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Gonadotropin-releasing hormone antagonists versus standard androgen suppression therapy for advanced prostate cancer? A systematic review with meta-analysis.

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Abstract

Purpose: To evaluate efficacy and safety of gonadotropin-releasing hormone (GnRH) antagonists compared to standard androgen suppression therapy for advanced prostate cancer.

Methods: We searched CENTRAL, MEDLINE, Web of Science, EMBASE, trial registries and conference books for randomized controlled trials (RCT) for effectiveness data analysis and randomized or non-randomized controlled studies (non-RCT) for safety data analysis. Two authors independently screened identified articles, extracted data, evaluated risk of bias and rated quality of evidence according to GRADE. The search strategy was updated in March 2015. The protocol was prospectively registered: www.crd.york.ac.uk/PROSPERO; CRD42012002751.

Results: 13 studies (10 RCTs, 3 non-RCTs) were included. No study reported cancer-specific survival or clinical progression. There were no statistically significant differences in overall mortality (RR 1.35, 95% CI 0.63-2.93), treatment failure (RR 0.91, 95% CI 0.70-1.17), or prostate-specific antigen progression (RR 0.83, 95%CI 0.64-1.06). While there was no statistically significant difference for quality of life related to urinary symptoms, improved quality of life regarding prostate symptoms, measured with the International Prostate Symptom Score (IPSS), for the use of GnRH antagonists compared with the use of standard androgen suppression therapy (mean score difference -0.40, 95%CI -0.94 to 0.14, and -1.84, 95%CI -3.00 to -0.69, respectively) was found. Quality of evidence for all assessed outcomes was rated low according to GRADE. The risk for injection-site events was increased (e.g. injection-site pain RR 7.88, 95% CI 5.65-10.98), but cardiovascular events may occur less often using GnRH antagonist (RR 0.60, 95% CI 0.38-0.94). Available evidence is hampered by risk of bias, selective reporting and limited follow-up.

Conclusion: There is currently insufficient evidence to make firm conclusive statements on the efficacy of GnRH antagonist compared to standard androgen suppression therapy for advanced prostate cancer. There is a need for further high quality research on GnRH antagonists with long-term follow-up.

Strengths and limitations of this study

- We searched CENTRAL, MEDLINE, Web of Science, EMBASE, trial registries and conference books.
- Two authors independently screened identified articles, extracted data, evaluated risk of bias and rated quality of evidence according to GRADE.
- There were no statistically significant differences in overall mortality, treatment failure, or prostate-specific antigen progression and no study reported cancer-specific survival or clinical progression.
- Quality of evidence for all assessed outcomes was rated low according to GRADE.
- Available evidence is hampered by risk of bias, selective reporting and limited follow-up.
- The question that was addressed by this systematic review was in some points different from the available evidence.
- There is currently insufficient evidence to make firm conclusive statements on the efficacy of GnRH antagonist compared to standard androgen suppression therapy for advanced prostate cancer and there is a need for further high quality research on GnRH antagonists with long-term follow-up.

Introduction

Gonadotropin-releasing hormone (GnRH) antagonists, such as abarelix or degarelix, are new agents for androgen suppression therapy in advanced prostate cancer. They act by competitively binding to receptors in the pituitary gland, leading to reduced amounts of luteinizing hormone and follicle-stimulating hormone. GnRH antagonists are thereby able to decrease the level of testosterone immediately to castration levels without flare [1-3]. Testosterone is important for the growth of prostate cells and its suppression slows disease progression and leads to a decrease in prostate-specific antigen (PSA).

Data from published randomized controlled trials support the use of degarelix as an alternative to standard androgen suppression therapies [4 5]. Abarelix also appears to be equally effective [2 6]. Androgen suppression therapy with degarelix may also be more cost-effective in patients with locally advanced prostate cancer [7-9] and may increase PSA-progression-free and overall survival [5 10]. Additionally, degarelix might also have beneficial effects on lower urinary tract symptoms [11]. Despite these positive findings, the current European guideline indicate that there is no definitive evidence that GnRH antagonists have advantages over GnRH agonists [12].

An analysis of pooled individual patient data of five randomized clinical trials found clinical benefits with degarelix compared with GnRH agonists [10]. However, no systematic review based on a comprehensive literature search using predefined methodology have yet evaluated the efficacy and tolerability of GnRH antagonists in comparison with standard androgen suppression therapy for advanced prostate cancer. Therefore, the objectives of this systematic review are to determine the efficacy and safety of GnRH antagonists compared with standard androgen suppression therapy for advanced prostate cancer treatment.

Methods

For details on our predefined methodology and outcomes see the prospective registry entry in the 'International Prospective Register of Systematic Reviews' (www.crd.york.ac.uk/PROSPERO;CRD42012002751).

We included studies that compared GnRH antagonists (abarelix, degarelix) with standard androgen suppression therapy in patients with advanced prostate cancer irrespective of their publication status or language of publication. Randomized controlled trials were included for efficacy and safety data analysis. In addition, prospective non-randomized controlled studies comparing GnRH antagonists with standard androgen suppression therapy were considered for adverse events and quality of life analysis. We included only the results of the first phase of cross-over interventions. We excluded no studies based on age or ethnicity of patients.

Standard androgen suppression therapy included monotherapy with surgical or medical castration, anti-androgen monotherapy, or maximal androgen blockade (combination of either surgical or medical castration with antiandrogens). Advanced disease included patients with locally advanced (T3-4, N0, M0), local to regionally advanced (T1-4, N1, M0), disseminated disease (T1-4, N0-1, M1) or PSA relapse after local therapy.

Our prospectively defined primary outcomes were overall survival and adverse events. We defined cancer-specific survival, clinical or PSA progression, treatment failure and quality of life as secondary outcomes. No study was excluded solely because the outcome of interest was not reported.

We searched the Cochrane Library (CENTRAL, Issue 2, 2015), MEDLINE (via Ovid; 1946 to February 2015), Web of Science (Thomson Reuters Web of Knowledge; 1970 to February 2015), and EMBASE (via DIMDI; 1947 to February 2015) databases. For details on the search strategy, see supplementary material Table 1.

Additionally, we searched three trial registries: Current Controlled Trials (ISRCTN; www.controlled-trials.com/; last searched February 2015), ClinicalTrials.gov (www.clinicaltrials.gov/; last searched 23 December 2013), and the World Health Organization International Clinical Trials Registry Platform Search Portal (WHO

ICTRP Search Portal; www.who.int/ictrp/en/; last searched February 2015). We used the following keywords for this search: 'abarelix', 'degarelix', 'plenaxis', 'firmagon'.

We also searched the electronically available abstract books from three major conferences: American Society of Clinical Oncology (ASCO; jco.ascopubs.org; 2004 to February 2015), European Association of Urology (EAU; www.uroweb.org; 2004 to February 2015), and American Urological Association (AUA; www.jurology.com/; 2008 to February 2015). We used the following keywords for this search: 'abarelix', 'degarelix', 'plenaxis', 'firmagon'.

Furthermore, reference lists of retrieved articles were also searched manually. We also used the safety data analyses from the websites of the Food and Drug Administration (FDA), and the European Medicines Agency (EMEA) to obtain additional information on studies that included patients treated with GnRH antagonists.

The search of all databases was initially conducted in March 2014 and was updated in March 2015. The search update included the studies only that were published since our initial search (studies published between March 2014 and March 2015). No language restrictions were applied.

Two authors independently screened retrieved references for inclusion (FK, HB), and two authors (FK, AB) independently extracted data using standardized data extraction forms and assessed each study's risk of bias. We resolved any disagreements through double-checking the respective articles, or through discussion with a third review author (JM). One review author performed the search update (FK). Randomized studies' risk of bias was assessed following the recommendations of the Cochrane Handbook by Higgins et al. [13]. We used the checklist recommended by Reeves et al. for data collection and study assessment for non-randomized studies [14].

We used the Cochrane RevMan 5.2 for statistical data analyses (http://tech.cochrane.org/revman/) and the GRADE working group's software GRADEpro to develop the GRADE evidence table (http://www.gradeworkinggroup.org/) [15 16]. We identified no studies evaluating time-to-event outcomes. Therefore, no hazard ratios (HRs) were extracted. We

extracted the proportions of participants with the respective outcomes to calculate risk ratios (RR) with their 95% confidence intervals (CI) and defined $p<0.05$ as statistically significant. Continuous outcomes were expressed as mean differences (MD) with 95% CI. We assessed statistical heterogeneity among studies (Chi^2, I^2), and employed a fixed effects model for $I^2 \leq 50\%$ and additionally a random effects model for $I^2 > 50\%$.

We performed subgroup analyses for the different doses of androgen suppression therapy and for the different GnRH antagonists (abarelix and degarelix). Initially, we also planned to perform subgroup analyses for non-metastatic versus metastatic disease. However, results were not reported for these subgroups in the included studies.

Results

Study characteristics

We identified 15 studies but only 13 (10 randomized and 3 non-randomized controlled trials) were included in this review. Two of the three non-randomized studies were cross-over studies (Zuckerman 2013, Garnick 2011). See Figure 1, 2 for details regarding the literature search.

Abarelix depot 100 mg intramuscularly administered on day 0, day 15, and every 4 weeks thereafter was evaluated in six studies:

- 149-97-04 [1 17 18],
- 149-98-02 [6 19-21],
- 149-98-03 [2 20-24],
- 149-99-03 [21 25],
- ABACS1 [21 26-28],
- Garnick 2011 [29].

Seven studies evaluated degarelix 240 mg subcutaneously administered as a starting dose and 80 mg or 160 mg subcutaneous maintenance doses every 4 weeks thereafter:

- CS21 [10 30-62];
- CS28 [10 30-33 59-61 63-65],
- CS30 [10 30-33 59-61 64-67];
- CS31 [10 30-33 59-61 64 65 68 69];
- CS35 [10 30-33 58-61],
- CS37 [30-33 59-61],
- Zuckerman 2013 [70 71].

The two excluded studies were retrieved from the FDA website (149-01-03 and 149-01-05). We identified no publications regarding these studies and were therefore not able to include the studies in our analyses because we found no further methodological information or study results. Study 149-01-03 was an open-label trial that compared neoadjuvant hormonal therapy with abarelix depot 100 mg intramuscularly with leuprolide depot 7,5 mg intramuscularly in patients with prostate

cancer planned to undergo brachytherapy or external-beam radiation therapy [21]. Study 149-01-05 was an open-label cross-over study to evaluate the feasibility of switching to treatment with a GnRH agonist following 12 weeks of treatment with abarelix in patients with prostate cancer [21].

The 13 included studies resulted in 55 citations (16 full journal publications, 34 abstracts, and 5 other data sources). Two studies were published as conference abstracts or within meta-analysis of several studies (CS35, CS37) only, one in conference abstracts (149-99-03), and one study as a conference abstract, FDA safety data publications or within narrative reviews (ABACS1). We did not identify journal publications that reported details of the methodology for any of these studies.

We did not identify any active controlled study with follow-up beyond 1 year. There are publications available for an extension of study CS21, which reports on outcomes with longer follow-up [72-76]. However, randomization was rescinded in study CS21 after 1 year of follow-up because all patients were switched from GnRH agonist intervention to GnRH antagonist treatment. So, after 1 year of follow-up, this study became an observational study without a control group, and results from this extension phase were not included in this systematic review. Study characteristics of the included studies are presented in Tables 1 and 2.

Risk of bias

Two trials were terminated early (CS28, CS35). Regarding randomized controlled trials, there was adequate information on random sequence generation in only one study (CS21) and on allocation concealment in four studies (CS21, 149-98-02, 149-98-03, 149-99-03). All studies included were open-label trials. Study results for adverse events, treatment failure and quality of life are therefore likely to be influenced by lack of blinding. Two studies did not report the dose of GnRH agonist and the number of patients per group included (CS35, CS37). In six studies (CS28, CS31, CS35, CS37, 149-99-03, ABACS1), there was insufficient reporting of attrition and exclusions to permit judgement on incomplete outcome data. One study did not report Gleason score (149-99-03), and four studies did not report either Gleason score or disease stage (ABACS1, 149-97-04, CS35, CS35).

All of the 10 randomized and 3 non-randomized controlled trials provided data on adverse events. However, in five studies several adverse events were reported incompletely and, therefore, could not be entered into our meta-analysis (CS28, CS35, CS37, ABACS1, Zuckerman 2013). There was no wash-out period between the different interventions of the two included cross-over studies (Zuckerman 2013, Garnick 2011).

Details on risk of bias assessment are presented in 'Supplementary Tables 2-4' and the GRADE evidence profile table (Table 3).

Overall mortality

Information on mortality presented as time-to-event data was not provided by a single study. Therefore we could not, as initially planned, analyze these data with hazard ratios, but had to report numbers of death during study duration. After screening the available entries of the study protocols in the registries, mortality was not predefined as primary or secondary outcome in any of the included studies but was only assessed as an adverse event outcome.

Nine studies reported number of patients that died during study conduct (149-98-02, 149-98-03, ABACS1, CS21, CS28, CS30, CS31, CS35, and CS37). There were no statistically significant differences in deaths between GnRH antagonists and standard androgen suppression therapy (RR 1.35, 95% CI 0.63-2.93, 3020 patients included), nor in the subgroup analyses of abarelix or degarelix compared with standard androgen suppression therapy (abarelix 100 mg: RR 3.49, 95% CI 0.77- 15.83, 697 patients included; degarelix 240/80 mg and 240/160 mg: RR 1.00, 95% CI 0.52-1.92, 2323 patients; Figure 3). Quality of evidence for this outcome was rated low due to study limitations and imprecision according to GRADE (Table 3).

Cancer-specific survival

No studies were identified that reported this outcome.

Clinical disease progression

No studies were identified that reported this outcome.

