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TABLE OF CONTENTS

[Intervention Review]

5-alpha-reductase inhibitors for prostate cancer prevention

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ABSTRACT

Background

Five-alpha-reductase inhibitors (5ARI) are frequently used to treat bothersome lower urinary tract symptoms associated with benign prostatic hyperplasia and male androgenic alopecia. They have potential as chemopreventive agents.

Objectives

We sought to estimate the effectiveness and harms of 5ARI in preventing prostate cancer.

Search methods

MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library were searched through April 2007 to identify randomized trials.

Selection criteria

For prostate cancer outcomes we included randomized controlled trials of at least 1 year in duration published after 1984. For non-prostate cancer outcomes, randomized trials were included if: they were at least 6 months in duration published after 1999.

Data collection and analysis

The primary outcome was prostate cancer period-prevalence "for-cause." "For-cause" was defined as prostate cancer clinically detected based on symptoms, an abnormal digital rectal exam, or detected as a result of an abnormal prostate specific antigen value. Trials were categorized as long (> 2 year), mid (1 to 2 years) and short (< 1 year) term.

Main results

Nine trials reported prostate cancer period-prevalence. Three trials using finasteride lasted four years or longer but only one (the Prostate Cancer Prevention Trial) was specifically designed to assess the impact of 5ARI on prostate cancer period-prevalence. The mean age of enrollees was 64.6 years, 91% were white, mean PSA was 2.1 ng/mL. For-cause prostate cancers comprised 54% of all cancers detected. Finasteride was associated with a 26% relative risk reduction in prostate cancers detected for-cause among all randomized subjects (relative risk 0.74 (95% CI 0.67 to 0.83); absolute risk reduction = 1.4% (3.5% versus 4.9%). Six trials assessed prostate cancers detected overall with a pooled 26% relative reduction favoring 5ARI (relative risk 0.74 (95% CI 0.55 to1.00); 2.9% absolute reduction (6.3% versus 9.2%). Reductions were observed regardless of age, race or family history of prostate cancer but not among men with baseline PSA > 4.0 ng/mL. A greater number of high Gleason score tumors (7 to 10 or 8 to 10) occurred in men on finasteride in the PCPT. Impaired sexual or erectile function or endocrine effects were more common with finasteride than placebo.

Authors' conclusions

Five-alpha-reductase inhibitors reduce prostate cancer risk but may increase the risk of high-grade disease in men who are undergoing regular screening for prostate cancer using prostate specific antigen and digital rectal examination. Effects are consistent across race, family history and age and possibly 5ARI but were limited to men with baseline PSA values < 4.0 ng/mL. The impact of 5ARI on absolute or relative rates of prostate cancer in men who are not being regularly screened is not clear. Information is inadequate to assess the impact of 5ARI on mortality.

PLAIN LANGUAGE SUMMARY

Five-alpha-reductase inhibitor drugs, such as finasteride or dutasteride, reduce the risk prostate cancer in men who have routine prostate cancer screening

Five-alpha-reductase inhibitor drugs have potential as chemopreventive agents. Reduction of prostate cancer was similar between racial groups, age groups (aged 65 years or older compared to younger age groups) and those with or without a family history of prostate cancer. Reduction of prostate cancer was limited to men who had a baseline prostate specific antigen (PSA) values less than 4.0 ng/mL. However, use of five-alpha-reductase inhibitors may also increase the risk of high-grade prostate cancer in men undergoing prostate cancer screening. Future research is needed to determine if the use of five-alpha-reductase inhibitors can reduce prostate cancer in men who are not being regularly screened for prostate cancer. Future studies should also determine whether five-alpha-reductase inhibitors can reduce death and prostate cancer death and further evaluate the risk of developing high-grade prostate cancer.

BACKGROUND

In 2007 an estimated 218,890 men will be diagnosed with, and 27,050 deaths attributed to, prostate cancer in the United States (ACS 2007). Costs associated with prostate cancer detection and treatment exceed $8 billion annually and represent 8% of cancer and 0.4% of all health related expenditures (Wilt 2008). Safe and effective methods to prevent or slow prostate cancer progression are needed. Because testosterone, after conversion to 5-alpha-dihydrotestosterone, controls prostate mitotic activity and potentially cancer development, interventions that alter circulating androgen levels or inhibit 5-alpha-reductase have potential as chemo preventive agents. Two 5-alpha-reductase inhibitors (5ARI) currently exist. Finasteride is selective for the type 2 isoenzyme. Dutasteride inhibits both Type 1 and type 2 isoenzymes. They are frequently used to treat bothersome lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) and male androgenic alopecia. Their potential role as chemo preventive agents has resulted in completion of one randomized trial assessing the impact of finasteride on the period prevalence of biopsy-proven prostate cancer, the initiation of another trial with dutasteride and reporting prostate cancer period-prevalence results from studies of BPH treatment (PCPT 2003; Andriole 2004).

We conducted a systematic review to provide evidence for a joint American Society of Clinical Oncology (ASCO) and American Urological Association (AUA) Clinical Practice Guideline Panel to address the following key question: Should men routinely be offered a 5ARI for the chemoprevention of prostate cancer based on the evidence related to the impact of 5ARI on prostate cancer detection, prostate cancer mortality, and/or overall mortality as well as other clinical benefits and harms associated with 5ARI?

OBJECTIVES

To evaluate the impact of 5ARI on the risk of incident prostate cancer. This includes the evaluation of whether benefits and harms of 5ARI vary among identifiable subgroups such as age, race/ethnicity, family history of prostate cancer, baseline risk for prostate cancer, histologic grades or stages of prostate cancer, and by type of 5ARI.

We also wished to evaluate: 1) the impact of 5ARI on the risk of prostate cancer mortality, and/or overall mortality; 2) what are other potential benefits of, and indications for, 5ARI use (e.g., BPH); 3) the impact of 5ARI on the need for treatment for benign and for malignant disease; and 4) the potential harms and side effects of 5ARI.

METHODS

Criteria for considering studies for this review

Types of studies

For prostate cancer outcomes we included randomized controlled trials of at least 1 year in duration published after 1984. For non-prostate cancer outcomes, randomized trials were included if: they were at least 6 months in duration published after 1999. This date was chosen because the American Urologic Association guideline on the management of BPH included studies published through 1999.

Types of participants

Adult men, aged 45 years or older, who are at risk for prostate cancer and have a life expectancy of at least 10 years
Subgroups of interest include:

- Age: 45-64 years / 65-74 years / 75 and older
- Race/ethnicity: Caucasian / African American / Asian / Hispanic / Other
- Baseline prostate specific antigen (PSA) values (ng/mL): 3 / >3 4 / >4 10
- Family history of prostate cancer (yes/no)
- Pre-existing BPH (yes/no)
- Pre-existing LUTS (yes/no)
- AUA/ International Prostate Symptom Score (IPSS) Symptom Severity: none to mild/moderate/severe
- Bother/Impact: moderate or greater
- Pre-existing high-grade prostatic intraepithelial neoplasia (PIN) (yes/no)

Types of interventions

5ARI (finasteride or dutasteride) versus placebo, no intervention, medical or herbal therapies, or surgical, device/minimally invasive therapies for nonmalignant prostate conditions.

Types of outcome measures

The primary outcome was prostate cancer detected "for-cause" period prevalence. For-cause prostate cancers include those that: 1) were suspected clinically during the course of the trial because of symptoms, abnormal digital rectal exam, or abnormal PSA, and were confirmed on biopsy; or 2) during the trial, a recommendation was made for biopsy per the study protocol (e.g. due to increasing PSA) which was never done, and end-of-study biopsy showed prostate cancer; or 3) end-of-study biopsy in the setting of a PSA > 4 ng/mL and/or suspicious digital rectal exam (DRE) showed prostate cancer.

Secondary outcomes included: 1) prostate cancers detected due to study protocol rather than clinical indication (see above); 2) overall mortality; and 3) prostate cancer-specific mortality. We also assessed the clinical benefits of 5ARI in the treatment of BPH. These outcomes included 1) change in urinary symptom scale scores (IPSS/AUA); 2) BPH progression; 3) development of acute urinary retention; and 4) need for interventions for treatment of LUTS. We also assessed the harms associated with 5ARI including 1) impotence/erectile dysfunction; 2) retrograde ejaculation; 3) decreased ejaculate volume; 4) decreased libido; and 5) gynecomastia.

Search methods for identification of studies

MEDLINE and the Cochrane Library were searched through April 2007. Results were supplemented with hand searching of reviews and personal files. The following MeSH terms and text words were used: "finasteride," "dutasteride," "prostatic neoplasms," "azasteroids," "reductase inhibitors" and "enzyme inhibitors." Unpublished information was provided from Prostate Cancer Prevention Trial (PCPT) authors.

Data collection and analysis

Trials were categorized as long (> 2 year), mid (1 to 2 years) and short (< 1 year) term; with trials of at least 1 year duration included for assessment of prostate cancer outcomes. Pooled analyses of outcomes data were conducted using RevMan 4.2 software. Relative risks and absolute risk differences with 95% confidence intervals were calculated for categorical outcomes. Weighted mean differences, the difference between treatment and control pooled means at endpoint, along with 95% confidence intervals were calculated for continuous variables. If heterogeneity was evident between the trials, based on the Chi^2 test for heterogeneity ($P < 0.1$) and the I^2 test (> 50%) (Higgins 2003), a DerSimonian and Laird random-effects model was utilized, exploration of potential clinical causes of heterogeneity conducted and/or results reported separately (DerSimonian 1986). A fixed-effects model was used if heterogeneity criteria were not present. Individual trials outcomes were assessed, with emphasis on the PCPT because it was designed to assess whether 5ARI prevent or delay prostate cancer (PCPT 2003).

RESULTS

Description of studies

Preliminary searches for trials with prostate cancer outcomes identified 728 MEDLINE/preMEDLINE abstracts. Cochrane Library search identified 315 abstracts. Abstract screening eliminated 919 abstracts that failed to meet criteria. The remaining 124 articles were reviewed in full. Following exclusion of publications that did not report data pertinent to the research questions, 13 reports were included.

The trials randomized 34,410 men (ARIA/ARIB 2004; Multicentre Investigation to Characterise the effect of Tamsulosin on Urinary Symptoms (MICTUS 2003); Medical Therapy of Prostatic Symptoms (MTOPS 2003); PCPT 2003; Prospective European Doxazosin and Combination Therapy Trial (PREDICT 2003); Lee 2002; Foley 2000; Cote 1998; Proscar Long-Term Efficacy and Safety Study Group (PLESS 1998); PROscar Safety Plus Efficacy Canadian Two-year Study (PROSPECT 1996); Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group (VA COOP 1996); Finasteride Study Group (International) (FSG Int. 1993); Finasteride Study Group (FSG American 1992)). Nine trials of at least one year duration (33,403 men) provided information related to prostate cancer period-prevalence (ARIA/ARIB 2004; PCPT 2003; Foley 2000; Cote 1998; PLESS 1998; FSG American 1992). Reports assessing the effectiveness and safety of dutasteride 0.5 mg/day were a pooled analysis of three trials (ARIA/ARIB 2004) and the Finasteride Study Group report consisted of two trials (FSG Int. 1993; FSG American 1992). Two trials lasting six months in duration provided outcomes related to BPH (MICTUS 2003; Lee 2002).

Study duration was 0.5 to 7 years with three trials enrolling 24,969 men lasting four years or longer (MTOPS 2003; PCPT 2003; PLESS 1998). All three of these trials used finasteride. Only the PCPT was designed to assess the impact of a 5ARI on prostate cancer period-prevalence as a primary endpoint (PCPT 2003). All trials except the ARIA/ARIB trials (dutasteride) used finasteride. Approximately 39% of enrollees were randomized to finasteride, 7% to dutasteride, 45% to placebo, 5% to alpha-blockers, 4% to combined finasteride and alpha-blocker therapy, and less than 1% to watchful waiting.

Overall mean age of the subjects was 63.8 years (range of means 62.6 to 77.5). Among the trials reporting race, 91% of the subjects were white, 4% black, and 5% Asian or other racial category (MTOPS 2003; PCPT 2003; Lee 2002 9 10,VA COOP 1996; FSG American 1992). The mean PSA level when excluding the PCPT was 3.3 ng/mL (range 2.0 to 9.8) (ARIA/ARIB 2004; MTOPS 2003; PREDICT 2003; Lee 2002; Cote 1998; PLESS 1998; VA COOP 1996; FSG Int. 1993; FSG American 1992) and mean prostate volume was 45.9 cc (range 29.8 to 55.0) (ARIA/ARIB 2004; MTOPS 2003; PREDICT 2003; Lee 2002; VA COOP 1996; FSG Int. 1993; FSG American 1992). The mean baseline PSA level for the PCPT was 1.2 ng/mL (range 0 to 3). Most trials enrolled men with symptomatic BPH. The mean AUA/IPSS score (range 0 to 35 points) in BPH trials was 16.5 (range 15 to 19.5) (ARIA/ARIB 2004; MTOPS 2003; PREDICT 2003; Lee 2002; PLESS 1998; VA COOP 1996), indicating moderate LUTS. In PCPT the mean AUA/IPSS score was 6.7. Approximately 70% of PCPT enrollees had AUA-SS < 8 and fewer then 2% had severe baseline symptoms (AUA-SS > 18).

Risk of bias in included studies

Three placebo-controlled studies met criteria for adequate treatment allocation concealment (central randomization by on site computer, telephone, opaque envelopes, etc.) (PLESS 1998; PROSPECT 1996; VA COOP 1996). Eight of the nine placebo-controlled studies indicated subjects and investigators were blinded to treatment assignment (ARIA/ARIB 2004; MTOPS 2003; PREDICT 2003; PLESS 1998; PROSPECT 1996; VA COOP 1996; FSG Int. 1993; FSG American 1992). One of the alpha-blocker trials reported double blinding (MICTUS 2003). Review of outcome events blinded to treatment assignment was reported in three trials (MTOPS 2003; PREDICT 2003; PLESS 1998). In the PCPT and Cote trials, laboratory and the pathologists reviewing the biopsies were blinded to the treatment assignment (PCPT 2003; Cote 1998). Eight studies specifically recorded using an intention to treat analysis (typically analyses of subjects who received at least one dose of the study treatment) (ARIA/ARIB 2004; MTOPS 2003; PCPT 2003; PREDICT 2003; PLESS 1998; PROSPECT 1996; VA COOP 1996; FSG American 1992). In the largest trial, PCPT, the primary intention to treat analysis included men receiving a diagnosis of prostate cancer during the study or who underwent an end-of-study biopsy (PCPT 2003). There was adequate description of study withdrawals and dropouts by treatment group in 10 studies (ARIA/ARIB 2004; MICTUS 2003; PCPT 2003; Lee 2002; PREDICT 2003; Foley 2000; Cote 1998; PLESS 1998; PROSPECT 1996; FSG American 1992). Pharmaceutical funding or support, either partial or full, was provided in nine trials (ARIA/ARIB 2004; MICTUS 2003; MTOPS 2003; PCPT 2003; PREDICT 2003; PLESS 1998; PROSPECT 1996; FSG Int. 1993; FSG American 1992).

Effects of interventions

Prostate cancer period prevalence

5ARI reduced the period-prevalence of "for-cause cancers". Six reports of eight trials provided data for "prostate cancer detected for cause among all subjects randomized" (ARIA/ARIB 2004; PCPT 2003; PLESS 1998; PROSPECT 1996; FSG Int. 1993; FSG American 1992). All but the Finasteride Study Group trial favored finasteride (FSG Int. 1993; FSG American 1992). For-cause prostate cancers comprised 53.8% (1189/2211) of all cancers. PCPT contributed 1006/1188 (84.6%) of "for cause" cancers (PCPT 2003). Finasteride resulted in a 26% relative reduction (pooled relative risk 0.74 (95% CI 0.67 to 0.83)) and an absolute reduction of 1.4%; risk difference

-0.01 (95% -0.02 to -0.01)) in for-cause cancer among all subjects randomized.

Overall prostate cancer period prevalence was obtained from five long-term (ARIA/ARIB 2004; PCPT 2003; PLESS 1998) and four mid-term RCTs (Cote 1998; PROSPECT 1996; FSG Int. 1993; FSG American 1992). Pooled results demonstrated a 26% relative reduction of borderline statistical significance; relative risk 0.74 (95% CI 0.55 to1.00) and a 2.9% absolute reduction in overall prostate cancers (6.3% versus 9.2%). Four of the trials (and all three longer term trials) had risk estimates favoring 5ARI, though only two were statistically significant. The test for heterogeneity was statistically significant (P = 0.04; I^2 = 56.0%). This was primarily based on one very small mid-term trial of men (n = 58) with PSA levels > 4 ng/mL that included some with baseline prostate biopsies positive for prostatic intraepithelial neoplasia (Cote 1998). When this trial was excluded the overall results became statistically significant (relative risk 0.72; (95% CI 0.58 to 0.88)). ARIA/ARIB, the only report evaluating dutasteride showed a 51% relative reduction in prostate cancers detected (relative risk 0.49 (95% CI 0.31 to 0.77) with an absolute reduction of 1.3% (1.2% versus 2.5%)) (ARIA/ARIB 2004). The PCPT provided 1950/2211 (88.2%) of overall prostate cancers (PCPT 2003).

There were no significant differences in prostate cancers detected due to study protocol in pooled analysis of three trials providing this information (PCPT 2003; PLESS 1998; Cote 1998). The criteria for protocol-directed prostate cancer assessment and diagnosis varied but typically involved obtaining an end-of-study prostate biopsy among men who had not previously been diagnosed with prostate cancer and had not had a biopsy within 1 year of study closure. After initiation of the PLESS, a protocol amendment recommended a repeat biopsy of all men with a baseline PSA of > 4.0 ng/mL who had not been diagnosed with prostate cancer, had not had a repeat biopsy for clinical reasons within the past year and would be candidates for prostate cancer therapy if prostate cancer were diagnosed (PLESS 1998). In contrast, PCPT recommended a prostate biopsy if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/mL (varying from a factor of 2.0 to 2.3) or if the DRE was abnormal (PCPT 2003). An end of study biopsy was planned for all men who had not been given a diagnosis of prostate cancer. The small trial by Cote was unique in that it only enrolled men with PSA levels > 4.0 ng/mL and required a baseline sextant prostate biopsy negative for prostate cancer (Cote 1998). However, 13 of the 58 enrolled subjects had prostatic intraepithelial neoplasia. All men underwent repeat biopsy at 12 months from enrollment.

In the PLESS trial, 27% of cancers diagnosed were detected on end-of-study biopsy; absolute detection rate of 4.9% (finasteride 4.7% versus placebo 5.1%) (PLESS 1998). All men with PSA >4 ng/mL were required to have a negative prostate biopsy prior to enrollment. Two-thirds of men with baseline PSA >4.0 ng/mL and 16% of men with PSA <4.0 ng/mL underwent biopsy. The PCPT noted a 2.2% absolute reduction (6.1% versus 3.9%) though pooled results demonstrated no reduction in prostate cancers detected due to study protocol (relative risk = 1.38 (95% CI 0.50 to 3.78)) (PCPT 2003). Ninety-eight percent of detected cancers were classified as T1 or T2. In the Cote trial, all 9 prostate cancers (8 in the finasteride group) were found on end-of study biopsy (Cote 1998). This included 6/8 men in the finasteride group with prostatic intraepithelial neoplasia at baseline but 0/5 in the placebo group.

Subgroup analysis

Risk reduction was associated with baseline PSA levels. Three trials provided data according to baseline PSA levels (PCPT 2003; PLESS 1998; Cote 1998) and two trials reported histologic grade (PCPT 2003; PLESS 1998). Only PCPT provided information related to race, age at entry and family prostate cancer history (PCPT 2003). Some subgroup results are available only on prostate cancer detected overall rather than prostate cancer detected for-cause. Risk reduction occurred among all randomized men with baseline PSA levels < 4.0 ng/mL (relative risk 0.70 (95% CI 0.64 to 0.77)). However, among the 783 men who had baseline PSA levels of > 4 ng/mL no reduction was observed (relative risk 2.08 (0.28 to 15.43)). All men with baseline PSA > 4 ng/mL had a prostate biopsy at entry that was negative for prostate cancer. Only PCPT limited enrollment to men with a PSA of 3.0 ng/mL or lower (PCPT 2003). The greatest relative reduction occurred in men with the lowest baseline PSA levels (relative risk 0.61 for baseline PSA 0.0-1.0 ng/mL and 0.73 for baseline PSA of 1.1 to 2.0 or 2.1 to 3.0 ng/mL).

A greater number of high Gleason score tumors (7 to 10 or 8 to 10) occurred in men on finasteride in the PCPT but not the smaller and shorter-term PLESS where scores of 8 to 10 were greater in the placebo arm. Considerable statistical heterogeneity existed (P = 0.02; I^2 = 81.3%) suggesting that pooled analysis may not be appropriate. Gleason score distribution in PLESS was reported "to be similar" between finasteride and placebo though no tests of statistical significance were provided (PLESS 1998). However, approximately 5% of all cancers were Gleason 8-10 with seven occurring in the placebo treated group and one on finasteride (relative risk 0.14 (95% CI 0.02 to 1.15)). Twelve prostate cancers had a Gleason score of 7 among men receiving placebo compared to 11 on finasteride.

