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Testosterone Replacement in Men with Age-Related Low Testosterone: What Did We Learn From The Testosterone Trials?

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Abstract

The T Trials were a coordinated set of seven double-blind, placebo-controlled trials to assess efficacy and safety of testosterone versus placebo gel treatment for one year in 788 older men 65 years or older with hypogonadism who had self-reported and objective impairment of sexual and physical function and/or vitality and an average of two morning serum testosterone concentrations < 275 ng/dL. Testosterone dose was adjusted to the mid-normal range for young men. Compared to placebo, testosterone treatment moderately improved sexual function, hemoglobin concentration and corrected anemia, and slightly improved walking distance, vitality, mood and depressive symptoms and bone density and strength, but did not improve cognitive function. Testosterone treatment slightly increased non-calcified and total plaque volume; while concerning, the clinical significance of this finding is not clear. Testosterone treatment also increased PSA levels and referral for urological evaluation, and caused erythrocytosis in some men. The T Trials provided definitive evidence for short-term clinically meaningful, albeit modest benefits and risks of testosterone treatment in older men with unequivocal age-related hypogonadism. Larger and longer-term placebo-controlled clinical trials are needed to assess the long-term benefits and risks of testosterone treatment on clinical outcomes such as frailty, depression, fractures, prostate cancer and cardiovascular events.

Keywords

testosterone; hypogonadism; older male; sexual function; physical function; vitality; cognitive function; anemia; bone mineral density; prostate; coronary artery disease

Introduction

As men age, serum testosterone (T) concentrations decline progressively in association with conditions such as reduced sexual function, energy, muscle mass and function, cognitive function, bone mass with increased fracture risk and anemia.[1–3] These age-associated conditions also occur in men with organic hypogonadism due to diseases affecting the

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hypothalamic-pituitary-testicular axis. The decline in serum T levels with age contributes to an increasing prevalence of levels below the normal range for young men. However, the prevalence of clinical hypogonadism is much less.[4–6] In the European Male Aging Study, only sexual symptoms (poor morning erections, low sexual desire and erectile dysfunction [ED]) had a syndromic association with low serum T concentrations and the overall prevalence of age-related hypogonadism (termed late-onset hypogonadism) was 2.1%.[6] The etiology of hypogonadism as men age is complex and largely due to potentially reversible or treatable age-related comorbidities (e.g., obesity, chronic illness) or medication use (e.g. opioids, glucocorticoids) that suppress gonadotropins and T, i.e. functional causes of secondary hypogonadism. Less commonly, with advanced older age (e.g., over age 70 years), testes function declines substantially, resulting in organic primary hypogonadism. [7,8]

From clinical experience and older clinical trials, it is well established that T replacement therapy in men with severe organic hypogonadism improves sexual function, energy, muscle mass, bone mineral density (BMD) and anemia.[9] However, at the beginning of the century, it was unclear whether T treatment of old men with low T levels would benefit from T treatment. Early trials investigating whether T treatment in older men yielded conflicting results because the populations of men studied were heterogeneous (including healthy men without symptoms of low T or who had low-normal T levels rather than unequivocally low T levels); T treatment resulted in either supra- or sub-physiological T levels; studies were under-powered for some outcomes; and the use of non-validated, insensitive or non-clinically relevant surrogate outcome measures were used.[10]

Because large long-term clinical outcomes studies of T treatment in older men were lacking, in 2000, we proposed a 6-year randomized, double-blind, placebo-controlled trial (known as the Efficacy and Safety of TEstosterone in Elderly Men [ESTEEM], Department of Veterans Affairs (VA) Cooperative Studies Program No. 490) to determine the effect of T gel treatment on fractures (primary outcome), incident prostate cancer, cardiovascular (CV) events, sexual function, vitality, cognitive function and invasive treatment of benign prostatic hyperplasia (BPH) in 6000 men ≥ 65 years with serum low T concentrations. After a long and extensive reviews both by the VA CSP and an National Institutes on Aging (NIA), the ESTEEM study was approved but not funded, largely because of concerns regarding the potential safety of long-term T treatment in older men, particularly the risk of prostate cancer.[11]

In 2002, an Institute of Medicine (IOM) committee was convened to assess the state of clinical research on T therapy in older men. In 2003, the IOM committee concluded that there was insufficient evidence that T treatment in older men with low T levels was beneficial and recommended that the NIA support a coordinated set of short-term efficacy trials in older men with low T levels and at least one symptom that might be related to low T to investigate the efficacy of T therapy on sexual function, vitality/well-being/quality of life, muscle strength/frailty/disability and cognitive function.[12] The committee further recommended that only if adequate short-term benefits were found, would a larger, longer-term clinical efficacy and safety study be recommended. The NIA followed the IOM committee recommendations and supported The Testosterone Trials (T Trials).

