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Non-steroidal antiandrogen monotherapy compared with luteinising hormone–releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer (Review)

Kunath F, Grobe HR, Rücker G, Motschall E, Antes G, Dahm P, Wullich B, Meerpohl JJ

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[Intervention Review]

Non-steroidal antiandrogen monotherapy compared with luteinising hormone–releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer

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ABSTRACT

Background

Non-steroidal antiandrogens and castration are the main therapy options for advanced stages of prostate cancer. However, debate regarding the value of these treatment options continues.

Objectives

To assess the effects of non-steroidal antiandrogen monotherapy compared with luteinising hormone–releasing hormone agonists or surgical castration monotherapy for treating advanced stages of prostate cancer.

Search methods

We searched the Cochrane Prostatic Diseases and Urologic Cancers Group Specialized Register (PROSTATE), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science with Conference Proceedings, three trial registries and abstracts from three major conferences to 23 December 2013, together with reference lists, and contacted selected experts in the field and manufacturers.

Selection criteria

We included randomised controlled trials comparing non-steroidal antiandrogen monotherapy with medical or surgical castration monotherapy for men in advanced stages of prostate cancer.

Data collection and analysis

One review author screened all titles and abstracts; only citations that were clearly irrelevant were excluded at this stage. Then, two review authors independently examined full-text reports, identified relevant studies, assessed the eligibility of studies for inclusion, assessed trial quality and extracted data. We contacted the study authors to request additional information. We used Review Manager 5 for data synthesis and used the fixed-effect model for heterogeneity less than 50%; we used the random-effects model for substantial or considerable heterogeneity.

Main results

Eleven studies involving 3060 randomly assigned participants were included in this review. The quality of evidence is hampered by risk of bias. Use of non-steroidal antiandrogens decreased overall survival (hazard ratio (HR) 1.24, 95% confidence interval (CI) 1.05 to 1.48, six studies, 2712 participants) and increased clinical progression (one year: risk ratio (RR) 1.25, 95% CI 1.08 to 1.45, five studies, 2067 participants; 70 weeks: RR 1.26, 95% CI 1.08 to 1.45, six studies, 2373 participants; two years: RR 1.14, 95% CI 1.04 to 1.25, three studies, 1336 participants), as well as treatment failure (one year: RR 1.19, 95% CI 1.02 to 1.38, four studies, 1539 participants; 70 weeks: RR 1.27, 95% CI 1.05 to 1.52, five studies, 1845 participants; two years: RR 1.14, 95% CI 1.05 to 1.24, two studies, 808 participants), compared with medical or surgical castration. The quality of evidence for overall survival, clinical progression and treatment failure was rated as moderate according to GRADE. Predefined subgroup analyses showed that use of non-steroidal antiandrogens, compared with castration, was less favourable for overall survival, clinical progression (at one year, 70 weeks, two years) and treatment failure (at one year, 70 weeks, two years) in men with metastatic disease. Use of non-steroidal antiandrogens also increased the risk for treatment discontinuation due to adverse events (RR 1.82, 95% CI 1.13 to 2.94, eight studies, 1559 participants), including events such as breast pain (RR 22.97, 95% CI 14.79 to 35.67, eight studies, 2670 participants), gynaecomastia (RR 8.43, 95% CI 3.19 to 22.28, nine studies, 2774 participants) and asthenia (RR 1.77, 95% CI 1.36 to 2.31, five studies, 2073 participants). The risk of other adverse events, such as hot flashes (RR 0.23, 95% CI 0.19 to 0.27, nine studies, 2774 participants), haemorrhage (RR 0.07, 95% CI 0.01 to 0.54, two studies, 546 participants), nocturia (RR 0.38, 95% CI 0.20 to 0.69, one study, 480 participants), fatigue (RR 0.52, 95% CI 0.31 to 0.88, one study, 51 participants), loss of sexual interest (RR 0.50, 95% CI 0.30 to 0.83, one study, 51 participants) and urinary frequency (RR 0.22, 95% CI 0.11 to 0.47, one study, 480 participants) was decreased when non-steroidal antiandrogens were used. The quality of evidence for breast pain, gynaecomastia and hot flashes was rated as moderate according to GRADE. The effects of non-steroidal antiandrogens on cancer-specific survival and biochemical progression remained unclear.

Authors' conclusions

Currently available evidence suggests that use of non-steroidal antiandrogen monotherapy compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of overall survival, clinical progression, treatment failure and treatment discontinuation due to adverse events. Evidence quality was rated as moderate according to GRADE. Further research is likely to have an important impact on results for patients with advanced but non-metastatic prostate cancer treated with non-steroidal antiandrogen monotherapy. However, we believe that research is likely not necessary on non-steroidal antiandrogen monotherapy for men with metastatic prostate cancer. Only high-quality, randomised controlled trials with long-term follow-up should be conducted. If further research is planned to investigate biochemical progression, studies with standardised follow-up schedules using measurements of prostate-specific antigen based on current guidelines should be conducted.

PLAIN LANGUAGE SUMMARY

Androgen suppression monotherapy for treatment of advanced prostate cancer

Review question

We reviewed the evidence on the effects of androgen suppression monotherapies (non-steroidal antiandrogens compared with medical or surgical castration monotherapy) in men with advanced prostate cancer.

Background

Prostate cancer is among the top six most lethal cancers, and treatment implies a high disease burden for patients. An advanced prostate cancer has spread outside the prostate gland or has metastasised to lymph nodes, bones and/or other areas. Currently no curative therapy for advanced prostate cancer is known, although androgen suppression therapy is commonly used to treat the disease at this stage. We wanted to discover the effects of androgen suppression monotherapies in the treatment of patients in advanced stages of prostate cancer.

Study characteristics

The evidence is current to December 2013. We included 11 studies involving 3060 randomly assigned participants at advanced stages of prostate cancer. The follow-up period of participants ranged from six months to six years. In seven studies, authors reported possible conflicts of interest. In three studies, no conflicts of interest were declared. In one study, authors reported that they had received an educational grant from the sponsor, who had no role in any aspect of analysis or data interpretation.

Key results

Use of non-steroidal antiandrogens decreased overall survival and increased clinical progression and treatment failure. Subgroup analyses showed that non-steroidal antiandrogens, compared with castration, were less favourable for overall survival, for clinical progression and for treatment failure in men with metastatic disease. Participants receiving antiandrogens were also more likely to stop treatment as the result of side effects. The risk of suffering breast pain, enlargement of breast tissue or symptoms of physical weakness was also increased with non-steroidal antiandrogens. The risks of feeling intense heat with sweating and rapid heartbeat and of bleeding, the need to get up in the night to urinate, loss of sexual interest, extreme tiredness and the need to urinate more often than usual were increased with castration. No difference was noted for other side effects. The effect of non-steroidal antiandrogens on cancer-specific survival and biochemical progression remained unclear.

Quality of the evidence

Included studies were poorly conducted, and the quality of evidence was rated as moderate. This means that further research is likely to have an important impact on our confidence in the accuracy of results.

Summary of findings for the main comparison. Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy for advanced prostate cancer

Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy for advanced prostate cancer

Patient or population: men with advanced prostate cancer
Settings: multi-centre (9 studies) and single-centre studies (2 studies) on outpatients
Intervention: non-steroidal antiandrogen monotherapy

Comparison: LHRH agonists or surgical castration monotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Hazard ratio/ Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Castration	Non-steroidal antiandrogen				
Overall survival Follow-up: median 1 to 6.3 years	**296 per 1000**	**353 per 1000** (308 to 405)	**HR 1.24** (1.05 to 1.48)	2712 (6 studies)	⊕⊕⊕⊖ **moderate** [1,6]	Overall survival was evaluated using the random-effects model because of heterogeneity (I^2 = 51%). Sensitivity analyses showed comparable results. Numbers of absolute risks relate to deaths
Clinical progression Follow-up: median 70 weeks	**420 per 1000**	**529 per 1000** (453 to 608)	**RR 1.26** (1.08 to 1.45)	2373 (6 studies)	⊕⊕⊕⊖ **moderate** [2,6]	Clinical progression after median 70 weeks was evaluated using the random-effects model because of heterogeneity (I^2 = 64%). Sensitivity analyses showed comparable results. After imputation of event numbers: RR 1.43, 95% CI 1.19 to 1.73, I^2 = 0%; fixed-effect model
Treatment failure Follow-up: median 70 weeks	**527 per 1000**	**669 per 1000** (553 to 801)	**RR 1.27** (1.05 to 1.52)	1845 (5 studies)	⊕⊕⊕⊖ **moderate** [3,6]	Treatment failure after median 70 weeks was evaluated using the random-effects model because of heterogeneity (I^2 = 81%). Sensitivity analyses showed comparable results. After imputation of event numbers: RR 1.21, 95% CI 1.09 to 1.35, I^2 = 0%; fixed-effect model
Breast pain Follow-up: median 1 to 6.3 years	**17 per 1000**	**397 per 1000** (256 to 617)	**RR 22.97** (14.79 to 35.67)	2670 (8 studies)	⊕⊕⊕⊖ **moderate** [4]	Breast pain was evaluated using the fixed-effect model (I^2 = 0%)

Gynaecomastia Follow-up: median 1 to 6.3 years	**44 per 1000**	**374 per 1000** (142 to 989)	**RR 8.43** (3.19 to 22.28)	2774 (9 studies)	⊕⊕⊕⊖ **moderate** [5,6]	Gynaecomastia was evaluated using the random-effects model because of heterogeneity (I^2 = 92%). Sensitivity analyses showed comparable results
Hot flashes Follow-up: median 1 to 6.3 years	**451 per 1000**	**104 per 1000** (86 to 122)	**RR 0.23** (0.19 to 0.27)	2774 (9 studies)	⊕⊕⊕⊖ **moderate** [5]	Hot flashes were evaluated using the fixed-effect model (I^2 = 0%)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
LHRH: Luteinising hormone-releasing hormone; **CI:** Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for study limitations (-1): high risk of bias: 'allocation concealment' (Tyrrell 2006); unclear risk of bias: 'random sequence generation' (Study 0301; Study 0302; Study 0303; Study 306; Study 307); 'allocation concealment' (Study 0301; Study 0302; Study 0303; Study 306; Study 307); 'blinding of participants and personnel' (all included studies); 'other bias' (all included studies).

[2]Downgraded for study limitations (-1): high risk of bias: 'blinding of participants and personnel' (all included studies); 'blinding of outcome assessment' (all included studies); 'incomplete outcome data' (Sciarra 2004a; Study 0301; Study 0302; Study 0303); 'selective reporting' (Sciarra 2004a); unclear risk of bias: 'random sequence generation' (all included studies); 'allocation concealment' (all included studies); 'other bias' (all included studies).

[3]Downgraded for study limitations (-1): high risk of bias: 'blinding of participants and personnel' (all included studies); 'blinding of outcome assessment' (all included studies); 'incomplete outcome data' (Study 0301; Study 0302; Study 0303); unclear risk of bias: 'random sequence generation' (all included studies); 'allocation concealment' (all included studies); 'other bias' (all included studies).

[4]Downgraded for study limitations (-1): high risk of bias: 'allocation concealment' (Tyrrell 2006); 'blinding of participants and personnel' (Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006); 'blinding of outcome assessment' (Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006); 'incomplete outcome data' (Study 0301; Study 0302; Study 0303); unclear risk of bias: 'random sequence generation' (Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307); 'allocation concealment' (Sieber 2004; Smith 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307); 'blinding of participants and personnel' (Smith 2004); 'blinding of outcome assessment' (Smith 2004); 'other bias' (all included studies).

[5]Downgraded for study limitations (-1): high risk of bias: 'allocation concealment' (Tyrrell 2006); 'blinding of participants and personnel' (Boccon-Gibod 1997; Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006); 'blinding of outcome assessment' (Boccon-Gibod 1997; Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006); 'incomplete outcome data' (Study 0301; Study 0302; Study 0303); unclear risk of bias: 'random sequence generation' (Boccon-Gibod 1997; Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307); 'allocation concealment' (Sieber 2004; Smith 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307); 'blinding of participants and personnel' (Smith 2004); 'blinding of outcome assessment' (Smith 2004); 'other bias' (all included studies).

[6]Heterogeneity was present but might be explained by subgroup or sensitivity analyses (see Effects of interventions; Quality of the evidence); therefore we did not downgrade for inconsistency.

BACKGROUND

Description of the condition

Prostate cancer is a frequently occurring tumour that leads to 85,200 cancer deaths per year in Europe (Boyle 2005). Worldwide, tumours of this type are associated with significant morbidity and are among the top six most lethal cancers (Eheman 2012; GLOBOCAN 2012); therefore, optimising therapy for prostate cancer is crucial.

Prostate cancer is usually classified as localised disease that is limited to the prostate gland (localised, stage T1-2, N0, M0) or more advanced disease that has spread locally outside the prostate gland (locally advanced, stage T3-4, N0, M0), disseminated to regional lymph nodes (local to regionally advanced, stage T1-4, N1, M0) or metastasised to bones and/or to other areas (advanced, stage T1-4, N0-1, M1). Localised and locally advanced prostate cancers are amenable to curative treatment. However, currently no curative therapy is known for patients at local to regionally advanced and advanced stages of prostate cancer. Androgen suppression therapy is usually recommended to treat patients at this stage of the disease (ASCO 2007; EAU 2013).

Description of the intervention

Several different approaches to androgen suppression monotherapy can be used at advanced stages of prostate cancer, including oestrogens, bilateral orchiectomy, luteinising hormone–releasing hormone (LHRH) agonists, LHRH antagonists, antiandrogens (non-steroidal antiandrogens and steroidal antiandrogens) and 5-alpha reductase inhibitors.

Oestrogens were among the first drugs used to treat patients at advanced stages of prostate cancer. They act through negative hormonal feedback. However, their side effects, even at low doses, are significantly greater than those observed with surgical castration. Therefore, their use is no longer recommended under current guidelines (ASCO 2007; EAU 2013).

Surgical castration removes the source of testicular androgen production and can be performed totally (bilateral orchiectomy) or by a subcapsular technique (preservation of tunica albuginea and epididymis). This intervention has been effectively used for decades, and current guidelines still consider it to be the 'gold standard' (EAU 2013). However, it is irreversible and might cause psychological distress.

LHRH agonists (e.g. leuprorelin, goserelin, buserelin, triptorelin) have been found to be as effective as surgical castration via orchiectomy, and no difference in overall survival has been reported among the different LHRH agonists (Seidenfeld 2000). These medications are recommended as standard initial treatment options for advanced stages of prostate cancer (ASCO 2007; EAU 2013).

LHRH antagonists are newer agents. They block hormonal effects at the pituitary gland. Whether they provide advantages over LHRH agonists has not yet been determined (EAU 2013).

Antiandrogens are classified as non-steroidal (e.g. bicalutamide, flutamide, nilutamide) or steroidal antiandrogens (e.g. cyproterone acetate). Non-steroidal antiandrogens are mentioned in current guidelines as an alternative to medical or surgical castration in selected patients with non-metastatic prostate cancer (ASCO 2007; EAU 2013).

5-alpha reductase inhibitors also have antiandrogenic activity. This form of androgen manipulation has a potential role in prevention and treatment of prostate cancer (Azzouni 2012). Antiandrogens combined with 5-alpha reductase inhibitors for the treatment of biochemical disease recurrence after local therapy might be a therapeutic option (EAU 2013), but discussions on this topic are still controversial.

Oestrogens, LHRH antagonists, steroidal antiandrogens and 5-alpha reductase inhibitors are not part of this review and will not be discussed further. This systematic review focuses on the effectiveness of non-steroidal antiandrogens compared with LHRH agonists or surgical castration.

How the intervention might work

All treatment modalities that reduce androgen activity are referred to as androgen suppression therapy (EAU 2013). Androgen suppression therapy is usually recommended for patients with advanced prostate cancer to slow down progression and to increase the chance of survival (EAU 2013; Schmitt 1999). The androgen testosterone is essential for the growth of prostate cells; suppression of testosterone is therefore important in prostate cancer therapy. Testosterone is produced mainly in the testes but also to a lesser extent in the adrenal glands. The release of testosterone is regulated by the hypothalamic-pituitary-gonadal axis. Hypothalamic LHRH stimulates the pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the testes to secrete testosterone. Testosterone is then converted to oestrogens, which contribute to negative feedback control of hypothalamic hormone secretion. This negative feedback in turn diminishes the secretion of LH, thereby reducing testicular testosterone production (Gibbs 1996; Huggins 2002).

Antiandrogens compete with testosterone and dihydrotestosterone at the receptor level in the prostate cell nucleus and thereby inhibit prostate cancer cell growth. Because non-steroidal antiandrogens do not affect the pituitary gland and do not block the negative feedback mechanism, testosterone levels are not affected, but testosterone is still converted to oestrogens. This provides potential benefits for sexual function, but it also stimulates gynaecomastia (Iversen 2002).

Bilateral orchiectomy and LHRH agonists reduce testosterone to a castration level and have been used for decades. Surgical castration removes the source of testicular androgen production, which leads to a rapid reduction in testosterone. LHRH agonists stimulate the pituitary gland continuously, which leads to desensitisation of LH and testosterone secretion (medical castration). However, before the hormonal receptors are downregulated, LHRH agonists cause an initial stimulation of LH, FSH and thereby testosterone. This process is called 'testosterone flare' and can lead to potential exacerbations of clinical symptoms in metastatic disease by stimulating the growth of prostate cancer cells. Premedication with antiandrogens can be used for a few days before the start of LHRH agonist therapy to prevent flares (Gibbs 1996). However, castration therapies do not affect adrenal secretion of testosterone.

Why it is important to do this review

A systematic review published in 2000 concluded that survival rates might be lower with non-steroidal antiandrogens than with medical or surgical castration (Seidenfeld 1999; Seidenfeld 2000). However, no update of the review has been performed, and no other current evaluation of this comparison has been published. Clinical practice guidelines on androgen suppression monotherapy for advanced stages of prostate cancer support antiandrogens for selected and motivated patients with low prostate-specific antigen (PSA) (EAU 2013). Non-steroidal antiandrogens have been argued to have fewer side effects (e.g. hot flashes), and they do not affect testosterone levels. This might offer potential benefits for sexual function. However, non-steroidal antiandrogens have other side effects; testosterone is converted to oestrogens, and this stimulates gynaecomastia (Iversen 2002). Additionally, effectiveness has been challenged, and the debate concerning the value of different treatment options, especially the comparison between non-steroidal antiandrogens and medical or surgical castration, continues. As current guidelines are based upon older literature, there is a need to revisit the topic to update our understanding in light of more recent data.

OBJECTIVES

To assess the effects of non-steroidal antiandrogen monotherapy compared with luteinising hormone–releasing hormone agonists or surgical castration monotherapy for treating advanced stages of prostate cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We reviewed parallel-group randomised controlled trials comparing non-steroidal antiandrogens versus castration (surgical or medical) for advanced stages of prostate cancer.

Types of participants

Studies recruiting men at advanced stages of prostate cancer who had not received prior androgen suppression therapy were eligible. We included studies evaluating men with prostate cancer that had spread locally outside the prostate gland (locally advanced, T3-4, N0, M0), to regional lymph nodes (local to regionally advanced, T1-4, N1, M0), to the bones or to other areas (advanced, T1-4, N0-1, M1), or those who had recurrent disease after local therapy. No exclusions were based on age or ethnicity.

Types of interventions

For androgen suppression monotherapies, the following comparison was considered: non-steroidal antiandrogen monotherapy versus medical or surgical castration monotherapy.

Medical castration and surgical castration are two different treatment options that are thought to be equally effective (EAU 2013; Seidenfeld 2000). For this reason, we decided to include randomised trials even if they did not differentiate between medical and surgical castration.

We defined medical castration monotherapy as androgen suppression therapy using LHRH agonists (e.g. leuprorelin, goserelin, buserelin, triptorelin).

Bilateral surgical castration included total and subcapsular techniques.

LHRH antagonists, oestrogen and steroidal antiandrogen monotherapies were not a topic of this review, and trials investigating these treatment options were not included in our analysis (see Description of the intervention). This review did not consider maximal androgen blockade (combination therapy of antiandrogens with medical or surgical castration). However, we did not exclude trials that used antiandrogens as short-term flare protection for up to four weeks after medical castration (see Description of the intervention).

Types of outcome measures

Primary outcomes

Overall survival.

Secondary outcomes

1. Cancer-specific survival (we assessed data for cancer-specific mortality because data for cancer-specific survival were not available).
2. Treatment discontinuation due to adverse events.
3. Clinical progression (time from random assignment to progression; determined by an increase in prostatic dimension, appearance of new or increase in existing bone or extraskeletal metastases confirmed by imaging or physical examination).
4. Biochemical progression (time from random assignment to progression; determined by an increase of more than 25% in serum PSA concentration from the nadir value on two determinations).
5. Treatment failure (determined by death; disease progression, i.e. an increase in prostatic dimensions, appearance of new or increase in existing bone or extraskeletal metastases confirmed by imaging or physical examination; addition of other systemic therapies for prostate cancer; loss to follow-up; refusal to begin or continue with randomly assigned therapy; or discontinuation due to adverse events or for other reasons).
6. Adverse events, such as breast pain, pelvic pain, bone pain, back pain, headache, abdominal pain, general pain, gynaecomastia, constipation, diarrhoea, vomiting, cardiovascular events, hypertension, loss of sexual interest, asthenia, insomnia, hot flashes, night sweats, anaemia, hepatic enzyme increase, rash, pruritus, dyspnoea, infection, pharyngitis, arthritis, sinusitis, urinary tract infection, dizziness, haemorrhage, haematuria, nocturia, urinary frequency, urinary retention, oedema, anorexia, gastrointestinal disorders, loss of sexual function and lethargy, as well as serious adverse events (defined as adverse events causing death or events that are life threatening, require inpatient hospitalisation, result in persistent or significant disability/incapacity or require intervention to prevent permanent impairment or damage).

Search methods for identification of studies

Both electronic and manual searches were conducted.

Electronic searches

We searched the following electronic databases on 26 February 2013 and updated the search on 23 December 2013: Cochrane Prostatic Diseases and Urologic Cancers Group Specialized Register (PROSTATE; 23 December 2013); Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 12 (part of *The Cochrane Library*); Ovid MEDLINE, In-Process & Other Non-Indexed Citations, Daily (1946 to 23 December 2013); EMBASE via DIMDI (www.dimdi.de/static/en/index.html; 1947 to 23 December 2013); and Web of Science with Conference Proceedings (Thomson Reuters Web of Knowledge; 1945 to 23 December 2013). The search strategy was adapted for each electronic database. For the search strategies used by the review authors, see Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5. No language restriction was applied.

Searching other resources

The reference lists of all identified articles were screened to identify additional potentially relevant citations. We contacted selected experts in the field as well as manufacturers of non-steroidal androgen suppression drugs to request information on unpublished studies. We searched all other resources on 26 February 2013 and updated the search on 23 December 2013.

We performed an electronic search of abstracts from three major conferences: the American Society of Clinical Oncology (ASCO; jco.ascopubs.org; 2004 to 23 December 2013), the European Association of Urology (EAU; www.uroweb.org; 2004 to 23 December 2013) and the American Urological Association (AUA; www.jurology.com/; 2008 to 23 December 2013). For keywords used to search meeting abstracts, see Appendix 6.

Additionally, we searched three trial registries for completed or ongoing studies: Current Controlled Trials (ISRCTN; www.controlled-trials.com/; last searched 23 December 2013), 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 23 December 2013). For keywords used to search trial registries, see Appendix 7.

Data collection and analysis

Selection of studies

For the initial search, one review author (FK) screened all titles and abstracts of records identified by the search for relevance. Only records that were clearly irrelevant were excluded at this stage (e.g. animal/in vitro research and testing). Next, two review authors (FK, HG) independently examined the full-text reports of the remaining records, identified relevant studies and assessed the eligibility of studies for inclusion. We resolved disagreements regarding study eligibility through discussion and consensus or, if necessary, with the help of a third review author (JM). We recorded details of excluded studies and the reasons for exclusion. One review author (FK) performed the search update, which included only records published since the time of our initial search (between 26 February 2013 and 23 December 2013). Few records were published since the time of our last search, and we retrieved no reference that fitted our inclusion criteria. Therefore we performed no full-text screening.

Data extraction and management

In addition to details related to the quality (risk of bias) of the included studies, we extracted the following types of data.

1. Study characteristics: population characteristics, setting, detailed nature of the intervention, detailed nature of the comparator and outcomes, place of publication and date of publication. The key purpose of collecting these data was to explore the clinical heterogeneity of the included studies.
2. Results of the included studies: We extracted the results with respect to each of the main outcomes (see Types of outcome measures). We recorded the reasons why an included study did not contribute data on a particular outcome and considered the possibilities of selective reporting of the results of particular outcomes.

Two review authors (FK, HG) independently extracted data using a data extraction form based on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). The review authors resolved disagreements by consensus or through discussion with a third review author (JM). In addition, when necessary, we contacted the original investigators.

Assessment of risk of bias in included studies

Two review authors (FK, HG) independently assessed all studies using our data extraction form and followed the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) to assess the following domains as low risk of bias, unclear risk of bias or high risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.

We reviewed the assessments and discussed inconsistencies in the interpretation of information given and their significance for the selected studies. We resolved disagreements through discussion with a third review author (JM). In assessing the risk of bias, we did not automatically exclude any study as a result of an unclear or high risk of bias rating.

Measures of treatment effect

We analysed extracted data using Review Manager 5 (Review Manager 2012).

We extracted hazard ratios (HRs) with 95% confidence intervals (CIs) for time-to-event outcomes. If HRs were not given, we used indirect estimation methods (described by Parmar et al (Parmar 1998) and Williamson et al (Williamson 2002)) to calculate them. If we were unable to extract these data from the study reports or to receive the necessary information from the primary investigators, we alternatively used the proportions of participants with the respective outcomes measured at certain time points to calculate risk ratios (RRs) with 95% CIs.

We expressed results for binary outcomes as RRs with 95% CIs as measures of uncertainty.

Unit of analysis issues

Only randomised controlled trials were included; cluster-randomised or cross-over trials were excluded.

Dealing with missing data

We contacted the original investigators to request missing data. We analysed the data using an intention-to-treat (ITT) analysis. If we did not receive all required data, and if a substantial departure of people assigned to the intervention or control group was noted, we conducted best-case and worst-case scenarios, as proposed by Gamble 2005 and described briefly in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 16.2.2; Higgins 2011c), and presented the results as sensitivity analyses.

Assessment of heterogeneity

Statistical heterogeneity was examined by using the I^2 statistic (Higgins 2002; Higgins 2003). Our definitions of the thresholds for interpretation of I^2 are consistent with the definitions presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2008): 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% substantial heterogeneity; 75% to 100% considerable heterogeneity. Clinical heterogeneity was examined by performing subgroup analyses. For details, see Subgroup analysis and investigation of heterogeneity section.

Assessment of reporting biases

To minimise the impact of possible publication bias, we conducted electronic and manual searches of multiple databases, without imposing a language restriction, to identify published and unpublished studies. We performed a funnel plot asymmetry analysis to assess possible publication bias.

Data synthesis

For data synthesis, we used Review Manager 5 (Review Manager 2012), as provided by The Cochrane Collaboration. Meta-analyses of the data from all contributing studies were conducted using a fixed-effect model if I^2 was less than 50%, and using a random-effects model for substantial or considerable heterogeneity if I^2 was greater than or equal to 50% (≥ 50%). We reported results from both models.

Subgroup analysis and investigation of heterogeneity

We explored the following potential sources of heterogeneity using subgroup analyses.

1. Disease stage: non-metastatic (M0) versus metastatic (M1) disease.
2. Dose of non-steroidal antiandrogen (e.g. bicalutamide 50 mg vs bicalutamide 150 mg).

We planned in advance to also evaluate a subgroup analysis regarding the effects of different control interventions (medical vs surgical castration). However, the largest included studies (Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) permitted both control interventions but did not report results of subgroups. This involves 925 of the 1288 participants randomly assigned to the control groups (72%). We decided therefore not to evaluate subgroup analyses regarding the effects of different control interventions.

A current guideline mentioned that non-steroidal antiandrogen monotherapy using bicalutamide at a dose of 150 mg daily for non-metastatic prostate cancer might be an alternative to castration for selected patients (EAU 2013). A narrative review suggested that non-steroidal antiandrogen monotherapy might be an established treatment option in patients with prostate cancer, but an unexplained trend towards decreased survival should prohibit their uncritical use (Wirth 2007). Therefore for the primary outcome of overall survival, we performed post hoc subgroup analyses regarding disease stage (non-metastatic or metastatic disease) in combination with different doses of non-steroidal antiandrogens (bicalutamide 50, 150, 450 or 600 mg daily; Analysis 1.1).

In accordance with the recommendation of Higgins et al, we did not perform subgroup analyses if only a few studies were included in the meta-analysis (Higgins 2004).

Sensitivity analysis

We performed sensitivity analyses to evaluate the effects of data imputations for best-case and worst-case scenarios (Analysis 1.5; Analysis 1.7; Analysis 1.9). Additionally, we investigated the robustness of results through sensitivity analyses when heterogeneity was substantial or considerable (I^2 50% to 90% or 75% to 100%, respectively) by excluding smaller studies from the meta-analysis (Analysis 1.1; Analysis 1.2; Analysis 1.4; Analysis 1.8; Analysis 1.17).

Summary of findings table

We summarised the findings in a summary of findings table (Summary of findings for the main comparison) in accordance with GRADE methodology (Guyatt 2011; Schünemann 2011).

RESULTS

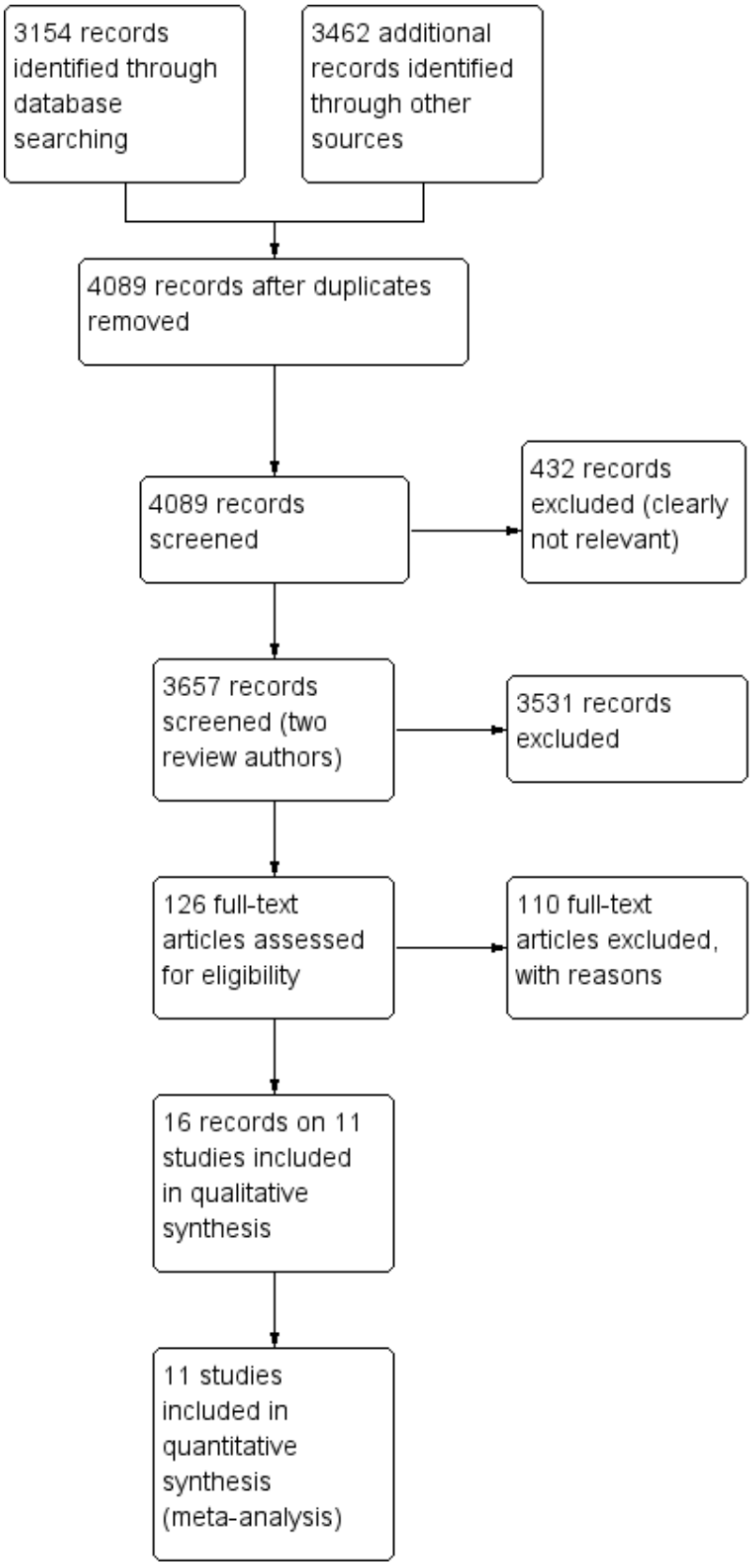
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

For details of the search results, see Figure 1. A total of 16 articles on 11 studies were finally included in the review. None of these studies was available in abstract form only. All included studies were published in English. We did not identify ongoing studies. We also did not identify further relevant studies through the search update.

Figure 1. Study flow diagram (searched 26 February 2013; updated 23 December 2013).



Included studies

For details on the included studies, see Characteristics of included studies.

We included 11 studies that randomly assigned 3060 participants. All of the included studies fit our inclusion criteria and provided information on study population demographics. The type of non-steroidal antiandrogen and the doses given varied among the included studies (flutamide 250 mg three times daily: Boccon-Gibod 1997; bicalutamide 50 mg daily: Study 0301, Study 0302 and Study 0303; bicalutamide 150 mg daily: Dockery 2009, Sciarra 2004a, Sieber 2004, Smith 2004, Study 306 and Study 307; bicalutamide 450 mg daily and 600 mg daily: Tyrrell 2006). Two studies (Boccon-Gibod 1997; Study 0301) used surgical castration, and four studies used medical castration (goserelin 10.8 mg three times monthly: Dockery 2009; triptorelin 3.75 mg monthly: Sciarra 2004a; leuprorelin 22.5 mg every three months: Smith 2004; drug not specified: Sieber 2004). In five studies, participants could choose between medical (using goserelin) and surgical castration (Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006). In two studies (Dockery 2009; Smith 2004), participants randomly assigned to castration also received a non-steroidal antiandrogen for two (Dockery 2009) or four weeks (Smith 2004) to prevent a flare reaction. Four studies included participants with non-metastatic prostate cancer (Dockery 2009; Sciarra 2004a; Sieber 2004; Smith 2004), and four studies included participants with metastatic prostate cancer (Boccon-Gibod 1997; Study 0301; Study 0302; Study 0303). Three studies included participants with non-metastatic or metastatic disease (Study 306; Study 307; Tyrrell 2006). The follow-up period of participants ranged from six months (Dockery 2009) to six years (Study 306; Study 307).

In seven studies (Boccon-Gibod 1997; Sieber 2004; Smith 2004; Study 0303; Study 306; Study 307; Tyrrell 2006), the trial authors reported possible conflicts of interest. In three studies (Sciarra 2004a; Study 0301; Study 0302), no conflicts of interest were declared. The authors of only one study (Dockery 2009) reported that they received an educational grant from the sponsor; however, they claimed that this sponsor had no role in any aspect of the study plan, protocol or analysis; data interpretation; or writing of the manuscript.

Excluded studies

Figure 1 and the table titled Characteristics of excluded studies provide information on the numbers of and reasons for exclusions from the review.

Risk of bias in included studies

We conducted a funnel plot asymmetry analysis for our primary outcome to assess potential publication bias (Figure 2). We found no indication of bias. However, the sensitivity of this analysis to assess publication bias might be low because fewer than 10 studies were included in the meta-analyses performed. All studies were published in peer-reviewed publications. For details on risk of bias, see Figure 3 and the table titled Characteristics of included studies.

Figure 2. Funnel plot: Outcome: 1.1 Overall survival, 1.1.1 Total.

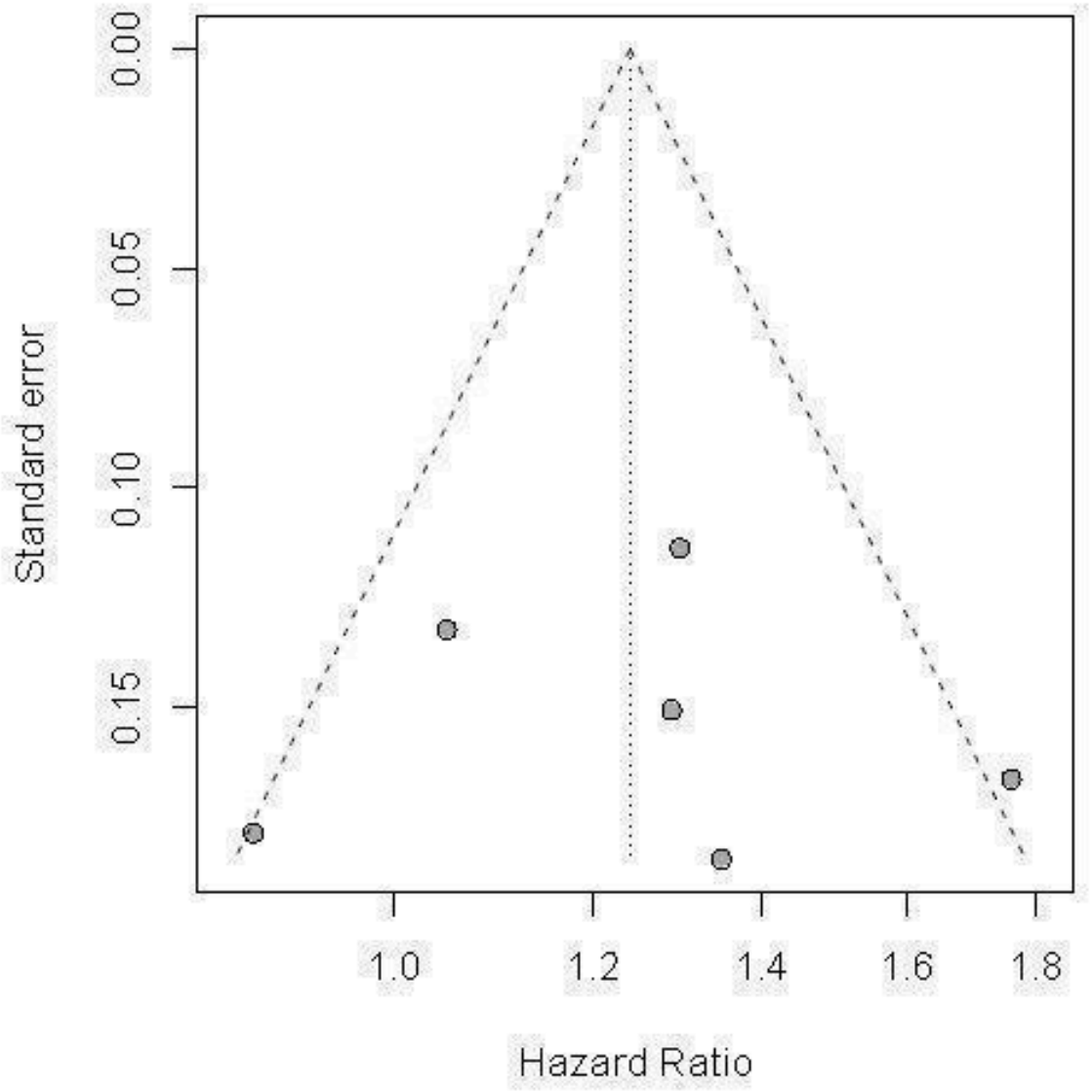


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

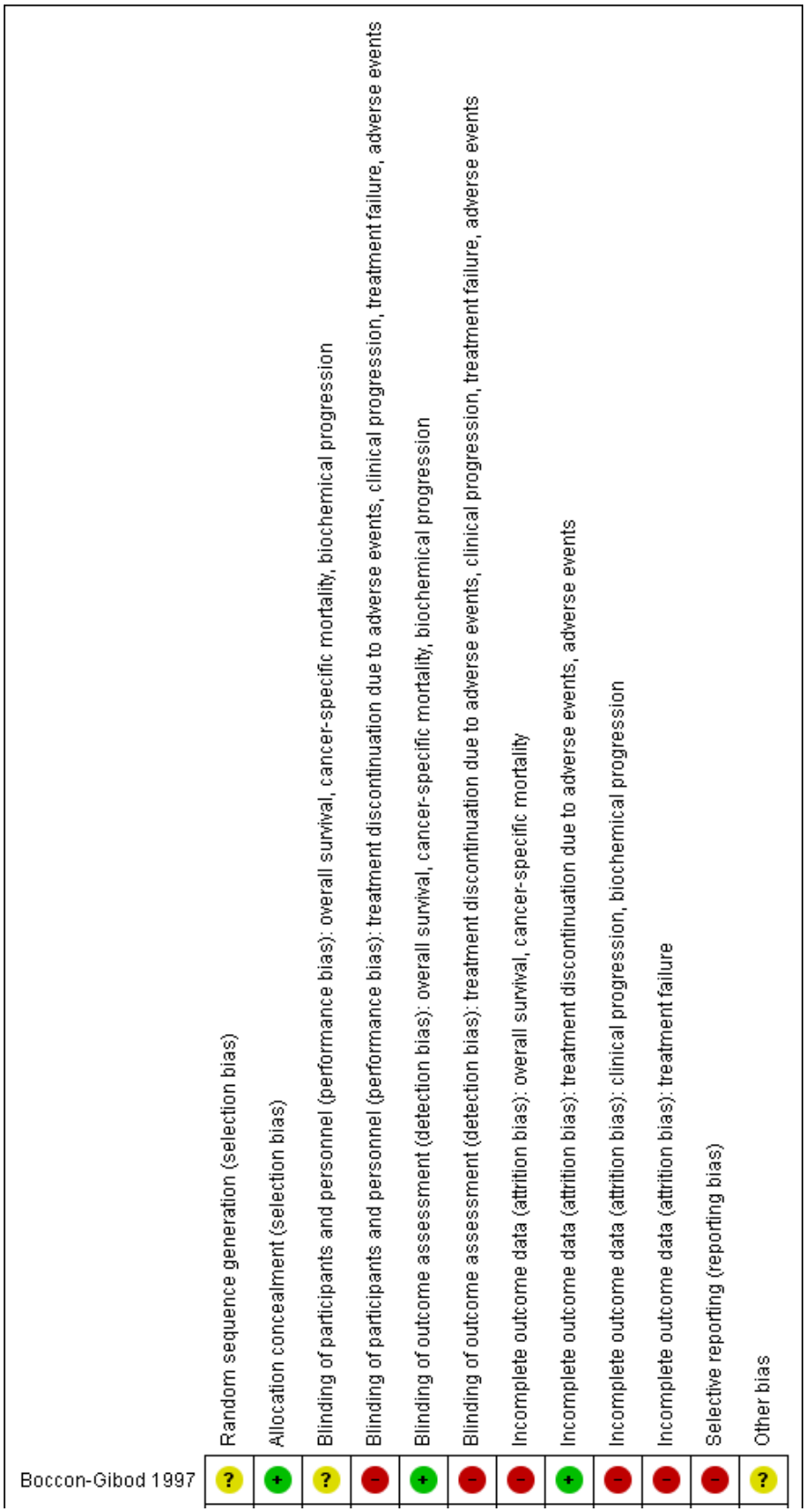
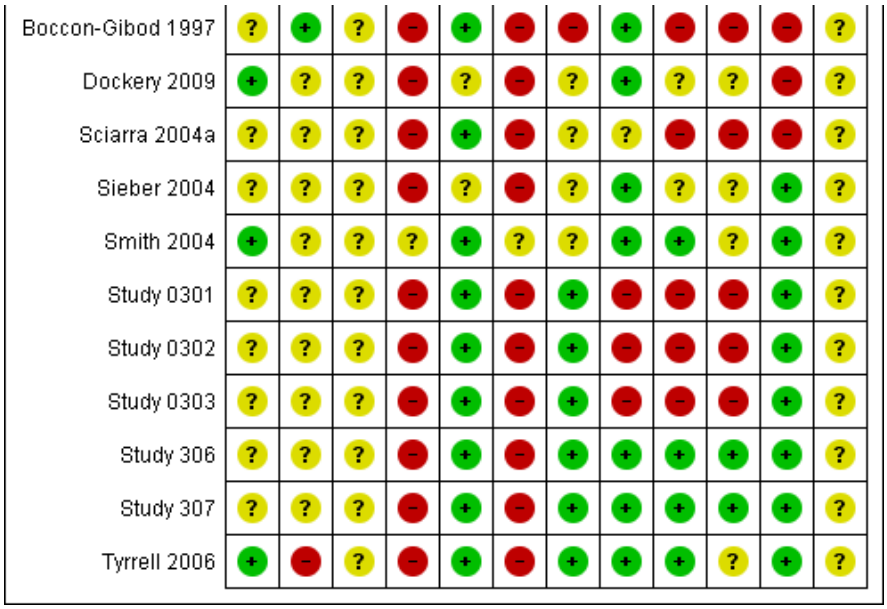


Figure 3. (Continued)



Allocation

Random sequence generation

Three studies (Dockery 2009; Smith 2004; Tyrrell 2006) reported adequate sequence generation (low risk of bias). In all of the other studies, information on sequence generation was not reported or was insufficient to permit a judgement (unclear risk of bias).

Allocation concealment

Only one study (Boccon-Gibod 1997) provided information indicating adequate allocation concealment using central random assignment (low risk of bias). One study (Tyrrell 2006) contained a high risk of bias because participant numbers were allocated sequentially as men entered the trial. No other studies reported information on allocation concealment (unclear risk of bias).

Blinding

We assessed risk of bias for blinding of participants and personnel and for blinding of outcome assessment on an outcome-specific basis.

Blinding of participants and personnel

All included studies were open randomised trials that did not involve blinding of participants and/or personnel. Blinding was not feasible because of differences in the interventions, which included surgical therapy (orchiectomy), medical castration by injection (LHRH agonists) and oral medications (non-steroidal antiandrogens).

Overall survival, cancer-specific mortality, biochemical progression

We were uncertain to what extent outcomes such as overall survival, cancer-specific mortality and biochemical progression were influenced by lack of blinding. We judged therefore that risk of bias regarding these outcomes for most of the included studies was unclear (Boccon-Gibod 1997; Sciarra 2004a; Smith 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006). Two studies (Dockery 2009; Sieber 2004) did not assess these outcomes (unclear risk of bias).

Clinical progression, treatment failure, treatment discontinuation due to adverse events, adverse events

Outcomes such as clinical progression, treatment failure, treatment discontinuation due to adverse events and adverse events could be influenced by lack of blinding. These outcomes therefore present a high risk of bias in most of the included studies (Boccon-Gibod 1997; Dockery 2009; Sciarra 2004a; Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006). Risk of bias was unclear for one study (Smith 2004). The original investigators responded that "subjects and study investigators were blinded to treatment assignment." However, the method of blinding bicalutamide 150 mg by mouth daily for 12 months compared with leuprorelin three-month depot (22.5 mg intramuscularly every three months) for treatment discontinuation due to adverse events and adverse events remained unclear (unclear risk of bias).

Blinding of outcome assessment

Overall survival, cancer-specific mortality, biochemical progression

In all studies, no blinding was provided or blinding was not reported. However, we judged that it was not likely that outcome assessments for overall survival, cancer-specific mortality and biochemical progression were influenced by lack of blinding (low risk of bias). Two studies (Dockery 2009; Sieber 2004) did not assess these outcomes (unclear risk of bias).

Clinical progression, treatment failure, treatment discontinuation due to adverse events, adverse events

We judged that for most studies (Boccon-Gibod 1997; Dockery 2009; Sciarra 2004a; Sieber 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) it was likely that outcome assessments of clinical progression, treatment failure, treatment discontinuation due to adverse events and adverse events were influenced by lack of blinding. For one study (Smith 2004), the original investigators responded that blinding was performed

("subjects and study investigators were blinded to treatment assignment"). However, blinding of outcome assessments for treatment discontinuation due to adverse events and adverse events remained unclear (unclear risk of bias).

Incomplete outcome data

We assessed risk of bias for incomplete outcome data on an outcome-specific basis.

Overall survival, cancer-specific mortality

Five studies (Study 0301; Study 0302; Study 0303; Study 306; Study 307) were judged to report adequate information leading to low risk of attrition bias. In the study published by Tyrrell et al, the proportion of missing outcomes might not have had a clinically relevant impact on the intervention effect estimate, leading to low risk of bias (Tyrrell 2006). Boccon-Gibod et al reported data on overall survival incompletely (Boccon-Gibod 1997). Therefore risk of bias regarding overall survival was high. Four studies (Dockery 2009; Sciarra 2004a; Sieber 2004; Smith 2004) did not measure/report these outcomes (unclear risk of bias).

Treatment discontinuation due to adverse events, adverse events

Three studies (Boccon-Gibod 1997; Study 306; Study 307) were judged to report adequate information leading to low risk of attrition bias. In four studies, the proportion of missing outcomes might not have had a clinically relevant impact on the intervention effect estimate, leading to low risk of bias (Dockery 2009; Sieber 2004; Smith 2004; Tyrrell 2006). One study (Sciarra 2004a) did not measure/report these outcomes (unclear risk of bias). Three studies (Study 0301; Study 0302; Study 0303) present high risk of attrition bias. These studies reported data on an 'as-treated' analysis with a high rate of dropout from the intervention assigned at randomisation.

Clinical progression, biochemical progression

Two studies (Study 306; Study 307) were judged to report adequate information leading to low risk of attrition bias. Five studies (Boccon-Gibod 1997; Sciarra 2004a; Study 0301; Study 0302; Study 0303) present high risk of attrition bias. These studies reported data on an 'as-treated' analysis with a high rate of dropout from the intervention group. Two studies (Dockery 2009; Sieber 2004) did not measure/report these outcomes (unclear risk of bias). In two studies, the proportion of missing outcomes might not have had a clinically relevant impact on the intervention effect estimate, leading to low risk of bias (Smith 2004; Tyrrell 2006).

Treatment failure

Two studies (Study 306; Study 307) were judged to report adequate information, leading to low risk of attrition bias. Four studies (Boccon-Gibod 1997; Study 0301; Study 0302; Study 0303) were judged as having high risk of attrition bias. These studies reported data on an 'as-treated' analysis with a high rate of dropout from the intervention group. One study (Sciarra 2004a) provided an outcome definition for treatment failure in the report but did not report any data for this outcome (high risk of bias). Four studies (Dockery 2009; Sieber 2004; Smith 2004; Tyrrell 2006) did not measure/report this outcome (unclear risk of bias).

Selective reporting

Three studies (Boccon-Gibod 1997; Dockery 2009; Sciarra 2004a) had a high risk of reporting bias. Boccon-Gibod et al reported incomplete data on overall survival at 69 months. They reported only "identical" survival in both groups, which was irrespective of the second-line treatment given (Boccon-Gibod 1997). Thus, their study could not be entered into the meta-analysis. Dockery et al reported data on treatment discontinuation due to adverse events but did not report any data concerning individual adverse events (Dockery 2009), and Sciarra et al did not report data on adverse events, treatment discontinuation due to adverse events or treatment failure (Sciarra 2004a). We expected that these outcomes would be reported for such studies. We did not identify study protocols with adequate information on primary or secondary outcomes for all other studies; however, published reports included all of the expected outcomes.

Other potential sources of bias

In seven studies (Boccon-Gibod 1997; Sieber 2004; Smith 2004; Study 0303; Study 306; Study 307; Tyrrell 2006), the trial authors reported possible conflicts of interest. In three studies (Sciarra 2004a; Study 0301; Study 0302), no conflicts of interest were declared. The authors of only one study (Dockery 2009) reported that they received an educational grant from the sponsor; however, they claimed that this sponsor had no role in any aspect of the study plan, protocol or analysis; data interpretation; or writing of the manuscript. Potential conflicts of interest may exist in any study, but we believe that in itself, this is not a reason for high risk of bias. Therefore, the risk of bias remains unclear for all studies.

