



# Testosterone Therapy in Men

Shehzad Basaria, M.D.

Section on Men's Health, Aging and Metabolism

Brigham and Women's Hospital

Harvard Medical School

# Shehzad Basaria, M.D.



- **Medical School:** The Aga Khan University Medical College
- **Medicine Residency:** University of Texas Health Science Center at Houston
- **Endocrinology Fellowship:** Johns Hopkins University School of Medicine
- Professor of Medicine at HMS / BWH
  - Clinical Focus: Male Reproductive Disorders
  - Research Focus:
    1. Male Androgen Deficiency
    2. Androgen Deprivation Therapy for Prostate Cancer
    3. Opioid-Induced Hypogonadism

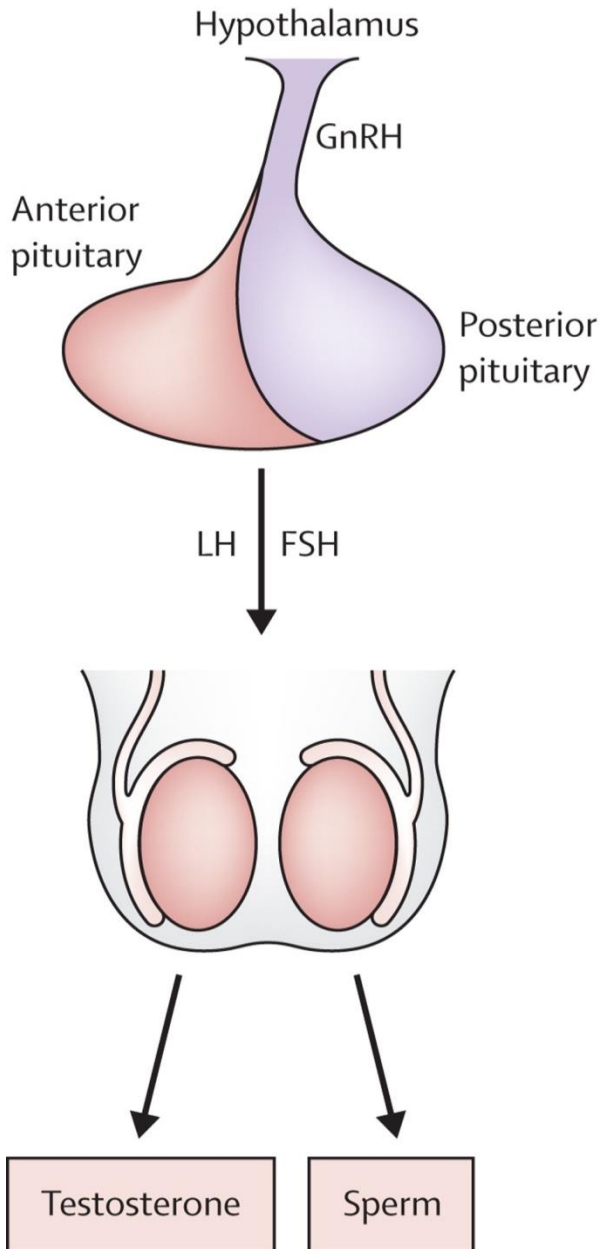
# Disclosures

- NIH funding (NCI, NIA)

# Outline

- Physiology of the Hypothalamic-Pituitary-Gonadal Axis
- Clinical Manifestations of Male Androgen Deficiency
- Diagnostic Work-up
- Benefits and Risks of Testosterone Replacement

# Hypothalamic-Pituitary-Gonadal Axis

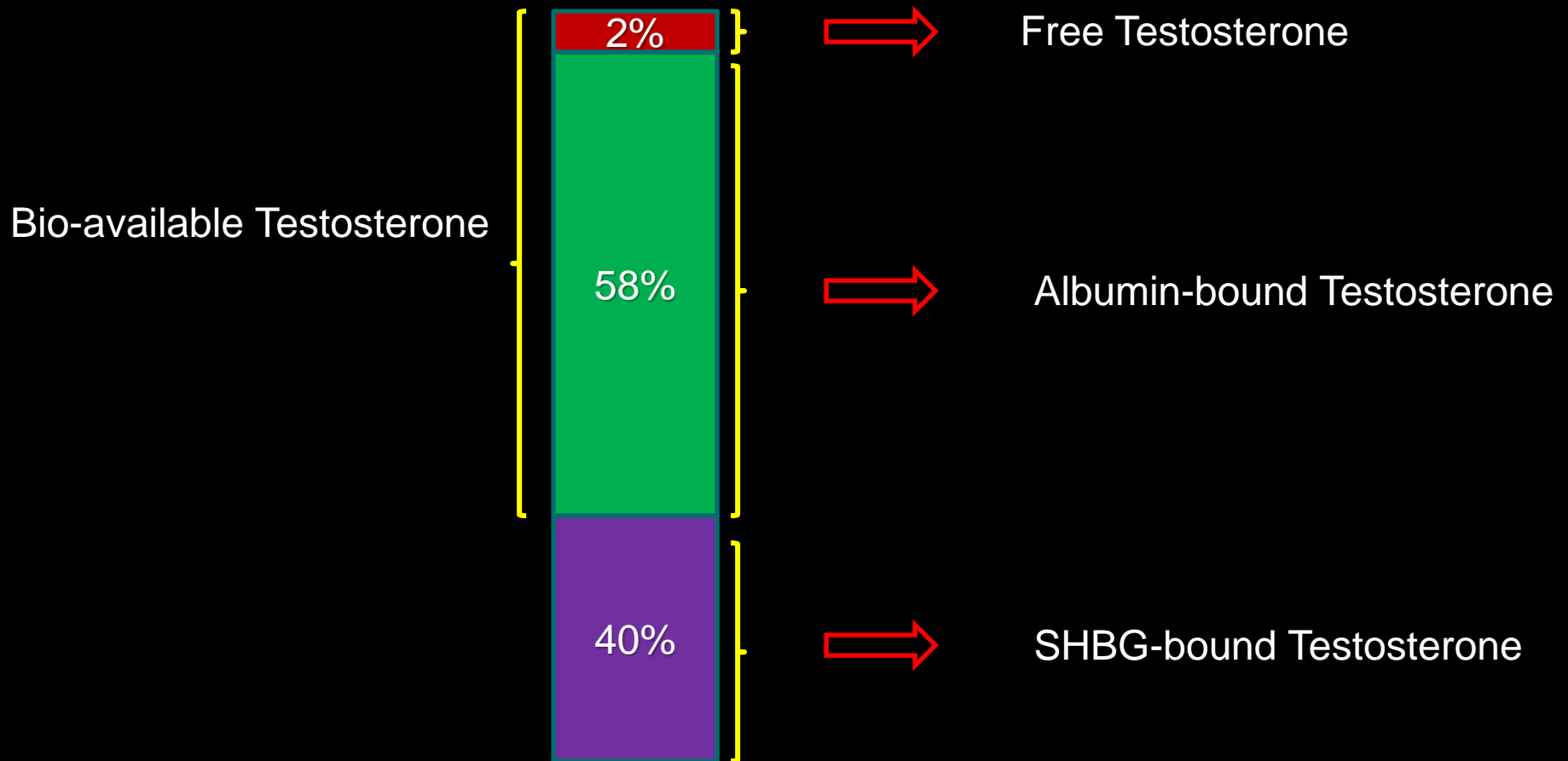


- ▶ Testes secrete 3-10 mg of Testosterone daily
- ▶ Normal range in serum 300-1000 ng/dl
- ▶ Diurnal rhythm in young men
- ▶ Peak levels 6-9 am

# Testosterone: A Prohormone

Mechanisms of Action of Testosterone			
	<pre> graph TD     Testosterone -- "5α-Reductase" --&gt; Dihydrotestosterone     Testosterone -- "Aromatase" --&gt; Estradiol     Testosterone --&gt; AndrogenReceptor1[Androgen receptor]     Dihydrotestosterone --&gt; AndrogenReceptor2[Androgen receptor]     Estradiol --&gt; EstrogenReceptor[Estrogen receptor]                     </pre>		
Tissues Affected			
	External genitalia, prostate, skin, hair	Muscle, bone marrow, bone, brain	Bone, brain
Potential Effects of Testosterone Treatment			
Benefits	Reproductive function	Muscle strength, erythropoiesis, bone strength, energy	Bone strength, epiphyseal closure, libido
Risks	Prostate cancer, benign prostatic hyperplasia	Erythrocytosis, ? sleep apnea	

