Late Onset Hypogonadism

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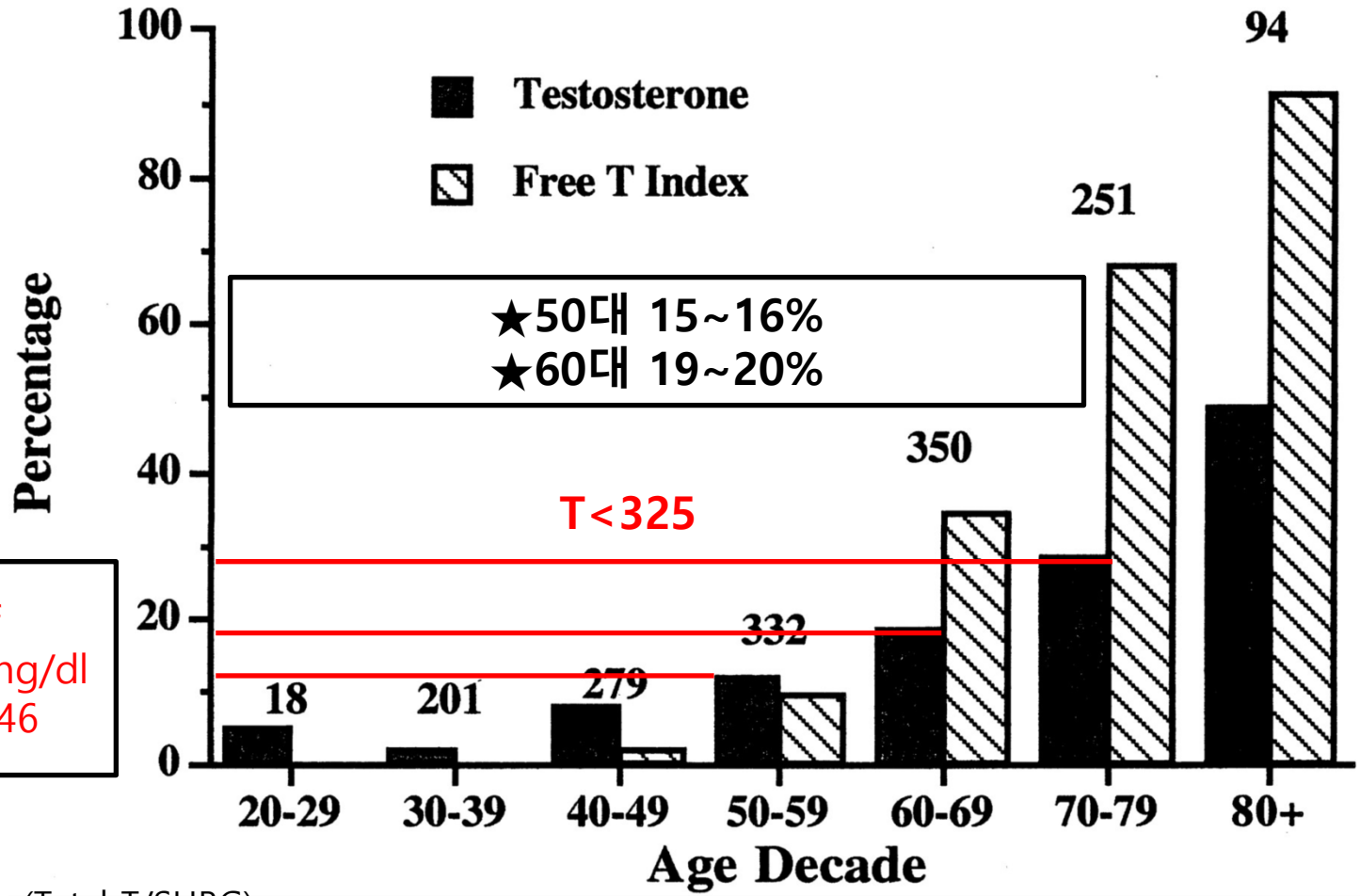
핵심 사항

- 진단, 치료, 잇점
- 생식관련 (Fertility)
- 전립선관련 (Prostate cancer, BPH)
- 심혈관계 영향 (Cardiovascular events)
- 비의도적 약물전파 (Transference)
- 추적관찰 (how: cessation, monitoring)

Prevalence of T def



※ Ref
AUA: 300 ng/dl
ISSM: 346

*FAI = 100x (Total T/SHBG)
Range: 30-150

Harman et al. J Clin Endocrinol Metab 2001; 86: 724

Physical Symptoms and Signs
★ Reduced energy
Reduced endurance
Diminished work performance
Diminished physical performance
Loss of body hair
Reduced beard growth
★ Fatigue
Reduced lean muscle mass
★ Obesity
Cognitive Symptoms and Signs
★ Depressive symptoms
Cognitive dysfunction
Reduced motivation
Poor concentration
★ Poor memory
★ Irritability
★ **Sexual Symptoms and Signs**
Reduced sex drive
Reduced erectile function

T검사 급여 기준 (code: testicular hypofunction)

Panel discussion: Diagnosis

- The diagnosis of testosterone deficiency must include the presence of symptoms and/or signs associated with low testosterone in combination with documented low total testosterone levels. (Grade B)

- Making a diagnosis of testosterone deficiency in the absence of signs and/or symptoms increases the likelihood of making a false diagnosis and reduces the potential benefit of testosterone therapy.

- Clinicians should refrain from measuring testosterone levels in patients who are asymptomatic.

American Association of Clinical Endocrinologists

British Society for Sexual Medicine

	AUA	AACE	BSSM
TT			
Threshold	<300 ng/dL (10.4 nmol/L)	NR	<345 ng/dL (12 nmol/L)
Assay	LCMS	NR	'Reliable method'
Timing	Early morning	Early morning	Early morningFasting
Second test required	Yes	Yes	Yes
Free testosterone			
To be used	with TT in equivocal range	If low or low–normal TT	If TT low–normalIf SHBG abnormal

EAU	ES	ISSM	ISSAM
			International Society for the Study of the Aging Male
<350 ng/dL (12.1 nmol/L)	'Consistently low'	<350 ng/dL (12.1 nmol/L)	<350 ng/dL (12.1 nmol/L
LCMS or immunoassay	'Reliable assay'	NR	LCMS
Early morningFasting	Early morningFasting	Early morning	Early morning
Yes	Yes	Yes	Yes
If TT low–normalIf SHBG abnormal	If TT low–normalwith SHBG-altering condition	NR	If TT does not suggest diagnosis Obese men

BJU Int 2019; 124: 722–729

Adjunctive Testings

	Guideline			
	AUA	EAU	Endocrine Society	ISSM
LH	Recommended	Recommended	Recommended	Recommended
FSH	If interested in fertility	Recommended	Recommended	NR
Hb/Hct	Recommended	NR	Recommended	Recommended
Prolactin	If LH low or low–normal	NR	If LH and FSH low or 'inappropriately normal'	Recommended
Pituitary MRI	High prolactinTT <150 ng/dL (5.2 nmol/L)	NR	High prolactinTT <150 ng/dL (5.2 nmol/L)	High prolactinTT <150 ng/dL (5.2 nmol/L)
PSA	Recommended for men aged ≥40 years	Recommended	If patient elects prostate cancer screening	NR
Oestradiol	In men with breast symptoms	NR	NR	NR
DEXA	Optional	Recommended	NR	NR
HbA1c	In men with DM risk	NR	NR	NR
Karyotype	In men with hypergonadotrophic hypogonadism without known cause	NR	Primary hypogonadism with testes volume <6 mL	NR
SHBG	NR	If free testosterone measured	If free testosterone measured	If TT low or low–normal

BJU Int 2019; 124: 722–729

남성갱년기 진단, 치료 적응증 AUA, EAU, ISSM

- 남성호르몬 치료는 언제 하는 것인가?

→ 증상이 있는 T<300~350

→ 증상이 있는 T>300 도 3~6개월간 시도해 볼 수 있다.