PSA progression

All included studies reported PSA levels, and seven studies reported PSA progression (ABACS1, CS21, CS28, CS30, CS31, CS35 and CS37). Only study CS21 was planned to evaluate time to PSA progression that was defined as two consecutive increases in PSA of 50% compared with nadir and ≥5ng/ml on two consecutive measurements at least 2 weeks apart [35]. We did not identify a definition for PSA progression for the other studies and the analyses for PSA progression might be of post-hoc nature. There was no statistically significant difference in PSA progression between GnRH antagonists and standard androgen suppression therapy (RR 0.83, 95%CI 0.64-1.06; subgroup abarelix: RR 1.05, 95% CI 0.41-2.66; degarelix 240/80 mg and 240/160 mg: 0.81, 95% CI 0.62-1.05; see Figure 2). We performed post-hoc subgroup analyses for patients treated with degarelix and different baseline PSA levels. There were no statistically significant differences for patients treated with different regimens of degarelix, i.e. 240/80 mg or 240/160 mg and PSA ≤50 ng/ml (PSA<20 ng/ml: RR 9.10, 95% CI 0.52-159.00, 1399 patients included; PSA ≥20-50 ng/ml: RR 0.81, 95% CI 0.34-1.90, 401 patients included; data not shown). GnRH antagonists decreased PSA progression in patients with baseline PSA levels >50 ng/ml compared with standard androgen suppression therapy (RR 0.74, 95% CI 0.56-0.98, 513 patients included; data not shown). Quality of evidence was rated low due to study limitations and imprecision according to GRADE (Table 3).

Treatment failure

Seven studies reported treatment failure (149-98-02, 149-98-03, 149-99-03, CS21, CS28, CS30, and CS31). No statistically significant differences were observed between GnRH antagonists and standard androgen suppression therapy (RR 0.91, 95% CI 0.70-1.17, 2200 patients included). While subgroup analyses demonstrated a favorable effect for abarelix compared with standard androgen suppression therapy (RR 0.66, 95% CI 0.45-0.98, 1110 patients included), there was no significant difference for degarelix compared with standard therapy (degarelix 240/80 mg: RR 1.03, 95% CI 0.65-1.63, 782 patients included; degarelix 240/160 mg: RR 1.33, 95% CI 0.79-2.24, 308 patients included). Quality of evidence was rated low due to study limitations and imprecision according to GRADE (Table 3).

At variance with the pre-specified outcomes in our protocol, we also included the outcome 'failure to achieve or maintain castration'. Castration was defined as no testosterone value >50 ng/ml under androgen suppression therapy. Five studies provided data (149-98-02, 149-98-03, 149-99-03, ABACS1, and CS21). We identified a statistically significant difference in favor of standard androgen suppression therapy (RR 1.80, 95% CI 1.37-2.35, 1889 patients included; data not shown). However, statistically significant differences did not persist after using the random effects model for heterogeneity (I^2=60%; RR 1.53, 95% CI 0.95-2.49). Therefore, the overall effect on this outcome remains unclear. Subgroup analyses showed that abarelix increased the failure to achieve or maintain castration, while there was no significant difference between degarelix and standard therapy (abarelix: RR 1.88, 95% CI 1.19-2.97; 1279 patients included; degarelix 240/80 mg: RR 0.61, 95% CI 0.17-2.22, 308 patients included; degarelix 240/160 mg: RR 0.50, 95% CI 0.10-2.41, 302 patients included; data not shown).

Adverse events

The data on adverse events are shown in table 4. We did not identify statistically significant differences for the predefined adverse events fatigue, hot flushes, infections, loss of sexual interest, sexual dysfunction, asthenia, urinary retention, diarrhea, or constipation (Table 4).

The risk of injection site pain or reaction significantly increased with GnRH antagonists compared with standard therapy (Table 4).

No significant difference in urinary tract infection was observed between the different therapy groups. However, subgroup analysis showed a significant positive effect for degarelix 240/80 mg or 240/160 mg compared with standard androgen therapy (RR 0.57; 95% CI 0.39-0.83, 2328 patients included; Table 4).

Cardiovascular events occurred less often with GnRH antagonist (degarelix 240/80 mg and 240/160 mg) than with standard therapy (RR 0.60, 95% CI 0.38-0.94, 2328 patients included; Table 4). Because of the reduced risk regarding cardiovascular events we also evaluated further adverse events regarding the cardiovascular system. Post-hoc analyses revealed no statistically significant differences regarding acute myocardial infarction or fatal cerebrovascular-related events, but showed that new diagnosis of ischemic heart diseases occurred significantly less often with the

use of GnRH antagonists compared with standard androgen suppression therapy (RR 0.42, 95% CI 0.23-0.77, 610 patients included). This was also seen for the subgroup of patients treated with degarelix 240/80 mg, but not for those treated with degarelix 240/160 mg. Therefore, the effect of GnRH antagonists on these post-hoc included outcomes remains unclear.

The risks of experiencing peripheral edema and musculoskeletal adverse events were decreased using GnRH antagonists compared with standard androgen suppression therapy (RR 0.51, 95% CI 0.32-0.81, 520 patients included and RR 0.65, 0.45-0.96, 408 patients included, respectively).

Arthralgia and back pain also occurred less often with GnRH antagonists (Table 4). However, this was only seen in the subgroup of patients treated with degarelix (RR 0.66, 0.46-0.94, 2680 patients included, and RR 0.68, 0.48-0.99, 2328 patients included, respectively).

Meta-analysis identified that the risk of chills was increased with GnRH antagonists (RR 9.38, 95% CI 1.26-69.58, 610 patients included). Interestingly, no chills occurred with standard androgen suppression therapy (18/409 degarelix vs. 0/201 standard androgen suppression therapy).

There were no statistically significant differences regarding serious adverse events (RR 0.82, 95% CI 0.62 to 1.08, 7 studies, 2179 patients included), severe/life-threatening adverse events (RR 0.76, 95% CI 0.58 to 1.00, 5 studies, 2064 patients included), or discontinuations due to adverse events (RR 0.86, 95% CI 0.57 to 1.31, 8 studies, 2290 patients included).

We identified no statistical significant differences between GnRH antagonists and standard androgen suppression therapy for immediate-onset allergic reactions (RR 2.36, 95% CI 0.55 to 10.12, 1694 patients included, table 4). However, this adverse event occurred in 9 of 1119 patients (0.8%) treated with abarelix but in no patient receiving standard androgen suppression therapy. We found no data for degarelix regarding this outcome.

We did not identify information about the occurrence of gynecomastia, breast pain, or sweating with the use of GnRH antagonist therapy.

Quality of life

Three studies were included for quality of life evaluation (CS28, CS20, and CS31). Further two studies (CS35 and CS37) were identified to measure quality of life outcomes through screening of protocol entries. However, we found no publications of these studies that reported this outcome. The question addressed by this systematic review was different from the results presented in included studies because we expected a measurement of quality of life related to general health but found an evaluation of quality of life related to urinary or prostate symptoms only.

While there was no statistically significant difference for quality of life related to urinary symptoms, improved quality of life regarding prostate symptoms, measured with the International Prostate Symptom Score (IPSS), for the use of GnRH antagonists (degarelix 240/80 mg) compared with the use of standard androgen suppression therapy (mean score difference -0.40, 95%CI -0.94 to 0.14, and -1.84, 95%CI -3.00 to -0.69, respectively) was found. Quality of evidence was rated low according to GRADE (Table 3).

Discussion

Based on the assessed evidence including trials not published as journal articles, the effects on efficacy of GnRH antagonist compared to standard androgen therapy are still unclear because no long-term follow-up data (>364 days) are available for any of the evaluated outcomes and because evidence is hampered by selective reporting of results, risk of bias and insufficient reporting of methodology. Fifteen studies were identified but only thirteen could be included. No study reported cancer-specific survival or clinical progression. There were no statistically significant differences in overall mortality, treatment failure, prostate-specific antigen progression or quality of life. However, quality of evidence according to GRADE was rated low for these outcomes.

The question that was addressed by this systematic review was in some points different from the available evidence. We planned to include studies evaluating efficacy and adverse events outcomes for patients with advanced prostate cancer. However, the primary outcome of two studies (CS30 and CS31) was the evaluation of prostate volume reduction and relief of lower urinary tract symptoms. In one study (CS21) many patients had localized disease or PSA relapse only. The majority of patients treated with androgen suppression therapy for prostate cancer had non-metastatic disease (range 58-96%), and the number of patients with Gleason score <7 ranged between 18% (CS31) and 57% (149-98-03).

The FDA required a black-box warning on the packaging and the patient instruction sheet of abarelix in USA because immediate-onset systemic allergic reactions occurred after administration of this drug. We found no statistically significant differences in immediate-onset allergic reactions between GnRH antagonists and standard androgen suppression therapy. However, it should be mentioned that 1.1% of patients included in FDA safety data analysis, treated with abarelix, discontinued therapy because of immediate onset of allergic-type adverse events, and 0.4-0.5% had serious anaphylactic-like reactions. There were no such events in the control groups treated with standard androgen suppression therapy [21]. Additionally, the risk for injection-site events was increased using GnRH antagonists. This result is consistent with the FDA safety data analysis, where 25% of patients treated with degarelix had injection site reactions (grade 3 or 4 events in 1% of patients) [49].

Fewer cardiovascular events occurred among patients using GnRH antagonists than among patients using standard androgen suppression therapy. This has been noted in the literature previously [59 77-79]. However, there is evidence for both medications that in patients with a pre-existing cardiovascular disease and/or corresponding risk factors that these drugs may increase the risk to suffer from cardiovascular events on the long-term and that these subgroup of patients may need careful clinical follow-up [78-81].

Conclusion

Evidence is hampered by risk of bias, selective reporting and limited follow-up. Quality of evidence for all assessed outcomes was rated low according to GRADE. There is currently insufficient evidence to make firm conclusive statements on the efficacy of GnRH antagonist compared to standard androgen suppression therapy for advanced prostate cancer. The risk for injection-site events was increased, but cardiovascular events may occur less often using GnRH antagonist. Further high-quality research on GnRH antagonists with long-term follow-up is required.

Figure legend

Figure 1: Flow Chart of initiall search in March 2014[1]

[1]Adapted to the flow chart recommended by Liberati et al. [82]

Figure 2: Flow Chart of search update in March 2015[1]

[1]Adapted to the flow chart recommended by Liberati et al. [82]

Figure 3: Overall Mortality

Table 1: Study Characteristics (Degarelix)

	Zuckerman 2013	CS21	CS28	CS30	CS31	CS35	CS37
Design (Duration of study)	non-randomized prospective cross-over study (90/90 days)	randomized controlled trial (364 days)	randomized controlled trial (84 days)	randomized controlled trial (84 days)	randomized controlled trial (84 days)	randomized controlled trial (364 days)	randomized controlled trial (364 days)
Patients included	48	620	42	246	182	859	405
Non-metastatic disease	43 (90%)	369/610 (61%)	9/40 (22%)	235/244 (96%)	109/179 (61%)	NR	NR
Metastatic disease	5 (10%)	125/610 (20%)	14/40 (35%)	0/244 (0%)	53/179 (30%)	NR	NR
Non-classified disease	-	116/610 (19%)	17/40 (43%)	9/244 (4%)	17/179 (9%)	NR	NR
Gleason-Score 2-6	9 (19%)	266/610 (43%)	2/40 (5%)	53/244 (22%)	33/179 (18%)	NR	NR
Gleason-Score 7	17 (35%)	181/610 (30%)	38/40 (95%)	139/244 (57%)	55/179 (31%)	NR	NR
Gleason-Score 8-10	22 (46)	163/610 (27%)		52/244 (21%)	91/179 (51%)	NR	NR
Gleason-Score nc	-	-	-	-	-	-	-
Intervention (N)	Degarelix 240/80 mg[1] (n=48) for 3 months	Degarelix 240/160 mg or 240/80 mg[1] (n=409)	Degarelix 240/80 mg[1] (n=27)	Degarelix 240/80 mg[1] (n=181)	Degarelix 240/80 mg[1] (n=84)	Degarelix 240/80 mg[1] (n=NR)	Degarelix 240/80 mg[1] (n=NR)
Control (N)	Leuprolide (22.5 mg) 3-month depot for 3 month	Leuprolide 7.5 mg (n=201) monthly	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=13)	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=65)	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=98)	Goserelin NR mg (n=NR)	Leuprolide NR mg (n=NR)
Outcomes	Ability to maintain medical castration (prevent a testosterone surge) during transition from degarelix to leuprolide, assessment of any PSA elevation after the degarelix to leuprolide transition, adverse events	Change in vital signs/body weigh/QTc Interval, adverse events, measurement of PSA levels/testosterone levels/testosterone surge, time to PSA failure	Change in vital signs/body weigh/Total International Prostate Symptom Score (IPSS)/Quality of Life/prostate size/maximum urine flow/residual volume, measurement of PSA levels/testosterone levels, adverse events	Change in vital signs and body weigh/laboratory variables/oestradiole levels/Total International Prostate Symptom Score (IPSS)/Quality of Life/prostate size, measurement of PSA levels/testosterone levels, adverse events	Change in vital signs/body weigh/laboratory variables/Total International Prostate Symptom Score (IPSS)/ Quality of Life/Benign Prostatic Hyperplasia Impact Index/prostate size, measurement of PSA levels/testosterone levels, adverse events	Change in Total International Prostate Symptom Score (IPSS)/Quality of Life, measurement of PSA levels/testosterone levels	Measurement of PSA levels, Change in quality of life

PSA, Prostate-Specific Antigen; NR, not reported; NC, not classified

[1] Degarelix 240 mg subcutaneous given as a starting dose and 80 mg or 160 mg subcutaneous maintenance doses every 4 weeks thereafter

Table 2: Study Characteristics (Abarelix)

