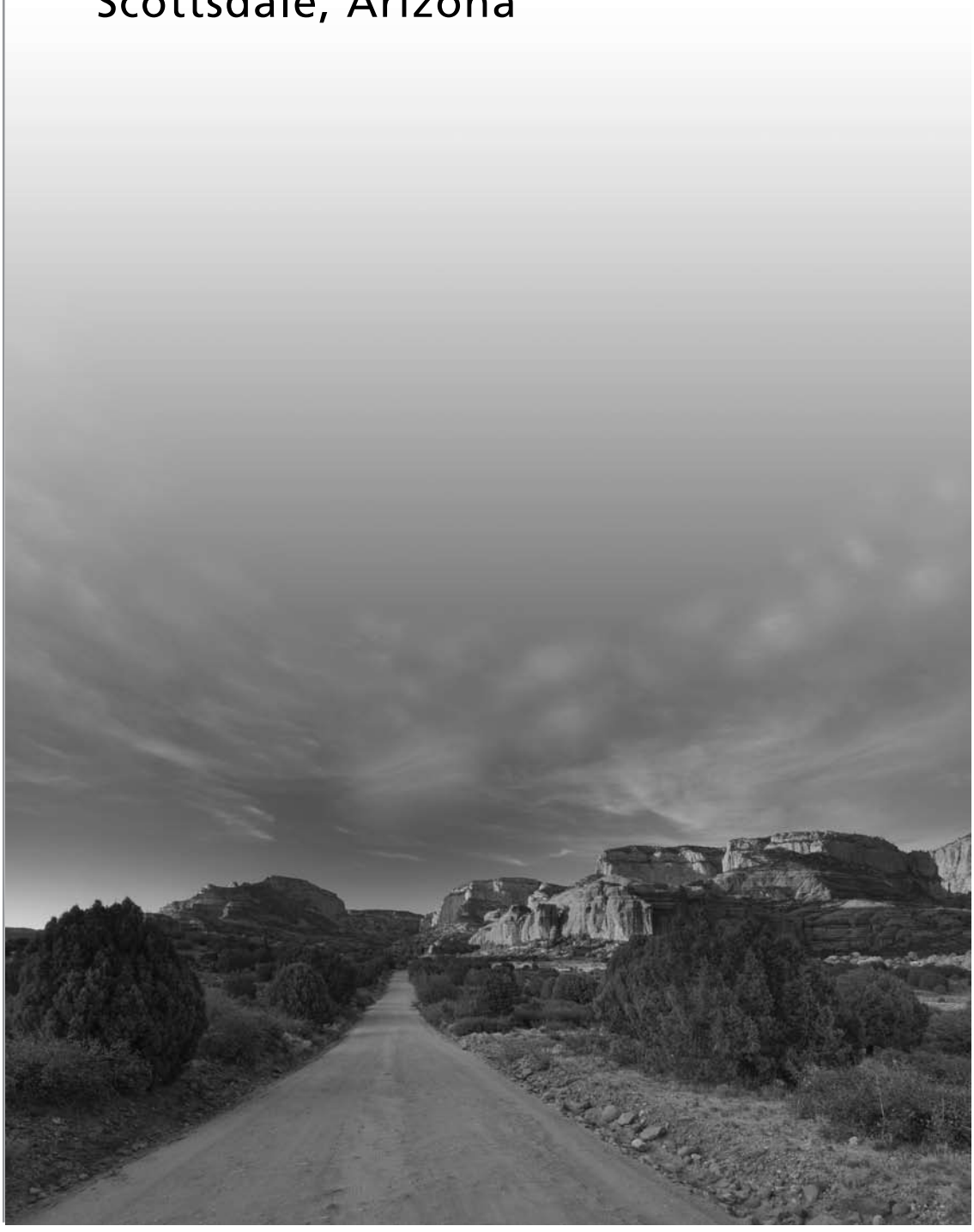
18th Annual

PERSPECTIVES IN UROLOGY

POINT COUNTERPOINT2009

Saturday, November 7, 2009
Ballroom E-F
The Scottsdale Plaza
Scottsdale, Arizona



Agenda

Saturday, November 7

		Page
7:15 – 8:00 am	Continental Breakfast in Exhibit Hall	
8:00 – 8:20 am	Chemotherapy for Urological Cancers *~ Matthew Rettig, MD*	17.1
8:20 – 8:25 am	Questions & Answers	
Prostate Conditions		
8:25 – 8:55 am	Increasing Awareness, Diagnosis, and Treatment of BPH, LUTS, and EP *~ E. David Crawford, MD*	18.1
8:55 – 9:25 am	Point-Counterpoint	19.1
	Are We Ignoring Level One Evidence by Not Prescribing Appropriate Medical Therapy? *~ E. David Crawford, MD* Alternative Medicine Should Be the Choice *~ Mark A. Moyad, MD, MPH*	
9:25 – 9:35 am	Questions & Answers	
Hypogonadism		
9:35 – 10:05 am	Increasing Awareness, Diagnosis, and Treatment of Hypogonadism *~ Jacob Rajfer, MD*	20.1
10:05 – 10:35 am	Point-Counterpoint: Late Onset Hypogonadism (LOH)	21.1
	We are Under-diagnosing and Treating Men with LOH *~ Jacob Rajfer, MD*	*21.1*
	LOH is a Non-existent Disease *~ Robert E. Donohue, MD*	21.8
10:35 – 10:45 am	Questions & Answers	
10:45 – 10:55 am	Break in Exhibit Hall	
Complementary Alternative Medicine		
10:55 – 11:55 am	Fad Diets and Dietary Supplements for Urology Patients: What Works and What's Worthless *~ Mark A. Moyad, MD, MPH*	22.1
11:55 – 12:10 pm	Pills and Tests: What Should I (the urologist) Be Taking and Getting? *~ Mark A. Moyad, MD, MPH*	23.1
12:10 – 12:30 pm	Point-Counterpoint:	24.1
	Why Every Man Should Be Offered Chemoprevention for Prostate Cancer *~ E. David Crawford, MD*	24.1
	Chemoprevention Is Not for Every Man *~ Mark A. Moyad, MD, MPH*	24.12
12:30 – 12:45 pm	Questions & Answers	
12:45 pm	Meeting Adjourns	

Chemotherapy for Urological Cancers

~ Matthew Rettig, MD

Chemotherapy for Urologic Cancers

Matthew Rettig, MD
Associate Professor
Department of Medicine
Division of Hematology-Oncology
Department of Urology
Medical Director, Prostate Cancer Program
Institute of Urologic Oncology
David Geffen School of Medicine at UCLA

- Q: What is Chemotherapy?
- A: In *oncologic* terms, chemotherapeutic agents are chemicals with varying mechanisms of action that influence cell survival by damaging DNA. May be:
  - Cytotoxic
  - Cytostatic

Chemotherapy Schemes

- Adjuvant/neoadjuvant
- Palliative
- Survival benefit
- Curative

- Various roles in:
  - RCC
  - Bladder cancer
  - Testicular cancer
  - Prostate cancer

Chemotherapy Principles

- Very narrow therapeutic index.
- We do not understand why cancer cells are preferentially responsive to chemotherapeutic agents. In fact, the abundance of data suggest that for the vast majority of human malignancies, the converse is true. That is, certain normal cellular compartments are *more* sensitive to the effects of chemotherapy than cancer cells.

RCC

- Chemotherapy has no role.

Bladder Cancer

- Neoadjuvant (pre-op): combination chemotherapy improves OS.
  - ~5% improvement at 5 years.
  - Applies to all stages.
- Data in adjuvant (post-op) setting is controversial and less robust.
- Chemotherapy (cisplatin) plus radiation is a bladder-sparing option for tumors optimally debulked by TURBT with no clear decrement in OS.
  - Bladder spared in ~50% of cases.
  - Prognostic factors: performance status, visceral involvement, p53 mutations, ERCC1 mutations.

Bladder Cancer

- Metastatic: Combination chemo improves OS.
  - ~12 mos vs. 6 mos for BSC.
  - Gemcitabine and cisplatin (GC) is "non-inferior" to MVAC, but less toxic.

Testicular Cancer

- Adjuvant chemotherapy for stage I and II markedly reduces recurrence risk, but does not affect overall survival because salvage therapy of patients managed by observation is effective.
- Metastatic disease: chemo is curative.
  - Good risk: 90% cure.
  - Intermediate risk: 70% cure.
  - Poor risk: 50% cure.

Testicular germ cell tumors risk stratification system
Seminomas
Good risk
All of the following:
Any primary site
No nonpulmonary visceral metastases
Normal serum AFP
Intermediate risk
All of the following:
Any primary site
Nonpulmonary visceral metastases present
Normal serum AFP

Non-seminomatous germ cell tumors
Good risk
All of the following:
Testicular or retroperitoneal primary tumors
No nonpulmonary visceral metastases
Serum AFP <1000 ng/mL, beta-hCG <5000 mIU/mL, and LDH <1.5 times upper limit of normal
Intermediate risk
All of the following:
Testicular or retroperitoneal primary tumors
No nonpulmonary visceral metastases
Intermediate level of any of the following:
AFP 1000 to 10,000 ng/mL
beta-hCG 5000 to 50,000 mIU/mL, or
LDH 1.5 to 10 times upper limit of normal
Poor risk
Any of the following:
Mediastinal primary, or
Nonpulmonary visceral metastases, or
Serum AFP >10,000 ng/mL, or
Serum beta-hCG >50,000 mIU/mL, or
LDH more than 10 times upper limit of normal

Prostate Cancer

- No established role for chemotherapy in the neoadjuvant/adjuvant setting.
- Metastatic disease:
  - Docetaxel improves OS
    - Median OS improved 2-3 mos.
    - Reduces risk of death by ~ 25%.
  - Mitoxantrone
    - No affect on survival.
    - Improves QOL of patients with bone pain.

Case 1

Date	Case History	PSA
2/2006	• 55 yo AAM undergoes open RRP: Gleason 5+4 = 9/10, SVI (pT3b), PNI, SM-.	8.5
5/2006		1.2
7/2006	• LHRH analog initiated.	3.8
9/2006		0.8
12/2006	• Patient c/o bone pain, fatigue. • Bone scan: widespread bone mets. • CT abd/pelvis: RPLAN and liver mets. • CRPC diagnosed based on clinical and radiographic progression.	0.8

What is the next step?

Case 1

Date	Case History	PSA
1/2007	• Liver biopsy → neuroendocrine (small cell) carcinoma. • Chemotherapy initiated (cisplatin/etoposide).	
3/2007	• Restaging CT abd/pelvis → partial response. • Chemotherapy continued for a total of four cycles.	
11/2007	• Restaging CT abd/pelvis → progression of liver mets. • Patient's performance status rapidly declines. • Referred for hospice care.	

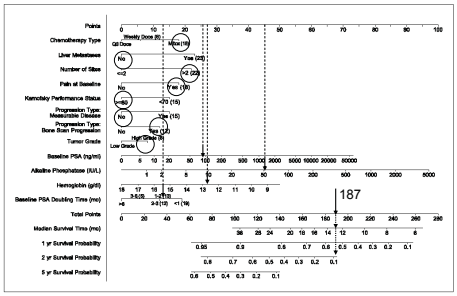
Case 2

Date	Case History	PSA
1991	• 62 yo WM. RRP: Gleason 4+4 = 8/10, pT2b.	6.2
1991-97		undetectable
1998	• Lupron/Casodex initiated.	3.7
1998-2007		undetectable
1/2007	• T = 4.0 ng/ml; CRPC diagnosed.	1.2
3/2007	• Casodex withdrawn.	4.8
5/2007	• Bone scan → widespread mets associated pain. CT abd/pelvis - • CRPC with clinical, radiographic and PSA progression. • Ketoconazole/hydrocortisone initiated.	11.8

Case 2

Date	Case History	PSA
6/2007	• LFTs elevated → ketoconazole/hc d/c'd.	38.4
7/2007	• LFTs normalize.	85.2

CRPC Nomogram



Clin Cancer Res 2007;13(21) November 1, 2007 6396

Case 2 (continued)

Date	Case History	PSA
8/2007	• Chemotherapy (docetaxel) initiated.	95.1
9/2007	• Bone pain resolved. • No significant chemotherapy-related toxicity.	31.5
10/2007		8.6
11/2007		4.6
12/2007		1.6
1/2008	• Bone scan: no evidence of progression.	0.8
5/2008	• Chemotherapy completed (10 of 10 planned cycles).	0.5

Survival by PSA Decline from TAX 327

	Median Survival (months)
PSA normalization (n=115)	33.3
≥ 90% PSA decline (n=106)	26.6
≥ 50% PSA decline (n=460)	22.4
≥ 30% PSA decline (n=591)	21.6
Any PSA decline (n=730)	20.7
No PSA decline (n=259)	11.7

Armstrong, AJ et al. *J Clin Oncol* 2007; 25 (18S Part I of II):237S (abstract and oral presentation 5009).

Case 2

Date	Case History	PSA
?	Progression	↑↑

No established therapy for docetaxel-resistant CRPC.

↓

Clinical trials.

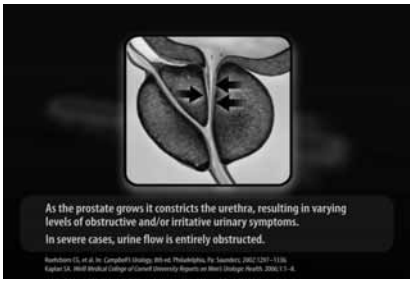
Increasing Awareness, Diagnosis, and Treatment of BPH, LUTS, and EP

~ E. David Crawford, MD

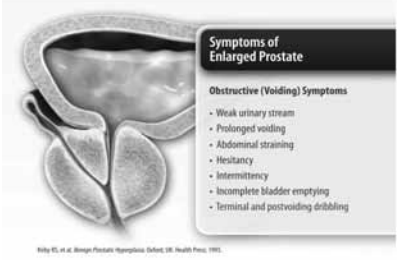
Introduction to Enlarged Prostate

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

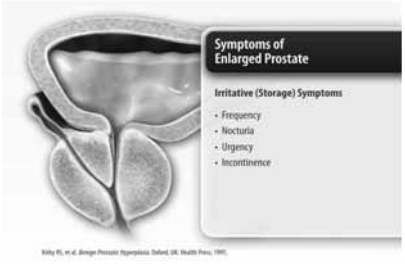
What is Enlarged Prostate (EP)?



Symptoms of Enlarged Prostate: Obstructive



Symptoms of Enlarged Prostate: Irritative



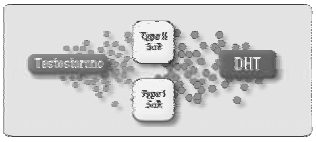
Overview of DHT in the Development of EP

- 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]

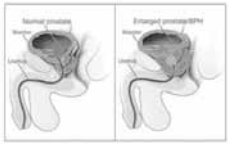
1. Steers W. *Urology.* 2001;58:17-24.
2. Tindall D. *J Urol.* 2008;179:1235-42.
3. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Philadelphia, Pa: Saunders; 2002:1297–336.

5ARs' Role in the Conversion of Testosterone to DHT



Characteristics of EP

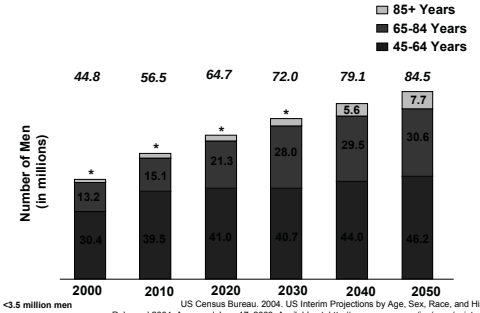
- Common prostate condition in men over 50[1]
- Prostate size ≥30 mL[1]
- Prostate-specific antigen (PSA) ≥1.5 ng/mL[1]
- Progressive disease[1]
- Major cause of urinary symptoms in older men[2]



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.

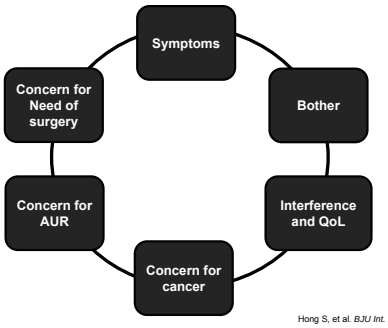
Economic Burden of EP

- 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

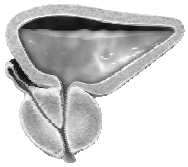
70 years old
PV: >61 mL

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

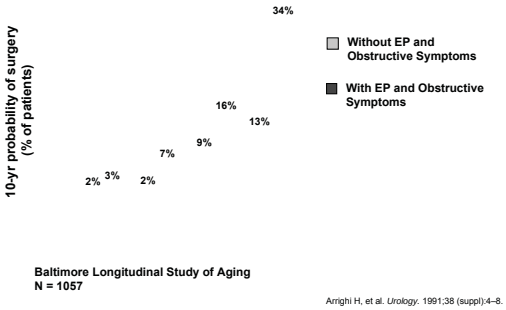
- Common urological emergency[1,2]
  - Greater resistance to urine flow
  - Bladder over-distention
  - Can have neuropathic causes
- Outcomes of AUR[2-4]
  - Inability to urinate with increasing pain
  - Visits to the emergency room
  - Emergency catheterization
  - Urinary tract infection
  - Continuing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

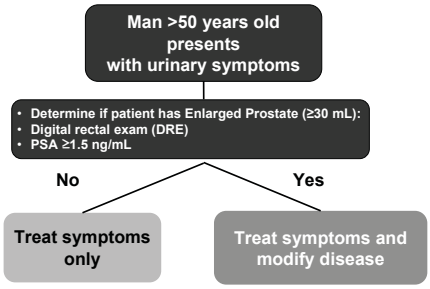
Arrighi H, et al. *Urology.* 1991;38 (suppl):4–8.

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



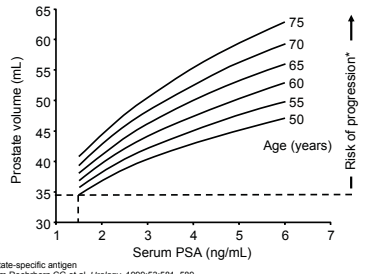
Adapted from Figure 3, entitled "Practical Algorithm for the treatment of EP in primary care" in Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health.* 2006;1(1):1–8.

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.

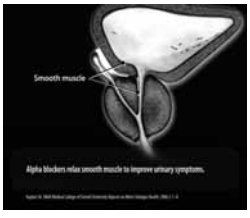
Summary of EP Diagnosis

- 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

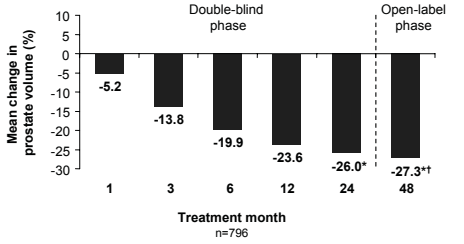
The clinical benefit of more complete DHT suppression has not been established.

