Assumed population risk[*]	Risk with treatment	Absolute difference			
Intention to treat	Follow-up: 6-36 months (29–33)	11 in 1000	7.1 per 1,000 (4.3 to 11.2)	3.9 fewer in 1000 (6.7 fewer to 0.2 more)	0.64 (0.39 to 1.02)		
		General population risk* (females)					
		20 in 1000	12.9 per 1,000 (7.9 to 20.4)	7.1 fewer in 1000 (12.1 fewer to 0.4 more)			
Clinical fragility fractures Intention to treat or ≥1 dose	5 RCT; 9,231 Follow-up: 12-36 months (21,26,29–32,34)	Control event rate (study data)			0.70 (0.59 to 0.82)	Moderate[b]	Probably reduces
		42 in 1000	29.8 per 1,000 (25.2 to 34.7)	12.2 fewer in 1000 (16.8 fewer to 7.3 fewer)			
		General population risk* (females)					
		202 in 1000	150.5 per 1,000 (129.9 to 171.9)	51.5 fewer in 1000 (72.1 fewer to 30.1 fewer)			
Clinical vertebral fractures Intention to treat or ≥1 dose	3 RCT; 8,397 Follow-up: 6-36 months (29,32,34–36)	Control event rate (study data)			0.32 (0.21 to 0.49)	Moderate[b]	Probably reduces
		24 in 1000	7.8 per 1,000 (5.1 to 11.9)	16.2 fewer in 1000 (18.9 fewer to 12.1 fewer)			
		General population risk* (females)					
		27 in 1000	8.8 per 1,000 (5.8 to 13.4)	18.2 fewer in 1000 (21.2 fewer to 13.6 fewer)			
All-cause mortality Intention to treat or ≥1 dose	5 RCT; 9,185 Follow-up: 6-36 months (21,26,29–32,34,36)	Control event rate (study data)			0.79 (0.58 to 1.08)	Moderate[b,d]	Probably does not reduce
		23 in 1000	18.3 per 1,000 (13.5 to 24.8)	4.7 fewer in 1000 (9.5 fewer to 1.8 more)			
		General population risk* (females)					
		57 in 1000	45.6 per 1,000 (33.9 to 61.3)	11.4 fewer in 1000 (23.1 fewer to 4.3 more)			
Health-related quality of life (OPAQ-SV; 0-100; higher = better) after 3-y of treatment	5 RCT; 9,185 (21,26,29–32,34,36)	Change from baseline: physical function (-1.3 vs. -1.2), emotional status (-1.4 vs. -1.6), and back pain (4.1 vs. 4.3) for denosumab vs. placebo.				Moderate[b,c]	Probably does not change
Denosumab vs placebo (men)							
Hip fractures Intention to treat	1 RCT; 242 Follow-up: 12 months (37)	Control event rate (study data)			1.00 (0.02 to 50.80)	Very low[a,b,d]	Very uncertain
		0 in 1000	0.0 per 1,000 (0 to 0)	No difference in 1000			
		General population risk* (males)					
		16 in 1000	16.0 per 1,000 (0.3 to 452.4)	No difference in 1000 (15.7 fewer to 436.4 more)			
Clinical fragility fractures Intention to treat	1 RCT; 242 Follow-up: 12 months (37)	Control event rate (study data)			0.5 (0.04 to 5.59)	Very low[a,b,d]	Very uncertain
		16 in 1000	8.6 per 1,000 (0.7 to 88.2)	8.4 fewer in 1000 (16.3 fewer to 71.2 more)			
		General population risk* (males)					

Outcome & Study approach	Studies; sample size; follow-up	Anticipated absolute effects (95% CI)			Relative OR (95% CI)	Certainty	Judgement
		Assumed population risk[*]	Risk with treatment	Absolute difference			
		105 in 1000	55.4 per 1,000 (4.7 to 396.1)	49.6 fewer in 1000 (100.3 fewer to 291.1 more)			
Clinical vertebral fractures Intention to treat	1 RCT; 242 Follow-up: 12 months (37)	Control event rate (study data)			1.00 (0.02 to 50.80)	Very low[a,b,d]	Very uncertain
		0 in 1000	0.0 per 1,000 (0 to 0)	No difference in 1000			
		General population risk* (males)					
		10 in 1000	9.8 fewer to 329.1 more	No difference in 1000			
All-cause mortality Exposed to ≥1 dose	1 RCT; 240 Follow-up: 12 months (37)	Control event rate (study data)			1.00 (0.06 to 16.17)	Very low[a,b,d]	Very uncertain
		8 in 1000	7.5 fewer to 107.4 more	No difference in 1000			
		General population risk* (males)					
		76 in 1000	(71.1 fewer to 494.8 more)	No difference in 1000			

CI=confidence interval; RCT=randomized controlled trial; NA=not applicable; OPAQ-SV=Osteoporosis Assessment Questionnaire-Short Version; OR = Odds ratio; y=years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision

[*] The effects without treatment (i.e., assumed population risk) for the general risk (Canadian) population (≥65 years) are estimated from Prior et al. based on 10 year follow-up (29)

Data for the general population <65 years is not included in the summary table.

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