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

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Background Testosterone exerts some effects on the cardiovascular system that could be considered beneficial; some other effects may potentially increase the risk of cardiovascular (CV) events. Neither the long-term efficacy nor safety of testosterone treatment has been studied in an adequately-powered randomized trial.

Methods The Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) study is a randomized, double-blind, placebo-controlled, parallel group, non-inferiority, multicenter study. Eligible participants are men, 45 to 80 years, with serum testosterone concentration <300 ng/dL and hypogonadal symptoms, who have evidence pre-existing CV disease or increased risk of CV disease. Approximately 6,000 subjects will be randomized to either 1.62% transdermal testosterone gel or a matching placebo gel daily for an anticipated duration of up to 5 years. The primary outcome is CV safety defined by the major adverse CV event composite of nonfatal myocardial infarction, nonfatal stroke, or death due to CV causes. The trial will continue 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 include prostate safety defined as the incidence of adjudicated high grade prostate cancer and efficacy in domains of sexual function, bone fractures, depression, anemia, and diabetes.

Results As of July 1, 2021, 5,076 subjects had been randomized.

Conclusions The TRAVERSE study will determine the CV safety and long-term efficacy of testosterone treatment in middle-aged and older men with hypogonadism with or at increased risk of CV disease. (Am Heart J 2022;245:41–50.)

Background

Testosterone replacement therapy (TRT) is approved for the treatment of hypogonadism associated with known diseases of the testis, pituitary and the hypothalamus, but it is not approved by the United States Food and Drug Administration (FDA) for the treatment of age-associated decline in testosterone levels.[1] Prior to the development of radioimmunoassays for the measurement of circulating testosterone levels, men diagnosed with severe hypogonadism typically suffered from clini-

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cally apparent testosterone deficiency, in whom the diagnosis relied upon the loss of secondary sex characteristics, gynecomastia, and small testes. In young men with severe hypogonadism, testosterone treatment induced visible changes in secondary sex characteristics and body habitus and restored sexual function with low frequency of adverse events. However, 80% of testosterone prescriptions have historically been written for men 45 to 74 years,[1-2] who often report symptoms that are also common with aging; testosterone levels in these middle-aged and older men are typically either in the low-normal range or only mildly reduced, and these men have few overt physical signs of testosterone deficiency. Neither the long-term efficacy nor the long-term safety of testosterone treatment in middle-aged and older men with age-related decline in testosterone levels has been demonstrated in adequately powered randomized trials.[3]

Between the years 2000 and 2013, the prescription sales of testosterone products underwent explosive growth,[4-5] driven by several historical factors, including direct-to-consumer advertising of testosterone products; the availability of easy-to-use transdermal testosterone products; and the development of men's health clinics that catered almost exclusively to men's sexual and genitourinary problems.[6] In 2013, in response to a petition by a citizen's interest group and conflicting reports of cardiovascular (CV) events from small clinical trials, retrospective analyses of medical records data, and pharmacovigilance studies of testosterone-treated men, the FDA conducted an extensive review of the available information.[7] FDA concluded that "*the studies...have significant limitations that weaken their evidentiary value for confirming a causal relationship between testosterone and adverse cardiovascular outcomes.*" An independent review conducted by the European Medicines Agency also found no consistent evidence of an increased risk of coronary heart disease associated with testosterone treatment of men with hypogonadism. Given the broad and growing use of TRT among middle-aged and older men with or at risk for CV disease, the FDA issued updated testosterone labeling inclusive of a limitation of use in men with "age-related hypogonadism," along with a guidance *"... 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."* The Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) study was designed in response to this FDA guidance to determine the effects of testosterone treatment on the incidence of major adverse CV events (MACE) in middle-aged and older men with hypogonadism with or at high risk for CV disease.

