Clinical and Economic Outcomes in Patients Treated for Enlarged Prostate

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Abstract

Background: Benign prostatic hyperplasia (BPH), also referred to as enlarged prostate, is a highly prevalent condition in men aged 50 years or older. It is a progressive disease with significant morbidity from complications.

Objective: The purpose of this study was to assess the likelihood of having acute urinary retention (AUR) and prostate surgery after initiating therapy with an alpha blocker or 5-alpha reductase inhibitor in a real-world setting.

Study Design: This was a retrospective study of patients who were treated for BPH between January 1, 2003, and November 30, 2003, in a large, national managed care claims database. Outcomes measures of interest included rate of AUR, prostate surgery, and surgical complications.

Results: There were 2959 patient records with a diagnosis of BPH who were taking prostate medications in the database. Eighty-nine percent of patients were receiving alpha blocker therapy, whereas 11% of patients were receiving 5-alpha reductase inhibitors. Overall, the 1-year AUR rate was 12.1%, and the prostate surgery rate was 5.8%. Patients who initiated 5-alpha reductase inhibitor therapy only were less likely to have AUR or surgery compared with patients taking alpha blockers, although surgical differences did not reach statistical significance ($P = .0576$). Overall, the surgical complication rate was 49.4%, and the rate of AUR within 180 days of prostate surgery was 30.6%. Rates of prostate surgery, AUR, and surgical complications all increased with age.

Conclusion: Patients receiving 5-alpha reductase inhibitor therapy alone were less likely to have AUR compared with patients receiving alpha blockers and tended to be less likely to have surgery ($P = .054$).

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Benign prostatic hyperplasia (BPH), also referred to as enlarged prostate, affects 50% of men between the ages of 51 and 60 and up to 90% of men in their 80s.[1] Characterized by symptoms of urinary frequency, urgency, nocturia, weak stream, hesitancy, and straining, enlarged prostate is responsible for 4.5 million physician office visits per year, resulting in $1.1 billion spent on enlarged prostate–related healthcare costs, excluding the cost of prostate medications.[2] As the US population ages, it is likely that prostate disease will consume increased resources from the healthcare system.

From a patient's perspective, enlarged prostate produces a negative impact on quality of life, interfering with common daily activities, decreasing psychological well-being, and in some instances, causing embarrassment from the urinary symptoms. Although enlarged prostate is more prevalent in older men, men of working age are commonly affected and may have productivity loss due to the condition. Saigal and Joyce found that 10% of patients with enlarged prostate younger than 65 years of age reported some work loss or disability, with an average of 7.3 hours of missed work annually, primarily due to 4.7 hours of outpatient care.[3]

The Urologic Diseases in America Project estimated that approximately 25% of white men 50 to 79 years of age would meet criteria for enlarged prostate–related treatment options.[2] Most men do not seek care for symptomatic BPH until their symptoms have significantly reduced their quality of life.[4] The progressive nature of enlarged prostate eventually results in decreased urinary flow and a higher symptom burden.[5-7] Patients may progress to more serious sequelae, such as acute urinary retention (AUR) and/or the need for prostate surgery.[4,6] Currently, the first-line treatment for BPH is the use of pharmacological agents, with alpha blockers being the most commonly prescribed drug

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Table 1. Inclusion and Exclusion *ICD-9* Codes

Inclusion *ICD-9* codes	
Enlarged prostate	222.2, 600
Exclusion *ICD-9* codes	
Prostate cancer	185, 198.82, 233.4, 236.5, 239.5, V10.46
Bladder cancer	188, 198.1, 233.7, 223.3, 236.7, 239.4, V10.51

ICD-9 indicates *International Classification of Diseases, Ninth Revision.*

class.[2,8] Clinical trials have shown that alpha blockers quickly improve the symptoms associated with BPH, however, there is no effect on reducing the likelihood of AUR or the need for surgery. Clinical trials have demonstrated that 5-alpha reductase inhibitors improve symptom control and slow the rate of disease progression, reducing the likelihood of AUR and the need for surgery.[7] However, these results have yet to be reproduced in a real-world practice setting in the United States. Previous naturalistic studies (evaluating outcomes in a real-world setting) conducted in the United Kingdom found that patients initiating 5-alpha reductase inhibitors were less likely to have AUR and surgeries compared with patients taking alpha blockers.[9,10] The present study was designed to assess the incidence of AUR and prostate surgery in men with BPH treated with an alpha blocker or 5-alpha reductase inhibitors in a US managed care setting.

