Male Hypogonadism with Special Consideration of the Aging Male

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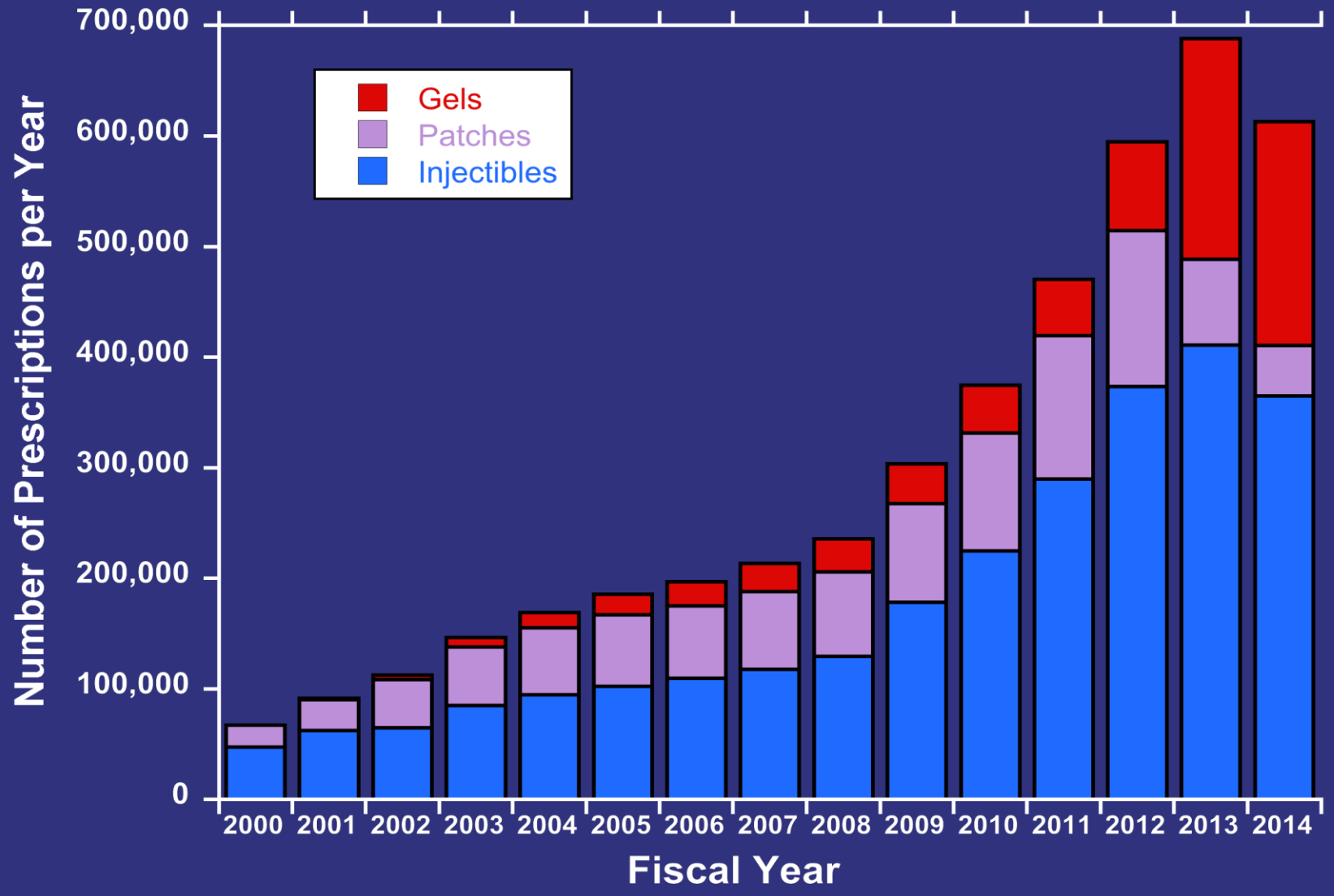
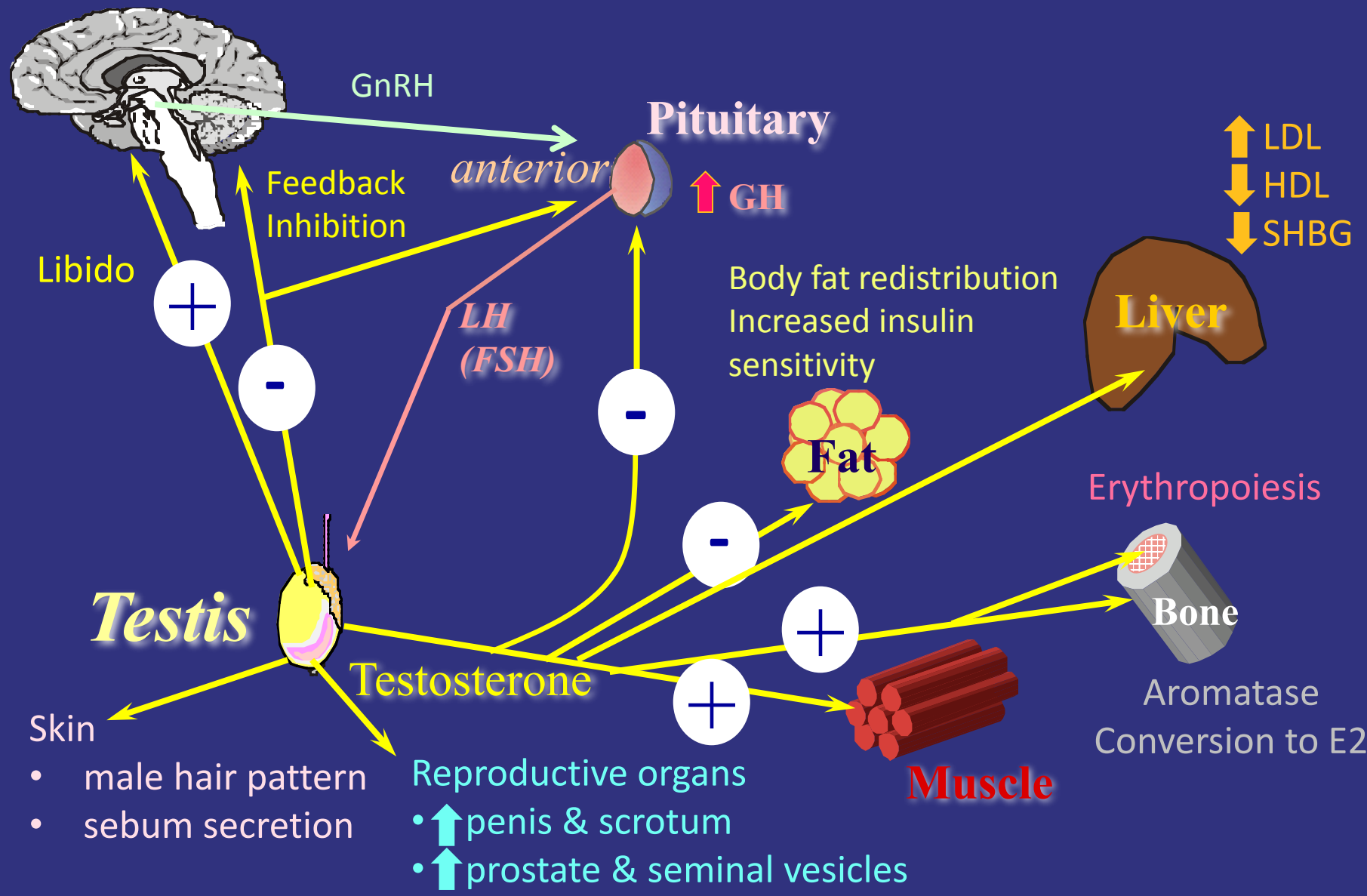
Annual Prescriptions for Testosterone in VA Health System by Type and Year



Courtesy of Dr. Winston Frank Evans, VA Pharmacy

SUMMARY OF TESTOSTERONE PHYSIOLOGY



Symptoms & Signs of Hypogonadism

- Enuchoid habitus (developmental)
- Reduced libido
- Erectile dysfunction
- Gynecomastia
- Infertility
- Osteoporosis
  - Height loss
  - Fractures
- Hot flushes
- Reduce shaving and loss of body hair
- Fatigue/depression/irritability
- Muscle weakness
- Poor concentration/memory

The Androgen Deficiency in Aging Men (ADAM) Questionnaire

1. Do you have a decrease in libido or 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 weight?
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?

The ADAM questionnaire is considered positive if the patient answers 'yes' to questions 1 and 7, as well as two to four of the other items

Morley, J et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 2000. 49:1239-42

Causes of Hypogonadism

- Primary (testicular)- T low, LH &FSH elevated
  - Developmental abnormalities
    - Undescended testes
    - Klinefelter's syndrome (XXY)
  - Acquired
    - Autoimmune disease
    - Infection (e.g. mumps, TB)
    - Trauma
    - Varicocoele
- Hypothalamic & Pituitary- T low, LH and FSH low or WNL
  - Genetic/developmental (e.g. Kallman's)
  - Intracranial tumors
    - Pituitary adenoma, esp. prolactinoma
    - Craniopharyngioma
  - Infections & inflammatory (TB, Eosinophilic granuloma)
  - Medications (esp. opiates, anti-depressive, anti-psychotic)
  - Chronic disease, incl. diabetes
  - Aging
  - Obesity

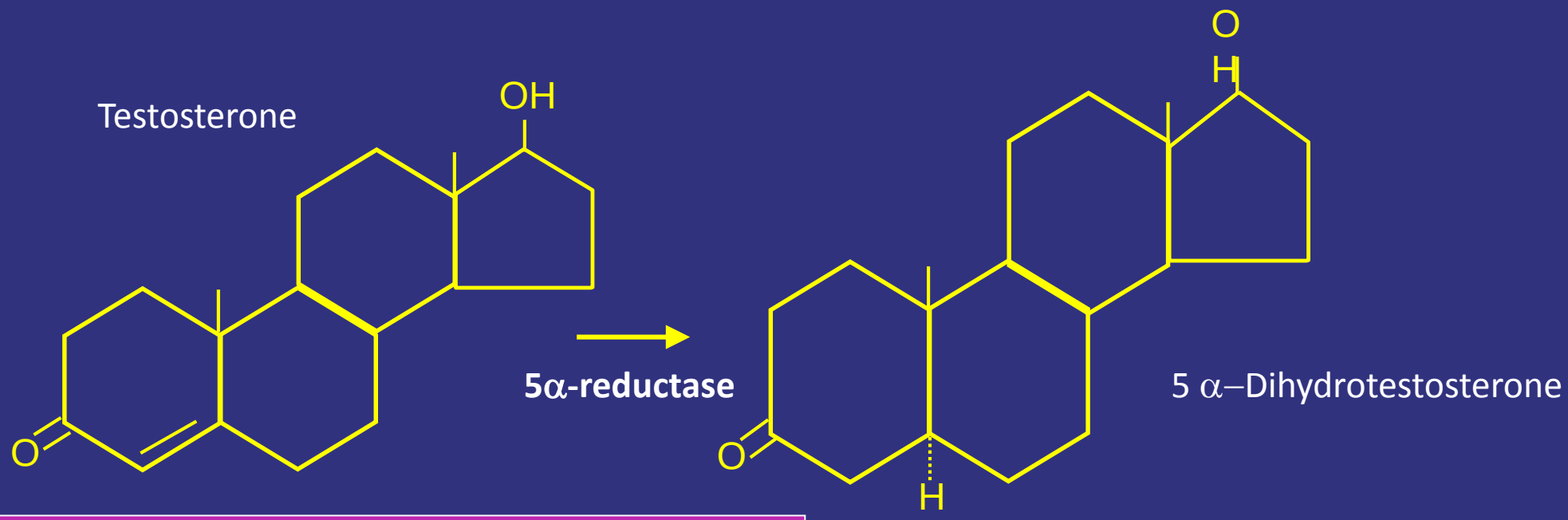
Assessment of Hypogonadism: Physical Examination

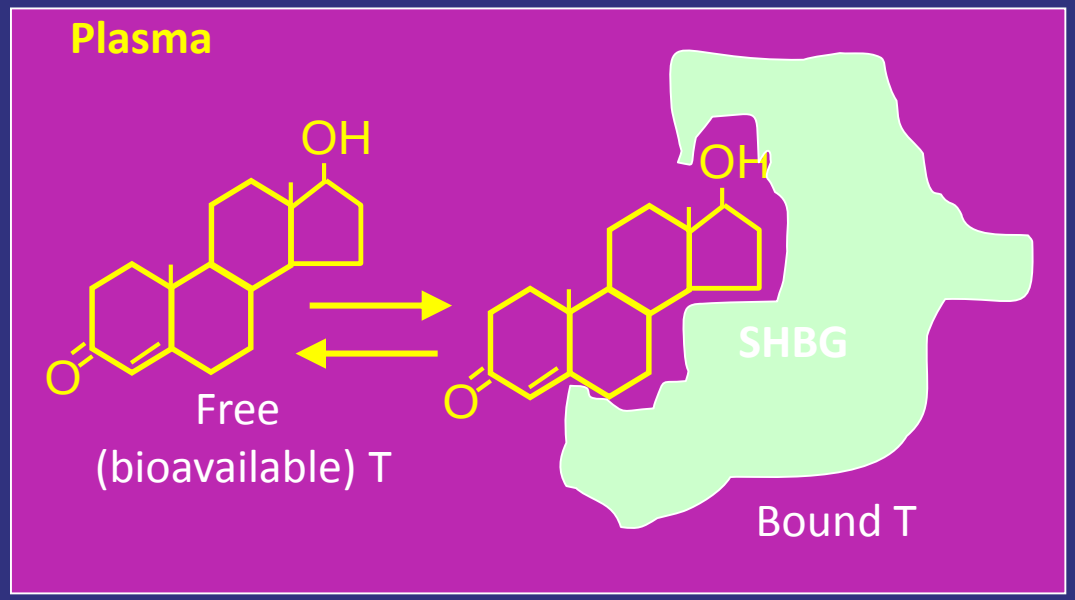
- Habitus (masculinized, feminized, immature)
  - Body shape (? Central obesity, Eunuchoid)
  - Skeletal muscle tone and strength
  - Hair distribution- beard, chest, pubic, and axillary hair
- Gynecomastia- present or absent, extent, Tanner stage
- Genitals
  - Phallus
    - Size (? micropenis)
    - Abnormalities of development-esp. hypospadias
  - Scrotum
    - Size, Pigmentation, Rugation
    - Contents- varicoele, cystocoele, other mass
  - Testes
    - Size in ml (estimate or use orchiometer)
    - Texture/turgor
      - Atrophy “ripe plum” vs. “overripe”
      - Small and hard (Kleinfelter’s)

Assessment of Hypogonadism: Lab Values

- Total testosterone (T) levels
  - Usually RIA or immunometric assays but LC Mass Spec. is “gold standard”
  - Range of “normal”
    - 350 to 1000+ ng/dl = WNL
    - 150 to 350 ng/dl = possibly abnormal, further assessment indicated
    - <150 ng/dl = low, consistent with hypogonadism
- Bioavailable and Free T levels (male)
  - Bioavailable (ammonium sulfate precipitation method)
    <110 ng/dl = hypogonadal
  - Free (dialysis or calculated from SHBG and albumin)
    <46 ng/dl = hypogonadal
- SHBG levels
  - < 22 nmol/L = low: may lead to factitious decrease in total T
  - >77 nmol/L = high: may cause high total T levels with low free or bioavailable levels
- Pituitary
  - Luteinizing hormone (LH) >12 mIU/ml, primary hypogonadism
  - Follicle stimulating hormone (FSH) > 8 mIU/ml, tubular atrophy
  - Prolactin (Prl) >100 ng/ml prolactinoma; 30-100 ng/ml medication or other cause

