ISSWSH/ISSM Atlanta

Testosterone Controversies: Lessons Learned from TRAVERSE 2025

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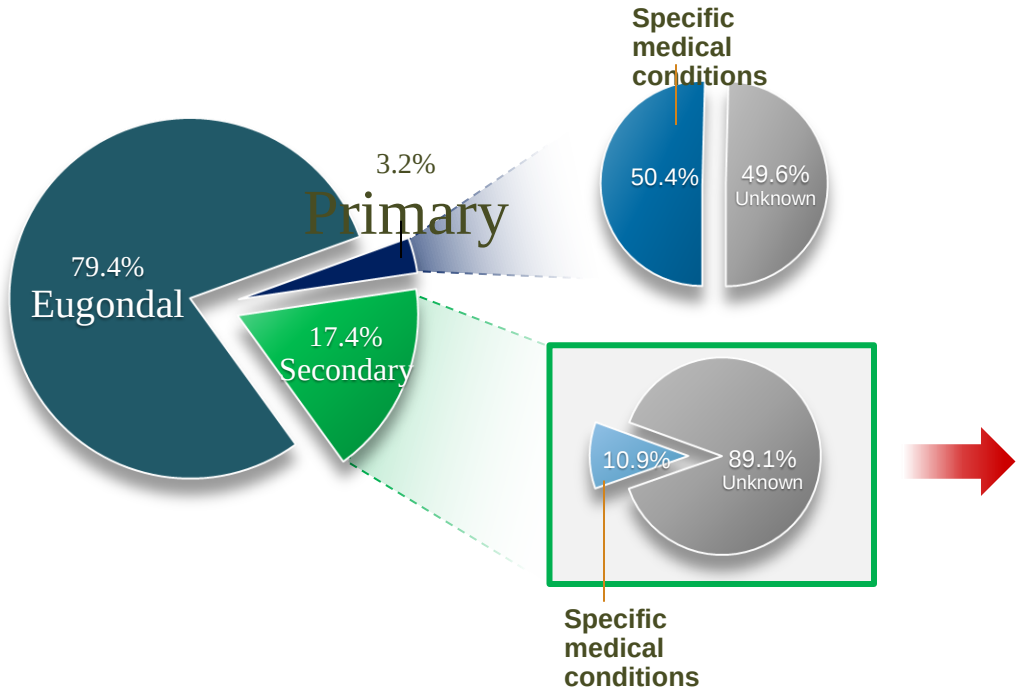
Disclosures

- Halozyme Pharmaceuticals – advisor
- Tolmar- ADT Guideline Management to Reduce CV Risk Author
- AUA Guidelines: ED, Peyronies; Testosterone; Screening for PCa

Objectives

- Discuss the present indications for testosterone therapy and actual real-life experience. Specific Medical Conditions. Treatment for Co-Morbid T Def is "off-label"
- Discuss the most current data on cardiometabolic risk and testosterone: TRAVERSE CVS STUDY
- Briefly summarize the findings of TRAVERSE Depression; Sexual Function; and Fracture Studies
- Present the current understanding of the relationship between testosterone and prostate cancer: TRAVERSE PROSTATE Safety Study

Prevalence of Hypogonadism



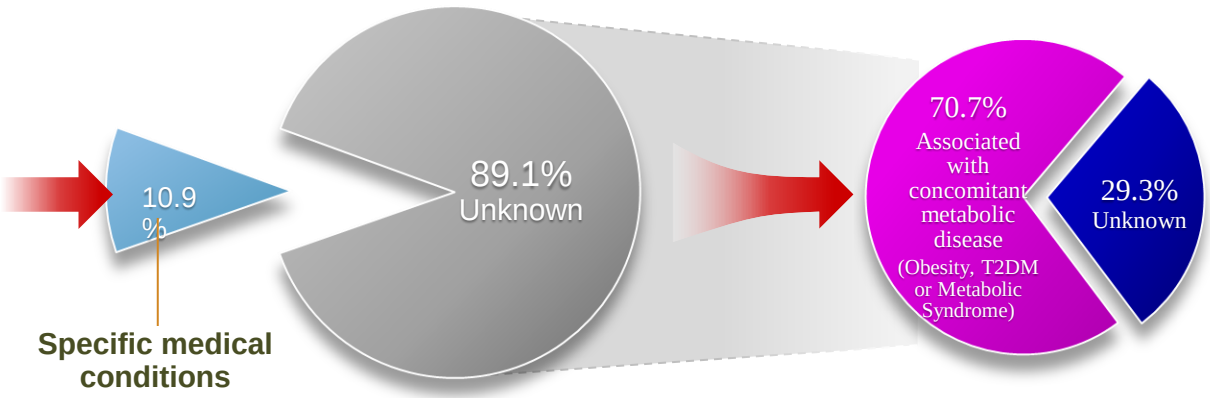
Corona et al *J Sex Med* 2015; 12 1690-1693)

Maseroli E, Corona G, Rastrelli G, Lotti F, Cipriani S, Forti G, Mannucci E, Maggi M. Prevalence of endocrine and metabolic disorders in subjects with erectile dysfunction: A comparative study. J Sex Med 2015;12:956–65.

Indications for Treatment: FDA

- The FDA cautions that prescribing T products is approved only for men who have low T levels caused by specific medical conditions
- Only subjects with primary or secondary HG resulting from problems within the testis, pituitary, or hypothalamus (e.g. genetic problems, or damage from surgery, chemotherapy, or infection) should be treated.

