Screening for the primary prevention of fragility fractures among adults aged 40 years and older in primary care: systematic reviews of the effects and acceptability of screening and treatment, and the accuracy of risk prediction tools

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Additional file 7. Risk of bias assessments

Additional Table 7.1. Risk of bias assessments for studies included in KQ2 on the predictive accuracy of screening tests

Study	Tool	Domain 1. Participants				Domain 2. Predictors							Domain 3. Outcomes									Domain 4. Analysis										Overall Appraisal	
		1.1 Data sources	1.2 Eligibility	Risk of bias	Applicability	2.1 Definitions	2.2 Blinding	2.3a Available	2.3b Collected/used	2.3c Missing data	Risk of bias	Applicability	3.1a Determination (CFF)	3.1b Determination (hip)	3.2 Definition	3.3 Predictors excluded	3.4 Similar definition	3.5 Knowledge of predictor	3.6 Interval	Risk of Bias	Applicability	4.1a No. outcomes (hip)	4.1b No. outcomes (CFF)	4.2 Predictor handling	4.3 Missing participants	4.4 Deaths/competing risk	4.5 Complexities in data	4.6a Performance data (hip)	4.6b Calibration plots (hip)	4.6c Performance data (CFF)	4.6d Calibration plots (CFF)	Risk of Bias	Risk of Bias	Applicability
Azagra 2016a	FRAX	Y	Y	Low	High	Y	NI	Y	Y	NI	Unclear	Low	Y	Y	Y	Y	Y	NI	Y	Low	Low	N	Y	PY	N	N	N	Y	Y	Y	Y	High	High	High
Azagra 2016b	FRAX	Y	Y	Low	Low	NI	NI	Y	NI	NI	Unclear	Low	Y	NA	Y	Y	Y	NI	Y	Low	Low	NA	Y	NI	N	N	N	NA	NA	PY	N	High	High	Low
Bolland 2011	FRAX	Y	Y	Low	Low	Y	NI	Y	Y	NI	Unclear	Low	N	Y	Y	Y	N	NI	Y	High	Low	N	Y	NI	Y	N	N	Y	Y	Y	Y	High	High	Low
	Garvan	Y	Y	Low	Low	Y	NI	Y	Y	NI	Unclear	Low	N	Y	Y	Y	N	NI	Y	High	Low	N	Y	NI	Y	N	N	Y	Y	Y	Y	High	High	Low
Crandall 2019a	FRAX	Y	Y	Low	High	N	NI	Y	Y	PY	Unclear	Low	PN	Y	Y	Y	Y	NI	Y	Unclear	Low	Y	Y	PN	Y	Y	Y	Y	Y	Y	Y	Unclear	Unclear	High
Crandall 2019b	FRAX	Y	Y	Low	High	Y	NI	Y	Y	PY	Unclear	Low	N	Y	Y	Y	Y	NI	Y	Unclear	Low	Y	Y	Y	N	N	N	Y	N	N	N	High	High	High
Crandall 2019b	Garvan	Y	Y	Low	High	Y	NI	Y	Y	PY	Unclear	Low	N	Y	Y	Y	Y	NI	Y	Unclear	Low	Y	Y	Y	N	N	N	Y	N	N	N	High	High	High
Czerwinski 2013	FRAX	PY	Y	Low	High	Y	NI	Y	Y	Y	Low	Low	N	Y	Y	Y	Y	NI	PY	High	Low	N	Y	Y	N	N	N	Y	N	Y	N	High	High	High
Dagan 2017	FRAX	Y	Y	Low	Unclear	Y	NI	Y	Y	Y	Low	Low	PN	Y	Y	Y	Y	NI	Y	Unclear	Low	Y	Y	PN	Y	Y	N	Y	Y	N	N	High	High	Unclear
	Garvan	Y	Y	Low	Unclear	Y	NI	Y	Y	Y	Low	Low	PN	Y	Y	Y	Y	NI	Y	Unclear	Low	Y	NA	PN	Y	Y	N	Y	Y	NA	NA	High	High	Unclear
	QFrac-ture	Y	Y	Low	Unclear	Y	NI	Y	Y	Y	Low	Low	PN	Y	Y	Y	Y	NI	Y	Unclear	Low	Y	Y	PN	Y	Y	N	Y	Y	N	N	High	High	Unclear

