

Review Article

# Current Status of 5 $\alpha$ -Reductase Inhibitors in Prostate Disease Management

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The key enzyme in the androgen synthesis and androgen receptor pathways is 5 $\alpha$ -reductase (5-AR), which occurs as three isoenzymes. Types I and II 5-ARs the most important clinically, and two different 5-AR inhibitors (5-ARIs), finasteride and dutasteride, have been developed. Several urology associations have recommended and upgraded the use of 5-ARIs for an enlarged prostate with lower urinary tract symptoms. In the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events Trial, 5-ARIs reduced the incidence of low-grade prostate cancer. However, despite the documented reductions in the overall incidence of prostate cancer, 5-ARIs are at the center of a dispute. The American Society of Clinical Oncology (ASCO) and the American Urology Association (AUA) presented clinical guidelines for the use of 5-ARIs for chemoprevention of prostate cancer in 2008. However, ASCO/AUA has eliminated these from the main "Clinical Guidelines" in 2012, because the U.S. Food and Drug Administration denied a supplemental New Drug Application for the use of dutasteride for prostate cancer chemoprevention. The 5-ARIs can also be used to manage hemospermia and prostatic hematuria, and to prevent intraoperative bleeding, although there is insufficient evidence for a standard strategy. This review summarizes the current use of 5-ARIs for prostate disease, including benign prostate hyperplasia, prostate cancer, prostate-related bleeding, and hemospermia.

**Keywords:** 5-alpha reductase inhibitor; Hemospermia; Prostatic hyperplasia; Prostate neoplasms

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## INTRODUCTION

Benign prostatic hyperplasia (BPH) and prostate cancer are the most common diseases of men, and the incidence of these diseases increases with age. Androgens cause the proliferation of prostate epithelial and stromal cells [1]. Testosterone is the most abundant androgen in the blood [2], whereas dihydrotestosterone (DHT) is the principle androgen in the prostate gland. 5 $\alpha$ -Reductase inhibitors (5-ARIs) inhibit the metabolism of testosterone to DHT by 5 $\alpha$ -reductase (5-AR). They are widely used for BPH, and the 5-ARIs, finasteride and dutasteride, reduce lower urinary tract symptoms (LUTS), prostate size, and gross hematuria due to prostatic bleeding. Use of 5-ARIs for 6 months diminishes the risk for acute urinary re-

tention and the need for prostate surgery. 5-ARIs decreased the overall incidence of prostate cancer in the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) Trial. The focus of this review is the current status of 5-ARIs for managing prostate disease, including prostate cancer and BPH.

## MECHANISM OF ACTION OF 5-ARIs

The regulation of the androgen-androgen receptor (AR) pathway is at the core of prostate development, prostate enlargement, and prostate cancer. Testosterone is produced by Leydig cells in the testis and by the adrenal cortex. Cholesterol, the steroid hormone precursor, can be synthe-

sized *de novo* in Leydig cells and is derived from plasma low-density lipoprotein.

Androgen biosynthesis is a multistep process in which cholesterol is converted to the active androgens testosterone and DHT. The conversion of cholesterol to testosterone involves enzymatic transformations by several different enzymes, including the cholesterol side chain cleavage enzyme (CYP11A), 3 $\beta$ -hydroxysteroid dehydrogenase isomerase II, 17 $\alpha$ -hydroxylase, and 17 $\beta$ -hydroxysteroid dehydrogenase III. Testosterone is secreted by the testis, enters cells by diffusion, and binds to the AR in the target cell, either directly or after conversion to DHT. After testosterone or DHT is bound to AR in the cytoplasm, the androgen-AR complex enters the nucleus. Although testosterone and DHT bind to the same AR, their roles are different. The actions of the testosterone-AR complex are gonadotropin regulation, spermatogenesis, and stimulation of the Wolffian duct during sexual differentiation. In contrast, the DHT-AR complex regulates external virilization and sexual maturation at puberty. In addition to AR signaling activation, the binding of DHT to the AR also affects prostate growth and differentiation. DHT is the primary prostatic androgen that combines with the AR because the affinity of the AR for DHT is 2–5 times that for testosterone [3]. Additionally, the testosterone-AR complex is less stable [3]. The potency of DHT for the induction of AR signaling is 10-fold that of testosterone [4].

