# The Association between Testosterone Treatment and Incident Cardiovascular Events Among Testosterone Deficient U.S. Veterans

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# Disclosure

Consultant:
- Coloplast
- Biote

Advisory Board:
- Boston Scientific
- Progyny

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- National Institutes of Health (NIA); 1R01AG042934-01: "Adverse Events Associated with Testosterone Treatment in Hypogonadal Men"
- Boston Scientific
- Coloplast
- Endo

# 66 year old man with decreased libido, mild erectile dysfunction and decreased energy

# “I don’t have the strength that I used to”

Testosterone 289 ng/dl (normal 348-1197ng/dl)
Free Testosterone 5.9 ng/dl (normal 6.6-18.1)
LH and Prolactin are normal
PSA  1.2 ng/dl
Hematocrit  45%

# Would you treat him with testosterone?

Does testosterone treatment place this man at higher risk of cardiovascular disease?

# FDA Statement

- [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.

Testosterone therapy is appropriate treatment for patients with clinically significant hypogonadism, after full discussion of potential adverse effects

*Adapted from AUA Position Statement on Testosterone Therapy, 2015*

Evidence that testosterone treatment may provide BENEFIT to this man's health

Evidence that testosterone treatment MAY BE HARMFUL to this man's health

Evidence for the ABSENCE of risk that testosterone treatment is bad for this man's health

Evidence that testosterone treatment may provide BENEFIT to this man's health

# Benefits of testosterone treatment

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## Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg, for the Testosterone Trials Investigators*

*Snyder et al.* ***N Engl J Med 2016;374:611-24.***

# Benefits of testosterone treatment

Placebo-controlled, double-blind, parallel-group randomized trials of 5 g of 1% Testosterone vs Placebo gel for 1 year

Primary outcomes

1) Sexual function 2) Physical function 3) Vitality

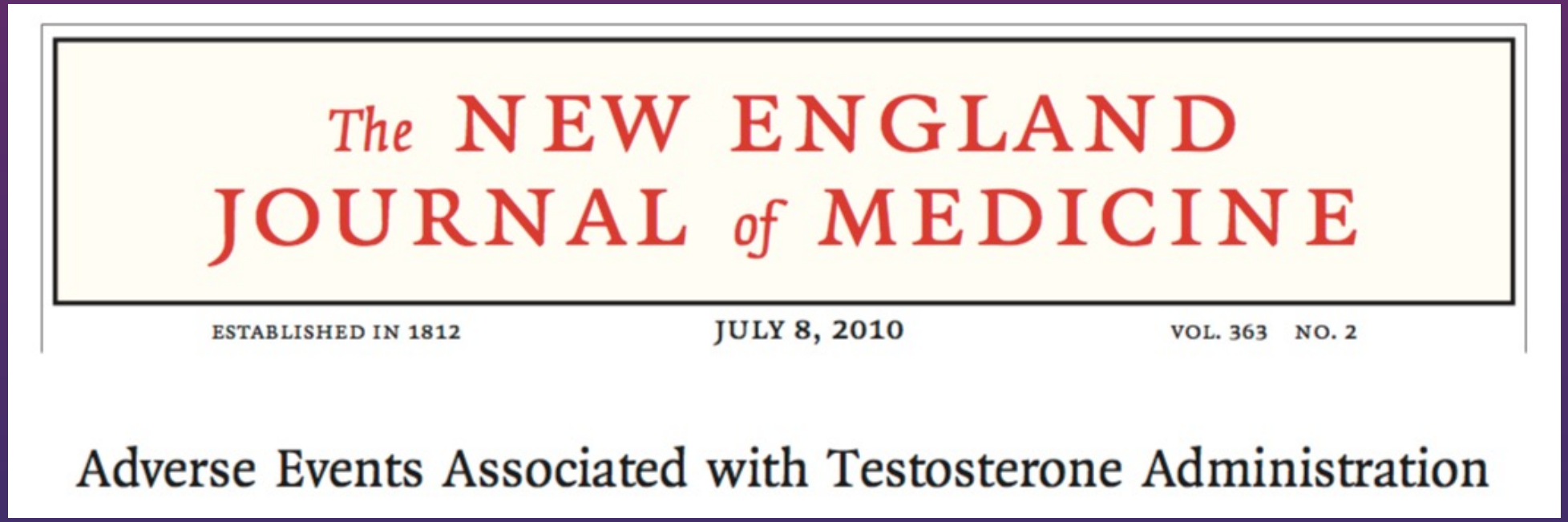
Findings:

- INCREASED SEXUAL ACTIVITY AND DESIRE
- IMPROVED ERECTILE FUNCTION
- IMPROVED PHYSICAL PERFORMANCE
- IMPROVED MOOD
- LOWER SEVERITY OF DEPRESSION

