Testosterone treatment and the Heart

Jorge A. Rohena-Santaella, MD

Disclosure

- I have no actual or potential conflict of interest in relation to this presentation

Objectives

- Review current literature regarding testosterone and the heart
- Controversial topic

Introduction

- Difficult to study heart disease
  - Multiple risks factors: fam hx, lipids, obesity, smoking, physical activity…
- Difficult to study testosterone
  - Variable levels…
- Difficult to study together

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ENDOCRINE SOCIETY

Summary of Recommendations

1.0 Diagnosis of hypogonadism in men

Diagnosis of men with suspected hypogonadism

1.1 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). (1|⊕⊕⊕O)

Screening and case detection for hypogonadism

1.2 We recommend against routine screening of men in the general population for hypogonadism. (1|⊕⊕OO)

https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines/testosterone-therapy

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

Specific symptoms and signs
Incomplete or delayed sexual development
Loss of body (axillary and pubic) hair
Very small testes (<6 mL)
Suggestive symptoms and signs
Reduced sexual desire (libido) and activity
Decreased spontaneous erections, erectile dysfunction
Breast discomfort, gynecomastia
Eunuchoidal body proportions
Inability to father children, low sperm count
Height loss, low-trauma fracture, low BMD
Hot flushes, sweats
Nonspecific symptoms and signs associated with testosterone deficiency
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild unexplained anemia (normochromic, normocytic)
Reduced muscle bulk and strength
Increased body fat, body mass index

Adapted with permission from Bhasin *et al.* (7).

Shalender Bhasin, Juan P Brito, Glenn R Cunningham, Frances J Hayes, Howard N Hodis, Alvin M Matsumoto, Peter J Snyder, Ronald S Swerdloff, Frederick C Wu, Maria A Yialamas, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

Treatment

Table 5. Clinical Pharmacology of T Formulations Approved in the United States and Europe

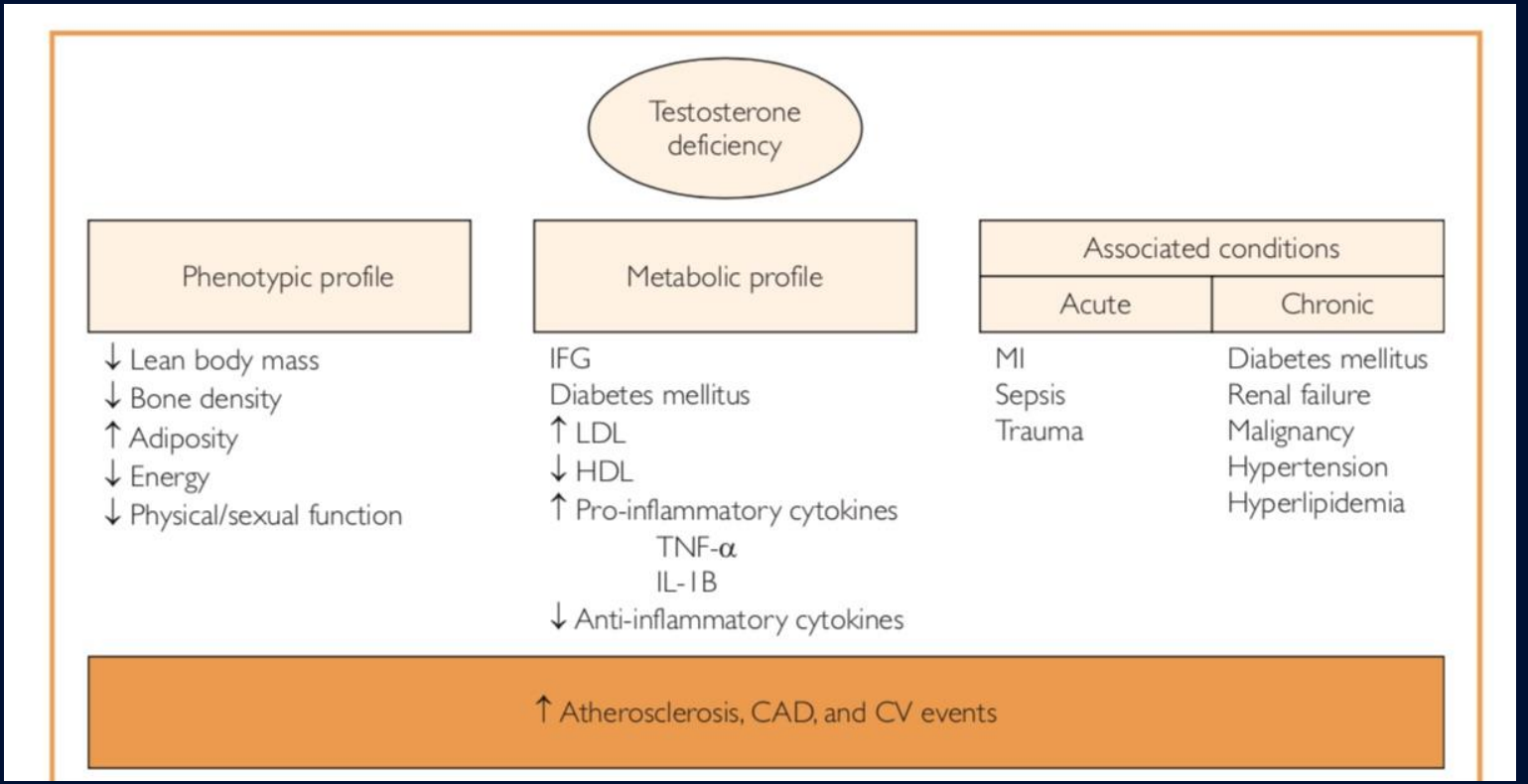
Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
T enanthate or cypionate	150–200 mg IM every 2 wk or 75–100 mg/wk	After a single IM injection, serum T concentrations rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval	Relatively inexpensive, if self-administered; flexibility of dosing	Requires IM injection; peaks and valleys in serum T concentrations that may be associated with fluctuations in symptoms
T transdermal gels: 1%, 1.62%, or 2%	50–100 mg of 1% transdermal gel; 20.25–81 mg of 1.62% gel or 40–70 mg of 2% transdermal gel applied to skin; check package insert for application site and instructions	With appropriate dose, restores serum T and E2 concentrations to the physiological male range; less fluctuation of T concentrations than T enanthate or cypionate	Provides flexibility of dosing, ease of application, good skin tolerability; less erythrocytosis than injectable T	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
T Axillary Solution	60 mg of T solution applied in the axillae	Restores serum T and E2 concentrations to the physiological male range	Provides, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
Transdermal T patch	One or two patches, designed to nominally deliver 2–4 mg of T during 24 h applied every day on nonpressure areas	Restores serum T, DHT, and E2 concentrations to the physiological male range	Ease of application	Serum T concentrations in some T-deficient men may be in the low-normal range; these men may need applications of two patches daily; skin irritation at the application site occurs frequently in many patients
Buccal, bioadhesive T tablets	30-mg controlled release, bioadhesive tablets twice daily	Restores serum T, DHT, and E2 concentrations to the physiological male range; absorbed from the buccal mucosa	Convenience and discreet	Gum-related adverse events in 16% of treated men
T pellets	Pellets containing 600–1200 mg T implanted SC; the number of pellets and the regimen may vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 mo, depending on formulation	Requires infrequent administration	Requires surgical incision for insertions; pellets may extrude spontaneously; rarely, local hematoma and infection may occur
Injectable long-acting T undecanoate in oil	United States regimen: 750 mg IM, followed by 750 mg at 4 wk, and 750 mg every 10 wk	When administered at a dose of 750 mg IM, serum T concentrations are maintained in the normal range in most treated men	Requires infrequent administration	Requires IM injection of a large volume (3 or 4 mL); coughing episode reported immediately after injection in a small number of men