Testosterone, the main circulating androgen, is converted to DHT by 5-AR isoenzymes. Three 5-AR isoenzymes have been identified to date, and these are encoded by different genes (*SRD5A1*, *SRD5A2*, and *SRD5A3*). Type I 5-AR is located predominantly in the skin, liver, brain, and prostate. Type II 5-AR is present in the prostate, seminal vesicles, and genital skin. Type III 5-AR is expressed in prostate cancer [5,6] and is currently being investigated. Type I and type III 5-ARs are upregulated in prostate cancer and hormone-refractory prostate cancer [5,6]. The 5-ARs finasteride inhibits type II 5-AR, while dutasteride inhibits type I and type II 5-AR. Both 5-ARs are used clinically. At a typical dosage, finasteride causes a profound decline in DHT levels in the prostate, but has little or no effect on serum testosterone or luteinizing hormone levels. Dutasteride decreases serum DHT by 90%, significantly decreases total prostate volume by 25.7%, and reduces total transitional volume by 20.4% (vs. placebo) at 2 years [7].

## 5-ARs AND BPH

Many clinical studies have reported that monotherapy or combination therapy with a 5-ARs or alpha-blocker for BPH improves LUTS and urine flow rates, and reduces the risk for acute urinary retention and the need for prostate surgery.

A total of 1,315 men with moderate to severe LUTS due to BPH were enrolled in a Korean multicenter, retro-

spective study [8]. The patients were treated with an alpha-blocker and/or a 5-ARs (finasteride). The total change in the International Prostate Symptom Score in the combination therapy group was –11.5 points over 4 years. The combination therapy group showed a 21% reduction in prostate volume after 1 year and achieved a prostate-specific antigen (PSA) reduction of 47% after 1 year. Men who received combination therapy with dutasteride had a prostate volume reduction of 23% over 1 year and 52% after more than 1 year [9].

Many urological associations have recommended the use of 5-ARs for BPH. Table 1 summarizes society-specific guidelines for the use of 5-ARs for LUTS and an enlarged prostate. The 2010 American Urology Association (AUA) guidelines on the management of BPH recommend 5-ARs (5 mg finasteride, 0.5 mg dutasteride daily) as a monotherapy or combined treatment for BPH based on the Medical Therapy of Prostatic Symptoms and Combination of Avodart and Tamsulosin Trials [10]. The panel consensus was as follows. The combination of an alpha-blocker and a 5-ARs (combination therapy) is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostate enlargement based on a volume measurement, PSA level as a proxy for volume, and/or enlargement on a digital rectal exam. They also stated that 5-ARs reduce the risk for complications (urinary retention) and BPH-related surgery. However, the AUA panel did not recommend 5-ARs for men without an enlarged prostate. The 2012 European Association of Urology (EAU) guidelines recommend 5-ARs for LUTS with benign prostatic obstruction [11]. They recommended that 5-ARs should be offered to men who have moderate to severe LUTS, prostate size  $\geq 40$  g, and a PSA level  $> 1.4$ – $1.6$   $\mu\text{g/L}$ , and they indicated that 5-ARs can prevent progression and the need for prostate surgery (level 1b evidence, grade A recommendation).

The Canadian Urological Association (CUA) also recommended 5-ARs as a single or combined treatment option for BPH [12]. The indications for a single 5-ARs are BPH or LUTS associated with prostate enlargement (level 1 evidence, grade A recommendation). In addition, they recommended 5-ARs in combination with an alpha blocker (level 1 evidence, grade A recommendation) and suggested that patients receiving combination therapy can stop the alpha blocker after 6–9 months of treatment. The CUA presented prognostic factors indicating the risk for BPH progression; these include serum PSA  $> 1.4$  ng/mL, age  $> 50$  years, and gland volume  $> 30$  cm<sup>3</sup>. The National Institute for Health and Clinical Excellence (NICE) in the UK developed the NICE guidelines for high-quality healthcare and encouraged healthy living based on the evidence. The NICE guidelines for LUTS, which are shown in a detail in [13], recommend 5-ARs for men with LUTS who have a prostate size  $\geq 30$  g, PSA  $\geq 1.4$  ng/mL, and a risk for progression. Combination therapy with an alpha blocker can be considered for patients with bothersome moderate to severe LUTS, prostate size  $\geq 30$  g, and PSA  $\geq 1.4$  ng/mL.

