

Bisfosfonaten

Key question

- a. *Wat is - bij patiënten met castratie resistente prostaatkanker met botmetastasen - het effect van bisfosfonaten (ZA, APD of CL) en denosumab (in vergelijking met placebo) op preventie en reductie van 'skeletal related events', pijn, morbiditeit en mortaliteit?*
- b. *Wat is - bij patiënten met castratie resistente prostaatkanker met botmetastasen - het effect van bisfosfonaten (alleen ZA) - in vergelijking met denosumab - op preventie en reductie van 'skeletal related events', pijn, morbiditeit en mortaliteit?*

P: Castration Resistant Prostate Cancer (CRPC), metastatic to the skeleton (M+) (CRPC is in de Nederlandse setting bijna altijd/99% CRPC én M+. In de US is een nieuwe groep ontstaan door zeer vroege hormonale therapie: CRPC M0)

I: Bone targeted therapies: bisphosphonates (BP: zoledronic acid [ZA], pamidronate [APD], clodronate [CL]) and denosumab (DEN)

C: Placebo versus BP (ZA, APD, CL) or DEN; BP (ZA) versus DEN

O: Reduction or prevention of SRE's, pain, morbidity, mortality by intervention

Searches were limited to studies published in English or Dutch, from 2002 up to May 11 2012

Search strategy

Searches were run on May 11 2012 for systematic reviews (SRs) and randomised controlled trials (RCTs). Pubmed Medline, OVID Embase and the Cochrane Database of Systematic Reviews (CDSR) were searched. Detailed search strings are given below. Systematic reviews and narrative reviews based on a systematic search were used to source older references.

Search results

Systematic reviews and meta-analyses

The Medline search yielded 15 hits, while the Embase search yielded 77 hits. The search in the CDSR yielded 2 Cochrane reviews.

Full-text evaluation

After merging the 3 search files into 1 file and removal of the duplicates, 79 records were screened on title and abstract. Of these 45 were excluded. The most important reasons for exclusion were that studies were on different patients, interventions or outcomes.

Of the remaining 34 studies, the full-text was retrieved. Table 11 provides an overview of the evaluation of these studies.

Table 11. Overview of reviews evaluated full-text

	Reference	In-/Excluded	Reason(s)
1	High-quality evidence in oncology from 18th May to 15th June 2004: A summary. Cancer Treatment Reviews. 2004;30(8):721-3	Ex	Summary of articles on cancer treatment. None within scope
	Bayes M, Rabasseda X, Prous JR. Gateways to Clinical Trials. Methods and Findings in Experimental and Clinical Pharmacology. 2004;26(9):723-53	Ex	List of clinical trials
	Beltran H, Beer TM, Carducci MA, De Bono J, Gleave M,	Ex	Narrative review based on a systematic