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

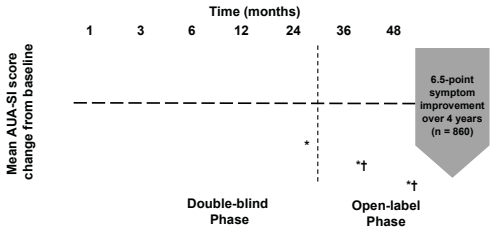


*P < 0.001 between treatment groups; †p < 0.07 vs month 24

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

AVODART Reduces Symptoms

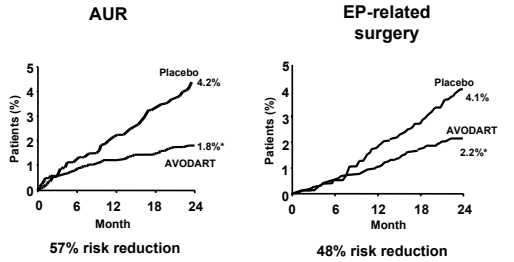
Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies with 2-year Open-label Extension Phase with AVODART 0.5 mg daily



*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



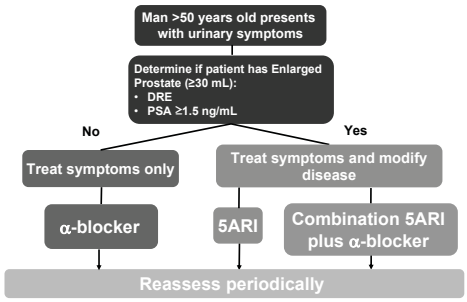
57% risk reduction

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.

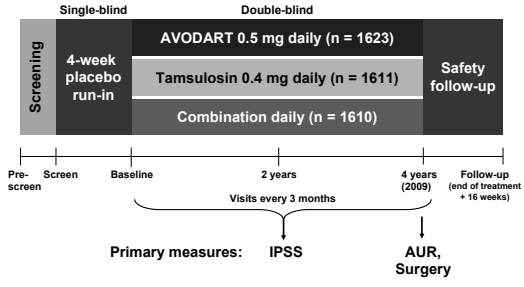
A Practical Algorithm for the Treatment of EP in Primary Care



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

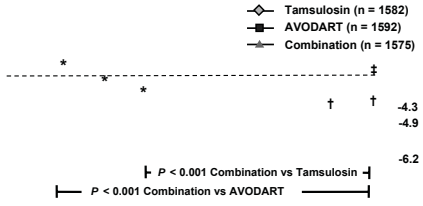
	All Patients N=4844	Combination* n=1610	AVODART n=1623	Tamsulosin n=1611
Mean age (years)	66.1	66.0	66.0	66.2
Caucasian ethnicity (%)	88	88	88	87
Mean IPSS score (points)	16.4	16.6	16.4	16.4
Mean prostate volume (cc)	55.0	54.7	54.6	55.8
Mean Qmax (mL/sec)	10.7	10.9	10.6	10.7
Mean serum PSA (ng/mL)	4.0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

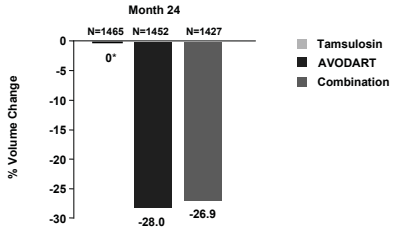


LOCF = last observation carried forward
*P <0.001 in post hoc analysis for tamsulosin vs. AVODART as monotherapy[2]
†P <0.05 in post hoc analysis for AVODART vs. tamsulosin as monotherapy[2]
‡Patients generally perceive a 3-point change in the AUA-SI score as meaningful[3]

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)

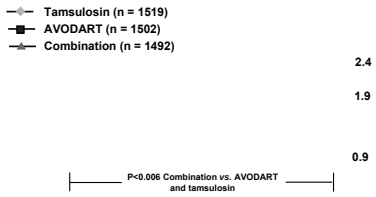


*P <0.001 Combination *vs.* tamsulosin

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

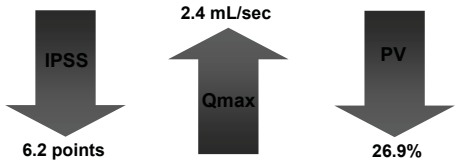
	Combination n = 1610	Tamsulosin n = 1611	AVODART n = 1623
Erectile dysfunction	7.4%	3.8%	6.0%
Retrograde ejaculation	4.2%	1.1%	0.6%
Libido decreased	3.4%	1.7%	2.8%
Ejaculation failure	2.4%	0.8%	0.5%
Semen volume decreased	1.8%	0.8%	0.3%
Loss of libido	1.7%	0.9%	1.3%
Dizziness	1.6%	1.7%	0.7%
Breast enlargement	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.

Point-Counterpoint:

Are We Ignoring Level One Evidence by Not Prescribing Appropriate Medical Therapy?

~ E. David Crawford, MD

Alternative Medicine Should Be the Choice

~ Mark A. Moyad, MD, MPH

CAM Should be the Choice: Can we really do any worse compared to the damage already done?

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Heart Healthy=Prostate Healthy

Heart Healthy=Prostate Healthy=Colon Healthy=Breast Healthy…

Moyad MA. Urol Nurs 2003;23(6):439-441.

BPH

Lifestyle factors

- Diet (energy restriction, fat, fruits & veggies…)
- Physical activity (HDL…)
- Obesity (BMI…)
- Hyperinsulinemia
- Smoking
- Other (age, height, HTN, vit. D…)

Moyad MA, Lowe FC. Am J Med 2008; 121 (8 Suppl 2):S34-S42.

Health Professionals-I

- N=51,529 men
- Mean age=53 +/- 9 years
- 8 yrs of follow-up
- Total cases=3523 (Surgery &/or AUA score)
- Noncases=24,388 (AUA score ≤7)

Suzuki S, et al. Am J Clin Nutr 75:689-697, 2002.

Health Professionals-II

- Total energy intake=51% increase
- Total dietary fat=No difference
- Increase in sympathetic activity?
- Increase in testosterone?
- Increase in abdominal obesity? Aromatization?

Bottom Line=Largest observational study.

Diet & BPH

- Higher caloric consumption=Higher risk
- Higher meat consumption=Higher risk
- More omega-3 fatty acids=Lower risk
- More fruits & veggies=Lower Risk

Bottom Line=Heart healthy=Prostate Healthy!!!

Koskimaki J, et al: Scand J Urol Nephrol 34:46-50, 2000. Yang YJ, et al: Clin Biochem 32:405-409, 1999.

Physical activity & BPH

- Health Professional Follow-up
- Walking=2-3 hours/wk=25% lower risk
- Total BPH (& surgery & symptoms)

Bottom Line=Walking/physical activity is good for your prostate.

Platz EA, et al: Arch Intern Med 158:2349-2356, 1998.

Exercise vs. Zoloft®

- Duke Trial, n=156, MDD
- 4 months-exercise (3x), zoloft® (150 mg), both
- Baseline, 4 & 6 months post-study
- 50% reduction w/exercise

Bottom Line=Zoloft® fast-exercise more effective.

Blumenthal, et al. Arch Intern Med 159:2349-56,1999./ Babyak,et al. Psychosom Med 62:633-8, 2000.

E=Exercise (resistance) (Bone Loss & LHRH?)

Increase:
-GH
-DHEA
-WBC…

- Australia Study (10 men, age=70)
- 20 wk high-intensity resistance exercise (5 months)
- 5 men on acute & 5 on chronic ADT

- Increased Muscle Strength, No change in Fat Mass
- No bone loss at any site + No Hgb change!

Bottom Line=Exaggerated? Moyad Experience.

Galvao DA, et al. (Spry N, Newton R…). Pros Cancer Prostat Dis, 2006.

Obesity & BPH

- Health professionals, Korean study
- Higher WHR/ waist circumference (≥43 vs <35 inches)
- Lower HDL

Bottom Line=WHR or waist circum= BPH risk (OR=2.38)

Giovannucci E, et al Am J Epidemiol 140:989-1002, 1994. Lee E, et al: Br J Urol 79:736-741, 1997

Smoking & BPH

- Population study (n=2100)
- OR=1.47 (current smokers)
- OR=1.38 (former smokers)
- Changes hormone levels (ATBC…)

Bottom Line=Reversible w/smoking cessation?

Koskimaki J, et al: J Urol 159:1580-1582, 1998.

Hyperinsulinemia & BPH

- Swedish study of 307 consecutive patients
- Annual BPH growth rate=higher in men with higher plasma insulin levels.

Bottom Line=Type II diabetes, HTN, obesity, & dyslipidemia=greater prostate growth.

Hammarsten J, Hogstedt B:Eur Urol 39:151-158, 2001.

Hyperinsulinemia/obesity & Urology

- BPH
- E.D.
- Prostate cancer
- Renal cell carcinoma (RCC)…

Bottom Line=Obesity epidemic=Urology case epidemic=Marriage of urology & preventive medicine.

Moyad MA: Urology January, 2002.

BPH

Supplements

- Saw palmetto (Serenoa repens=Sabal serrulata)
- Pygeum africanum (African plum)
- B-sitosterol (Hypoxis rooperi)
- Cernilton (Secale cercale=rye pollen)

Lowe FC, et al: Prostate 37:187-193, 1998. Moyad MA: Urol Clin N America, 2001.

Plant extract components of BPH supplements

- Phytosterols
- B-sitosterol
- Alpha-5-sterols
- Alpha-7-sterols
- Campesterol
- Stigmasterol
- Lupenone

Lowe FC, et al: Prostate 37:187-193, 1998. Moyad MA: Urol Clin N America, 2001

Plant extract components cont.

- Lupeol
- Terpenoids
- Fatty acids
- Lectins
- Plant oils
- Polysaccharides
- Flavonoids

Lowe FC, et al: Prostate 37:187-193, 1998. Moyad MA: Urol Clin N America, 2001

Plant extract components cont.

- Phyto-estrogens
- Coumestrol
- Genistein
- Daidzein
- Bowman-Birk inhibitor

Lowe FC, et al: Prostate 37:187-193, 1998.

Potential mechanisms of BPH supp & Lifestyle Changes.

- Placebo effect (1/3rd rule)
- Antiinflammatory
- Cholesterol absorption & metabolism
- SHBG
- Inhibition of 5-alpha-reductase
- Inhibition of aromatase
- Other antiandrogenic and/or antiestrogenic effects

Potential mechanisms cont.

- Detrusor function improvement
- Effect on growth factors=antiproliferative effects
- Block alpha-adrenergic receptors
- Free radical scavengers

Lowe FC, et al: Prostate 37:187-193, 1998. Moyad MA: Urol Clin N America, 2001.

Saw palmetto (meta-analysis)

- 18 randomized trials (n=2939)-Permixon®
- Decreased symp. scores, nocturia,peak urine flow
- Similar to finasteride

Bottom line=Mean study duration=9 weeks???

Wilt TJ, et al: JAMA 280:1604-1609, 1998

Saw palmetto (meta-analysis)

- Mean dose=320 mg/day
- No PSA change at this dose, 1-2% E.D. rate
- Use in Europe decreasing (Insurance???)

Bottom line=Mechanism of action???

Wilt TJ, et al: JAMA 280:1604-1609, 1998

Saw palmetto-UCLA

- N=44 (age 45-80), 6 months vs. placebo & finast.
- Clinical parameters not different from placebo
- Epithelial contraction

Bottom line=Mechanism of action???

Marks LS, et al: Urology 57:999-1005, 2001

Saw palmetto-mild finasteride or dutasteride effect?

	Finasteride	Saw palmetto
PSA	50% decrease	No change
DHT	70% decrease	No change
Testost.	10-20% increase	No change
Gland-vol.	20% decrease	No change
Epith. (%)	55% decrease	40% decrease
Gland-DHT	80% decrease	32-50% decrease
Gland-Tes.	5-10x increase	0-125% increase

Marks LS, et al: Urology 57:999-1005, 2001.

Permixon® vs. Tamsulosin-I

- 1 yr (n=542 from an n=704)
- 320 mg/day vs. 0.4 mg/day
- IPSS $\geq$ 10
- 11 European countries
- BMI=26-27
- Age=65 years

Debruyne F, et al. European Urology Annual Meeting, 2002.

Permixon® vs. Tamsulosin-II

- Equivalent results
- IPSS=-4.4
- Qmax=similar=1.8-1.9 mL/s
- No diff in irritative vs. obstructive sympt improve
- PSA stable + prostate vol decline w/permixon
- Ejac. Disorders=0.6% vs 4.2%

Debruyne F, et al. European Urology Annual Meeting, 2002.

Saw palmetto=hair tonic…?

- Inhibits 5-alpha reductase type II & I???
- Similar to propecia® & avodart®???
- Prostate cancer prevention=PCPT Trial???
- COX-inhibition???

Bottom line=millions in sales=an option

Moyad MA: Urol Clin N Am Feb, 2002.

Pygeum africanum (meta-analysis)

- Extract-bark of African plum evergreen tree
- 18 randomized trials (n=1,562 men)-Tadenan®
- Mean study=64 days (range 1-4 months)-100 mg

Bottom Line=Modestly but significantly improves urologic symptoms & flow measures. Long term?

Ishani A, et al: Am J Med 109:654-664, 2000.

B-sitosterol

- Extract of African star grass=Harzol®
- >70% dry weight=B-sitosterol (cholesterol?)
- 6 month trials (benefits up to 18 months)
- No effect on prostate size (stromal TGFbeta?)

Bottom Line=20 mg tid-symptoms not obstruction.

Berges RR, et al: BJU Intl 85:842-846, 2000.

Cernilton® (rye-grass pollen)

- Prostatitis and/or BPH
- Not improve flow rates, residual vol., prost. size
- Improves symptoms-esp. nocturia (anti-inflamm)
- N=444 (2 trials) 3-6 months

Bottom Line=60 mg tid for prostatitis. BPH?

Macdonald R, et al: BJU Intl 85:836-841, 1999.

Quercetin

- Naturally occurring bioflavonoid
- High conc. in red wine, onions, green tea
- Anti-oxidant
- Tyrosine kinase inhib.
- Nitric oxide inhibitor
- Anti-inflammatory….(COX…)

Moyad MA: Urology January, 2001

Quercetin trial

- N=30
- 500 mg twice daily vs. placebo (1 month)
- Non-bacterial chronic prostatitis
- NIH chronic prostatitis symptom score

Shoskes DA: Urology 54:960-963, 1999

Quercetin trial

	Placebo	Quercetin
Age (yr)	43.5	46.2
Symp. Duration	11.5 yr	10.5 yr
Initial WBC/hpf	13.1	16.9
Final WBC/hpf	8.3	2.9
NIH symp. Score (pain,urin,QOL)	20.2 to 18.8	21.0 to 13.1 (significant)

Shoskes DA: Urology 54:960-963, 1999

Quercetin-Conclusions

- Case-series
- 1 randomized small trial for 1 month
- Prosta-Q® (quercetin, bromelain, papain,…)
- Wine, green-tea??? Why not.

Bottom Line=Conflict of intererst? Be careful-Walmart sells it for 50-75% less. Cysta-Q®……

Shoskes DA: Urology 54:960-963, 1999

Cernilton®-Pollen extract

- 1 tablet tid (180 mg)-6 months (n=90)
- Similar results to quercetin trial
- Reduction in WBC,
- Decrease in complement C3 in ejaculate

Bottom Line=Cernitin company of Ohio. Prostaglandin & leukotriene inhibitor?…

Rugendorff EW, et al: BJU 71,433-438, 1993.

BPH & Prostatitis-Bottom Line

- Lifestyle changes=Primary Prevention
- Saw palmetto=320 mg/d (Quality control…)
- Pygeum africanum=100 mg/day
- B-sitosterol (Af. star grass=Harzol®)-20 mg TID
- Cernilton®=rye grass pollen=60 mg TID
- Quercetin=Prosta-Q®?=500 mg BID

Risk factors for ED

- Alcohol abuse
- Anemia
- CHD or PVD
- Depression
- Drug abuse
- Endocrine disorders
- Hyperlipidemia
- Hypertension
- Hypogonadism
- Peyronie's disease
- Smoking
- Trauma (bike seats??) or surgery to the pelvis or spine
- Vascular surgery

Moyad MA. Contemp Urology: submitted.

Lifestyle & ED

- N=1156, follow-up=8.8 yrs (Mass Male Aging)
- Ages 40-70
- Obesity status=significantly higher ED
- Physical activity=low ED risk (OR=0.5-0.8)
- Changes in smoking & alcohol=no effect

Derby CA, et al. Urology 56:302-306, 2000.

Randomized Trial-I

- Italian Study
- Randomized, 2-yrs!!!, n=110 obese (BMI ≥30)
- No diabetes, HTN, or dyslipidemia w/ED
- 21 or less on IIEF
- 55 men reduced calories, increase exercise

Esposito K, et al. JAMA 291:2978-2984, 2004.

Randomized Trial-II

- Age=43, BMI=36-37
- ED score=13-14 (range=1-25)
- hs-CRP=3.3-3.4 mg/L

Esposito K, et al. JAMA 291:2978-2984, 2004.

Randomized Trial-III

- BMI reduced 36.9 to 31.2
- Exercise increase from 48 to 195 min/week
- IIEF from 13 to 17 (17 men IIEF of 22 or more)
- BMI, Exercise, & hs-CRP associated w/IIEF
- hs-CRP=1.9 mg/L, HDL=48

Bottom Line=WOW!!!

Esposito K, et al. JAMA 291:2978-2984, 2004.

Moyad Secret=I Found the Magic Pill!

DRUG/MEDICAL CONDITION	SUGAR PILL IMPACT
E.D./F.S.D./BPH	25%
Hair Loss	42%
Hot Flashes (B. cohosh)	25-50%
Sleep (Insomnia)	25-50%
Weight Loss	6 pounds

#1 Magic Pill=Motivation (like smoking cessation)

Moyad MA. Urol Clin N Am, 2004

Placebo Effect

- Sildenafil=25% (women???)
- Apomorphine (40%)
- Vardenafil… (30-40%)
- Tadalafil (30%)

Bottom Line=Remember this???

Moyad MA. Urol Clin N Amer 29:11-22, 2002.

Lets Give Conventional Medicine More Opportunities?-I

- Provenge Example…just give us a chance

Moyad MA. Promoting Wellness, Ann Arbor Media Group, 2009.

Lets Give Conventional Medicine More Opportunities?-II

- ANEMIA DRUGS?
- ANGIOPLASTY
- ARTHROSCOPIC DEBRIDEMENT for OA
- ASPIRIN?
- BILATERAL LAPAROSCOPIC UTEROSACRAL NERVE ABLATION (LUNA) vs. Laparoscopy (no denervation) alone for CPP

Moyad MA. No BS Health Advice, Ann Arbor Media Group, 2009.

Lets Give Conventional Medicine More Opportunities?-III

- BLOOD PRESSURE DRUGS
- CHEMOTHERAPY FOR P. Ca..
- CHOLESTEROL-DRUGS (novel-torceptrapib)
- COLD REMEDIES
- COX-2 Inhibitors (Vioxx, 2-others…)
- CT SCANS…
- DIABETES (type II Medication)

Moyad MA. No BS Health Advice, Ann Arbor Media Group, 2009.