	149-98-02	149-98-03	149-99-03	ABACS 1	149-97-04	Garnick 2011
Design (Duration of study)	randomized controlled trial (169 days)	randomized controlled trial (169 days)	randomized controlled trial (169 days)	randomized controlled trial (364 days)	prospective non-randomized controlled clinical trial (27 days)	non-randomized prospective cross-over study (84/56 days)
Patients included	271	255	584	177	242	176
Non-metastatic disease	165/269 (61%)	145/251 (58%)	NR	NR	NR	143/176 (80%)
Metastatic disease	104/269 (39%)	106/251 (42%)	30/582 (5%)	NR	NR	12/176 (8%)
Non-classified disease	-	-	552/582 (95%)	-	-	21/176 (12%)
Gleason-Score 2-6	121/269 (45%)	144/251 (57%)	NR	NR	NR	97/176 (55%)
Gleason-Score 7	81/269 (30%)	61/251 (24%)	NR	NR	NR	73/176 (41%)
Gleason-Score 8-10	56/269 (21%)	34/251 (14%)	NR	NR	NR	6/176 (3%)
Gleason-Score non-classified	11/269 (4%)	12/251 (5%)	-	-	-	-
Intervention (N)	Abarelix 100 mg* (n=180)	Abarelix 100 mg* (n=170)	Abarelix 100 mg* (n=390)	Abarelix 100 mg* (n=87)	Abarelix 100 mg* (n=209)	Abarelix 100 mg* (n=176)
Control (N)	Leuprolide 7.5mg monthly (n=91)	Leuprolide 7.5 mg monthly + Bicalutamide 50 mg daily (n=85)	Leuprolide 7.5 mg monthly (n=194)	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=90)	Leuprolide or Goserelin with(out) Antiandrogen (n=33)	Leuprolide 7.5 mg monthly or Goserelin 3.6 mg monthly (n=176)
Outcomes	Achievement of castration (day <8, <29, <365); Measurement of testosterone levels/endocrine efficacy/PSA levels, adverse events	Achievement of castration (day <8, <29, <365); Measurement of testosterone levels/endocrine efficacy/PSA levels, adverse events	Achievement of castration (day <8, <365); adverse events, discontinuation of treatment, measurement of PSA levels	Achievement of castration (day <8, <365), measurement of testosterone levels, adverse events,	Achievement of castration (day <8, <365), Measurement of testosterone levels/endocrine efficacy/PSA levels, adverse events	Achievement of castration (day <8, <365), measurement of testosterone levels, adverse events,

PSA, Prostate-Specific Antigen; NR, not reported

* Abarelix depot 100 mg intramuscular given on day 0, day 15 and every 4 weeks thereafter

Table 3: GRADE evidence profile table

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GnRH antagonists	Standard androgen suppression therapy	Relative (95% CI)	Absolute	
Overall mortality (follow-up 84-364 days)											
9	randomized trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	see comment[4]	35/1923 (1.8%)	16/1097 (1.5%)	RR 1.35 (0.63 to 2.93)	5 more per 1000 (from 6 fewer to 30 more)	⊕⊕OO LOW
Treatment failure (follow-up 84-364 days)											
7	randomized trials[5]	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	146/1450 (10.1%)	81/750 (10.8%)	RR 0.92 (0.64 to 1.33)	9 fewer per 1000 (from 39 fewer to 36 more)	⊕⊕OO LOW
PSA progression (follow-up 84-364 days)											
7	randomized trials[7]	serious[8]	no serious inconsistency	no serious indirectness	serious[3]	none	115/1566 (7.3%)	75/923 (8.1%)	RR 0.83 (0.64 to 1.06)	14 fewer per 1000 (from 29 fewer to 5 more)	⊕⊕OO LOW
Quality of life related to International Prostate Symptom Score (IPSS, follow-up 84 days; Better indicated by lower values)											
3	randomized trials[9]	serious[10]	no serious inconsistency	serious[11]	no serious imprecision	none	286	173	-	MD 1.84 lower (3 to 0.69 lower)	⊕⊕OO LOW
Quality of Life related to urinary symptoms (follow-up 84 days; Better indicated by lower values)											
3	randomized trials[9]	serious[10]	no serious inconsistency	serious[11]	no serious imprecision	none	288	173	-	MD 0.4 lower (0.94 lower to 0.14 higher)	⊕⊕OO LOW

[1] The following studies were included: 149-98-02, 149-98-03, ABACS1, CS21, CS28, CS30, CS31, CS35, CS37

[2] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables in 'supplementary material'). Despite the methodological limitations, we don't feel that results are likely to be influenced by lack of blinding. However, there was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28, CS31, CS35, CS37, and ABACS1. Studies CS35 and CS37 were reported as conference abstracts or data presentation within combined data analyses. Study ABACS1 was reported as conference abstract or the trial information was published within narrative reviews or FDA safety data publications. Studies CS35 and CS37 were terminated early. Studies CS35 and CS37 reported patient baseline characteristics incompletely.

[3] Downgraded for imprecision (-1): Imprecision due to low number of events and wide confidence intervals.
[4] Information on mortality was not provided by a single study as time to event data. Therefore we could not, as initially planned, analyze these data with hazard ratios, but have to report numbers of death during study duration. After screening the available entries of the study protocols in the registries, mortality was not predefined as primary/secondary outcome in any of the included studies but was only assessed as an adverse event outcome.
[5] The following studies were included: 149-98-02, 149-98-03, 149-99-03, CS21, CS28, CS30, CS31
[6] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables in 'supplementary material'). Study 149-99-03 was reported as conference abstract only. There was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28, CS31, and 149-99-03. Study CS28 was terminated early.
[7] The following studies were included: CS21, CS28, CS30, CS31, CS35, CS37, ABACS1
[8] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables in 'supplementary material'). Despite the methodological limitations, we don't feel that results are likely to be influenced by lack of blinding. However, there was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28, CS31, CS35, CS37, and ABACS1. Studies CS35 and CS37 were reported as conference abstracts or data presentation within combined data analyses only. Study ABACS1 was reported as conference abstract or the trial information was published within narrative reviews or FDA safety data publications. Studies CS35 and CS37 were terminated early. Studies CS35 and CS37 reported patient baseline characteristics incompletely.
[9] The following studies were included: CS28, CS30, CS31.
[10] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables in 'supplementary material'). There was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28 and CS31. Studies CS35 and CS37 were identified to measure quality of life outcomes. However, we found no publications of these studies that reported this outcome.
[11] Downgraded for indirectness (-1): The question addressed by this systematic review was different from the results presented in the available evidence. We expected a measurement of quality of life related to general health but found only an evaluation of quality of life related to urinary symptoms or International Prostate Symptom Score (IPSS).

Table 4: Adverse events

Outcome or Subgroup	Studies	Patients	Effect Estimate[95% CI], Heterogeneity (I^2)
Serious adverse events	7	2179	RR 0.82 [0.62, 1.08], 4%[1]
Subgroup: Abarelix 100 mg	3	1102	RR 0.88 [0.60, 1.28], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.85 [0.46, 1.57], NA[1]
Subgroup: Degarelix 240/80 mg	4	775	RR 0.68 [0.39, 1.19], 35%[1]
Severe/life-threatening adverse event	5	2064	RR 0.76 [0.58, 1.00], 4%[1]
Subgroup: Abarelix 100 mg	4	1454	RR 0.79 [0.60, 1.05], 0%[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 0.16 [0.02, 1.54], NA[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.50 [0.07, 3.46], NA[1]
Discontinuation due to adverse events	8	2290	RR 0.86 [0.57, 1.31], 25%[1]
Subgroup: Abarelix 100 mg	3	1110	RR 0.58 [0.31, 1.08], 39%[1]
Subgroup: Degarelix 240/80 mg	5	872	RR 0.95 [0.44, 2.04], 0%[1]
Subgroup: Degarelix 240/160 mg	1	308	RR 1.57 [0.65, 3.81], NA[1]
Fatigue	10	3784	RR 0.88 [0.72, 1.08], 0%[1]
Subgroup: Abarelix 100 mg	4	1456	RR 0.96 [0.73, 1.26], 0%[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.80 [0.59, 1.08], NA[1]
Hot flush	8	3264	RR 1.00 [0.92, 1.08], 0%[1]
Subgroup: Abarelix 100 mg	2	936	RR 1.01 [0.93, 1.10], 0%[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.99 [0.88, 1.11], NA[1]
Infection (Abarelix 100 mg)	2	520	RR 0.93 [0.42, 2.05], NA[1]
Urinary tract infection	8	2848	RR 0.71 [0.41, 1.25], 54%[2]
Subgroup: Abarelix 100 mg	2	520	RR 1.03 [0.52, 2.07], NA[2]
Subgroup: Degarelix 240/80 and 240/160 mg	6	2328	RR 0.57 [0.39, 0.83], NA[2]
Loss of sexual interest	2	597	RR 1.05 [0.38, 2.91], 0%[1]
Subgroup: Abarelix 100 mg	1	352	RR 1.00 [0.06, 15.86], NA[1]
Subgroup: Degarelix 240/80 mg	1	245	RR 1.06 [0.35, 3.17], NA[1]
Sexual dysfunction (Degarelix 240/80 mg)	2	427	RR 0.83 [0.40, 1.71], 0%[1]

Acute myocardial infarction	1	610	RR 0.49 [0.07, 3.48], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 1.49 [0.06, 36.31], NA[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 0.16 [0.01, 3.98], NA[1]
Cardiovascular events (Degarelix 240/80 and 240/160 mg)	6	2328	RR 0.60 [0.38, 0.94], NA[3]
Ischemic heart disease	1	610	RR 0.42 [0.23, 0.77], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.50 [0.21, 1.15], NA[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 0.35 [0.15, 0.85], NA[1]
Fatal cerebrovascular-related events (Degarelix 240/80 mg and 240/160 mg)	1	610	RR 0.49 [0.12, 1.94], NA[1]
Asthenia (Degarelix 240/80 mg)	2	427	RR 0.91 [0.39, 2.13], 0%[1]
Urinary retention	4	1077	RR 0.39 [0.12, 1.32], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.99 [0.09, 10.79], NA[1]
Subgroup: Degarelix 240/80 mg	4	775	RR 0.28 [0.06, 1.23], 0%[1]
Immediate onset allergic reactions (<1h) (Abarelix 100 mg)	5	1694	RR 2.36 [0.55, 10.12], 0%[1]
Injection-site pain Degarelix 240/80 mg and 240/160 mg	6	2328	RR 7.88 [5.65, 10.98], NA[1]
Injection-site reaction (Degarelix 240/80 mg and 240/160 mg)	1	610	RR 79.61 [11.23, 564.49], NA[1]
Diarrhea (Abarelix 100 mg)	3	872	RR 1.21 [0.81, 1.80], 0%[1]
Peripheral edema (Abarelix 100 mg)	2	520	RR 0.51 [0.32, 0.81], NA[1]
Constipation	5	1522	RR 0.99 [0.64, 1.53], 0%[1]
Subgroup: Abarelix 100 mg	3	872	RR 1.00 [0.58, 1.75], 0%[1]
Subgroup: Degarelix 240/160 mg	1	303	RR 0.60 [0.19, 1.92], NA[1]
Subgroup: Degarelix 240/80 mg	2	347	RR 1.28 [0.49, 3.33], 0%[1]
Arthralgia	7	2680	RR 0.64 [0.45, 0.91], 0%[1]
Subgroup: Abarelix 100 mg	1	352	RR 0.40 [0.08, 2.03], NA[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.66 [0.46, 0.94], NA[1]
Musculoskeletal adverse events (Degarelix 240/80 mg)	1	408	RR 0.65 [0.45, 0.96], NA[1]
Chills	1	610	RR 9.38 [1.26, 69.58], 0%[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 11.28 [0.67, 189.51], NA[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 7.46 [0.43, 129.37], NA[1]
Back pain	9	3200	RR 0.74 [0.56, 0.97], 4%[1]

Subgroup: Abarelix 100 mg	3	872	RR 0.81 [0.54, 1.23], 38%[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.68 [0.48, 0.99], NA[1]

NA, Not applicable; RR, risk ratio; CI, Confidence Interval; MD, Mean Difference

[1] Statistical method: *Mantel-Haenszel*, Fixed-effect model
[2] Statistical method: *Mantel-Haenszel*, Random-effects model
[3] Statistical method: Generic inverse variance, Fixed-effect model

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Conflict of interest

The authors confirm that they have no conflicts of interest.