Specific Medical Conditions Associated with Secondary Hypogonadism



Of the 89% of men without a known cause of TD, 71% will have one of 3 conditions: diabetes; obesity or metabolic syndrome

Thus, the majority of patients we treat for TD are "off-label"

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

T Def: A barometer of overall poor health: ?Reversible with lifestyle changes

- The diagnosis of functional (age-related) hypogonadism should prompt thorough assessment & optimization of general health including:

Lifestyle changes

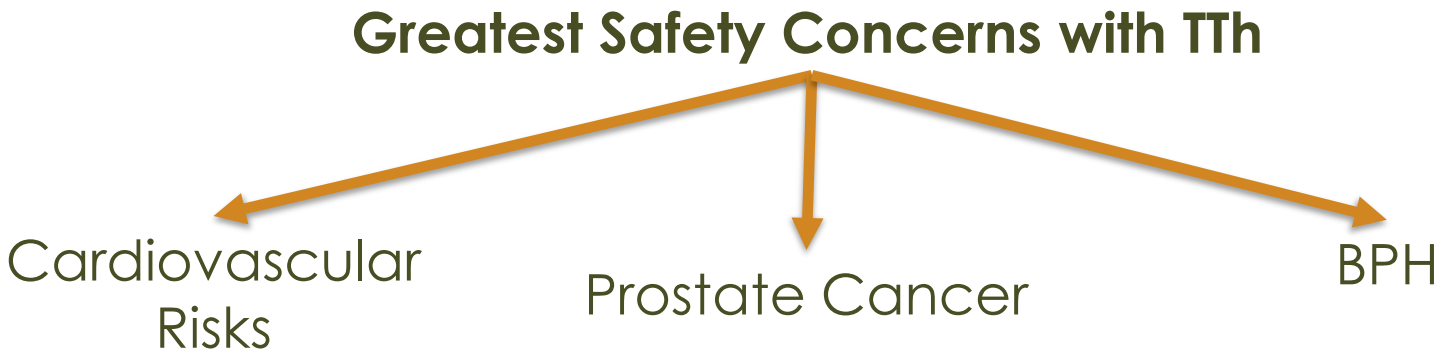
- Weight reduction
- Enhanced care of comorbidities
- T Treatment improves libido, may be less effective for erectile dysfunction (ED)
- TTh may have modest positive effects on insulin resistance, bone strength, some measures of physical strength and mild depressive symptoms

→ TTh should be offered to men with "age-related" hypogonadism with sx & sy

Ageing male (Part 2): Management of functional hypogonadism in older men, a patient-centric holistic approach Frederick C.W. Wu]*DOI: https://doi.org/10.1016/j.beem.2022*

Risks of Testosterone Therapy?

Adverse effects may accompany <u>any</u> treatment



<u>Other Common Risks of TTh:</u>

- Male infertility / testicular atrophy
- Erythrocytosis
- Gynecomastia
- Others…DVT/PE?