Effects of interventions

See: **Summary of findings for the main comparison** Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy for advanced prostate cancer

Overall survival

Of the 11 included studies, six studies (Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) involving 2712 randomly assigned participants measured overall survival. The quality of evidence for this outcome was moderate (Summary of findings for the main comparison). One study (Boccon-Gibod 1997) reported incomplete data and therefore could not be entered into the meta-analysis. Overall survival was significantly decreased when non-steroidal antiandrogens were used as opposed to castration (HR 1.24, 95% CI 1.10 to 1.40, fixed-effect model; not shown). A random-effects model for heterogeneity (I^2 = 51%) still revealed a significant result (HR 1.24, 95% CI 1.05 to 1.48, 2712 participants; Analysis 1.1). We performed a sensitivity analysis because heterogeneity was noted (I^2 = 51%). After exclusion of the smallest study (Tyrrell 2006), results still showed significant differences with lower heterogeneity (HR 1.31, 95% CI 1.12 to 1.53, I^2 = 33%; not shown).

Subgroup: disease stage

A meta-analysis of three studies (Study 306; Study 307; Tyrrell 2006) on non-metastatic disease showed no significant difference in overall survival between non-steroidal antiandrogens and castration (HR 1.00, 95% CI 0.79 to 1.26, 608 participants; Analysis 1.1). However, a meta-analysis of six studies (Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006)

showed that overall survival was significantly decreased with non-steroidal antiandrogens in participants with metastatic disease when compared with castration (HR 1.34, 95% CI 1.14 to 1.57, 2103 participants; Analysis 1.1).

Subgroup: dose of non-steroidal antiandrogen

The non-steroidal antiandrogen bicalutamide given in doses of 50 mg daily or 150 mg daily significantly decreased overall survival when compared with castration using the fixed-effect model (bicalutamide 50 mg daily: HR 1.45, 95% CI 1.20 to 1.74, 1196 participants; bicalutamide 150 mg daily: HR 1.19, 95% CI 1.00 to 1.41, 1288 participants; not shown). However, the random-effects model showed that bicalutamide 50 mg daily still significantly decreased overall survival (HR 1.45, 95% CI 1.19 to 1.75, 1196 participants), although the effect was compatible with benefit or harm when bicalutamide 150 mg daily was used (HR 1.18, 95% CI 0.96 to 1.45, 1288 participants; Analysis 1.1). No significant difference was noted between high-dose bicalutamide (450 mg daily or 600 mg daily) and castration (HR 0.88, 95% CI 0.62 to 1.25, 228 participants; Analysis 1.1).

Subgroup (post hoc analysis): non-metastatic disease and dose of non-steroidal antiandrogen

No significant difference was found between non-steroidal antiandrogens (bicalutamide 150 mg daily compared with 450 mg daily or 600 mg daily) and castration in participants with non-metastatic prostate cancer (Analysis 1.1).

Subgroup (post hoc analysis): metastatic disease and dose of non-steroidal antiandrogen

The non-steroidal antiandrogen bicalutamide given in doses of 50 mg daily or 150 mg daily decreased overall survival in participants with metastatic disease when compared with castration (bicalutamide 50 mg daily: HR 1.45, 95% CI 1.19 to 1.75, 1196 participants; bicalutamide 150 mg daily: HR 1.30, 95% CI 1.04 to 1.63, 808 participants; Analysis 1.1). No significant difference was found between high-dose bicalutamide (450 mg daily or 600 mg daily) and castration in participants with metastatic disease (HR 0.91, 95% CI 0.56 to 1.48, 99 participants; Analysis 1.1).

Cancer-specific mortality

We presented data for cancer-specific mortality in place of cancer-specific survival based on availability of data in the included studies. Three studies (Study 0301; Study 0302; Tyrrell 2006) involving 904 randomly assigned participants provided data on cancer-specific mortality. Non-steroidal antiandrogens probably increased cancer-specific mortality when compared with castration (RR 1.26, 95% CI 1.00 to 1.59, fixed-effect model; not shown). However, this difference was no longer statistically significant when a random-effects model was applied as the result of heterogeneity (I^2 = 67%, RR 1.32, 95% CI 0.86 to 2.05, 904 participants; Analysis 1.2). We performed a sensitivity analysis because heterogeneity was noted (I^2 = 67%). After the smallest study had been excluded (Tyrrell 2006), results were still comparable but heterogeneity was greater (RR 1.63, 95% CI 0.71 to 3.73, I^2 = 79%; not shown). The included studies reported cancer-specific mortality based on different follow-up periods (Study 0301 and Study 0302: after a minimum 12 months of follow-up; Tyrrell 2006: after a median of five years of follow-up). Analysis of the different follow-up periods showed that non-steroidal antiandrogens might increase cancer-specific mortality after a minimum of 12 months when compared with castration (RR 1.43, 95% CI 1.05 to 1.95, fixed-effect model; not shown). However, this difference was no longer significant after a random-effects model was applied because of heterogeneity (RR 1.63, 95% CI 0.71 to 3.73, 680 participants, I^2 = 79%; Analysis 1.2). We performed a sensitivity analysis because heterogeneity was present (I^2 = 79%). After the smaller of the two included studies had been excluded (Study 0302), results of Study 0301 showed a significant difference (RR 2.60, 95% CI 1.30 to 5.07; not shown). No difference was found between these therapies after a median of five years (RR 1.04, 95% CI 0.73 to 1.47, 224 participants; Analysis 1.2). The overall effect of non-steroidal antiandrogens on cancer-specific mortality and even more on cancer-specific survival therefore remains unclear.

Subgroup: disease stage

We did not perform subgroup analyses because very few studies were included for this outcome for which results were reported after different follow-up periods. The conduct and presentation of meta-analyses therefore did not seem appropriate.

Subgroup: dose of non-steroidal antiandrogen

We did not perform subgroup analyses because very few studies were included for this outcome for which results were reported after different follow-up periods. The conduct and presentation of meta-analyses therefore did not seem appropriate.

Treatment discontinuation due to adverse events

Eight studies (Boccon-Gibod 1997; Dockery 2009; Sieber 2004; Smith 2004; Study 0301; Study 0302; Study 0303; Tyrrell 2006) involving 1559 randomly assigned participants reported data on treatment discontinuation due to adverse events. Non-steroidal antiandrogens significantly increased the rate of withdrawal due to adverse events (RR 1.82, 95% CI 1.13 to 2.94, 1559 participants; Analysis 1.3).

Two studies (Study 306; Study 307) provided incomplete data on treatment discontinuation due to adverse events; thus, the data from these studies could not be included in the meta-analysis. The trial authors reported that after 6.3 years, 4.1% of participants with non-metastatic disease treated with bicalutamide (n = 314) were withdrawn; 1.3% of these withdrawals were due to breast pain and/or gynaecomastia (Study 306; Study 307). They reported no data for participants treated with castration. Two studies (Study 0301; Tyrrell 2006) did not specify the adverse events that led to discontinuation, and four studies (Sieber 2004; Study 0303; Study 306; Study 307) provided only partial information on adverse events. Smith et al reported that two participants in the leuprorelin group discontinued treatment early as the result of adverse events such as hot flashes and fatigue (Smith 2004). Additionally, treatment with bicalutamide was interrupted in one participant for three months because of elevated liver enzymes (Smith 2004). In the study conducted by Sieber et al, five of nine participants who withdrew from the study in the bicalutamide group discontinued treatment as the result of asthenia (Sieber 2004). In another study, four participants discontinued treatment because of adverse events; two participants withdrew because of impotence (one in each group for bicalutamide and castration) and two withdrew because of a skin reaction (both in the bicalutamide group) (Dockery 2009). In Study 0303, six participants discontinued treatment (three with rash and one with constipation), and

in Study 0302, three participants withdrew from the study (in the group treated with bicalutamide, one withdrew because of gynaecomastia and back pain; in the group treated with castration, one withdrew because of severe hot flashes). Boccon-Gibod et al reported that four participants discontinued therapy; two were suffering from nausea or vomiting, one reported diarrhoea and another showed an increase in hepatic enzymes before discontinuing therapy (Boccon-Gibod 1997).

Subgroup: disease stage

The subgroup analysis included seven studies: three studies (Dockery 2009; Sieber 2004; Smith 2004) including participants with non-metastatic disease, and four studies (Boccon-Gibod 1997; Study 0301; Study 0302; Study 0303) including participants with metastatic disease. No significant difference was found between non-steroidal antiandrogens and castration for participants with non-metastatic (RR 1.47, 95% CI 0.66 to 3.28, 194 participants) or metastatic disease (RR 1.39, 95% CI 0.54 to 3.54, 1141 participants; Analysis 1.3). Data reported by Tyrrell et al could not be included into this analysis because they were not reported for subgroups of participants on the basis of disease stage (Tyrrell 2006).

Subgroup: dose of non-steroidal antiandrogen

One study evaluated the non-steroidal antiandrogen flutamide 250 mg three times daily (Boccon-Gibod 1997), three studies evaluated the non-steroidal antiandrogen bicalutamide 50 mg daily (Study 0301; Study 0302; Study 0303), three studies evaluated bicalutamide 150 mg daily (Dockery 2009; Sieber 2004; Smith 2004) and one study evaluated bicalutamide 450 mg daily and 600 mg daily (Tyrrell 2006). No significant differences were found for bicalutamide 50 mg daily, bicalutamide 150 mg daily or flutamide 250 mg three times daily (Analysis 1.3). However, the numbers of treatment discontinuations due to adverse events were significantly increased when bicalutamide 450 mg daily was used (RR 2.66, 95% CI 1.17 to 6.01, 182 participants). No significant differences were found between bicalutamide 600 mg daily and castration (RR 2.45, 95% CI 0.95 to 6.31, 132 participants; Analysis 1.3).

Clinical progression

Seven studies (Sciarra 2004a; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) involving 2591 randomly assigned participants were included in the meta-analyses for clinical progression. For the definitions of clinical progression, see the Characteristics of included studies table. Two studies (Boccon-Gibod 1997; Smith 2004) reported data on an outcome they referred to as “clinical progression.” However, we included the data in an analysis of biochemical progression because the definition provided in the reports was consistent with our previously established definition of biochemical progression. Non-steroidal antiandrogens significantly increased clinical progression at one year, at 70 weeks and at two years when compared with castration, but no significant differences were found at three, four or five years when the fixed-effect model was used (at one year: RR 1.27, 95% CI 1.14 to 1.41, 2067 participants; at 70 weeks: RR 1.27, 95% CI 1.16 to 1.38, 2373 participants; at two years: RR 1.13, 95% CI 1.03 to 1.24, 1336 participants; at three years: RR 1.04, 95% CI 0.87 to 1.23, 480 participants; at four years: RR 1.07, 95% CI 0.91 to 1.26, 480 participants; at five years: RR 0.96, 95% CI 0.87 to 1.06, 698 participants; not shown). The random-effects model due to heterogeneity (I^2 = 64%) at 70 weeks still showed comparable results (at one year: RR 1.25, 95% CI 1.08 to 1.45, 2067 participants; at 70 weeks: RR 1.26, 95% CI 1.08 to 1.45, 2373 participants; at two years: RR 1.14, 95% CI 1.04 to 1.25, 1336 participants; at three years: RR 1.04, 95% CI 0.87 to 1.23, 480 participants; at four years: RR 1.07, 95% CI 0.91 to 1.26, 480 participants; at five years: RR 0.96, 95% CI 0.88 to 1.06, 698 participants; Analysis 1.4). We performed a sensitivity analysis for clinical progression at 70 weeks because we noted heterogeneity (I^2 = 64%). After the smallest study had been excluded (Study 0302), results still showed significant differences with lower heterogeneity (RR 1.33, 95% CI 1.19 to 1.48, I^2 = 13%; not shown). Five studies (Sciarra 2004a; Study 0301; Study 0302; Study 0303; Tyrrell 2006) did not report ITT analysis data, but findings were summarised instead according to treatment received. An analysis that considered data imputations for the best-case and worst-case scenarios still showed significant results at one year, 70 weeks and two years but not at five years (Analysis 1.5). This analysis involved 2771 randomly assigned participants. The quality of evidence for clinical progression was moderate (Summary of findings for the main comparison).

Subgroup: disease stage

No significant differences were found between non-steroidal antiandrogens and castration for participants with non-metastatic disease at all evaluated time points (Analysis 1.4). An analysis considering data imputations for the best-case and worst-case scenarios showed comparable results (Analysis 1.5). Five studies were included in the subgroup analysis of participants with metastatic disease (Study 0301; Study 0302; Study 0303; Study 306; Study 307). Clinical progression at one year (RR 1.25, 95% CI 1.05 to 1.49, I^2 = 64%, 1539 participants), at 70 weeks (RR 1.27, 95% CI 1.07 to 1.51, I^2 = 74%, 1845 participants) and at two years (RR 1.17, 95% CI 1.05 to 1.29, 808 participants) increased with non-steroidal antiandrogens when compared with castration in participants with metastatic disease (Analysis 1.4). We performed sensitivity analyses for clinical progression at one year and at 70 weeks because heterogeneity was present. After the smallest study had been excluded (Study 0302), results still showed significant differences with lower heterogeneity (at one year: RR 1.35, 95% CI 1.13 to 1.61, I^2 = 42%; at 70 weeks: RR 1.35, 95% CI 1.18 to 1.55, I^2 = 34%; not shown). The results remained significant after an analysis was performed by considering data imputations for best-case and worst-case scenarios (Analysis 1.5).

Subgroup: dose of non-steroidal antiandrogen

The non-steroidal antiandrogen bicalutamide at a dose of 50 mg daily showed no significant difference when compared with castration (at one year: RR 1.27, 95% CI 0.91 to 1.76, I^2 = 83%, 731 participants; at 70 weeks: RR 1.30, 95% CI 0.99 to 1.71, 1037 participants, I^2 = 84%; Analysis 1.4). We performed sensitivity analyses because heterogeneity was present. After the smallest study had been excluded (Study 0302), results showed significant differences with lower heterogeneity (at one year: RR 1.49, 95% CI 1.21 to 1.85; at 70 weeks: RR 1.47, 95% CI 1.26 to 1.72, I^2 = 0%; not shown). The analysis considering data imputations for best-case and worst-case scenarios showed a significant increase in clinical progression with bicalutamide 50 mg daily at 70 weeks (RR 1.40, 95% CI 1.04 to 1.88, 1196 participants), but no difference was found at one year (Analysis 1.5). The non-steroidal antiandrogen bicalutamide at a dose of 150 mg daily might increase clinical progression at one year (RR 1.25, 95% CI 1.07 to 1.46, 1336

participants), at 70 weeks (RR 1.22, 95% CI 1.07 to 1.39, 1336 participants) or at two years (RR 1.14, 95% CI 1.04 to 1.25, 1336 participants), but no differences were noted when compared with castration at three, four or five years (Analysis 1.4). An analysis considering data imputations for best-case and worst-case scenarios showed comparable results (Analysis 1.5). No significant differences were found between high-dose bicalutamide (450 mg daily or 600 mg daily) and castration at five years.

Biochemical progression

Three studies (Boccon-Gibod 1997; Sciarra 2004a; Smith 2004) involving 185 randomly assigned participants were included in the analysis of biochemical progression. For the definitions of biochemical progression in included studies, see the Characteristics of included studies table. The analysis considering data imputations for best-case and worst-case scenarios involved 214 randomly assigned participants. No significant differences were found between the non-steroidal antiandrogen and castration groups at any of the evaluated time points (Analysis 1.6; Analysis 1.7). The study conducted by Smith et al was not designed to evaluate clinical cancer outcomes including clinical or biochemical progression (for details, see Characteristics of included studies). The overall effect on biochemical progression therefore remains unclear.

Subgroup: disease stage

We did not perform subgroup analyses because very few studies were included for this outcome for which results were reported after different follow-up periods. The conduct and presentation of meta-analyses therefore did not seem appropriate.

Subgroup: dose of non-steroidal antiandrogen

We did not perform subgroup analyses because very few studies were included for this outcome for which results were reported after different follow-up periods. The conduct and presentation of meta-analyses therefore did not seem appropriate.

Treatment failure

Six studies (Boccon-Gibod 1997; Study 0301; Study 0302; Study 0303; Study 306; Study 307) involving 2411 randomly assigned participants reported data on treatment failure. For the definition of treatment failure, see the Characteristics of included studies table. Non-steroidal antiandrogens increased treatment failure at one year, at 70 weeks and at two years, but no difference was found at three or four years (Analysis 1.8). The random-effects model for heterogeneity revealed significant results (at one year: I^2 = 63%, RR 1.19, 95% CI 1.02 to 1.38, 1539 participants; at 70 weeks: I^2 = 81%, RR 1.27, 95% CI 1.05 to 1.52, 1845 participants; at two years: RR 1.14, 95% CI 1.05 to 1.24, 808 participants; Analysis 1.8). We performed sensitivity analyses because heterogeneity was present. After the smallest study had been excluded (Study 0302), results still showed significant differences with lower heterogeneity (at one year: RR 1.26, 95% CI 1.08 to 1.47, I^2 = 53%; at 70 weeks: RR 1.36, 95% CI 1.14 to 1.62, I^2 = 69%; not shown). An analysis considering data imputations for best-case and worst-case scenarios showed comparable results (Analysis 1.9). This analysis involved 2004 randomly assigned participants. The quality of evidence for treatment failure was moderate (Summary of findings for the main comparison).

Subgroup: disease stage

The subgroup analysis for non-metastatic prostate cancer included two studies (Study 306; Study 307) and showed no significant differences between non-steroidal antiandrogens and castration at four years (RR 1.04, 95% CI 0.93 to 1.16, 480 participants; Analysis 1.8). For participants with metastatic prostate cancer, non-steroidal antiandrogens increased treatment failure at one year (RR 1.19, 95% CI 1.02 to 1.38, I^2 = 63%, 1539 participants), at 70 weeks (RR 1.27, 95% CI 1.05 to 1.52, I^2 = 81%, 1845 participants) and at two years (RR 1.14, 95% CI 1.05 to 1.24, 808 participants). We performed sensitivity analyses for treatment failure at one year and at 70 weeks because heterogeneity was present. After the smallest study had been excluded (Study 0302), results still showed significant differences with lower heterogeneity (at one year: RR 1.26, 95% CI 1.08 to 1.47, I^2 = 53%; at 70 weeks: RR 1.36, 95% CI 1.14 to 1.62, I^2 = 69%; not shown). No significant difference was found at three years (Analysis 1.8). An analysis considering data imputations for best-case and worst-case scenarios revealed comparable results (Analysis 1.9).

Subgroup: dose of non-steroidal antiandrogen

No significant differences were found between the non-steroidal antiandrogen bicalutamide at a dose of 50 mg daily and castration at any of the time points assessed using the random-effects model for heterogeneity (Analysis 1.8). However, the analysis considering data imputations for best-case and worst-case scenarios showed that without heterogeneity, bicalutamide at 50 mg daily significantly increased treatment failure at one year and at 70 weeks (Analysis 1.9). Additionally, the non-steroidal antiandrogen bicalutamide at a dose of 150 mg daily significantly increased treatment failure at one year (RR 1.17, 95% CI 1.01 to 1.35, 808 participants), at 70 weeks (RR 1.18, 95% CI 1.05 to 1.34, 808 participants) and at two years (RR 1.14, 95% CI 1.05 to 1.24, 808 participants). No difference was found at four years (Analysis 1.8; Analysis 1.9). One study (Boccon-Gibod 1997) assessed the non-steroidal antiandrogen flutamide at a dose of 250 mg three times daily compared with castration and showed no significant differences at three years (Analysis 1.8; Analysis 1.9).

Adverse events

Nine studies (Boccon-Gibod 1997; Sieber 2004; Smith 2004; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) reported data on adverse events associated with treatment with non-steroidal antiandrogens compared with castration.

Non-steroidal antiandrogens were associated with a significantly increased occurrence of breast pain (RR 22.97, 95% CI 14.79 to 35.67, 2670 participants; Analysis 1.10). Subgroup analyses showed that this was also evident for bicalutamide at a dose of 50 mg, 150 mg, 450 mg or 600 mg daily (Analysis 1.10).

The risk of suffering gynaecomastia was increased with non-steroidal antiandrogens (RR 8.43, 95% CI 3.19 to 22.28, 2774 participants; Analysis 1.17). We performed a sensitivity analysis because considerable heterogeneity was noted (I^2 = 92%). After the smallest study had been excluded (Smith 2004), results still showed significant differences with lower heterogeneity (RR 9.34, 95% CI 5.43 to 16.05, I^2 = 53%; not shown). Subgroup analyses showed that gynaecomastia occurred more often with bicalutamide 50 mg daily (RR 14.07, 95% CI 3.74 to 52.85), flutamide 250 mg three times daily

(RR 3.70, 95% CI 1.33 to 10.33), bicalutamide 450 mg daily (RR 27.88, 95% CI 7.02 to 110.79) and bicalutamide 600 mg daily (RR 20.36, 95% CI 4.97 to 83.40). However, no significant difference was found between bicalutamide 150 mg daily and castration. We performed a sensitivity analysis because heterogeneity (I^2 = 97%) was present for this comparison. After the smallest study had been excluded (Smith 2004), a significant increase in gynaecomastia with reduced heterogeneity was found with bicalutamide 150 mg daily (RR 8.79, 95% CI 3.88 to 18.94, I^2 = 67%; not shown).

The occurrence of asthenia was significantly increased when non-steroidal antiandrogens were used compared with castration (RR 1.77, 95% CI 1.36 to 2.31, 2073 participants; Analysis 1.23). Subgroup analyses showed higher incidences of asthenia with bicalutamide 50 mg, 150 mg and 450 mg daily (Analysis 1.23). No significant difference was found between bicalutamide 600 mg daily and castration (RR 2.45, 95% CI 0.95 to 6.31, 132 participants; Analysis 1.23).

No differences in the risk of suffering arthralgia were found between non-steroidal antiandrogens and castration in overall analysis and subgroup analysis for bicalutamide 600 mg daily (Analysis 1.46). However, the occurrence of arthralgia was significantly increased with the non-steroidal antiandrogen bicalutamide at a dose of 450 mg daily compared with castration (RR 1.96, 95% CI 1.01 to 3.80, 182 participants; Analysis 1.46).

One small study (Smith 2004) of participants receiving bicalutamide 150 mg daily showed that non-steroidal antiandrogens might preserve sexual interest compared with castration (RR 0.50, 95% CI 0.30 to 0.83, 51 participants; Analysis 1.22).

Risk of hot flashes (RR 0.23, 95% CI 0.19 to 0.27, 2774 participants; Analysis 1.25), haemorrhage (RR 0.07, 95% CI 0.01 to 0.54, 546 participants; Analysis 1.38), nocturia (RR 0.38, 95% CI 0.20 to 0.69, 480 participants; Analysis 1.40), urinary frequency (RR 0.22, 95% CI 0.11 to 0.47, 480 participants; Analysis 1.41) and occurrence of fatigue (RR 0.52, 95% CI 0.31 to 0.88, 51 participants; Analysis 1.49) was decreased with non-steroidal antiandrogens compared with castration. These significant differences were also evident for all subgroup analyses regarding the different doses of non-steroidal antiandrogens.

The overall risk to suffer night sweats was decreased with non-steroidal antiandrogens compared with castration (RR 0.29, 95% CI 0.17 to 0.49, 1571 participants; Analysis 1.26). However, although a significant difference was noted in the subgroup of participants treated with bicalutamide 150 mg daily (RR 0.26, 95% CI 0.14 to 0.49, 1268 participants), this finding was not evident for participants treated with bicalutamide 50 mg daily (RR 0.36, 95% CI 0.12 to 1.09, 303 participants).

Infection occurred less frequently with bicalutamide at 50 mg daily but showed no significant difference for overall analysis or bicalutamide at 150 mg daily when compared with castration (Analysis 1.32).

The occurrence of peripheral oedema was significantly decreased for bicalutamide at 50 mg daily (RR 0.42, 95% CI 0.21 to 0.82, 480 participants); however, we found no statistically significant difference for bicalutamide at 150 mg daily compared with castration and in overall analysis (Analysis 1.43).

We found an increased occurrence of constipation (Analysis 1.18) and a decreased risk of anaemia (Analysis 1.27) with higher doses of non-steroidal antiandrogens compared with castration.

No significant difference between non-steroidal antiandrogens and castration was noted for occurrence of haematuria (Analysis 1.39). However, results of the meta-analysis including two studies (Study 0303; Study 306) show considerable heterogeneity (I^2 = 97%). Subgroup analyses showed a significantly decreased risk with bicalutamide 50 mg daily but an increased risk with bicalutamide 150 mg daily to suffer haematuria when compared with castration (bicalutamide 50 mg daily: RR 0.41, 95% CI 0.26 to 0.67, 480 participants; bicalutamide 150 mg daily: RR 3.49, 95% CI 2.01 to 6.05, 474 participants; Analysis 1.39).

Conflicting results were found for the occurrence of vomiting because events in both groups were very rare (Analysis 1.20).

We identified no statistically significant differences for the following adverse events when we compared non-steroidal antiandrogens with castration: pelvic pain (Analysis 1.11), bone pain (Analysis 1.12), back pain (Analysis 1.13), headache (Analysis 1.14), abdominal pain (Analysis 1.15), general pain (Analysis 1.16), gastralgia (Analysis 1.47), diarrhoea (Analysis 1.19), hypertension (Analysis 1.21), nausea (Analysis 1.48), insomnia (Analysis 1.24), hepatic enzyme increase (Analysis 1.28), rash (Analysis 1.29), pruritus (Analysis 1.30), dyspnoea (Analysis 1.31), pharyngitis (Analysis 1.33), arthritis (Analysis 1.34), sinusitis (Analysis 1.35), urinary tract infection (Analysis 1.36), dizziness (Analysis 1.37), urinary retention (Analysis 1.42), anorexia (Analysis 1.44), loss of sexual function (Analysis 1.45), dry skin (Analysis 1.50), aggravation reaction (Analysis 1.51) and serious adverse events (Analysis 1.52).

No study reported data on the predefined outcomes of cardiovascular events, gastrointestinal disorders and lethargy.

The quality of evidence for breast pain, gynaecomastia and hot flashes was moderate (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

Eleven studies were included. The quality of the evidence for overall survival, clinical progression, treatment failure, breast pain, gynaecomastia and hot flashes was moderate (Summary of findings for the main comparison). Non-steroidal antiandrogens significantly decreased overall survival and increased clinical progression as well as treatment failure. Subgroup analyses showed that non-steroidal antiandrogens, compared with castration, were consistently less favourable for overall survival, clinical progression and treatment failure in men with metastatic disease. Additionally, less favourable effects were seen with the non-steroidal antiandrogen bicalutamide 50 mg daily for overall survival, clinical progression with imputed event numbers at 70 weeks and treatment failure with imputed event numbers at 70 weeks, as well as for the non-steroidal antiandrogen bicalutamide 150 mg daily for clinical progression and treatment failure at one year, 70 weeks and two years, when compared with castration. Non-steroidal antiandrogens also increased the risk for treatment discontinuation due to adverse events and increased the risk of breast pain, gynaecomastia and asthenia. The risk of other

adverse events, such as hot flashes, fatigue, loss of sexual interest, haemorrhage, nocturia and urinary frequency, was significantly increased with castration. Effects of non-steroidal antiandrogens on cancer-specific survival and biochemical progression remained unclear.

Overall completeness and applicability of evidence

The included studies examined clinically important populations that were representative of patients seen in routine clinical practice. These participants and assessed interventions directly conformed to the review question. However, several points must be considered regarding the applicability of evidence.

The included studies provided data on our predefined outcomes. However, four studies (Dockery 2009; Sciarra 2004a; Sieber 2004; Smith 2004) did not address the review question directly and instead assessed primary outcomes that were not relevant to the review question, such as bone mineral density (Sieber 2004; Smith 2004), arterial stiffness (Dockery 2009), metabolic changes (Sieber 2004; Smith 2004) and markers of neuroendocrine differentiation (Sciarra 2004a). However, these studies also reported data on adverse events and/or progression and therefore were included in the review.

Only three studies were evaluated for biochemical progression. However, this outcome was defined by the authors in two of the three studies (Boccon-Gibod 1997; Smith 2004) as clinical progression. In accordance with our predetermined definition, we classified these reported outcomes as biochemical progression because a PSA measurement was used for the definition of this outcome. The definition of biochemical progression varied among the included studies. The results of this outcome assessment should be interpreted carefully.

The two largest included studies (Study 306; Study 307) assessed participants with non-metastatic and metastatic prostate cancer. PSA values were measured for participants with non-metastatic disease only. For participants in the non-steroidal antiandrogen group, these values ranged between 0.1 and 7691 ng/mL (median 69.2 ng/mL, mean 173.2 ng/mL). These rather high PSA values might no longer represent populations with non-metastatic disease and might lead to bias in the evaluations.

We included seven studies (Boccon-Gibod 1997; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) that assessed men treated with surgical castration. This therapy is suggested as a potential alternative to medical castration (Abrahamsson 2005; ASCO 2004; ASCO 2007; Seidenfeld 1999; Seidenfeld 2000). However, surgical castration could lead to potential psychological strain, and the resulting adverse events are only partially treatable. Nyman et al suggested that when patients can choose between different androgen suppression therapy options (non-steroidal antiandrogens and medical or surgical castration) and receive comprehensive information about the treatment, nearly all patients are satisfied with their choice after three months of treatment (Nyman 2005). However, it should be mentioned that the clinical heterogeneity of these treatments might lead to bias in our results regarding treatment discontinuation due to adverse events because reversal of surgical castration is not possible.

Quality of the evidence

Most of the included studies reported insufficient information on sequence generation and allocation concealment.

No study performed blinding of participants and personnel because different therapy options were included (surgical castration, oral medication and injection therapy). Opinions vary as to whether lack of blinding has a relevant impact on outcomes such as overall survival, cancer-specific mortality and biochemical progression. It might be conceivable that these outcomes are influenced by lack of blinding. Therefore we judged that risk of bias for most of the included studies is unclear regarding overall survival, cancer-specific mortality and biochemical progression. Outcomes such as clinical progression, treatment failure, treatment discontinuation due to adverse events and adverse events could be influenced by lack of blinding, presenting a high risk of bias in most of the included studies. Therefore the effects of intervention may have been overestimated (Als-Nielsen 2004; Pildal 2007; Wood 2008).

In all studies, no blinding of outcome assessment was performed or blinding was not reported or underlying methodology remained unclear. However, this type of blinding would have been feasible and could have been expected in all studies. We suggest that it is not likely that outcome assessments for overall survival, cancer-specific mortality and biochemical progression are influenced by lack of blinding. For outcomes such as clinical progression, treatment failure, treatment discontinuation due to adverse events and adverse events, this lack of blinding might, however, introduce detection bias due to potentially overestimated intervention effects (Pildal 2007).

The results of five studies (Boccon-Gibod 1997; Sciarra 2004a; Study 0301; Study 0302; Study 0303) were based on data for which risk for incomplete outcomes was high. A risk of bias is present because per-protocol analyses may lead to overestimated effects (Akl 2012; Meerpohl 2010; Porta 2007; Schulz 1996; Tierney 2005; Wood 2004). We performed sensitivity analyses based on best-/worst-case scenarios for outcomes such as treatment failure (Analysis 1.9), biochemical progression (Analysis 1.7) and clinical progression (Analysis 1.5) with imputations of missing data to minimise this bias because ITT analyses are regarded as the preferred way to estimate the effects of interventions in randomised controlled trials (Newell 1992).

Possible conflicts of interest should be considered for all of the included studies because the trial authors reported a possible conflict of interest or provided no disclosure statement. Conflicts of interest are common in the field of urology (Hampson 2012; Ramm 2012). Conflicts of interest may introduce a risk of bias because studies funded by industry have been shown to be more likely to report positive results than studies with other funding sources (Gøtzsche 2006; Okike 2007; Shah 2005). However, the risk of bias remains unclear because lack of a disclosure statement in itself is not an indicator of bias. Peer reviewers and journal editors may require conflict of interest disclosures at any step of the peer review process without providing a summary statement on the issue (Meerpohl 2010).

Non-steroidal antiandrogens were assessed using subgroup analyses regarding disease stage. The two largest included studies (Study 306; Study 307) recruited participants with metastatic

or non-metastatic prostate cancer. However, participants with metastatic disease withdrew from the study early (after 100 weeks) and were excluded from further evaluations. We did not examine the protocols for these studies; it is therefore unclear whether the subgroup analyses were predefined. Post hoc subgroup analyses are common and might introduce a risk that differences in effect sizes across subgroups could produce statistically significant differences (Sun 2009; Sun 2012; Wang 2010). The influence of subgroup effects might be low (Sun 2012; Wang 2010) and should be interpreted carefully.

Overall, we identified several methodological limitations during our assessment of risk of bias, leading to downgrading of the quality of evidence for study limitations (section Characteristics of included studies; Figure 3). No indication of publication bias was found by funnel plot asymmetry analysis for our primary outcome, and we believe that risk of publication bias might be low (Risk of bias in included studies; Figure 2). Heterogeneity was noted for overall survival, clinical progression, treatment failure and gynaecomastia. However, this heterogeneity might be explained by subgroup or sensitivity analyses (see Effects of interventions); we believe that it should not be required that the quality of the evidence should be downgraded for inconsistency. Additionally, we believe that it might not be necessary to downgrade the quality of the evidence because of imprecision. The quality of the body of evidence for outcomes such as overall survival, clinical progression, treatment failure, breast pain, gynaecomastia and hot flashes was therefore rated as moderate (Summary of findings for the main comparison).

Potential biases in the review process

Limitations of the review at the study or outcome level

All studies were published in peer-reviewed publications. However, results might be hampered by several limitations. As discussed above, included participants might no longer represent the contemporary population (see Overall completeness and applicability of evidence). Additionally, only two included studies (Sciarra 2004a; Smith 2004) measured PSA as a marker for clinical or biochemical progression. Nowadays, PSA plays an important role in the follow-up of patients with prostate cancer and in early detection of disease progression. This certainly has an effect on clinical and biochemical progression and might be important for outcomes such as overall and cancer-specific mortality.

Limitations of the review at the review level

We followed the recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to minimise potential biases (Higgins 2011a). We performed an extensive literature search and contacted selected experts in the field, as well as manufacturers of non-steroidal androgen suppression drugs, to request information on unpublished studies. Therefore it is not likely that relevant studies were overlooked. Two review authors independently assessed the information given in the reports of included studies and contacted the investigators of the identified studies to request supplemental data. This review therefore assessed the best evidence available from published randomised controlled trials. Unfortunately, even after contacting the primary investigators, we received no additional data.

Limitations of the review related to detection of serious and/or rare adverse events

We considered only randomised controlled trials for inclusion in this review. However, for evaluation of serious and/or rare adverse events, it is also necessary to consider non-randomised studies such as controlled clinical trials, cohort studies and case-control studies. Observational studies often utilise large databases and likely or possibly show greater external validity when compared with data from randomised controlled trials (Gartlehner 2008). Additionally, data on adverse events from randomised controlled trials could underestimate rare but serious adverse events as the result of small sample size and might be susceptible to bias due to the inclusion of highly selected participants (Chou 2010).

Agreements and disagreements with other studies or reviews

We identified that overall survival was significantly decreased with non-steroidal antiandrogens when compared with castration. This is consistent with the findings of other studies. A systematic review published in 2000 by Seidenfeld et al already suggested that overall survival might be lower when non-steroidal antiandrogens are used (Seidenfeld 1999; Seidenfeld 2000). However, no update was performed of the review published by Seidenfeld et al, and no other systematic review evaluating overall or cancer-specific survival was published comparing non-steroidal antiandrogens with medical or surgical castration. A narrative review suggested that non-steroidal antiandrogen monotherapy is an established treatment option in men with prostate cancer, but that an unexplained trend towards increased mortality should prohibit their uncritical use (Wirth 2007). The Early Prostate Cancer program investigated the effect of bicalutamide 150 mg daily compared with placebo. It showed that bicalutamide might delay clinical progression, but that for overall survival, it provided an advantage only when combined with external beam radiotherapy for locally advanced prostate cancer (EPC program; Wirth 2008).

Non-steroidal antiandrogens are thought to provide advantages such as oral application and the potential preservation of libido, potency and muscle mass or bone mineral density when compared with castration (EAU 2013; Daniell 1997; Prezioso 2007; Sciarra 2004b; Sieber 2004; Smith 2002; Smith 2004; Study 306; Study 307; Wadhwa 2011). However, adverse events should be considered. This review suggests that the occurrence of adverse events such as breast pain, gynaecomastia and asthenia is increased with non-steroidal antiandrogens. Breast events were the most common adverse events in recent reports of treatment with non-steroidal antiandrogens (Boccardo 1999; Boccardo 2002; EPC program; Kotake 1996b; Lunglmayr 1995; Raina 2007; Tyrrell 1994; Wadhwa 2011), and hot flashes occurred in approximately 30% to 40% of these participants (Boccardo 1999; EPC program; Lunglmayr 1995). Results of studies evaluating non-steroidal antiandrogens assume that the incidence of adverse events ranges between 40% and 74% (EPC program; Kotake 1996b; Raina 2007). Castration, on the other hand, increased adverse events such as hot flashes, haemorrhage, nocturia, urinary frequency, fatigue and loss of sexual interest, as indicated by this review. Side effects that have an impact on physiological and psychological health should be considered when androgen suppression therapies are prescribed because these effects can interfere with compliance as soon as the patient notices symptoms; thus, these patients might require additional treatment (Kunath 2012).

Non-steroidal antiandrogens lead to an increased rate of treatment discontinuation compared with castration because of their associated adverse events. This finding is consistent with the results of the systematic review published by Seidenfeld et al, as well as other studies, and accounts for 4% to 10% of patients receiving non-steroidal antiandrogens (EPC program; Seidenfeld 2000; Study 306; Study 307; Tyrrell 1994). The main reasons for discontinuing treatment were elevated liver enzymes (Boccon-Gibod 1997; Smith 2004; Tyrrell 1994) and breast events (EPC program).

We found no data on the impact of androgen suppression therapy on cardiovascular events. However, androgen suppression might adversely affect cardiovascular risk (Dockery 2002; Dockery 2009), and men with existing cardiovascular disease might have increased mortality (Efstathiou 2009). However, adjuvant castration does not appear to increase cardiovascular mortality in men with advanced prostate cancer who do not have notable cardiovascular risk (Efstathiou 2008; Nguyen 2011).

In the included studies, bicalutamide was the most frequently assessed non-steroidal antiandrogen. Only one study (Boccon-Gibod 1997) with a small sample size evaluated flutamide; we identified no studies evaluating nilutamide. This observation is consistent with common prescribing practices. A recent study evaluated men registered in the National Prostate Cancer Register of Sweden to determine the prescribing patterns of therapy with bicalutamide (Grundmark 2012). Of the 58,143 patients with prostate cancer registered in the National Prostate Cancer Register of Sweden, 4.4% (n = 2558) were treated with non-steroidal antiandrogens and 1406 received bicalutamide monotherapy. Of these, 79% received a dosage of 150 mg per day. The prescription of other antiandrogens was very rare (n = 88) (Grundmark 2012).

We did not include studies that compared non-steroidal antiandrogens with placebo. Evidence from large randomised controlled trials suggests that non-steroidal antiandrogens (bicalutamide at 150 mg daily) given as an adjuvant to radiotherapy significantly improve progression-free survival compared with radiotherapy alone. However, these studies showed no significant differences in overall survival after 9.7 years (EPC program).

AUTHORS' CONCLUSIONS

Implications for practice

Based on our assessment of the best available evidence, use of non-steroidal antiandrogen monotherapy rather than medical or surgical castration monotherapy is less effective for treating men with advanced prostate cancer with respect to overall survival, clinical progression, treatment failure and treatment discontinuation due to adverse events. Some of the variation in study results may be attributable to disease stage, as subgroup analyses showed that these effects were more pronounced in men with metastatic disease. Additionally, subgroup analyses by dose showed less favourable effects regarding the non-steroidal antiandrogen bicalutamide 50 mg daily for overall survival, clinical progression with imputed event numbers at 70 weeks and treatment failure with imputed event numbers at 70 weeks, as well as for the non-steroidal antiandrogen bicalutamide 150 mg daily for clinical progression and treatment failure at one year, 70 weeks and two years compared with castration. However, subgroup analyses could be confounded because their results are observational in nature and contain greater uncertainty. Adverse events should be considered in both non-steroidal antiandrogen and castration therapies.

Implications for research

The quality of evidence according to GRADE is only moderate. However, we believe that further research on non-steroidal antiandrogen monotherapy is likely not necessary for the subgroup of men with metastatic prostate cancer. Further research is likely to have an important impact on results for the subgroup of patients with advanced but non-metastatic prostate cancer treated with non-steroidal antiandrogen monotherapy. Only high-quality, randomised controlled trials with long-term follow-up should be conducted. If further research is planned to investigate biochemical progression, studies with standardised follow-up schedules using measurements of PSA based on current guidelines should be conducted.

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Wood 2008

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boccon-Gibod 1997

Methods	Start date, end date of recruitment: April 1989 to June 1991 Follow-up period: minimum follow-up of 36 months Design: randomised controlled trial
Participants	Population/Inclusion criteria: newly diagnosed hormone-naive metastatic prostate cancer; histologically proven prostate cancer with documented metastatic disease beyond pelvic lymph nodes, no prior hormonal manipulation, chemotherapy or radiation therapy outside of the primary tumour, normal liver function test, ECOG performance status 0 to 2 and absence of any previous malignant disease except skin cancer Setting: multi-centre (7 institutions) Geographical location: France Exclusion criteria: not reported Total number randomly assigned: 104 Baseline imbalances: balanced Number of participants with non-metastatic disease: 0 Number of participants with metastatic disease: 104 Age (mean ± SD): intervention: 72.3 ± 8.5 years; control: 73.8 ± 8 years PSA (mean ± SD): intervention: 666 ± 961 ng/mL; control: 681 ± 1073 ng/mL

Boccon-Gibod 1997 *(Continued)*

	Subgroup measured: no
Interventions	**Intervention** Description/Timing: flutamide 250 mg 3 times daily; tablets were taken after each meal Number randomly assigned to this group: 54 **Control** Description/Timing: orchiectomy (formal or subcapsular orchiectomy at the discretion of each urologist) Number randomly assigned to this group: 50
Outcomes	**Overall survival** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: minimum follow-up of 36 months; at 69 months Time points reported: at 69 months Number of participants randomly assigned: intervention: 54; control: 50 Number of participants in evaluation for ITT: unclear **Cancer-specific mortality** Outcome not reported/measured **Treatment discontinuation due to adverse events** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: minimum follow-up of 36 months Time points reported: minimum follow-up of 36 months Number of participants randomly assigned: intervention: 54; control: 50 Number of participants in evaluation for ITT: intervention: 54; control: 50 **Clinical progression** Not measured/reported **Biochemical progression** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: minimum follow-up of 36 months Time points reported: minimum follow-up of 36 months Outcome definition in report: defined by an increase in serum PSA > 50% of its nadir value confirmed over 2 months or a PSA rise > 50% over the nadir in association with another objective parameter (newly proven metastasis) Number of participants randomly assigned: intervention: 54; control: 50

Boccon-Gibod 1997 *(Continued)*

Number of participants in evaluation for ITT: intervention 44; control: 42

Note: This outcome was named as clinical progression by the primary investigators. However, because of the outcome definition reported, we classified it as biochemical progression. The primary investigators reported that at progression, treatment was left to the discretion of the urologist. Participants treated by orchiectomy could receive flutamide or another antiandrogen. Participants receiving flutamide were treated with orchiectomy or medical castration using an LHRH agonist. Continuation of flutamide was done at the urologist's discretion. Also investigators reported no significant differences whether the progression-free survival plot concerned only follow-up participants or all included participants

Treatment failure

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: minimum follow-up of 36 months

Time points reported: minimum follow-up of 36 months

Outcome definition in report: not reported

Number of participants randomly assigned: intervention: 54; control: 50

Number of participants in evaluation for ITT: intervention: 44; control: 42

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: minimum follow-up of 36 months

Time points reported: minimum follow-up of 36 months

Number of participants randomly assigned: intervention: 54; control: 50

Number of participants in evaluation for ITT: intervention: 54; control: 50

Other outcomes reported

Serum testosterone, salvage therapy by second-line flutamide

Notes

Sexual function was not assessable because of advanced age of participants. Study authors reported no data on overall survival at 69 months but noted an "identical" survival, irrespective of second-line treatment. They reported no definition of hepatic enzyme increase

Study funding source: not reported

Possible conflict of interest: Co-author is a member of Schering-Plough

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Participants centrally randomly assigned after signing the informed consent form

Boccon-Gibod 1997 *(Continued)*

Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for overall survival and biochemical progression. Blinding was not possible because of different interventions provided. It might be conceivable that outcomes such as overall survival, cancer-specific mortality or biochemical progression are influenced by lack of blinding. We finally judge that risk of bias regarding these outcomes is unclear
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided. We judge that outcomes such as treatment discontinuation due to adverse events, adverse events and treatment failure are likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	No blinding for overall survival and biochemical progression. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely that outcome assessment for overall survival and biochemical progression are influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression, treatment failure, adverse events and treatment discontinuation due to adverse events is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	High risk	Data on overall survival were reported incompletely (Boccon-Gibod et al reported only "identical" survival in both groups)
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Low risk	Intention-to-treat analysis for adverse events and treatment discontinuation due to adverse events
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	High risk	'As-treated' analysis on biochemical progression done with substantial departure of the intervention received from that assigned at randomisation
Incomplete outcome data (attrition bias) treatment failure	High risk	'As-treated' analysis on treatment failure done with substantial departure of the intervention received from that assigned at randomisation
Selective reporting (reporting bias)	High risk	Data on overall survival were reported incompletely and could not be entered into the meta-analysis
Other bias	Unclear risk	Unclear risk for conflict of interest

Dockery 2009

Methods	Start date, end date of recruitment: unclear Follow-up period: All participants had atrial stiffness measures at baseline and at 12 and 24 weeks Design: randomised controlled trial
Participants	Population/Inclusion criteria: men with localised prostate cancer who were deemed as requiring hormonal treatment by local urology or oncology services Setting: single centre Geographical location: UK (London) Exclusion criteria: metastatic cancer, atrial fibrillation, severe hepatic renal or cardiac failure, any acute illness and any recent (in the preceding 12 months) hormone treatment Total number randomly assigned: 43 Baseline imbalances: balanced Number of participants with non-metastatic disease: 42 Number of participants with metastatic disease: 0 Age (mean ± SD): intervention: 71.1 ± 6.1 years; control: 71.3 ± 6.6 years PSA: not reported Subgroup measured: no
Interventions	**Intervention** Description/Timing: bicalutamide 150 mg once daily for 6 months Number randomly assigned to this group: 21 (1 participant excluded) **Control** Description/Timing: goserelin depot injection 10.8 mg 3 times monthly (1 injection preceded by 2 weeks of flutamide, an androgen receptor blocker, 250 mg 3 times daily, as per standard guidelines) Number randomly assigned to this group: 21
Outcomes	**Overall survival** Outcome not measured/reported **Cancer-specific mortality** Outcome not measured/reported **Treatment discontinuation due to adverse events** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: at 6 months Time points reported: at 3 months Number of participants randomly assigned: intervention: 22; control: 21 Number of participants in evaluation for ITT: intervention: 21; control: 21 **Clinical progression**

Dockery 2009 *(Continued)*

	Outcome not measured/reported **Biochemical progression** Outcome not measured/reported **Treatment failure** Outcome not measured/reported **Adverse events** Outcome not measured/reported **Other outcomes reported** Metabolic parameters, carotid-femoral and carotid-radial pulse wave velocity, blood pressure
Notes	Study funding source: educational grant from AstraZeneca Possible conflict of interest: Sponsor had no role in any aspect of the study plan, conduct or analysis; interpretation of data; or writing of manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated and was balanced for every 6 participants
Allocation concealment (selection bias)	Unclear risk	Randomly allocated; no other statement reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	Not measured/reported
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for treatment discontinuation due to adverse events. Blinding was not possible because of different interventions provided. We judge that the outcome of treatment discontinuation due to adverse events is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	Not measured/reported
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progres-	High risk	No blinding for treatment discontinuation due to adverse events. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for treatment discontinuation due to adverse events is influenced by lack of blinding

Dockery 2009 *(Continued)*

sion, treatment failure, adverse events		
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Unclear risk	Not measured/reported
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Low risk	One man in intervention arm dropped out after his baseline visit, leaving 42 participants available for analysis. The proportion of missing outcomes compared with observed event risk is not enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	Unclear risk	Not measured/reported
Incomplete outcome data (attrition bias) treatment failure	Unclear risk	Not measured/reported
Selective reporting (reporting bias)	High risk	Only adverse events leading to discontinuation reported; no other adverse events reported
Other bias	Unclear risk	Unclear risk for conflict of interest

Sciarra 2004a

Methods	Start date, end date of recruitment: between December 1998 and January 2001 Follow-up period: After radical retropubic prostatectomy, when serum PSA levels exceeded 0.2 ng/mL, PSA determinations were repeated every 2 weeks. Participants entered the study once their PSA level progressed, defined as 3 or more consecutive elevated levels (greater than 0.4 ng/mL) Serum CgA levels were analysed at baseline (PSA progression) and at 1, 3, 6, 12, 18 and 24 months after random assignment. Total PSA levels were measured every 4 weeks for the first 12 months of treatment and every 8 weeks thereafter Design: randomised controlled trial
Participants	Population/Inclusion criteria: Men with pT3pN0M0 prostate cancer and biochemical progression (defined as PSA level greater than 0.4 ng/mL) within 12 months of radical retropubic prostatectomy were enrolled. Other inclusion criteria were histologically proven prostate cancer; no preoperative hormonal therapy or radiotherapy; radical retropubic prostatectomy with regional lymphadenectomy performed at our institution; and negative surgical margins Setting: single centre Geographical location: Italy Exclusion criteria: not reported Total number randomly assigned: 186 men with clinically localised prostate cancer underwent radical retropubic prostatectomy and bilateral pelvic lymphadenectomy at our institution; 59 fulfilled inclusion criteria and agreed to random assignment. Only the 48 men who concluded and successfully responded to the first 24 months of treatment were analysed

Sciarra 2004a *(Continued)*

	Baseline imbalances: balanced Number of participants with non-metastatic disease: 48 Number of participants with metastatic disease: 0 Age (mean ± SD): intervention: 64.2 ± 3.7 years (range 54 to 70 years); control: 64.8 ± 3.5 years (range 56 to 70 years) PSA (mean ± SD): PSA at baseline (progression after prostatectomy) in non-steroidal antiandrogen group: 1.12 ± 0.32 ng/mL (median 1.0 ng/mL; range 0.60 to 1.80 ng/mL); PSA at baseline (progression after prostatectomy) in castration group: 1.05 ± 0.30 ng/mL (median 1.0 ng/mL; range 0.60 to 1.60 ng/mL) Subgroup measured: no
Interventions	**Intervention** Description/Timing: bicalutamide 150 mg daily Number randomly assigned to this group: unclear (analysed and reported: 24) **Control** Description/Timing: triptorelin 3.75 mg monthly Number randomly assigned to this group: unclear (analysed and reported: 24)
Outcomes	**Overall survival** Outcome not measured/reported **Cancer-specific mortality** Outcome not measured/reported **Treatment discontinuation due to adverse events** Outcome not measured/reported **Clinical progression** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: at 24 months Time points reported: at 24 months Outcome definition in report: Treatment was considered to have failed when the PSA level increased to greater than 0.4 ng/mL or at clinical progression. Biopsy of the urethrovesical anastomosis, abdominal-pelvic magnetic resonance imaging and a total body bone scan were performed 12 and 24 months after random assignment or at PSA progression Number of participants randomly assigned: intervention: unclear; control: unclear Number of participants in evaluation for ITT: intervention: 24; control: 24 **Biochemical progression** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: at 24 months