METHODS

Data Source

Medical and pharmacy claims data were abstracted from the Integrated Health Care Information Solutions National Managed Care Benchmark database (Waltham, Mass). This database is nationally representative and includes data from 30 health plans covering more than 25 million lives.

Sample Selection

Patients aged ≥50 years who were taking an alpha blocker (ie, alfuzosin, doxazosin, tamsulosin, or terazosin) and/or a 5-alpha reductase inhibitor (ie, dutasteride or finasteride, excluding dosage forms for male pattern baldness) for BPH between January 1, 2003, and November 30, 2003, were identified in the database. The index date for each patient was the date of the first prostate medication prescription within this time frame. Patients who started both an alpha blocker and a 5-alpha reductase inhibitor within a 10-day period were considered to be receiving combination therapy (alpha blocker + 5-alpha reductase inhibitor) and were excluded from the analyses. All patients were required to have a coded diagnosis for BPH in a 6-month period before or after their index date. Diagnoses were determined using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes, as shown in **Table 1**. Patients were required to be continuously eligible for medical and pharmacy services 6 months before and at least 12 months after their index date, with no evidence of drug therapy or surgery for enlarged prostate in the 6-month period before their index date. Patients were excluded if they had an *ICD-9-CM* code for prostate or bladder cancer for the 18-month eligible period.

Outcomes and Adverse Events

Patients meeting all selection criteria were followed for 12 months to assess clinical outcomes. Patients who had prostate surgery were followed for an additional 6 months after the surgical procedure to evaluate the incidence of surgery complications, which included AUR, urinary tract infection (UTI), erectile dysfunction, bladder dysfunction, urinary incontinence, and additional prostate surgery. UTIs were deemed surgery related when the UTI occurred within 30 days of prostate surgery, whereas other outcomes were deemed surgery related when they occurred within 6 months of surgery. **Table 2** presents the *ICD-9* codes used for surgical adverse events. **Table 3** presents the *Current Procedural Terminology 4* procedure codes for prostate surgeries.

Comorbidity Assessment

To assess comorbidities in the population with enlarged prostate, the Charlson index, with Dartmouth-Manitoba and Deyo modification, was utilized.[11,12] This index contains 19 categories of comorbidities primarily defined by *ICD-9-CM* diagnosis codes with higher numbers representing a higher burden of comorbidity. Charlson index scores for this

study (range 0-14) were derived from the presence of various *ICD-9-CM* codes in the 6-month period before each patient's index date. Additional summary variables used to assess comorbidities in the 6-month period before each patient's index date were a unique count of disease states beyond those used to calculate the Charlson index, the total number of prescriptions received, and a unique count of prescription drug categories received.

Analysis of Outcomes

Univariate analyses of frequencies and means were performed to describe the study population. Logistic regression was used to compare outcomes across drug cohorts controlling for age, comorbidities, and non–BPH-related prescriptions.

RESULTS

Population Overview

There were 1 134 491 men ≥50 years of age identified during the 2003 study period. Of this cohort, 13.5% (153 156) had a coded diagnosis of BPH, with only 9091 (5.9%) receiving pharmaceutical treatment. After removing patients not meeting eligibility criteria (5320), patients with prostate cancer (1214), patients with bladder cancer (311), patients with evidence of receiving combination therapy (127), and those with surgery before index (156), 2959 patients remained. (Each criterion was not mutually exclusive.)