T Trials Design

The design of the T Trials addressed the limitations of earlier trials of T therapy in older men and followed the recommendations of the IOM committee to assess the short-term benefits and risks of T treatment in older men.[13] The T Trials were a coordinated set of seven double-blind, placebo-controlled trials of T versus placebo gel treatment for one year in men 65 years or older who had an average of two morning serum T concentrations < 275 ng/dL, and self-reported and objective impairment in sexual function, physical function and/or vitality. Men were enrolled in one or more main trials: Sexual Function Trial (men with self-reported low libido and low sexual desire on a sexual function inventory); Physical Function Trial (men with self-reported difficulty walking or climbing stairs and gait speed < 1.2 m/sec on a 6-minute walk test); Vitality Trial (men with self-reported low vitality and low score on a validated fatigue scale).

Subsets of men were enrolled in one or more four other trials: Cognitive Function Trial (men with Age-Associated Memory Impairment [AAMI] who had self-reported memory complaint and verbal or visual memory impairment relative to young men); Anemia Trial (men with unexplained mild anemia defined as hemoglobin concentration [Hgb] < 12.7 g/dL but > 10.0 g/dL without a known etiology); Bone Trial (men with at least one computed tomography (CT)-evaluable lumbar vertebrae and not taking medications known to affect bone); Cardiovascular Trial (men with no contraindications to coronary computed tomographic angiography [CCTA] and no previous coronary artery bypass surgery).[13]

There were inclusion and exclusion criteria for the T Trials in general as well as specific criteria for each individual trial. Notably, men with prostate cancer and > 35% risk of any or > 7% risk of high-grade prostate cancer (by the Prostate Cancer Risk Calculator) were excluded. Also, men at high CV risk were excluded (myocardial infarction [MI] or stroke within 3 months, unstable angina, class III or IV heart failure, systolic blood pressure [BP] > 160 mm Hg or diastolic BP > 100 mm Hg). Participants were allocated to treatment by minimization that permitted balancing of a greater number of baseline variables than randomization with stratification.[13]

The initial T gel (AndroGel 1%) dosage of 5 g daily was adjusted according to serum T levels measured at months 1, 2, 3, 6 and 9 to maintain serum T concentrations within the normal range for young men. To maintain blinding, the dose of placebo gel was adjusted in another individual when T gel dose was adjusted. In the three main trials, the primary outcomes were chosen because they were deemed clinically important and each trial had 90% power to detect a clinically meaningful change in the primary outcome.[13]

Recruitment and Baseline Characteristics

51,085 men recruited initially called study sites and underwent an initial telephone screening and subsequent two-stage, in-person screening visits. Of those who expressed interest in participating, only 1.5% of men were enrolled in the T Trials. The main reason of exclusion of men was insufficiently low serum T concentrations. Only 14.7% of men screened had sufficiently low serum T levels on two occasions to qualify. Recruitment for the T Trials

confirmed that while symptoms that might be attributable low T levels are common, only a minority of older men have consistently and unequivocally low serum T concentrations in association with these symptoms.[14]

At baseline, men enrolled in the T Trials had an average age of 72 years and the majority were white, obese and had hypertension and unequivocally low serum T (Table 1). Approximately 37% had diabetes and 19% had sleep apnea. Importantly, men in the T Trials had a relatively low-risk of prostate cancer (18%), including high-grade prostate cancer (3%). Baseline characteristics were similar in men treated with T and placebo.[15]

Results of the T Trials

Testosterone Concentrations

705 of 788 (89%) of men enrolled in the T Trials completed all 12 months of treatment and evaluations.[10,15] In the 394 men treated with T, serum T concentrations increased from levels unequivocally below the normal range to the mid-normal range for young men by month 3 and were maintained at that level for the 12 months of treatment. However, to maintain serum T levels within the mid-normal range, 504 adjustments in the T dose were required in 301 of the 394 men treated with T. These results demonstrated that maintaining serum T concentrations within a target range is achievable but requires dose adjustments in most men.