Sciarra 2004a *(Continued)*

Time points reported: at 24 months

Outcome definition in report: Treatment was considered to have failed when the PSA level increased to greater than 0.4 ng/mL or at clinical progression. Biopsy of the urethrovesical anastomosis, abdominal-pelvic magnetic resonance imaging and a total body bone scan were performed 12 and 24 months after random assignment or at PSA progression

Number of participants randomly assigned: intervention: unclear; control: unclear

Number of participants in evaluation for ITT: intervention: 24; control: 24

Treatment failure (outcome measured but not reported)

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: at 24 months

Time points reported: at 24 months

Outcome definition in report: Treatment was considered to have failed when the PSA level increased to greater than 0.4 ng/mL or at clinical progression. Biopsy of the urethrovesical anastomosis, abdominal-pelvic magnetic resonance imaging and a total body bone scan were performed 12 and 24 months after random assignment or at PSA progression

Number of participants randomly assigned: intervention: unclear; control: unclear

Number of participants in evaluation for ITT: intervention: 24; control: 24

Adverse events

Outcome not measured/reported

Other outcomes reported

Serum CgA levels

Notes	During the first 24 months of follow-up, no participant showed evidence of clinical progression, and the PSA serum levels remained at 0.4 ng/mL or less Study funding source: unclear Possible conflict of interest: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for biochemical progression. Blinding was not possible because of different interventions provided. It might be conceivable that biochemical progression is influenced by lack of blinding. We finally judge that risk of bias regarding this outcome is unclear

Sciarra 2004a *(Continued)*

Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression and treatment failure. Blinding was not possible because of different interventions provided. We judge that outcomes such as clinical progression and treatment failure are likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	No blinding for biochemical progression. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely that outcome assessment for biochemical progression is influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression and treatment failure. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression and treatment failure is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Unclear risk	Not measured/reported
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Unclear risk	Not measured/reported
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	High risk	'As-treated' analysis on clinical/biochemical progression done with substantial departure of the intervention received from that assigned at randomisation (59 men fulfilled the inclusion criteria and agreed to random assignment; only the 48 participants who concluded and successfully responded to the first 24 months of treatment were analysed)
Incomplete outcome data (attrition bias) treatment failure	High risk	Outcome measured but not reported
Selective reporting (reporting bias)	High risk	Study report fails to include results for a key outcome that would be expected to have been reported for such a study (no data on adverse events, treatment discontinuation due to adverse events or treatment failure reported). No protocol available
Other bias	Unclear risk	Unclear risk for conflict of interest

Sieber 2004

Methods	Start date, end date of recruitment: not reported Follow-up period: Subsequent assessments were obtained within 7 days of weeks 24, 48, 72 and 96

Sieber 2004 *(Continued)*

	Design: randomised controlled trial
Participants	Population/Inclusion criteria: Study population consisted of men with histologically confirmed prostate cancer with no distant metastases (T1–T4, Nx, M0) for whom immediate androgen deprivation was indicated Inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0 or 1; life expectancy greater than 6 months; no history or presence of metabolic bone disease, renal failure, malabsorption, rheumatoid arthritis, recent fracture or any other condition known to affect bone metabolism; no hormone therapy within the previous 6 months, no concomitant treatment with any drugs known to affect calcium or vitamin D metabolism and no treatment with systemic steroids. Participants were also required to have a baseline testosterone level greater than the lower limit of normal (194 ng/dL or greater), a calcium level less than the upper limit of normal (10.6 mg/dL or less), a thyroid-stimulating hormone level within normal limits (0.4 to 10 mg/mL) and a bone mineral density (BMD) within 2 standard deviations of age-matched controls Setting: multi-centre (11 locations) Geographical location: United States Exclusion criteria: not reported Total number randomly assigned: 103 Baseline imbalances: balanced Number of participants with non-metastatic disease: 103 Number of participants with metastatic disease: 0 Age: intervention: mean 74.6 years (range 53 to 87 years); control: mean 75.2 years (range 61 to 90 years) PSA: not reported Subgroup measured: no
Interventions	**Intervention** Description/Timing: bicalutamide 150 mg once daily for 96 weeks Number randomly assigned to this group: 51 **Control** Description/Timing: medical castration with an LHRH agonist for 96 weeks (drug not specified) Number randomly assigned to this group: 52
Outcomes	**Overall survival** Outcome not measured/reported **Cancer-specific mortality** Outcome not measured/reported **Treatment discontinuation due to adverse events** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: at 96 weeks

Sieber 2004 *(Continued)*

Time points reported: at 96 weeks

Number of participants randomly assigned: intervention: 51; control: 52

Number of participants in evaluation for ITT: intervention: 50; control: 51

Clinical progression

Outcome not measured/reported

Biochemical progression

Outcome not measured/reported

Treatment failure

Outcome not measured/reported

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: at 96 weeks

Time points reported: at 96 weeks

Number of participants randomly assigned: intervention: 51; control: 52

Number of participants in evaluation for ITT: intervention: 50; control: 51

Other outcomes reported

Primary efficacy end points were mean percentage change in lumbar spine BMD, hip BMD and fat-free mass (FFM) from baseline to 96 weeks. Secondary efficacy end points included mean percentage change in lumbar spine (L2 to L4) BMD, hip BMD and FFM from baseline to 24, 48 and 72 weeks; and mean change from baseline in serum lipid levels of HDL, LDL, total and very low-density lipoprotein (VLDL) cholesterol and triglycerides. Lumbar spine BMD, hip BMD and FFM were assessed by dual-energy x-ray absorptiometry within 6 weeks before random assignment

Notes	Study funding source: supported by a research grant from AstraZeneca Possible conflict of interest: financial interest and/or other relationship with AstraZeneca. Two authors had financial interest and/or another relationship with AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement (eligible participants were randomly assigned in a 1:1 ratio to receive bicalutamide 150 mg once daily or medical castration with an LHRH analogue for 96 weeks)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	Not measured/reported

Sieber 2004 *(Continued)*

Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for treatment discontinuation due to adverse events and adverse events. Blinding was not possible because of different interventions provided. We judge that outcomes such as treatment discontinuation due to adverse events and adverse events are likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	Not measured/reported
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for treatment discontinuation due to adverse events and adverse events. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for treatment discontinuation due to adverse events and adverse events are influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Unclear risk	Not measured/reported
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. The proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate (2 participants, 1 in each treatment group, who did not receive randomly assigned therapy and were excluded from the analysis of adverse events). For analyses of all efficacy variables, a modified per-protocol data set was used. Participants were included according to the treatment received but, unlike in a true per-protocol data set, participants with major protocol violations were not excluded
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	Unclear risk	Not measured/reported
Incomplete outcome data (attrition bias) treatment failure	Unclear risk	Not measured/reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest

Smith 2004

Methods	Start date, end date of recruitment: Study participants were recruited between May 2000 and May 2002

Smith 2004 *(Continued)*

	Follow-up period: treatment time: 12 months. Participants were evaluated at baseline and at 3, 6, 9 and 12 months Design: randomised controlled trial
Participants	Population/Inclusion criteria: Participants had locally advanced, lymph node–positive or recurrent prostate cancer. Men with prior neoadjuvant or adjuvant hormone therapy were included if the interval between completion of treatment and study entry was longer than 1 year; 10 men (5 men in each group) had received neoadjuvant or adjuvant treatment with a gonadotropin-releasing hormone agonist Setting: single-centre trial Geographical location: United States Exclusion criteria: Men with bone metastases by radionuclide bone scan were excluded. Men with Karnofsky performance status less than 90, history of hypogonadism, history of growth hormone or anabolic steroid use, Paget's disease, hyperthyroidism, Cushing's disease, hyperprolactinaemia, chronic liver disease, corrected serum calcium 8.4 mg/dL or 10.6 mg/dL or serum creatinine concentration 2.0 mg/dL (177 mol/L) were also excluded. Men were excluded if they had received bisphosphonate, calcitonin or glucocorticoid therapy, or suppressive doses of thyroxine, within 1 year Total number randomly assigned: 52 Baseline imbalances: unclear: balanced for data reported; data for staging not reported Number of participants with non-metastatic disease: 51 (52 men were randomly assigned to leuprorelin monotherapy or bicalutamide monotherapy. Fifty-one men completed the baseline evaluation and initiated study treatment; 51 participants completed the study. All 51 participants are included in the analyses, including 3 men who discontinued treatment early) Number of participants with metastatic disease: 0 Age: intervention: mean 63 ± 8 years; control: mean 65 ± 10 years PSA (mean ± SD): intervention: 158 ± 670 ng/mL; control: 40 ± 119 ng/mL Subgroup measured: no
Interventions	**Intervention** Description/Timing: bicalutamide 150 mg by mouth daily for 12 months Number randomly assigned to this group: 25 **Control** Description/Timing: Leuprorelin 3-month depot (Lupron Depot; TAP Pharmaceuticals Inc, Deerfield, Illinois; 22.5 mg intramuscularly every 3 months). Men assigned to leuprorelin treatment also received bicalutamide (50 mg by mouth daily) for 1 month to prevent the potential disease flare associated with initial leuprorelin administration Number randomly assigned to this group: 26
Outcomes	**Overall survival** Outcome not measured/reported **Cancer-specific mortality** Outcome not measured/reported **Treatment discontinuation due to adverse events** Comparison: non-steroidal antiandrogen versus castration

Smith 2004 *(Continued)*

Subgroup: no

Time points measured: at 12 months

Time points reported: at 12 months

Number of participants randomly assigned: intervention: 25; control: 26

Number of participants in evaluation for ITT: intervention: 25; control: 26

Clinical progression

Outcome not measured/reported

Biochemical progression

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: at 12 months

Time points reported: at 12 months

Outcome definition in report: Disease progression was defined as new metastatic disease or a greater than 25% increase in serum PSA concentration from nadir value on 2 determinations and 5 ng/mL absolute increase in PSA

Number of participants randomly assigned: intervention: 25; control: 26

Number of participants in evaluation for ITT: intervention: 25; control: 26

Note: This outcome was named as clinical progression by the study authors. However, because of the outcome definition reported, we classified it as biochemical progression

Treatment failure

Outcome not measured/reported

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: at 12 months

Time points reported: at 12 months

Number of participants randomly assigned: intervention: 25; control: 26

Number of participants in evaluation for ITT: intervention: 25; control: 26

Other outcomes reported

Primary study end points were percentage change in bone mineral density in posterior-anterior lumbar spine and percentage change in thigh muscle area from baseline to 12 months

Notes	Email response: "Subjects and study investigators were blinded to treatment assignment. The main outcomes for this 1-year study were bone mineral density and body composition and the study was NOT designed to evaluate clinical cancer outcomes including time to progression" Study funding source: supported by research award from AstraZeneca PLC Possible conflict of interest: Study authors indicated no potential conflicts of interest

Smith 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	Email response: "Subjects and study investigators were blinded to treatment assignment." However, the method of blinding bicalutamide 150 mg by mouth daily for 12 months and leuprorelin 3-month depot (22.5 mg intramuscularly every 3 months) for biochemical progression remains unclear
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	Unclear risk	Email response: "Subjects and study investigators were blinded to treatment assignment." However, the method of blinding bicalutamide 150 mg by mouth daily for 12 months compared with leuprorelin 3-month depot (22.5 mg intramuscularly every 3 months) for treatment discontinuation due to adverse events and adverse events remains unclear
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	Not reported. However, we judge that it is not likely that outcome assessment for biochemical progression is influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	Unclear risk	Not reported. However, original investigators responded that blinding was performed ("Subjects and study investigators were blinded to treatment assignment"). However, blinding of outcome assessment for treatment discontinuation due to adverse events and adverse events remains unclear
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Unclear risk	Not measured/reported
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Low risk	Proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate (52 men were randomly assigned to leuprorelin monotherapy or bicalutamide monotherapy. Fifty-one men completed baseline evaluation and initiated study treatment; 51 participants completed the study. All 51 participants are included in the analyses, including 3 men who discontinued treatment early)
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	Low risk	Proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate (52 men were randomly assigned to leuprorelin monotherapy or bicalutamide monotherapy. Fifty-one men completed the baseline evaluation and initiated

Smith 2004 *(Continued)*

		study treatment; 51 participants completed the study. All 51 participants are included in the analyses, including 3 men who discontinued treatment early)
Incomplete outcome data (attrition bias) treatment failure	Unclear risk	Not measured/reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest

Study 0301

Methods	Start date, end date of recruitment: June 1990 to February 1992 Follow-up period: follow-up of a minimum of 12 months; mean duration for all 376 participants was 67 weeks for intervention and 75 weeks for control (for all analyses except survival, a data cutoff point was used when a minimum follow-up of 3 months was reached for the first 306 participants; for the analyses of survival, information from all 376 participants was used with a minimum follow-up of 12 months) Design: randomised controlled trial
Participants	Population/Inclusion criteria: histologically or cytologically diagnosed prostate cancer with evaluable distant metastases and suitable for orchiectomy Setting: multi-centre Geographical location: Denmark, Norway, Sweden Exclusion criteria: Men who had received or were receiving systemic treatment for prostate cancer (including radiotherapy, antiandrogen, oestrogen, LHRH analogue, ketoconazole or cytotoxic therapy) or who had previously received radiotherapy to the prostate within 3 months of entry into the study were excluded. Other exclusion criteria were history or presence of an invasive malignancy within the past 5 years (other than prostate cancer or squamous/basal cell carcinoma of the skin), an ECOG performance score of 3 or 4, a bilirubin value 1.26 times the upper limit of the reference range or greater and any severe concomitant medical condition that would limit participation in the study. No other treatment for prostate cancer or drugs that could affect sex hormone status were allowed during the follow-up period Total number randomly assigned: 376 Baseline imbalances: balanced Number of participants with non-metastatic disease: 0 Number of participants with metastatic disease: 376 Age: intervention: mean 71.5 years (range 54 to 80 years); control: mean 70.3 years (range 49 to 85 years) PSA: not reported Subgroup measured: no
Interventions	**Intervention** Description/Timing: bicalutamide 50 mg once daily Number randomly assigned to this group: 186

Study 0301 *(Continued)*

Control

Description/Timing: bilateral orchiectomy

Number randomly assigned to this group: 190

Outcomes

Overall survival

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: For analyses of survival, information from all 376 participants was used, with a minimum follow-up of 12 months

Time points reported: For analyses of survival, information from all 376 participants was used, with a minimum follow-up of 12 months

Number of participants randomly assigned: intervention: 186; control: 190

Number of participants in evaluation for ITT: intervention: 186; control: 190

Cancer-specific mortality

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: For analyses of survival, information from all 376 participants was used, with a minimum follow-up of 12 months

Time points reported: For analyses of survival, information from all 376 participants was used, with a minimum follow-up of 12 months

Number of participants randomly assigned: intervention: 186; control: 190

Number of participants in evaluation for ITT: intervention: 186; control: 190

Treatment discontinuation due to adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: minimum follow-up of 3 months

Time points reported: mean duration for all 376 participants was 67 weeks for intervention and 75 weeks for control

Number of participants randomly assigned: intervention: 186; control: 190

Number of participants in evaluation for ITT: intervention: 153; control: 153

Clinical progression

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: minimum follow-up of 3 months

Time points reported: mean duration for all 376 participants was 67 weeks for intervention and 75 weeks for control

Outcome definition in report: an increase in prostatic dimensions (product of 2 greatest perpendicular diameters) by 50% or more (1 initial diameter at least 3 cm) compared with the minimum dimensions recorded during the study; appearance of any new or worsening of existing bone metastases on x-ray

Study 0301 *(Continued)*

	or isotope bone scan; appearance of any new extraskeletal metastasis or an increase in dimensions (by 25% or more) of any existing extraskeletal metastasis compared with the minimum dimensions recorded during the study; death occurring before evidence of objective progression Number of participants randomly assigned: intervention: 186; control: 190 Number of participants in evaluation for ITT: intervention: 153; control: 153 **Biochemical progression** Outcome not measured/reported **Treatment failure** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: minimum follow-up of 3 months Time points reported: Mean duration for all 376 participants was 67 weeks for intervention and 75 weeks for control Outcome definition in report: death (in the absence of disease progression); objective disease progression; addition of any recognised systemic treatment for prostate cancer before objective progression; patient lost to follow-up; cessation of therapy because of adverse event, at the discretion of the investigator or at the request of the participant (applicable only to participants receiving bicalutamide) Number of participants randomly assigned: intervention: 186; control: 190 Number of participants in evaluation for ITT: intervention: 153; control: 153 **Adverse events** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: minimum follow-up of 3 months Time points reported: mean duration for all 376 participants was 67 weeks for intervention and 75 weeks for control Number of participants randomly assigned: intervention: 186; control: 190 Number of participants in evaluation for ITT: intervention: 153; control: 150 (3 refused surgery) **Other outcomes reported** Subjective response, quality of life
Notes	Study funding source: not reported Possible conflict of interest: not reported; the assistance of a member of Zeneca in preparation of the manuscript was gratefully acknowledged

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Study 0301 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for overall survival and cancer-specific mortality. Blinding was not possible because of different interventions provided. It might be conceivable that outcomes such as overall survival and cancer-specific mortality are influenced by lack of blinding. We finally judge that risk of bias regarding these outcomes is unclear
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided. We judge that outcomes such as clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure are likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	No blinding for overall survival and cancer-specific mortality. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely that outcome assessment for overall survival and cancer-specific mortality is influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression, treatment failure, adverse events and treatment discontinuation due to adverse events is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Low risk	Intention-to-treat analysis and therefore low risk of bias for incomplete outcome data for overall survival
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	High risk	'As-treated' analysis on adverse events done with substantial departure of the intervention received from that assigned at randomisation (participants included who had at least 3 months of follow-up)
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	High risk	'As-treated' analysis on clinical progression done with substantial departure of the intervention received from that assigned at randomisation (participants included who had at least 3 months of follow-up)
Incomplete outcome data (attrition bias) treatment failure	High risk	'As-treated' analysis on treatment failure done with substantial departure of the intervention received from that assigned at randomisation (participants included who had at least 3 months of follow-up)
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest

Study 0302

Methods	Start date, end date of recruitment: May 1990 to December 1991 Follow-up period: study closed in September 1993; median duration of treatment at the time of data cutoff for analysis was 35.3 weeks and 37.7 weeks for participants in the bicalutamide and castration groups, respectively Design: randomised controlled trial
Participants	Population/Inclusion criteria: histologically or cytologically confirmed prostate cancer, presence of evaluable metastatic disease and fitness for orchiectomy Setting: multi-centre (3 countries) Geographical location: United Kingdom, The Netherlands, Austria Exclusion criteria: Men who had received or who were receiving systemic therapy for prostate cancer were excluded. Those who had received radiotherapy to the prostate gland within 3 months of entry of the study and those men with a history in the previous 5 years of invasive malignancy (other than prostate cancer or squamous/basal cell carcinoma of the skin) were also excluded, as were patients with an ECOG performance score of 3 or 4. Patients with a bilirubin value greater than 1.26 times the upper limit of the reference range were also excluded Total number randomly assigned: 304 Baseline imbalances: data presented only for subgroup (characteristics of participants who completed 3 months of treatment; 245 participants instead of 304) Number of participants with non-metastatic disease: intervention: 0; control: 1 Number of participants with metastatic disease: intervention: 119; control: 125 Age (mean ± SD): intervention: 71.9 ± 8.2 years; control: 72.1 ± 7.8 years PSA: not reported Subgroup measured: no
Interventions	**Intervention** Description/Timing: bicalutamide 50 mg once daily Number randomly assigned to this group: 150 **Control** Description/Timing: Participants were offered a choice between Zoladex (goserelin 3.6 mg subcutaneous every 28 days) and surgical bilateral orchiectomy (complete or subcapsular); goserelin: 60, orchiectomy: 65 (126 participants included in 'as-treated' analysis; 1 participant excluded; distribution of participants receiving medical or surgical castration for ITT analysis not reported) Number randomly assigned to this group: 154
Outcomes	**Overall survival** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: median follow-up 61 weeks for intervention and 66 weeks for control Time points reported: median follow-up 61 weeks for intervention and 66 weeks for control

Study 0302 *(Continued)*

Number of participants randomly assigned: intervention: 150; control: 154

Number of participants in evaluation for ITT: intervention: 150; control: 154

Cancer-specific mortality

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: median follow-up 61 weeks for intervention and 66 weeks for control

Time points reported: median follow-up 61 weeks for intervention and 66 weeks for control

Number of participants randomly assigned: intervention: 150; control: 154

Number of participants in evaluation for ITT: intervention: 150; control: 154

Treatment discontinuation due to adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: median follow-up 61 weeks for intervention and 66 weeks for control

Time points reported: median follow-up 61 weeks for intervention and 66 weeks for control

Number of participants randomly assigned: intervention: 150; control: 154

Number of participants in evaluation for ITT: intervention: 119; control: 126

Clinical progression

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: median follow-up 61 weeks for intervention and 66 weeks for control

Time points reported: median follow-up 35.3 weeks for intervention and 37.7 weeks for control

Outcome definition in report: any of the following defined objective progressions: increase in prostatic dimensions (product of 2 greatest perpendicular diameters) by 50% or more compared with minimum dimensions recorded during study; appearance of any new or worsening of existing bone metastasis on x-ray or isotope bone scan; appearance of any new extraskeletal metastasis or increase in dimensions (by 25% or more) of any existing extraskeletal metastasis compared with minimum dimensions recorded during the study; death occurred before evidence of objective progression

Number of participants randomly assigned: intervention: 150; control: 154

Number of participants in evaluation for ITT: intervention: 119; control: 126

Biochemical progression

Outcome not measured/reported

Treatment failure

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: median follow-up 61 weeks for intervention and 66 weeks for control

Time points reported: median follow-up 35.3 weeks for intervention and 37.7 weeks for control

Study 0302 *(Continued)*

Outcome definition in report: earliest occurrence of any of the following defined treatment failures: death (in the absence of progression); objective disease progression; addition of any recognised systemic treatment for prostate cancer before objective progression; participants lost to follow-up; cessation of therapy because of adverse events, at the discretion of the investigator or at the request of the participant (applicable only to participants in the bicalutamide group)

Number of participants randomly assigned: intervention: 150; control: 154

Number of participants in evaluation for ITT: intervention: 119; control: 126

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: median follow-up 61 weeks for intervention and 66 weeks for control

Time points reported: median follow-up 35.3 weeks for intervention and 37.7 weeks for control

Number of participants randomly assigned: intervention: 150; control: 154

Number of participants in evaluation for ITT: intervention: 118; control: 125

Other outcomes reported

PSA levels, subjective response, quality of life

Notes

Study funding source: not reported

Possible conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for overall survival and cancer-specific mortality. Blinding was not possible because of different interventions provided. It might be conceivable that outcomes such as overall survival and cancer-specific mortality are influenced by lack of blinding. We finally judge that risk of bias regarding these outcomes is unclear
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided. We judge that outcomes such as clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure are likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	No blinding for overall survival and cancer-specific mortality. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely

Study 0302 *(Continued)*

overall survival, cancer-specific mortality, biochemical progression		that outcome assessment for overall survival and cancer-specific mortality is influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Low risk	Intention-to-treat analysis and therefore low risk of bias for incomplete outcome data for overall survival (once randomly assigned, all participants were followed for survival regardless of reason for discontinuation)
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	High risk	'As-treated' analysis for treatment discontinuation due to adverse events and adverse events done with substantial departure of the intervention received from that assigned at randomisation (efficacy and tolerability analysis was restricted to 245 participants who completed 3 months of treatment)
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	High risk	'As-treated' analysis for clinical progression done with substantial departure of the intervention received from that assigned at randomisation (efficacy and tolerability analysis was restricted to 245 participants who completed 3 months of treatment)
Incomplete outcome data (attrition bias) treatment failure	High risk	'As-treated' analysis for treatment failure done with substantial departure of the intervention received from that assigned at randomisation (efficacy and tolerability analysis was restricted to 245 participants who completed 3 months of treatment)
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest

Study 0303

Methods	Start date, end date of recruitment: March 1990 to October 1991 Follow-up period: All randomly assigned participants who reached treatment failure endpoints or completed at least 3 months of follow-up as of November 1991 (n = 486) were evaluated. Mean time on randomly assigned therapy was 39 weeks for the bicalutamide treatment group and 42 weeks for the castration group Design: randomised controlled trial
Participants	Population/Inclusion criteria: men with untreated stage D2 prostate cancer; confirmation of metastatic disease was based on results of scintigraphy, radiography or computed tomography Setting: multi-centre (31 locations) Geographical location: United States Exclusion criteria: Men physically unfit to undergo orchiectomy were excluded before random assignment

Study 0303 *(Continued)*

	Total number randomly assigned: 516 Baseline imbalances: balanced Number of participants with non-metastatic disease: 516 Number of participants with metastatic disease: 0 Age: intervention: median 70 years; control: median 71 years PSA: intervention: median 187.3 µg/L; control: median 147.3 µg/L Subgroup measured: no
Interventions	**Intervention** Description/Timing: bicalutamide 50 mg daily Number randomly assigned to this group: 259 **Control** Description/Timing: Participants randomly assigned to undergo castration chose the method of castration: bilateral orchiectomy or a depot injection of the LHRH analogue goserelin acetate (Zoladex, Zeneca Pharmaceuticals) every 28 days Number randomly assigned to this group: 257
Outcomes	**Overall survival** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: unclear Time points reported: 39 weeks for bicalutamide group and 42 weeks for castration group; survival analysis approximately 1 year later was based on data collected through December 1992 (n = 516) Number of participants randomly assigned: intervention: 259; control: 257 Number of participants in evaluation for ITT: intervention: 259; control: 257 **Cancer-specific mortality** Outcome not measured/reported **Treatment discontinuation due to adverse events** Comparison: non-steroidal antiandrogen versus castration Subgroup: no Time points measured: unclear Time points reported: 39 weeks for bicalutamide group and 42 weeks for castration group Number of participants randomly assigned: intervention: 259; control: 257 Number of participants in evaluation for ITT: intervention: 243; control: 243 **Clinical progression** Comparison: non-steroidal antiandrogen versus castration Subgroup: no

Study 0303 *(Continued)*

Time points measured: unclear

Time points reported: 39 weeks for bicalutamide group and 42 weeks for castration group

Outcome definition in report: an increase of 50% or more in prostatic dimensions compared with the minimum dimensions recorded during the trial, provided that 1 perpendicular diameter was at least 3 cm; 1 or more new or worsening bone metastases; or 1 or more new extraskeletal metastases or an increase in linear dimensions of at least 25% in any existing measurable extraskeletal metastasis. Increases in serum PSA alone were not considered evidence of progression. Findings from digital rectal examination and changes in acid phosphatase concentrations were not used as tumour markers

Number of participants randomly assigned: intervention: 259; control: 257

Number of participants in evaluation for ITT: intervention: 243; control: 243

Biochemical progression

Outcome not measured/reported

Treatment failure

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: unclear

Time points reported: 39 weeks for bicalutamide group and 42 weeks for castration group

Outcome definition in report: time from random assignment to treatment failure (death from any cause; objective progression; addition of any recognised systematic treatment; any adverse event leading to discontinuation; discontinuation due to discretion of investigator or request of participant; loss to follow-up)

Number of participants randomly assigned: intervention: 259; control: 257

Number of participants in evaluation for ITT: intervention: 243; control: 243

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: no

Time points measured: unclear

Time points reported: 39 weeks for bicalutamide group and 42 weeks for castration group

Number of participants randomly assigned: intervention: 259; control: 257

Number of participants in evaluation for ITT: intervention: 242; control: 238

Other outcomes reported

Subjective response, quality of life

Notes	Prostate-specific antigen (PSA) was measured before treatment began, every 3 months thereafter and at time of progression. Increases in serum PSA alone were not considered evidence of progression Study funding source: Trial was supported by a grant from Zeneca Pharmaceuticals, Zeneca Inc Possible conflict of interest: Co-author is a member of Zeneca Pharmaceuticals

Risk of bias

Study 0303 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for overall survival. Blinding was not possible because of different interventions provided. It might be conceivable that overall survival is influenced by lack of blinding. We finally judge that risk of bias regarding this outcome is unclear
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided. We judge that outcomes such as clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure are likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	No blinding for overall survival. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely that overall survival is influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression, treatment failure, adverse events and treatment discontinuation due to adverse events is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Low risk	Intention-to-treat analysis and therefore low risk of bias for incomplete outcome data for overall survival (once randomly assigned, all participants were followed for survival regardless of reason for discontinuation)
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	High risk	'As-treated' analysis for treatment discontinuation due to adverse events and adverse events done with substantial departure of the intervention received from that assigned at randomisation (efficacy and tolerability analysis was restricted to 486 participants who completed 3 months of treatment)
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	High risk	'As-treated' analysis for clinical progression done with substantial departure of the intervention received from that assigned at randomisation (efficacy and tolerability analysis was restricted to 486 participants who completed 3 months of treatment)
Incomplete outcome data (attrition bias) treatment failure	High risk	'As-treated' analysis for treatment failure done with substantial departure of the intervention received from that assigned at randomisation (efficacy and tolerability analysis was restricted to 486 participants who completed 3 months of treatment)

Study 0303 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest

Study 306

Methods	Study 306 and Study 307 are 2 individual randomised controlled trials, but with very similar methodology. These studies were planned for pooled analysis, and publications report mostly combined data analysis. We present therefore a summary of the 2 studies Start date, end date of recruitment: January 1992 to June 1993 Follow-up period: non-metastatic participants: 6.3 years; metastatic participants: 100 weeks Design: randomised controlled trial Trial registration number of study 307: ISRCTN44967321
Participants	Population/Inclusion criteria: PSA > 20 ng/mL and T3/4 M0 or M1; men with histologically or cytologically diagnosed stage who were considered candidates for palliative hormonal management; metastatic status was assessed for bone metastases by bone scan or x-ray and for non-skeletal metastases by x-ray, computed tomography scan, clinical examination, ultrasound or other relevant test Setting: multi-centre Geographical location: Study 306: Denmark, Norway, Finland, Sweden; Study 307: UK, South Africa, Austria, The Netherlands, Spain, Australia, Germany, Belgium, Italy Exclusion criteria: previous systemic therapy for prostate cancer; radiation therapy in previous 3 months; invasive malignancy in previous 5 years; ECOG 3 to 4; serum bilirubin ≥ 1.26 times the upper reference range Total number randomly assigned: 1450 (a total of 1453 men were recruited for the 2 studies (Study 306 and Study 307), of whom 1450 received their randomly assigned treatment (bicalutamide 100 mg daily: 165 participants; bicalutamide 150 mg daily: 862 participants; castration: 423 participants); of bicalutamide 150 mg and castration: 480 metastatic participants, 805 non-metastatic participants) Baseline imbalances: balanced Number of participants with non-metastatic disease: 480 Number of participants with metastatic disease: 805 Age: intervention: Study 306: mean 71.0 years (range 47 to 88 years); Study 307: mean 72.2 years (range 49 to 92 years); control: Study 306: mean 72.4 years (range 46 to 94 years); Study 307: mean 73.4 years (range 50 to 93 years) PSA: reported only for non-metastatic participants: intervention (n = 320): range 0.1 to 7691 ng/mL, median 69.2 ng/mL, mean 173.2 ng/mL; control (n = 160): range 8.6 to 6267.7 ng/mL, median 65.3 ng/mL, mean 194.5 ng/mL Subgroup measured: non-metastatic and metastatic participants (metastatic participants later withdrawn from study after 100 weeks—they received standard therapy; participants with non-metastatic disease continued); data reported only for bicalutamide 150 mg versus castration
Interventions	**Intervention** Description/Timing: bicalutamide 100 mg or 150 mg daily

Study 306 *(Continued)*

Number randomly assigned to this group: 864; data reported only for bicalutamide 150 mg versus castration

Note: "Initially patients were randomised on a 2:2:1 basis to receive either bicalutamide 100 mg daily, bicalutamide 150 mg daily or castration. The dose of bicalutamide was blinded. After 3 months the higher dose of bicalutamide showed a greater fall in PSA. This dose was selected for further investigation. Patients were then randomised to either bicalutamide 150 mg daily or castration on a 2:1 basis." Investigators presented no data for bicalutamide 100 mg daily

Control

Description/Timing: bilateral orchiectomy or goserelin acetate 3.6 mg every 28 days at the discretion of participants and investigators

Number randomly assigned to this group: 424

Outcomes

Overall survival

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants; data reported only for bicalutamide 150 mg versus castration

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred

Time points reported: non-metastatic and metastatic participants after 100 weeks; non-metastatic participants after median follow-up of 202 to 205 weeks and 6.3 years

Number of participants randomly assigned: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Number of participants in evaluation for ITT: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Cancer-specific mortality

Outcome not measured/reported

Treatment discontinuation due to adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: reported only for non-metastatic participants (data reported only for bicalutamide 150 mg vs castration)

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after randomisation and at 12-week intervals thereafter until death occurred

Time points reported: at 6.3 years

Number of participants randomly assigned: intervention: 320; control: 160

Number of participants in evaluation for ITT: intervention: 314; control: 160

Clinical progression

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for bicalutamide 150 mg vs castration)

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after randomisation and at 12-week intervals thereafter until death occurred

Study 306 *(Continued)*

Time points reported: metastatic participants after 12 months and 24 months; non-metastatic and metastatic participants after 100 weeks; non-metastatic participants after median follow-up of 202 to 205 weeks and 6.3 years

Outcome definition in report: time of random assignment to 50% or greater increase in prostatic dimension (product of the 2 largest perpendicular dimensions) from the minimum recorded during the trial, bony metastases on x-ray or isotope bone scan or appearance of extraskeletal metastases

Number of participants randomly assigned: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Number of participants in evaluation for ITT: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Biochemical progression

Outcome not measured/reported

Treatment failure

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for bicalutamide 150 mg vs castration)

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred

Time points reported: median 202 to 205 weeks

Outcome definition in report: death from any cause; objective progression; addition of other systemic therapy for prostate cancer; loss to follow-up; refusal to take or continue with randomly assigned therapy; cessation due to adverse events or other reasons (bicalutamide and medical castration only)

Number of participants randomly assigned: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Number of participants in evaluation for ITT: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for bicalutamide 150 mg vs castration)

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred

Time points reported: after 100 weeks, at 202 to 205 weeks and after 6.3 years

Number of participants randomly assigned: intervention: 320, control: 160

Number of participants in evaluation for ITT: intervention: 314; control: 160

Other outcomes reported

Subjective response, quality of life, bone mineral density (evaluated in only 29 non-metastatic participants)

Notes	Study funding source: not reported Possible conflict of interest: Seven trial authors had a financial interest and/or relationship with AstraZeneca; co-author is a member of sponsor (AstraZeneca)

Study 306 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for overall survival. Blinding was not possible because of different interventions provided. It might be conceivable that overall survival is influenced by lack of blinding. We finally judge that risk of bias regarding this outcome is unclear Note: Comparison of bicalutamide 100 mg daily versus 150 mg daily was blinded, but participants receiving bicalutamide 100 mg daily discontinued
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided. We judge that outcomes such as clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure are likely to be influenced by lack of blinding Note: Comparison of bicalutamide 100 mg daily versus 150 mg daily was blinded, but participants receiving bicalutamide 100 mg daily discontinued
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	No blinding for overall survival. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely that outcome assessment for overall survival is influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression, treatment failure, adverse events and treatment discontinuation due to adverse events is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Low risk	Data are reported on intention-to-treat
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Low risk	Data are reported on intention-to-treat. Proportion of missing outcomes for treatment discontinuation due to adverse events and adverse events data compared with observed event risk were not enough to have a clinically relevant impact on the intervention effect estimate
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	Low risk	Data are reported on intention-to-treat
Incomplete outcome data (attrition bias)	Low risk	Data are reported on intention-to-treat

Study 306 *(Continued)*
treatment failure

Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest Note: A protocol interim analysis after a median of approximately 100 weeks revealed a statistically significant qualitative interaction between randomly assigned treatment group and stage of disease at entry (M0 and M1); consequently, data from these subgroups were analysed separately. At that time, the M1 data were considered mature (43% deaths, combined trials) and indicated a significant survival advantage of 6 weeks for participants treated by castration. In accordance with DMSC advice, the M1 participants were withdrawn from the trial, and no further data for this subgroup are presented here. The M0 data, at that time, were considered immature (13% of cases resulting in death, combined trials), and so these participants remained in the trial

Study 307

Methods	Study 306 and Study 307 are individual randomised controlled trials, but with very similar methodology. These studies were planned for pooled analysis, and publications report mostly combined data analysis. We present therefore a summary of the 2 studies Start date, end date of recruitment: January 1992 to June 1993 Follow-up period: non-metastatic participants: 6.3 years; metastatic participants: 100 weeks Design: randomised controlled trial Trial registration number of study 307: ISRCTN44967321
Participants	Population/Inclusion criteria: PSA > 20 ng/mL and T3/4 M0 or M1; men with histologically or cytologically diagnosed stage who were considered candidates for palliative hormonal management; metastatic status was assessed for bone metastases by bone scan or x-ray and for non-skeletal metastases by x-ray, computed tomography scan, clinical examination, ultrasound or other relevant test Setting: multi-centre Geographical location: Study 306: Denmark, Norway, Finland, Sweden; Study 307: UK, South Africa, Austria, The Netherlands, Spain, Australia, Germany, Belgium, Italy Exclusion criteria: previous systematic therapy for prostate cancer; radiation therapy in previous 3 months; invasive malignancy in previous 5 years; ECOG 3 to 4; serum bilirubin ≥ 1.26 times the upper reference range Total number randomly assigned: 1450 (a total of 1453 men were recruited for the 2 studies (Study 306 and Study 307), of whom 1450 received their randomly assigned treatment (bicalutamide 100 mg daily: 165 participants; bicalutamide 150 mg daily: 862 participants; castration: 423 participants); of bicalutamide 150 mg and castration: 480 metastatic participants, 805 non-metastatic participants) Baseline imbalances: balanced Number of participants with non-metastatic disease: 480 Number of participants with metastatic disease: 805 Age: intervention: Study 306: mean 71.0 years (range 47 to 88 years), Study 307: mean 72.2 years (range 49 to 92 years); control: Study 306: mean 72.4 years (range 46 to 94 years), Study 307: mean 73.4 years (range 50 to 93 years)

Study 307 *(Continued)*

PSA: reported only for non-metastatic participants: intervention (n = 320): range 0.1 to 7691 ng/mL, median 69.2 ng/mL, mean 173.2 ng/mL; control (n = 160): range 8.6 to 6267.7 ng/mL, median 65.3 ng/mL, mean 194.5 ng/mL

Subgroup measured: non-metastatic and metastatic participants (metastatic participants later withdrawn from study after 100 weeks—they received standard therapy; participants with non-metastatic disease continued); data reported only for bicalutamide 150 mg versus castration

Interventions	**Intervention** Description/Timing: bicalutamide 100 mg daily or 150 mg daily Number randomly assigned to this group: 864; data reported only for bicalutamide 150 mg versus castration Note: "Initially patients were randomised on a 2:2:1 basis to receive either bicalutamide 100 mg daily, bicalutamide 150 mg daily or castration. The dose of bicalutamide was blinded. After 3 months the higher dose of bicalutamide showed a greater fall in PSA. This dose was selected for further investigation. Patients were then randomised to either bicalutamide 150 mg daily or castration on a 2:1 basis." Investigators presented no data for bicalutamide 100 mg daily **Control** Description/Timing: bilateral orchiectomy or goserelin acetate 3.6 mg every 28 days at the discretion of participants and investigators Number randomly assigned to this group: 424
Outcomes	**Overall survival** Comparison: non-steroidal antiandrogen versus castration Subgroup: non-metastatic and metastatic participants; data reported only for bicalutamide 150 mg versus castration Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred Time points reported: non-metastatic and metastatic participants after 100 weeks; non-metastatic participants after median follow-up of 202 to 205 weeks and 6.3 years Number of participants randomly assigned: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264 Number of participants in evaluation for ITT: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264 **Cancer-specific mortality** Outcome not measured/reported **Treatment discontinuation due to adverse events** Comparison: non-steroidal antiandrogen versus castration Subgroup: reported only for non-metastatic participants (data reported only for bicalutamide 150 mg vs castration) Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred Time points reported: at 6.3 years Number of participants randomly assigned: intervention: 320; control: 160

Study 307 *(Continued)*

Number of participants in evaluation for ITT: intervention: 314; control: 160

Clinical progression

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for bicalutamide 150 mg vs castration)

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred

Time points reported: metastatic participants after 12 months and 24 months; non-metastatic and metastatic participants after 100 weeks; non-metastatic participants after median follow-up of 202 to 205 weeks and 6.3 years

Outcome definition in report: time of random assignment to 50% or greater increase in prostatic dimension (product of the 2 largest perpendicular dimensions) from the minimum recorded during the trial, bony metastases on x-ray or isotope bone scan or appearance of extraskeletal metastases

Number of participants randomly assigned: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Number of participants in evaluation for ITT: intervention: non-metastatic participants: 320, metastatic participants: 544; control: non-metastatic participants: 160, metastatic participants: 264

Biochemical progression

Outcome not measured/reported

Treatment failure

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for bicalutamide 150 mg vs castration)

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred

Time points reported: median 202 to 205 weeks

Outcome definition in report: death from any cause; objective progression; addition of other systemic therapy for prostate cancer; loss to follow-up; refusal to take or continue with randomly assigned therapy; cessation due to adverse events or other reasons (bicalutamide and medical castration only)

Number of participants randomly assigned: intervention: non-metastatic participants: 320; metastatic participants: 544; control: non-metastatic participants: 160; metastatic participants: 264

Number of participants in evaluation for ITT: intervention: non-metastatic participants: 320; metastatic participants: 544; control: non-metastatic participants: 160; metastatic participants: 264

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for bicalutamide 150 mg vs castration)

Time points measured: Clinical visits were scheduled at 4, 8 and 12 weeks after random assignment and at 12-week intervals thereafter until death occurred

Time points reported: after 100 weeks, at 202 to 205 weeks and after 6.3 years

Number of participants randomly assigned: intervention: 320; control: 160

Study 307 *(Continued)*

	Number of participants in evaluation for ITT: intervention: 314; control: 160 **Other outcomes reported** Subjective response, quality of life, bone mineral density (evaluated in only 29 non-metastatic participants)
Notes	Study funding source: not reported Possible conflict of interest: Seven study authors had a financial interest and/or relationship with AstraZeneca; co-author is a member of sponsor (AstraZeneca)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for overall survival. Blinding was not possible because of different interventions provided. It might be conceivable that overall survival is influenced by lack of blinding. We finally judge that risk of bias regarding this outcome is unclear Note: Comparison of bicalutamide 100 mg daily versus 150 mg daily was blinded, but participants receiving bicalutamide 100 mg daily discontinued
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided. We judge that outcomes such as clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure are likely to be influenced by lack of blinding Note: Comparison of bicalutamide 100 mg daily versus 150 mg daily was blinded, but participants receiving bicalutamide 100 mg daily discontinued
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	No blinding for overall survival. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely that overall survival is influenced by lack of blinding
Blinding of outcome assessment (detection bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events, adverse events and treatment failure. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression, treatment failure, adverse events and treatment discontinuation due to adverse events is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Low risk	Data are reported on intention-to-treat

Study 307 *(Continued)*

Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Low risk	Data are reported on intention-to-treat. Proportions of missing outcomes for safety data compared with observed event risk were not enough to have a clinically relevant impact on the intervention effect estimate
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	Low risk	Data are reported on intention-to-treat
Incomplete outcome data (attrition bias) treatment failure	Low risk	Data are reported on intention-to-treat
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest Note: A protocol interim analysis after a median of approximately 100 weeks revealed a statistically significant qualitative interaction between randomly assigned treatment group and stage of disease at entry (M0 and M1); consequently, data from these subgroups were analysed separately. At that time, the M1 data were considered mature (43% deaths, combined trials) and indicated a significant survival advantage of 6 weeks for participants treated by castration. In accordance with DMSC advice, M1 participants were withdrawn from the trial, and no further data for this subgroup are presented here. The M0 data, at that time, were considered immature (13% of cases resulting in death, combined trials), and so these participants remained in the trial

Tyrrell 2006

Methods	Start date, end date of recruitment: between November 1994 and September 1996 Follow-up period: Mean duration of treatment in months was 27.6 (range 1.9 to 75.6) in the bicalutamide 300 mg group, 30.0 (range 2.0 to 78.7) in the 450 mg group and 29.2 (range 0.5 to 73.5) in the 600 mg group. Mean duration of treatment in the castration group was 33.5 (range 1.0 to 78.2) months; median follow-up: 5 years Design: randomised controlled trial Trial registration number: ISRCTN16559899
Participants	Population/Inclusion criteria: Men with histologically or cytologically confirmed M0 (T3 or T4) or M1 prostate cancer were included in the trial, provided they had a PSA level ≥ 20 ng/mL, a life expectancy greater than 3 months and evaluable disease and were considered fit enough to receive any of the randomly assigned treatments Setting: multi-centre Geographical location: conducted at 26 centres across Belgium, Denmark, Finland, France, Norway, Portugal, Spain, Sweden and the UK Exclusion criteria: any previous or concurrent systemic therapy for prostate cancer; previous radiotherapy to the prostate within 3 months before trial entry Total number randomly assigned: 248

Tyrrell 2006 *(Continued)*

	Baseline imbalances: balanced Number of participants with non-metastatic disease: 139 Number of participants with metastatic disease: 109 Age: bicalutamide 300 mg daily: mean 69.5 years (range 46 to 82 years); bicalutamide 450 mg daily: mean 71.2 years (range 52 to 89 years); bicalutamide 600 mg daily: mean 72.1 years (range 56 to 84 years); castration: mean 71.3 years (range 51 to 86 years) PSA: bicalutamide 300 mg daily: mean 76.5 ng/mL (range 21 to 545 ng/mL); bicalutamide 450 mg daily: mean 105.9 ng/mL (range 20 to 7008 ng/mL); bicalutamide 600 mg daily: mean 89.4 ng/mL (range 19 to 965 ng/mL); castration: mean 91.2 ng/mL (range 16 to 2000 ng/mL) Subgroup measured: Results are presented for the overall participant population and by disease stage (M0 or M1); however data for these subgroups were reported only for overall survival
Interventions	**Intervention** Description/Timing: bicalutamide 300 mg daily or 450 mg daily or 600 mg daily Number randomly assigned to this group: 21 participants received bicalutamide 300 mg daily, 95 participants received bicalutamide 450 mg daily and 43 participants received bicalutamide 600 mg daily Note: "Patients were initially recruited into a non-randomised phase to assess the tolerability of oral bicalutamide 300 mg (two 150 mg tablets) given once daily. Tolerance was assessed in these patients after 6 weeks of treatment and, if acceptable, future patients were randomised on 1:1 to either bicalutamide 450 mg (three 150 mg tablets) or castration (bilateral orchidectomy or goserelin acetate 3.6 mg depot every 28 days). If, after 6 weeks, tolerance at the 450 mg dose was acceptable, further patients were to be randomised at 1:1:1 to bicalutamide 450 mg, bicalutamide 600 mg (four 150 mg tablets) or castration. However, if tolerance at the 450 mg dose was unacceptable, future patients were to be randomised to bicalutamide 300 mg or castration. If the 600 mg dose was acceptable (after 6 weeks of follow-up), recruitment to the bicalutamide 450 mg dose was ended and all future patients entering the study were to be randomised at 1:1:1 to bicalutamide 600 mg, bicalutamide 750 mg (5 150 mg tablets) or castration. If tolerance at the 600 mg dose was unacceptable, new patients were to be randomised to bicalutamide 450 mg or castration. If tolerability at the 750 mg dose was acceptable, a further and final dose escalation to 900 mg (six 150 mg tablets) was to be done. Recruitment of 20 patients per treatment group was planned for each dose-escalation stage"; "As patients who received bicalutamide at the 300 mg dose were not randomised, it was considered inappropriate to provide any comparisons with the other treatments" **Control** Description/Timing: goserelin acetate or bilateral orchidectomy Number randomly assigned to this group: Of 90 participants randomly assigned to castration, 82 received goserelin acetate and 8 underwent bilateral orchiectomy
Outcomes	**Overall survival** Comparison: non-steroidal antiandrogen versus castration Subgroup: non-metastatic and metastatic participants Time points measured: median follow-up of 5 years Time points reported: median follow-up of 5 years Number of participants randomly assigned: intervention: bicalutamide 450 mg daily: 95; bicalutamide 600 mg daily: 43; control: 90 (non-metastatic disease: bicalutamide 450/600 mg daily: 74, castration: 54; metastatic disease: bicalutamide 450/600 mg daily: 63; castration: 36) Number of participants in evaluation for ITT: intervention: bicalutamide 450 mg daily: 92; bicalutamide 600 mg daily: 42; control: 90

Tyrrell 2006 *(Continued)*

Cancer-specific mortality

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for combined population)

Time points measured: median follow-up of 5 years

Time points reported: median follow-up of 5 years

Number of participants randomly assigned: intervention: bicalutamide 450 mg daily: 95; bicalutamide 600 mg daily: 43; control: 90

Number of participants in evaluation for ITT: intervention: bicalutamide 450 mg daily: 92; bicalutamide 600 mg daily: 42; control: 90

Treatment discontinuation due to adverse events

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for combined population)

Time points measured: median follow-up of 5 years

Time points reported: median follow-up of 5 years

Number of participants randomly assigned: intervention: bicalutamide 450 mg daily: 95; bicalutamide 600 mg daily: 43; control: 90

Number of participants in evaluation for ITT: intervention: bicalutamide 450 mg daily: 92; bicalutamide 600 mg daily: 42; control: 90

Clinical progression

Comparison: non-steroidal antiandrogen versus castration

Subgroup: non-metastatic and metastatic participants (data reported only for combined population)

Time points measured: median follow-up of 5 years

Time points reported: median follow-up of 5 years

Outcome definition in report: Objective evidence for disease progression was considered to include any of the following: ≥ 50% increase in prostatic dimensions compared with the minimum dimensions recorded during the trial (provided 1 of the dimensions was > 3 cm at the time of assessment); the appearance of new or worsening of existing bone metastases on x-ray or isotopic bone scan; or the appearance of new extraskeletal metastases or a ≥ 25% increase in the dimensions of any existing extraskeletal metastases compared with the minimum dimensions recorded during the trial

Number of participants randomly assigned: intervention: bicalutamide 450 mg daily: 95; bicalutamide 600 mg daily: 43; control: 90

Number of participants in evaluation for ITT: intervention: bicalutamide 450 mg daily: 92; bicalutamide 600 mg daily: 42; control: 90

Biochemical progression

Outcome not measured/reported

Treatment failure

Outcome not measured/reported

Adverse events

Comparison: non-steroidal antiandrogen versus castration

Tyrrell 2006 *(Continued)*

	Subgroup: non-metastatic and metastatic participants (data reported only for combined population) Time points measured: median follow-up of 5 years Time points reported: median follow-up of 5 years Number of participants randomly assigned: intervention: bicalutamide 450 mg daily: 95; bicalutamide 600 mg daily: 43; control: 90 Number of participants in evaluation for ITT: intervention: bicalutamide 450 mg daily: 92; bicalutamide 600 mg daily: 42; control: 90 **Other outcomes reported** Pharmacokinetic, change in serum PSA level from baseline after 12 weeks of treatment
Notes	Study funding source: AstraZeneca Possible conflict of interest: Five study investigators were funded by sponsor; author is a paid consultant to sponsor; another author is an employee of sponsor; editorial support was provided; financial assistance for this support was provided by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned treatment was assigned according to a scheme prepared by AstraZeneca using appropriate computer software. Random assignment was co-ordinated in the UK by the Clinical Trials Unit, Queen Elizabeth Hospital, Birmingham; in Sweden, Denmark, Finland and Norway by the Randomisation Bureau, Danish Cancer Society, Aarhus, Denmark; and for all other centres by the local AstraZeneca Pharma Office
Allocation concealment (selection bias)	High risk	Participant numbers were allocated sequentially by entry as participants entered the trial
Blinding of participants and personnel (performance bias) overall survival, cancer-specific mortality, biochemical progression	Unclear risk	No blinding for overall survival and cancer-specific mortality. Blinding was not possible because of different interventions provided. It might be conceivable that outcomes such as overall survival and cancer-specific mortality are influenced by lack of blinding. We finally judge that risk of bias regarding these outcomes is unclear
Blinding of participants and personnel (performance bias) treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events	High risk	No blinding for clinical progression, treatment discontinuation due to adverse events and adverse events. Blinding was not possible because of different interventions provided. We judge that outcomes such as clinical progression, treatment discontinuation due to adverse events and adverse events are likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) overall survival, cancer-specific mortality, biochemical progression	Low risk	No blinding for overall survival and cancer-specific mortality. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. However, we judge that it is not likely that outcome assessment for overall survival and cancer-specific mortality is influenced by lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding. Blinding was not possible because of different interventions provided, and study authors reported insufficient information only. We judge that it is likely that outcome assessment for clinical progression, treatment failure,