(Continued)

Shalender Bhasin, Juan P Brito, Glenn R Cunningham, Frances J Hayes, Howard N Hodis, Alvin M Matsumoto, Peter J Snyder, Ronald S Swerdloff, Frederick C Wu, Maria A Yialamas, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-testosterone-capsule-treatment-men-certain-forms-hypogonadism

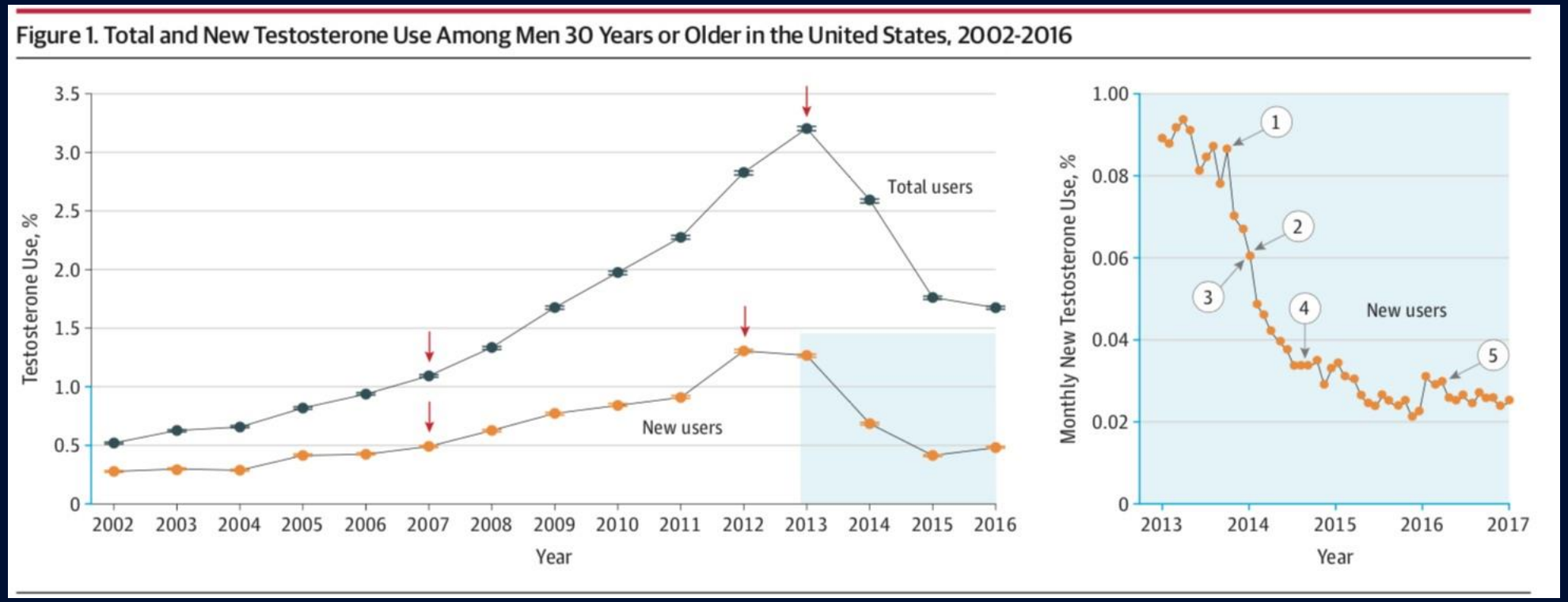
Hypogonadism and increased cardiovascular risk