In a sub-study of the T Trials that assessed pharmacokinetics of the T gel, after an average of 4 months of treatment with dose adjustments, 47 men had serum T measured 2 hours following application of T or placebo gel at two outpatient visits and at multiple time points over 24 hours during an inpatient stay.[16] T levels 2 hours after T gel application correlated poorly with each other and with the 24-hour average serum T concentration. While 81.5% of men on T had levels within the normal range, only 22.2% of men had serum T concentrations in the mid-normal range. These findings demonstrated the large within-individual variations in serum T levels after T gel application and the limited utility of dose adjustments based on a single serum T measurement during treatment.

Sexual Function Trial

Compared to placebo, T treatment modestly increased sexual activity (primary outcome), libido and to a lesser degree erectile function in both the 459 men enrolled in the Sexual Function Trial and all men enrolled in the T Trials (Table 2).[15] T increased most types of sexual activity assessed, including sexual daydreams, flirting, sexual intercourse, masturbation and spontaneous erections at night.[17] Men treated with T reported an improvement in Patient Global Impression of Change (PGIC) in sexual desire.[15]

Increases in serum total and free T (and estradiol) were associated with improvements in sexual activity and libido, but not erectile function.[17] Using PGIC as an anchor, clinically meaningful improvements in the sexual activity and libido instruments used in the T Trials were ascertained.[18] Together, these findings demonstrated that T treatment improves sexual activity and libido more than erectile function in older men with low T levels.

Physical Function Trial

In the 387 men enrolled in the Physical Function Trial, compared to placebo, T treatment did not increase the percentage of men who demonstrated a significant increase in walking distance (> 50 m) (primary outcome) or absolute increase in walking distance; but there was an increase in perceived physical function.[15] However, across all T Trials, T treatment slightly increased the percentage of men who demonstrated a significant increase in walking distance and absolute walking distance; perceived physical function; and improvement in PGIC in walking ability.

In a secondary analysis, T-treated men who reported difficulty walking or had a gait speed 1.2 m/s at baseline had greater improvements in 6-minute walking distance and perceived physical function.[19] Changes in 6-minute walking distance were associated with changes in total and free T (dihydrotestosterone and estradiol) and Hgb. The frequency of falls was identical in T-and placebo-treated men. The consistent results in all T Trials men demonstrated that T treatment in older men with low T levels has a small effect to improve mobility, but it is unclear whether these small improvements will substantially improve day-to-day function in older men.

Vitality Trial

In the 474 men enrolled in the Vitality Trial, compared to placebo, T treatment did not increase the percentage of men who demonstrated a significant increased score (≥ 4) on a validated fatigue scale (primary outcome) or absolute vitality score.[15] However, T treatment slightly increased perceived vitality, improved positive and negative moods and decreased depressive symptoms on a validated depression scale. Across all T Trials, T treatment did not increase the percentage of men who demonstrated a significant increased vitality score, but did increase the absolute vitality score and improved PGIC in energy level. These results demonstrated that T treatment in older men with low T levels has a small effect to improve mood and depressive symptoms and to a lesser extent vitality. It is possible that the small effect of T treatment was related to modestly low serum T levels in T Trials men.

Cognitive Function Trial

In the 493 men enrolled in the Cognitive Function Trial who had AAMI, compared to placebo, T treatment did not improve verbal memory (primary outcome), visual memory, spatial ability, executive function or global cognitive function.[20] In all men in the T Trials, T treatment slightly increased executive function but did not improve performance on other cognitive function measures. These results demonstrated that T treatment in older men with low T levels and AAMI does not improve memory or other cognitive functions.