Demographics

There were 2959 men ≥50 years of age identified from the database who met the study criteria. The mean age of the sample was 62.6 years, with a range of 50 to 79 years (**Table 4**). Most patients (88.9%) initiated an alpha blocker alone, although 11.1% initiated 5-alpha reductase inhibitor therapy. In addition to enlarged prostate–related prescriptions, these men filled an average of 10.5 prescriptions from 4.1 therapeutic categories during the 6-month pre-index period. In terms of comorbidities, the average Charlson comorbidity score was 0.9, indicating a low level of comorbidity associated with mortality. These men, however, had an average of 8.4 different nonenlarged prostate–related diagnoses over 6 months. The most common diagnoses for long-term conditions were hypertension (67%), osteoarthritis (37%), and coronary artery disease (37%).

Patients who initiated alpha blocker therapy were younger and had a lower number of nonenlarged prostate–related diagnoses compared with patients taking 5-alpha reductase inhibitors; however, other background covariates were statistically similar.

Table 2. *ICD-9* Codes for Adverse Outcomes and Surgical Complications

Acute urinary retention	788.2 (excluding 788.21), 599.6
Urinary tract infection	599.0
Erectile dysfunction	607.84
Bladder dysfunction	596.59, 596.0, 598.2, 598.9
Incontinence	788.30, 788.31, 788.32, 788.38, 788.37

ICD-9 indicates *International Classification of Diseases, Ninth Revision.*

Acute Urinary Retention and Surgery

The 1-year AUR rate (not associated with prostate surgery) was 12.1% in the study cohort, whereas the overall prostate-related surgery rate was 5.8%. Of all prostate surgeries for enlarged prostate, 46.5% were for transurethral electrosurgical resection of the prostate, 28.3% were for transurethral microwave thermotherapy, 10% were for transurethral needle ablation, and the remaining 15.2% were for other prostate surgical procedures.

Rates of AUR and surgeries tended to increase as patients aged, with AUR rates

Table 3. *CPT* Codes for Prostate Surgeries

Transurethral incision of prostate	52450
Transurethral electrosurgical resection of the prostate	52601
Transurethral resection of the prostate	52612, 52614, 52620, 52640
Laser coagulation	52647
Laser vaporization	52648
Prostatectomy	55801, 55821, 55831
Transurethral microwave thermotherapy	53850
Transurethral needle ablation	53852
Transurethral water-induced thermotherapy	53853

CPT indicates *Current Procedural Terminology.*

Table 4. Demographic Characteristics

	Alpha blocker (n = 2630)	5-alpha reductase inhibitor (n = 329)	Overall (n = 2959)
Age by age groups			
Mean age, years*	62.4	64.7	62.6
50-59			1257 (40.7%)
60-65			882 (28.6%)
≥66			947 (30.7%)
Charlson, mean score (SD)†	0.9 (1.6)	0.9 (1.7)	0.9 (1.6)
Number of prescriptions, mean (SD)†	10.4 (11.4)	11.2 (10.3)	10.5 (11.3)
Number of prescription categories, mean (SD)†	4.1 (3.5)	4.3 (3.4)	4.1 (3.5)
Number of unique diagnoses, mean (SD)*†	8.3 (6.2)	9.0 (6.0)	8.4 (6.2)
Type of health plan			
HMO	38.4%	40.7%	38.6%
PPO	45.4%	44.7%	45.4%
Other	16.2%	14.6%	16.0%

*P <.05 when comparing alpha blockers to 5-alpha reductase inhibitors.
†Assessed over 6 months before the prescription index date.
SD indicates standard deviation; HMO, health maintenance organization; PPO, preferred provider organization.

being 10.7% in patients 50 to 59 years of age, 10.6% in patients 60 to 65 years of age, and 15.3% in patients >65 years of age. For surgeries, rates were 4.7% in patients 50 to 59 years of age, 5.85% in patients 60 to 65 years of age, and 7.1% in patients >65 years of age.