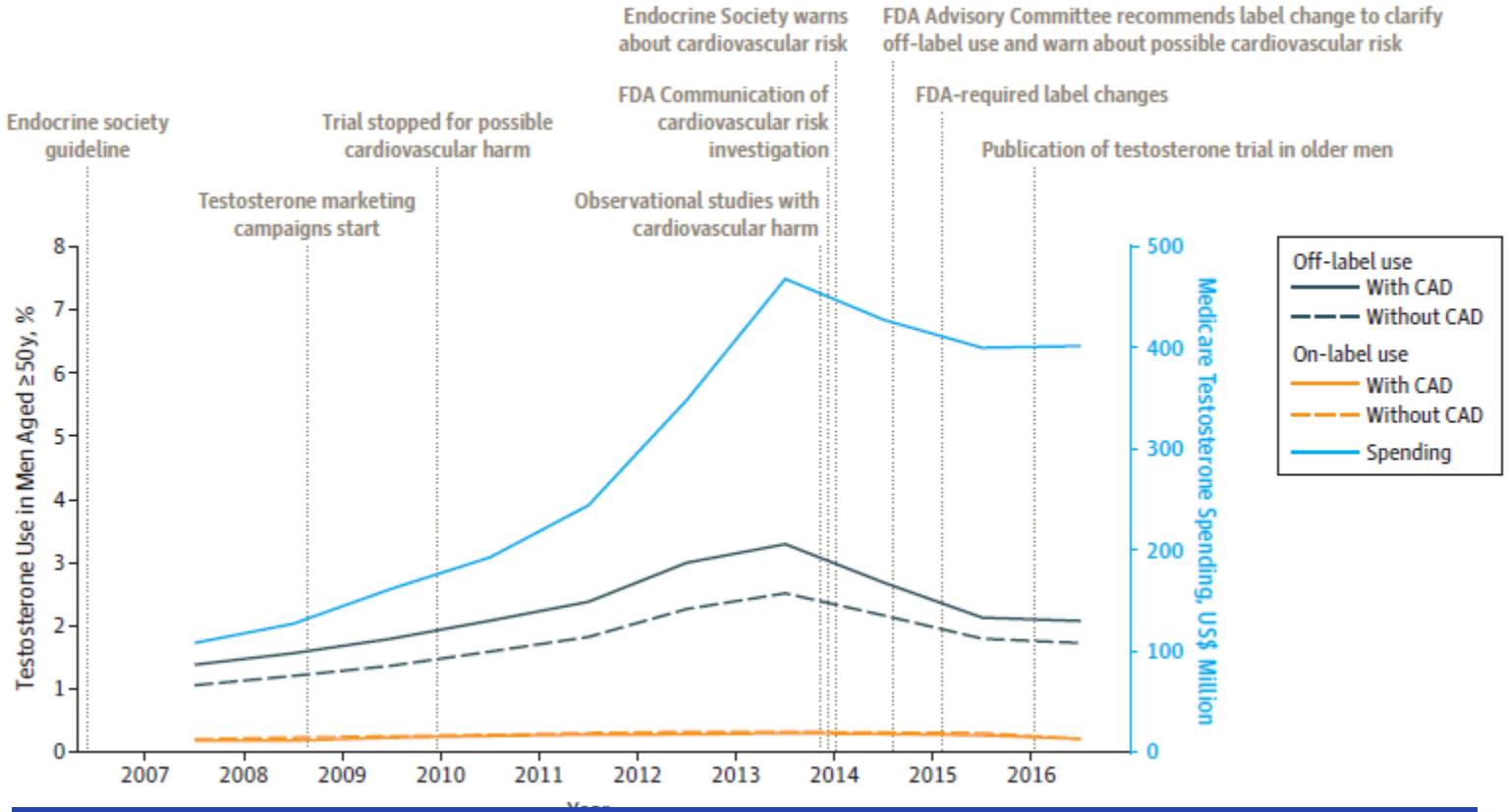
Cardiometabolic Risk and TTh

https://www.diagnoptics.com/cardiovascular-risk/

Understanding the History Testosterone Th

- In late 1980s, rarely used and almost not at all in urology
- Reserved for men with unequivocal or severe testosterone deficiencies
  - Absent testes
  - Pituitary/hypothalamic tumors or resection
  - Genetic abnormalities, eg, Klinefelter syndrome
- Not recognized as useful in otherwise healthy men with sexual or other symptoms
- Until the FDA approval of topical gel: Androgel 1% in 2001 broadened its use.

Off-Label Prescription Testosterone Use and Medicare Testosterone Expenditure



2012: TTh fastest growing med in US: Sales growth 33%/yr

Morden et al JAMA Internal Medicine March 2019 ;179(3)

T Sales grow unparalleled until:

Nov 2013
JAMA

Vigen

Research

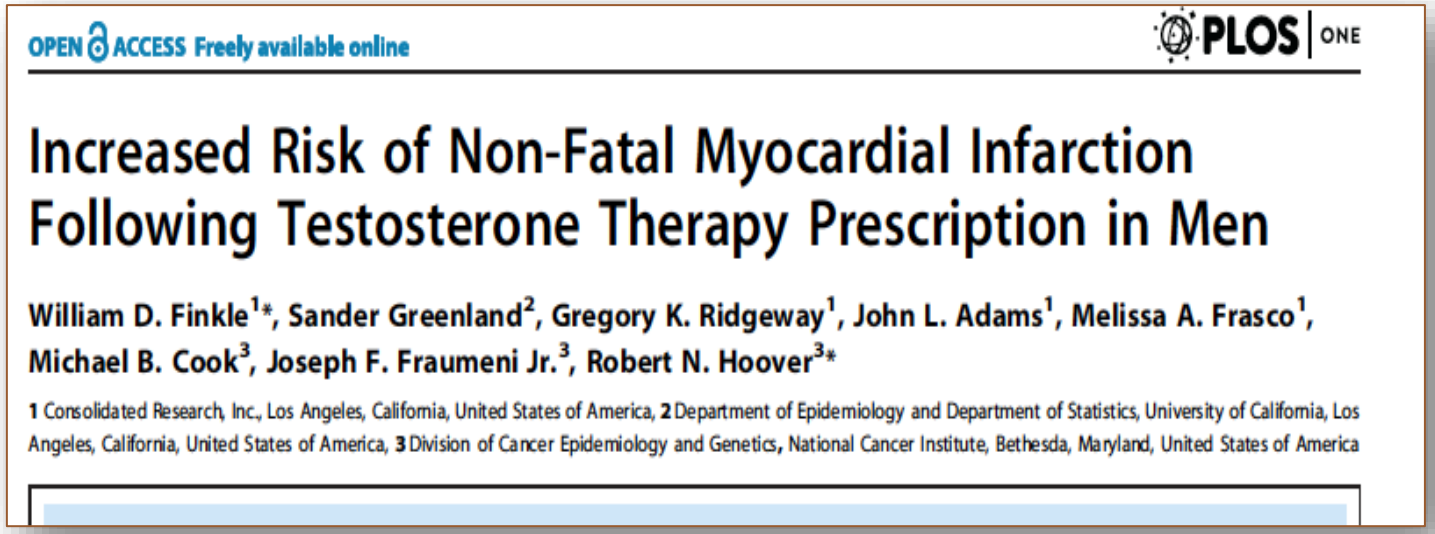
Original Investigation

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

Jan 2014
PLUS One

Finkle



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PLOS ONE

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

No Strong Evidence that TTh Increases CV Risk

Basaria et al. *NEJM* 2010

- RPCT – frail elderly men
- 15 g of testosterone
- CVD NOT an endpoint
- Greater CV risk in treatment arm
- 5 vs. 2 major CV events
- ***No difference*** if exclude CHF

Vigen et al.

- No randomization / placebo
- Exclusion of 1132 men
- ***RETRACTION***

2013

events in 27 RC studies of >12 weeks

- Just 2 studies → 30% of events in treatment arm

studies, CV events in T and placebo are ***identical***

- 90 days after start of TTh
  - ***Pre-rx MI rate → 3.48/1000***
  - ***Post-rx MI rate → 4.75/1000***

Finkle et al. *PLoS One* 2014

- No randomization / placebo
- No control group / clinical data
- Health insurance database

Evidence supporting a relationship between TTh and increased CV risk is INCONCLUSIVE

Basaria S et al. *N Engl J Med*. 2010; 363: 109.
Vigen R et al. *JAMA*. 2013; 310: 1829.
Finkle WD et al. *PLoS One*. 2014; e85805.
Xu L et al. *BMC Med*. 2013; 11: 108.

Cardiovascular Risk Since the FDA Labeling Change 2015

2015 FDA Advis

- "…available s lar safety signal with testostero quality, design, and size. Nor ***diovascular risk*** emerged fro epidemiologic studies."

----------WARNINGS AND PRECAUTIONS----------

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid unintentional exposure of women or children to Testim. Secondary exposure to testosterone can produce signs of virilization. Testim should be discontinued until the cause of virilization is identified. (5.2)
- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE. (5.4)
- Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.5)
- Exogenous administration of androgens may lead to azoospermia. (5.7)
- Edema, with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease. (5.9, 6.2)
- Sleep apnea may occur in those with risk factors. (5.11)
- Monitor prostate specific antigen (PSA), hematocrit, and lipid concentrations periodically. (5.1, 5.3, 5.12)
- Testim is flammable until dry. (5.15)

Goodman N. et al. *Endocrine Practice*. 2015; 21: 1066.

