Published in final edited form as:

Curr Sex Health Rep. 2014 December 1; 6(4): 235–243. doi:10.1007/s11930-014-0030-x.

The implications of low testosterone on mortality in men

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Abstract

Testosterone levels in men slowly decline with aging and also decline more abruptly due to medical illness or medications. Prescriptions for testosterone have increased dramatically over the past decade, since a testosterone-gel formulation was approved and since numerous studies reported an association between low serum testosterone and increased mortality. However, recent observational studies of testosterone treatment have reported conflicting results with some studies reporting decreased risks for mortality while others reported increased mortality risks with testosterone treatment. This paper will summarize recent studies of low serum testosterone and mortality and testosterone treatment and mortality and what the potential implications of these studies are for the clinician.

Keywords

Testosterone; Androgens; Hypogonadism; Testosterone treatment; Mortality; Cardiovascular events

Introduction

Testosterone levels in men slowly decline by approximately 1% per year beginning at ages 30–40. [1] Testosterone levels also decrease with acute illness, such as myocardial infarction (MI), stroke, or trauma, and with chronic illnesses, such as diabetes, end stage liver disease, renal disease, and with medications such as steroids, opiates, or spironolactone. [2–4] Testosterone levels decline more rapidly in medically ill or obese men, [5] but most older men, particularly healthy older men, have normal testosterone levels into old age. [6, 7] In contrast to women, who have a complete cessation of gonadal hormone secretion following menopause, the decline in testosterone in men is variable, gradual, and potentially reversible. The decline in testosterone levels may be reversible, as testosterone levels may increase with recovery from acute or chronic illness, with discontinuation of opiates or steroids, and with weight loss and exercise. [8, 9]

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Molly M. Shores reports no conflict of interest.

The diagnosis of hypogonadism is based on two low morning testosterone levels and the presence of signs and symptoms of low testosterone which include irritability, decreased concentration, fatigue, decreased libido, erectile dysfunction, hot flushes or sweats, gynecomastia and decreased muscle mass and strength. [10, 11] Several of the signs and symptoms of hypogonadism are nonspecific and could be caused by aging, medical illness, or medications. In addition to these symptoms, low testosterone levels are also associated with insulin resistance, metabolic syndrome, diabetes, increased central obesity, dyslipidemia, decreased bone mineral density, and osteoporosis [10, 11]. Treatment guidelines recommend considering a diagnosis of hypogonadism if a man has signs or symptoms of hypogonadism and total testosterone levels of 230–350 ng/dl and to strongly consider the diagnosis at total testosterone levels less than 230 ng/d. [10, 11]. However, there is no consensus for a specific threshold for low testosterone in older men. Most thresholds are based on what would be considered a normal testosterone level in younger men, while some studies have suggested that thresholds be based on the lowest decile of testosterone in a community sample of older men. [12–14] Given the lack of a clear threshold level for low testosterone in older men and that older men are more likely to have acute and chronic medical conditions and medications that affect testosterone levels, the diagnosis of hypogonadism is more complex in older men than younger men. [15] A recent study examined various testosterone levels and symptoms to validate those that predicted hypogonadism in older men. The study found that late onset hypogonadism (LOH) was defined by a total testosterone level less than 320 ng/dl and 3 sexual symptoms and that severe LOH was a total testosterone less than 230 ng/dl and 3 sexual symptoms. [16]

Over the past decade there has been a 10-fold increase in testosterone prescriptions in the United States [17] which occurred following the introduction of testosterone-gels and after several studies reported that low serum testosterone levels were associated with an increased risk for mortality. However, the only approved indication for the use of testosterone is a diagnosis of hypogonadism and it is unlikely that the incidence of hypogonadism has increased that markedly over the past 10 years. Furthermore, it appears that many men are being prescribed testosterone inappropriately as a recent study found that approximately 25% of men who received a new prescription for testosterone did not have serum testosterone levels obtained prior to receiving a prescription for testosterone. [18] This is particularly concerning. [17, 19] since some recent studies have reported that testosterone treatment is associated with an increased risk for mortality or serious cardiovascular (CV) events [20–22] while others have not. [23–25] The purpose of this paper will be to summarize recent studies that have examined the association of serum testosterone and testosterone treatment with mortality and what the implications of these recent studies may be for the clinical practitioner.