*Snyder et al. N Engl J Med 2016;374:611-24.*

Evidence that testosterone treatment MAY BE HARMFUL to this man's health

# Risk of testosterone treatment



The NEW ENGLAND JOURNAL of MEDICINE

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Adverse Events Associated with Testosterone Administration

- Efficacy NOT safety
- Adverse events were NOT adjudicated

*N Engl J Med.* ***2010*** *Jul 8;363(2):109-22*

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# Risk of testosterone treatment

## Vigan (2013)

"use of testosterone therapy was associated with increased risk of mortality, MI and stroke"

*JAMA, 2013; 310(17): 1829-1836*

## Finkle (2014)

"the risk of MI follow testosterone treatment is substantially increased"

*PloS ONE, 2014; 9(1): e85805*

## Layton (2015)

"testosterone injections were associated with greater risk of CV events, hospitalizations, and deaths compared to gels"

*JAMA Intern Med, 2015; 175(7): 1187-1196*

Evidence for the ABSENCE of risk that testosterone treatment is bad for this man's health

# Evidence for the absence of risk

Research

Original Investigation

## Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels

### A Randomized Clinical Trial

Shehzad Basaria, MBBS; S. Mitchell Harman, MD, PhD; Thomas G. Travison, PhD; Howard Hodis, MD; Panayiotis Tsitouras, MD; Matthew Budoff, MD; Karol M. Pencina, PhD; Joseph Vita, MD; Connie Dzekov, BS; Norman A. Mazer, MD, PhD; Andrea D. Coviello, MD, MS; Philip E. Knapp, MD; Kathleen Hally, BS; Emma Pinjic, MD, MPH; Mingzhu Yan, MD; Thomas W. Storer, PhD; Shalender Bhasin, MBBS

*Basaria et al. JAMA. 2015;314(6):570-581*

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

- Placebo-controlled, double-blind, parallel-group randomized trial
- Testosterone vs Placebo gel for 3 years
- Primary outcomes:
  1. Common carotid artery intimal thickness
  2. Coronary artery calcium
- Findings
  1. NO DIFFERENCE IN PRIMARY OUTCOMES
  2. NO DIFFERENCE IN ADVERSE EVENTS

*Basaria et al. JAMA. 2015;314(6):570-581*

# Similarly…

Research

JAMA Internal Medicine | Original Investigation

## Association of Testosterone Replacement With Cardiovascular Outcomes Among Men With Androgen Deficiency

T. Craig Cheetham, PharmD, MS; JaeJin An, BPharm, PhD; Steven J. Jacobsen, MD, PhD; Fang Niu, MS; Stephen Sidney, MD, MPH; Charles P. Quesenberry, PhD; Stephen K. VanDenEeden, PhD

*Cheetham et al, AMA Intern Med. 2017 Apr 1;177(4):491-499*

# More evidence for the absence of risk

- Retrospective cohort study, 40 years and older, T< 300 or coded dx
- 8808 men ever-treated compared to 35,527 never-treated
- Composite cardiovascular outcome
- Propensity scores to account for clinical differences

- ❖ Decreased risk of composite CV event in ever-TRT treated men
- ❖ Results were consistent across all subcategories of CV event

*Cheetham et al, JAMA Intern Med. 2017 Apr 1;177(4):491-499*

# Summary of T and CVD risk

There is evidence for the benefit of testosterone treatment in select men with hypogonadism

Evidence for the detrimental effects of testosterone is highly variable, and challenging to interpret

# The VA Testosterone Treatment Study

A Pharmacoepidemiologic study of Veterans with low serum testosterone aged 40 to 89 years from 2002 to 2012

T R*e*x Study

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# Hypothesis

Treatment with exogenous testosterone may increase the risk of incident cardiovascular events.

1. Composite major event:  myocardial infarction, stroke, thrombosis
2. Individual component events

# Setting for Observational Study

Excellent setting in which to respond to testosterone treatment safety questions:

1. Large population of men (~8M users in a year)
2. National electronic health record
3. National prescription dispensing data
4. testosterone treatment relatively common
5. Can easily include CMS data
6. Uniformity of health care access

# Study Cohort

Cohort of men with low serum testosterone

1. Men aged 40-89 years
2. Cohort entry at first lab measure of low endogenous T
3. Users of VA primary care: 2 or more outpatient visits in 12 months before cohort entry
4. Exclusion: histories of MI, VTE, stroke, prostate or breast cancer, PSA ≥4.0 ng/dL, T treatment prior to cohort entry, missing data: race, BMI, region

# Basic Study Design

# Outcomes

Primary:

Incident composite cardiovascular events

- ✓Myocardial infarction
- ✓Ischemic stroke
- ✓Deep venous thromboembolism

Secondary:

- ✓Incident individual outcomes

# Exposure-Outcome Models

- Time-varying testosterone exposure as current use, former use, no use.
- All subjects were non-users at the time of cohort entry
- Current use for prescription duration plus 20% overrun
- Testosterone use continuously updated during the study
- Analysis by testosterone formulation

# Bias: how to account for the differences between those who were and were not prescribed testosterone (confounding by indication)?