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Supplementary material

Table 1: Search strategy

CENTRAL	1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
(The Cochrane Library)	2	(prostat* near (cancer* or tumo* or neoplas* or carcinom* or malign*))
01/03/2014	3	(#1 or #2)
	4	(LHRH antagonist* or LH RH antagonist* or GNRH antagonist* or GN RH antagonist*)
	5	(FE200486* or FE 200486*)
	6	(firmagon* or degarelix*)
	7	(PPI149* or PPI 149*)
	8	(abarelix* or plenaxis*)
	9	(#4 or #5 or #6 or #7 or #8)
	10	(#3 and #9)
MEDLINE (Ovid)	1	Prostatic Neoplasms/
1946-01/03/2014	2	(prostat* adj3 (cancer* or tumo* or neoplas* or carcinom* or malign*)).tw.
	3	1 or 2
	4	(LHRH antagonist* or LH RH antagonist* or GNRH antagonist* or GN RH antagonist*).tw.
	5	(FE200486* or FE 200486*).mp.
	6	(firmagon* or degarelix*).mp.
	7	(PPI149* or PPI 149*).mp.
	8	(abarelix* or plenaxis*).mp.
	9	4 or 5 or 6 or 7 or 8
	10	3 and 9
EMBASE (DIMDI)	1	EM74
1947-01/03/2014	2	CT=("PROSTATE TUMOR"; "PROSTATE CANCER"; "PROSTATE ADENOCARCINOMA"; "PROSTATE CARCINOMA")
	3	(prostat* and (cancer* or tumo* or neoplas* or carcinom* or malign*))/same sent
	4	2 OR 3
	5	(LHRH antagonist* or LH RH antagonist* or GNRH antagonist* or GN RH antagonist*)/same sent
	6	(FE200486* or FE 200486*)/same sent
	7	(firmagon* or degarelix*)/same sent
	8	(PPI149* or PPI 149*)/same sent
	9	(abarelix* or plenaxis*)/same sent

	10	5 OR 6 OR 7 OR 8 OR 9
	11	4 AND 10
Web of Science	1	TS=(prostat* same (cancer* or tumo* or neoplas* or carcinom* or malign*))
1970-01/03/2014	2	TS=((LHRH same antagonist*) or (LH same RH same antagonist*))
	3	TS=((gnrh same antagonist*) OR (gn same rh same antagonist*))
	4	TS=(FE200486*)
	5	TS=(FE same 200486*)
	6	TS=(abarelix* OR plenaxis*)
	7	TS=(firmagon* OR degarelix*)
	8	TS=(PPI149*)
	9	TS=(PPI same 149*)
	10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
	11	#10 AND #1

Table 2: Risk of bias of randomized studies evaluating degarelix

	CS21	CS28	CS30	CS31	CS35	CS37
Random sequence generation	Low risk[1]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Allocation concealment	Low risk[2]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Blinding of participants and personnel: Mortality, PSA progression	Low risk[3]	Unclear risk (NR)	Low risk[3]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Blinding of participants and personnel: Adverse events, treatment failure, quality of life	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]
Blinding of outcome assessment: Mortality, PSA progression	Low risk[3]	Unclear risk (NR)	Low risk[3]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Blinding of outcome assessment: Adverse events, treatment failure, quality of life	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]
Incomplete outcome data: Mortality, PSA progression	Low risk[5]	Unclear risk (NR)	Low risk[5]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Incomplete outcome data: Adverse events, treatment failure, quality of life	Low risk[5]	Unclear risk (NR)	Low risk[5]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Selective reporting	Low risk[6]	High risk[7]	Low risk[6]	Low risk[6]	High risk[7]	High risk[7]

NR, not reported

[1] Random number generator (computer program)
[2] Central allocation
[3] Open-label study but personnel were unaware of blood values
[4] Open-label study but results are likely to be influenced by lack of blinding
[5] Missing outcome data balanced in numbers across intervention groups.
[6] The study protocol is available and all outcomes that are of interest have been reported.
[7] Averse events are reported incompletely or study report fails to include results for this outcome

Table 3: Risk of bias of randomized studies evaluating abarelix

	149-98-02	149-98-03	149-99-03	ABACS1
Random sequence generation	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Allocation concealment	Low risk[1]	Low risk[1]	Low risk[1]	Unclear risk (NR)
Blinding of participants and personnel: Mortality, PSA progression	Low risk[2]	Low risk[2]	Unclear risk (NR)	Unclear risk (NR)
Blinding of participants and personnel: Adverse events, treatment failure, quality of life	High risk[3]	High risk[3]	High risk[3]	High risk[3]
Blinding of outcome assessment: Mortality, PSA progression	Low risk[2]	Low risk[2]	Unclear risk (NR)	Unclear risk (NR)
Blinding of outcome assessment: Adverse events, treatment failure, quality of life	High risk[3]	High risk[3]	High risk[3]	High risk[3]
Incomplete outcome data: Mortality, PSA progression	Low risk[4]	Low risk[4]	Unclear risk (NR)	Unclear risk (NR)
Incomplete outcome data: Adverse events, treatment failure, quality of life	Low risk[4]	Low risk[4, 5]	Unclear risk (NR)	Unclear risk (NR)
Selective reporting	Low risk[6]	Low risk[6]	Unclear risk[7]	High risk[8]

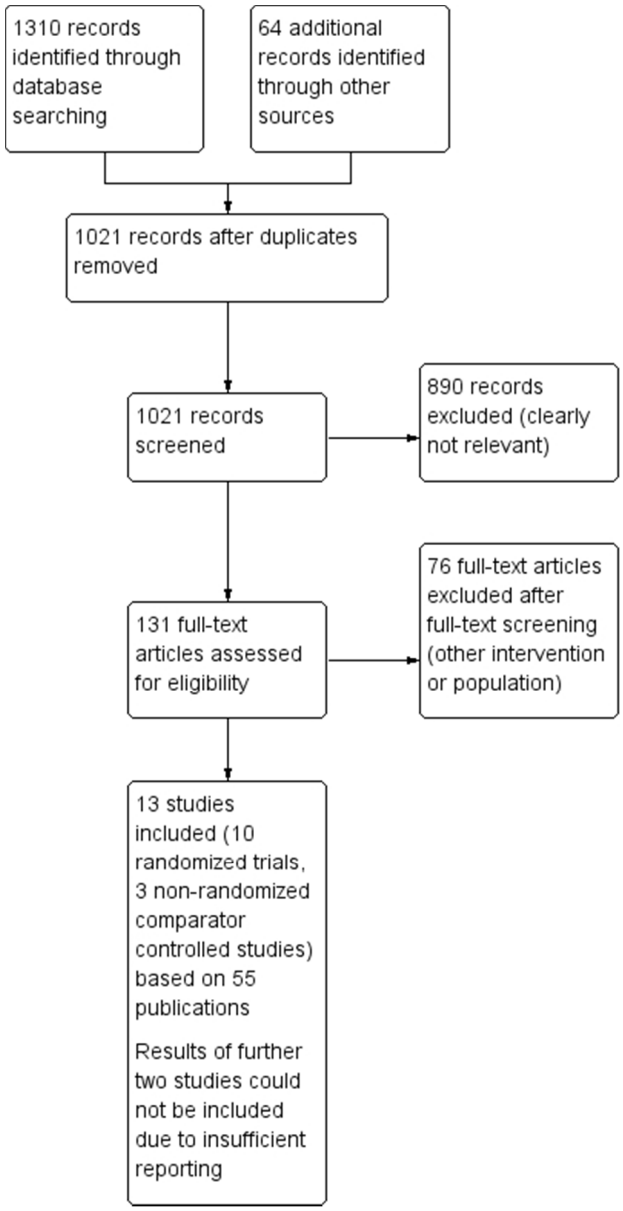
NR, not reported

[1] Central allocation
[2] Open-label study but personnel were unaware of blood values
[3] Open-label study but results are likely to be influenced by lack of blinding
[4] Proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate
[5] Missing outcome data balanced in numbers across intervention groups.
[6] The study protocol is not available but it is clear that the published reports include all expected outcomes
[7] No protocol available
[8] Averse events are reported incompletely or study report fails to include results for this outcome

Table 4: Risk of bias of prospective non-randomized comparator controlled studies[1]

	149-97-04	Zuckerman 2013	Garnick 2011
Study type	controlled clinical trial	cross-over study	cross-over study
Prospective study?	Yes	Yes	Yes
Was there a comparison?	Yes	Yes	Yes
Was there a baseline assessment?	Yes	Yes	Yes
Blinding of outcome assessment?	Unclear	No	No
Incomplete outcome data?	Yes	No	No
Selective outcome reporting?	Unclear	Yes	Unclear
Patient selection method			
Random sample generation	No	No	No
Consecutive enrollment	Yes	Unclear	Yes
Selected subset of patients	Yes	Unclear	No
Time difference	No	No	No
Location difference	No	No	No
Treatment decision	Yes	No	No
Patients preferences	Yes	No	No
On the basis of outcome	No	No	No
Predefinition of adverse events?	Unclear	Unclear	Unclear
Reporting of all adverse events?	Unclear	No	Unclear
Are all patients evaluated for adverse events?	Unclear	Yes	Unclear
Dropouts because of adverse events?	Unclear	No	Unclear

[1]Adapted to the checklist recommended by Reeves et al. for data collection and study assessment for non-randomized studies [14].



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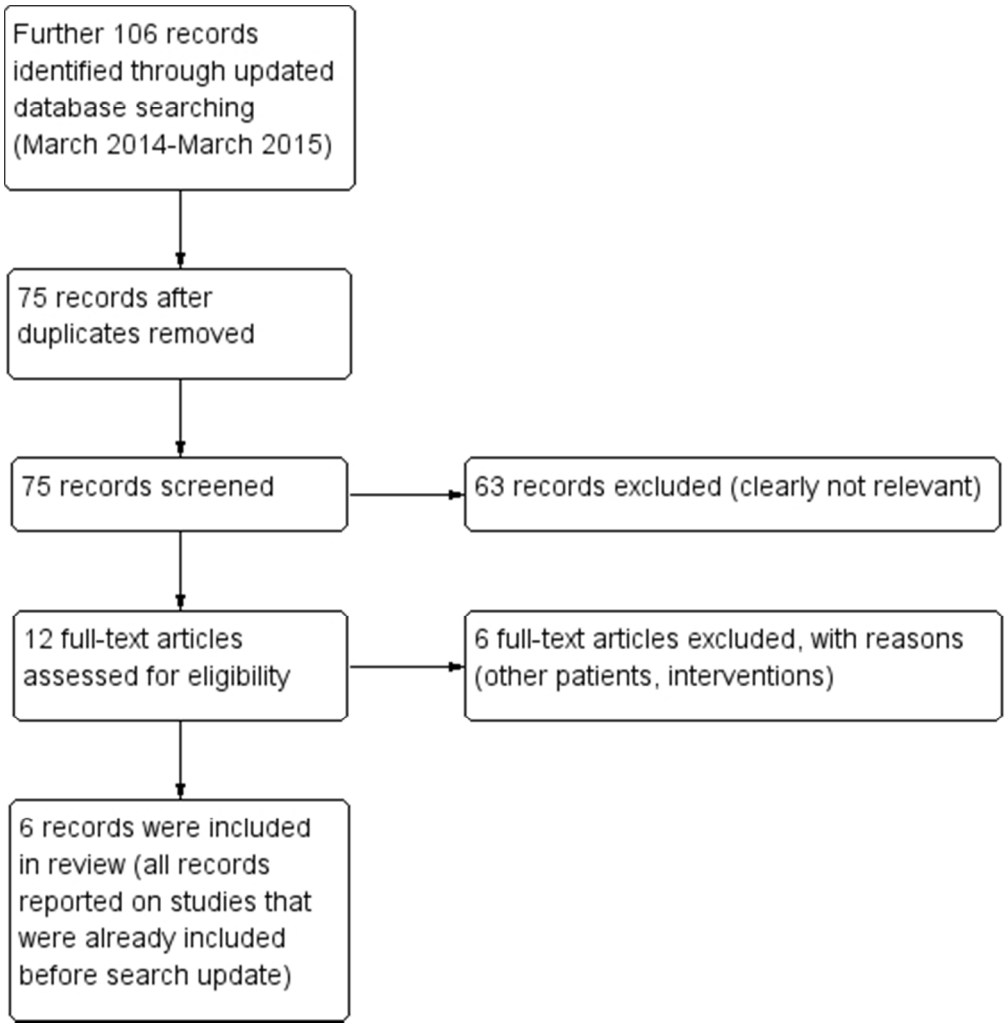

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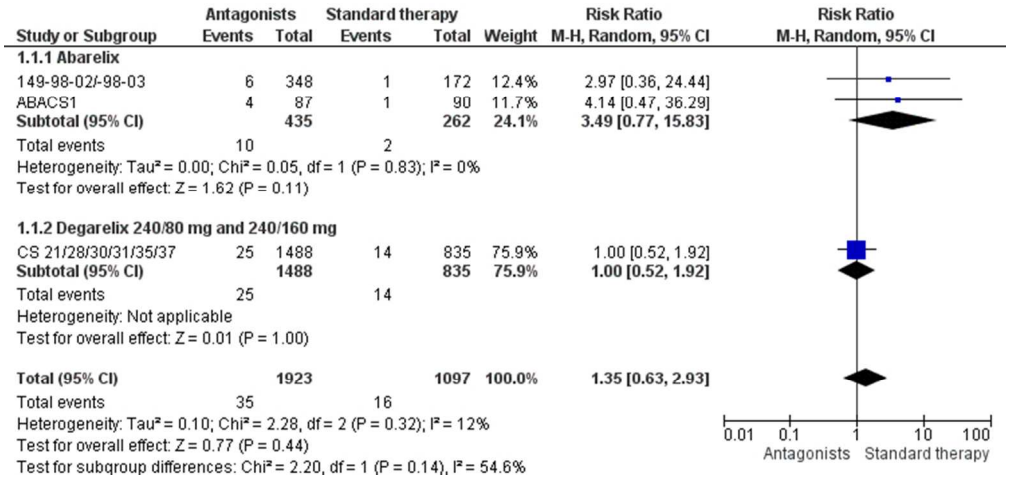

263x124mm (72 x 72 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	32
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6; Figure 1,2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6,7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 3 + supplementary data table 2-4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1,2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1,2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3 + supplementary data table 2-4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3, Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14, Table 3, 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3 + supplementary data table 2-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Gonadotropin-releasing hormone antagonists versus standard androgen suppression therapy for advanced prostate cancer? A systematic review with meta-analysis.

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Secondary Subject Heading:	Oncology
Keywords:	Urological tumours < UROLOGY, Prostate disease < UROLOGY, Adult urology < UROLOGY

Gonadotropin-releasing hormone antagonists versus standard androgen suppression therapy for advanced prostate cancer? A systematic review with meta-analysis.

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Abstract

Objectives: To evaluate efficacy and safety of gonadotropin-releasing hormone (GnRH) antagonists compared to standard androgen suppression therapy for advanced prostate cancer.

Setting: The international review team included methodologists of the German Cochrane Centre and clinical experts.

Participants: We searched CENTRAL, MEDLINE, Web of Science, EMBASE, trial registries and conference books for randomized controlled trials (RCT) for effectiveness data analysis and randomized or non-randomized controlled studies (non-RCT) for safety data analysis (March 2015). Two authors independently screened identified articles, extracted data, evaluated risk of bias and rated quality of evidence according to GRADE.

Results: 13 studies (10 RCTs, 3 non-RCTs) were included. No study reported cancer-specific survival or clinical progression. There were no differences in overall mortality (RR 1.35, 95% CI 0.63-2.93), treatment failure (RR 0.91, 95% CI 0.70-1.17), or prostate-specific antigen progression (RR 0.83, 95%CI 0.64-1.06). While there was no difference for quality of life related to urinary symptoms, improved quality of life regarding prostate symptoms, measured with the International Prostate Symptom Score (IPSS), for the use of GnRH antagonists compared with the use of standard androgen suppression therapy (mean score difference -0.40, 95%CI -0.94 to 0.14, and -1.84, 95%CI -3.00 to -0.69, respectively) was found. Quality of evidence for all assessed outcomes was rated low according to GRADE. The risk for injection-site events was increased, but cardiovascular events may occur less often using GnRH antagonist. Available evidence is hampered by risk of bias, selective reporting and limited follow-up.