Tyrrell 2006 *(Continued)*

treatment discontinuation due to adverse events, clinical progression, treatment failure, adverse events		adverse events and treatment discontinuation due to adverse events is influenced by lack of blinding
Incomplete outcome data (attrition bias) overall survival, cancer-specific mortality	Low risk	Proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate (all participants were evaluable except for 3 in the bicalutamide 450 mg group and 1 in the bicalutamide 600 mg group, who received no study treatment)
Incomplete outcome data (attrition bias) treatment discontinuation due to adverse events, adverse events	Low risk	Proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate (all participants were evaluable except for 3 in the bicalutamide 450 mg group and 1 in the bicalutamide 600 mg group, who received no study treatment)
Incomplete outcome data (attrition bias) clinical progression, biochemical progression	Low risk	Proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate (all participants were evaluable except for 3 in the bicalutamide 450 mg group and 1 in the bicalutamide 600 mg group, who received no study treatment)
Incomplete outcome data (attrition bias) treatment failure	Unclear risk	Not measured/reported
Selective reporting (reporting bias)	Low risk	Study protocol was not available, but it was clear that published reports included all expected outcomes
Other bias	Unclear risk	Unclear risk for conflict of interest Note: Allocation of bicalutamide 300 mg was not randomly assigned in this trial, and random assignment to the higher doses was done in 2 sections. Consequently, although the similar demographics of the treatment groups offer reassurance as to the validity of the results, the efficacy data should still be interpreted with some caution. Analysis of time to death was one of the endpoints not specified in the protocol that were analysed retrospectively to compare the effect of high doses (450 mg to 600 mg) of bicalutamide or castration on survival rates of participants with advanced prostate cancer

BMD, bone mineral density; CgA, chromogranin A; DMSC, Data Management Sub-Committee; ECOG, Eastern Cooperative Oncology Group; FFM, fat-free mass; HDL, high-density lipoprotein; ITT, intention-to-treat; LDL, low-density lipoprotein; LHRH, luteinising hormone–releasing hormone; PSA, prostate-specific antigen; SD, standard deviation; VLDL, very low-density lipoprotein; x-ray, x-radiation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akaza 1993	Comparison of other androgen suppression therapies
Akaza 2003	Comparison of other androgen suppression therapies
Alberts 2006	Patients not fitting to inclusion criteria. Comparison of other androgen suppression therapies
Aso 1993a	Comparison of other androgen suppression therapies
Aso 1993b	Comparison of other androgen suppression therapies

Study	Reason for exclusion
Auvinen 2004	Different topic
Ayub 1990	Comparison of other androgen suppression therapies
Blackledge 1996	Not a randomised controlled study (review article)
Boccardo 2002	Comparison of other androgen suppression therapies
Bono 2007	Not a randomised controlled study. Patients not fitting to inclusion criteria
Bruun 1996	Comparison of other androgen suppression therapies
Chang 1996	Comparison of other androgen suppression therapies
Chatelain 1994	Comparison of other androgen suppression therapies
Cockshott 1990	No comparison with control group
Colquhoun 2012	Different topic
Dawson 1997	Comparison of other androgen suppression therapies
Decensi 2007	Comparison of bicalutamide versus no treatment
Ekwueme 2012	Not a randomised controlled study
EPC program	Comparison of bicalutamide versus placebo
Eri 1993	Patients not fitting to inclusion criteria. Comparison of bicalutamide versus placebo
Eri 2001	Comparison of bicalutamide versus placebo. Patients not fitting to inclusion criteria
Festuccia 2007	Different topic. Comparison of other androgen suppression therapies
Gravina 2007	Different topic
Henderson 2003	Not a randomised controlled study. Different topic
Iida 2011	Comparison of other androgen suppression therapies. Not a randomised controlled study
Jacobo 1976	Comparison of other androgen suppression therapies
Johansson 1988	Comparison of other androgen suppression therapies
Jones 1994	Not a randomised controlled study
Kaisary 1994	Not a randomised controlled study
Kariakin 2001	No comparison with control group
Kasimis 2000	Not a randomised controlled study
Kotake 1996a	Not a randomised controlled study
Kotake 1996b	Comparison of different doses of bicalutamide (no comparison with castration)

Study	Reason for exclusion
Kulkarni 2003	Comparison of other androgen suppression therapies
Lazzaro 2007	Different topic
Lee 2009	Comparison of other androgen suppression therapies. Randomised cross-over study. Patients not fitting to inclusion criteria
Lee 2010	Comparison of other androgen suppression therapies. Randomised cross-over study. Patients not fitting to inclusion criteria
Lehmusvaara 2012	Not a randomised controlled study. Different topic
Lin 2011	Comparison of other androgen suppression therapies
Lissoni 2002	No comparison with control group
Loran 2001	Comparison of other androgen suppression therapies. Not a randomised controlled study. Patients not fitting to inclusion criteria
Lund 1988	Comparison of other androgen suppression therapies
Lunglmayr 1995	No comparison with control group
McGivern 2011	Different topic. Not a randomised controlled study
McGivern 2012	Different topic. Not a randomised controlled study
Migliari 1991	Not a randomised controlled study
Migliari 1992	No comparison with control group
Motofei 2011	Not a randomised controlled study
Murphy 2004	Comparison of different doses of flutamide. No comparison with castration
Newling 1989	Not a randomised controlled study
Noldus 1996	Comparison of other androgen suppression therapies
Nyman 2005	Not a randomised controlled study. Different topic
Oosterlinck 1996	Comparison of other androgen suppression therapies. Not a randomised controlled study
Ostri 1991	Comparison of other androgen suppression therapies
Petit 2008	Not a randomised controlled study
Prezioso 2007	Not a randomised controlled study
Raina 2007	Not a randomised controlled study
Raynaud 1988	Not a randomised controlled study
Scattoni 2006	Comparison of bicalutamide versus no treatment

Study	Reason for exclusion
Scher 1997	No comparison with control group. Patients not fitting to inclusion criteria
Schröder 2000	Comparison of other androgen suppression therapies
Schröder 2004	Comparison of other androgen suppression therapies
Sciarra 2004b	Not a randomised controlled study
See 2004	Not a randomised controlled study
Shipley 2011	Comparison of bicalutamide versus placebo
Smith 2003	Not a randomised controlled study
Soloway 1996	No comparison with control group
Thorpe 1996	Comparison of other androgen suppression therapies
Thrasher 2000	Comparison of other androgen suppression therapies
Tyrrell 1998	No comparison with castration
Verhelst 1994	No comparison with control group
Wadhwa 2009	Not a randomised controlled study
Wadhwa 2011	Not a randomised controlled study
Wirth 2004	Comparison of flutamide versus no treatment
Yoshimura 2003	Not a randomised controlled study. Different topic
Zanardi 2009	Patients not fitting to inclusion criteria. Not a randomised controlled study
Zhigang 2008	Patients not fitting to inclusion criteria. Comparison of flutamide with placebo

DATA AND ANALYSES

Comparison 1. Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	6		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 Total	6	2712	Hazard Ratio (Random, 95% CI)	1.24 [1.05, 1.48]
1.2 Subgroup analysis: non-metastatic disease	2	608	Hazard Ratio (Random, 95% CI)	1.00 [0.79, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Subgroup analysis: metastatic disease	5	2103	Hazard Ratio (Random, 95% CI)	1.34 [1.14, 1.57]
1.4 Subgroup analysis: bicalutamide 50 mg daily	3	1196	Hazard Ratio (Random, 95% CI)	1.45 [1.19, 1.75]
1.5 Subgroup analysis: bicalutamide 150 mg daily	2	1288	Hazard Ratio (Random, 95% CI)	1.18 [0.96, 1.45]
1.6 Subgroup analysis: bicalutamide 450 mg daily or 600 mg daily	1	228	Hazard Ratio (Random, 95% CI)	0.88 [0.62, 1.25]
1.7 Subgroup analysis: non-metastatic disease and bicalutamide 150 mg daily	1	480	Hazard Ratio (Random, 95% CI)	1.05 [0.81, 1.36]
1.8 Subgroup analysis: non-metastatic disease and bicalutamide 450 mg daily or 600 mg daily	1	128	Hazard Ratio (Random, 95% CI)	0.79 [0.46, 1.36]
1.9 Subgroup analysis: metastatic disease and bicalutamide 50 mg daily	3	1196	Hazard Ratio (Random, 95% CI)	1.45 [1.19, 1.75]
1.10 Subgroup analysis: metastatic disease and bicalutamide 150 mg daily	1	808	Hazard Ratio (Random, 95% CI)	1.30 [1.04, 1.63]
1.11 Subgroup analysis: metastatic disease and bicalutamide 450 mg daily or 600 mg daily	1	99	Hazard Ratio (Random, 95% CI)	0.91 [0.56, 1.48]
2 Cancer-specific mortality	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Total	3	904	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.86, 2.05]
2.2 Total after a minimum 12 months	2	680	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.71, 3.73]
2.3 Total after median 5 years	1	224	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.73, 1.47]
3 Treatment discontinuation due to adverse events	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Total	8	1559	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.13, 2.94]
3.2 Subgroup analysis: non-metastatic disease	3	194	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.66, 3.28]
3.3 Subgroup analysis: metastatic disease	4	1141	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.54, 3.54]
3.4 Subgroup analysis: bicalutamide 50 mg daily	3	1037	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.29, 2.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 Subgroup analysis: bicalutamide 150 mg daily	3	194	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.66, 3.28]
3.6 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Fixed, 95% CI)	8.35 [0.46, 151.19]
3.7 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [1.17, 6.01]
3.8 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.95, 6.31]
4 Clinical progression	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Total at 1 year	5	2067	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.08, 1.45]
4.2 Total at 70 weeks	6	2373	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.08, 1.45]
4.3 Total at 2 years	3	1336	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.04, 1.25]
4.4 Total at 3 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.23]
4.5 Total at 4 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.91, 1.26]
4.6 Total at 5 years	2	698	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.06]
4.7 Subgroup analysis: non-metastatic disease at 1 year	2	528	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.82, 1.96]
4.8 Subgroup analysis: non-metastatic disease at 70 weeks	2	528	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.83, 1.68]
4.9 Subgroup analysis: non-metastatic disease at 2 years	2	528	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.81, 1.31]
4.10 Subgroup analysis: non-metastatic disease at 3 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.23]
4.11 Subgroup analysis: non-metastatic disease at 4 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.91, 1.26]
4.12 Subgroup analysis: non-metastatic disease at 5 years	1	480	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.06]
4.13 Subgroup analysis: metastatic disease at 1 year	3	1539	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.05, 1.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.14 Subgroup analysis: metastatic disease at 70 weeks	4	1845	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.07, 1.51]
4.15 Subgroup analysis: metastatic disease at 2 years	1	808	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.05, 1.29]
4.16 Subgroup analysis: bicalutamide 50 mg daily at 1 year	2	731	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.91, 1.76]
4.17 Subgroup analysis: bicalutamide 50 mg daily at 70 weeks	3	1037	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.99, 1.71]
4.18 Subgroup analysis: bicalutamide 150 mg daily at 1 year	3	1336	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.07, 1.46]
4.19 Subgroup analysis: bicalutamide 150 mg daily at 70 weeks	3	1336	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.07, 1.39]
4.20 Subgroup analysis: bicalutamide 150 mg daily at 2 years	3	1336	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.04, 1.25]
4.21 Subgroup analysis: bicalutamide 150 mg daily at 3 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.23]
4.22 Subgroup analysis: bicalutamide 150 mg daily at 4 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.91, 1.26]
4.23 Subgroup analysis: bicalutamide 150 mg daily at 5 years	1	480	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.06]
4.24 Subgroup analysis: bicalutamide 450 mg daily at 5 years	1	177	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.54, 1.86]
4.25 Subgroup analysis: bicalutamide 600 mg daily at 5 years	1	127	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.33, 1.86]
5 Clinical progression (with imputed event numbers)	7		Risk Ratio (Fixed, 95% CI)	Subtotals only
5.1 Total (with imputed event numbers) at 1 year	5	2167	Risk Ratio (Fixed, 95% CI)	1.43 [1.16, 1.76]
5.2 Total (with imputed event numbers) at 70 weeks	6	2543	Risk Ratio (Fixed, 95% CI)	1.43 [1.19, 1.73]
5.3 Total (with imputed event numbers) at 2 years	3	1347	Risk Ratio (Fixed, 95% CI)	1.39 [1.09, 1.78]
5.4 Total (with imputed event numbers) at 5 years	2	708	Risk Ratio (Fixed, 95% CI)	0.86 [0.56, 1.31]
5.5 Subgroup analysis: non-metastatic disease (with imputed event numbers) at 1 year	2	539	Risk Ratio (Fixed, 95% CI)	1.33 [0.80, 2.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.6 Subgroup analysis: non-metastatic disease (with imputed event numbers) at 70 weeks	2	539	Risk Ratio (Fixed, 95% CI)	1.23 [0.78, 1.94]
5.7 Subgroup analysis: non-metastatic disease (with imputed event numbers) at 2 years	2	539	Risk Ratio (Fixed, 95% CI)	1.05 [0.71, 1.55]
5.8 Subgroup analysis: non-metastatic disease (with imputed event numbers) at 5 years	1	480	Risk Ratio (Fixed, 95% CI)	0.84 [0.52, 1.36]
5.9 Subgroup analysis: metastatic disease (with imputed event numbers) at 1 year	3	1628	Risk Ratio (Fixed, 95% CI)	1.45 [1.16, 1.82]
5.10 Subgroup analysis: metastatic disease (with imputed event numbers) at 70 weeks	4	2004	Risk Ratio (Fixed, 95% CI)	1.48 [1.20, 1.83]
5.11 Subgroup analysis: metastatic disease (with imputed event numbers) at 2 years	1	808	Risk Ratio (Fixed, 95% CI)	1.69 [1.22, 2.32]
5.12 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 1 year	2	820	Risk Ratio (Fixed, 95% CI)	1.40 [0.99, 1.98]
5.13 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 70 weeks	3	1196	Risk Ratio (Fixed, 95% CI)	1.40 [1.04, 1.88]
5.14 Subgroup analysis: bicalutamide 150 mg daily (with imputed event numbers) at 1 year	3	1347	Risk Ratio (Fixed, 95% CI)	1.45 [1.12, 1.87]
5.15 Subgroup analysis: bicalutamide 150 mg daily (with imputed event numbers) at 70 weeks	3	1347	Risk Ratio (Fixed, 95% CI)	1.46 [1.14, 1.87]
5.16 Subgroup analysis: bicalutamide 150 mg daily (with imputed event numbers) at 2 years	3	1347	Risk Ratio (Fixed, 95% CI)	1.39 [1.09, 1.78]
5.17 Subgroup analysis: bicalutamide 150 mg daily (with imputed event numbers) at 5 years	1	480	Risk Ratio (Fixed, 95% CI)	0.84 [0.52, 1.36]
5.18 Subgroup analysis: bicalutamide 450 mg daily (with imputed event numbers) at 5 years	1	185	Risk Ratio (Fixed, 95% CI)	1.00 [0.41, 2.47]
5.19 Subgroup analysis: bicalutamide 600 mg daily (with imputed event numbers) at 5 years	1	133	Risk Ratio (Fixed, 95% CI)	0.78 [0.27, 2.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Biochemical progression	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Total at 1 year	2	99	Risk Ratio (M-H, Fixed, 95% CI)	3.12 [0.13, 73.06]
6.2 Total at 2 years	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Total at 3 years	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.94, 1.26]
7 Biochemical progression (with imputed event numbers)	3		Risk Ratio (Fixed, 95% CI)	Subtotals only
7.1 Total (with imputed event numbers) at 1 year	2	110	Risk Ratio (Fixed, 95% CI)	2.29 [0.15, 34.62]
7.2 Total (with imputed event numbers) at 2 years	1	59	Risk Ratio (Fixed, 95% CI)	0.96 [0.00, 196.72]
7.3 Total (with imputed event numbers) at 3 years	1	104	Risk Ratio (Fixed, 95% CI)	1.07 [0.72, 1.58]
8 Treatment failure	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Total at 1 year	3	1539	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.02, 1.38]
8.2 Total at 70 weeks	4	1845	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.05, 1.52]
8.3 Total at 2 years	1	808	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.05, 1.24]
8.4 Total at 3 years	1	86	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.63, 3.99]
8.5 Total at 4 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.16]
8.6 Subgroup analysis: non-metastatic disease at 4 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.16]
8.7 Subgroup analysis: metastatic disease at 1 year	3	1539	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.02, 1.38]
8.8 Subgroup analysis: metastatic disease at 70 weeks	4	1845	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.05, 1.52]
8.9 Subgroup analysis: metastatic disease at 2 years	1	808	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.05, 1.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.10 Subgroup analysis: metastatic disease at 3 years	1	86	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.63, 3.99]
8.11 Subgroup analysis: bicalutamide 50 mg daily at 1 year	2	731	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.90, 1.57]
8.12 Subgroup analysis: bicalutamide 50 mg daily at 70 weeks	3	1037	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.98, 1.75]
8.13 Subgroup analysis: bicalutamide 150 mg daily at 1 year	1	808	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.01, 1.35]
8.14 Subgroup analysis: bicalutamide 150 mg daily at 70 weeks	1	808	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.05, 1.34]
8.15 Subgroup analysis: bicalutamide 150 mg daily at 2 years	1	808	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.05, 1.24]
8.16 Subgroup analysis: bicalutamide 150 mg daily at 4 years	1	480	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.16]
8.17 Subgroup analysis: flutamide 250 mg 3 times daily at 3 years	1	86	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.63, 3.99]
9 Treatment failure (with imputed event numbers)	5		Risk Ratio (Fixed, 95% CI)	Subtotals only
9.1 Total (with imputed event numbers) at 1 year	3	1628	Risk Ratio (Fixed, 95% CI)	1.19 [1.06, 1.35]
9.2 Total (with imputed event numbers) at 70 weeks	4	2004	Risk Ratio (Fixed, 95% CI)	1.21 [1.09, 1.35]
9.3 Total (with imputed event numbers) at 3 years	1	104	Risk Ratio (Fixed, 95% CI)	1.51 [0.32, 7.06]
9.4 Subgroup analysis: metastatic disease (with imputed event numbers) at 1 year	3	1628	Risk Ratio (Fixed, 95% CI)	1.19 [1.06, 1.35]
9.5 Subgroup analysis: metastatic disease (with imputed event numbers) at 70 weeks	4	2004	Risk Ratio (Fixed, 95% CI)	1.21 [1.09, 1.35]
9.6 Subgroup analysis: metastatic disease (with imputed event numbers) at 3 years	1	104	Risk Ratio (Fixed, 95% CI)	1.51 [0.32, 7.06]
9.7 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 1 year	2	820	Risk Ratio (Fixed, 95% CI)	1.27 [1.01, 1.60]
9.8 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 70 weeks	3	1196	Risk Ratio (Fixed, 95% CI)	1.29 [1.05, 1.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.9 Subgroup analysis: bicalutamide 150 mg daily (with imputed event numbers) at 1 year	1	808	Risk Ratio (Fixed, 95% CI)	1.17 [1.01, 1.35]
9.10 Subgroup analysis: bicalutamide 150 mg daily (with imputed event numbers) at 70 weeks	1	808	Risk Ratio (Fixed, 95% CI)	1.18 [1.05, 1.34]
9.11 Subgroup analysis: flutamide 250 mg 3 times daily (with imputed event numbers) at 3 years	1	104	Risk Ratio (Fixed, 95% CI)	1.51 [0.32, 7.06]
10 Breast pain	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Total	7	2670	Risk Ratio (M-H, Fixed, 95% CI)	22.97 [14.79, 35.67]
10.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Fixed, 95% CI)	19.39 [10.26, 36.66]
10.3 Subgroup analysis: bicalutamide 150 mg daily	3	1420	Risk Ratio (M-H, Fixed, 95% CI)	25.82 [13.34, 49.97]
10.4 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	23.48 [5.88, 93.73]
10.5 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	25.71 [6.37, 103.78]
11 Pelvic pain	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Total	5	2395	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.24]
11.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.22]
11.3 Subgroup analysis: bicalutamide 150 mg daily	2	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.79, 1.53]
12 Bone pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.68, 1.72]
13 Back pain	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Total	5	1351	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.54, 1.94]
13.3 Subgroup analysis: bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.54, 7.71]
13.4 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.59, 1.80]
13.5 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.29, 1.57]
14 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Total	2	584	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.24, 1.15]
14.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.20, 1.05]
14.3 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.12, 66.75]
15 Abdominal pain	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Total	3	1058	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.90, 2.48]
15.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.58, 2.70]
15.3 Subgroup analysis: bicalutamide 150 mg daily	1	474	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.92, 3.81]
15.4 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.42]
16 General pain	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Total	4	2073	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.16]
16.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.65, 1.32]
16.3 Subgroup analysis: bicalutamide 150 mg daily	2	1369	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.16]
16.4 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.80, 2.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.5 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.67, 2.70]
17 Gynaecomastia	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 Total	8	2774	Risk Ratio (M-H, Random, 95% CI)	8.43 [3.19, 22.28]
17.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Random, 95% CI)	14.07 [3.74, 52.85]
17.3 Subgroup analysis: bicalutamide 150 mg daily	3	1420	Risk Ratio (M-H, Random, 95% CI)	5.01 [0.88, 28.69]
17.4 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Random, 95% CI)	3.70 [1.33, 10.33]
17.5 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Random, 95% CI)	27.88 [7.02, 110.79]
17.6 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Random, 95% CI)	20.36 [4.97, 83.40]
18 Constipation	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Total	4	1250	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.65, 1.95]
18.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.50, 1.73]
18.3 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.84, 2.81]
18.4 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.03, 3.85]
19 Diarrhoea	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 Total	7	1929	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.80, 3.71]
19.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.00, 3.82]
19.3 Subgroup analysis: bicalutamide 150 mg daily	2	575	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.14, 12.28]
19.4 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Random, 95% CI)	8.35 [0.46, 151.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.5 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.57, 3.19]
19.6 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Random, 95% CI)	2.14 [0.86, 5.32]
20 Vomiting	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Total	3	650	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [1.38, 10.87]
20.2 Subgroup analysis: bicalutamide 50 mg daily	2	546	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [0.99, 9.35]
20.3 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Fixed, 95% CI)	10.2 [0.58, 179.88]
21 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.34]
22 Loss of sexual interest	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Bicalutamide 150 mg daily	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.83]
23 Asthenia	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Total	4	2073	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.36, 2.31]
23.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.11, 2.72]
23.3 Subgroup analysis: bicalutamide 150 mg daily	2	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.10, 2.28]
23.4 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [1.38, 6.84]
23.5 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.95, 6.31]
24 Insomnia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 Total	2	325	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.11, 2.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.2 Subgroup analysis: bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.36]
24.3 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.38, 2.06]
24.4 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.29, 2.58]
25 Hot flashes	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 Total	8	2774	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.19, 0.27]
25.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.15, 0.27]
25.3 Subgroup analysis: bicalutamide 150 mg daily	3	1420	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.19, 0.30]
25.4 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.10, 0.82]
25.5 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.12, 0.40]
25.6 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.15, 0.63]
26 Night sweats	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Total	2	1571	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.17, 0.49]
26.2 Subgroup analysis: bicalutamide 50 mg daily	1	303	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.12, 1.09]
26.3 Subgroup analysis: bicalutamide 150 mg daily	1	1268	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.14, 0.49]
27 Anaemia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 Total	2	294	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.16, 5.35]
27.2 Subgroup analysis: bicalutamide 50 mg daily	1	243	Risk Ratio (M-H, Random, 95% CI)	3.18 [0.34, 30.13]
27.3 Subgroup analysis: bicalutamide 150 mg daily	1	51	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28 Hepatic enzyme increase	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 Total	2	205	Risk Ratio (M-H, Fixed, 95% CI)	4.91 [0.59, 40.86]
28.2 Subgroup analysis: bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	7.14 [0.38, 134.72]
28.3 Subgroup analysis: flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.12, 66.75]
29 Rash	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 Total	3	805	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.77, 2.16]
29.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.50, 1.92]
29.3 Subgroup analysis: bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	5.10 [0.62, 42.12]
29.4 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.47, 3.61]
29.5 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.58, 5.52]
30 Pruritus	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 Total	2	723	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [0.93, 7.19]
30.2 Subgroup analysis: bicalutamide 50 mg daily	2	723	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [0.93, 7.19]
31 Dyspnoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 Bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.24, 1.31]
32 Infection	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 Total	4	2294	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.03]
32.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.34, 0.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32.3 Subgroup analysis: bicalutamide 150 mg daily	1	1268	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.65, 1.33]
33 Pharyngitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 Total	2	325	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.47, 1.34]
33.2 Subgroup analysis: bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.11, 1.36]
33.3 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.56, 1.93]
33.4 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.34, 1.91]
34 Arthritis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 Bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.12, 1.60]
35 Sinusitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 Bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.36, 4.48]
36 Urinary tract infection	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
36.1 Total	2	698	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.19]
36.2 Subgroup analysis: bicalutamide 150 mg daily	1	474	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.43, 1.14]
36.3 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.40, 1.99]
36.4 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.57, 3.27]
37 Dizziness	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 Total	2	581	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.61, 1.95]
37.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.49, 1.97]

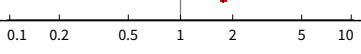
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.3 Subgroup analysis: bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.49, 4.20]
38 Haemorrhage	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 Total	2	546	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]
38.2 Subgroup analysis: bicalutamide 50 mg daily	2	546	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]
39 Haematuria	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
39.1 Total	2	954	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.14, 9.87]
39.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.26, 0.67]
39.3 Subgroup analysis: bicalutamide 150 mg daily	1	474	Risk Ratio (M-H, Random, 95% CI)	3.49 [2.01, 6.05]
40 Nocturia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.1 Bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.20, 0.69]
41 Urinary frequency	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
41.1 Bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.11, 0.47]
42 Urinary retention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
42.1 Bicalutamide 150 mg daily	1	1268	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.55, 1.24]
43 Peripheral oedema	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
43.1 Total	2	1748	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.33, 1.15]
43.2 Subgroup analysis: bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.21, 0.82]
43.3 Subgroup analysis: bicalutamide 150 mg daily	1	1268	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.54, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44 Anorexia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
44.1 Bicalutamide 50 mg daily	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.57, 2.18]
45 Loss of sexual function	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
45.1 Bicalutamide 50 mg daily	1	303	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.87]
46 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
46.1 Total	1	224	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.86, 3.15]
46.2 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.01, 3.80]
46.3 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.36, 2.63]
47 Gastralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
47.1 Flutamide 250 mg 3 times daily	1	104	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.12, 66.75]
48 Nausea	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
48.1 Total	3	1026	Risk Ratio (M-H, Random, 95% CI)	3.24 [0.95, 11.02]
48.2 Subgroup analysis: bicalutamide 50 mg daily	3	1026	Risk Ratio (M-H, Random, 95% CI)	3.24 [0.95, 11.02]
49 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
49.1 Bicalutamide 150 mg daily	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.31, 0.88]
50 Dry skin	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
50.1 Total	1	224	Risk Ratio (M-H, Fixed, 95% CI)	7.41 [0.42, 132.46]
50.2 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	8.81 [0.48, 161.24]

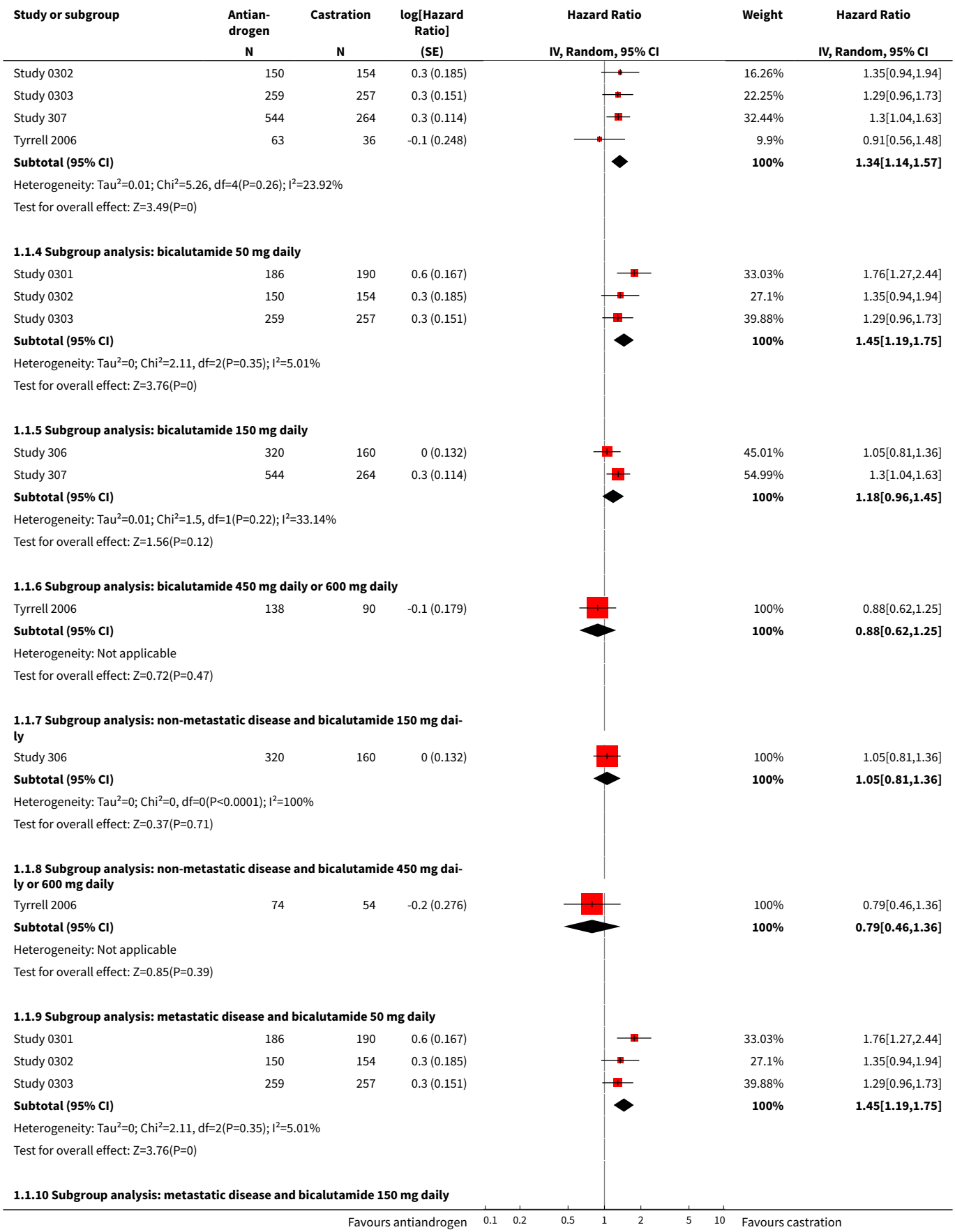
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
50.3 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	6.35 [0.26, 152.67]
51 Aggravation reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
51.1 Bicalutamide 150 mg daily	1	474	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.45, 1.05]
52 Serious adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
52.1 Total	2	325	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.28]
52.2 Subgroup analysis: bicalutamide 150 mg daily	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.49, 4.20]
52.3 Subgroup analysis: bicalutamide 450 mg daily	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.25]
52.4 Subgroup analysis: bicalutamide 600 mg daily	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.37]

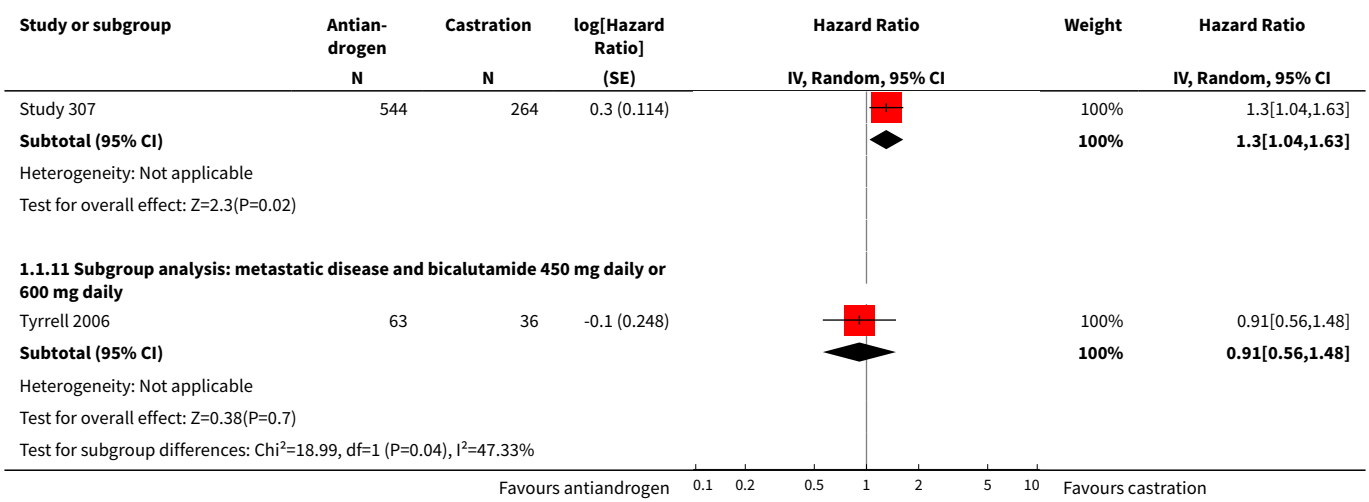
Analysis 1.1. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 1 Overall survival.

Study or subgroup	Antiandrogen N	Castration N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 Total						
Study 0301	186	190	0.6 (0.167)		15.19%	1.76[1.27,2.44]
Study 0302	150	154	0.3 (0.185)		13.49%	1.35[0.94,1.94]
Study 0303	259	257	0.3 (0.151)		16.86%	1.29[0.96,1.73]
Study 306	320	160	0 (0.132)		19.01%	1.05[0.81,1.36]
Study 307	544	264	0.3 (0.114)		21.42%	1.3[1.04,1.63]
Tyrrell 2006	138	90	-0.1 (0.179)		14.03%	0.88[0.62,1.25]
Subtotal (95% CI)					**100%**	**1.24[1.05,1.48]**
Heterogeneity: Tau^2=0.02; Chi^2=10.14, df=5(P=0.07); I^2=50.67%						
Test for overall effect: Z=2.47(P=0.01)						
1.1.2 Subgroup analysis: non-metastatic disease						
Study 306	320	160	0 (0.132)		81.28%	1.05[0.81,1.36]
Tyrrell 2006	74	54	-0.2 (0.276)		18.72%	0.79[0.46,1.36]
Subtotal (95% CI)					**100%**	**1[0.79,1.26]**
Heterogeneity: Tau^2=0; Chi^2=0.86, df=1(P=0.35); I^2=0%						
Test for overall effect: Z=0.04(P=0.97)						
1.1.3 Subgroup analysis: metastatic disease						
Study 0301	186	190	0.6 (0.167)		19.15%	1.76[1.27,2.44]

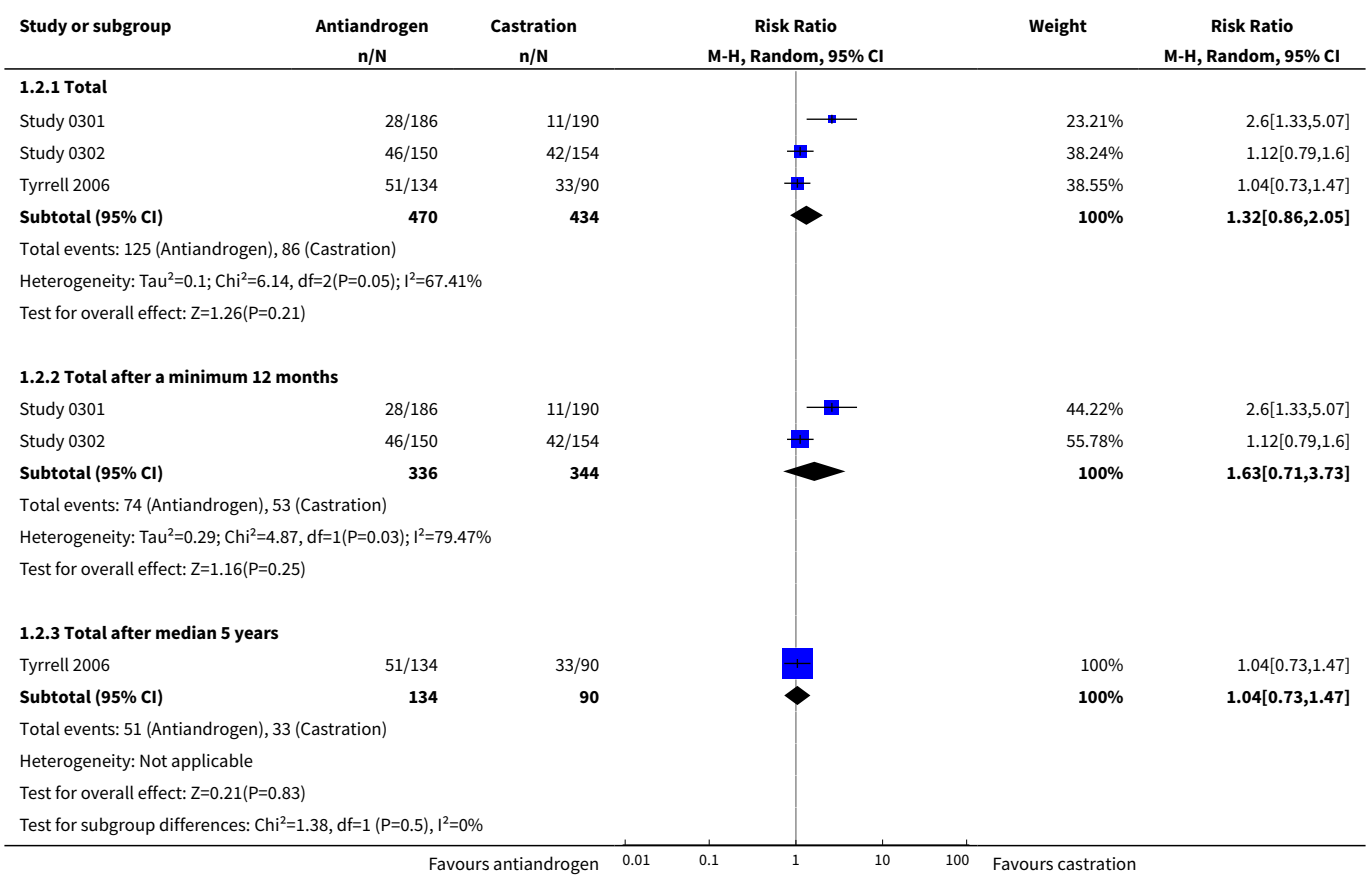


Favours antiandrogen — Favours castration



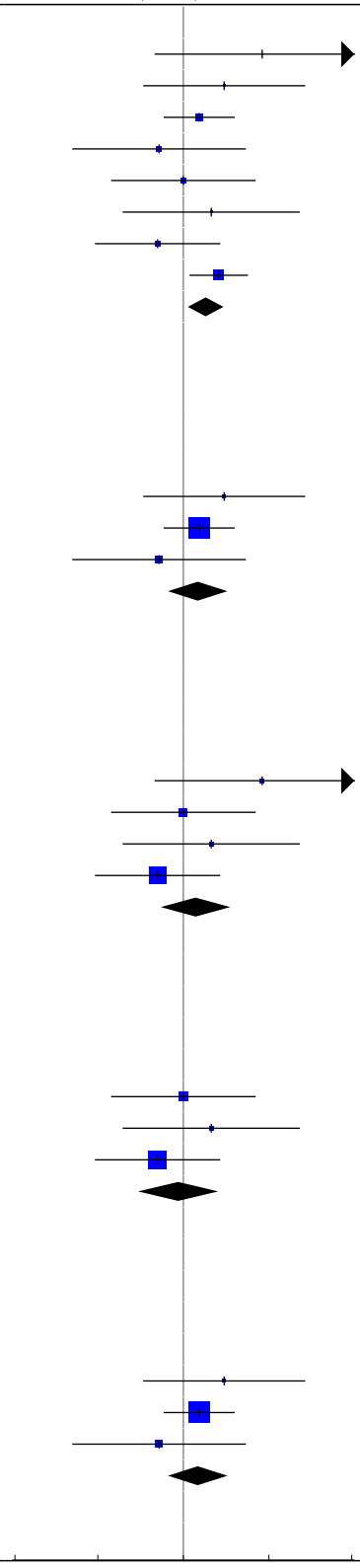


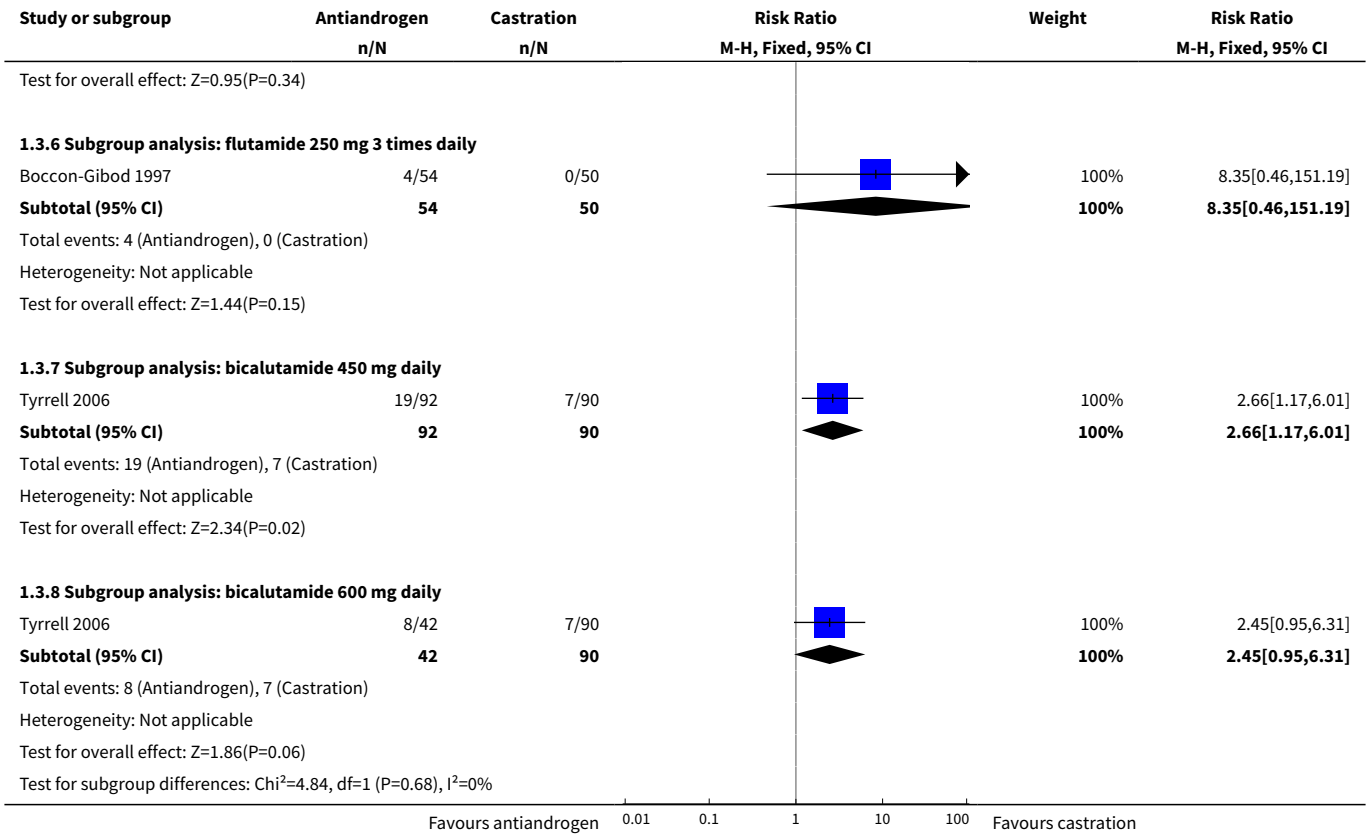
Analysis 1.2. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 2 Cancer-specific mortality.



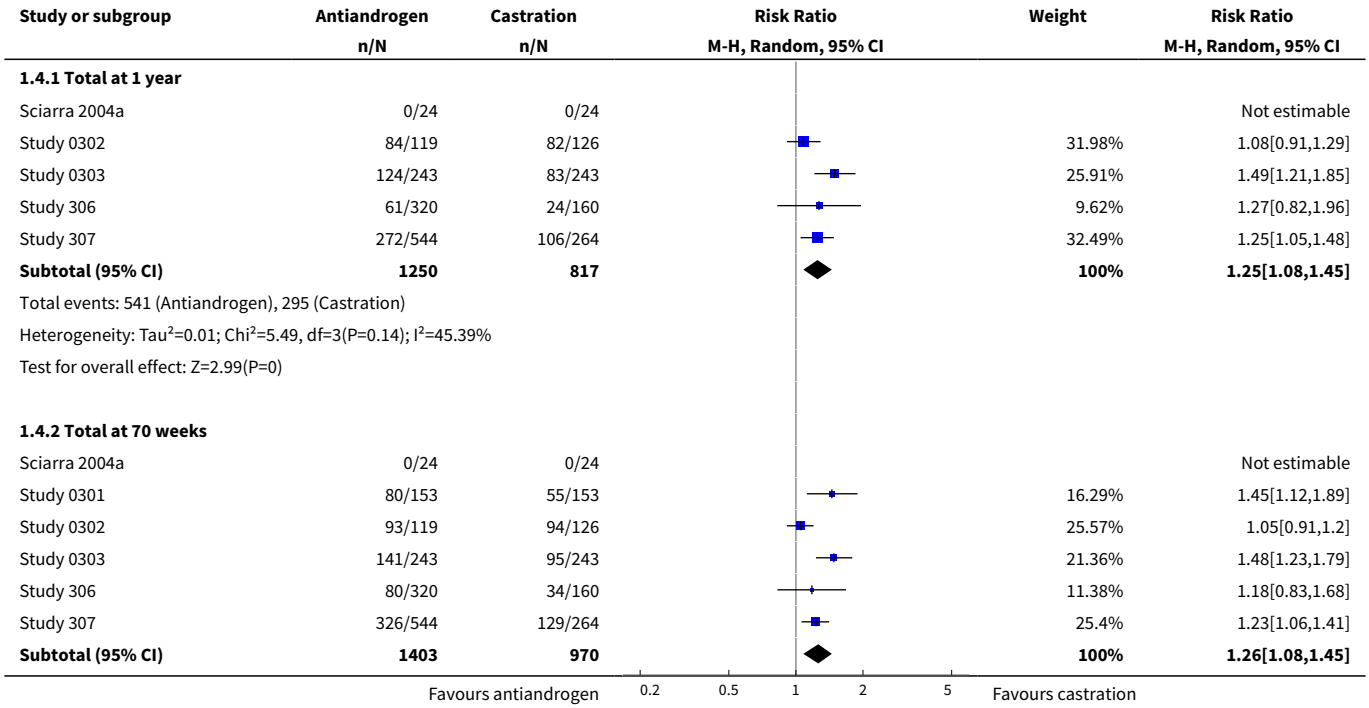
Analysis 1.3. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 3 Treatment discontinuation due to adverse events.