# Testosterone in Circulation

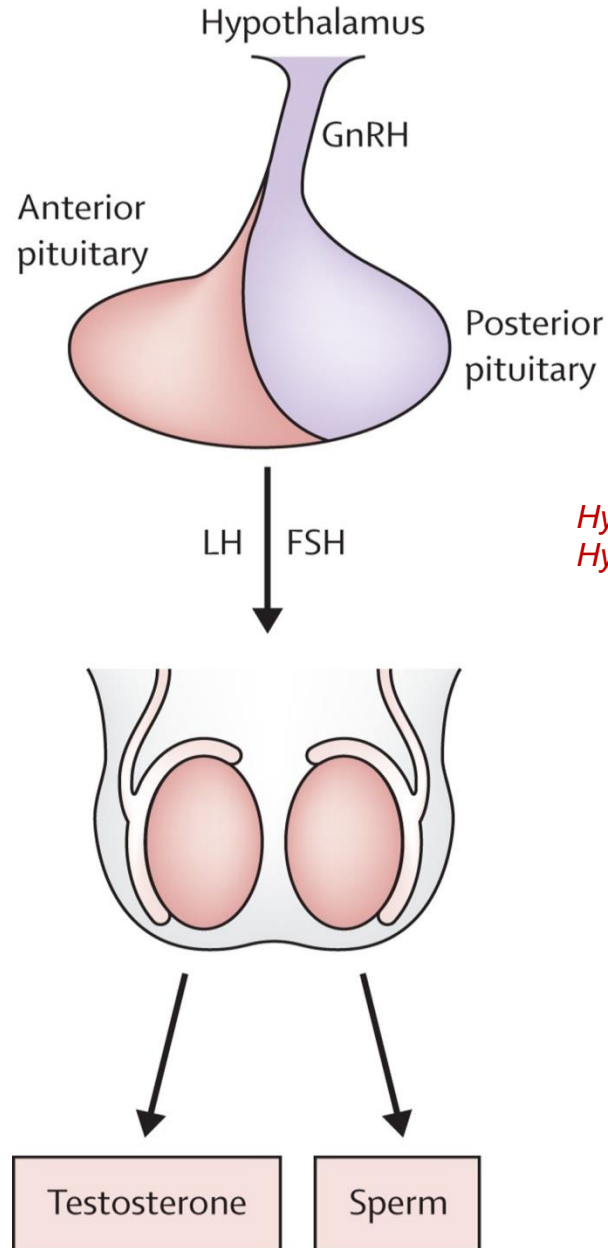


# Male Hypogonadism: Definition and Etiologies

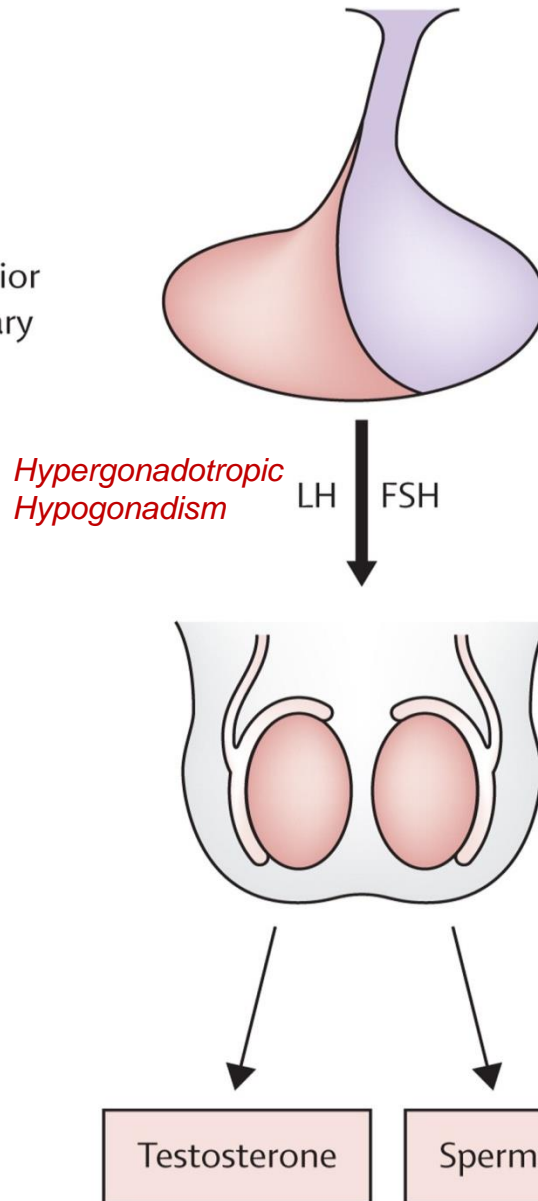


# Types of Hypogonadism

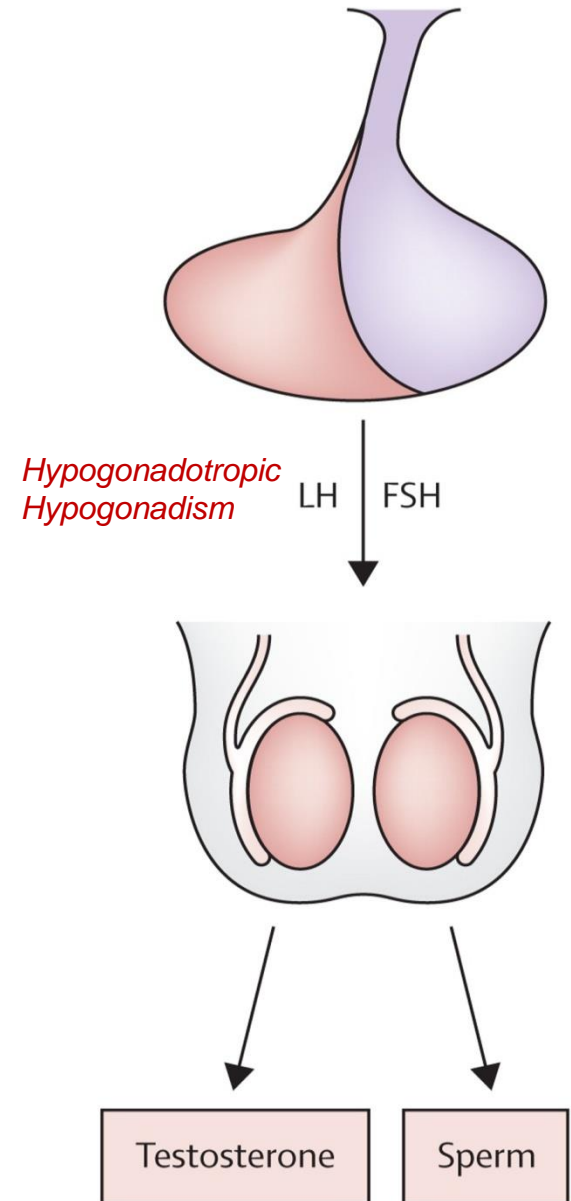
## A Normal HPG axis



## B Primary hypogonadism



## C Secondary hypogonadism



## Primary Hypogonadism

### Congenital:

- Klinefelter's syndrome
- Y-chromosome microdeletions
- LH & FSH receptor mutations
- Myotonic dystrophy
- Cryptorchidism

### Acquired:

- Testicular trauma/torsion
- Testicular radiation
- Orchitis (mumps)
- Chemotherapy (alkylating agents)
- Medications (ketoconazole)
- Autoimmune testicular failure
- Infiltrative disease (hemochromatosis)
- Varicocele
- Sickle cell disease
- Cirrhosis
- Alcohol abuse