Testosterone and Cardiovascular Health
Elagizi, Andrew et al.
Mayo Clinic Proceedings , Volume 93 , Issue 1 , 83 - 100

Testosterone Prescribing in the United States, 2002-2016

Baillargeon J, Kuo Y, Westra JR, Urban RJ, Goodwin JS. *JAMA.* 2018;320(2):200–202. doi:10.1001/jama.2018.7999



Adverse events associated with testosterone administration

Basaria S, Coviello AD, Travison TG, et al.
N Engl J Med. 2010;363(2):109–122. doi:10.1056/NEJMoa1000485

- Testosterone in Older Men with Mobility Limitations trial (TOM trial)
  - 209 men
  - mean age 74 years
  - with limitations in mobility and low total serum testosterone levels
    - (climb 10 steps or walking 2 blocks)
  - high prevalence of comorbidities, including hypertension, diabetes, congestive heart failure, and renal insufficiency.

Adverse events associated with testosterone administration

Basaria S, Coviello AD, Travison TG, et al.
N Engl J Med. 2010;363(2):109–122. doi:10.1056/NEJMoa1000485

- randomly assigned a placebo gel or testosterone gel, to be applied daily for 6 months
- 23 subjects in the T group vs. 5 in the placebo group had cardiovascular-related adverse events, including 1 death in the treatment group.
- halted because of these adverse effects.

Adverse events associated with testosterone administration

Basaria S, Coviello AD, Travison TG, et al.
N Engl J Med. 2010;363(2):109–122. doi:10.1056/NEJMoa1000485

- Goal of study improvement in physical function not cardiovascular disease
- Cardiovascular event not defined prior to study
  - Cardiovascular related events: peripheral edema, htn, tachycardia, non specific EKG changes

- Higher T doses – higher T levels

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

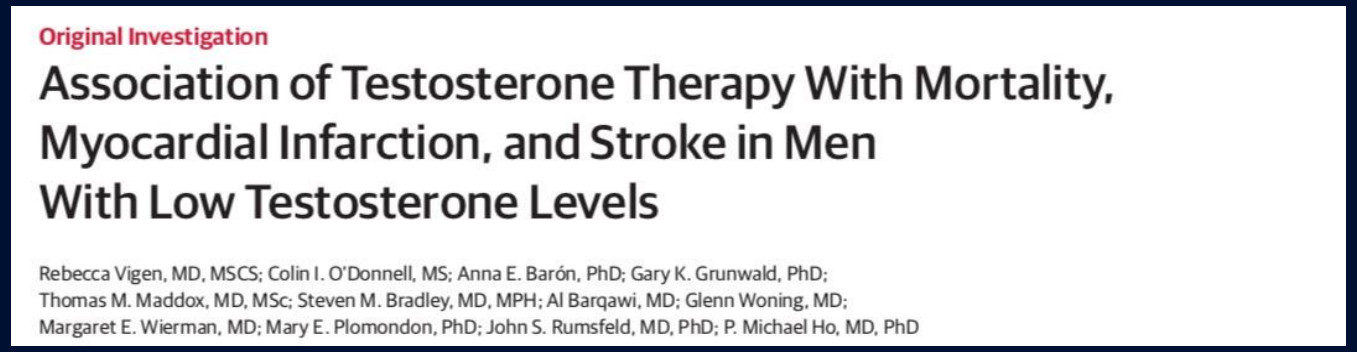
Nov 6, 2013

-Observational study 8709 men in VA who underwent cardiac angiography and had low T
-MI, stroke or death at 3 yrs. following angiography

- Men who subsequently received TTh 25.7%

- Untreated 19.9%

Vigen R, ODonnell CI, Barón AE, et al. Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels. *JAMA*. 2013;310(17):1829–1836. doi:10.1001/jama.2013.280386



Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

- Limitations:
- Observational - no chart review
  - Based on ICD9
- Unknown when T was measured
  - 40% T not measured.
  - The rest T levels only 332 ng/dl (adequately replaced??, compliance??)