Study	Tool	Domain 1. Participants				Domain 2. Predictors							Domain 3. Outcomes									Domain 4. Analysis											Overall Appraisal	
		1.1 Data sources	1.2 Eligibility	Risk of bias	Applicability	2.1 Definitions	2.2 Blinding	2.3a Available	2.3b Collected/used	2.3c Missing data	Risk of bias	Applicability	3.1a Determination (CFF)	3.1b Determination (hip)	3.2 Definition	3.3 Predictors excluded	3.4 Similar definition	3.5 Knowledge of predictor	3.6 Interval	Risk of Bias	Applicability	4.1a No. outcomes (hip)	4.1b No. outcomes (CFF)	4.2 Predictor handling	4.3 Missing participants	4.4 Deaths/competing risk	4.5 Complexities in data	4.6a Performance data (hip)	4.6b Calibration plots (hip)	4.6c Performance data (CFF)	4.6d Calibration plots (CFF)	Risk of Bias	Risk of Bias	Applicability
Desbiens 2020	FRAX	Y	Y	●Low	●Low	Y	NI	N	PY	N	●Unclear	●Low	NI	NA	Y	Y	Y	NI	Y	● Unclear	●Low	NA	Y	PN	PY	N	N	NA	NA	Y	Y	●High	●High	●Low
	Garvan	Y	Y	●Low	●Low	Y	NI	N	PY	N	●Unclear	●Low	NI	NA	Y	Y	Y	NI	Y	● Unclear	●Low	NA	Y	PN	PY	N	N	NA	NA	Y	Y	●High	●High	●Low
	QFrac-ture	Y	Y	●Low	●Low	Y	NI	N	PY	N	●Unclear	●Low	NI	NA	Y	Y	Y	NI	Y	● Unclear	●Low	NA	Y	PN	PY	N	N	NA	NA	Y	Y	●High	●High	●Low
Ettinger 2012	FRAX	Y	Y	●Low	●High	Y	NI	Y	Y	N	●High	●Low	Y	Y	Y	Y	Y	NI	PY	●Low	●Low	Y	Y	Y	N	N	N	Y	Y	Y	PY	●High	●High	●High
Ettinger 2013	FRAX	Y	Y	●Low	●High	Y	NI	Y	N	PN	●High	●Low	Y	Y	Y	Y	Y	NI	PY	●High	●Hig h	Y	Y	Y	N	Y	PN	Y	Y	Y	PY	●High	●High	●High
Fraser 2011	FRAX	Y	Y	●Low	● bUnclear	N	NI	Y	Y	NI	●Unclear	●Low	PY	Y	Y	Y	Y	Y	Y	● Unclear	●Low	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	● Unclear	● Unclear	● Unclear
Goldshtein 2018	FRAX	Y	Y	●Low	●High	Y	NI	Y	PY	Y	●Low	●Low	PN	Y	Y	Y	Y	NI	Y	● Unclear	●Low	Y	Y	N	Y	Y	N	Y	PY	Y	PY	●High	●High	●High
Gourlay 2017	FRAX	Y	Y	●Low	●Low	NI	NI	Y	NI	N	●High	●Low	Y	Y	Y	Y	Y	NI	N	●High	●Low	Y	Y	PY	NI	Y	N	PY	Y	N	N	●High	●High	●Low
	Garvan	Y	Y	●Low	●Low	NI	NI	Y	NI	N	● High	●Low	Y	Y	Y	Y	Y	NI	N	●High	●Low	Y	Y	PY	NI	Y	N	PY	Y	N	N	●High	●High	●Low
	QFrac-ture	Y	Y	●Low	●Low	NI	NI	Y	NI	N	● High	●Low	Y	Y	Y	Y	Y	NI	N	●High	●Low	Y	Y	PY	NI	Y	N	PY	Y	N	N	●High	●High	●Low
Holloway 2018	FRAX	Y	Y	●Low	●Low	Y	NI	Y	Y	Y	● Low	●Low	PN	Y	Y	Y	Y	NI	Y	● Unclear	●Low	N	N	Y	Y	Y	N	Y	N	Y	N	●High	●High	●Low
Iki 2015	FRAX	Y	Y	●Low	●High	Y	NI	Y	Y	Y	● Low	●Low	N	NA	Y	Y	Y	NI	N	●High	●Low	NA	N	N	PY	NI	N	NA	NA	Y	PY	●High	●High	●Uncle ar
Langsetmo 2011	Garvan	Y	Y	●Low	●Low	Y	NI	Y	Y	NI	●Unclear	●Low	PN	Y	Y	Y	N	NI	PY	●High	●Low	N	Y	PN	NI	Y	N	Y	Y	Y	Y	●High	●High	●Low
Leslie 2016	FRAX	Y	Y	●Low	●High	N	NI	Y	Y	Y	●Unclear	●Low	PN	NA	Y	Y	Y	NI	Y	● Unclear	●Low	NA	Y	PN	Y	Y	Y	NA	NA	Y	PY	● Unclear	● Unclear	●High
	CAROC	Y	Y	●Low	●High	N	NI	Y	Y	Y	●Unclear	●Low	PN	NA	Y	Y	Y	NI	Y	● Unclear	●Low	NA	Y	Y	Y	Y	Y	NA	NA	Y	PY	● Unclear	● Unclear	●High
Leslie 2017b	FRAX	Y	Y	●Low	●High	N	NI	Y	Y	PY	●Unclear	●Low	PN	Y	Y	Y	Y	NI	PY	● Unclear	●Low	Y	Y	N	Y	Y	Y	PY	Y	PY	Y	● Unclear	● Unclear	●High
Li 2015	FRAX	Y	Y	●Low	● Unclear	Y	NI	Y	Y	N	●High	●Low	N	Y	Y	Y	Y	NI	N	●High	●Low	NA	Y	NI	PY	N	N	NA	NA	Y	N	●High	●High	● Unclear