Physiology of Circulating Testosterone





Common causes of altered SHBG

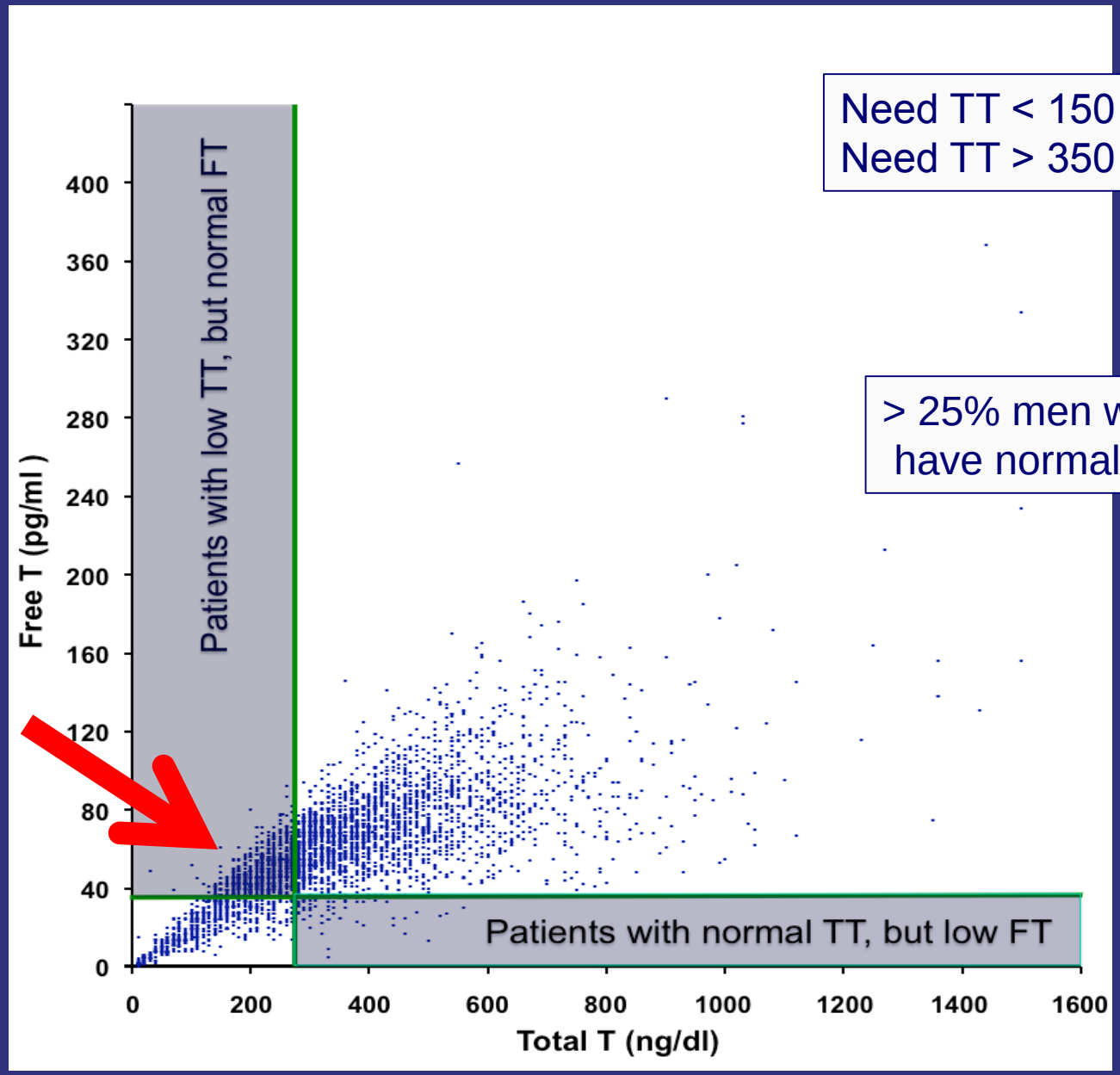
Low SHBG

- Obesity
- Diabetes mellitus
- Metabolic syndrome
- Corticosteroids
- Anabolic steroids
- Hypothyroidism

High SHBG

- Aging
- Medications
  - (anti-epileptics)
- Cirrhosis, hepatitis
- Estrogens
- Hyperthyroidism

Distribution of Total and Free T in Men



Need TT < 150 ng/dl to "rule in" low free T
Need TT > 350 ng/dl to "rule out" low free T

> 25% men with low total testosterone levels have normal free testosterone levels

N = 3600 veterans
~ 30% diabetic
~ 50% obese (BM > 30)

Anawalt. J Urol. 2012;187:1369-73

Other Assessment of Hypogonadism

- Primary hypogonadism
  - Varicocoele (scrotal ultrasound)
- Secondary hypogonadism
  - MRI of pituitary, with contrast preferable
  - Other conditions (diabetes, obesity, Cushing's, cancers, etc.)
- DEXA Scan for bone density
- Review medications
  - Opiates
  - Psychotropic agents
  - Steroids

Treatment of Hypogonadism

- Goals
  - Total T level of 450- 700 ng/dl
  - Relief of symptoms- energy, libido, strength
  - Improvements in body composition, bone mass, metabolism
- Testosterone administration
  - Testosterone (enanthate or other) injections 100 mg IM q week
  - Testosterone gels (transdermal 50, 100, or 150 mg/ day)
  - Testosterone transdermal patches
- When fertility is an issue
  - hCG (1500 to 2000 IU 3x weekly)
  - Add FSH (hMG or recombinant FSH) - at 75 IU 3x weekly for oligospermia
  - Clomiphene citrate (Off-label)
    - Only if no pituitary disease
    - Effective at 50 mg tiw in 85% for raising T level to goal
    - May be less effective at improving libido than other modalities

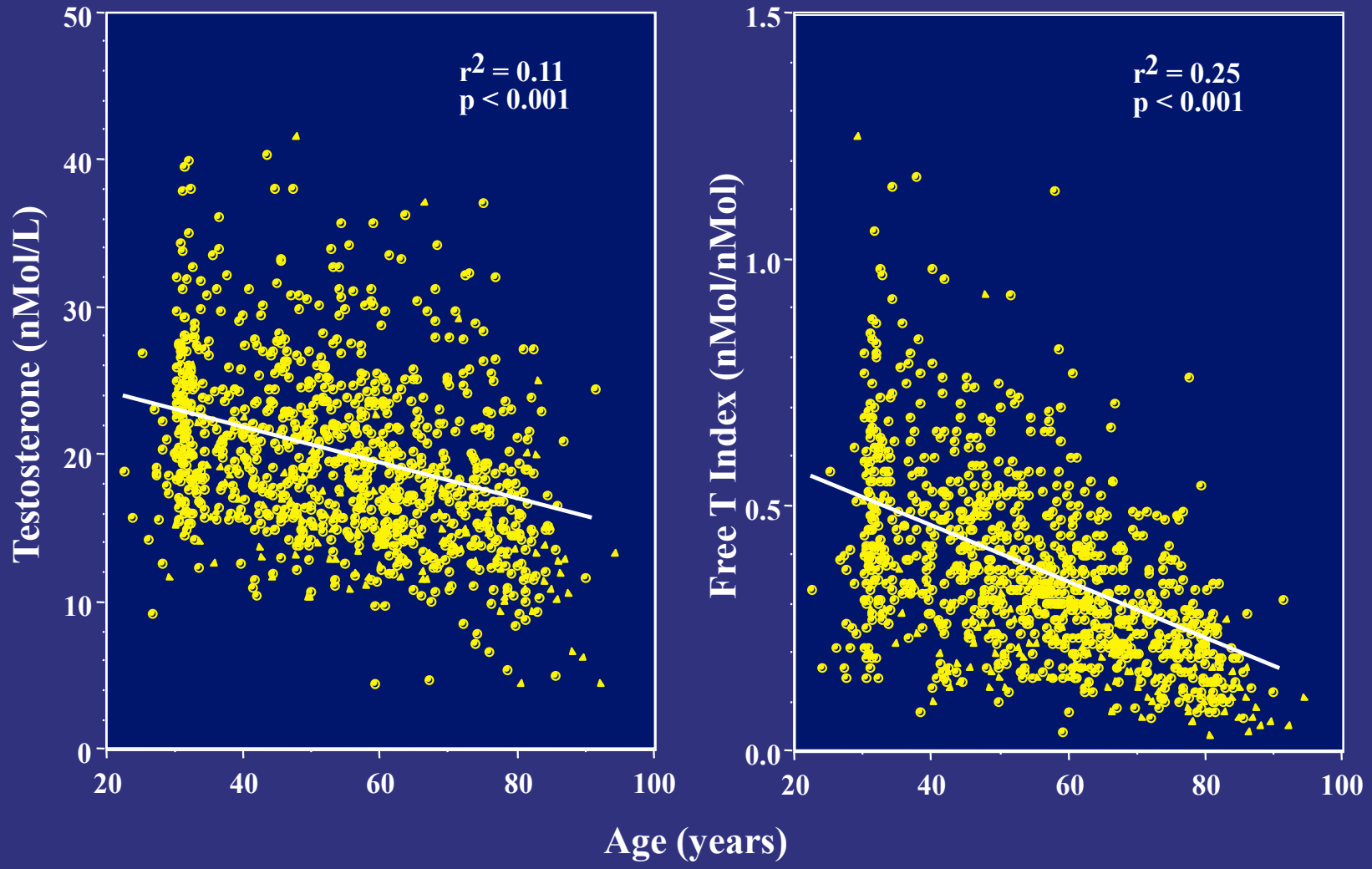
Adverse Effects of Treatment

- Commonly observed and accepted risks
  - Increases in PSA – usually by no more than 0.2 to 0.3 units
  - Modest decreases in HDL cholesterol
  - Erythrocytosis - Increased hemoglobin and hematocrit >15 g dl and 55%
  - Worsening sleep apnea
  - Testicular atrophy
  - Oily skin, acne
- Controversial areas of concern
  - Cardiovascular disease
  - Venous thromboembolic events
  - Prostate cancer

Questions Regarding Older Men and Testosterone

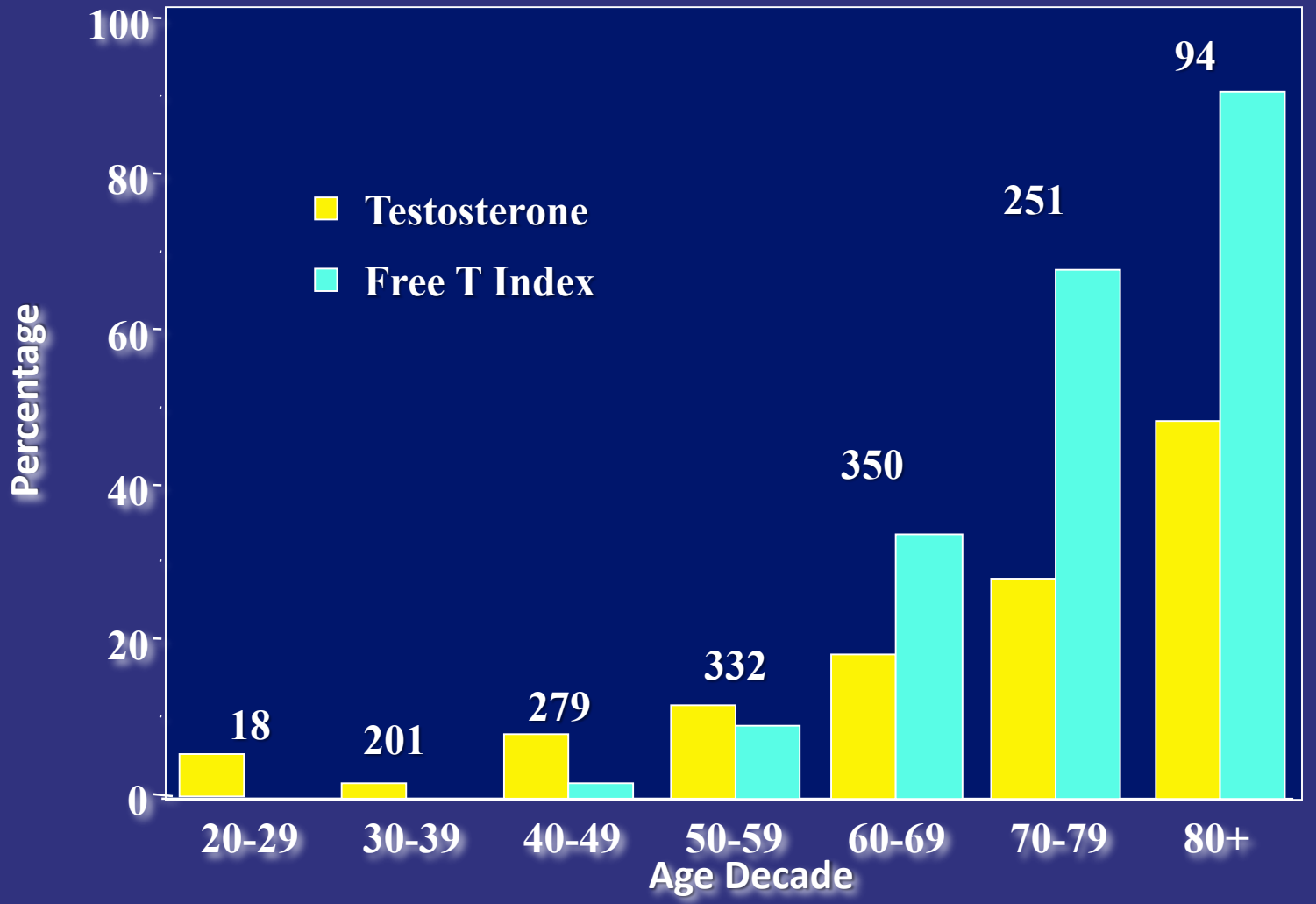
- Is there an “Andropause?”
- Are there relationships between problems of aging and androgen levels in men?
- Are there demonstrated benefits of treating older men with androgens?
- Are there additional risks of androgen treatment in elderly men?
  - Prostate cancer?
  - Cardiovascular disease?