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

Nov 6, 2013

-Observational study 8709 men in VA who underwent cardiac angiography and had low T
-MI, stroke or death at 3 yrs. following angiography

- Men who subsequently received TTh ~~25.7%~~ 10.1%

- Untreated ~~19.9%~~ 21.2%

Miscategorized ~1000 individuals (~10% women)

Vigen R, ODonnell CI, Barón AE, et al. Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels. *JAMA*. 2013;310(17):1829–1836. doi:10.1001/jama.2013.280386

Adverse events…

Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

William D. Finkle[1]*, Sander Greenland[2], Gregory K. Ridgeway[1], John L. Adams[1], Melissa A. Frasco[1], Michael B. Cook[3], Joseph F. Fraumeni Jr.[3], Robert N. Hoover[3]*

1 Consolidated Research, Inc., Los Angeles, California, United States of America, **2** Department of Epidemiology and Department of Statistics, University of California, Los Angeles, California, United States of America, **3** Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, United States of America

PLoS One. 2014 Jan 29;9(1):e85805. doi: 10.1371/journal.pone.0085805. eCollection 2014.

- Info obtained form healthcare database
- Information available: procedure codes, diagnosis codes and prescription data
- incidence rate of MI in the 90 days following the initial prescription vs. rate in the one year prior to the initial prescription (N=55,593)
- Same in a cohort of men prescribed phosphodiesterase type 5 inhibitors (PDE5I; sildenafil or tadalafil, N = 167,279)
- TT prescription post/pre rates vs.PDE5I post/pre rates

Adverse events…

Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

William D. Finkle[1]*, Sander Greenland[2], Gregory K. Ridgeway[1], John L. Adams[1], Melissa A. Frasco[1], Michael B. Cook[3], Joseph F. Fraumeni Jr.[3], Robert N. Hoover[3]*

1 Consolidated Research, Inc., Los Angeles, California, United States of America, 2 Department of Epidemiology and Department of Statistics, University of California, Los Angeles, California, United States of America, 3 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, United States of America

PLoS One. 2014 Jan 29;9(1):e85805. doi: 10.1371/journal.pone.0085805. eCollection 2014.

- No control group (12 mo. Prior not adequate control) - retrospective
- comparison made between men given T and men given PDE5i
- MI rates determined by dx codes
- no other clinical data such as pre or post treatment testosterone levels, BMI, smoking, BP
- Diagnostic indication for using T ???
- T exposure defined as receiving a Rx
  - unknown if filled, used it, or obtained and used refills

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-cautions-about-using-testosterone-products-low-testosterone-due

AACE/ACE Position Statement

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF TESTOSTERONE AND CARDIOVASCULAR RISK

Neil Goodman, MD, FACE[1]; Andre Guay, MD, FACE[2,]; Paresh Dandona, MD, PhD, FACE[3]; Sandeep Dhindsa, MD[4]; Charles Faiman, MD, MACE[5]; Glenn R. Cunningham, MD[6]; for the AACE Reproductive Endocrinology Scientific Committee*

MAYO CLINIC

DIAGNOSIS AND TREATMENT GUIDELINES

Consensus Recommendations

Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions

Abraham Morgentaler, MD (Chairman); Michael Zitzmann, MD (Cochairman);
Abdulmaged M. Traish, PhD (writing group);
Anthony W. Fox, MSc, MD (writing group); T. Hugh Jones, MD (writing group);
Mario Maggi, MD (writing group); Stefan Arver, MD; Antonio Aversa, MD;
Juliana C.N. Chan, MD; Adrian S. Dobs, MD; Geoffrey I. Hackett, MD;
Wayne J. Hellstrom, MD; Peter Lim, MD; Bruno Lunenfeld, MD;
George Mskhalaya, MD; Claude C. Schulman, MD; and Luiz O. Torres, MD

Morgentaler, Abraham et al.
Mayo Clinic Proceedings , Volume 91 , Issue 7 , 881 - 896

Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions

Morgentaler, Abraham et al.
Mayo Clinic Proceedings , Volume 91 , Issue 7 , 881 - 896

RESOLUTION 1. TD is a Well-established, Significant Medical Condition That Negatively Affects Male Sexuality, Reproduction, General Health, and Quality of Life

RESOLUTION 2. The Symptoms and Signs of TD Occur as a Result of Low Levels of T and may Benefit From Treatment Regardless of Whether There is an Identified Underlying Etiology

RESOLUTION 3. TD is a Global Public Health Concern

RESOLUTION 4. T Therapy for Men With TD is Effective, Rational, and Evidence Based

Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions

Morgentaler, Abraham et al.
Mayo Clinic Proceedings , Volume 91 , Issue 7 , 881 - 896