Increasing Awareness, Diagnosis, and Treatment of Hypogonadism

~ Jacob Rajfer, MD

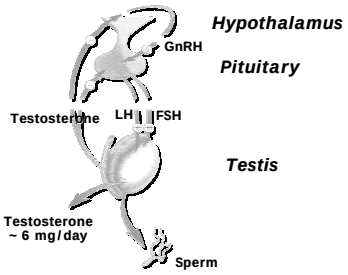
HYPOGONADISM

DEFINITION: PRODUCTION OF SEX HORMONES AND GERM CELLS IS INADEQUATE (ENDOCRINE SOCIETY)

DEFECT OF THE REPRODUCTIVE SYSTEM THAT RESULTS IN LACK OF FUNCTION OF THE GONADS (Wikipedia)

REDUCTION IN TESTICULAR FUNCTION
(www.nature.com/nrg/journal/v2/n4/glossary/nrg0401_245a_glossary.html)

FUNCTION OF TESTIS



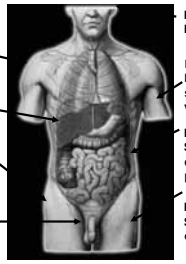
Adapted from Bagatell CJ, Bremner WJ. *N Engl J Med.* 1996;334:707-714.

FUNCTION OF TESTIS

1. SPERMATOGENESIS
   - A. BEGINS AT PUBERTY
   - B. CONTRIBUTES TO ABOUT 80% OF TESTIS VOLUME
   - C. DECREASES WITH AGING (FSH may increase)

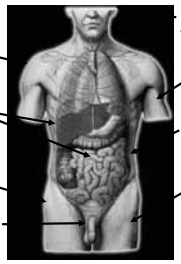
2. TESTOSTERONE PRODUCTION
   - A. BEGINS TO INCREASE AT PUBERTY
   - B. PRODUCES ABOUT 6 mg of T per day adult
   - B. DECREASES WITH AGING (LH may increase)

THE IMPACT OF TESTOSTERONE



Ref: AACE Hypogonadism Task Force. *Endocrinol Pract.* 2002;8:439-456
Morley JE, et al. *Metabolism.* 2000;49:1239-1242.

THE IMPACT OF ↓ TESTOSTERONE



Ref: AACE Hypogonadism Task Force. *Endocrinol Pract.* 2002;8:439-456
Morley JE, et al. *Metabolism.* 2000;49:1239-1242.

What Is a "Low" Level of Testosterone?

- Definition of "low T" varies widely
- Most labs define "low T" based on lowest 2.5% of values
- Yet prevalence is >2.5%
- Most clinical trials use threshold values ranging from 325-400 ng/dL
- Each person may have his own individual threshold value

Diagnosis of Androgen Deficiency/Hypogonadism

- Signs/symptoms of hypogonadism
  and
- Confirmatory blood test (sT, f T, bT)

(SALIVARY T MEASUREMENT OK BUT NOT STANDARDIZED)

Prevalence of Study-Defined Testosterone Deficiency in Older Men

Study	Ages	N	Serum total testosterone (mg/dL)	Prevalence
Lungimayr	50-87	817	<300	11.4%
Tenover	20-100	300	<317	22% (80-100y) 36% (80-100y)
Tenover (unpublished)	60-83	379	<350 <300 <250	36% 19% 8%
Morley (unpublished)	75-101	77	<245	33%

What is the most common cause of hypogonadism in men > 50 y age

- HIV
- Obesity
- Aging
- Hyperprolactinemia
- Medications

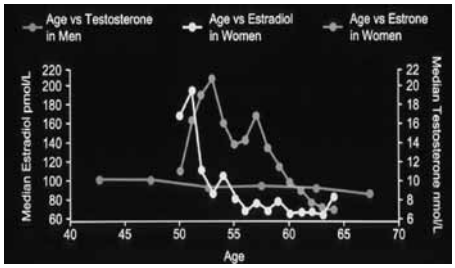
CAUSES OF HYPOGONADISM

- PRIMARY TESTICULAR FAILURE
- HYPOGONADOTROPIC HYPOGONADISM (KALLMANN'S SYNDROME, PITUITARY ADENOMA)
- TRAUMA
- IDIOPATHIC
- OBESITY
- SEVERE SYSTEMIC ILLNESS (INCLUDING HIV)
- MEDICATIONS
- CHANGES IN GnRH, PROLACTIN, CORTISOL, AND THYROID HORMONES
- NORMAL AGING

GnRH=gonadotropin-releasing hormone

Winters SJ. *Arch Fam Med.* 1999;8:257-263.
Tenover JL. *Endocrinol Metab Clin North Am.* 1998;27:969-987.

T in Men and E2 in Women During the Middle Years



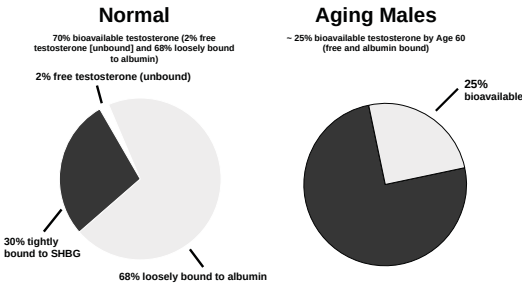
Massachusetts Women's Health Study (1981-1996) and Massachusetts Male Aging Study (1986-1989)

Age-related Changes in Testosterone Level

- New Mexico Aging Process Study
  - Men, 61-87 years old
  - Average rate of decrease in serum testosterone concentration is 110 ng/dL per decade

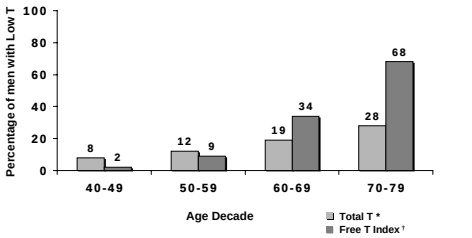
Morley JE, et al. *Metabolism.* 1997;46:410-413.

Testosterone Levels in Aging Males



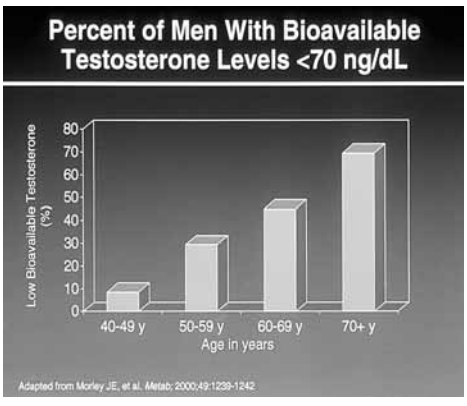
SHBG=Sex Hormone-Binding Globulin.

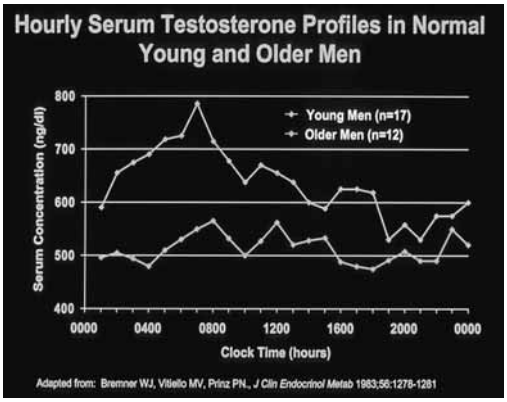
Prevalence of Low T in Men



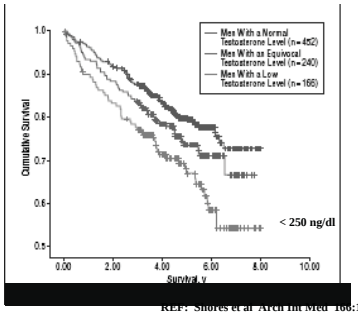
* <325 ng/dL
† <0.153 nmol/nmol (lowest value observed in normal men 21-45 years of age)

Harman SM, et al. *J Clin Endocrinol Metab.* 2001;86:724-731.





LOW T & MORTALITY



REF: Shores et al Arch Int Med 166:1660-1665, 2006

SERUM T & MORTALITY

n = 794, AGE X = 73.6y, 11.8 y f/u, 538 deaths
Rancho Bernardo, CA, pop based study

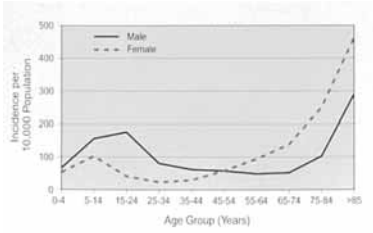
sT < 241 ng/dl had a > 40% greater mortality if sT > 370 ng/dl

It predicted increased CV and Respiratory but not cancer death

REF: Laughlin et al: JCEM 93:68-75, 2008

Long-term Consequences of Andropause

Annual Fracture Incidence



Donaldson LJ, et al. *J Epidemiol Community Health.* 1990;44:241-245.

THE AGING MALE : ANDROPAUSE

CLINICAL SYMPTOMS

1. LOSS OF LIBIDO, ED - 1st RECOGNITION
2. TIREDNESS, LETHARGY
3. DECREASED COGNITION
4. RESTLESSNESS, DEPRESSION
5. LOSS OF STRENGTH

ANDROPAUSE CAN BE DEFINED AS A SYMPTOM COMPLEX IN THE PRESENCE OF LOW LEVELS OF TESTOSTERONE

THE AGING MALE : ANDROPAUSE

CLINICAL SIGNS

- OSTEOPENIA / OSTEOPOROSIS
- LOSS OF MUSCLE MASS
- INCREASED VISCERAL ADIPOSITY
- TESTICULAR ATROPHY
- GYNECOMASTIA

REF: JCEM 71: 963-69, 1990; JCEM 85: 3276-82, 2000; Am J PSYCH 155: 1310-8, 1998; BEHAV NEUROSCI 108: 325-32, 1994; J Bone Miner Res 12:1883-43, 1997 Aging Male 2:8-15, 1999; Clin Endocrinol 47: 379, 403, 1997

The ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased “enjoyment of life”?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Positive questionnaire result is defined as a “yes” answer to questions 1 or 7 or any 3 other questions.

Morley JE. *J Gend Specif Med.* 2001;4:49-53.

TRT - WHEN?

- **HYPOGONADISM**
  OVERT LOW T LEVEL
  AT ANY AGE
- **ANDROPAUSE[1]**
  CLINICAL AGING SYNDROME

[1] F & S: 81:1437-40, 2004

DIAGNOSTIC TESTOSTERONE TESTING

(IF T LEVEL IS OR SUSPECTED TO BE LOW)

Additional Tests:

- **LH and FSH**
  - **To ascertain whether cause is primary or secondary**
- **Serum prolactin**
  - **High prolactin levels may suggest presence of pituitary tumor**

BENEFITS OF T – TX OF HYPOGONADISM (LOW T)

- **Preserve or improve bone mass**
- **Increase muscle mass, rearrange fat**
- **Increase strength, stamina and physical function**
- **Improve libido and mood, HRQoL**
- **Possibly decrease cardiovascular risk**

(MOST DATA ARE IN YOUNG MEN)

REF: Snyder et al, 1999, 2001; Sih et al, 1997; Kenny et al., 2001, 2002

ANDROGEN R_X OLDER MEN

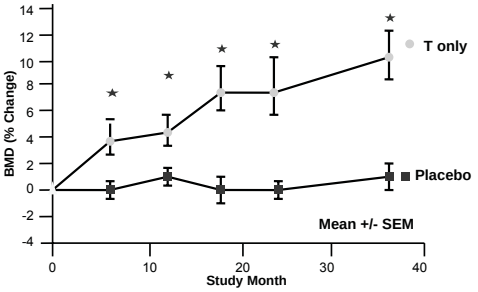
1. **BMD -spine_____ ⇧ 8% over 3 yrs**
   -hip_____ ⇧ 3% over 3 yrs
2. **Lean Body Mass ⇧ 8% over 3 yrs**
3. **Body Fat ⇩ 15% over 3 yrs**

REF: Adapted from Tenover. *Int J Androl.* 1999;22:300.

How long after starting TRT will a hypgonadal symptom start to improve

- 3 months
- 6 months
- 9 months
- 12 months.

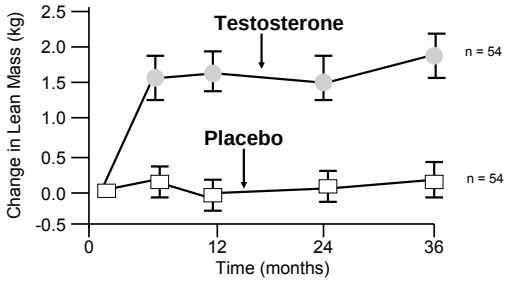
LS Spine BMD with TRT Aging Men



Amory JK, et al. J Clin Endocrinol Metab. 2004;89:503-510.

EFFECT OF T ON LEAN MASS

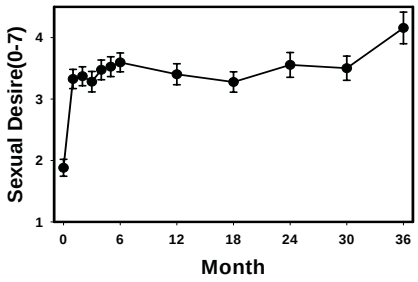
ELDERLY MEN (>65y)



Snyder PJ, et al. *J Clin Endocrinol Metab.* 1999;84:2647-2653.

NZ1

EFFECT OF T ON LIBIDO Hypogonadal Men (19-68y)



Wang, et al. *J Clin Endo Metab. 2004;89:2085-2998.*

Slide 30

NZ1 Change Y axis to 1 to 5. Text from previous slide added to notes here. Previous slide deleted

Nick Zitelli, 8/8/2006

CONTRAINDICATIONS OF TESTOSTERONE REPLACEMENT THERAPY IN MEN

- KNOWN OR SUSPECTED PROSTATE CANCER
- MALE BREAST CANCER
- KNOWN OR SUSPECTED SENSITIVITY TO INGREDIENTS USED IN TESTOSTERONE THERAPY SYSTEMS
- ELEVATED HEMOCRIT

ANDROGEN PREPARATIONS

ORAL

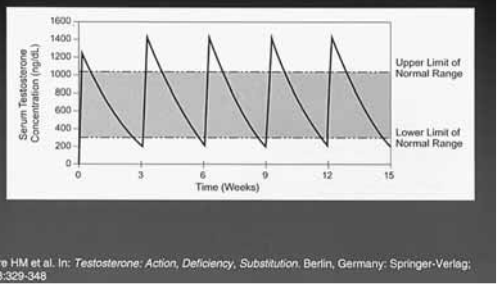
BUCCAL

PARENTERAL

TRANSDERMAL PATCH

TRANSDERMAL GEL

Testosterone Enanthate 250 mg Administered IM Every 3 Weeks



Behre HM et al. In: *Testosterone: Action, Deficiency, Substitution*. Berlin, Germany: Springer-Verlag; 1998:329-348

ANDROGEN PREPARATIONS

TRANSDERMAL PATCH

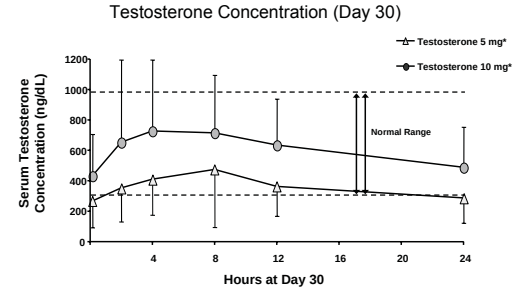
- **Testoderm (scrotal) - Delivers 4-6 mg testosterone daily**
- **Testoderm TTS (arm/torso/thigh skin)**
  Delivers 5 mg testosterone daily
- **Androderm (arm/torso/thigh skin)**
  Delivers 2.5-5 mg testosterone daily

ANDROGEN PREPARATIONS

TRANSDERMAL GEL

- **ANDROGEL OR TESTIM 1% (ARM/TORSO SKIN)**
  5 G/DAY

Testosterone 1% Gel



Steidle C, *et al. J Clin Endocrinol Metab.* 2003;88:2673. *Approx. delivered testosterone dose

CLOMIPHENE CITRATE

WORKS WHEN LH IS LOW

EFFECTIVE AS A Q O D PILL (25 – 50 mg)

MINIMAL SIDE EFFECTS

DOES NOT SUPPRESS SPERMATOGENESIS

CHECK SERUM T IN 2- 3 WEEKS

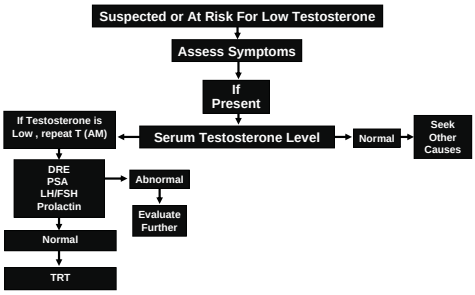
Rajfer J; Personal experience

TRT : NOT RECOMMENDED

hCG, DHEA, DHEAS, DHT

http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf

Diagnosis and Treatment Algorithm for Testosterone Deficiency



DRE=Digital Rectal Exam, PSA=Prostate Specific Antigen, TRT=Testosterone Replacement Therapy, LH=Luteinizing Hormone, FSH=Follicle Stimulating Hormone.

Patient Monitoring with Testosterone Replacement Therapy

Baseline, Pre-therapy:	**Testosterone levels** **Hgb and Hct** **PSA level** **DRE** **IPSS**
Day 30:	**Testosterone levels**
Day 90:	**Hgb and Hct** **PSA level** **DRE** **IPSS**
Repeat Day 90 Measures:	**Month 9 and every 6-12 months thereafter**

Hgb=Hemoglobin, Hct=Hematocrit, PSA=Prostate-Specific Antigen, DRE=Digital Rectal Exam, IPSS=International Prostate Symptom Score.

LOH

LOH: underdx. & undertx

LOH is a syndrome characterized primarily by:

(1) The easily recognized features of **diminished sexual desire (libido) and erectile quality** and frequency,particularly nocturnal erections.

(2) Changes in **mood** with concomitant **decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability**.

(3) **Sleep disturbances**.

(4) **Decrease in lean body mass** with associated diminution in muscle volume and strength.

(5) **Increase in visceral fat.**

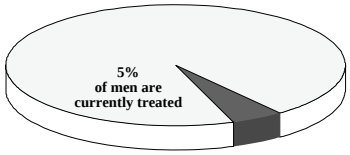
(6) **Decrease in body hair and skin alterations.**

(7) **Decreased bone mineral density** resulting in **osteopenia, osteoporosis** and increased risk of bone fractures.

Ref: ISA*, ISSAM, and EAU recommendations**
http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf

PREVALENCE OF HYPOGONADISM

4 TO 5 MILLION MEN WITH HYPOGONADISM



US Food and Drug Administration Updates. Skin patch replaces testosterone. Available at: http://www.fda.gov/fdac/departs/196_upd.html. Accessed January 19, 2004.

LOH : why is it under tx?