Anemia Trial

In the 62 men enrolled in the Anemia Trial, compared to placebo, T treatment increased the percentage of men who demonstrated a significant increase (≥ 1.0 g/dL) in Hgb (primary outcome); resulted in large absolute Hgb increase; and increased percentage of men who were no longer anemic.[21] T treatment resulted in similar outcomes in the 64 men with anemia of known cause and 657 men who did not have anemia at baseline. Increase in Hgb was associated with small increases in 6-minute walking distance and vitality and improved

PGIC in vitality, suggesting that increases in Hgb were clinically significant. These results demonstrated that T treatment of older men with low T levels and anemia (unexplained or of known cause) improves Hgb and corrects anemia. Of the 336 men who were not anemic and treated with T, 6 (2%) developed erythrocytosis, supporting the recommendation to monitoring Hgb and hematocrit during T treatment.[22]

Bone Trial

In the 211 men enrolled in the Bone Trial (most of whom did not have osteoporosis), compared to placebo, T treatment slightly increased vBMD and estimated bone strength in trabecular > peripheral and whole bone of the spine > hip, and areal BMD in the lumbar spine but not total hip or femoral neck.[23] The effects of T treatment on vBMD after only one year of treatment were impressive and similar in magnitude to that of bisphosphonate therapy in women with osteoporosis.[24,25] These results demonstrated that T treatment in older men with low T levels increases BMD and bone strength in trabecular > cortical bone of the spine > hip. They provide a strong rationale for larger and longer-term studies to determine whether T treatment of older men with low T levels will reduce fractures.

Cardiovascular Trial

The 138 men enrolled in the Cardiovascular Trial had high baseline rates of cardiovascular risk factors with a very high ACC/AHA atherosclerotic CV disease 10-year risk score (27% and 24% in placebo and T treated men, respectively).[26,27] Also, these men had severe coronary atherosclerosis with coronary artery calcium (CAC) score > 300 in 50.7%. Compared to placebo, T treatment slightly increased non-calcified (primary outcome) and total coronary artery plaque volume, but not CAC score. However, men in the placebo group had higher non-calcified coronary artery plaque volume and CAC scores at baseline. Although analyses were adjusted for these baseline differences and there was no association between baseline and change in plaque volume from baseline to month 12, it is still possible that baseline imbalance could have influenced the results.

The increase non-calcified plaque volume with T treatment is concerning as it has been associated with subsequent CV adverse events in other studies, and any compromise of the coronary artery lumen could be deleterious. However, the clinical implications of these initial findings need to be confirmed in larger studies.

Adverse Events

Among all 788 men enrolled in the T Trials, more men treated with T than placebo developed a confirmed PSA ≥ 1.0 ng/mL that triggered a referral for urological evaluation (23 vs. 8 T-vs. placebo-treated men, respectively) and erythrocytosis defined as a Hgb ≥ 17.5 dL (7 vs. 0 T-vs. placebo-treated men, respectively).[15] However, a similar number of men developed severe lower urinary tract symptoms (IPSS score >19 in 27 vs. 26 T-vs. placebo-treated men, respectively). Despite relatively intensive PSA monitoring during treatment, only 3 men underwent prostate biopsy.

The T Trials were not designed nor powered to adequately assess clinical prostate cancer or CV adverse events. Prostate cancer was diagnosed in one man in T arm during the 12-month

treatment period.[15] Major cardiovascular events (MI, stroke or cardiovascular death) occurred in 7 men in each treatment arm.[15]

These results demonstrated that increase in PSA and erythrocytosis are short-term adverse events of T treatment of older men with low T levels. Although few prostate biopsies resulted from PSA monitoring, the findings highlight the need for studies to evaluate best practice to avoid excessive prostate cancer monitoring during T treatment. Even though the incidence of erythrocytosis was relatively low, the results also support recommendations for monitoring Hgb or hematocrit during T treatment.[22]

What Did We Learn From The T Trials?

In older men over the age of 65 years with symptomatic, unequivocal hypogonadism, T treatment that increased and maintained T levels in the mid-normal range for young men for one-year moderately improves sexual function, Hgb and corrects anemia, and slightly improves walking distance, vitality, mood and depressive symptoms and bone density and strength, but does not improve cognitive function. T treatment slightly increases non-calcified and total plaque volume; although the clinical significance of this increase is not clear. T treatment also increased PSA and referral for urological evaluation, and caused erythrocytosis.

In summary, the T Trials provided definitive evidence for short-term clinically meaningful, albeit modest benefits and risks of T treatment in a large number of older men with symptomatic, unequivocal age-related hypogonadism. They provide a strong rationale and impetus for larger and longer-term placebo-controlled clinical trials to assess the benefits and risks of T treatment on clinical outcomes such as frailty, depression, fractures, prostate cancer and cardiovascular events.