The TRAVERSE Trial

- TRAVERSE is a response to the FDA directive in 2015
- "We are also requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question
of whether an increased risk of heart attack or stroke exists among users of these products"

Effects of long-term testosterone treatment on cardiovascular outcomes in men with hypogonadism: Rationale and design of the TRAVERSE study

Shalender Bhasin, MBBS[a,†], A. Michael Lincoff, MD[b,†], Shehzad Basaria, MD[a], Douglas C. Bauer, MD[c], William E. Boden, MD[d], Glenn R. Cunningham, MD[e], Deborah Davey, RN[b], Elena Dubcenco, MD, MS[f], Sandra Fukumoto, MBA[f], Michelle Garcia, RN, BSN[b], Christopher B. Granger, MD[g], Vidyasagar Kalahasti, MD, FACC[b], Mohit Khera, MD, MBA, MPH[c], Michael G. Miller, PharmD[f], Lisa M. Mitchell, RN, BSN[b], Michael P. O'Leary, MD, MPH[h], Karol M. Pencina, PhD[a], Peter J. Snyder, MD[i], Ian M. Thompson Jr., MD[j], Thomas G. Travison, PhD[k], Kathy Wolski, MPH[b], and Steven E. Nissen, MD[b], for the TRAVERSE Study Investigators[a] *Boston, MA; Cleveland, OH; Francisco, CA; Houston, TX; and Chicago, IL, San Antonio, TX, Philadelphia, PA*

- Randomized, double-blinded, placebo-controlled trial multicenter study
- Men 45-80 years of age
- CV disease or increased risk of CV disease
- T <300ng/dl and hypogonadal symptoms
- 6000 patients randomized to either testosterone gel or placebo
- Up to 5 years follow-up

Bhasin et al Am Heart J. 2022 Mar;245:41-50

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

- Cardiovascular safety of long-term testosterone therapy in hypogonadal men with existing CV disease or risk factors was recently reported June 2023
- Based on results of a prospective, placebo-controlled trial of testosterone gel versus placebo in 5,246 men aged 45-80 years, **testosterone is not associated with increased overall cardiovascular risk,** despite, a higher incidence of pulmonary embolism (0.9% vs 0.5%), acute kidney injury (2.3% vs 1.5%), and atrial fibrillation (3.5% vs 2.4%) in the testosterone group.

CV Eligibility Criteria: 3 or more Risk factors

Pre-existing cardiovascular disease	
Coronary artery disease	• Acute myocardial infarction >4 mo prior to screening • Coronary artery disease (at least a 50% lesion in two of the major coronary artery distributions including their branches) as documented by angiogram • Coronary revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]) >4 mo prior to screening
Cerebrovascular disease	• Stroke excluding hemorrhagic >4 mo prior to screening • Transient ischemic attack that required treatment >4 mo prior to screening • Catheter-based or surgical revascularization of the carotid or middle cerebral arteries >4 mo prior to screening • Extracranial carotid artery stenosis >50%, excluding intracranial vessels
Peripheral arterial disease	• Symptomatic peripheral arterial disease (ie, lower extremity arterial disease documented by ankle/brachial index <0.9 with claudication or resting limb ischemia obtained in the prior 12 mo) • Peripheral arterial revascularization or amputation due to arterial obstructive disease >4 mo prior to screening • Peripheral arterial stenosis >50% • Abdominal aortic aneurysm not due to connective tissue disorders
Cardiovascular risk factors	
Hypertension	• Hypertensive and taking prescription anti-hypertensive medication OR • Systolic blood pressure (SBP) >140 or diastolic blood pressure (DBP) >90 mmHg during Screening Period
Dyslipidemia	• Dyslipidemic and taking prescription anti-dyslipidemic medication OR • Low-density lipoprotein cholesterol (LDL-C) >160 mg/dL or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL during Screening Period
Current smoker	• Current daily cigarette/cigar smoker (e-cigarette smoking alone does not satisfy this criterion)
Stage 3 chronic kidney disease	• Estimated Glomerular Filtration Rate (eGFR) >30 and <60 mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation during Screening Period
Elevated hsCRP	• History of high-sensitivity C-reactive protein (hsCRP) ≥2.0 mg/L (≥0.2 mg/dL) and confirmed at screening visit
Diabetes	• Diabetic and currently taking prescription anti-diabetic medication OR • Hemoglobin A1c (HbA1c) ≥6.5% or fasting glucose of ≥126 mg/dL during Screening Period
Agatston coronary calcium score	• Agatston Coronary Calcium Score >75th percentile for age and race (a link is provided for calculation of the 75th percentile calcium score)
≥65 yrs of age	

Bhasin et al Am Heart J. 2022 Mar;245:41-50

TRAVERSE Trial Design

Study Drug Management

Randomized double blind, 1:1 ratio
Stratified by pre-existing CV Disease vs CV Risk Factors

Testosterone 1.62% gel

Placebo gel

Patients and trial team blinded to post-baseline testosterone levels measured at central lab*
(*drawn at weeks 2, 4, 12, 26 and months 12, 18, 24, 36, 48)

Dose titrations by automated algorithm to maintain testosterone levels 350-750ng/dL and Hct ≤54%

Sham titrations in placebo arm to facilitate blinding

Primary Endpoints

- Time from randomization to first occurrence of any component of the MACE composite of nonfatal myocardial infarction, nonfatal stroke, or death due to CV causes
  - Trial continued until at least 256 adjudicated major adverse CV event endpoints have occurred to assess whether the 95% (2-sided) upper confidence limit for a hazard ratio of 1.5 can be ruled out

Secondary Endpoints

- Cardiovascular safety: incidence of MACE or cardiac revascularization procedures/ cardiac percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)
- Prostate safety: incidence of high-grade prostate cancer, defined as a pathologically confirmed prostate cancer with Gleason score 4 + 3 or higher

Secondary Endpoints

Efficacy domain	Condition/Study population	Efficacy endpoint
Sexual function	Randomized participants with low libido	Change from baseline in overall sexual activity per PDQ Question 4
Low grade, PDD (Dysthymia)	Randomized participants with late-onset, low grade, PDD (dysthymia)	Proportion of men whose PDD remits during intervention per remission definition
Fracture	All randomized participants	Proportion of men with adjudicated clinical bone fractures
Diabetes	Randomized participants with pre-diabetes at baseline	Proportion of men, who had pre-diabetes at baseline, and who progress to diabetes; and the proportion of men who had diabetes at baseline who undergo glycemic remission
Anemia	Randomized participants with unexplained anemia	Proportion of anemic men whose anemia is corrected during the intervention period

PDD, persistent depressive disorder; *PDQ*, psychosexual daily questionnaire.

