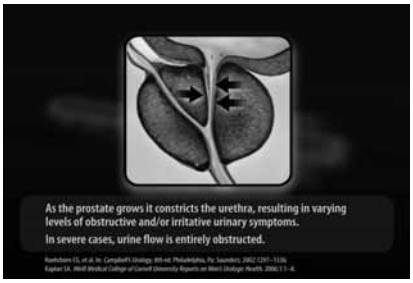
Increasing Awareness, Diagnosis, and Treatment of BPH, LUTS, and EP

~ E. David Crawford, MD

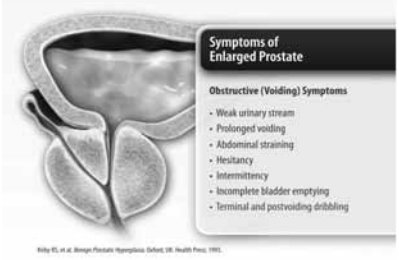
Introduction to Enlarged Prostate

E. David Crawford, MD
Professor of Surgery (Urology) and Radiation Oncology
Head, Urologic Oncology
E. David Crawford Endowed Chair in Urologic Oncology
University of Colorado Health Sciences Center
Denver, Colorado

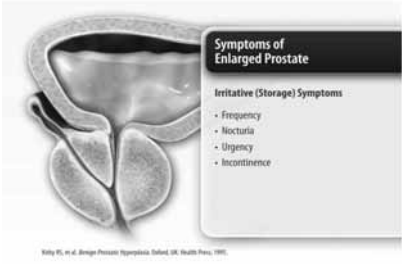
What is Enlarged Prostate (EP)?



Symptoms of Enlarged Prostate: Obstructive



Symptoms of Enlarged Prostate: Irritative



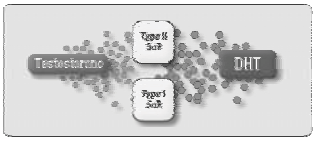
Overview of DHT in the Development of EP

- The development and growth of the prostate gland depends on androgen stimulation.[1]
- In men, testosterone is converted to dihydrotestosterone (DHT),[1] a more potent androgen,[2] by 5-alpha-reductase (5AR) enzymes[1]
- In the prostate, two types of 5ARs exist: Type I and Type II.[1]
- It is known that DHT levels in the prostate remain high with aging, despite a decrease in the production of testosterone[3]

DHT is primarily responsible for the development of EP[1]

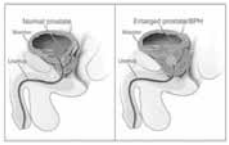
1. Steers W. *Urology.* 2001;58:17-24.
2. Tindall D. *J Urol.* 2008;179:1235-42.
3. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Philadelphia, Pa: Saunders; 2002:1297–336.

5ARs' Role in the Conversion of Testosterone to DHT



Characteristics of EP

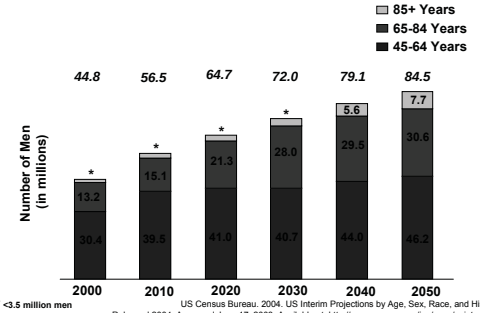
- Common prostate condition in men over 50[1]
- Prostate size ≥30 mL[1]
- Prostate-specific antigen (PSA) ≥1.5 ng/mL[1]
- Progressive disease[1]
- Major cause of urinary symptoms in older men[2]



1. Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health.* 2006;1(1):1–8.
2. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Saunders; 2002:1297–336.

The Burden of EP in the United States (US)

Population Growth of Men At-Risk for EP



* <3.5 million men

US Census Bureau. 2004. US Interim Projections by Age, Sex, Race, and Hispanic. Released 2004. Accessed June 17, 2008. Available at: http://www.census.gov/ipc/www/usinterimproj/

Prevalence of EP

- EP affects 50% of men over age 50 and 90% of men over the age of 80[1,2]
- In a recent survey of men over age 50 in the United States[3]
  - 25% reported moderate to severe symptoms of EP
  - 55% of those consulting a doctor were diagnosed with EP

EP is significantly underreported and underdiagnosed[1,3]

1. AUA guideline on management of benign prostatic hyperplasia (2003). *J Urol.* 2003; 170:530-47.
2. Berry S. *J Urol.* 1984;132:474-79.
3. Roehrborn C, et al. *Pros Cancer and Prostatic Dis.* 2006;9:30-4.