Testosterone treatment and the risk of cardiovascular events

Physiologic effects of testosterone on the cardiovascular system

Testosterone exerts diverse effects on CV physiology, some of which may theoretically increase the risk of CV events, while others could be considered potentially beneficial. Testosterone administration reduces plasma high-density lipoprotein cholesterol by a magnitude that is related to the administered dose, the route of administration, and the extent to which it can be aromatized.[3] Testosterone induces platelet aggregation by stimulating thromboxane A2 and promotes sodium and water retention, which can contribute to edema and may worsen pre-existing heart failure. In pre-clinical models, testosterone promotes smooth muscle proliferation and increases the expression of vascular cell adhesion molecules. Testosterone increases hematocrit by stimulating iron-dependent erythropoiesis by suppressing hepcidin,[8] increasing erythropoietin, and by direct effects on the bone marrow that increase hematopoietic progenitors. Older men experience greater increases in hematocrit than younger men.[9]

Testosterone also exerts potentially beneficial effects on the CV system. Testosterone inhibits L-type calcium channels, resulting in coronary vasodilatation and increased coronary blood flow.[10] Testosterone improves endothelial function, reduces vascular reactivity,[11] prolongs time to ST segment depression in men with known coronary artery disease,[12] and shortens QTc interval. Testosterone administration also decreases whole body, subcutaneous and intra-abdominal fat.[13]

Testosterone administration increases the circulating levels of both prothrombotic and anti-thrombotic factors. It does not significantly affect myocardial infarct size in pre-clinical models of myocardial infarction. Testosterone has been shown to retard atherosclerosis in some preclinical models and induce myocardial hypertrophy in some mouse strains. The effects of testosterone on measures of insulin sensitivity have been inconsistent in intervention trials.[14-15] Acute sex steroid withdrawal or rapid induction of testosterone deficiency by the administration of a gonadotropin releasing hormone agonist or an antagonist is associated with an acute worsening of insulin sensitivity.[16-17] In a randomized trial in middle-aged and older men who had impaired glucose tolerance or new diagnosis of type 2 diabetes, but who were not hypogonadal, the combined administration of testosterone treatment plus a lifestyle program for 2 years reduced the proportion of men who developed type 2 diabetes compared with the lifestyle program alone.[18]

Epidemiological studies of the association of endogenous testosterone levels with cardiovascular disease

Prospective longitudinal studies have not found a consistent relationship between endogenous testosterone levels and incident CV events,[19-20] although in a meta-analysis of epidemiologic studies, lower testosterone levels were associated with increased risk of all-cause mortality, especially CV mortality.[21] Circulating testosterone concentrations are inversely associated with common carotid artery intima-media thickness, a measure of subclinical atherosclerosis.[22] In an observational study of men with prostate cancer, the use of androgen deprivation therapy was associated with increased risk of incident coronary artery disease, myocardial infarction, stroke and sudden cardiac death.[23] However, epidemiological studies can only show association and cannot prove causality. It is possible that testosterone is a marker of health, and those who are higher risk of dying have lower testosterone levels.

In Mendelian randomization analyses of the UK Biobank data, the genetically determined testosterone levels were associated with type 2 diabetes in a sexually dimorphic manner; lower genetically determined testosterone levels in men but higher genetically determined testosterone levels in women were associated with increased risk of type 2 diabetes, even after adjusting for sex-hormone binding globulin levels.[24] Mendelian randomization studies did not observe a significant association between genetically determined total or free testosterone levels and CV disease risk.[25]

Retrospective analyses of testosterone replacement therapy

Retrospective analyses of electronic medical records or Medicare data have reported conflicting findings on the association of testosterone treatment with CV events.[26-30] Of five published retrospective studies considered by the FDA in its 2014 guidance,[26-30] two reported increased risk of CV events, one showed a trend toward decreased risk, and two reported lower risk for all-cause mortality associated with TRT. These studies suffer from the many limitations intrinsic to their design, including heterogeneity of study populations and differences in the duration of intervention and study design. The studies used variable definitions and varying rigor in ascertainment of CV outcomes. The indications for treatment, treatment regimens, on-treatment testosterone levels and exposure were somewhat unclear and differed in these publications. The studies also suffered from a potential for residual confounding, since the participants assigned to testosterone therapy differed from comparators in baseline CV risk factors. Because of these limitations and inconsistency of findings, these epidemiologic studies do not permit strong inferences about the relationship between testosterone therapy and mortality and CV outcomes.