In contrast, while Gleason score 7 tumors in the PCPT trial were similar between finasteride and placebo (2.0% versus 1.9%), there were statistically significantly more Gleason 8-10 tumors identified overall (0.96% versus 0.56%; relative risk 1.70 (95% CI 1.22 to 2.39)) and for-cause with finasteride than with placebo (PCPT 2003). Relative risk increases ranged from 56% for Gleason 8 to 10 cancers diagnosed for cause among all men randomized to 84% of prostate cancers detected for cause when confined to men receiving a biopsy for cause. Of all-cancers in PCPT, 22.2% in the placebo group compared to 37.0% in the finasteride group were Gleason 7 to 10 (PCPT 2003). Among cancers diagnosed in biopsies performed for-cause the cumulative percents were 29.4 and 47.8 for placebo and finasteride, respectively. Slightly smaller differences were observed in cancers protocol-driven diagnosed in end-of study biopsies (25.3% versus 15.8%). Among all men evaluated Gleason score 7 to 10 tumors were found in 11.5% on finasteride and 7.7% on placebo (relative risk 1.50 (95%CI 1.22 to 1.84)) (PCPT 2003).

Reduction in overall prostate cancers detected due to finasteride was consistent regardless of race or family history. In the placebo group between 9.7% (Hispanic ethnicity) to 14.2% (Black ethnicity) of men were diagnosed with prostate cancer. Relative risk reductions due to finasteride ranged from 25 to 33% and absolute risk reductions ranged from 2.4 to 3.7%. Because fewer than 10% of men were of nonwhite race confidence intervals were wide and risk reductions not statistically significant. Both the relative and absolute reductions due to finasteride in detected prostate cancers were similar among men with versus without a 1st degree family history of prostate cancer.

Only PCPT provided information regarding the cumulative period-prevalence of prostate cancer (PCPT 2003). The cumulative period-prevalence of prostate cancer diagnosed in a biopsy performed for-cause was lower in finasteride treated men than placebo (relative risk 0.90 (95% CI 0.81 to 1.00)) with differences noted after approximately two years following randomization. Throughout the first six years of study follow-up the biopsy rate remained about 2-3% of men at risk. In year 7 there was a three-fold increase in the biopsy rate (7%) and number of total and Gleason grade 7 to 10 prostate cancers diagnosed. The cumulative period-prevalence of prostate cancers detected among men with an endpoint assessed just prior to end-of study biopsies was 9% in the finasteride group versus 12% with placebo. This increased to 22% versus 29% when including end of trial protocol driven biopsy detected cancers.

Mortality

There were no differences in overall or prostate cancer mortality between finasteride and placebo in any trial. No trial was designed to assess these outcomes though the pooled overall mortality estimates favored placebo with wide and statistically non significant confidence intervals (relative risk 1.06 (95% CI 0.95 to1.18)) (PCPT 2003; PREDICT 2003; PROSPECT 1996; VA COOP 1996; FSG American 1992). In the PCPT trial, five subjects in each treatment arm died of prostate cancer (PCPT 2003). Overall and prostate cancer mortality was 5% and 0.05%, respectively.

Benign Prostatic Hyperplasia Progression and Treatments

Trials examined the effectiveness of 5ARI, alone or in combination with other medications, in doses used to improve bothersome lower urinary tract symptoms or prevent symptomatic progression in men with BPH (finasteride = 5 mg/day; dutasteride = 0.5 mg/day). In contrast to PCPT participants, BPH treatment trials targeted men with moderate to severe lower urinary tract symptoms. Effectiveness and adverse effects derived from BPH trials may differ from men taking 5ARI primarily for prostate cancer chemoprevention.

In placebo-controlled trials lasting between 1-4 years, 5ARI reduced AUA symptom scale scores by 20 to 39% compared to 13 to 29% with placebo Table 1(ARIA/ARIB 2004; MTOPS 2003; PREDICT 2003; PLESS 1998; PROSPECT 1996; VA COOP 1996; FSG Int. 1993; FSG American 1992). Results were statistically significant versus placebo in most trials. However, the mean change in AUA-symptom-scale scores versus placebo generally did not achieve the three to four point change previously demonstrated to be clinically noticeable. The risk of acute urinary retention was reduced by one-half in long term trials of 5ARI that included PCPT (relative risk 0.51 (95% CI 0.38 to 0.69); absolute risk reduction 2.2%) (ARIA/ARIB 2004; MTOPS 2003; PCPT 2003; PREDICT 2003; PLESS 1998; FSG Int. 1993). Surgical intervention due to BPH progression was also lower by one-half (relative risk 0.50 (95% CI 0.43 to 0.58); absolute risk reduction 1.7%) (ARIA/ARIB 2004; MTOPS 2003; PCPT 2003; PREDICT 2003; Foley 2000; PLESS 1998; PROSPECT 1996; VA COOP 1996; FSG Int. 1993; FSG American 1992). Relative risk reductions were seen in both mid and long-term BPH treatment trials as well as PCPT (absolute risk reduction 1.8%). The largest benefits were observed in men with baseline PSA > 4.0 ng/ml. Pooled results from BPH trials indicated that finasteride was superior to placebo, comparable to alpha-blockers but inferior to combination alpha-blocker and finasteride therapy at reducing long-term BPH progression. These findings are in agreement with those published in the AUA guideline on the management of BPH. One trial showed a statistically significant reduction in BPH-associated hematuria with finasteride compared to placebo (Foley 2000).

Study discontinuations/lost to follow-up and Adverse effects

Overall study discontinuations and/or lost to follow-up did not differ among men assigned to placebo or 5ARI. Discontinuation due to adverse events also did not differ by treatment assignment and was approximately 7% in mid-term and long-term BPH trials. Adverse effects of finasteride represented the primary reason for the difference in the proportion of men who temporarily discontinued treatment in the PCPT trial, 18% in the finasteride group versus 10% in the placebo group (PCPT 2003). Impaired sexual or erectile function or endocrine effects were more common with finasteride than placebo. Pooled absolute differences were 2% (95% CI 1 to 2) for gynecomastia (ARIA/ARIB 2004; PCPT 2003), 3% (95% CI 1 to 6) for decreased libido (ARIA/ARIB 2004; PCPT 2003; PREDICT 2003; PROSPECT 1996; VA COOP 1996; FSG American 1992), 4% (95% CI -1 to 8) for impotence/erectile dysfunction (ARIA/ARIB 2004; PCPT 2003; PREDICT 2003; PROSPECT 1996; VA COOP 1996; FSG Int. 1993; FSG American 1992), and 4% (95% CI -8 to 17) for reduced volume of ejaculate (PCPT 2003; PLESS 1998; VA COOP 1996; FSG American 1992). The degree to which a particular side effect might have driven withdrawal is not known. In the PCPT trial, there was one breast cancer diagnosis reported in each group (PCPT 2003). Dizziness, fatigue and postural hypotension were more frequent with use of alpha-blockers compared to finasteride (PREDICT 2003; VA COOP 1996).

DISCUSSION

Five-alpha-reductase inhibitors reduce the absolute period-prevalence of "for-cause" detected prostate cancer in all men randomized by about 1% but increase detection of Gleason 8 to 10 tumors by 0.3% in absolute terms. The reduction in prostate cancer was limited to men with baseline PSA levels < 4.0 ng/mL, though relatively few men had baseline PSA levels > 4.0 ng/ml. Reduction was observed regardless of race, family history or age. Five-alpha-reductase inhibitors when taken for periods longer than one year reduced progression of lower urinary tract symptoms associated with BPH, acute urinary retention and the need for surgical intervention especially in men with enlarged prostate glands (PSA > 4.0 ng/mL or volume > 40 cc). 5ARI were well tolerated among trial participants for up to seven years with overall discontinuations and discontinuations due to adverse events similar to placebo. However, adverse events with 5ARI were increased, particularly those related to sexual and erectile dysfunction.

The findings and clinical interpretations have limitations. While 9 trials involving 34,410 men and lasting at least 1 year were included for prostate cancer outcomes, only the PCPT trial was specifically designed to prospectively assess the impact of 5ARI on prostate cancer period-prevalence. Data from other long-term BPH treatment trials that provide information on prostate cancer detection are generally consistent with PCPT findings. Uncertainty relates to the impact of 5ARI on the incidence Gleason grade 8-10 cancers. While PLESS reported a reduction in high-grade tumors on finasteride, PCPT found the opposite effect. Only one modest size BPH trial evaluated dutasteride. It is not possible to determine if the impact on prostate cancer period-prevalence is a 5ARI class effect or varies according to type, mechanism of action or dose of 5ARI. The Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), is assessing the impact of dutasteride on prostate

cancer period-prevalence in men aged 50 to 75 judged to be at increased risk for prostate cancer (clinicaltrials.gov identifier number = NCT00056407) (Andriole 2004).

Methodological and clinical concerns include whether: 1) estimates of prostate cancer period-prevalence should be based on overall prostate cancers detected (which included clinically detected prostate cancers as well as those due to study protocol) rather than "for-cause"; 2) estimates of period-prevalence should incorporate all randomized patients or be limited to those with a diagnosis of prostate cancer or biopsy evaluation to rule out prostate cancer; 3) the proposed alteration in the sensitivity and specificity of prostate cancer detection due to finasteride impacts effect estimates; and 4) the increase in high-grade tumors seen in PCPT is actual or due to pathologic or sampling artifact or is due to the effects of 5ARI on the sensitivity/specificity of PSA testing (Thompson 2007; D'Amico 2006; Thompson 2006).

Our report emphasized prostate cancers detected for-cause among all men randomized. This decision, made after extensive discussion with panel members, resulted in a strong consensus that this approach was representative of outcomes that would occur in clinical settings, reduced bias by preserving the randomization process and focused on clinically relevant prostate cancers. This also reduces selection bias that could occur if only enrollees receiving end-of-study evaluation were analyzed. Our use of "for-cause cancers among patients randomized" in PCPT resulted in a relative risk reduction of 26% and an absolute risk reduction of 1.4%. This contrasts to the 10% relative reduction and 3% absolute reduction noted by PCPT authors who limited their definition to patients undergoing a prostate biopsy for cause. Even so, trial authors' definitions of "for-cause" included some cancers detected due to study protocol directed biopsies. Findings likely overestimate the number of cancers detected compared to clinical settings. However, indications for prostate biopsies and thresholds for labeling a man as having an abnormal PSA value or velocity continue to evolve. This has resulted in more men undergoing prostate biopsies with increased sampling of prostate glands. It is likely that the number of men with prostate cancer detected "for cause" in future clinical settings will increase compared to current practice. Some are likely to be detected for reasons closely approximating protocol driven biopsies from trials included here.

Uncertainty has developed around whether the increase in high-grade tumors observed in PCPT is due to histopathologic artifact caused by 5ARI rather than to an accurate representation of the biologic activity of the tumor. An expert panel of pathologists evaluating high-grade tumor biopsies as well as radical prostatectomy specimens from PCPT concluded that the finasteride effects on tumor morphology did not explain the increase in high-grade cancer. (Lucia 2007). Reports have discussed the impact of finasteride on prostate volume and sampling and the potential role this may play in a changed sensitivity for prostate cancer detection and detection of high grade disease (Lucia 2007; D'Amico 2006). A history of 5ARI use will change PSA thresholds for biopsy. However, men and their physicians will likely make future treatment decisions related to tumor (PSA levels/velocity, stage, histologic grade) patient (age, comorbidities, personal and family preferences), treatment (relative effectiveness and adverse effects) and provider factors rather than a history of 5ARI use.

The ultimate goal of preventing prostate cancer is to reduce overall and disease specific morbidity and mortality. Reduction of prostate cancer detection is a surrogate for that. The majority of men with PSA detected tumors have asymptomatic, clinically localized prostate cancer that is unlikely to result in morbidity or mortality for decades even if not treated. None of the trials were designed to assess the impact on mortality and pooled evidence is insufficient to determine whether 5ARI improves overall or disease specific morbidity or mortality. A diagnosis of prostate cancer can trigger a cascade of events frequently involving interventions that can result in morbidity, cost, and treatment-related mortality. Chemoprevention options that reduce detection and treatment of prostate cancer would be beneficial even in the absence of definitive information regarding mortality in men who are actively screened for prostate cancer.

Results indicate that 71 men aged 55 or greater would need to be treated with a 5ARI for up to seven years in order to prevent detection of one case of prostate cancer. The risk that any detected prostate cancer would be judged high grade, and thus potentially clinically more serious, might be increased by chemoprevention. The relative reduction in prostate cancers detected would not greatly differ based on race, family history or age but is confined to men with baseline PSA levels < 4.0 ng/mL. Other considerations include the impact on lower urinary tract symptoms due to BPH and the risk of adverse effects. While the average change in overall urinary symptom scale scores is unlikely to be noticeable, approximately 2 men (of 71) would be prevented from developing acute urinary retention and two would avoid need for surgical intervention for benign urinary symptoms. Conversely, two to three men would develop gynecomastia, four would become impotent, four develop decreased libido and 13 would notice decreased or abnormal ejaculate volume.

The existing evidence does not provide sufficient information regarding optimal age to initiate treatment or duration of chemoprevention. The mean age of enrollees ranged from 63 to 77 years with none less than age 55. The longest duration of treatment and follow up was seven years. Greater than 80% reduction in PSA levels due to 5ARI occurs within 12 weeks of initiation and PSA values return to baseline within a similar period of time after discontinuation. Effects on other biomarkers such as testosterone levels and 5 hydroxytestosterone are also seen within a few weeks. Whether this is directly associated with initiation and/or loss of prostate cancer prevention activity is not known. If chemoprevention with 5ARI is recommended the most appropriate age to initiate and terminate prevention should balance potential impact on the growth and development of prostate cancer and the likelihood that tumors could cause long-term problems. Long-term cancer prevention might be of greatest magnitude in younger men, though these potential benefits must be balanced with adverse effects regarding sexual function that may be of greater importance in younger individuals. Because the presence and severity of BPH symptoms is less common in younger men the potential advantage for relieving bothersome symptoms or preventing 2 to 10 year BPH progression may be of less importance. Potential candidates for chemoprevention include men who express interest in chemoprevention and are considered likely to benefit from prostate cancer screening.

AUTHORS' CONCLUSIONS

Implications for practice

Five-alpha-reductase inhibitors reduce prostate cancer risk but may increase the risk of high grade disease in men who are undergoing regular screening for prostate cancer using PSA and digital rectal examination. The impact of 5ARI on absolute or relative rates of prostate cancer in men who are not being regularly screened is not clear. Effects are consistent across race, family history and age and possibly 5ARI but were limited to men with baseline PSA values < 4.0 ng/mL. Information is inadequate to assess the impact on mortality. Long term compliance in randomized trials is high. Decisions to initiate chemoprevention with 5ARI should incorporate this information.

Implications for research

Future research is needed to determine whether 5ARI reduce overall and disease-specific morbidity and mortality; whether any beneficial effect is drug or class-specific; whether the increase in high-grade tumors is real or artifactual. Future trials should also determine appropriate "PSA adjustments"/indications for prostate biopsy in men on 5ARI.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

ARIA/ARIB 2004

Methods	Randomization allocation: Unclear Blinding: Subject and provider Intention-to-treat analysis: Partial (subjects had at least one dose of study medication) Funding: Pharmaceutical PCa diagnosis for cause: Yes
Participants	Multinational men, mean age 66.3 (years), with lower urinary tract symptoms (LUTS) secondary benign prostatic hyperplasia (BPH) (all subjects had IPSS at least 12). Race: white 92%; black 4%; Hispanic 7.3%; Asian 1%; other 1.5%. Mean PSA (ng/ml): 4.0 (SD 2.1). Mean prostate volume (cc): 54.5 Mean baseline AUA/IPSS score: 17.05
Interventions	A. Dutasteride 0.5mg (n=2167) B. Placebo (n=2158) Study duration: 2 years
Outcomes	Prostate cancer detected for-cause; Prostate cancer detected overall; BPH symptom score improvement; Acute urinary retention; Surgical intervention for BPH progression; Adverse events
Notes	A pooled analysis of three trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cote 1998

Methods	Randomization allocation: Unclear Blinding: Outcome assessor Intention-to-treat analysis: No Funding: Government (NIH) and private (academic) PCa diagnosis for cause: No

Cote 1998 *(Continued)*

Participants	American men aged at least 50 years (mean 68) with elevated PSA (> 4.0 ng/ml). Study objective was to examine effect of finasteride on prostate cellular proliferation and high-grade prostatic intraepithelial neoplasia (PIN). Race: Not reported. Mean PSA (ng/mL): 9.8 Mean baseline AUA/IPSS score: Not reported. Pre-existing high-grade PIN: Observation 5 men; Finasteride 8 men.
Interventions	A. Observation (Watchful waiting (n=29) B. Finasteride 5 mg (n=29) Study duration: 1 year
Outcomes	Prostate cancer detected overall; Prostate cancer detected due to study protocol
Notes	Only enrolled men with PSA levels > 4.0 ng/mL and required a baseline sextant prostate biopsy negative for prostate cancer. 13 of the 58 enrolled subjects had prostatic intraepithelial neoplasia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Foley 2000

Methods	Randomization allocation: Unclear Blinding: None Intention-to-treat analysis: No Funding: Non-funded. PCa diagnosis for cause: No
Participants	British men, mean age 77.5 (range 55 to 89), with hematuria associated with BPH. Race: Not reported. Mean PSA (ng/ml): Not reported. Mean baseline AUA/IPSS score: Not reported.
Interventions	A. Finasteride 5 mg (n=29) B. Watchful waiting (n=28) Study duration: 1 year
Outcomes	Surgical intervention for BPH progression;
Notes	Trial assessed the effect of finasteride on chronic hematuria associated with BPH.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

FSG American 1992

Methods	Randomization allocation: Unclear Blinding: Subject and provider Intention-to-treat analysis: Unclear Funding: Pharmaceutical PCa diagnosis for cause: Yes
Participants	American men, mean age 64 (range 40 to 83), with LUTS secondary BPH. Race: white 96%; black 3%; other 1%. Mean PSA (ng/ml): 3.8 Mean prostate volume (gm): NR Mean baseline Boyarsky score: 10.2
Interventions	A. Finasteride 1 mg (n=298) B. Finasteride 5 mg (n=297) C. Placebo (n=300) Study duration: 1 year
Outcomes	Prostate cancer detected for-cause; Prostate cancer detected overall; Overall mortality; BPH symptom score improvement; Surgical intervention for BPH progression; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

FSG Int. 1993

Methods	Randomization allocation: Unclear Blinding: Subject and provider Intention-to-treat analysis: Unclear Funding: Pharmaceutical PCa diagnosis for cause: Yes
Participants	European men, mean age 66 (range 46 to 83), with LUTS secondary BPH. Race: Not reported. Mean PSA (ng/ml): 5.7 Mean prostate volume (gm): 46.9 Mean baseline Boyarsky score: 18.5
Interventions	A. Finasteride 1 mg (n=249) B. Finasteride 5 mg (n=246) C. Placebo (n=255) Study duration: 1 year
Outcomes	Prostate cancer detected for-cause; Prostate cancer detected overall; BPH symptom score improvement; Acute urinary retention; Surgical intervention for BPH progression; Adverse events
Notes	

FSG Int. 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Lee 2002

Methods	Randomization allocation: Unclear Blinding: Subject Intention-to-treat analysis: No Funding: Pharmaceutical PCa diagnosis for cause: No
Participants	Korean men, mean age 64.7, with LUTS secondary to BPH (all subjects had Korean IPSS > 8). Race: Asian 100%. Mean PSA (ng/ml): 2.0 Mean prostate volume (cc): 29.8 Mean baseline AUA/IPSS score: 19.5
Interventions	A. Finasteride 5 mg (n=102) B. Tamsulosin 0.2 mg (n=103) Study duration: 24 weeks
Outcomes	BPH symptom score improvement; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

MICTUS 2003

Methods	Randomization allocation: Unclear Blinding: Subject and provider Intention-to-treat analysis: No Funding: Pharmaceutical PCa diagnosis for cause: No
Participants	Italian men, mean age 63 (SD 7.1), with LUTS secondary to BPH (all subjects had IPSS at least 13). Race: Not reported. Mean PSA (ng/ml): Not reported. Mean baseline AUA/IPSS score: NR
Interventions	A. Finasteride 5 mg (n=204) B. Tamsulosin 0.4 mg (n=199) Study duration: 26 weeks

MICTUS 2003 *(Continued)*

Outcomes	BPH symptom score improvement; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

MTOPS 2003

Methods	Randomization allocation: Unclear Blinding: Subject, provider, and outcome assessor Intention-to-treat analysis: Yes Funding: Government (NIH) and pharmaceutical PCa diagnosis for cause: No
Participants	American men, mean age 62.6 (SD 7.3), with LUTS secondary to BPH. Race: white 82.3%; black 8.9%; Hispanic 7.3%; other 1.5%. Mean PSA (ng/ml): 2.4 (SD 2.1). Mean prostate volume (gm): 36.3 (20.1); small (median) 19.8, moderate 31.0, large 52.0. Mean baseline AUA/IPSS score: 16.9 (SD 5.9).
Interventions	A. Finasteride 5 mg (n=768) B. Doxazosin 4-8 mg (n=756) C. Combination Finasteride and Doxazsoin (n=786) D. Placebo (n=737) Study duration: 4.5 years
Outcomes	BPH symptom score improvement; Acute urinary retention; Surgical intervention for BPH progression; Overall BPH progression; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

