ORIGINAL RESEARCH

Benefits of Testosterone Replacement Therapy in Hypogonadal Males

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Importance: **Hypogonadism is defined by consistently low serum testosterone levels in conjunction with clinical symptoms. Testosterone replacement therapy (TRT) can be used to achieve physiologic levels of testosterone. Testosterone deficiency is associated with increased mortality and poorer health outcomes.**

Purpose: **To compare rates of mortality, atrial fibrillation (AF), stroke, myocardial infarction (MI), and prostate cancer in hypogonadal men who received TRT versus those who did not.**

Methods: **The TriNetX database was utilized to access deidentified, retrospective propensity matched EMR data from 57 participating health care organizations between 2005 to 2020. Cohorts included males 40 to 80 years old diagnosed with hypogonadism who were prescribed TRT versus no TRT. Propensity matching was performed to reduce bias and balance confounding factors between the 2 groups. The following 3-year outcomes were analyzed: mortality, AF, stroke, MI, and prostate cancer.**

Results: **There were 163,456 male patients identified with hypogonadism, and 133,584 were included after propensity matching. There was a lower mortality rate, (3.1% vs 3.6%; RR, 0.886; $P < .001$), decreased risk of AF (3.6% vs 4.0%; RR 0.900; $P < .001$), less stroke (1.6% vs 1.8%; RR, 0.898; $P < .011$), and fewer cases of prostate cancer (1.9% vs 2.9%; RR 0.648; $P < .001$) for patients on TRT.**

Conclusions: **Using TRT is associated with moderately lower rates of mortality, atrial fibrillation, stroke, and prostate cancer in hypogonadal men versus no TRT. There is potential for missed cases of stroke, prostate cancer, and cardiovascular disease incidence not captured by the database. As prescriptions of TRT increase, understanding risks and benefits will help guide future practice. (J Am Board Fam Med 2024;37:816–825.)**

Keywords: **Cardiovascular Diseases, Chronic Disease, Hormone Replacement Therapy, Hypogonadism, Lifestyle, Preventive Medicine, Primary Health Care, Reproductive Health, Testosterone**

Introduction

Hypogonadism is failure of the testes to produce physiologic levels of testosterone (T).[1] It is defined by consistently low serum testosterone levels in conjunction with clinical symptoms.[2] Testosterone levels vary significantly, due to diurnal and seasonal changes as well as between individuals. For this reason, at least 2 measurements of fasting, morning serum T should be acquired 4 weeks apart to establish the diagnosis.[3] Multiple guidelines propose different serum T cut offs for male

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hypogonadism, ranging from 231 ng/dL to 300 ng/dL, so it is important to look at the entire clinical picture.[4] Clinical manifestations of testosterone deficiency (TD) present sexually, physically, and psychologically.

The rate of testosterone prescription has increased 3- to 8-fold in the United States since 2008.[5,6] However, during the years 2013 and 2014, testosterone replacement therapy prescriptions had a tumultuous decline owing in part to a change in guidelines and mention of a possible increase in suspected cardiovascular risk.[7] Since then, after further investigation and an accruing evidence base in favor of decreased negative cardiovascular outcomes, along with favorable insurance and industry sentiments, TRT prescription rates benefited from a resurgence. It is estimated that 10 to 31% of men diagnosed with hypogonadism have a testosterone prescription, equating to 0.8-2.91% of the total population.[8]

Most longitudinal community-based population studies have demonstrated significant associations between TD and all-cause mortality.[9] A meta-analysis of 12 community-based studies demonstrated a 35% increased risk of all-cause mortality and a 25% increase in Cardiovascular Disease (CVD) mortality in association with a 2.18 standard deviation decrease of serum T.[10] As such, this study is significant in adding to existing literature to answer the question of whether TRT prescriptions in select males with hypogonadism are safe and possibly protective from a cardiovascular disease and prostate cancer risk standpoint.