FEAR OF ADVERSE EVENTS

1. PROSTATE CANCER
2. BPH / LUTS
3. SLEEP APNEA
4. C V EVENTS
5. NO DATA TO SUPPORT ↓ MORTALITY

ARE THESE FEARS APPROPRIATE?

The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate

In men with metastatic prostate carcinoma to bone:
Acid phosphatase:

- **Rose in 3 men after testosterone injection**
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Since low T causes prostate cancer to shrink, it has been assumed that higher T causes prostate cancer to grow. There are little data to support this.

REF: Huggins, Hodges. *Cancer Research* 1941; 1: 293-297.

Are Serum Hormones Associated With The Risk Of Prostate Cancer?
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- **N = 1,576 men - Approximately 8 year follow-up**
- **70 men (4%) developed prostate cancer**
  - **Correlated positively with PSA levels**
- **No correlation with:**
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  - **Androstenedione**
  - **Estradiol**

Mohr, et al. Urology 2001; 57: 930-935

A Ten-Year Safety Study of the Oral Androgen Testosterone Undecanoate

N = 33/35 men followed for 10-year minimum; 8/33 >50 y age

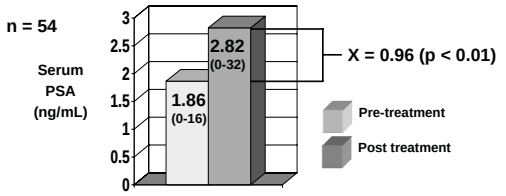
- No gynecomastia
- No liver abnormalities
- No prostate abnormalities
- 2/8 > 50y age showed slight decrease in urine flow
- Levels of T remained stable
  - No liver enzyme activation

REF: Gooren. J Androl. 1994; 15: 212-215.

Effect of Testosterone Supplementation on Serum PSA

Dose = 200-300 mg, Q2-4wks Mean F/U = 30.2 mos

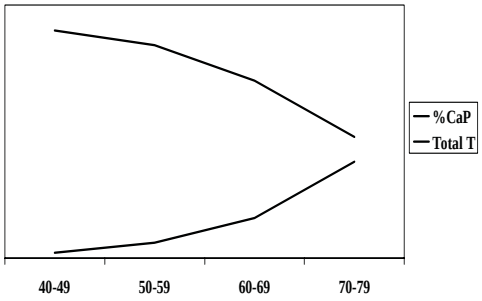
6 biopsies (11%), 1 PCa Mean Age = 60.4 yrs



(MEDIAN PSA : 1.01 → 1.56)

Gerstenbluth RE, et al. *J Androl.* 2002; 23:922-926.

CaP Prevalence Increases as T Levels Decline



Case series: reports of clinically apparent tumor diagnosed in men while on TRT

	TRT (months)	Patients	Prostate Cancer
Hajjar,1997	24	45	-
Sih,1997	12	17	-
Dobs,1999	24	66	3
Snyder,1999	36	54	1
Snyder, 2000	36	18	0
Wang, 2000	6	76	0
Kenny, 2001	12	34	0
Wang,2004	36	123	3
Total		433	**7 (1.6%)**

Effects of Exogenous Testosterone on PSA Levels

166 hypogonadal men
3 years of 1% testosterone gel
mean PSA increase of 0.37 ng/ml
3 men diagnosed with cancer (1.8%)

NOTE: THE PSA RISE OCCURS IN THE FIRST 6 MONTHS OF TREATMENT AND REMAINS STABLE THEREAFTER

Swerdloff et al. Aging Male 2003:6;207

Is the incidence in Hypogonadal men different?

- 345 "hypogonadal" men (<300 ng/dl)
  - PSA ≤ 4: 15% positive biopsy
  - Markedly suppressed T level: 20% positive biopsy
  - Low T and PSA≥2.0: 30% positive biopsy
  - Is this any different than the "baseline" established in PCPT?

Rhoden & Morgentaler. JUrol,2003

High Levels of Circulating Testosterone Are Not Associated With Increased Prostate Cancer Risk: A Pooled Prospective Study

- **N = 708 men (Finland, Norway, Sweeden) with prostate cancer**
- **N = 2,242 men without prostate cancer**
- **Mean lag time from blood draw to diagnosis was 14 years.**
- **Decrease in risk of prostate cancer for increasing levels of:**

Total Testosterone	**OR**	**0.80**
SHBG	**OR**	**0.76**
Free Testosterone	**OR**	**0.82**

Stattin, et al. Int J Cancer 2004; 108: 418-424

Testosterone Replacement in Hypogonadal Men With Prostatic Intraepithelial Neoplasia (PIN)

75 hypogonadal men (TT <300ng/dL) after 12 mo TRT

	With PIN	Without PIN
	PSA	
Before TRT	1.49	1.53
After TRT	1.82	1.78
	Biopsy for ↑ PSA	
Bx +	1	0
Bx -	2	4

Overall, one cancer in 75 men (1.3%). No sig difference with PIN

Rhoden et al. J Urol. 2003; 170: 2348-2351

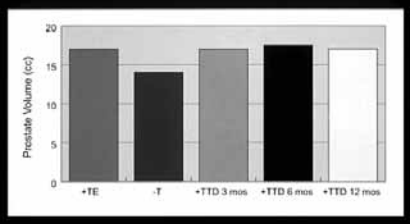
EFFECTS OF TRT ON PROSTATE

- PBO (n = 19) vs T (n = 21: TE 150 mg/2 wk) x 6 mo., TRUS + Bx @ baseline and 6 mo.
- T: 282 ⟶ 640 ng/dl (@ 6 mo); no diff PBO
- No increased CA with T tx
- No difference in pT or pDHT with TRT
- No change in PSA, genes for prostate growth

44-78y

REF: Marks et al., JAMA 2006:296:2351-61

Mean Prostate Volume +/- Treatment With Testosterone Enanthate (TE) or Transdermal Patch (TTD)



TRT and PSA

T trials have *inconsistently* shown a rise in PSA- the mean increase has been 0.3-0.43 ng/mL

Study	Duration	Increase in PSA	
		Placebo	Testosterone
	mo		*number/t*
Hajjar et al. (1997)[32]	24	–	–
Sih et al. (1997)[9]	12	0/15	0/17
Dobs et al. (1999)[11]	24	–	1/33
		–	0/33
Snyder et al. (1999)[8]	36	7/54	13/54
Snyder et al. (2000)[6]	36	–	–
Wang et al. (2000)[20]	6	–	0/76
		–	1/73
		–	4/78
Kenny et al. (2001)[7]	12	3/33	8/34

Duval reported no significant PSA changes in 50 men treated for over 5 years. (Aging Male, 2001)

TRT and BPH?

- **Results of studies are conflicting or insignificant**
- **No well-designed study yet done**
- **What we have so far:**
  7 studies of 3–36 months' duration conclude:
  - **Prostate volume** **No change**
  - **IPSS** **No change**
  - **Average urine stream** **No change**

Gettman M, et al. *AUA Update Series* 2001

• Despite decades of research there is no compelling evidence that T has a causative role in prostate cancer, that men with higher T levels are at greater risk of prostate cancer or that treating hypogonadal men with androgens increases the risk of converting the biological behaviour of prostate cancer

T & SLEEP APNEA

THERE IS LACK OF EVIDENCE TO SUPPORT ANY LINK BETWEEN OSA AND TRT

REF: Hanafy HM J Sex Med 4:1241-6, 2007.

ANDROGENS AND CV SYSTEM

Age = 51 y, n = 25 in each group; case control study for plasma total T; no TRT.

- **Lipid metabolism**
- **Insulin sensitivity**
- **Coagulation factors**
- **Vascular responsiveness**

DATA ARE INCONCLUSIVE AT THIS TIME

Simon D. JCEM 82:682-685, 1997

Androgens And Coronary Artery Disease

- **430 references**
- **"Cross-sectional data have suggested coronary heart disease can be associated with low T in men"**
  - **But no independent association in prospective studies**
- **"Based on current evidence, the therapeutic use of T in men need not be restricted by concerns regarding cardiovascular side effects"**
- **Hypoandrogenemia in men are associated with:**
  - **Visceral obesity**
  - **Insulin resistance**
  - **Low HDL cholesterol**
  - **Elevated: Triglycerides, LDL cholesterol**

Wu and von Eckardstein. Endocrine Reviews. 2003; 24: 183-217

Effects of Testosterone on Serum Lipid Profile in Middle Aged-Men: A Meta-Analysis

Hypoandrogenemia in men are associated with:
- Visceral obesity
- Insulin resistance
- Low HDL cholesterol
- Elevated: Triglycerides, LDL cholesterol

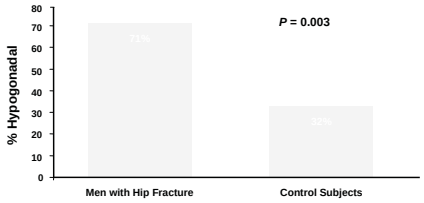
- Review of randomized- controlled trials (#29) OF TRT
- n = 1,083
- Mean age 64.5 yrs

- Total and LDL chol ↓
- HDL Chol mixed:
  - Small ↓, esp. in men with higher testosterones
  - Do not give supraphysiological levels

Isidori, et al. Clinical Endocrinology 2005; 63: 280-293

Hip Fractures in Aging Males

Increased Hypogonadism With Hip Fractures



Jackson JA et al. *Am J Med Sci.* 1992;304(1):4-8.

Elderly Population >65
% of the Total

Continents	1950	2000	2025	2050
Europe	8.2	14.6	20.2	25.8
North America	**8.2**	**12.4**	**18.5**	**21.5**
Latin America	3.7	5.4	9.6	16.7
Asia	4.1	5.8	9.6	15.9
World	5.2	6.8	10.0	15.1

U.N. Data

Conclusions

Testosterone Therapy is Safe In:
- Benign prostate disease (BPH)
- Risk of prostate cancer
  - Men receiving testosterone therapy
  - Men with high normal levels of T
  - Men at higher risk for prostate cancer (PIN)
- Effect on lipids and cardiovascular disease

Low Testosterone May Be Unsafe For:
- Incidence of prostate cancer
- Prognosis of prostate cancer
- Prevention of cardiovascular disease
- Prevention of osteoporosis / fractures
- Overall longevity ?

Point-Counterpoint: Late Onset Hypogonadism (LOH)

We are Under-diagnosing and Treating Men with LOH

~ Jacob Rajfer, MD

LOH is a Non-existent Disease

~ Robert E. Donohue, MD

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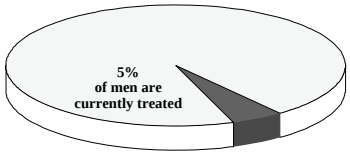

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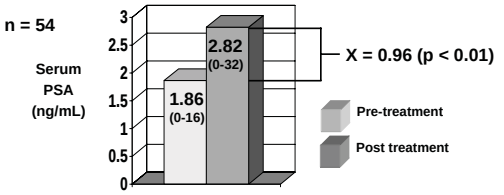
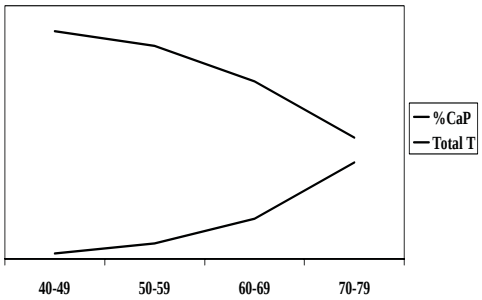


(MEDIAN PSA : 1.01 → 1.56)

Gerstenbluth RE, et al. *J Androl.* 2002; 23:922-926.

CaP Prevalence Increases as T Levels Decline



Case series: reports of clinically apparent tumor diagnosed in men while on TRT

	TRT (months)	Patients	Prostate Cancer
Hajjar,1997	24	45	-
Sih,1997	12	17	-
Dobs,1999	24	66	3
Snyder,1999	36	54	1
Snyder, 2000	36	18	0
Wang, 2000	6	76	0
Kenny, 2001	12	34	0
Wang,2004	36	123	3
Total		433	**7 (1.6%)**

Effects of Exogenous Testosterone on PSA Levels

166 hypogonadal men
3 years of 1% testosterone gel
mean PSA increase of 0.37 ng/ml
3 men diagnosed with cancer (1.8%)

NOTE: THE PSA RISE OCCURS IN THE FIRST 6 MONTHS OF TREATMENT AND REMAINS STABLE THEREAFTER

Swerdloff et al. Aging Male 2003:6;207

Is the incidence in Hypogonadal men different?

- 345 "hypogonadal" men (<300 ng/dl)
  - PSA ≤ 4: 15% positive biopsy
  - Markedly suppressed T level: 20% positive biopsy
  - Low T and PSA≥2.0: 30% positive biopsy
  - Is this any different than the "baseline" established in PCPT?

Rhoden & Morgentaler. JUrol,2003

High Levels of Circulating Testosterone Are Not Associated With Increased Prostate Cancer Risk: A Pooled Prospective Study

- **N = 708 men (Finland, Norway, Sweeden) with prostate cancer**
- **N = 2,242 men without prostate cancer**
- **Mean lag time from blood draw to diagnosis was 14 years.**
- **Decrease in risk of prostate cancer for increasing levels of:**

Total Testosterone	**OR**	**0.80**
SHBG	**OR**	**0.76**
Free Testosterone	**OR**	**0.82**

Stattin, et al. Int J Cancer 2004; 108: 418-424

Testosterone Replacement in Hypogonadal Men With Prostatic Intraepithelial Neoplasia (PIN)

75 hypogonadal men (TT <300ng/dL) after 12 mo TRT

	With PIN	**Without PIN**
	PSA	
Before TRT	**1.49**	**1.53**
After TRT	**1.82**	**1.78**
	Biopsy for ↑ PSA	
Bx +	**1**	**0**
Bx -	**2**	**4**

Overall, one cancer in 75 men (1.3%). No sig difference with PIN

Rhoden et al. J Urol. 2003; 170: 2348-2351

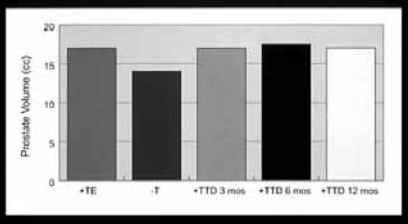
EFFECTS OF TRT ON PROSTATE

- **PBO (n = 19) vs T (n = 21: TE 150 mg/2 wk) x 6 mo., TRUS + Bx @ baseline and 6 mo.**
- **T: 282 → 640 ng/dl (@ 6 mo); no diff PBO**
- **No increased CA with T tx**
- **No difference in pT or pDHT with TRT**
- **No change in PSA, genes for prostate growth**

44-78y

REF: Marks et al., JAMA 2006:296:2351-61

Mean Prostate Volume +/- Treatment With Testosterone Enanthate (TE) or Transdermal Patch (TTD)



TRT and PSA

T trials have *inconsistently* shown a rise in PSA- the mean increase has been 0.3-0.43 ng/mL

Study	Duration	Increase in PSA	
		Placebo	Testosterone
	mo		*number/t*
Hajjar et al. (1997)[32]	24	–	–
Sih et al. (1997)[9]	12	0/15	0/17
Dobs et al. (1999)[11]	24	– –	1/33 0/33
Snyder et al. (1999)[8]	36	7/54	13/54
Snyder et al. (2000)[6]	36	–	–
Wang et al. (2000)[20]	6	– – –	0/76 1/73 4/78
Kenny et al. (2001)[7]	12	3/33	8/34

Duval reported no significant PSA changes in 50 men treated for over 5 years. (Aging Male, 2001)

TRT and BPH?

- **Results of studies are conflicting or insignificant**
- **No well-designed study yet done**
- **What we have so far:**
  7 studies of 3–36 months' duration conclude:
  - **Prostate volume** **No change**
  - **IPSS** **No change**
  - **Average urine stream** **No change**

Gettman M, et al. *AUA Update Series* 2001

• Despite decades of research there is no compelling evidence that T has a causative role in prostate cancer, that men with higher T levels are at greater risk of prostate cancer or that treating hypogonadal men with androgens increases the risk of converting the biological behaviour of prostate cancer

T & SLEEP APNEA

THERE IS LACK OF EVIDENCE TO SUPPORT ANY LINK BETWEEN OSA AND TRT

REF: Hanafy HM J Sex Med 4:1241-6, 2007.

ANDROGENS AND CV SYSTEM

Age = 51 y, n = 25 in each group; case control study for plasma total T; no TRT.

- **Lipid metabolism**
- **Insulin sensitivity**
- **Coagulation factors**
- **Vascular responsiveness**

DATA ARE INCONCLUSIVE AT THIS TIME

Simon D. JCEM 82:682-685, 1997

Androgens And Coronary Artery Disease

- **430 references**
- **"Cross-sectional data have suggested coronary heart disease can be associated with low T in men"**
  - **But no independent association in prospective studies**
- **"Based on current evidence, the therapeutic use of T in men need not be restricted by concerns regarding cardiovascular side effects"**
- **Hypoandrogenemia in men are associated with:**
  - **Visceral obesity**
  - **Insulin resistance**
  - **Low HDL cholesterol**
  - **Elevated: Triglycerides, LDL cholesterol**

Wu and von Eckardstein. Endocrine Reviews. 2003; 24: 183-217

Effects of Testosterone on Serum Lipid Profile in Middle Aged-Men: A Meta-Analysis

Hypoandrogenemia in men are associated with:
Visceral obesity
Insulin resistance
Low HDL cholesterol
Elevated: Triglycerides, LDL cholesterol

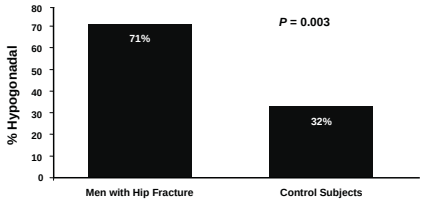
- **Review of randomized- controlled trials (#29) OF TRT**
- **n = 1,083**
- **Mean age 64.5 yrs**

- **Total and LDL chol ↓**
- **HDL Chol mixed:**
  - **Small ↓, esp. in men with higher testosterones**
  - **Do not give supraphysiological levels**

Isidori, et al. Clinical Endocrinology 2005; 63: 280-293

Hip Fractures in Aging Males

Increased Hypogonadism With Hip Fractures



Jackson JA et al. *Am J Med Sci.* 1992;304(1):4-8.

Elderly Population >65
% of the Total

Continents	1950	2000	2025	2050
Europe	8.2	14.6	20.2	25.8
North America	**8.2**	**12.4**	**18.5**	**21.5**
Latin America	3.7	5.4	9.6	16.7
Asia	4.1	5.8	9.6	15.9
World	5.2	6.8	10.0	15.1

U.N. Data

Conclusions

Testosterone Therapy is Safe In:

- Benign prostate disease (BPH)
- Risk of prostate cancer
  - Men receiving testosterone therapy
  - Men with high normal levels of T
  - Men at higher risk for prostate cancer (PIN)
- Effect on lipids and cardiovascular disease

Low Testosterone May Be Unsafe For:

- Incidence of prostate cancer
- Prognosis of prostate cancer
- Prevention of cardiovascular disease
- Prevention of osteoporosis / fractures
- Overall longevity ?