RESOLUTION 5. There is No T Concentration Threshold That Reliably Distinguishes Those Who Will Respond to Treatment From Those Who Will Not
RESOLUTION 6. There is No Scientific Basis for Any Age-specific Recommendations Against the Use of T Therapy in Men
RESOLUTION 7. The Evidence Does Not Support Increased Risks of CV Events With T Therapy
RESOLUTION 8. The Evidence Does Not Support Increased Risk of PCa With T Therapy
RESOLUTION 9. The Evidence Supports a Major Research Initiative to Explore Possible Benefits of T Therapy for Cardiometabolic Disease, Including Diabetes

Testosterone Trials

- 7 coordinated trials of testosterone treatment in elderly men
- First large, government funded, multicenter, placebo-controlled
- 790 men 65 yrs. or greater assigned to either t gel or placebo
  - (mean age 72)

Testosterone trials

1. Physical function trial
2. Sexual function trial
3. Vitality trial
4. Cognitive function trial
5. Anemia trial
6. Cardiovascular trial
7. Bone trial

Noncalcified coronary artery plaque
volume by computed tomographic angiography

Table 1. Characteristics of Men Enrolled in Testosterone Trials at Baseline

Characteristics	Treatment Group	
	Placebo	Testosterone
Participants, n	395	395
Demographic data		
Age, y	72.3 ± 5.8	72.1 ± 5.7
Race, n		
White	351 (88.9)	349 (88.4)
Black	20 (5.1)	21 (5.3)
Other (%)	24 (6.1)	25 (6.3)
Concomitant conditions		
BMI (kg/m^2)	31.0 ± 3.6	31.0 ± 3.5
BMI >30, n (%)	246 (62.3)	251 (63.5)
Alcohol use, drinks/wk	3.4 ± 5.0	3.0 ± 4.3
Smoking		
Current smoker, n	34 (8.6)	30 (7.6)
Ever smoker, n	268 (67.9)	256 (64.8)
Diabetes, n	144 (36.5)	148(37.5)
Hypertension, n	280 (70.9)	286 (72.4)
History of myocardial infarction, n	63 (16.0)	53 (13.4)
History of stroke, n	17 (4.3)	16 (4.1)
Sleep apnea, n	76 (19.2)	78 (19.8)

Snyder et al., 20818. Lessons From the Testosterone Trials, *Endocrine Reviews*, Volume 39, Issue 3, June 2018, Pages 369–386, https://doi.org/10.1210/er.2017-00234

Cardiovascular trial

Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone.

Budoff et al. JAMA 2017 Feb 21;317(7):708-716. doi: 10.1001/jama.2016.21043.

- ~ 170 subjects
- Primary outcome
  - noncalcified coronary artery plaque volume, as determined by coronary computed tomographic angiography.
- Secondary outcomes
  - total coronary artery plaque volume
  - coronary artery calcium score (range of 0 to >400 Agatston units, higher values = more severe atherosclerosis)

Cardiovascular trial

Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone.

Budoff et al. JAMA 2017 Feb 21;317(7):708-716. doi: 10.1001/jama.2016.21043.

- 73 testosterone vs. 65 placebo
- mean (SD) age was 71.2 (5.7) years
- 81% were white
- high rates of obesity, hypertension, hyperlipidemia, and diabetes
- relatively high 10-year risk of a cardiovascular event by the American College of Cardiology/American Heart Association risk calculator (ASCVD)
  - 24% [95% CI, 2.6%-45.4%] in the testosterone group vs. 27% [95% CI, 6.4%-47.6%] in the placebo group

Cardiovascular trial

Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone.

Budoff et al. JAMA 2017 Feb 21;317(7):708-716. doi: 10.1001/jama.2016.21043.

- prevalence of atherosclerosis
- high coronary artery calcification score (higher than 300 Agatston units)
- 70 men [50.7%] overall
  - 60.3% in the placebo group
  - 43.8% in the testosterone group

Cardiovascular trial

Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone.

Budoff et al. JAMA 2017 Feb 21;317(7):708-716. doi: 10.1001/jama.2016.21043.

- Primary outcome
- testosterone vs. placebo
- greater increase in noncalcified plaque volume from baseline to 12 months
    - median values of 204 mm3 to 232 mm3 vs 317 mm3 to 325 mm3 (estimated difference, 41 mm3; 95% CI, 14 to 67 mm3; P = .003)
    - (baseline 60 to 420 mm^3 vs. 168 to 589 mm^3)

Cardiovascular trial

Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone.

Budoff et al. JAMA 2017 Feb 21;317(7):708-716. doi: 10.1001/jama.2016.21043.