PCPT 2003

Methods	Randomization allocation: Unclear Blinding: Subject, and outcome assessor Intention-to-treat analysis: Partial (men receiving diagnosis of prostate cancer during the study or who underwent an end-of-study biopsy). Funding: Government (NIH) and pharmaceutical PCa diagnosis for cause: Yes

PCPT 2003 *(Continued)*

Participants	American men enrolled in a prostate cancer prevention trial. Age, 45-64 years 62%; at least 65 years 38%. Race: white 92%; black 3.8%; Hispanic 2.6%; other 1.5%. PSA (ng/ml), at least 3: 100%. Family history of PCa (1st degree relative): 15.4% Mean baseline AUA/IPSS score: 6.7 (SD 4.8)
Interventions	A. Finasteride 5 mg (n= 9423) B. Placebo (n=9459) Study duration: 7 years
Outcomes	Prostate cancer detected for-cause; Prostate cancer detected overall; Prostate cancer detected due to study protocol; Overall mortality; Prostate cancer-specific mortality; Acute urinary retention; Surgical intervention for BPH progression; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

PLESS 1998

Methods	Randomization allocation: Yes Blinding: Subject and provider Intention-to-treat analysis: Yes Funding: Pharmaceutical PCa diagnosis for cause: Yes
Participants	American men, mean age 64 (SD 6.4), with LUTS secondary BPH. Race: white 95.5%. Mean PSA (ng/ml): 2.8 (SD 2.1). Mean baseline AUA/IPSS score: 15 (SD 5.7). History of sexual dysfunction: 46% of men in each group at screening.
Interventions	A. Finasteride 5 mg (n=1524) B. Placebo (n=1516) Study duration: 4 years
Outcomes	Prostate cancer detected for-cause; Prostate cancer detected overall; Prostate cancer detected due to study protocol; BPH symptom score improvement; Acute urinary retention; Surgical intervention for BPH progression; Overall BPH progression; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

PREDICT 2003

Methods	Randomization allocation: Unclear Blinding: Subject, provider, and outcome assessor Intention-to-treat analysis: Partial (subjects had at least one dose of study medication) Funding: Pharmaceutical PCa diagnosis for cause: No
Participants	European men, mean age 64 (range 50 to 80), with LUTS secondary BPH (all subjects had IPSS 12). Race: Not reported. Mean PSA (ng/ml): 2.6 Mean prostate volume (gm): 36 Mean baseline AUA/IPSS score: 17.2
Interventions	A. Finasteride 5 mg (n=264) B. Doxazosin 4-8 mg (n=275) C. Combination Finasteride and Doxazsoin (n=286) D. Placebo (n=270) Study duration: 1 year
Outcomes	Overall mortality; BPH symptom score improvement; Acute urinary retention; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

PROSPECT 1996

Methods	Randomization allocation: Adequate Blinding: Subject, provider Intention-to-treat analysis: Yes Funding: Pharmaceutical PCa diagnosis for cause: No
Participants	Canadian men in good health, mean age 63.3 (range 46 to 80) with LUTS secondary BPH. Race: Not reported. Mean PSA (ng/ml): Not reported. Mean baseline AUA/IPSS score: 16.2
Interventions	A. Finasteride 5 mg (n=310) B. Placebo (n=303) Study duration: 2 years
Outcomes	Prostate cancer detected for-cause; Prostate cancer detected overall; Overall mortality; BPH symptom score improvement; Surgical intervention for BPH progression; Adverse events
Notes	

Risk of bias

PROSPECT 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

VA COOP 1996

Methods	Randomization allocation: Adequate Blinding: Subject and provider Intention-to-treat analysis: Partial (subjects with any follow up data available). Funding: Government (VA) PCa diagnosis for cause: No
Participants	American men, mean age 65, with symptomatic BPH. Race: white 80% Race (from Lepor): white 87%; black 11%; Asian 1%; Native American 0.5%. Mean PSA (from Lepor) (ng/ml): 2.3 Mean prostate volume (gm): 37.6 Mean baseline AUA/IPSS score: 16.1
Interventions	A. Finasteride 5 mg (n=252) B. Terazosin 10 mg (n=262) C, Combination Finasteride and Terazosin (n=272) D. Placebo (n=254) Study duration: 1 year
Outcomes	Overall mortality; BPH symptom score improvement; Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

DATA AND ANALYSES

Comparison 1. 5-alpha-reductase Inhibitors versus placebo

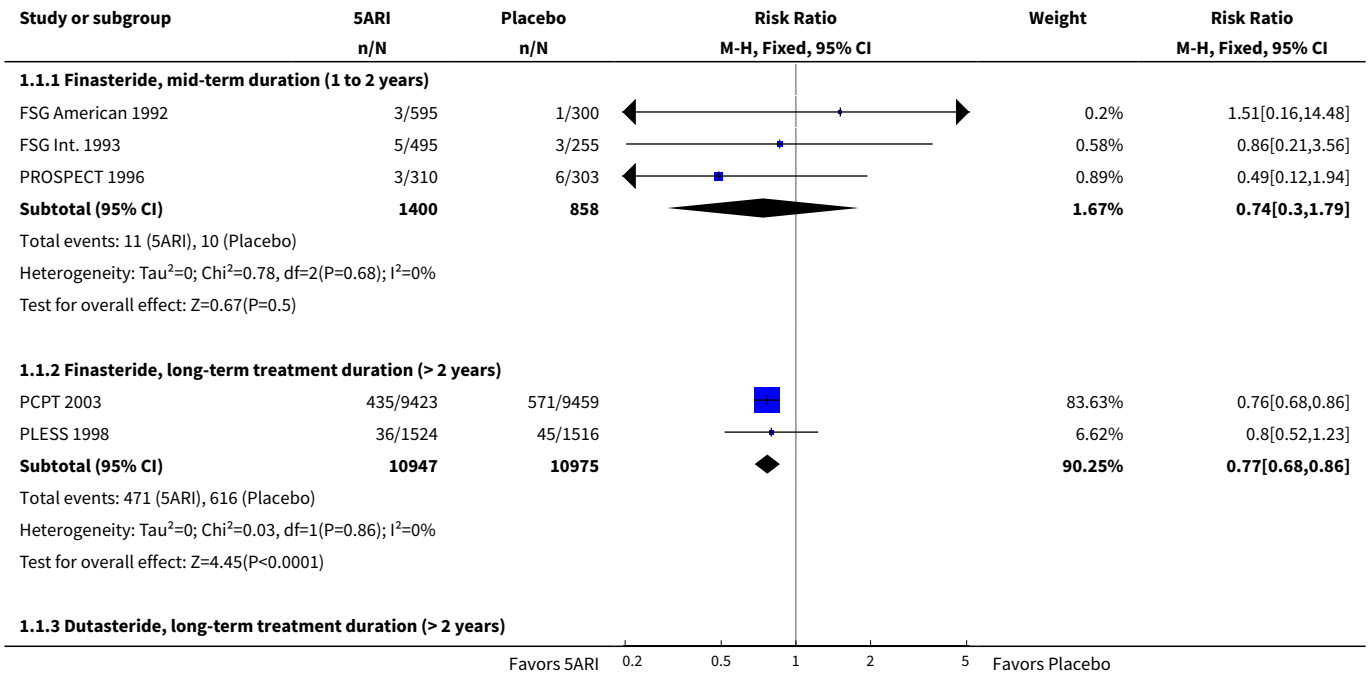
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prostate cancer detected "for-cause"	6	28505	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.67, 0.83]
1.1 Finasteride, mid-term duration (1 to 2 years)	3	2258	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.30, 1.79]

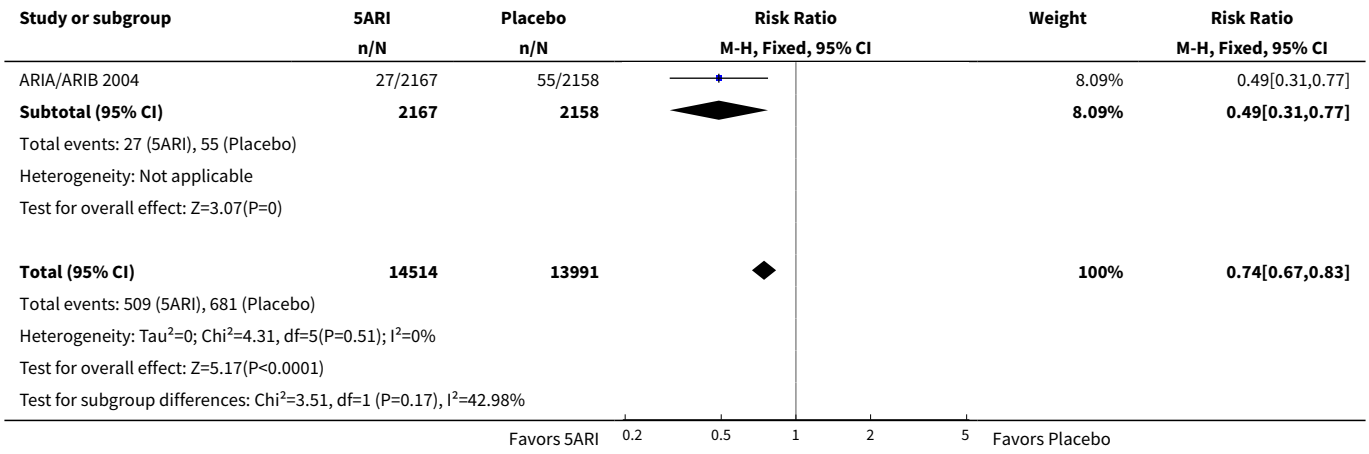
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Finasteride, long-term treatment duration (> 2 years)	2	21922	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.68, 0.86]
1.3 Dutasteride, long-term treatment duration (> 2 years)	1	4325	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.31, 0.77]
2 Prostate cancer detected overall	7	28557	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.56, 0.98]
2.1 Finasteride, mid-term treatment duration (1 to 2 years)	4	2310	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.40, 3.78]
2.2 Finasteride, long-term treatment duration (> 2 years)	2	21922	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.01]
2.3 Dutasteride, long-term treatment duration (> 2 years)	1	4325	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.31, 0.77]
3 Prostate cancer detected due to study protocol	3	21968	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.50, 3.78]
3.1 Finasteride: Mid-term treatment duration (1 to 2 years)	1	52	Risk Ratio (M-H, Random, 95% CI)	7.41 [1.00, 55.09]
3.2 Finasteride: Long-term treatment duration (> 2 years)	2	21916	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.39, 2.46]
4 Overall mortality	5	21539	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.18]
4.1 Finasteride: Mid-term treatment duration (1 to 2 years)	4	2657	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.78, 4.11]
4.2 Finasteride: Long-term treatment duration (> 2 years)	1	18882	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.93, 1.17]
5 Prostate cancer-specific mortality	1	18882	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.29, 3.47]
5.1 Finasteride: Long-term treatment duration (> 2 years)	1	18882	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.29, 3.47]
6 BPH progression: Overall	2	4521	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.46, 0.65]
6.1 Finasteride: Long-term treatment duration (> 2 years)	2	4521	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.46, 0.65]
7 BPH progression: Acute urinary retention	6	29009	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.38, 0.69]
7.1 Finasteride: Mid-term treatment duration (1 to 2 years)	2	1283	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.29, 2.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Long-term treatment duration (> 2 years)	3	23401	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.33, 0.77]
7.3 Dutasteride: Long-term treatment duration (> 2 years)	1	4325	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.30, 0.63]
8 BPH progression: Surgical interventions for treatment	10	31187	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.43, 0.58]
8.1 Finasteride, mid-term treatment duration (1 to 2 years)	5	2848	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.05]
8.2 Finasteride, long-term treatment duration (> 2 years)	4	24014	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.42, 0.58]
8.3 Dutasteride, long-term treatment duration (> 2 years)	1	4325	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.37, 0.75]
9 Study withdrawals	9	29019	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.07]
9.1 Mid-term treatment duration (1 to 2 years)	7	7097	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.06]
9.2 Long-term treatment duration (> 2 years)	2	21922	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.72, 1.24]
10 Study withdrawals due to adverse events	6	10021	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.83, 1.52]
10.1 Mid-term treatment duration (1 to 2 years)	5	6981	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.32]
10.2 Long-term treatment duration (> 2 years)	1	3040	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.16, 2.72]
11 Impotence/erectile dysfunction	7	25446	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.11, 2.65]
11.1 Mid-term treatment duration (1 to 2 years)	6	6566	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.27, 3.00]
11.2 Long-term treatment duration (> 2 years)	1	18880	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.07, 1.12]
12 Decreased ejaculate volume	4	23430	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.07, 2.85]
12.1 Mid-term treatment duration (1 to 2 years)	2	1510	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.00, 4.53]
12.2 Long-term treatment duration (> 2 years)	2	21920	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.80, 3.70]

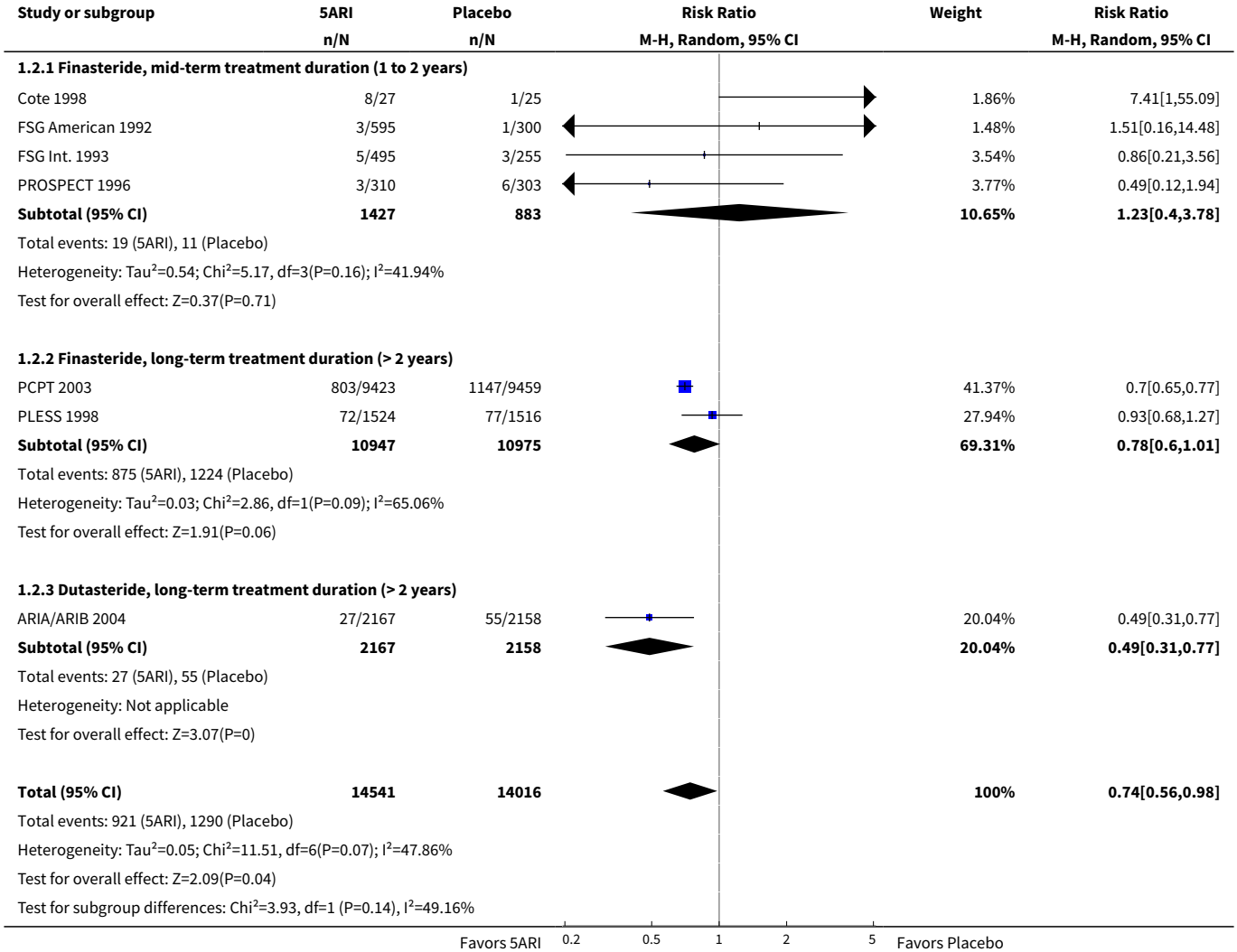
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Decreased libido	6	25861	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.19, 2.81]
13.1 Mid-term treatment duration (1 to 2 years)	5	6981	Risk Ratio (M-H, Random, 95% CI)	2.02 [1.55, 2.64]
13.2 Long-term treatment duration (> 2 years)	1	18880	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.07, 1.12]
14 Gynecomastia	2	23205	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.15, 3.95]
14.1 Mid-term treatment duration (1 to 2 years)	1	4325	Risk Ratio (M-H, Random, 95% CI)	3.11 [1.78, 5.45]
14.2 Long-term treatment duration (> 2 years)	1	18880	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.41, 1.91]
15 Incontinence	2	20385	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.08]
15.1 Long-term treatment duration (> 2 years)	2	20385	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.08]
16 Increased urinary frequency/urgency	1	18880	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.77, 0.89]

Analysis 1.1. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 1 Prostate cancer detected "for-cause".

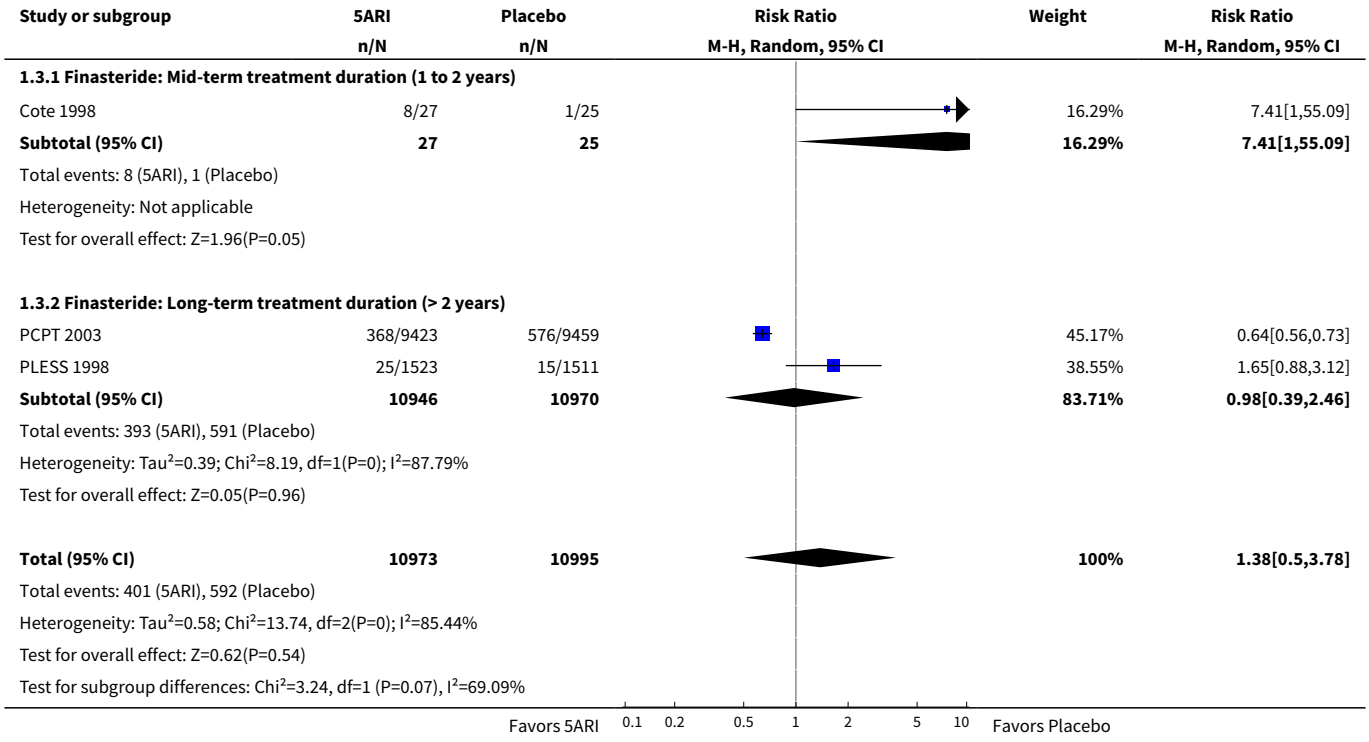




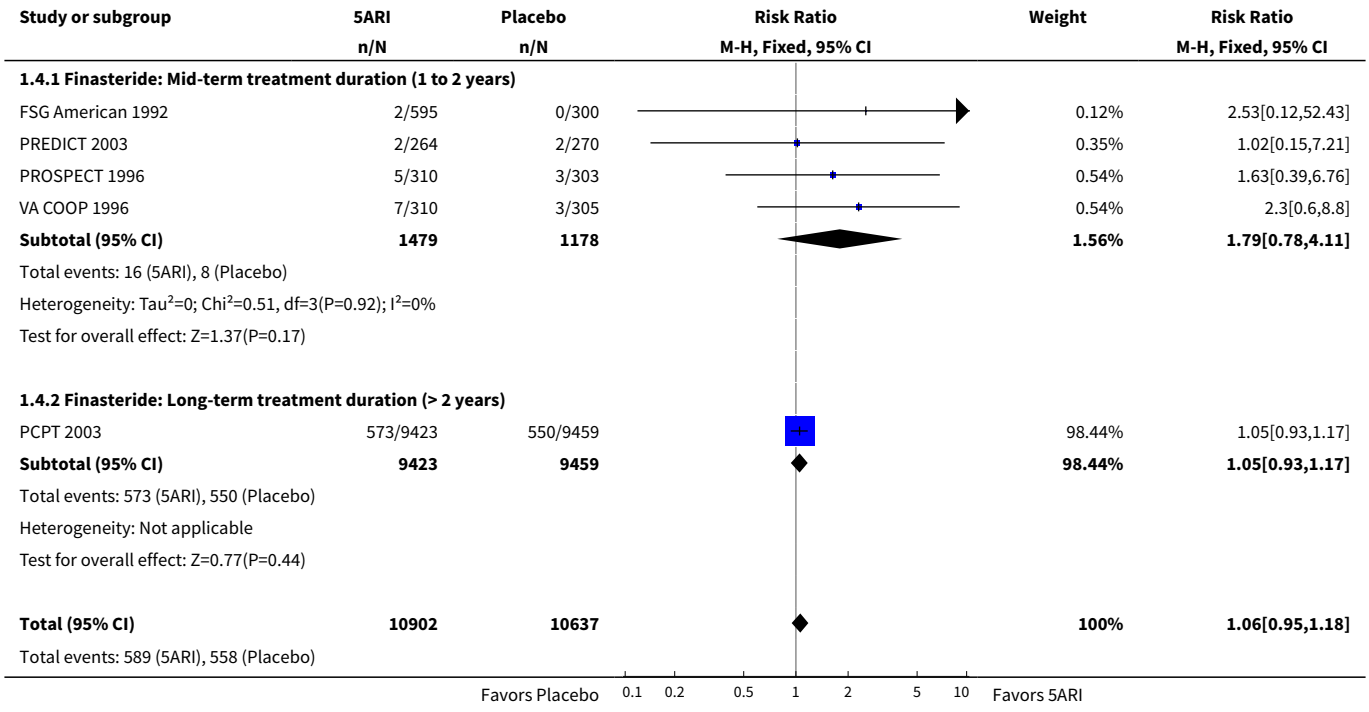
Analysis 1.2. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 2 Prostate cancer detected overall.

