

A Large Retrospective Analysis of Acute Urinary Retention and Prostate-related Surgery in BPH Patients Treated with 5-alpha Reductase Inhibitors: Dutasteride Versus Finasteride

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Abstract

Objective: The purpose of this study was to examine the rates of acute urinary retention (AUR) and surgery after initiating 5-alpha reductase inhibitor (5ARI) therapy and to compare the 2 currently available 5ARIs, dutasteride and finasteride, in a real-world, managed care setting. This study constitutes the first direct comparison of therapeutic outcome between a mono 5ARI (finasteride) and a dual 5ARI (dutasteride).

Methods: This is a retrospective descriptive and comparative analysis of the rates of AUR and prostate surgery in patients with benign prostatic hyperplasia (BPH) treated with 5ARI therapy, either dutasteride or finasteride. Data were obtained from the PharMetrics Integrated Medical and Pharmaceutical Database (PIMPD) (Watertown, Mass) during a 6-year period. The PIMPD is a large national healthcare database that represents a total of 85 managed health plans and covers more than 45 million patients. The data analysis included all patients aged 50 years or older diagnosed with BPH who were treated with 5ARIs (dutasteride 0.5 mg/day or finasteride 5 mg/day) for up to 12 months during the 6-year period of January 1, 1999, to March 1, 2005. Patients meeting the selection criteria were evaluated for a total of 12 months with regard to the likelihood of experiencing AUR or prostate-related surgery.

Results: After 5 months of 5ARI therapy, the rate of AUR during months 5 to 12 was found to be significantly lower in the dutasteride group compared with the finasteride group (5.3% vs 8.3%). After controlling for background covariates, dutasteride-treated patients were 49.1% less likely to experience AUR than patients treated with finasteride ($P = .0207$). Patients treated with dutasteride were also less likely to undergo prostate-related surgery, with 1.4% of dutasteride-treated patients and 3.4% of patients receiving finasteride undergoing surgery; differences in surgery rates, however, were not statistically significant ($P = .0745$), even after controlling for background covariates.

Conclusion: Although the 2 drugs, dutasteride and finasteride, belong to the same category of 5ARIs, this large retrospective multivariate analysis potentially indicates differences in therapeutic outcomes. In this study, patients treated with dutasteride were less likely to experience AUR and demonstrated a trend toward being less likely to experience surgery than patients treated with finasteride.

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Enlarged prostate (EP), also known as benign prostatic hyperplasia (BPH), is the fourth most commonly diagnosed disorder in men 50 years of age and older,¹ accounting for almost 4.5 million outpatient visits and \$1.1 billion in total medical services costs each year, exclusive of outpatient pharmaceuticals.¹⁻³ EP can cause bothersome urinary symptoms and may progress to acute urinary retention (AUR) and other complications requiring BPH-related surgery.^{4,5} Patients with an EP and lower urinary tract symptoms are commonly treated with alpha blockers, which are considered purely symptom-modifying treatment (ie, they do not address or impact the underlying disease process of EP). Recently, more awareness of the need to treat the disease process has led to an increase in the utilization of disease-modifying therapy, namely 5-alpha reductase inhibitors (5ARIs). 5ARIs decrease a patient's likelihood of developing AUR and the need for prostate-related surgery, while also providing long-term symptom control.⁶

Dutasteride and finasteride, the only 5ARIs currently available in the United States, work by blocking the 5-alpha reductase enzyme, which converts testosterone to dihydrotestosterone (DHT), the primary androgen responsible for prostatic growth.⁶ There are 2 types (isozymes) of 5-alpha reductase isozymes, type 1 and type 2. Finasteride inhibits the type-2 isozyme only, resulting in what is considered a partial (approximately 70%) suppression of DHT.⁷ Dutasteride, on the other hand, inhibits both type-1 and type-2 5-alpha reductase isozymes, leading to a more complete suppression (>90%) of DHT.^{7,8}

In a 2-year, placebo-controlled trial,⁸ dutasteride reduced total prostate volume by 26%, and this reduction was sustained for an additional 2 years in an open-label extension of that trial.⁹ American Urological Association Symptom Index (AUASI)

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improved by 6.4 points compared with baseline among patients receiving dutasteride for 4 years.⁹ In contrast, finasteride reduced prostate volume by 18% and AUASI by 3.3 points over a similar time period in a 4-year placebo-controlled trial.¹⁰ Further, in a prospective observational study, a significantly greater percentage of dutasteride-treated patients experienced symptom improvement within 3 months compared with finasteride-treated patients.¹¹

Despite these observations, debate continues because no published randomized head-to-head study has directly compared outcomes between dutasteride and finasteride. Meanwhile, in the absence of randomized comparative trials, there is a need to convey scientific evidence to medical decision makers to allow them to differentiate between these two 5ARIs.