- 남성호르몬 검사시 고려해야 할 추가검사?
  - Hb/Hct → 필수검사 → 낮다면 Anemia study (소화기, 혈액내과 의뢰)
  - 50% 이상이라면 호르몬보충 못함
  - LH, FSH: T가 낮게 나오면 검사 → if low LH, FSH, check prolactin
    → if high LH, FSH, check Karyotype
  - Brain MRI → prolactin이 높을 때
  - HbA1c → 당뇨상병 (의증) 넣고.
  - 골밀도검사→ Osteoporosis 의증상병 넣고 1년에 1회 보험.
  - Lipid profile → Total chol. LDL, HDL, TG (4종을 하면 삭감, 2종 추천함)
  - PSA (40세 이상)

When T should be measured? (Grade B)

※ 다음을 알게 되었을 때 환자 동의하에 검사

- **Unexplained anemia**
- **Bone density loss**
- **Diabetes**
- **Chemotherapy (직장/대장 암 등)**
- **Testicular radiation Tx (직장/대장 암 등)**
- HIV
- Chronic narcotic use
- Infertility
- **Steroid use (류마티스, 신장, 신경외과 등)**

Beneficials and safety of TTh

Table 1. Summarized effect of TTh on specific symptom and on development of unfavorable condition in TD

	EAU [4]	AUA [5]	ISSM [6][a]	SR in JSM [7]	ES [8]
Symptom/sign					
Documentation[b]	Strong/weak R or LE	Recommendation grade	Recommendation grade	Mild/moderate/strong effect	+/++/+++/++++
Sexual function					
Libido (desire)	IR	↑ R (Grade B)	↑ R (Grade C)	↑ Strong effect	↑ (++)
Erectile function	In TD, start PDE5I as first line treatment and add T in case of a poor response (Strong R).	↑ R (Grade B)	↑ R (Grade C)	↑ Moderate effect	IR
Ejaculatory function	IR		↑ R (Grade C)	↑ Mild effect	
Physical function			↑ R (Grade C)	↑ Mild effect	IR
Mood	↑ (LE 3)	↑ R (Grade B)	↑ R (Grade C)	↑ Mild effect	
Cognition	↑ (LE 3)	↔ R (Grade B)	↑ R (Grade C)	↔ no effect	
Metabolic syndrome	↑ (LE 3)	↔ R (Grade B)		↑/↔ Mild/no effect	
DM	↑ (LE 3)	↔ R (Grade B)		Not suggested as an alternative Tx for DM or MetS.	↔ Not recommended only for glycemic control (++).
Body composition (muscle/fat ratio)	↑ (LE 3)	↑ R (Grade B)	IR	↑ Mild effet TTh+LSM>LSM	IR
Bone density	IR	↑ R (Grade B)	IR	↑ Mild effect	IR
Quality of life		↔ R (Grade B)			↔
Vitality		↔ R (Grade B)			↔
Adverse effects					
Patients with LUTS	Marginal increase in prostate volume		↓	↓ or ↔	↔
Pca development	↔ (LE1b)	↔ R (Grade B)	↔ R (Grade C)	↔	↔

DS Lee and HJ Park. WJMH 2020

Beneficials of TTh

	EAU [4]	AUA [5]	ISSM [6][a]	SR in JSM [7]	ES [8]
Patients with Pca history (comments)	In treated Pca without evidence of active disease, TTh can be introduced after 1 year follow-up in cases of low risk for recurrence (Weak R).	Inadequate evidence	Possible candidate in successfully treated Pca with symptomatic TD with a prudent interval and without no evidence of residual cancer (Grade C).	IR	Recommended against T supplementation in men with prostate cancer.
Fertility	↓ (Strong R) Only use hCG treatment	↓ R (Grade A) AI, hCG, SERMS can be used (Grade C)	↓ (Grade A) hCG, hMG, SERMS, AI (short-term) can be used (Grade B/C).	↓	↓ (++)
Cardiovascular	↔ (LE1a) Assess for cardiovascular risk factors before commencing TTh (Strong R). In hypogonadal men TTh has been demonstrated to have a positive impact on cardiovascular risks.	↔ R (Grade B) Not recommended until 6 months in pt with CVD.	↔ (Grade B) Possibility of beneficial effect	↔	↔

DS Lee and HJ Park. WJMH 2020

생식 (Fertility)

Counseling

- Long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Grade A)

- TRT → LH ↓, FSH ↓ by negative feedback → endogenous T ↓, Spermatogenesis ↓

Spermatogenesis

- The vast majority of healthy men with normal testosterone levels will recover sperm production after cessation of exogenous testosterone.

- 67% within 6 months, 90% within 12 months, 96% within 16 months, and 100% within 24 months

Bachman et al. J Gerontol A Biol Sci Med Sci 2014; 69: 725
Samplaski et al. Fertil Steril 2014; 101: 64

T with hCG, SERM, AI (Grade C)

- Aromatase Inhibitor to low T/E ratio

→ improve T/E and semen parameters (debates)

→ AIs can significantly suppress E2, which is essential in maintaining bone density.

- hCG to hypogonadotrophic hypogonadism

→ Serum T↑, intratesticular T↑ and preserve spermatogenesis

→ Good to facilitate recovery of spermatogenesis prior use of exo. T and or anabolic steroid abuse

- SERM (e.g. Clomiphen)

→ oral agent; E2 feedback blocking → LH↑ → T↑

→ Sperm concentration was maintained (comparable to placebo) for males treated with the SERMs, but was significantly decreased for males on exogenous testosterone

hCG, SERM, AI

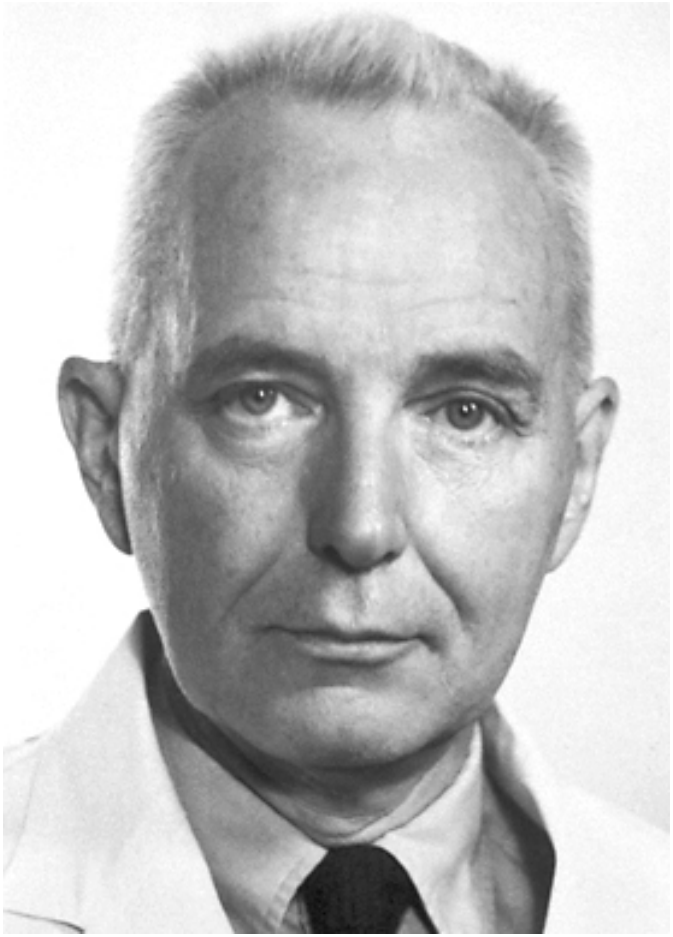
- SERM (Not FDA-approved for use in males)
  → Clomiphen citrate (50mg qd daily or with drug holiday), Tamoxifen

- AI (Not FDA-approved for use in males)
  → Anastrozole

- hCG (FDA approved for use in males with hypogonadotropic hypogonadism and pediatric patients with cryptorchidism)
  → 500-4000 IU units SQ or IM 2-3 times per week

전립선

Testosterone and Prostate cancer



- Charles Huggins (1901~1997)
- 1941 report

  - P-ca is activated by testosterone injection.
- 1966 Nobel Prize
- High T maybe aggravate P-ca
- Low T maybe protective against P-ca

Serum phosphatase in P-ca

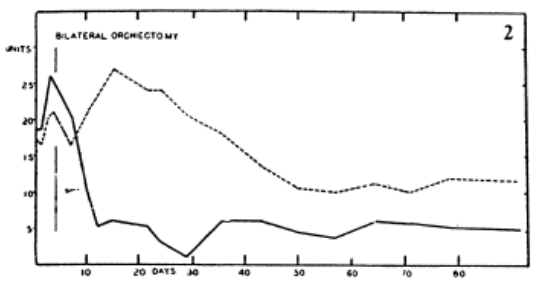
Studies on Prostatic Cancer

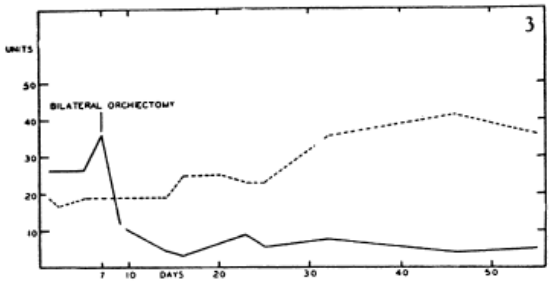
I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

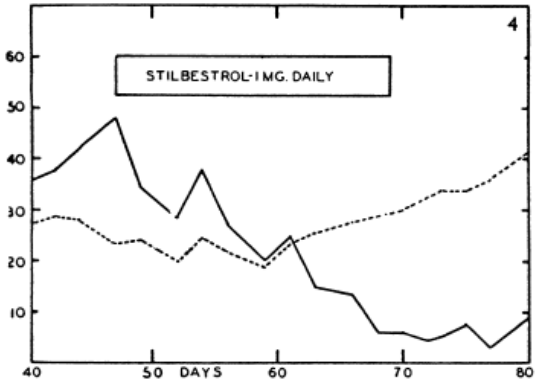
Orchiectomy

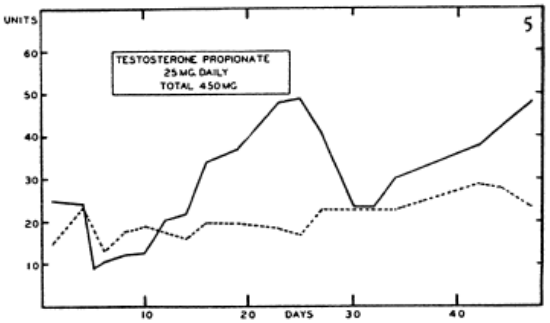




Orchiectomy

Estrogen





Androgen

Testosterone and Prostate cancer

- There is no evidence that high T levels contribute to increased PCa risk
- Low T levels are not protective.
- The important exception is androgen-deprived men!