- Secondary outcomes:
- median total plaque volume increased in both from baseline to 12 months
  - Testosterone group: 272 mm3 to 318 mm3
  - Placebo group: 499 mm3 to 541 mm3
  - (estimated difference, 47 mm3; 95% CI, 13 to 80 mm3; P = .006)
- median coronary artery calcification score changed in both
  - Testosterone group: 255 to 244 Agatston units
  - Placebo group: 494 to 503 Agatston units
  - (estimated difference, -27 Agatston units; 95% CI, -80 to 26 Agatston units).
- No adverse cardiovascular events

Table 2. Adverse Events During 1 Year of Treatment in TTrials

Event	Treatment	
	Placebo	Testosterone
Participants, n	394	394
Prostate events, n		
PSA increase ≥1.0 ng/mL	8	23
Prostate cancer	0	1
IPSS >19	26	27
Hemoglobin ≥17.5 g/dL	0	7
CV events,[a] n		
MI (definite/probable)	1	2
Stroke (definite/probable)	5	5
CV death	1	0
Total (MI, stroke, CV death)	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other[b]	6	7

Snyder et al., 20818. Lessons From the Testosterone Trials, *Endocrine Reviews*, Volume 39, Issue 3, June 2018, Pages 369–386, https://doi.org/10.1210/er.2017-00234

Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM)

Basaria et al., JAMA 2015 Aug 11;314(6):570-81. doi: 10.1001/jama.2015.8881.

- placebo-controlled, double-blind, parallel-group randomized trial
- 308 men 60 years or older with low or low-normal testosterone levels (100-400 ng/dL; free testosterone <50 pg/mL)
- 156 received 7.5 g of 1% testosterone and 152 received placebo gel packets daily for 3 years
- dose was adjusted to achieve testosterone levels between 500 and 900 ng/dL
- Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium

Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM)

Basaria et al., JAMA 2015 Aug 11;314(6):570-81. doi: 10.1001/jama.2015.8881.

- Rate of change in intima-media thickness
  - Placebo group: 0.010 mm/year
  - Testosterone group: 0.012 mm/year
  - (mean difference adjusted for age and trial site, 0.0002 mm/year; 95% CI, -0.003 to 0.003, P = .89).
- Rate of change in the coronary artery calcium score
  - Placebo group: 41.4 Agatston units/year
  - Testosterone group: 31.4 Agatston units/year
  - (adjusted mean difference, -10.8 Agatston units/year; 95% CI, -45.7 to 24.2; P = .54).
- No CV events – designed to measure atherosclerosis

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Sharma et al., Eur Heart J. 2015 Oct 21;36(40):2706-15. doi: 10.1093/eurheartj/ehv346. Epub 2015 Aug 6.

- retrospectively examined 83,010 males > 50 yrs. with documented low T levels (from VA 1999-2014) without prior MI or stroke
  - Gp1: TRT with resulting normalization of T levels (43,931)
  - Gp2: TRT without normalization of TT levels (25,701)
  - Gp3: Did not receive TRT (13,378)
- Matched for age, BMI, various chronic diseases, LDL levels, medications
- F/u period: 4.6-6.2 yrs.

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Sharma et al., Eur Heart J. 2015 Oct 21;36(40):2706-15. doi: 10.1093/eurheartj/ehv346. Epub 2015 Aug 6.

- Results
- Gp1 vs Gp3 (lower)
  - all-cause mortality (HR:0.44, CI 0.42-0.46)
  - risk of MI (HR: 0.76, CI 0.63-0.93)
  - stroke (HR: 0.64, CI 0.43-0.96)
- Gp1 vs Gp2 (lower)
  - all-cause mortality (HR: 0.53, CI 0.50-0.55)
  - risk of MI (HR: 0.82, CI 0.71-0.95
  - stroke (HR: 0.70, CI 0.51-0.96)
- no difference in MI or stroke risk between Gp2 and Gp3.

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Sharma et al., Eur Heart J. 2015 Oct 21;36(40):2706-15. doi: 10.1093/eurheartj/ehv346. Epub 2015 Aug 6.

- Limitations
- Observational
- ?? When T measured
- ?? Indication for T
- Who received T Rx :
  - ?? Healthier subjects
- Why lower levels in Gp2?
  - Compliance??
  - Better medical care??
- At least T levels post TTh available=adherence

Cardiovascular Risks of Exogenous Testosterone Use Among Men: A Systematic Review and Meta-Analysis

Alexanderet al., Am J Med. 2017 Mar;130(3):293-305. doi: 10.1016/j.amjmed.2016.09.017. Epub 2016 Oct 14.

- Meta-analysis was done using data from 30 RCTs.
- randomized controlled trials (RCTs) that enrolled men aged 18 years or older receiving exogenous testosterone for 3 or more days
- Primary outcomes:
  - death due to all causes, myocardial infarction, and stroke
- Compared with placebo, exogenous testosterone treatment did not show any significant increase in risk of myocardial infarction (odds ratio [OR] 0.87; 95% CI, 0.39-1.93; 16 RCTs), stroke (OR 2.17; 95% CI, 0.63-7.54; 9 RCTs), or mortality (OR 0.88; 95% CI, 0.55-1.41; 20 RCTs)

Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies

Corona et at., J Sex Med. 2018 Jun;15(6):820-838. doi: 10.1016/j.jsxm.2018.04.641

- whether T therapy represents a possible risk factor for CV morbidity and mortality
- 93 RCT
- TTh had no clear effect, either beneficial or detrimental, on the incidence of CV events
- an increased risk of CV diseases was observed in RCTs when T preparations were prescribed at dosages above those normally recommended, or when frail men were considered.

