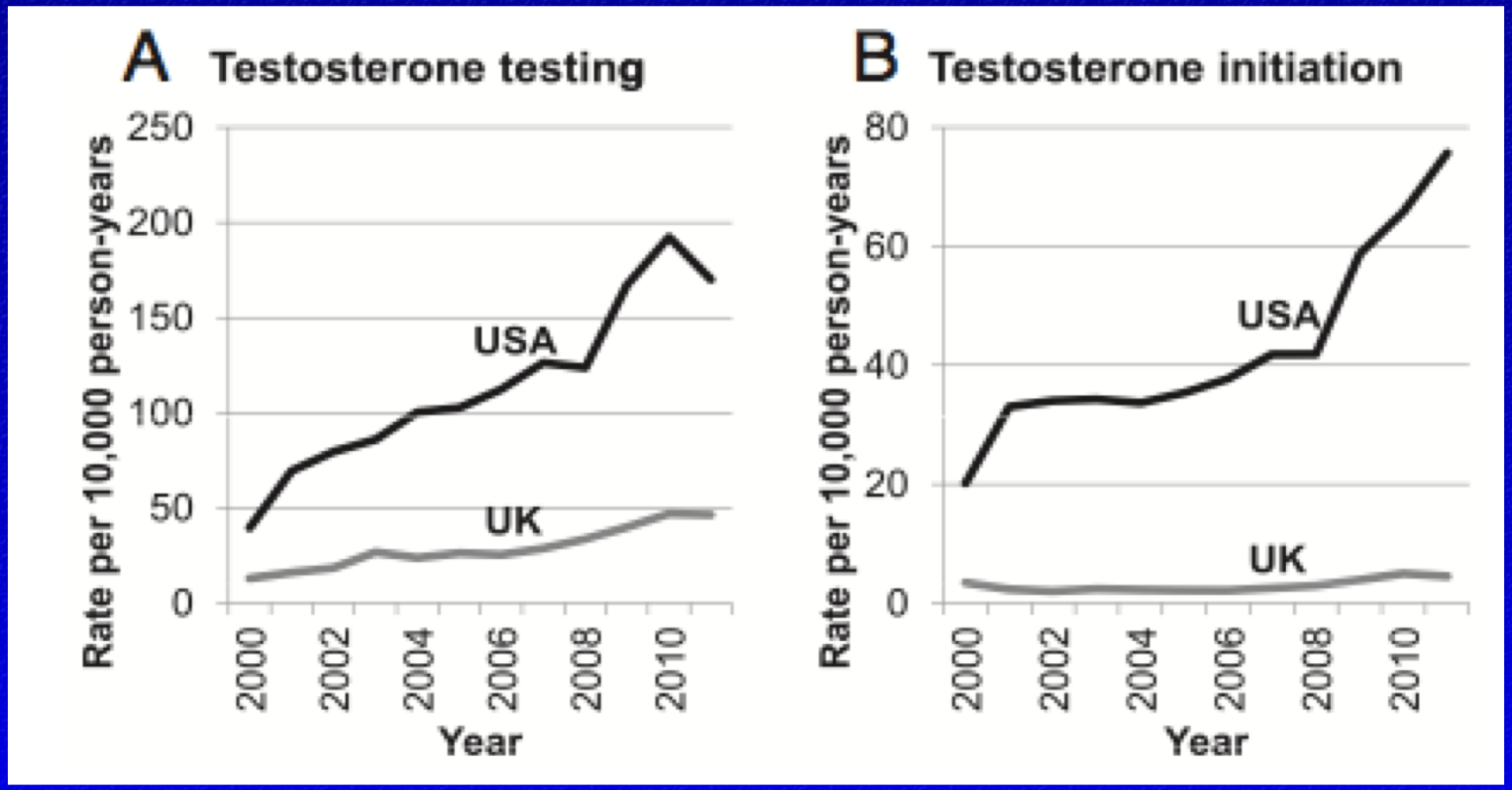
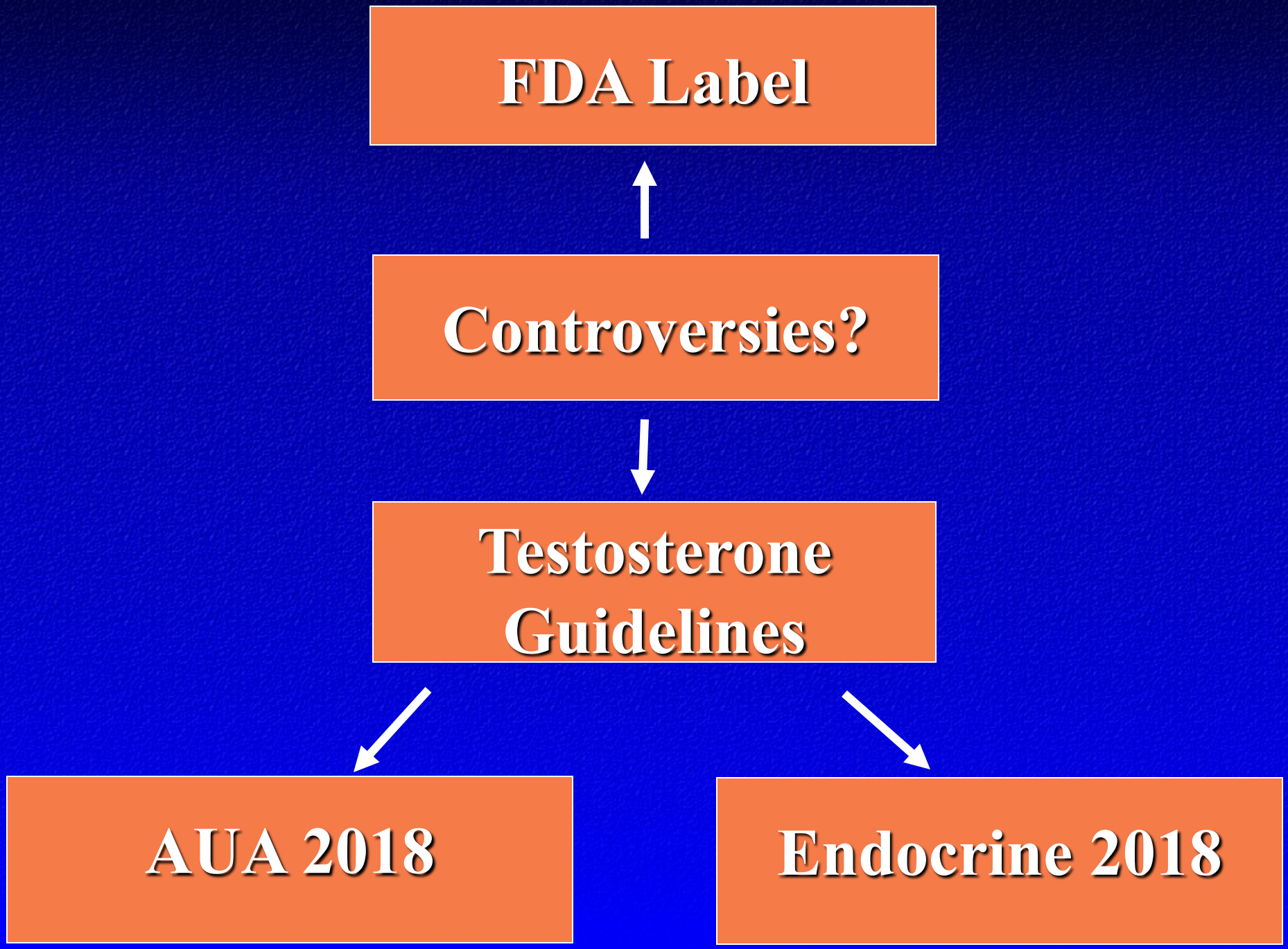
Controversies in the Diagnosis and Treatment of Hypogonadism