Study	Tool	Domain 1. Participants				Domain 2. Predictors							Domain 3. Outcomes									Domain 4. Analysis											Overall Appraisal	
		1.1 Data sources	1.2 Eligibility	Risk of bias	Applicability	2.1 Definitions	2.2 Blinding	2.3a Available	2.3b Collected/used	2.3c Missing data	Risk of bias	Applicability	3.1a Determination (CFF)	3.1b Determination (hip)	3.2 Definition	3.3 Predictors excluded	3.4 Similar definition	3.5 Knowledge of predictor	3.6 Interval	Risk of Bias	Applicability	4.1a No. outcomes (hip)	4.1b No. outcomes (CFF)	4.2 Predictor handling	4.3 Missing participants	4.4 Deaths/competing risk	4.5 Complexities in data	4.6a Performance data (hip)	4.6b Calibration plots (hip)	4.6c Performance data (CFF)	4.6d Calibration plots (CFF)	Risk of Bias	Risk of Bias	Applicability
Lo 2011	FRC	Y	PY	●Low	●High	Y	NI	Y	N	NI	●Unclear	●Low	NA	Y	Y	Y	Y	NI	PY	●Low	●Low	Y	NA	Y	Y	Y	N	Y	PY	NA	NA	●High	●High	●High
Marques 2017	FRAX	Y	Y	●Low	●High	Y	Y	Y	Y	Y	●Low	●Low	N	Y	Y	Y	PY	Y	PN	●High	●Low	N	Y	Y	N	Y	N	Y	N	Y	N	●High	●High	● Unclear
Melton 2012	FRAX	Y	Y	●Low	●Low	Y	Y	Y	Y	NI	●Unclear	●Low	Y	Y	Y	Y	Y	NI	PY	● Unclear	●Low	N	N	Y	Y	N	Y	N	N	Y	N	●High	●High	●Low
Pluskiewicz 2015	FRAX	Y	Y	●Low	●Low	Y	NI	Y	Y	NI	●Unclear	●Low	N	Y	Y	Y	N	NI	N	●High	●Low	N	N	PY	N	N	N	Y	N	Y	N	●High	●High	●Low
	Garvan	Y	Y	●Low	●Low	Y	NI	Y	Y	NI	●Unclear	●Low	N	Y	Y	Y	N	NI	N	●High	●Low	N	N	PY	N	N	N	Y	N	Y	N	●High	●High	●Low
Premaor 2013	FRAX	Y	Y	●Low	● Unclear	Y	NI	Y	Y	N	●High	●Low	Y	Y	Y	Y	Y	NI	PY	●Low	●Low	Y	Y	N	Y	Y	N	Y	PY	Y	PY	●High	●High	● Unclear
Pressman 2011	FRAX	Y	PY	●Low	●High	Y	NI	Y	N	NI	●Unclear	●Low	NA	Y	Y	Y	Y	NI	PY	●Low	●Low	Y	NA	Y	Y	N	N	Y	N	NA	NA	●High	●High	●High
Reyes Dominguez 2019	Garvan	Y	NI	● Unclear	●High	NI	NI	Y	PY	NI	●Unclear	●Low	N	Y	NI	Y	Y	NI	Y	●High	●Low	N	N	NI	N	Y	N	Y	N	Y	N	●High	●High	●High
Sornay-Rendu 2010	FRAX	Y	PY	●Low	●Low	Y	NI	Y	Y	NI	●Unclear	●Low	Y	Y	Y	Y	Y	NI	Y	●Low	●Low	N	N	NI	Y	Y	Y	Y	N	Y	N	●High	●High	●Low
Tamaki 2011	FRAX	Y	Y	●Low	●Low	Y	NI	Y	Y	NI	●Unclear	●Low	PN	Y	Y	Y	N	NI	Y	●High	●Low	N	N	N	N	N	N	Y	PY	Y	PY	●High	●High	● Unclear
Tamaki 2019	FRAX	Y	Y	●Low	●Low	Y	NI	Y	Y	NI	●Unclear	●Low	N	NA	Y	Y	Y	NI	Y	●High	●Low	NA	N	N	N	N	N	NA	NA	Y	N	●High	●High	● Unclear
Tanaka 2010	FRAX	Y	Y	●Low	●Low	PN	NI	Y	N	N	●High	●Low	NI	NA	Y	Y	NI	NI	Y	● Unclear	●Low	NA	N	PY	PY	N	N	NA	NA	Y	N	●High	●High	●Low
	FRISC	Y	Y	●Low	●Low	PY	NI	Y	N	N	●High	●Low	NI	NA	Y	Y	NI	NI	Y	● Unclear	●Low	NA	N	PY	PY	N	N	NA	NA	Y	N	●High	●High	●Low
Tebe Cordomi 2013	FRAX	Y	Y	●Low	●High	Y	NI	Y	PY	NI	●Unclear	●Low	N	NA	Y	Y	N	NI	Y	●High	●Low	NA	Y	NI	N	N	N	NA	NA	Y	PY	●High	●High	●High
Tremoll-ieres 2010	FRAX	Y	Y	●Low	●High	N	NI	Y	Y	NI	●Unclear	●Low	Y	NA	Y	Y	Y	NI	N	●High	●Low	NA	N	PY	N	N	N	NA	NA	Y	N	●High	●High	●High
Yin 2016	FRAX	Y	Y	●Low	●High	Y	NI	Y	N	N	● High	●Low	PN	Y	Y	Y	Y	NI	Y	● Unclear	●Low	Y	Y	PN	NI	N	N	Y	N	Y	PY	●High	●High	●High