	Reference	In-/Excluded	Reason(s)
	Hussain M, et al. New therapies for castration-resistant prostate cancer: Efficacy and safety. <i>European Urology</i> . 2011;60(2):279-90		search. Used for reference tracking
	Berry S, Waldron T, Winquist E, Lukka H. The use of bisphosphonates in men with hormone-refractory prostate cancer: a systematic review of randomized trials. <i>Can J Urol</i> . 2006;13(4):3180-8	Ex	Systematic review in scope. No meta-analysis. Includes four RCTs on clodronate published before 2002 that were requested full text (see below)
5	Burkiewicz JS, Scarpace SL, Bruce SP. Denosumab in osteoporosis and oncology. <i>Ann Pharmacother</i> . 2009;43(9):1445-55	Ex	Narrative review based on a systematic search. Used for reference tracking
	Campbell-Baird C, Polderdijk H, Kofler C, Zhou L, Yeh H, Braun A. Comparing the incidence of acute phase reactions in patients with advanced cancer or multiple myeloma (MM) following treatment with denosumab or zoledronic acid (ZA): Results from a metaanalysis of two phase 3 randomized trials. <i>Supportive Care in Cancer</i> . 2010;18:S77	Ex	Not on prostate cancer patients
	Chi KN, Bjartell A, Dearnaley D, Saad F, Schroder FH, Sternberg C, et al. Castration-resistant Prostate Cancer: From New Pathophysiology to New Treatment Targets. <i>European Urology</i> . 2009;56(4):594-605	Ex	Narrative review based on a systematic search. Used for reference tracking
	Clarke NW. Management of the Spectrum of Hormone Refractory Prostate Cancer. <i>European Urology</i> . 2006;50(3):428-39	Ex	Narrative review based on a systematic search. Used for reference tracking
	Crawford ED. Skeletal complications in men with prostate cancer: Effects on quality-of-life outcomes throughout the continuum of care. <i>European Urology, Supplements</i> . 2004;3(5 SPEC. ISS.):10-5	Ex	Narrative review based on a systematic search. Used for reference tracking
10	Gomella LG. Contemporary use of hormonal therapy in prostate cancer: Managing complications and addressing quality-of-life issues. <i>BJU International</i> . 2007;99(SUPPL. 1):25-9	Ex	Narrative review (no systematic search, no explicit selection criteria and no quality assessment)
	Graham JD. Chemotherapy for metastatic disease: Current status. <i>Clinical Oncology</i> . 2005;17(7):572-8	Ex	Narrative review
	Hei YJ. Future directions for zoledronic acid and new agents for the treatment of bone metastases. <i>European Urology, Supplements</i> . 2004;3(5 SPEC. ISS.):55-62	Ex	Narrative review based on a systematic search. Used for reference tracking
	Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, et al. EAU Guidelines on Prostate Cancer. <i>European Urology</i> . 2008;53(1):68-80	Ex	Systematic review without a quality assessment (other than levels of evidence). Used for reference tracking
	Horwich A. Prostate cancer management. <i>Annals of Oncology</i> . 2004;15(SUPPL. 4):iv307-iv12	Ex	Narrative review (no systematic search, no explicit selection criteria and no quality assessment)
15	Hunfeld NGM, Sleeboom HP, Kropman RF, Pelger RCM, Le Brun PPH. Evidence for bisphosphonates in prostate cancer. [Dutch] Bewijs voor bisfosfonaten bij prostaatkanker." <i>Nederlands Tijdschrift voor Urologie</i> . 2006;14(1): 25-29.	Ex	Systematic review without a quality assessment (other than levels of evidence). Used for reference tracking. Included 4 RCTs published before 2002 (references 6, 7, 9, 10) (see below)
	Leo S, Accettura C, Lorusso V. Castration-resistant prostate cancer: Targeted therapies. <i>Chemotherapy</i> . 2011;57(2):115-27	Ex	Narrative review based on a systematic search. Used for reference tracking
	Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. <i>Clin Ther</i> . 2003;25(11):2669-708	Ex	Narrative review based on a systematic search. Used for reference tracking
	Machado M, Cruz LS, Tannus G, Fonseca M. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: A meta-analysis of randomized clinical trials. <i>Clinical Therapeutics</i> . 2009;31(5):962-79	Ex	Systematic review with meta-analysis, but includes other patient groups. Used for reference tracking
	Maung K, Higano C. Zoledronic acid is effective in the treatment of prostate cancer patients with bone metastases. <i>Clinical Prostate Cancer</i> . 2002;1(1):12-3	Ex	Summary of an included RCT
20	Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. <i>European Urology</i> . 2011;59(4):572-83	Ex	Summary of the EUA guidelines
	Ok JH, Meyers FJ, Evans CP. Medical and surgical palliative care of patients with urological malignancies. <i>Journal of Urology</i> . 2005;174(4 I):1177-82	Ex	Narrative review based on a systematic search. Used for reference tracking
	Saad F. Preventing bone complications in patients with	Ex	Narrative review based on a systematic

	Reference	In- /Excluded	Reason(s)
	prostate cancer: The emerging role of zoledronic acid. <i>European Urology, Supplements</i> . 2004;3(5 SPEC. ISS.):25-33		search. Used for reference tracking
	Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: quality-of-life considerations throughout the continuum of care. <i>Eur Urol</i> . 2004;46(6):731-39; discussion 9-40	Ex	Narrative review based on a systematic search. Used for reference tracking
	Saad F, Schulman CC. Role of bisphosphonates in prostate cancer. <i>Eur Urol</i> . 2004;45(1):26-34	Ex	Narrative review based on a systematic search. Used for reference tracking
25	Saad F, Karakiewicz P, Perrotte P. The role of bisphosphonates in hormone-refractory prostate cancer. <i>World J Urol</i> . 2005;23(1):14-8	Ex	Narrative review based on a systematic search. Used for reference tracking
	Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumour effects. <i>Cancer Treat Rev</i> . 2008;34(2):183-92	Ex	Narrative review based on a systematic search. Used for reference tracking
	Saad F, Adachi JD, Brown JP, Canning LA, Gelmon KA, Josse RG, et al. Cancer treatment-induced bone loss in breast and prostate cancer. <i>Journal of Clinical Oncology</i> . 2008;26(33):5465-76	Ex	Narrative review based on a systematic search. Used for reference tracking
	Serpa Neto A, Tobias-Machado M, Esteves MA, Senra MD, Wroclawski ML, Fonseca FL, et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. <i>Prostate Cancer Prostatic Dis</i> . 2012;15(1):36-44	Ex	Studies with patients with and without bone metastases included; 'Studies were excluded if fracture outcome or BMD data were not provided', so studies with only mortality or pain data would be missed. Used for reference tracking
	Smith MR. Bisphosphonates to prevent skeletal complications in men with metastatic prostate cancer. <i>J Urol</i> . 2003;170(6 Pt 2):S55-7; discussion S7-8	Ex	Narrative review based on a systematic search. Used for reference tracking
30	Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and osteonecrosis of the jaw: Cause and effect or a post hoc fallacy? <i>Annals of Oncology</i> . 2006;17(8):1197-204	Ex	Review of retrospective chart studies
	Van den Wyngaert T, Wouters K, Huizing MT, Vermorken JB. RANK ligand inhibition in bone metastatic cancer and risk of osteonecrosis of the jaw (ONJ): Non bis in idem? <i>Supportive Care in Cancer</i> . 2011;19(12):2035-40	Ex	Meta-analysis of the risk of osteonecrosis of the jaw in divers population
	Wong RKS, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. <i>Cochrane Database of Systematic Reviews</i> . 2009;(4)(CD002068)	Ex	On all patients with metastatic bone disease. Used for reference tracking. Includes two references published before 2002 (see below)
	Wu S, Dahut WL, Gulley JL. The use of bisphosphonates in cancer patients. <i>Acta Oncologica</i> . 2007;46(5):581-91	Ex	Narrative review based on a systematic search (no selection criteria, no quality assessment). Used for reference tracking
34	Yuen KY, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. <i>Cochrane Database of Systematic Reviews</i> . 2006;(4)(CD006250)	Ex	Systematic review with meta-analysis, including etidronate. Used for reference tracking. Includes 5 RCTs published before 2002 (see below)