Conclusions: There is currently insufficient evidence to make firm conclusive statements on the efficacy of GnRH antagonist compared to standard androgen suppression therapy for advanced prostate cancer. There is a need for further high quality research on GnRH antagonists with long-term follow-up.

Trial registration: www.crd.york.ac.uk/PROSPERO; CRD42012002751

Strengths and limitations of this study

- We searched CENTRAL, MEDLINE, Web of Science, EMBASE, trial registries and conference books.
- Two authors independently screened identified articles, extracted data, evaluated risk of bias and rated quality of evidence according to GRADE.
- There were no statistically significant differences in overall mortality, treatment failure, or prostate-specific antigen progression and no study reported cancer-specific survival or clinical progression.
- Quality of evidence for all assessed outcomes was rated low according to GRADE.
- Available evidence is hampered by risk of bias, selective reporting and limited follow-up.
- The question that was addressed by this systematic review was in some points different from the available evidence.
- There is currently insufficient evidence to make firm conclusive statements on the efficacy of GnRH antagonist compared to standard androgen suppression therapy for advanced prostate cancer and there is a need for further high quality research on GnRH antagonists with long-term follow-up.

Introduction

Gonadotropin-releasing hormone (GnRH) antagonists, such as abarelix or degarelix, are new agents for androgen suppression therapy in advanced prostate cancer. They act by competitively binding to receptors in the pituitary gland, leading to reduced amounts of luteinizing hormone and follicle-stimulating hormone. GnRH antagonists are thereby able to decrease the level of testosterone immediately to castration levels without flare [1-3]. Testosterone is important for the growth of prostate cells and its suppression slows disease progression and leads to a decrease in prostate-specific antigen (PSA).

Data from published randomized controlled trials support the use of degarelix as an alternative to standard androgen suppression therapies [4 5]. Abarelix appears to be equally effective [2 6]. Androgen suppression therapy with degarelix may also be more cost-effective in patients with locally advanced prostate cancer [7-9] and may increase PSA-progression-free and overall survival [5 10]. Additionally, degarelix might also have beneficial effects on lower urinary tract symptoms [11]. Furthermore, GnRH antagonists might provide an alternative to castration in symptomatic patients with advanced prostate cancer because there is no risk for testosterone flare associated with GnRH agonists that might aggravate clinical symptoms [12]. Despite these positive findings, the current European guideline indicate that there is no definitive evidence that GnRH antagonists have advantages over GnRH agonists [13].

An analysis of pooled individual patient data of five randomized clinical trials found clinical benefits with degarelix compared with GnRH agonists [10]. However, no systematic review based on a comprehensive literature search using predefined methodology have yet evaluated the efficacy and tolerability of GnRH antagonists in comparison with standard androgen suppression therapy for advanced prostate cancer. Therefore, the objectives of this systematic review are to determine the efficacy and safety of GnRH antagonists compared with standard androgen suppression therapy for advanced prostate cancer treatment.

Methods

For details on our predefined methodology and outcomes see the prospective registry entry in the 'International Prospective Register of Systematic Reviews' (www.crd.york.ac.uk/PROSPERO;CRD42012002751).

We included studies that compared GnRH antagonists (abarelix, degarelix) with standard androgen suppression therapy in patients with advanced prostate cancer. Included studies had to be randomized controlled trials (that were used for efficacy and safety analysis) or prospective non-randomized controlled studies (that were used for adverse events and quality of life analysis). If randomized controlled trials were identified with cross-over design, we only included the data just before cross-over started. We did not exclude studies because of publication status or language of publication, nor did we make restrictions based on age or ethnicity of patients.

We included all patients with advanced prostate cancer. Advanced disease was defined as either locally advanced (T3-4, N0, M0), local to regionally advanced (T1-4, N1, M0), disseminated disease (T1-4, N0-1, M1) or PSA relapse after local therapy.

Included studies had to compare GnRH antagonists (abarelix or degarelix) with standard androgen suppression. The standard androgen suppression therapy included monotherapy with surgical or medical castration, anti-androgen monotherapy or maximal androgen blockade (combination of either surgical or medical castration with antiandrogens).

Our prospectively defined primary outcomes were overall survival and adverse events. We defined cancer-specific survival, clinical or PSA progression, treatment failure and quality of life as secondary outcomes. No study was excluded solely because the outcome of interest was not reported.

Unit of analysis was the study rather than publications and we named the studies according to their study identification numbers assigned by the sponsors. We used the sponsors identification numbers for differentiation because several authors were involved in more than one study, publications were identified reporting information on several studies (pooled analyses of individual patient data of five randomized controlled trials: CS21, CS28, CS30, CS31, CS35), and because of the fact that for

some studies there are several publications available (e.g. different follow-up time or reporting different outcomes).

We searched the Cochrane Library (CENTRAL, Issue 3, 2015), MEDLINE (via Ovid; 1946 to March 2015), Web of Science (Thomson Reuters Web of Knowledge; 1970 to March 2015), and EMBASE (via DIMDI; 1947 to March 2015) databases. For details on the search strategy, see Table 1.

Additionally, we searched three trial registries: Current Controlled Trials (ISRCTN; www.controlled-trials.com/; last searched March 2015), ClinicalTrials.gov (www.clinicaltrials.gov/; last searched March 2015), and the World Health Organization International Clinical Trials Registry Platform Search Portal (WHO ICTRP Search Portal; www.who.int/ictrp/en/; last searched March 2015). We used the following keywords for this search: 'abarelix', 'degarelix', 'plenaxis', 'firmagon'.

We also searched the electronically available abstract books from three major conferences: American Society of Clinical Oncology (ASCO; jco.ascopubs.org; 2004 to March 2015), European Association of Urology (EAU; www.uroweb.org; 2004 to March 2015), and American Urological Association (AUA; www.jurology.com/; 2008 to March 2015). We used the following keywords for this search: 'abarelix', 'degarelix', 'plenaxis', 'firmagon'.

Furthermore, reference lists of retrieved articles were also searched manually. We also used the safety data analyses from the websites of the Food and Drug Administration (FDA), and the European Medicines Agency (EMEA) to obtain additional information on studies that included patients treated with GnRH antagonists.

The search of all databases was initially conducted in March 2014 and was updated in March 2015. The search update included the studies only that were published since our initial search (studies published between March 2014 and March 2015). No language restrictions were applied.

Two authors independently screened retrieved references for inclusion (FK, HB), and two authors (FK, AB) independently extracted data using standardized data extraction forms and assessed each study's risk of bias. We resolved any

disagreements through double-checking the respective articles, or through discussion with a third review author (JM). One review author performed the search update (FK). Randomized studies' risk of bias was assessed following the recommendations of the Cochrane Handbook by Higgins et al. [14]. We used the checklist recommended by Reeves et al. for data collection and study assessment for non-randomized studies [15].

We used the Cochrane RevMan 5.2 for statistical data analyses (http://tech.cochrane.org/revman/) and the GRADE working group's software GRADEpro to develop the GRADE evidence table (http://www.gradeworkinggroup.org/) [16 17]. We identified no studies evaluating time-to-event outcomes. Therefore, no hazard ratios (HRs) were extracted.

We extracted outcomes data relevant to this review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals to calculate pooled risk ratios (RR) with their 95% confidence intervals (CI) using Mantel-Haenszel method. Continuous outcomes were analyzed using the inverse variance method and were expressed as mean differences (MD) with 95% CI. We defined $p<0.05$ as statistically significant. We assessed statistical heterogeneity among studies (Chi^2, I^2), and employed a fixed effects model for $I^2 \leq 50\%$ and additionally a random effects model for $I^2 > 50\%$ as a sensitivity analysis.

We performed subgroup analyses for the different doses of androgen suppression therapy and for the different GnRH antagonists (abarelix and degarelix). Initially, we also planned to perform subgroup analyses for non-metastatic versus metastatic disease. However, results were not reported for these subgroups in the included studies.

Results

Study characteristics

We identified 15 studies but only 13 (10 randomized and 3 non-randomized controlled trials) were included in this review. Two of the three non-randomized

studies were cross-over studies (Zuckerman 2013, Garnick 2011). See Figure 1, 2 for details regarding the literature search.

Abarelix depot 100 mg intramuscularly administered on day 0, day 15, and every 4 weeks thereafter was evaluated in six studies:

- 149-97-04 [1 18 19],
- 149-98-02 [6 20-22],
- 149-98-03 [2 21-25],
- 149-99-03 [22 26],
- ABACS1 [22 27-29],
- Garnick 2011 [30].

Seven studies evaluated degarelix 240 mg subcutaneously administered as a starting dose and 80 mg or 160 mg subcutaneous maintenance doses every 4 weeks thereafter:

- CS21 [10 31-63];
- CS28 [10 31-34 60-62 64-66],
- CS30 [10 31-34 60-62 65-68];
- CS31 [10 31-34 60-62 65 66 69 70];
- CS35 [10 31-34 59-62],
- CS37 [31-34 60-62],
- Zuckerman 2013 [71 72].

The two excluded studies were retrieved from the FDA website (149-01-03 and 149-01-05). We identified no publications regarding these studies and were therefore not able to include the studies in our analyses because we found no further methodological information or study results. Study 149-01-03 was an open-label trial that compared neoadjuvant hormonal therapy with abarelix depot 100 mg intramuscularly with leuprolide depot 7,5 mg intramuscularly in patients with prostate cancer planned to undergo brachytherapy or external-beam radiation therapy [22]. Study 149-01-05 was an open-label cross-over study to evaluate the feasibility of switching to treatment with a GnRH agonist following 12 weeks of treatment with abarelix in patients with prostate cancer [22].

The 13 included studies resulted in 55 citations (16 full journal publications, 34 abstracts, and 5 other data sources). Two studies were published as conference abstracts or within meta-analysis of several studies (CS35, CS37) only, one in conference abstracts (149-99-03), and one study as a conference abstract, FDA safety data publications or within narrative reviews (ABACS1). We did not identify journal publications that reported details of the methodology for any of these studies.

We did not identify any active controlled study with follow-up beyond 1 year. There are publications available for an extension of study CS21, which reports on outcomes with longer follow-up [73-77]. However, randomization was rescinded in study CS21 after 1 year of follow-up because all patients were switched from GnRH agonist intervention to GnRH antagonist treatment. So, after 1 year of follow-up, this study became an observational study without a control group, and results from this extension phase were not included in this systematic review. Study characteristics of the included studies are presented in Tables 2 and 3.

Risk of bias

Two trials were terminated early (CS28, CS35). Regarding randomized controlled trials, there was adequate information on random sequence generation in only one study (CS21) and on allocation concealment in four studies (CS21, 149-98-02, 149-98-03, 149-99-03). All studies included were open-label trials. Study results for adverse events, treatment failure and quality of life are therefore likely to be influenced by lack of blinding. Two studies did not report the dose of GnRH agonist and the number of patients per group included (CS35, CS37). In six studies (CS28, CS31, CS35, CS37, 149-99-03, ABACS1), there was insufficient reporting of attrition and exclusions to permit judgement on incomplete outcome data. One study did not report Gleason score (149-99-03), and four studies did not report either Gleason score or disease stage (ABACS1, 149-97-04, CS35, CS35).

All of the 10 randomized and 3 non-randomized controlled trials provided data on adverse events. However, in five studies several adverse events were reported incompletely and, therefore, could not be entered into our meta-analysis (CS28, CS35, CS37, ABACS1, Zuckerman 2013). There was no wash-out period between the different interventions of the two included cross-over studies (Zuckerman 2013, Garnick 2011).

Details on risk of bias assessment are presented in table 4, 5, 6 and the GRADE evidence profile table (Table 7).

Overall mortality

Information on mortality presented as time-to-event data was not provided by a single study. Therefore we could not, as initially planned, analyze these data with hazard ratios, but had to report numbers of death during study duration. After screening the available entries of the study protocols in the registries, mortality was not predefined as primary or secondary outcome in any of the included studies but was only assessed as an adverse event outcome.

Nine studies reported number of patients that died during study conduct (149-98-02, 149-98-03, ABACS1, CS21, CS28, CS30, CS31, CS35, and CS37). There were no statistically significant differences in deaths between GnRH antagonists and standard androgen suppression therapy (RR 1.35, 95% CI 0.63-2.93, 9 studies with 3020 patients included), nor in the subgroup analyses of abarelix or degarelix compared with standard androgen suppression therapy (abarelix 100 mg: RR 3.49, 95% CI 0.77- 15.83, 3 studies with 697 patients included; degarelix 240/80 mg and 240/160 mg: RR 1.00, 95% CI 0.52-1.92, 6 studies with 2323 patients included; Figure 3). Quality of evidence for this outcome was rated low due to study limitations and imprecision according to GRADE (Table 7).

Cancer-specific survival

No studies were identified that reported this outcome.

Clinical disease progression

No studies were identified that reported this outcome.

