"T Party" – Should We Protest the Use of Testosterone Therapy?

Tanner Moser, PharmD
PGY1 Pharmacy Resident
Seton Healthcare Family
September 9th, 2016

WELCOME TO HUMANCARE | Seton

Objectives

- Describe the epidemiology and proper diagnosis of hypogonadism in men
- Report current recommendations for testosterone replacement therapy (TRT)
- Assess the link between TRT and major adverse cardiovascular events (MACE)
- Provide recommendations on proper testosterone use in hypogonadal men

Patient Case

- DT is a 62 year old male presenting to his outpatient clinic
  - **CC**:
    - "I just don't have the energy or desire to do anything"
  - **PMH**:
    - Hypertension, hyperlipidemia, type 2 diabetes, obesity, depression, osteopenia, and recently diagnosed hypogonadism
  - **Medications**:
    - Lisinopril, hydrochlorothiazide, atorvastatin, metformin, and escitalopram

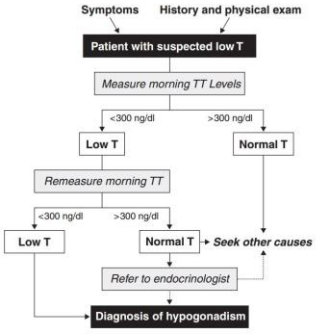
What else do you want to know?

Hypogonadism

- **The Endocrine Society**
  - Failure of the testes to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular (HPT) axis

Bhasin et al. *J Clin Endocrinol Metab.* 2010;95:2536-59.

Diagnosis



Dandona et al. *Int J Clin Pract.* 2010;64(6):682-696.

Treatment

- **Supplement testosterone**
  - TRT (e.g., intramuscular, transdermal, subcutaneous)
- **Contraindications**
  - **Absolute**: Prostate or breast cancer
  - **Relative**: Elevated hematocrit, severe untreated sleep apnea, unstable congestive heart failure, and severe lower urinary tract symptoms
- **Goal**
  - Replace to mid-normal testosterone levels
  - Monitor

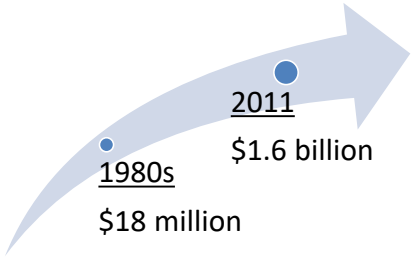
Epidemiology

- **Age**
  - Gradual decrease in testosterone after ~30 years of age
- **Prevalence**
  - 6 – 12% for men aged 40 – 60 years
- **Risk factors**
  - Acute
  - Chronic

WELCOME TO HUMANCARE | Seton

Oskui et al. *J Am Heart Assoc.* 2013;2(6):e000272.
Araujo et al. *J Clin Endocrinol Metab.* 2004;89:5920–5926.

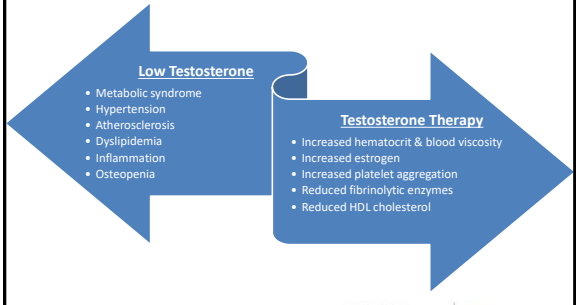
Testosterone Prescribing Pattern



WELCOME TO HUMANCARE | Seton

Handelsman et al. *Med J Aust.* 2013;199(8):S48-S51

Cardiovascular (CV) Risk



WELCOME TO HUMANCARE | Seton

Reshmi et al. *J Endocrinol Diabetes Obes.* 2014;2:1-5.
Traish et al. *Steroids.* 2014;88:106-116.

Controversy

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*

WELCOME TO HUMANCARE | Seton

Basaria et al. *J Gerontol A Biol Sci Med Sci*. 2013;68(2):153-160.
Goodman et al. *Endocr Pract*. 2015;21(9):1066-1073.