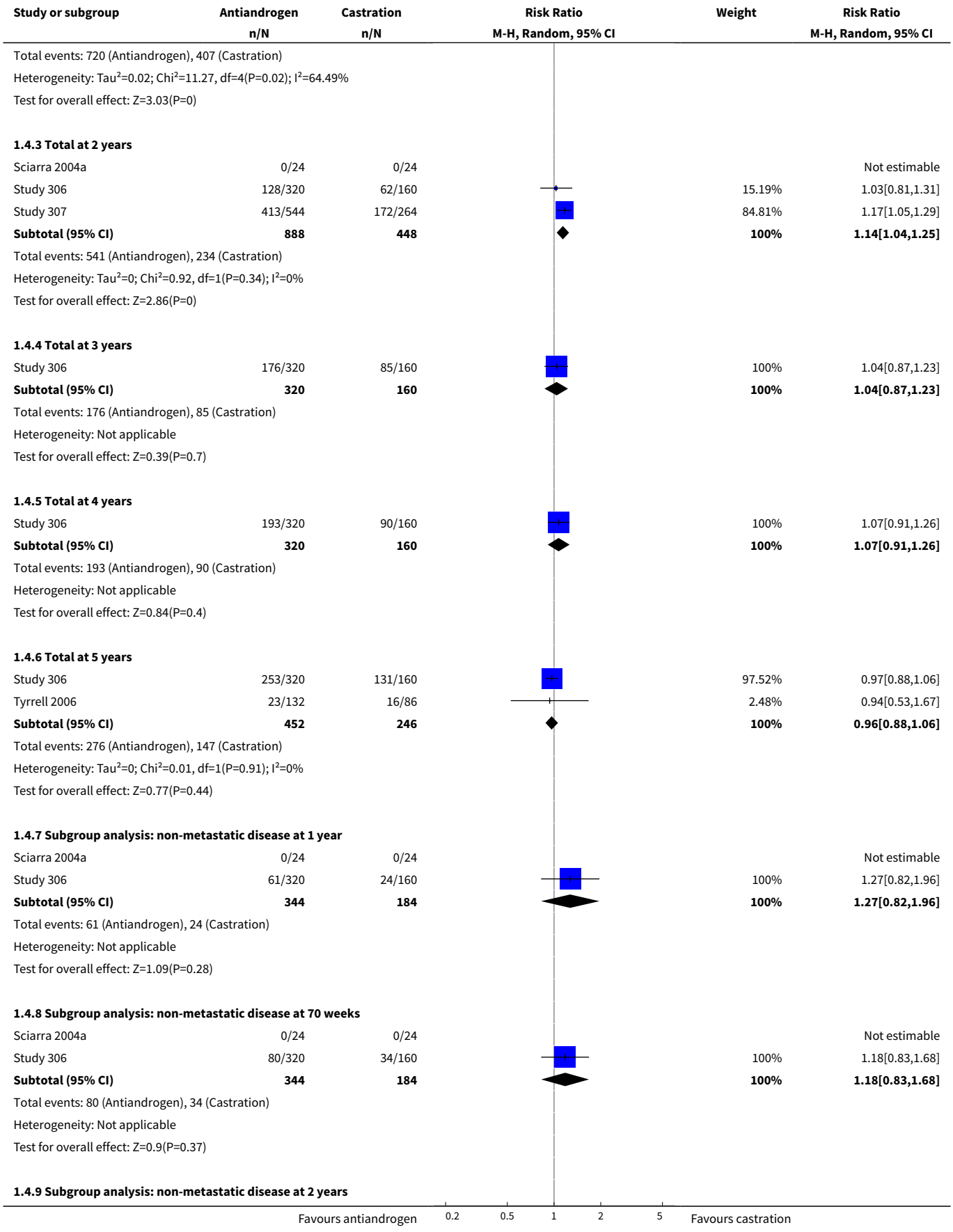
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Total					
Boccon-Gibod 1997	4/54	0/50		2.1%	8.35[0.46,151.19]
Dockery 2009	3/21	1/21		4.04%	3[0.34,26.56]
Sieber 2004	9/50	6/51		23.99%	1.53[0.59,3.98]
Smith 2004	1/25	2/26		7.92%	0.52[0.05,5.38]
Study 0301	2/153	2/153		8.08%	1[0.14,7.01]
Study 0302	2/119	1/126		3.92%	2.12[0.19,23.05]
Study 0303	2/243	4/243		16.15%	0.5[0.09,2.7]
Tyrrell 2006	27/134	7/90		33.82%	2.59[1.18,5.69]
Subtotal (95% CI)	**799**	**760**		**100%**	**1.82[1.13,2.94]**
Total events: 50 (Antiandrogen), 23 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=5.9, df=7(P=0.55); I^2=0%					
Test for overall effect: Z=2.47(P=0.01)					
1.3.2 Subgroup analysis: non-metastatic disease					
Dockery 2009	3/21	1/21		11.23%	3[0.34,26.56]
Sieber 2004	9/50	6/51		66.74%	1.53[0.59,3.98]
Smith 2004	1/25	2/26		22.03%	0.52[0.05,5.38]
Subtotal (95% CI)	**96**	**98**		**100%**	**1.47[0.66,3.28]**
Total events: 13 (Antiandrogen), 9 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=1.18, df=2(P=0.56); I^2=0%					
Test for overall effect: Z=0.95(P=0.34)					
1.3.3 Subgroup analysis: metastatic disease					
Boccon-Gibod 1997	4/54	0/50		6.93%	8.35[0.46,151.19]
Study 0301	2/153	2/153		26.7%	1[0.14,7.01]
Study 0302	2/119	1/126		12.97%	2.12[0.19,23.05]
Study 0303	2/243	4/243		53.4%	0.5[0.09,2.7]
Subtotal (95% CI)	**569**	**572**		**100%**	**1.39[0.54,3.54]**
Total events: 10 (Antiandrogen), 7 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=3.11, df=3(P=0.38); I^2=3.43%					
Test for overall effect: Z=0.68(P=0.49)					
1.3.4 Subgroup analysis: bicalutamide 50 mg daily					
Study 0301	2/153	2/153		28.69%	1[0.14,7.01]
Study 0302	2/119	1/126		13.93%	2.12[0.19,23.05]
Study 0303	2/243	4/243		57.38%	0.5[0.09,2.7]
Subtotal (95% CI)	**515**	**522**		**100%**	**0.87[0.29,2.56]**
Total events: 6 (Antiandrogen), 7 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=0.97, df=2(P=0.62); I^2=0%					
Test for overall effect: Z=0.25(P=0.8)					
1.3.5 Subgroup analysis: bicalutamide 150 mg daily					
Dockery 2009	3/21	1/21		11.23%	3[0.34,26.56]
Sieber 2004	9/50	6/51		66.74%	1.53[0.59,3.98]
Smith 2004	1/25	2/26		22.03%	0.52[0.05,5.38]
Subtotal (95% CI)	**96**	**98**		**100%**	**1.47[0.66,3.28]**
Total events: 13 (Antiandrogen), 9 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=1.18, df=2(P=0.56); I^2=0%					

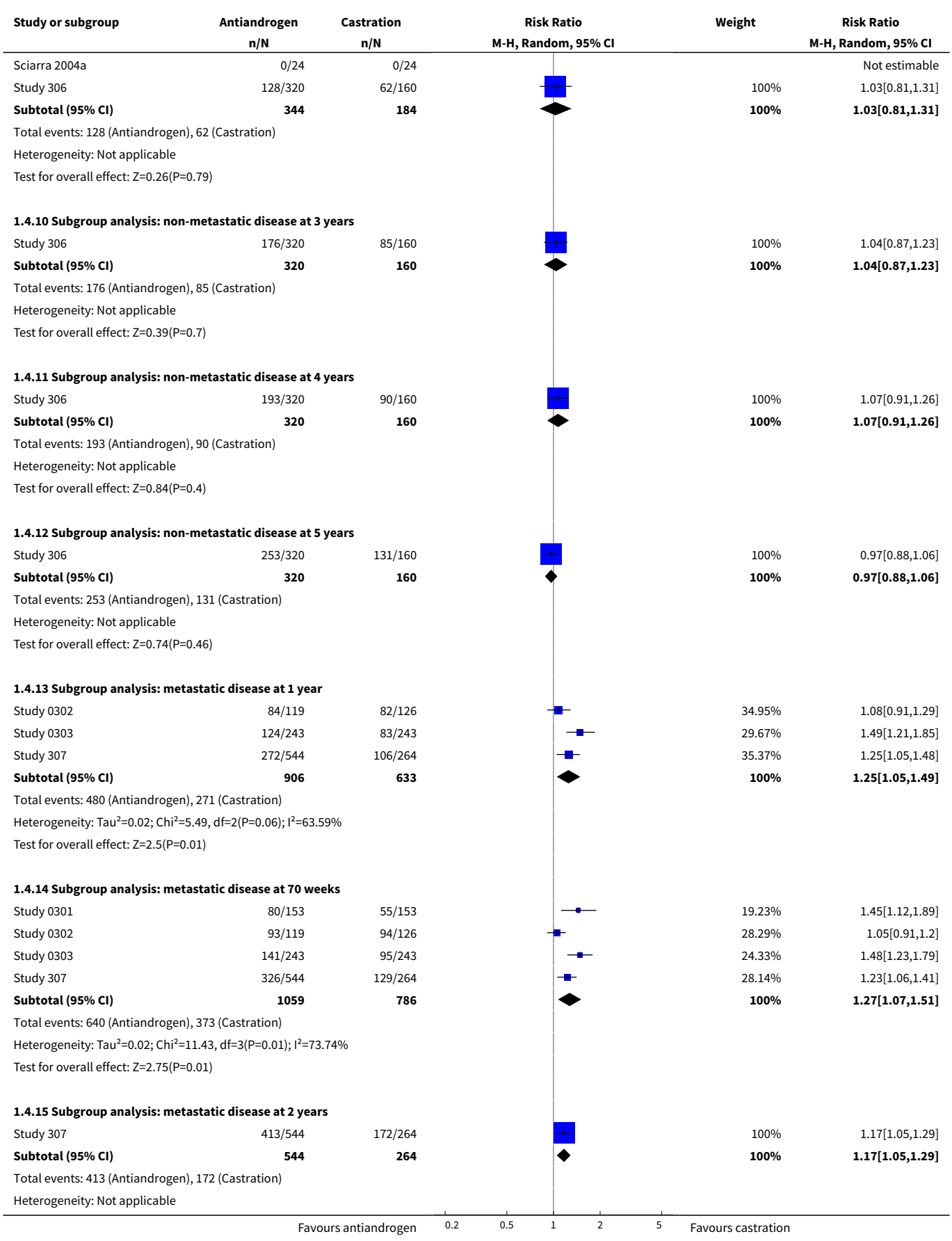


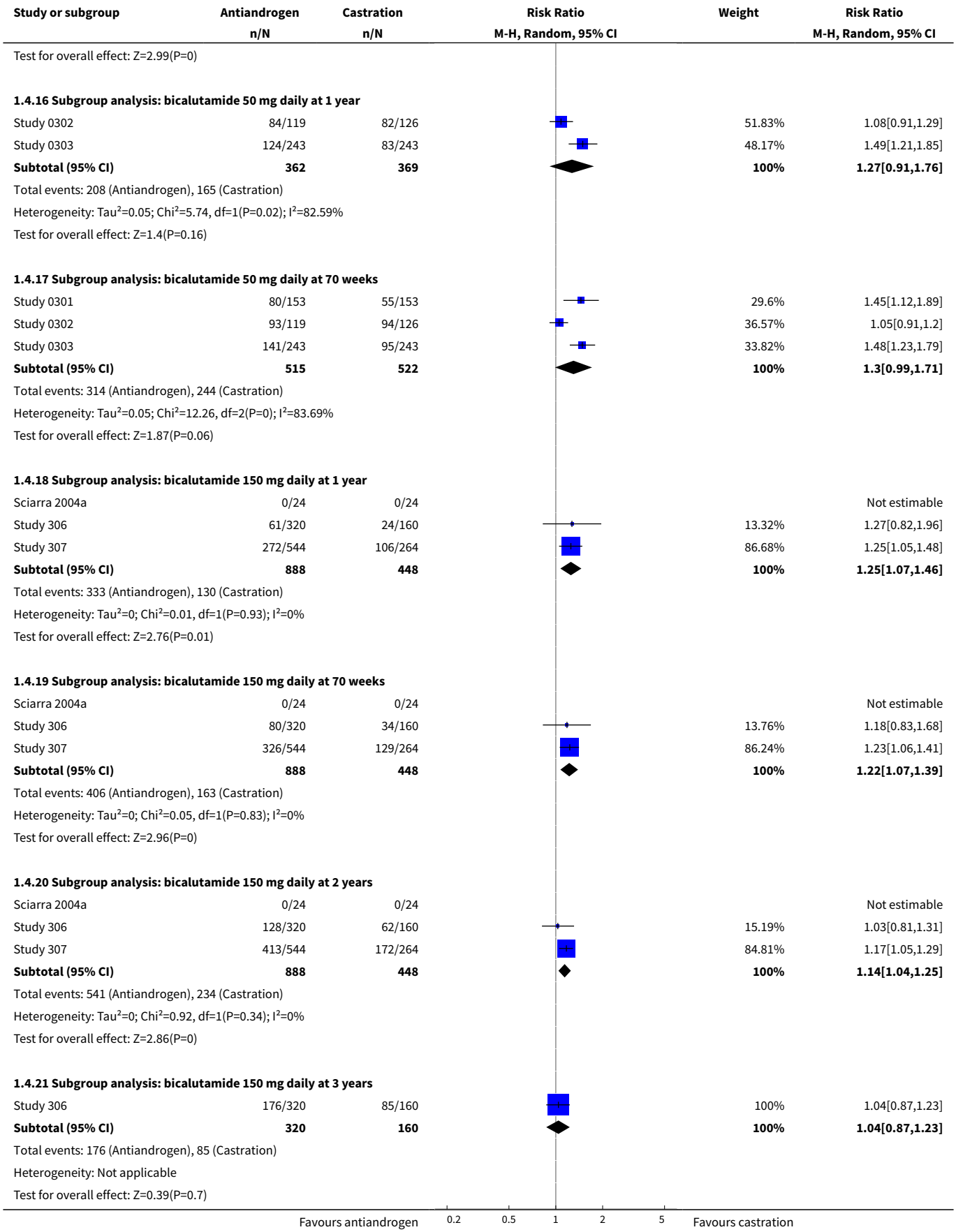


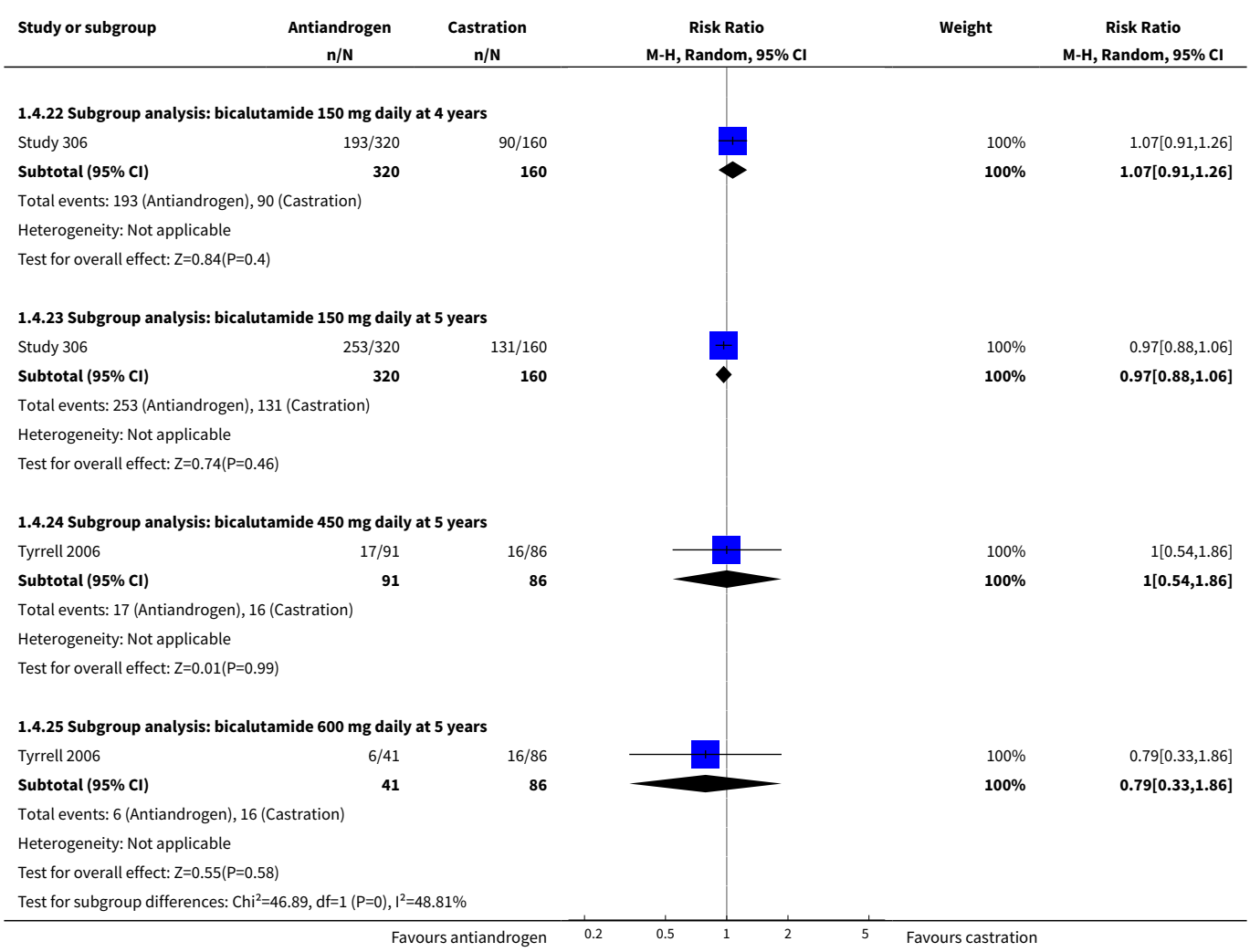
Analysis 1.4. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 4 Clinical progression.



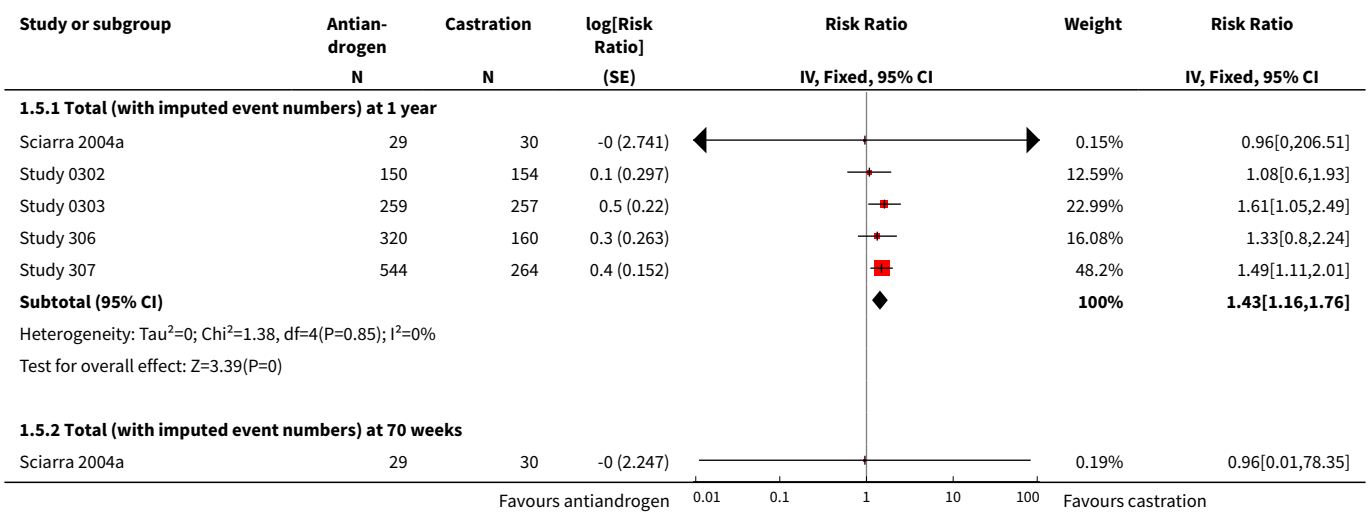


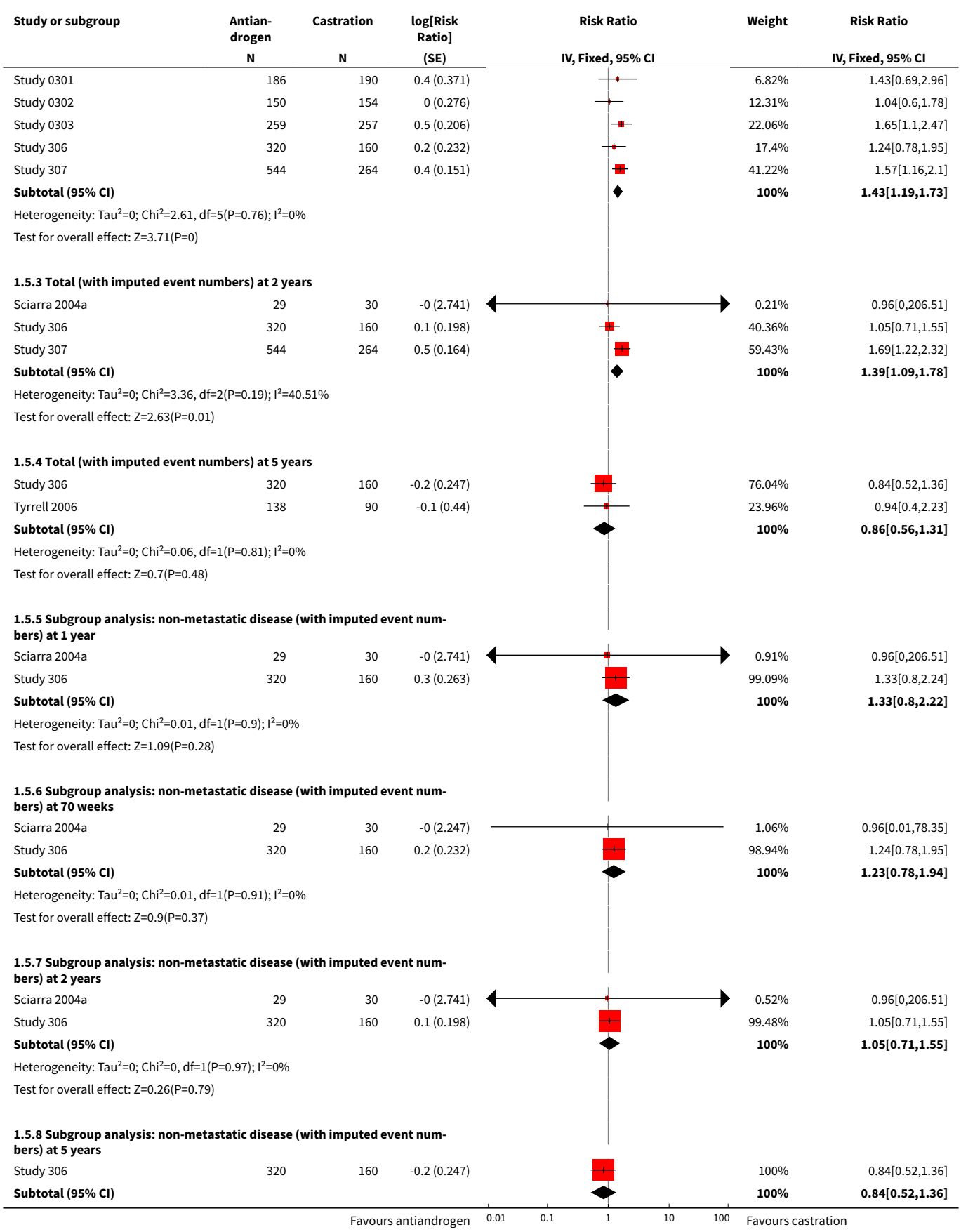




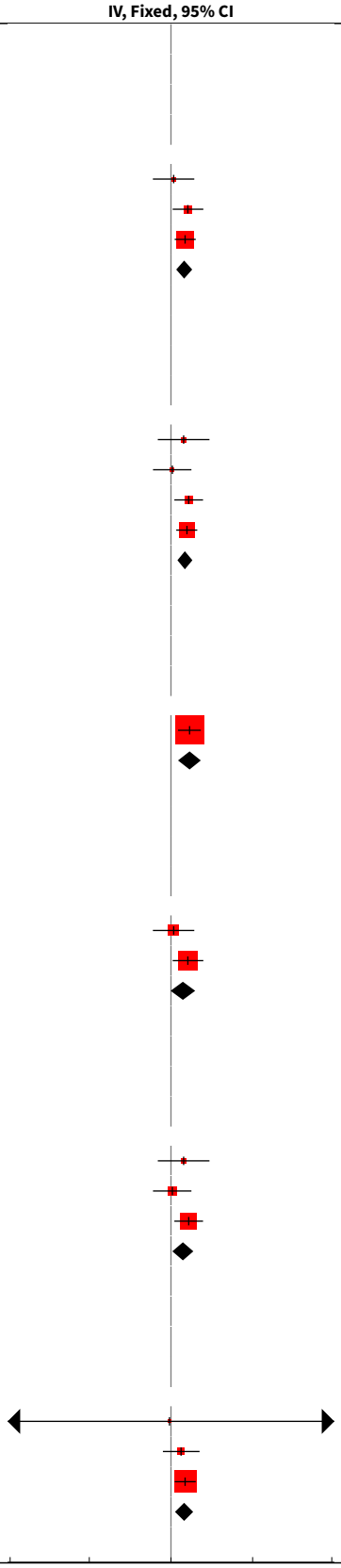


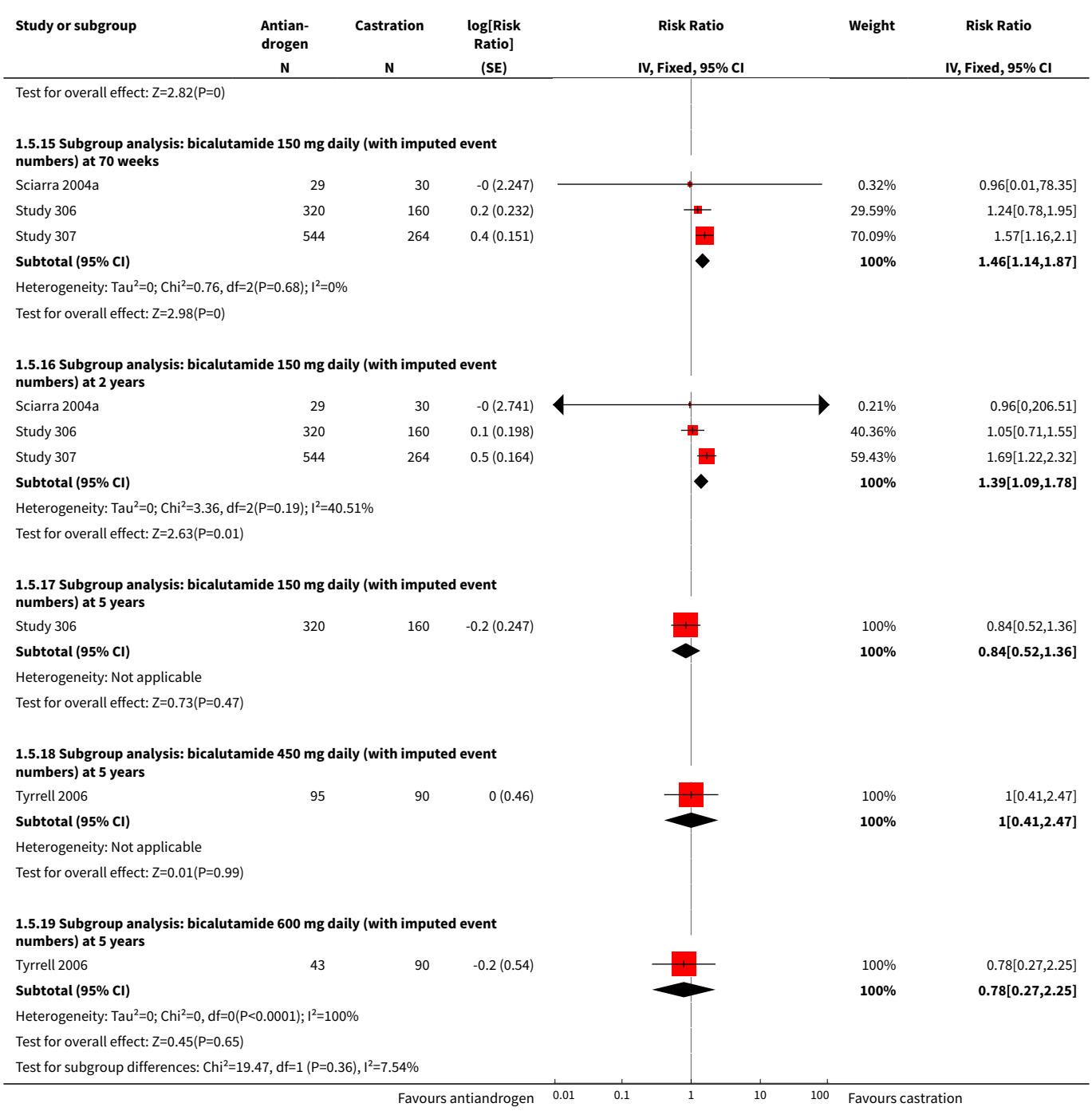
Analysis 1.5. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 5 Clinical progression (with imputed event numbers).



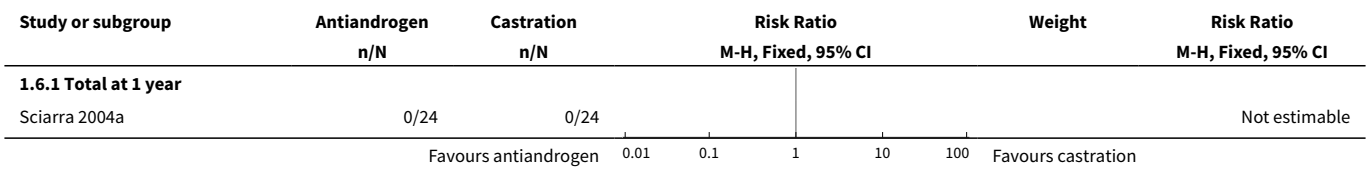


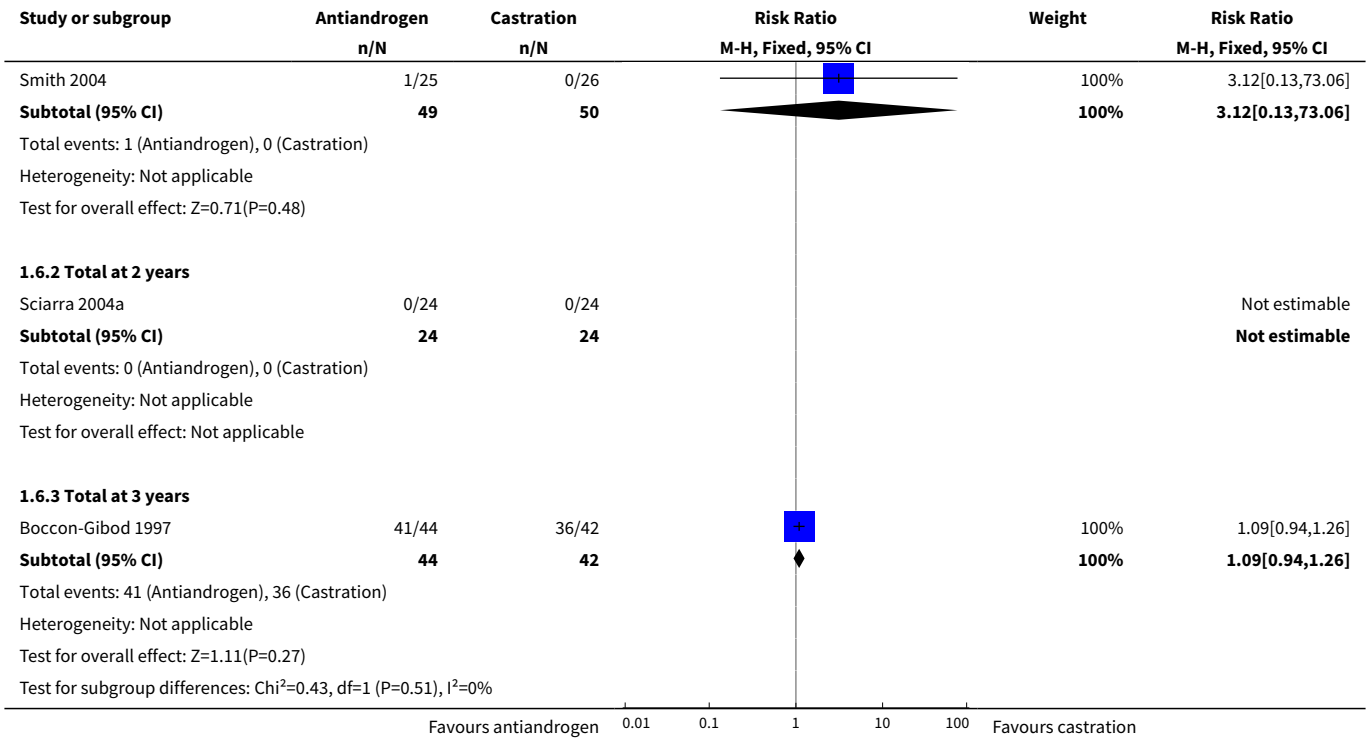
Study or subgroup	Antian-drogen N	Castration N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Heterogeneity: Not applicable						
Test for overall effect: Z=0.73(P=0.47)						
1.5.9 Subgroup analysis: metastatic disease (with imputed event numbers) at 1 year						
Study 0302	150	154	0.1 (0.297)		15.03%	1.08[0.6,1.93]
Study 0303	259	257	0.5 (0.22)		27.44%	1.61[1.05,2.49]
Study 307	544	264	0.4 (0.152)		57.53%	1.49[1.11,2.01]
Subtotal (95% CI)					**100%**	**1.45[1.16,1.82]**
Heterogeneity: Tau²=0; Chi²=1.28, df=2(P=0.53); I²=0%						
Test for overall effect: Z=3.23(P=0)						
1.5.10 Subgroup analysis: metastatic disease (with imputed event numbers) at 70 weeks						
Study 0301	186	190	0.4 (0.371)		8.28%	1.43[0.69,2.96]
Study 0302	150	154	0 (0.276)		14.94%	1.04[0.6,1.78]
Study 0303	259	257	0.5 (0.206)		26.77%	1.65[1.1,2.47]
Study 307	544	264	0.4 (0.151)		50.01%	1.57[1.16,2.1]
Subtotal (95% CI)					**100%**	**1.48[1.2,1.83]**
Heterogeneity: Tau²=0; Chi²=2.08, df=3(P=0.56); I²=0%						
Test for overall effect: Z=3.67(P=0)						
1.5.11 Subgroup analysis: metastatic disease (with imputed event numbers) at 2 years						
Study 307	544	264	0.5 (0.164)		100%	1.69[1.22,2.32]
Subtotal (95% CI)					**100%**	**1.69[1.22,2.32]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.2(P=0)						
1.5.12 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 1 year						
Study 0302	150	154	0.1 (0.297)		35.39%	1.08[0.6,1.93]
Study 0303	259	257	0.5 (0.22)		64.61%	1.61[1.05,2.49]
Subtotal (95% CI)					**100%**	**1.4[0.99,1.98]**
Heterogeneity: Tau²=0; Chi²=1.2, df=1(P=0.27); I²=16.83%						
Test for overall effect: Z=1.9(P=0.06)						
1.5.13 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 70 weeks						
Study 0301	186	190	0.4 (0.371)		16.57%	1.43[0.69,2.96]
Study 0302	150	154	0 (0.276)		29.88%	1.04[0.6,1.78]
Study 0303	259	257	0.5 (0.206)		53.55%	1.65[1.1,2.47]
Subtotal (95% CI)					**100%**	**1.4[1.04,1.88]**
Heterogeneity: Tau²=0; Chi²=1.81, df=2(P=0.4); I²=0%						
Test for overall effect: Z=2.23(P=0.03)						
1.5.14 Subgroup analysis: bicalutamide 150 mg daily (with imputed event numbers) at 1 year						
Sciarra 2004a	29	30	-0 (2.741)		0.23%	0.96[0,206.51]
Study 306	320	160	0.3 (0.263)		24.95%	1.33[0.8,2.24]
Study 307	544	264	0.4 (0.152)		74.82%	1.49[1.11,2.01]
Subtotal (95% CI)					**100%**	**1.45[1.12,1.87]**
Heterogeneity: Tau²=0; Chi²=0.16, df=2(P=0.93); I²=0%						



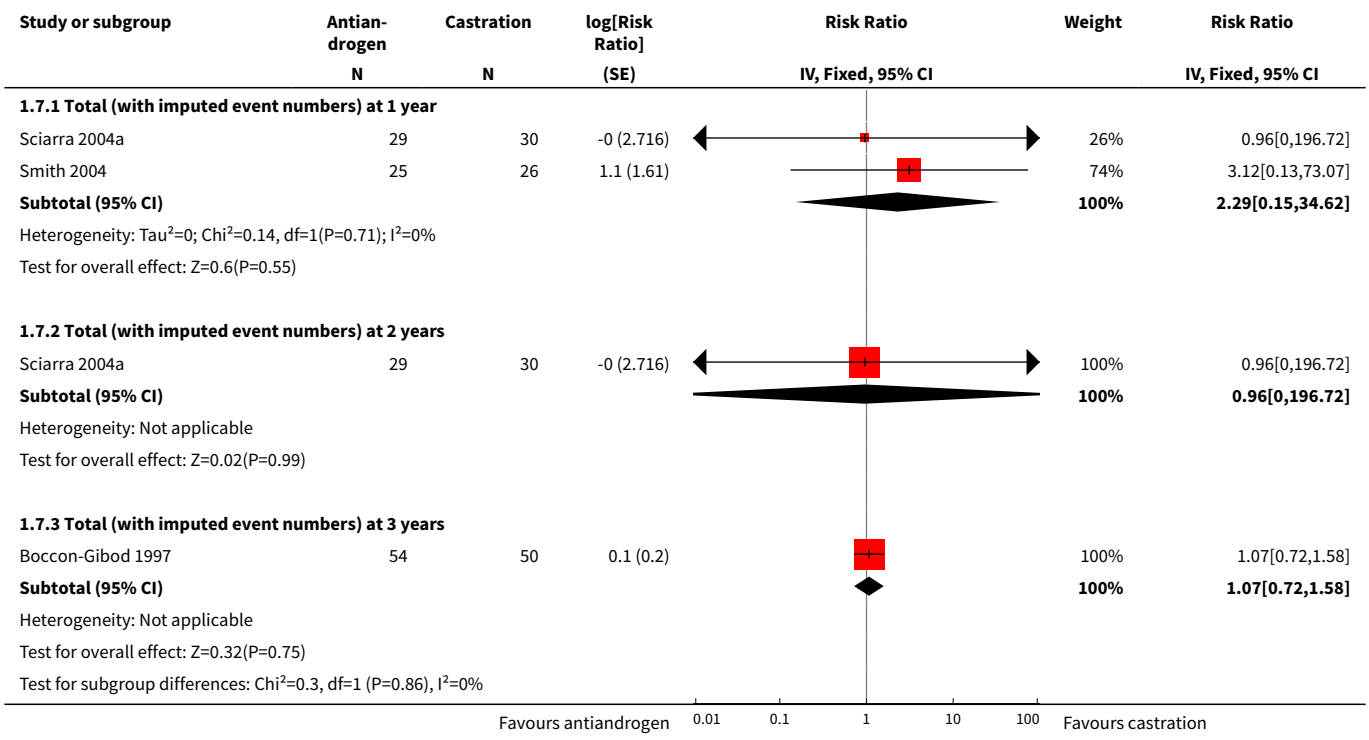


Analysis 1.6. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 6 Biochemical progression.



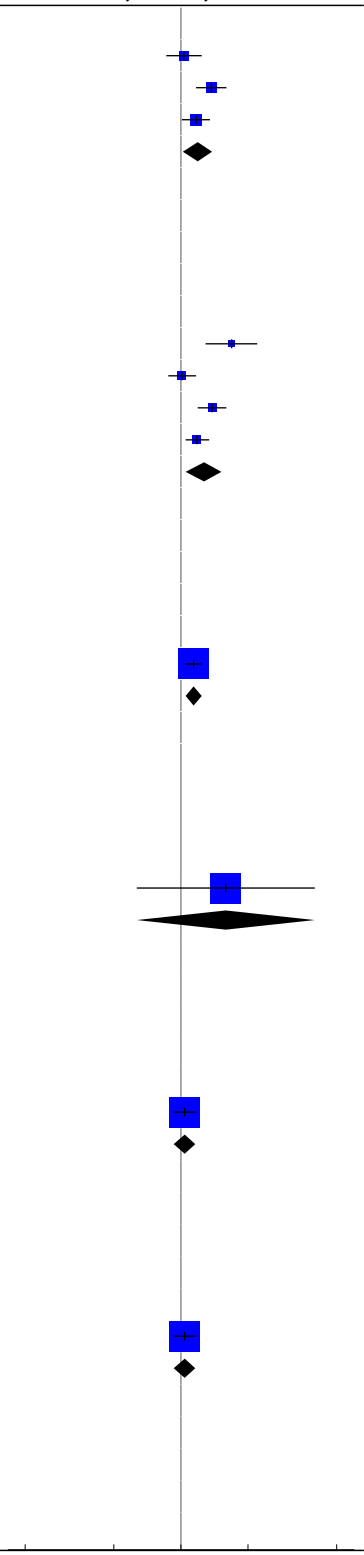


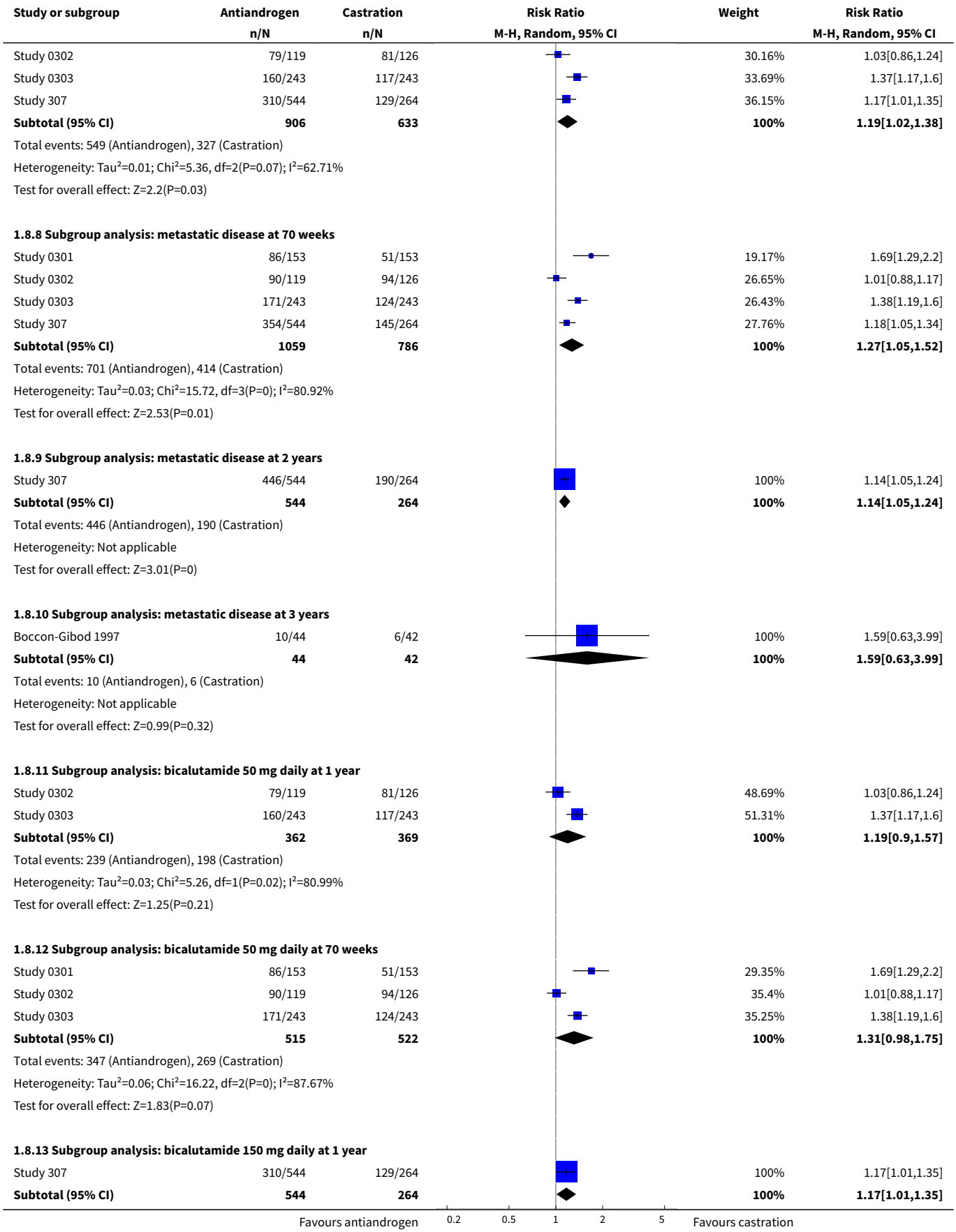
Analysis 1.7. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 7 Biochemical progression (with imputed event numbers).

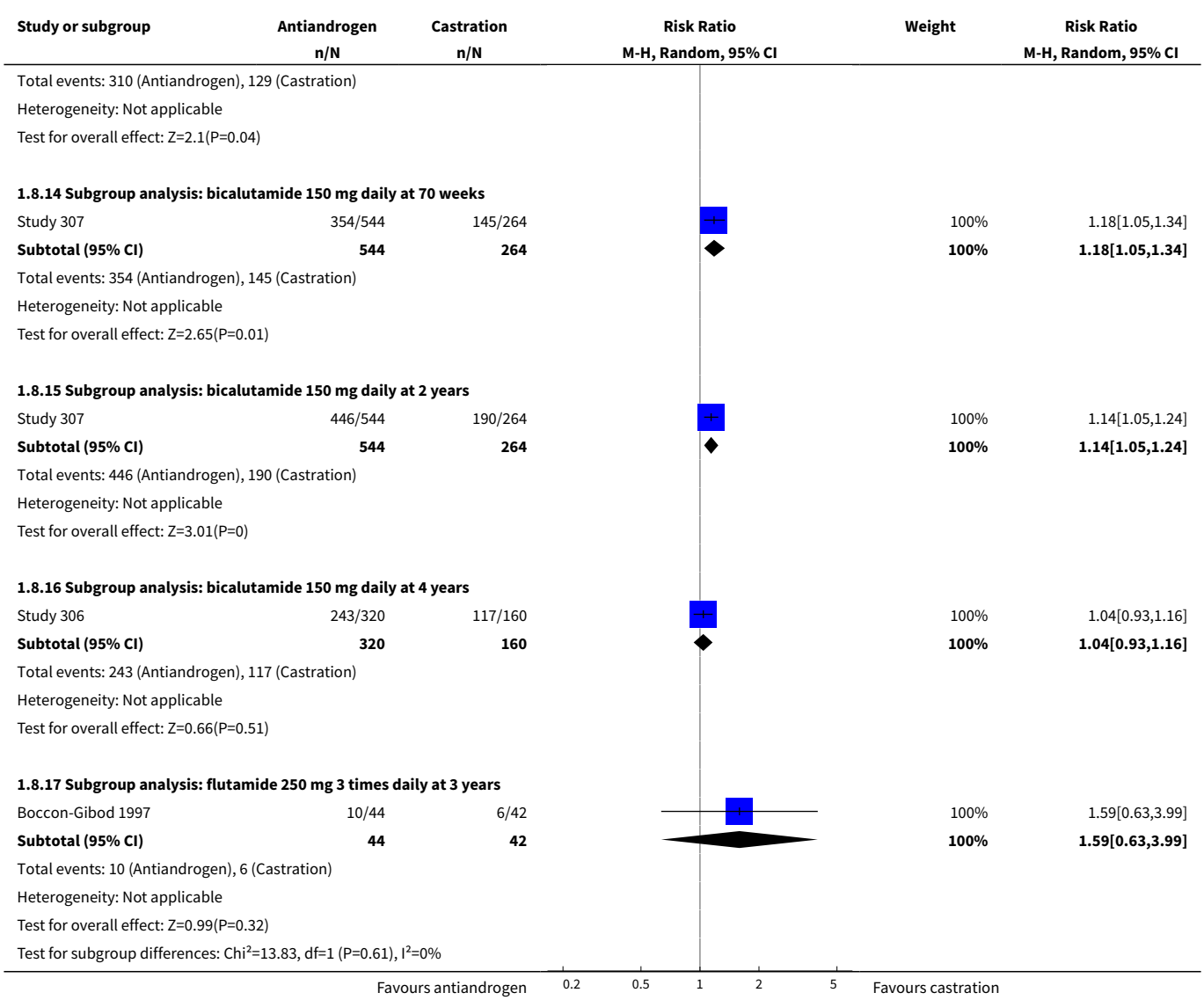


Analysis 1.8. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 8 Treatment failure.

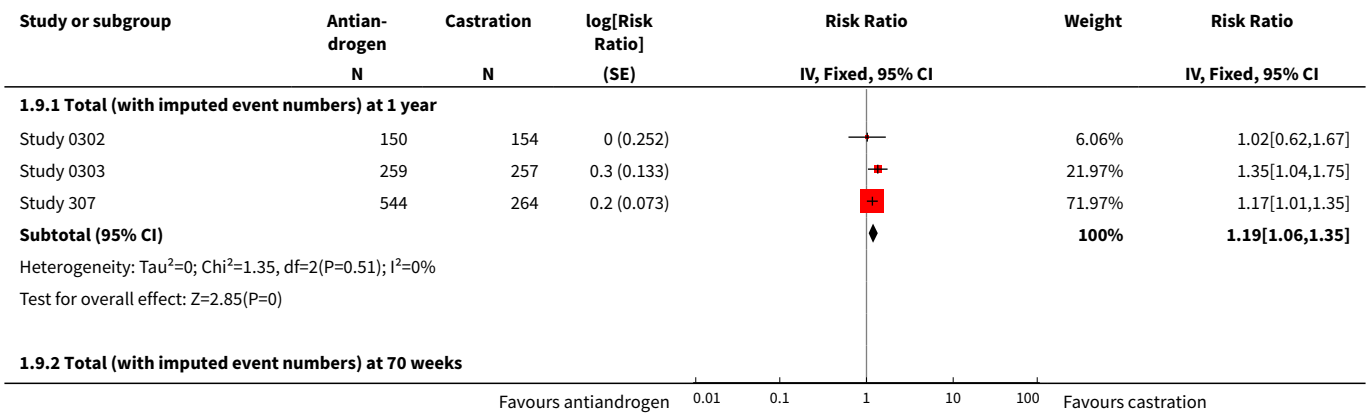
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Total at 1 year					
Study 0302	79/119	81/126		30.16%	1.03[0.86,1.24]
Study 0303	160/243	117/243		33.69%	1.37[1.17,1.6]
Study 307	310/544	129/264		36.15%	1.17[1.01,1.35]
Subtotal (95% CI)	**906**	**633**		**100%**	**1.19[1.02,1.38]**
Total events: 549 (Antiandrogen), 327 (Castration)					
Heterogeneity: Tau^2=0.01; Chi^2=5.36, df=2(P=0.07); I^2=62.71%					
Test for overall effect: Z=2.2(P=0.03)					
1.8.2 Total at 70 weeks					
Study 0301	86/153	51/153		19.17%	1.69[1.29,2.2]
Study 0302	90/119	94/126		26.65%	1.01[0.88,1.17]
Study 0303	171/243	124/243		26.43%	1.38[1.19,1.6]
Study 307	354/544	145/264		27.76%	1.18[1.05,1.34]
Subtotal (95% CI)	**1059**	**786**		**100%**	**1.27[1.05,1.52]**
Total events: 701 (Antiandrogen), 414 (Castration)					
Heterogeneity: Tau^2=0.03; Chi^2=15.72, df=3(P=0); I^2=80.92%					
Test for overall effect: Z=2.53(P=0.01)					
1.8.3 Total at 2 years					
Study 307	446/544	190/264		100%	1.14[1.05,1.24]
Subtotal (95% CI)	**544**	**264**		**100%**	**1.14[1.05,1.24]**
Total events: 446 (Antiandrogen), 190 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.01(P=0)					
1.8.4 Total at 3 years					
Boccon-Gibod 1997	10/44	6/42		100%	1.59[0.63,3.99]
Subtotal (95% CI)	**44**	**42**		**100%**	**1.59[0.63,3.99]**
Total events: 10 (Antiandrogen), 6 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.99(P=0.32)					
1.8.5 Total at 4 years					
Study 306	243/320	117/160		100%	1.04[0.93,1.16]
Subtotal (95% CI)	**320**	**160**		**100%**	**1.04[0.93,1.16]**
Total events: 243 (Antiandrogen), 117 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
1.8.6 Subgroup analysis: non-metastatic disease at 4 years					
Study 306	243/320	117/160		100%	1.04[0.93,1.16]
Subtotal (95% CI)	**320**	**160**		**100%**	**1.04[0.93,1.16]**
Total events: 243 (Antiandrogen), 117 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
1.8.7 Subgroup analysis: metastatic disease at 1 year					



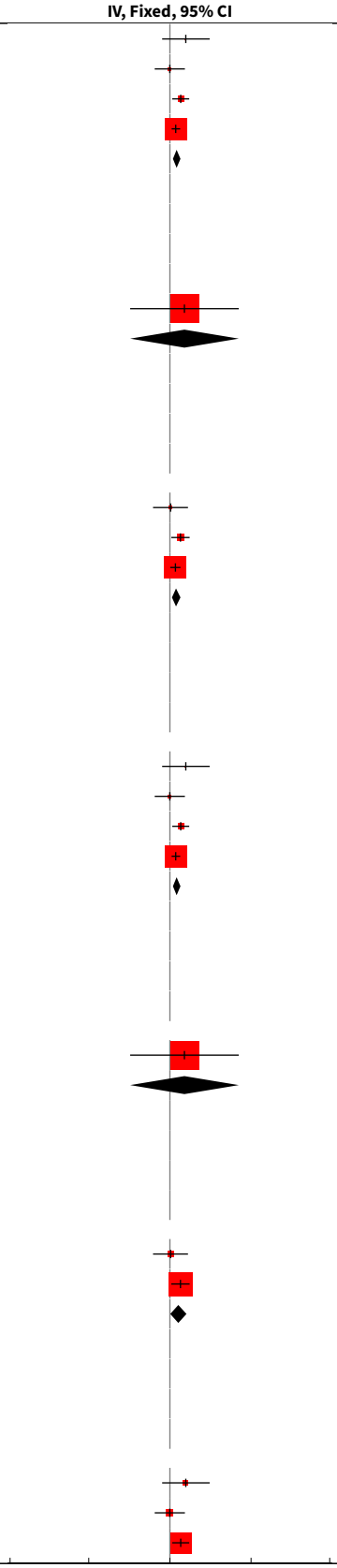


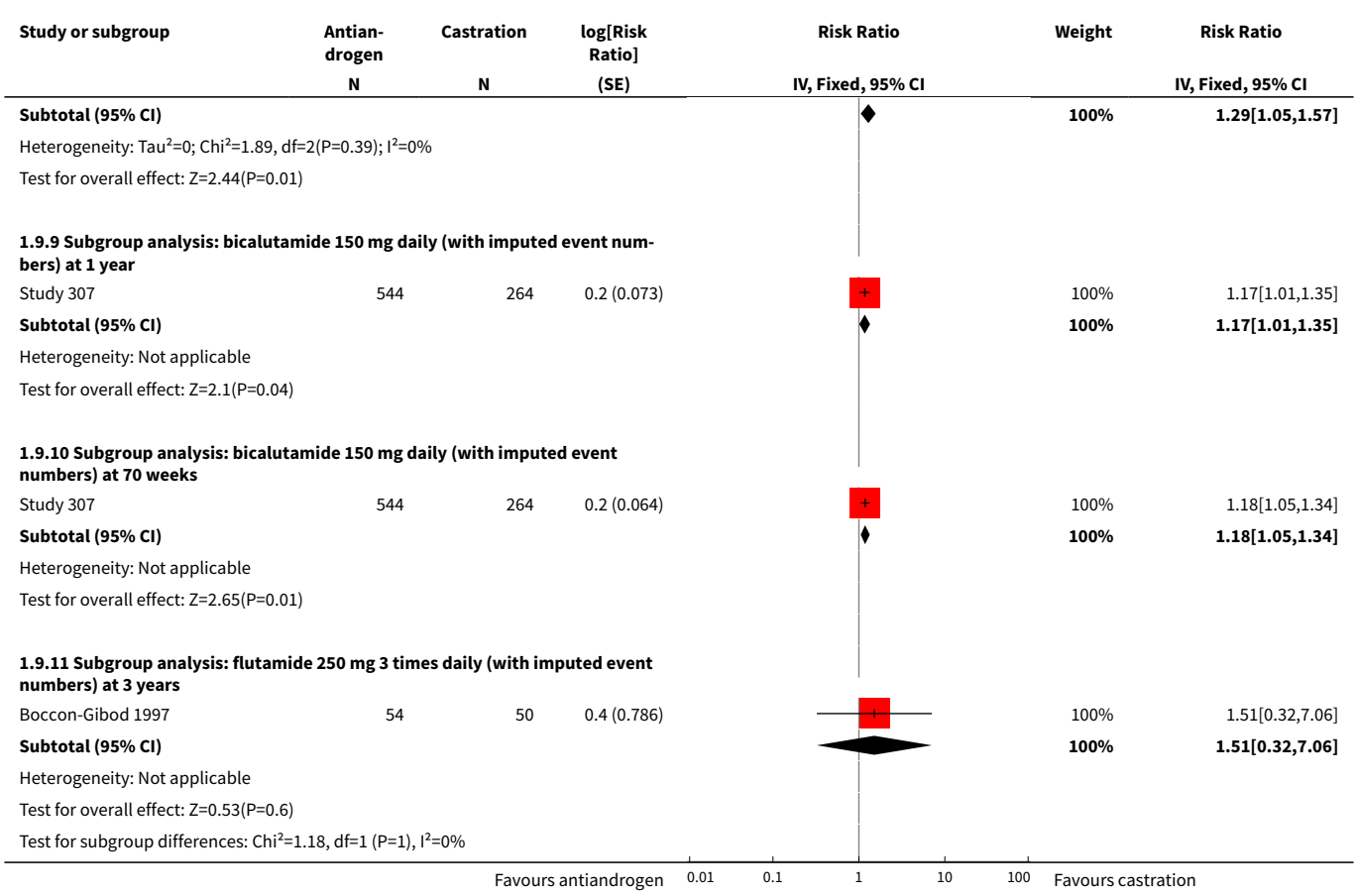


Analysis 1.9. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 9 Treatment failure (with imputed event numbers).