LOH is a non-existent disease

Robert E. Donohue M.D.

Denver V.A. Medical Center

University of Colorado

Hypogonadism

Hypogonadism in men is a clinical syndrome that results from the failure of the testis to produce physiologic levels of Testosterone and the normal levels of spermatozoa due to disruption of one or more levels of the HPG axis.

Disease

Any deviation from or interruption of the normal structure or function of any part, organ or system, or combination thereof, of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology and prognosis may be known or unknown

Syndrome

A set of symptoms which occur together; the sum or signs of a morbid state,

Hypogonadism

sub-categories

Rx young males with Androgen deficiency with T

Rx Sexual disfunction with T

Older men with lower serum T

Chronic illness and lower serum T

Gluco-corticosteroid treated men

Hypogonadism

serum Testosterone

< 325 ng/dL

60's	20%
70's	30%
80's	50%

Baltimore Longitudinal Study of Aging 2001

Hypogonadism

serum Testosterone

secondary; not primary

[role of obesity ?]

LH 9.4 to 13.8 15yers

FSH 14.1 to 27.4

New Mexico Aging Process 1997

LH 0.9% / year

FSH 1.3% / year

Massachusetts Male Aging Study 2002

Hypogonadism

serum Testosterone

total

free

bound to albumin

SHBG

bio-available free + albumin

Am Soc Repro Med, F&S 86, S236, 2006

Hypogonadism

benefits of therapy
older men

long term benefit in
conditions of concern
to patient and MD ?

Hypogonadism

serum total Testosterone
assay is widely available
bio-available and free* T levels
are not widely available;

***free - challenged assay**

Hypogonadism

total Testosterone
free Testosterone index*
total Testosterone / SHBG

*** bio-available Testosterone**

Hypogonadism

concensus
androgen replacement candidates
hormonal criteria, No
clinical criteria, No
additional studies to elucidate
patients who might benefit from
androgen replacement

Hypogonadism

Endocrine Society

Testosterone total

< 200 ng / dL; treat

200 – 400 ; beneficial ??

> 400 ng / dL; unlikely to benefit

Bhasin JCE&M; 91: 1995, 2007

Hypogonadism

Endocrine Society

measure LH when serum Testosterone low, < 150 ng / dL

if LH normal or low order Prolactin, pituitary MRI,

Hypogonadism

candidates

clinical manifestations of ADAM

ostepenia, muscle mass strength down, stamina energy down,

low libido, E quality, irritability, impaired cognition,

Androgen Deficiency suggestive

sexual development
libido and activity
decreased erections
breast discomfort
gynecomastia
loss of body hair
shrinking testes
infertility
height loss
muscle bulk/ strength less
hot flashes
sweats

Androgen Deficiency associated

decreased energy, motivation, initiative, aggressiveness,
self confidence, physical or work performance
feeling sad or blue, depressed, weak
poor concentration, memory
sleep disturbance, anemia,
increased body fat, BMI

Hypogonadism

candidates
clinical manifestations of ADAM
ostepenia, low libido,
muscle mass E quality,
strength down, irritability,
stamina impaired
energy down, cognition,

Hypogonadism

candidates
clinical manifestations of ADAM
PLUS
low serum Testosterone or
bio-available Testosterone or
FTI
No contraindications to treatment!

Hypogonadism

candidates
threshold Testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur is not known !

Hypogonadism

candidates

Testosterone concentration below which T administration improves outcome is unknown and may vary patient to patient and among target organs

Hypogonadism

candidates

available evidence does not support the use of an arbitrary threshold for T below which clinical androgen deficiency occurs and that confirms the diagnosis of hypogonadism.

Hypogonadism

candidates

threshold Testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur is not known !

Hypogonadism

concensus

androgen replacement candidates

hormonal criteria, No

clinical criteria, No

additional studies to elucidate patients who might benefit from androgen replacement

Hypogonadism

Sex Hormone Binding Globulin
- **increases with age**
- **decline in bio-available**

Testosterone with normal aging is greater than for total Testosterone

Sex Hormone Binding Globulin

decreased	increased
obesity	aging
nephrotic Syn	cirrhosis
hypothyroidism	hyperthyroidism
steroids, progestins androgens	anticonvulsants estrogens HIV infection

Hypogonadism

- **bio-available Testosterone**

epidemiological studies
- **bone mineral density**
- **sexual function**
- **cognition**

- **metabolites**

Estrogen bone; DHT prostate

Hypogonadism

libido	osteopenia
potency	osteoporosis
fatigue	lipid profile
strength loss	cholesterol
muscle loss	trigylycerides
weight gain	LDL, VLDL
anemia	HDL

Hypogonadism

initial evaluation

breast
heart
lungs
rectal **23,580 rectal tumors**

CBC, PSA

Hypogonadism

No evidence that clinical response depends on Testosterone form.

Benefits relate to level achieved !

endogenous / exogenous

goal – raise T over pretreatment values but not exceeding levels of normal young adult males

Hypogonadism

normal range

Testosterone 300 ng / dL*****

free Testosterone 50 pg / dL

*** Use your reference laboratory**

Hypogonadism

lack on consensus on

1] case definition

2] extent to which androgen deficiency is an important health problem

3] lack of data on screening tools, population screening cannot be evaluated at present.

Hypogonadism

long term health consequences are unknown in two largest subsets of men with low Testosterone: 1] older men and 2] men with chronic diseases Impact, untreated, on mortality is unclear.

Hypogonadism

dehydro-epiandrostene, DHT
50 – 100 mg
does not increase serum T
androgen deficiency benefit ???

Hypogonadism

replacement side effects
IM pain, mood swings,
elevated hematocrit,
patch
scrotal site irritation
non-scrotal " , urticaria
gel skin irritation

Hypogonadism

measure Testosterone
IM T 350 – 700 ng / dL
controversial –at 8 AM best
patch T 3 to 12 hours
gel T 1 to 2 weeks
buccal T before fresh tablet

Hypogonadism

monitoring

weight gain	**LUTs**
peripheral edema	**sleep state**
breast tenderness	**DRE**
gynecomastia	

measure T, Hgb, PSA
LFTs and lipids, No

Hypogonadism

monitoring
examination @ 3 and 9 months
yearly thereafter
CBC, PSA*, T
bone mineral density – at 2 years
*** Rapid PSA rise – unmasked Ca P**

Hypogonadism

therapy risks

fluid retention
erythrocytosis
sleep apnea worsened*
benign* or malignant* prostate problems * YES * No
cardiovascular disease risk

Hypogonadism

contraindications

absolute	**relative**
Ca prostate	**severe apnea**
breast Ca	**LUTs**
Hematocrit > 55%	**> 52%**
sensitivity	**fluid retention**

Testosterone trials

testosterone – young men

Improvement in overall sexual activity, sexual thoughts and fantasies, attention to erotic stimuli, frequency and duration of nighttime erections, hair growth, increases in fat-free mass, muscle strength, decrease in fat mass.

Testosterone trials

Bone mineral density increases but effect on fracture risk is unknown. T improves positive and reduces the negative aspects of mood, improves energy and sense of well-being, and some studies report improvement in visuospatial cognition and verbal memory.

Testosterone trials

recommendations

The recommendations to treat young, healthy, hypo-gonadal men with T places a higher value on alleviating hypo-gonadal symptoms and other benefits , and lower value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

Testosterone trials

testosterone - older men

There are no randomized, placebo- controlled trials of T therapy on depression, cognition, fracture fragility, quality of life and cardiovascular outcomes; libido improved but no significant improvement in self-reported erectile function.

Testosterone trials

bone mineral density [BMD]

Inconsistent and imprecise data

@ 1 year - insignificant

longer trials – 1 to 3 years

lumbar BMD 2% increase

femoral neck, No

Testosterone trials

bone fracture

No trial reporting the effect of Testosterone on bone fractures was reported.

Testosterone trials

body composition

Significantly greater increase in LBM [lean body mass] and reduction in fat mass.

Body weight change did not differ significantly.

Testosterone trials

muscle strength and physical function

Greater improvement in grip, lower extremity strength but measures of physical function were inconsistent .

Testosterone trials

11 randomized clinical trials, 474 men

muscle strength

larger effects for lower extremity muscle strength than upper extremity - injected >topical

Ottenbacher J Am Ger Soc 54: 1666, 2006

Testosterone trials

sexual function

Two placebo- controlled trials on overall sexual satisfaction yielded imprecise results.

Testosterone trials

sexual function

17 trials - 862 men

low T; moderate, non-significant and inconsistent effect of T on satisfaction with erectile function;

large effect on libido

none on sexual satisfaction

Testosterone trials

sexual function

17 trials - 862 men

low normal and normal T

small satisfaction of EF effect

moderate, non-significant libido

no effect sexual satisfaction

Bologa Mayo Cl Pro 82: 20, 2007

Testosterone trials

quality of life

The results were imprecise and inconsistent across trials.

There was improvement in physical function domain.

Testosterone trials

depression

Three randomized T trials for 3 months or longer showed no significant effects on depression.

Inconsistent and imprecise results limit the inferential strength.

Testosterone trials

cognition

Three placebo-controlled randomized trials, one which studied men with Alzheimer's Disease and low Testosterone, reported imprecise effects on several aspects of cognition; none of which were significant after pooling data.

Testosterone trials

adverse outcomes

19 randomized trials

Prostate Events

Rates of prostate Ca, PSA > 4 ng and prostate biopsies were numerically higher but not significantly higher.

Testosterone trials

adverse outcomes

Erythrocytosis

T treated men were four times as likely to experience a rise in hematocrit above 50%.

Testosterone trials

adverse outcomes

The frequency of cardiovascular events, sleep apnea or death did not differ significantly between groups.

Cardiovascular risk

30 trials; 1642 men

Low Testosterone

inconsequential changes in BP and gylcemia; lipd profile shows

Cholesterol [-0.22],

HDL [-0.04],

LDL [0.06]

Trig [-0.27]

Cardiovascular risk

30 trials; 1642 men

Currently available evidence weakly supports the inference that T use is men is not associated with important cardiovascular effects. We need large, randomized, clinical trials of men at risk for CVD.

Haddad Mayo Cl Pro 82: 29., 2007

Testosterone trials

adverse outcomes
Lipid profiles
5 trials reported insignificant changes in major lipid fractions.
Cholesterol - 4mg/dl
HDL - 6 mg/dl
triglycerides - 9 mg/dl

Testosterone trials

HIV infected men
Low T yielded weight loss*, lean body mass*, AIDS wasting* AIDS progression, depression* and loss of muscle mass*, mood** exercise capacity, and QoL**.
* Improved ** minimal to none

Testosterone trials

gluco-corticoid- treated men
5 – 7.5 mg Prednisone or > changes in muscle mass and BMD
bronchial asthma and COPD
greater gain in LBM and decrease in fat mass; increase in lumbar, +/- femoral BMD; no fracture data

Testosterone trials

gluco-corticoid- treated men
higher value on potential benefit and lower value of avoiding adverse events, burdens of T administration, monitoring and cost and long term safety

Testosterone trials

summary – older men

small sample size, healthy men, normal or low T, asymptomatic, Insufficient power to detect meaningful gains in outcomes or changes in cardiovascular or prostate event rates

Testosterone trials

recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

References

1

References

Testosterone trials

recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

Testosterone trials

recommendations

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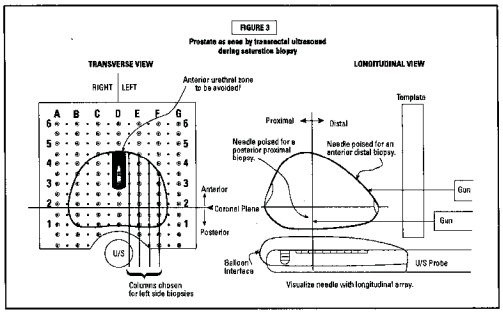
Testosterone trials

recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

Prostate Biopsy

transition zone biopsies
suspicious; PSA rise, velocity +,
negative biopsies,
negative repeat biopsies,
negative 12 or + core biopsies,
biopsy TZ and anterior, separate specimens from repeat PZ cores



Prostate Biopsy

146 patients

PNBx		Saturation Bx
12	cores	59 [17-124]
1	positive	2 [0-19]

Prostate Biopsy

technique

combination

TRUS-guided transrectal biopsies for diagnostic biopsies

TRUS-guided perineal biopsies for saturation biopsies

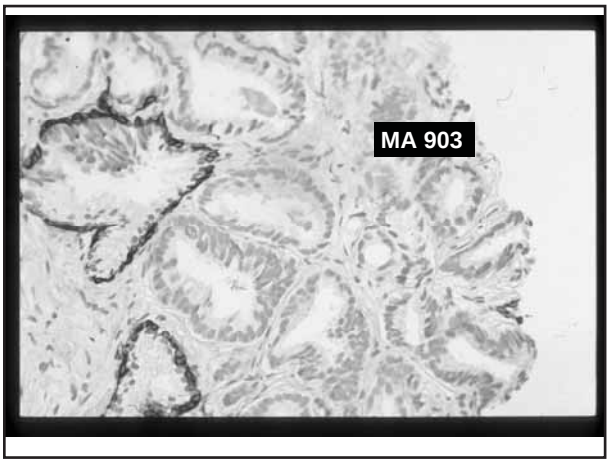
Prostate Biopsy

146 patients

PNBx	Saturation Bx Gleason
1	5 0
119	6 62
12	7 49
0	8 5
14	neg 30

Thompson

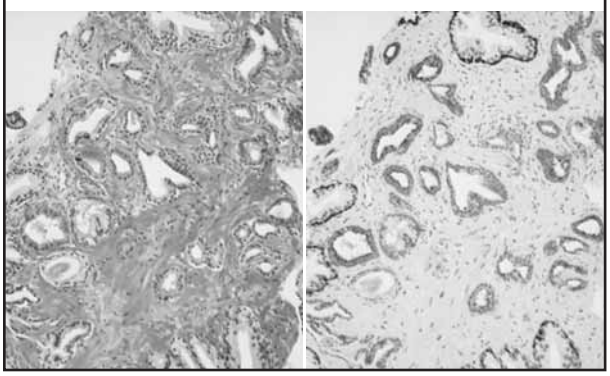
Google
Prostate Cancer Risk Calculator
risk 44%
high grade 14%



Racemase and P^{63}

stains
MA 903 - basal cell cytoplasm;
benign, 2 layer prostate glands
no basal layer = malignancy
Racemase – cytoplasmic epithelial cell; stains = malignancy
P^{63} – basal cell nuclei, basal cells present, stain = benign gland
R +, P^{63} - = Ca;

AMACR + p63 in PCa



Prostate Biopsy

43 patients

PNBx	Saturation Bx	
11	cores	61.8
1.5	positive	3.9

Prostate Biopsy

43 patients

PNBx	Saturation Bx	
	Gleason	
41	6	24
2	7	10
0	8	7

Prostate Biopsy

43 patients

PNBx	Saturation Bx	
43	unilateral	20
0	bilateral	16
0	negative	7

Prostate Biopsy

43 patients

PNBx	Saturation Bx	
43	unilateral	20
0	bilateral	16
0	negative	7

Prostate Biopsy

The future

Djavan's technique

Thompson's risk calculator

tumor localization technique

PCA 3

Prostate Biopsy
Oct 2000 – September 2007

percentage positive

#	pos / total	percentage
3 cores	106 / 433	24.4%
4 cores	115 / 407	28.2%
5 cores	152 / 449	33.8%
6 cores	154 / 418	36.8%
7 cores	128 / 364	36.2%

Biopsy Results

technique altered

7/01/07 to 11/28/2007; 41+ / 165, 25%

technique corrected

12/01/07 to 3/30/08; 77+ / 273, 28%

technique re-corrected; re-re-corrected

March 08 46%; October 08 50%

April 08 41%;

BUT 31 / 85 36% [4-6]; 37 / 100 37% [7-9,08]

FIGURE 1. Prostatic adenocarcinoma (histologic patterns). Standardized drawing for grading system.

~ Robert E. Donohue, MD

Testis Pain

42 year old male,
bilateral testicular pain,
chronic, intermittent,
No other GU or GI symptoms
nor fever,
left testis lower than right

Testis Pain

no history of
cryptorchidism,
atrophy,
trauma,
surgery in groins,

Testis Pain

history
hypertension
Rx Lisinopril
left knee pain,
arthrosocpy

Testis Pain

physical examination
scalenus anticus nodes normal
no gynecomastia
no upper abdominal mass
no groin scars

Testis Pain

physical examination
pubic hair pattern normal
penis circumcised, normal
left testis, epididymis, vas normal, varicocele

Testis Pain

physical examination
right testis located higher than normal in the scrotum,
smaller than the left testis
no mass palpable in testis,
normal epididymis and vas

Testis Pain

chest x-ray nomral
alpha feto-protein 2.9
beta HCG < 2

Fad Diets and Dietary Supplements for Urology Patients: What Works and What's Worthless

~ Mark A. Moyad, MD, MPH

Diet & Dietary Supplements: What works & what is worthless from A to Z?!

Mark A. Moyad, MD, MPH
Jenkins/Pokempner Director of Preventive/Alternative Medicine
University of Michigan Medical Center
Dept of Urology
Ann Arbor, MI
moyad@umich.edu

Hobbies: Telling you that less is More!

Disclosure Statement

- I am a consultant for Abbott Labs Inc., NBTY, Embria, Farr Labs, FTC, & Guthy-Renker, Inc & may receive royalties for product invention from Guthy-Renker and on the speakers bureau for Abbott Labs, Inc. I will not be discussing drugs that are unlabeled or used for investigational purposes.

Overview of the Talk

- Pre-Game Locker Room Speech
- A-Z=Lifestyle/Pill=Game time
- Post-Game Summary

Dietary Supplements=Big Business (Where is the Objectivity?)

Annual Sales of nutritional supplements in the U.S. (CDC/NIH)?

A) 1 Billion
B) 3 Billion
C) 5 Billion

(Nahin RL, et al for the National Health Statistics Report 2009;18, July 30, 1-14)

Moyad Rule

- "Approximately 2-3 weeks before any surgical or radiation procedure please stop the use of **most OTC dietary supplements…"**
- LESS IS MORE! (FDA/Canada & 2010 Maybe)
- Most natural products are not better for you…

Moyad MA. Promoting Wellness for Prostate Cancer Patients, 2006.

PRE-GAME-Probability Diet

BOTTOM LINE=Heart Healthy=Bladder Healthy=Bone Healthy=Brain Healthy=Breast Healthy=Colon Healthy=Eye Healthy=Joint Healthy=Kidney Healthy=Prostate Healthy=Skin Healthy=Sexual Health=ALL HEALTHY!!!

(Vioxx vs. Vitamin E vs. Fish Oil…?)

Moyad MA. Promoting wellness for prostate cancer patients. JW Edwards Publishing, 2006.
Moyad MA, Carroll PR. Urol Clin N Am 2004;31:289-300.

