

5-Alpha Reductase Inhibitors in Men With an Enlarged Prostate: An Evaluation of Outcomes and Therapeutic Alternatives

Michael Naslund, MD, MBA; Timothy S. Regan, BPharm, RPh, CPh;
Christine Ong, PharmD, MBA, BS; and Susan L. Hogue, PharmD, MPH

Abstract

This article presents background information and highlights key findings from a managed care perspective related to enlarged prostate (EP) in Medicare-eligible patients. This article does not provide a comprehensive review of EP but instead attempts to increase the current understanding of EP through discussion of its prevalence in men aged ≥ 65 years, its associated economic burden, and some available treatment options.

This supplement includes 3 additional articles, all of which present data from a naturalistic, managed care setting. The article by Fenter et al assesses differences in outcomes between elderly EP patients treated with finasteride and those treated with dutasteride in relation to the risks of acute urinary retention and prostate-related surgery. Issa et al conduct a comparative analysis of the combined use of alpha-blockers and 5-alpha reductase inhibitors to treat EP. The final article compares medical costs incurred within the first year of initiating treatment for EP patients receiving finasteride versus dutasteride.

This supplement is intended to assist managed care formulary decision makers in evaluating key clinical and economic data that differentiate dutasteride and finasteride within the Medicare-aged population. Although the information presented is not designed to illustrate the superiority of one product over the other, it answers important questions in relation to treating EP in elderly men and raises substantial issues beyond medication costs.

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**For author information and disclosures,
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Benign prostatic hyperplasia (BPH), which leads to an enlarged prostate (EP), is the fourth most prevalent health-care condition in older men.¹ Prostate enlargement is an age-dependent, progressive condition that affects more than 50% of men aged ≥ 50 years and close to 90% of men by 80 years of age.^{2,4} EP can cause bothersome lower urinary tract symptoms (LUTS), which can significantly affect a patient's quality of life. EP tends to progress with advancing age and, left untreated, can result in the development of complications such as acute urinary retention (AUR) or the need for prostate surgery. It has been estimated that EP accounts for 4.5 million outpatient visits and \$1.1 billion in total direct medical services costs annually.⁵ The burden of EP is expected to grow as the population of men aged ≥ 65 years increases from 17 million in 2010 to approximately 30 million by 2030.⁶ Because of the significant impact of EP on aging males and the potential for increased treatment costs, optimizing the management of EP is important to reduce the clinical and economic burden of this condition.

The clinical and economic implications of EP underscore the necessity of assessing various treatment options and their corresponding treatment-related outcomes. For healthcare providers and payers, determining the safest, most efficacious, and cost-effective treatments for EP is important. Although there is a good understanding of the pharmacology and clinical effects of 5-alpha reductase inhibitors (5ARIs),^{7,8} there are few studies that have addressed treatment outcome differences between the 2 available 5ARI agents on the market: dutasteride and finasteride.⁹⁻¹⁴ In this supplement, we will focus on the therapeutic role of 5ARIs in EP and analyze available data on outcome differences between dutasteride and finasteride in elderly men.

EP Disease Overview

BPH, also known as EP, is a progressive disease that can cause bothersome urinary symptoms and urinary obstruction. Patients diagnosed with the disease often experience nonspecific LUTS, such as a decreased urinary stream, incomplete bladder emptying, urinary frequency and hesitancy, and straining to void—all of which can impair a patient's quality of life.¹⁵ The landmark epidemiologic study demonstrating the clinical progression of EP, the Olmsted County Study, reported a 2% reduction per year in peak urinary flow rates in men¹⁶

and a mean increase of 1.6% in prostate volume per year.¹⁷ Symptom severity progresses with age, including greater increases in men in their 60s compared with men in their 40s.¹⁸ The prevalence of moderate to severe LUTS, defined by the American Urological Association Symptom Index (AUA-SI) as a score of ≥ 8 , has been reported to approach 50% by 80 years of age.¹⁸

One of the most significant complications of disease progression is the onset of AUR, resulting in the inability to urinate. Although the exact etiology of AUR is incompletely understood, prostate infarction has been noted to be a common cause.¹⁹ The occurrence of AUR is a major event that presents acutely and requires emergency catheterization in most instances. In men experiencing LUTS, Marberger et al showed that patients with prostate volume >40 mL and serum prostate-specific antigen (PSA) over 1.4 ng/mL were at 3 to 8 times higher risk for AUR.²⁰ Among those diagnosed with EP, prominent predictors for the development of AUR include subjective ratings of symptom severity, including symptom severity scores ≥ 8 (symptom scale: mild, 0-7; moderate or severe, >7) and each of the 7 LUTS measures compiled by the AUA-SI.²¹⁻²³ Among men with moderate to severe urinary symptoms, the risk of AUR was 3 times higher than in men with no or mild symptoms.²⁴ The general risk for AUR with advancing age has a reported incidence of 0.5% to 2.5% per year.¹⁹ This risk progressively increases with advancing age. Men with moderate symptoms in their 50s, 60s, and 70s will have incremental risks of 20%, 23%, and 30%, respectively, by 80 years of age. The risk for AUR is even higher among patients already diagnosed with EP.¹⁹ In a large retrospective analysis of a managed care database, the likelihood of experiencing a clinical event such as AUR and/or surgery within 1 year of medical treatment initiation for EP was about 19% in men ≥ 50 years of age.²⁵