Therefore, the purpose of this study was to examine the rates of AUR and surgery after initiation of 5ARI therapy, comparing the 2 currently available 5ARIs, dutasteride and finasteride.

METHODS

This is a retrospective descriptive and comparative analysis of the rates of AUR and prostate surgery in BPH patients treated with 5ARI therapy, either dutasteride or finasteride. Data were obtained from the PharMetrics Integrated Medical and Pharmaceutical Database (PIMPD) during a 6-year period (1999-2005). The PIMPD, based in Watertown, Mass, is a large national healthcare database that represents a total of 85 managed health plans and covers more than 45 million patients. Available data included inpatient and outpatient diagnoses as determined by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes,¹² and procedures as determined by *Current Procedural Terminology 4 (CPT-4)* formats, as well as prescription records. Dates of service and both paid and charged amounts were available for all services rendered.

The data analysis included all patients older than 50 years of age diagnosed with prostatic enlargement due to BPH or benign neoplasms who were treated with 5ARIs (dutasteride 0.5 mg/day or finasteride 5 mg/day) for up to 12 months during the 6-year period from January 1, 1999, to March 1,

■ **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, 223.3, 233.7, 236.7, 239.4, V10.51
<i>ICD-9 indicates International Classification of Diseases, Ninth Revision.</i>	

2005. The analysis excluded patients who were ≤30% adherent to 5ARI therapy, and those who were receiving nontherapeutic doses of 5ARI, such as individuals treated for male pattern baldness. Patients were also excluded if they were diagnosed with prostate or bladder cancer during the 18-month eligibility period. **Table 1** lists all relevant inclusion and exclusion ICD-9 codes.

Assessment of AUR and Surgery

Patients meeting the selection criteria were evaluated for a total of 12 months with regard to the likelihood of experiencing AUR or prostate-related surgery. Patients having AUR in months 0 to 5 were excluded to avoid including outcomes that might be due to insufficient duration of 5ARI therapy.^{13,14}

A separate subanalysis of the same outcomes occurring as early as 4 months was also conducted. This subanalysis was an attempt to test the hypothesis that dual 5ARI inhibition (dutasteride) may achieve an earlier therapeutic benefit compared with single-isozyme 5ARI inhibition (finasteride).

Table 2 presents the ICD-9-CM and CPT-4 procedure codes used to identify AUR and prostate-related surgeries.

Comorbidity Assessment

To assess comorbidities present in the study population during the 6-month period before the starting date of the analysis, the Charlson Comorbidity Index with Dartmouth-Manitoba and Deyo modification was utilized.^{15,16} The Charlson Index encompasses 19 medical conditions, each assigned a weight ranging from 1 to 6. Possible total scores range from 0 to 37; the higher the score, the more severe the burden of comorbidity.¹⁶ The Deyo

■ **Table 2.** ICD-9-CM and CPT-4 Codes for Acute Urinary Retention and Prostate-related Surgeries

Outcomes of interest	CPT or ICD-9-CM codes
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
Acute urinary retention*	788.2 (excluding 788.21), 599.6

*ICD-9-CM codes were used to identify this outcome.
 ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*; CPT, *Current Procedural Terminology*.

modification is an adaptation of the Charlson Index for use with ICD-9-CM diagnosis codes.¹⁵

Severity and Sequelae of EP

The Thomson Medstat Disease Staging coding criteria were used to identify the various complications and sequelae of prostate enlargement that were present before the patient was placed on 5ARI therapy. The Thomson Medstat method is based on electronic screening and identification of a comprehensive map of ICD-9-CM diagnosis codes. The proprietary coding criteria, developed by physicians and medical records professionals employed by Thomson Medstat, have been widely used as a

classification system for diagnostic categories—1 of 4 systems selected for dissemination with the Healthcare Cost and Utilization Project Nationwide Inpatient Sample.

The Thomson Medstat system defines 7 ascending ICD-9-CM code criteria for staging the severity of prostate enlargement (Table 3).¹⁷ In our study, each patient initiated on 5ARI therapy was placed into 1 of the 7 disease severity stages based on the presence of ICD-9-CM codes in the 6-month period before the index date (Table 3). Additionally, patients having hematuria (ICD-9-CM code 599.7) and/or bladder stones (ICD-9-CM codes 592.0, 592.1, 592.9, and 594.1) in the 6-month pre-period were identified, because these outcomes may also be indicative of disease severity.