Testosterone and HF

- 25 % Pts T deficiency
- Lower T levels associated with HF progression and severity

Toma et al., Testosterone Supplementation in Heart Failure A Meta-Analysis, Circulation: Heart Failure. 2012 May 1;5:315–321

- Improved exercise function
- No safety concerns

Testosterone and HF

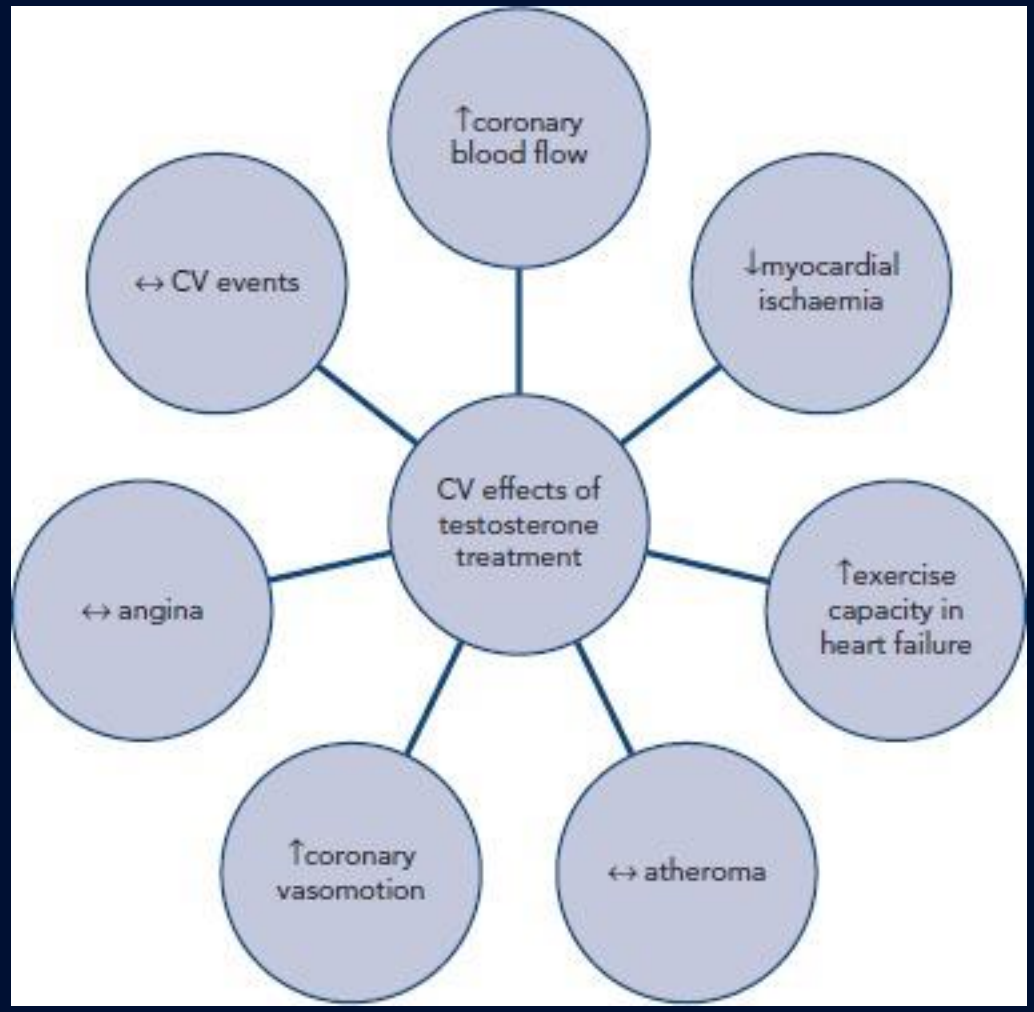
- Caminiti et al., **Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study**

  J Am Coll Cardiol. 2009 Sep 1;54(10):919-27.

  - 70 patients median age 70
  - NYHA class II or III HF clinically stable
  - Randomly assigned IM T undecanoate or saline for 6 wks.
  - improved exercise capacity, muscle strength and baroreflex sensitivity.

Testosterone and HF

- No studies found that reported improvement in left ventricular EF after T therapy in patients with HF
- Improvement in functional/exercise may be related to peripheral mechanisms



M Webb C, Collins P. Role of Testosterone in the Treatment of Cardiovascular Disease. *Eur Cardiol*. 2017;12(2):83–87. doi:10.15420/ecr.2017:21:1

Conclusions

- No study to provide evidence to support concern that T therapy increases cv risk

Conclusions

- Endocrine Society Guidelines:
- There have been no RCTs that were large enough or long enough to determine the effects of T-replacement therapy on major adverse cardiovascular events (MACE). Additionally, there is no conclusive evidence that T supplementation is associated with increased cardiovascular risk in hypogonadal men.
- There are no adequately powered RCTs on the effects of T replacement on MACE.