Serum Testosterone and Free Testosterone Index vs. Age in 890 BLSA Men



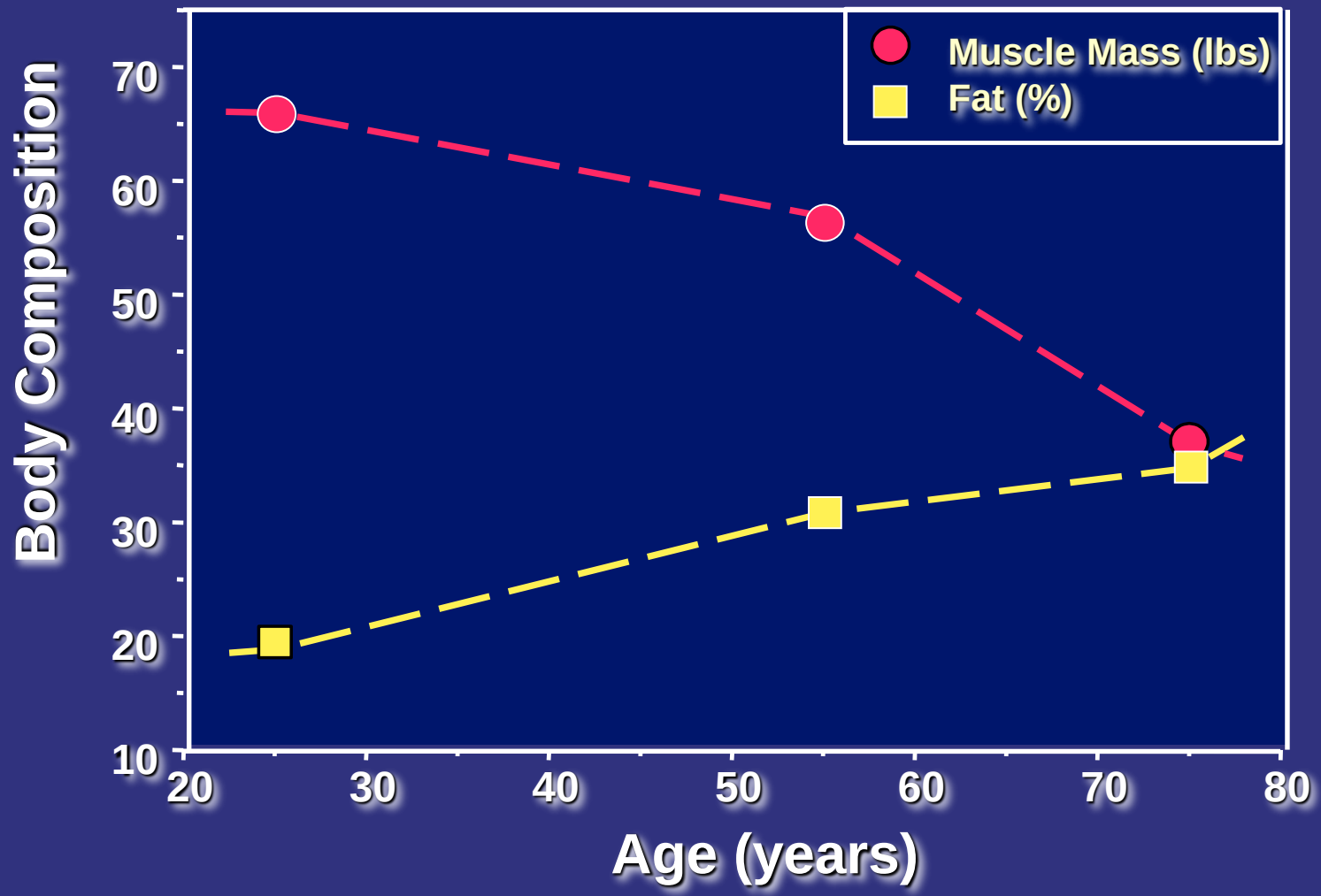
(Harman et al. J Clin Endocrinol Metab, 2001)

Percentage of Healthy BLSA Men by Decade Hypogonadal by Total T and Free T Criteria



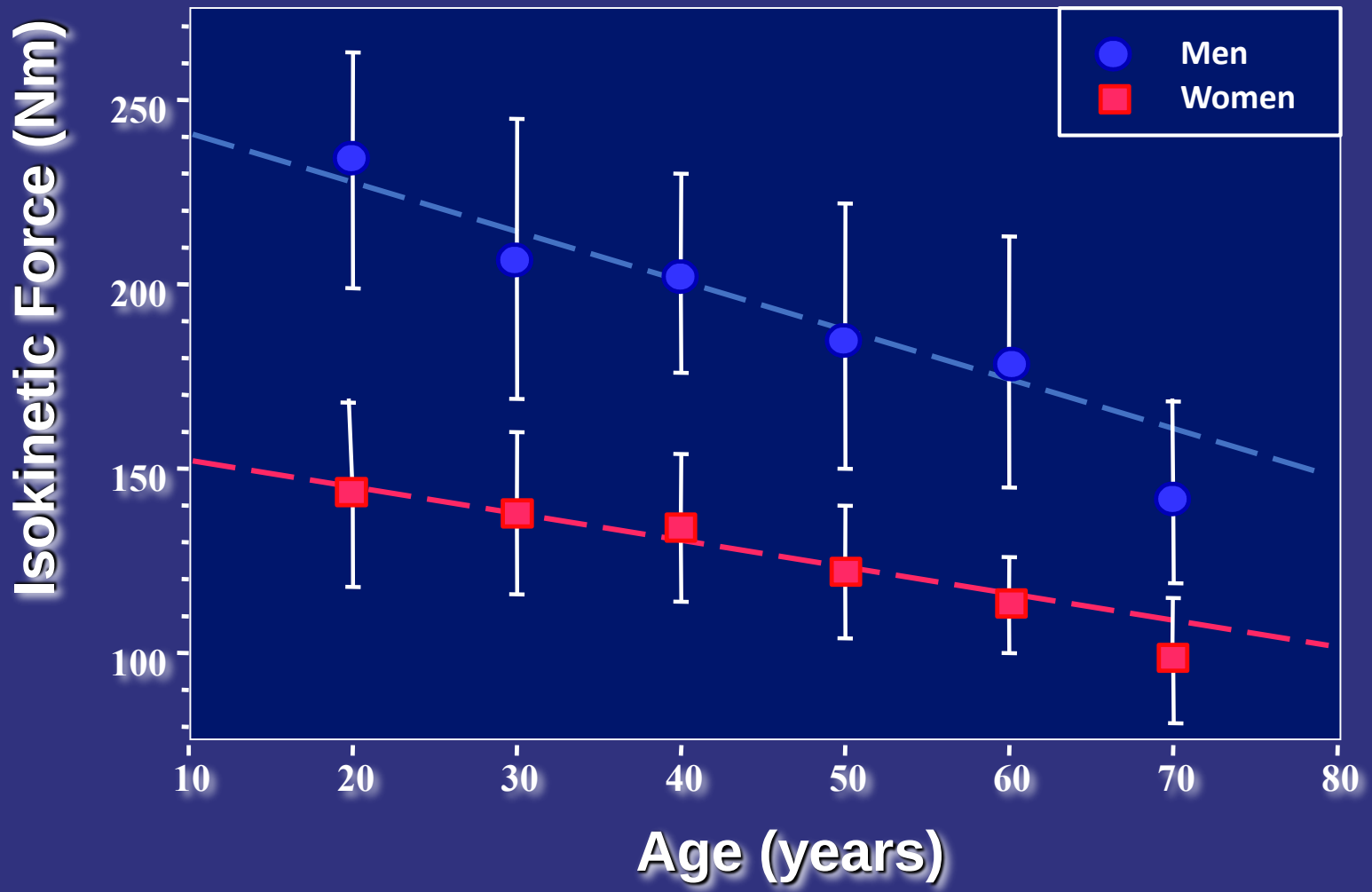
(Harman et al. J Clin Endocrinol Metab, 2001)

Age-related Changes in Body Composition in Normal Sedentary Men



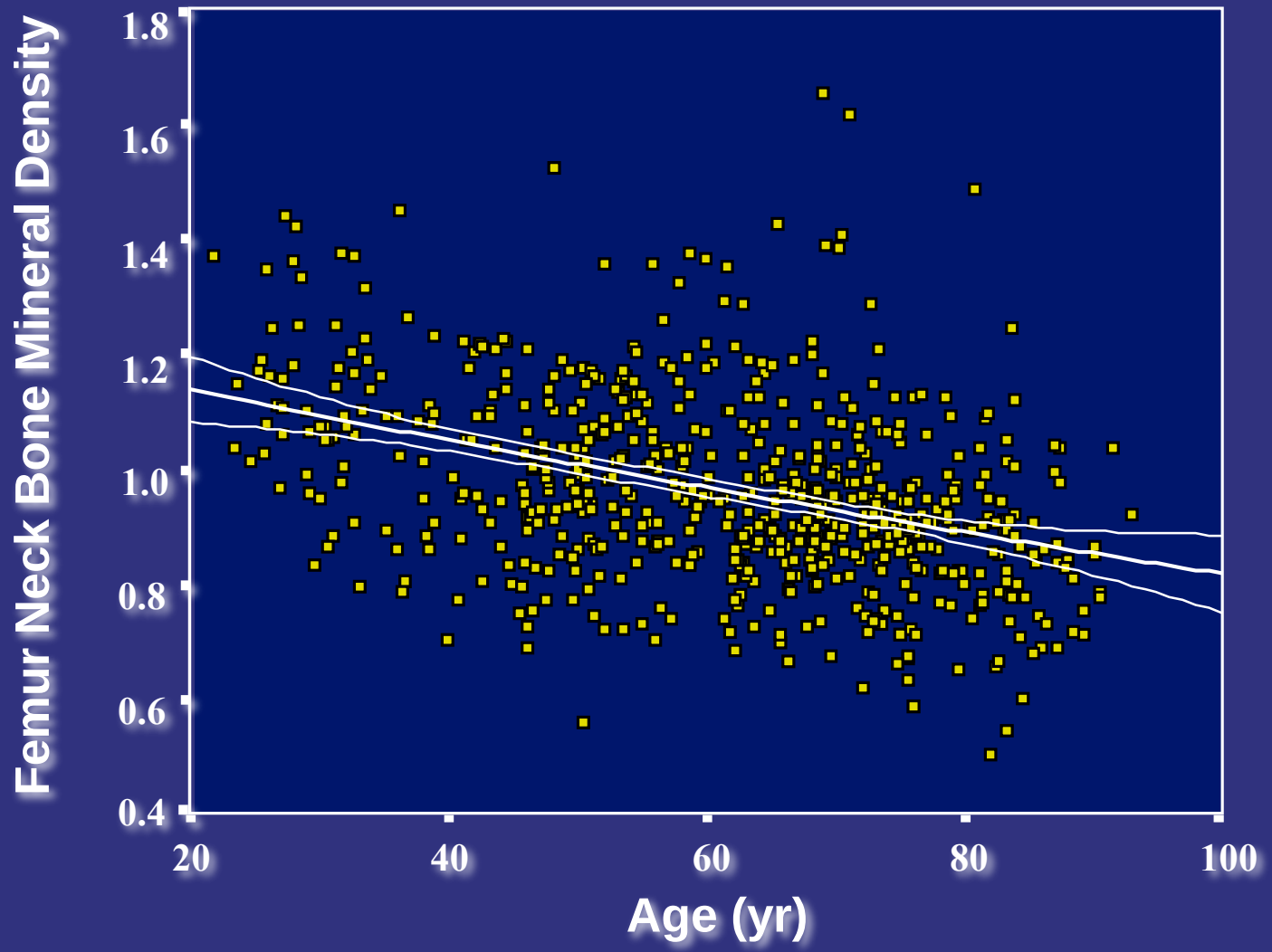
Balagopal et al., Endocrine, 1997

Decreases in Muscle Strength with Age

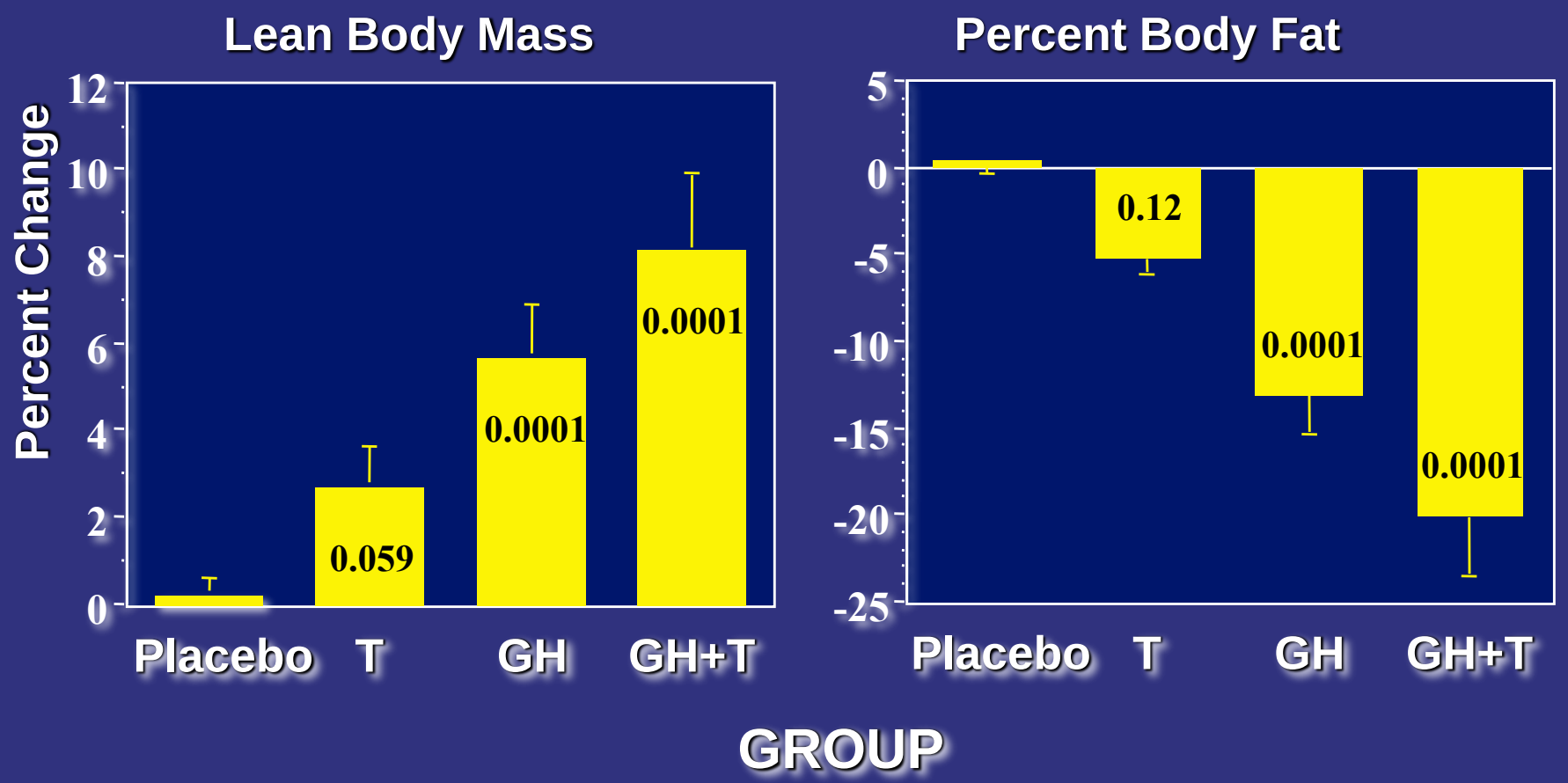


Borges, Scand J Rehabil Med,1989

Femoral Bone Density by DEXA in BLSA Men Ages 20 to 85 Years

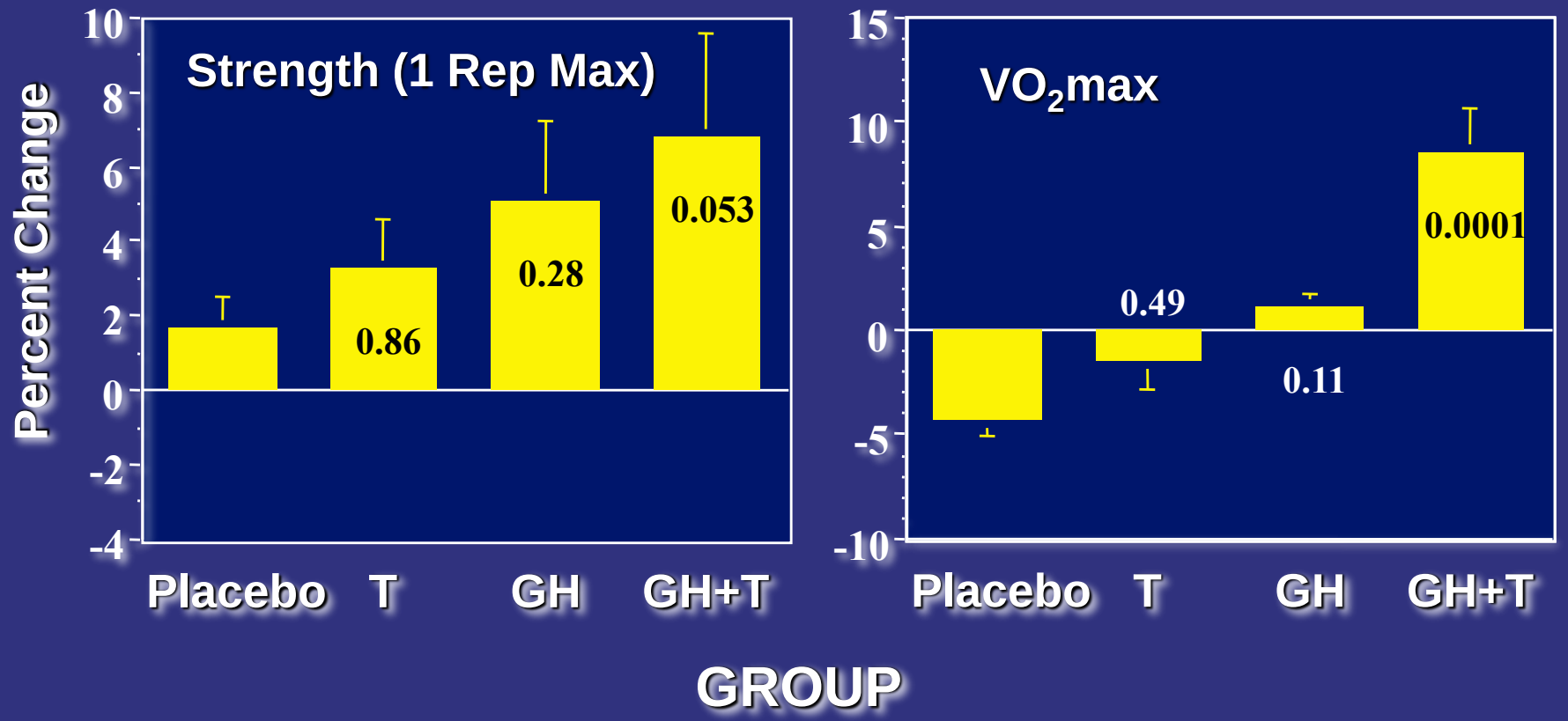


Effects of 6 Months Hormone Administration on Lean and Fat Mass (DEXA) in Healthy Elderly Men