PSA progression

All included studies reported PSA levels, and seven studies reported PSA progression (ABACS1, CS21, CS28, CS30, CS31, CS35 and CS37). Only study CS21 was planned to evaluate time to PSA progression that was defined as two consecutive increases in PSA of 50% compared with nadir and ≥5ng/ml on two

consecutive measurements at least 2 weeks apart [36]. We did not identify a definition for PSA progression for the other studies and the analyses for PSA progression might be of post-hoc nature. There was no statistically significant difference in PSA progression between GnRH antagonists and standard androgen suppression therapy (RR 0.83, 95%CI 0.64-1.06, 7 studies with 2489 patients included; subgroup abarelix: RR 1.05, 95% CI 0.41-2.66, 1 study with 176 patients included; degarelix 240/80 mg and 240/160 mg: 0.81, 95% CI 0.62-1.05, 6 studies with 2313 patients included). We performed post-hoc subgroup analyses for patients treated with degarelix and different baseline PSA levels. There were no statistically significant differences for patients treated with different regimens of degarelix, i.e. 240/80 mg or 240/160 mg and PSA ≤50 ng/ml (PSA<20 ng/ml: RR 9.10, 95% CI 0.52-159.00, 6 studies with 1399 patients included; PSA ≥20-50 ng/ml: RR 0.81, 95% CI 0.34-1.90, 6 studies with 401 patients included). GnRH antagonists decreased PSA progression in patients with baseline PSA levels >50 ng/ml compared with standard androgen suppression therapy (RR 0.74, 95% CI 0.56-0.98, 6 studies with 513 patients included). Quality of evidence was rated low due to study limitations and imprecision according to GRADE (Table 7).

Treatment failure

Seven studies reported treatment failure (149-98-02, 149-98-03, 149-99-03, CS21, CS28, CS30, and CS31). No statistically significant differences were observed between GnRH antagonists and standard androgen suppression therapy (RR 0.91, 95% CI 0.70-1.17, 7 7 studies with 2200 patients included). While subgroup analyses demonstrated a favorable effect for abarelix compared with standard androgen suppression therapy (RR 0.66, 95% CI 0.45-0.98, 3 studies with 1110 patients included), there was no significant difference for degarelix compared with standard therapy (degarelix 240/80 mg: RR 1.03, 95% CI 0.65-1.63, 4 studies with 782 patients included; degarelix 240/160 mg: RR 1.33, 95% CI 0.79-2.24, 1 study with 308 patients included). Quality of evidence was rated low due to study limitations and imprecision according to GRADE (Table 7).

At variance with the pre-specified outcomes in our protocol, we also included the outcome ‘failure to achieve or maintain castration’. Castration was defined as no testosterone value >50 ng/ml under androgen suppression therapy. Five studies

provided data (149-98-02, 149-98-03, 149-99-03, ABACS1, and CS21). We identified a statistically significant difference in favor of standard androgen suppression therapy (RR 1.80, 95% CI 1.37-2.35, 5 studies with 1889 patients included). However, statistically significant differences did not persist after using the random effects model for heterogeneity (I^2=60%; RR 1.53, 95% CI 0.95-2.49, 5 studies with 1889 patients included). Therefore, the overall effect on this outcome remains unclear. Subgroup analyses showed that abarelix increased the failure to achieve or maintain castration, while there was no significant difference between degarelix and standard therapy (abarelix: RR 1.88, 95% CI 1.19-2.97; 4 studies with 1279 patients included; degarelix 240/80 mg: RR 0.61, 95% CI 0.17-2.22, 1 study with 308 patients included; degarelix 240/160 mg: RR 0.50, 95% CI 0.10-2.41, 1 study with 302 patients included).

Adverse events

The data on adverse events are shown in table 8. We did not identify statistically significant differences for the predefined adverse events fatigue, hot flushes, infections, loss of sexual interest, sexual dysfunction, asthenia, urinary retention, diarrhea, or constipation (Table 8).

The risk of injection site pain or reaction significantly increased with GnRH antagonists compared with standard therapy (Table 8).

No significant difference in urinary tract infection was observed between the different therapy groups. However, subgroup analysis showed a significant positive effect for degarelix 240/80 mg or 240/160 mg compared with standard androgen therapy (RR 0.57; 95% CI 0.39-0.83, 6 studies with 2328 patients included; Table 8).

Cardiovascular events occurred less often with GnRH antagonist (degarelix 240/80 mg and 240/160 mg) than with standard therapy (RR 0.60, 95% CI 0.38-0.94, 6 studies with 2328 patients included; Table 8). Because of the reduced risk regarding cardiovascular events we also evaluated further adverse events regarding the cardiovascular system. Post-hoc analyses revealed no statistically significant differences regarding acute myocardial infarction or fatal cerebrovascular-related events, but showed that new diagnosis of ischemic heart diseases occurred significantly less often in patients who were using GnRH antagonists compared with patients on standard androgen suppression therapy (RR 0.42, 95% CI 0.23-0.77, 1

study with 610 patients included). This was also seen for the subgroup of patients treated with degarelix 240/80 mg, but not for those treated with degarelix 240/160 mg. Therefore, the effect of GnRH antagonists on these post-hoc included outcomes remains unclear. Additionally, it was also unclear if these results are also applicable for patients that already had a history of cardiovascular events because original publications did not report if this was evaluated during study screening phase or if this was an exclusion criteria.

The risks of experiencing peripheral edema and musculoskeletal adverse events were decreased using GnRH antagonists compared with standard androgen suppression therapy (RR 0.51, 95% CI 0.32-0.81, 2 studies with 520 patients included and RR 0.65, 0.45-0.96, 1 study with 408 patients included, respectively).

Arthralgia and back pain also occurred less often with GnRH antagonists (Table 8). However, this was only seen in the subgroup of patients treated with degarelix (RR 0.66, 0.46-0.94, 6 studies with 2328 patients included, and RR 0.68, 0.48-0.99, 6 studies with 2328 patients included, respectively).

Meta-analysis identified that the risk of chills was increased with GnRH antagonists (RR 9.38, 95% CI 1.26-69.58, 1 study with 610 patients included). Interestingly, no chills occurred with standard androgen suppression therapy (18/409 degarelix vs. 0/201 standard androgen suppression therapy).

There were no statistically significant differences regarding serious adverse events (RR 0.82, 95% CI 0.62 to 1.08, 7 studies with 2179 patients included), severe/life-threatening adverse events (RR 0.76, 95% CI 0.58 to 1.00, 5 studies with 2064 patients included), or discontinuations due to adverse events (RR 0.86, 95% CI 0.57 to 1.31, 8 studies with 2290 patients included).

We identified no statistical significant differences between GnRH antagonists and standard androgen suppression therapy for immediate-onset allergic reactions (RR 2.36, 95% CI 0.55 to 10.12, 5 studies with 1694 patients included, table 8). However, this adverse event occurred in 9 of 1119 patients (0.8%) treated with abarelix but in no patient receiving standard androgen suppression therapy. We found no data for degarelix regarding this outcome.

We did not identify information about the occurrence of gynecomastia, breast pain, or sweating with the use of GnRH antagonist therapy.

Quality of life

Three studies were included for quality of life evaluation (CS28, CS20, and CS31). Further two studies (CS35 and CS37) were identified to measure quality of life outcomes through screening of protocol entries. However, we found no publications of these studies that reported this outcome. The question addressed by this systematic review was different from the results presented in included studies because we expected a measurement of quality of life related to general health but found an evaluation of quality of life related to urinary or prostate symptoms only.

While there was no statistically significant difference for quality of life related to urinary symptoms, improved quality of life regarding prostate symptoms, measured with the International Prostate Symptom Score (IPSS), for the use of GnRH antagonists (degarelix 240/80 mg) compared with the use of standard androgen suppression therapy (mean score difference -0.40, 95%CI -0.94 to 0.14, 3 studies with 461 patients included, and -1.84, 95%CI -3.00 to -0.69, 3 studies with 459 patients included, respectively) was found. Quality of evidence was rated low according to GRADE (Table 7).

Discussion

Based on the assessed evidence including trials not published as journal articles, the effects on efficacy of GnRH antagonist compared to standard androgen therapy are still unclear because no long-term follow-up data (>364 days) are available for any of the evaluated outcomes and because evidence is hampered by selective reporting of results, risk of bias and insufficient reporting of methodology. Fifteen studies were identified but only thirteen could be included. No study reported cancer-specific survival or clinical progression. There were no statistically significant differences in overall mortality, treatment failure, prostate-specific antigen progression or quality of life. However, quality of evidence according to GRADE was rated low for these outcomes.

The question addressed by this systematic review could partly not be answered with the available evidence. We aimed to assess efficacy and safety of GnRH antagonists compared with standard androgen suppression therapy for advanced prostate cancer treatment. However, most of the studies available were not intended to provide, as their primary endpoint, safety and efficacy data. The majority of studies included were performed or sponsored by the manufacturing companies to gain regulatory approval for marketing authorization. The studies aimed to assess the pharmacodynamic metrics of obtaining a level of testosterone </= 50 ng/dl by day 28 and maintaining that level through 365 days. The primary outcome of two studies (CS30 and CS31) was the evaluation of prostate volume reduction and relief of lower urinary tract symptoms. In one study (CS21) many patients had localized disease or PSA relapse only. The majority of patients treated with androgen suppression therapy for prostate cancer had non-metastatic disease (range 58-96%), and the number of patients with Gleason score <7 ranged between 18% (CS31) and 57% (149-98-03). Future studies therefore should focus on patient-relevant outcomes to inform decision making in clinical practice.

The FDA required a black-box warning on the packaging and the patient instruction sheet of abarelix in USA because immediate-onset systemic allergic reactions occurred after administration of this drug. We found no statistically significant differences in immediate-onset allergic reactions between GnRH antagonists and standard androgen suppression therapy. However, it should be mentioned that 1.1% of patients included in FDA safety data analysis, treated with abarelix, discontinued therapy because of immediate onset of allergic-type adverse events, and 0.4-0.5% had serious anaphylactic-like reactions. There were no such events in the control groups treated with standard androgen suppression therapy [22]. Additionally, the risk for injection-site events was increased using GnRH antagonists. This result is consistent with the FDA safety data analysis, where 25% of patients treated with degarelix had injection site reactions (grade 3 or 4 events in 1% of patients) [50].

Fewer cardiovascular events occurred among patients using GnRH antagonists than among patients using standard androgen suppression therapy. This has been noted in the literature previously [60 78-80]. However, there is evidence for both medications that in patients with a pre-existing cardiovascular disease and/or corresponding risk factors that these drugs may increase the risk to suffer from

cardiovascular events on the long-term and that these subgroup of patients may need careful clinical follow-up [79-82].

Conclusion

Evidence is hampered by risk of bias, selective reporting and limited follow-up. Quality of evidence for all assessed outcomes was rated low according to GRADE. There is currently insufficient evidence to make firm conclusive statements on the efficacy of GnRH antagonist compared to standard androgen suppression therapy for advanced prostate cancer. The risk for injection-site events was increased, but cardiovascular events may occur less often using GnRH antagonist. Further high-quality research on GnRH antagonists with long-term follow-up is required.

Figure legend

Figure 1: Flow Chart of initially search in March 2014[1]

[1]Adapted to the flow chart recommended by Liberati et al. [83]

Figure 2: Flow Chart of search update in March 2015[1]

[1]Adapted to the flow chart recommended by Liberati et al. [83]

Figure 3: Overall Mortality

Table 1: Search strategy

CENTRAL	1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
(The Cochrane Library)	2	(prostat* near (cancer* or tumo* or neoplas* or carcinom* or malign*))
03/2015	3	(#1 or #2)
	4	(LHRH antagonist* or LH RH antagonist* or GNRH antagonist* or GN RH antagonist*)
	5	(FE200486* or FE 200486*)
	6	(firmagon* or degarelix*)
	7	(PPI149* or PPI 149*)
	8	(abarelix* or plenaxis*)
	9	(#4 or #5 or #6 or #7 or #8)
	10	(#3 and #9)
MEDLINE (Ovid)	1	Prostatic Neoplasms/
1946-03/2015	2	(prostat* adj3 (cancer* or tumo* or neoplas* or carcinom* or malign*)).tw.
	3	1 or 2
	4	(LHRH antagonist* or LH RH antagonist* or GNRH antagonist* or GN RH antagonist*).tw.
	5	(FE200486* or FE 200486*).mp.
	6	(firmagon* or degarelix*).mp.
	7	(PPI149* or PPI 149*).mp.
	8	(abarelix* or plenaxis*).mp.
	9	4 or 5 or 6 or 7 or 8
	10	3 and 9
EMBASE (DIMDI)	1	EM74
1947-03/2015	2	CT=("PROSTATE TUMOR"; "PROSTATE CANCER"; "PROSTATE ADENOCARCINOMA"; "PROSTATE CARCINOMA")
	3	(prostat* and (cancer* or tumo* or neoplas* or carcinom* or malign*))/same sent
	4	2 OR 3
	5	(LHRH antagonist* or LH RH antagonist* or GNRH antagonist* or GN RH antagonist*)/same sent
	6	(FE200486* or FE 200486*)/same sent
	7	(firmagon* or degarelix*)/same sent
	8	(PPI149* or PPI 149*)/same sent
	9	(abarelix* or plenaxis*)/same sent
	10	5 OR 6 OR 7 OR 8 OR 9
	11	4 AND 10

Web of Science	1	TS=(prostat* same (cancer* or tumo* or neoplas* or carcinom* or malign*))
1970-03/2015	2	TS=((LHRH same antagonist*) or (LH same RH same antagonist*))
	3	TS=((gnrh same antagonist*) OR (gn same rh same antagonist*))
	4	TS=(FE200486*)
	5	TS=(FE same 200486*)
	6	TS=(abarelix* OR plenaxis*)
	7	TS=(firmagon* OR degarelix*)
	8	TS=(PPI149*)
	9	TS=(PPI same 149*)
	10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
	11	#10 AND #1

Table 2: Study Characteristics (Degarelix)