Mohit Khera, M.D., M.B.A., M.P.H.
Professor of Urology
Scott Department of Urology
Baylor College of Medicine
Houston, TX

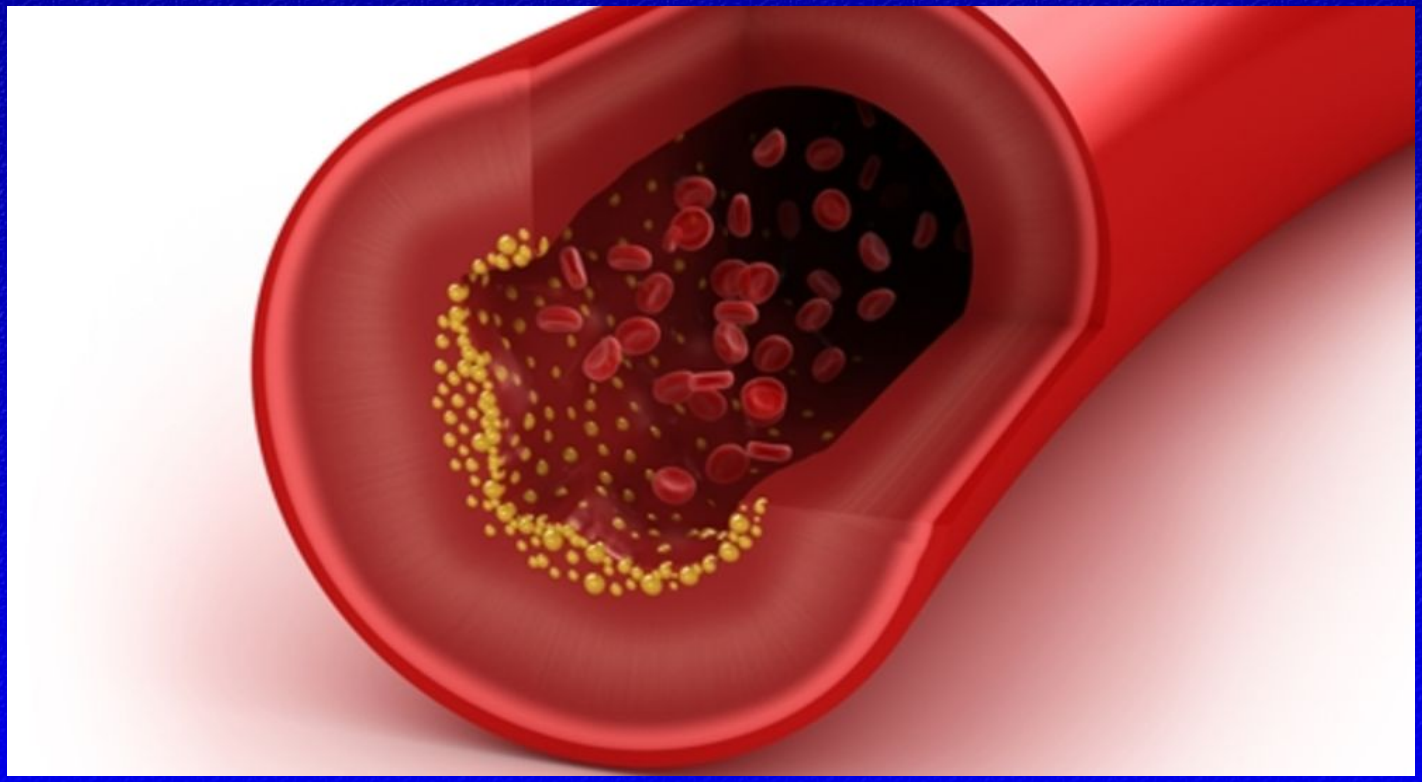
Testosterone Testing and Initiation



Layton et al. J Clin Endocrinol Metab 2014; 99(3):835-842


FDA Label
Controversies?
Testosterone Guidelines
AUA 2018
Endocrine 2018

Venous Thromboembolism (VTE)



FDA Label (2014): Venous Thromboembolism

"Warnings and Precaution" Section

5.4 Venous Thromboembolism

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products such as AndroGel 1%. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with AndroGel 1% and initiate appropriate workup and management *[see Adverse Reactions (6.2)]*.