The majority of patients suffering from AUR who are unable to void after catheter removal will eventually undergo surgery.¹⁹ In patients with spontaneous AUR, as many as 85% will undergo prostate-related surgery within 1 to 2 years of follow-up.^{26,27} AUR-related surgeries have been correlated with significant morbidity and mortality. In a prospective study by Pickard et al, 1242 patients who had prostate surgery after AUR had a postoper-

ative excess risk of death at 30 days (relative risk [RR], 26.6; confidence interval [CI], 3.5-204.5) and at 90 days (RR, 4.4; CI, 2.5-7.6). Furthermore, prostate-related surgery caused by AUR has been reported to have an increased risk of intra- and perioperative complications.²⁸ In a recent study evaluating EP-related treatment outcomes in a managed care setting (N = 77,040), more than 20% of patients experienced at least 1 adverse event after an EP-related surgical intervention.²⁹ One of the most costly observations noted in the study was the need for another surgical procedure within 6 months in approximately 18% of patients. The total cost for surgery, including management of related complications, was estimated at approximately \$8 million annually, ranging from approximately \$5600 to \$10,400 per patient treated.²⁹ It is important to note that this study also had a relatively young male population with a mean age of 58.1 years (range, 56-64 years). In accounting for natural age-dependent disease progression, the clinical and cost implications among Medicare-aged patients may be greater. AUR and prostate-related surgery represent the most significant risks of EP progression in the elderly population. Lowering progression risk would have significant impact in reducing costs as well as decreasing the morbidity and mortality from EP.

EP Treatment

The basis of current pharmacologic treatments for EP targets the static and dynamic pathophysiologic effects of the disease. Enlargement of the prostate is primarily mediated by the stimulatory effects of the androgen known as dihydrotestosterone (DHT). BPH is typically characterized by an increase in total prostate volume (>30 mL) and an increase in transition zone volume. The static effects arise from the mechanical obstruction of the bladder outlet because of the proliferative growth of the prostatic tissue. The dynamic component of EP pertains to increased smooth muscle tone in the bladder neck and prostatic urethra as men age. This process accounts for up to 40% of the obstruction seen in EP.³⁰ Treating both the static and dynamic aspects of EP may therefore offer the best opportunity to comprehensively treat the disease. Alpha-adrenergic antagonists (alpha-blockers) have been shown to reduce smooth muscle tone, whereas 5ARIs have been shown to inhibit prostatic growth and

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decrease prostate volume.^{31,32} It should be noted that only 5ARIs have been shown to reduce the incidence of AUR and the risk for prostate-related surgery.^{8,31,33}

Historically, the primary disease management approach for EP has been symptom driven. In primary care practice, alpha-blockers are used extensively, with up to 85% of patients initiated on these agents to relieve symptoms.²⁵ With greater understanding of the progressive nature of BPH, disease modification has become a vital component of medical management in patients who are at increased risk for progression. Several treatment options exist for managing EP, including watchful waiting, pharmacologic treatment, and surgery. Treatment goals of EP aim to relieve LUTS and prevent disease progression typified by worsening LUTS, a decrease in urinary flow, an increase in prostate size, and related complications such as AUR and need for surgery.³⁴

5ARIs have been shown to modify the disease and reduce EP-related complications. 5ARIs work by lowering serum levels of DHT, thereby inhibiting prostatic growth.³⁵ Dutasteride and finasteride are the two 5ARIs currently available in the US market and are recommended by the American Urological Association in patients with EP.²² Their short- and long-term (ie, ≥ 4 years) efficacy and safety profiles have been demonstrated in numerous clinical studies.^{7,8,31,32,36} Patients treated with 5ARIs have shown significant improvement in symptomatic control of EP secondary to prostate size reduction. These agents effectively decrease prostate volume by 20% to 26%, thereby relieving the urinary symptoms caused by the static component of the disease.^{7,31}