## Secondary Hypogonadism

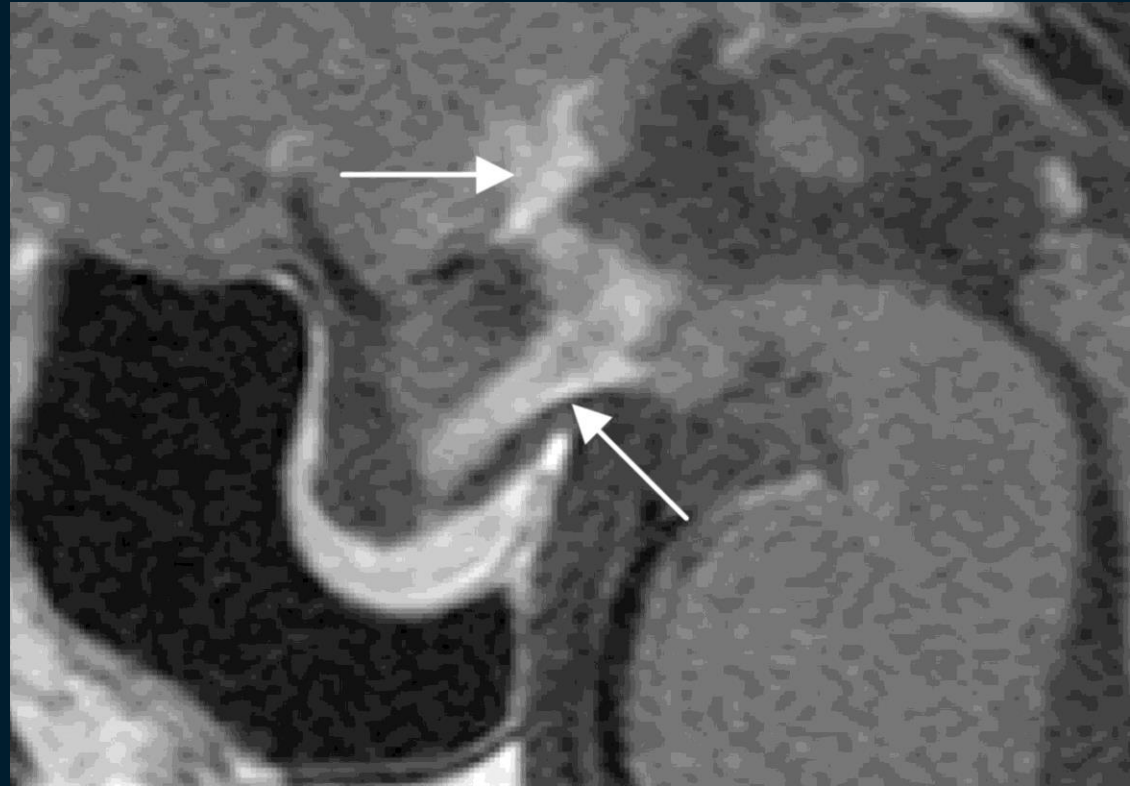
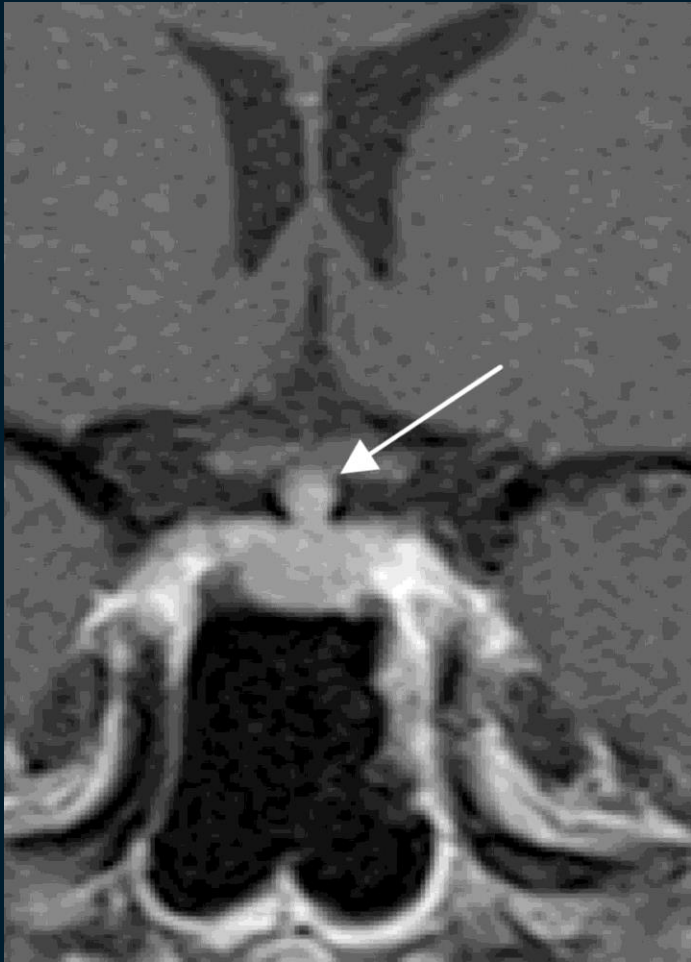
### Congenital:

- Isolated hypogonadotropic hypogonadism (Kallmann's syndrome)
- Prader-Willi syndrome
- Mutations of  $\beta$  subunit of LH and FSH

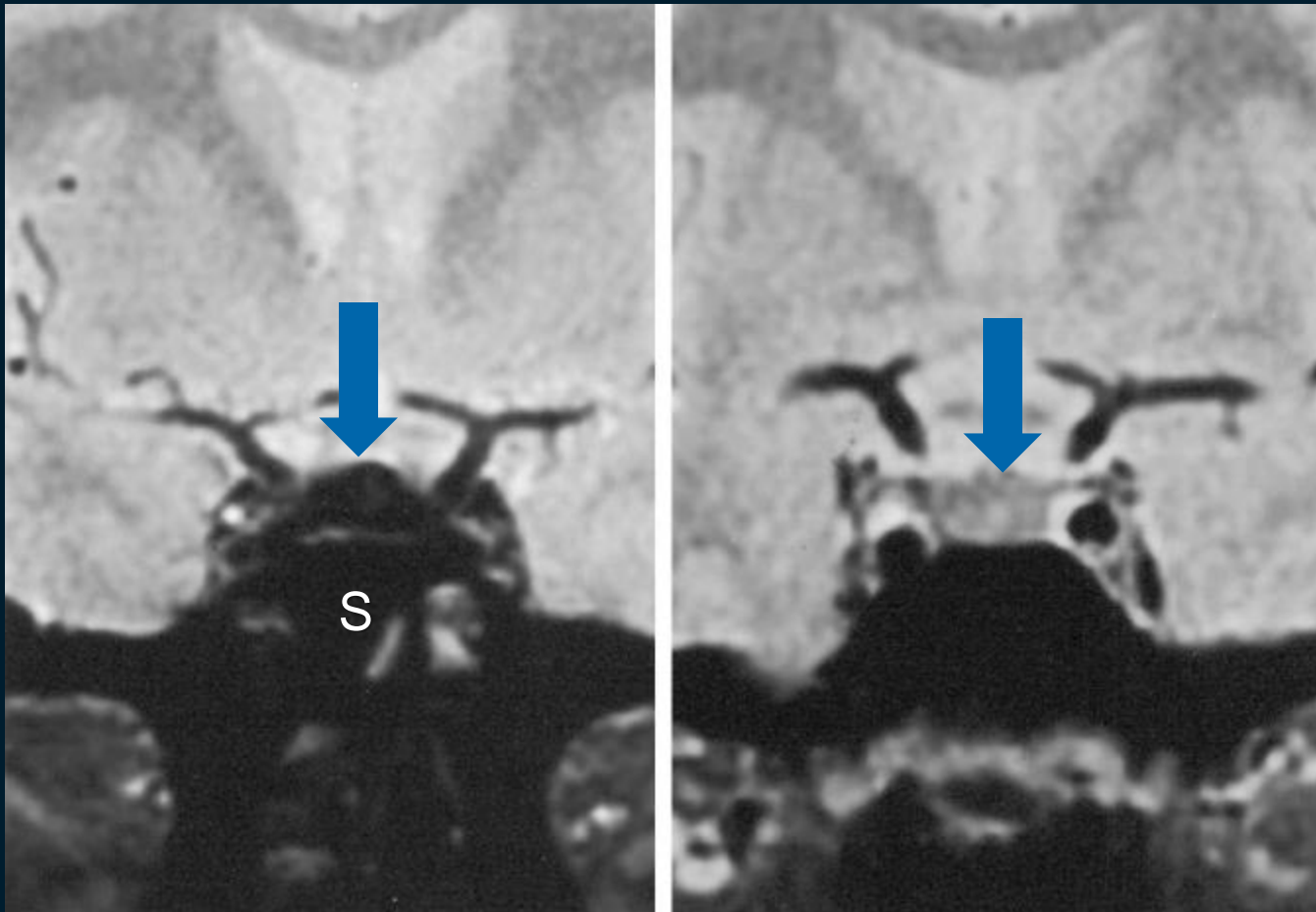
### Acquired:

- Hyperprolactinemia
- Pituitary damage [tumors, apoplexy, infection, infiltrative (hemochromatosis, sarcoidosis, histiocytosis)]
- Head trauma (stalk injury)
- Acute systemic illness
- Medications (opioids, glucocorticoids)
- Morbid obesity/diabetes (*functional*)
- Cirrhosis
- Idiopathic hypogonadotropic hypogonadism

# Infiltrative Diseases



# Infiltrative Diseases



# Clinical Features of Male Hypogonadism

# Symptoms of Androgen Deficiency

(Adapted from Endocrine Society --- JCEM 2018)

## Suggestive Symptoms

- Reduced Libido and activity
- Decreased spontaneous erections
- Incomplete/delayed puberty
- Gynecomastia
- Loss of body hair
- Testicular atrophy (<6 cc)
- Infertility
- Hot flushes

## Non-Specific Symptoms

- Decreased energy
- Decreased motivation
- Depressed mood
- Sleepiness
- Reduced muscle bulk
- Increased body fat and BMI
- Poor concentration and memory
- Mild unexplained anemia

# Clinical Manifestations of Hypogonadism

## Pre-pubertal Onset

- Testes volume <5 cc
- Micropenis
- Cryptorchidism
- Scrotum: hypopigmented, lack rugae
- Anosmia (Kallmann's syndrome)
- Visual field defects (pituitary lesion)
- Gynecomastia
- Eunuchoidal Proportions
- Decreased body hair
- High-pitched voice
- Low hair line
- Decreased libido
- Decreased bone mass
- Decreased muscle mass
- Small prostate

## Post-pubertal Onset

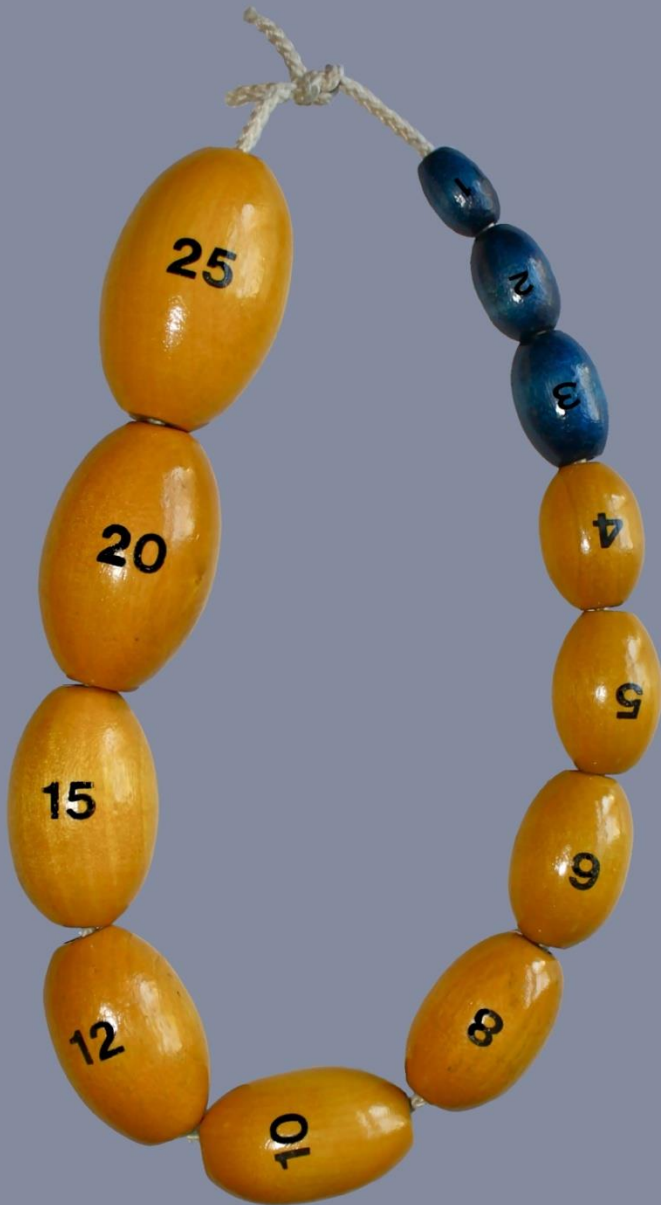
- Decreased libido
- Decreased spontaneous erections
- Decrease in testicular volume
- Gynecomastia
- Hot flashes
- Decreased bone mass
- Height loss / minimal trauma fracture
- Decreased hair/shaving frequency
- Galactorrhea (prolactinoma) (rare)
- Visual field defects (pituitary lesion)
- Decreased muscle mass
- Decreased energy and motivation

### These patients have:

- Normal skeletal proportions
- Normal penile length
- Normal voice
- Normal prostate size



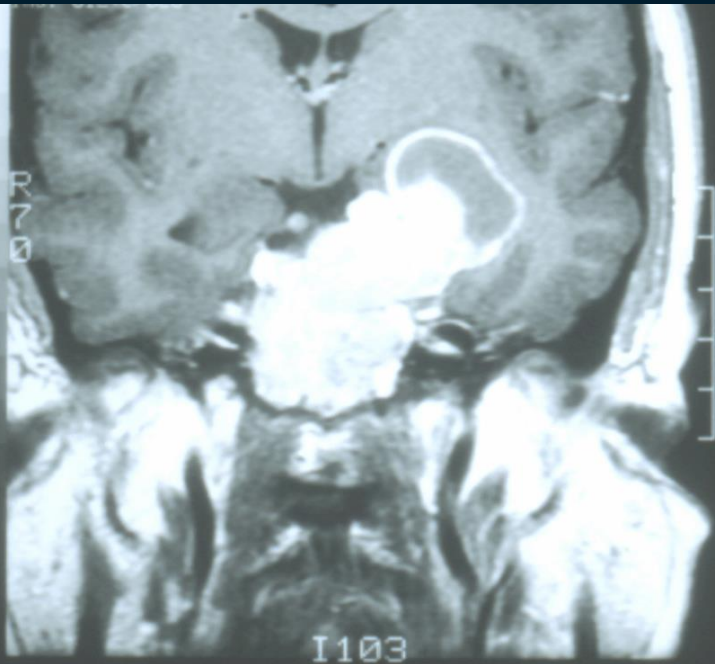
# Prader Orchidometer







## Macroprolactinoma



Response to Dopamine agonist  
(2-year therapy)



# Diagnostic Work-up

Postpone Evaluation if the patient:

- \*Recently hospitalized
- \*Recovering from acute/subacute illness
- \*Reversible systemic illness
- \*Severe nutritional deficiency
- \*On drugs that lower T

## Signs & Symptoms of Hypogonadism

Total Testosterone (morning, fasting, reliable assay)

Normal  
Testosterone

Total Testosterone <264 ng/dl

Repeat morning, fasting, Total Testosterone

Total Testosterone <264 ng/dl

(Measure Free Testosterone if SHBG variations expected)

Free Testosterone cut-off--- lab-specific

Measure Gonadotropins (LH/FSH)

Hypogonadism  
Unlikely

Other causes of symptoms

High  
(Primary Hypogonadism)

Low or Inappropriately normal  
(Secondary Hypogonadism)

- Iron studies
- Karyotype (rule out Klinefelter's Syndrome)

- Prolactin
- Iron studies
- Exclude Opioids / Glucocorticoids
- Other Pituitary Hormones
- MRI (T<150 ng/dl)

# Question 1

- Which of the following conditions result in reduced serum sex hormone binding globulins (SHBG) levels?
- A. Hyperthyroidism
- B. Liver disease
- C. Obesity
- D. HIV



# Conditions Influencing SHBG Concentrations

## Increase

- Aging
- Hyperthyroidism
- Hyperestrogenemia
- Liver disease
- HIV
- Anticonvulsant Use
- SHBG gene polymorphisms

## Decrease

- Obesity
- Insulin Resistance and Diabetes
- Hypothyroidism
- GH, Androgens, Progestins
- Glucocorticoids
- Nephrotic Syndrome
- SHBG gene polymorphisms

# Contraindications to Testosterone Replacement Therapy

Metastatic Prostate Cancer

Severe Lower Urinary Tract  
Symptoms (IPSS>19)

Breast Cancer

Hematocrit >48%

(>50% for men living at high altitude)

Prostate Nodule/ Induration

(unless urology evaluation negative)