Venous Thromboembolism

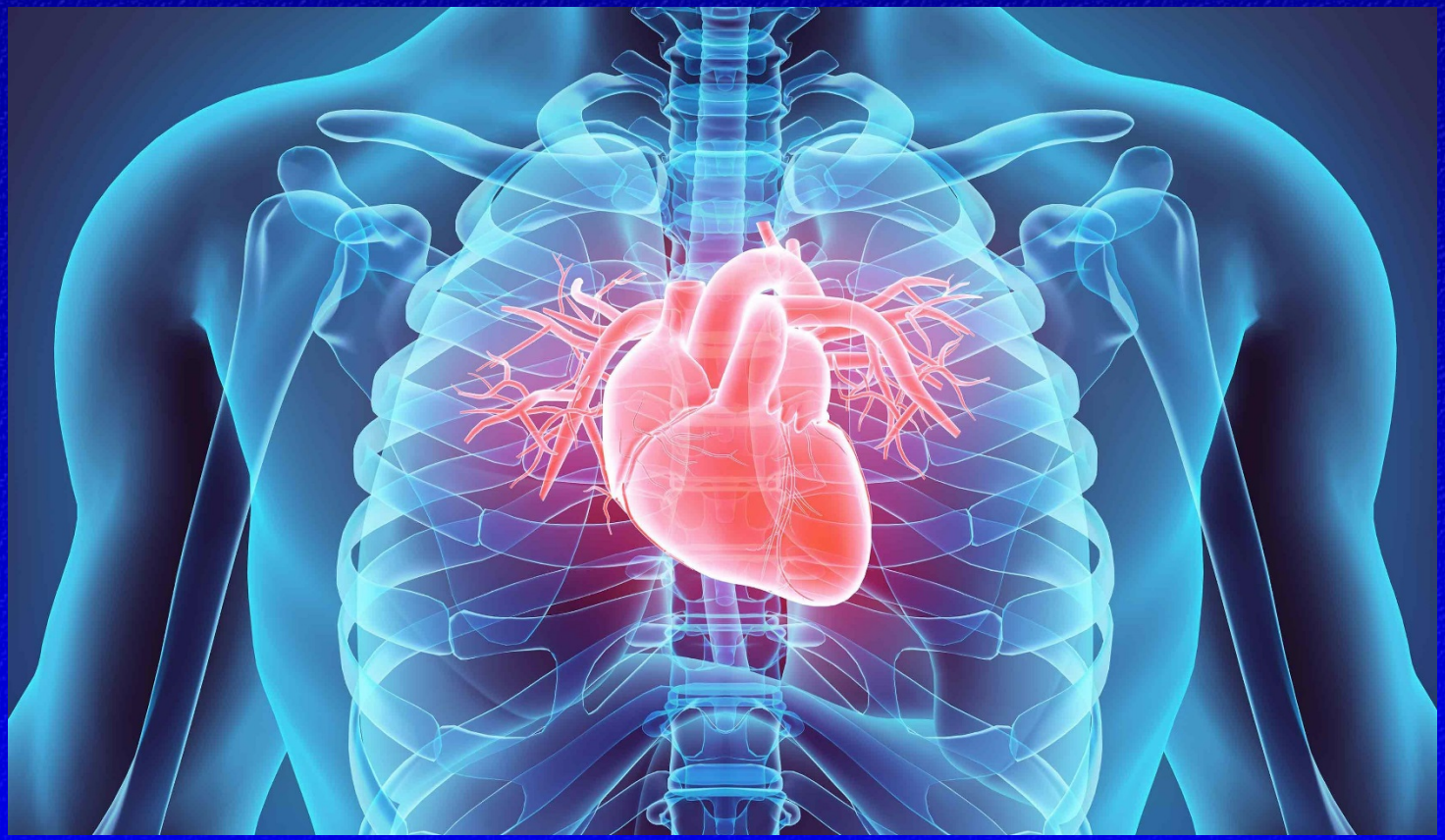
AUA 2018 Guidelines

Patients should be informed that there is no definitive evidence linking testosterone therapy to a higher incidence of venothrombolic events (Moderate Recommendation; Evidence Level: Grade C)

Endocrine 2018 Guidelines