**TABLE 1.** Comparison of recommended guidelines for use of 5-ARIs

|                  |  |
|------------------|--|
| AUA [10]         | The combination of an alpha-blocker and 5 $\alpha$ -reductase inhibitors (5-ARIs) (combination therapy) is an appropriate and effective treatment for patients with lower urinary tract symptoms (LUTS) associated with demonstrable prostatic enlargement based on volume measurement, prostate-specific antigen (PSA) level as a proxy for volume, and/or enlargement on digital rectal examination.<br>5-ARIs may be used to prevent progression of LUTS secondary to benign prostatic hyperplasia (BPH) and to reduce the risk of urinary retention and future prostate-related surgery.<br>5-ARIs should not be used in men with LUTS secondary to BPH without prostatic enlargement.<br>The 5-ARIs are an appropriate and effective treatment alternative for men with LUTS secondary to BPH who have demonstrable prostate enlargement. |
| EAU [11]         | 5-ARIs should be offered to men who have moderate to severe LUTS and enlarged prostates ( $\geq 40$ mL) or elevated PSA concentrations ( $> 1.4$ - $1.6$ $\mu\text{g/L}$ ).<br>5-ARIs can prevent disease progression with regard to acute urinary retention and need for surgery (level 1b evidence, grade A recommendation).   |
| CUA, Canada [12] | The 5-ARIs are appropriate and effective treatments for patients with LUTS associated with demonstrable prostatic enlargement (level 1 evidence, grade A recommendation).<br>Combination therapy of an alpha-adrenergic receptor blocker and a 5-ARIs is an appropriate and effective treatment strategy for patients with LUTS associated with prostatic enlargement. Combination medical therapy can effectively delay symptomatic disease progression, while combination therapy and/or 5-ARIs monotherapy is associated with decreased risk of urinary retention and/or prostate surgery (level 1 evidence, grade A recommendation).   |
| NICE, UK [13]    | Offer a 5-ARIs to men with LUTS who have prostates estimated to be larger than 30 g or a PSA level greater than $> 1.4$ ng/mL, and who are considered to be at high risk of progression (for example, older men).<br>Consider offering a combination of an alpha blocker and a 5-ARIs to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 g or a PSA level greater than $> 1.4$ ng/mL.   |

AUA, American Urology Association; EAU, European Association of Urology; CAU, Canadian Urological Association; NICE, National Institute for Health and Clinical Excellence.

## 5-ARIs AND PROSTATE CANCER CHEMOPREVENTION

Prostate cancer is the most common incident cancer in western countries, and the incidence of prostate cancer has increased in Korea. According to the Korean National Cancer Incidence Database, the estimated crude incidence rate was 43.3 per 100,000 population from 1993 to 2010, and the estimated age-standardized incidence rate was 32.5 per 100,000 population in 2012. The estimated crude prostate cancer mortality rate was 6.1 per 100,000 [14].

Prostate cancer is an androgen-stimulated cancer, and DHT is the main stimulant [15]. DHT upregulates the expression of PSA and stimulates prostate cancer cells, whereas no prostate cancer occurs in males with 5-AR deficiency [16-18]. The upregulation of 5-AR also occurs in men with prostate cancer [6,19,20]. Type I and type III 5-ARs are upregulated in prostate cancer and in castration-refractory prostate cancer. Type III 5-AR is being investigated intensively in the prostate cancer research field [5,6]. Additionally, variations in the steroid 5-AR type II gene (*SRD5A2*) may contribute to the development of prostate cancer [21].