Literature Review

- **Objective**
  - Does the use of testosterone replacement therapy increase the risk of MACE in hypogonadal men?

Vigen 2013 → Sharma 2015 → Corona 2014

WELCOME TO HUMANCARE | Seton

Vigen R, O'Donnell C, Baron A, et al.

Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels.

JAMA 2013; 310:1829-36.

WELCOME TO HUMANCARE | Seton

Vigen et al. (2013)

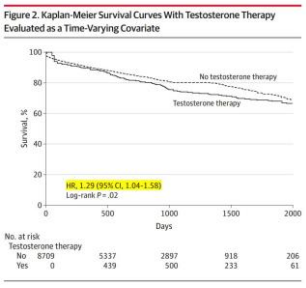
Objective	Assess the association between total testosterone (TT) and all-cause mortality, myocardial infarction (MI), or stroke
Design	Retrospective cohort study using Veterans Affairs (VA) database

Population	Male veterans with TT levels less than 300 ng/dL and a history of coronary angiography completed between 2005 – 2011
	• TRT:
	  • Mean age (yrs): 61
	  • Mean TT (ng/dL): 176
	• Untreated:
	  • Mean age (yrs): 64
	  • Mean TT (ng/dL): 207

Intervention (n = 8,709)	TRT (n = 1,223) vs. Untreated (n = 7,486) • Mean follow-up (months): 27.5

Absolute Outcomes

Intervention	Mortality	MI	Stroke	Composite
TRT (n = 1,223)	67 (5.5%)	23 (1.9%)	33 (2.7%)	10.1%
Untreated (n = 7,486)	681 (9.1%)	420 (5.6%)	486 (6.5%)	21.2%



Vigen et al. (2013) (cont.)

Strengths	+ Sensitivity analyses + VA database + High CV-risk population
Limitations	- Retrospective database review - Differing baseline characteristics - Patient prescription rates utilized for defining treatment - Fairly short treatment duration and follow-up - Repeat TT levels not always assessed - Data collection errors
Conclusions	-Shows that TRT may increase the risk of MACE in a high risk population of hypogonadal men

Sharma R, Oni OA, Gupta K, et al.

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

Eur Heart J 2015; 36:2706-15.

Sharma et al. (2015)

Objective	Examine the effect of TRT on cardiovascular outcomes by comparing the incidence of MI, stroke, and all-cause mortality among treated and untreated patients
Design	Retrospective cohort study utilizing the VA database
Population	Male veterans with TT levels lower than the respective laboratory reference range, collected from 1999 – 2014 • Excluded those with history of MI or ischemic stroke • Median age (yrs): 66
Intervention (n = 83,010)	1. TRT with a normalized TT (n = 43,931) 2. TRT without a normalized TT reached (n = 25,701) 3. Untreated (n = 13,378) • Mean follow-up (yrs): 5 • Mean TRT duration for normalized group (yrs): 3

Table 2 Unadjusted and adjusted hazard ratios for all-cause mortality, MI, and stroke

Model	All-cause mortality			Myocardial infarction			Stroke		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Comparing normalized treated vs. untreated (ref = untreated)									
Univariate N = 43 931 vs. 13 378	0.40	0.39–0.43	<0.001	0.70	0.59–0.83	<0.001	0.57	0.40–0.82	0.002
Propensity matched (stabilized inverse probability of treatment weights) N = 40 852 vs. 11 957	0.44	0.42–0.46	<0.001	0.76	0.63–0.93	0.005	0.64	0.43–0.96	0.031
Comparing normalized treated vs. non-normalized treated (ref = non-normalized treated)									
Univariate N = 43 931 vs. 25 701	0.49	0.47–0.51	<0.001	0.74	0.64–0.85	<0.001	0.64	0.48–0.87	0.004
Propensity matched (stabilized inverse probability of treatment weights) N = 40 852 vs. 23 953	0.53	0.50–0.55	<0.001	0.82	0.71–0.95	0.008	0.70	0.51–0.96	0.028
Comparing non-normalized treated vs. untreated (ref = untreated)									
Univariate N = 25 701 vs. 13 378	0.83	0.79–0.87	<0.001	0.95	0.79–1.15	0.599	0.90	0.61–1.34	0.610
Propensity matched (stabilized inverse probability of treatment weights) N = 23 953 vs. 11 957	0.84	0.80–0.89	<0.001	0.98	0.80–1.19	0.811	0.94	0.64–1.44	0.675