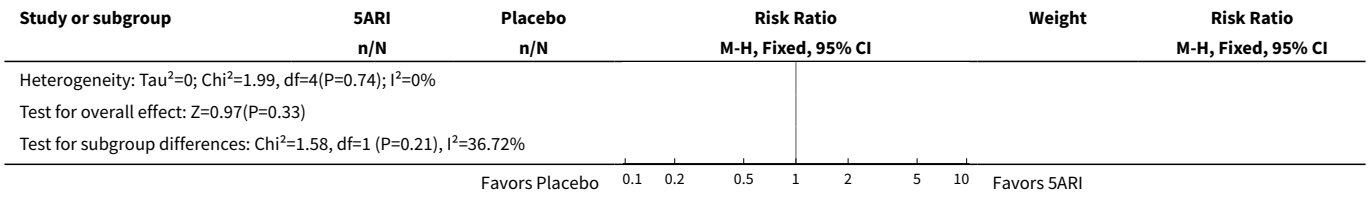


Analysis 1.3. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 3 Prostate cancer detected due to study protocol.

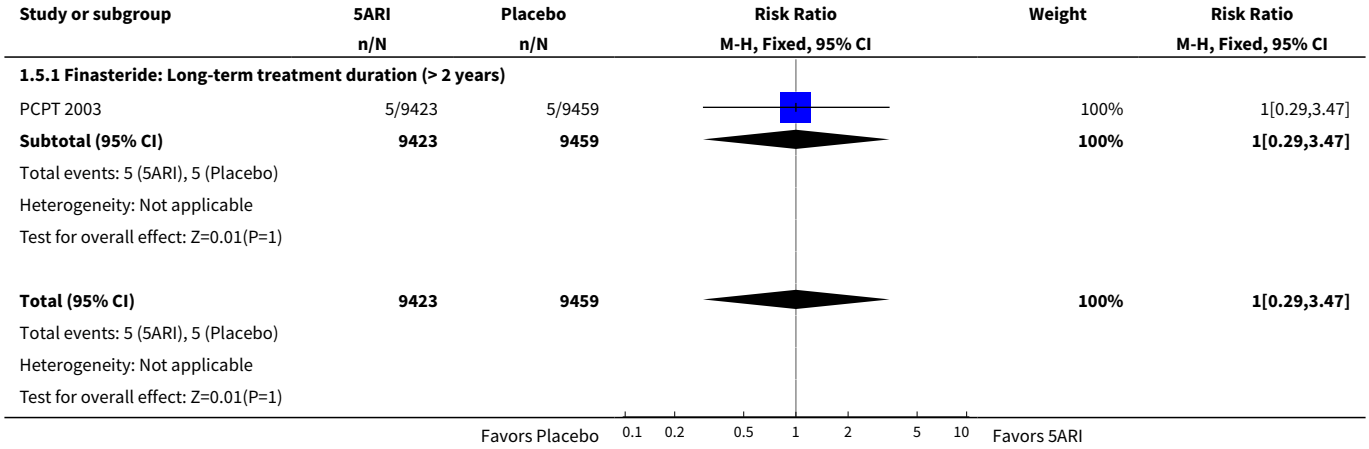


Analysis 1.4. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 4 Overall mortality.

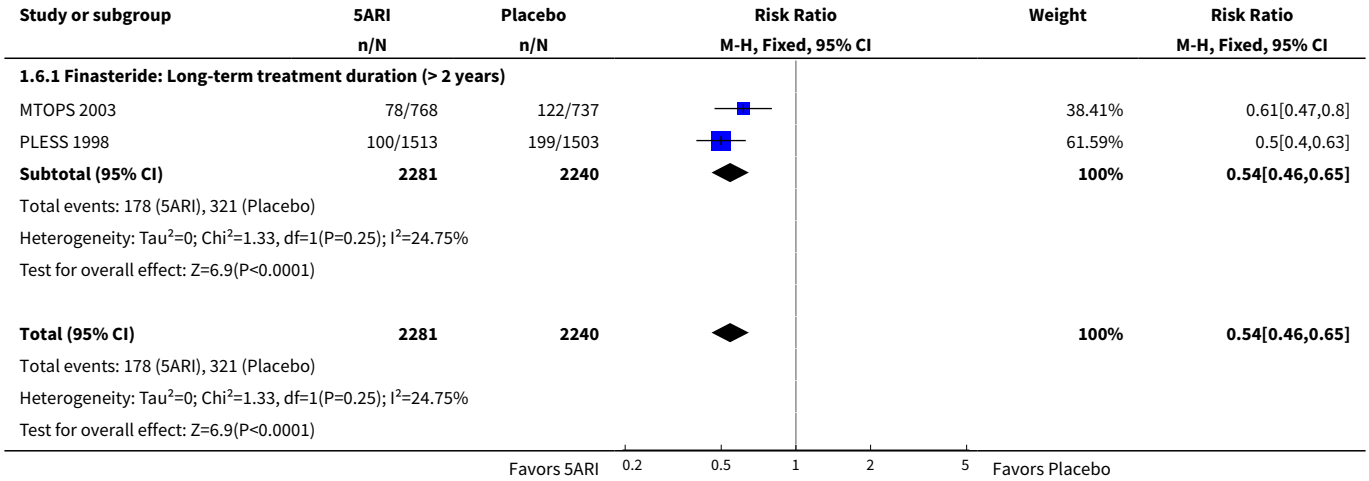




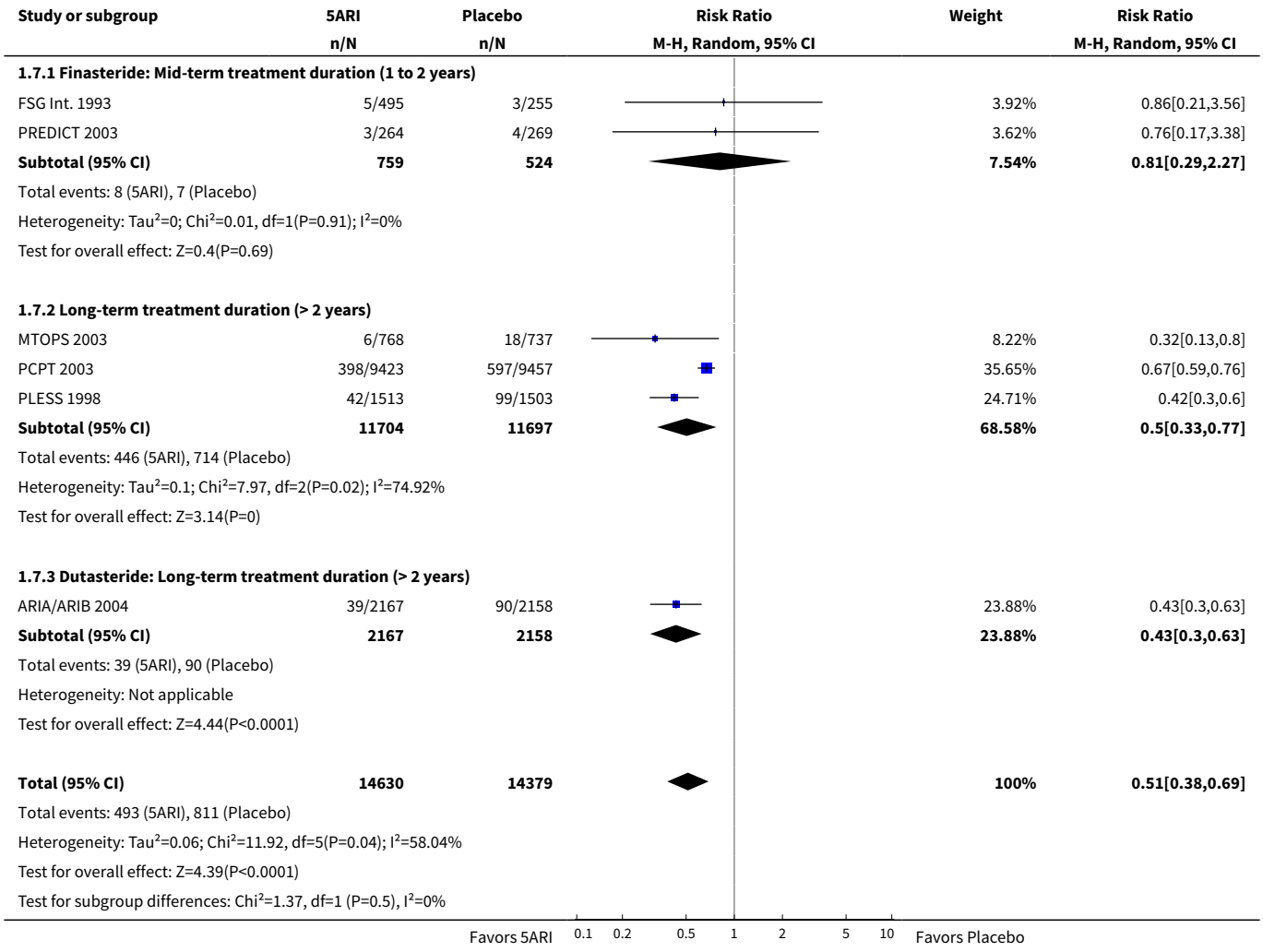
Analysis 1.5. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 5 Prostate cancer-specific mortality.



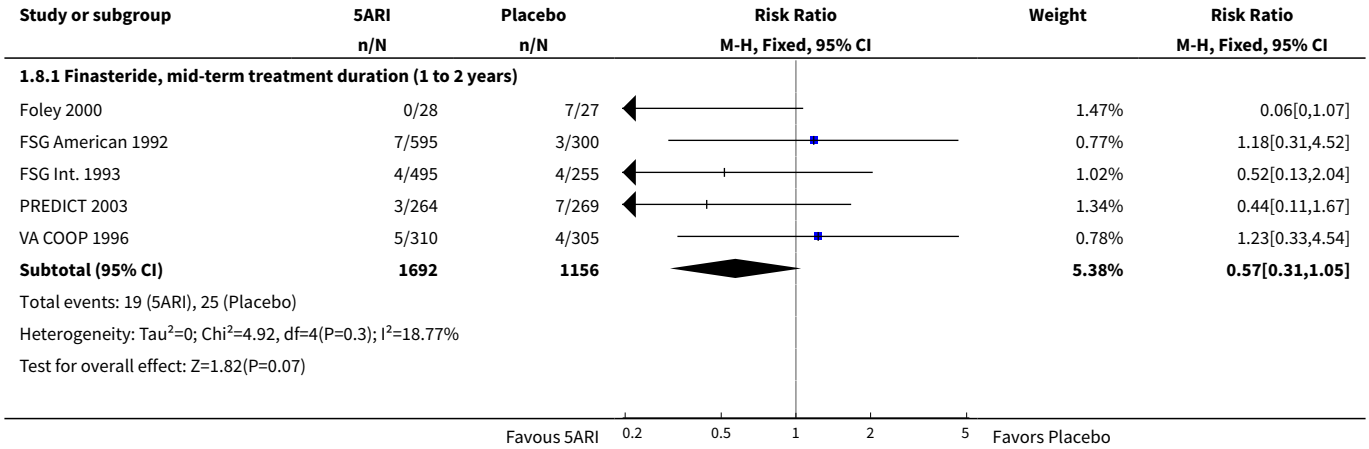
Analysis 1.6. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 6 BPH progression: Overall.

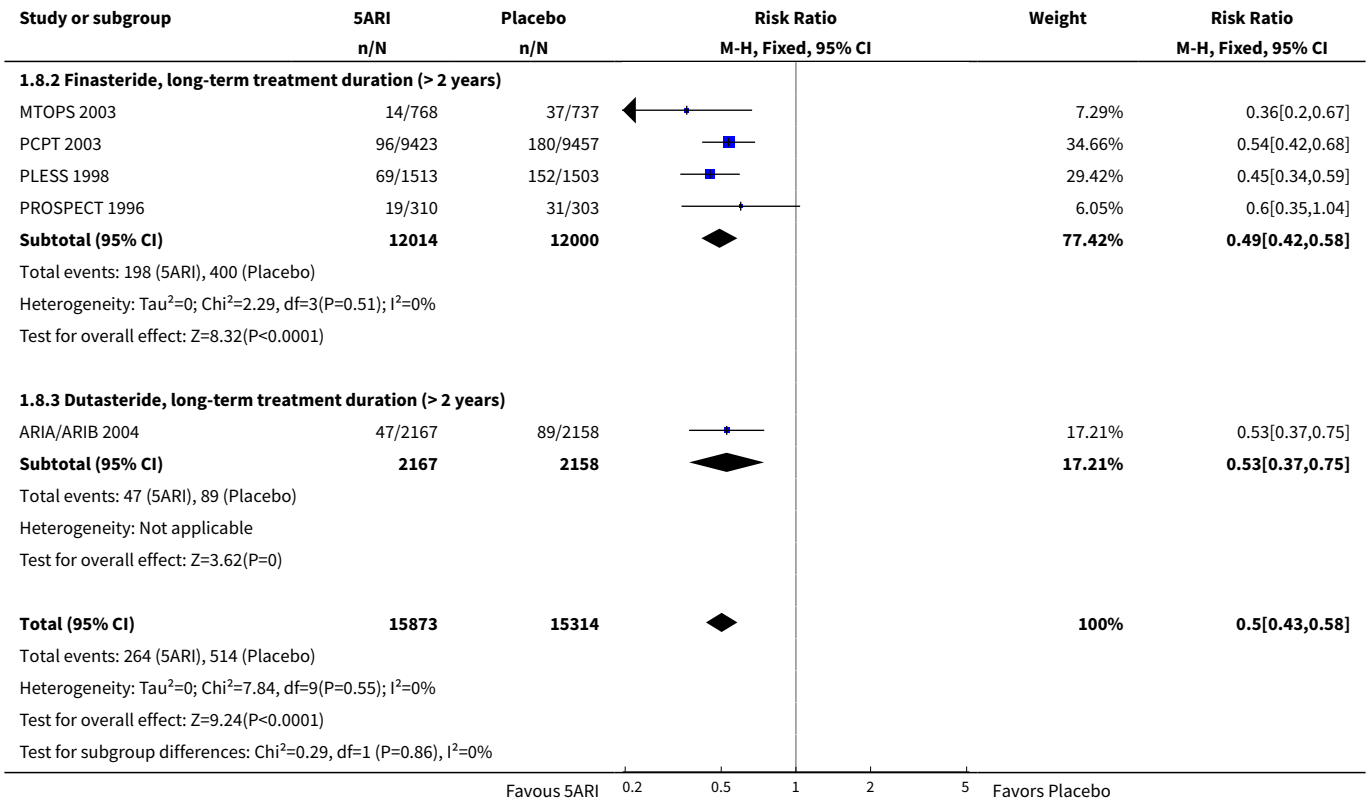


Analysis 1.7. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 7 BPH progression: Acute urinary retention.

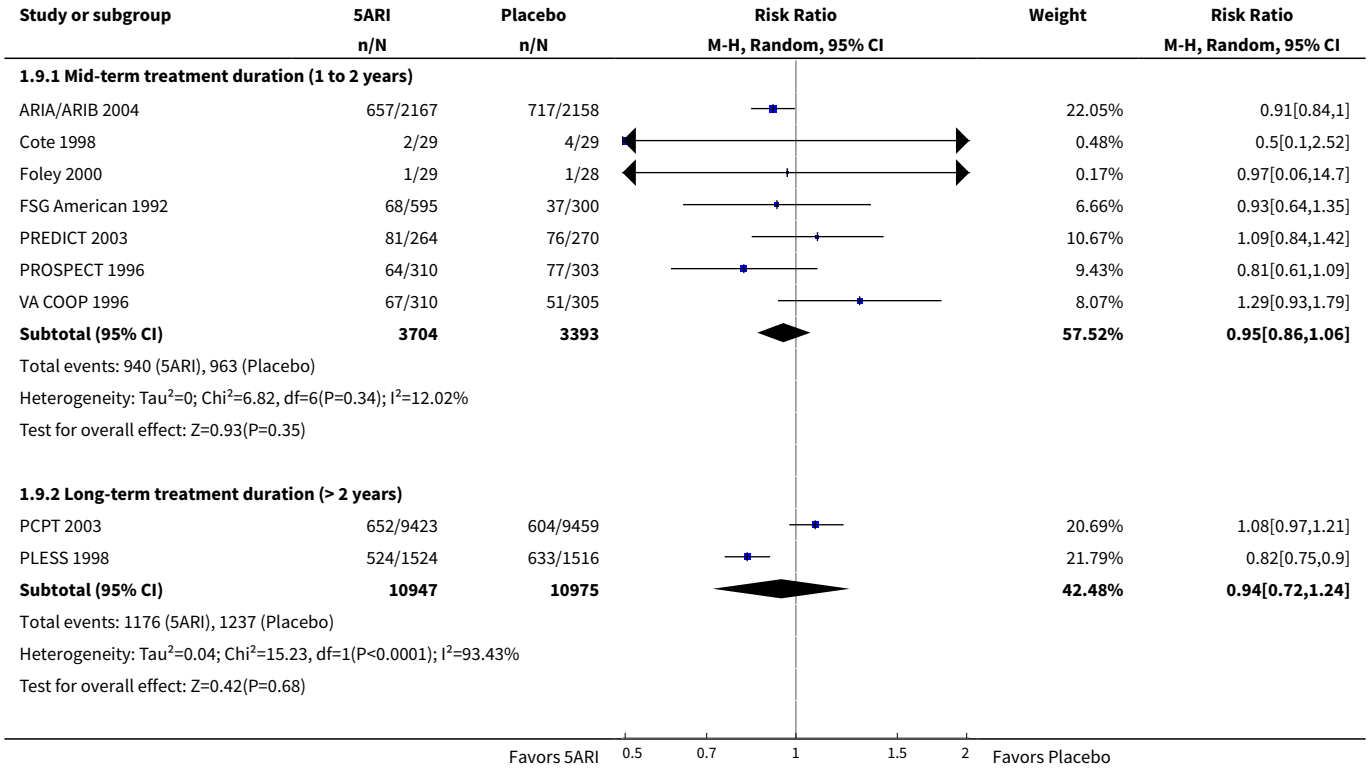


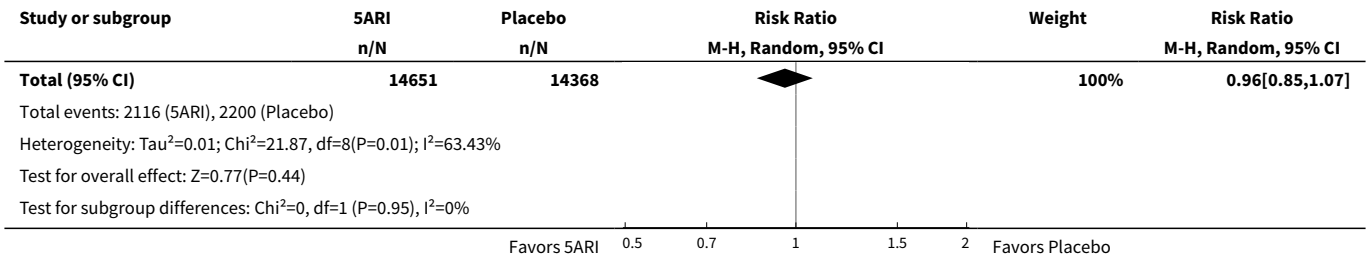
Analysis 1.8. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 8 BPH progression: Surgical interventions for treatment.