Traditional myths

- P-ca caused by androgen **Wrong!**

- Low T is protective against P-ca

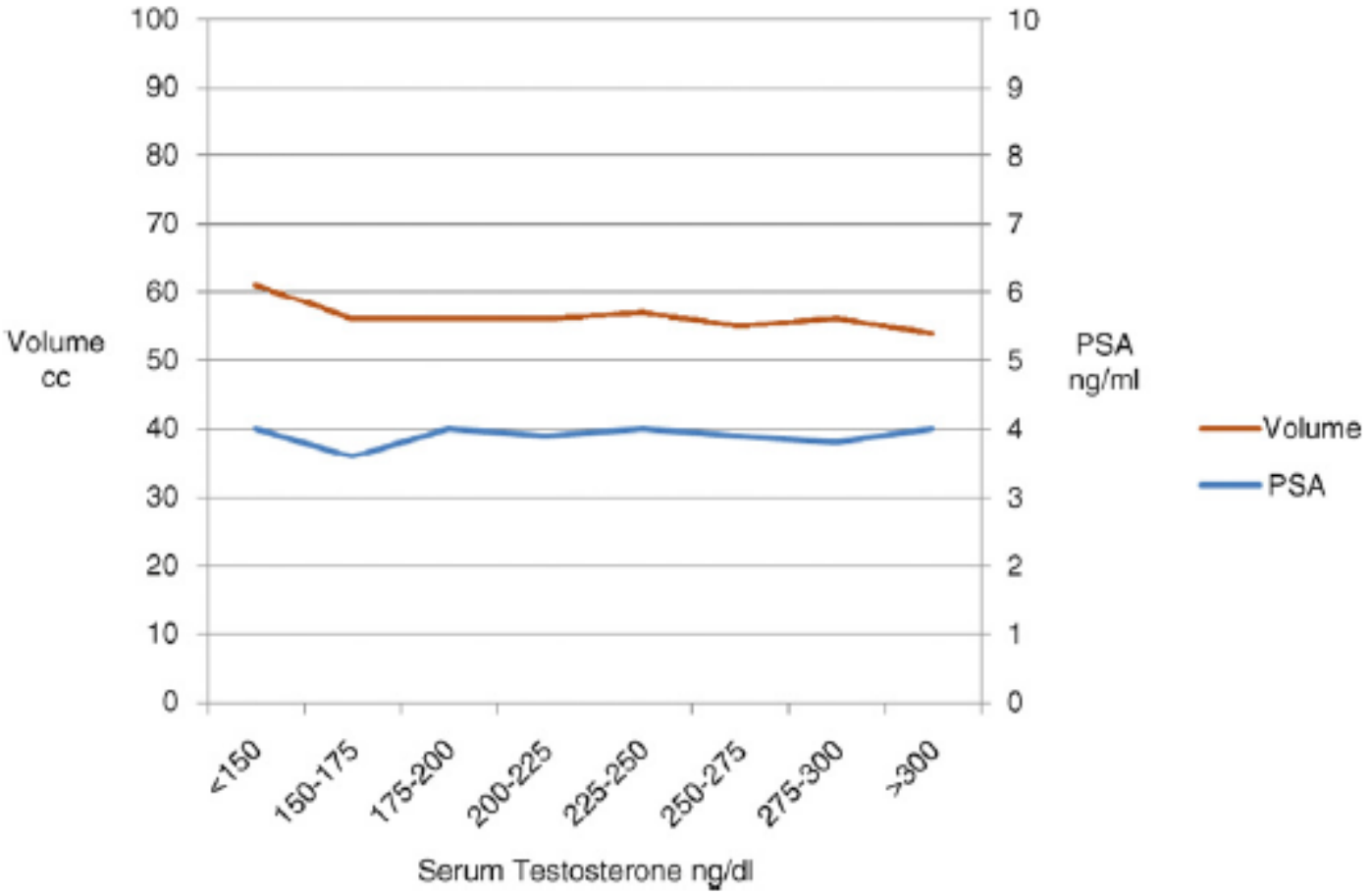
Wrong! But androgen deprivation suppress P-ca

- High T causes rapid P-ca growth

May be Wrong! But we need more information

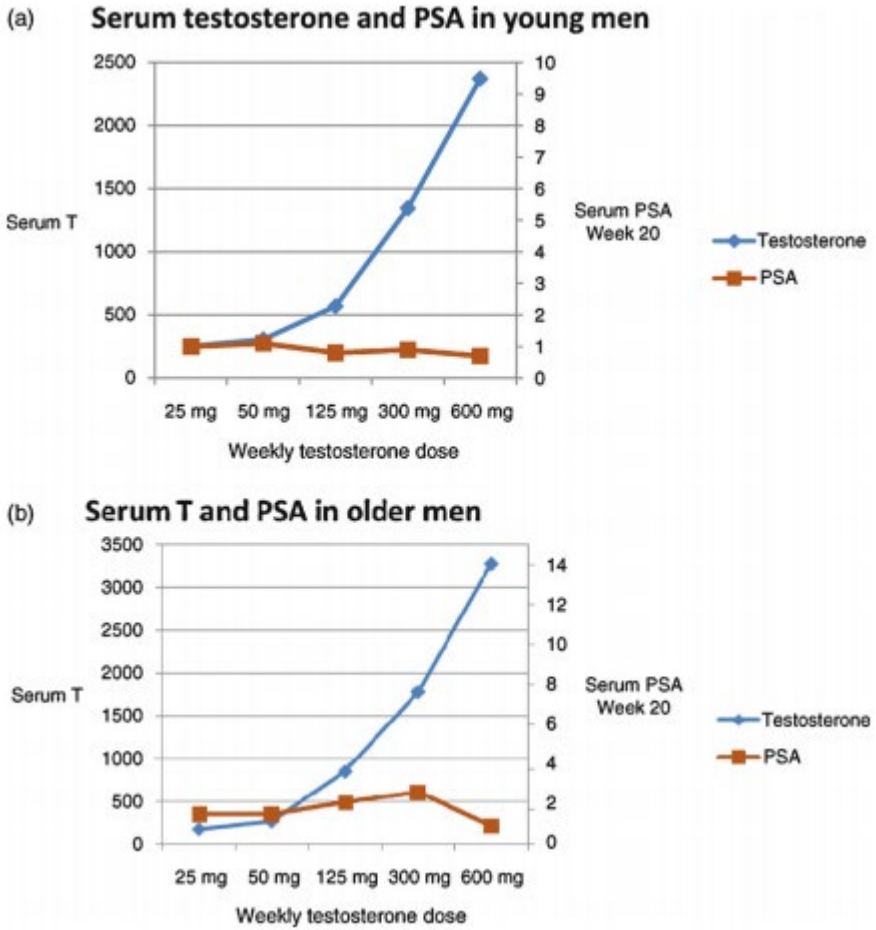
Morgentaler, Abraham "Testosterone and Prostate Cancer: Is There a Link?" March 16, 2017. Accessed Mar 2019. https://grandroundsinurology.com/testosterone-prostate-cancer-link