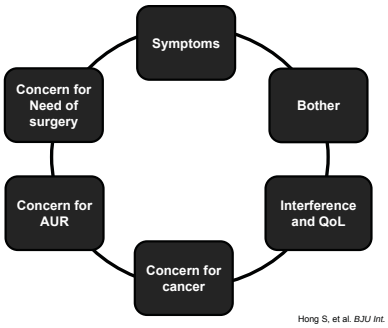
Economic Burden of EP

- In 2000, the direct cost of EP reached $1.1 billion in the US alone (not including outpatient pharmaceuticals)
  - Medical services at hospital inpatient and outpatient settings
  - Emergency departments and physician office visits
- In a 2-year period, outpatient prescription drugs for EP were estimated to cost $194 million a year*

*from 1996-1998

Wei J, et al. *J Urol.* 2005:173;1256-61.

The Personal Impact of EP



Hong S, et al. *BJU Int.* 2005;95:15-19.

Summary of Disease Burden of EP

- The majority of men over age 50 are affected by BPH, which can include EP
- Considerably underdiagnosed and undertreated
- Economic and societal burden
- Can decrease quality of life
  - Creates strains on personal life
  - Interferes with daily activities
  - Causes concerns about AUR and prostate-related surgery

Enlarged Prostate: A Progressive Disease

Predictors of Clinical Progression of EP

	Age Progression	Symptoms	Prostate Volume	PSA
Olmsted County Study[1,2] (n = 2,115)	>50 years	Moderate-to-severe symptoms (AUA-SI >7)	>30 mL	≥1.4 ng/mL
Baltimore Longitudinal Study of Aging[3,4] (n = 1,057)	≥50 years	Obstructive symptoms	Clinical EP diagnosed by DRE	>1.4 ng/mL for 50-59 years*, >1.7 ng/mL for 60-69 years*
Medical Therapy of Prostatic Symptoms[5] (n = 737)	≥62 years	4-point increase in AUA-SI	≥31 mL	≥1.6 ng/mL

*PSA level associated with prostate enlargement

1. Jacobsen S, et al. *J Urol.* 1997;158:481–7.
2. Jacobsen S, et al. *J Urol* 1999;162:1301-1306.
3. Arrighi H, et al. *Urology.* 1991;38 (suppl):4–8.
4. Wright E et al. *J Urol.* 2002;167:2484-2488.
5. Crawford E, et al. *J Urol.* 2006;175:1422–7.

Natural History of Untreated EP Progression

Male patient, age 55 years:
symptomatic EP, PSA = 1.5 ng/mL, negative for prostate cancer

55 years old
PV: 30 mL
PSA = 1.5 ng/mL

60 years old
PV: >40 mL

65 years old
PV: >50 mL

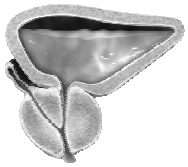
70 years old
PV: >61 mL

Disease progression can increase the risk of AUR and prostate-related surgery[1,2]

Figure based on Roehrborn C, et al. *J Urol.* 2000;163:13–20.
1. Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health.* 2006;1(1):1–8.
2. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Saunders; 2002:1297–336.

Overview and Outcomes of AUR

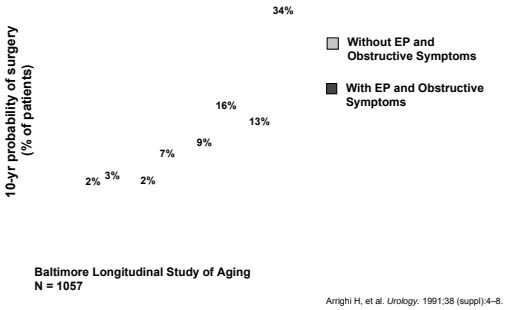
- Common urological emergency[1,2]
  - Greater resistance to urine flow
  - Bladder over-distention
  - Can have neuropathic causes
- Outcomes of AUR[2-4]
  - Inability to urinate with increasing pain
  - Visits to the emergency room
  - Emergency catheterization
  - Urinary tract infection
  - Continuing failure to spontaneously void
  - Surgery



AUR is a painful, time-consuming, and feared condition that often results in emergency catheterization[4]

1. Fitzpatrick J, et al. *BJU Int.* 2006;97 (Suppl 2):16-20.
2. Choong S, et al. *BJU Int.* 2000;85:186-201.
3. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Saunders; 2002:1297–336.
4. Roehrborn C, et al. *Rev Urol.* 2001;3:187-92.