Randomized trials

The rate of atherogenesis progression, assessed using the common carotid artery intima media thickness or the coronary calcium scores did not differ between testosterone-treated and placebo-treated men either in the Cardiovascular Testosterone Trial of the TTrials[31] that enrolled older men with hypogonadism, 65 years or older, for an intervention duration of one year, or in the Testosterone Effects on Atherosclerosis in Aging Men (TEAAM) Trial that enrolled older men, 60 years or older, with low or low normal testosterone levels, for an intervention duration of 3 years.[32] In the CV trial of the TTrials,[31] testosterone treatment was associated with greater increase in the volume of noncalcified plaque in the coronary arteries compared with placebo. Cardiovascular events were evaluated in the TTrials but the number of CV events did not differ significantly between the testosterone and placebo arms (7 MACE events in each of the two study arms).[31] However, neither the TTrials nor any other trial to-date had sufficient size or duration to determine the effects of testosterone treatment on major adverse CV events in men with hypogonadism. A number of meta-analyses of randomized trials have evaluated the effects of testosterone treatment on CV outcome and mortality.[33-37] These meta-analyses have not shown significant associations between testosterone and CV events, major CV events, or mortality. The meta-analyses are limited by the heterogeneity of eligibility criteria, testosterone dose and formulation, and intervention durations. The included trials were small, and the total number of major CV events was too small to draw strong inferences. CV outcomes were not pre-specified or formally adjudicated, were often defined post-hoc, and varied in clinical importance.

Additionally, there is no evidence of a significant association between testosterone treatment and increased risk of venous thromboembolic events,[38] although the risk for venous thromboembolic events may be increased in participants with hypercoagulable states,[39] especially within the first few months after starting testosterone treatment.

Uncertainty about the effects of testosterone therapy on prostate health

The prostate volume is smaller in men with hypogonadism than in age-matched eugonadal men and TRT increases prostate volume to the size observed in age-matched controls. In meta-analyses of randomized trials, TRT has not been associated with worsening of lower urinary tract symptoms in hypogonadal men who do not have severe lower urinary tract symptoms prior to treatment. In epidemiologic studies, neither circulating testosterone or dihydrotestosterone levels nor poly-

morphisms in genes associated with testosterone action and metabolism have been associated with an increased risk of prostate cancer.[40-43] However, androgen receptor signaling plays an important role in the pathobiology of prostate cancer, and testosterone administration promotes the growth of metastatic prostate cancer. The guidelines of professional societies recommend against testosterone treatment in men with prostate cancer.[3,42] A Mendelian randomization analysis of the UK Biobank data found that higher genetically-determined testosterone level is associated with an increased risk of clinically diagnosed prostate cancer.[24] Similarly, registries of men with Klinefelter Syndrome report a lower incidence of prostate cancer than the general population.[44] Taken together, these data suggest that life-long exposure to higher testosterone levels could increase the risk of prostate cancer.

Serum prostate-specific antigen (PSA) levels are lower in men with hypogonadism and increase in response to testosterone treatment. The PSA increase after initiation of testosterone treatment may lead to consideration of prostate biopsy and thereby increase the likelihood of detection of low-grade prostate cancers.[3] In a meta-analysis of randomized studies,[45] a greater proportion of men randomized to testosterone treatment, compared with those assigned to placebo treatment, were referred for prostate biopsies, had PSA levels exceeding 4 ng/ml, or had prostate cancer diagnoses.

Many middle-aged and older adults harbor small subclinical cancers in the prostate, and it remains uncertain whether long-term TRT might cause these small subclinical foci of cancer to grow. Previous testosterone trials have not had sufficient treatment duration or a large enough sample size to evaluate the effects of testosterone treatment on prostate outcomes, such as incidence of prostate cancer, including high grade prostate cancer; acute urinary retention; and invasive or noninvasive surgical procedures for benign prostatic hyperplasia. The TRAVERSE trial is designed to address this knowledge gap about prostate safety with long-term testosterone treatment.