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Table 1.

T Trials Baseline Characteristics[#]

	Placebo	Testosterone
Number	395	395
Age (years)	72.3 ± 5.8	72.1 ± 5.7
White/Black/Collage (%)	88.9%/5.1%/50.1%	88.4%/5.3%/54.2%
BMI (kg/m ²)/BMI>30 (%)	31 ± 3.6/62.3%	31 ± 3.5/63.5%
Current smoker	8.6%	7.6%
Diabetes (%)	36.5%	37.5%
Hypertension (%)	70.9%	72.4%
History of MI/stroke (%)	16%/4.3%	13.4%/4.1%
Sleep apnea	19.2%	19.8%
Risk All Prostate Cancer [*] (%)	17.6 ± 6%	17.3 ± 6%
Risk High-Grade Prostate Cancer [*] (%)	3 ± 1.7%	2.9 ± 1.7%
IPSS score (0–35)	9.6 ± 5.3	9 ± 5.2
Alpha adrenergic blocking agent (%)	12%	14%
5-alpha reductase inhibitor (%)	4.1%	3.8%
Phosphodiesterase 5 inhibitor (%)	9.1%	7.6%
Total T (ng/dL)	236 ± 67	232 ± 63
SHBG (nM)	29.5 ± 14.7	31.4 ± 15.2
DISF-M-II score (0–33)	14 ± 7.8	13.9 ± 7.7
Gait Speed (m/sec)	1.1 ± 0.2	1.1 ± 0.2
FACIT-Fatigue score (0–52)	36.8 ± 8.8	37 ± 8.6

[#] Adapted from Snyder PJ, et al. Effects of testosterone treatment in older men. *N Engl J Med* 374:611–624, 2016.[15]

BMI = body mass index

MI = myocardial infarction

^{*} As assessed by the Prostate Cancer Risk Calculator (using prostate specific antigen [PSA] adjusted for low T level)

IPSS = International Prostate Symptom Score

T = testosterone

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SHBG = sex hormone binding globulin

DISF-M-II = Derogatis Inventory of Sexual Function-Men-II, sexual desire domain (DISF-M-II) Gait speed on 6-minute walk test

FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue

Table 2.

Summary of T Trials Results

Outcome	Testosterone vs. Placebo Treatment Effect
Sexual Function	All T Trials Men
Sexual Function Trial [*]	Moderate ↑ sexual activity
Moderate ↑ sexual activity ^{1,2}	↑ global impression of in sexual desire ⁵
Moderate ↑ sexual desire ³	
Moderate ↑ erectile function ⁴	
Physical Function	All T Trials Men
Physical Function Trial [^]	Slight ↑ % significant improvement in walking ^{1,6}
No % significant improvement in walking ^{1,6}	Slight ↑ walking distance
No walking distance ⁷	Slight ↑ % significant perceived physical function
No % significant perceived physical function ⁸	Slight ↑ perceived physical function
Slight ↑ perceived physical function ⁹	↑ global impression of in walking ability ⁵
Vitality	All ↑ Trials Men
Vitality Trial ^v	No % significant improvement in vitality
No % significant improvement in vitality ^{1,10}	Slight ↑ vitality
No vitality ¹¹	↑ global impression of in energy level ⁵
Slight ↑ perceived vitality ¹²	
Slight ↑ positive and ↓ negative moods ¹³	
Slight ↓ depressive symptoms ¹⁴	
Cognitive Function	All T Trials Men
Cognitive Function Trial (AAMI [#])	No verbal memory
No verbal memory ^{1,15}	No visual memory
No visual memory ¹⁶	No spatial ability
No spatial ability ¹⁷	Slight ↑ executive function
No executive function ¹⁸	No global cognitive function
No global cognitive function ¹⁹	

Outcome	Testosterone vs. Placebo Treatment Effect	
Anemia	Anemia Trial (Unexplained Anemia) ^{\$}	Anemia of Known Cause and No Anemia
	↑ % significant improvement in hemoglobin ^{1,20}	↑ % significant improvement in hemoglobin
	Large ↑ hemoglobin ²¹	Large ↑ hemoglobin
	↑ % men no longer anemic	↑ % men no longer anemic
Bone	Bone Trial [%]	
	Slight ↑ spine trabecular vBMD ^{1,22} and bonestrength ^{1,23}	
	Slight ↑ spine peripheral and whole bone vBMD and bone strength	
	Slight ↑ hip trabecular, peripheral and whole bone vBMD and bone strength	
Cardiovascular	Slight ↑ lumbar spine aBMD ²⁴	
	No total hip and femoral neck aBMD	
	Cardiovascular Trial [‡]	
	Slight ↑ non-calcified coronary artery plaque volume ^{1,25}	
	Slight ↑ total coronary artery plaque volume ²⁶	
	No coronary artery calcium score ²⁷	