Rates of AUR and surgery for alpha blockers and 5-alpha reductase inhibitors are presented in **Figures 1** and **2**. Patients who initiated 5-alpha reductase inhibitor therapy alone were less likely to experience AUR (8.2%) or surgery (3.7%) compared with patients taking alpha blockers alone (12.6% and 6.01%, respectively). After accounting for background covariates, patients taking alpha blockers were 74.0% more likely (P = .0088) to have AUR and 80.6% more likely (P = .0576) to have surgery compared with patients receiving 5-alpha reductase inhibitors alone.

Surgical Complication

Of men having surgery, 49.4% had at least 1 surgical complication. AUR occurred in 30.6% of men during the first 6 months after surgery, making AUR the most common prostate surgery complication. Of these AURs, 51.9% occurred within 7 days of the surgery. In addition, UTI occurred in 7.1% of post-surgical patients within 30 days of surgery (**Figure 3**). Surgical complication rates also increased with age to 51.7% in patients 50 to 59 years of age, 61.2% in patients 60 to 65 years of age, and 63.5% in patients >65 years of age.

DISCUSSION

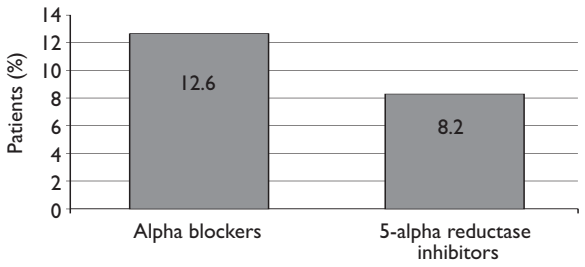
The purpose of this study was to assess the likelihood of having AUR and prostate surgery after initiating therapy with an alpha blocker or 5-alpha reductase inhibitor in a real-world setting. This study found that patients treated with 5-alpha reductase inhibitors alone were less likely to have AUR or surgery than patients taking alpha blockers alone; however, surgical differences did not reach statistical significance (P = .0576). Trends observed between 5-alpha reductase inhibitors and alpha blocker therapy are critical, because this is the first naturalistic study in the United States to assess differences between these 2 classes. The Medical Therapy of Prostatic Symptoms (MTOPS) study demonstrated that the risks of AUR and the need for invasive therapy were significantly reduced by long-term treatment with 5-alpha reductase inhibitors.[7] Alpha blockers delayed the onset of AUR, but did not reduce the overall incidence. Taken with the results of MTOPS, this study suggests that the rates of AUR and surgery are reduced in patients treated with 5-alpha reductase inhibitors.

Additionally, the rates of AUR and surgery in this study increased with age, highlighting the progressive nature of BPH. The rate of AUR (12.1% without surgery and 30.6% with surgery) was higher than expected in this study compared with clinical trials. It was initially thought that rates of AUR and surgery would be higher in this study than in other epidemiologic studies because treated patients were analyzed. Clinical practice guidelines recommend initiation of BPH treatment when patients develop bothersome symptoms, which may indicate more advanced disease.[13] Because this study selected patients who initiated treatment, these patients may be more likely to have advanced disease and therefore be more likely to experience significant clinical events than patients who are undergoing watchful waiting, the primary focus in previous studies. Although other studies indicated surgical rates of 8.7% and 15.2%,[9,10] higher than the 5.8% rates shown in this study, the rate of AUR for Boyle was only 3.5%, similar to rates seen in clinical trials.[14] Differences in the real-world AUR rates of Boyle et al[9] and this study may be due to the criteria used to identify AURs, however this information was not fully specified in Boyle's study and cannot be determined.

AUR is an important clinical outcome of enlarged prostate because it is a manifestation of persistent bladder obstruction, a common symptom of enlarged prostate. In a recent review, Tubaro and colleagues assessed evidence suggesting that bladder obstruction can lead to bladder decompensation and permanent bladder damage.[15] The authors argued that symptomatic patients with enlarged prostate should be treated, and that early treatment may preserve bladder function. The ability of 5-alpha reductase inhibitors to reduce the risk of AUR by means of reducing prostate volume represents an important treatment strategy for patients with enlarged prostate.