Gaps in the current understanding of the efficacy of testosterone replacement therapy

Most studies of the effects of TRT have been open-label trials and only a few relatively short-term placebo-controlled randomized trials have evaluated the efficacy of testosterone's efficacy in men who met the Endocrine Society's criteria for hypogonadism.[46-48] Among the small number of randomized trials of testosterone's efficacy, the TTrials are perhaps the most important.

The TTrials comprised of seven NIH-funded, coordinated, placebo-controlled trials of testosterone replacement conducted in 788 community-dwelling older men, 65 years or older, who had an average of two morning fasting total testosterone levels, measured using liquid chromatography tandem mass spectrometry (LC-MS/MS), less than 275 ng/dL, and one or more symptoms of low libido, mobility limitation, and/or fatigue.[46] The eligible participants were allocated using minimization to receive either placebo gel or testosterone gel for 1 year. The dose of testosterone gel was adjusted to achieve and maintain serum testosterone levels in the mid-range for healthy young men. Compared to placebo, testosterone treatment was associated with significantly greater improvements in overall sexual activity, sexual desire, and erectile function[49]; increases in volumetric bone mineral density and estimated bone strength in the spine and hip[50]; small improvements in mobility[51] and depressive symptoms[46]; and a greater proportion of men increasing their hemoglobin level by more than 1.0 g/dL and correcting unexplained anemia.[52] Testosterone treatment did not significantly improve vitality or cognitive function in men who did not have cognitive deficit at baseline.[46]

No trials have been large enough nor long enough to determine the long-term benefits of testosterone treatment on clinically important outcomes such as bone fractures; progression from prediabetes to diabetes or induction of glycemic remission; remission of late-life persistent depressive disorder (PDD); and sustained improvement in sexual function and activity in men who rigorously meet the Endocrine Society's criteria for hypogonadism.

Traverse study objectives and design

TRAVERSE (clinicaltrials.gov NCT03518034) is a phase 4, randomized, double-blind, placebo-controlled, noninferiority, parallel group, multicenter study of transdermal TRT in symptomatic men with hypogonadism who have pre-existing CV disease or increased risk for CV disease. The primary aim of the TRAVERSE study is to determine the safety of TRT with regard to MACE in middle-aged and older men with hypogonadism. The study will enroll approximately 6,000 participants and continue until 256 primary major adverse CV events have been positively adjudicated, with an anticipated study duration of up to 5 years. Because of its long duration and large sample size, the study also provides an opportunity to evaluate prostate safety and several efficacy outcomes, including clinical fractures; sexual activity, sexual desire, and erectile function; remission of late life PDD (dysthymia); progression from prediabetes to diabetes and remission of diabetes; and correction of anemia and incidence of anemia.

Study population

The study population consists of men, 45 to 80 years of age, with confirmed low serum testosterone concentrations (<300 ng/dL) who report hypogonadal symptoms and have evidence of CV disease or are at an increased

Table I. Cardiovascular inclusion criteria

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	

risk for CV disease. The CV eligibility criteria are listed in Table I and described below.

The inclusion criteria were designed to enroll middle-aged and older men who met the Endocrine Society's criteria for the diagnosis of hypogonadism, defined as the presence of: a) two serum testosterone levels < 300 ng/dL, measured using liquid chromatography tandem mass spectrometry in fasting specimens obtained between 5 AM and 11 AM local time, plus b) self-report of one or more of the following symptoms related to testosterone deficiency: decreased sexual desire, decreased spontaneous erections, low energy or fatigue, low mood or depressed moo,; loss of body hair or reduced shaving, or hot flashes. To enrich the study population with those at increased risk of CV events, the participants were also required to have evidence of either pre-existing CV disease indicated by clinical or angiographic evidence of coronary artery disease, cerebrovascular disease, or peripheral vascular disease or increased CV risk defined by the presence of three or more of the following risk factors : hypertension, dyslipidemia, current smoking, stage 3 kidney disease, diabetes, elevated high sensitivity C-reactive protein, age 65 years or older, documented historical Agatston coronary calcium score greater than 75th percentile for age and race.