Additional references sourced through reviews:

	Reference	In- /Excluded	Reason(s)
1	Adami S, Mian M. Clodronate therapy of metastatic bone disease in patients with prostatic carcinoma. Recent results in cancer research. <i>Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer</i> . 1989;116:67-72.	In	
	Elomaa I, Kylmala T, Tammela T, Viitanen J, Ottelin J, Ruutu M, et al. Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostatic cancer. <i>International urology and nephrology</i> . 1992;24(2):159-66.	Ex	Other comparison (estramustine phosphate + clodronate vs. estramustine phosphate + placebo)
	Kylmala T, Tammela T, Risteli L, Risteli J, Taube T, Elomaa I. Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. <i>European Journal of Cancer</i> .	Ex	No placebo for clodronate

	1993;29A(6):821-5		
	Kylmala T, Taube T, Tammela TL, Risteli L, Risteli J, Elomaa I. Concomitant i.v. and oral clodronate in the relief of bone pain--a double-blind placebo-controlled study in patients with prostate cancer. British journal of cancer. 1997;76(7):939-42.	Ex	Other comparison (estrामustine phosphate + clodronate vs. estrामustine phosphate + placebo)
5	Strang P, Nilsson S, Brandstedt S, Sehlin J, Borghede G, Varenhorst E, et al. The analgesic efficacy of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. Anticancer research. 1997;17(6D):4717-21.	Ex	Mean pain intensity was significantly higher in the placebo group (39 in the clodronate group vs. 53 in the placebo group on a visual analogue scale of 10; p=0.02) which undermines the validity of the sole reported outcome, pain
6	Taube T, Kylmala T, Lamberg-Allardt C, Tammela TL, Elomaa I. The effect of clodronate on bone in metastatic prostate cancer. Histomorphometric report of a double-blind randomised placebo-controlled study. European Journal of Cancer. 1994;30A(6):751-8.	Ex	Other outcomes

Randomized controlled trials

The Medline search yielded 386 hits, while the Embase search yielded 889 hits.

Full-text evaluation

After merging the 2 search files into 1 file and removal of the duplicates, 1061 hits were screened on title and abstract. Of these, 966 were excluded. The most important reasons for exclusion were that studies were no RCT or studied different patients, interventions or outcomes.

Of the remaining 95 studies, the full-text was retrieved. Table 12 provides an overview of the evaluation of these studies.

Table 12. Overview of full-text evaluated RCTs

	Reference	In-/Excluded	Reason(s)
1	Denosumab: New drug - Limited efficacy in fracture prevention, too many adverse effects. Prescrire International. 2011;20(117):145-8.	Ex	Narrative review based on a systematic search. Used for reference tracking
	Altundag K, Altundag O, Morandi P, Gunduz M. High-dose calcitriol, zoledronate, and dexamethasone for the treatment of progressive prostate carcinoma. Cancer. 2004;101(5):1101-2; author reply 2-3.	Ex	Letter
	Altundag K, Altundag O, Morandi P, Gunduz M. Imatinib mesylate and zoledronic acid in androgen-independent prostate cancer. Urology. 2005;65(1):211-2; author reply 2.	Ex	Letter
	Amir E, Tannock IF. Prostate cancer: Androgen deprivation therapy and bone loss. Nature Reviews Urology. 2009;6(12):642-4.	Ex	Narrative review
5	Atkins CD. Re: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2003;95(4):332; author reply 3-4.	Ex	Letter
	Banal F, Briot K, Ayoub G, Dougados M, Roux C. Unilateral anterior uveitis complicating zoledronic acid therapy in prostate cancer. J Rheumatol. 2008;35(12):2458-9.	Ex	Case report
	Barni S, Mandala M, Cazzaniga M, Cabiddu M, Cremonesi M. Bisphosphonates and metastatic bone disease. Annals of Oncology. 2006;17(SUPPL. 2):ii91-ii5.	Ex	Narrative review
	Berruti A, Tucci M, Terrone C, Scarpa RM, Angeli A, Dogliotti L. Re: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2003;95(4):332-3; author reply 3-4.	Ex	Letter
	Body JJ. Tumor bone disease. Annales d'Endocrinologie. 2006;67(2):166-72.	Ex	Narrative review
10	Body JJ, Lipton A, Gralow J, Steger GG, Gao G, Yeh H, et al. Effects of denosumab in patients with bone metastases with and without previous bisphosphonate exposure. Journal of Bone and Mineral Research. 2010;25(3):440-6.	Ex	Uses the data from an included study