■ **Table 3.** Thomson Medstat Staging Criteria for Enlarged Prostate

Stage	Description	ICD-9-CM codes
1.1	Benign prostatic hypertrophy	222.2, 600.xx
1.2	with urinary tract infection	Stage 1.1 + 599.0
2.1	with bladder outlet obstruction	Stage 1.1 + 593.5, 596.0, 599.6
2.2	with hydronephrosis	Stage 1.1 + 591.xx
3.1	with renal failure	Stage 1.1 + 584.xx, 586.xx
3.2	with sepsis	Stage 1.1 + 038.xx
3.3	with shock	Stage 1.1 + 785.50, 785.59

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*.
 Source: Reference 17.

Analysis of Outcomes

The likelihood and timing of AUR and surgery were assessed via survival analysis techniques. Time to event (AUR or surgery) was modeled using a Cox proportional hazards model. Cox proportional hazards models measure the likelihood of an event occurring over a defined time period in the presence of condition A compared with condition B. This likelihood is expressed as a hazard ratio. Hazard ratios greater than 1 are interpreted to mean that an event is more likely to occur under condition A versus B; ratios less than 1 indicate that an event is less likely to occur under condition A; and ratios equal to 1 indicate that an event is equally

likely to occur under either condition. In our study, the following covariates, which may be relevant severity indices for EP, were included in the model: age, Charlson Comorbidity Index score, Thomson Medstat stage, the presence of hematuria and/or bladder stones, number of alpha blocker prescriptions before the index date, the number of office visits related to EP, and the timing of the alpha blocker prescription. Alpha blocker timing was defined as pre-index if the first alpha blocker acquired was dispensed before the first 5ARI, and defined as same day if the alpha blocker was dispensed at the same time as the first 5ARI. Univariate analyses of frequencies and means were performed to describe the demographic characteristics of the study population. When appropriate, chi-square tests were used to compare differences in dichotomous variables and *t*-tests were used to compare differences in continuous variables.

and were included in the analysis. The mean age for the combined dutasteride and finasteride groups was 62.8 years, with a mean Charlson score of 0.8 (range, 0-11), indicating an overall low level of comorbidity in this sample. The majority of the men (94.6%) were classified as stage 1—ie, having EP without bladder outlet obstruction, hydronephrosis, renal failure, sepsis, or shock. When comparing the groups receiving dutasteride (*n* = 366) and finasteride (*n* = 1626), the men in the finasteride-treated group were slightly older (mean age 63.4 vs 59.9 years; *P* <.0001) and were less likely to have hematuria before initiating therapy. The Charlson Comorbidity Index, presence of bladder stones, timing of alpha blocker treatment, and Thomson Medstat stage were comparable between groups (Table 4).

Assessment of AUR and Surgery

After the first 150 days of 5ARI therapy, the rate of AUR during days 150 to 365 was found to be significantly lower in the dutasteride group compared with the finasteride group (5.3% vs 8.3%), as shown in Figure 1. After controlling for background covariates, dutasteride-treated patients were

RESULTS

Demographics

A total of 1992 men met all selection criteria

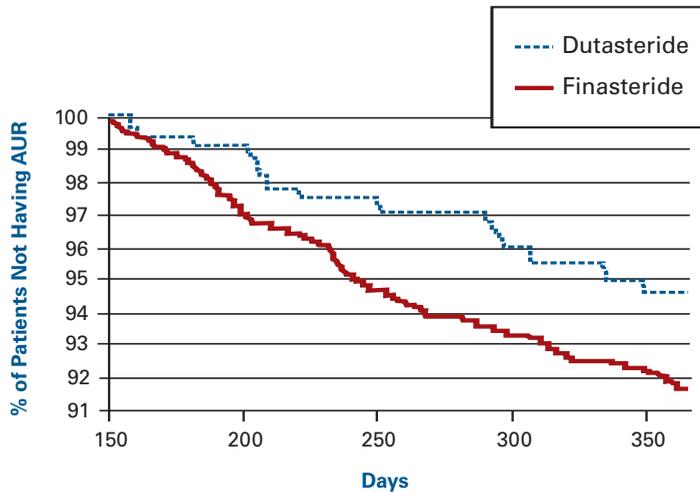
■ **Table 4.** Demographics of Study Population (N = 1992)