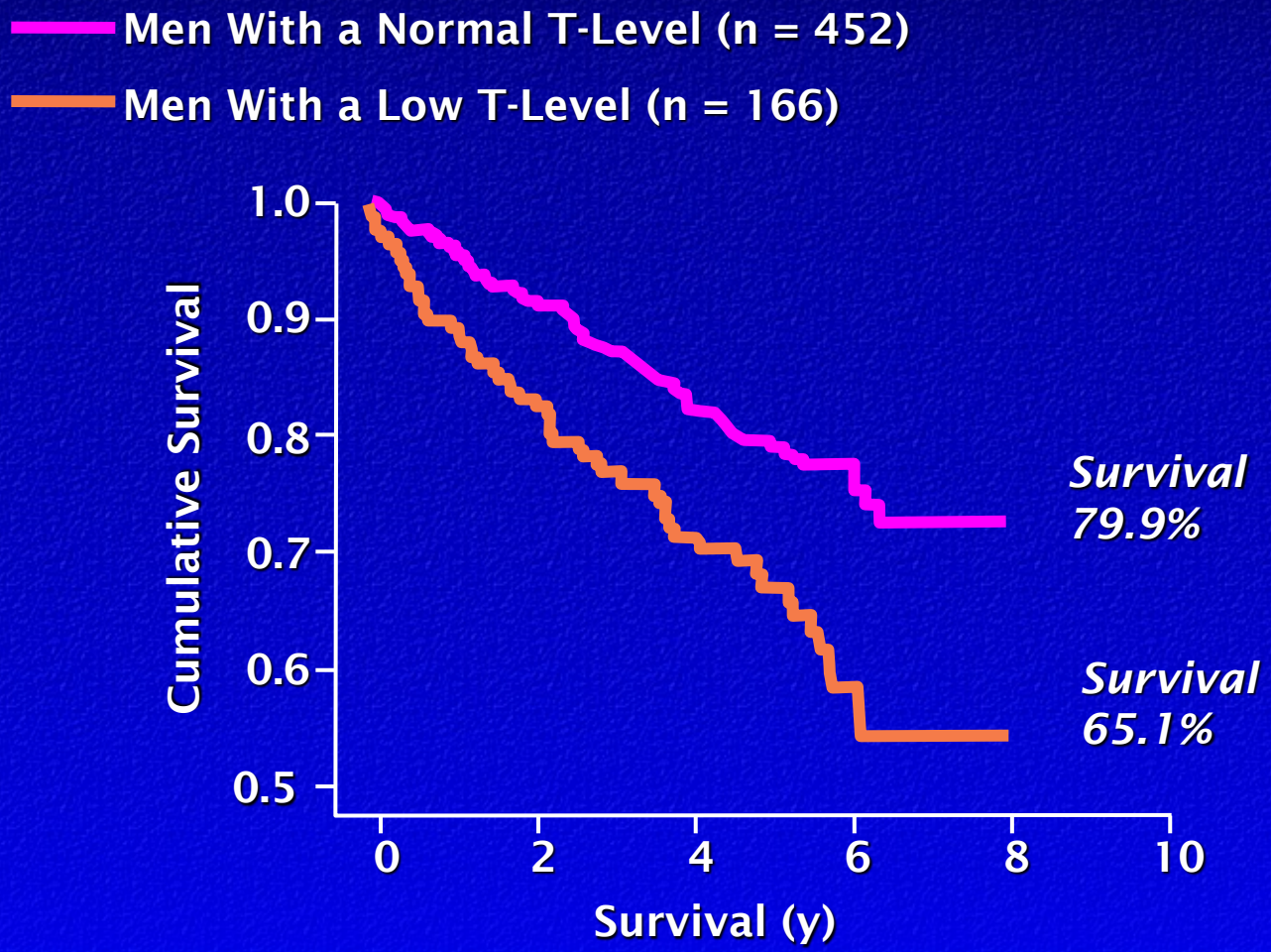
- No guideline statement
- "Case-control and pharmacoepidemiologic studies have not shown a consistent increase in the risk of venous thromboembolism (VTE) with T treatment. However, there are too few T-associated VTE events in RCTs to draw meaningful inferences."