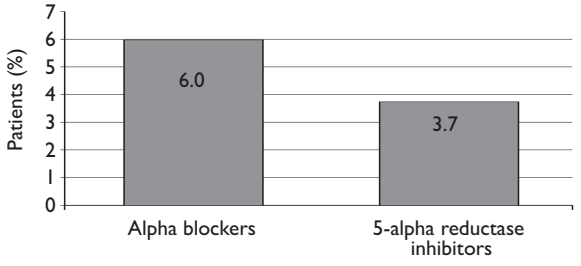
Even with the favorable results of this study, the analysis has several limitations. The Integrated Health Care Information Solutions database contains medical and pharmacy claims data for a large managed care population across a wide geographic range; thus, the generalizability of the study

Figure 1. AUR Rates Across Medication Cohorts



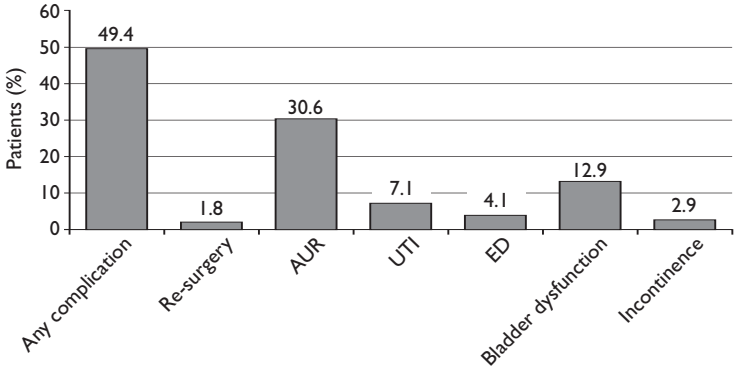
After controlling for age, comorbidities, and additional pharmaceutical use, $P = .0088$.
AUR indicates acute urinary retention.

Figure 2. Prostate Surgery Rates Across Medication Cohorts



After controlling for age, comorbidities, and additional pharmaceutical use, $P = .0576$.

Figure 3. Surgical Complication Rates of Men ≥50 Years of Age



Patients were tracked for 6 months after surgery for all complications except for UTI, which was tracked for 30 days post-surgery. Of AUR, 51.9% occurred within 7 days.
AUR indicates acute urinary retention; UTI, urinary tract infection; ED, erectile dysfunction.

results is good, but not without drawbacks. The database primarily contains claims data generated by health plan members who are primarily working-age adults and their dependents. Therefore, the study results are most generalizable among managed care members and employees and less so in other settings.

Rates presented in this report were based on a cross-sectional analysis, and the method cannot capture a longitudinal cohort effect. The study design is unable to ascertain if men in various age groups had different unmeasured risks of adverse clinical outcomes due to potential unknown generation effects. However, the increasing trend of AUR and prostate surgery with age is consistent with that found in the literature.[2,6,16]

The use of claims data for research carries the intrinsic weakness that only information required for billing is available for the analysis. Baseline demographic information is limited, and clinical characteristics (such as symptom scores, urinary flow rate, and prostate-specific antigen levels) are not available. For the purpose of our analysis, however, the claims data provided sufficient information to observe the event rates and age trends.

Despite these discussed limitations, this study describes rates of AUR, surgeries, and surgical complications. Future studies should further evaluate the economic benefit of initiating treatment with 5-alpha reductase inhibitor therapy and assess the value of combination therapy, while adequately reducing issues with selection bias. Future studies should also assess the place of BPH in the entire spectrum of health conditions in middle-aged and elderly men.

CONCLUSION

This study supports previous clinical trials and naturalistic research documenting the value of 5-alpha reductase inhibitors in reducing the likelihood of AUR compared with alpha blocker treatment. Patients initiating 5-alpha reductase inhibitor therapy were less likely to have AUR and tended to be less likely to have prostate surgery than patients initiating alpha blockers.

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