	Zuckerman 2013	CS21	CS28	CS30	CS31	CS35	CS37
Design (Duration of study)	non-randomized prospective cross-over study (90/90 days)	randomized controlled trial (364 days)	randomized controlled trial (84 days)	randomized controlled trial (84 days)	randomized controlled trial (84 days)	randomized controlled trial (364 days)	randomized controlled trial (364 days)
Setting/ Geographical region	Single center/ US	Multicenter/ international	Multicenter/ Europe	Multicenter/ US, Europe	Multicenter/ Europe	Multicenter/ international	Multicenter/ US
Patients included	48	620	42	246	182	859	405
Non-metastatic disease	43 (90%)	369/610 (61%)	9/40 (22%)	235/244 (96%)	109/179 (61%)	NR	NR
Metastatic disease	5 (10%)	125/610 (20%)	14/40 (35%)	0/244 (0%)	53/179 (30%)	NR	NR
Non-classified disease	-	116/610 (19%)	17/40 (43%)	9/244 (4%)	17/179 (9%)	NR	NR
Gleason-Score 2-6	9 (19%)	266/610 (43%)	2/40 (5%)	53/244 (22%)	33/179 (18%)	NR	NR
Gleason-Score 7	17 (35%)	181/610 (30%)	38/40 (95%)	139/244 (57%)	55/179 (31%)	NR	NR
Gleason-Score 8-10	22 (46)	163/610 (27%)		52/244 (21%)	91/179 (51%)	NR	NR
Gleason-Score nc	-	-	-	-	-	-	-
Intervention (N)	Degarelix 240/80 mg[1] (n=48) for 3 months	Degarelix 240/160 mg or 240/80 mg[1] (n=409)	Degarelix 240/80 mg[1] (n=27)	Degarelix 240/80 mg[1] (n=181)	Degarelix 240/80 mg[1] (n=84)	Degarelix 240/80 mg[1] (n=NR)	Degarelix 240/80 mg[1] (n=NR)
Control (N)	Leuprolide (22.5 mg) 3-month depot for 3 month	Leuprolide 7.5 mg (n=201) monthly	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=13)	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=65)	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=98)	Goserelin NR mg (n=NR)	Leuprolide NR mg (n=NR)
Outcomes	Ability to maintain medical castration (prevent a testosterone surge) during transition from degarelix to leuprolide, assessment of any PSA elevation after the degarelix to leuprolide transition, adverse events	Change in vital signs/body weigh/QTc Interval, adverse events, measurement of PSA levels/testosterone levels/testosterone surge, time to PSA failure	Change in vital signs/body weigh/Total International Prostate Symptom Score (IPSS)/Quality of Life/prostate size/maximum urine flow/residual volume, measurement of PSA levels/testosterone levels, adverse events	Change in vital signs and body weigh/laboratory variables/oestradiole levels/Total International Prostate Symptom Score (IPSS)/Quality of Life/prostate size, measurement of PSA levels/testosterone levels, adverse events	Change in vital signs/body weigh/laboratory variables/Total International Prostate Symptom Score (IPSS)/ Quality of Life/Benign Prostatic Hyperplasia Impact Index/prostate size, measurement of PSA levels/testosterone levels, adverse events	Change in Total International Prostate Symptom Score (IPSS)/Quality of Life, measurement of PSA levels/testosterone levels	Measurement of PSA levels, Change in quality of life

PSA, Prostate-Specific Antigen; NR, not reported; NC, not classified

[1]Degarelix 240 mg subcutaneous given as a starting dose and 80 mg or 160 mg subcutaneous maintenance doses every 4 weeks thereafter

Table 3: Study Characteristics (Abarelix)

	149-98-02	149-98-03	149-99-03	ABACS 1	149-97-04	Garnick 2011
Design (Duration of study)	randomized controlled trial (169 days)	randomized controlled trial (169 days)	randomized controlled trial (169 days)	randomized controlled trial (364 days)	prospective non-randomized controlled clinical trial (27 days)	non-randomized prospective cross-over study (84/56 days)
Geographical region	Multicenter/ US	Multicenter/ US	Multicenter/ US	Multicenter/ Europe	Multicenter/ US	Multicenter/ US
Patients included	271	255	584	177	242	176
Non-metastatic disease	165/269 (61%)	145/251 (58%)	NR	NR	NR	143/176 (80%)
Metastatic disease	104/269 (39%)	106/251 (42%)	30/582 (5%)	NR	NR	12/176 (8%)
Non-classified disease	-	-	552/582 (95%)	-	-	21/176 (12%)
Gleason-Score 2-6	121/269 (45%)	144/251 (57%)	NR	NR	NR	97/176 (55%)
Gleason-Score 7	81/269 (30%)	61/251 (24%)	NR	NR	NR	73/176 (41%)
Gleason-Score 8-10	56/269 (21%)	34/251 (14%)	NR	NR	NR	6/176 (3%)
Gleason-Score non-classified	11/269 (4%)	12/251 (5%)	-	-	-	-
Intervention (N)	Abarelix 100 mg[1] (n=180)	Abarelix 100 mg[1] (n=170)	Abarelix 100 mg[1] (n=390)	Abarelix 100 mg[1] (n=87)	Abarelix 100 mg[1] (n=209)	Abarelix 100 mg[1] (n=176)
Control (N)	Leuprolide 7.5mg monthly (n=91)	Leuprolide 7.5 mg monthly + Bicalutamide 50 mg daily (n=85)	Leuprolide 7.5 mg monthly (n=194)	Goserelin 3.6 mg monthly + Bicalutamide 50 mg daily (n=90)	Leuprolide or Goserelin with(out) Antiandrogen (n=33)	Leuprolide 7.5 mg monthly or Goserelin 3.6 mg monthly (n=176)
Outcomes	Achievement of castration (day <8, <29, <365); Measurement of testosterone levels/endocrine efficacy/PSA levels, adverse events	Achievement of castration (day <8, <29, <365); Measurement of testosterone levels/endocrine efficacy/PSA levels, adverse events	Achievement of castration (day <8, <365); adverse events, discontinuation of treatment, measurement of PSA levels	Achievement of castration (day <8, <365), measurement of testosterone levels, adverse events,	Achievement of castration (day <8, <365), Measurement of testosterone levels/endocrine efficacy/PSA levels, adverse events	Achievement of castration (day <8, <365), measurement of testosterone levels, adverse events,

PSA, Prostate-Specific Antigen; NR, not reported

[1] Abarelix depot 100 mg intramuscular given on day 0, day 15 and every 4 weeks thereafter

Table 4: Risk of Bias assessment per randomized controlled trial (Degarelix)

	CS21	CS28	CS30	CS31	CS35	CS37
Random sequence generation	Low risk[1]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Allocation concealment	Low risk[2]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Blinding of participants and personnel: Mortality, PSA progression	Low risk[3]	Unclear risk (NR)	Low risk[3]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Blinding of participants and personnel: Adverse events, treatment failure, quality of life	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]
Blinding of outcome assessment: Mortality, PSA progression	Low risk[3]	Unclear risk (NR)	Low risk[3]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Blinding of outcome assessment: Adverse events, treatment failure, quality of life	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]	High risk[4]
Incomplete outcome data: Mortality, PSA progression	Low risk[5]	Unclear risk (NR)	Low risk[5]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Incomplete outcome data: Adverse events, treatment failure, quality of life	Low risk[5]	Unclear risk (NR)	Low risk[5]	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Selective reporting	Low risk[6]	High risk[7]	Low risk[6]	Low risk[6]	High risk[7]	High risk[7]

NR, not reported

[1] Random number generator (computer program)
[2] Central allocation
[3] Open-label study but personnel were unaware of blood values
[4] Open-label study but results are likely to be influenced by lack of blinding
[5] Missing outcome data balanced in numbers across intervention groups.
[6] The study protocol is available and all outcomes that are of interest have been reported.
[7] Averse events are reported incompletely or study report fails to include results for this outcome

Table 5: Risk of Bias assessment per randomized controlled trial (Abarelix)

	149-98-02	149-98-03	149-99-03	ABACS1
Random sequence generation	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)	Unclear risk (NR)
Allocation concealment	Low risk[1]	Low risk[1]	Low risk[1]	Unclear risk (NR)
Blinding of participants and personnel: Mortality, PSA progression	Low risk[2]	Low risk[2]	Unclear risk (NR)	Unclear risk (NR)
Blinding of participants and personnel: Adverse events, treatment failure, quality of life	High risk[3]	High risk[3]	High risk[3]	High risk[3]
Blinding of outcome assessment: Mortality, PSA progression	Low risk[2]	Low risk[2]	Unclear risk (NR)	Unclear risk (NR)
Blinding of outcome assessment: Adverse events, treatment failure, quality of life	High risk[3]	High risk[3]	High risk[3]	High risk[3]
Incomplete outcome data: Mortality, PSA progression	Low risk[4]	Low risk[4]	Unclear risk (NR)	Unclear risk (NR)
Incomplete outcome data: Adverse events, treatment failure, quality of life	Low risk[4]	Low risk[4, 5]	Unclear risk (NR)	Unclear risk (NR)
Selective reporting	Low risk[6]	Low risk[6]	Unclear risk[7]	High risk[8]

NR, not reported

[1] Central allocation
[2] Open-label study but personnel were unaware of blood values
[3] Open-label study but results are likely to be influenced by lack of blinding
[4] Proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate
[5] Missing outcome data balanced in numbers across intervention groups.
[6] The study protocol is not available but it is clear that the published reports include all expected outcomes
[7] No protocol available
[8] Averse events are reported incompletely or study report fails to include results for this outcome

Table 6: Risk of Bias assessment per prospective non-randomized comparator controlled studies (Degarelix + Abarelix) [1]

	149-97-04	Zuckerman 2013	Garnick 2011
Study type	controlled clinical trial	cross-over study	cross-over study
Prospective study?	Yes	Yes	Yes
Was there a comparison?	Yes	Yes	Yes
Was there a baseline assessment?	Yes	Yes	Yes
Blinding of outcome assessment?	Unclear	No	No
Incomplete outcome data?	Yes	No	No
Selective outcome reporting?	Unclear	Yes	Unclear
Patient selection method			
Random sample generation	No	No	No
Consecutive enrollment	Yes	Unclear	Yes
Selected subset of patients	Yes	Unclear	No
Time difference	No	No	No
Location difference	No	No	No
Treatment decision	Yes	No	No
Patients preferences	Yes	No	No
On the basis of outcome	No	No	No
Predefinition of adverse events?	Unclear	Unclear	Unclear
Reporting of all adverse events?	Unclear	No	Unclear
Are all patients evaluated for adverse events?	Unclear	Yes	Unclear
Dropouts because of adverse events?	Unclear	No	Unclear

[1]Adapted to the checklist recommended by Reeves et al. for data collection and study assessment for non-randomized studies [15].

Table 7: GRADE evidence table: quality of evidence assessment (confidence in effect estimates) per endpoint

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GnRH antagonists	Standard androgen suppression therapy	Relative (95% CI)	Absolute	
Overall mortality (follow-up 84-364 days)											
9	randomized trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	see comment[4]	35/1923 (1.8%)	16/1097 (1.5%)	RR 1.35 (0.63 to 2.93)	5 more per 1000 (from 6 fewer to 30 more)	⊕⊕OO LOW
Treatment failure (follow-up 84-364 days)											
7	randomized trials[5]	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	146/1450 (10.1%)	81/750 (10.8%)	RR 0.92 (0.64 to 1.33)	9 fewer per 1000 (from 39 fewer to 36 more)	⊕⊕OO LOW
PSA progression (follow-up 84-364 days)											
7	randomized trials[7]	serious[8]	no serious inconsistency	no serious indirectness	serious[3]	none	115/1566 (7.3%)	75/923 (8.1%)	RR 0.83 (0.64 to 1.06)	14 fewer per 1000 (from 29 fewer to 5 more)	⊕⊕OO LOW
Quality of life related to International Prostate Symptom Score (IPSS, follow-up 84 days; Better indicated by lower values)											
3	randomized trials[9]	serious[10]	no serious inconsistency	serious[11]	no serious imprecision	none	286	173	-	MD 1.84 lower (3 to 0.69 lower)	⊕⊕OO LOW
Quality of Life related to urinary symptoms (follow-up 84 days; Better indicated by lower values)											
3	randomized trials[9]	serious[10]	no serious inconsistency	serious[11]	no serious imprecision	none	288	173	-	MD 0.4 lower (0.94 lower to 0.14 higher)	⊕⊕OO LOW

[1] The following studies were included: 149-98-02, 149-98-03, ABACS1, CS21, CS28, CS30, CS31, CS35, CS37

[2] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables). Despite the methodological limitations, we don't feel that results are likely to be influenced by lack of blinding. However, there was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28, CS31, CS35, CS37, and ABACS1. Studies CS35 and CS37 were reported as conference abstracts or data presentation within combined data analyses. Study ABACS1 was reported as conference abstract or the trial information was published within narrative reviews or FDA safety data publications. Studies CS35 and CS37 were terminated early. Studies CS35 and CS37 reported patient baseline characteristics incompletely.

[3] Downgraded for imprecision (-1): Imprecision due to low number of events and wide confidence intervals.
[4] Information on mortality was not provided by a single study as time to event data. Therefore we could not, as initially planned, analyze these data with hazard ratios, but have to report numbers of death during study duration. After screening the available entries of the study protocols in the registries, mortality was not predefined as primary/secondary outcome in any of the included studies but was only assessed as an adverse event outcome.
[5] The following studies were included: 149-98-02, 149-98-03, 149-99-03, CS21, CS28, CS30, CS31
[6] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables). Study 149-99-03 was reported as conference abstract only. There was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28, CS31, and 149-99-03. Study CS28 was terminated early.
[7] The following studies were included: CS21, CS28, CS30, CS31, CS35, CS37, ABACS1
[8] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables). Despite the methodological limitations, we don't feel that results are likely to be influenced by lack of blinding. However, there was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28, CS31, CS35, CS37, and ABACS1. Studies CS35 and CS37 were reported as conference abstracts or data presentation within combined data analyses only. Study ABACS1 was reported as conference abstract or the trial information was published within narrative reviews or FDA safety data publications. Studies CS35 and CS37 were terminated early. Studies CS35 and CS37 reported patient baseline characteristics incompletely.
[9] The following studies were included: CS28, CS30, CS31.
[10] Downgraded for study limitations (-1): High or unclear risk of bias in included studies (for details see 'risk of bias' tables). There was insufficient reporting of attrition and exclusions to permit judgment on incomplete outcome data in studies CS28 and CS31. Studies CS35 and CS37 were identified to measure quality of life outcomes. However, we found no publications of these studies that reported this outcome.
[11] Downgraded for indirectness (-1): The question addressed by this systematic review was different from the results presented in the available evidence. We expected a measurement of quality of life related to general health but found only an evaluation of quality of life related to urinary symptoms or International Prostate Symptom Score (IPSS).