	Overall (N = 1992)	Dutasteride (n = 366)	Finasteride (n = 1626)
Age group, years, n (%)			
50-55	363 (18.2)	78 (21.3)	285 (17.5)
56-64	1087 (54.6)	250 (68.3)	837 (51.5)
65 and older	542 (27.2)	38 (10.4)	504 (31.0)
Enlarged prostate stage, n (%)			
1	1885 (94.6)	348 (95.1)	1537 (94.5)
2	87 (4.4)	11 (3.0)	76 (4.7)
3+	20 (1.0)	7 (1.9)	13 (0.8)
Age, mean (SD)	62.8 (9.2)	59.9 (6.8)	63.4 (9.5)*
Charlson rating, mean (SD)	0.8 (1.4)	0.7 (1.4)	0.8 (1.3)
Presence of hematuria, n (%)	233 (11.7)	54 (14.8)	179 (11.0)†
Presence of bladder stones, n (%)	82 (4.1)	21 (5.7)	61 (3.8)
Timing of alpha blocker treatment			
Pre-index period, n (%)	1481 (74.3)	272 (74.3)	1209 (74.4)
Same day, n (%)	511 (25.7)	94 (25.7)	417 (25.6)

**P* <.0001.
 †*P* = .0446.
 SD indicates standard deviation.

■ Reports

■ **Figure 1.** Time to Acute Urinary Retention (AUR)



49.1% less likely to experience AUR than patients receiving finasteride ($P = .0207$) (Table 5).

An additional analysis and sensitivity assessment were conducted using a shorter period (120 days vs 150 days) of initial 5ARI therapy. This analysis showed dutasteride-treated patients were 32.8% less likely to develop AUR than finasteride-treated patients.

Patients treated with dutasteride were also less likely to undergo prostate-related surgery during days 150 to 365 (1.4% of dutasteride-treated patients vs 3.4% of patients receiving finasteride) (Figure 2). After adjusting for covariates, dutasteride patients

were 45.1% less likely to have surgery, however this was not statistically significant ($P = .0745$) (Table 6). A similar trend was seen in the 120-day sensitivity analysis.

DISCUSSION

Dutasteride blocks both the type-1 and type-2 5-alpha reductase isozymes, achieving 50% more DHT suppression than finasteride, which inhibits type 2 only.⁷ Because DHT is the primary hormone responsible for prostatic growth,¹⁸ it seems reasonable to postulate that greater DHT suppression would result in greater prostate volume reduction and lower risk of BPH progression to AUR. To date, however, the relationship between the aforementioned measures and the risk of AUR and surgery has not been substantiated.^{6,7}

Placebo-controlled studies have shown reduced rates of AUR and surgical therapy with both 5ARIs.^{13,14,19,20} Although AUR and surgery rates in pivotal trials were lower with dutasteride (1.8% and 2.2%, respectively¹⁴) than with finasteride (2.8% and 4.6%, respectively¹³), results from these studies cannot be directly compared, because the 2 drugs were not compared head to head and differences in patient populations may have affected the outcomes.

The purpose of this study was to compare the likelihood of experiencing AUR or prostate-related surgery after initiating dutasteride or finasteride therapy in a real-world, managed care setting. This retrospective analysis was the first direct comparison of therapeutic outcome with a single-isozyme 5ARI (finasteride) versus a dual 5ARI (dutasteride). The results support the hypothesis that, although both drugs are 5ARIs, there may be differences in their therapeutic outcomes. In this study, patients treated with dutasteride were less likely to experience AUR and demonstrated a trend toward less prostate-related surgery than patients treated with finasteride.

The development of AUR in BPH patients causes considerable distress that includes lower abdominal pain and overflow incontinence in addition to the usual BPH voiding symptoms. Further hardship results from the need to visit the emergency department and the discomfort and potential complications associated with catheterization of the

■ **Table 5.** Cox Regression Model Results—Days Until First Postindex EP-related Acute Urinary Retention

Model term	Point estimate (95% CI)	P value
Dutasteride	0.509 (0.287, 0.902)	.0207
Aged 55 to 64 years	0.786 (0.484, 1.277)	.3309
Aged 65 years and older	0.727 (0.462, 1.145)	.1690
EP stage	0.983 (0.641, 1.507)	.9358
Charlson Comorbidity Index	0.973 (0.845, 1.121)	.7039
Number of alpha blocker prescriptions	0.998 (0.968, 1.029)	.9071
Number of office visits related to EP	1.255 (1.144, 1.377)	<.0001
Presence of stones	0.994 (0.400, 2.467)	.9889
Presence of hematuria	1.156 (0.677, 1.971)	.2815
Index before 2003	0.818 (0.551, 1.215)	.3203

EP indicates enlarged prostate; CI, confidence interval.

bladder.²¹ Surgical therapies add inconvenience, cost, and risk of adverse events such as infection, erectile and bladder dysfunction, and the need for retreatment.²²