BUCKLE UP!-Last sec. Tips…

- Nutrients can be added back to diet-unlike Rx (selenium, folic acid)="Over-Anti-Oxidation Of Our Population!"

LESS IS MORE…
LESS IS MORE…
LESS IS MORE…
LESS IS MORE…

Moyad MA, Carroll PR. Urol Clin N Am 2004;31:289-300. & Moyad MA. AUA Update 37 & 38, 2008.

B=Belly Fat

Just Released!
-EPIC Study!
-9 countries

-360,000!!!
-Most Accurate
-10 years
-15,000 deaths

-BMI=25-26 men

-BMI=24-25 women


General and Abdominal Adiposity and Risk of Death in Europe

-BMI & WC= General + Abdominal Obesity

-CVD
-Cancer
-Overall Mortality

(Pischon T, et al. N Engl J Med 359:2105-2120, 2008).

B=BELLY FAT
(WC=Waist Circumference=Belly)

WC (U.S.)	WC (METRIC)	What this means?
Men-<35 inches	<89 cm	"Normal"
Men-35-39 inches	89-100 cm	"Overweight"
Men-≥40 inches	≥101 cm	"Obese"
Women-<32.5	<83 cm	"Normal"
Women-32.5-36	83-93 cm	"Overweight"
Women-≥37	≥94 cm	"Obese"

Moyad MA. Promoting Wellness, 2009 & No BS Health Advice, 2009.

B=BELLY FAT/FAT (Moyad MA. ABCs Nutr, 2004)
(HEART HEALTHY=ALL HEALTHY)

FAT TYPE	PRIMARY SOURCE	COMMENT
Monounsaturated (Oleic acid…)	Cooking oils + nuts..	GOOD
Polyunsaturated (Omega-3s)	Soy, Flax, Fish…	GOOD
Saturated (hydrogenated)	Dairy/non-game-meat…	BAD? Not Exactly!
Trans (partially hydrogenated)	Marg/shorten/deep fried/fast-food…	BAD

B=BELLY FAT (surgery)
(Saturated Fat=Higher Calories!)

TYPE OF MILK	SATURATED FAT (8 oz)	TOTAL CALORIES
Skim Milk	0 grams	80 Calories
1% Milk	1.5 grams	100 Calories
2% Milk	3 grams	120 Calories
Whole Milk	5 grams	150 Calories
Reindeer Milk	Does it matter?!	580 Calories

Moyad MA. No BS Health Advice, 2009. & Strom SS, et al. Int J Cancer 2008;122:2581-2585.

B=BELLY FAT (Just In-2 year Harvard Trial)

SPEICAL DIET (1400 Calories) (n=811)	RESULTS (2-years)
Fad Diet I	-9 lbs=4 kg, -2 inches=5 cm
Fad Diet II	SAME
Fad Diet III	SAME
Fad Diet IV	SAME

N Engl J Med, On-Line, March, 2009.

B=Belly Fat Calerie/CR Study (acts like LHRH)

- n=48, 6-months, 37-39 yrs, BMI=27-28, 175-180 lbs
- Control=2 lbs
- CR (25%)=17-18 lbs
- CR (12.5%) + Exercise (12.5%)=17-18 lbs
- Severe CR (890 cal/day until 15% loss)=24-25 lbs
- Insulin reduced, core temp reduced, thyroid, DNA damage…

Heilbronn LK et al. JAMA 295(13):1539-1548, 2006.

B=BELLY FAT/FAT= The Magic Pill?

- Rimonabant (Acomplia®)=No Chance!
- "ALLI" ($2/day)=Not exciting!
- Meridia (Sibutramine)=Maybe!
- Green Tea=Why?
- FISH OIL & EXERCISE=Why not?
- Fiber (30gram/d)=Why not?

Moyad MA. No BS Health Advicce, 2009.

C=Calcium (Tang BMP, et al. Lancet 2007;370:657-666_ 1200-1500 mg/d for men (11-18%)!

CALCIUM CARBONATE (40% elem)	Caltrate, Oscal…	-W/Meals -Colon? -PSA? (PCPT…)
CALCIUM CITRATE (21% elem)	Citracal…	-W/or w/out meal -Best for stone patients…
CALCIUM PHOSPHATE (39% elem)	Posture-D…	-W/or w/out meal

Moyad MA. Promoting Wellness for Prostate Cancer Patients, 2009. & Panju AH, et al BJU Int 2009;103:753-7.

Would You Take This Pill If It was Free & Had No Side Effects?

Physical health	Mental Health
• Premature death=30-50%	-Depression
• Heart disease=40-50%	
• Stroke=30-50%	
• Type II diabetes=30-40%	
• BREAST CANCER=20-30%	
• Colon cancer…=30-50%	
• Osteoporosis=40-50%	
• Kidney stones, E.D., & FATAL P.C.!!!	

(Manson J, Amend P. The 30-minute fitness solution, 2006.)

E=Exercise/Fatigue… (Weight Lifting & Cancer Study)

2 sets
8-12 repetitions
3 times per week

- Calf raise
- Leg extension
- Leg curl
- Chest press
- Latissimus pull-down
- Overhead press
- Triceps extension
- Biceps curl
- Modified curl-up

Segal RJ, et al. *J Clin Oncol.* 2003; 21:1653-1659.

Just Released!

-Randomized Trial of Weight-Lifting In LHRH & Radiation.

-Univ of PA Lymphedema Study
N Engl J Med (n=141, 2x/wk, 1-year)

Segal RJ, et al. J Clin Oncol 2009;27:344-351. & Schmitz KH, et al. N Engl J Med 2009;361:664-673.

E=Exercise/Wt Lifting (Bone Loss & LHRH?)

Increase:
-GH
-DHEA
-WBC…

- Australia Study (10 men, age=70)
- 20 wk high-intensity resistance exercise (5 months)
- 5 men on acute & 5 on chronic ADT

- Increased Muscle Strength, No change in Fat Mass
- No bone loss at any site + No Hgb change!

Bottom Line=Rx-Exaggerated? Moyad Experience.

Galvao DA, et al. (Spry N, Newton R…). Pros Cancer Prostat Dis, 2006.

E=Exercise
Aerobic vs. Weight Lifting

HEALTH AREA	AEROBIC	WT. LIFTING
Bone Health		Yes!!!
Burn Fat/Metab	Yes!!!	Yes!!!
Strength		Yes!!!
Glucose/Insulin	Yes!!!	Yes!!!
Lipids + hs-CRP	Yes!!!	
HR/BP at rest	Yes!!!	
Mental Health	Yes!!!	Yes!!!
Overall Survival	Yes!!!	Yes!!!

Braith RW, Stewart KJ. Circulation 113:2642-2650, 2006.

AMERICAN GINSENG

Rx for Fatigue?!-Maybe! N=282!

(Barton DL, et al. Mayo Clinic. Abstact 9001, page 493s, ASCO, 2007, Brief Fatigue Inventory)

8 wk data

ENDPT	Placebo	750 mg/d	1000 mg/d	2000 mg/d
BFI-sub	---	---	---	Best
BFI	---	---	---	Best
Scale	---	---	Best	Best
Physical	---	---	Best	Best
% Perceived	---	---	Best	Best (25-27%)
% Satisfied	---	---	Best	Best (34%)

F=FATIGUE
(Summary)

- Lifestyle Option=Weight-Lifting
- American Ginseng-1000-2000 mg/day-New possibility?
- Rx=Provigil (modafanil=100-200 mg/d)

Barton DL et al: ASCO/AUA-2007

Moyad MA et al: Sem Prev Alt Med-2007

F=FIBER (internal Anti-Aging)

20-30 Grams Per day for:
-Acid Reflux
-BP
-Cholesterol
-Constipation
-Diverticulitis
-Glucose
-Hem..
-PSA
-Prebiotic!!
-Weight Loss…

SOLUBLE (VISCOUS) FIBER SHOULD BE INCREASED!

WHAT ABOUT INSOLUBLE FIBER? (All-Bran, Flax…)

Moyad MA, et al. No BS Health Advice, 2009. & Anderson JW, et al. Nutr Rev 2009; 67:188-205.

Flaxseed-Presurgical Rand Trial (30 grams--6 wks pre-surg, n=161)

	Placebo	Flaxseed	Low-Fat	Flax+LF
TC (mg/dl)	+9	-26	-46	-37
LDL	-14	-17	-29	-21
Weight	+0.3 kg	-1.3 kg	-1.7	-1.1
Pathology	---	Sign Ki-67	----	Sign Ki-67

Demark-Wahnefried W, et al. Cancer Epidemiol Biomarkers Prev 2008;17:3577-3587.
George SL, et al. Abstract 1510, pg 63S, ASCO, 2007

F=Flaxseed (2-3 Tablespoons pre/post surgery)

GOOD NEWS	BAD NEWS
FIBER	FIBER (golden?)
OMEGA-3	PILLS/OIL
PLANT ESTROGENS	CHIA SEEDS ARE HERE!!
HEART HEALTHY	
CHEAP/Powdered/grounded	

Ki-67. Sesame seed?

Demark-Wahnefried W, et al. Cancer Epidemiol Biomarkers Prev 2008;17:3577-3587. & Moyad MA

F=Fruits & Veggies (Pills)? MORE is not MORE

- WHEL=Women's Healthy Eating & Living
- Treated for early-stage breast cancer
- 7.3 years (n= >3000)
- Veggies, fruit, fiber & low-fat

Bottom Line=NOTHING!

Pierce JP, et al. JAMA 298(3):289-298, 2007.

Remember the Obesity Epidemic?

BEVERAGE	CALORIES (8 oz)
Acai Juice	150-200
Cranberry/Grape Juice	140-160
Pomegranate Juice	140-160
Tomato/Carrot	50-60
Light Beer	70-80
Beer/Wine/Hard Liquor	100-150 (Low-carb diet)

Moyad MA. Dr. Moyad's Diet Book. 2008.

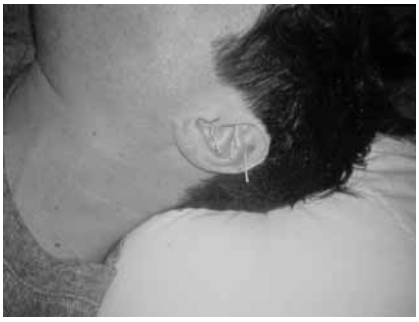
Calories=Antioxidants!

H=HOT FLASHES (Treatments?)

HOT FLASH TREATMENTS	COMMENTS
Lifestyle Changes/Diary Flax, Sesame, Mag, Acup	Mild to Moderate Hot Flashes
Estrogens (Topical?)	Clots, DVT, Stroke, CVD
Progesterone	HDL drop, wt gain, CVD
SSRI, SNRI	CVD, Bone Loss…
OTHER	Gabapentin…(side effects)

Moyad MA. Promoting Wellness. 2009.

A=ACUPUNCTURE



-N/V=Yes!
-Pain=Yes!
-Xerostomia=Yes!
-Hot Flashes=?
-Low Back Pain=?

(Johnstone PAS, et al. Cancer 2002;94:1151-56., Moyad MA. Sem Prev Alt Med 2006.)

F=FOLIC ACID & Polyp Prevention Study Group (1mg/d)

SIDE EFFECT	FOLIC ACID (n=516)	PLACEBO (n=505)	RESULT
Died	10 (2%)	19 (4%)	Non-sign (p=0.09)
Colon Cancer	3 (0.5%)	4 (1%)	No impact
Other Cancers	54 (10.5%) (24=p ca)	32 (6.3%) (9=p ca)	P=0.02!!! (BPH)

Cole BF, et al: JAMA 297:2351-2359, 2007.

M=Multivitamin-SU.VI.MAX-French Study

- N=13,017 (5141 men, age=45-60)
- 120 mg vit C + 30 mg vit E + 6 mg beta-carot + 100 mcg selenium, + 20 mg zinc vs. placebo
- 7.5 years
- Men=31% reduction in cancer & 37% all-cause mortality! PCa=REDUCED 48%, but…!!!!

Hercberg S, et al. Arch Intern Med 164:2335-2342, Nov. 22, 2004 & 2005.

MULTIVITAMINS (& Zinc) (LESS IS MORE!)

- 295,344 (NIH-AARP study) or WHI
- 10,241 cases
- Double the risk of fatal p. cancer or no impact

Bottom Line =Men Take Women's Multi OR KIDS MULTI! (Max 1 pill a day). Zinc=15-20 mg/d---that is all (Zicam anyone?).

Lawson KA, et al. J Natl Cancer Inst 99:754-764, 2007.

Ornish Trial?

- N=87 (Pca, PSA=4-10, Gleason<7)
- Combo lifestyle change + supplements???
- 1yr=Mean PSA decrease 3%
- Increase=7% w/control

Bottom Line=??? Catch_____???.

Ornish D, et al. J Urol 174:1065-1070, 2005. & Ornish D, et al. AUA Annual Meeting 169:page 74 (abstract #286), 2003.

Ornish (1-yr)

(Ornish D, et al. J Urol 174:1065-1070, 2005)

-Vegan Diet (no animal products)
-**10% or less calories from fat**
-Soy products (1 serving tofu + 58g soy protein beverage)
-Fish Oil supplement (3g daily)
-Vitamin E supplement (400 IU/day)
-Selenium supplement (200 mcg/day)
-Vitamin C supplement (2000 mg/day)
-**Moderate exercise (walking-30 min/d/6 days-wk)**
-Stress reduction/mgmt (yoga, meditation..60-min/d)
-Support Group Meeting (1-hour wk)

Ornish Plan-I

(Ornish D, et al. J Urol 174:1065-1070, 2005)

PARAMETER	LIFESTYLE(44)	CONTROL(49)
TC (mg/dL)*	-32	-2
LDL*	-30	-1
HDL*	-5	+1
TG	+5	+1
Testost (ng/dl)	+29	+48
Weight (lbs)*	-10	No change
PSA*	-0.25	+0.38

Quality of life? N=44 & 49, Age=66, Gleason=6 or less

PHYSICAN'S HEALTH STUDY II- (just released)


Vitamins E and C in the Prevention of Cardiovascular Disease in Men
The Physicians' Health Study II Randomized Controlled Trial

-NO IMPACT ON CVD, P. Cancer

-VIT E & HEM STROKE!

Heart Unhealthy= Prostate Unhealthy …

N=14,641

Gaziano JM, et al. PHS II. JAMA 2009;301:52-62.

SELECT (just released) -35,000 men

-300 sites

-150 million Dollars

-Phase 2 to 3


JAMA

-400 IU Vitamin E Increased risk of Prostate Cancer (bleeding)

-200 mcg Selenium increased Risk of type II diabetes

-QUERCETIN?

(Sel=70-100 mcg) (Vit E=15-30 IU)

1 Death From Prostate Cancer…& _____ deaths from heart disease

Lippman SM, et al. SELECT. JAMA 2009;301:39-51.

SELECT TRIAL- More is Not Better!

- Nutritional Prevention of Cancer (NPC) Trial of Selenium in 1996 the median Baseline Selenium Level=114 ng/ml (Clark LC, et al. Br J Urol 1998;81:730-734.)
- Median baseline selenium level in 2003 of SELECT=135 ng/ml & (Final Level at 5.5 years=251 ng/ml)
- Sel=70-100 mcg & Vit E=15-30 IU

Lippman SM, et al. SELECT. JAMA 2009;301:39-51

Natural Vitamin E* Is Obviously Better For You???????????

Lung	No impact
Colon	No impact
Melanoma	No impact
Heart failure hospitalization	Increased risk

*7,030 patients randomized to vitamin E 400 IU/day or placebo.

(Radiation & Vitamin E)

HOPE-TOO=Heart Outcomes Prevention Evaluation Study Extension
Lonn E, et al. *JAMA*. 2005;293:1338-1347.

Zinc & Cancer

- Zinc & BPH + immune-supp (1970s)
- HPFS (N=47,974 US men-14 yr follow-up)
- 2901 New cancers (434 advanced)
- >100 mg/d=RR=2.29
- 10 or more yrs=RR=2.37

Bottom Line=Stop high-dose zinc now!!!

Leitzmann MF, et al. JNCI 95:1004-1007, 2003.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

- 90-95% REDUCTION!
- 70% Chance of living to the age of 85 without mental or physical disability.

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?
2) Low CHOLESTEROL (LDL<100, hs-CRP)

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?
2) Low CHOLESTEROL (LDL<100, hs-CRP)?
3) Normal BLOOD PRESSURE (not pre-hypertension)

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?
2) Low CHOLESTEROL (LDL<100, hs-CRP)?
3) Normal BLOOD PRESSURE (not pre-hyperten)
4) Normal GLUCOSE

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?
2) Low CHOLESTEROL (LDL<100, hs-CRP)?
3) Normal BLOOD PRESSURE (not pre-hyperten)
4) Normal GLUCOSE
5) Normal WC/WHR/No Belly Fat

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?
2) Low CHOLESTEROL (LDL<100, hs-CRP)?
3) Normal BLOOD PRESSURE (not pre-hyperten)
4) Normal GLUCOSE
5) Normal WC/WHR/No Belly Fat
6) Normal MENTAL HEALTH/STRESS

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?
2) Low CHOLESTEROL (LDL<100, hs-CRP)?
3) Normal BLOOD PRESSURE (not pre-hyperten)
4) Normal GLUCOSE
5) Normal WC/WHR/No Belly Fat
6) Normal MENTAL HEALTH/STRESS
7) FRUITS & VEGGIES>1 serving/day

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?
2) Low CHOLESTEROL (LDL<100, hs-CRP)?
3) Normal BLOOD PRESSURE (not pre-hyperten)
4) Normal GLUCOSE
5) Normal WC/WHR/No Belly Fat
6) Normal MENTAL HEALTH/STRESS
7) FRUITS & VEGGIES>1 serving/day
8) MODERATE ALCOHOL

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.

FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

1) Do you SMOKE?=10-15%
2) Low CHOLESTEROL (LDL<100, hs-CRP)?=10%
3) Normal BLOOD PRESSURE (not pre-hyperten)=10%
4) Normal GLUCOSE=10%
5) Normal WC/WHR/No Belly Fat=10-15%
6) Normal MENTAL HEALTH/STRESS=10%
7) FRUITS & VEGGIES>1 serving/day=5%
8) MODERATE ALCOHOL=10%
9) EXERCISE AVERAGE OF 30 MIN/DAY=10%
10) ???=2%

Pills and Tests: What Should I (the urologist) Be Taking and Getting?

~ Mark A. Moyad, MD, MPH

›

Pills & Tests: What should I (the urologist) be taking and getting?!

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Hobbies: Telling you that less is More!

Lets Take a Doctor Moyad Quiz! Part I

- Angelina Jolie is married to _____ Pitt
- Oprah _____ has a good TV show!
- The actor that played Moses in the movie the Ten Commandments was_____ Heston.
- This actor (Sally _____) said "You like me…you really really like me" after winning her oscar!

Moyad MA. No BS Health Advice, Ann Arbor Media Group, 2009.