	Reference	In- /Excluded	Reason(s)
	Botteman M, Carter J, Kaura S. A comparison of the cost-effectiveness of zoledronic acid for preventing skeletal-related events in patients with bone metastases from prostate cancer in 4 European countries. <i>Value in Health</i> . 2010;13 (7):A264.	Ex	Cost-effectiveness study with no reference as to the clinical data used
	Botteman M, Logman F, Kaura S. Analysis of the cost-effectiveness of zoledronic acid for the prevention of skeletal-related events in patients with prostate cancer and bone metastases: A comparison across four European countries. <i>Journal of Clinical Oncology</i> . Conference. 2010;28(15 SUPPL. 1).	Ex	Cost-effectiveness study with no reference as to the clinical data used
	Carter JA, Bains M, Chandiwana D, Kaura S, Botteman MF. Cost effectiveness of zoledronic acid vs. pamidronate or no therapy for the treatment of bone metastases secondary to prostate cancer. <i>Value in Health</i> . 2011;14 (7):A447.	Ex	Cost-effectiveness study based on effectiveness data from an included trial
	Carter JA, Joshi A, Kaura S, Botteman MF. Cost effectiveness of zoledronic acid in the management of skeletal metastases in hormone-refractory prostate cancer patients in France, Germany, Portugal, and the Netherlands. <i>J Med Econ</i> . 2011;14(3):288-98.	Ex	Cost-effectiveness study based on effectiveness data from an included trial
15	Casey R, Gesztesi Z, Rochford J. Long term zoledronic acid during androgen blockade for prostate cancer. <i>Can J Urol</i> . 2010;17(3):5170-7.	Ex	Patients without bone metastases
	Cleeland CS, Patrick DL, Fallowfield L, Von Moos R, Body J, Egerdie B, et al. Effects of denosumab vs zoledronic acid (ZA) on pain in patients (PTS) with advanced cancer and bone metastases: An integrated analysis of 3 pivotal trials. <i>Annals of Oncology</i> . 2010;21:viii380.	Ex	Narrative review
	Cleeland SC, Patrick LD, Fallowfield L, Von Moos R, Body J, Egerdie B, et al. Denosumab vs zoledronic acid (ZA) effect on pain in patients with advanced cancer and bone metastases: An integrated analysis of 3 trials. <i>Asia-Pacific Journal of Clinical Oncology</i> . 2011;7:55.	Ex	Narrative review
	Crawford BS, McNulty RM, Kraut EH, Turowski RC. Extended use of intravenous bisphosphonate therapy for the prevention of skeletal complications in patients with cancer. <i>Cancer Invest</i> . 2009;27(10):984-8.	Ex	Retrospective chart review
	Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). <i>J Natl Cancer Inst</i> . 2003;95(17):1300-11.	In	
20	Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes MR. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. <i>Lancet Oncol</i> . 2009;10(9):872-6.	In	Long-term follow up of Dearnaley 2003
	Demirtas A, Sahin N, Caniklioglu M, Kula M, Ekmekcioglu O, Tatlisen A. Assessment of the effects of zoledronic Acid therapy on bone metabolic indicators in hormone-resistant prostate cancer patients with bone metastasis. <i>ISRN Urol</i> . 2011;2011:392014.	Ex	No control group
	DePuy V, Anstrom KJ, Castel LD, Schulman KA, Weinfurt KP, Saad F. Effects of skeletal morbidities on longitudinal patient-reported outcomes and survival in patients with metastatic prostate cancer. <i>Support Care Cancer</i> . 2007;15(7):869-76.	Ex	Post hoc analysis of clinical trial data (Saad 2002), quantifying the longitudinal effects of multiple SREs on HRQOL and survival
	Dranitsaris G, Hatzimichael E. Interpreting results from oncology clinical trials: a comparison of denosumab to zoledronic acid for the prevention of skeletal-related events in cancer patients. <i>Support Care Cancer</i> . 2012.	Ex	Narrative review based on a systematic search. Used for reference tracking
	Dubin CH. Weekly, oral zoledronic acid can improve quality of life for bone metastases sufferers. <i>Drug Delivery Technology</i> . 2010;10(9):30-3	Ex	Narrative review
25	Egerdie B, Smith MR, Tammela TLJ, Saad F, Ke C, Goessl C, et al. A responder analysis of the effects of denosumab on bone mineral density in men with prostate cancer receiving androgen deprivation therapy. <i>Journal of Urology</i> . 2009;1:611.	Ex	Bone mineral density as the sole outcome
	Ernst DS, Tannock IF, Winquist EW, Venner PM, Reyno L, Moore MJ, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. <i>J Clin Oncol</i> . 2003;21(17):3335-42.	Ex	Different intervention: mitoxantrone + prednisone + clodronate vs. mitoxantrone + prednisone
	Fallowfield L, Von Moos R, Patrick D, Cleeland CS, Henry DH, Hirsh V, et al. Pain outcomes in a randomized phase 3 clinical trial of denosumab vs zoledronic acid (ZA) in patients with solid tumours and bone metastases. <i>European Journal of Cancer</i> . 2011;47:S485.	Ex	No prostate cancer patients included
	Fizazi K, Bosserman L, Gao G, Skacel T, Markus R. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates:	In	Prostate cancer patients only