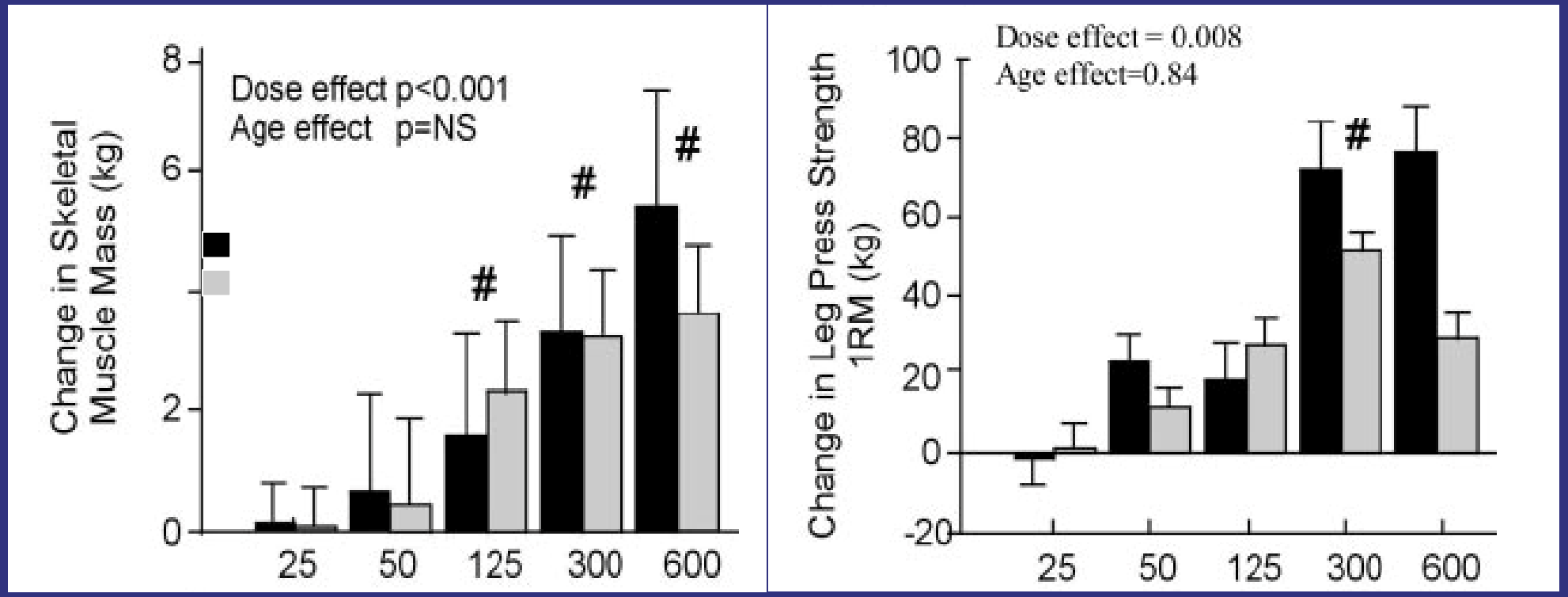
Blackman et al., JAMA 2003; 288:2282-92

Effects of Hormone Administration on Muscle Strength and VO_2 max in Healthy Elderly Men



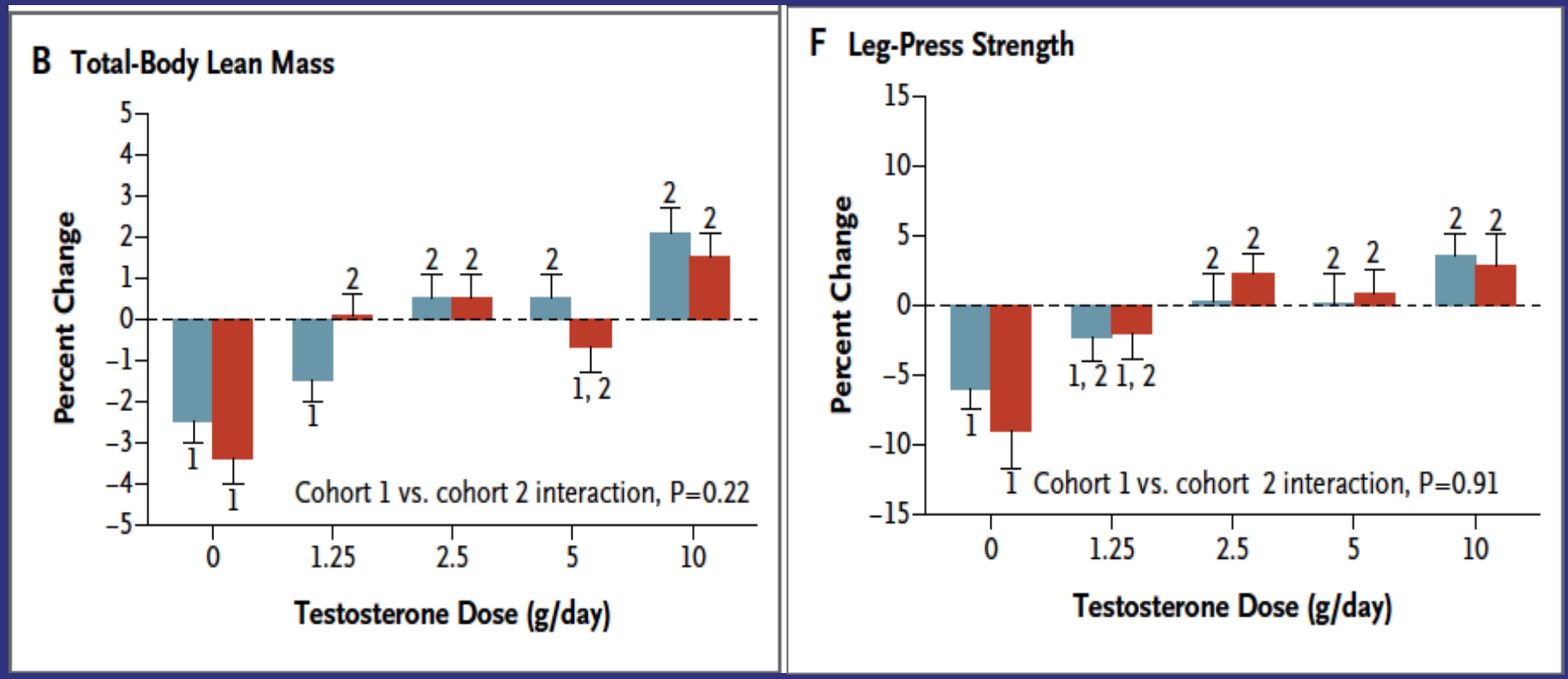
Blackman et al. JAMA. 2003; 288:2282-92

Testosterone Effects on Muscle Mass and Strength in Young and Old Men



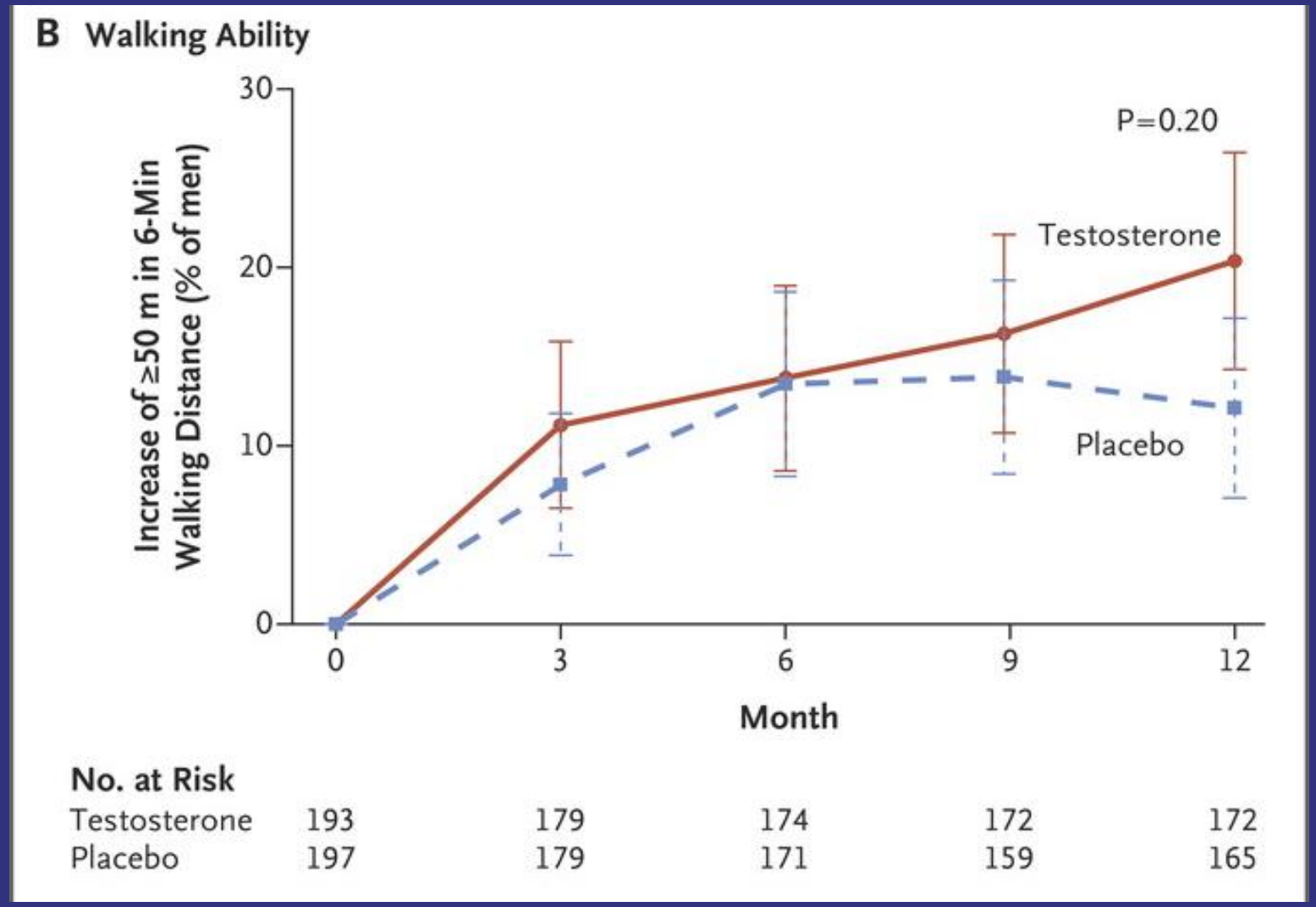
Bhasin S, et al. J Clin Endocrinol Metab. 2005;90:678

Effects of T Dose in Goserelin Hypogonadal Men Treated with Varying Doses of T with and without Anastrazole on LBM and Muscle Strength



Finklestein JS, et al. New Engl J Med. 2013, 369:1011-22

Primary Outcome in the Physical Function Trial of the Testosterone Trials in 65+ Year Old Men.



Snyder PJ et al. N Engl J Med 2016;374:611-624.