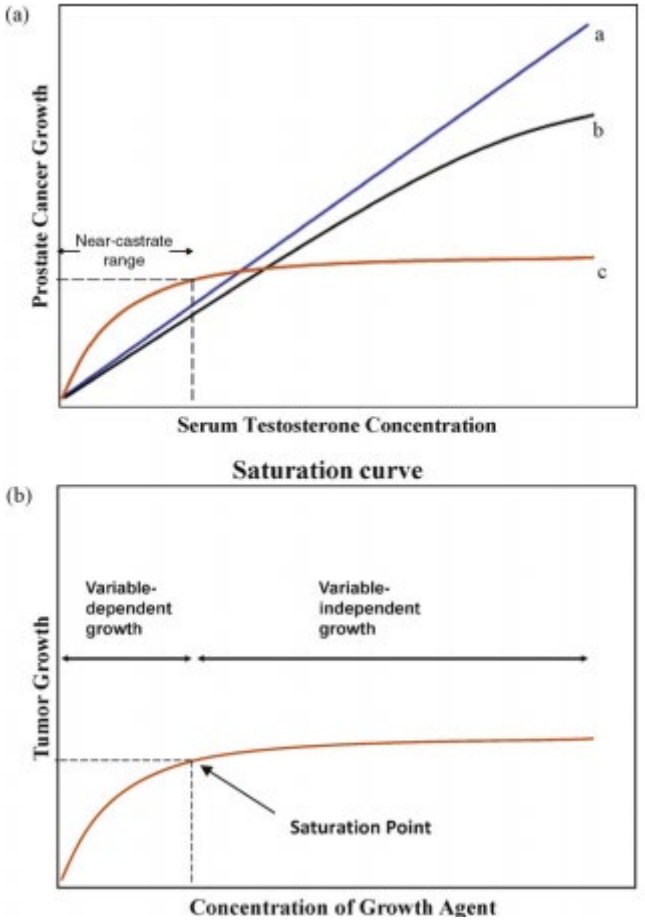
Serum T and Prostate volume



Marberger et al. J Clin Endocrinol Metab 2006;91:1323–8.

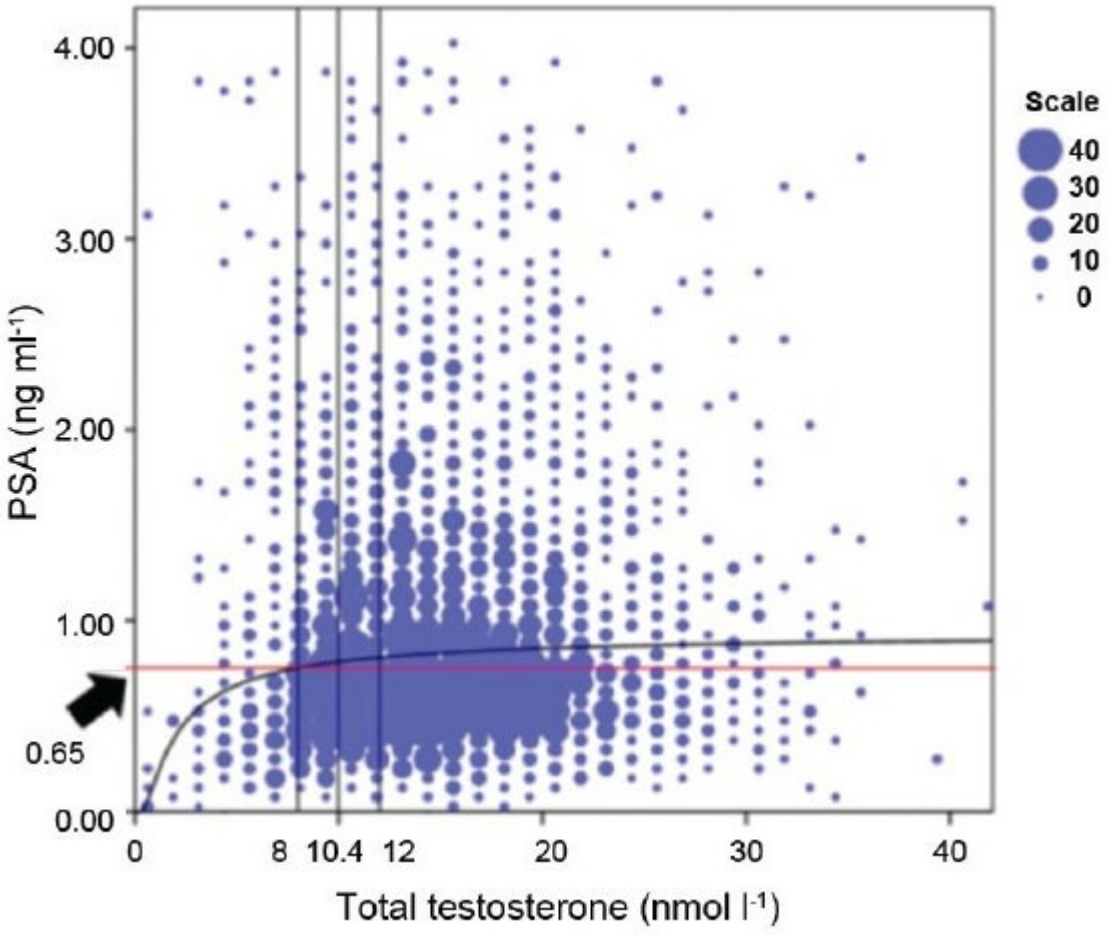
Saturation model by Abraham Morgentaler





Morgentaler et al. Eur Urol 2009;55:310

Saturation point



Rastrelli et al. J Sex Med 2013;10:2518

T Tx vs. Prostate cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2016 VOL. 374 NO. 7

Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg, for the Testosterone Trials Investigators*

Table 4. Adverse Events during the First Year (Treatment Period) of the Testosterone Trials.*

Event	Placebo (N=394)	Testosterone (N=394)
	no. of participants	
Prostate-related event		
Increase in PSA level by ≥1.0 ng/ml	8	23
Prostate cancer	0	1
IPSS >19†	26	27
Hemoglobin ≥17.5 g/dl	0	7
Cardiovascular event‡		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other§	6	7

Meta-analysis from 13 RCTs

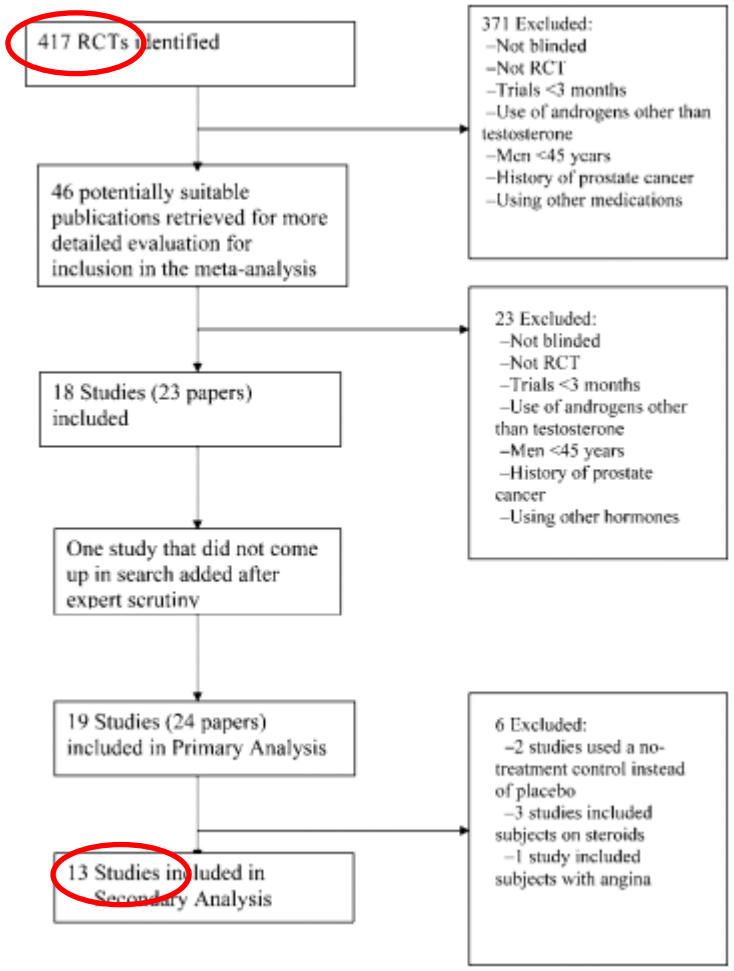


Table 2. Characteristics of Participants

Characteristics	Testosterone Group	Placebo Group
Number of participants	643	427
Age, years	62.9 ± 9.0	64.4 ± 8.2
Baseline testosterone, ng/dl	320 ± 78	344 ± 91
Testosterone levels during treatment, ng/dl	536 ± 173	339 ± 105
Baseline PSA levels, ng/ml	1.3 ± 1.0	1.3 ± 1.0

Event	Testosterone: Adverse Event Rate per 1000 Patient-Years*	Placebo: Adverse Event Rate per 1000 Patient-Years*	Pooled Odds Ratio	95% Confidence Interval
Prostate biopsies	46.1	3.6	2.30	0.92, 5.77
Prostate cancers	11.0	7.3	1.14	0.44, 2.97
PSA >4 ng/ml or 1.5 ng/ml increase during study	59.2	50.9	1.22	0.67, 2.24
Increase in IPSS score	6.6	3.6	1.12	0.42, 3.04
Acute urinary retention	2.2	0	1.00	0.34, 2.97
All prostate events	122.9	65.5	1.90†	1.11, 3.24
Hematocrit >50%	76.8	3.6	5.07†	2.30, 11.14
Atrial fibrillation/arrhythmia	11.0	3.6	1.32	0.50, 3.51
Myocardial infarction	4.4	7.3	0.91	0.38, 2.46
Chest pain/ischemia	0	10.9	0.68	0.23, 1.99
Coronary procedure/CABG	4.4	18.2	0.74	0.29, 1.91
Vascular events/cerebrovascular accidents	6.6	10.9	0.91	0.35, 2.38
All cardiovascular events	19.7	47.3	0.94	0.43, 2.04
Death	0	7.3	0.72	0.24, 2.11

Notes: *The rate per 1000 patient-years was calculated based on average study duration of 10 months, standardized to 1 year and multiplied by 1000.
†Odds ratios significantly different from placebo.
PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; CABG = coronary artery bypass graft.