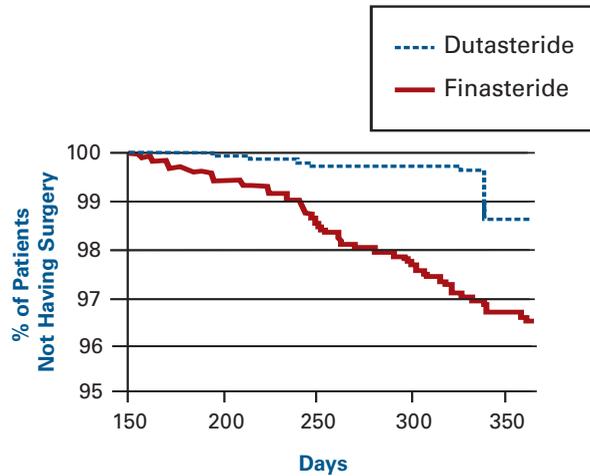
The impact of the information presented by this study is important not only to patients but also to primary care providers and third party payers. The ability to reduce BPH progression and AUR risk is a key factor that both patients and clinicians should consider when deciding to begin 5ARI treatment. Once the decision is made to start a 5ARI, one must consider all factors, including success rates, when choosing the specific medication.

Although the result of this study favors dutasteride over finasteride in reducing the risk of AUR, the differences in surgery were not statistically meaningful ($P = .0745$). It is possible that a study with increased sample size and a longer follow-up may have a greater likelihood of detecting a difference in surgical outcomes between these 2 products. Future studies should re-examine this issue.

Although our results suggest outcome differences between the two 5ARIs, interpretation of the results is limited by the retrospective nonrandomized nature of the study. To minimize the influence of selection bias, our analysis was adjusted for variations in age, disease severity staging, timing of treatment initiation, the presence of bladder stones and/or hematuria, Charlson Comorbidity Index score, use of alpha blockers, and number of prostate-related office visits before initiating the 5ARI. Even so, the results may have been influenced by other confounding factors such as symptom severity and/or prostate volume, or by unknown confounding factors. Although the timing of treatment initiation was included in the model, a post-hoc sensitivity analysis for treatment timing was conducted. An analysis of patients from 2003 and later revealed that dutasteride patients were 49% less likely to have AUR ($P = .0207$) and 41% less likely to have prostate surgery ($P = .1160$).

This study used survival analysis as the primary analytical technique. One of the principal assumptions with survival analysis is the independence of survival time and censoring. Censoring could be positively correlated with survival time, however, which would overestimate the survival function of each 5ARI.²³ The extent of the upward shift due to censoring cannot be determined, but is thought to

■ **Figure 2.** Time to Surgery



be equal across both cohorts. The effect is thought to be minimal, because the rates of AUR and surgery reported in this study are similar to those found among patients taking 5ARIs in another retrospective real-world study that did not employ survival analysis techniques (AUR, 8.2%; surgery, 3.7%).²⁴

This study is the first to highlight outcome differences between dutasteride and finasteride. Patients initiated on dutasteride were significantly less likely to have AUR and were slightly (though nonsignificantly) less likely to undergo prostate-related surgical intervention. Future studies should evaluate the economic differences between the 5ARIs while further exploring additional cost driv-

■ **Table 6.** Cox Regression Model Results—Days Until First Postindex EP-related Surgery

Model term	Point estimate (95% CI)	P value
Dutasteride	0.549 (0.285, 1.061)	.0745
Aged 55 to 64 years	0.971 (0.565, 1.670)	.9160
Aged 65 years and older	0.374 (0.191, 0.731)	.0040
EP stage	1.241 (0.842, 1.831)	.2751
Charlson Comorbidity Index	0.978 (0.815, 1.173)	.8120
Number of alpha blocker prescriptions	0.973 (0.936, 1.011)	.1633
Number of office visits related to EP	1.518 (1.376, 1.675)	<.0001
Presence of stones	1.079 (0.335, 3.469)	.8990
Presence of hematuria	0.967 (0.478, 1.956)	.9258
Index before 2003	0.692 (0.419, 1.143)	.1505

EP indicates enlarged prostate; CI, confidence interval.

ers, such as absenteeism and other measures of work productivity.

CONCLUSION

Patients treated with dutasteride were less likely to have AUR than patients receiving finasteride. Although patients taking dutasteride were slightly less likely to have prostate-related surgery, this difference was not statically significant due to a lack of power. Overall, patients treated with dutasteride tended to have fewer EP-related progression events compared with patients treated with finasteride.

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