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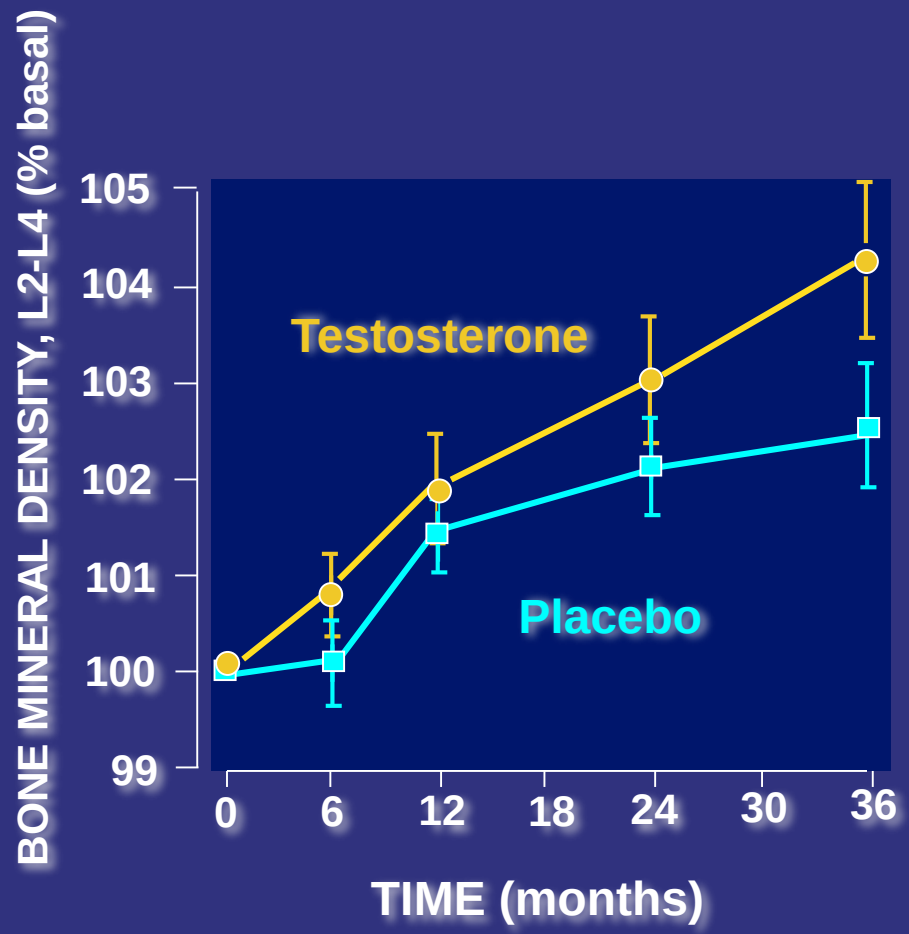
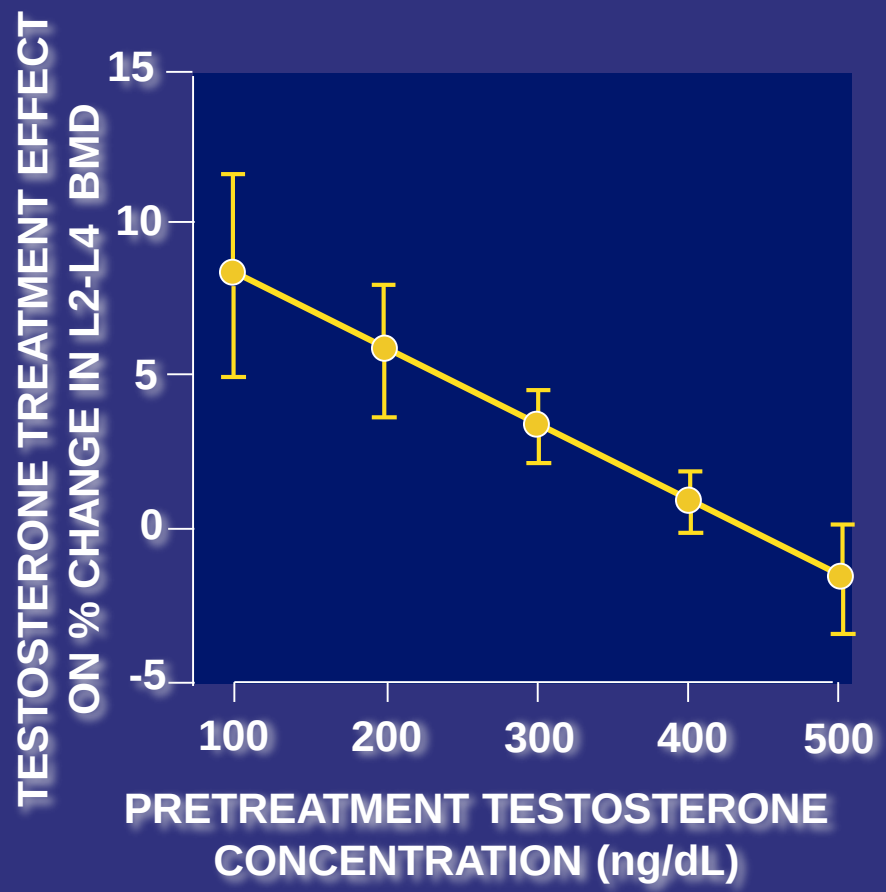
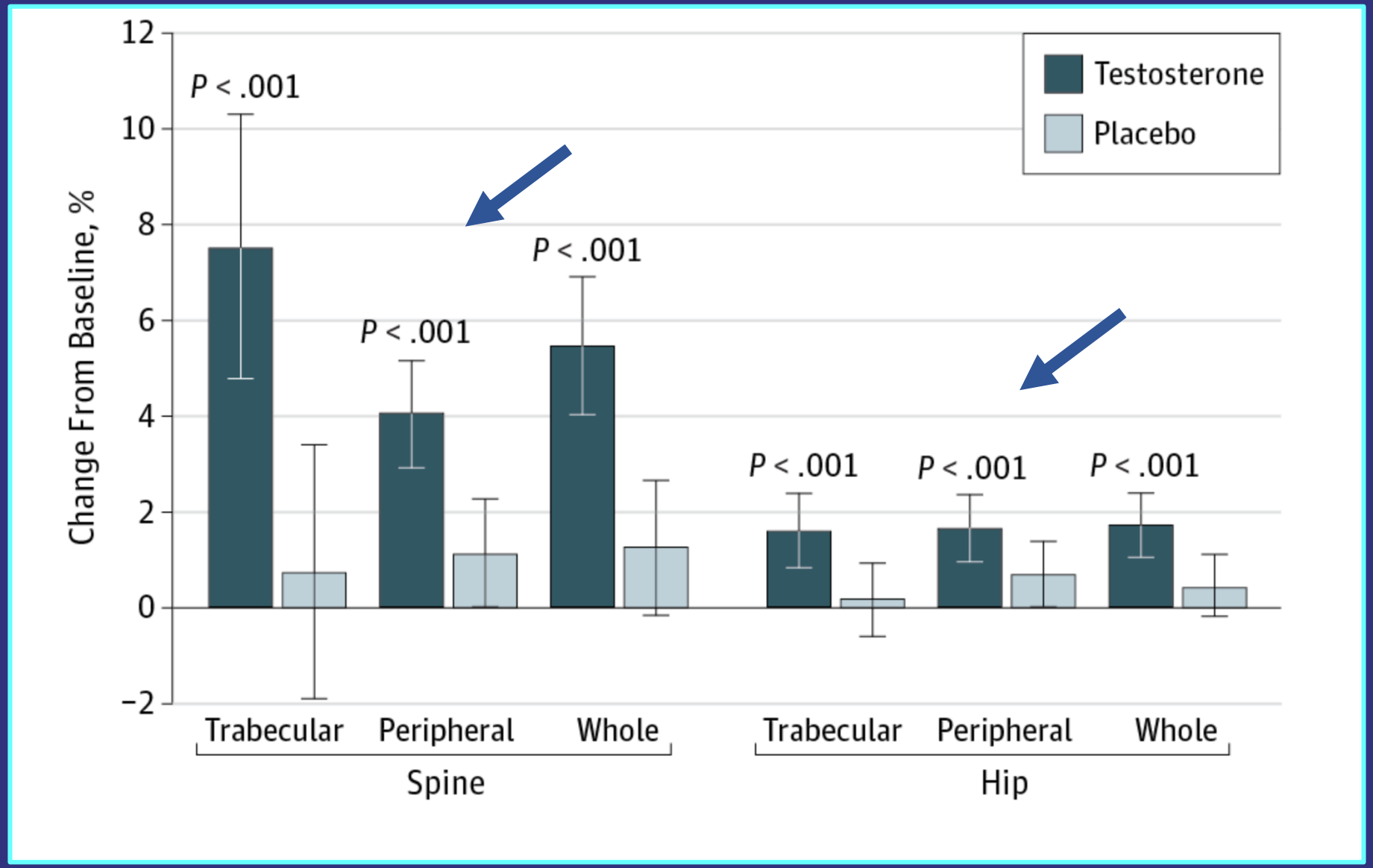
Effects of 3 Years of Testosterone Treatment on Bone Mineral Density in Healthy Older Men





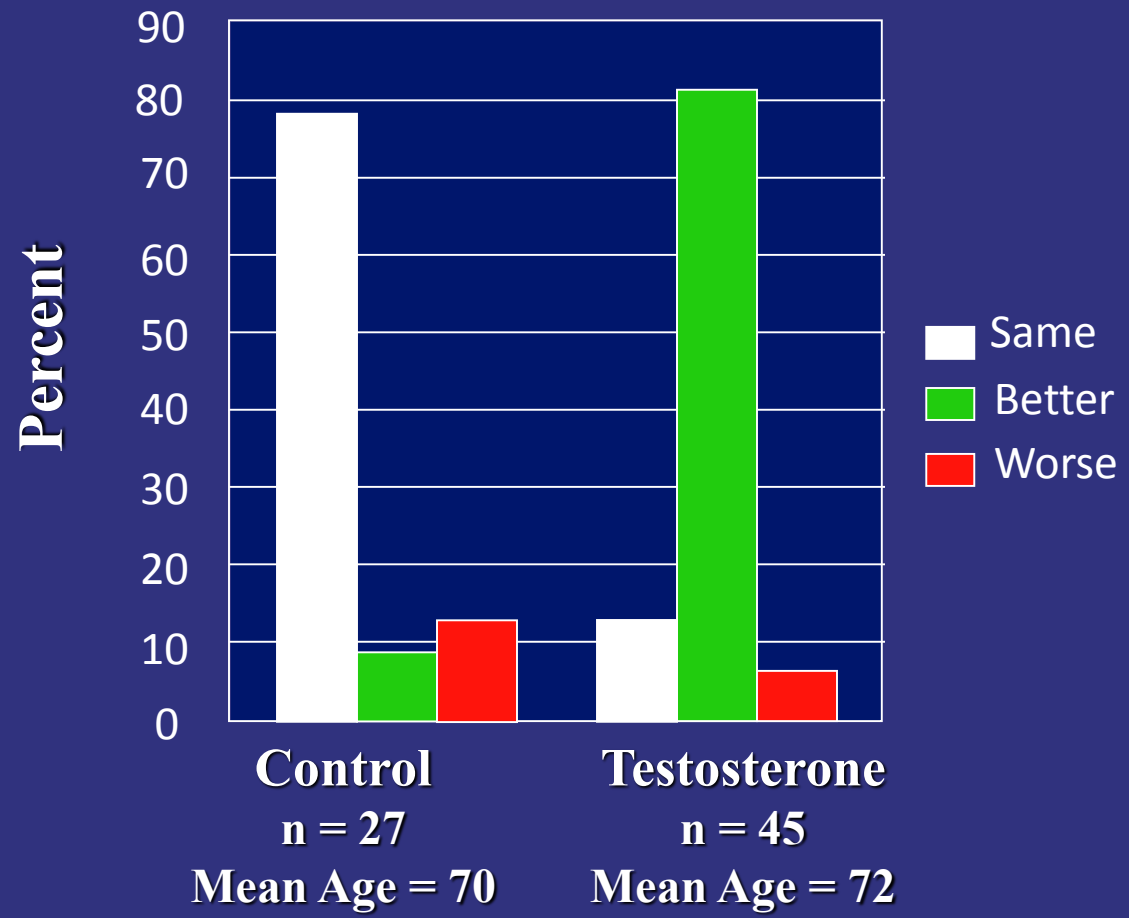
From: Snyder et al. J Clin Endocrinol Metab, 84:1966-78, 1999

United States T trial: T Gel ↑ volumetric BMD (CT) in 1 year



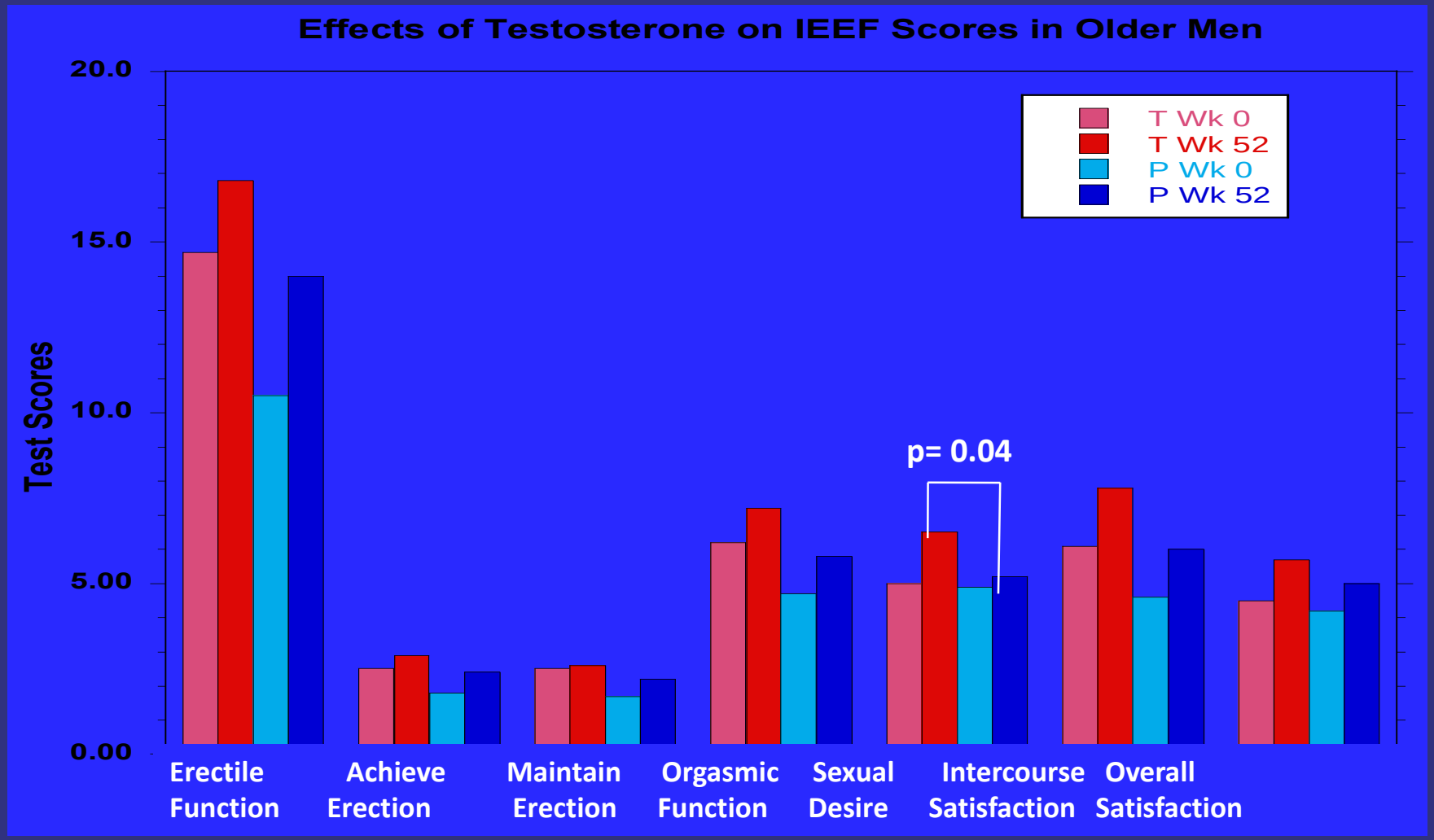
BDA

Perceived Libido in Testosterone and Placebo Treated Old Men



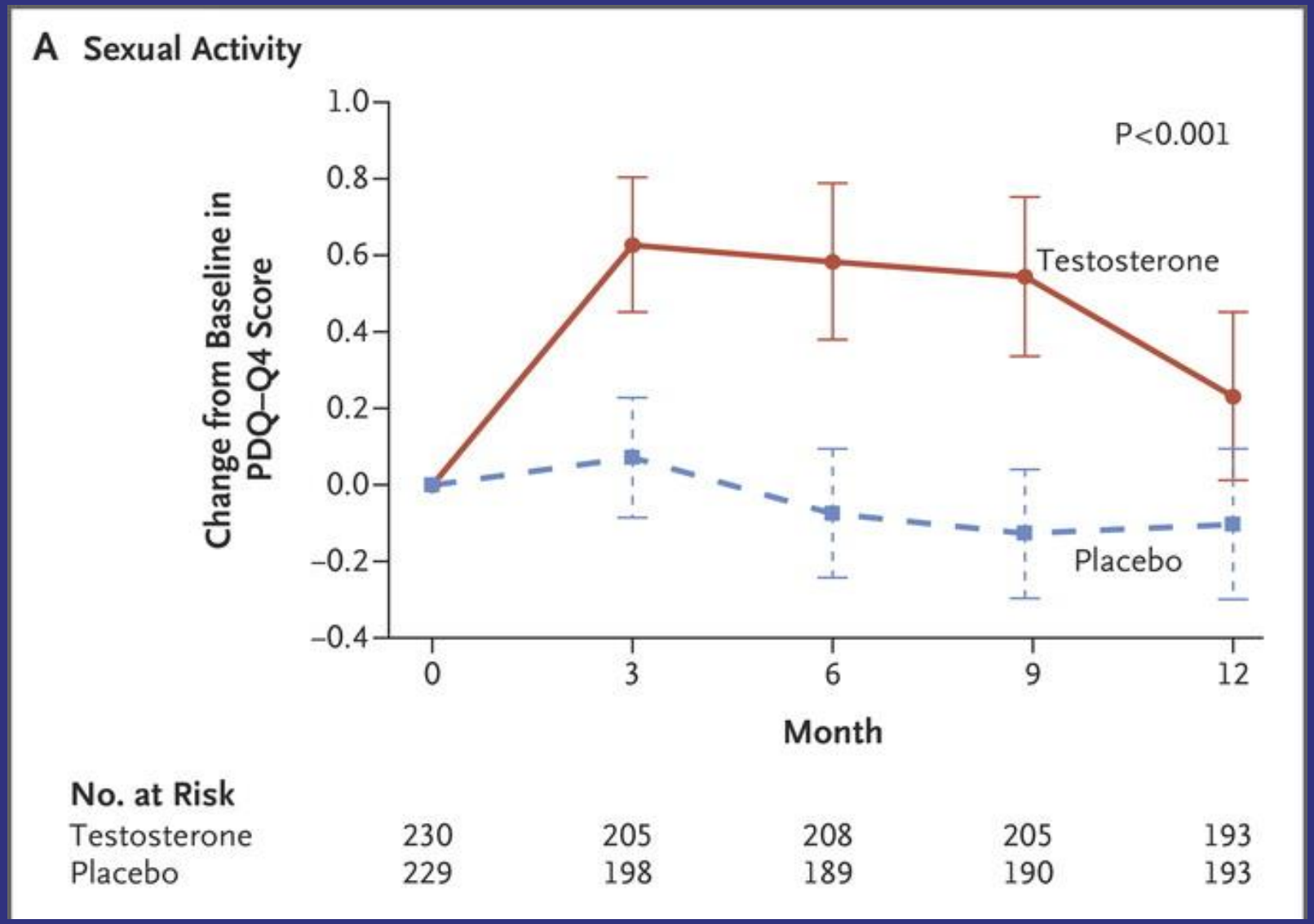
Morley, J.E. et al. *J Clin Endocrinol Metab* 82: 3793–3796, 1997

Transdermal Testosterone and Sexual Function in Old Men with Low to Low Normal Testosterone



Allan CA, et al. Int J Impot Res 2008;20:396

Primary Outcome in the Sexual Function Trial of the Testosterone Trials in 65+ Year Old Men.