Possible remediation:

- Comparison of “current” to “former” users
- Characterization of baseline and emerging medical conditions (with continuous readjustment)

# Adjustment for medical conditions

Baseline

- Age
- Race
- Region
- Year of cohort entry
- BMI
- Hospitalization
- Medical comorbidity
- Prevalent CVD

Time-varying Emergence

- Hospitalization
- Medical comorbidity
- Prevalent CVD

# What is medical comorbidity?

- Chronic kidney disease
- Chronic lung disease
- Diabetes mellitus
- Erectile dysfunction
- Hospitalization in prior year
- Hyperlipidemia
- Hypertension
- Major depression
- Malignancy
- Morbid obesity
- Polycythemia
- Sleep apnea
- Smoking

# Additional analyses:  its all about the testosterone

- Sensitivity analysis:  vary the overrun from 0% to 40%
- Compare event rates for men with continuous T treatment:  3, 6 and 12 months
- Exploratory case-cross over investigation for composite outcomes: allow subjects to serve as their own controls

# Results

- 300,631 with low serum testosterone;  of 204,857 after the application of exclusions
- Mean age 60.9 (9.9) years
  - Hypertension 62%; Diabetes 33%, obesity 62%, prevalent CVD 40%
- Testosterone Treatment
  - 28% received only transdermal T
  - 40% received only intramuscular T
  - 22% received both formulations of T
  - Median cumulative treatment time of 4.8 months for transdermal and 11.1 months for intramuscular users.

# Baseline Characteristics of Men in the Analytic Cohort

| | No use (122,302) | Initiated TD (43,502) | Initiated IM (39,053) |
|---|---|---|---|
| Age, y, mean | 61.7 | 59.8 | 60.9 |
| BMI, mean | 31.5 | 32.6 | 32.8 |
| Race, n (%) | | | |
| White | 97,589 (79.8) | 35,548 (81.7) | 33,158 (84.9) |
| Black | 21,102 (17.3) | 6,722 (15.5) | 4,609 (11.8) |
| Other | 3,611 (3.0) | 1,232 (2.8) | 1,286 (3.3) |
| Prevalent CVD, n (%) | 50,292 (79.8) | 16,481 (37.9) | 14,441 (37.0) |
| Arrhythmia | 20,813 (17.0) | 6,309 (14.5) | 5,869 (15.0) |
| Cardiomyopathy | 3,681 (3.0) | 1,146 (2.6) | 814 (2.1) |
| CAD or angina | 32,055 (26.2) | 10,390 (23.9) | 8,914 (22.8) |
| Cerebrovascular disease or TIA | 4,690 (3.8) | 1,494 (3.4) | 1,137 (2.9) |
| CHF | 9,949 (8.1) | 2,978 (6.8) | 2,177 (5.6) |
| PVD | 11,626 (9.5) | 3,539 (8.1) | 2,885 (7.4) |
| MI | 3,904 (3.2) | 1,127 (2.6) | 900 (2.3) |
| Stroke, ischemic | 1,800 (1.5) | 490 (1.1) | 342 (0.9) |
| VTE (DVT or PE) | 1,175 (1.0) | 388 (0.9) | 248 (0.6) |
| No. of medical comorbidities, mean (sd) | 4.8 (3.6) | 4.7 (3.5) | 4.5 (3.4) |

# Baseline Characteristics of Men in the Analytic Cohort

| | No use (122,302) | Initiated TD (43,502) | Initiated IM (39,053) |
|---|---|---|---|
| Age, y, mean | 62 | 60 | 61 |
| BMI, mean | 32 | 33 | 33 |
| Race, % | | | |
| White | 80 | 82 | 85 |
| Black | 17 | 16 | 12 |
| Other | 3 | 3 | 3 |
| Prevalent CVD, % | 80 | 38 | 37 |
| Arrhythmia | 17 | 15 | 15 |
| Cardiomyopathy | 3 | 3 | 2 |
| CAD or angina | 26 | 24 | 23 |
| Cerebrovascular disease or TIA | 4 | 3 | 3 |
| CHF | 8 | 7 | 6 |
| PVD | 10 | 8 | 7 |
| MI | 3 | 3 | 2 |
| Stroke, ischemic | 2 | 1 | 1 |
| VTE (DVT or PE) | 1 | 1 | 1 |
| No. of medical comorbidities, mean | 5 | 5 | 5 |