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide, affecting 2.7 to 6.1 million US individuals in 2010, and prevalence of the dysrhythmia is expected to double in the year 2030.[11] Prevalence of AF is higher in men than women and increases with age.[12] It has been shown that normalization of T levels by TRT is associated with a significantly lower incidence of AF when compared with non-normalized treated and untreated groups.[11] However, other studies noted a modest positive association between the incidence of AF in men and total serum testosterone concentrations.[13,14]

For individuals over 20 years of age, stroke was the fifth leading cause of death in the United States between 2009 and 2012.[15] One prospective observational study with a median follow-up period of 3.5 years consisting of 3,775 males over the age of 70 correlated free testosterone levels at baseline below 222 pmol/L with a higher incidence of stroke in older men when adjusting for confounding variables.[16] Another, smaller scale study corroborated these findings by measuring levels of sex hormones including free and total testosterone levels in a broad array of males aged between 35 and 92 years with ischemic strokes and noted a decrease of 18 to 20% in total and free serum testosterone in subjects with strokes when compared with an age-approximated control population.[17]

Cardiovascular death is the leading cause of death in the United States, with over half of those being from acute myocardial infarction.[18] Recent studies have reported a relationship between TD and atherosclerosis, coronary artery disease, and Cardiovascular (CV) events.[19] Previously, the cardiovascular safety of TRT in hypogonadal men had not been determined, but the TRAVERSE study shows promising results.[14] This randomized, placebo controlled trial enrolled 5,246 clinically hypogonadal men between the ages of 45 to 80 who had preexisting or high risk of CV disease and the TRT group was found to be noninferior to placebo in incidence of major adverse cardiac events.[14]

TRT was once contraindicated in men with prostate cancer based on the hormonal dependence of prostate cancer.[20,21] A systematic review of 44 studies concluded that TRT does not have a significant effect on serum PSA levels.[21,22] In addition, studies have found that patients treated for age-related hypogonadism do not develop prostate cancer at a higher incidence than the general population of untreated men.[21] This is in balance and contrast to a 2004 case report which mentions a marginal increase in PSA in a male on TRT, which decreased when discontinued; however, the article makes an important acknowledgment that a rising PSA level in the setting of androgen therapy does not necessarily mean the patient has prostate cancer.[23]

The goal of this investigation is to use the TriNetX database to compare health outcomes in hypogonadal men who received TRT and those who did not to determine the safety of exogenous testosterone.

Methods

TriNetX is a global health care research network that provides access to deidentified, retrospective EMR data. This study utilized the US Collaborative

Network consisting of 57 health care organizations (HCOs) and approximately 100 million patients. The participating HCOs are predominantly located in the US and include academic medical centers, specialty physician practices, and community hospitals.

Study Cohort

The platform was used to generate 2 cohorts consisting of men between 40 and 80 years old at the time of their hypogonadism diagnosis, identified using the International Statistical Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10) codes E29.1. The first cohort included patients who were prescribed testosterone (T) within 3 months on or after hypogonadism was diagnosed. Inclusion criteria for the second cohort consisted of male patients without a prescription of testosterone before or up to 3 years after the diagnosis of hypogonadism. The second cohort did not receive any prescription of testosterone through any route, including buccal, gel, transdermal, pellets or clomiphene citrate. The 3-year time frame was set for the second cohort to exclude any patients who may have been started on testosterone replacement therapy within the outcome period. Prescription of testosterone was identified using RXNORM:10379. Data were analyzed within the time window of January 1, 2005, through May 1, 2020. Patients were excluded if the index event occurred greater than 20 years before the time of analysis.

Outcomes

For each cohort the following 3-year outcomes were analyzed: mortality, AF, stroke, myocardial infarction (MI), and prostate cancer (PC). Patients with any outcomes before the 3-year period of analysis were excluded to maintain the structural integrity of the cohort study. We evaluated patient diagnoses with hypogonadism from the years 2005 - 2020 and excluded the following 3 years (2020 to 2023) as these were potential follow-up years for outcomes of interest in patients diagnosed in 2018 to 2020. Limitations of the database restrict data collection behind 20 years from the present.