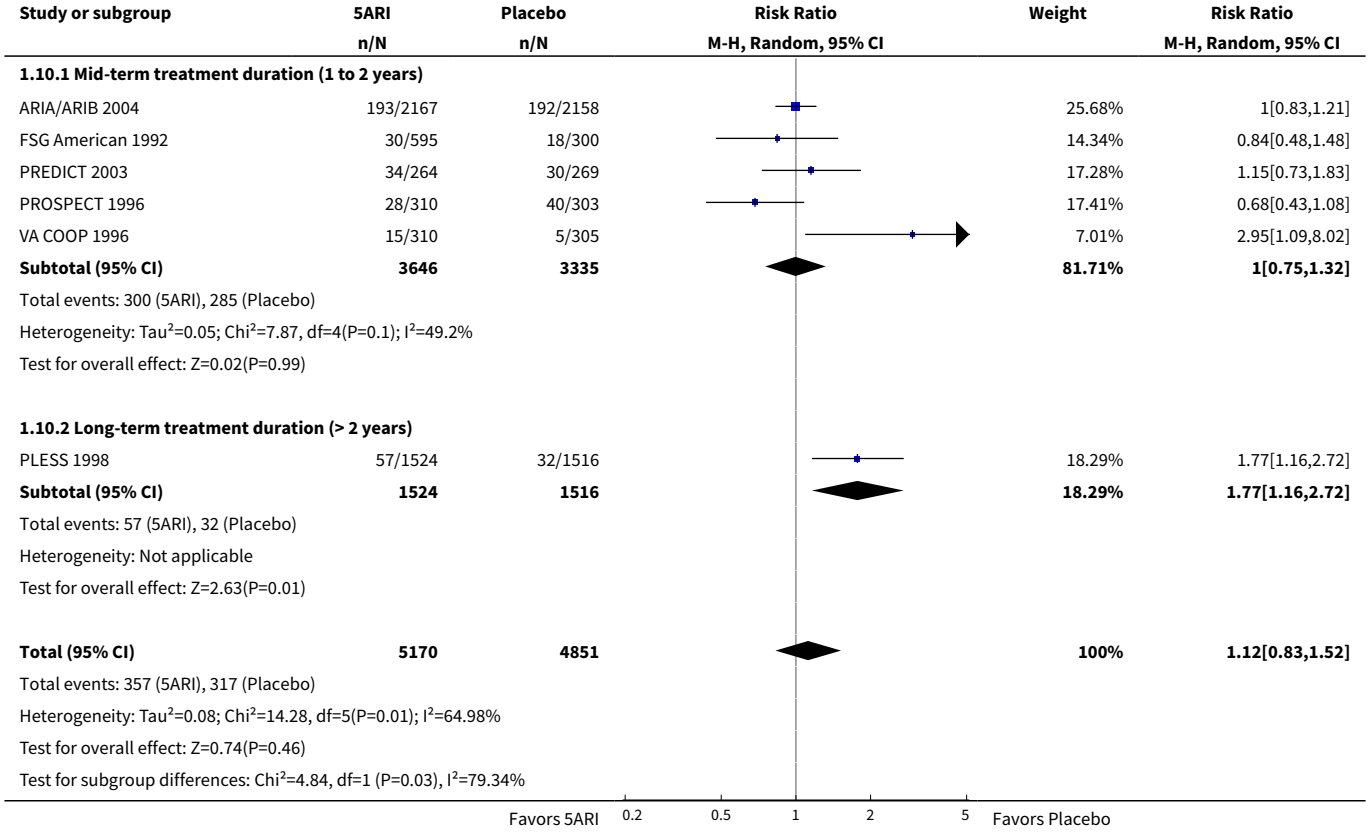


Analysis 1.9. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 9 Study withdrawals.

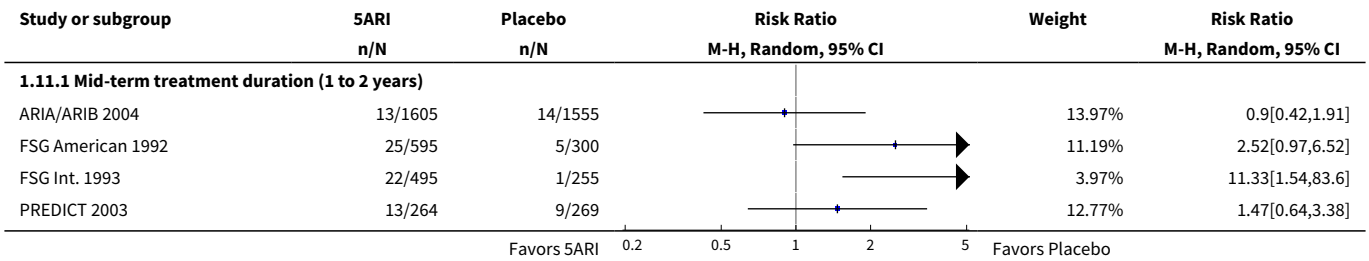




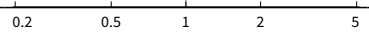
Analysis 1.10. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 10 Study withdrawals due to adverse events.



Analysis 1.11. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 11 Impotence/erectile dysfunction.

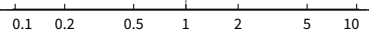


Study or subgroup	5ARI n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
PROSPECT 1996	49/310	19/303		18.08%	2.52[1.52,4.18]
VA COOP 1996	29/310	14/305		16.14%	2.04[1.1,3.78]
Subtotal (95% CI)	**3579**	**2987**		**76.13%**	**1.95[1.27,3]**
Total events: 151 (5ARI), 62 (Placebo)					
Heterogeneity: Tau^2=0.12; Chi^2=8.95, df=5(P=0.11); I^2=44.15%					
Test for overall effect: Z=3.03(P=0)					
1.11.2 Long-term treatment duration (> 2 years)					
PCPT 2003	6349/9423	5816/9457		23.87%	1.1[1.07,1.12]
Subtotal (95% CI)	**9423**	**9457**		**23.87%**	**1.1[1.07,1.12]**
Total events: 6349 (5ARI), 5816 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.42(P<0.0001)					
Total (95% CI)	**13002**	**12444**		**100%**	**1.71[1.11,2.65]**
Total events: 6500 (5ARI), 5878 (Placebo)					
Heterogeneity: Tau^2=0.21; Chi^2=23.62, df=6(P=0); I^2=74.6%					
Test for overall effect: Z=2.42(P=0.02)					
Test for subgroup differences: Chi^2=6.82, df=1 (P=0.01), I^2=85.34%					



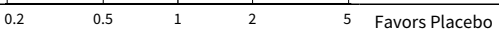
Analysis 1.12. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 12 Decreased ejaculate volume.

Study or subgroup	5ARI n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Mid-term treatment duration (1 to 2 years)					
FSG American 1992	26/595	5/300		17.37%	2.62[1.02,6.76]
VA COOP 1996	6/310	4/305		11.64%	1.48[0.42,5.18]
Subtotal (95% CI)	**905**	**605**		**29.01%**	**2.13[1,4.53]**
Total events: 32 (5ARI), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=1.96(P=0.05)					
1.12.2 Long-term treatment duration (> 2 years)					
PCPT 2003	5690/9423	4473/9457		49.67%	1.28[1.24,1.31]
PLESS 1998	23/1524	8/1516		21.31%	2.86[1.28,6.37]
Subtotal (95% CI)	**10947**	**10973**		**70.99%**	**1.72[0.8,3.7]**
Total events: 5713 (5ARI), 4481 (Placebo)					
Heterogeneity: Tau^2=0.24; Chi^2=3.9, df=1(P=0.05); I^2=74.33%					
Test for overall effect: Z=1.39(P=0.16)					
Total (95% CI)	**11852**	**11578**		**100%**	**1.75[1.07,2.85]**
Total events: 5745 (5ARI), 4490 (Placebo)					
Heterogeneity: Tau^2=0.13; Chi^2=6.18, df=3(P=0.1); I^2=51.44%					
Test for overall effect: Z=2.24(P=0.03)					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					



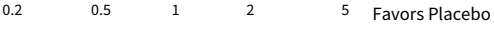
Analysis 1.13. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 13 Decreased libido.

Study or subgroup	5ARI n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Mid-term treatment duration (1 to 2 years)					
ARIA/ARIB 2004	91/2167	46/2158		23.18%	1.97[1.39,2.79]
FSG American 1992	32/595	4/300		10.67%	4.03[1.44,11.3]
PREDICT 2003	9/264	5/269		10.06%	1.83[0.62,5.4]
PROSPECT 1996	31/310	19/303		18.94%	1.59[0.92,2.76]
VA COOP 1996	14/310	4/305		9.83%	3.44[1.15,10.34]
Subtotal (95% CI)	**3646**	**3335**		**72.67%**	**2.02[1.55,2.64]**
Total events: 177 (5ARI), 78 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.45, df=4(P=0.49); I^2=0%					
Test for overall effect: Z=5.19(P<0.0001)					
1.13.2 Long-term treatment duration (> 2 years)					
PCPT 2003	6163/9423	5635/9457		27.33%	1.1[1.07,1.12]
Subtotal (95% CI)	**9423**	**9457**		**27.33%**	**1.1[1.07,1.12]**
Total events: 6163 (5ARI), 5635 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.24(P<0.0001)					
Total (95% CI)	**13069**	**12792**		**100%**	**1.83[1.19,2.81]**
Total events: 6340 (5ARI), 5713 (Placebo)					
Heterogeneity: Tau^2=0.18; Chi^2=24.08, df=5(P=0); I^2=79.24%					
Test for overall effect: Z=2.74(P=0.01)					
Test for subgroup differences: Chi^2=20.15, df=1 (P<0.0001), I^2=95.04%					

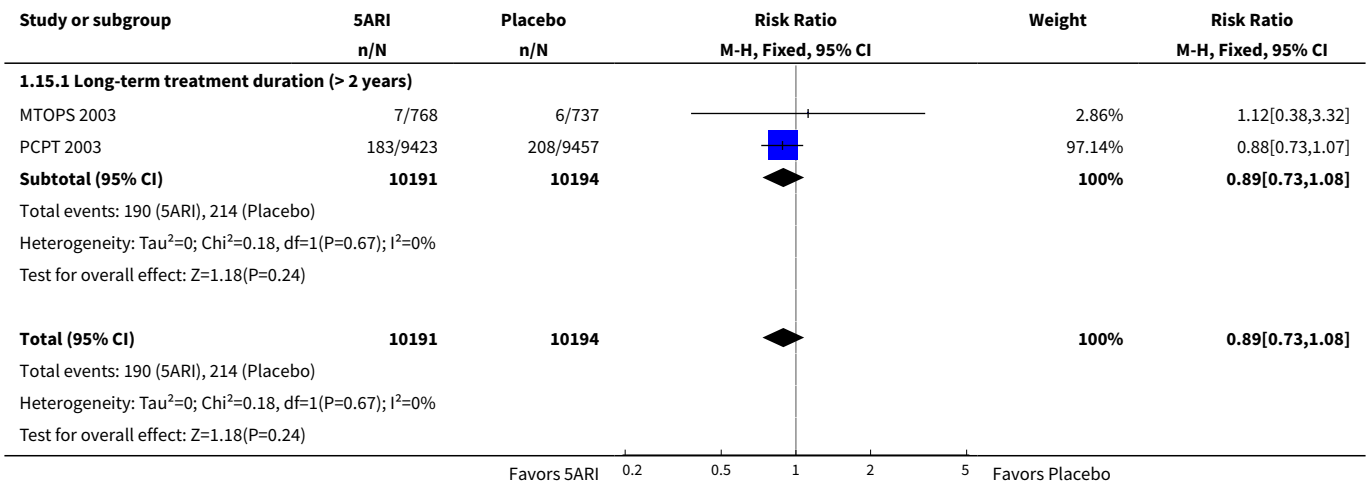


Analysis 1.14. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 14 Gynecomastia.

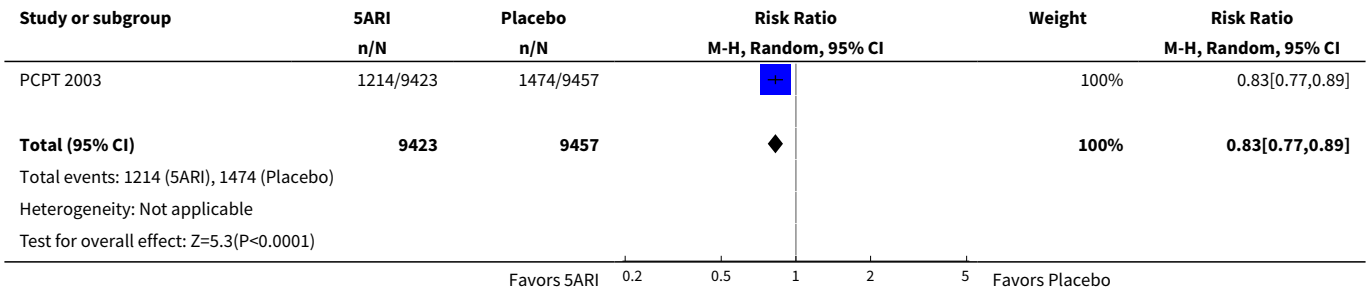
Study or subgroup	5ARI n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Mid-term treatment duration (1 to 2 years)					
ARIA/ARIB 2004	50/2167	16/2158		40.84%	3.11[1.78,5.45]
Subtotal (95% CI)	**2167**	**2158**		**40.84%**	**3.11[1.78,5.45]**
Total events: 50 (5ARI), 16 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.97(P<0.0001)					
1.14.2 Long-term treatment duration (> 2 years)					
PCPT 2003	426/9423	261/9457		59.16%	1.64[1.41,1.91]
Subtotal (95% CI)	**9423**	**9457**		**59.16%**	**1.64[1.41,1.91]**
Total events: 426 (5ARI), 261 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.39(P<0.0001)					
Total (95% CI)	**11590**	**11615**		**100%**	**2.13[1.15,3.95]**
Total events: 476 (5ARI), 277 (Placebo)					
Heterogeneity: Tau^2=0.16; Chi^2=4.71, df=1(P=0.03); I^2=78.78%					
Test for overall effect: Z=2.39(P=0.02)					
Test for subgroup differences: Chi^2=4.7, df=1 (P=0.03), I^2=78.74%					



Analysis 1.15. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 15 Incontinence.



Analysis 1.16. Comparison 1 5-alpha-reductase Inhibitors versus placebo, Outcome 16 Increased urinary frequency/urgency.



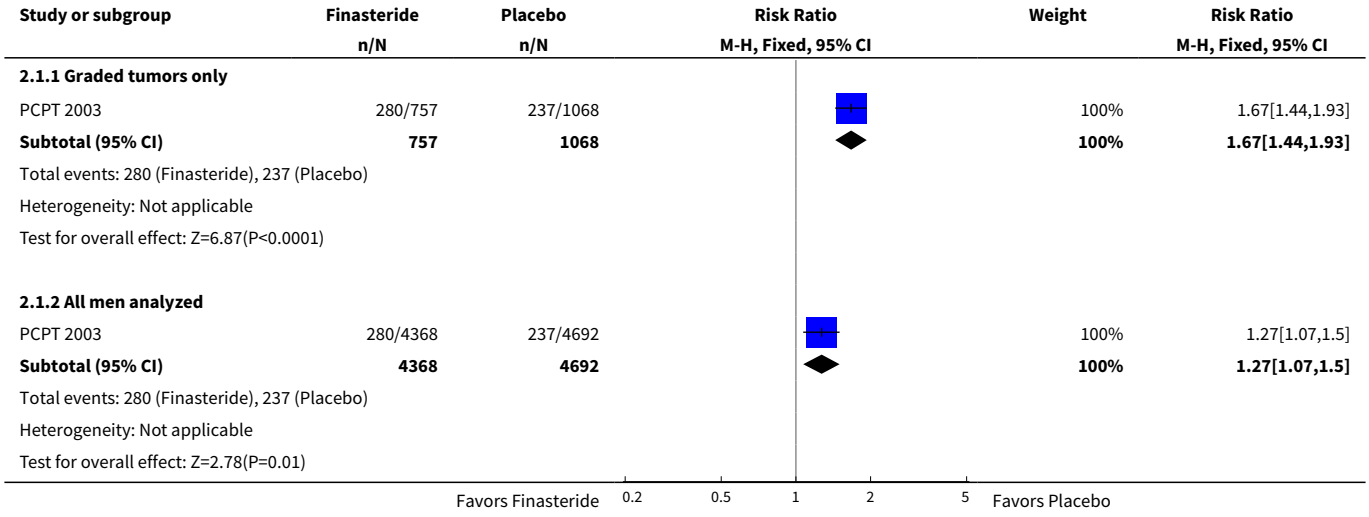
Comparison 2. Finasteride versus placebo; Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prostate cancer detected: Gleason scores 7-10, all cancers	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Graded tumors only	1	1825	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.44, 1.93]
1.2 All men analyzed	1	9060	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.07, 1.50]
2 Prostate cancer detected "for-cause": Gleason scores 7-10	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Graded tumors only	1	897	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.37, 1.93]
2.2 All men analyzed	1	3573	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.22, 1.84]

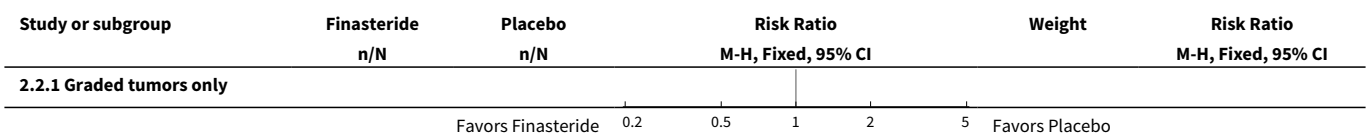
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 All men randomized	2	21920	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.97, 1.35]
2.4 All analyzed "for-cause"	1	18880	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.03, 1.58]
3 Prostate cancer detected: Gleason score 7, all cancers	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All cancers/ # randomized	2	21922	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
3.2 All Cancers/ # men evaluated	1	9060	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.91, 1.35]
3.3 Detected "for cause" /# randomized	1	18882	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.88, 1.50]
3.4 Detected "for cause" /# biopsies performed for cause	1	3573	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.05, 1.75]
4 Prostate cancer detected: Gleason scores 8-10, all cancers	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 All cancers/ # randomized	2	21922	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.05, 6.87]
4.2 All cancers/ # men evaluated	1	9060	Risk Ratio (M-H, Random, 95% CI)	1.82 [1.30, 2.55]
4.3 Detected "for cause" /# randomized	1	18882	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.07, 2.27]
4.4 Detected "for cause" /# biopsies performed for cause	1	3573	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.27, 2.65]
5 Prostate cancer detected: PSA at study entry	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 < 4.0 ng/mL	2	21182	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.65, 0.77]
5.2 > or = 4.0 ng/mL	2	783	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.28, 15.43]
6 Prostate cancer detected: PSA at study entry	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 0.0 to 1.0 ng/mL	1	9132	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.52, 0.72]
6.2 1.1 to 2.0 ng/mL	1	6708	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.64, 0.84]
6.3 2.1 to 3.0 ng/mL	1	3039	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]
6.4 > or = 4.0 ng/mL	2	783	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.74, 1.56]
7 Prostate cancer detected overall according to age	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Age 55-59 years	1	5908	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.56, 0.79]
7.2 Age 60-64 years	1	5795	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.79]