Snyder PJ et al. N Engl J Med 2016;374:611-624.

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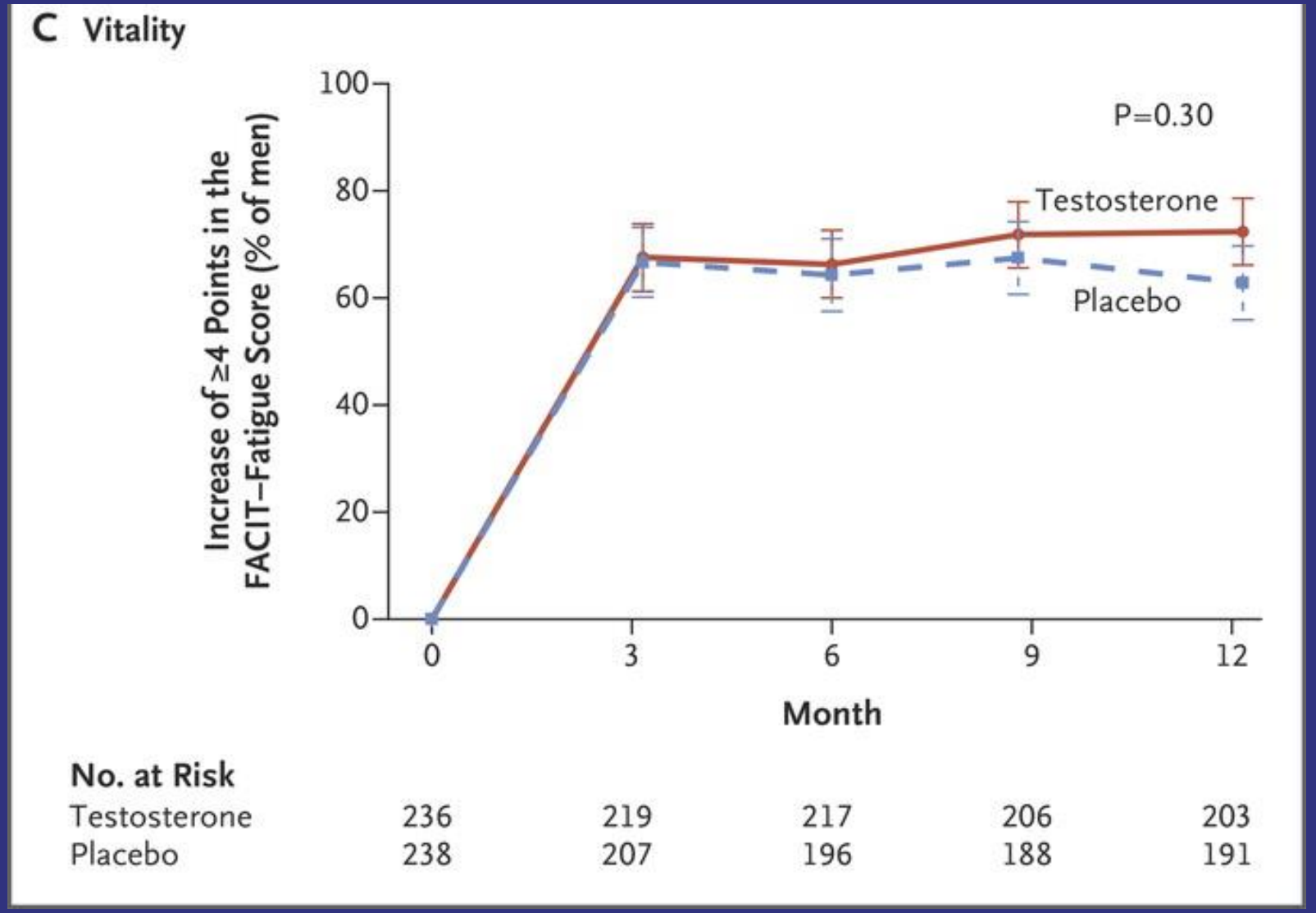
Primary Outcome in the Vitality Trial of the Testosterone Trials in 65+ Year Old Men.



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Change in Symptoms in Aged Men Treated with T vs. Placebo

Parameter	T Group Median [IQR]	Placebo Group Median [IQR]	Mean Adjusted Difference [95% CI][a]	*P* Value[b]
AMS total	n = 44	n = 41		
0 wk	32 [27, 38]	35 [28, 40]		
18 wk	31 [22, 35]	31 [27, 40]		
40 wk	28 [24, 36]	31 [26, 41]	−0.9 (−4.1, 2.2)	.67
AMS psychological	n = 44	n = 41		
0 wk	7 [5, 11]	8 [6, 11]		
18 wk	8 [5, 10]	8 [5, 10]		
40 wk	7 [5, 10]	8 [6, 12]	0.2 (−0.9, 1.3)	.90
AMS somatic	n = 44	n = 41		
0 wk	14 [11, 19]	13 [11, 18]		
18 wk	14 [11, 19]	13 [10, 16]		
40 wk	13 [10, 15]	14 [10, 16]	−0.6 (−2.1, 0.9)	.15
AMS sexual	n = 44	n = 41		
0 weeks	11 [8, 12]	12 [9, 14]		
18 weeks	10 [6, 13]	11 [6, 13]		
40 weeks	9 [7, 14]	10 [7, 15]	−0.4 (−1.8, 1.0)	.78
Sexual desire question 17 AMS	n = 44	n = 41		
0 weeks	2 [1, 3]	2 [1, 3]		
18 weeks	2 [1, 2]	2 [1, 3]		
40 weeks	1 [1, 3]	2 [1, 3.5]	−0.3 [−0.8, 0.2]	.17
IIEF-5 total	n = 23	n = 25		
0 weeks	18 [13, 21]	17 [10, 22]		
18 weeks	19 [13, 22]	19 [15, 22]		
40 weeks	16 [14, 22]	19 [12, 23]	−2.0 (−3.4, −0.6)	.02

Abbreviations: AMS psychological, AMS score, psychological subscale; AMS somatic, AMS score, somatic subscale.

[a] Mean adjusted difference refers to the change over 40 weeks across groups (mixed model).

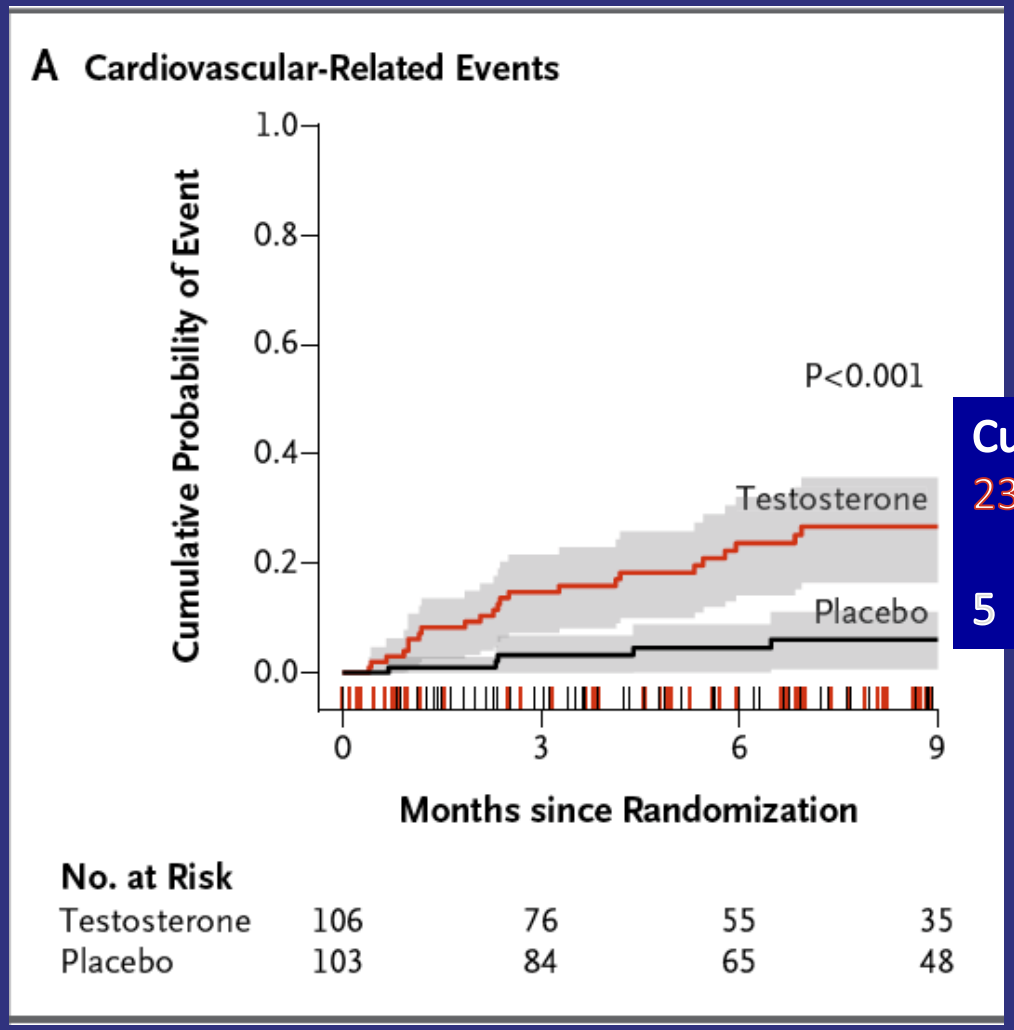
[b] The *P* value refers to the overall significance of the change between groups during follow-up. AMS range is 17–85 and sexual desire AMS question 17 is 1–5, with a higher value denoting more severe symptoms. IIEF-5 range is 5–25, with a lower value denoting more severe symptoms.

Gianatti et al. J Clin Endocrinol Metab 2014, 99:3821

Questions Regarding Older Men and Testosterone

- Is there an “Andropause?”
- Are there relationships between problems of aging and androgen levels in men?
- Are there potential benefits of treating older men with androgens?
- What are the risks of androgen replacement in elderly men?

Cumulative Cardiovascular Adverse Events Apparently Due to Testosterone in the TOM Study



Cumulative Events

23 **Adjusted Odds Ratio: 5.8 (2.0 – 16.8)**

5

Basaria S, et al. 2010. N Engl J Med 363:109

“Cardiovascular” Events Reported in the TOM Study

NONSPECIFIC	**9**	**OTHER CARDIOVASCULAR**	**4**
Chest pain nonspecific	1	Stroke	1
Peripheral edema	5	Elevated blood pressure	2
Syncope	2	CHF exacerbation	1
Sinus tachycardia, fatigue	1	**EKG CHANGES**	**2**
CORONARY	**5**	Exercise induced LV Strain pattern	1
Acute coronary syndrome	1	Exercise induced ST depression	1
Myocardial infarction	2	**ARRHYTMIAS**	**3**
MI suspected, death	1	PVC's	1
Angioplasty required	1	AF with hypertension	1
		AF with CHF exacerbation	1

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

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

Snyder PJ et al. N Engl J Med 2016;374:611-624.

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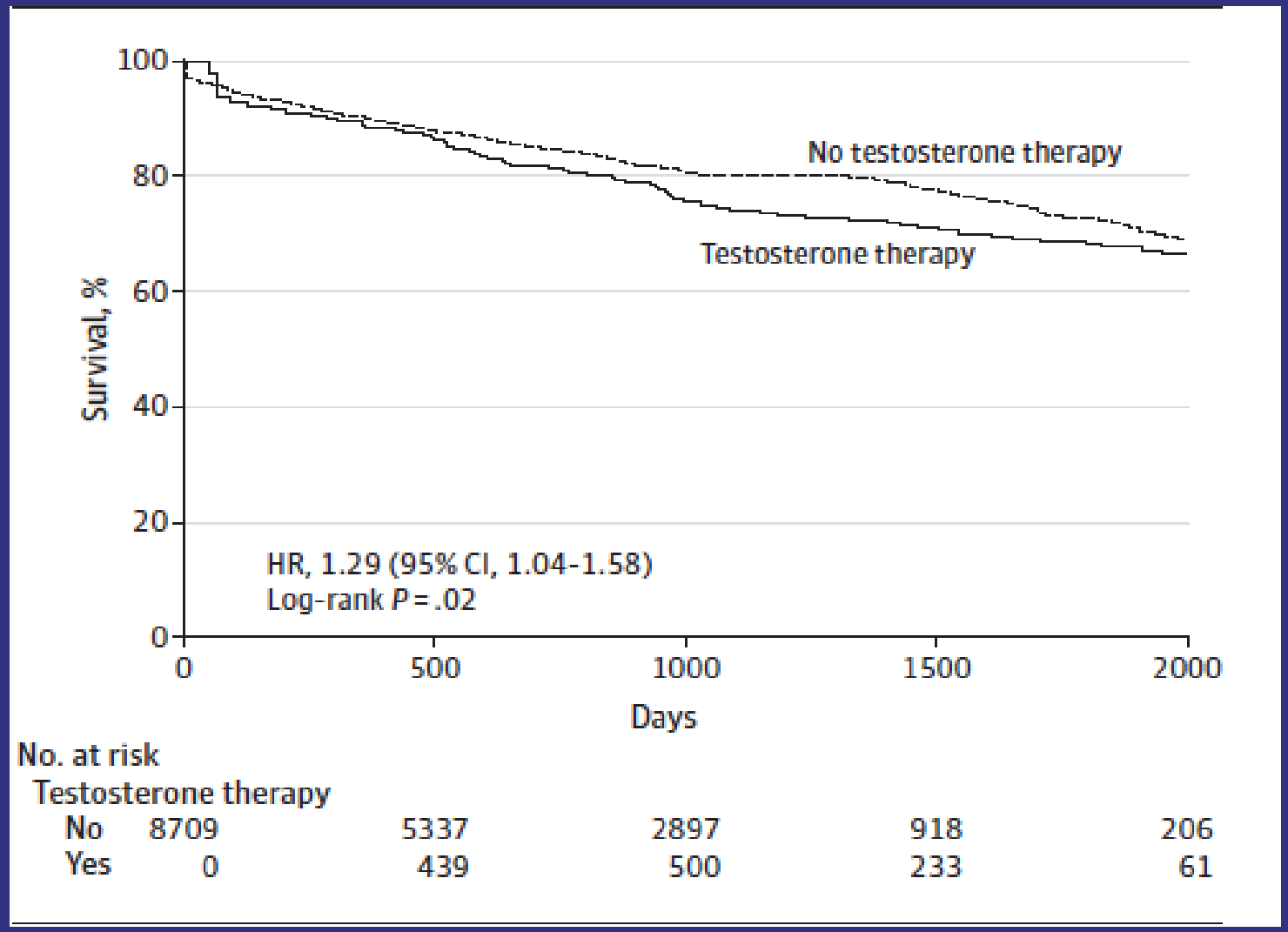
Adverse Events During 36 months in the TEAAM Trial