The respective ICD-10 codes used to identify these diagnoses within the cohorts were: I48, I63, I21, and C61. Mortality is identified in the database as a demographic. Mortality data within the TriNetX platform is obtained from EMR data and HCOs, in conjunction with national death registries. There is potential for missed death events when a patient is treated at an HCO not affiliated with the TriNetX network and subsequently experiences a fatal outcome outside of this network. However, this represents only a minor issue, as currently, 94% of Health care Organizations (HCOs) within the TriNetX network are also linked to the US death registries. The search was generated on August 16, 2023.

Propensity Matching

A 1:1 propensity score matching was conducted with linear and logistic regression to limit confounding variables. Linear regression was used for any continuous variables for which propensity scoring was done such as age. Logistic regression was done for those items that were dichotomous. Variables included were age, race/ethnicity, and preexisting conditions including hypertensive diseases (I10-I16), diabetes mellitus (E08-E13), acute kidney failure and chronic kidney disease (N17-N19), overweight and obesity (E66), heart failure (I50), cardiac arrest (I46), ischemic heart diseases (I20-I25), and malignant neoplasm of the bronchus and lung (C34). These preexisting conditions were included in propensity matching because they are known risk factors for the analyzed outcomes. Greedy nearest-neighbor matching was used with a tolerance of 0.1 and a difference between propensity scores less than or equal to 0.1. The order of data rows is randomized in TriNetX to mitigate bias introduced by the nearest-neighbor algorithm. These methods have been previously validated.[24]

Statistical Analysis

Statistical analysis was completed through the TriNetX platform. Univariate analysis was performed using the measure of association tool with Chi-Square and t-testing to provide comparisons of patients with measured outcomes in each cohort, risk (within cohort), risk difference (between cohorts), risk ratio (RR), accompanied by 95% confidence intervals (CI) with *P*-values. Statistical significance was set with a 2-sided α of less than 0.05. Patients with outcomes from before the time window or with previous outcome diagnoses were excluded. Comparisons were made before and after propensity matching.

IRB Approval

Utilization of the data from TriNetX does not require UTMB IRB review as this is secondary analysis of deidentified data. The UTMB IRB

determined that this project is considered "not human subjects research."

Results

The queries returned a total of 163,456 patients, before propensity matching for demographics and risk factors from 57 HCOs within the US Collaborative network. Cohort 1 was prescribed testosterone after a diagnosis of hypogonadism. Cohort 2 was not prescribed testosterone before or within 3 years of a hypogonadism diagnosis. The query for cohort 1 included 57 HCOs with 68,448 patients. The query for cohort 2 included 57 HCOs with 95,008 patients. Following propensity matching, there were a total of 133,584 patients diagnosed with hypogonadism. The cohorts were thus well-balanced with 66,792 patients each in the testosterone and no testosterone groups. Outcomes were tabulated 3 years following the initial diagnosis of hypogonadism.

Before propensity matching, there was statistical significance between all demographic groups except Native Hawaiian or Other Pacific Islander. All preexisting risk factor groups before propensity matching were significantly different between cohorts 1 and 2 except for Malignant Neoplasm of Bronchus & Lung. Table 1 presents demographic trends in cohorts 1 and 2 before and after propensity matching. Table 2 presents preexisting risk factor trends in cohorts 1 and 2 before and after propensity matching. After propensity matching, most of the differences between demographic factors and preexisting conditions were eliminated.

Analysis of the 2 cohorts showed statistically significant differences in all outcomes except MI (Table 3 and 4). There was a lower mortality rate, (3.1% vs 3.6%; RR, 0.886; $P < .001$), decreased risk of AF (3.6% vs 4.0%; RR 0.900; $P < .001$), decreased risk of stroke (1.6% vs 1.8%; RR, 0.898; $P < .011$), and fewer cases of prostate cancer (1.9% vs 2.9%; RR 0.648; $P < .001$) for patients on TRT when compared against patients with hypogonadism who were not prescribed TRT. These results were similar in the nonpropensity-matched groups,