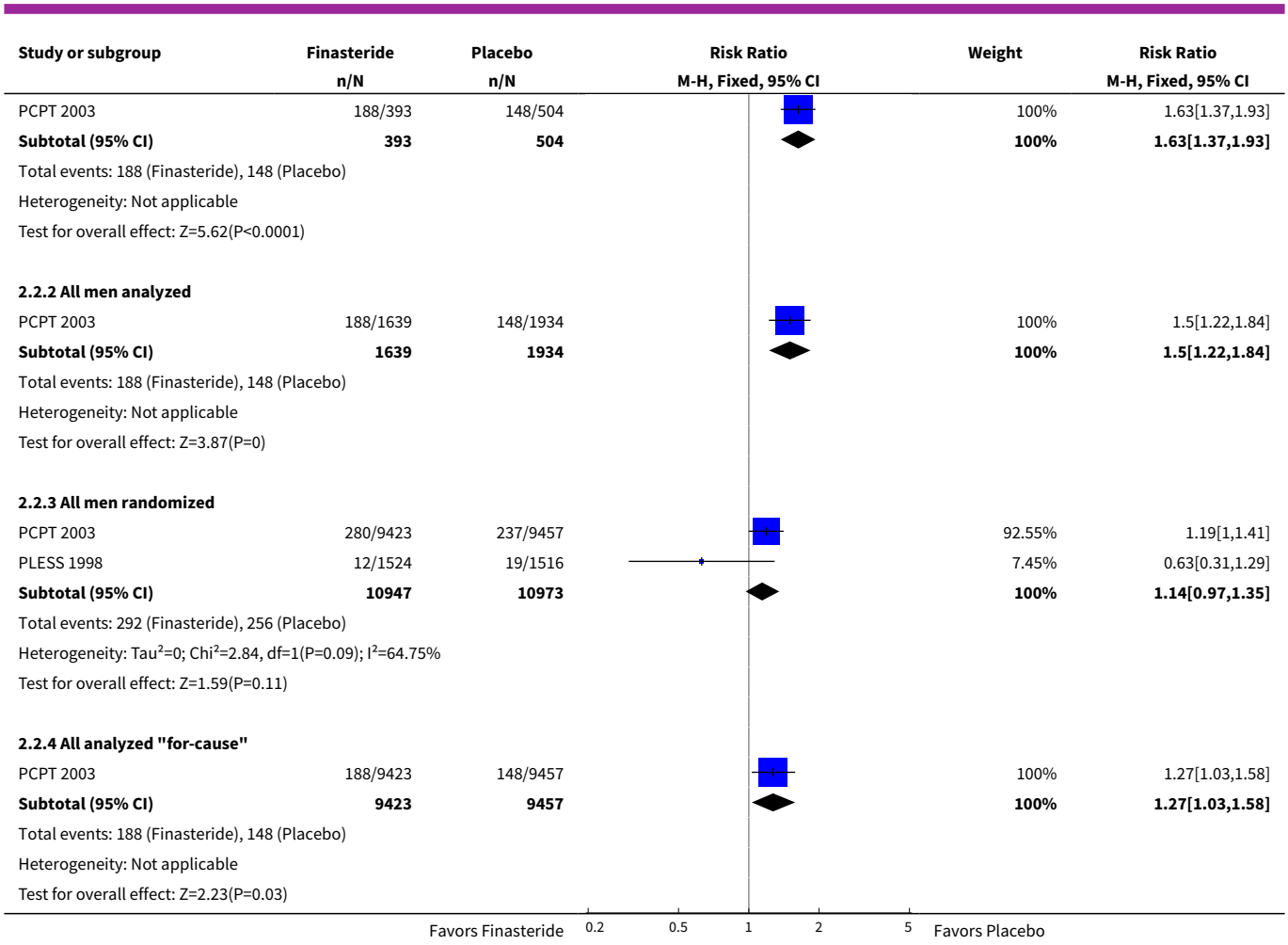
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Age > or = 65 years	1	7175	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.66, 0.86]
8 Prostate cancer detected overall according to race	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 White	1	17380	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.64, 0.76]
8.2 Black	1	709	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.55, 1.20]
8.3 Hispanic	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.42, 1.34]
8.4 Other	1	292	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.19, 2.13]
9 Prostate cancer detected: Prostate cancer in a first degree relative	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Yes	1	2913	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]
9.2 No	1	15967	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.63, 0.77]

Analysis 2.1. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 1 Prostate cancer detected: Gleason scores 7-10, all cancers.

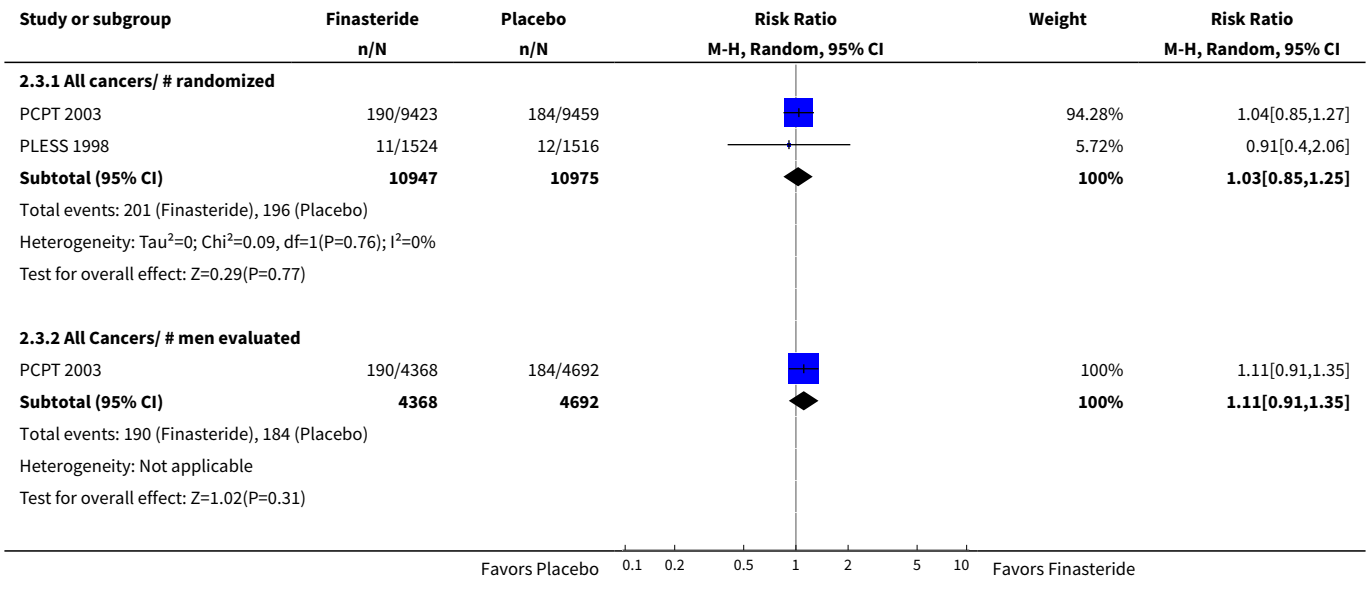


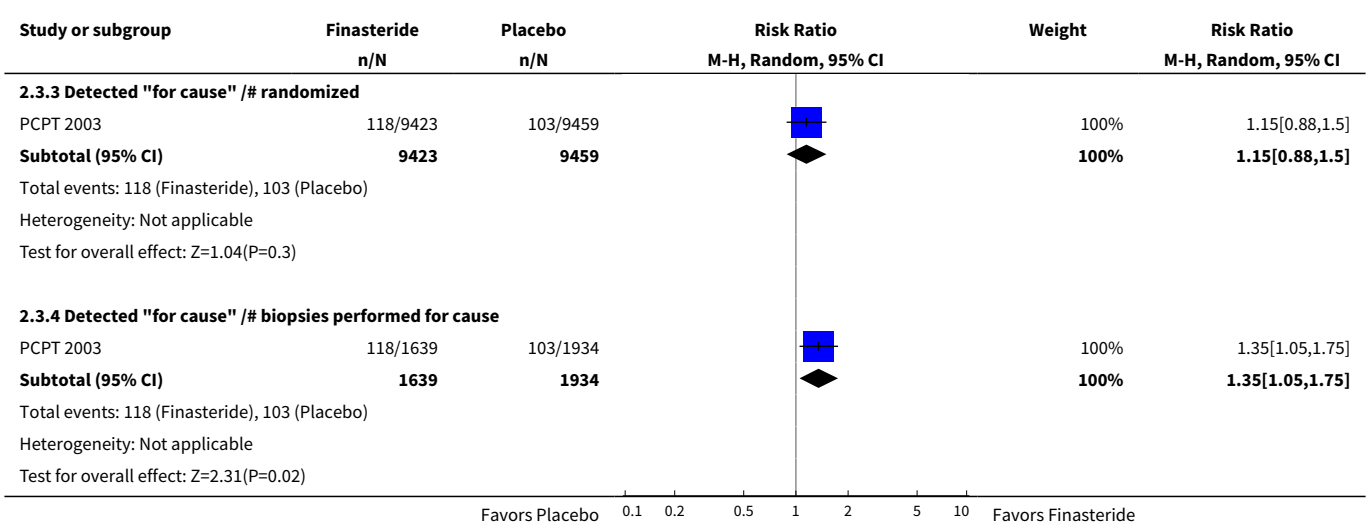
Analysis 2.2. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 2 Prostate cancer detected "for-cause": Gleason scores 7-10.



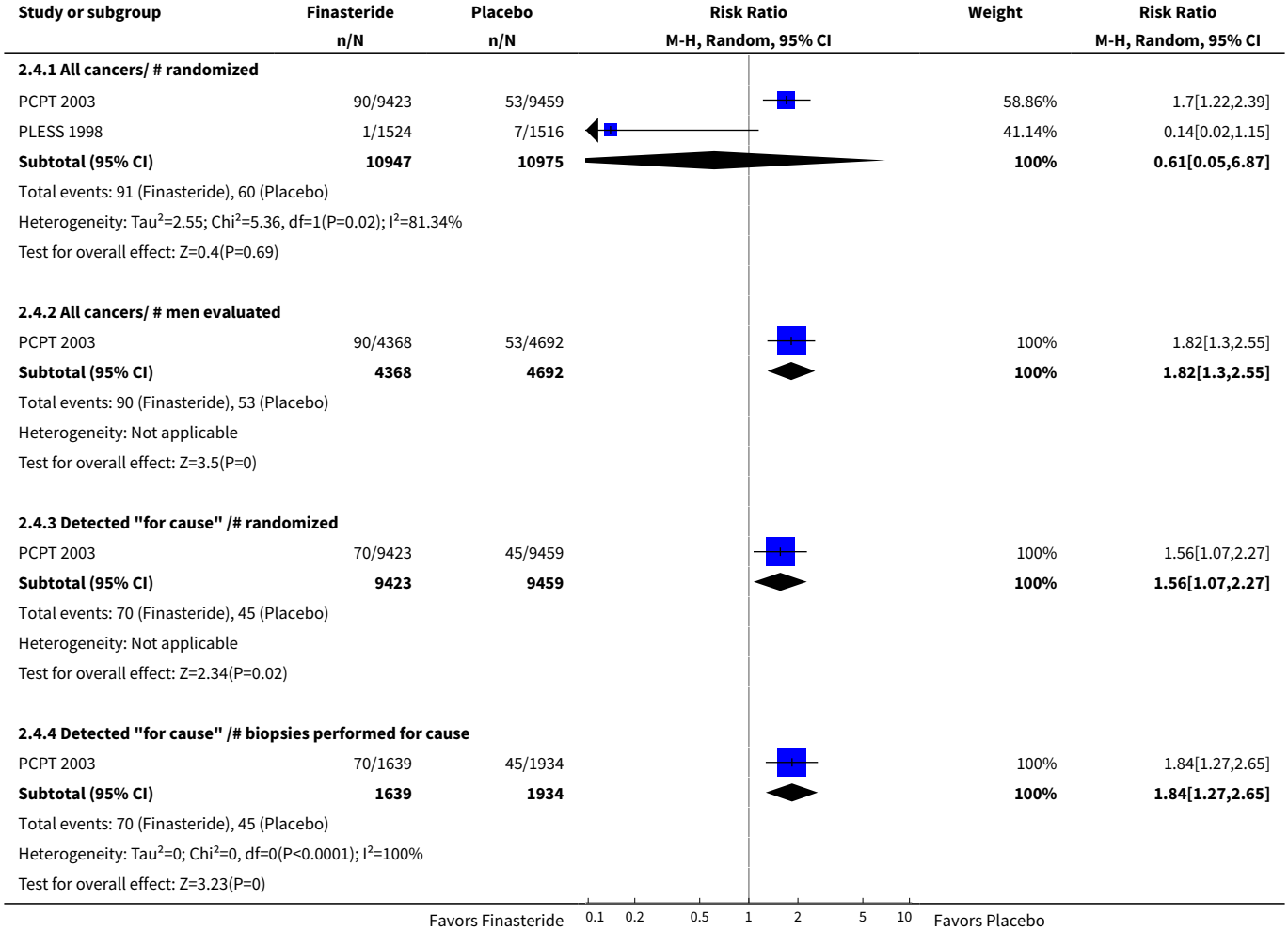


Analysis 2.3. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 3 Prostate cancer detected: Gleason score 7, all cancers.





Analysis 2.4. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 4 Prostate cancer detected: Gleason scores 8-10, all cancers.



Analysis 2.5. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 5 Prostate cancer detected: PSA at study entry.

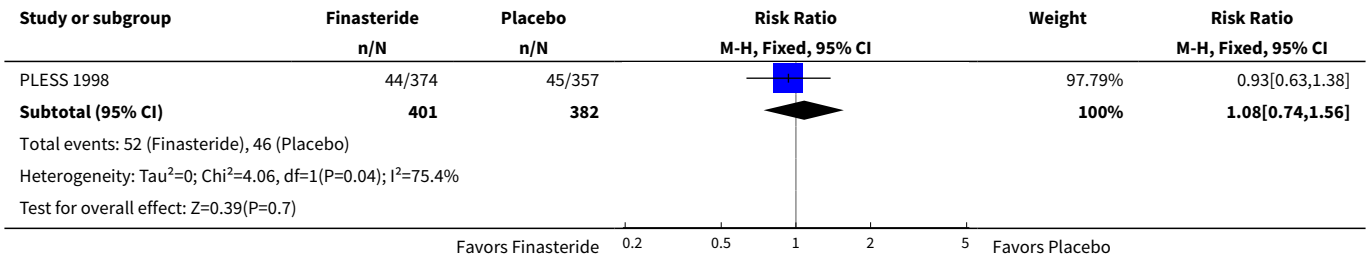
Study or subgroup	Finasteride n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 < 4.0 ng/mL					
PCPT 2003	803/9423	1147/9456		97.16%	0.7[0.64,0.77]
PLESS 1998	28/1149	32/1154		2.84%	0.88[0.53,1.45]
Subtotal (95% CI)	**10572**	**10610**		**100%**	**0.71[0.65,0.77]**
Total events: 831 (Finasteride), 1179 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=8.06(P<0.0001)					
2.5.2 > or = 4.0 ng/mL					
Cote 1998	8/27	1/25		38.59%	7.41[1,55.09]
PLESS 1998	44/374	45/357		61.41%	0.93[0.63,1.38]
Subtotal (95% CI)	**401**	**382**		**100%**	**2.08[0.28,15.43]**
Total events: 52 (Finasteride), 46 (Placebo)					
Heterogeneity: Tau^2=1.67; Chi^2=4.06, df=1(P=0.04); I^2=75.4%					
Test for overall effect: Z=0.71(P=0.48)					

Favors Finasteride — Favors Placebo

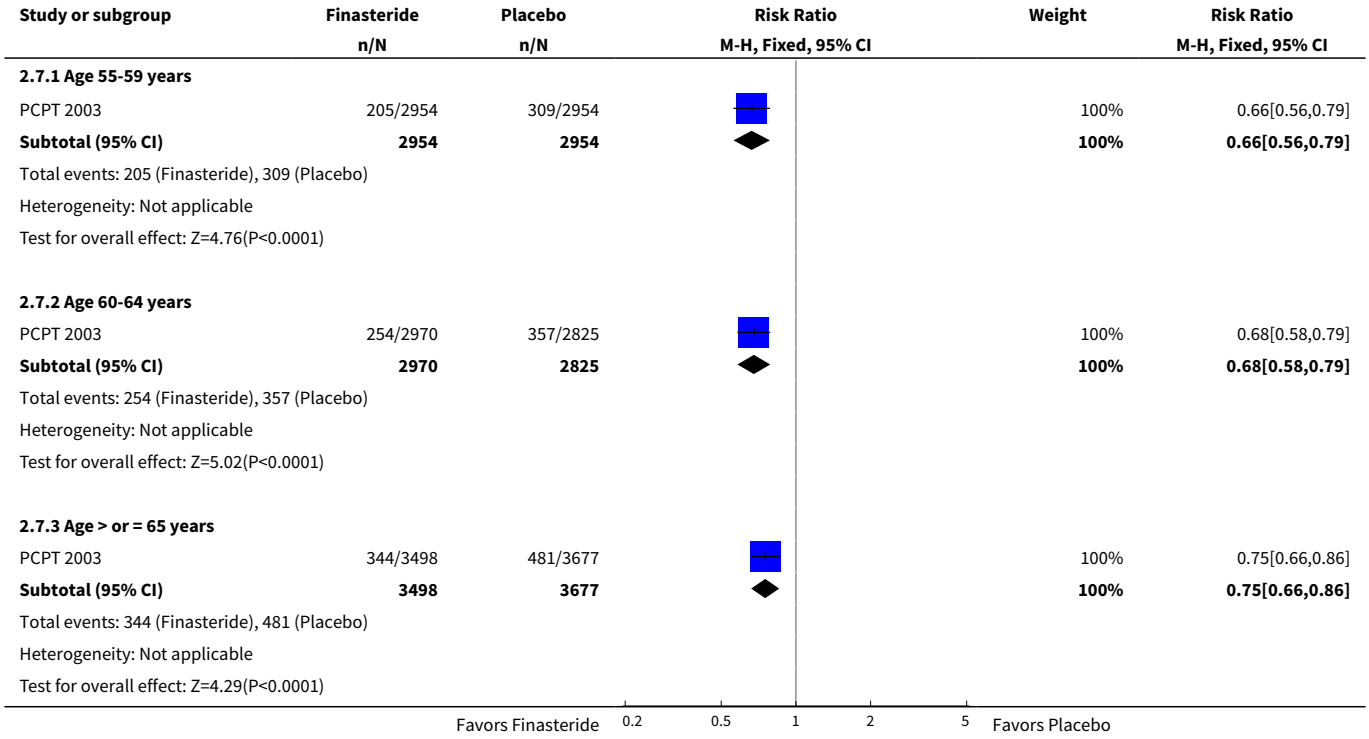
Analysis 2.6. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 6 Prostate cancer detected: PSA at study entry.

Study or subgroup	Finasteride n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 0.0 to 1.0 ng/mL					
PCPT 2003	212/4493	357/4639		100%	0.61[0.52,0.72]
Subtotal (95% CI)	**4493**	**4639**		**100%**	**0.61[0.52,0.72]**
Total events: 212 (Finasteride), 357 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.81(P<0.0001)					
2.6.2 1.1 to 2.0 ng/mL					
PCPT 2003	344/3397	457/3311		100%	0.73[0.64,0.84]
Subtotal (95% CI)	**3397**	**3311**		**100%**	**0.73[0.64,0.84]**
Total events: 344 (Finasteride), 457 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.62(P<0.0001)					
2.6.3 2.1 to 3.0 ng/mL					
PCPT 2003	247/1533	332/1506		100%	0.73[0.63,0.85]
Subtotal (95% CI)	**1533**	**1506**		**100%**	**0.73[0.63,0.85]**
Total events: 247 (Finasteride), 332 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.14(P<0.0001)					
2.6.4 > or = 4.0 ng/mL					
Cote 1998	8/27	1/25		2.21%	7.41[1,55.09]

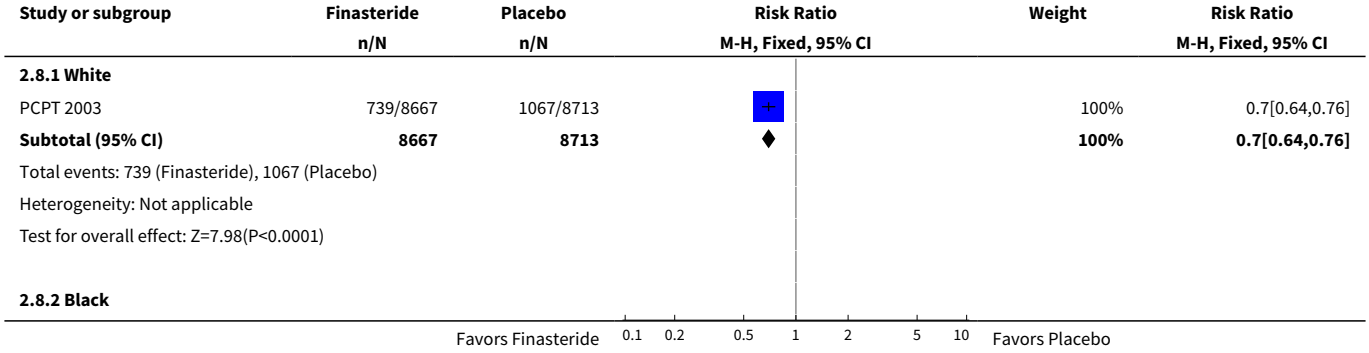
Favors Finasteride — Favors Placebo

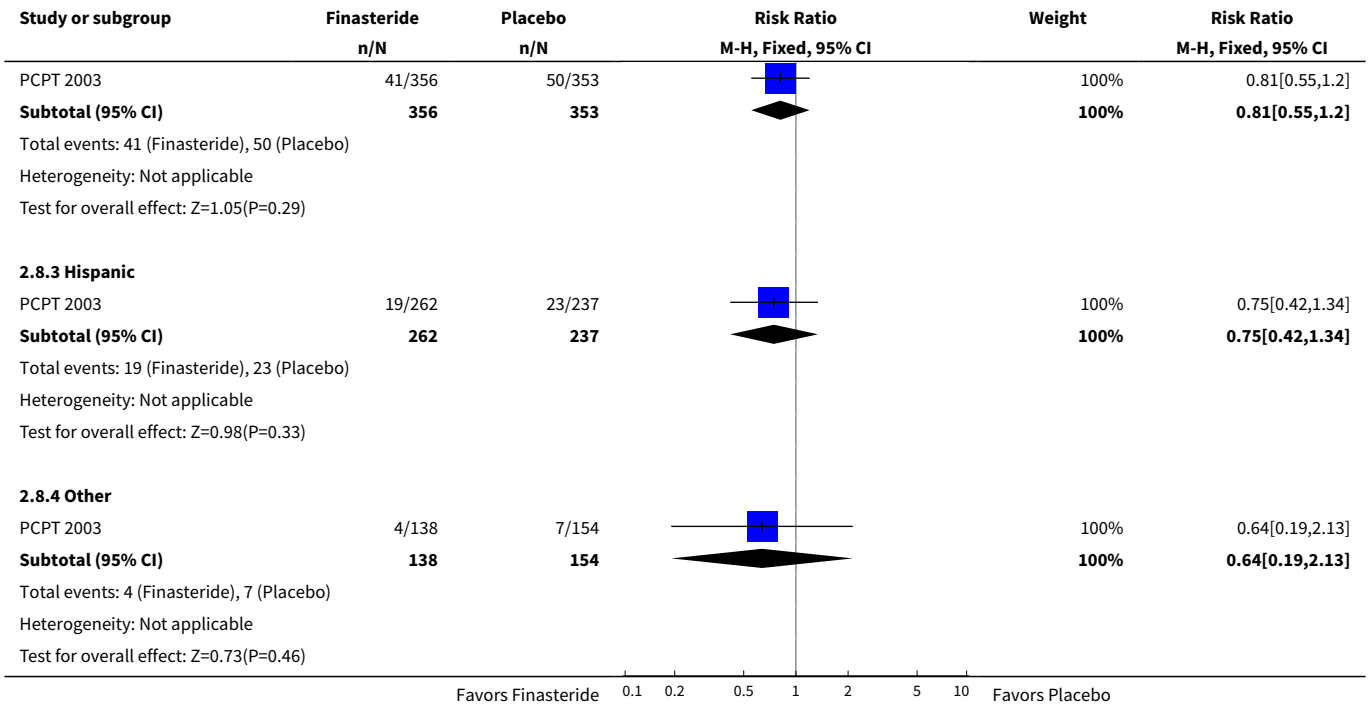


Analysis 2.7. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 7 Prostate cancer detected overall according to age.