Sexual Activity & Remission of Depression

Bhasin et al Am Heart J. 2022 Mar;245:41-50

Tertiary Endpoints

- CV safety: include all-cause mortality; hospitalization or urgent visit for heart failure; venous thromboembolic events (including DVT, PE and venous thromboembolism); or peripheral arterial revascularization
- Prostate safety: include prostate biopsy; any prostate cancer; acute urinary retention; starting pharmacologic treatment for LUTS; and invasive prostate surgical procedures (ie, prostatectomy, TURP, brachytherapy or other prostate surgical procedure for BPH)

Patients Completing the Trial:

5204 Patients Randomized (with no duplicates) 2601 Testosterone		2603 Placebo
5 not treated		1 not treated
2596 Testosterone treated	Safety Set	2602 Placebo Treated
1593 (61.4%) d/c'd study drug		1605 (61.7%) d/c'd study drug
1003 completed study drug		997 completed study placebo
21.8 +/- 14.2 mo	Duration Rx	21.6 +/- 14.0 mo
67.5%	% time treated	67.3%
1007 (38.8%) withdrew from study		1023 (39.3%) withdrew from study
1594 completed study		1580 completed study
33.1 +/- 12.0 mo	Duration F/U	32.9 +/- 12.1 mo
82.7%	% possible F/U	81.7%

Baseline Characteristics:

Characteristic	Testosterone Group (N = 2601)	Placebo Group (N = 2603)
Mean Age - years	63.3 ± 7.9	63.3 ± 7.9
45 - <65 years	1360 (52.3)	1392 (53.5)
Age ≥65 years	1241 (47.7)	1211 (46.5)
Race – no. (%)		
White	2070 (79.6)	2084 (80.1)
Black or African American	445 (17.1)	432 (16.6)
Unspecified or other	86 (3.3)	87 (3.3)
Ethnicity of Hispanic or Latino – no. (%)	409 (15.7)	439 (16.9)
Body-mass index, kg/m^2	35.0 ± 5.7	34.8 ± 6.0
Testosterone – ng/dL	220.5 ±- 47.0	220.2 ± 48.2
Prior testosterone use – no. (%)	5 (0.2)	10 (0.4)
Prostate specific antigen – ng/mL	0.91 ± 0.65	0.94 ± 0.68
Hematocrit – %	42 ± 4	42 ± 4