Cardiovascular Risk



Aging Males and Mortality

Low Serum T and Mortality in Male Veterans



Shores M, et al. *Arch Intern Med.* 2006;166:1660-1665.

Low Testosterone and Increased Mortality (N >500)

Recent Studies	HR (95% CI)	Nature	Men, n	Follow-Up, y	Mortality
Shores, 2006	1.88 (1.34–2.63)	Retrospective	858	8	All-cause
Laughlin, 2008	1.38 (1.02–1.85)	Prospective	794	20	CVD
Khaw, 2007	2.29 (1.60–3.26)	Prospective	2314 of 11,606	10	All-cause and CVD
Haring, 2010	2.32 (1.38–3.89)	Prospective	1954	7.2	All-cause
	2.56 (1.15-6.52)				CVD
Malkin, 2010	2.27 (1.45–3.60)	Prospective	930	6.9	All-cause in men with coronary disease
Tivesten, 2009	1.65 (1.29–2.12)	Prospective	3014	4.5	All-cause
Menke, 2010	1.43 (1.09–1.87)	Prospective	1114	9	All-cause
Vikan, 2009	1.24 (1.01–1.54)	Prospective	1568	11.2	All-cause
Corona, 2010	7.1 (1.8–28.6)	Prospective	1687	4.3	CVD

HR=hazard ratio; CI=confidence interval.

SPECIAL ARTICLE

MAYO CLINIC

Testosterone Therapy and Cardiovascular Risk: Advances and Controversies

Abraham Morgentaler, MD; Martin M. Miner, MD; Monica Caliber, MSc; Andre T. Guay, MD†; Mohit Khera, MD; and Abdulmaged M. Traish, PhD

- **Review of all articles from 1940-2014 relating to T and CVD**
- **Over 200 articles identified**
- **Only 4 articles suggesting increased CV risk with T**
- **Several dozen studies demonstrated beneficial effects of normal T on CV risk and mortality**
- **Low levels of T associated with increased risk of mortality and CVD (LOE IIa)**
- **Severity of CAD inversely correlated with serum T levels (LOE IIa)**

Morgentaler et al. Mayo Clin Proc. 2014 Nov 1

Studies Claiming TTh Causes CVD

Basaria et al NEJM 2010

- RPCT frail elderly men
- 15 grams of testosterone
- CVD not an endpoint
- Treatment arm greater CV risks
- 5 vs 2 major CV events (ie MI)
- No difference if exclude CHF

Vigen et al JAMA 2013

- No randomization or placebo
- 2 major corrections
  - "Absolute risk" of MI (19.9 vs 25.7%) vs (21 vs 10%)
  - Exclusion of 1132 men
- RETRACTION 29 societies

Finkle et al PLoS One 2014

- No randomization or placebo
- No control group or clinical info
- Health insurance database
- 90 days after start testosterone
- Pre-prescription MI rate 3.48/1000
  Post-prescription MI rate 4.75/1000

Xu et al BMC 2013

- Meta- analysis of CV events in 27 PC studies of >12 weeks
- Just 2 studies provided 1/3 of all CV events in T treat arm
- If exclude 2 studies CV events in T and placebo are identical

FDA Label (2015): Cardiovascular Risk

"Warnings and Precaution" Section

5.5 Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men.

Patients should be informed of this possible risk when deciding whether to use or to continue to use AndroGel 1%.

European Medicines Agency (EMA) performed its own review and declined to add a new CV warning

The state of testosterone therapy since the FDA's 2015 labelling changes: Indications and cardiovascular risk

Martin Miner[1,2] | Abraham Morgentaler[3] | Mohit Khera[4] | Abdulmaged M. Traish[5]

- **T and CV studies from September 2014 to July 2017**
- **23 studies (12 clinical trials, 11 observational studies)**
- **Results:**
  - No study reported increased MACE with TTh
  - Men whose T normalized with TTh had reduced risk of MI and death compared with men whose T levels failed to normalize

Miner et al. Clinical Endocrinology 2018

Cardiovascular Risk

AUA 2018 Guidelines

- Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B)
- Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). (Moderate Recommendation; Evidence Level: Grade B)
- Testosterone therapy should not be commenced for a period of three to six months in patients with a history of cardiovascular events. (Expert Opinion)

Endocrine 2018 Guidelines

- We recommend against testosterone therapy in men with…. heart failure, myocardial infarction or stroke within the last 6 months… (Low quality evidence)
- "…there is no conclusive evidence that T supplementation is associated with increased cardiovascular risk in hypogonadal men."
- "Thus, there are insufficient data to establish a causal link between T therapy and cardiovascular events."

Indications for Testosterone Therapy

FDA Androgen Class Labeling Guideline (1981)

- "Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.
  a) Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy.
  b) Hypogonadotropic hypogonadism (congenital or acquired)—idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation."

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.

Safety Announcement

[03-03-2015] The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.