Table 8: Adverse events

Outcome or Subgroup	Studies	Patients	Effect Estimate[95% CI], Heterogeneity (I^2)
Serious adverse events	7	2179	RR 0.82 [0.62, 1.08], 4%[1]
Subgroup: Abarelix 100 mg	3	1102	RR 0.88 [0.60, 1.28], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.85 [0.46, 1.57], NA[1]
Subgroup: Degarelix 240/80 mg	4	775	RR 0.68 [0.39, 1.19], 35%[1]
Severe/life-threatening adverse event	5	2064	RR 0.76 [0.58, 1.00], 4%[1]
Subgroup: Abarelix 100 mg	4	1454	RR 0.79 [0.60, 1.05], 0%[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 0.16 [0.02, 1.54], NA[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.50 [0.07, 3.46], NA[1]
Discontinuation due to adverse events	8	2290	RR 0.86 [0.57, 1.31], 25%[1]
Subgroup: Abarelix 100 mg	3	1110	RR 0.58 [0.31, 1.08], 39%[1]
Subgroup: Degarelix 240/80 mg	5	872	RR 0.95 [0.44, 2.04], 0%[1]
Subgroup: Degarelix 240/160 mg	1	308	RR 1.57 [0.65, 3.81], NA[1]
Fatigue	10	3784	RR 0.88 [0.72, 1.08], 0%[1]
Subgroup: Abarelix 100 mg	4	1456	RR 0.96 [0.73, 1.26], 0%[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.80 [0.59, 1.08], NA[1]
Hot flush	8	3264	RR 1.00 [0.92, 1.08], 0%[1]
Subgroup: Abarelix 100 mg	2	936	RR 1.01 [0.93, 1.10], 0%[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.99 [0.88, 1.11], NA[1]
Infection (Abarelix 100 mg)	2	520	RR 0.93 [0.42, 2.05], NA[1]
Urinary tract infection	8	2848	RR 0.71 [0.41, 1.25], 54%[2]
Subgroup: Abarelix 100 mg	2	520	RR 1.03 [0.52, 2.07], NA[2]
Subgroup: Degarelix 240/80 and 240/160 mg	6	2328	RR 0.57 [0.39, 0.83], NA[2]
Loss of sexual interest	2	597	RR 1.05 [0.38, 2.91], 0%[1]
Subgroup: Abarelix 100 mg	1	352	RR 1.00 [0.06, 15.86], NA[1]
Subgroup: Degarelix 240/80 mg	1	245	RR 1.06 [0.35, 3.17], NA[1]
Sexual dysfunction (Degarelix 240/80 mg)	2	427	RR 0.83 [0.40, 1.71], 0%[1]

Acute myocardial infarction	1	610	RR 0.49 [0.07, 3.48], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 1.49 [0.06, 36.31], NA[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 0.16 [0.01, 3.98], NA[1]
Cardiovascular events (Degarelix 240/80 and 240/160 mg)	6	2328	RR 0.60 [0.38, 0.94], NA[3]
Ischemic heart disease	1	610	RR 0.42 [0.23, 0.77], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.50 [0.21, 1.15], NA[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 0.35 [0.15, 0.85], NA[1]
Fatal cerebrovascular-related events (Degarelix 240/80 mg and 240/160 mg)	1	610	RR 0.49 [0.12, 1.94], NA[1]
Asthenia (Degarelix 240/80 mg)	2	427	RR 0.91 [0.39, 2.13], 0%[1]
Urinary retention	4	1077	RR 0.39 [0.12, 1.32], 0%[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 0.99 [0.09, 10.79], NA[1]
Subgroup: Degarelix 240/80 mg	4	775	RR 0.28 [0.06, 1.23], 0%[1]
Immediate onset allergic reactions (<1h) (Abarelix 100 mg)	5	1694	RR 2.36 [0.55, 10.12], 0%[1]
Injection-site pain Degarelix 240/80 mg and 240/160 mg	6	2328	RR 7.88 [5.65, 10.98], NA[1]
Injection-site reaction (Degarelix 240/80 mg and 240/160 mg)	1	610	RR 79.61 [11.23, 564.49], NA[1]
Diarrhea (Abarelix 100 mg)	3	872	RR 1.21 [0.81, 1.80], 0%[1]
Peripheral edema (Abarelix 100 mg)	2	520	RR 0.51 [0.32, 0.81], NA[1]
Constipation	5	1522	RR 0.99 [0.64, 1.53], 0%[1]
Subgroup: Abarelix 100 mg	3	872	RR 1.00 [0.58, 1.75], 0%[1]
Subgroup: Degarelix 240/160 mg	1	303	RR 0.60 [0.19, 1.92], NA[1]
Subgroup: Degarelix 240/80 mg	2	347	RR 1.28 [0.49, 3.33], 0%[1]
Arthralgia	7	2680	RR 0.64 [0.45, 0.91], 0%[1]
Subgroup: Abarelix 100 mg	1	352	RR 0.40 [0.08, 2.03], NA[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.66 [0.46, 0.94], NA[1]
Musculoskeletal adverse events (Degarelix 240/80 mg)	1	408	RR 0.65 [0.45, 0.96], NA[1]
Chills	1	610	RR 9.38 [1.26, 69.58], 0%[1]
Subgroup: Degarelix 240/80 mg	1	308	RR 11.28 [0.67, 189.51], NA[1]
Subgroup: Degarelix 240/160 mg	1	302	RR 7.46 [0.43, 129.37], NA[1]
Back pain	9	3200	RR 0.74 [0.56, 0.97], 4%[1]

Subgroup: Abarelix 100 mg	3	872	RR 0.81 [0.54, 1.23], 38%[1]
Subgroup: Degarelix 240/80 mg and 240/160 mg	6	2328	RR 0.68 [0.48, 0.99], NA[1]

NA, Not applicable; RR, risk ratio; CI, Confidence Interval; MD, Mean Difference

[1] Statistical method: *Mantel-Haenszel*, Fixed-effect model
[2] Statistical method: *Mantel-Haenszel*, Random-effects model
[3] Statistical method: Generic inverse variance, Fixed-effect model

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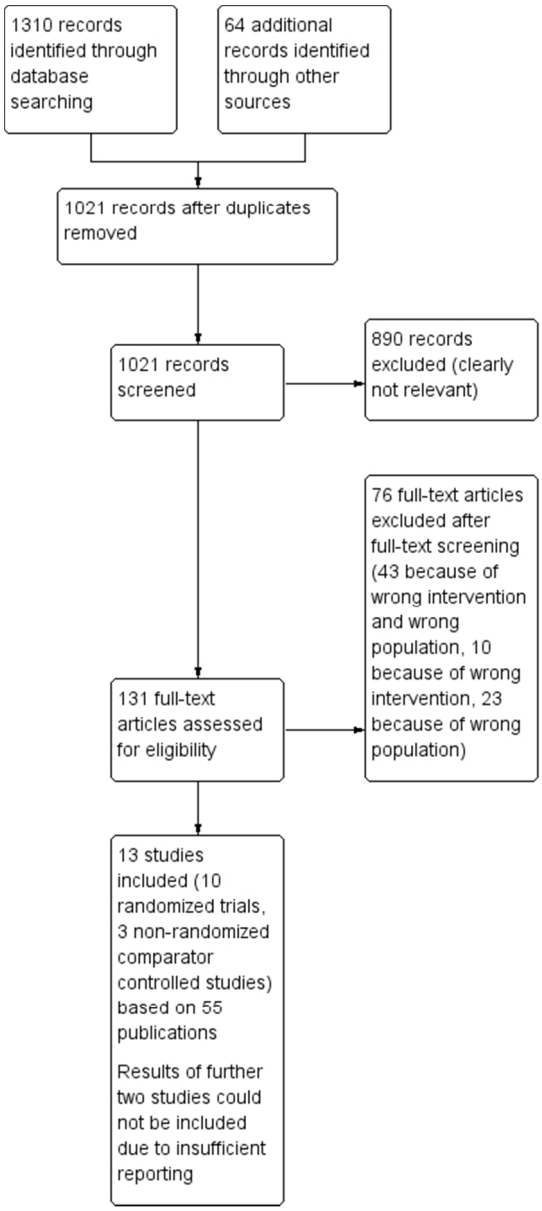

Figure 1: Flow Chart of initially search in March 2014
141x316mm (72 x 72 DPI)

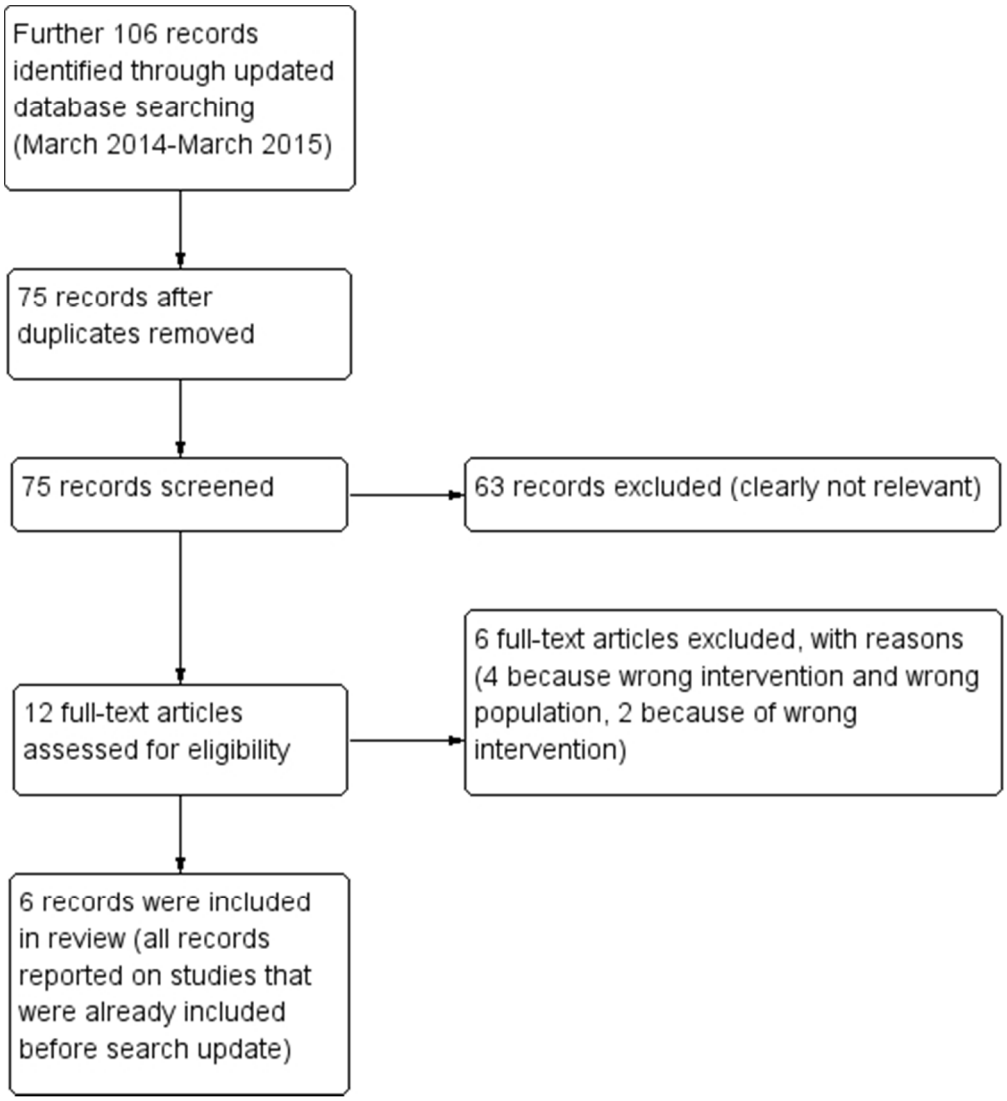

Figure 2: Flow Chart of search update in March 2015
182x198mm (72 x 72 DPI)

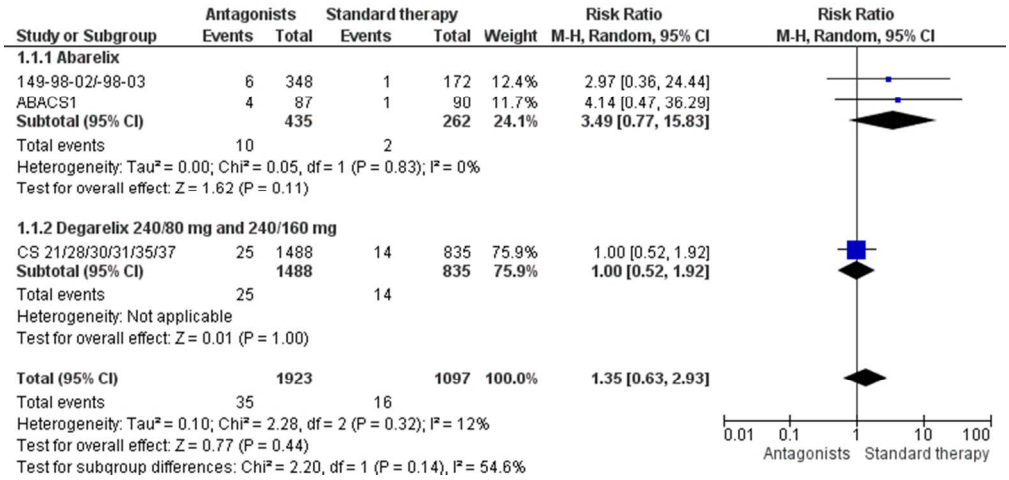

Figure 3: Overall Mortality
263x124mm (72 x 72 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6; Figure 1,2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Table 4-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6,7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 4-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1,2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2,3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 4-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 7, Figure 3, 10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14, Table 7. Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15, Table 7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	30

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

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