Table 1. Patient Demographics Before and After Propensity Matching

		Before Propensity Matching				After Propensity Matching			
Cohort	Demographics	Mean ± SD	Patients	% of Cohort	*P*-value	Mean ± SD	Patients	% of Cohort	*P*-value
1	Male sex		68,448	100	–		66,792	100	–
2			95,008	100			66,792	100	
1	Age at index	56.6 ± 9.8	68,448	100	<0.001	56.7 ± 9.8	66,792	100	0.013
2		57.4 ± 10.3	95,008	100		56.8 ± 10.0	66,792	100	
1	White		54,326	79.4	<0.001		52,777	79.0	0.809
2			71,724	75.5			52,741	79.0	
1	Not Hispanic or Latino		48,285	70.5	<0.001		46,797	70.1	0.862
2			62,407	65.7			46,826	70.1	
1	Unknown ethnicity		17,364	25.4	<0.001		17,208	25.8	0.535
2			27,735	29.2			17,109	25.6	
1	Unknown race		7,819	11.4	<0.001		7,770	11.6	0.308
2			13,099	13.8			7,651	11.5	
1	Black or African American		5,062	7.4	<0.001		5,024	7.5	0.010
2			8,077	8.5			5,274	7.9	
1	Hispanic or Latin		2,799	4.1	<0.001		2,787	4.2	0.341
2			4,866	5.1			2,857	4.3	
1	Asian		894	1.3	<0.001		894	1.3	0.030
2			1,653	1.7			805	1.2	
1	American Indian or Alaska Native		190	0.3	0.005		171	0.3	0.785
2			198	0.2			166	0.2	
1	Native Hawaiian or Other Pacific Islander		157	0.2	0.103		156	0.2	0.955
2			257	0.3			155	0.2	

Abbreviation: SD, Standard deviation.

Table 2. Preexisting Conditions Associated with Mortality Before and After Propensity Matching

			Before Propensity Matching			After Propensity Matching		
Cohort	I-10	Condition	Patients	% of Cohort	*P*-value	Patients	% of Cohort	*P*-value
1	I10-I16	Hypertensive diseases	31,527	46.1	<0.001	29,941	44.8	0.010
2			34,736	36.6		30,409	45.5	
1	E08-E13	Diabetes mellitus	15,137	22.1	<0.001	14,304	21.4	0.009
2			17,220	18.1		14,697	22.0	
1	E66	Overweight & obesity	13,768	20.1	<0.001	12,367	18.5	0.366
2			12,804	13.5		12,239	18.3	
1	I20-I25	Ischemic heart diseases	8,081	11.8	<0.001	7,815	11.7	0.037
2			10,086	10.6		8,062	12.1	
1	N17-N19	Acute kidney failure & chronic kidney disease	5,689	8.3	<0.001	5,319	8.0	0.992
2			6,098	6.4		4,320	8.0	
1	I50	Heart failure	2,765	4.0	<0.001	2,639	3.9	0.544
2			3,209	3.4		2,595	3.9	
1	C34	Malignant neoplasm of bronchus & lung	280	0.4	0.080	280	0.4	0.439
2			262	0.4		262	0.4	
1	I46	Cardiac arrest	137	0.2	<0.001	110	0.2	0.405
2			107	0.1		98	0.1	

Abbreviation: ICD-10, International Statistical Classification of Diseases, Tenth Revision.

with a significantly decreased mortality rate (3.2% vs 3.4%; RR 0.940; $P = .023$), decreased risk of AF (3.6% vs 4.2%; RR 0.873; $P < .001$), decreased risk of stroke (1.6% vs 1.7%; RR 0.915; $P = .023$), and fewer cases of prostate cancer (1.9% vs 3.3%; RR 0.575; $P < .001$). See Table 5 for a representation of exclusions from each cohort for each outcome; patients were excluded if they had one of the outcomes before the diagnosis of hypogonadism.