Risk of EP-Related Surgery in Men with EP



Baltimore Longitudinal Study of Aging
N = 1057

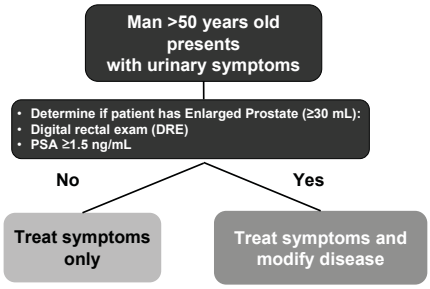
Arrighi H, et al. *Urology.* 1991;38 (suppl):4–8.

Summary of Progressive Disease

- Age, severity of urinary symptoms, PSA and prostate volume are predictors of clinical progression of EP
- Disease progression increases the risk of AUR and EP-related surgery
  - Men 70 to 79 years of age are up to 3 times more likely to have AUR
  - Men with a baseline prostate volume >30 mL are at greater risk for AUR, as are men with greater PSA and symptom severity at baseline
- AUR is a painful condition that results in emergency catheterization
- As men age, their risk for developing EP, and progressing to AUR and prostate-related surgery increases

Diagnosing EP

A Practical Algorithm for the Diagnosis and Management of EP



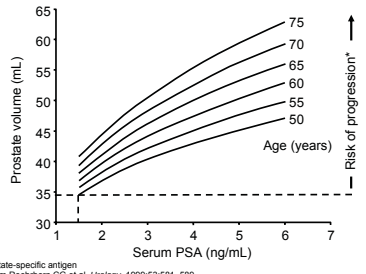
Adapted from Figure 3, entitled "Practical Algorithm for the treatment of EP in primary care" in Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health.* 2006;1(1):1–8.

Symptom Assessments for EP

- American Urological Association Symptom Index (AUA-SI)[1]
  - 7 item, patient-rated questionnaire to evaluate symptom severity
  - Scaled 0-5, with a maximum score of 35:
    - ≤7 mild symptoms
    - 8-19 moderate symptoms
    - 20-35 severe symptoms
- International Prostate Symptom Score (IPSS)[2]
  - Same 7 questions as the AUA SI, with the addition of a disease-specific quality of life question

1. Barry M, et al. *J Urol.* 1992;148:1558.
2. AUA guideline on management of benign prostatic hyperplasia (2003). *J Urol.* 2003;170:530-47.

Serum PSA ≥ 1.5 ng/mL Can Predict Prostate Enlargement and Risk of Progression



PSA = prostate-specific antigen
Adapted from Roehrborn CG et al. *Urology.* 1999;53:581–589.
*Crawford ED et al. *J Urol.* 2006;175:1422–1427.

Arresting Disease Progression

Symptom worsening[1]

Decreased urinary flow[2]

AUR[3] Prostate-related surgery[4]

1. Sarma A, et al. *J Urol.* 2002;168 (4 part 1):1446-52.
2. Roberts R, et al. *J Urol.* 2000;163:107-13.
3. Jacobson S, et al. *Urology.* 2001; (suppl 6A):5-16.
4. Arrighi H, et al. *Urology.* 1991;38:4-8.

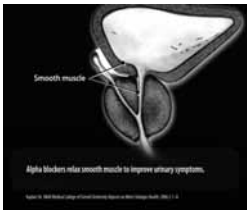
Summary of EP Diagnosis

- Diagnosis involves assessment of symptom severity and determination of prostate volume
- The PSA test is an effective tool to estimate prostate size
- PSA of 1.5 ng/mL suggests a prostate volume ≥30 mL
- The goal of medical therapy should be to arrest disease progression and reduce the risk of long-term disease complications

Pharmacologic Treatment Goals and Options for EP

Treatment Options: Alpha Blockers

- Alpha blockers:[1,2]
  - Relax smooth muscle
  - Ease pressure on urethra and bladder
  - Improve urinary flow (Q_{max}) and bothersome symptoms



1. Weill Medical College of Cornell University Reports on Men's Urologic Health. 2006;1(1):1-8.
2. McConnell J, et al. *NEJM.* 2003;349:2387-98.

Treatment Options: AVODART - A 5AR Inhibitor

- Dutasteride (AVODART)
  - Dual Type I and II inhibitor
  - Dual 5ARI blocks the conversion of testosterone to DHT by competitively inhibiting both Type I and Type II pathways

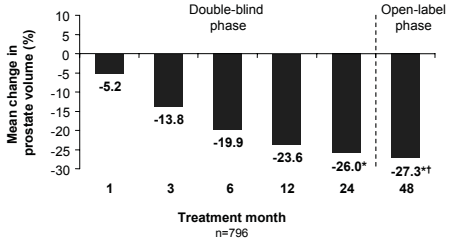
The clinical benefit of more complete DHT suppression has not been established.