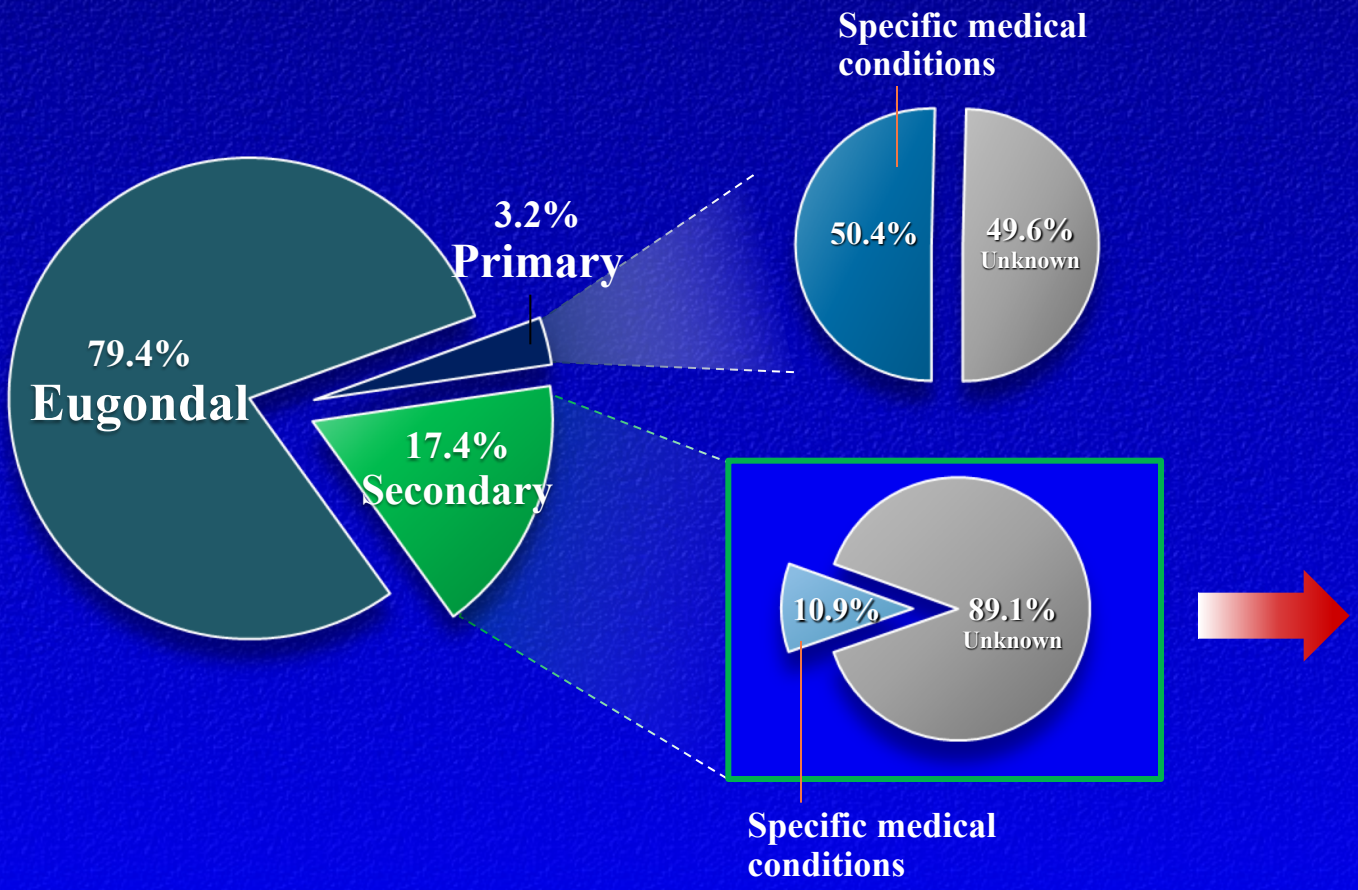
FDA Label (2015): Indications for Testosterone Therapy

1 INDICATIONS AND USAGE

AndroGel 1% is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

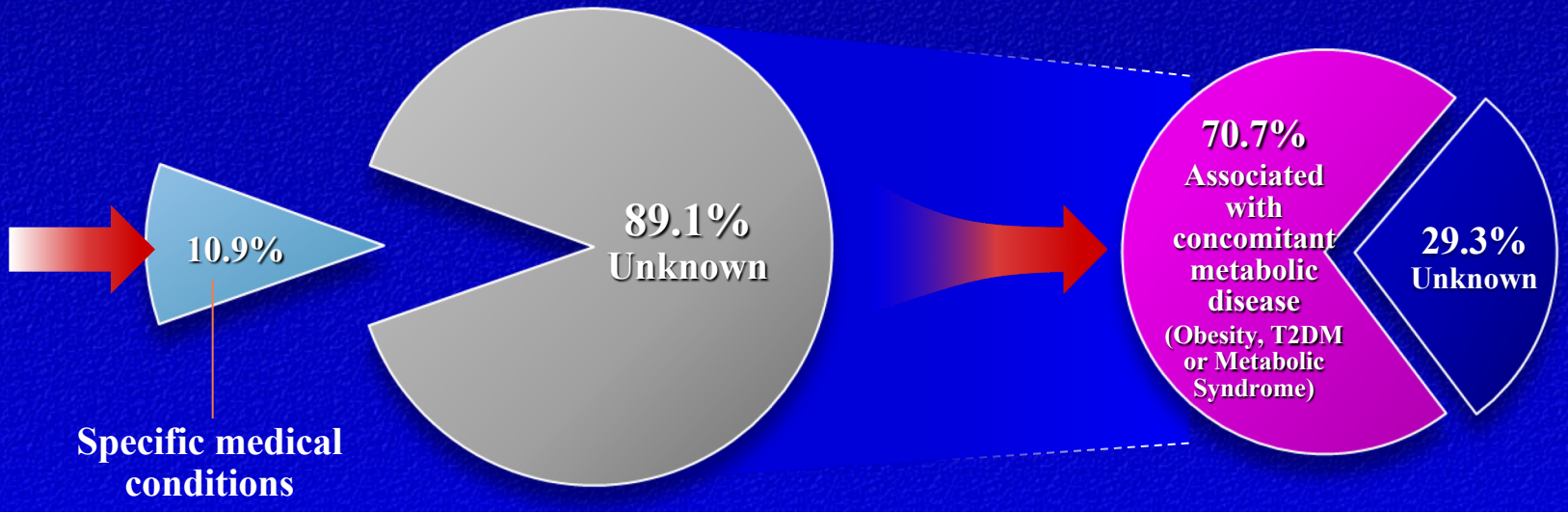
- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): ~~idiopathic~~ gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