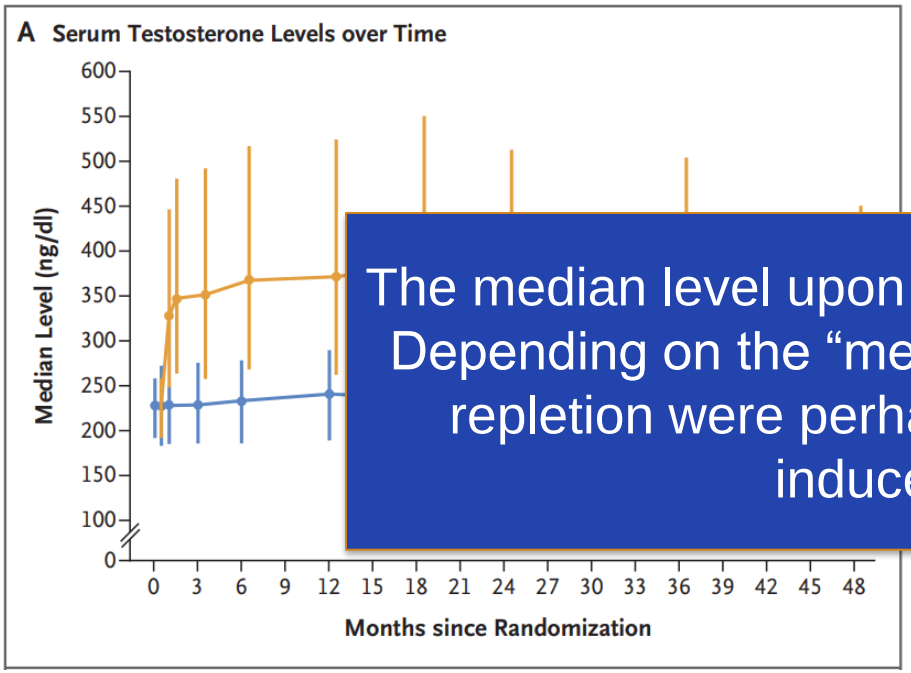
Cardiovascular Disease and Risk Factors

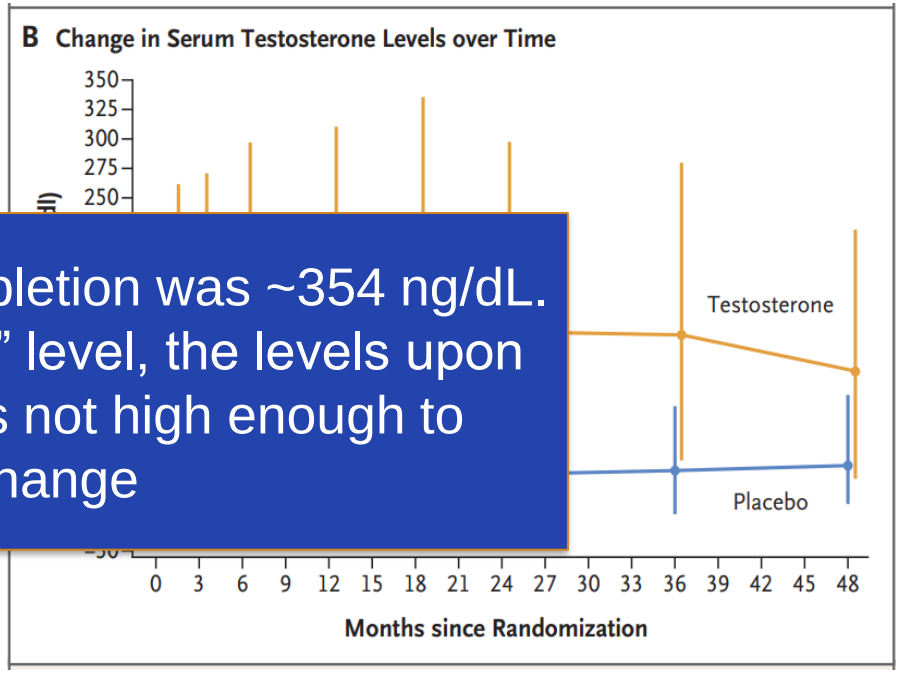
Characteristic	Testosterone Group (N = 2601)	Placebo Group (N = 2603)
Cardiovascular risk category – no. (%)		
Pre-existing cardiovascular disease	1410 (54.2)	1437 (55.2)
Increased cardiovascular risk	1191 (45.8)	1166 (44.8)
Coronary artery disease – no. (%)	1158 (44.5)	1160 (44.6)
Cerebrovascular disease – no. (%)	304 (11.7)	318 (12.2)
Peripheral vascular disease – no. (%)	158 (6.1)	153 (5.9)
Diabetes, type 1 or type 2	1788 (68.7)	1844 (70.8)
Hypertension	2423 (93.2)	2402 (92.3)
Dyslipidemia	2344 (90.1)	2332 (89.6)
hs-CRP ≥ 2 mg/dL	61.8%	61.0%

Baseline Medication and Lipids

	Testosterone Group (N = 2601)	Placebo Group (N = 2603)
Medications		
Aspirin - % of pts	60.4	59.5
Lipid lowering therapy - % of pts	84.0	83.7
Lipids		
LDL cholesterol – mg/dL	80.2 +- 34.0	79.3+-33.9
HDL cholesterol – mg/dL	41.9 +- 11.2	41.7 +- 10.9
Median triglycerides (IQR) - mg/dL	154.6 [108.1, 227.6]	157.7 [112.5, 226.7]

Testosterone Levels





The median level upon repletion was ~354 ng/dL. Depending on the "mean" level, the levels upon repletion were perhaps not high enough to induce change

Average daily dose: 65 +/- 22mg

Change at 12 months:
Testosterone – 148 ng/dL [34, 312]
Placebo – 14 ng/dL [-21, 56]

Primary and Secondary CV Safety Endpoints

Outcome	Testosterone Group (N=2601)	Placebo Group (N=2603)	Hazard Ratio (95% CI)
	number of patients (percent)		
Primary safety endpoint (MACE)*	182 (7.00)	190 (7.30)	0.96 (0.78, 1.17)
Secondary CV safety endpoint	269 (10.34)	264 (10.14)	1.02 (0.86, 1.21)
Components of composite endpoints			
Death due to cardiovascular causes	87 (3.34)	103 (3.96)	0.84 (0.63, 1.12)
Nonfatal myocardial infarction	68 (2.61)	62 (2.38)	1.10 (0.78, 1.56)
Nonfatal stroke	36 (1.38)	38 (1.46)	0.94 (0.60, 1.49)
Coronary revascularization	144 (5.54)	121 (4.65)	1.20 (0.95, 1.53)

1° CV Composite (MACE) = CV death, non-fatal MI, non-fatal stroke
2° CV Composite = CV death, non-fatal MI, non-fatal stroke, coronary revascularization

*P-value for noninferiority <0.001 (rejection of inferiority of testosterone vs placebo)

Tertiary CV Safety Endpoints

Outcome	Testosterone Group (N=2601)	Placebo Group (N=2603)	Hazard Ratio (95% CI)
	Percent of patients		
All-cause mortality	5.5	5.7	0.98 (0.78-1.23)
Heart failure hospitalization	2.1	1.9	1.11 (0.76-1.62)
Peripheral arterial revascularization	1.2	1.3	0.92 (0.56-1.51)
Venous thromboembolic events (VTE)	1.7	1.2	1.46 (0.92-2.32)
Components of VTE			
Pulmonary embolism	0.9	0.5	
DVT	0.6	0.5	
Other peripheral thrombosis	0.4	0.5	

Investigator Reported Adverse Events

Event	Testosterone Group (N=2596)	Placebo Group (N=2602)	P Value†
	number of patients (percent)		
Any adverse event	1187 (45.7)	1164 (44.7)	0.47
Serious adverse event	721 (27.8)	697 (26.8)	0.42
Adverse event leading to discontinuation of testosterone or placebo	244 (9.4)	226 (8.7)	0.37
Prespecified adverse events of special interest	196 (7.6)	167 (6.4)	0.11
Hospitalization for unstable angina	44 (1.7)	60 (2.3)	0.12
Nonfatal arrhythmia warranting intervention	134 (5.2)	87 (3.3)	0.001
Cardiovascular disease causing syncope	27 (1.0)	32 (1.2)	0.52
Transient ischemic attack	15 (0.6)	17 (0.7)	0.73
Other adverse events			
Diabetes mellitus	189 (7.3)	213 (8.2)	0.22
~~Coronavirus disease 2019~~	~~121 (4.7)~~	~~117 (4.5)~~	~~0.78~~
Atrial fibrillation	91 (3.5)	63 (2.4)	0.02
Pneumonia	64 (2.5)	56 (2.2)	0.45
Acute kidney injury	60 (2.3)	40 (1.5)	0.04
~~Benign prostatic hyperplasia~~	~~45 (1.7)~~	~~46 (1.8)~~	~~0.92~~
Acute respiratory failure	52 (2.0)	37 (1.4)	0.11
Urinary retention	50 (1.9)	34 (1.3)	0.08
Cellulitis	35 (1.3)	46 (1.8)	0.22
Congestive cardiac failure	34 (1.3)	41 (1.6)	0.42

* The safety population consisted of all patients who had undergone randomization and received at least one dose of testosterone or placebo. Events are classified according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 25.0.