* Sexual Function Trial: men with self-reported decrease in libido and DISF-M-II score 20/33; partner willing to have intercourse twice monthly

^ Physical Function Trial: men with self-reported difficulty walking or climbing stairs and gait speed 1.2 m/sec on the 6-minute walk test; ambulatory and no disabling neuromuscular or arthritic condition

v Vitality Trial: men with self-reported low vitality and FACIT-Fatigue score < 40/52

Cognitive Function Trial: men with age-associated memory impairment (AAMI) = self-reported subjective memory complaint (score on Memory Assessment Clinics Questionnaire, MAC-Q) and objective memory impairment (delayed paragraph recall or Benton Visual Retention test) scores > 1 SD lower than young men but not > 2 SD lower than age-matched men; Mini-Mental State Examination score 24

\$ Anemia Trial: men with anemia (hemoglobin concentration 12.7 g/dL but 10.0 g/dL) with unexplained etiology

% Bone Trial: men with at least on evaluable lumbar vertebrae; no medications known to affect bone (except calcium and vitamin D); and DXA T-score -3.0

& Cardiovascular Trial: men with estimated glomerular filtration rate 60 mL/min/1.73 m²; no known allergy to iodinated contrast medium; weight 136 kg; ability to hold breath for 10 seconds; no prior diagnosis of tachycardia or irregular heart beat; no previous coronary artery bypass graft surgery

No = no difference in testosterone vs. placebo group; ↑ = increase in testosterone vs. placebo group; ↓ = decrease in testosterone vs. placebo group; % = percentage of men Slight-small effect size; Moderate = medium effect size; Large = large effect size

- ¹ = Primary outcome
- ² = Psychosexual Daily Questionnaire, question 4 (PDQ-Q4)
- ³ = Derogatis Inventory of Sexual Function-Men-II, sexual desire domain (DISF-M-II)
- ⁴ = International Index of Erectile Function, erectile function domain (IIEF)
- ⁵ = Patient global impression of change (PGIC) questionnaire ("much better, a little better, not changed, a little worse or much worse")
- ⁶ = % of men with increase in walking distance 5 meters in the 6-minute walk test
- ⁷ = Total walking distance in the 6-minute walk test
- ⁸ = Increase in score of 8 in Physical Function scale (PF-10) of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)
- ⁹ = Increase in PF-10 score
- ¹⁰ = % of men with increase in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score 4
- ¹¹ = Increase in FACIT-Fatigue score
- ¹² = Increase in Vitality scale of the SF-36 score
- ¹³ = Increase and decrease in Positive and Negative Affect Schedule (PANAS) scales, respectively
- ¹⁴ = Decrease in Patient Health Questionnaire 9 (PHQ-9) score
- ¹⁵ = Delayed paragraph recall (Wechsler Memory Scale-Revised Logical Memory II) test
- ¹⁶ = Benton visual retention test
- ¹⁷ = Card rotation test
- ¹⁸ = Trail-Making (B-A) test
- ¹⁹ = Modified Mini-Mental State Examination (3MSE)
- ²⁰ = % of men with increase in hemoglobin concentration 1.0 g/dL
- ²¹ = Increase in hemoglobin concentration
- ²² = Volumetric trabecular bone mineral density (vBMD) of the lumbar spine by quantitative computed tomography (QCT)
- ²³ = Estimated bone strength by finite element analysis (FEA)
- ²⁴ = Areal bone mineral density (aBMD) by dual-energy x-ray absorptiometry (DXA)
- ²⁵ = Increase in non-calcified coronary artery plaque volume by coronary computed tomographic angiography (CCTA)

²⁶ = Increase in total coronary artery plaque volume by CCTA

²⁷ = Increase in coronary artery calcium score on precontrast CT scans (prior to CCTA)

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