Discussion

In this study, the hypogonadal men treated with TRT within 3 months of diagnosis had significantly lower rates of mortality, atrial fibrillation, stroke, and prostate cancer compared with the hypogonadal men who received no testosterone within 3 years of diagnosis following propensity matching. There was a nonsignificant lower rate of myocardial infarction in the treatment cohort. This high-powered study is currently the largest analysis concerning testosterone replacement therapy and mortality, with generalizable findings after propensity matching.

Testosterone status has been linked to the general health of the male population.[9] Whether this is an etiology or an association is not entirely known. Low testosterone has also been linked to increased all-cause mortality in disease-specific populations, such as type 2 diabetes mellitus and acute MI.[9] The Seattle study retrospectively analyzed 1031

Table 3. Mortality, Cardiovascular, and Prostate Cancer 3-Year Outcomes After Propensity Score Matching

Outcome	ICD-10	Cohort 1 (Prescribed T)	Cohort 2 (Not Prescribed T)	Risk Ratio	95% CI	*P*-value
Mortality	–	0.031	0.036	0.886	(0.836, 0.939)	<0.001
AF	I48	0.036	0.040	0.900	(0.851, 0.951)	<0.001
Stroke	I63	0.016	0.018	0.898	(0.826, 0.975)	0.011
MI	I21	0.018	0.019	0.977	(0.903, 1.057)	0.559
PC	C61	0.019	0.029	0.648	(0.603, 0.695)	<0.001

Abbreviations: ICD-10, International Statistical Classification of Diseases, Tenth Revision; T, testosterone; AF, atrial fibrillation; MI, myocardial infarction; PC, prostate cancer.

Table 4. Mortality, Cardiovascular, and Prostate Cancer 3-Year Outcomes Before Propensity Score Matching

Outcome	ICD-10	Cohort 1 (Prescribed T)	Cohort 2 (Not Prescribed T)	Risk Ratio	95% CI	*P*-value
Mortality	–	0.032	0.034	0.940	(0.890, 0.991)	0.023
AF	I48	0.036	0.042	0.873	(0.830, 0.918)	<0.001
Stroke	I63	0.016	0.017	0.915	(0.848, 0.988)	0.023
MI	I21	0.019	0.018	1.032	(0.960, 1.110)	0.392
PC	C61	0.019	0.033	0.575	(0.539, 0.614)	<0.001

Abbreviations: ICD-10, International Statistical Classification of Diseases, Tenth Revision; T, testosterone; AF, atrial fibrillation; MI, myocardial infarction; PC, prostate cancer; CI, Class interval.

hypogonadal (T < 250 ng/dL) male veterans over the age of 40 and compared survival rates in those who received TRT and those who did not. After propensity score adjustment, they found TRT was associated with a decreased risk of death.[25]

In their retrospective observational VA cohort study, Sharma et al. analyzed 3 groups of propensity-matched male veterans aged between 40 to 69 with documented low testosterone levels: those who received testosterone replacement with normalization, those who received therapy without normalization, and those who did not receive any testosterone replacement therapy. The study found that all-cause mortality, risk of MI, and stroke were significantly lower in those males who received testosterone replacement therapy with normalization than those whose testosterone levels did not normalize. While their study relied on a different database and cohorts, these findings are supported by our much larger study.[26] Fantus et al. showed that hypogonadal men were more likely to have obesity, diabetes mellitus, hypertension, CHF, MI, walking disability, and a higher atherosclerotic cardiovascular disease risk.[27] This study also demonstrated an increased incidence of premature mortality associated with untreated hypogonadism.[27]

Table 5. Patients Excluded If the Outcome Occurred Before the 3-Year Time Frame Evaluated

Outcome	Cohort 1 Exclusion	Cohort 2 Exclusion
Mortality	277	272
AF	3,136	3,236
Stroke	1,086	1,210
MI	1,321	1,352
PC	1,837	3,425

Abbreviations: AF, atrial fibrillation; MI, myocardial infarction; PC, prostate cancer.