Risk of bias assessed using the PROBAST tool: Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A tool to assessed risk of bias and applicability of prediction model studies. Ann Intern Med. 2019;170:51-58.

NI = No Information; N = No; PN = Probably No; PY = Probably Yes; Y = Yes; CFF = Clinical fragility fracture

Additional Table 7.2. Risk of bias assessments for trials included for KQ3a on the benefits of pharmacologic treatments

Study	Random sequence generation	Allocation concealment	Blinding – participants and personnel	Blinding – outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Hip fractures								
Ascott-Evans 2003	● Low	● Unclear	● Low	● Low	● High	● High	● Low	● High
Boonen 2012	● Low	● Unclear	● Low	● Low	● Unclear	● Low	● Low	● Unclear
Chesnut 1995	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Low	● High
Cummings 1998	● Low	● Low	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Cummings 2009	● Low	● Unclear	● Low	● Low	● Unclear	● Low	● Low	● Unclear
Grey 2009	● Low	● Low	● Low	● Low	● Low	● High	● Low	● High
Grey 2014	● Low	● Low	● Low	● Low	● Low	● High	● Low	● High
Hosking 1998	● Unclear	● Unclear	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Li 2005	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Unclear	● Low	● High
Liberman 1995	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
McClung 2001	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Unclear	● Low	● High
Mortensen 1998	● Low	● Unclear	● Unclear	● Unclear	● High	● High	● Low	● High
Orwoll 2012	● Low	● Low	● Low	● Low	● Low	● High	● Low	● High
Pitale 2015	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● High	● Low	● High
Pols 1999	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear	● Low	● Unclear
Reid 2018	● Low	● Low	● Low	● Low	● Low	● Low	● Low	● Low
Välimäki 2007	● Unclear	● Unclear	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Yan 2009	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Low	● High
Zhu 2017	● Unclear	● Unclear	● Low	● Low	● Low	● High	● Low	● High
Clinical fragility fractures								
Ascott-Evans 2003	● Low	● Unclear	● Low	● Low	● High	● High	● Low	● High
Bell 2002	● Unclear	● Unclear	● Unclear	● Unclear	● High	● High	● Low	● High
Bone 2008	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
Boonen 2012	● Low	● Unclear	● Low	● Low	● Unclear	● Low	● Low	● Unclear
Chesnut 1995	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Low	● High
Cummings 1998	● Low	● Low	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Cummings 2009	● Low	● Unclear	● Low	● Low	● Unclear	● Low	● Low	● Unclear
Fogelman 2000	● Low	● Unclear	● Unclear	● Unclear	● High	● Unclear	● Low	● High
Grey 2009	● Low	● Low	● Low	● Low	● Low	● High	● Low	● High
Grey 2014	● Low	● Low	● Low	● Low	● Low	● High	● Low	● High
Hooper 2005	● Low	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
Hosking 1998	● Unclear	● Unclear	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Hosking 2003	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear

Study	Random sequence generation	Allocation concealment	Blinding – participants and personnel	Blinding – outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Lewiecki 2007 (alendronate)	● Low	● Low	● High	● High	● Unclear	● High	● Low	● High
Lewiecki 2007 (denosumab)	● Low	● Low	● Low	● Low	● Unclear	● High	● Low	● High
Li 2005	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Unclear	● Low	● High
Liberman 1995	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
McClung 2001	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Unclear	● Low	● High
McClung 2009	● Low	● Low	● Low	● Low	● Low	● Unclear	● Low	● Low
Mortensen 1998	● Low	● Unclear	● Unclear	● Unclear	● High	● High	● Low	● High
Orwoll 2012	● Low	● Low	● Low	● Low	● Low	● High	● Low	● High
Pitale 2015	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● High	● Low	● High
Pols 1999	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear	● Low	● Unclear
Reid 2002	● Unclear	● Low	● Low	● Low	● Unclear	● Unclear	● Low	● Unclear
Reid 2018	● Low	● Low	● Low	● Low	● Low	● Low	● Low	● Low
Välimäki 2007	● Unclear	● Unclear	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Yan 2009	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● High	● Low	● High
Zhu 2017	● Unclear	● Unclear	● Low	● Low	● Low	● High	● Low	● High
All-cause mortality								
Bone 2008	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
Boonen 2012	● Low	● Unclear	● Low	● Low	● Unclear	● Unclear	● Low	● Unclear
Chesnut 1995	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
Cummings 1998	● Low	● Low	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Cummings 2009	● Low	● Unclear	● Low	● Low	● Unclear	● Low	● Low	● Unclear
Grey 2014[a]	● Low	● High	● Unclear	● Unclear	● High	● High	● Low	● High
Lewiecki 2007 (alendronate)	● Low	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
Lewiecki 2007 (denosumab)	● Low	● Low	● Low	● Low	● Unclear	● Unclear	● Low	● Unclear
McClung 2009	● Low	● Low	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Orwoll 2012	● Low	● Low	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Pitale 2015	● Unclear	● Unclear	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Reid 2018	● Low	● Low	● Low	● Low	● Low	● Low	● Low	● Low
Välimäki 2007	● Unclear	● Unclear	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Yan 2009	● Low	● Unclear	● Unclear	● Unclear	● Unclear	● Unclear	● Low	● Unclear
Zhu 2017	● Unclear	● Unclear	● Low	● Low	● Low	● Low	● Low	● Unclear

Study	Random sequence generation	Allocation concealment	Blinding – participants and personnel	Blinding – outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Quality of life								
Cummings 2009	● Low	● Unclear	● Low	● Low	● Unclear	● Unclear	● Low	● Unclear

Risk of bias assessed using the Cochrane Risk of Bias Tool, v. 2011: Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ;2011;343:d5928.

[a]Mortality data are from the 5-year open-label extension (participants remained in originally randomized groups)

Additional Table 7.3. Quality appraisals of the systematic reviews included for KQ3b on the harms of pharmacologic treatments