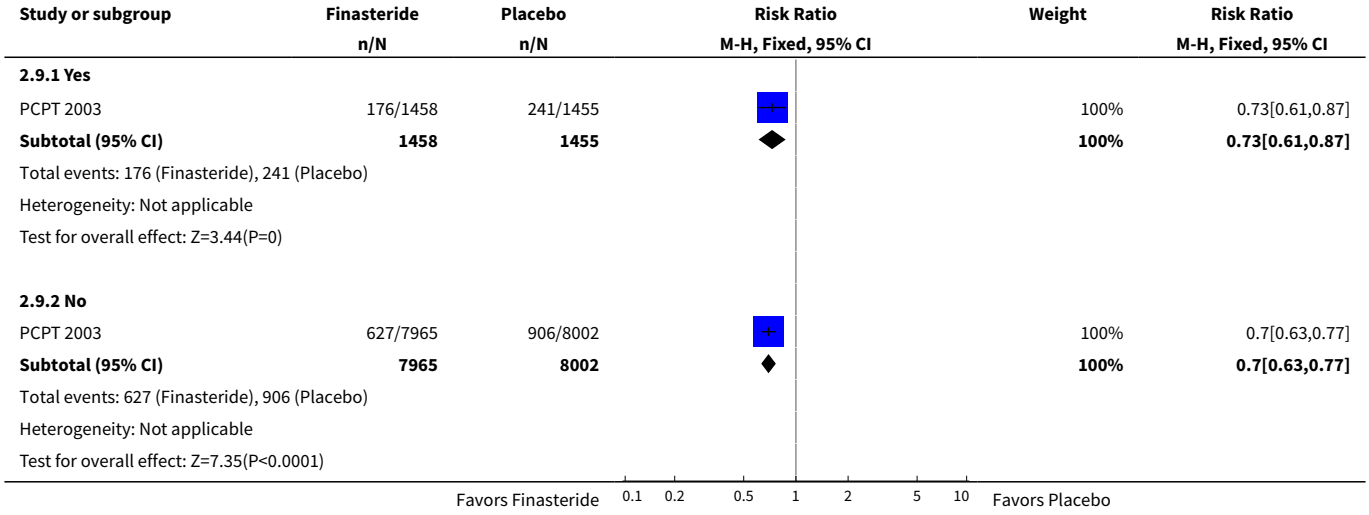


Analysis 2.8. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 8 Prostate cancer detected overall according to race.





Analysis 2.9. Comparison 2 Finasteride versus placebo; Subgroup analyses, Outcome 9 Prostate cancer detected: Prostate cancer in a first degree relative.



Comparison 3. 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks)

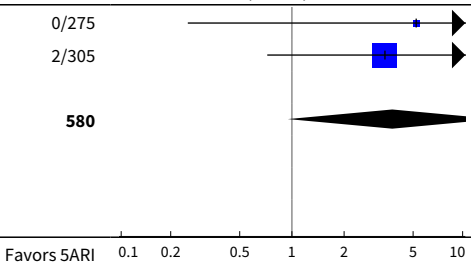
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall mortality	2	1154	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [0.95, 15.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Study withdrawals	5	3286	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
2.1 Finasteride versus Tamsulosin	2	608	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.59, 1.00]
2.2 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.96, 1.88]
2.3 Finasteride versus Doxazosin	2	2063	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.96, 1.28]
3 Study withdrawals due to adverse events	4	1762	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.49]
3.1 Finasteride versus Tamsulosin	2	608	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.19, 13.89]
3.2 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.42, 1.60]
3.3 Finasteride versus Doxazosin	1	539	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.70, 1.74]
4 Any adverse events	2	608	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.34, 13.90]
4.1 Finasteride versus Tamsulosin	2	608	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.34, 13.90]
5 Impotence/erectile dysfunction	4	1762	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.76, 2.16]
5.1 Finasteride versus Tamsulosin	2	608	Risk Ratio (M-H, Random, 95% CI)	2.45 [0.27, 22.31]
5.2 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.90, 2.79]
5.3 Finasteride versus Doxazosin	1	539	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.42, 1.73]
6 Decreased libido	3	1386	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.66, 3.45]
6.1 Finasteride versus Tamsulosin	1	232	Risk Ratio (M-H, Random, 95% CI)	11.45 [0.62, 210.19]
6.2 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.73, 4.05]
6.3 Finasteride versus Doxazosin	1	539	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.39, 2.27]
7 Decreased or abnormal ejaculate volume	4	1762	Risk Ratio (M-H, Random, 95% CI)	2.56 [0.46, 14.31]
7.1 Finasteride versus Tamsulosin	2	608	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.06, 24.48]
7.2 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Random, 95% CI)	5.90 [0.71, 48.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Finasteride versus Doxazosin	1	539	Risk Ratio (M-H, Random, 95% CI)	6.25 [0.76, 51.56]
8 Asthenia	2	1154	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.72]
8.1 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.33, 0.87]
8.2 Finasteride versus Doxazosin	1	539	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.20, 0.77]
9 Dizziness	2	1154	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.26, 0.62]
9.1 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.21, 0.49]
9.2 Finasteride versus Doxazosin	1	539	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.31, 0.83]
10 Postural hypotension	2	1154	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.11, 0.47]
10.1 Finasteride verus Terazosin	1	615	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.13, 0.69]
10.2 Finasteride versus Doxazosin	1	539	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.03, 0.56]

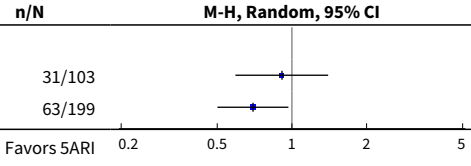
Analysis 3.1. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 1 Overall mortality.

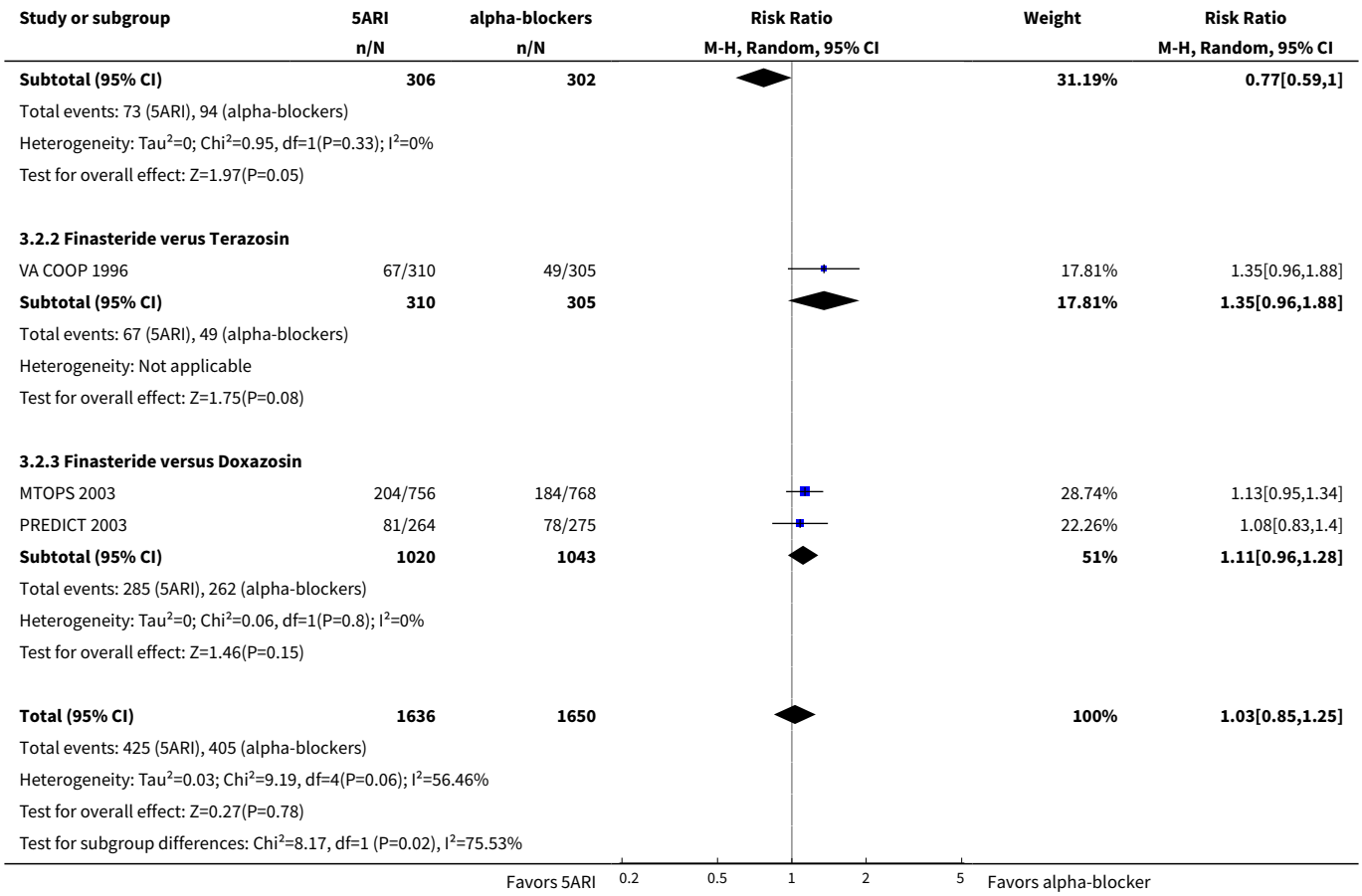
Study or subgroup	5ARI n/N	alpha-blockers n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
PREDICT 2003	2/264	0/275		19.55%	5.21[0.25,107.96]
VA COOP 1996	7/310	2/305		80.45%	3.44[0.72,16.44]
Total (95% CI)	**574**	**580**		**100%**	**3.79[0.95,15.15]**
Total events: 9 (5ARI), 2 (alpha-blockers)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%					
Test for overall effect: Z=1.88(P=0.06)					



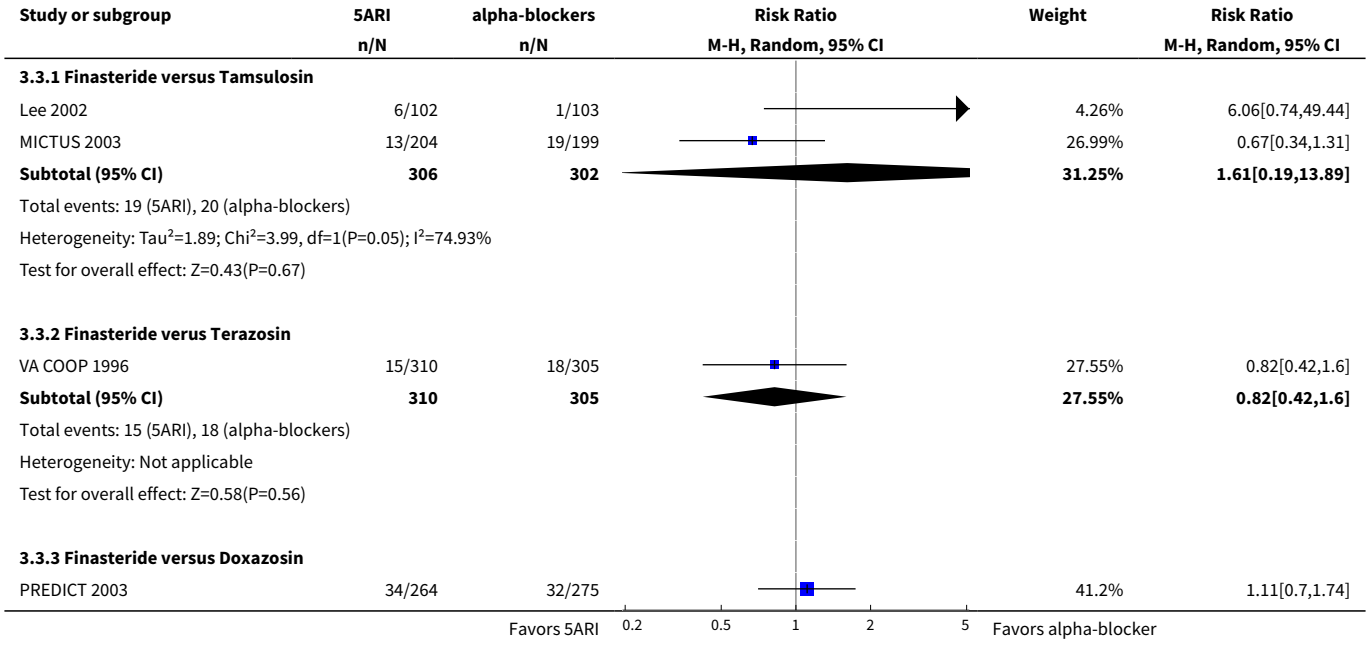
Analysis 3.2. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 2 Study withdrawals.

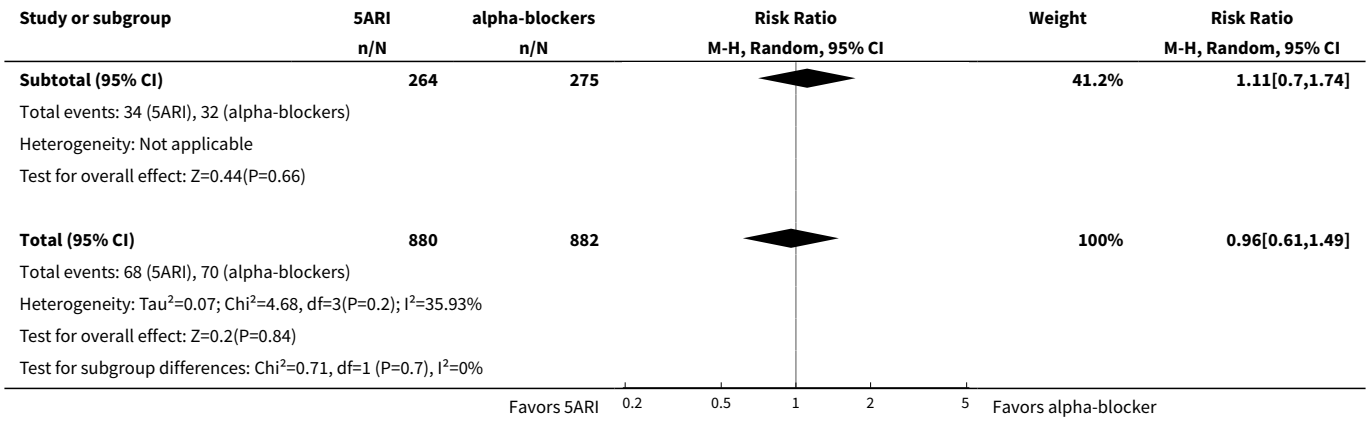
Study or subgroup	5ARI n/N	alpha-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Finasteride versus Tamsulosin					
Lee 2002	28/102	31/103		13.16%	0.91[0.59,1.4]
MICTUS 2003	45/204	63/199		18.03%	0.7[0.5,0.97]



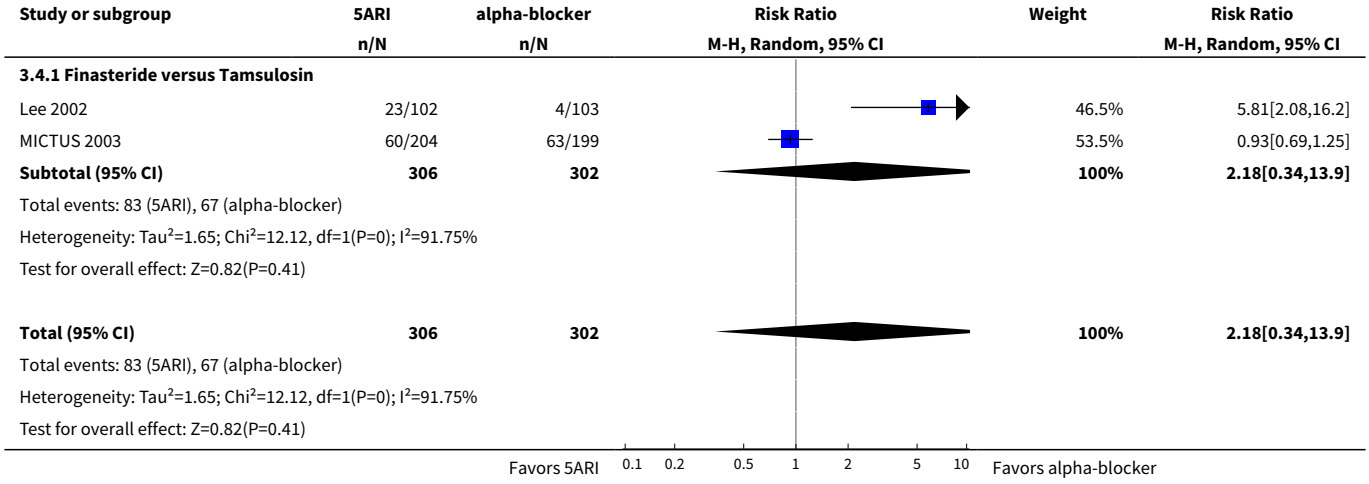


Analysis 3.3. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 3 Study withdrawals due to adverse events.