TEAAM Adverse Events by Physiologic System					
	Placebo		Testosterone		
	# Events	# Participants	# Events	# Participants	[a]p
Cardiovascular	**24**	**16**	**28**	**20**	**0.65**
Dermatologic	13	12	15	14	0.76
Endocrine/Metabolic	6	6	8	7	0.63
Gastrointestinal	17	12	14	11	0.54
Genital/Urinary	31	27	41	32	0.29
Hematologic	4	4	17	15	0.011
Hepatic/Biliary	1	1	1	1	0.99
Infectious Disease	3	3	-	-	>0.99
Lymphatic	2	2	-	-	>0.99
Musculoskeletal	36	27	37	30	>0.99
Neurologic	5	4	4	4	0.71
Other	21	18	18	16	0.57
Psychiatric	5	5	4	4	0.71
Pulmonary	33	27	21	20	0.09
All SAE's	**33**	**24**	**33**	**25**	**0.92**

Basaria et al. JAMA, 2015; 314:570-581

Survival Curves in VA Patients with Significant Comorbidities with and without T Treatment



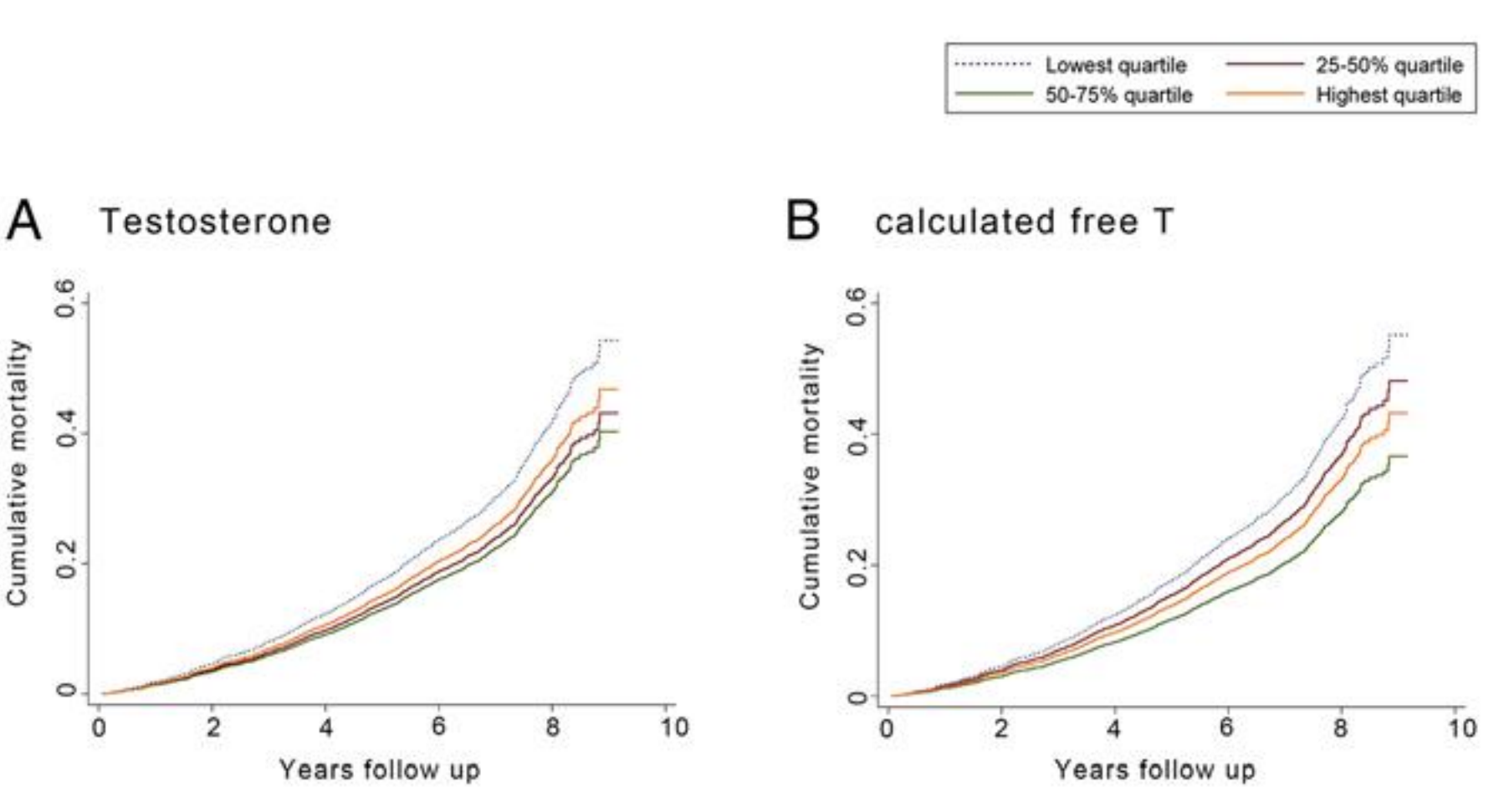
Vigen R, et al. JAMA. 2013, 310:1829-36

Absolute Values for Events in VA Patients with Significant Comorbidities with and without T Treatment

Group	**TT**		**No TT**		**All Patients**	
Total N	1223		7486		8709	
	N	%	N	Percent	N	Percent
Deaths	67	5.5%	681	9.1%	748	8.6%
MI's	23	1.9%	420	5.6%	443	5.1%
Strokes	33	2.7%	486	6.5%	519	6.0%
All Events	123	10.1%	1587	21.2%	1710	19.6%

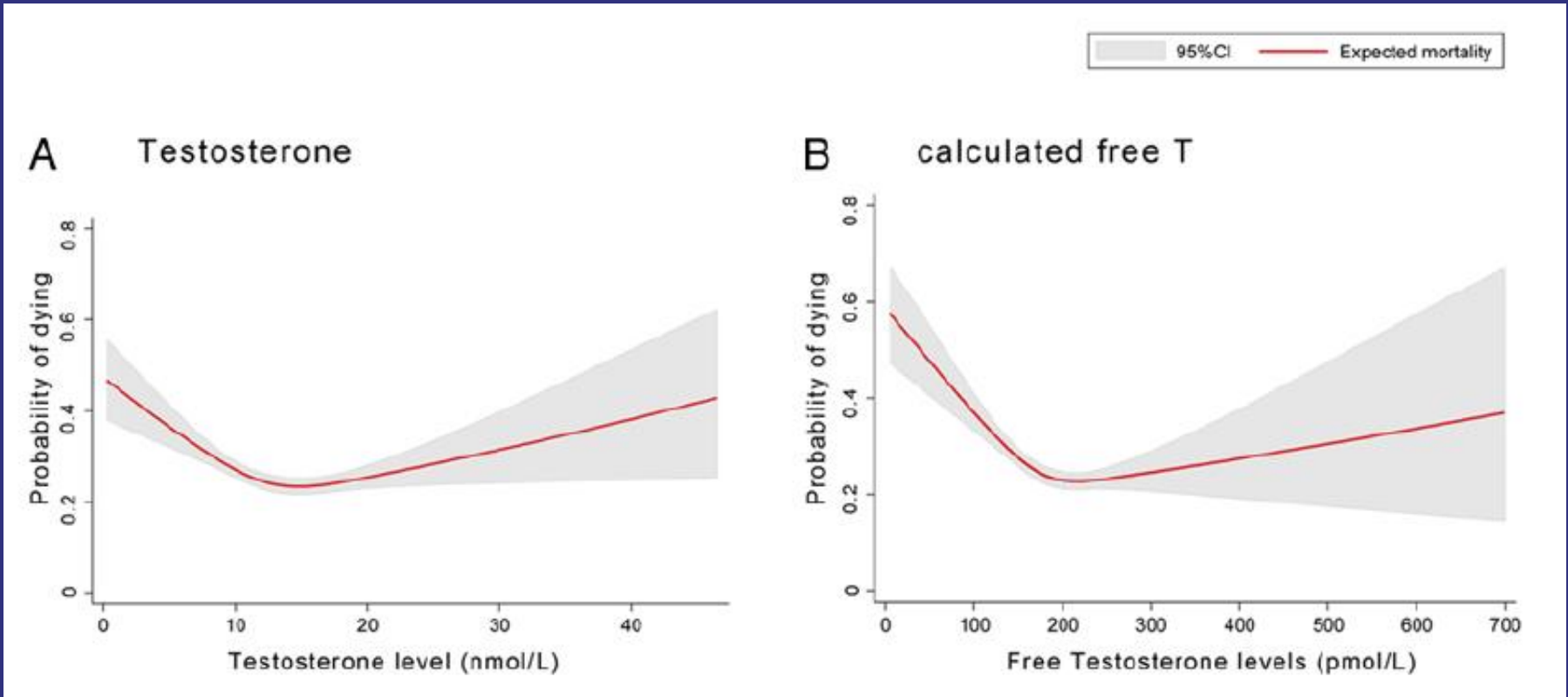
Vigen R, et al. JAMA. 2013, 310:1829-36

Mortality Curves in Men at Various Quartiles of T Levels



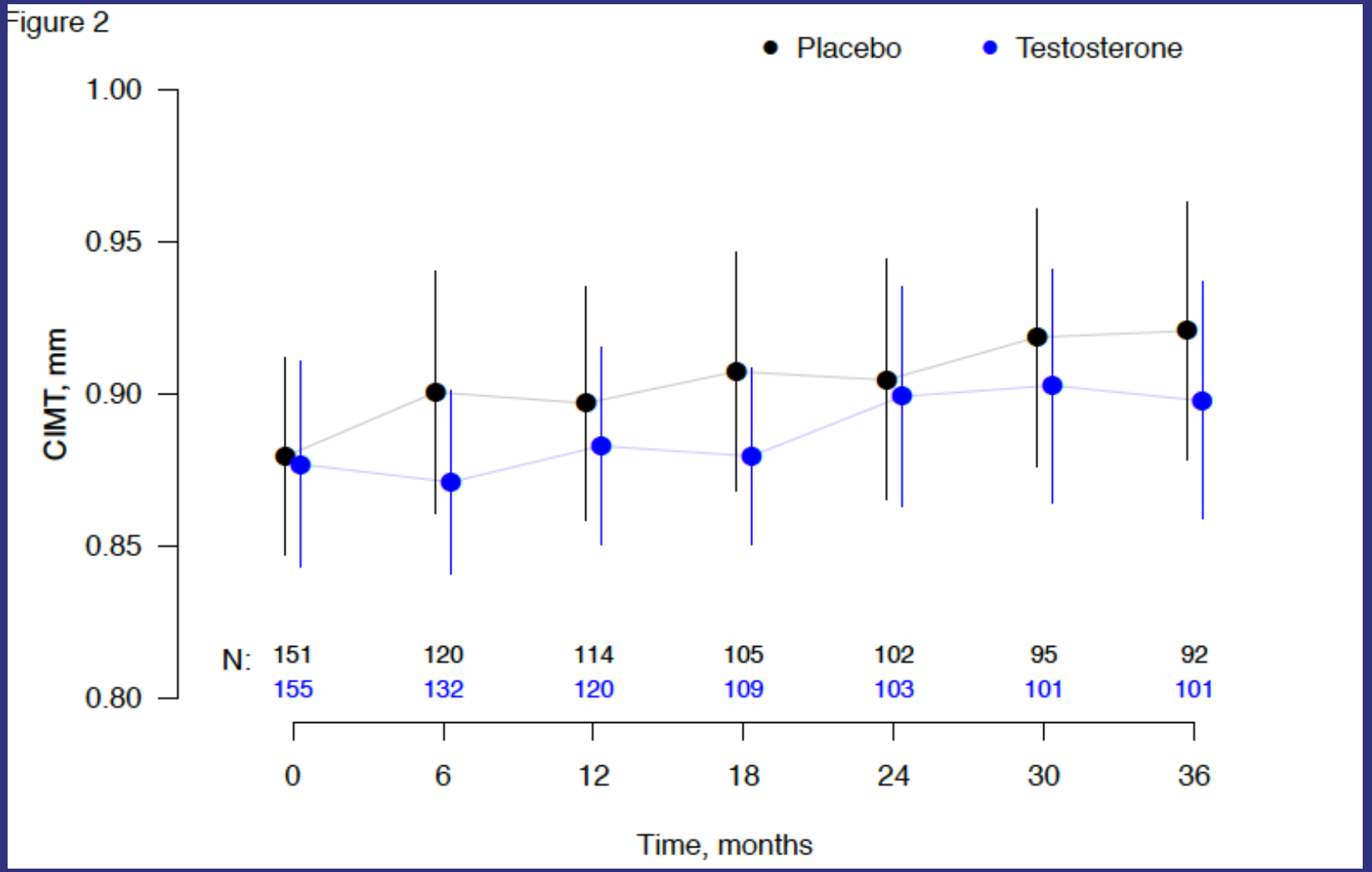
Yeap et al. J Clin Endocrinol Metab. 2014, 99 E9-18

Relationship of Survival to Prevalent Endogenous T Levels in Elderly Men



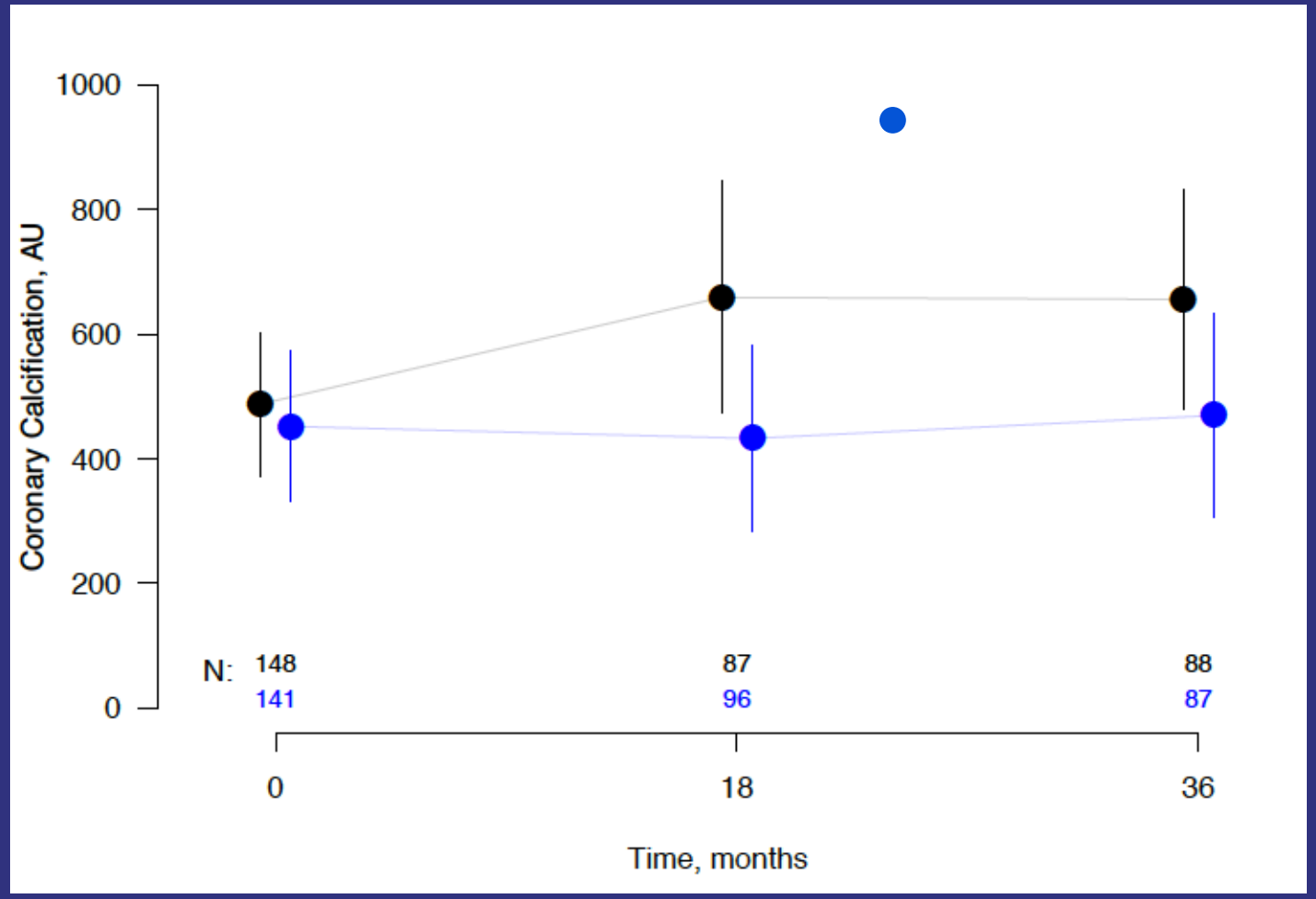
Yeap et al. J Clin Endocrinol Metab. 2013, 99 ePub

Progression of Carotid Artery Intima Media Thickness in the TEAAM Study



Basaria S, Harman SM, Travison TG, et al. JAMA. 2015, 314:570-81.