Bachman et al. J Gerontol A Biol Sci Med Sci 2014; 69: 725

T Tx. in men with Hx. of P-ca

Table 1 – Results of testosterone therapy in men with prostate cancer

Study	No. of patients	Intervention	Follow-up, mo	Gleason score (no. of patients)	Pretreatment PSA	Post-treatment PSA	Pretreatment testosterone, ng/dl	Post-treatment testosterone, ng/dl	Comments
Agarwal et al. [39]	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1	<0.1	197	591	No PSA recurrences
Kaufman et al. [38]	7	RP	24	6 (6) 7 (1)	<0.1	<0.1	97	434	No PSA recurrences; longest follow-up = 12 yr
Khera et al. [40]	57	RP	13	≤6 (24) 7 (26) 8 (4)	0.005	0.005	255	459	No PSA recurrences
Pastuszak et al. [41]	103	RP	27.5	<6 (1) 6,7 (72) ≥8 (9)	0.004	0.007	261	460	Included 26 men with high-risk PCa and positive margins or nodes or Gleason score >8; comparison group of 49 men with RP without testosterone therapy; four PSA recurrences in the testosterone therapy group (4%), eight recurrences in the comparison group (16%)
Sarosdy [42]	31	Brachytherapy	60	5 (3) 6 (19) 7 (6) 8/9 (3)	NA	<1	188	489	No PSA recurrences
Morales et al. [43]	5	EBRT	14.5	6 (2) 7 (1) 8 (2)	0.1–0.97	<0.1–1.08	150 (5.2 nmol/l)	507 (17.6 nmol/l)	One patient had a transitory increase in PSA; none had PSA increase >1.5 ng/ml
Pastuszak et al. [44]	13	Brachytherapy and EBRT	29.7	6 (4) 7 (7) 8 (2)	0.30	0.66	178	368	No PSA recurrences
Morgentaler et al. [8]	13	AS	30	6 (12) 7 (1)	5.5	3.6	238	664	Follow-up biopsies in all men; no definite PCa progression in any patient; no increase in mean PSA or prostate volume; no cancer in 54% of follow-up biopsies
Morales et al. [45]	6	AS	NA	6 (5) 8 (1)	5.66	NA	259 (9 nmol/l)	NA	Variable PSA response in several men; no follow-up biopsies reported; one man subsequently underwent RP

PSA = prostate-specific antigen; RP = radical prostatectomy; PCa = prostate cancer; NA = not available; EBRT = external-beam radiation therapy; AS = active surveillance.

Khera et al. Eur Urol. 2014;65(1):115-23.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

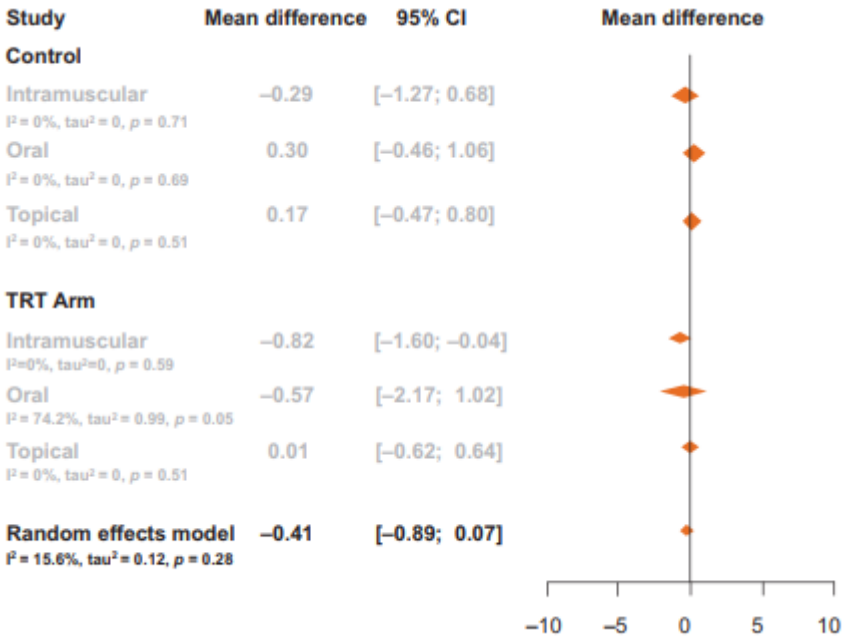
European Association of Urology

Review – Benign Prostatic Hyperplasia

Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis

Taylor P. Kohn [a,†], *Douglas A. Mata* [b,†], *Ranjith Ramasamy* [c], *Larry I. Lipshultz* [d,*]

[a] *Baylor College of Medicine, Houston, TX, USA;* [b] *Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [c] *Department of Urology, Miller School of Medicine, University of Miami, Miami, FL, USA;* [d] *Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA*



Prostate cancer

- Absence of evidence linking testosterone therapy to the development of prostate cancer (Grade B)
- Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)

Offer testosterone treatment cautiously in symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis): treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score < 8; pathological stage pT1-2; pre-operative PSA < 10 ng/ml) and should not start before one year of follow-up.	Weak

Cardiovascular events

Results from JAMA (2013)

- 8709 with T<300 : 결론 → TRT가 심혈관 mortality 높인다
- Methods and Results
- F/U after coronary angiography (m 531days)
- 7486 no TRT (real event 21.2%)
- 1223 TRT (real event 10.1%)

Vigen et al. JAMA. 2013;310(17):1829-1836

- Criticism (Bias): 후향적 연구; 실제 event는 TRT group에서 훨씬 낮은데 통계로 장난쳤다 (50개의 confounding factor); TRT 직전에 발생한 MI는 no TRT group 으로 했어야 함; 표본집단이 모집단을 반영하기 어렵다 (veterans affair system에서만 모집)

COMMENT & RESPONSE

Deaths and Cardiovascular Events in Men Receiving Testosterone

To the Editor As clinicians and researchers in the testosterone field, we found surprising the results reported by Dr Vigen and colleagues[1] of increased deaths and cardiovascular events in male veterans receiving testosterone following coronary angiography because these results contradict a literature spanning more than 20 years.[2] Should testosterone therapy be considered unsafe based on this study? We do not believe so.

This study was not a straightforward 2-group comparison in which there were a higher number of events in men who received testosterone. Rather, this was a complex retrospective study with a messy data set, containing a serious flaw that distorted the conclusion.

The authors wrote, "... the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group ..." at 3 years following coronary angiography. However, we note the raw rate of events in the testosterone group was only 10.1% (123 events in 1223 men) compared with 21.2% (1587 events in 7486 men) in the no testosterone group. The authors neither acknowledged these data favoring the testosterone group, nor did they explain what drove results to an opposite conclusion.

The Kaplan-Meier curves are similarly misleading because the approximately 30% event rate for the testosterone group at the end of the study is a 3-fold multiple of the actual event rate. We assume the disparity is derived from calculated estimates based on statistical adjustment for more than 50 variables, thus magnifying potential errors.

Both groups began as a single population, with men joining the testosterone group as they began treatment, thus contributing to both event curves. A myocardial infarction was attributed to the testosterone group if a man filled his testosterone prescription the same day, but to the no testosterone group if he had not yet filled his prescription. This does not make sense.

In addition, basic information was not provided. Did time zero begin for the testosterone group at angiography or testosterone initiation? Could raw event data be provided for years 1 to 3? What was the mean time to events after receiving testosterone therapy? What were the person-years of exposure for both groups?

Our greatest concern is that 1132 men with myocardial infarction or stroke who subsequently received testosterone were incorrectly excluded from the study. It was irrelevant what happened after their event. All these events should have been included in the no testosterone group, increasing the number of events by 71%, thereby yielding an outcome consistent with 2 recent studies,[3,4] and demonstrating a reduction in mortality with testosterone therapy.