The ability of 5ARIs to decrease prostatic size has been correlated with the risk reductions in AUR and prostate-related surgeries.^{7,8,33} Pivotal studies for 5ARIs have shown significant risk reductions in AUR (finasteride, 57%; dutasteride, 48%) and prostate-related surgery (finasteride, 51%; dutasteride, 57%) versus placebo.^{7,8} Treatment with alpha-blockers does not significantly lower the risk of progression to AUR or prostate surgery. Patients treated with alpha-blockers are significantly more likely to develop AUR (hazard ratio [HR], 2.35) or undergo prostate surgery (HR, 1.52-1.78) than patients treated with 5ARIs.^{37,38} Moreover, a study of a managed care national claims database reported a 74% ($P = .0088$) higher likelihood for AUR and an 80% ($P = .0576$)

higher likelihood for surgery in patients treated with alpha-blockers compared with patients treated with 5ARIs.³⁶

It is common clinical practice to initially prescribe alpha-blockers concurrently with 5ARIs for rapid symptom relief in the early part of the treatment phase.¹⁴ Because the subsequent effect of reducing prostate volume through hormonal inhibition is a process that takes time, the clinical benefits from 5ARIs are typically not seen until after a few months of therapy.^{7,31} Several studies have evaluated the efficacy of combination therapy using 5ARIs with alpha-blockers. In a landmark study, the Medical Therapy of Prostatic Symptoms (MTOPS) trial of 3047 men aged ≥ 50 years, the overall progression of EP and treatment outcomes of 5ARIs \pm alpha-blockers were evaluated over a 4-year period. Patients were treated with finasteride, doxazosin, a combination of both, or received placebo. Treatment with finasteride alone and in combination with doxazosin resulted in 68% ($P = .002$) and 81% ($P < .001$) decreases, respectively, in the risk of AUR compared with placebo. In contrast, doxazosin alone did not significantly reduce the cumulative incidence of AUR compared with placebo ($P = .23$). Patients who received finasteride had a median prostate volume reduction of 24% compared with those who received placebo or doxazosin.³¹

In a multinational, multicenter study involving 327 men with EP, patients received 24 weeks of combination therapy with dutasteride and tamsulosin followed by 12 weeks of either continued combination therapy or monotherapy with dutasteride and placebo.³² At week 30, 77% of patients withdrawn from alpha-blocker treatment reported feeling their urinary symptoms were the same or better than at week 24 compared with 91% of patients who remained on combination therapy.

Dutasteride vs Finasteride

The need to analyze any clinical or economic outcome differences between finasteride and dutasteride is important to clinicians and managed care decision makers. This issue is potentially relevant to clinicians when dealing with patients at high risk for progression and to managed care decision makers given that finasteride has become available in a generic version that is less costly than dutasteride. Although there are limited data directly

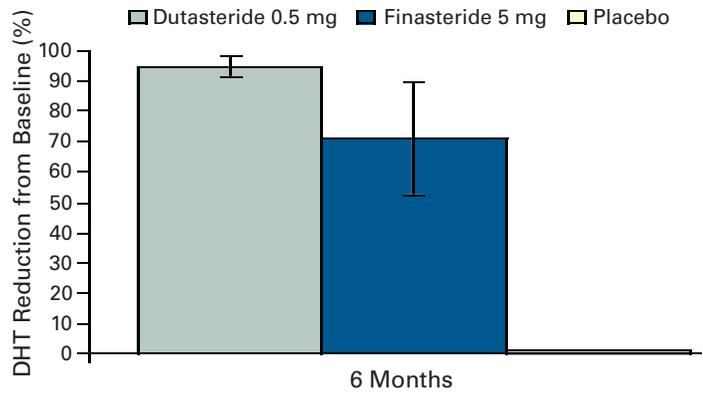
comparing dutasteride and finasteride, several studies suggest potential outcome differences between these 2 medications.

Pharmacologically, finasteride and dutasteride have different selectivity for inhibition of the 2 5ARI isoenzymes that are responsible for the conversion of testosterone to DHT. Finasteride inhibits the type 2 isoenzyme. Dutasteride inhibits both the conversion of type 1 and type 2 isoenzymes.^{39,40} Since DHT plays a critical role in the pathophysiologic development and progression of EP, greater suppression of DHT may provide better treatment benefits. In a placebo-controlled, comparative study investigating DHT suppression with finasteride and dutasteride in men with EP, dutasteride-treated men had greater suppression of DHT over a 6-month period compared with finasteride and placebo ($P < .001$). Dutasteride reduced serum DHT levels by approximately 94% from baseline compared with a 70% reduction with finasteride (Figure).¹⁰

In particular, greater suppression of DHT may correlate with greater efficacy in alleviating urinary symptoms. In a prospective, 3-month, open-label study evaluating the onset of symptomatic relief for dutasteride versus finasteride, Hagerly et al demonstrated significant improvements in AUA-SI score associated with dutasteride-treated patients compared with finasteride-treated patients (43% vs 23%, $P < .001$). Higher AUA-SI improvements of 1 point (30% vs 18%) and 2 points (12% vs 4%) were observed with dutasteride compared with finasteride during the first 3 months of therapy.⁹ The open-label, short duration of the study, however, does not provide firm conclusions on differences between the 2 agents. It does suggest that greater DHT suppression with dutasteride may lead to more rapid symptomatic relief in men with symptomatic BPH.