Uncontrolled CHF

PSA>4 ng/ml

PSA>3ng/ml \* African-Americans

\* Pca

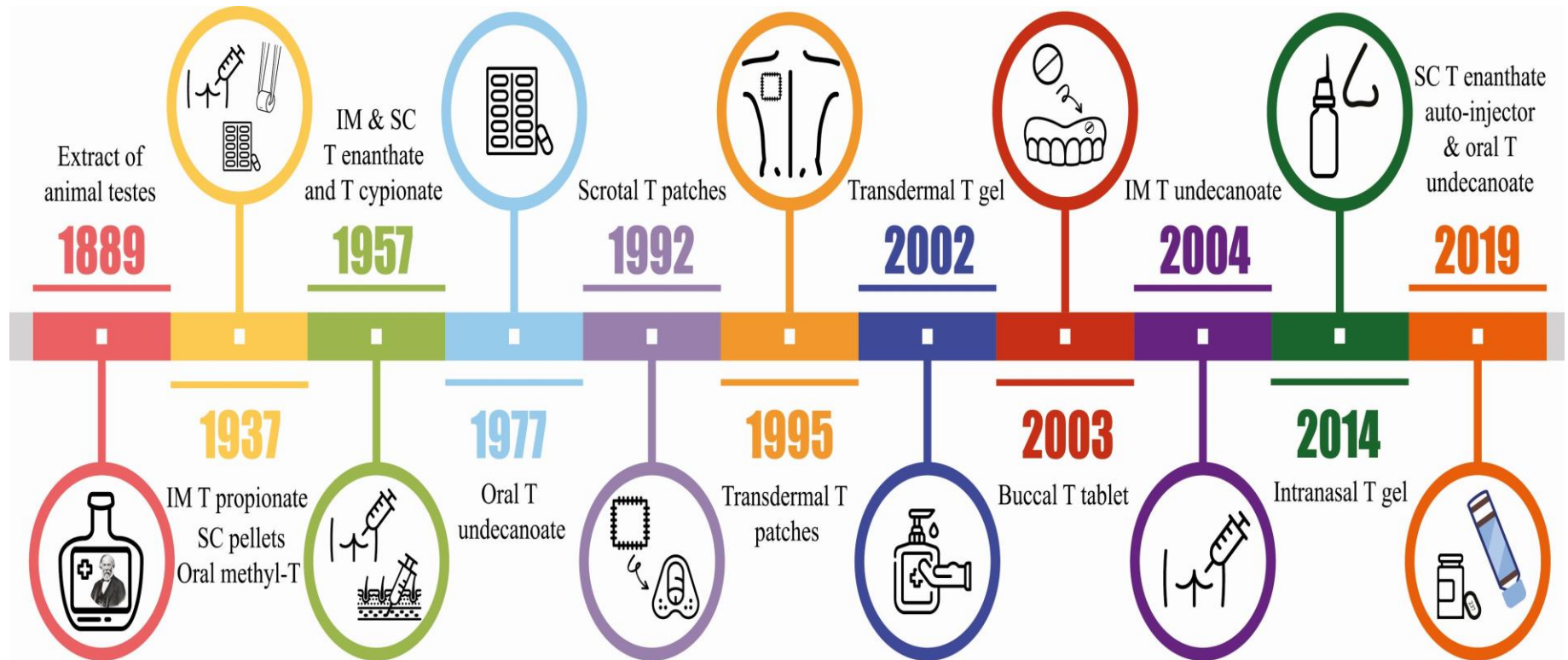
(unless urology evaluation negative)

Desire for Fertility

# Modalities of Testosterone Replacement



# Timeline of Testosterone Formulations



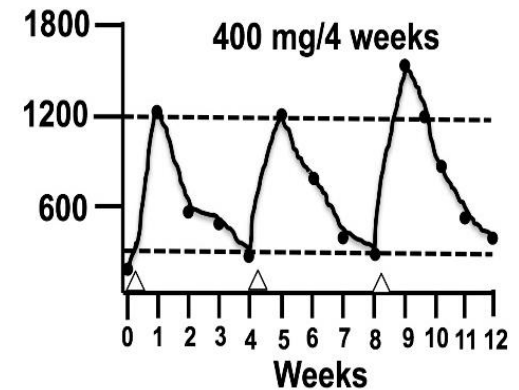
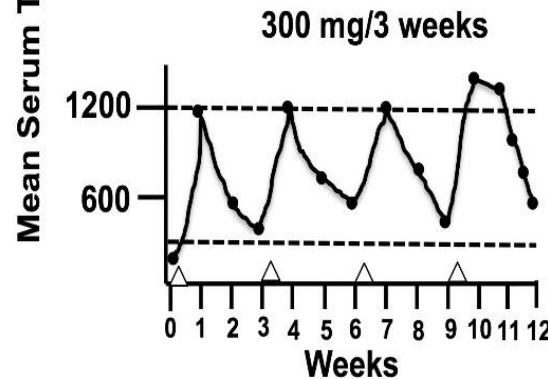
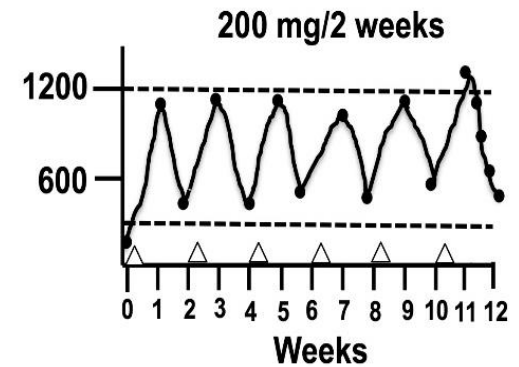
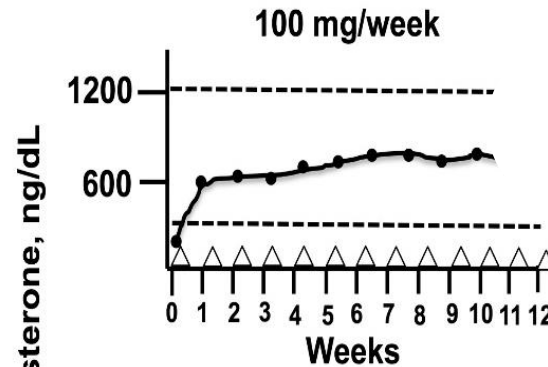
# Intramuscular Injections