Prevalence of Hypogonadism



Corona et al *J Sex Med* 2015; 12 1690-1693)

Specific Medical Conditions Associated with Secondary Hypogonadism



Corona et al *J Sex Med* 2015; 12 1690-1693)

SPECIAL ARTICLE

MAYO CLINIC

CrossMark

Adult-Onset Hypogonadism

Mohit Khera, MD, MBA, MPH; Gregory A. Broderick, MD; Culley C. Carson III, MD; Adrian S. Dobs, MD, MHS; Martha M. Faraday, PhD; Irwin Goldstein, MD; Lawrence S. Hakim, MD; Wayne J.G. Hellstrom, MD; Ravi Kacker, MD; Tobias S. Köhler, MD, MPH; Jesse N. Mills, MD; Martin Miner, MD; Hossein Sadeghi-Nejad, MD; Allen D. Seftel, MD; Ira D. Sharlip, MD; Stephen J. Winters, MD; and Arthur L. Burnett, MD, MBA

- AOH is a clinical and biochemical syndrome characterized by a deficiency of testosterone with signs and symptoms that can be caused by testicular and/or hypothalamic-pituitary dysfunction
- AOH is clinically distinct from classical primary and secondary hypogonadism
- AOH more often occurs in men who have chronic medical conditions

Khera et al. Mayo Clin Proc. 2016 Jul;91(7):908-26

Indications

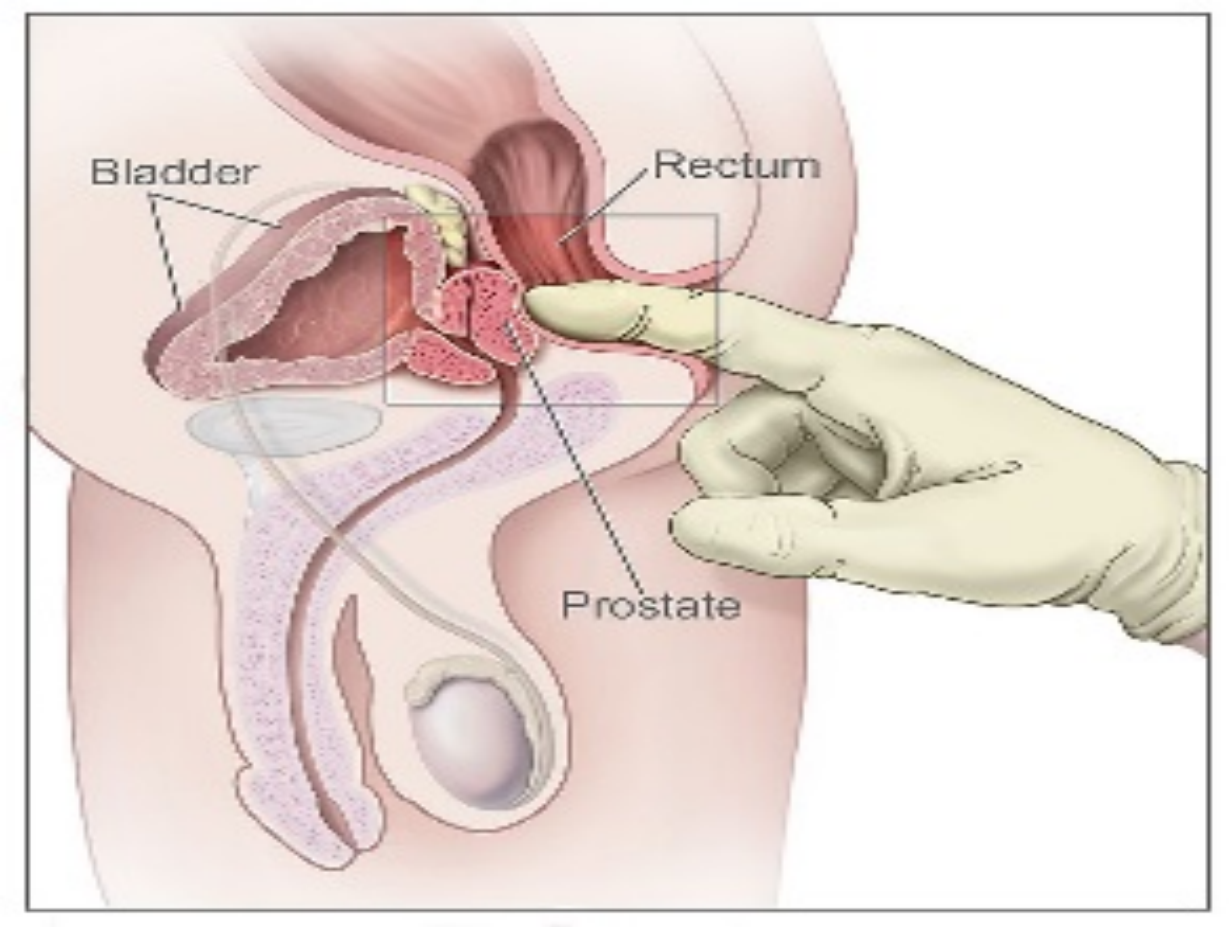
AUA 2018 Guidelines

The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs (Moderate Recommendation; Evidence Level: Grade B)

Endocrine 2018 Guidelines

We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated) (Moderate quality evidence)

Prostate Cancer and BPH



FDA Label: Prostate Cancer and BPH

"Warnings and Precaution" Section

5.1 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens *[see Contraindications (4), Adverse Reactions (6.1)* and *Nonclinical Toxicology (13.1)]*.

"Contraindications" Section

- AndroGel 1% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1), Adverse Reactions (6.1),* and *Nonclinical Toxicology (13.1)]*.

Prostate Cancer and BPH

AUA 2018 Guidelines

Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong Recommendation; Evidence Level: 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)

Endocrine 2018 Guidelines

We recommend against testosterone therapy in men with…. prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level >4 ng/mL, a prostate-specific antigen level >3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation)….severe lower urinary tract symptoms,…. (Low quality evidence)

T and BPH Studies

Table 1
Outcomes of studies assessing the effect of TRT on the Prostate/LUTS