Progression of Coronary Artery Calcium in the TEAAM Study



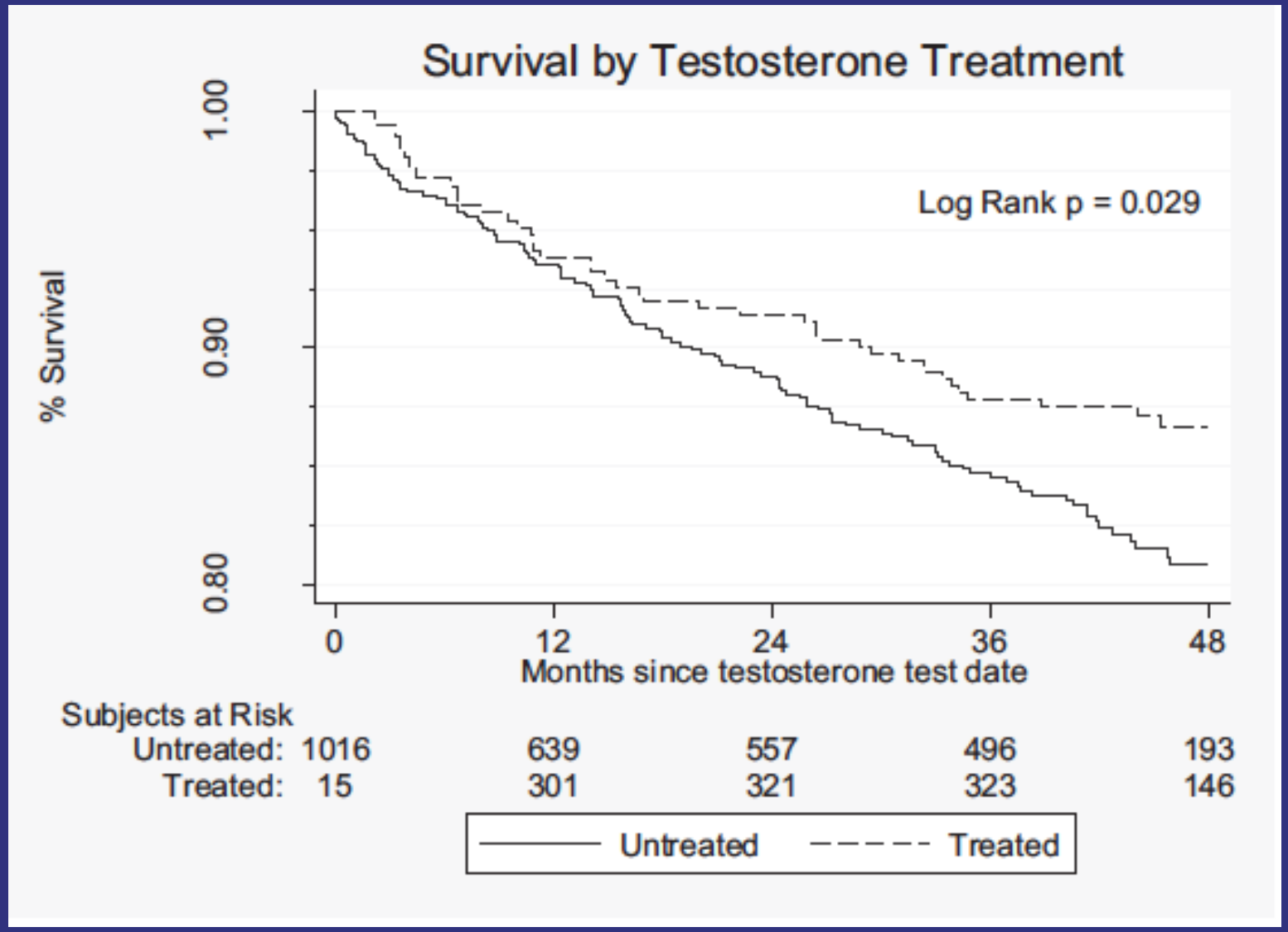
Basaria S, Harman SM, Travison TG, et al. JAMA. 2015, 314:570-81.

Progression of Coronary Calcium in the United States T Trial

- No difference after 1 year of T gel vs. placebo in adjudicated CV events (7 each)
- T gel ↑ coronary artery noncalcified plaque volume *vs*. placebo gel, but 50% baseline difference between groups, too
- Mean age ~ 70
- Need for hard outcomes
- Need data in younger men

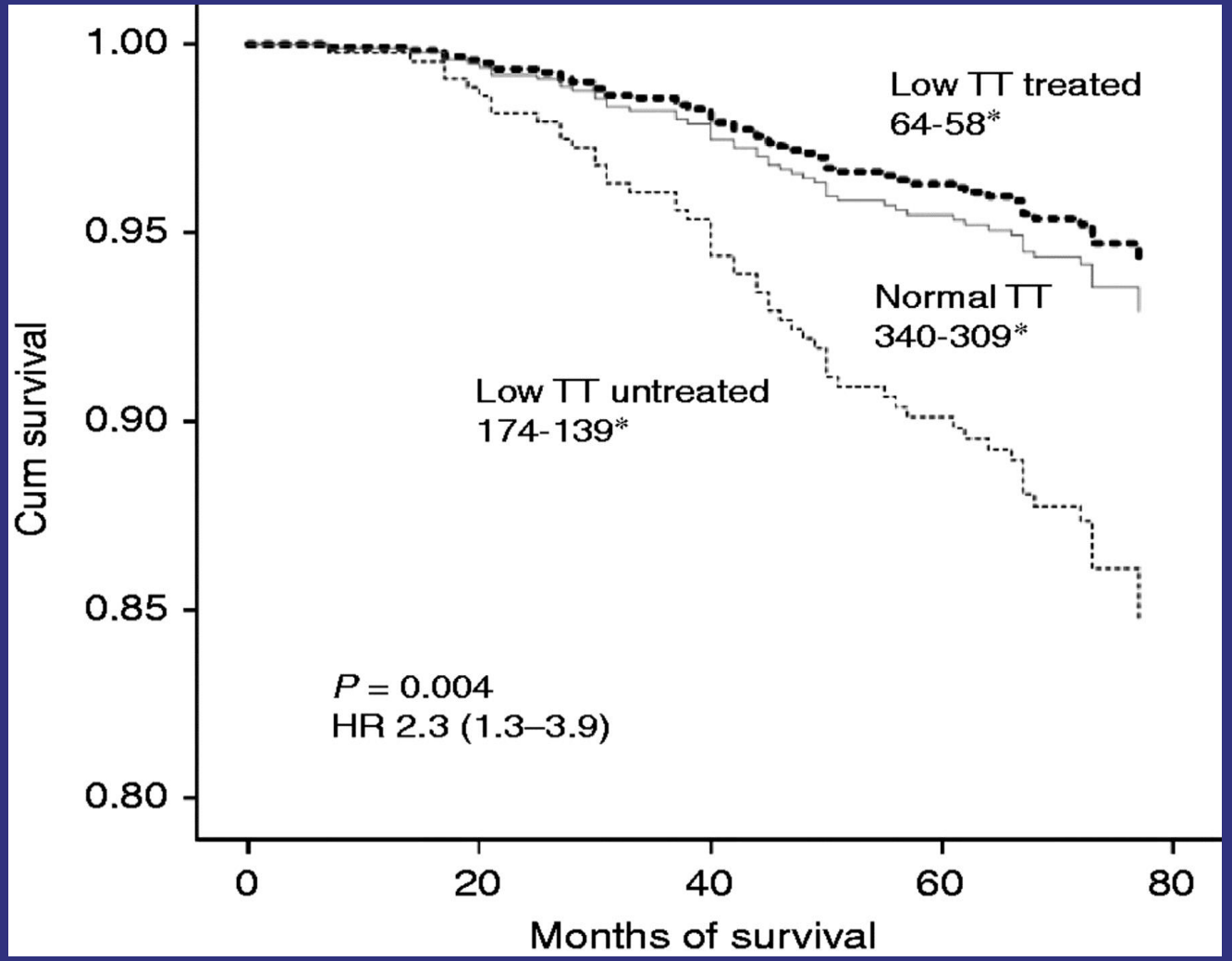
Budoff, et al. JAMA.2017;317:708-716

Survival Curves in VA Patients with and without T Treatment



Shores MM, et al. Journal Clin Endocrinol Metab. 2012, 97:2050-8

Multivariate-adjusted Survival Curves (Cox Regression) for T treated and Untreated Type 2 Diabetic Men with Low T vs. Those with Normal T.



Muraleedharan V, et al. Eur J Endocrinol 2013;169(6):725-33

T Rx and Thromboembolism

Glueck, et al.

- 2011 report of 6 ♂ with thromboses after T Rx
- All 6 with thrombophilia
- 2014 report of 13 ♂ & 1 ♀ with thromboses short time after T Rx initiated (mean = 11 mos)

  (deep venous or osteonecrosis of hips or knees)

  12 of 13 had a clotting disorder

  ‘Thrombophilia should be excluded before administration of exogenous testosterone.”
- More accurate: Consider evaluation for clotting disorder if unexplained thrombosis while on T Rx

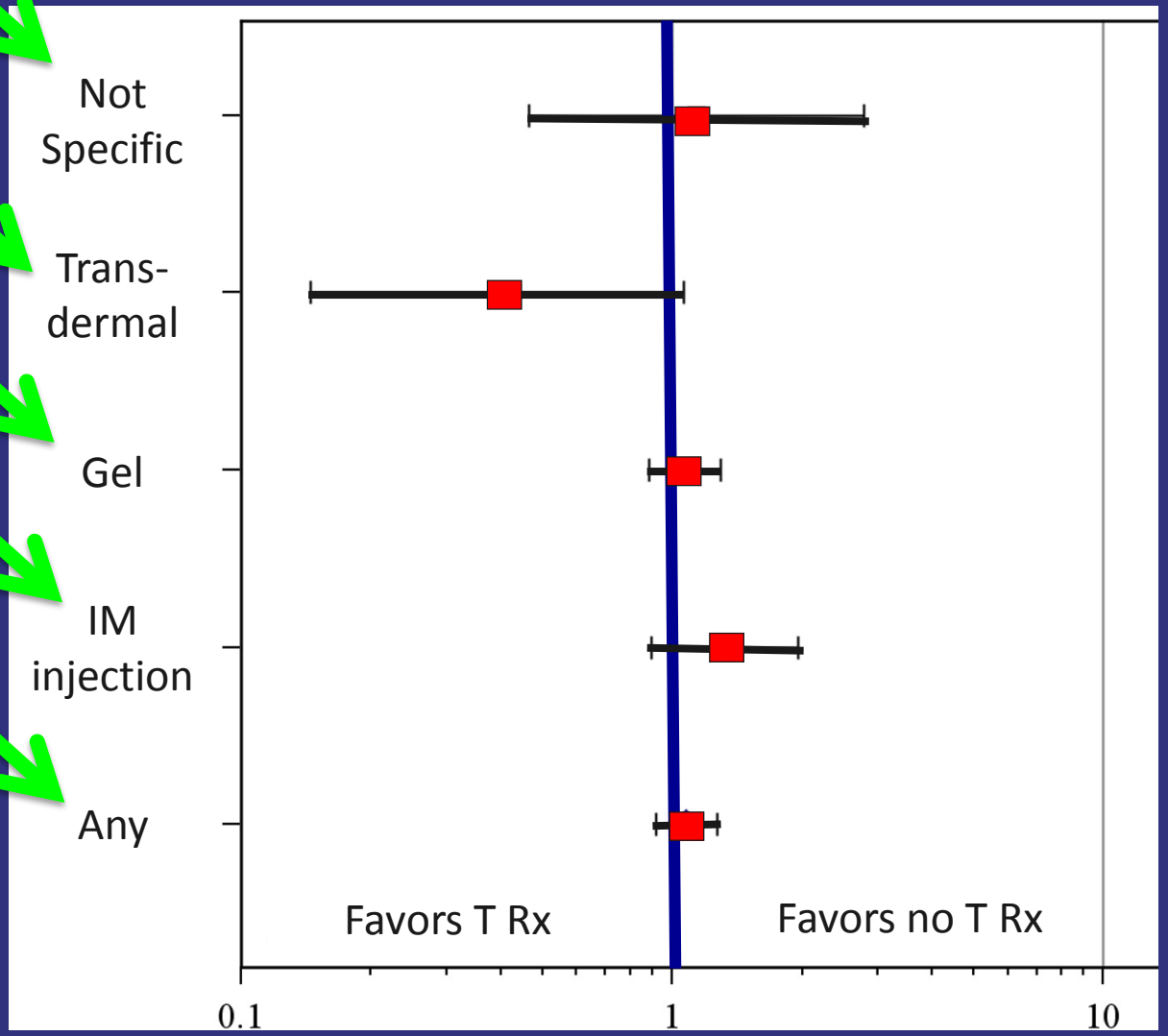
Clin Appl Thromb Hemost. 2014;20:244-9. (+ more case reports since)

Epidemiology: T Treatment and Risk of VTE

Martinez BMJ 2016;355: i5968	Controls (~200K) vs. (~19K) DVT/PE	UK database Mean age 65	No baseline serum T No hx of DVT/PE	No difference in DVT with T RX
Sharma Chest 2016;150:563-571	No T Rx T Rx with low T T Rx with nl T	> 70K US veterans mean age 64-67	Baseline low T x 2 No hx of DVT/PE	No difference in DVT with T RX
Baillargeon Mayo Clin Proc 2015;90:1038-1045	Controls (~22K) vs. (~8K) DVT/PE	Insurance claims > 40 years old	No baseline serum T No history of DVT/PE	No difference in DVT with T RX

T Treatment Does Not Increase Idiopathic DVT or PE

> 100,000 T users *vs.* equal # of untreated ♂ with Dx. of hypogonadism Cohort analysis



J Urol. 2016;195: 1065-1072

Summary- Take Home

- Complaints associated with hypogonadism are non-specific
  - Symptoms such as fatigue, ED, and loss of libido are often associated with co-morbid conditions such as diabetes, depression, chronic infections, malignancy, other endocrine disorders
  - Co-morbid conditions themselves may reduce T levels
- Decision to treat hypogonadism should be based on both symptoms and accepted laboratory criteria
- Patients should be worked up for CAUSE of hypogonadism
- Patients should be monitored for T levels and adverse effects
- Elderly men have a high incidence of low T
  - Treatment of old men is less likely to produce significant benefits
  - Older age is associated with greater risks of adverse outcomes, altering the therapeutic index
- Risks of cardiovascular and thromboembolic disease have likely been exaggerated and remain controversial