## Dose

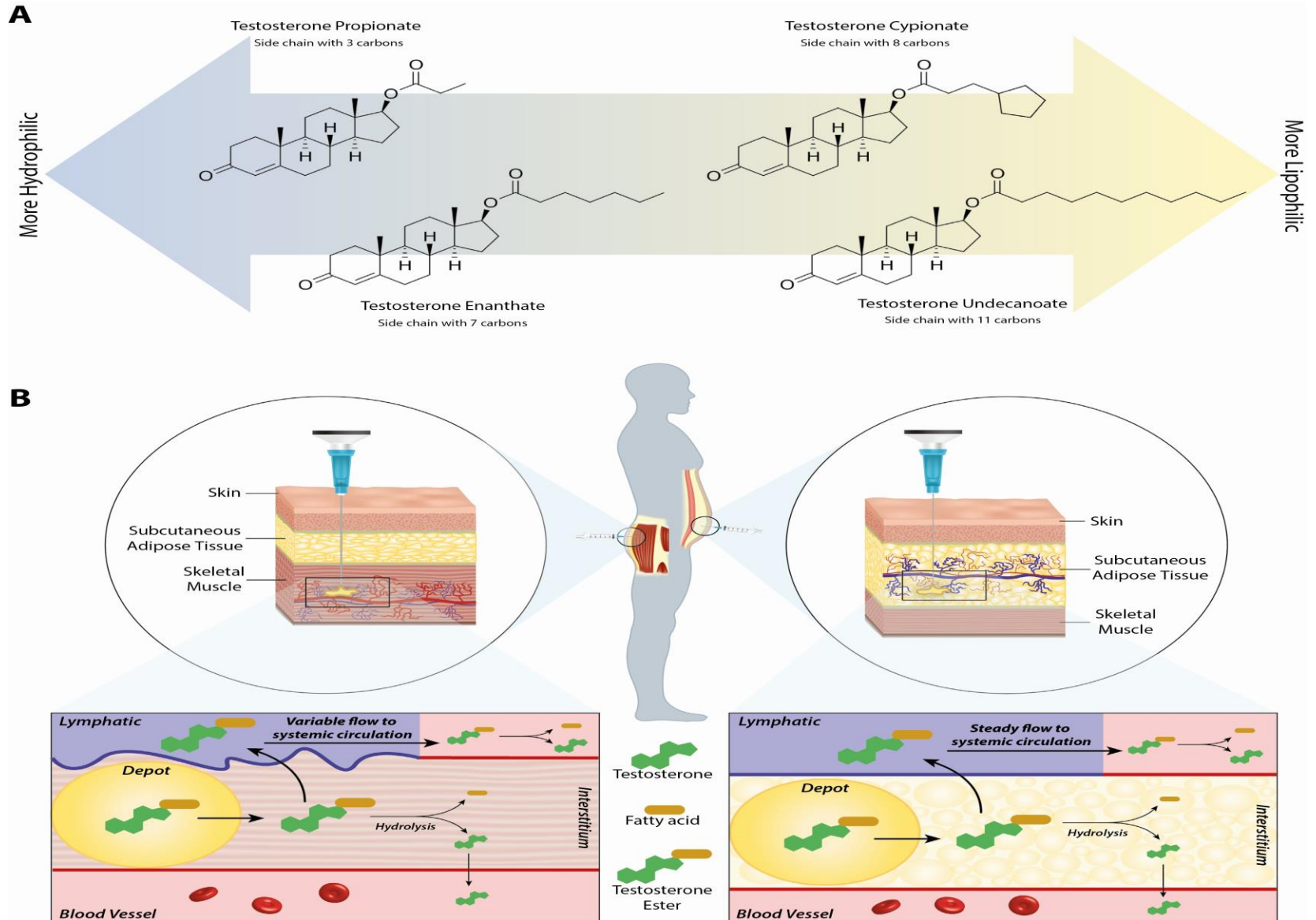
*T. enanthate / cypionate*

200 mg q 2 weeks

75-100 mg weekly (most physiologic)



# Subcutaneous Testosterone Injection



# Subcutaneous Injections (with syringe)

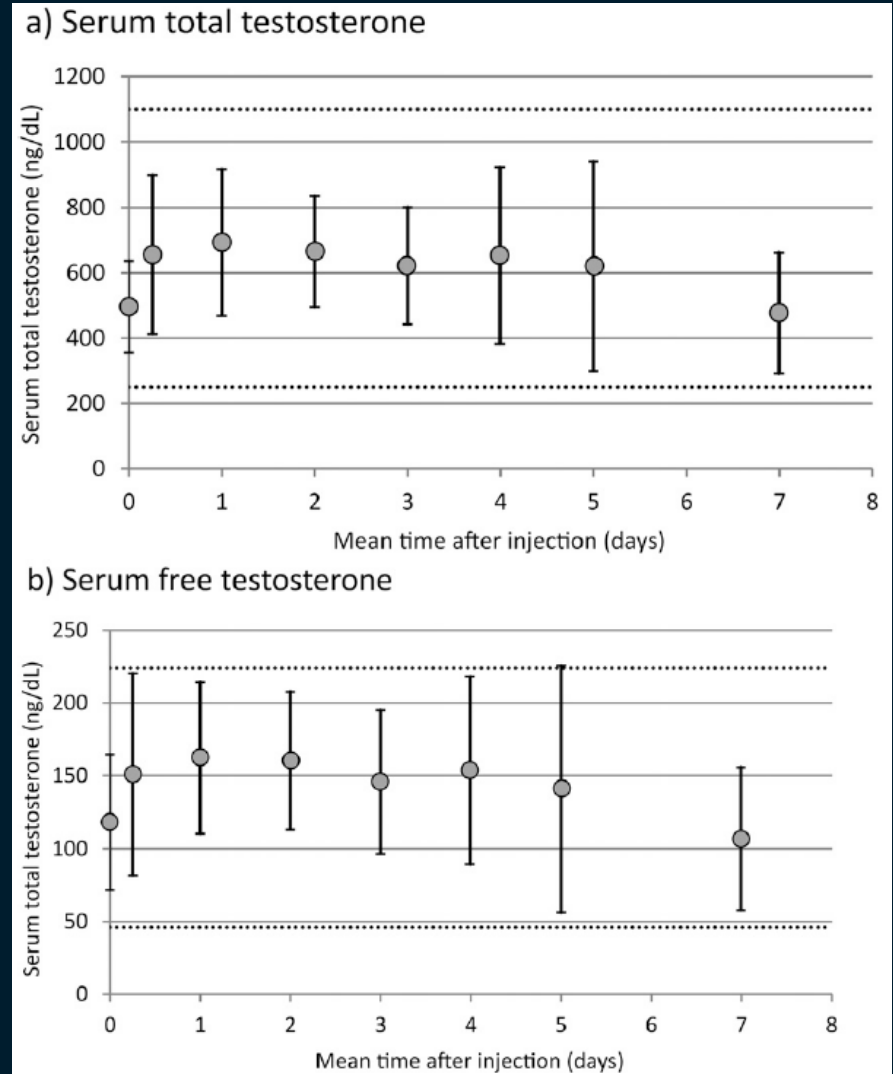
## Data from 11 Female-to-Male Transgender Patients

*T. cypionate*

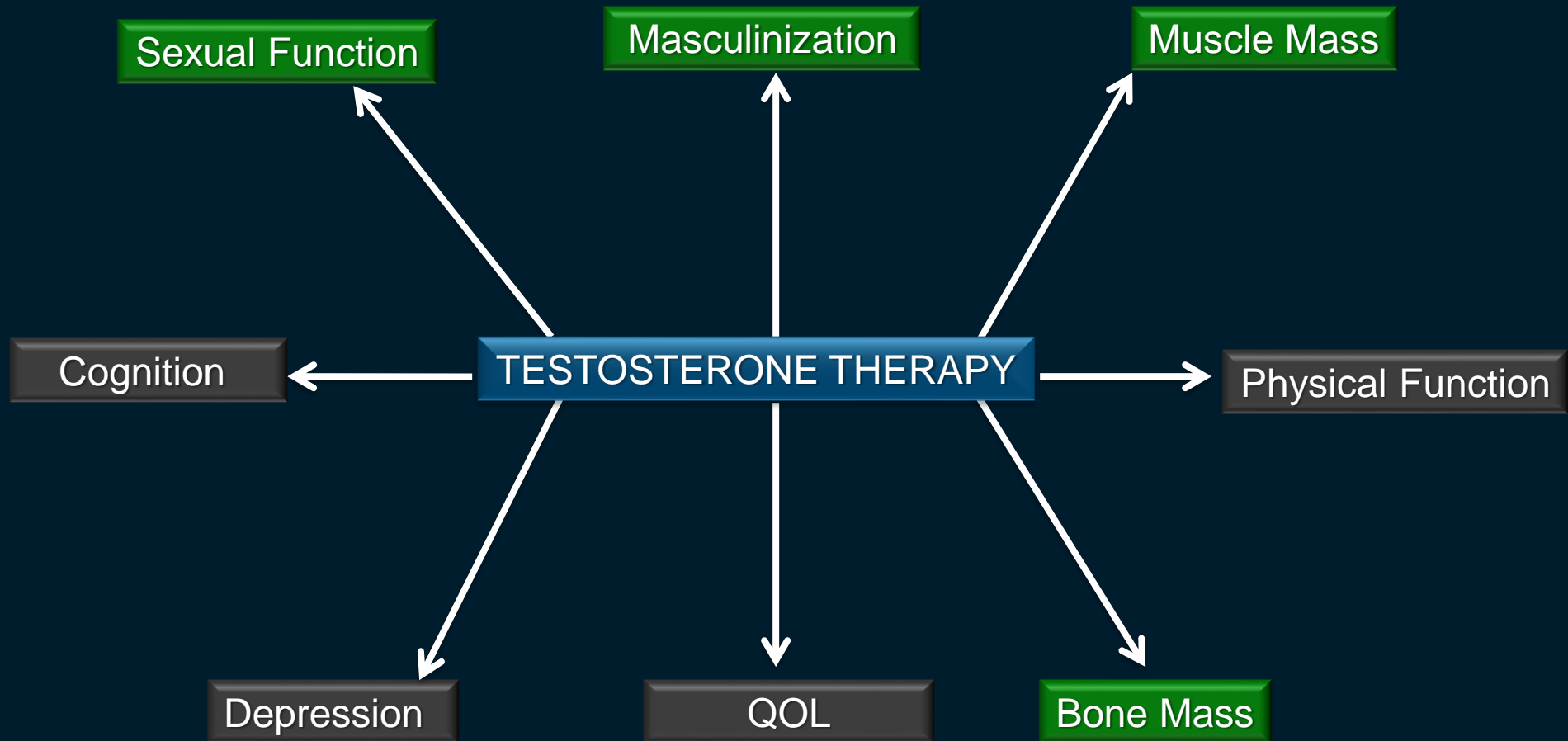
- Weekly injections
  - 1 ml syringe
  - 25G needle 5/8"
- 2-6" lateral to umbilicus or thigh