Systematic review	Intervention[a]	Components of PICO	Protocol & deviations	Selection of designs	Comprehen-sive search	Duplicate selection	Duplication data extraction	Excluded studies	Study description	ROB appraisal[b]	Funding sources	Appropriate statistics	Impact of ROB on synthesis	Impact of ROB on results	Heterogeneity explained	Publication bias	Conflict of interest	Overall Confidence
Any non-serious AE																		
Davis 2016	ALE	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● No	● No	● No	● No	● No	● Yes	Low
Davis 2016	RIS, ZOL	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● No	● Yes	Low
Davis 2020	DEN	● Yes	● Yes	● No	● Yes	● No	● No	● Yes	● Yes	● Yes	● No	NA	NA	● No	● Yes	NA	● Yes	Low
Non-serious GI AE																		
Crandall 2014	ALE, DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● Yes	● No	● Yes	● No	● Yes	● Yes	Low
Crandall 2014	RIS, ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● Yes	● No	● No	● No	● No	● Yes	Critically Low
Influenza-like symptoms																		
Davis 2016	ALE	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● No	● Yes	Low
Crandall 2014	ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Low
Influenza, Pharyngitis																		
Davis 2016	RIS	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	NA	NA	● No	● Yes	● No	● Yes	Low
Pyrexia, Headache																		
Davis 2016	ZOL	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● No	● No	● No	● Yes	Low
Chills																		
Davis 2016	ZOL	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	Low
Musculoskeletal pain																		
Diedhou 2015	DEN	● Yes	● No	● No	● No	● No	● No	● No	● Yes	● No	● No	NA	NA	● No	● Yes	NA	● Yes	Critically Low
Arthritis and arthralgia																		
Crandall 2014	ALE, RIS, ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● No	● No	● No	● Yes	Critically Low
Myalgias, cramps, or limb pain																		
Crandall 2014	ALE, ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● No	● No	● No	● Yes	Critically Low
Crandall 2014	RIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
Composite: arthralgia, myalgia, pyrexia, chills, and influenza-like symptoms																		
Crandall 2014	ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Low
Infections																		
Crandall 2014	DEN	● Yes	● Yes	● No	● Yes	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● Yes	● No	● Yes	● Yes	Low
Dermatologic AE																		
Injection site reactions																		
Crandall 2014	DEN	● Yes	● Yes	● No	● Yes	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● Yes	● Yes	Low

Systematic review	Intervention[a]	Components of PICO	Protocol & deviations	Selection of designs	Comprehen-sive search	Duplicate selection	Duplication data extraction	Excluded studies	Study description	ROB appraisal[b]	Funding sources	Appropriate statistics	Impact of ROB on synthesis	Impact of ROB on results	Heterogeneity explained	Publication bias	Conflict of interest	Overall Confidence
Rash/eczema																		
Crandall 2014	DEN	● Yes	● Yes	● No	● Yes	● Yes	● No	● No	● PYes	● No	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Low
Rash																		
Viswanathan 2018	DEN	● Yes	● Yes	● No	● Yes	● Yes	● No	● No	● Yes	● Yes	● No	NA	NA	● Yes	● Yes	● Yes	● Yes	Moderate
Eczema																		
Viswanathan 2018	DEN	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● No	NA	NA	● Yes	● Yes	● Yes	● Yes	Moderate
Any serious AE																		
Viswanathan 2018	ALE, RIS, ZOL, DEN	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Moderate
Serious gastrointestinal AE (excluding cancers)																		
Crandall 2014	ALE, RIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● Yes	● No	● No	● Yes	● No	● Yes	Critically Low
Crandall 2014	ZOL, DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
GI perforation, ulcers, or bleeds																		
Crandall 2014	ALE	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● Yes	● No	● No	● Yes	● No	● Yes	Critically Low
Crandall 2014	RIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● No	● No	● No	● Yes	Critically Low
Crandall 2014	ZOL, DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
Serious esophageal AE																		
Crandall 2014	ALE, RIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● No	● No	● No	● Yes	Critically Low
Crandall 2014	ZOL, DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
Serious hepatobiliary AE																		
Crandall 2014	ALE, RIS, ZOL, DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
GI cancer																		
Crandall 2014	RIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● No	● Yes	● No	● Yes	Critically Low
Colon or colorectal																		
Chen 2015	ALE	● Yes	● No	● No	● No	● Yes	● No	● Yes	● No	● Yes	● No	● No	● No	● Yes	● No	● Yes	● Yes	Critically Low
Crandall 2014	DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Low
Gastric																		
Chen 2015	ALE	● Yes	● No	● No	● No	● Yes	● No	● Yes	● No	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Critically Low
Esophageal																		
Chen 2015	ALE	● Yes	● No	● No	● No	● Yes	● No	● Yes	● No	● Yes	● No	● No	● No	● Yes	● No	● Yes	● Yes	Critically Low
Crandall 2014	BIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● No	● Yes	● No	● Yes	Low
Liver																		