In men, the prevalence of AF ranges from 0.2% for those younger than 55 to more than 11% among those over the age of 85.[28] In this study, TRT was associated with an approximately 9% risk reduction in atrial fibrillation rates. It is unclear whether low testosterone has a causal relationship to atrial fibrillation, and if it does, it is most likely multifactorial and heterogeneous.[13] Evidence supports a relationship between TD and increased risk factors for AF.[29] Diabetes mellitus, hypertension, obesity, and metabolic syndrome have been associated with lowered testosterone in men.[29] Animal models have demonstrated that modification of systemic hormones can alter atrial electrophysiology: orchiectomized rats showed greater repetitive atrial responses compared with controls.[30]

A population-based study of 1,482 men found that lower total testosterone levels were significantly related to increased carotid intima-media thickness, an indicator for general atherosclerosis.[31] Hypogonadism has also been linked to risk factors associated with cerebrovascular disease, such as blood pressure, increased serum cholesterol, diabetes, AF, obesity, and smoking.[17,32] In a study of 167 men with acute ischemic stroke, total and free serum T concentrations were 18% and 20% lower, respectively, than healthy control subjects.[17]

Three studies published from 2010 to 2014 suggested an association between adverse CV events and exogenous testosterone use.[33,34] In March of 2015, the Food and Drug Administration (FDA) changed the labeling for testosterone prescriptions to reflect the possible increased risk of heart attacks and strokes.[35] This action may have been in response to the literature written by Vigen et al.,[7] a retrospective national cohort study of all males with low testosterone in the VA system who received a coronary angiogram and had serum testosterone levels checked.[7] The study had noted a significant

increase of death, MI and stroke in the population, and the resulting data were implicated in the premature discontinuation of the Testosterone in Older Men with Mobility Limitations (TOM) trial conducted in older frail men with a high prevalence of cardiovascular diseases.[33]

Many studies since this label change have shown the opposite association, including our study. Although our query did not find a statistically significant reduction in MI when comparing the TRT group with the control group, the TRT group had slightly lower rates of MI (1.8% vs 1.9%) and a higher-powered patient population could show a significant protective association. The findings in our study also agree with a meta-analysis of 70 studies which demonstrated significantly lower T and higher 17-β estradiol levels in patients with CV disease, even after adjusting for age and body mass index.[19,36] The TRAVERSE study further provides clarity on the safety of TRT in men with CV risk factors and established CVD.[13] Baillargeon et al. demonstrated that older men treated with IM testosterone did not have an increased risk of MI. Testosterone use was also found to be modestly protective for men with high MI risk.[37]

Prostate cancer has historically been a feared complication of TRT, due to the androgen dependency of these tumors[38]; however, our findings demonstrate a 35.2% reduction in PC in the treated group. There is no conclusive evidence that high serum T levels are associated with increased prostate cancer risk.[38] Several trials have demonstrated no increase in the risk of prostate cancer in hypogonadal men on TRT versus the general population.[39] The saturation theory proposes that prostate growth is extremely sensitive to variations in testosterone at very low concentrations, but becomes insensitive to changes in testosterone concentrations at higher levels.[40] This could explain why men with baseline total T less than 250 ng/dL are more likely to have increased prostate specific antigen (PSA) levels after TRT than those with a baseline total T of 250 ng/dL or greater.[41]

A significant limitation of this study is that it is assumed that the men in Cohort 1 reached physiologic levels of testosterone with TRT. In other words, the numeric testosterone values of men on TRT after prescription was not obtained, and it is unknown whether males who received this therapy remained subtherapeutic, normalized, or were supratherapeutic. If some of the men in Cohort 1 remained hypogonadal or supratherapeutic with treatment, the observed relationship in the variables studied may be skewed. Future studies demonstrating an assessment of the proportion of each arm that reached eugonadal levels after approximately 3 months of prescription following established guidelines would be beneficial to address this.