Study	Location	# of Patients	Follow-up	Design	Data Followed	Therapy	Outcomes
Emmelot-Vonk et al,[41] 2008	The Netherlands	207	6 mo	RCT, double-blind, placebo-controlled	Prostate volume measured by TRUS, PSA, IPSS	IM Testosterone Undecanoate vs placebo	No increase in TRUS volume with TRT No change in IPSS or PSA
Kalinchenko et al,[42] 2010	Russia	184	30 wk	RCT, double-blind, placebo-controlled	IPSS	IM Testosterone Undecanoate vs placebo	No change in IPSS
Haider et al,[44] 2009	Multinational	122	24 mo	Prospectively Followed cohort	IPSS	IM Testosterone Undecanoate vs placbo	Decrease in IPSS with TU treatment ($P<.05$)
Kenny et al,[47] 2010	United States	27	3 mo	Prospective Open-label study	IPSS	Transdermal testosterone	No change in IPSS with TRT
Tan et al,[48] 2013	Malaysia	114	48 wk	RCT, double-blind, placebo-controlled	IPSS	IM Testosterone Undecanoate vs placebo	No Change in IPSS with TRT
Shigehara et al,[49] 2011	Japan	46	12 mo	RCT with untreated control group	IPSS Qmax PVR Prostate volume	IM Testosterone Enthanate vs placebo	Decrease in IPSS & Qmax with TRT ($P<.05$)
Saad et al,[50] 2007	Germany	28	12 mo	Prospective Uncontrolled	IPSS	IM Testosterone Undecanoate vs Transdermal testosterone	Both arms Demonstrated a decrease in IPSS compared to baseline ($P = .05$)
Yassin et al,[51] 2014	Germany	152	5.5 y	Prospective Uncontrolled Registry study	IPSS	IM Testosterone Undecanoate	Decrease in IPSS from 10.35 to 6.31 with no statistical analysis
Karazindiyaoğlu et al,[52] 2008	Turkey	25	12 mo	Prospective cohort study	IPSS, bladder compliance, maximal bladder capacity	Transdermal testosterone	Increase in bladder capacity and compliance with TRT ($P<.05$).

DeLay KJ and Kohler TS Urol Clin North Am. 2016 Aug;43(3):405-12

Conclusion

- Diagnosis of hypogonadism can be challenging with majority of men being treated off-label
- Clinicians prescribing testosterone therapy should be aware of the 2018 AUA and Endocrine Guidelines and the recent FDA label changes
- TTh has been shown to improve BPH and LUTS
- Low serum testosterone has been associated with an increased risk of MI and CV risk factors
- There is no convincing data to support that TTh causes prostate cancer
- Patients should be appropriately counseled on the risks of VTE, CVE, BPH and prostate cancer when prescribing testosterone therapy


Thank You
Texas Medical Center, Houston