Lets Take a Doctor Moyad Quiz! Part I

- A normal vitamin D blood level may reduce my risk of osteoporosis and may reduce my risk of certain autoimmune diseases, cancers, & heart disease. Anyhow, my last vitamin D blood test was _____ ng/ml and the number that is ideal for me _____ ng/ml.
- A normal hs-CRP test has been shown to reduce the risk of the number 1 cause of death in men & women, & my last test was _____mg/L
- My Framingham Risk Score or Reynolds Risk Score (paid for by the tax payers) that can determine my risk of the 1 cause of death in men & women is _____
- The Over the Counter product that costs pennies that works as well as the number 1 selling expensive medicine in the U.S. to fight cough and colds is known as _____

Moyad MA. No BS Health Advice, Ann Arbor Media Group, 2009.

PRE-GAME = Vaccines……

COLONOSCOPY	Cure at biopsy?!
FLU VACCINE (& H1N1)	Right now! (other benefits--imm boost)
PNEUMONIA	Age 60-65 & over!
SHINGLES	APPROVED (Zostavax®)

Hep A/B= down 90%!!!

Moyad MA. Sem Prev Alt Med, 2007

Overview of the Talk

- Pre-Game Locker Room Speech
- A-Z=Lifestyle/Pill=Game time
- Post-Game Summary

PRE-GAME for MEN

1. CVD	426,772
2. Cancer	286,741
3. Accidents	67,923
4. Respiratory Diseases*	60,456
5. Diabetes*	35,217

Moyad MA. Sem Prev Alt Men, 2008

PRE-GAME for WOMEN

1. CVD (since 1984)	483,842
2. Cancer	267,902
3. Respiratory Diseases*	65,672
4. Alzheimer's Disease	45,058
5. Diabetes*	35,748

Moyad MA. Sem Prev Alt Men, 2008

PRE-GAME-Probability Diet

- #1 cause of death for 107 out of 108 years?
- #1 cause of death post-localized trt for ca (Moyad…)
- #1 in cancer prevention trials?

BOTTOM LINE=Heart Healthy=Bladder Healthy=Bone Healthy=Brain Healthy=Breast Healthy=Colon Healthy=Eye Healthy=Joint Healthy=Kidney Healthy=Prostate Healthy=Skin Healthy=Sexual Health=ALL HEALTHY!!!
(Vioxx vs. Vitamin E vs. Fish Oil…?)

Moyad MA. Promoting wellness for prostate cancer patients. JW Edwards Publishing, 2006.
Moyad MA, Carroll PR. Urol Clin N Am 2004;31:289-300.

STATINS
LDL CHOLESTEROL

LDL (mg/dL)	LDL (mmol/L)	COMMENT
<70	<1.81	High-Risk
<100	<2.59	Optimal
100-129	2.59-3.34	Near optimal
130-159	3.37-4.12	Borderline High
160-189	4.14-4.90	High
≥190	≥4.92	Very High

NCEP Guidelines. JAMA 285:2486-2497, 2001.

STATINS
HDL CHOLESTEROL

HDL (mg/dL)	HDL (mmol/L)	COMMENT
<40	<1.04	Low
40-59	1.04-1.53	Normal
≥60	≥1.55	IDEAL

NCEP Guidelines. JAMA 285:2486-2497, 2001.

STATINS
TRIGLYCERIDES

TRIGLYCERIDE (mg/dL)	TRIGLYCERIDE (mmol/L)	COMMENT
<150	<1.70	Normal
150-199	1.70-2.25	Borderline High
200-499	2.26-5.64	High
≥500	≥5.65	High

NCEP Guidelines. JAMA 285:2486-2497, 2001.

Have you had this test? (hs-CRP)

High-sensitivity C-reactive protein	Number
< 1 mg/L	Low risk (normal)
1-3 mg/L	Moderate risk
> 3 mg/L	High risk

www.Reynoldsriskscore.org

Ridker PM. *Circulation.* 2003;107:363-369.

Framingham CHD 10-yr Risk For Men: Step 1 (NCEP. JAMA 2001;285:2486-2497.)

Age	Points	Age	Points
20-34	-9	65-69	11
35-39	-4	70-74	12
40-44	0	75-79	13
45-49	3		
50-54	6	Moyad=0	
55-59	8		
60-64	10		

NCEP Guidelines. JAMA 285:2486-2497, 2001.

Framingham CHD 10-yr Risk: Step 2 (Moyad=0)

TC	20-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

NCEP Guidelines. JAMA 285:2486-2497, 2001.

Framingham-10 yr Risk: Step 3

	20-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs
Non-smoker	0	0	0	0	0
Smoker	8	5	3	1	1

NCEP Guidelines. JAMA 285:2486-2497, 2001.

Framingham 10 yr-Risk: Step 4

HDL (mg/dl)	POINTS
≥60	-1
50-59	0 (Moyad)
40-49	1
<40	2

NCEP Guidelines. JAMA 285:2486-2497, 2001.

Framingham 10-yr Risk: Step 5

Systolic Blood Pressure (mm Hg)	If Untreated	If Treated
<120	0 (Moyad)	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

NCEP Guidelines. JAMA 285:2486-2497, 2001.

NCEP Guidelines. JAMA 285:2486-2497, 2001.

Framingham Risk-10 yr: Step 6

TOTAL POINTS	10-YR RISK (%)
<0	<1
0, 1, 2, 3, 4	1
5, 6	2
7	3
8	4
9	5
10	6
11	8
12	10

Framingham Risk 10-yr: Step 6

TOTAL POINTS	10-YR RISK (%)
13	12
14	16
15	20
16	25
≥17	30
TOTAL SCORE	=??? (Moyad=0=1% risk)

NCEP Guidelines. JAMA 285:2486-2497, 2001.

REYNOLDS RISK SCORE-I?! (www.reynoldsriskscore.org)

- Family History (before age of 60 yrs)
- Hs-CRP

REYNOLDS RISK SCORE-II?! (www.reynoldsriskscore.org)

- AGE
- CURRENTLY SMOKE?
- SYSTOLIC BP
- TOTAL CHOLESTEROL (mg/dL)
- HDL
- Hs-CRP
- GENETICS (Mother or Father w/MI before age 60)

10-year Risk? No diabetes?

REYNOLDS RISK SCORE-III?! (www.reynoldsriskscore.org)

- AGE=65
- CURRENTLY SMOKE=No
- SYSTOLIC BP=120
- TOTAL CHOLESTEROL (mg/dL)=160
- HDL=60
- Hs-CRP=1 mg/L
- GENETICS (Mother or Father w/MI before age 60)=Y

=2% 10-YEAR RISK (age 75=5%, age 85=10%…)

Vitamin D Blood Test

VITAMIN D BLOOD TEST	NORMAL LEVLES
25 (OH)-hydroxy-vitamin D	35-40 ng/ml (90-100 nmol/l)

NEED 800-1000 IU (20-25 mcg)/day!

SEND YOUR RESULTS TO ME PLEASE!!!

Bischoff-Ferrari HA et al. Am J Clin Nutr 84:18-28, 2006

A=Alcohol

MODERATION:
- HDL
- Heart health
- Estrogenic
- Bone health (not hard liq?)

EXCESS:
- Increases triglycerides
- Calories
- Increases BP
- Immune-Suppressive
- Reduces folic acid/EFA..
- Oral/Esophageal cancer
- Breast/colon cancer…
- OSTEOPOROSIS
- CALORIES PER GRAM???

Moyad MA. Sem Prev Alt Med, Dec, 2007.

A=Aspirin

- "Aspirin is a miracle drug for the people who NEED it (>10% Reynold's Risk), but it is a potential disaster for the people that do not need it!"
- -New Meta-Analysis of 6 Studies
- Worried about Tylenol?! ASA is everywhere!

ATT Collaboration. Lancet 2009;373:1849-1860.

A=Aspirin=WHS-39,876 Women

CONDITION	RISK REDUCTION-ASA
Heart Attack-age 65+	34% Reduction
Ischemic Stroke-age 65+	30% Reduction
Hemorrhagic Stroke	24% Increase
Major GI Bleed	40% Increase
Peptic Ulcer	32% Increase

Ridker PM, et al. N Engl J Med March 9, 2005;352

Low-Dose ASA per 1000 treated for 5 years (meta=5 trials=>55,000)

CHD event risk/yr	CHD Events Avoided	Ischemic Strokes Avoided	Hem Strokes from ASA	Major Bleeds from ASA
Low= <10%	5	0	1	5
Moderate =10-20%	14	0	1	5
High= >20%	25-50	25-50	1	5

NCEP Guidelines. JAMA 285:2486-2497, 2001. ALL-CAUSE MORTALITY?

WHICH ONE IS BEST?

F=FISH OIL & AHA

SITUATION?	Recommendation
Perfectly Healthy (from food)	2 Fish Meals/wk Pills?
CHD (food and/or pill)	1 g
Pregnancy (food/pill)	200-500 mg…
Triglycerides (Wt loss/pills)	2-4 g

Depression, Weight loss…

Autism-1.5 g/d -Hyperactivity

Moyad MA: Sem in Urol Oncol 23:28-35 & 36-48, Part I & II, 20055

WHAT ABOUT COD LIVER OIL? (Consumer Reports, 2009.)

F=Fish oil pills

1) Kirkland Signature (Costco) (0.06 day/$22-yr)	9) GNC
2) Member's Mark (Sam's Club)	10) Nature's Bounty-Salmon Oil
3) Spring Valley	11) Rite Aid
4) Walgreens	12) YourLife
5) Vitasmart (Kmart)	13) Country Life
6) CVS Pharmacy	14) Eckerd
7) Natrol	15) Spectrum Essentials
8) Sundown	16) Solgar-Omega-3 "700"

S=STATINS/Cholesterol (N=938, 9-years)

PARAMETER	STATINS	NON-STATINS
Disease-Specific Survival	98%	95%
Overall Survival	94%	81%

(Moyad MA, et al. Urol August/Sept 2006)

How about after adjusting for confounding variables? YES! YES!

Jacobs (2007)	N=55,454 (317 adv)	Followed= 6-years	-40% Adv/ Fatal P Ca.
Flick (2007)	69,047 (131)	14 years	-43%
Murtola (2007)	49,446 (3680)	8 years	-25% (CC)
Platz (2006)	34,989 (316)	13 years	-50%
Marcella (2009)	380 cases	10 years	-63% DEATHS!!!

Adjusting for PSA testing…=More Robust!!! Murtola TJ, et al. Nat Clin Prac Uro 2008;5(7):376-387.

Red Yeast Rice (600 mg=1-2.5 mg)……..VYTORIN (2011)

C=CHOLESTEROL=Statins!

Atorvastatin=Lipitor®	?
Fluvastatin=Lescol®	?
Lovastatin=Mevacor®	Patent lost
Pravastatin=Pravachol®	Patent lost-06
Rosuvastatin=Crestor®	? (once a week?!)
Simvastatin=Zocor®	Patent lost-June 06

Moyad once a week solution???

JUPITER SHOULD CHANGE YOUR LIFE (less is more)!

LDL "bad cholesterol"	hs-CRP	WHAT HAPPENED?
≥70	≥1 mg/L	-9% Reduction
≥70	≤1 mg/L	-35% Reduction
<70	≥1 mg/L	-50% Reduction
<70	≤1 mg/L	-79% Reduction!!!

Ridker PM, et al. Lancet 373:1175-1182, April 4, 2009. Justification for the Use of Statins in Prevention

-DVT?

Arthritis Pills (OA) (Summary)

- Pycnogenol (100 mg/d)
- Glucosamine…
- SAM-e
- Tylenol/Aleve
- Capsaicin?
- Hyaluronic Acid?
- Vitamin C?

Moyad MA et al: Sem Prev Alt Med-2007

F=FOLIC ACID & Polyp Prevention Study Group (1mg/d)

SIDE EFFECT	FOLIC ACID (n=516)	PLACEBO (n=505)	RESULT
Died	10 (2%)	19 (4%)	Non-sign (p=0.09)
Colon Cancer	3 (0.5%)	4 (1%)	No impact
Other Cancers	54 (10.5%) (24=p ca)	32 (6.3%) (9=p ca)	P=0.02!!! (BPH)

Cole BF, et al: JAMA 297:2351-2359, 2007.

M=Multivitamin-SU.VI.MAX-French Study

- N=13,017 (5141 men, age=45-60)
- 120 mg vit C + 30 mg vit E + 6 mg beta-carot + 100 mcg selenium, + 20 mg zinc vs. placebo
- 7.5 years
- Men=31% reduction in cancer & 37% all-cause mortality! PCa=REDUCED 48%, but…

Hercberg S, et al. Arch Intern Med 164:2335-2342, Nov. 22, 2004 & 2005.

MULTIVITAMINS (LESS IS MORE!)

- 295,344 (NIH-AARP study)
- 10,241 cases
- Double the risk of fatal p. cancer

Bottom Line =Men Take Women's Multi OR KIDS MULTI! (Max 1 pill a day)

Lawson KA, et al. J Natl Cancer Inst 99:754-764, 2007.

Point-Counterpoint:

Why Every Man Should Be Offered Chemoprevention for Prostate Cancer

~ E. David Crawford, MD

Chemoprevention Is Not for Every Man

~ Mark A. Moyad, MD, MPH

Chemoprevention
Prostate
Cancer

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

The Clinical and Economic Burden of Prostate Cancer

Expenditures

- Prostate- 8 billion 11.2%
- Lung- 9.6 billion 13.3%
- Breast 8.1 billion 11.2&

Presentation Outline

- Study Design
- Research Objectives
- Results
- Next Steps

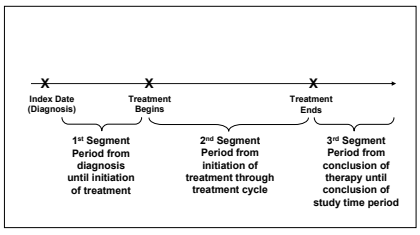
5

Selection Criteria

- **Inclusion Criteria**
  - Men ≥ 40 years of age
  - Index date occurs during the enrollment period
  - Continuously eligible for at least 18 months (6-month pre-period and a minimum 12-month post-period)
- **Exclusion Criteria**
  - Members with ICD-9 claims for any other cancer

6

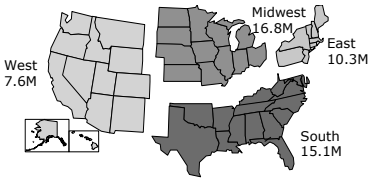
Measurement Segments



7

Data Sources

- PharMetrics
  - Data from over 85 health plans and 45 million lives
  - Mostly a commercial population (80%)
  - Timeframe of the dataset is 1995 to present (approximately a 6-month lag)



8

Patient Selection

Men with Prostate Cancer Diagnosis
N = 109,029

Exclusion Criteria	Men Excluded
Men less than 40 years of age	587
Index date not within enrollment period	33,628
Not continuously eligible for 6 months pre- and 12 months post-PCa diagnosis	89,033
ICD-9 for any other cancer	20,941

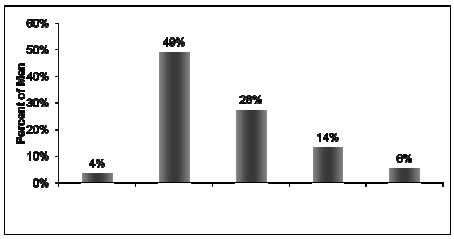
An excluded patient may have met >1 exclusion criterion.

Final Study Population
N = 23,278

9

Age

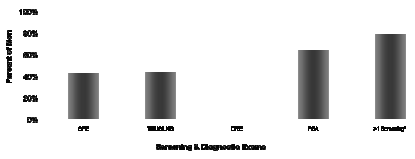
Mean age = 61.2 years



10

Screening & Diagnostics

80% of men had screening/diagnostic exam(s) in the 6-month pre-period through the cancer index date. Men had PSA most often.



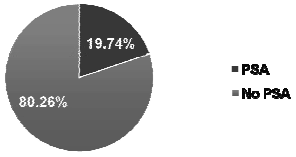
*35% had 1, 16% had 2, and 30% had ≥3 screening or diagnostic exams

DRE - Digital Rectal Exam, PSA -Prostate Specific Antigen, SPE - Surgical Pathological Exam, TRUS - Transrectal Ultrasound, LNB - Lymph Node Biopsy

11

Screening & Diagnostics

80% of men had a PSA test at some time in the database.

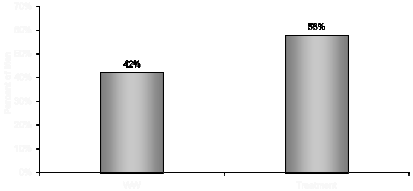


N=23,278
PSA -Prostate Specific Antigen

12

Treatment or Watchful Waiting?

More than half of the men that were diagnosed with prostate cancer received some treatment during the follow-up period.

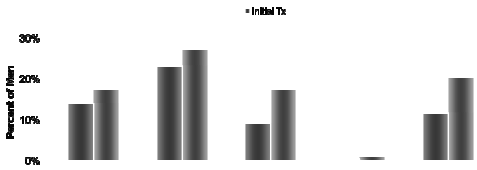


N=11,227
WW – Watchful Waiting

13

Type of Treatment

Of men that were treated, the most common treatment was surgery.

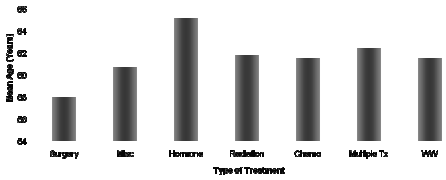


The percentages add to more than 100% as there were patients that received more than one treatment
*Misc=ketoconazole, aminoglutethimide, and any corticosteriod

14

Characteristics of Treatment Cohorts

Men receiving surgery as their initial treatment were younger.

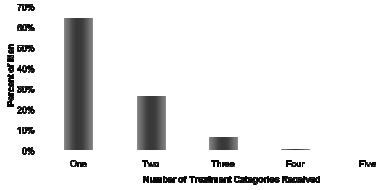


WW – Watchful Waiting

15

Number of Treatments

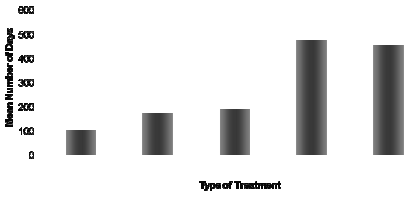
Of men that were treated, the majority received one type of treatment.



16

Time to Treatment

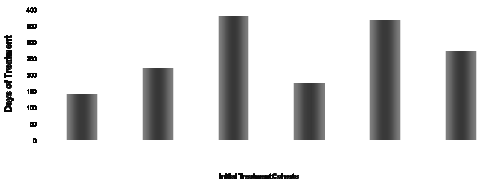
Of all men that received treatment, surgery occurred closest to diagnosis, and miscellaneous treatments occurred furthest from diagnosis (1.31 years).



17

Average Duration of Treatment

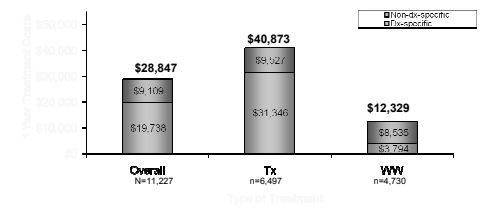
Mean days from first to last treatment ranged from 141 days for surgery cohort to 381 days for hormone therapy cohort.