	Reference	In-/Excluded	Reason(s)
	results of a randomized phase II trial. <i>J Urol.</i> 2009;182(2):509-15; discussion 15-6.		
	Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. <i>J Clin Oncol.</i> 2009;27(10):1564-71.	In	
30	Fizazi K, Carducci MA, Smith MR, Damiao R, Brown JE, Karsh L, et al. A randomized phase III trial of denosumab versus zoledronic acid in patients with bone metastases from castration-resistant prostate cancer. <i>Journal of Clinical Oncology. Conference.</i> 2010;28(18 SUPPL. 1).	Ex	Double publication in abstract form of Fizazi 2011
	Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. <i>Lancet.</i> 2011;377(9768):813-22.	In	
	Grenader T, Shavit L, Uziely B, Peretz T. Re: Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. <i>J Natl Cancer Inst.</i> 2005;97(3):235-6.	Ex	Letter
	Hyer R. Denosumab prevents or stalls skeletal events in prostate cancer. <i>Oncology Report.</i> 2010(JULY-AUGUST):22-3.	Ex	Summary of an included trial
	Ignatoski KM, Friedman J, Escara-Wilke J, Zhang X, Daignault S, Dunn RL, et al. Change in markers of bone metabolism with chemotherapy for advanced prostate cancer: interleukin-6 response is a potential early indicator of response to therapy. <i>J Interferon Cytokine Res.</i> 2009;29(2):105-12.	Ex	Bone markers as the sole outcome
35	Israeli RS, Rosenberg SJ, Saltzstein DR, Gottesman JE, Goldstein HR, Hull GW, et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. <i>Clin Genitourin Cancer.</i> 2007;5(4):271-7.	Ex	Patients without bone metastases
	James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Anderson J, et al. STAMPEDE: Systemic Therapy for Advancing or Metastatic Prostate Cancer--a multi-arm multi-stage randomised controlled trial. <i>Clin Oncol (R Coll Radiol).</i> 2008;20(8):577-81.	Ex	On an ongoing trial
	Kapoor A, Gupta A, Desai N, Ahn H. Effect of zoledronic acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog. <i>Prostate Cancer.</i> 2011;2011:176164.	Ex	Bone mineral density and biochemical markers of bone turnover as outcomes
	Lipton A, Small E, Saad F, Gleason D, Gordon D, Smith M, et al. The new bisphosphonate, Zometa (zoledronic acid), decreases skeletal complications in both osteolytic and osteoblastic lesions: a comparison to pamidronate. <i>Cancer Invest.</i> 2002;20 Suppl 2:45-54.	Ex	Narrative review
	Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Saad F, et al. Prevention of skeletal-related events with denosumab or zoledronic acid - Combined analysis from 3 registrational trials. <i>European Journal of Cancer.</i> 2011;47:S240.	Ex	Review in abstract form
40	Major P, Cook R, Saad F. The prognostic value of pain scores for clinical outcomes in advanced breast cancer (BC), prostate cancer (PC), and other solid tumors (OST). <i>Annals of Oncology.</i> 2008;19 (S8):viii255.	Ex	Review in abstract form
	Meijboom M, Botteman M, Kaura S, Durand-Zaleski I. Cost effectiveness of zoledronic acid for the prevention of skeletal related events in prostate cancer patients with bone metastases in France. <i>Annals of Oncology.</i> 2008;19 (S8):viii201.	Ex	Cost-effectiveness study with no reference as to the clinical data used
	Meijboom M, Botteman MF, Kaura S. Zoledronic acid is cost effective for the prevention of skeletal-related events in patients with prostate cancer and bone metastases in France and Germany. <i>Journal of Urology.</i> 2009;1):295.	Ex	Cost-effectiveness study with no reference as to the clinical data used
	Meijboom M, Botteman MF, Kaura S. Cost effectiveness of zoledronic acid for the prevention of skeletal related events in prostate cancer patients with bone metastases in France and Germany. <i>European Urology, Supplements.</i> 2009;8 (4):132.	Ex	Cost-effectiveness study with no reference as to the clinical data used
	Michaelson MD, Kaufman DS, Kantoff P, Oh WK, Smith MR. Randomized phase II study of atrasentan alone or in combination with zoledronic acid in men with metastatic prostate cancer. <i>Cancer.</i> 2006;107(3):530-5.	Ex	Other outcomes (biochemical markers of bone turnover, PSA response, disease progression by scheduled bone scan)
45	Miller K, Fizazi K, Smith M, Moroto JP, Klotz L, Brown J, et al. Benefit of denosumab therapy in patients with bone metastases from castrate resistant prostate cancer: A number-needed-to-treat (NNT) analysis. <i>Journal of Urology.</i> 2011;1):e262.	In	NNT for Fizazi Lancet 2011