The National Cancer Institute (NCI) and American Society of Clinical Oncology (ASCO) define chemoprevention as suppression or delay of cancer development or cancer recurrence by a natural, synthetic, or biological substance [22]. Since finasteride was approved by the U.S. Food and Drug Administration (FDA) in 1992, several re-

searchers have reported using 5-ARIs to prevent prostate cancer. The PCPT and REDUCE clinical trials for prostate cancer chemoprevention are notable as well-designed, randomized placebo controlled trials [23,24].

In the PCPT, 18,882 men were randomized into a finasteride (5 mg) arm and a placebo arm over 7 years [23]. The risk for the incidence of low-grade prostate cancer declined by 25%, and the risk for high-grade prostatic intraepithelial neoplasia declined by 21.4% relative to placebo after a 7-year finasteride administration period. An increased risk for high-grade (Gleason score, 7 to 10) prostate cancer was observed in the finasteride group compared with the risk in the placebo group. In the REDUCE trial, similar to the PCPT trial, 4-year administration of dutasteride reduced prostate cancer incidence by 22.8% (overall hazard ratio, 0.77; 95% confidence interval [CI], 0.70 to 0.85), but increased the risk for high-grade prostate cancer (Gleason score, 8 to 10; 0.5% vs. 1.0%;  $p=0.02$ ) [24,25]. Thus, the use of 5-ARIs for preventing prostate cancer remains controversial based on the PCPT and REDUCE analyses.

All investigators agree that 5-ARIs reduce the incidence of low grade prostate cancer, but their use for high-grade prostate cancer is controversial. It is not clear whether 5-ARIs produce high-grade prostate cancer or increase the rate of detection of high-grade prostate cancer. Additional analysis of PCPT data has suggested the latter option. 5-ARIs reduce prostate size and advance the sensitivity of prostate biopsy by improving the digital rectal examination and PSA level [26,27]. Redman et al. [28] reported that

**TABLE 2.** Comments of the FDA and ASCO/AUA for use of 5-ARIs in prostate cancer chemoprevention

| Organization  | Comments  |
|---------------|---|
| FDA [30]      | <p>Be aware that 5-ARIs may increase the risk of high-grade prostate cancer.</p> <p>Prior to initiating therapy with 5-ARIs, consideration should be given to other urological conditions that might mimic benign prostatic hyperplasia (BPH).</p> <p>Be aware that treatment with 5-ARIs causes an approximate 50% reduction in prostate-specific antigen (PSA) values by 6 months; however, individual patients receiving 5-ARIs may experience varying decreases in PSA values. Therefore, any confirmed increase in PSA while on a 5-ARI may signal the presence of prostate cancer and should be evaluated, even if that PSA is in the normal range of men not taking a 5-ARI.</p> <p>Know that 5-ARIs are not approved for the prevention of prostate cancer.</p> |
| ASCO/AUA [32] | <p>The ASCO and AUA have archived this collaborative 2008 guideline on the use of 5-ARIs for prostate cancer chemoprevention. The guideline has been removed from the main "Clinical Guidance" of the www.AUAnet.org website, but is available in the "Archived Guidelines" section. This is in response to the FDA's denial of the supplemental New Drug Application for dutasteride for prostate cancer chemoprevention.</p> <p>The AUA recommends to its members that using 5-ARIs solely for prostate cancer prevention is not FDA-approved and should be performed with caution. 5-ARIs maintain an FDA-approved indication to treat symptomatic BPH (update 12/11/12).</p>  |

FDA, U.S. Food and Drug Administration; ASCO, American Society of Clinical Oncology; AUA, American Urology Association; 5-ARIs, 5  $\alpha$ -reductase inhibitors.

finasteride does not increase the risk for high-grade prostate cancer. They found two problems with the PCPT trial. First, the PCPT randomized 18,882 men, but only 15,990 (85%) of the 18,882 men were assessable at the endpoint, and only 9,989 (52.9%) of the 18,882 (finasteride arm, 4,847 men; placebo arm, 5,142 men) were included in the final analysis. Second, the trial lacked prostatectomy data, as only 500 radical prostatectomy data were available. When Redman et al. [28] reanalyzed the data using a bias-adjusted modeling approach, the overall estimated rate of prostate cancer was 21.1% in the placebo arm and 14.7% in the finasteride arm, representing a 30% reduction. The estimated rates of high-grade prostate cancer were 4.2% and 4.8%, respectively. The incidence of high-grade prostate cancer based on the prostatectomy data were estimated at 8.2% and 6.0%, respectively. Because of the discrepancy between the observed and estimated data, the authors suggested that men who were administered finasteride had an opportunity to prevent cancer.