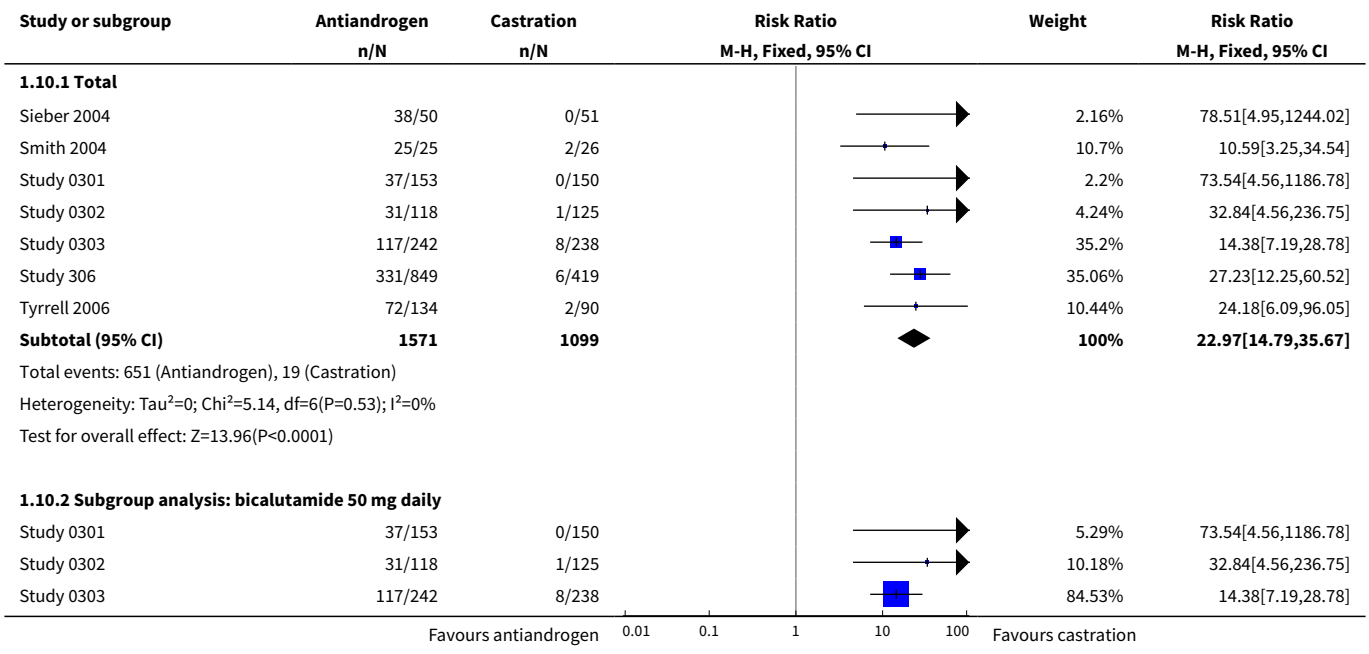


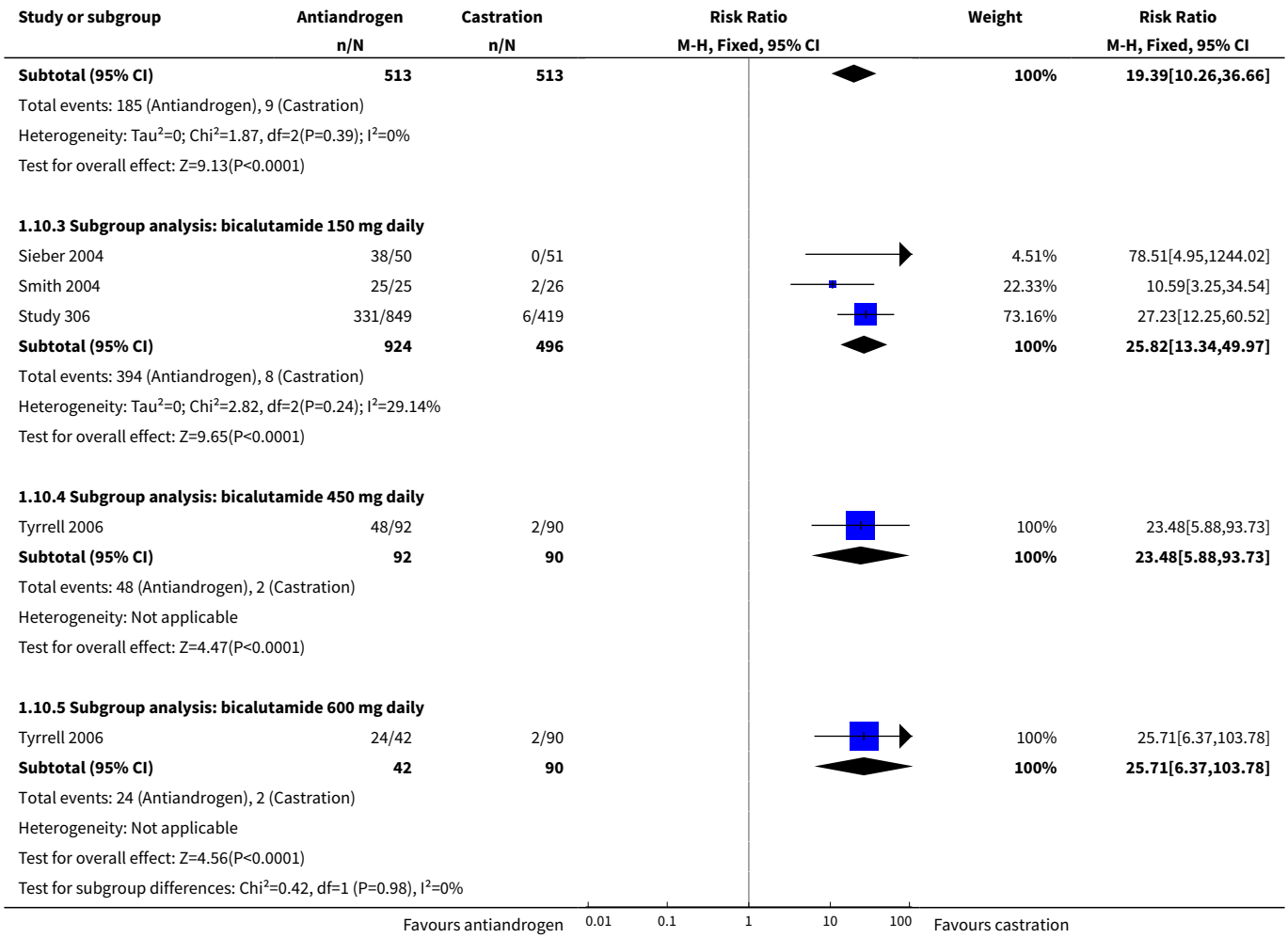
Study or subgroup	Antian-drogen N	Castration N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Study 0301	186	190	0.5 (0.344)		2.51%	1.57[0.8,3.09]
Study 0302	150	154	-0 (0.219)		6.16%	1[0.65,1.53]
Study 0303	259	257	0.3 (0.124)		19.14%	1.36[1.07,1.73]
Study 307	544	264	0.2 (0.064)		72.19%	1.18[1.05,1.34]
Subtotal (95% CI)					**100%**	**1.21[1.09,1.35]**
Heterogeneity: Tau²=0; Chi²=2.34, df=3(P=0.5); I²=0%						
Test for overall effect: Z=3.54(P=0)						
1.9.3 Total (with imputed event numbers) at 3 years						
Boccon-Gibod 1997	54	50	0.4 (0.786)		100%	1.51[0.32,7.06]
Subtotal (95% CI)					**100%**	**1.51[0.32,7.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.53(P=0.6)						
1.9.4 Subgroup analysis: metastatic disease (with imputed event numbers) at 1 year						
Study 0302	150	154	0 (0.252)		6.06%	1.02[0.62,1.67]
Study 0303	259	257	0.3 (0.133)		21.97%	1.35[1.04,1.75]
Study 307	544	264	0.2 (0.073)		71.97%	1.17[1.01,1.35]
Subtotal (95% CI)					**100%**	**1.19[1.06,1.35]**
Heterogeneity: Tau²=0; Chi²=1.35, df=2(P=0.51); I²=0%						
Test for overall effect: Z=2.85(P=0)						
1.9.5 Subgroup analysis: metastatic disease (with imputed event numbers) at 70 weeks						
Study 0301	186	190	0.5 (0.344)		2.51%	1.57[0.8,3.09]
Study 0302	150	154	-0 (0.219)		6.16%	1[0.65,1.53]
Study 0303	259	257	0.3 (0.124)		19.14%	1.36[1.07,1.73]
Study 307	544	264	0.2 (0.064)		72.19%	1.18[1.05,1.34]
Subtotal (95% CI)					**100%**	**1.21[1.09,1.35]**
Heterogeneity: Tau²=0; Chi²=2.34, df=3(P=0.5); I²=0%						
Test for overall effect: Z=3.54(P=0)						
1.9.6 Subgroup analysis: metastatic disease (with imputed event numbers) at 3 years						
Boccon-Gibod 1997	54	50	0.4 (0.786)		100%	1.51[0.32,7.06]
Subtotal (95% CI)					**100%**	**1.51[0.32,7.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.53(P=0.6)						
1.9.7 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 1 year						
Study 0302	150	154	0 (0.252)		21.63%	1.02[0.62,1.67]
Study 0303	259	257	0.3 (0.133)		78.37%	1.35[1.04,1.75]
Subtotal (95% CI)					**100%**	**1.27[1.01,1.6]**
Heterogeneity: Tau²=0; Chi²=0.98, df=1(P=0.32); I²=0%						
Test for overall effect: Z=2.02(P=0.04)						
1.9.8 Subgroup analysis: bicalutamide 50 mg daily (with imputed event numbers) at 70 weeks						
Study 0301	186	190	0.5 (0.344)		9.01%	1.57[0.8,3.09]
Study 0302	150	154	-0 (0.219)		22.15%	1[0.65,1.53]
Study 0303	259	257	0.3 (0.124)		68.83%	1.36[1.07,1.73]



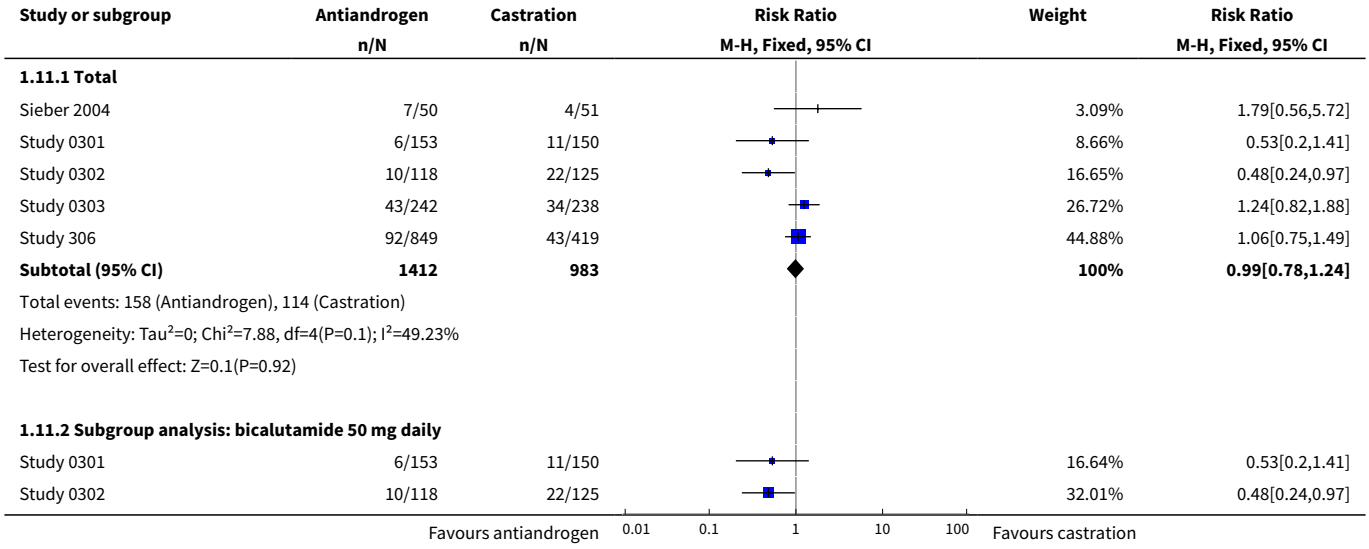


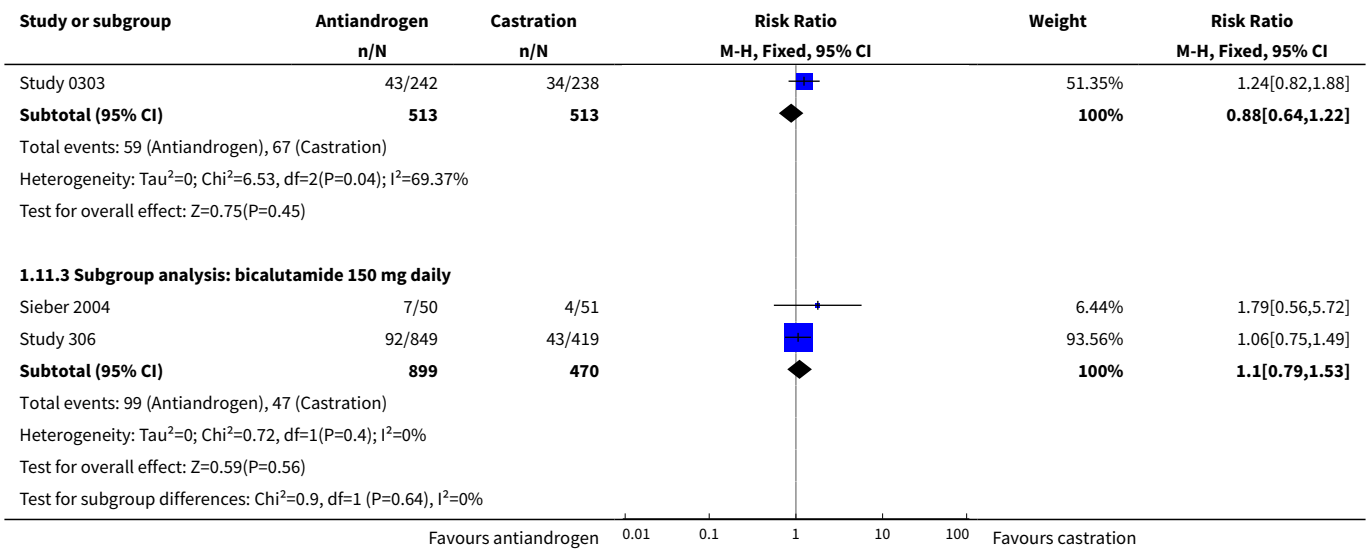
Analysis 1.10. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 10 Breast pain.



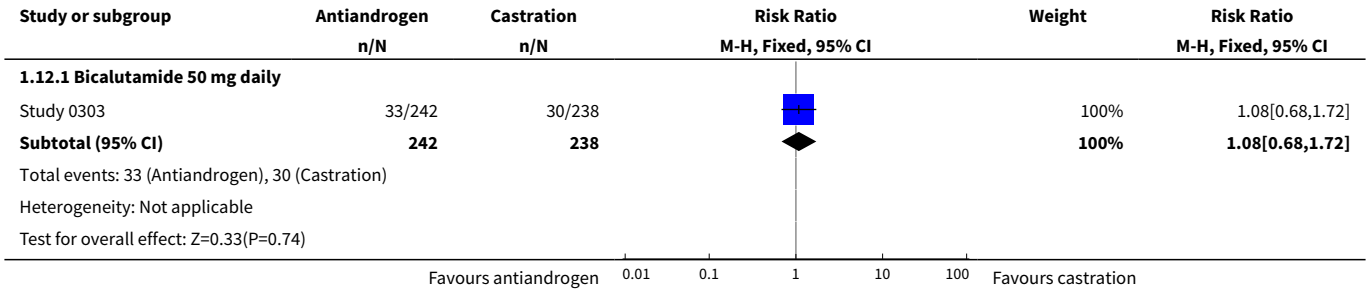


Analysis 1.11. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 11 Pelvic pain.

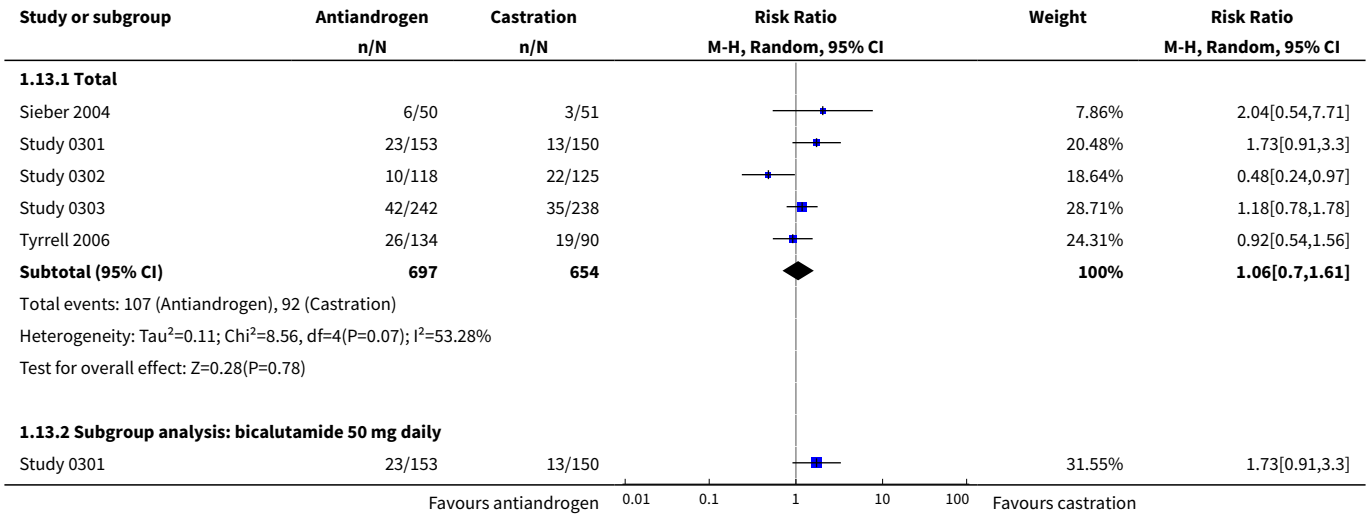


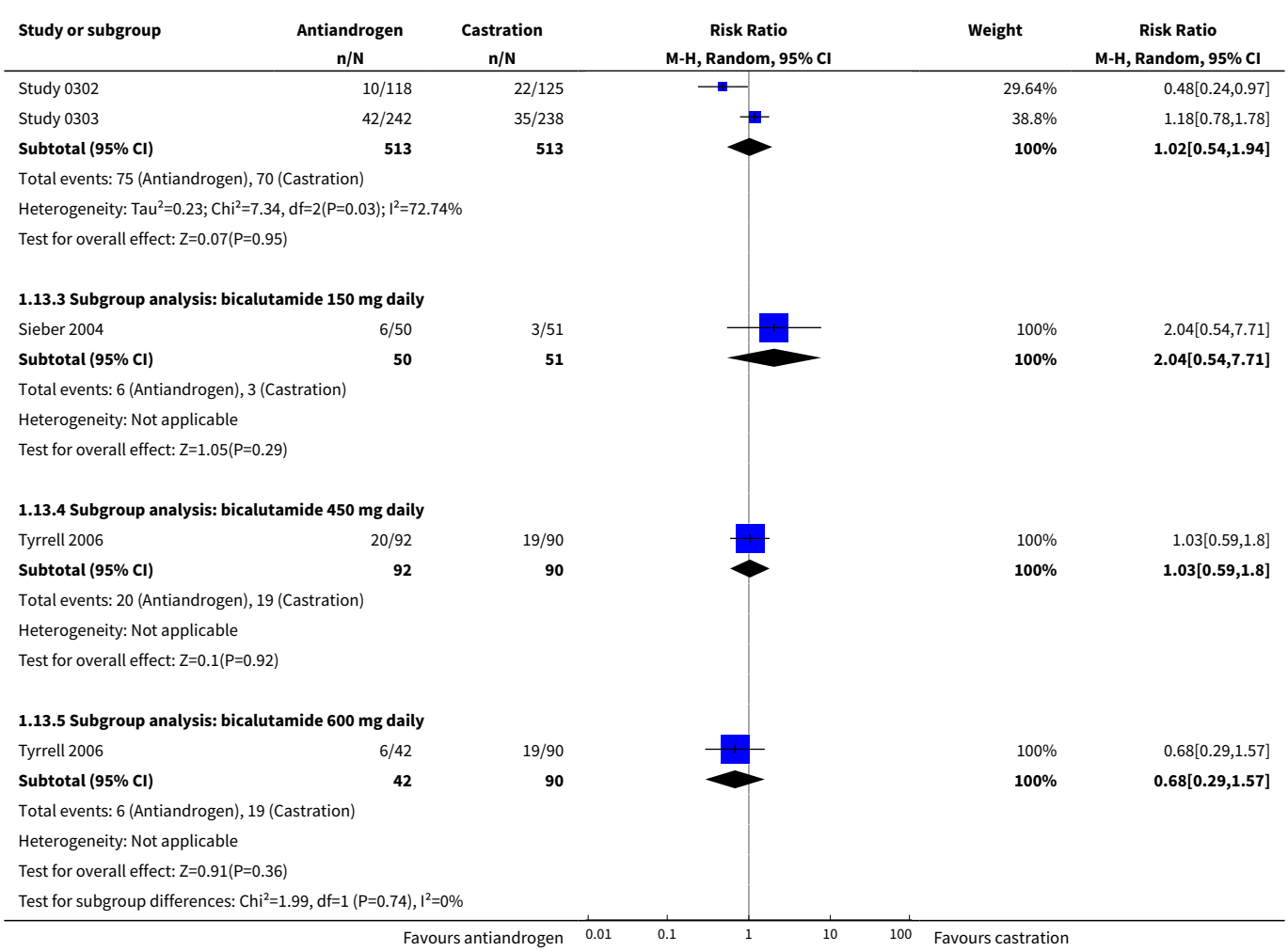


Analysis 1.12. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 12 Bone pain.

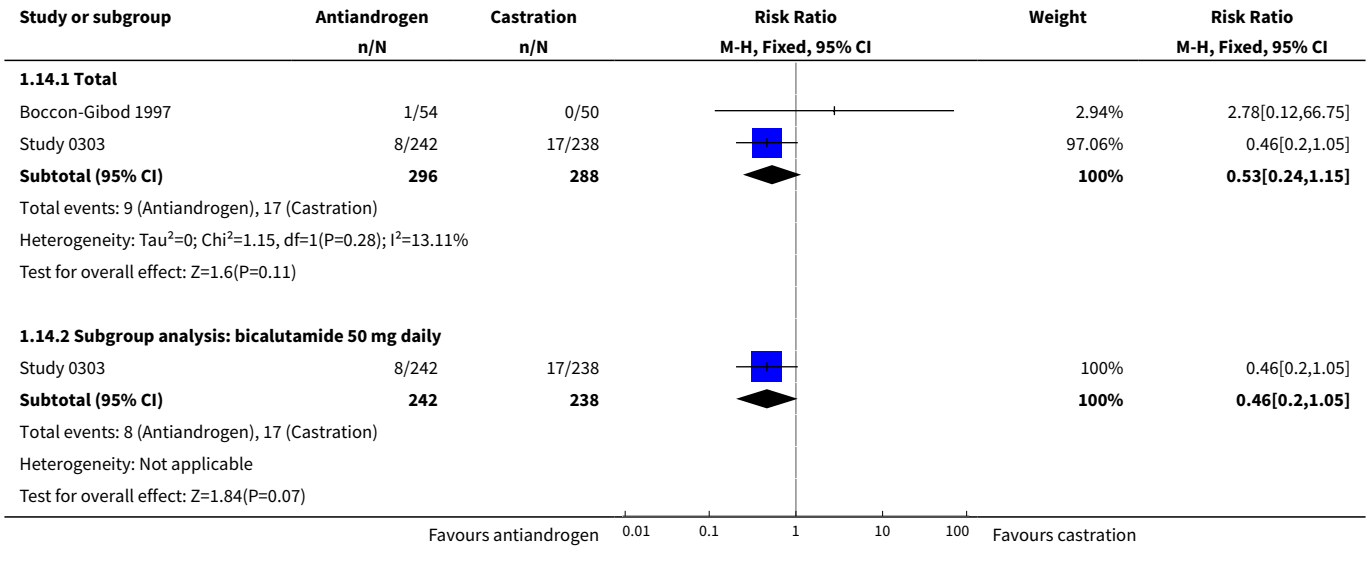


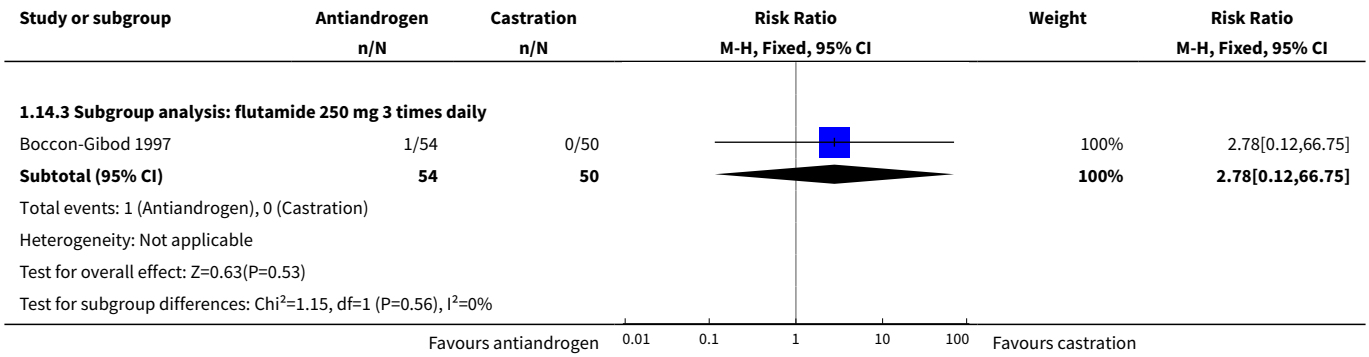
Analysis 1.13. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 13 Back pain.



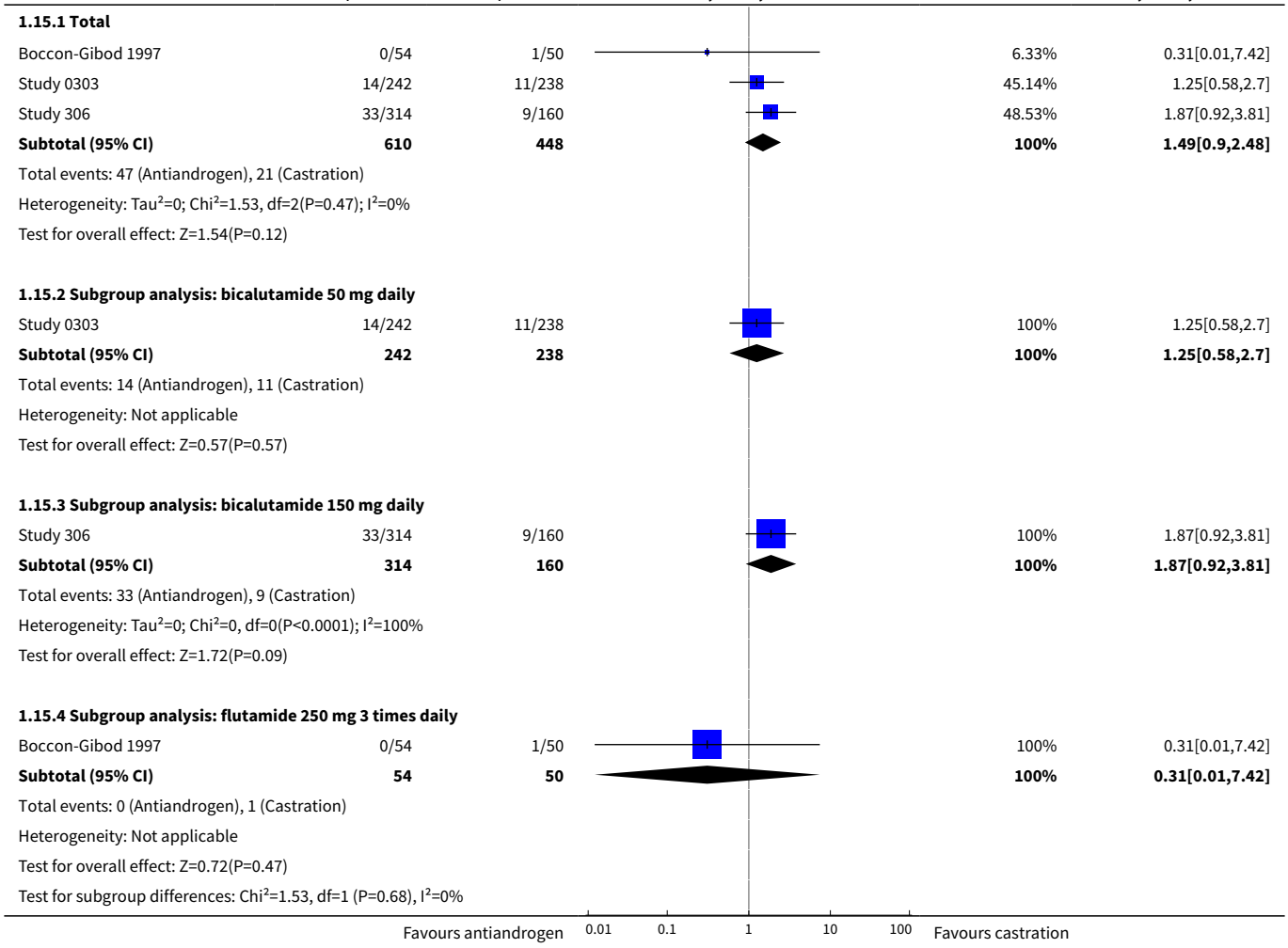


Analysis 1.14. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 14 Headache.



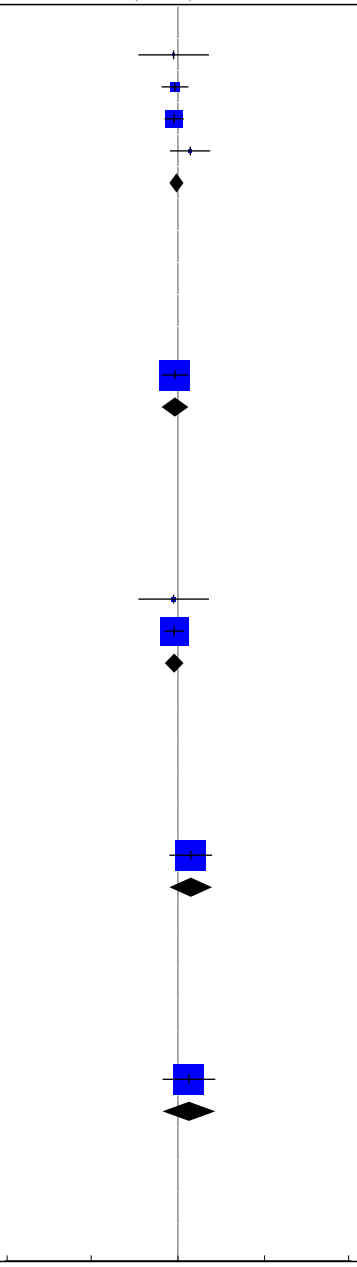


Analysis 1.15. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 15 Abdominal pain.



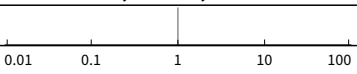
Analysis 1.16. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 16 General pain.

Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Total					
Sieber 2004	7/50	8/51		4.49%	0.89[0.35,2.28]
Study 0303	47/242	50/238		28.55%	0.92[0.65,1.32]
Study 306	136/849	74/419		56.12%	0.91[0.7,1.17]
Tyrrell 2006	33/134	16/90		10.84%	1.39[0.81,2.36]
Subtotal (95% CI)	**1275**	**798**		**100%**	**0.96[0.8,1.16]**
Total events: 223 (Antiandrogen), 148 (Castration)					
Heterogeneity: Tau²=0; Chi²=2.06, df=3(P=0.56); I²=0%					
Test for overall effect: Z=0.39(P=0.7)					
1.16.2 Subgroup analysis: bicalutamide 50 mg daily					
Study 0303	47/242	50/238		100%	0.92[0.65,1.32]
Subtotal (95% CI)	**242**	**238**		**100%**	**0.92[0.65,1.32]**
Total events: 47 (Antiandrogen), 50 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.43(P=0.67)					
1.16.3 Subgroup analysis: bicalutamide 150 mg daily					
Sieber 2004	7/50	8/51		7.4%	0.89[0.35,2.28]
Study 306	136/849	74/419		92.6%	0.91[0.7,1.17]
Subtotal (95% CI)	**899**	**470**		**100%**	**0.91[0.71,1.16]**
Total events: 143 (Antiandrogen), 82 (Castration)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.97); I²=0%					
Test for overall effect: Z=0.78(P=0.44)					
1.16.4 Subgroup analysis: bicalutamide 450 mg daily					
Tyrrell 2006	23/92	16/90		100%	1.41[0.8,2.48]
Subtotal (95% CI)	**92**	**90**		**100%**	**1.41[0.8,2.48]**
Total events: 23 (Antiandrogen), 16 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.18(P=0.24)					
1.16.5 Subgroup analysis: bicalutamide 600 mg daily					
Tyrrell 2006	10/42	16/90		100%	1.34[0.67,2.7]
Subtotal (95% CI)	**42**	**90**		**100%**	**1.34[0.67,2.7]**
Total events: 10 (Antiandrogen), 16 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
Test for subgroup differences: Chi²=2.82, df=1 (P=0.59), I²=0%					

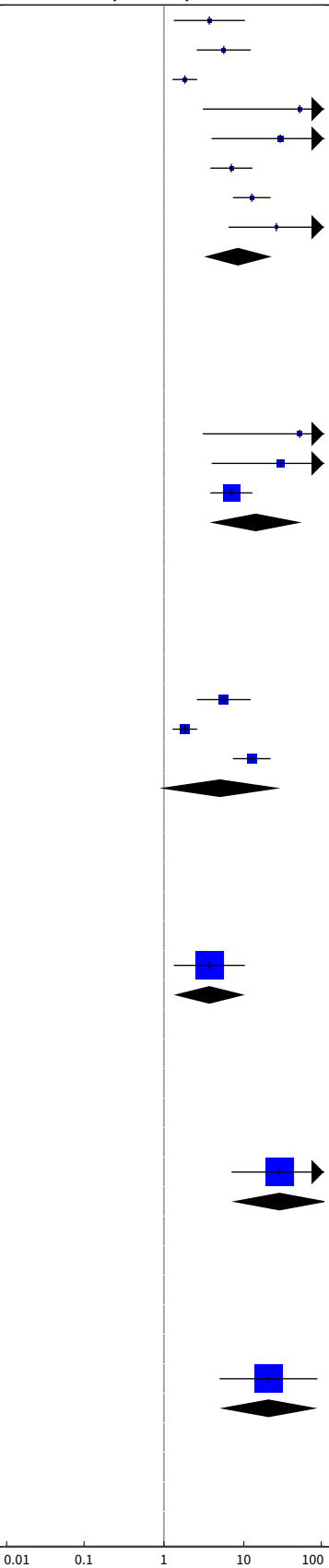


Analysis 1.17. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 17 Gynaecomastia.

Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Total					

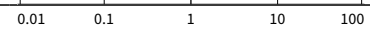


Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Boccon-Gibod 1997	16/54	4/50		13.22%	3.7[1.33,10.33]
Sieber 2004	33/50	6/51		14.11%	5.61[2.58,12.21]
Smith 2004	25/25	14/26		15.19%	1.83[1.28,2.6]
Study 0301	25/153	0/150		6.81%	50.01[3.07,814.02]
Study 0302	27/118	1/125		9.43%	28.6[3.95,207.16]
Study 0303	78/242	11/238		14.63%	6.97[3.81,12.78]
Study 306	331/849	13/419		14.79%	12.57[7.31,21.6]
Tyrrell 2006	76/134	2/90		11.82%	25.52[6.43,101.28]
Subtotal (95% CI)	**1625**	**1149**		**100%**	**8.43[3.19,22.28]**
Total events: 611 (Antiandrogen), 51 (Castration)					
Heterogeneity: Tau^2=1.59; Chi^2=84.39, df=7(P<0.0001); I^2=91.71%					
Test for overall effect: Z=4.3(P<0.0001)					
1.17.2 Subgroup analysis: bicalutamide 50 mg daily					
Study 0301	25/153	0/150		16.69%	50.01[3.07,814.02]
Study 0302	27/118	1/125		26.41%	28.6[3.95,207.16]
Study 0303	78/242	11/238		56.89%	6.97[3.81,12.78]
Subtotal (95% CI)	**513**	**513**		**100%**	**14.07[3.74,52.85]**
Total events: 130 (Antiandrogen), 12 (Castration)					
Heterogeneity: Tau^2=0.71; Chi^2=3.88, df=2(P=0.14); I^2=48.48%					
Test for overall effect: Z=3.91(P<0.0001)					
1.17.3 Subgroup analysis: bicalutamide 150 mg daily					
Sieber 2004	33/50	6/51		32.38%	5.61[2.58,12.21]
Smith 2004	25/25	14/26		34.12%	1.83[1.28,2.6]
Study 306	331/849	13/419		33.49%	12.57[7.31,21.6]
Subtotal (95% CI)	**924**	**496**		**100%**	**5.01[0.88,28.69]**
Total events: 389 (Antiandrogen), 33 (Castration)					
Heterogeneity: Tau^2=2.29; Chi^2=64.06, df=2(P<0.0001); I^2=96.88%					
Test for overall effect: Z=1.81(P=0.07)					
1.17.4 Subgroup analysis: flutamide 250 mg 3 times daily					
Boccon-Gibod 1997	16/54	4/50		100%	3.7[1.33,10.33]
Subtotal (95% CI)	**54**	**50**		**100%**	**3.7[1.33,10.33]**
Total events: 16 (Antiandrogen), 4 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.5(P=0.01)					
1.17.5 Subgroup analysis: bicalutamide 450 mg daily					
Tyrrell 2006	57/92	2/90		100%	27.88[7.02,110.79]
Subtotal (95% CI)	**92**	**90**		**100%**	**27.88[7.02,110.79]**
Total events: 57 (Antiandrogen), 2 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.73(P<0.0001)					
1.17.6 Subgroup analysis: bicalutamide 600 mg daily					
Tyrrell 2006	19/42	2/90		100%	20.36[4.97,83.4]
Subtotal (95% CI)	**42**	**90**		**100%**	**20.36[4.97,83.4]**
Total events: 19 (Antiandrogen), 2 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.19(P<0.0001)					
Test for subgroup differences: Chi^2=7.61, df=1 (P=0.18), I^2=34.28%					



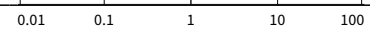
Analysis 1.18. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 18 Constipation.

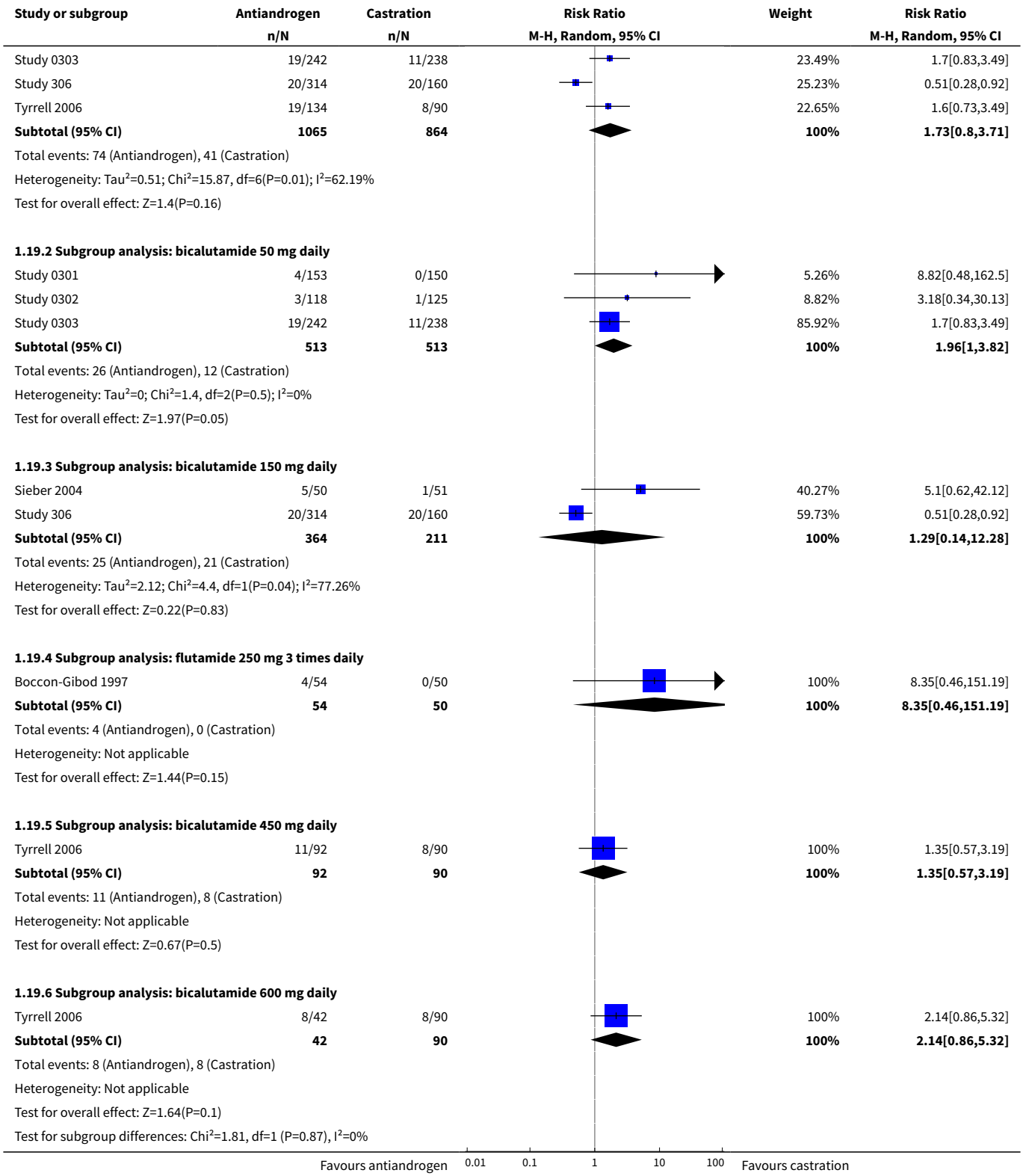
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Total					
Study 0301	14/153	11/150		24.73%	1.25[0.59,2.66]
Study 0302	7/118	5/125		15.92%	1.48[0.48,4.54]
Study 0303	13/242	23/238		27.98%	0.56[0.29,1.07]
Tyrrell 2006	35/134	14/90		31.37%	1.68[0.96,2.94]
Subtotal (95% CI)	**647**	**603**		**100%**	**1.12[0.65,1.95]**
Total events: 69 (Antiandrogen), 53 (Castration)					
Heterogeneity: Tau^2=0.17; Chi^2=6.72, df=3(P=0.08); I^2=55.36%					
Test for overall effect: Z=0.41(P=0.68)					
1.18.2 Subgroup analysis: bicalutamide 50 mg daily					
Study 0301	14/153	11/150		36.16%	1.25[0.59,2.66]
Study 0302	7/118	5/125		22.21%	1.48[0.48,4.54]
Study 0303	13/242	23/238		41.63%	0.56[0.29,1.07]
Subtotal (95% CI)	**513**	**513**		**100%**	**0.93[0.5,1.73]**
Total events: 34 (Antiandrogen), 39 (Castration)					
Heterogeneity: Tau^2=0.13; Chi^2=3.53, df=2(P=0.17); I^2=43.42%					
Test for overall effect: Z=0.24(P=0.81)					
1.18.3 Subgroup analysis: bicalutamide 450 mg daily					
Tyrrell 2006	22/92	14/90		100%	1.54[0.84,2.81]
Subtotal (95% CI)	**92**	**90**		**100%**	**1.54[0.84,2.81]**
Total events: 22 (Antiandrogen), 14 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.4(P=0.16)					
1.18.4 Subgroup analysis: bicalutamide 600 mg daily					
Tyrrell 2006	13/42	14/90		100%	1.99[1.03,3.85]
Subtotal (95% CI)	**42**	**90**		**100%**	**1.99[1.03,3.85]**
Total events: 13 (Antiandrogen), 14 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.04(P=0.04)					
Test for subgroup differences: Chi^2=3.29, df=1 (P=0.35), I^2=8.8%					



Analysis 1.19. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 19 Diarrhoea.

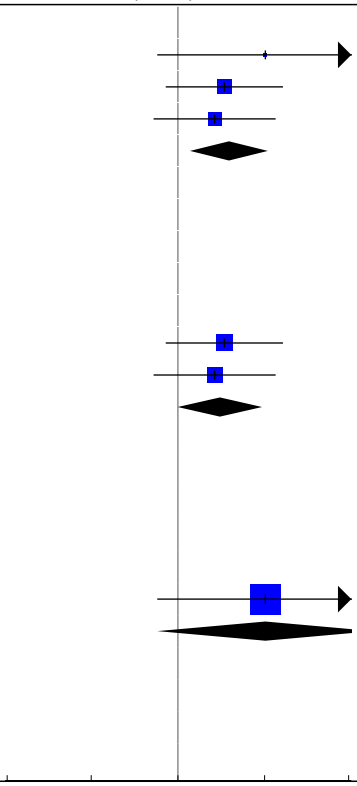
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Total					
Boccon-Gibod 1997	4/54	0/50		5.64%	8.35[0.46,151.19]
Sieber 2004	5/50	1/51		9.09%	5.1[0.62,42.12]
Study 0301	4/153	0/150		5.59%	8.82[0.48,162.5]
Study 0302	3/118	1/125		8.31%	3.18[0.34,30.13]





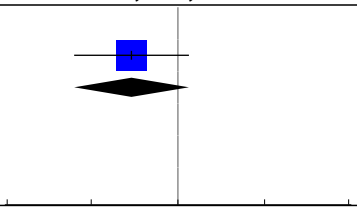
Analysis 1.20. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 20 Vomiting.

Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 Total					
Boccon-Gibod 1997	5/54	0/50		11.58%	10.2[0.58,179.88]
Study 0301	7/153	2/150		45.07%	3.43[0.72,16.25]
Study 0302	5/118	2/125		43.35%	2.65[0.52,13.39]
Subtotal (95% CI)	**325**	**325**		**100%**	**3.88[1.38,10.87]**
Total events: 17 (Antiandrogen), 4 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=2.58(P=0.01)					
1.20.2 Subgroup analysis: bicalutamide 50 mg daily					
Study 0301	7/153	2/150		50.98%	3.43[0.72,16.25]
Study 0302	5/118	2/125		49.02%	2.65[0.52,13.39]
Subtotal (95% CI)	**271**	**275**		**100%**	**3.05[0.99,9.35]**
Total events: 12 (Antiandrogen), 4 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					
1.20.3 Subgroup analysis: flutamide 250 mg 3 times daily					
Boccon-Gibod 1997	5/54	0/50		100%	10.2[0.58,179.88]
Subtotal (95% CI)	**54**	**50**		**100%**	**10.2[0.58,179.88]**
Total events: 5 (Antiandrogen), 0 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.59(P=0.11)					
Test for subgroup differences: Chi^2=0.6, df=1 (P=0.74), I^2=0%					



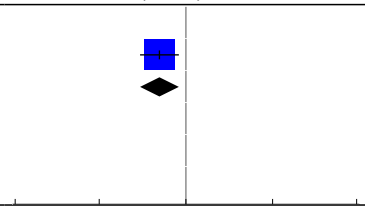
Analysis 1.21. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 21 Hypertension.

Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.21.1 Bicalutamide 150 mg daily					
Sieber 2004	2/50	7/51		100%	0.29[0.06,1.34]
Subtotal (95% CI)	**50**	**51**		**100%**	**0.29[0.06,1.34]**
Total events: 2 (Antiandrogen), 7 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.59(P=0.11)					



Analysis 1.22. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 22 Loss of sexual interest.

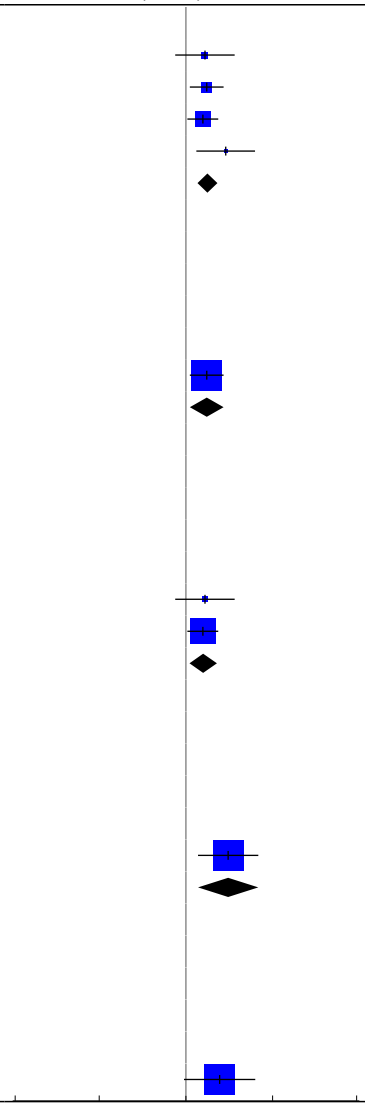
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 Bicalutamide 150 mg daily					
Smith 2004	10/25	21/26		100%	0.5[0.3,0.83]
Subtotal (95% CI)	**25**	**26**		**100%**	**0.5[0.3,0.83]**
Total events: 10 (Antiandrogen), 21 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.67(P=0.01)					



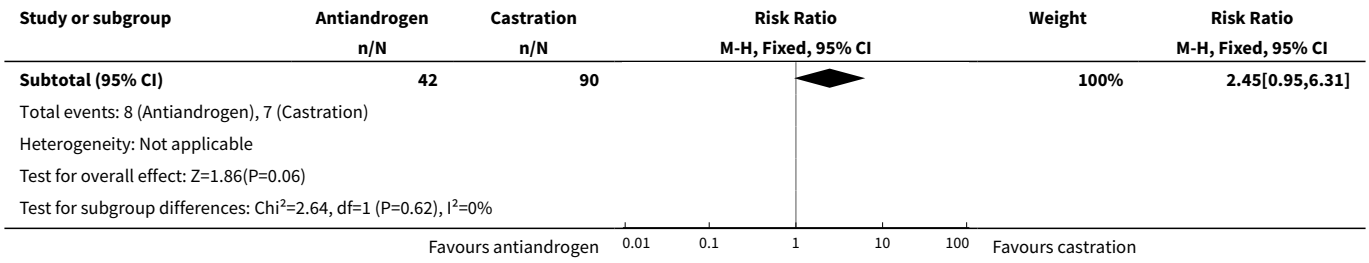
Favours antiandrogen — Favours castration

Analysis 1.23. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 23 Asthenia.

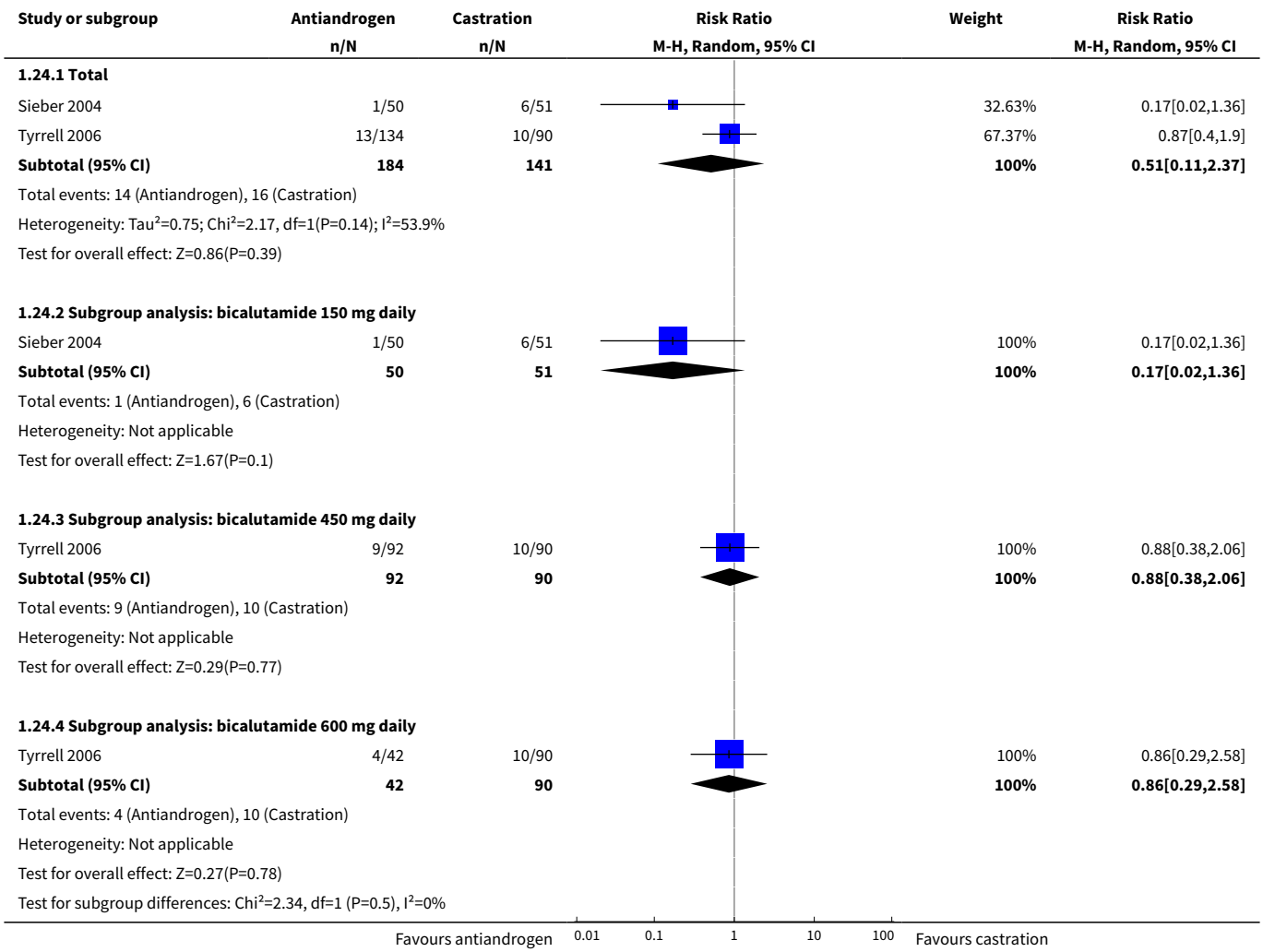
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.23.1 Total					
Sieber 2004	13/50	8/51		9.9%	1.66[0.75,3.65]
Study 0303	46/242	26/238		32.77%	1.74[1.11,2.72]
Study 306	89/849	28/419		46.86%	1.57[1.04,2.36]
Tyrrell 2006	30/134	7/90		10.47%	2.88[1.32,6.27]
Subtotal (95% CI)	**1275**	**798**		**100%**	**1.77[1.36,2.31]**
Total events: 178 (Antiandrogen), 69 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=3(P=0.6); I^2=0%					
Test for overall effect: Z=4.23(P<0.0001)					
1.23.2 Subgroup analysis: bicalutamide 50 mg daily					
Study 0303	46/242	26/238		100%	1.74[1.11,2.72]
Subtotal (95% CI)	**242**	**238**		**100%**	**1.74[1.11,2.72]**
Total events: 46 (Antiandrogen), 26 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.43(P=0.02)					
1.23.3 Subgroup analysis: bicalutamide 150 mg daily					
Sieber 2004	13/50	8/51		17.44%	1.66[0.75,3.65]
Study 306	89/849	28/419		82.56%	1.57[1.04,2.36]
Subtotal (95% CI)	**899**	**470**		**100%**	**1.58[1.1,2.28]**
Total events: 102 (Antiandrogen), 36 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=2.48(P=0.01)					
1.23.4 Subgroup analysis: bicalutamide 450 mg daily					
Tyrrell 2006	22/92	7/90		100%	3.07[1.38,6.84]
Subtotal (95% CI)	**92**	**90**		**100%**	**3.07[1.38,6.84]**
Total events: 22 (Antiandrogen), 7 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.75(P=0.01)					
1.23.5 Subgroup analysis: bicalutamide 600 mg daily					
Tyrrell 2006	8/42	7/90		100%	2.45[0.95,6.31]



Favours antiandrogen — Favours castration

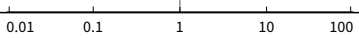


Analysis 1.24. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 24 Insomnia.

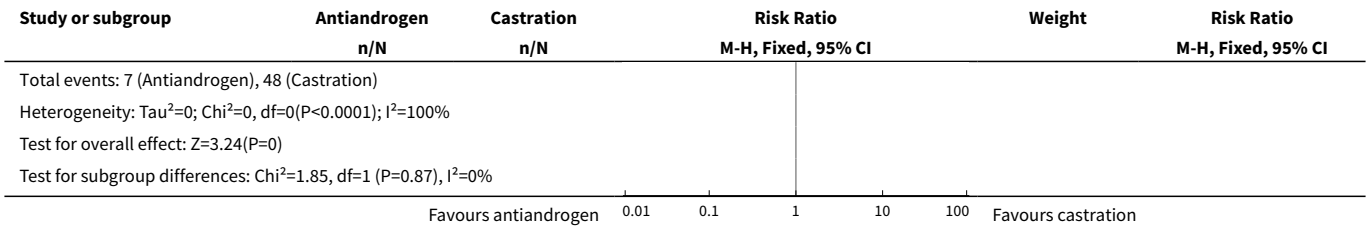


Analysis 1.25. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 25 Hot flashes.

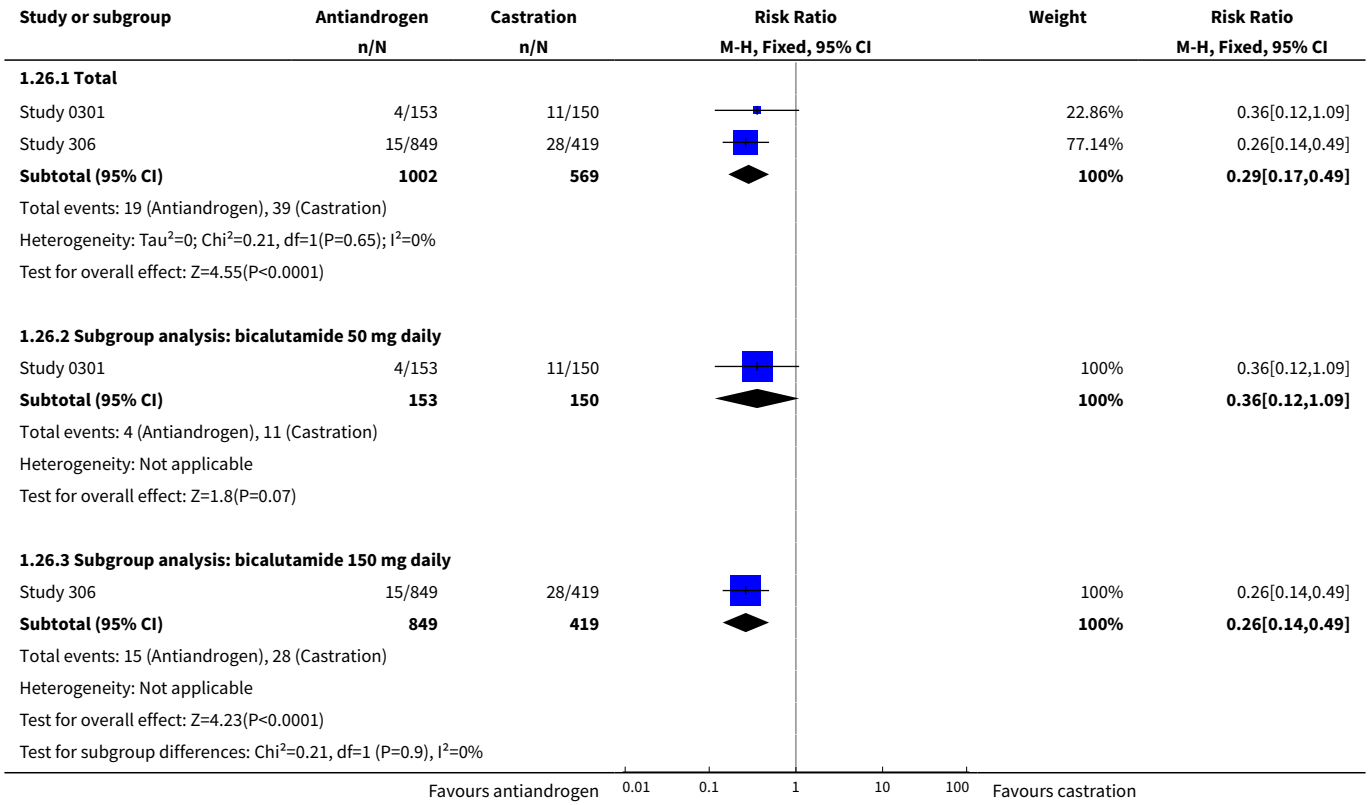
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.25.1 Total					
Boccon-Gibod 1997	4/54	13/50		2.3%	0.28[0.1,0.82]
Sieber 2004	8/50	33/51		5.55%	0.25[0.13,0.48]
Smith 2004	2/25	25/26		4.17%	0.08[0.02,0.32]
Study 0301	8/153	62/150		10.64%	0.13[0.06,0.26]
Study 0302	11/118	50/125		8.26%	0.23[0.13,0.43]
Study 0303	25/242	107/238		18.34%	0.23[0.15,0.34]
Study 306	93/849	180/419		40.98%	0.25[0.2,0.32]
Tyrrell 2006	18/134	48/90		9.76%	0.25[0.16,0.4]
Subtotal (95% CI)	**1625**	**1149**		**100%**	**0.23[0.19,0.27]**
Total events: 169 (Antiandrogen), 518 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=6.32, df=7(P=0.5); I^2=0%					
Test for overall effect: Z=18.03(P<0.0001)					
1.25.2 Subgroup analysis: bicalutamide 50 mg daily					
Study 0301	8/153	62/150		28.58%	0.13[0.06,0.26]
Study 0302	11/118	50/125		22.17%	0.23[0.13,0.43]
Study 0303	25/242	107/238		49.25%	0.23[0.15,0.34]
Subtotal (95% CI)	**513**	**513**		**100%**	**0.2[0.15,0.27]**
Total events: 44 (Antiandrogen), 219 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=2.34, df=2(P=0.31); I^2=14.7%					
Test for overall effect: Z=10.5(P<0.0001)					
1.25.3 Subgroup analysis: bicalutamide 150 mg daily					
Sieber 2004	8/50	33/51		10.96%	0.25[0.13,0.48]
Smith 2004	2/25	25/26		8.22%	0.08[0.02,0.32]
Study 306	93/849	180/419		80.83%	0.25[0.2,0.32]
Subtotal (95% CI)	**924**	**496**		**100%**	**0.24[0.19,0.3]**
Total events: 103 (Antiandrogen), 238 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=2.73, df=2(P=0.26); I^2=26.65%					
Test for overall effect: Z=13.39(P<0.0001)					
1.25.4 Subgroup analysis: flutamide 250 mg 3 times daily					
Boccon-Gibod 1997	4/54	13/50		100%	0.28[0.1,0.82]
Subtotal (95% CI)	**54**	**50**		**100%**	**0.28[0.1,0.82]**
Total events: 4 (Antiandrogen), 13 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.34(P=0.02)					
1.25.5 Subgroup analysis: bicalutamide 450 mg daily					
Tyrrell 2006	11/92	48/90		100%	0.22[0.12,0.4]
Subtotal (95% CI)	**92**	**90**		**100%**	**0.22[0.12,0.4]**
Total events: 11 (Antiandrogen), 48 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.99(P<0.0001)					
1.25.6 Subgroup analysis: bicalutamide 600 mg daily					
Tyrrell 2006	7/42	48/90		100%	0.31[0.15,0.63]
Subtotal (95% CI)	**42**	**90**		**100%**	**0.31[0.15,0.63]**



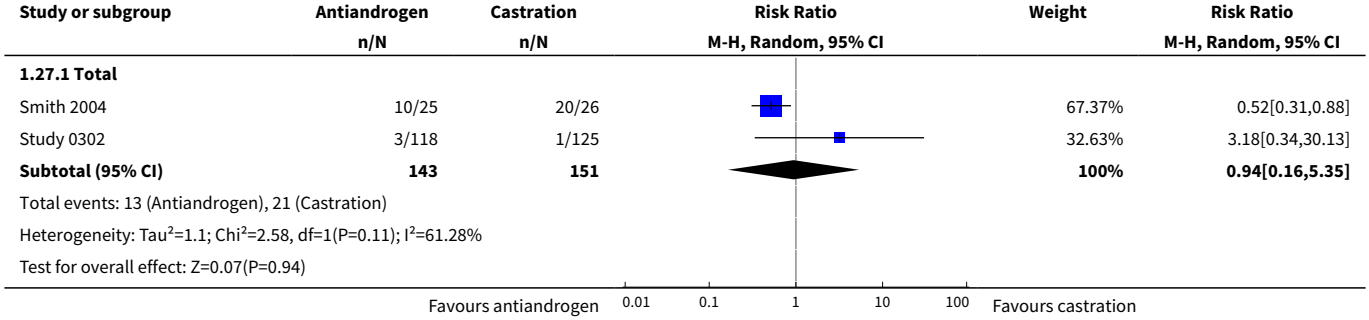
Favours antiandrogen — Favours castration

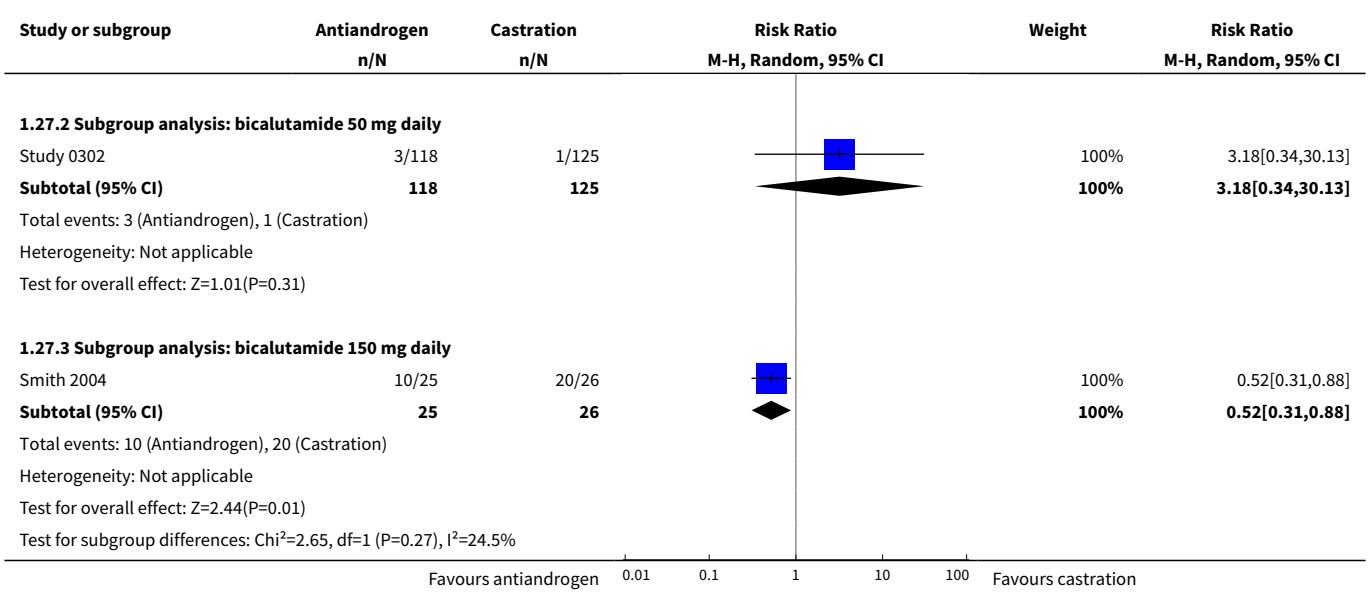


Analysis 1.26. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 26 Night sweats.

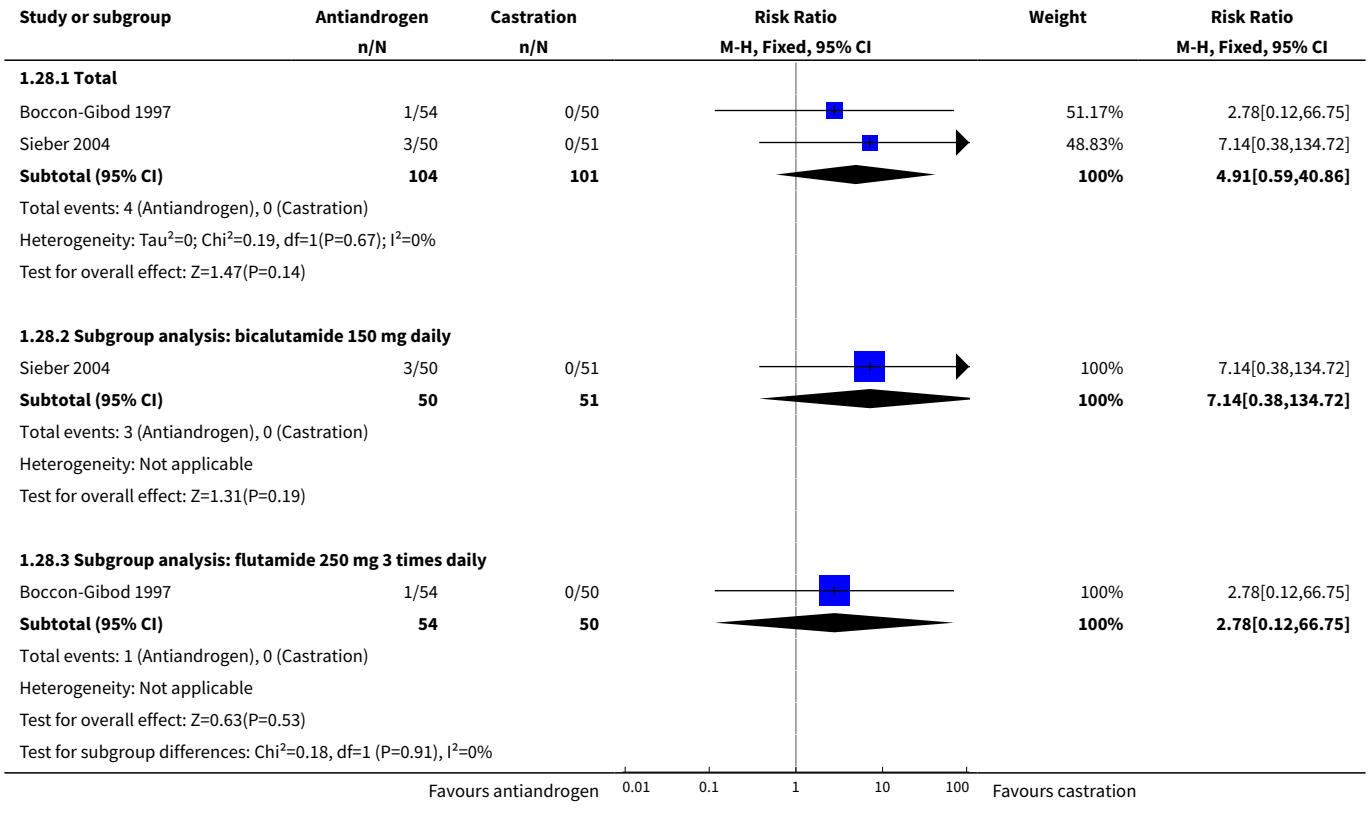


Analysis 1.27. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 27 Anaemia.





Analysis 1.28. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 28 Hepatic enzyme increase.



Analysis 1.29. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 29 Rash.

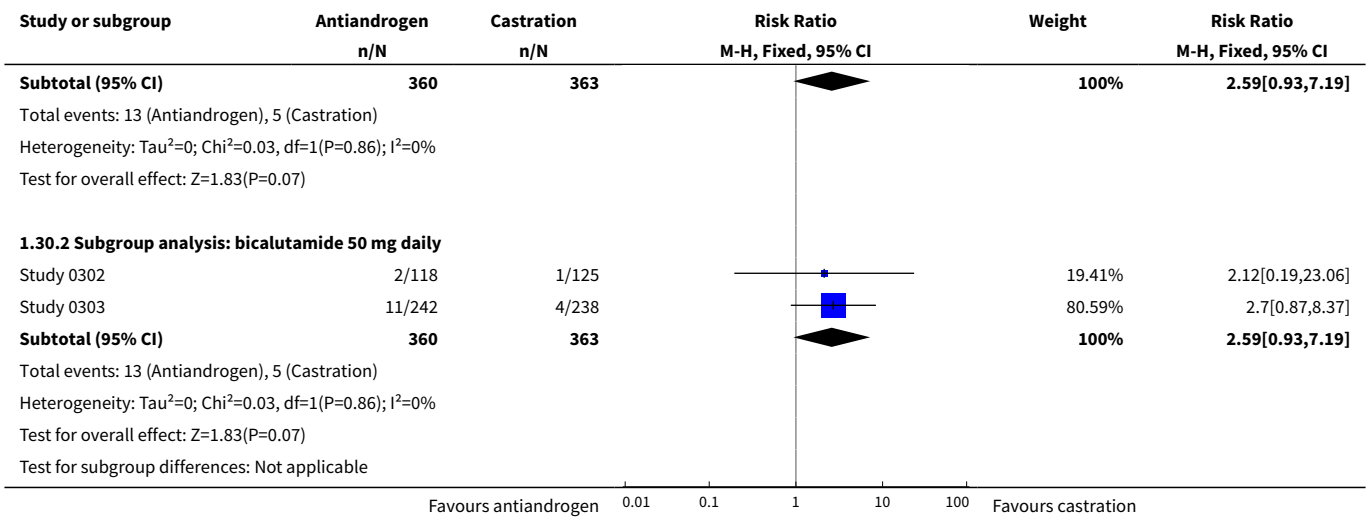
Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.29.1 Total					
Sieber 2004	5/50	1/51		4.07%	5.1[0.62,42.12]
Study 0303	16/242	16/238		66.39%	0.98[0.5,1.92]
Tyrrell 2006	13/134	6/90		29.54%	1.46[0.57,3.69]
Subtotal (95% CI)	**426**	**379**		**100%**	**1.29[0.77,2.16]**
Total events: 34 (Antiandrogen), 23 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=2.32, df=2(P=0.31); I^2=13.95%					
Test for overall effect: Z=0.97(P=0.33)					
1.29.2 Subgroup analysis: bicalutamide 50 mg daily					
Study 0303	16/242	16/238		100%	0.98[0.5,1.92]
Subtotal (95% CI)	**242**	**238**		**100%**	**0.98[0.5,1.92]**
Total events: 16 (Antiandrogen), 16 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
1.29.3 Subgroup analysis: bicalutamide 150 mg daily					
Sieber 2004	5/50	1/51		100%	5.1[0.62,42.12]
Subtotal (95% CI)	**50**	**51**		**100%**	**5.1[0.62,42.12]**
Total events: 5 (Antiandrogen), 1 (Castration)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.51(P=0.13)					
1.29.4 Subgroup analysis: bicalutamide 450 mg daily					
Tyrrell 2006	8/92	6/90		100%	1.3[0.47,3.61]
Subtotal (95% CI)	**92**	**90**		**100%**	**1.3[0.47,3.61]**
Total events: 8 (Antiandrogen), 6 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
1.29.5 Subgroup analysis: bicalutamide 600 mg daily					
Tyrrell 2006	5/42	6/90		100%	1.79[0.58,5.52]
Subtotal (95% CI)	**42**	**90**		**100%**	**1.79[0.58,5.52]**
Total events: 5 (Antiandrogen), 6 (Castration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					
Test for subgroup differences: Chi^2=2.58, df=1 (P=0.63), I^2=0%					

Favours antiandrogen — Favours castration

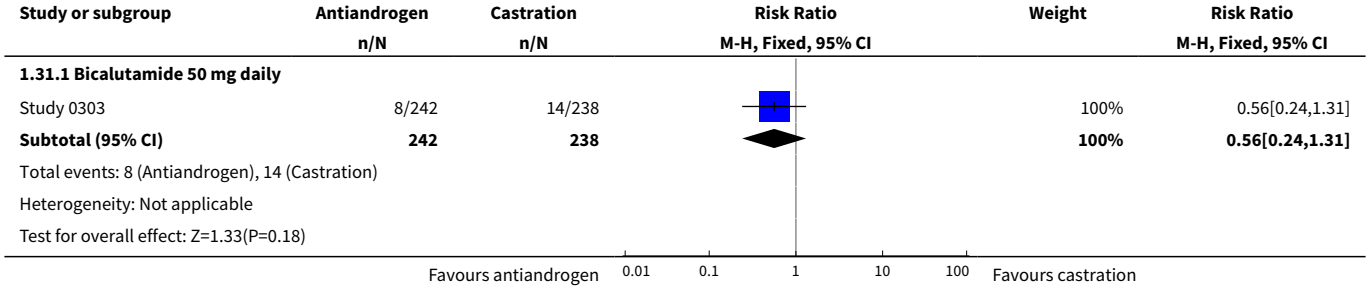
Analysis 1.30. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 30 Pruritus.

Study or subgroup	Antiandrogen n/N	Castration n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.30.1 Total					
Study 0302	2/118	1/125		19.41%	2.12[0.19,23.06]
Study 0303	11/242	4/238		80.59%	2.7[0.87,8.37]

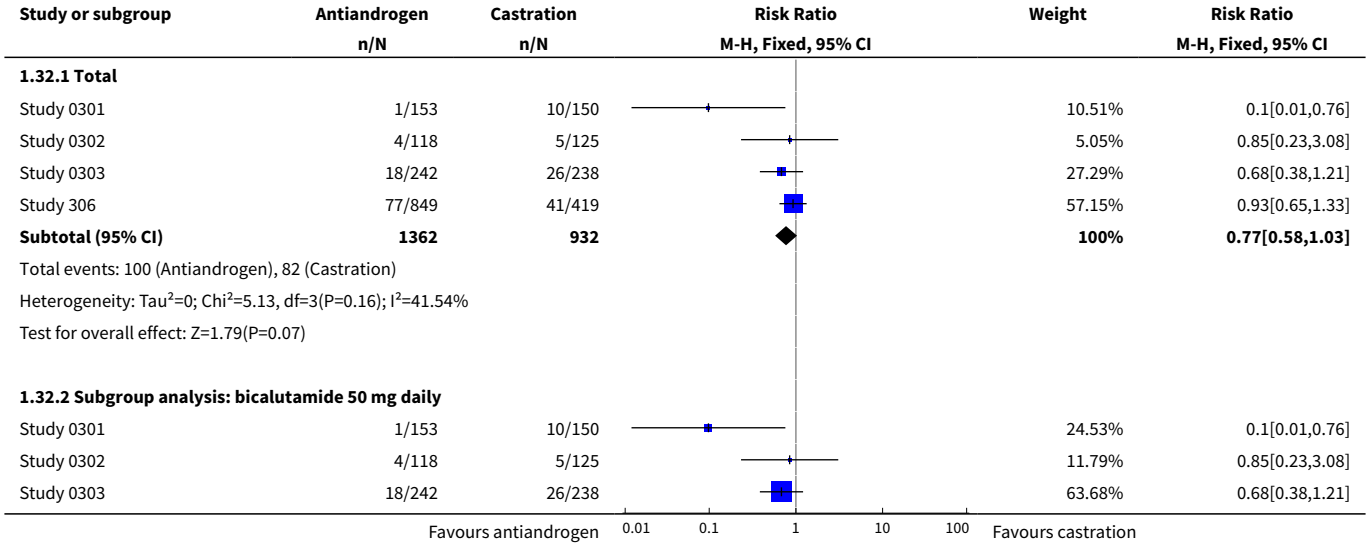
Favours antiandrogen — Favours castration

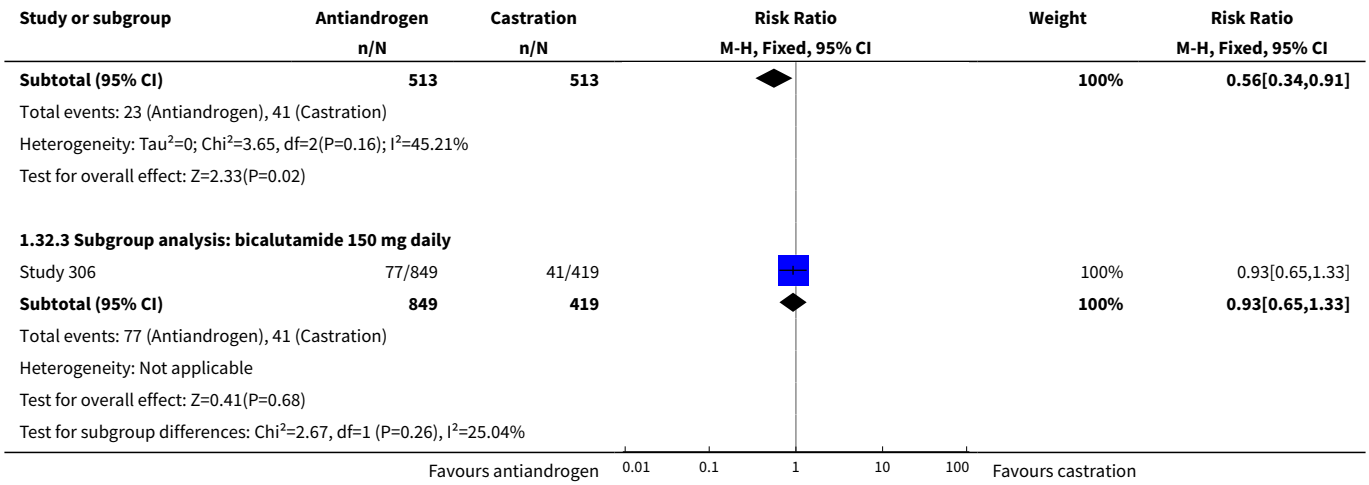


Analysis 1.31. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 31 Dyspnoea.

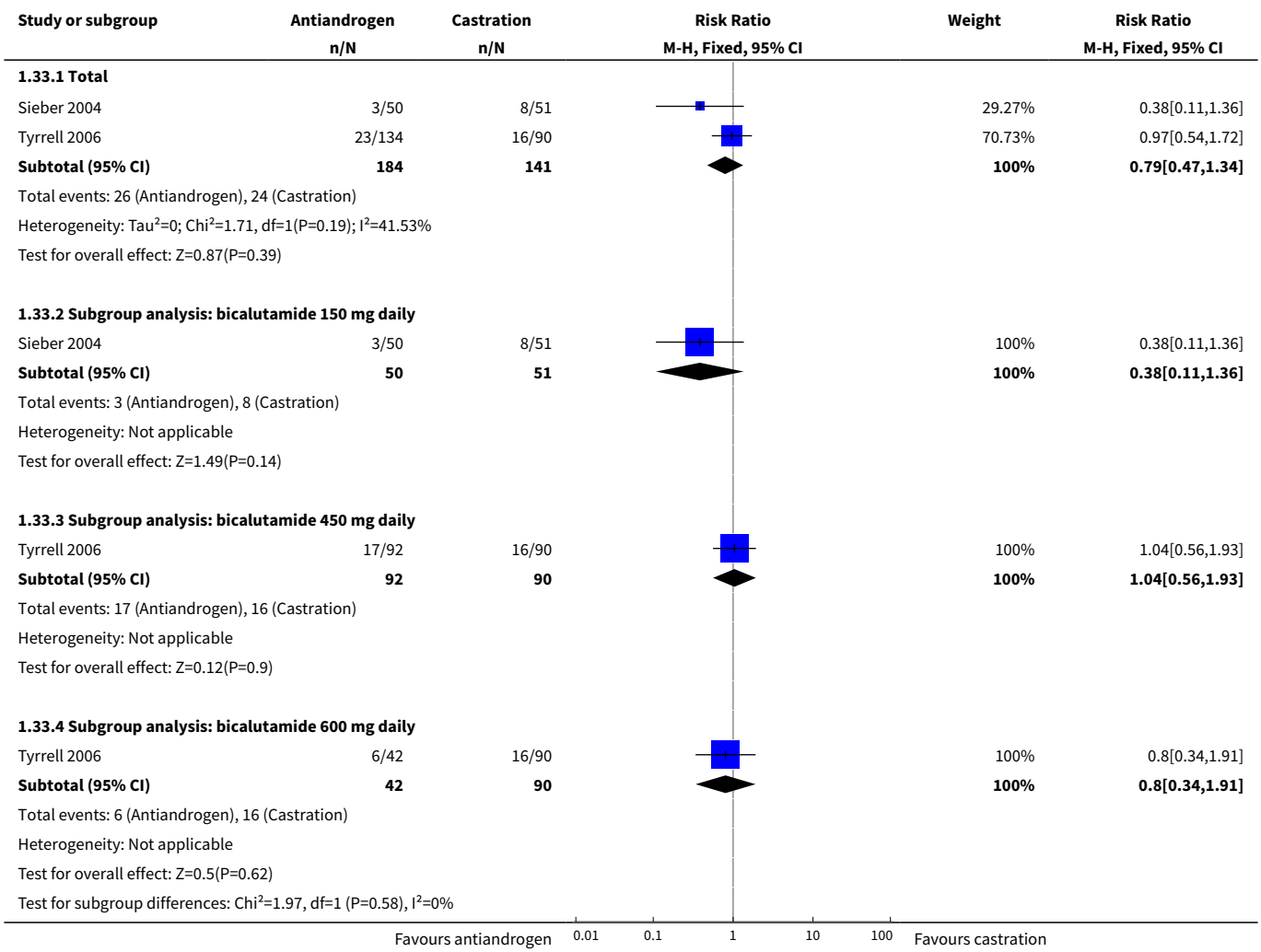


Analysis 1.32. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 32 Infection.

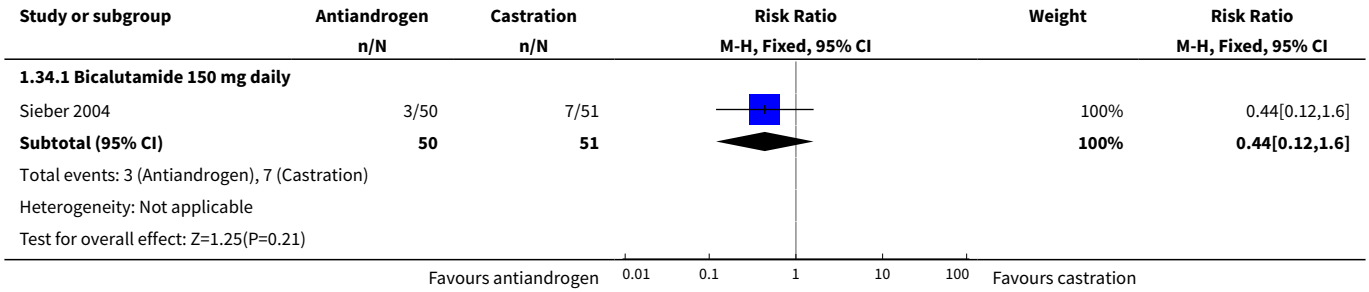




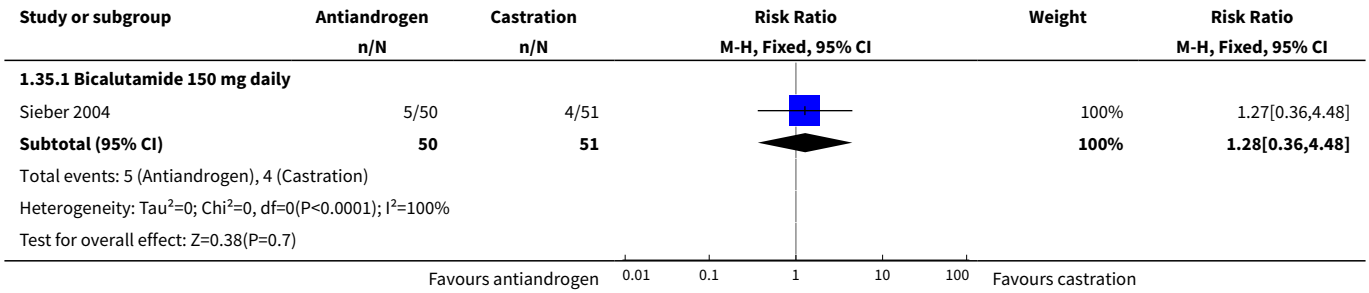
Analysis 1.33. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 33 Pharyngitis.



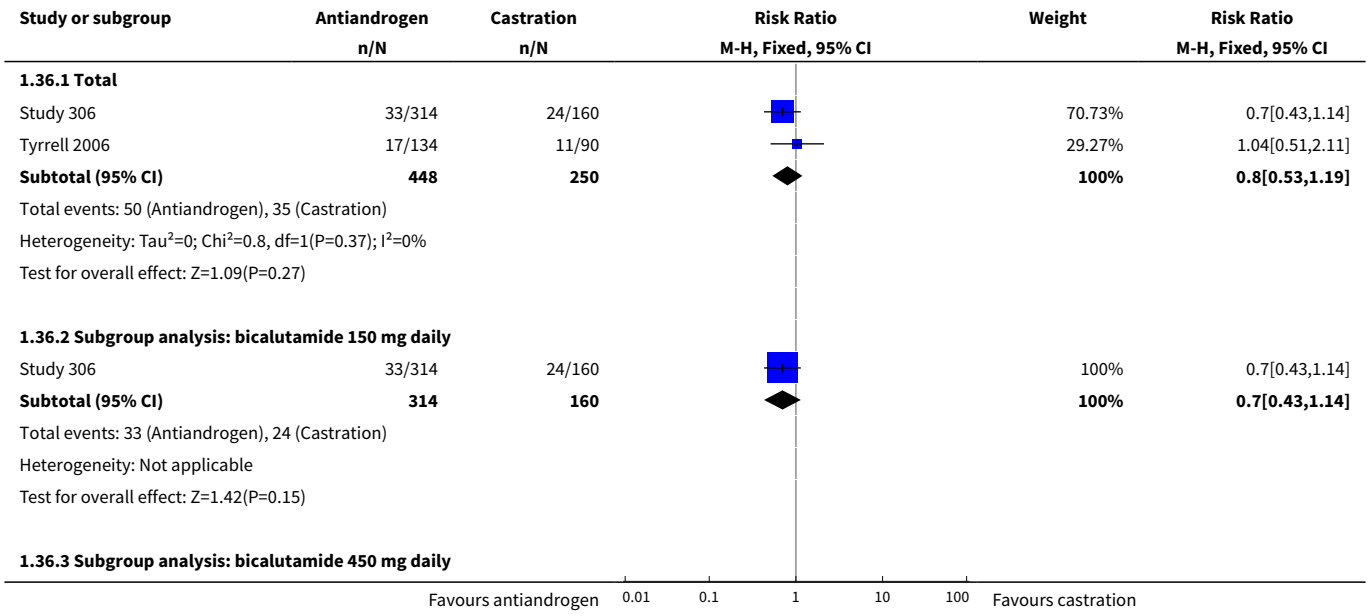
Analysis 1.34. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 34 Arthritis.

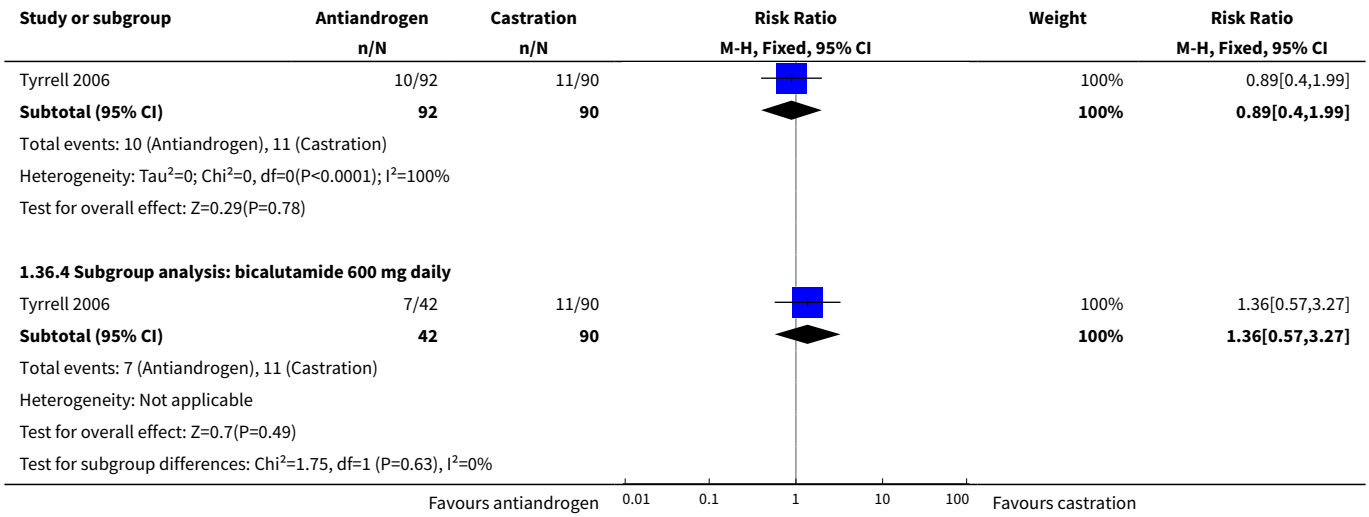


Analysis 1.35. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 35 Sinusitis.

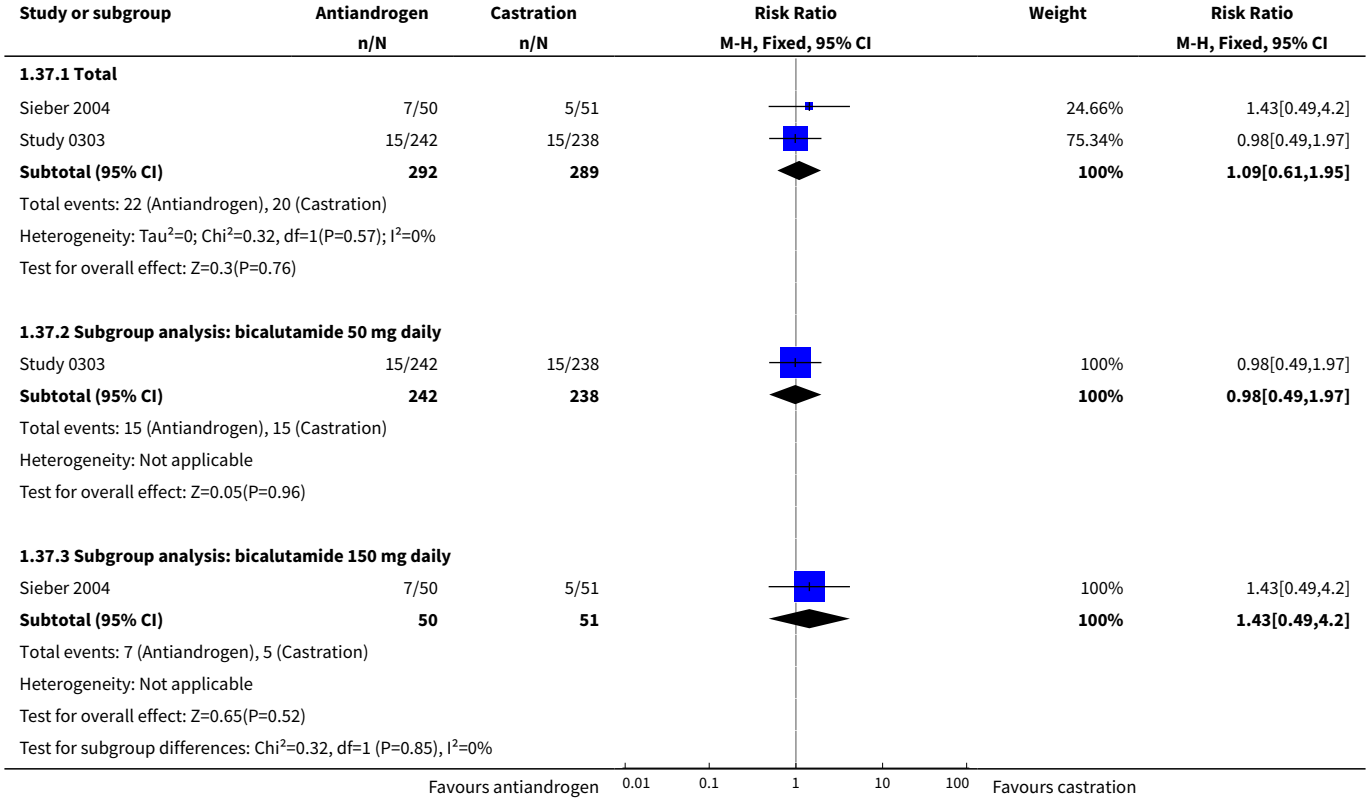


Analysis 1.36. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 36 Urinary tract infection.