To reach the intended event rate of the primary outcome, the protocol initially specified that at least 30% of randomized participants meet the criteria for pre-existing CV disease criteria (secondary prevention) but allowed the Executive Steering Committee and AbbVie to cap the cohort with CV risk factors (primary prevention stratum) if that cohort exceeded 70% of the total enrollment or if the pooled primary event rate fell below pro-

jections. The first participant was enrolled in May 2018. In April 2019, blinded data from the first 2,669 enrolled participants, of which 1,799 (67%) were in the primary prevention stratum and 870 (33%) in the secondary prevention stratum, showed a pooled primary event rate in the CV risk factor cohort below the 1.5% per year projection. The decision was therefore made to cease enrollment of study participants who qualified via CV risk factors on May 31, 2019 and subsequently enroll only those with pre-existing CV disease.

The study excludes men with congenital or acquired hypogonadism for whom long-term therapy with placebo would not be medically appropriate (eg, men with two testosterone levels <100 ng/dL) and men with conditions that constitute a contraindication for testosterone therapy, including unstable medical conditions that might compromise the subject's safety or render it difficult or unsafe to apply transdermal testosterone gel. Thus, men are excluded if they had history of prostate or breast cancer; undiagnosed prostate nodule or prostate induration; severe lower urinary tract symptoms (International Prostate Symptom Score >19); screening PSA >3 ng/mL (or >1.5 ng/mL if they were taking a 5-alpha reductase inhibitor); erythrocytosis; thrombophilia, unprovoked deep vein thrombosis or pulmonary embolism; hematocrit >50%; uncontrolled heart failure; untreated severe obstructive sleep apnea; severe or end stage chronic kidney disease (estimated GFR <30 mL/min/1.73m^2); or body mass index >50 kg/m^2. The participants are ineligible within the first 4 months after documented myocardial infarction, stroke, percutaneous coronary angioplasty, coronary artery bypass graft surgery, unstable angina; or procedures to treat critical limb ischemia. To avoid confounding due to the use of other medications or conditions that might affect testosterone levels or its action, the study design excludes men who during the preceding 6 months had received testosterone replacement, clomiphene, anabolic steroids, compounded or over-the-counter androgenic steroid derivatives and dehydroepiandrosterone, including investigational products that may affect the reproductive hormonal system.

Intervention and management

Eligible subjects are randomized using an interactive response technology system in a 1:1 ratio to receive either transdermal 1.62% testosterone gel or a matching placebo gel daily. The study drug is provided in metered dose pumps containing testosterone 1.62% gel or matching placebo gel. The subjects apply the study drug once daily in the morning to the shoulder(s) or upper arm(s).

The subjects, study personnel, and the sponsor are blinded to the subject's allocation. The central interactive response technology and designated central laboratory staff, who are unblinded to serum testosterone levels, manage the dose titrations and protocol-mandated actions needed to manage sustained high testosterone levels, and elevated hematocrit and PSA levels to assure participants' safety. All subjects randomized to the testosterone treatment group initiate therapy with the 40.5 mg dose (2 actuations of the pump, each actuation delivering 20.25 mg testosterone) once daily. The dose is titrated based on the measurement of testosterone levels to achieve and maintain levels between 350 ng/dL and 750 ng/dL. If serum testosterone level measured 24-hours after the application of the transdermal gel 2 weeks after randomization is less than 350 ng/dL, the dose is increased in increments of 20.25 mg until the level rises above 350 ng/dL or a maximum dose of 101.25 mg is reached. If the testosterone level is greater than 750 ng/dL, the dose is reduced in steps of 20.25 mg each until the serum testosterone level falls below 750 ng/dL. If the testosterone level stays above 750 ng/dL at the lowest dose of 20.25 mg daily, the study drug is discontinued, and the subject followed per study protocol. The subjects randomized to placebo arm also undergo sham titrations to maintain blinding. If the hematocrit is >54%, testosterone dose is decreased by one actuation of the pump (20.25 mg).