Xu et al. [29] reported that dutasteride inhibits the growth of prostate cancer cells by inhibiting SRD5A1 and SRD5A2 expression. In an *in vivo* study, dutasteride inhibited human prostate tumor growth compared with that in the finasteride and control groups (dutasteride 1.89  $\mu\text{mol/kg/d}$  vs. finasteride 1.89  $\mu\text{mol/kg/d}$  vs. control, 5.2 $\pm$ 0.7 g vs. 7.5 $\pm$ 0.8 g vs. 0.9 $\pm$ 1.1 g). The authors explained that the SRD5A2 (type II)-selective inhibitor induced regression of the non-malignant prostate tissue and that SRD5A1 participated in prostate carcinogenesis. Therefore, dual 5-ARIs or dutasteride with standard hormonal ablation therapy may have additive tumor-suppressing effects [29].

FDA researchers confirmed that both chemopreventive trials showed a reduction in the overall incidence of prostate cancer, by about 25%, but the incidence of high-grade (Gleason score, 7 to 10) prostate cancer was significantly

increased in both trials [25]. When the FDA reassessed all biopsy specimens using the modified Gleason scale, they found no reduction in high-grade tumor occurrence. Furthermore, a 0.5–0.7% increase in the incidence of high-grade prostate cancer (Gleason score, 8 to 10) was observed with 5-ARIs administration (finasteride 0.7%: relative risk, 1.7; dutasteride 0.5%: relative risk, 2.06). In 2011, the FDA announced a label change for 5-ARIs because of the possible increased risk for high-grade prostate cancer, but the use of 5-ARIs treatment for BPH was maintained (Table 2) [30]. The FDA decision was based on the PCPT and the REDUCE trials, two large, randomized, placebo-controlled trials. The ASCO and AUA deleted the use of 5-ARIs for prostate cancer chemoprevention from the main "Clinical Guidelines" on the AUA homepage, after the FDA denied a supplemental New Drug Application for dutasteride for prostate cancer chemoprevention (Table 2) [31,32].

The use of 5-ARIs is still disputed based on its risk for cancer development. Several investigators have reported the use of 5-ARIs to delay cancer progression. In The Reduction by Dutasteride of Clinical Progression Events in Expectant Management of Prostate Cancer Trial, a randomized, double-blind, placebo-controlled study, the use of dutasteride and active surveillance of low-risk prostate cancer delayed prostate cancer progression [33]. After 3 years, 38% (54/147) of the dutasteride group had pathological or therapeutic progression of cancer, whereas 45% (70/155) of the control group had progressed to prostate cancer (hazard ratio, 0.62; 95% CI, 0.43 to 0.89; log-rank  $p=0.009$ ). Schroder et al. [34] reported that dutasteride retarded the biochemical progression of cancer after radical prostatectomy or radiation therapy. In a multicenter, randomized, double-blind, placebo-controlled trial, 294 men with biochemical failure after radical therapy for localized prostate cancer were randomized for treatment

with 0.5 mg dutasteride or placebo for 2 years. The primary endpoint was PSA doubling time, and the secondary endpoint was disease progression. Eighty-two subjects (57%) in the placebo group and 41 (28%) in the dutasteride group showed PSA doubling, with 456 days (range, 53 to 771 days) and 722 days (range, 22 to 805), respectively, from the randomized start date to the PSA doubling date or the censored date. The relative risk reduction for PSA doubling was 66.1% (95% CI, 5.04 to 7.90). Forty-nine patients (34%) in the placebo group and 25 (17%) in the dutasteride group showed disease progression, which is a relative risk reduction for disease progression of 59% (95% CI, 32.53 to 75.09).