18

Average Annual Cost per Patient

Patients with prostate cancer cost $28,847 in the 1 year following diagnosis. Those who received any treatment were more costly.

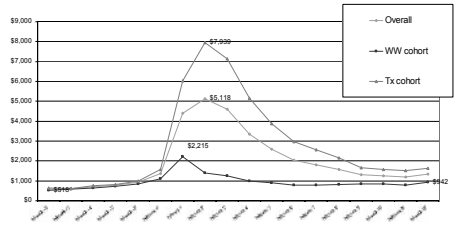


Costs were calculated from diagnosis through 1 year
WW – Watchful Waiting

19

Average Total Monthly Medical Costs

Costs peak in the month following diagnosis and are highest for patients who receive treatment

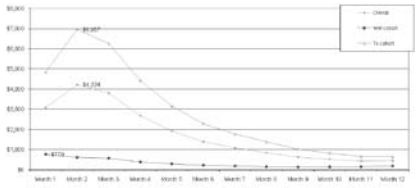


WW – Watchful Waiting

20

Average Prostate Cancer-specific Monthly Medical Costs

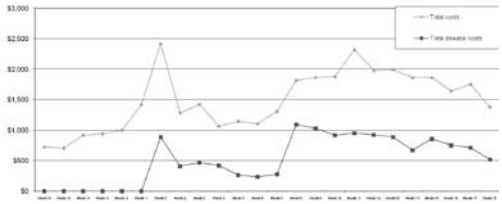
Disease-specific costs account for a high proportion of total costs



WW – Watchful Waiting

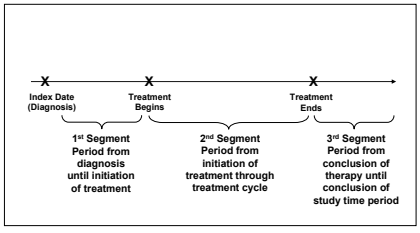
21

Average Monthly Medical Costs: Patients Starting Therapy at ≥8 Months



22

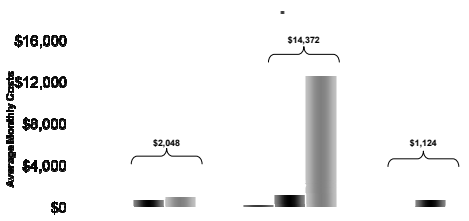
Measurement Segments



23

Costs

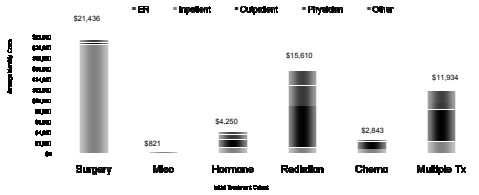
The majority of costs are accrued during treatment; almost all medical costs during treatment are related to prostate cancer.



24

During-treatment Costs

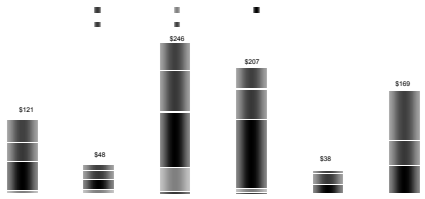
The surgery cohort had the highest during-treatment costs, driven by inpatient costs. Outpatient costs were the drivers in the radiation and multiple treatment cohorts.



25

After-treatment Costs

Prostate cancer-related medical costs were highest among the hormone and radiation cohorts. In most cohorts, outpatient costs were the highest.



26

Clinical Events

Men who received treatment were more likely to experience an event than the watchful waiting cohort. Men who received surgery were the most likely to experience at least one event.

WW – Watchful Waiting

27

Summary

- The majority of men receive one type of treatment.
- Surgery was the most common treatment. It was received by the youngest men and resulted in the highest costs and most clinical events.
- Annual costs, regardless of treatment pattern, were $30K per patient in the year following diagnosis.
- Costs peaked in the month following diagnosis.
- The watchful waiting cohort had the lowest costs and fewest clinical events.

28

Why Prostate Cancer Prevention?

- Significant public health risk
  - 186,000 new cases and 26,000 deaths yearly (2008)
- Risk factors (age, race, genes) are not modifiable
- Benefit of screening on mortality is unproven
- Therapy is associated with morbidity

- That Leaves Prevention

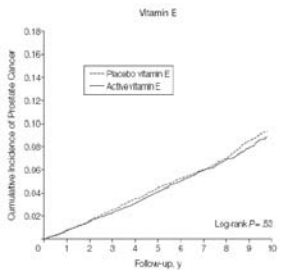
Prostate Cancer Diet & Exercise Risk Factors

- May *Increase* Risk
  - Fat / Red Meat
    - Cooking methods
  - Dairy/Calcium
  - Smoking
  - Total Calories, Body size

- May *Decrease* Risk
  - Plant-based Foods/ Vegetables
    - Tomatoes
    - Cruciferous
    - Soy/Legumes
  - Specific Nutrients
    - Selenium
    - Vitamin E
    - Carotenoids/Lycopene
    - Total Antioxidants
  - *Fish / Marine Omega 3 Fatty acids*
  - *Moderate to Vigorous Exercise*

Courtesy J. Chan, UCSF

Vitamin E and Prostate Cancer
Physicians Health Study II



N = 14,641

Gaziano et al, JAMA (in press)

Effect of Dutasteride on Cancer in BPH Trials

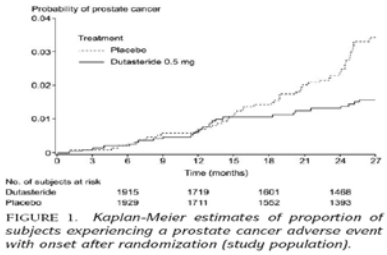
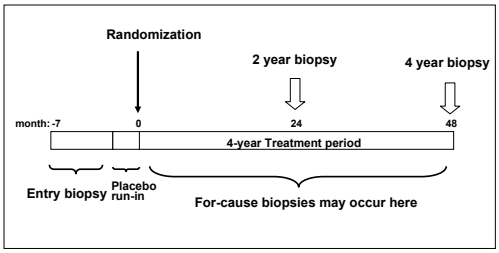


FIGURE 1. *Kaplan-Meier estimates of proportion of subjects experiencing a prostate cancer adverse event with onset after randomization (study population).*

Andriole et al, Urology 64: 537, 2004

REDUCE Schema



Andriole et al, J Urol 172:1314, 2004

REDUCE and PCPT Study Design Differences

Parameter	REDUCE	PCPT
Study drug	AVODART 0.5 mg daily	Finasteride 5 mg daily
Study duration	4 years	7 years
Number of patients	8,250	18,882
Age (years)	50 to 75	≥ 55
Baseline biopsies	Yes (1 negative biopsy)	No
Follow up (planned) biopsies	Year 2 and Year 4 (mandatory)	Year 7 (recommended)
PSA entry criteria	2.5 – 10 ng/mL if 50-60 years; 3 – 10 ng/mL if > 60	≤ 3 ng/mL
Location	International	United States

Note: Due to the differences in study design and patient population, comparisons of the results from REDUCE and PCPT cannot be made.

1. Thompson IM et al. *NEJM* 2003;349(3):215-224. 2. Andriole G et al for the REDUCE Study Group. *J Urol* 2004;172:1314-1317. 3. Gomella LG. *Curr Opin Uro* 2005;15:2932. 4. Musquera M et al. *Expert Reviews* 2008;8(7):1073-1079.

REDUCE: Primary endpoint (analysis ongoing)

Dutasteride reduced the risk of prostate cancer over 4 years by

23%

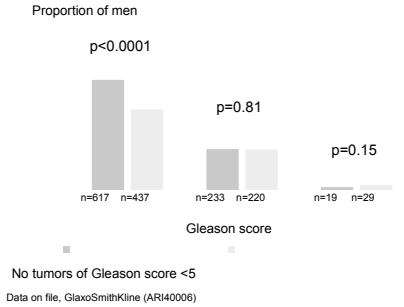
p<0.0001

(857 placebo *vs* 659 dutasteride)

Note: Analysis of data from the REDUCE trial is ongoing. Once the analysis is complete, the results will be published.

Data on file, GlaxoSmithKline (ARI40006)

REDUCE: Gleason score distribution (analysis ongoing)



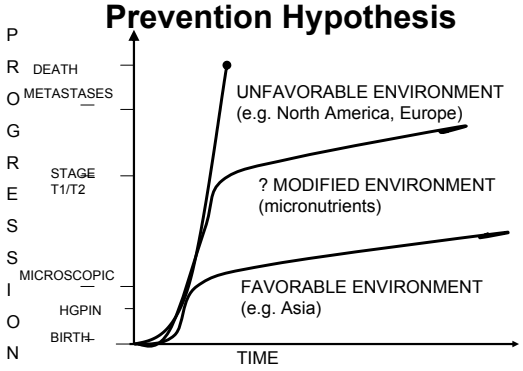
No tumors of Gleason score <5

Data on file, GlaxoSmithKline (ARI40006)

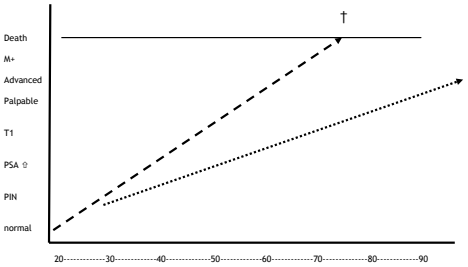
Consensus Meeting Panelists

From left to right: Jørgen Nordling, Manfred Wirth, Pierre Teillac, Per-Anders Abrahamsson, David Crawford (key note speaker on the PCPT data), Christopher Chapple, Adrian Joyce, Cle´ment-Claude Abbou, Jean-Louis Misset, Andrea Tubaro, Eduardo Solsona.
Professor Pierre Teillac, France Professor Per-Anders Abrahamsson, Sweden Professor Clement Claude Abbou, France.Mr Christopher Chapple, United Kingdom Mr Adrian Joyce, United Kingdom. Professor Jean-Louis Misset, France Professor Jørgen Nordling, Denmark. Dr Eduardo Solsona, Spain Professor Andrea Tubaro, Italy. Professor Manfred Wirth, Germany

Prevention Hypothesis

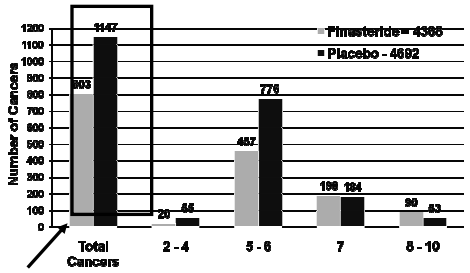


Delaying cancer = preventing it !



Eric Klein,. www.urologyrounds.com

Total Number of Cancers by Gleason Score



25% Risk Reduction

Thompson et al, NEJM 349:215, 2003

Statins and Prostate Cancer Risk

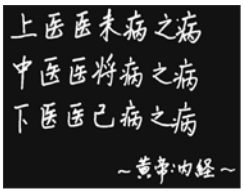
Risk Group	Risk Ratio
Any Px Cancer	**1.09**
Advanced Px Cancer	
Any use	**0.51**
Use < 5 yrs	**0.60**
Use > 5 yrs	**0.26**

Health Professionals Follow-up Study, N = 34,989

Platz et al, JNCI 98:1819-25, 2006

Prevention: What to Tell Patients

Historical Imperative for Prevention



- **Superior doctors prevent the disease.**
- **Mediocre doctors treat the disease before evident.**
- **Inferior doctors treat the full blown disease.**

Nai-Ching (2600 B.C. 1st Chinese Medical Text)

Chemoprevention for prostate cancer is not for every man!

Mark A. Moyad, MD, MPH
Jenkins/Pokempner Director of Preventive/Alternative Medicine
University of Michigan Medical Center
Dept of Urology
Ann Arbor, MI
moyad@umich.edu

Hobbies: Forest over the tree & why there are no support groups for men that have…!

1. CVD= #1 cause of death in men & women in the U.S.!

- Since 1900!
- Under the age of 65=50% diagnosed CVD &
- 15-20% of CVD deaths
- Cancer>>CHD???

(Bonow RO. Circulation 2002;106:3140-3141)

Top Killers of Men

(CDC 2006)

1. CVD	426,772
2. Cancer	286,741
3. Accidents	67,923
4. Respiratory Diseases*	60,456
5. Diabetes*	35,217

Top Killers of WOMEN

((Moyad MA. Sem Prev Alt Men, 2006)

1. CVD (since 1984)	483,842
2. Cancer	267,902
3. Respiratory Diseases*	65,672
4. Alzheimer's Disease	45,058
5. Diabetes*	35,748

predictor CVD/all-cause mortality!!

- 3-largest prospective investigations
- Follow-up 16-34 years

(Stamler J, et al. JAMA 2000;284:311-318)

3. CVD is #1 cause of death in largest U.S./world Rx prev. trials!!!

- P-1 tamoxifen trial
- PCPT (10 deaths vs. _____)

(Fisher B, et al. J Natl Cancer Inst 1998;90:1371-1388. &
Thompson IM, et al. N Engl J Med 2003;349:215-224)

4. CVD= #1 cause of death in largest diet/supplement prev. trials!

- ATBC
- Selenium supplement trial
- SELECT (1 death vs. _____)

(The ATBC Study Group. JAMA 2003;290:476-485. &
Clark LC, et al. JAMA 1996;276:1957-1963.)

5. CVD= #1 cause of death in largest PSA screening trials!

- PLCO??????????????????????????
- 1700 CHD vs. 174 Pca.
- 472 from “accidents”
- ERSPC? Where are they??? (appendix 8?)

(Andriole GL, Crawford D, et al. for PLCO Project team. N Engl J Med 2009;360:1310-1319.)

6. Most dietary supplements do not impact CVD? (Eidelman RS, et al. Arch Intern Med 2004;164:1552-1556)

China (1993)	ATBC (1994)	CHAO (1996)	GISSI (1999)	HOPE (2000)	PPP (2001)	HPS (2002)
5 yrs -29500	6.1 yrs -29133	1.5 yrs -2002	3.5 yrs -11324	4.5 yrs -9541	3.6 yrs -4495	5 yrs -20536
30 mg	50 mg	800 to 400 mg (n)	300 mg	400 mg (n)	300 mg	600 mg

Zinc & Cancer

- HDL, LDL, Bisphosphonates…
- HPFS (N=47,974 US men-14 yr follow-up)
- 2901 New cancers (434 advanced)
- >100 mg/d=RR=2.29
- 10 or more yrs=RR=2.37

Bottom Line=Why?

Leitzmann MF, et al. JNCI 95:1004-1007, 2003.

7. Some dietary supplements attenuate CVD agents?

- N=160, 3-yr randomized trial
- 800 IU vitamin E +
- 100 mcg selenium +
- 1000 mg vitamin C +
- 25 mg beta-carotene

Brown BG et al: N Engl J Med 345:1583-1592, 2001.

8. PSA Screening=lipid disorders?

- Over 1000 men= 3 cities
- 8% abnormal PSA/DRE…
- 52% w/dyslipidemia!

Moyad MA, et al. ASCO 2005.

9. Majority of diet/lifestyle changes for prostate cancer=heart healthy?

- Exercise
- Fat in the diet
- Flaxseed, Fruits & veggies
- Lycopene-diet & CVD
- Soy
- Weight Control…

(Moyad MA. Urol Oncol 2004;22:466-471)

10. CVD=#1 cause of death in men post-dx & treatment!

- 14,000 men (307,931 records)
- 66% die from non-prostate causes!

Bottom Line=Heart healthy=Prostate Healthy!

Sun L, et al. AACR 43:page 932, abstract 4616, 2002

Klotz-Canada WW

- "Most men with favorable risk prostate cancer will die of unrelated causes."
- PSA<10, Gleason=6 or less, T2a or less
- N=299, mean age >70 yrs
- 8 yrs=overall survival=85%,
- Disease Specific Survival=99%…

Klotz L. J Urol 2004;172(5,pt 2 of 2):S48-S51.

11. Mechanisms increase risk of CVD=increase p.ca risk-MSR-1…

- Prospective study (Austria)=862 patients
- Group 1=P.cancer (n=291)
- Group 2=2 biopsies (no cancer) (n=340)
- Group 3=no prostate cancer (n=231)

Bottom Line=Signif. elevated cholesterol/HDL

Sonnleithner M, et al. AUA Annual Meeting J Urol 169: page 76-abstract #294, 2003.

12. Statins & laboratory data

- Cholesterol increased in solid tumors.
- Prostate synthesizes cholesterol at a rate=liver.
- Inhibits all cell lines=PC-3, LNCaP…
- Add LDL=increase tumor growth…
- SCID mice=increase cholesterol=HRPC

(Moyad MA. Urol Oncol 23:49-55, 2005)

13. Pleiotropic effects & secondary benefits?

- Alzheimer's disease
- Mac. Degen.
- E.D./F.S.D.
- M.S.
- Osteoporosis
- R.A…

Moyad MA. Urol Oncol 2004;22:466-471, 472-477.

Biologic Properties of Statins-Apart from Cholesterol Reduction?

- Inhibit thrombotic process
- Inhibit tumor cell proliferation
- Inhibit angiogenesis
- Modulate immune responses
- Reduce inflammation
- Improve vascular endothelium function
- Stimulate bone growth/prevent bone loss
- Reduce oxidative stress
- Modulate smooth muscle cell proliferation
- Stabilize plaques
- Enhance fibrinolysis

Stamm JA, Ornstein DL. Oncology 19(6):739-754, May, 2005.

14. P Ca. Effects (aka forest over the tree)?

Jacobs (2007)	N=55,454 (317 adv)	Followed= 6-years	-40% Adv/ Fatal P Ca.
Flick (2007)	69,047 (131)	14 years	-43%
Murtola (2007)	49,446 (3680)	8 years	-25% (CC)
Platz (2006)	34,989 (316)	13 years	-50%
Marcella (2009)	380 cases	10 years	-63% DEATHS!!!

Adjusting for PSA testing…=More Robust!!! Murtola TJ, et al. Nat Clin Prac Uro 2008;5(7):376-387.

15. Cost?

Atorvastatin=Lipitor®	?
Fluvastatin=Lescol®	?
Lovastatin=Mevacor®	Patent lost
Pravastatin=Pravachol®	Patent lost-06
Rosuvastatin=Crestor®	? (once a week?!)
Simvastatin=Zocor®	Patent lost-June 06

Moyad once a week solution???

death/clinical endpoints) Evidence Exists?

LDL "bad cholesterol"	hs-CRP	WHAT HAPPENED?
≥70	≥1 mg/L	-9% Reduction
≥70	≤1 mg/L	-35% Reduction
<70	≥1 mg/L	-50% Reduction
<70	≤1 mg/L	-79% Reduction!!!

Ridker PM, et al. Lancet 373:1175-1182, April 4, 2009. Justification for the Use of Statins in Prevention:

-DVT?

NUMBER 17=I am tired! Other promising agents?

- COX-II inhibitors
- Finasteride
- Toremifene
- Vitamin E
- Selenium

Moyad MA. Urol Oncol 2004;22:466-471, 472-477.