Morgentaler et al. JAMA. 2014;311(9):961-962

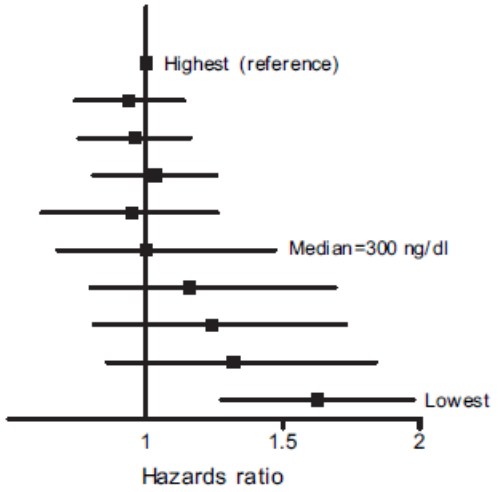


FIG. 1. All-cause mortality according to deciles of total testosterone adjusting for age, BMI, waist to hip ratio, current smoking, alcohol use, and exercise. The *squares* represent point estimates for HRs, the *lines* indicate 95% CIs. The median total testosterone values for deciles 1–10 were 171, 209, 241, 266, 288, 314, 338, 370, 422, and 507 ng/dl, respectively.

TABLE 4. HRs of low total testosterone and low bioavailable testosterone for all-cause mortality adjusting for (or excluding) potential covariates and mediators

	Low T HR (95% CI)	Low BioT HR (95% CI)
Lowest quartile *vs.* higher[a]	1.40 (1.14, 1.71)	1.44 (1.19, 1.74)
Plus hypertension[b]	1.39 (1.14, 1.70)	1.45 (1.19, 1.75)
Plus diabetes	1.37 (1.12, 1.69)	1.47 (1.21, 1.79)
Plus CVD	1.35 (1.11, 1.64)	1.44 (1.19, 1.75)
Plus metabolic syndrome	1.30 (1.06, 1.61)	1.45 (1.19, 1.76)
Plus health status markers[c]	1.36 (1.10, 1.67)	1.57 (1.29, 1.92)
Plus HOMA-IR[d]	1.41 (1.08, 1.85)	1.61 (1.24, 2.10)
Plus adiponectin, leptin	1.43 (1.16, 1.77)	1.45 (1.20, 1.77)
Plus CRP, IL-6[e]	1.27 (0.96, 1.57)	1.23 (0.96, 1.58)
Plus estradiol	1.35 (1.08, 1.68)	1.40 (1.15, 1.70)
Plus bioavailable estradiol	1.34 (1.09, 1.66)	1.39 (1.12, 1.71)
Excluding prevalent:		
Diabetes (n = 116)	1.45 (1.15, 1.82)	1.34 (1.09, 1.66)
CVD (n = 274)	1.39 (1.09, 1.77)	1.40 (1.12, 1.76)
Metabolic syndrome (n = 140)	1.43 (1.12, 1.83)	1.32 (1.06, 1.64)

TABLE 5. HRs of low total testosterone and low bioavailable testosterone for cause-specific mortality by years of follow-up

Cause of death	0–20 yr follow-up n	0–20 yr follow-up HR (95% CI)	5–20 yr follow-up n	5–20 yr follow-up HR (95% CI)
Low total testosterone[a]				
All-cause	529	1.38 (1.12, 1.69)	409	1.60 (1.27, 2.02)
CVD	264	1.38 (1.02, 1.85)	199	1.73 (1.23, 2.45)
Cancer	127	1.34 (0.89, 2.00)	90	1.22 (0.75, 1.99)
Respiratory disease	54	2.29 (1.25, 4.20)	46	2.67 (1.37, 5.20)
Other	96	1.13 (0.68, 1.88)	83	1.51 (0.89, 2.56)
Low biotestosterone[b]				
All-cause	529	1.44 (1.19, 1.74)	409	1.44 (1.16, 1.80)
CVD	264	1.36 (1.04, 1.79)	199	1.39 (1.01, 1.92)
Cancer	127	1.50 (0.99, 2.26)	90	1.38 (0.82, 2.31)
Respiratory disease	54	1.84 (1.03, 3.28)	46	1.65 (0.86, 3.14)
Other	96	1.43 (0.91, 2.24)	83	1.56 (0.96, 2.53)

Adjusted for age, BMI, waist to hip ratio, alcohol use, current smoking, and exercise.

[a] Reference is total testosterone 241 ng/dl or greater.

[b] Reference is bioavailable testosterone 78 ng/dl or greater.

Laughlin et al. J Clin Endocrinol Metab. 2008 Jan;93(1):68-75

Re: Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels

R. Vigen, C. I. O'Donnell, A. E. Barón, G. K. Grunwald, T. M. Maddox, S. M. Bradley, A. Barqawi, G. Woning, M. E. Wierman, M. E. Plomondon, J. S. Rumsfeld and P. M. Ho

University of Texas at Southwestern Medical Center, Dallas, Texas

*JAMA 2013; **310:** 1829–1836.*

Abstract for this article http://dx.doi.org/10.1016/j.juro.2014.04.069 available at http://jurology.com/

Editorial Comment: Another article that has fueled debate. The authors assessed the association between testosterone therapy and all cause mortality, myocardial infarction and stroke among male veterans to determine whether this association is modified by underlying coronary artery disease. This is a retrospective national cohort study of men with low testosterone levels (less than 300 ng/dl) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011. Primary outcome was a composite of all cause mortality, myocardial infarction and ischemic stroke. Among a cohort of men in the VA health care system who underwent coronary angiography and had low serum testosterone levels the use of testosterone therapy was associated with an increased risk of adverse outcomes.

Limitations of the study included its retrospective nature, a unique population of patients and the inability to extrapolate these data to the general population. Perhaps a consensus conference needs to be initiated to discuss these issues.