Prescribing Information for AVODART. 2008.

AVODART® (dutasteride) - Phase III Data: Reducing Size, Symptoms, and Risk

AVODART Reduces Size

Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies Followed by 2-year Open-label Extension Phase of AVODART 0.5 mg daily

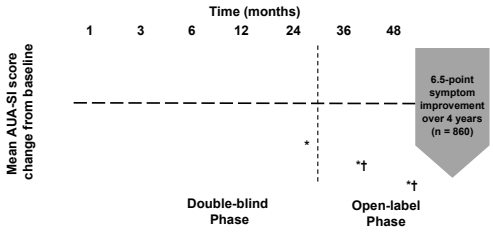


*P < 0.001 between treatment groups; †p < 0.07 vs month 24

Debruyne F, et al. *Eur Urol*. 2004;46:488-94.

AVODART Reduces Symptoms

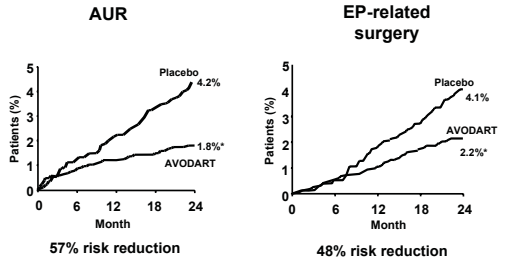
Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies with 2-year Open-label Extension Phase with AVODART 0.5 mg daily



*P <0.001 between treatment groups
†P <0.001 vs month 24

Debruyne F, et al. *Eur Urol*. 2004;46:488-94.

AVODART Reduces the Risk



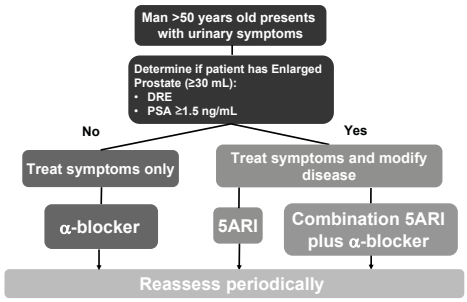
57% risk reduction

48% risk reduction

*P <0.001 vs placebo.
Results of 3 combined, double-blind, pivotal studies of 4325 men with BPH.

Roehrborn C, et al. *Urology*. 2002;60:434-41.

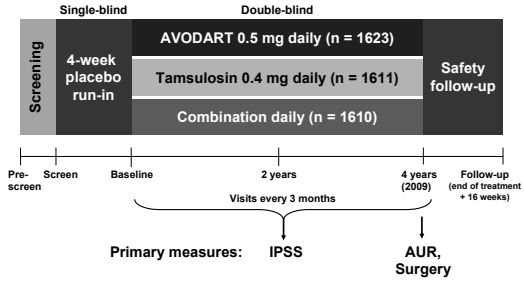
A Practical Algorithm for the Treatment of EP in Primary Care



Adapted from Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health*. 2006;1(1):1-8.

Two-year Results From the Combination of AVODART and Tamsulosin (CombAT) Study

CombAT Study Design



Roehrborn C, et al. *J Urol*. 2008;179:616-21.
Siami P, et al. *Contemp Clin Trials*. 2007;28:770-9.

CombAT Major Entry Criteria

Age	≥50 years
EP diagnosis	Diagnosis by history and DRE
IPSS	≥12 (moderate-to-severe symptoms)
Prostate volume	≥30 cc by TRUS
Serum PSA	1.5 – 10.0 ng/mL
Q_{max}	>5 and ≤15 mL/sec (moderate-to-severe impairment)
Minimum voided volume	≥125 mL (based on two voids at screening)

DRE = digital rectal exam; TRUS = transrectal ultrasound; Qmax = maximum urinary flow.

Roehrborn C, et al. *J Urol.* 2008;179:616-21.
Siami P, et al. *Contemp Clin Trials.* 2007;28:770-9.