### Disadvantages

- Nodule formation (resolved 1-2 days)
  - Localized urticaria
  - Cellulitis (transient)



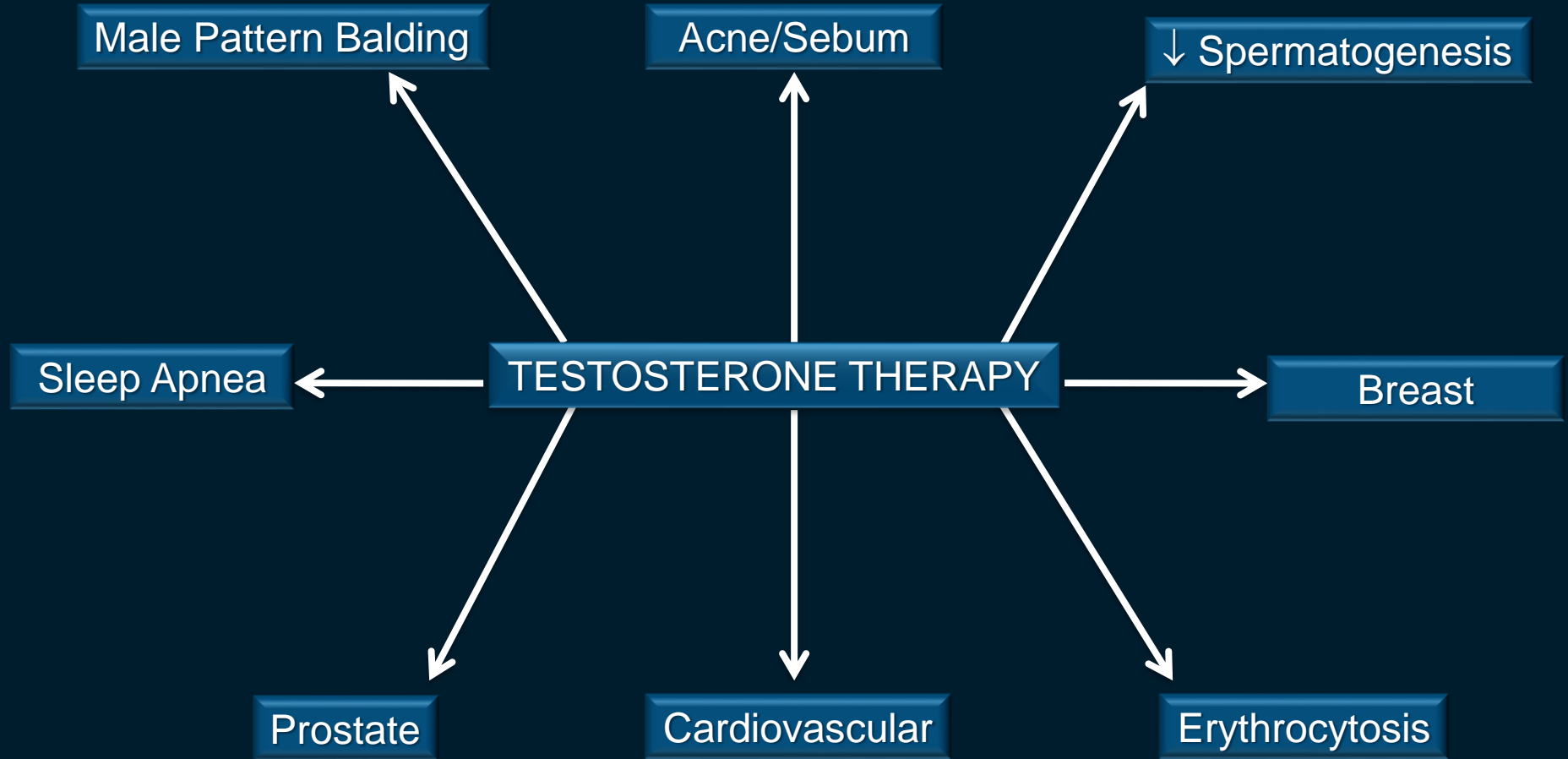
# Potential Benefits of Testosterone Therapy



## Question 2

- What is the most common adverse effect observed in clinical trials of testosterone replacement?
- A. Thromboembolism
- B. Erythrocytosis
- C. Prostate cancer
- D. Obstructive sleep apnea

# Potential Adverse Effects of Testosterone Therapy

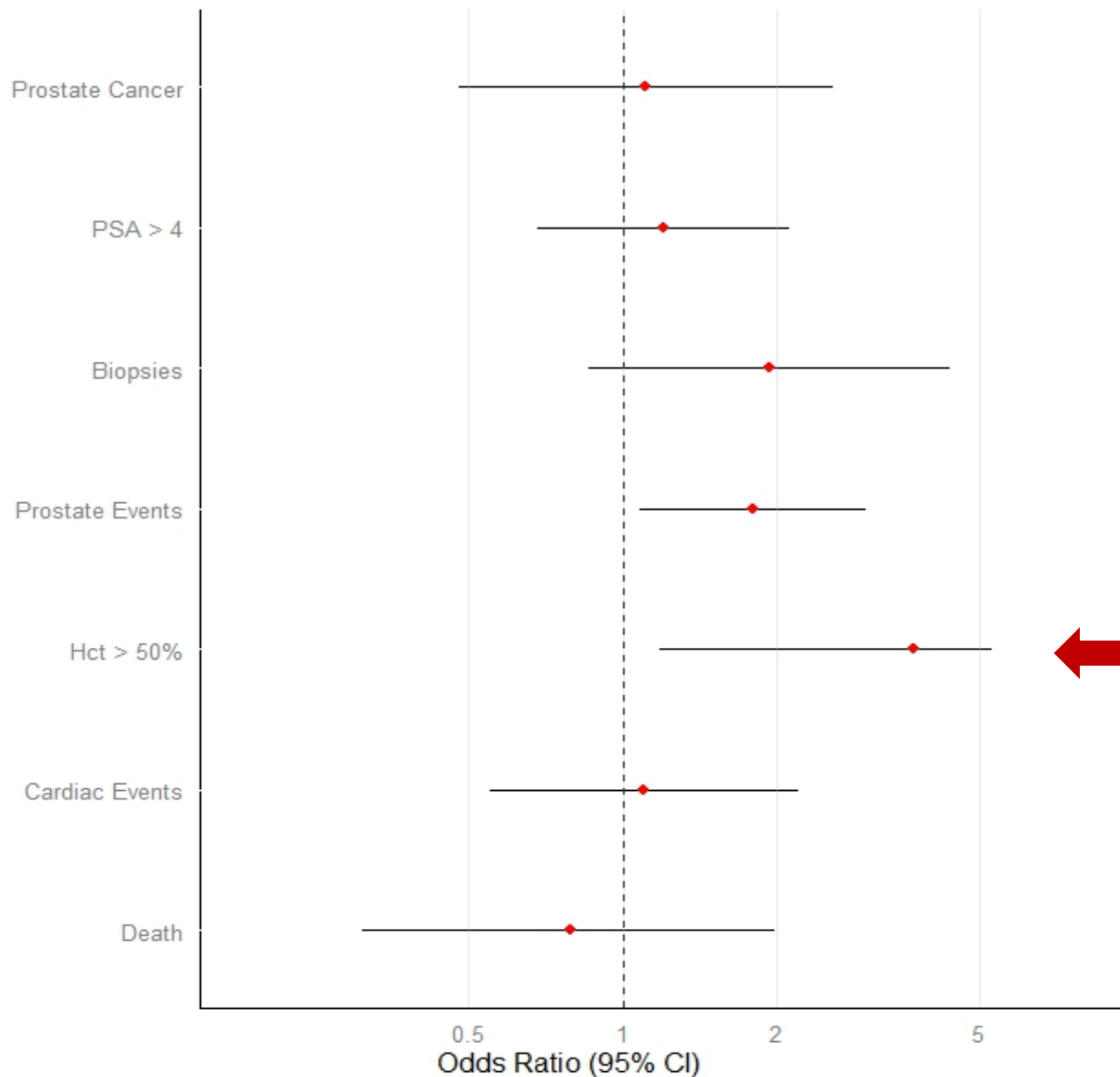


# Testosterone and Erythrocytosis



# Testosterone Related Polycythemia

Calof et al. J Gerontol Biol Sci Med Sci 2005;60:1451



# Endocrine Society Guidelines

## Erythrocytosis

### Treatment Initiation

Baseline Hct >48% (>50% high altitude)  
(further evaluation needed)