Allen Seftel, MD

INVITED COMMENTARY

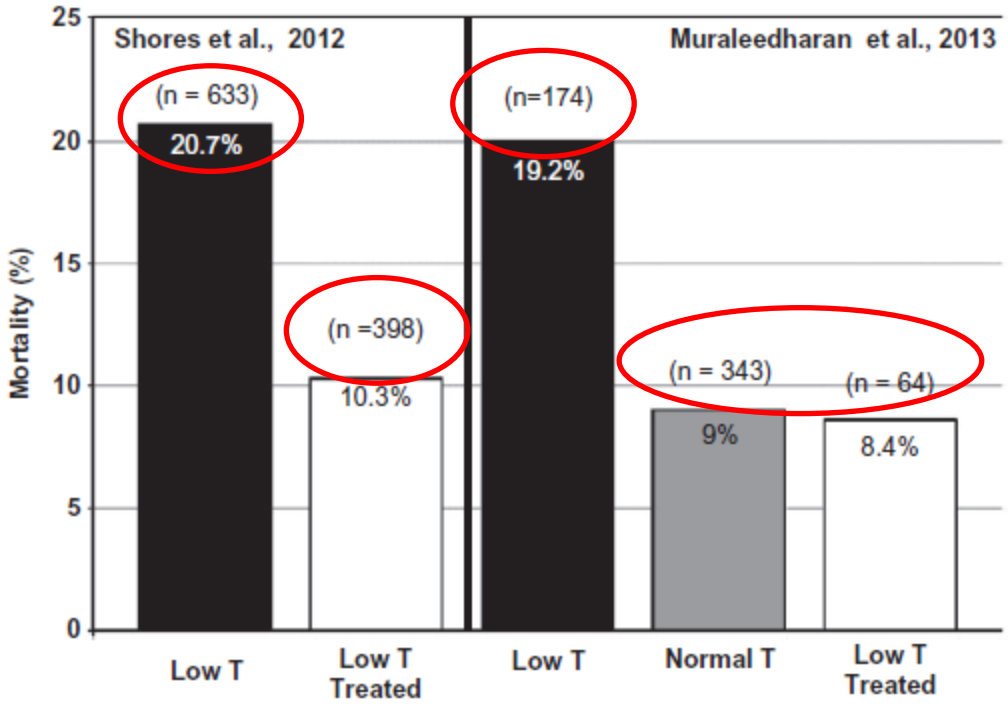
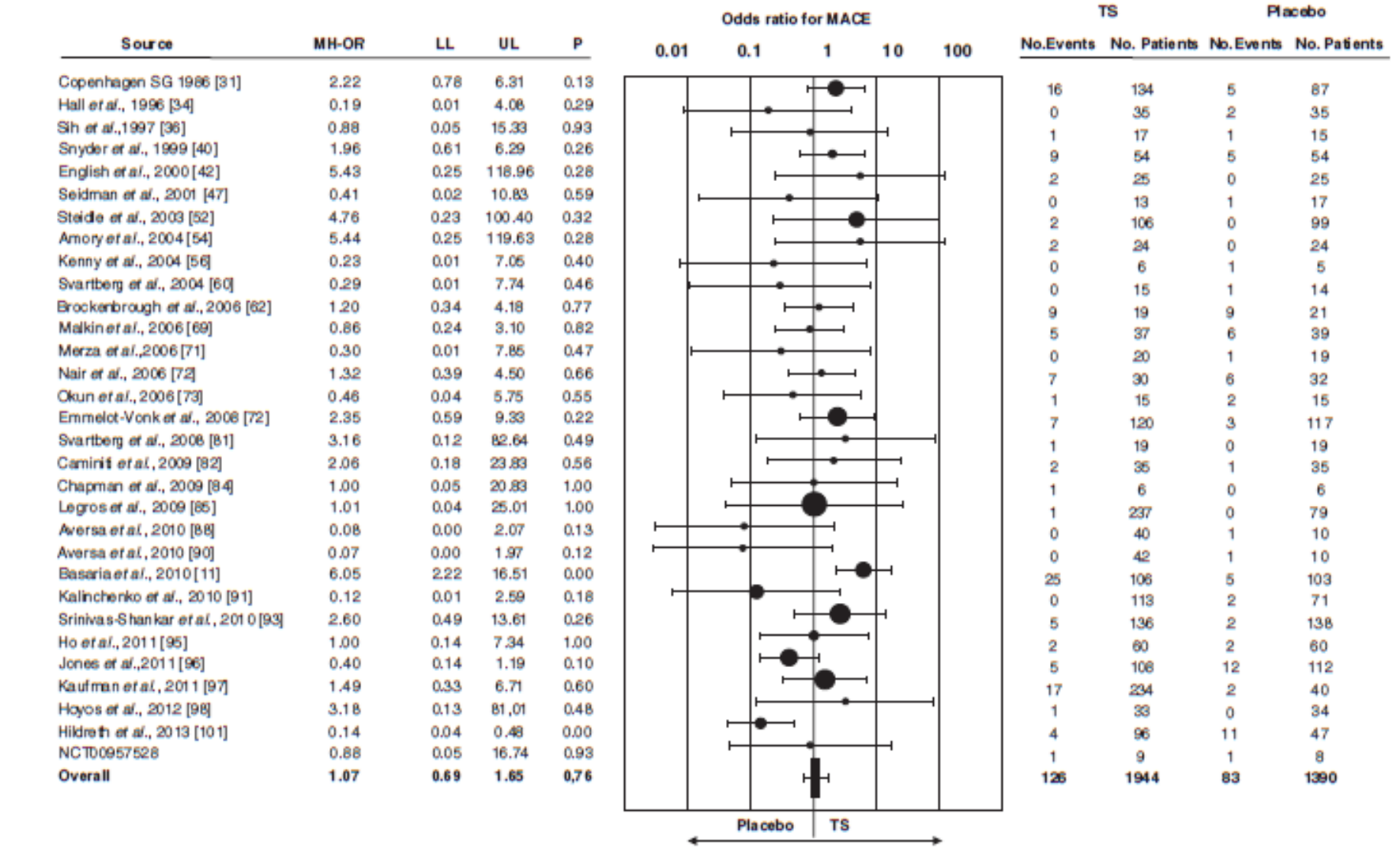


Figure 2 Testosterone treatment of men with low testosterone (T) reduces mortality. Left panel, percent of mortality in men with low T who were untreated (black bar) or treated with T (white bar) (Shores et al. [6]). Right panel: percent of mortality in men with low T who were untreated (black bar) or treated with T (white bar). Percent mortality in men with normal T levels are shown in the gray bar (Muraleedharan et al. [7]).

Journal of Medicine in 2010 in which a T trial in elderly frail men was terminated prematurely because of increased cardiovascular events in men who received T compared with men who received placebo [2]. Given the rapid increase in

revise their article, replacing the term "absolute risk" with a term that more properly reflected the fact that their conclusions represented a highly statistical approach to a messy dataset rather than being supported by raw data: "*At 3 years after coro-*



Source	MH-OR	LL	UL	P	TS No.Events	TS No. Patients	Placebo No.Events	Placebo No. Patients
Copenhagen SG 1986 [31]	2.22	0.78	6.31	0.13	16	134	5	87
Hall *et al.*, 1996 [34]	0.19	0.01	4.08	0.29	0	35	2	35
Sih *et al.*,1997 [36]	0.88	0.05	15.33	0.93	1	17	1	15
Snyder *et al.*, 1999 [40]	1.96	0.61	6.29	0.26	9	54	5	54
English *et al.*, 2000 [42]	5.43	0.25	118.96	0.28	2	25	0	25
Seidman *et al.*, 2001 [47]	0.41	0.02	10.83	0.59	0	13	1	17
Steidle *et al.*, 2003 [52]	4.76	0.23	100.40	0.32	2	106	0	99
Amory *et al.*, 2004 [54]	5.44	0.25	119.63	0.28	2	24	0	24
Kenny *et al.*, 2004 [56]	0.23	0.01	7.05	0.40	0	6	1	5
Svartberg *et al.*, 2004 [60]	0.29	0.01	7.74	0.46	0	15	1	14
Brockenbrough *et al.*, 2006 [62]	1.20	0.34	4.18	0.77	9	19	9	21
Malkin *et al.*, 2006 [69]	0.86	0.24	3.10	0.82	5	37	6	39
Merza *et al.*,2006 [71]	0.30	0.01	7.85	0.47	0	20	1	19
Nair *et al.*, 2006 [72]	1.32	0.39	4.50	0.66	7	30	6	32
Okun *et al.*, 2006 [73]	0.46	0.04	5.75	0.55	1	15	2	15
Emmelot-Vonk *et al.*, 2008 [72]	2.35	0.59	9.33	0.22	7	120	3	117
Svartberg *et al.*, 2008 [81]	3.16	0.12	82.64	0.49	1	19	0	19
Caminiti *et al.*, 2009 [82]	2.06	0.18	23.83	0.56	2	35	1	35
Chapman *et al.*, 2009 [84]	1.00	0.05	20.83	1.00	1	6	0	6
Legros *et al.*, 2009 [85]	1.01	0.04	25.01	1.00	1	237	0	79
Aversa *et al.*, 2010 [88]	0.08	0.00	2.07	0.13	0	40	1	10
Aversa *et al.*, 2010 [90]	0.07	0.00	1.97	0.12	0	42	1	10
Basaria *et al.*, 2010 [11]	6.05	2.22	16.51	0.00	25	106	5	103
Kalinchenko *et al.*, 2010 [91]	0.12	0.01	2.59	0.18	0	113	2	71
Srinivas-Shankar *et al.*, 2010 [93]	2.60	0.49	13.61	0.26	5	136	2	138
Ho *et al.*, 2011 [95]	1.00	0.14	7.34	1.00	2	60	2	60
Jones *et al.*,2011 [96]	0.40	0.14	1.19	0.10	5	108	12	112
Kaufman *et al.*, 2011 [97]	1.49	0.33	6.71	0.60	17	234	2	40
Hoyos *et al.*, 2012 [98]	3.18	0.13	81,01	0.48	1	33	0	34
Hildreth *et al.*, 2013 [101]	0.14	0.04	0.48	0.00	4	96	11	47
NCT00957528	0.88	0.05	16.74	0.93	1	9	1	8
Overall	**1.07**	**0.69**	**1.65**	**0,76**	**126**	**1944**	**83**	**1390**

Figure 5. Odds ratio for overall cardiovascular (CV) events in subjects treated with testosterone substitution (TS) or placebo.
LL: Lower limit; MH-OR: Mantel-Haenszel odds ratio; UL: Upper limit.

Corona et al. Expert Opin Drug Saf. 2014 Oct;13(10):1327-51

Thrombolic, Cardiovascular

- No definitive evidence linking testosterone therapy to a higher incidence of veno-thrombolic events. (Grade C)

- It cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (Grade B)

There is no substantive evidence that testosterone treatment, when replaced to the normal physiological range, is related to the development of major adverse cardiovascular events.	1a
In hypogonadal men testosterone treatment has been demonstrated to have a positive impact on cardiovascular risks.	1b

TRT to the Pts with cardiovascular events

- Avoid TRT within recent 3~6 months (Expert opinion)

Treat men with hypogonadism and either pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require testosterone treatment with caution by monitoring carefully with clinical assessment, haematocrit (not exceeding 0.54%) and testosterone levels maintained as best possible for age within the mid-normal healthy range.	Strong

Life-style modification (Grade B)

- T level ↑ and T-related symptom ↓
  Losing weight, recommended range, increasing physical activity

In patients with adult-onset hypogonadism, only prescribe testosterone treatment in men with multiple symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	Strong

비의도적 약물전파
(Transference)

Risk of Transference (gel/creams)

- Consider and discuss (Grade A)
- Child and woman
- Wash hands after applying
- Residual T on laundered clothing (13% of dose)

치료의 조지중단

- Cessation of TRT three to six months after commencement of treatment in patients who fail to achieve symptom or sign improvement.