† P values were calculated with the use of a chi-square test.

Limitations of TRAVERSE:

- Adherence and retention in this trial was lower than in most cardiovascular outcomes, but similar to other trials in symptomatic condition
- "Cardiovascular safety findings are limited to that population, not to men who do not have indications for testosterone therapy but who nevertheless may receive it through "low T centers" or other unscrupulous prescribers."
- "This study should not be used as a justification for the widespread prescription of testosterone to aging men"

---Steven Nissen, MD, Chief Academic Officer of Cleveland Clinic's Heart, Vascular & Thoracic Institute

Conclusion

- TRAVERSE is the largest randomized placebo-controlled trial in hypogonadal men to date
- Among middle-aged or older men with hypogonadism, who had a history of established CV disease or who were at high risk for incident CV events, TRT for a mean duration of 22 months did not increase the risk of major CV events

Effect of Testosterone Replacement Therapy on Sexual Function and Hypogonadal Symptoms in Men with Hypogonadism

Karol M. Pencina,[1,*] Thomas G. Travison,[2,*] Glenn R. Cunningham,[3] A. Michael Lincoff,[4] Steven E. Nissen,[4] Mohit Khera,[3] Michael G. Miller,[5] Panagiotis Flevaris,[5] Xue Li,[5] Kathleen Wannemuehler,[6] and Shalender Bhasin[1]

- 1161 hypogonadal men with low libido enrolled in the Sexual Function Study
  - 587 1.62% testosterone gel
  - 574 placebo gel
- Primary outcome: change from baseline in sexual activity (PDQ-4)
- Secondary outcomes: hypogonadal symptoms, EF, and sexual desire (HIS-Q, IIEF-EF, Patient Global Impression of Improvement in Libido question)

Results:

- TTh associated with significantly greater improvement in sexual activity than placebo
- TTh improved hypogonadal symptoms and sexual desire, but not erectile function, compared with placebo
- Treatment effect was maintained at 24 months

Pencina et al. JCEM, epub August 2023

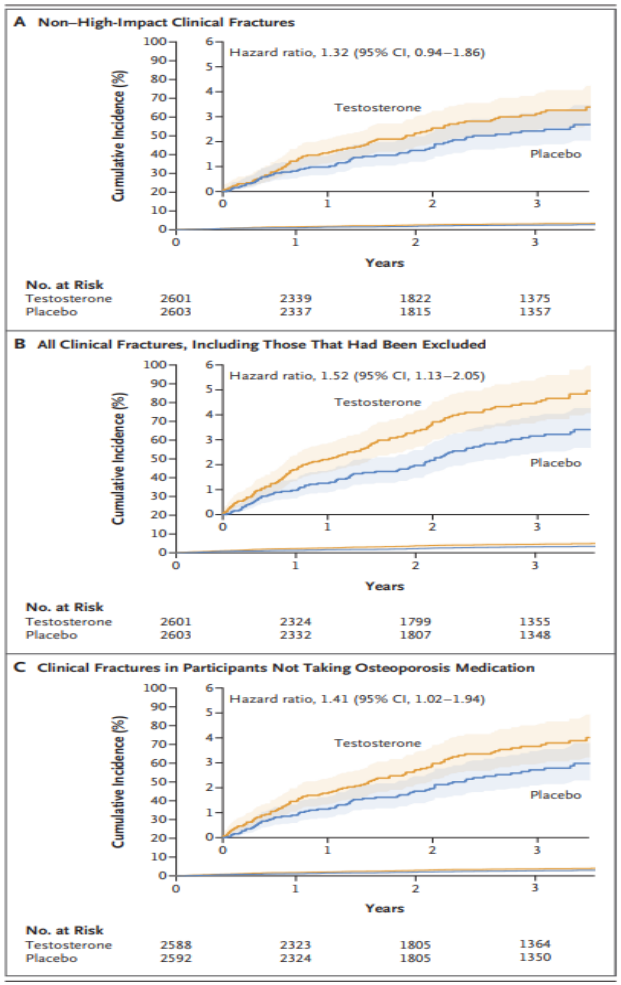
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 18, 2024 VOL. 390 NO. 3

Testosterone Treatment and Fractures in Men with Hypogonadism

Peter J. Snyder, M.D., Douglas C. Bauer, M.D., Susan S. Ellenberg, Ph.D., Jane A. Cauley, Dr.P.H., Kevin A. Buhr, Ph.D., Shalender Bhasin, M.B., B.S., Michael G. Miller, Pharm.D., Nader S. Khan, M.D., Xue Li, Ph.D., and Steven E. Nissen, M.D.