### Monitoring

- Hematocrit at 3 & 6 months---then annually
- Older age and T injections at higher risk

### Cessation and Referral

Hct >54%

- Evaluate for hypoxia / sleep apnea
- Re-initiate T at lower dose once Hct at safe level
- Therapeutic phlebotomy is efficacious

# Testosterone and Prostate

# Endocrine Society Guidelines

## Prostate

### Screening

- 55-69 yrs (40-69 yrs at increased risk)
- No screening for men <40 yrs

### Monitoring

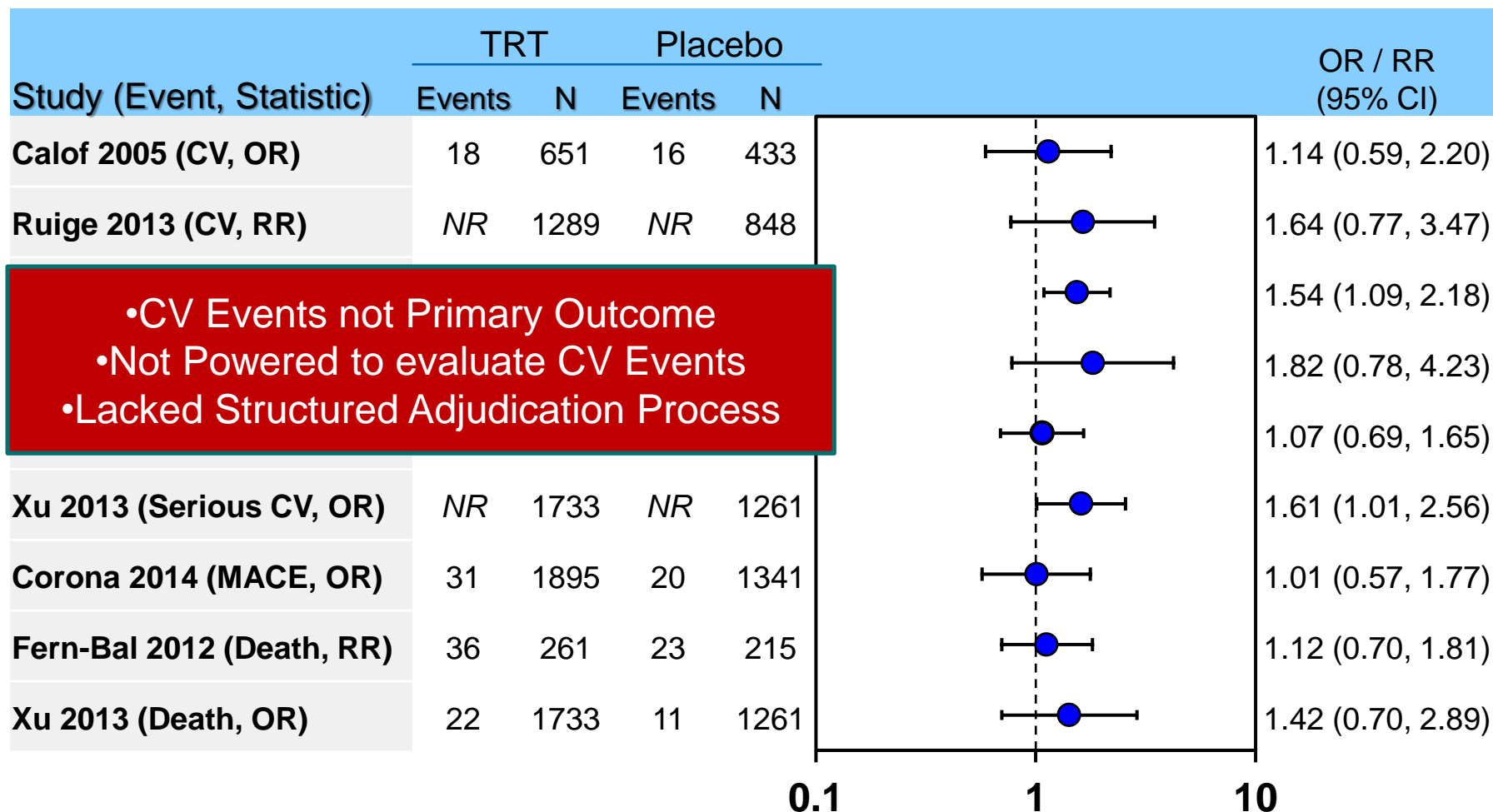
PSA at 3-12 months---then based on age/race recommendations

### Cessation and Referral

- Nodule
- $\Delta$  PSA change >1.4 ng/ml

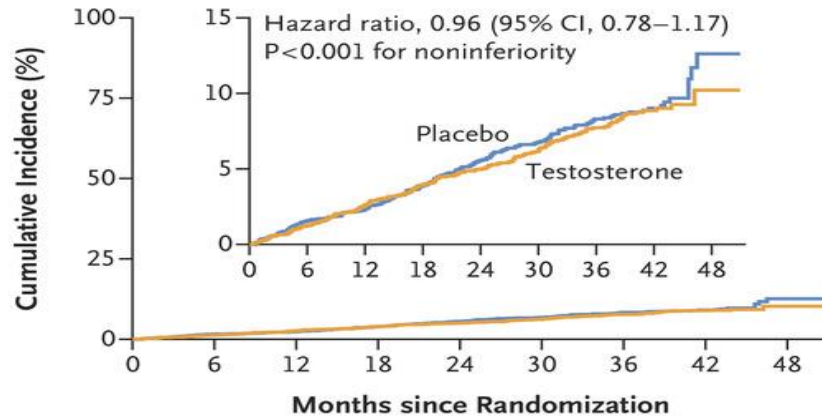
# Testosterone and Cardiovascular Disease

# Summary of Meta Analyses



# Time-to-Event Analysis for the Primary and Secondary Cardiovascular Safety End Points

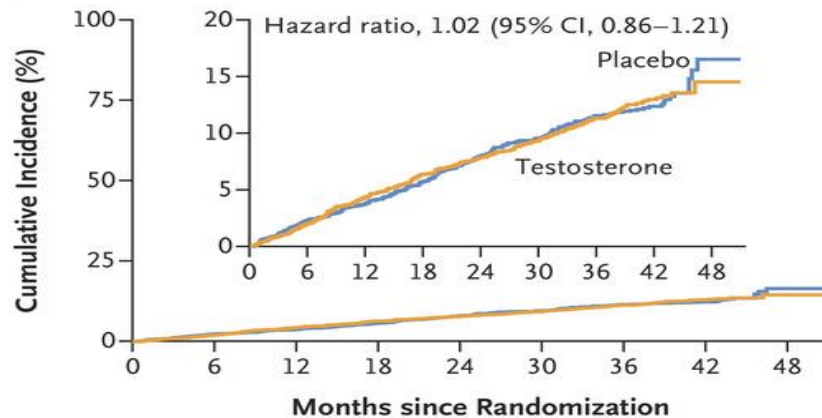
## A Primary Cardiovascular Composite Safety End Point: Safety Population



### No. at Risk

Placebo	2602	2507	2323	2088	1792	1568	1337	598	33
Testosterone	2596	2504	2339	2120	1829	1605	1380	653	39

## C Secondary Cardiovascular Composite Safety End Point: Safety Population



### No. at Risk

Placebo	2602	2488	2289	2048	1747	1522	1293	575	31
Testosterone	2596	2484	2295	2065	1776	1555	1330	625	37

# Conclusions

- Diagnosis of hypogonadism should be made in a **symptomatic** patient who has **consistently low** serum testosterone levels
- Testosterone levels should be measured in the **morning**, **fasting**, on at least **2 occasions**, with a **reliable assay**
- Consider measuring **free testosterone** in men with suspected **binding protein abnormalities**
- Choice of testosterone replacement modality should be based on **patient preference**, **cost**, **availability** and **formulation-specific properties**
- Testosterone replacement in older men results in **modest benefits**; reassuring recent data on **cardiovascular** & **prostate** safety
- Continue to monitor **efficacy** and **adverse effects**