Conclusions

- Ideal Study
- Large prospective
- Randomized, placebo-controlled, double-blinded
- Long term (1yr-more)
- Symptomatic hypogonadism dx made according to current guidelines
- Two types of T preparation (IM, Topical)
- Monitor T levels throughout study
- Primary endpoint: MI, stroke, CV death

Conclusions

- Ideal Study
- Secondary end: hospitalizations for ACS and/or HF
- Heart rate, BP, ECG
- Prostate abnormalities
- Questionnaires on sexual health(ED-libido)
- Tests of muscle strength, mass, adiposity
- T effects on lipids, glucose, psa, insulin resistance
- $$$

AACE position statement on the association of testosterone and CV risk

- The decision to replace testosterone therapy should be guided by the signs/symptoms and testosterone concentrations rather than the underlying cause.
- These men should be told that we do not have definitive studies demonstrating risk for treating men with these conditions
- Health care professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy.

Acknowledgements

- Cynthia Alvarez, RPT, MBA

References

- Baillargeon J, Kuo Y, Westra JR, Urban RJ, Goodwin JS. Testosterone Prescribing in the United States, 2002-2016. *JAMA.* 2018;320(2):200–202. doi:10.1001/jama.2018.7999
- Corona, Giovanni et al. Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies. The Journal of Sexual Medicine , Volume 15 , Issue 6 , 820 – 838
- Elagizi, Andrew et al., Testosterone and Cardiovascular Health Mayo Clinic Proceedings , Volume 93 , Issue 1 , 83 – 100
- Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9(1):e85805. Published 2014 Jan 29. doi:10.1371/journal.pone.0085805
- Neil Goodman, Andre Guay, Paresh Dandona, Sandeep Dhindsa, Charles Faiman, Glenn R. Cunningham, and for the AACE Reproductive Endocrinology Scientific Committee. **AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF TESTOSTERONE AND CARDIOVASCULAR RISK** Endocrine Practice 2015 21:9, 1066-1073
- Abraham Morgentaler & Bruno Lunenfeld (2014) Testosterone and cardiovascular risk: world's experts take unprecedented action to correct misinformation, The Aging Male, 17:2, 63-65, DOI: 10.3109/13685538.2014.913413
- Snyder PJ, Ellenberg SS, Cunningham GR, et al. The Testosterone Trials: Seven coordinated trials of testosterone treatment in elderly men [published correction appears in Clin Trials. 2015 Jun;12(3):291]. *Clin Trials*. 2014;11(3):362–375. doi:10.1177/1740774514524032
- Peter J Snyder, Shalender Bhasin, Glenn R Cunningham, Alvin M Matsumoto, Alisa J Stephens-Shields, Jane A Cauley, Thomas M Gill, Elizabeth Barrett-Connor, Ronald S Swerdloff, Christina Wang, Kristine E Ensrud, Cora E Lewis, John T Farrar, David Cella, Raymond C Rosen, Marco Pahor, Jill P Crandall, Mark E Molitch, Susan M Resnick, Matthew Budoff, Emile R Mohler, Nanette K Wenger, Harvey Jay Cohen, Stanley Schrier, Tony M Keaveny, David Kopperdahl, David Lee, Denise Cifelli, Susan S Ellenberg, Lessons From the Testosterone Trials, *Endocrine Reviews*, Volume 39, Issue 3, June 2018, Pages 369–386, https://doi.org/10.1210/er.2017-00234
- Vigen R, ODonnell CI, Barón AE, et al. Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels. *JAMA.* 2013;310(17):1829–1836. doi:10.1001/jama.2013.280386

References

- Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109–122. doi:10.1056/NEJMoa1000485
- Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. *JAMA.* 2017;317(7):708–716. doi:10.1001/jama.2016.21043
- Caminiti et al., **Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study**J Am Coll Cardiol. 2009 Sep 1;54(10):919-27
- Morgentaler, Abraham et al. Fundamental Concepts Regarding Testosterone Deficiency and Treatment Mayo Clinic Proceedings , Volume 91 , Issue 7 , 881 – 896
- Shalender Bhasin, Juan P Brito, Glenn R Cunningham, Frances J Hayes, Howard N Hodis, Alvin M Matsumoto, Peter J Snyder, Ronald S Swerdloff, Frederick C Wu, Maria A Yialamas, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229
- **Toma et al., Testosterone Supplementation in Heart Failure** A Meta-Analysis, Circulation: Heart Failure. 2012 May 1;5:315–321
- Yeap BB, Dwivedi G, Chih HJ, et al. Androgens and Cardiovascular Disease in Men. 2019 Feb 2. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279151/
- Webb C, Collins P. Role of Testosterone in the Treatment of Cardiovascular Disease. *Eur Cardiol*. 2017;12(2):83–87. doi:10.15420/ecr.2017:21:1
- https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-testosterone-capsule-treatment-men-certain-forms-hypogonadism
- https://www.renalandurologynews.com/home/departments/mens-health-update/hypogonadism/new-oral-tx-approved-for-males-with-certain-types-of-hypogonadism/