- Objective: To determine whether testosterone treatment would reduce the risk of clinical fractures in hypogonadal men
- 5204 participants (2601 in TTh group and 2603 in placebo group)
- Median follow-up of 3.19 years
- Clinical fracture occurred in 91 participants (3.50%) in the testosterone group and 64 participants (2.46%) in the placebo group (hazard ratio, 1.43; 95% CI, 1.04 to 1.97)



Reasons:

1. Increased activity due to being on testosterone
2. Fractures seemed to occur early on before T could have had any benefit
3. Only a modest increase in T and E, 148, which may not have been enough

Snyder et al N Engl J Med. 2024 Jan 18;390(3):203-211

Depressive Syndromes in Men With Hypogonadism in the TRAVERSE Trial: Response to Testosterone-Replacement Therapy

Shalender Bhasin,[1] Stuart Seidman,[2] Thomas G. Travison,[3] Karol M. Pencina,[1] A. Michael Lincoff,[4] Steven E. Nissen,[4] Michael G. Miller,[5] Panagiotis Flevaris,[5] Xue Li,[5] Kathleen A. Wannemuehler,[6] and Harrison G. Pope[7,8]

- Of 5204 randomly assigned participants
- 3 subgroups:
  - All randomly assigned men
  - All men with significant depressive symptoms (Patient Health Questionnaire-9 Score >4)
  - Men with rigorously defined, late on-set, low-grade persistent depressive disorder [LG-PDD] previously "dysthymia"
- Outcomes:
  - Men meeting criteria for LG-PDD or significant depressive symptoms
  - Changes in depressive symptoms, energy, sleep quality, and cognition in using the Hypogonadism Impact of Symptoms Questionnaire (HIS-Q) at baseline and at months 6, 12, and 24

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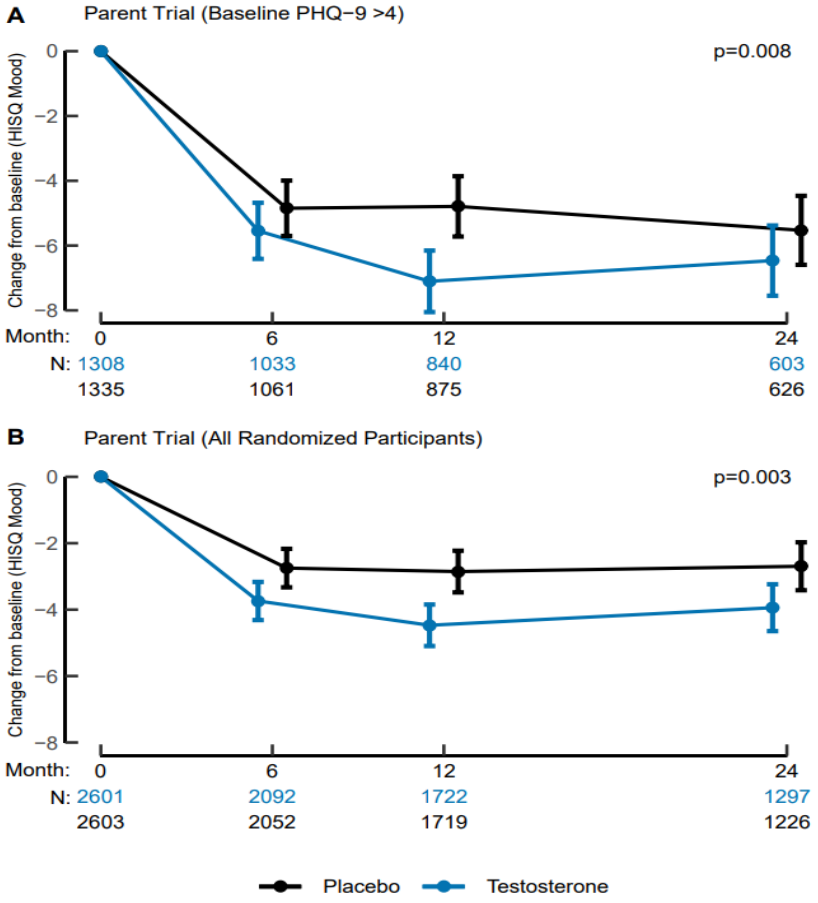
- Results:
  - 2643 (50.8%) had significant depressive symptoms
    - TTh was associated with modest but significantly greater improvements in mood and energy but not cognition or sleep quality
  - 1.5% men met rigorous criteria for LG-PDD
    - No significant difference in any outcome measure between the TTh and placebo groups



Bhasin et al J Clin Endocrinol Metab. 2024 Jan 11

T & P Ca & Traverse :FDA Label

"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)]*.

FDA Label: Prostate Cancer and BPH

"Warnings and Precautions" 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)]*.

T & P Ca: Key Issue

Does giving testosterone to men with a history of *treated* or *untreated* prostate cancer increase the risk of recurrence / progression?

JAMA Network Open

Original Investigation | Diabetes and Endocrinology

Prostate Safety Events During Testosterone Replacement Therapy in Men With Hypogonadism

A Randomized Clinical Trial

Shalender Bhasin, MB, BS; Thomas G. Travison, PhD; Karol M. Pencina, PhD; Michael O'Leary, MD, MPH; Glenn R. Cunningham, MD; A. Michael Lincoff, MD; Steven E. Nissen, MD; M. Scott Lucia, MD; Mark A. Preston, MD; Mohit Khera, MD; Nader Khan, MD; Michael C. Snabes, MD, PhD; Xue Li, PhD; Catherine M. Tangen, DrPH; Kevin A. Buhr, PhD; Ian M. Thompson Jr, MD

TRAVERSE Prostate Safety Study Negative!!

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- y

retention, invasive surg procedures, & new pharm treatments were low

- *Incidence of high-grade prostate cancer (5 of 2596 [0.19%] in the TRT group vs 3 of 2602 [0.12%] in the placebo group; hazard ratio, 1.62; 95%CI, 0.39-6.77; P = .51) did not differ significantly between groups*

TRAVERSE Trials Summary

Trial	Risks	Benefits
CV	MACE- No PE- ?	
Prostate	Cancer- No BPH/LUTS- No	
Sexual Function		ED - No Libido- Yes
Depression		Yes
Bone Fracture		No
Anemia		Yes
Diabetes		No

Conclusions

- Low testosterone is associated with increased CV risk
- Current data support a low CV risk in men on TTh and improvements in cardiometabolic parameters
- Normalization of T levels may reduce risk of death, MI and stroke
- There are no data currently supporting an increased risk of prostate cancer or prostate cancer recurrence / progression in men on TTh