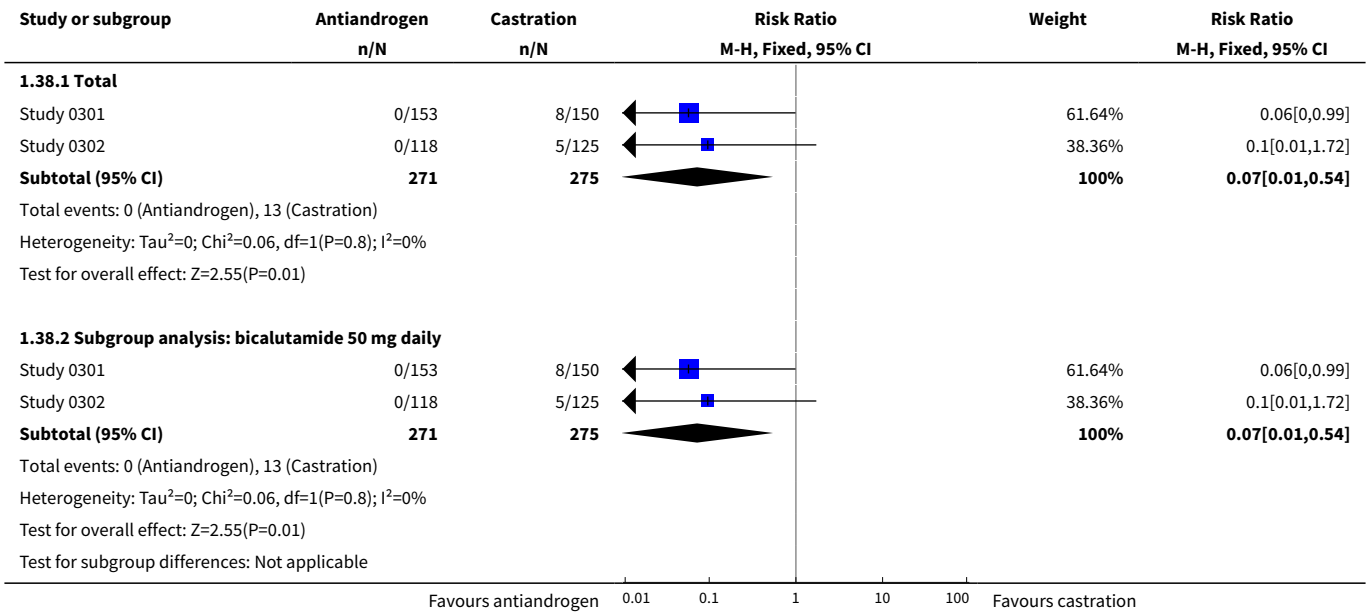




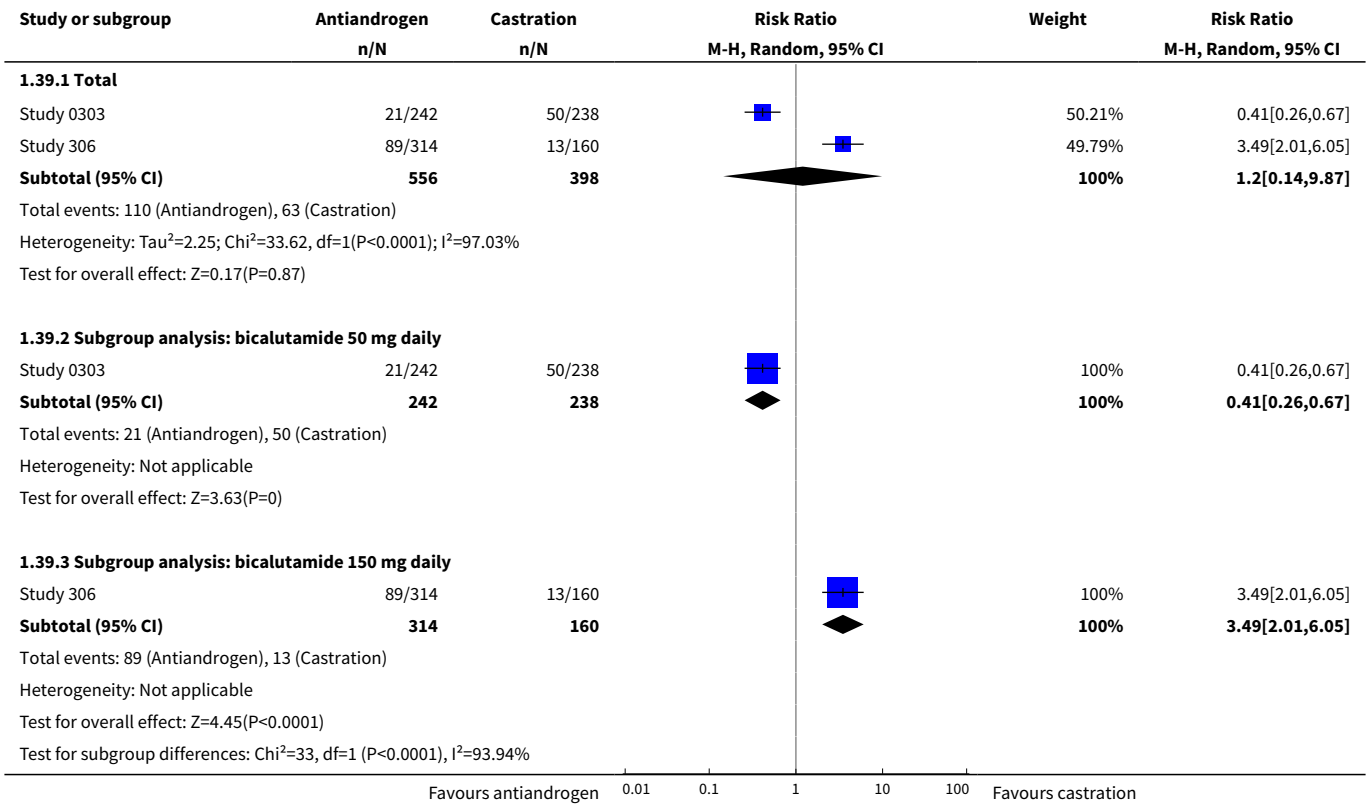
Analysis 1.37. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 37 Dizziness.



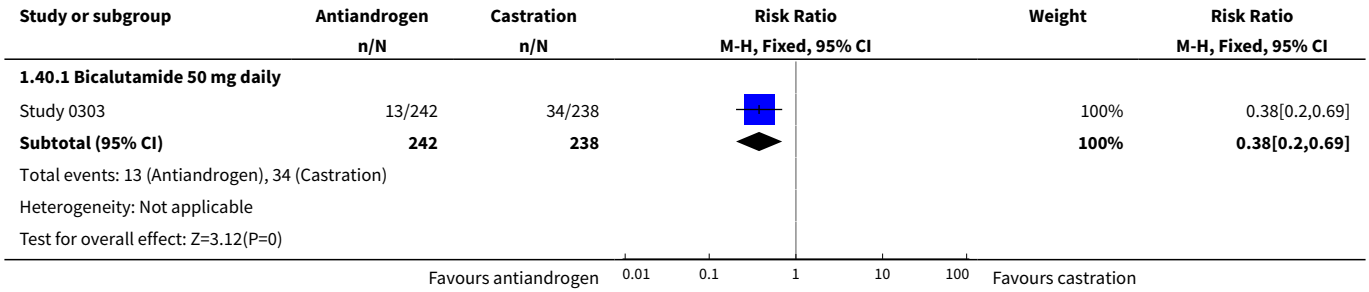
Analysis 1.38. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 38 Haemorrhage.



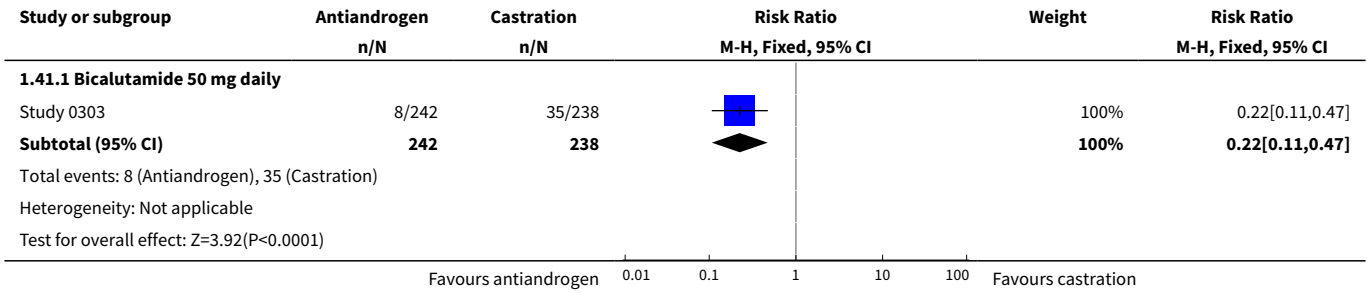
Analysis 1.39. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 39 Haematuria.



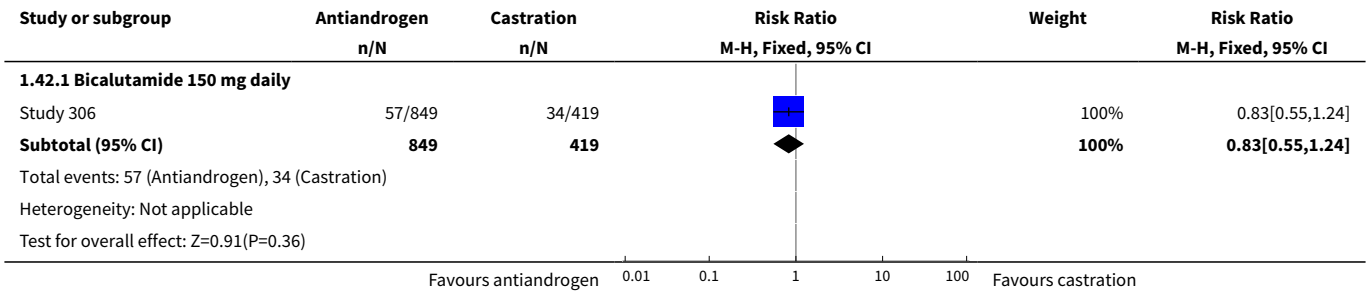
Analysis 1.40. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 40 Nocturia.



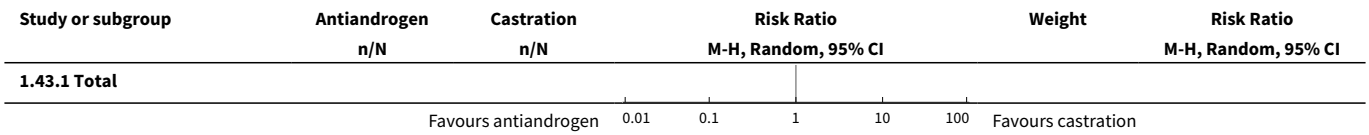
Analysis 1.41. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 41 Urinary frequency.

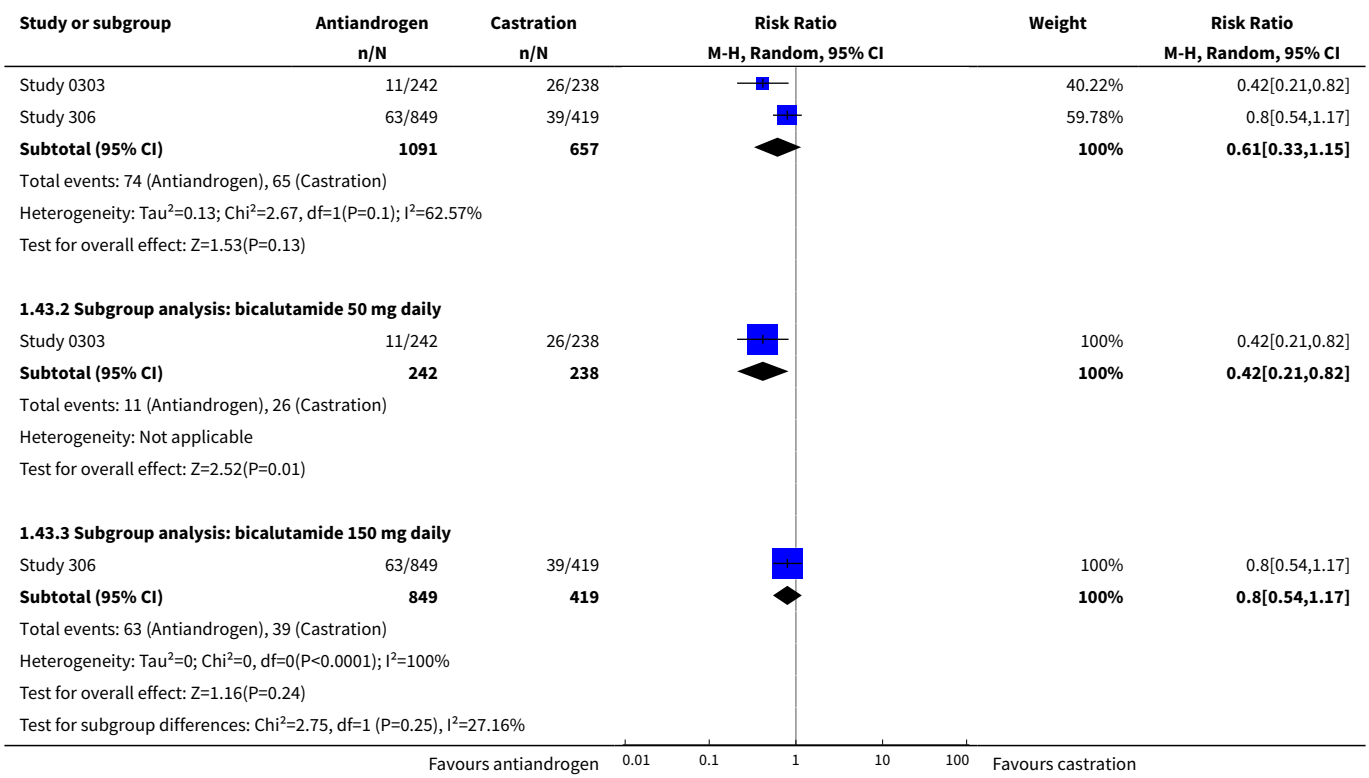


Analysis 1.42. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 42 Urinary retention.

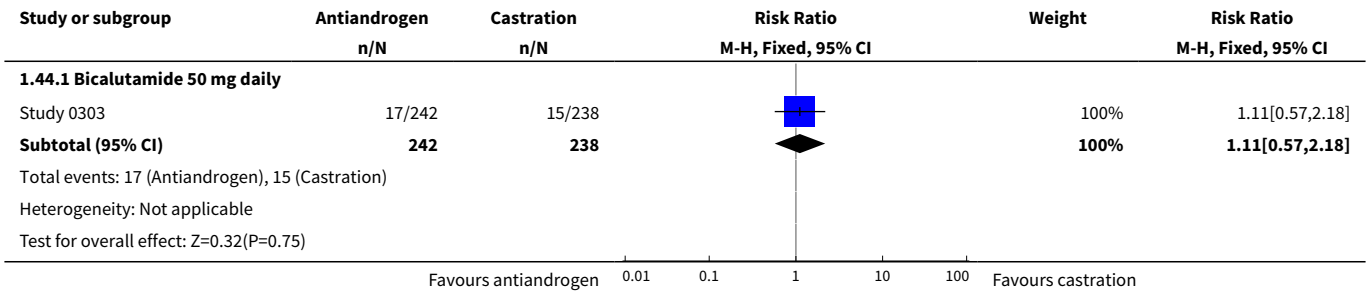


Analysis 1.43. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 43 Peripheral oedema.

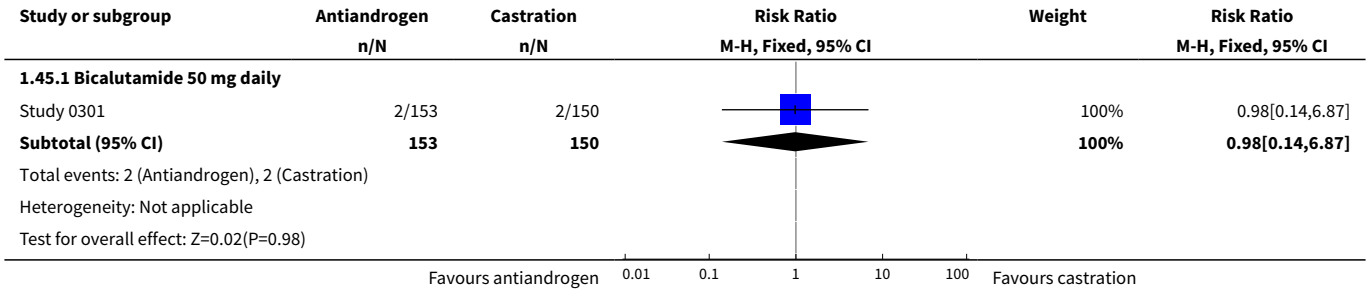




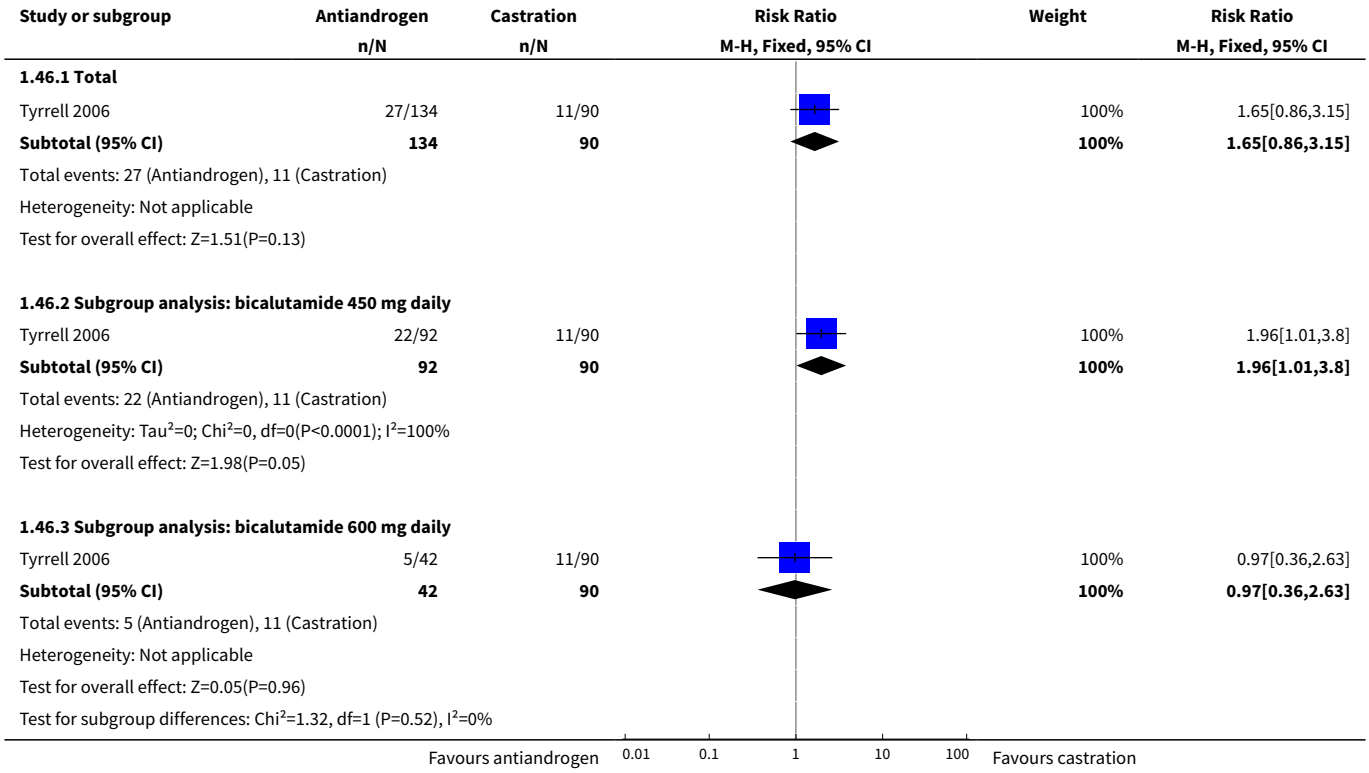
Analysis 1.44. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 44 Anorexia.



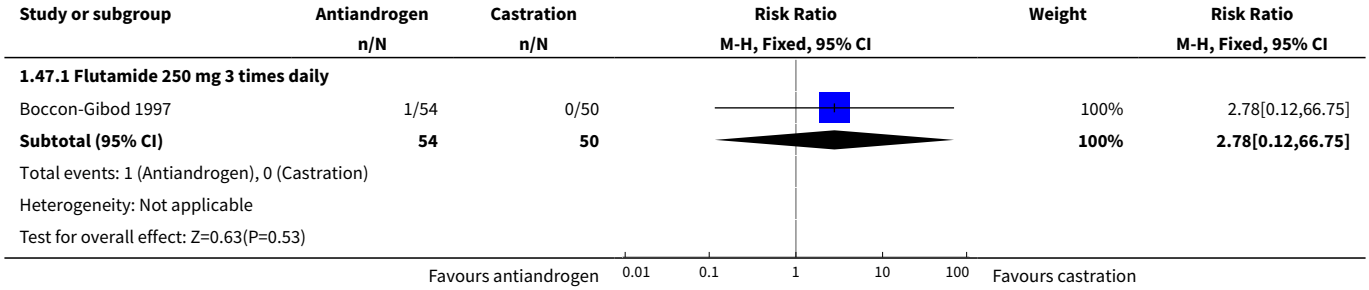
Analysis 1.45. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 45 Loss of sexual function.



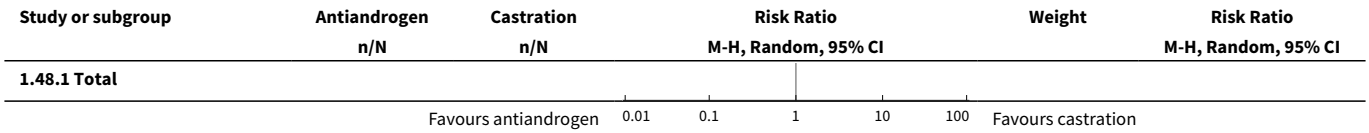
Analysis 1.46. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 46 Arthralgia.

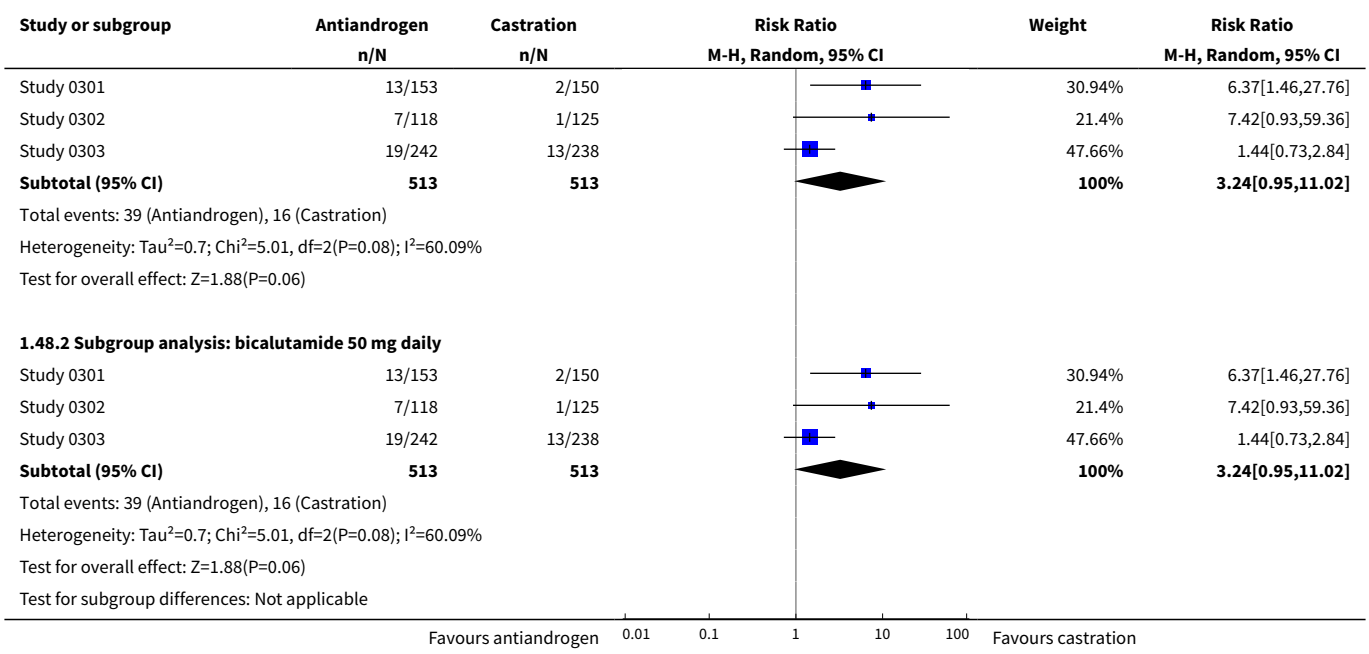


Analysis 1.47. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 47 Gastralgia.

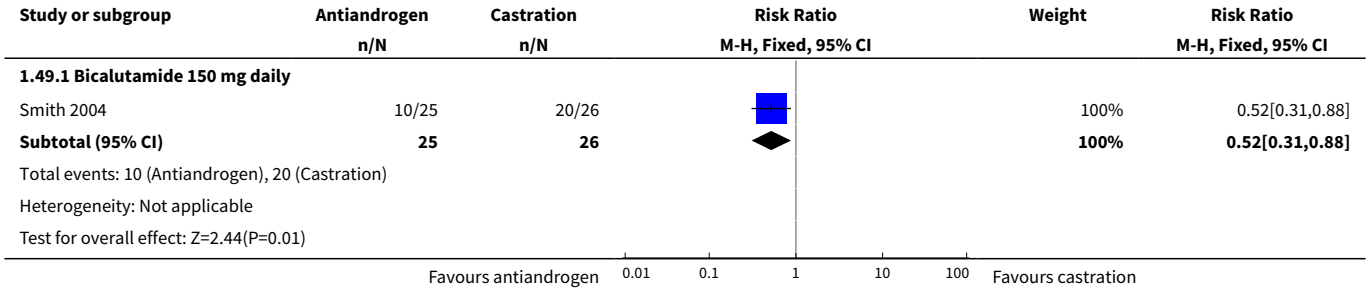


Analysis 1.48. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 48 Nausea.

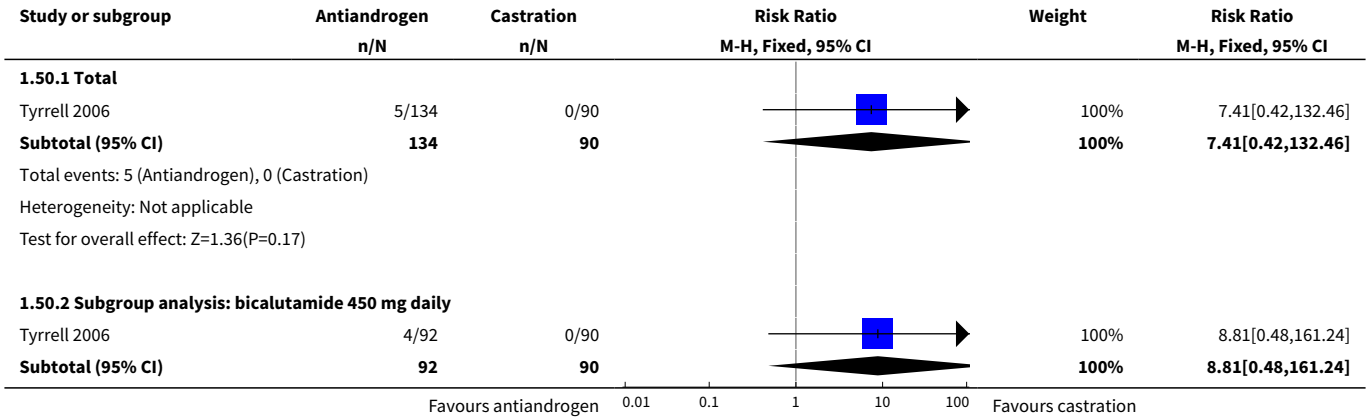


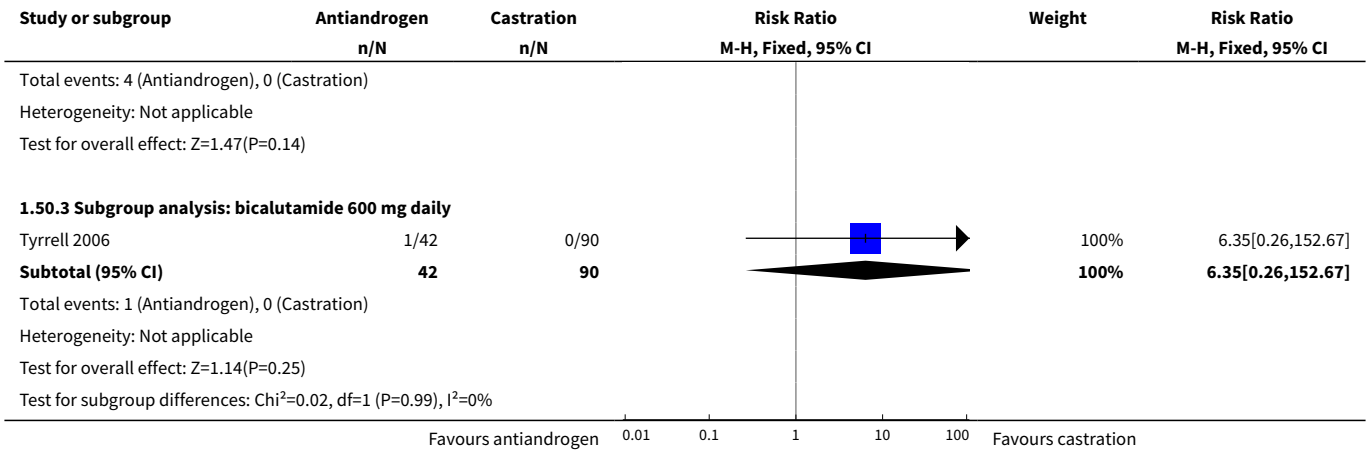


Analysis 1.49. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 49 Fatigue.

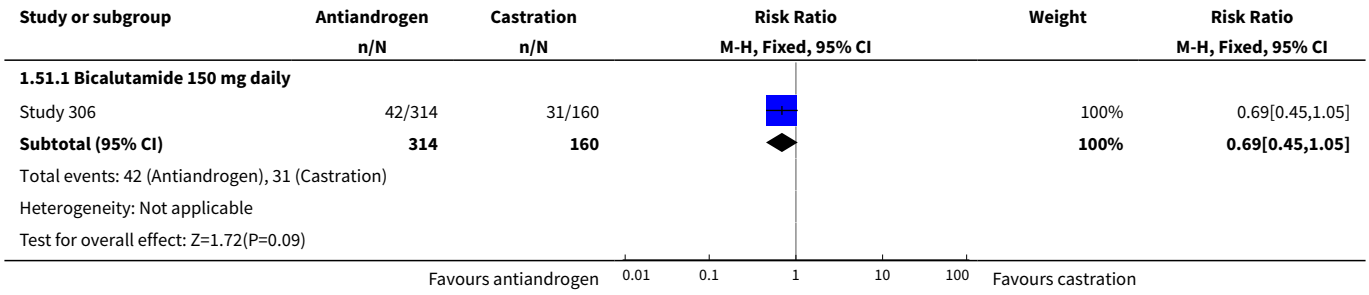


Analysis 1.50. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 50 Dry skin.

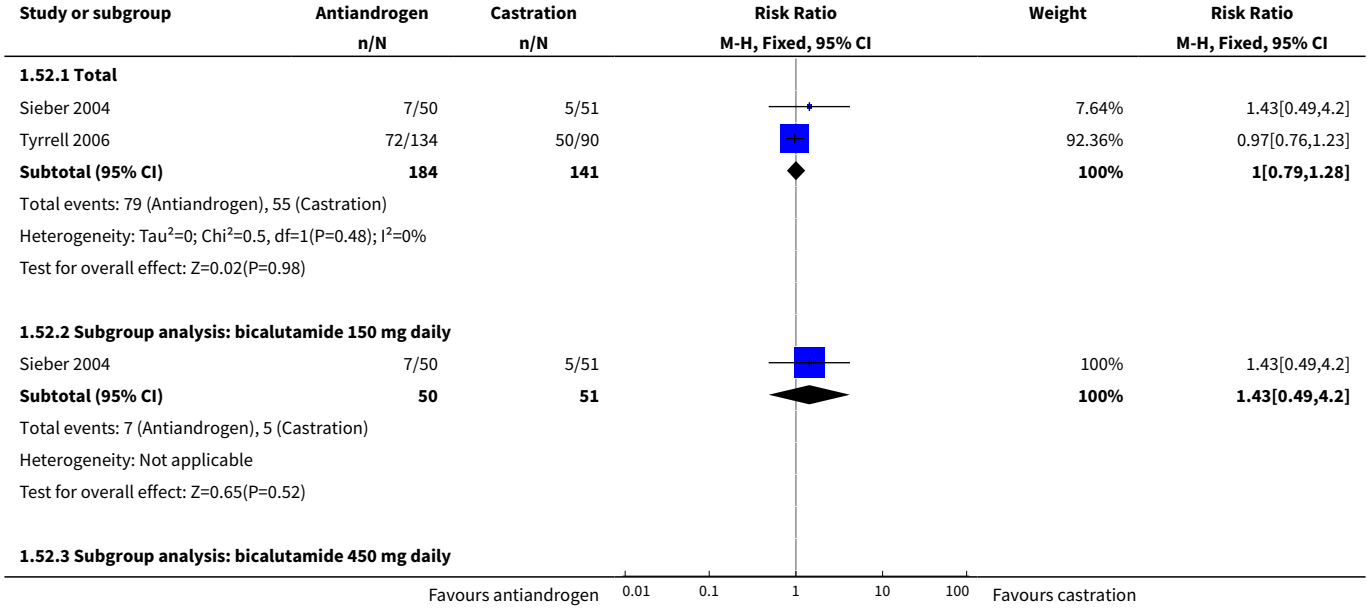


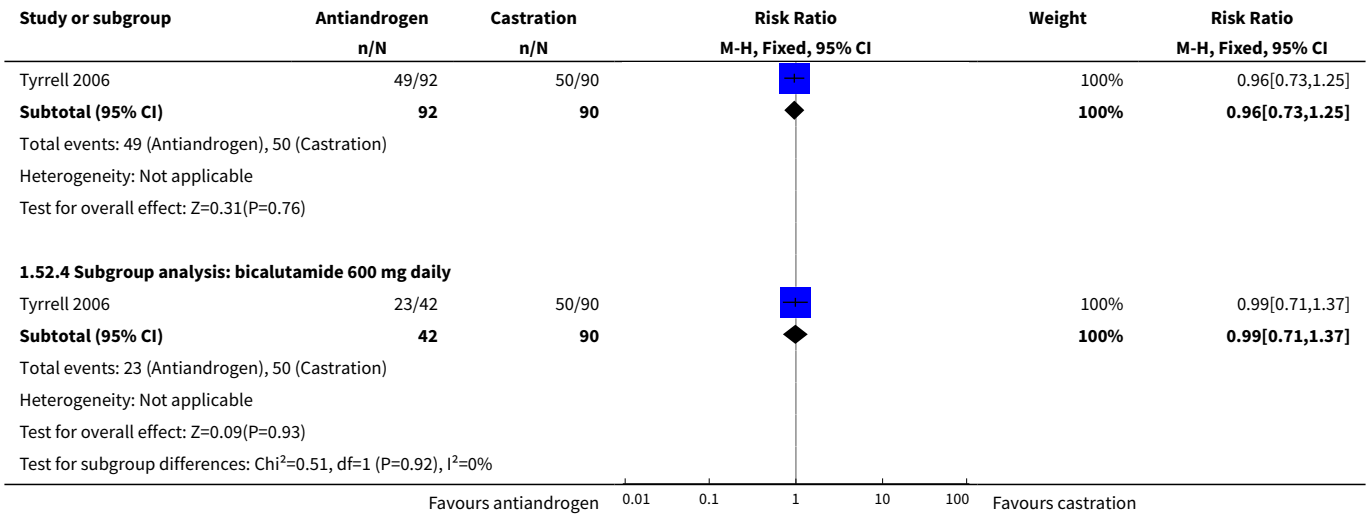


Analysis 1.51. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 51 Aggravation reaction.



Analysis 1.52. Comparison 1 Non-steroidal antiandrogen monotherapy versus LHRH agonists or surgical castration monotherapy, Outcome 52 Serious adverse events.





APPENDICES

Appendix 1. PROSTATE register search strategy

#1	SR-Prostate
#2	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#3	(prostat* near (cancer* or tumo* or neoplas* or carcinom* or malign*))
#4	#2 or #3
#5	MeSH descriptor: [Androgen Antagonists] explode all trees
#6	MeSH descriptor: [Flutamide], this term only
#7	(androgen* near antagonist*) or nilutamid* or nilandron* or anandron* or (RU next 23908*) or bicalutamid* or casodex* or casudex* or (ICI next 176334*) or fluta* or niftolid* or chimax* or cytamid* or eulexin* or drogenil* or euflex* or fluken* or flulem* or flumid* or flutamid* or flutexin* or fugerel* or grisetin* or oncosal* or prostacur* or prostica* or SCH13521* or (SCH next 13521*) or prostogenat* or testotard* or apimid*
#8	#5 or #6 or #7
#9	#1 and #4 and #8

Appendix 2. CENTRAL search strategy

#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	(prostat* near (cancer* or tumo* or neoplas* or carcinom* or malign*))

(Continued)

#3	(#1 OR #2)
#4	MeSH descriptor: [Castration], this term only
#5	MeSH descriptor: [Orchiectomy] explode all trees
#6	(orchiectom* or (surg* near castrat*))
#7	(#4 OR #5 OR #6)
#8	MeSH descriptor: [Androgen Antagonists] explode all trees
#9	MeSH descriptor: [Flutamide], this term only
#10	(androgen* near antagonist*) or nilutamid* or nilandron* or anandron* or (RU next 23908*) or bicalutamid* or casodex* or casudex* or (ICI next 176334*) or fluta* or niftolid* or chimax* or cytamid* or eulexin* or drogenil* or euflex* or fluken* or flulem* or flumid* or flutamid* or flutexin* or fugerel* or grisetin* or oncosal* or prostacur* or prostica* or SCH13521* or (SCH next 13521*) or prostogenat* or testotard* or apimid*
#11	(#8 OR #9 OR #10)
#12	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#13	(LHRH next agonist*) or (LH next RH next agonist*)
#14	luteinizing next hormone next releasing hormone*
#15	gonadotropin next releasing next hormone*
#16	(gnrh next agonist*) or (gn next rh next agonist*)
#17	gonadorelin* or leuprolid* or leuprorelin* or enanton* or lupron* or eligard* or (TAP next 144*) or TAP144* or (A next 43818*) or A43818* or goserelin* or ICI118630* or (ICI next 118630*) or zoladex* or buserelin* or receptal* or bigonist* or tiloryth* or profact* or suprecur* or suprefact* or HOE766* or (HOE next 766*) or triptorelin* or Wy42462* or (Wy next 42462*) or decapeptyl* or trelstar* or trimestral* or AY25650* or (AY next 25650*) or CL118532* or (CL next 118532*)
#18	MeSH descriptor: [Leuprolide] explode all trees
#19	MeSH descriptor: [Goserelin] explode all trees
#20	MeSH descriptor: [Buserelin] explode all trees
#21	MeSH descriptor: [Triptorelin] explode all trees
#22	(#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23	(#7 OR #22)
#24	(#11 AND #23)
#25	(#3 AND #24)

Appendix 3. MEDLINE (Ovid) search strategy

#1	Prostatic Neoplasms/
#2	(prostat* adj3 (cancer* or tumo* or neoplas* or carcinom* or malign*)).tw.
#3	1 or 2
#4	castration/ or orchiectomy/
#5	(orchiectom* or (surg* adj3 castrat*)).tw.
#6	4 or 5
#7	exp Androgen Antagonists/
#8	(androgen* adj3 antagonist*).mp.
#9	(nilutamid* or nilandron* or anandron* or RU 23908*).mp.
#10	(bicalutamid* or Casodex* or Casudex* or ICI 176334*).mp.
#11	(flutamid* or fluta* or niftolid* or chimax* or cytamid* or eulexin* or drogenil* or euflex* or fluken* or flulem* or flumid* or flutexin* or fugerel* or grisetin* or oncosal* or prostacur* or prostica* or SCH13521* or SCH 13521* or prostogenat* or restotard* or apimid*).mp.
#12	Flutamide/
#13	7 or 8 or 9 or 10 or 11 or 12
#14	exp Gonadotropin-Releasing Hormone/
#15	(LHRH agonist* or LH RH agonist*).tw.
#16	luteinizing hormone releasing hormone*.mp.
#17	Gonadotropin Releasing Hormone*.mp.
#18	(gnrh agonist* or gn rh agonist*).mp.
#19	gonadorelin*.mp.
#20	(leuprolid* or leuprorelin* or enanton* or lupron* or eligard* or TAP 144* or TAP144* or A 43818* or A43818*).mp.
#21	(goserelin* or ICI118630* or ICI 118630* or zoladex*).mp.
#22	(buserelin* or receptal* or bigonist* or tiloryth* or profact* or suprecur* or suprefact* or HOE766* or HOE 766*).mp.
#23	(triptorelin* or Wy42462* or Wy 42462* or decapeptyl* or trelstar* or trimestral* or AY25650* or AY 25650* or CL118532* or CL 118532*).mp.
#24	buserelin/ or goserelin/ or triptorelin pamoate/
#25	Leuprolide/

(Continued)

#26	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
#27	randomized controlled trial.pt.
#28	controlled clinical trial.pt.
#29	random*.ab.
#30	clinical trials as topic.sh.
#31	trial.ti.
#32	27 or 28 or 29 or 30 or 31
#33	exp animals/ not humans.sh.
#34	32 not 33
#35	6 or 26
#36	13 and 35
#37	3 and 36
#38	34 and 37
#39	remove duplicates from 38
#40	39 not retracted publication.pt.

Appendix 4. EMBASE (DIMDI) search strategy

#1	EM74
#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	CT=("CONTROLLED CLINICAL TRIAL"; "RANDOMIZED CONTROLLED TRIAL")
#6	CT="RANDOMIZATION"
#7	CT="DOUBLE BLIND PROCEDURE"
#8	CT="SINGLE BLIND PROCEDURE"
#9	CT="PROSPECTIVE STUDY"
#10	RANDOM*

(Continued)

#11	((SINGL* OR DOUBL*) AND (BLIND* OR MASK*))/SAME SENT
#12	(CONTROLLED AND TRIAL)/SAME SENT
#13	ti=trial
#14	groups
#15	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
#16	CT="ORCHIECTOMY"
#17	CT="CASTRATION"
#18	(orchiectom* or (surg* and castrat*))/same sent
#19	16 OR 17 OR 18
#20	CT="ANTIANDROGEN"
#21	CT="BICALUTAMIDE"
#22	CT="NILUTAMIDE"
#23	CT="FLUTAMIDE"
#24	(androgen* and antagonist*)/same sent
#25	(nilutamid* or nilandron* or anandron* or bicalutamid* or casodex* or casudex*)/same sent
#26	(flutamid* or fluta* or niftolid* or chimax* or cytamid* or eulexin* or drogenil* or euflex* or fluken* or flulem* or flumid* or flutexin* or fugerel* or grisetin* or oncosal* or prostacur* or prostica* or prostogenat* or testotard* or apimid*)/same sent
#27	20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26
#28	CT="GONADORELIN"
#29	CT="LEUPRORELIN"
#30	CT="GOSERELIN"
#31	CT="BUSERELIN"
#32	CT="TRIPTORELIN"
#33	((LHRH and agonist*) or (LH RH and agonist*))/same sent
#34	((luteinizing hormone releasing hormone*) or (gonadotropin releasing hormone*))/same sent
#35	((GnRH and agonist*) or (gn rh and agonist*))/same sent
#36	(gonadorelin* or leuprolid* or leuprorelin* or enanton* or lupron* or eligard* or goserelin* or zoladex* or buserelin* or receptal* or bigonist* or tiloryth* or profact* or suprecur* or suprefact*)/same sent

(Continued)

#37	(triptorelin* or decapeptyl* or trelstar* or trimestral*)/same sent
#38	28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
#39	19 OR 38
#40	4 AND 15 AND 27 AND 39
#41	su=medline
#42	40 NOT 41

Appendix 5. Web of Science search strategy

#1	ts=(prostat* same (cancer* or tumo* or neoplas* or carcinom* or malign*))
#2	ts=(orchiectom* or (surg* same castrat*))
#3	ts=(Androgen* same Antagonist*)
#4	ts=(nilutamid* or nilandron* or anandron* or "RU 23908*")
#5	ts=(bicalutamid* or casodex or casudex or "ICI 176334")
#6	ts=(fluta* or niftolid* or chimax* or cytamid* or eulexin* or drogenil* or euflex* or fluken* or flulem* or flumid* or flutamid* or flutexin* or fugerel* or grisetin* or oncosal* or prostacur* or prostica* or SCH13521* or "SCH 13521" or prostogenat* or testotard* or apimid*)
#7	#3 OR #4 OR #5 OR #6
#8	ts=(Gonadotropin same Releasing same Hormone*)
#9	ts=((LHRH same agonist*) or (LH same RH same agonist*))
#10	ts=(luteinizing same hormone same releasing same hormone*)
#11	ts=(gonadorelin* or (gnrh same agonist*) or (gn same rh same agonist*))
#12	ts=(leuprolid* or leuprorelin* or enanton* or lupron* or eligard* or "TAP 144" or TAP144* or "A 43818" or A43818* or goserelin* or ICI118630* or (ICI same 118630*) or zoladex* or buserelin* or receptal* or bigonist* or tiloryth* or profact* or suprecur* or suprefact* or HOE766* or "HOE 766" or triptorelin* or Wy42462* or "Wy 42462" or decapeptyl* or trelstar* or trimestral* or AY25650* or "AY 25650" or CL118532* or "CL 118532")
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	#2 OR #13
#15	#14 AND #7
#16	#15 AND #1

(Continued)

#17	ts=(rando* or (controlled same trial) or (clinical same trial) or (double* same blind*) or (singl* same blind*)) or ti=trial
#18	#16 AND #17

Appendix 6. Keywords used to search meeting abstracts

bicalutamide	casodex	nilutamide	apimid	flutamide
nilandron	anandron	casudex	niftolid	chimax
cytamid	eulexin	drogenil	euflex	fluken
flulem	flumid	flutexin	fugerel	grisetin
oncosal	prostacur	prostica	SCH-13521	prostogenat

Appendix 7. Keywords used to search trial registries

bicalutamide	casodex	nilutamide	apimid	flutamide
nilandron	anandron	casudex	niftolid	chimax
cytamid	eulexin	drogenil	euflex	fluken
flulem	flumid	flutexin	fugerel	grisetin
oncosal	prostacur	prostica	SCH-13521	prostogenat

CONTRIBUTIONS OF AUTHORS

Frank Kunath: correspondence, design and coordination of the review, search for trials, selection of studies for inclusion, extraction of data, assessment of risk of bias, entry of data, data analysis, interpretation of data analyses and final approval.

Henrik R Grobe: search for trials, selection of studies for inclusion, data collection and data management.

Gerta Rücker: statistical advice and methodological support, general advice on the review and final approval.

Edith Motschall: trial search co-ordinator, advice on search strategy, general advice on the review and final approval.

Gerd Antes: methodological support, general advice on the review and final approval.

Philipp Dahm: methodological support, urological/clinical advice on the review and final approval.

Bernd Wullich: urological/clinical advice on the review and final approval.

Joerg J Meerpohl: data collection, interpretation of data, methodological support, general advice, involvement in writing the review and final approval.

DECLARATIONS OF INTEREST

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We revised the title to clarify that non-steroidal antiandrogen monotherapy was compared with luteinising hormone–releasing hormone agonists or surgical castration monotherapy. Consequently, we also changed the objective section from 'To determine the effects of non-steroidal antiandrogen monotherapy compared to surgical/medical castration monotherapy for advanced stages of prostate cancer' to 'To assess the effects of non-steroidal antiandrogen monotherapy compared with luteinising hormone–releasing hormone agonists or surgical castration monotherapy for treating advanced stages of prostate cancer' for consistency with the review title.

For clarification, we specified the information regarding assessment of heterogeneity and data synthesis.

We revised the section Assessment of heterogeneity for consistency with the thresholds for interpretation of I^2 presented in the *Cochane Handbook for Systematic Reviews of Interventions* (Deeks 2008). It now reads: 'Statistical heterogeneity was examined by using the I^2 statistic (Higgins 2002; Higgins 2003). Our definitions of the thresholds for interpretation of I^2 are consistent with the definitions presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2008): 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% substantial heterogeneity; 75% to 100% considerable heterogeneity. Clinical heterogeneity was examined by performing subgroup analyses. For details, see Subgroup analysis and investigation of heterogeneity section.'

We revised the section Data synthesis to clarify the I^2 value threshold for which the random-effects model was used. It now reads: 'For data synthesis, we used Review Manager 5 (Review Manager 2012), as provided by The Cochrane Collaboration. Meta-analyses of the data from all contributing studies were conducted using a fixed-effect model if I^2 was less than 50%, and using a random-effects model for substantial or considerable heterogeneity if I^2 was greater than or equal to 50% (≥ 50%). We reported results from both models.'

We changed designations but not definitions of the following outcomes: 'discontinuation due to adverse events,' 'time to clinical progression,' 'time to biochemical progression' and 'time to treatment failure.' These are now: 'treatment discontinuation due to adverse events,' 'clinical progression,' 'biochemical progression' and 'treatment failure,' respectively.

We adapted our review to the MECIR recommendations. The names of the risk of bias domains "randomisation, concealment of allocation, blinding (of patients, personnel and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias" have been changed to "random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias," for consistency with the updated risk of bias tool included in the 2011 update of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

We planned in advance to evaluate subgroup analyses regarding the effects of different control interventions (medical vs surgical castration). However, the largest included studies permitted both control interventions but did not report results of subgroups. This involves 925 of the 1288 participants randomly assigned to control groups (72%). We therefore abstained from subgroup analyses regarding the effects of different control interventions.

A current guideline mentioned that non-steroidal antiandrogen monotherapy using bicalutamide with a dose of 150 mg daily for non-metastatic prostate cancer might be an alternative to castration for selected patients (EAU 2013). A narrative review suggested that non-steroidal antiandrogen monotherapy might be an established treatment option in patients with prostate cancer, but an unexplained trend towards decreased survival should prohibit their uncritical use (Wirth 2007). Therefore for the primary outcome of overall survival, we performed post hoc planned subgroup analyses regarding non-metastatic or metastatic disease in combination with different doses of non-steroidal antiandrogens.

We revised the name of our subgroup analysis to allow assessment of other doses. It now reads: 'dose of non-steroidal antiandrogen' (formerly: 'bicalutamide 50 mg (milligrams) versus bicalutamide 150 mg').

We revised the section Sensitivity analysis to be more precise. It now reads: 'We performed sensitivity analyses to evaluate the effects of data imputations for best-case and worst-case scenarios (Analysis 1.5; Analysis 1.7; Analysis 1.9). Additionally, we investigated the robustness of results through sensitivity analyses when heterogeneity was substantial or considerable (I^2 50% to 90% or 75% to 100%, respectively) by excluding smaller studies from the meta-analysis (Analysis 1.1; Analysis 1.2; Analysis 1.4; Analysis 1.8; Analysis 1.17).'

We revised the section Measures of treatment effect. It now reads: 'We analysed extracted data using Review Manager 5 (Review Manager 2012). We extracted hazard ratios (HRs) with 95% confidence intervals (CIs) for time-to-event outcomes. If HRs were not given, we used indirect estimation methods (described by Parmar et al (Parmar 1998) and Williamson et al (Williamson 2002)) to calculate them. If we were unable to extract these data from the study reports or to receive the necessary information from the primary investigators, we alternatively used the proportions of participants with the respective outcomes measured at certain time points to calculate risk ratios (RRs) with 95% CIs. We expressed results for binary outcomes as RRs with 95% CIs as measures of uncertainty' (formerly: '[...] If we will be unable to either extract these data from the study reports or receive the necessary information from the primary investigators, we will use as an alternative the proportions of participants with the respective outcomes measured at certain time points (i.e. six months, then 12-monthly intervals) to calculate risk ratios (RRs). If outcome data are presented for other time periods, we will give consideration to examine these as well [...]').

We extended the definition of 'cancer-specific survival' with a statement on cancer-specific mortality because of data availability in the included studies.

NOTES

For the next update of this review, we will adapt our search strategy to the recommendations of the trial search co-ordinators of the Cochrane Prostatic Diseases and Urologic Cancers Group. We will add the following search terms to our search strategy: "antiandrogen*", "anti androgen*", "testectomy", and "orchidectomy". Addtionally, we will search EMBASE without The 'SAME SENT' adjacency operator (e.g. change in search strategy from '(nilutamid* or nilandron* or anandron* or bicalutamid* or casodex* or casudex*)/same sent' to '(nilutamid* or nilandron* or anandron* or bicalutamid* or casodex* or casudex*).' We will also prespecify outcomes for summary of findings tables to minimise bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Androgen Antagonists [adverse effects] [*therapeutic use]; Anilides [adverse effects] [therapeutic use]; Antineoplastic Agents, Hormonal [adverse effects] [*therapeutic use]; Disease Progression; Flutamide [adverse effects] [therapeutic use]; Gonadotropin-Releasing Hormone [adverse effects] [*therapeutic use]; Goserelin [adverse effects] [therapeutic use]; Leuprolide [adverse effects] [therapeutic use]; Medication Adherence [statistics & numerical data]; Nitriles [adverse effects] [therapeutic use]; Orchiectomy [*methods] [mortality]; Prostatic Neoplasms [mortality] [pathology] [*therapy]; Randomized Controlled Trials as Topic; Tosyl Compounds [adverse effects] [therapeutic use]; Triptorelin Pamoate [adverse effects] [therapeutic use]

MeSH check words

Humans; Male