Study drug is permanently discontinued in subjects with confirmed testosterone levels >750 ng/dL or hematocrit >54% even after down-titration to the lowest dose, those with a new prostate cancer diagnosis, or subjects deemed at risk for suicide as determined by the Investigator or by response to the Patient Health Questionnaire-9 in the PDD substudy (see below). Specific criteria are provided for management or referral to a urologist for elevated prostate specific antigen values. Otherwise, participants who discontinue study drug for other reasons may be restarted at any time when deemed medically appropriate by the Investigator.

Study outcomes

Safety outcomes

The primary CV safety outcome of the study is the 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. The secondary CV safety endpoint is the time to first occurrence of any component of the composite endpoint of nonfatal myocardial infarction, nonfatal stroke, death due to CV causes, or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting). The secondary prostate safety endpoint is the incidence of high-grade prostate cancer, defined as a pathologically confirmed prostate cancer with Gleason score 4 + 3 or higher.

Tertiary safety CV endpoints include all-cause mortality; hospitalization or urgent visit for heart failure; venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, venous thromboembolism; or peripheral arterial revascularization. Tertiary

Table II. Secondary efficacy 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.

prostate safety endpoints include prostate biopsy; any prostate cancer; acute urinary retention; starting pharmacologic treatment for lower urinary tract symptoms; and invasive prostate surgical procedures (eg, prostatectomy, transurethral prostate resection, brachytherapy or other prostate surgical procedure for benign prostatic hyperplasia).

CV, prostate and bone fracture events during the study are adjudicated using pre-specified criteria and processes that are described in separate charters for each of adjudication committees for the three event categories.

Efficacy outcomes

A limited number of pre-specified efficacy endpoints are included as secondary outcomes in five efficacy domains (Table II). The following efficacy endpoints will be evaluated in sub-studies or analyses of subpopulations using validated patient reported outcome (PRO) questionnaires:

1. Improvement in sexual activity in hypogonadal men with low libido.
2. Remission of depression in hypogonadal men with late-onset, low grade PDD.
3. Reduction in incidence of clinical fractures.
4. Correction of anemia in subset of participants with baseline anemia, and incidence of anemia among randomized subjects who did not have anemia at baseline.
5. Reduction in progression from pre-diabetes to diabetes in subset of participants with pre-diabetes at baseline, and glycemic remission in subset of participants with diabetes at baseline.

Statistical analyses

The Full Analysis Set (FAS) comprising all randomized participants will be used for the summary of participants' disposition and summary of participants' demographics and baseline characteristics for the study. The Safety Set consists of all randomized participants who receive at least one dose of study drug (TRT or placebo). The Safety Set will be used for the analysis of all safety endpoints of the study, including the primary endpoint. The Efficacy Analysis Sets are pre-specified subgroups of the FAS comprising of eligible participants from the main study who satisfy the criteria for sub-studies for sexual function, PDD, anemia and diabetes, except for the bone fracture substudy for which all randomized participants are eligible. For instance, the Efficacy Analysis Sets for the analysis of sexual function substudy will include participants with Baseline DISF- Sexual Desire domain score $\leq$20.

A Cox proportional-hazards regression model will be used to estimate the hazard ratio (HR) of TRT to placebo and its two-sided 95% confidence interval (CI) for the primary MACE endpoint, using the prior CV disease/risk as a covariate. Non-inferiority of TRT to placebo is defined as an upper limit of the 95% CI for HR < 1.5. Median time to event and its 95% CI, as well as Kaplan Meier estimates of the incidence function (cumulative event rates over time) will be determined. The primary analyses will use the Safety Set and will be repeated using the FAS as supportive analyses. Principal Sensitivity analysis will also be performed based on the period of drug exposure that includes MACE occurring during the period from randomization to 365 days post last dose, while events occurring after 365 days post last dose will be censored. Two additional sensitivity analyses of the primary endpoint will also be performed: (1) an analysis that includes MACE occurring during the period from randomization to 30-days-post last dose, events occurring after 30-days-post last dose will be censored and (2) for participants with drug interruption(s) 3 months or longer and events occurring after 30-days-post the start date of the first dose interruption of 3 months or longer, the follow up time will be censored at 30 days from the start date of the first interruption of 3 months or longer.