	Reference	In- /Excluded	Reason(s)
	Ortega C, Faggiuolo R, Vormola R, Montemurro F, Nanni D, Goia F, et al. Jaw complications in breast and prostate cancer patients treated with zoledronic acid. <i>Acta Oncol.</i> 2006;45(2):216-7.	Ex	Cohort study
	Panese MD, Bracco A, Macarios D, Chung K, Barlev A, Halperin M, et al. Modeling the lifetime effectiveness of denosumab and zoledronic acid (ZA) in the prevention of skeletal related events (SRE) in patients with bone metastases from solid tumors. <i>Value in Health.</i> 2011;14 (3):A179.	Ex	Modeling study with no references on the trials used
	Parker CC. Re: Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. <i>J Natl Cancer Inst.</i> 2004;96(19):1480; author reply -1.	Ex	Comment on Saad
	Patrick D, Cleeland C, Fallowfield L, Smith MR, Trachtenberg J, Chilingirov P, et al. Effects of denosumab and zoledronic acid on pain interference with daily functioning in patients with castrate-resistant prostate cancer. <i>Journal of Urology.</i> 2011;1:e286.	Ex	Pain interference with daily functioning as the sole outcome
50	Patrick D, Cleeland C, Fallowfield L, Smith M, Trachtenberg J, Oudard S, et al. Pain interference with daily functioning in patients with castrate-resistant prostate cancer: A comparison of denosumab and zoledronic acid. <i>Journal of Urology.</i> 2012;1:e384.	Ex	Pain interference with daily functioning as the sole outcome
	Porfiri E, Collins SI, Barton D, Billingham L, McLaren D, Nixon GG, et al. Initial feasibility and safety results from a phase II/III clinical trial to evaluate docetaxel (D) therapy in combination with zoledronic acid (ZA) +/- strontium-89 (Sr89) in hormone-refractory prostate cancer patients: ISRCTN12808747. <i>Journal of Clinical Oncology. Conference.</i> 2010;28(15 SUPPL. 1).	Ex	No efficacy data
	Price N. Benefit of extended zoledronate therapy for patients with bone metastases from hormone-refractory prostate cancer. <i>Clin Prostate Cancer.</i> 2004;3(2):77-9.	Ex	Summary of the Saad trial
	Reed SD, Radeva JI, Glendenning GA, Saad F, Schulman KA. Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. <i>J Urol.</i> 2004;171(4):1537-42.	Ex	Uses the trial data from Saad 2002
	Richardson G, Siena S, Lipton A, Brown J, Stopeck A, Fizazi K, et al. Comparison of denosumab versus zoledronic acid (ZA) for the prevention of skeletal-related events in patients with bone metastases from solid tumors. <i>Asia-Pacific Journal of Clinical Oncology.</i> 2011;7:91.	Ex	No separate data for prostate cancer patients
55	Rizzoli R, Yasothan U, Kirkpatrick P. Denosumab. <i>Nat Rev Drug Discov.</i> 2010;9(8):591-2.	Ex	Narrative review
	Rodrigues P, Hering FO, Bruna P, Meller A, Afonso Y. Comparative study of the protective effect of different intravenous bisphosphonates on the decrease in bone mineral density in patients submitted to radical prostatectomy undergoing androgen deprivation therapy. A prospective open-label controlled study. <i>Int J Urol.</i> 2007;14(4):317-20.	Ex	No metastases
	Rosenthal M. Re: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. <i>J Natl Cancer Inst.</i> 2003;95(4):332; author reply 3-4.	Ex	Comment
	Ryan CW, Huo D, Bylow K, Demers LM, Stadler WM, Henderson TO, et al. Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid. <i>BJU Int.</i> 2007;100(1):70-5.	Ex	Mixed patient group, both with and without bone metastases. The sole outcome reported was bone density
	Saad F, Gleason DM, Murray R, Tchekmedyan S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. <i>J Natl Cancer Inst.</i> 2002;94(19):1458-68.	In	See also comments by Atkins and Rosenthal
60	Saad F, Gleason DM, Murray R, Tchekmedyan S, Venner P, Lacombe L, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. <i>J Natl Cancer Inst.</i> 2004;96(11):879-82.	In	Long term report of Saad 2002
	Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. <i>Clin Prostate Cancer.</i> 2005;4(1):31-7.	Ex	Narrative review
	Saad F. Bone-Directed Treatments for Prostate Cancer. <i>Hematology/Oncology Clinics of North America.</i> 2006;20(4):947-63.	Ex	Narrative review
	Saad F. Bisphosphonates Can Prevent Skeletal Complications of Malignant Bone Disease from Prostate Cancer and Renal Cell Carcinoma. <i>European Urology, Supplements.</i> 2007;6(11):683-8.	Ex	Narrative review
	Saad F, Chen YM, Gleason DM, Chin J. Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. <i>Clin Genitourin Cancer.</i> 2007;5(6):390-6.	Ex	Exploratory analyses of the original trial that only looks at months 16-24, and excludes