Studies of serum testosterone and mortality

Many studies have been published on the association of serum testosterone and mortality over the past decade. The most recent meta-analysis, published in 2011, included 12 studies of over 16,000 men and reported that low serum testosterone levels were associated with a 35% increased risk for mortality with a HR of 1.35 (1.13–1.62) [26]. Studies that included older men (mean age greater than 60 years) or that had lower mean testosterone levels were

more likely to report an association with low testosterone and mortality. [26]. Since then, 20 additional studies that include over 38,000 men have been published. Most of these studies (85%) found that low levels of testosterone or dihydrotestosterone (DHT), an active metabolite of testosterone, were associated with increased overall mortality [13, 14, 23, 27–38] but some did not. [38–42]. Two studies found that high levels of testosterone were associated with increased mortality in men with cancer. [38, 42] (Table 1).

These recent studies generally used a clearly low threshold to define low testosterone, one that would likely to be consistent with hypogonadism. One study reported that a low threshold level for total testosterone (less than 230 ng/dl) was associated with a more than doubling in the risk for mortality with a hazards ratio (HR) for overall mortality of 2.3 (1.2–4.2), but found no association with testosterone and mortality at higher levels of testosterone. [31] Furthermore, in that study men who had both low testosterone levels and symptoms of sexual dysfunction had a much greater risk for overall mortality with a HR of 5.5 (2.7–11.4), than men who had low testosterone but no sexual symptoms. Three other studies reported that androgens had a curvilinear relationship with mortality and CV events, in which both low and high levels were associated with an increased risk and that an intermediate level was associated with the lowest risk. [28, 29, 36] In one study, free testosterone was associated with overall and cardiovascular (CV)-mortality in a curvilinear manner, with HRs of 1.62 and 1.71 respectively. [36] In another study, total and free testosterone and DHT had a curvilinear relationship with overall mortality in which the third quartile was associated with the lowest risk and levels above or below this were associated with increased risk. [28] In a final study, DHT had a curvilinear relationship with total mortality in which an intermediate DHT level of 50–74 ng/dl, which was slightly above the average DHT level, was associated with the lowest risk and levels above and below this were associated with increased risk. [29] The results of curvilinear relationships are consistent with a study that reported a curvilinear relationship with testosterone and ischemic events. [43]. Given the possibility of a curvilinear association, men who are treated with testosterone should be monitored to ensure that testosterone levels have increased to a therapeutic, but not to a high testosterone level, as either low or high levels may be associated with increased risk.

Low testosterone and mortality in specific medical conditions

Most of the recent studies examined community dwelling men. However, a few studies focused on men with specific medical conditions including renal disease, sexual dysfunction, diabetes, prostate cancer and cancer. [44]

Renal disease—In two different studies, men on hemodialysis with low total testosterone levels (less than 230 ng/dL) had nearly a tripling in overall mortality risk with a HR of 2.8 (1.2–6.3) in one study [34] and 2.93 (1.10–7.78) in another study in men who were less than 63 years old. [37] In a third study of men with chronic kidney disease who were not on dialysis, increases in the log of serum total testosterone were associated with a 30% decrease in mortality with a HR of 0.70 (0.55–0.89). [45]

Sexual dysfunction—Erectile dysfunction (ED) is known to be a risk factor for CV events and CV-mortality [46, 47] and recent studies reported that men with both sexual dysfunction and low testosterone levels were at an increased risk for CV events and CV-mortality. [31, 48, 49] One study found that in men with ED each additional sexual symptom increased the risk for CV mortality, with a HR of 1.2 (1.0–1.5) for each sexual symptom, and that men who had both low total testosterone and ED had a marked increase in CV mortality with a HR of 7.1(1.8–28.6) [48]

Prostate Cancer—A concern about testosterone treatment has been that it may increase the risk for incident prostate cancer or increase the risk for aggressive prostate cancer, as testosterone is known to stimulate the growth of prostate cancer in vitro. However, there have been no studies that have found that serum testosterone levels are a risk factor for incident prostate cancer and a recent large, longitudinal study reported that there was no association between pre-diagnostic testosterone levels and risk for prostate cancer mortality or overall mortality. [40]

Androgen Deprivation Therapy—Androgen deprivation therapy (ADT), which decreases testosterone to castrate levels, is a common treatment for men with prostate cancer as it is associated with decreased prostate specific antigen (PSA) levels, increased survival time and improved symptoms in men with metastatic prostate cancer. [50] However, several studies have noted that men treated with ADT, develop increased insulin resistance, metabolic syndrome, diabetes and have increased CV events, CV mortality, and overall mortality within months of starting ADT compared to men who are not treated with ADT. [51–53] This remains an evolving research area, however, as a recent study reported no increase in CV mortality associated with ADT of 6 months or less when men were followed for up to 10 years. [54]