Systematic review	Intervention[a]	Components of PICO	Protocol & deviations	Selection of designs	Comprehen-sive search	Duplicate selection	Duplication data extraction	Excluded studies	Study description	ROB appraisal[b]	Funding sources	Appropriate statistics	Impact of ROB on synthesis	Impact of ROB on results	Heterogeneity explained	Publication bias	Conflict of interest	Overall Confidence
Chen 2015	ALE	● Yes	● No	● No	● No	● Yes	● No	● Yes	● No	● Yes	● No	● No	● No	● Yes	● No	● Yes	● Yes	Critically Low
Pancreas																		
Chen 2015	ALE	● Yes	● No	● No	● No	● Yes	● No	● Yes	● No	● Yes	● No	● No	● No	● Yes	● Yes	● Yes	● Yes	Critically Low
Oral, bile duct, small intestine																		
Chen 2015	ALE	● Yes	● No	● No	● No	● Yes	● No	● Yes	● No	● Yes	● No	NA	NA	● Yes	● Yes	● Yes	● Yes	Critically Low
Serious cardiovascular AEs																		
Kranenburg 2016	BIS, ZOL	● Yes	● No	● No	● PYes	● Yes	● Yes	● No	● Yes	● PYes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Low
Acute coronary syndrome																		
Crandall 2014	ALE, RIS, ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● No	● No	● No	● Yes	Critically Low
Cerebrovascular events																		
Crandall 2014	ALE, RIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
Crandall 2014	ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● No	● No	● No	● Yes	Critically Low
Crandall 2014	DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● No	● Yes	● No	● Yes	Critically Low
Davis 2020 (stroke)	DEN	● Yes	● Yes	● No	● Yes	● No	● No	● Yes	● Yes	● Yes	● No	NA	NA	● No	● Yes	NA	● Yes	Low
Pulmonary embolism																		
Crandall 2014	ALE, ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
Thromboembolic events																		
Crandall 2014	ALE, RIS, ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● No	● Yes	● No	● Yes	Critically Low
Crandall 2014	DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● No	● Yes	Critically Low
Davis 2020 (venous thromboembolism)	DEN	● Yes	● Yes	● No	● Yes	● No	● No	● Yes	● Yes	● Yes	● No	NA	NA	● No	● Yes	NA	● Yes	Low
Cerebrovascular death																		
Crandall 2014	ALE, RIS, ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● No	● No	● No	● Yes	Critically Low
Composite cardiovascular outcomes																		
Lv 2020	DEN	● Yes	● Yes	● No	● No	● Yes	● Yes	● Yes	● PYes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Moderate
Serious cardiac rhythm disturbances																		
Atrial fibrillation																		
Viswanathan 2018	BIS	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● No	NA	NA	● Yes	● Yes	NA	● Yes	Moderate
Crandall 2014	ALE, RIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● Yes	● Yes	Low
Crandall 2014	ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	● No	● No	● Yes	● No	● Yes	● Yes	Low

Systematic review	Intervention[a]	Components of PICO	Protocol & deviations	Selection of designs	Comprehen-sive search	Duplicate selection	Duplication data extraction	Excluded studies	Study description	ROB appraisal[b]	Funding sources	Appropriate statistics	Impact of ROB on synthesis	Impact of ROB on results	Heterogeneity explained	Publication bias	Conflict of interest	Overall Confidence
Crandall 2014	DEN	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● No	● Yes	● No	● Yes	Critically Low
Atypical femoral fractures																		
Crandall 2014	BIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● Yes	● Yes	Low
Fink 2019	ALE, ZOL, DEN (LT)[c]	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● Yes	NA	NA	● Yes	● Yes	● Yes	● Yes	Moderate
Davis 2020	DEN	● Yes	● Yes	● No	● Yes	● No	● No	● Yes	● Yes	● Yes	● No	NA	NA	● No	● Yes	NA	● Yes	Low
Osteonecrosis of the jaw																		
Crandall 2014	BIS	● Yes	● Yes	● No	● No	● Yes	● No	● No	● PYes	● No	● No	NA	NA	● Yes	● Yes	● Yes	● Yes	Low
Fink 2019	BIS, ALE, ZOL (LT)	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● Yes	NA	NA	● Yes	● Yes	● Yes	● Yes	Moderate
Davis 2020	DEN	● Yes	● Yes	● No	● Yes	● No	● No	● Yes	● Yes	● Yes	● No	NA	NA	● No	● Yes	NA	● Yes	Low
Fink 2019	DEN (LT)	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● Yes	NA	NA	● Yes	● Yes	● Yes	● Yes	Moderate
Discontinuation due to AE																		
Viswanathan 2018	ALE	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Moderate
Viswanathan 2018	RIS	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Moderate
Viswanathan 2018	ZOL	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● No	NA	NA	● Yes	● Yes	NA	● Yes	Moderate
Viswanathan 2018	DEN	● Yes	● Yes	● No	● No	● Yes	● No	● Yes	● Yes	● Yes	● No	● Yes	● Yes	● Yes	● Yes	● Yes	● Yes	Moderate
Rebound fractures after stopping treatment																		
Tsourdi 2020	DEN	● Yes	● No	● Yes	● No	● No	● No	● No	● PYes	● No	● No	NA	NA	● No	● Yes	NA	● Yes	Critically Low