	Reference	In- /Excluded	Reason(s)
			the first 15 months
65	Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. <i>Cancer</i> . 2007;110(8):1860-7.	Ex	Narrative review
	Saad F, Eastham J. Zoledronic Acid improves clinical outcomes when administered before onset of bone pain in patients with prostate cancer. <i>Urology</i> . 2010;76(5):1175-81.	In	Post-hoc analysis of Saad 2002
	Saad F, Perez J, Cook R, Segal S. Evaluation of prostate-specific antigen kinetics during zoledronic acid therapy for bone metastases in patients with castration-resistant prostate cancer. <i>Journal of Urology</i> . 2011;1:e288.	Ex	PSA kinetics as the sole outcome
	Sartor O. Survival analyses overview in hormone-refractory prostate cancer clinical trials in the prostate-specific antigen era. <i>Clinical Genitourinary Cancer</i> . 2007;5(7):420-1.	Ex	Editorial
	Satoh T, Kimura M, Matsumoto K, Tabata K, Okusa H, Bessho H, et al. Single infusion of zoledronic acid to prevent androgen deprivation therapy-induced bone loss in men with hormone-naive prostate carcinoma. <i>Cancer</i> . 2009;115(15):3468-74.	Ex	Bone mineral density as the sole outcome
70	Scott LJ, Muir VJ. Denosumab: in the prevention of skeletal-related events in patients with bone metastases from solid tumours. <i>Drugs</i> . 2011;71(8):1059-69.	Ex	Narrative review based on a systematic search. Used for reference tracking
	Seth A, Anderson DP, Albiani DA, Barton JJ. Orbital inflammation and optic neuropathy with zoledronic acid for metastatic prostate cancer. <i>Can J Ophthalmol</i> . 2009;44(4):467-8.	Ex	Case report
	Shore ND, Smith MR, Jievaltas M, Fizazi K, Damiao R, Chin J, et al. Effect of denosumab versus zoledronic acid in patients with castrate-resistant prostate cancer and bone metastases: Subgroup analyses by prior SRE and baseline pain. <i>Journal of Clinical Oncology</i> . Conference: ASCO Annual Meeting. 2011;29(15 SUPPL. 1).	In	Post-hoc subgroup analysis of Fizazi
	Shroff S, Martin M, Kearney M, Lothgren M, Bracco A. A cost-effectiveness analysis (CEA) for denosumab, a fully human monoclonal antibody for cancer treatment-induced bone loss (CTIBL) in non-metastatic prostate cancer (PrCa): A Swedish perspective. <i>Value in Health</i> . 2010;13(7):A266-A7.	Ex	On patients without metastases
	Silver DS. Denosumab reduces the incidence of new vertebral fractures in men with prostate cancer. <i>Current Osteoporosis Reports</i> . 2010;8(1):1-3.	Ex	Report of a trial on patients with nonmetastatic prostate cancer
75	Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. <i>J Clin Oncol</i> . 2003;21(23):4277-84.	In	
	Smith MR. CALGB 90202: A randomized double-blind, placebo-controlled phase III study of early vs standard zoledronic acid to prevent skeletal-related events in men with prostate cancer metastatic to the bone. <i>Clinical Advances in Hematology and Oncology</i> . 2006;4(12):897-8.	Ex	Summary of a trial
	Smith MR, Cook RJ, Coleman R, Brown J, Lipton A, Major P, et al. Predictors of skeletal complications in men with hormone-refractory metastatic prostate cancer. <i>Urology</i> . 2007;70(2):315-9.	Ex	Outcomes were variables associated with a greater risk of skeletal complications
	Smith MR, Saad F, Egerdie B, Szwedowski M, Tammela TL, Ke C, et al. Effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. <i>J Urol</i> . 2009;182(6):2670-5.	Ex	Subgroup analyses of a trial on patients with nonmetastatic prostate cancer
	Smith MR, Saad F, Egerdie B, Szwedowski M, Tammela TLJ, Ke C, et al. Effects of Denosumab on Bone Mineral Density in Men Receiving Androgen Deprivation Therapy for Prostate Cancer. <i>Journal of Urology</i> . 2009;182(6):2670-6.	Ex	Same as above
80	Smith MR, Saad F, Egerdie B, Sieber P, Tammela T, Leder BZ, et al. Denosumab and changes in bone turnover markers during androgen deprivation therapy for prostate cancer. <i>J Bone Miner Res</i> . 2011;26(12):2827-33.	Ex	Subgroup analyses of a trial on patients with nonmetastatic prostate cancer
	Stopeck A, Rader M, Henry D, Danese M, Halperin M, Cong Z, et al. Cost-effectiveness of denosumab vs zoledronic acid for prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. <i>J Med Econ</i> . 2012.	Ex	Cost-effectiveness study that uses the effectiveness data from an included trial (Fizazi)
	Stopeck AT, Richardson G, Siena S, Lipton A, Brown J, Fizazi K, et al. Denosumab versus zoledronic acid for the prevention of skeletal-related events in patients with bone metastases secondary to solid tumours: An integrated analysis of three phase 3 studies. <i>European Journal of Cancer</i> . 2012;48:S8.	Ex	Narrative review