모니터링

Target T level

- Middle tertile of the normal reference range (Grade C): 450~600ng/dL
- If injection Tx → centre point of inj.
- Achieving testosterone levels in this window should ameliorate any symptoms that are genuinely associated with testosterone deficiency.

T initial dosing monitoring

Table 2: Dosing Profiles of Available Testosterone Formulations (as of 2018)

Drug Name	Brand Name	Delivery System	Dose	Starting Dose	Dose Range	Application Site	Monitoring
Topical							
1% gel	Testim®	5g Tube	50mg/tube	50mg	50-100mg	Shoulders, upper arms	T within 4 weeks
1% gel	Vogelxo®	5g Tube 5g Packet 5g Pump	50mg/tube 50mg packet 12.25mg/actuation	50mg 50mg 4 actuations	50-100mg	Shoulders, upper arms	T within 4 weeks
1% gel	Androgel®	Packet Pump	50mg 12.25mg/actuation	50mg 4 actuations	50-100mg	Shoulders, upper arms	T within 4 weeks
1.62% gel	Androgel®	Packet Pump	40.5mg packet 20.25mg/actuation	40.5mg 2 actuations	20.25-81mg	Shoulders, upper arms	T within 4 weeks
2% gel pump	Fortesta®	Pump	10mg/actuation	4 actuations	10-70mg	Thigh	T within 4 weeks
2% solution	Axiron®	Pump	30mg/actuation	2 actuations	30-120mg	Axilla	T within 4 weeks
Patch	Androderm®	Patch	2 or 4mg/patch	4mg	2-6mg	Back, abdomen, upper arms or thighs	T within 4 weeks

T initial dose monitoring

Intramuscular							
T cypionate	*	Injection (1 and 10mL vials)		100 mg	50-200mg every 7-14 days	Gluteal muscle or lateral upper thigh	After cycle 4
T enanthate	*	Injection (5mL vials)		100 mg	50-200mg every 7-14 days	Gluteal muscle or lateral upper thigh	After cycle 4
T undecanoate	Aveed®	Injection– (750mg/3mL)	750mg (single dose)	750mg injection at weeks 0, 4, and every 10 weeks thereafter	750mg	Gluteal muscle	After cycle 4

Testosterone gel

Testosterone solution

악세론외용액2% [한국릴리]

보관 : 실온(1-30도) 보관

[처방에]
남성호르몬 부족으로 인한 질환(성기능저하, 남성 불임증, 갱년기장애 등)에 사용합니다.

[주 의]
진료 시마다 처방된 용량을 잘 확인합니다. 1번 펌프당 테스토스테론 30mg에 해당하며 보통 1~4번 펌프까지 사용됩니다. 전립선비대증 환자는 처방 전에 미리 의사에게 알리도록 합니다. 바른 부위에 부종, 자극감, 홍반, 뜨거운 느낌 등이 나타날 수 있습니다.

성분/함량 : Testosterone 2g

의사가 정해준 용량대로 도포용 도구 컵에 담아 그 컵채로 겨드랑이에 아래위로 문지릅니다. 가능한 오전에 겨드랑이를 깨끗이 씻고 건조시킨 후 발라줍니다. 한 쪽 겨드랑이 당 1회 1번 펌프한 양만 바를 수 있으며, 더 발라야 할 경우 다른 쪽 겨드랑이에 번갈아가며 바르도록 합니다(같은 쪽 겨드랑이에 재도포가 필요한 경우 약품이 건조된 후 바름). 타인에게 묻지 않도록 바르는 부위는 겨드랑이로 한정하고 손에 묻은 경우에도 깨끗이 씻어냅니다. 상처가 있는 부위에는 바를 수 없으며 손으로 문지르지 않도록 하고, 바른 후 2시간 내에 수영을 하거나 바른 부위를 씻어내지 않도록 합니다. (맨 처음 사용 시 3회 정도 펌프해 초기화시킴)

Testosterone patch

테스토패취1.8mg/24h(테스토스테론) TESTOPATCH 1.8mg/24h

성분/함량

Testosterone 22.50mg

제조사 (주)대웅제약

판매사 (주)대웅제약

전문의약품 | 비급여 <허가취하>

수입의약품

Andriol
(oral testosterone undecanoate)

안드리올 테스토캡스 연질캡슐
ANDRIOL TESTOCAPS SC

인쇄 공유

- 구분: 전문 (오·남용우려의약품)
- 제조사: N.V. Organon
- 판매사: 한국엠에스디(유)
- 수입사: 한국엠에스디(유)
- 생산발매현황: 생산/유통 중 (발매일 : 2010-06-01)
- 보험정보: 655501280(보)₩470/1캡슐 급여(2017-02-01) 약가이력정보 >
- 복지부 분류: 246 - 남성호르몬제
- KIMS 분류: 6a - 안드로겐, 관련제제
- ATC 코드: G03BA03 - testosterone 코드정보 상세
- 주성분코드: 236301ACS 대체가능의약품 >
- 성분 및 함량: testosterone undecanoate 40mg
- 포장정보(표준코드): 40밀리그램 x 60캡슐/PTP 8806555012817

더보기 >

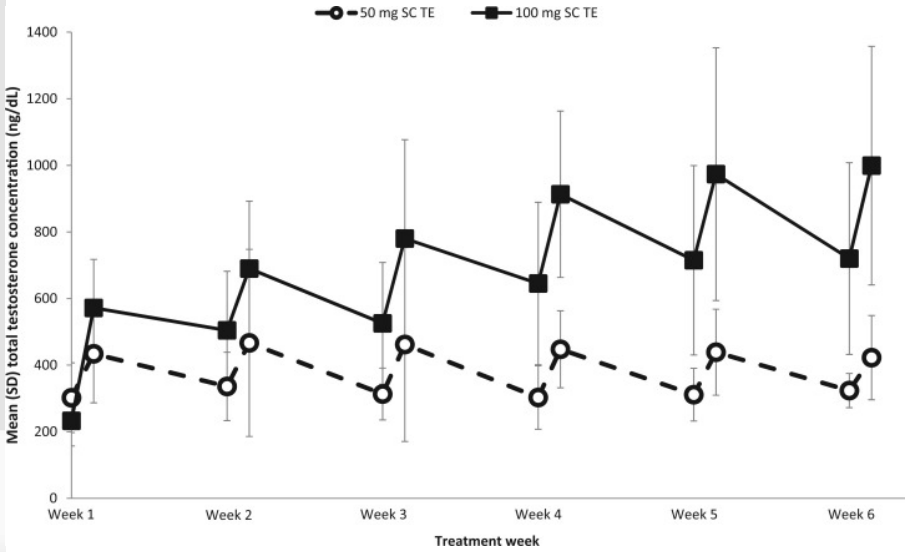
노란 유상 내용물이 들어있는 오렌지색의 광택이 있고 투명한 타원형의 연질 캡슐

식별정보 상세 이전 식별사진

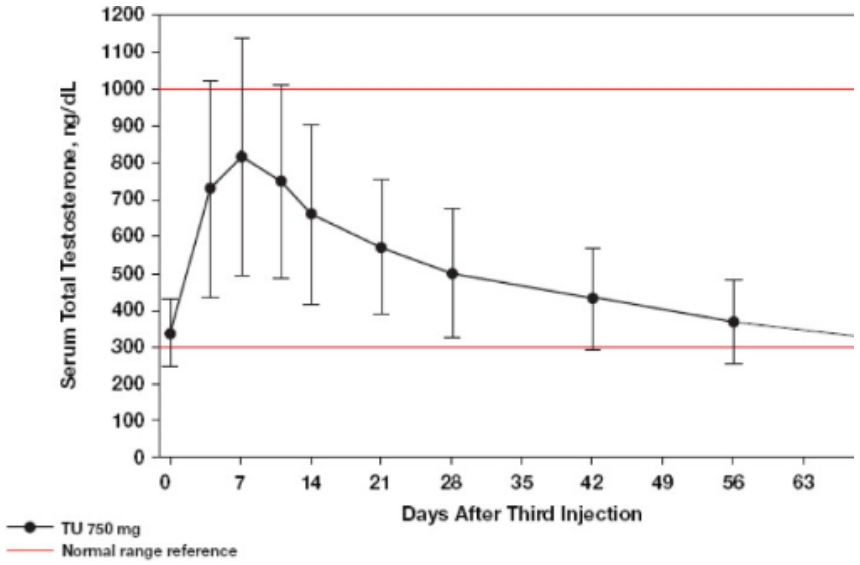
Jenasteron

예나스테론

테스토스테론 남성호르몬 주사



Sex Med 2015;3:263–73



J Urol 2008;180:2307-13

경청해주셔서 감사합니다.

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