Time to the secondary CV composite endpoint will be analyzed using methods similar to the primary endpoint. Other safety endpoint rates include all-cause mortality, heart failure events (hospitalization or urgent visit), deep vein thrombosis/pulmonary embolism/venous thromboembolism (excluding superficial thrombophlebitis) and peripheral arterial revascularization.

Determination of sample size

This non-inferiority study plans to observe a total of 256 primary composite MACE endpoints to rule out a HR of 1.5 at the 95% (2-sided) upper confidence limit (ie, 1-sided alpha = 2.5%) with 90% power. With an estimated annual placebo event rate of 1.5%, an accrual period of 3.5 years, and an annualized lost to follow-up rate of 2%, approximately 5,400 participants (2,700 per treatment arm) are needed to observe the 256 required events for the primary analysis. However, in order to achieve similar power for the principal sensitivity analysis (ie, analysis to censor participants after 365 days post last dose), approximately 6,000 participants (in a 3.5-year accrual period) will be needed, assuming the treatment discontinuation rate is 20% in the first year, and 10% in subsequent years. Therefore, the study plans to enroll approximately 6,000 participants (3,000 per treatment arm) and will be concluded after 256 MACE are observed. The study duration is projected to be 5.2 years under the alternative hypothesis (True HR = 1.0, ie, no increased risk with TRT) and 4.4 years under the null hypothesis (True HR = 1.5).

The protocol specified a blinded review of pooled study data after randomization of ~4,500 subjects or at approximately 2.5 years from the first subject enrolled to evaluate rates of the MACE endpoint, accrual, lost to follow-up, and treatment discontinuation against the original estimates used in the study design. This blinded sample size re-estimation review took place on December 14, 2020, at which time the decision was made to maintain the planned 6,000 patient sample size. As of July 1, 2021, 5,076 subjects had been randomized.

Study organization

The TRAVERSE Study is funded by a consortium of testosterone manufacturers led by AbbVie, Inc (North Chicago, IL), and coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research, Cleveland, OH). LabCorp Drug Development serves as the Contract Research Organization and provides data and site management. The physician leadership and the sponsor designed the study. The Executive Steering Committee, consisting of 9 academic members with expertise in cardiology, endocrinology, urology and biostatistics, and the Physician Leadership Committee have the responsibility for scientific and medical conduct of the study and publication of results. An independent Data Monitoring Committee, consisting of endocrinologists, cardiologists, urologists, clinical trialists, and statisticians supported by an independent data analysis center at the University of Wisconsin, Madison, monitors the safety of the study and has access to unblinded data. The efficacy and prostate substudies are coordinated by the Research Program in Men's Health, Aging and Metabolism, Brigham and Women's Hospital, Boston, MA. The bone fracture substudy is coordinated through University of Pennsylvania, Philadelphia. The appropriate national and institutional review boards approved the protocol, and all subjects provided written informed consent. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting, editing and final content of the manuscript, and the decision to submit.

Perspective

TRAVERSE is the largest and longest duration randomized study of TRT ever conducted. With a greater number of MACE endpoints than all other randomized trials to date combined, TRAVERSE will address the uncertainty regarding CV safety of this therapy among middle-aged or older men with or at high risk for CV disease. By virtue of its large sample size and treatment duration, this study will also allow assessment of prostate safety and provide potentially useful information regarding the long-term efficacy of TRT in improving sexual function, depressive symptoms, anemia, progression from prediabetes to diabetes or glycemic remission in those with diabetes, and risk of bone fractures.

Conflict of interest

Dr. Bhasin reports receiving research grants from NIA, NINR, NICHD-NCMRR, Alivegen, AbbVie, and Metro International Biotech, and consultation fees from OPKO. These grants are managed by the Brigham and Women's Hospital.

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