For these reasons, the 5-ARIs debate continues. Nevertheless, 5-ARIs remain the most promising chemopreventive agent for prostate cancer.

### 5-ARIs AND HEMOSPERMIA

Hemospermia or hematospermia is defined as bloody semen. The causes of hemospermia are multifactorial and include inflammation, infection (prostatitis, seminal vesiculitis, or orchitis), BPH, trauma, and an ejaculator duct obstruction [35]. The treatment depends on the cause, but there is insufficient evidence to recommend using 5-ARIs to treat hemospermia. Only Badawy et al. [36] reported a small prospective placebo-controlled trial in 70 men with hemospermia; only 24 men with idiopathic refractory hemospermia were enrolled and randomized into two groups (5 mg finasteride daily for 3 month vs. placebo). The hemospermia remission rates were 66.7% (8/12) in the finasteride group and 25% (3/12) in the placebo group. A large-scale well-designed, randomized, placebo-controlled trial is needed to assess the utility of 5-ARIs for the management of hemospermia.

### 5-ARIs AND HEMATURIA: PREVENTING INTRAOPERATIVE BLEEDING

The AUA panel recommended 5-ARIs for treating hematuria due to an enlarged prostate; hematuria due to any other cause was excluded [10]. Finasteride is considered effective management for refractory hematuria presumably due to prostate bleeding. Although dutasteride does not have a similar level of evidence, the AUA panel suggested that dutasteride is likely to function in a similar fashion.

5-ARIs are not appropriate for reducing bleeding due to transurethral resection of the prostate (TURP) [10]. However, several clinical researchers have reported positive effects of 5-ARIs for reducing bleeding. A randomized controlled study conducted by Ozdal et al. [37] suggested that 4 weeks of finasteride treatment before TURP reduces total blood loss and bleeding per gram of resected prostate. Other nonrandomized trials have found similar results [38,39]. Conversely, several studies have reported no significant reduction of blood loss after the use of 5-ARIs. Investigators who conducted prospective randomized trials in Denmark concluded that finasteride does not reduce

**TABLE 3.** Role of 5 $\alpha$ -reductase inhibitors in guideline of AUA and EAU

|                                       | AUA [10]         | EAU [11] |
|---------------------------------------|------------------|----------|
| Benign prostatic hyperplasia          |                  |          |
| Monotherapy                           | O <sup>a</sup>   | O        |
| Combined therapy with alpha-blocker   | O                | O        |
| Hematuria due to an enlarged prostate | O                | (-)      |
| Prevention of intraoperative bleeding | x <sup>b</sup>   | O        |
| Hemospermia                           | (-) <sup>c</sup> | (-)      |
| Prostate cancer chemoprevention       | x                | (-)      |

AUA, American Urology Association; EAU, European Association of Urology.

<sup>a</sup>:Recommended. <sup>b</sup>:Not recommended. <sup>c</sup>:Not comment.

perioperative bleeding during TURP [40]. Additionally, Hahn et al. [41], who conducted a double-blind, randomized, placebo-controlled, multicenter study, reported that pretreatment with 0.5 mg dutasteride for 2 or 4 weeks before TURP did not reduce blood loss during the surgery. The AUA panel concluded that there is unsatisfactory evidence to propose 5-ARIs pretreatment for preventing intraoperative or postoperative prostate bleeding [10]. However, the EAU panel considered that 5-ARIs (finasteride) may diminish bleeding during transurethral prostate surgery [11,42]. Table 3 summarized the role of 5-ARIs in guideline of AUA and EAU.

### CONCLUSIONS

5-ARIs have been developed for treating BPH, and long-term use of finasteride (20 years) and dutasteride (10 years) has shown their safety and usefulness for moderate to severe BPH with LUTS. 5-ARIs consistently induce a decrease in prostate size and improve the urine flow rate and LUTS. Many investigators are currently studying the further development of 5-ARIs to prevent prostate cancer, although 5ARIs have not yet been approved for preventing prostate cancer. The treatment of hemospermia and the reduction of prostate-related and intraoperative bleeding are optional uses for 5-ARIs.

### CONFLICTS OF INTEREST

The authors have no conflicts to disclose.

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