# Serum Testosterone Levels

| | Testosterone treatment status | | |
|---|---|---|---|
| **Total Testosterone Level (ng/dL)** | No use (29,954) | Transdermal (5,953) | Intramuscular (7,337) |
| **Baseline, Mean (SD)** | 195 (105) | 165 (81) | 166 (71) |
| **Baseline, Median (IQR)** | 190 (145-230) | 165 (119-210) | 170 (125-210) |
| **Follow-up, Mean (SD)** | 276 (167) | 312 (212) | 455 (321) |
| **Follow-up, Median (IQR)** | 249 (182-330) | 260 (173-399) | 372 (215-620) |

# Composite Cardiovascular Risk by Treatment Type Among men WITHOUT prevalent cardiovascular disease

| **Transdermal treatment** | | | | |
|---|---|---|---|---|
| Treatment | PY/1000 | Events | IR | HR (95%CI) |
| Former | 71.5 | 688 | 9.62 | 1.0 (ref) |
| Current | 20.7 | 180 | 8.68 | 0.89 (0.76-1.05) |
| No use | 332.2 | 3424 | 10.31 | 1.02 (0.94-1.11) |
| **Intramuscular treatment** | | | | |
| Former | 71.5 | 688 | 9.62 | 1.0 (ref) |
| Current | 20.7 | 180 | 8.68 | 0.89 (0.76-1.05) |
| No use | 332.2 | 3424 | 10.31 | 1.02 (0.94-1.11) |

PY: person-years
IR: unadjusted incidence rate
HR: adjusted hazard ratio
CI: confidence interval

# Composite Cardiovascular Risk by Treatment Type Among men WITH prevalent cardiovascular disease

| **Transdermal treatment** | | | | |
|---|---|---|---|---|
| Treatment | PY/1000 | Events | IR | HR (95%CI) |
| Former | 68.3 | 1415 | 20.73 | 1.0 (ref) |
| Current | 16.1 | 254 | 15.74 | 0.80 (0.70-0.91)* |
| No use | 299.0 | 6684 | 22.35 | 1.03 (0.97-1.09) |
| **Intramuscular treatment** | | | | |
| Former | 58.7 | 1250 | 21.29 | 1.0 (ref) |
| Current | 31.1 | 596 | 19.16 | 0.98 (0.89-1.09) |
| No use | 293.6 | 6507 | 22.16 | 0.96 (0.90-1.02) |

PY: person-years
IR: unadjusted incidence rate
HR: adjusted hazard ratio
CI: confidence interval
*p<0.05

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# Interpretation

The use of testosterone does NOT appear to increase risk of composite cardiovascular events (MI, stroke, & DVT)

- Consistent for individual outcomes
- Consistent regardless of prevalent cardiovascular disease
- Consistent across treatment modality

# Limitations

- Generalizability:  the population of study US male veterans with a high degree of medical comorbidity
- Clinical indications for testosterone treatment were not known
- Cardiovascular outcomes and medical comorbidities were assessed by diagnostic codes, procedural codes, pharmacy, and laboratory data and not by chart review
- Observational study design
- Residual confounding

# TRAVERSE Study – what's the answer?

- Three- year, multicenter, randomized, double-blind, placebo-controlled, noninferiority trial
- Specific intent to determine the cardiovascular safety of testosterone replacement.
  - 5,246 men aged 45 to 80 years
  - Symptoms of hypogonadism
  - T < 300 ng/dl
  - Treated to achieve serum T 350 to 750 ng/dl
- First occurance: MI, stroke, coronary artery revascularization

Lincoff, et al. NEJM, 2023, 389(2): 107-117

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# Cardiovascular Safety of Testosterone-Replacement Therapy

A.M. Lincoff, S. Bhasin, P. Flevaris, L.M. Mitchell, S. Basaria, W.E. Boden, G.R. Cunningham, C.B. Granger, M. Khera, I.M. Thompson, Jr., Q. Wang, K. Wolski, D. Davey, V. Kalahasti, N. Khan, M.G. Miller, M.C. Snabes, A. Chan, E. Dubcenco, X. Li, T. Yi, B. Huang, K.M. Pencina, T.G. Travison, and S.E. Nissen, for the TRAVERSE Study Investigators*

"In men with hypogonadism and preexisting cardiovascular disease, TRT was noninferior to placebo with respect to the incidence of major cardiac events"

Lincoff, et al. NEJM, 2023, 389(2): 107-117

66 year old man with decreased libido, mild erectile dysfunction and decreased energy

Would you treat him with testosterone?

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# Questions

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