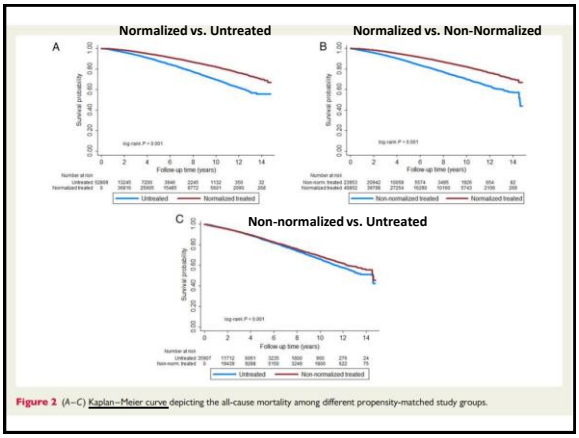


Figure 2 (A–C) Kaplan–Meier curve depicting the all-cause mortality among different propensity-matched study groups.

Sharma et al. (2015) (cont.)

Strengths	+ Large sample size and long follow-up period + Required repeat low TT measurements for inclusion + Institution specific cutoff values for low TT + VA database
Limitations	- Retrospective database review - Excluded patients with prior cardiovascular events - Patient prescription rates utilized for defining treatment - Relatively short mean duration of TRT - Normalized levels not defined
Conclusions	• MACE rates appear to be reduced when testosterone supplementation is used to completely normalize TT levels in a relatively low risk population

Corona G, Maseroli E, Rastrelli G, et al.

Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis.

Expert Opin Drug Saf 2014; 13:1327-51.

Corona et al. (2014)

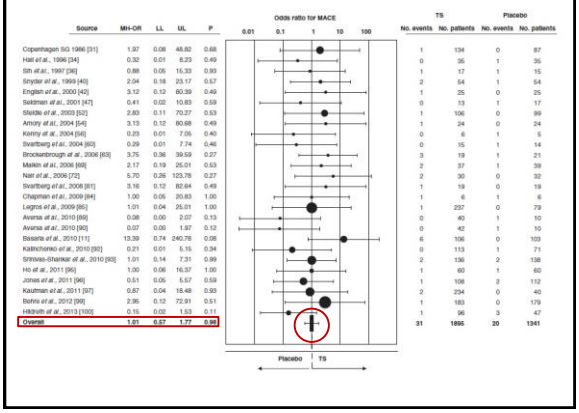
Objective	Determine the effect of testosterone supplementation, as compared to placebo, on the incidence of MACE (CV death, non-fatal MI, stroke, acute coronary syndromes, and heart failure)
Design	• Meta-analysis reviewing randomized controlled trials with CV events as primary or secondary outcomes between Jan. 1969 and Jan. 2014 • Searched Medline, Embase, and Cochrane using text and MeSH term "testosterone," and limited to Clinical Trials, Humans, and English • Utilized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Study Selection (n = 75)	• Inclusion:
	  • All RCTs enrolling men and comparing the effect of testosterone supplementation versus placebo on CV-related events
	• Exclusion:
	  • Simultaneous treatment with other hormones and drugs
	  • Studies not stating the occurrence or absence of CV-related events

Study Characteristics

- 6/75 studies included with CV events as a primary endpoint
- 31/75 studies included hypogonadal patients only
- 47/73 did not detect any MACE outcomes

Baseline Characteristics	
Total patients	3016 TRT, 2448 placebo
Mean trial duration (wks)	35
Mean age (yrs)	60
Mean baseline TT (ng/dL)	323
Mean BMI (kg/m^2)	28.1



Corona et al. (2014) (cont.)