CombAT Patient Characteristics at Baseline

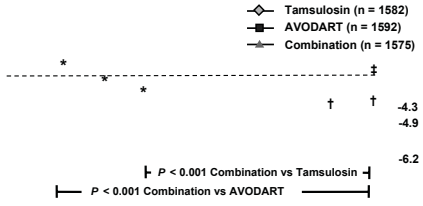
	All Patients N=4844	Combination* n=1610	AVODART n=1623	Tamsulosin n=1611
Mean age (years)	66.1	66.0	66.0	66.2
Caucasian ethnicity (%)	88	88	88	87
Mean IPSS score (points)	16.4	16.6	16.4	16.4
Mean prostate volume (cc)	55.0	54.7	54.6	55.8
Mean Qmax (mL/sec)	10.7	10.9	10.6	10.7
Mean serum PSA (ng/mL)	4.0	4.0	3.9	4.0
Previous 5ARI use (%)	11	11	12	11
Previous alpha blocker use (%)	50	50	51	51

*AVODART plus tamsulosin

Roehrborn C, et al. *J Urol.* 2008;179:616-21.

CombAT: Reduction in Urinary Symptoms

IPSS - Adjusted Mean Change From Baseline (LOCF)[1]

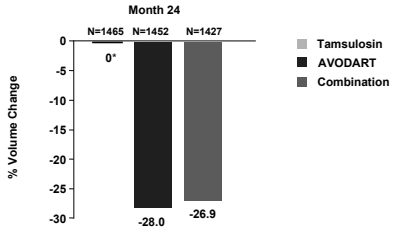


LOCF = last observation carried forward
*P <0.001 in post hoc analysis for tamsulosin vs. AVODART as monotherapy[2]
†P <0.05 in post hoc analysis for AVODART vs. tamsulosin as monotherapy[2]
‡Patients generally perceive a 3-point change in the AUA-SI score as meaningful[3]

1. Roehrborn C, et al. *J Urol.* 2008;179:616-21.
2. Data on file, GlaxoSmithKline.
3. Barry J, et al. *J Urol.* 1995;154:1770-74.

CombAT: Reduction in Total PV

Adjusted Mean Percentage Change from Baseline (LOCF)

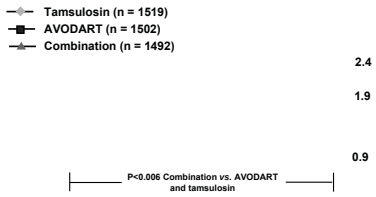


*P <0.001 Combination *vs.* tamsulosin

Roehrborn C, et al. *J Urol.* 2008;179:616-21.

CombAT: Continuous Improvement in Qmax

Adjusted Mean Change From Baseline (LOCF)[1]



Roehrborn C, et al. *J Urol.* 2008;179:616-21.

Most Common Drug-related Adverse Events* - CombAT

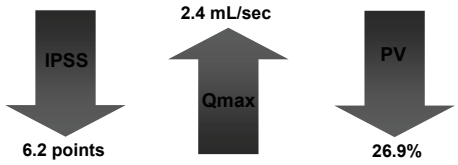
	Combination n = 1610	Tamsulosin n = 1611	AVODART n = 1623
Erectile dysfunction	7.4%	3.8%	6.0%
Retrograde ejaculation	4.2%	1.1%	0.6%
Libido decreased	3.4%	1.7%	2.8%
Ejaculation failure	2.4%	0.8%	0.5%
Semen volume decreased	1.8%	0.8%	0.3%
Loss of libido	1.7%	0.9%	1.3%
Dizziness	1.6%	1.7%	0.7%
Breast enlargement	1.4%	0.8%	1.8%
Nipple pain	1.2%	0.3%	0.6%
Breast tenderness	1.0%	0.3%	1.0%
Discontinued due to drug-related AEs	**5%**	**3%**	**3%**

*Drug-related AEs occurring in ≥1% of subjects within any treatment group.

Roehrborn C, et al. *J Urol.* 2008;179:616-21.

CombAT Summary

- Clinical trial in >4,800 men with moderate to severe lower urinary tract symptoms and enlarged prostate
- The CombAT study demonstrated a benefit for combination therapy over monotherapies in the first 12 months of therapy.
- Significant improvement in urinary symptoms and prostate size with combination therapy at 24 months



Roehrborn C, et al. *J Urol.* 2008;179:616-21.

PSA in Relation to the Prostate

- PSA production and use in EP[1]
  - DHT stimulates the growth of glandular epithelial cells in the prostate, which produce high levels of PSA[1]
  - Predictive of prostate volume in men with EP[2]
- PSA is prostate-specific, not cancer-specific
- Prostate cancer cells also produce PSA[3]
- PSA ≥1.5 ng/mL suggests EP[4]

1. Schalken J. *BJU Inter.* 2004;93 (suppl 1):5-9.
2. Roehrborn C, et al. *Urology.* 1999;53:581-9.
3. Balk S, et al. *J Clin Oncol.* 2003;21:383-91.
4. Kaplan SA. *Weill Medical College of Cornell University Reports on Men's Urologic Health.* 2006;1(1):1-8.