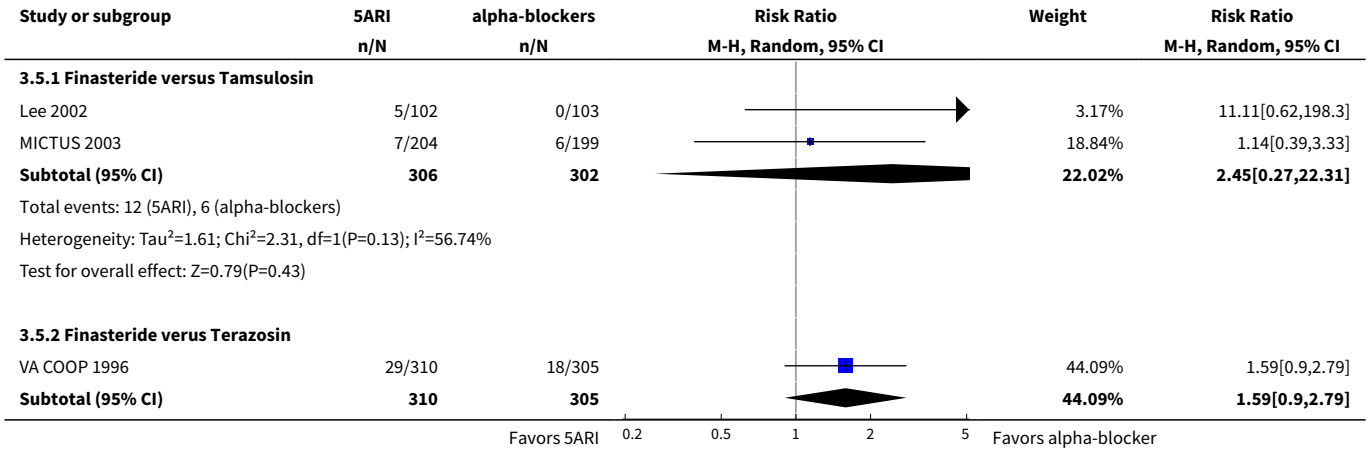


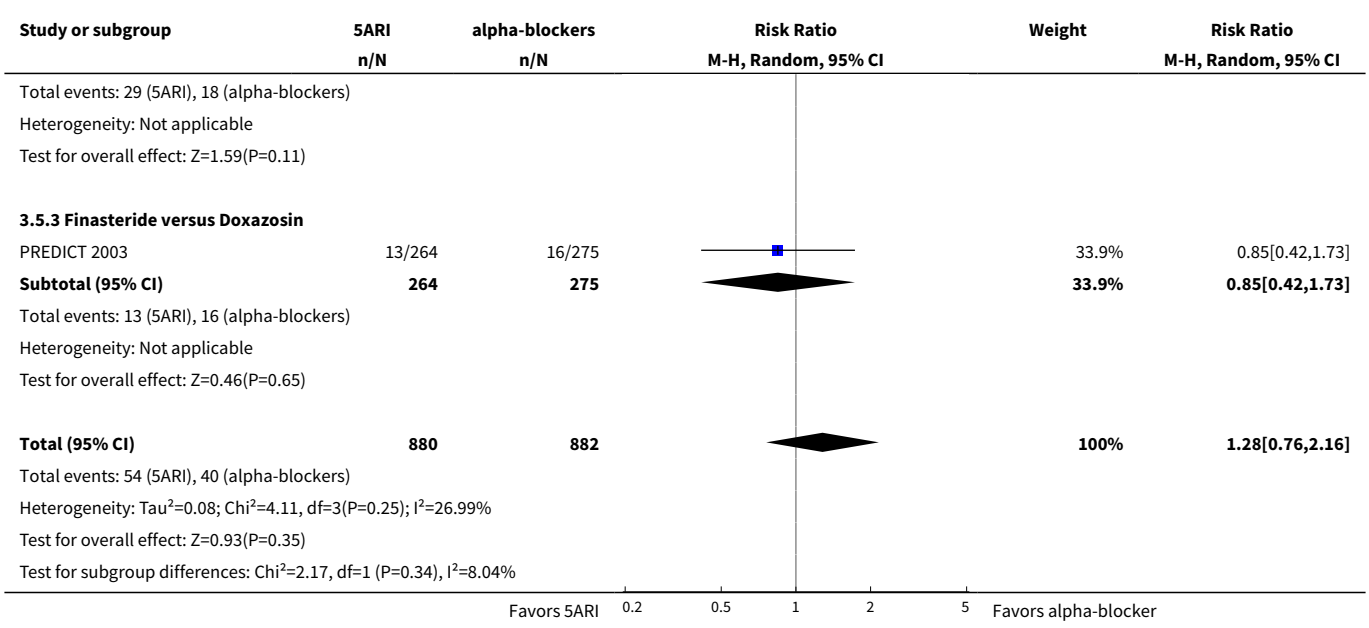


Analysis 3.4. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 4 Any adverse events.

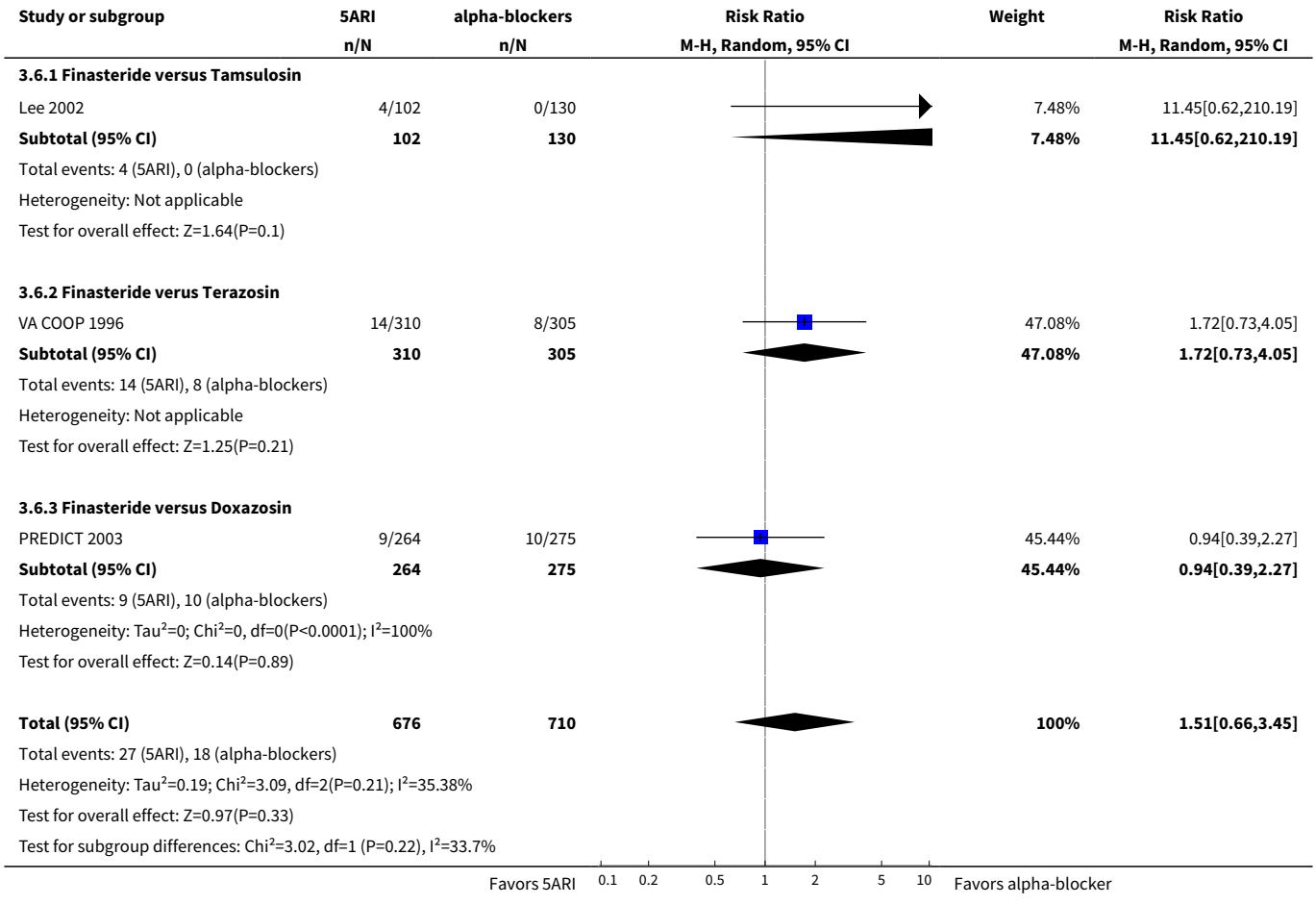


Analysis 3.5. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 5 Impotence/erectile dysfunction.



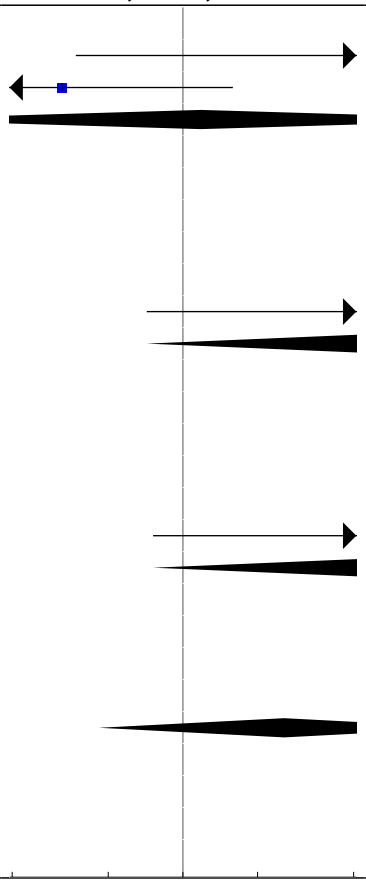


Analysis 3.6. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 6 Decreased libido.



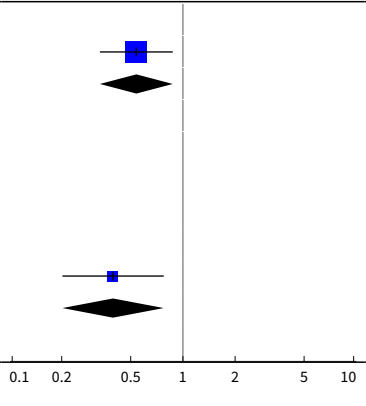
Analysis 3.7. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 7 Decreased or abnormal ejaculate volume.

Study or subgroup	5ARI n/N	alpha-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Finasteride versus Tamsulosin					
Lee 2002	3/102	0/103		18.63%	7.07[0.37,135.13]
MICTUS 2003	2/204	6/199		30.49%	0.33[0.07,1.59]
Subtotal (95% CI)	**306**	**302**		**49.13%**	**1.18[0.06,24.48]**
Total events: 5 (5ARI), 6 (alpha-blockers)					
Heterogeneity: Tau^2=3.46; Chi^2=3.37, df=1(P=0.07); I^2=70.31%					
Test for overall effect: Z=0.11(P=0.92)					
3.7.2 Finasteride verus Terazosin					
VA COOP 1996	6/310	1/305		25.43%	5.9[0.71,48.74]
Subtotal (95% CI)	**310**	**305**		**25.43%**	**5.9[0.71,48.74]**
Total events: 6 (5ARI), 1 (alpha-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
3.7.3 Finasteride versus Doxazosin					
PREDICT 2003	6/264	1/275		25.44%	6.25[0.76,51.56]
Subtotal (95% CI)	**264**	**275**		**25.44%**	**6.25[0.76,51.56]**
Total events: 6 (5ARI), 1 (alpha-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
Total (95% CI)	**880**	**882**		**100%**	**2.56[0.46,14.31]**
Total events: 17 (5ARI), 8 (alpha-blockers)					
Heterogeneity: Tau^2=1.87; Chi^2=7.88, df=3(P=0.05); I^2=61.91%					
Test for overall effect: Z=1.07(P=0.28)					
Test for subgroup differences: Chi^2=0.91, df=1 (P=0.64), I^2=0%					



Analysis 3.8. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 8 Asthenia.

Study or subgroup	5ARI n/N	alpha-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.8.1 Finasteride verus Terazosin					
VA COOP 1996	23/310	42/305		66%	0.54[0.33,0.87]
Subtotal (95% CI)	**310**	**305**		**66%**	**0.54[0.33,0.87]**
Total events: 23 (5ARI), 42 (alpha-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.51(P=0.01)					
3.8.2 Finasteride versus Doxazosin					
PREDICT 2003	11/264	29/275		34%	0.4[0.2,0.77]
Subtotal (95% CI)	**264**	**275**		**34%**	**0.4[0.2,0.77]**
Total events: 11 (5ARI), 29 (alpha-blockers)					



Study or subgroup	5ARI n/N	alpha-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=2.7(P=0.01)					
Total (95% CI)	**574**	**580**		**100%**	**0.48[0.33,0.72]**
Total events: 34 (5ARI), 71 (alpha-blockers)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=3.61(P=0)					
Test for subgroup differences: Chi^2=0.54, df=1 (P=0.46), I^2=0%					

Favors 5ARI 0.1 0.2 0.5 1 2 5 10 Favors alpha-blocker

Analysis 3.9. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 9 Dizziness.

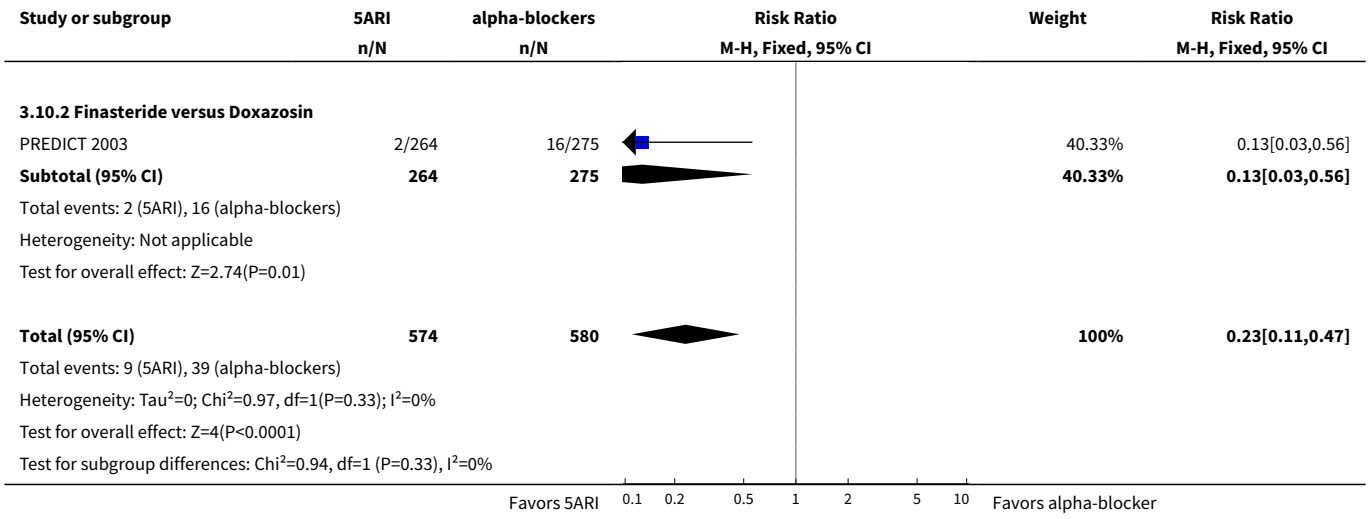
Study or subgroup	5ARI n/N	alpha-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Finasteride verus Terazosin					
VA COOP 1996	26/310	79/305		54.61%	0.32[0.21,0.49]
Subtotal (95% CI)	**310**	**305**		**54.61%**	**0.32[0.21,0.49]**
Total events: 26 (5ARI), 79 (alpha-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.34(P<0.0001)					
3.9.2 Finasteride versus Doxazosin					
PREDICT 2003	21/264	43/275		45.39%	0.51[0.31,0.83]
Subtotal (95% CI)	**264**	**275**		**45.39%**	**0.51[0.31,0.83]**
Total events: 21 (5ARI), 43 (alpha-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.68(P=0.01)					
Total (95% CI)	**574**	**580**		**100%**	**0.4[0.26,0.62]**
Total events: 47 (5ARI), 122 (alpha-blockers)					
Heterogeneity: Tau^2=0.05; Chi^2=1.89, df=1(P=0.17); I^2=47.09%					
Test for overall effect: Z=4.1(P<0.0001)					
Test for subgroup differences: Chi^2=1.89, df=1 (P=0.17), I^2=47.05%					

Favors 5ARI 0.1 0.2 0.5 1 2 5 10 Favors alpha-blocker

Analysis 3.10. Comparison 3 5-alpha-reductase Inhibitors versus alpha-blockers (24 to 52 weeks), Outcome 10 Postural hypotension.

Study or subgroup	5ARI n/N	alpha-blockers n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.10.1 Finasteride verus Terazosin					
VA COOP 1996	7/310	23/305		59.67%	0.3[0.13,0.69]
Subtotal (95% CI)	**310**	**305**		**59.67%**	**0.3[0.13,0.69]**
Total events: 7 (5ARI), 23 (alpha-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.84(P=0)					

Favors 5ARI 0.1 0.2 0.5 1 2 5 10 Favors alpha-blocker



ADDITIONAL TABLES

Table 1. Benign prostatic hyperplasia symptom score outcomes

Study (duration)	Score: Study entry	Mean change	Percent change	P-value vs. control
PCPT (>2 yrs): All subjects	AUA: 6.7 (4.8)	Not reported		
MTOPS (>2 yrs): finasteride (FIN)	AUA: 17.6 (5.9)	-5.6	-32%	0.001 vs. PBO
MTOPS (>2 yrs): doxazosin (DOX)	AUA: 17.0 (5.8)	-6.6	-39%	<0.001 vs. FIN, PBO
MTOPS (>2 yrs): combination FIN+DOX	AUA: 16.8 (5.8)	-7.4	-44%	<0.001 vs. FIN, PBO; 0.035 vs.DOX
MTOPS (>2 yrs): placebo (PBO)	AUA: 16.8 (5.9)	-4.9	-29%	
PLESS (>2 yrs): finasteride, all subjects	AUA: 15 (6)	-2.6	-17%	<0.001 vs. PBO
PLESS (>2 yrs): finasteride, subjects completing study	AUA: 15 (6)	-3.3	-22%	<0.001 vs. PBO
PLESS (>2 yrs): placebo, all subjects	AUA: 15 (6)	-1.0	-7%	
PLESS (>2 yrs): placebo, subjects completing study	AUA: 15 (6)	-1.3	-9%	
ARIA/ARIB (1-2 years): dutasteride	AUA: 17.0 (6.0)	-4.5 (6.6)	-26%	<0.001 vs. PBO
ARIA/ARIB (1-2 years): placebo	AUA: 17.1 (6.1)	-2.3 (6.8)	-13%	
PROSPECT (1-2 years): finasteride	Boyarsky: 15.8 (7.6)	-2.1	-13%	<0.01 vs. PBO
PROSPECT (1-2 years): placebo	Boyarsky: 16.6 (7.2)	-0.7	-4%	

Table 1. Benign prostatic hyperplasia symptom score outcomes *(Continued)*

PREDICT (1-2 years): finasteride (FIN)	AUA: 17.1 (4.4)	-6.6 (0.4)	-39%	Not significant vs. PBO
PREDICT (1-2 years): doxazosin (DOX)	AUA: 17.1 (4.2)	-8.3 (0.4)	-49%	<0.05 vs. FIN, PBO
PREDICT (1-2 years): combination FIN+DOX	AUA: 17.3 (4.7)	-8.5 (0.4)	-49%	<0.05 vs. FIN, PBO
PREDICT (1-2 years): placebo (PBO)	AUA: 17.2 (4.5)	-5.7 (0.4)	-33%	
VA COOP (1-2 years): finasteride (FIN)	AUA: 16.2 (5.4)	-3.2	-20%	0.63 vs. PBO
VA COOP (1-2 years): doxazosin (DOX)	AUA: 16.2 (5.5)	-6.1	-38%	<0.001 vs. PBO
VA COOP (1-2 years): combination FIN+DOX	AUA: 15.9 (5.7)	-6.2	-39%	<0.001 vs. FIN, PBO
VA COOP (1-2 years): placebo (PBO)	AUA: 15.8 (5.5)	-2.6	-16%	
FSG-American (1-2 years): finasteride	Boyarsky: 10.2 (5.5)	-2.7	-21%*	<0.05 vs. PBO
FSG-American (1-2 years): placebo	Boyarsky: 9.8 (5.3)	-1.0	-2%*	
FSG-International (1-2 years): finasteride	Boyarsky: 18.6 (6.0)	-3.3	-18%	0.005
FSG-International (1-2 years): placebo	Boyarsky: 18.2 (5.9)	-2.0	-11%	
MICTUS (< 1 year): finasteride	SPI**: 14.0 (4.2)	-4.5 (5.0)	-32%	0.055
MICTUS (< 1 year): tamsulosin	SPI**: 13.6 (4.4)	-5.2 (5.0)	-37%	
Lee (< 1 year): finasteride	AUA: 19.0 (7.2)	-5.8	-31%	Not significant
Lee (< 1 year): tamsulosin	AUA: 19.9 (7.2)	-6.9	-35%	

* Study authors noted that the values are the means of the percent changes from baseline in each man and therefore cannot be derived from the baseline and 12-month results shown

** Symptom problem Index

WHAT'S NEW

Date	Event	Description
17 January 2012	Amended	added grant info

HISTORY

Review first published: Issue 2, 2008

Date	Event	Description
15 March 2011	Amended	Few, minor edits.
13 May 2008	Amended	Converted to new review format.
14 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Wilt TJ: Development of criteria for study inclusion, conceptual design, data review and analysis, initial draft of manuscript, review and editing.

MacDonald R: Data extraction and analysis, manuscript review and editing.
Hagerty K: Data extraction and analysis, manuscript review and editing.

Schellhammer P: Data extraction and analysis, development of criteria for study inclusion, manuscript review and editing.

Kramer BS: Development of the analytic framework, development of criteria for study inclusion, data review, manuscript review and editing.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

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INDEX TERMS

Medical Subject Headings (MeSH)

*5-alpha Reductase Inhibitors; Enzyme Inhibitors [*therapeutic use]; Finasteride [therapeutic use]; Prostate-Specific Antigen [blood]; Prostatic Hyperplasia [drug therapy]; Prostatic Neoplasms [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Male