Results	A causal role between testosterone supplementation and adverse CV events (composite or single events) is not supported
Strengths	+ Utilized controlled trials only + Largest number of studies combined to date + Tested for effect of drug company influence
Limitations	- Small number of trials with MACE as primary outcome - Short average trial duration - Unclear if all TT levels normalized - Many studies with no events eliminated from analysis - Quality of the included studies
Conclusions	• Short-term use of TRT is not associated with increased or decreased risk of MACE

Literature Summary

Vigen	• Increased risk of MACE with TRT in high risk hypogonadal men
Sharma	• Decreased risk of MACE with TRT in low risk hypogonadal men
Corona	• Neutral effect on MACE with TRT in a diverse patient population

 26

Recommendations

Diagnosis
- Symptoms of low testosterone with multiple levels drawn correctly

Treatment
- Assess risk factors for MACE
- Thoroughly counsel on potential benefits and risks of TRT
- Provide testosterone therapy for properly diagnosed hypogonadal men who are not at a high risk of MACE

Monitoring
- Obtain normalized testosterone levels
- Trial period lasting 3 months
- Watch for contraindications and adverse effects

 27

Patient Case

- DT is a 62 year old male presenting to his outpatient clinic
  - **CC**:
    - "I just don't have the energy or desire to do anything"
  - **PMH**:
    - Hypertension, hyperlipidemia, type 2 diabetes, obesity, depression, osteopenia, and recently diagnosed hypogonadism
  - **Medications**:
    - Lisinopril, hydrochlorothiazide, atorvastatin, metformin, and escitalopram

Patient Case (cont.)

- **Increased risk**
  - Age
  - Comorbidities
    - Obesity
    - Hypertension
    - Diabetes
    - Dyslipidemia
- **Decreased risk**
  - No history of major adverse cardiovascular events
  - No family history of clotting
  - No contraindications to TRT
  - Non-smoker
  - Reasonably controlled comorbidities

Would you recommend TRT?

References

1. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;95:2536-59.
2. Goodman N, Guay A, Dandona P, et al.; 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. *Endocr Pract.* 2015;21(9):1066-73.
3. Oskui PM, French WJ, Herring MJ, et al. Testosterone and the cardiovascular system: a comprehensive review of the clinical literature. *J Am Heart Assoc.* 2013;2(6):e000272.
4. Araujo AB, O'Donnell AB, Brambilla DJ, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab.* 2004;89:5920-26.
5. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *Int J Clin Pract.* 2010;64(6):682-96.
6. PL Detail-Document #311005, Comparison of Testosterone Products. *Pharmacist's Letter*. October 2015.
7. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: Expanding the spectrum of prescription drug misuse. *Med J Aust.* 2013;199(8):548-51.
8. Reshmi S, Faraday N, Dobs A, et al. Testosterone and Arterial Thrombosis. *J Endocrinol Diabetes Obes.* 2014;2:1-5.
9. Traish AM. Adverse health effects of testosterone deficiency (TD) in men. *Steroids.* 2014;88:106-16.
10. Basaria S, Davda MN, Travison TG, et al. Risk factors associated with cardiovascular events during testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci.* 2013;68(2):153-60.
11. Vigen R, O'Donnell CI, Baron AE, et al. Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels. *JAMA.* 2013;310(17):1829.
12. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J.* 2015;36(40):2706-15.
13. Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systemic review and meta-analysis. *Expert Opin Drug Saf* 2014;13:1327-51.
14. Tanna MS, Schwartzbard A, Berger JS, Underberg J, Gianos E, Weintraub HS. Management of Hypogonadism in Cardiovascular Patients. *Urol Clin North Am.* 2016;43(2):247-60.
15. Morgentaler A, Miner MM, Caliber M, et al. Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc.* 2015;90(2):224-51.
16. McBride JA, Carson CC, Coward RM. Testosterone deficiency in the aging male. *Ther Adv Urol.* 2016;8(1):47-60.

Acknowledgements

- **Evaluator**:
  - Dr. Lindsay Vasquez, PharmD, BCPS, BCACP, CDE
- **Preceptors**:
  - Dr. Evan Peterson, PharmD, BCPS
  - Dr. Neil Pan, PharmD, BCPS

WELCOME TO HUMANCARE | Seton

 31