There is a potential for missed cases of atrial fibrillation, stroke, myocardial infarction and prostate cancer if the patient was treated at an HCO not affiliated with the TriNetX network. Limiting the analyses to men who have at least 2 visits after their hypogonadism diagnoses could reduce the bias for men who seek treatments at non-TriNetX health care organizations and could serve as a sensitivity analysis. Diagnoses of intermediate endpoints between cohorts like total testosterone, BMI, total cholesterol, HgbA1c or new antihypertensives were not available on the database at the time of data collection; the inclusion of such data if it were available could serve to further reduce confounding bias.

Another limitation of this study is that it is retrospective. Retrospective studies can suggest associations between treatment groups and health outcomes, but due to confounding it can be difficult to establish causality. By using propensity matching and analyzing present outcomes after a retrospective review as has been done in this study, it is plausible to draw causal inferences. While propensity matching for several comorbidities was performed, there may be other conditions (for example, smoking history) during data collection that could serve as confounding variables. Unfortunately, such characteristics were not accessed from the database. The corollary to this is that major articles in the literature that have influenced the prescription of TRT have been retrospective in nature. Noting this, further investigation through a prospective randomized controlled study could strengthen the causality between these variables and address a gap in the literature.

Overall, the use of TRT to achieve physiologic testosterone levels is associated with a decrease in mortality, AF, stroke, and prostate cancer. The prevalence of age-related hypogonadism is not known with certainty due to variations in diagnostic criteria between organizations, but it is projected to be up to 25%.[42] Normalizing testosterone levels in these men through the use of TRT can improve quality of life and reduce risk factors associated with increased morbidity/mortality. Future studies

should aim to measure testosterone levels after TRT and determine threshold levels for both risks and benefits for various outcomes to determine the optimal therapeutic level of testosterone. This data would guide clinicians in determining optimal replacement dosing for patients.

The goal of this study is to evaluate health outcomes in hypogonadal men receiving TRT compared with those who did not. In the largest study to date, TRT in hypogonadal men was associated with significantly lower rates of mortality, atrial fibrillation, stroke, and prostate cancer. Testosterone's effects on risk factors associated with these outcomes is an important area of study that should be further expanded on in the future. As the rates of testosterone prescribing increase, it is important to investigate the benefits/risks and optimal levels for TRT. This will help guide physicians in their prescribing practices and patient education.[43]

To see this article online, please go to: http://jabfm.org/content/37/5/816.full.

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Appendix 1

Greedy Nearest Neighbor Matching (NNM)

The most common implementation of propensity matching is pair-matching, in which pairs of treated and control participants are formed. There are several common implementations of pair-matching. The most commonly used is greedy nearest neighbor matching (NNM), which we used, in which a treated participant is selected at random and then matched to the control participant whose propensity score is closest to that of the treated participant. The process is described as greedy because at each stage the control is selected who is closest to the currently considered treated participant, even if that untreated participant would serve better as a control for a subsequently treated participant. This process is then repeated until a matched control participant has been selected for each treated participant. This process generally uses matching without replacement, so that once a control participant is matched to a treated participant, that control participant is no longer available for matching to a subsequent treated participant. A refinement to NNM is NNM with a caliper restriction. Using this approach, a control participant is an acceptable match for a treated participant only if the difference in their propensity scores is less than a maximum amount (the caliper width or distance). For technical reasons, one typically matches on the logit of the propensity score and uses a caliper width that is defined as a proportion of the (0.1–0.2) SD of the logit of the propensity score. A crucial step in any study that uses propensity score matching is to assess the degree to which matching on the propensity score resulted in the formation of a matched sample in which the distribution of baseline characteristics is similar between treated and control participants. This assessment is critical as it allows both the researcher and readers to assess whether matching on the estimated propensity score has removed systematic baseline differences between treatment. The use of the standardized difference, which is the difference in means in units of SD, is often used for assessing the similarity of matched treated and control participants. Some authors have suggested that a threshold of 0.10 (or 10%) be used to denote acceptable balance after matching. Once acceptable balance has been achieved, analysts can unblind themselves to the outcome and compare outcomes between treated and control participants in the matched sample. The analyses conducted in the propensity score–matched sample can be similar to those that would be done in an Randomized Controlled Trial (RCT) with a similar outcome.