	Reference	In-/Excluded	Reason(s)
	Subramanian PS, Kerrison JB, Calvert PC, Miller NR. Orbital inflammatory disease after pamidronate treatment for metastatic prostate cancer. Arch Ophthalmol. 2003;121(9):1335-6.	Ex	Case report
	Tchekmedyan NS, Chen Y, Saad F. Bone disease progression (BDP) and overall disease progression (ODP) correlate with significantly decreased time to onset of skeletal-related events (SRES) and increased risks of SREs. Annals of Oncology. 2008;19 (S8):viii254.	Ex	On risk factors for SRE within the Saad 2001 trial
85	Tu SM, Lin SH, Logothetis C. Re: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2003;95(15):1174-5; author reply 5.	Ex	Comment
	Uemura H, Yanagisawa M, Ikeda I, Fujinami K, Iwasaki A, Noguchi S, et al. Possible anti-tumor activity of initial treatment with zoledronic acid with hormonal therapy for bone-metastatic prostate cancer in multicenter clinical trial. Int J Clin Oncol. 2012.	Ex	Historical control group
	Vassiliou V, Bruland O, Janjan N, Lutz S, Kardamakis D, Hoskin P. Combining Systemic Bisphosphonates with Palliative External Beam Radiotherapy or Bone-Targeted Radionuclide Therapy: Interactions and Effectiveness. Clinical Oncology. 2009;21(9):665-7.	Ex	Narrative review
	von Moos R, Skacel T. Denosumab: first data and ongoing studies on the prevention of bone metastases. Recent Results Cancer Res. 2012;192:187-96.	Ex	Narrative review
	Von Moos R, Skacel T. Denosumab: First data and ongoing studies on the prevention of bone metastases. In: Joerger M, Gnant M, editors. Prevention of Bone Metastases. 233 Springer Street, New York NY 10013-1578, United States: Springer New York; 2012. p. 187-96.	Ex	Narrative review
90	Walsh PC. Re: Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. Journal of Urology. 2011;186(6):2254-5.	Ex	Summary of Fizazi 2011 + editorial
	Walsh PC. The antisteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade. A double blind, randomized, placebo-controlled crossover study. J Urol. 2002;168(4 Pt 1):1642-3.	Ex	Summary of a trial with bone density as the sole outcome
	Weinfurt KP, Anstrom KJ, Castel LD, Schulman KA, Saad F. Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. Ann Oncol. 2006;17(6):986-9.	In	Analysis of the Saad 2002 trial data
	Winqvist E, Berry S. Re: A Randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2004;96(15):1183; author reply -4.	Ex	Comment on Saad 2002
	Wong RK. No difference between pamidronate disodium and placebo in relieving bone pain in men with advanced prostate cancer. Cancer Treat Rev. 2004;30(4):395-400.	Ex	Summary of an excluded trial
95	Xie J, Namjoshi M, Wu EQ, Parikh K, Diener M, Yu AP, et al. Economic evaluation of denosumab compared with zoledronic acid in hormone-refractory prostate cancer patients with bone metastases. J Manag Care Pharm. 2011;17(8):621-43.	Ex	Cost-effectiveness study based on the effectiveness data of an included trial

Included sR and RCT from the SR and RCT searches

1 RCTs referenced from systematic reviews or narrative reviews with a systematic search, and 5 additional RCTs were included. Data were extracted according to a predefined format. Missing 95% confidence intervals and p-values were calculated using STATA 10.1, if appropriate.

GRADING the evidence

The quality of the evidence was graded according to GRADE methodology (<http://www.gradeworkinggroup.org/>). Absolute measures of effect rather than relative measures were chosen to GRADE, when available. The item 'imprecision' was scored according to imprecision for guidelines. When determining the overall quality of evidence across outcomes only those outcomes that were deemed 'critical' were considered.

Table 13. Rating of the importance of outcomes

Outcome	Average rating	relative importance
Pain	8	Critical
Analgesic use	5	Important
Skeletal related events	7	Critical
Survival	6	Important
Survival free from skeletal related events	7	Critical
Progression	6	Important
Quality of life	8	Critical
Adverse events	5	Important

Average rating across five panel members, including two patient' representatives