Quality assessment performed using AMSTAR-2: Shea BJ, Reeves BC, Thuku M, Hamel C, Moran J, Moher D, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomized or non-randomised studies of healthcare interventions or both. BMJ. 2017;358:j4008.

ALE: alendronate; LT: long-term; DEN: denosumab; NA: not applicable (no meta-analysis); PYes: probably yes; RIS: risedronate; ZOL: zoledronic acid

[a] All interventions are compared to placebo, unless otherwise denoted

[b] Note that the following reviews assessed the risk of bias of their included studies, but these were not assessed by outcome (i.e., specifically for harms): Davis 2016, Davis 2020, Fink 2019, Viswanathan 2018.

[c] compared to no treatment

Table 7.4. Risk of bias of cohort studies included for KQ3b on harms of pharmacologic therapy

Study	Newcastle Ottawa Risk of Bias Domain								
	Was the exposed cohort representative?	Was the non-exposed cohort selected appropriately?	How was the exposure ascertained?	Was the outcome of interest present at start of study?	Does the study control for confounders (age + other)?	Does the study control for additional factors?	How is the outcome assessed?	Length of follow-up sufficient for outcome?	Adequate follow-up?
Tripto-Shkolnik 2020	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes

Additional Table 7.5. Risk of bias appraisals of the studies include for KQ4 on the acceptability of screening and/or treatment

Study	Participant selection	Completeness of data			Measurement instrument					Participant understanding	Data analysis	Overall risk of bias
		Adequate participation rate	Losses to follow-up	Sample size justification	Valid, reliable, administered as intended	Outcome assessors blinded	Valid representation of benefits	Valid representation of harms	Timeframe sufficient			
de Bekker-Grob 2008	● Low	● Unclear	● Unclear	● Unclear	● Low	NA	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Fuzzell 2020	● Low	● Unclear	● Low	● Unclear	● Low	NA	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Hudson 2011	● Low	● High	● Low	● Low	● Low	NA	● Unclear	● Low	● Low	● Unclear	● Low	● High
Hudson 2012	● Low	● High	● Low	● Unclear	● Low	NA	● Unclear	● High	● Low	● Unclear	● Low	● High
Kalluru 2017	● Low	● Low	● Low	● Low	● Low	● Low	● Unclear	● High	● Low	● Unclear	● Low	● High
LeBlanc 2015	● Low	● Low	● High	● Low	● Low	NA	● Unclear	● Low	● Low	● Low	● High	● High
Liu 2020 & Billington 2019	● Low	● Unclear	● Low	● Unclear	● Low	NA	● Unclear	● Low	● Low	● Low	● Low	● Unclear
Montori 2011	● Low	● Low	● Low	● Low	● Low	NA	● Unclear	● Low	● Low	● Low	● Low	● Unclear
Neuner 2014	● Low	● High	● Low	● Unclear	● Low	NA	● Low	● Low	● Low	● Unclear	● Low	● High
Sheridan 2016	● Low	● High	● Low	● Low	● Low	● Low	● Low	● Low	● Low	● Low	● Low	● High
Si 2019	● Low	● Low	● Low	● Low	● Low	NA	● Low	● Low	● Low	● Unclear	● Low	● Unclear
Smallwood 2017	● Low	● Low	● Low	● High	● Low	NA	● High	● Unclear	● Low	● Low	● High	● High

Risk of bias assessment informed by the risk of bias subdomains included within the GRADE guidance for assessing the certainty of evidence in studies of the importance of outcomes or values and preferences. We adapted the questions to be relevant to the assessment of acceptability: Zhang Y, Alonso-Coello P, Guyatt GH, Yepes-Nuñez JJ, Akl EA, Hazlewood G, et al. GRADE guidelines: 19. Assessing the certainty of evidence in the importance of outcomes or values and preferences – risk of bias and indirectness. J Clin Epidemiol. 2019;11;94-104.

NA=not applicable