In another 12-month, randomized, comparative study, the Enlarged Prostate International Comparator Study (EPICS), dutasteride (0.5 mg) and finasteride (5 mg) were compared among men with EP aged >50 years.¹¹ The goal of the study was to determine any differences in the clinical outcomes between the 2 agents. After 1 year of treatment, prostate volume reductions from baseline were similar in both groups at 27%. Improvements in AUA-SI scores (6.2 vs 5.8) and peak urinary flow rate (Q_{max} , 2.1 vs 1.8 mL/s) were greater for dutasteride than finasteride but were not

Figure. Percentage of DHT Suppression at 6 Months in Men Treated With Dutasteride, Finasteride, and Placebo



DHT indicates dihydrotestosterone.

Source: Clark RV, et al. *J Clin Endocrinol Metab.* 2004;89(5):2179-2184.

statistically significant. Dutasteride also had a greater reduction in postvoid residual volume compared with finasteride (21.8% vs 16.1%),¹¹ although this difference was also not statistically significant.

The above-mentioned studies⁹⁻¹¹ are the only identified head-to-head trials comparing dutasteride with finasteride. Studies evaluating EP treatment outcomes in a managed care setting are also limited. Two studies have retrospectively evaluated EP clinical outcomes in a managed care setting. Data from the PharMetrics Integrated Medical and Pharmaceutical Database (PIMPD) from 1999 to 2005, covering 45 million patients and representing 85 managed care plans, were obtained and analyzed. In the first study, the rates of AUR and surgery in men with EP aged ≥ 50 years were determined for dutasteride and finasteride. A total of 1992 men were included in the analysis. In the study, dutasteride-treated patients experienced significantly less AUR compared with those on finasteride (5.3% vs 8.3%; $P = .021$). The likelihood of AUR occurrence with dutasteride was 49.1% ($P = .027$) lower than with finasteride. The data also reported a trend for lower prostate-related surgeries with dutasteride than with finasteride (1.4% vs 3.4%, respectively), although the difference was not statistically significant.¹²

Using the same database, a second study evaluated the rate of alpha-blocker discontinuation among dutasteride- and finasteride-treated patients. Since alpha-blocker discontinuation is thought to indicate symptomatic stabilization with 5ARI,

higher rates of withdrawal may correlate with greater symptomatic improvement with 5ARIs. In this study by Naslund et al, the overall rate of alpha-blocker discontinuation in a given year was approximately 20% higher with dutasteride-treated patients compared with finasteride.¹⁴ Although these studies are limited by their retrospective nature, the lower AUR rates, lower predisposition to prostate surgery, and earlier alpha-blocker withdrawal suggest that there may be clinically relevant advantages of increased DHT suppression associated with dutasteride.¹⁰

Implications for Managed Care

5ARIs have been shown to decrease EP disease progression. Given that the risk for disease progression increases with advancing age, complications from EP such as AUR and prostate-related surgery create a significant burden for aging men, particularly men ≥ 65 years. Understanding differences in clinical outcomes between dutasteride and finasteride may help guide managed care organizations and healthcare providers in selecting the most appropriate treatments for men with EP.

In this supplement, we will focus on the therapeutic role of 5ARIs in EP and the recent data suggesting outcome differences between finasteride and dutasteride in men aged ≥ 65 years. Specifically, we will assess the rate of AUR and prostatic surgical events in this high-risk population within a managed care environment. In addition, an assessment of the rate of alpha-blocker discontinuation associated with the use of each agent (when used in combination therapy) will be presented. Finally, an analysis of the economic differences between dutasteride and finasteride based on treatment outcomes will be discussed to further highlight the distinctions between the 2 agents.

Author Affiliations: (MN) Professor of Urology, University of Maryland School of Medicine, Director, Maryland Prostate Center, Baltimore, MD; (TSR) Executive Director, Xcenda, Palm Harbor, FL; (CO) Assistant Director, Xcenda, Palm Harbor, FL; (SLH) Director, Global Health Outcomes, GlaxoSmithKline, Research Triangle Park, NC.

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Address Correspondence to: Michael Naslund, MD, Director, Maryland Prostate Center, 419 W Redwood Street, Ste 320, Baltimore, MD 21201. E-mail: mnaslund@smail.umaryland.edu.

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