Cardiovascular disease and cardiovascular mortality—The most common type of specific mortality associated with low testosterone is cardiovascular (CV) mortality, which includes mortality due to coronary heart disease, myocardial infarction, heart failure, arrhythmia, sudden cardiac death, thrombosis, and stroke. Several reviews [55–58] have recently summarized the association between low testosterone and CV-mortality and reported that in most studies low testosterone is associated with increased CV-mortality. Some factors that may explain the pathophysiologic basis for an association between low testosterone and CV-mortality are that low testosterone is associated with several risk factors for cardiovascular disease and mortality including decreased insulin sensitivity, metabolic syndrome, diabetes, atherosclerosis, and endothelial dysfunction. [55] In recent studies that examined the association of low testosterone and CV mortality, 6/7 found an association with low testosterone and CV mortality [13, 27, 30, 33, 36, 48] while one did not,. [41]

Testosterone treatment and mortality

Testosterone treatment had been thought to be potentially protective against CV disease and mortality due to beneficial metabolic effects of testosterone treatment, including decreased central obesity and body mass index (BMI), improved insulin sensitivity and hemoglobin

A1c and decreased inflammatory markers. In small clinical trials, testosterone treatment has also been associated with beneficial CV effects including a shorter QTc interval, decreased time to ischemic EKG changes during exercise and improved function and exercise tolerance in patients with heart failure but without an improvement in the ejection fraction. [59] Furthermore, three meta-analyses reported that testosterone treatment was not associated with mortality or major adverse CV events in past clinical trials. [60–62] However, recently a clinical trial of testosterone in hypogonadal elderly men with mobility limitations was stopped due to increased CV events in the testosterone-treated men. [22, 63] Subsequent analyses indicated that the increased CV events were associated with a greater increase in free testosterone levels, but were not associated with age or traditional CV risk factors. [63] The significance of these results is unclear as the study was not designed or powered to assess CV-outcomes and the CV events consisted of both minor events (edema and hypertension) and major events (MI and stroke). In addition to that clinical trial, a recent meta-analysis reported an increased risk for CV-events, but no increased risk for CV-mortality in testosterone-treated men. [64] The risk for CV events varied by funding source, with non-industry funded trials with a risk of 2.06 (1.34–3.17) while there was no significant risk in industry funded trials with a HR of 0.89 (0.50–1.60). [64] It is unclear if the lower risk for CV events in industry-funded trials was due to a reporting bias or if there were methodological factors such as healthier subjects or the use of lower doses of testosterone in industry-funded trials.

Recently, large observational studies have reported conflicting results on the association of testosterone treatment with mortality or major adverse CV events.. Three studies reported that testosterone treatment was associated with a decreased risk for overall mortality or MI, [23–25] while two studies found that testosterone treatment was associated with an increased risk for MI or for mortality, MI and stroke compared to men who were not treated with testosterone. [20, 21] See Table 2.

Studies that found that testosterone treatment was associated with a decreased risk for mortality included a study that used a VA clinical database and found that men with low testosterone levels who were treated with testosterone treatment had a 39% decreased risk for mortality with a HR of 0.61(0.42–0.88) compared to men with low testosterone levels who weren't treated with testosterone. [24] Strengths of that study were that a time-varying treatment analysis was used and a propensity score adjustment was done to adjust for the observational study design and the non-randomization to treatment. Limitations were that the men were not randomized to treatment, indications for treatment were unknown and there was limited data on follow-up testosterone levels. In a study of hypogonadal men with type II diabetes, men who were not treated with testosterone had an increased mortality risk with a HR of 2.02 (1.2–3.4) compared to treated men. [23] Strengths of this study were that the men had diagnosed hypogonadism and follow-up testosterone levels were obtained to maintain testosterone levels within a therapeutic range. Weaknesses of the study were that the treated men were not randomized to testosterone treatment and no adjustments were made for the propensity for treatment. In addition, men who had less than one year of testosterone treatment were excluded from the study, which could bias the results against detecting an association of testosterone treatment with early mortality. In a Medicare database study, testosterone treatment was associated with a decreased risk for MI of 31%

with a HR of 0.69 (0.53–0.9) in men who were at a high risk for an MI. [25] Strengths of this study were that it was a large study with a long follow-up period. Limits of this study were that men were not randomly assigned to treatment, indications for treatment were unknown, no baseline testosterone levels were available and treatment was of short duration with 58% of men having 6 weeks or less of testosterone treatment.

Studies that found that testosterone treatment was associated with an increased risk for mortality or CV events included a study of male veterans with low total testosterone levels who had undergone coronary angiography. The men in this study had a high degree of medical morbidity, with documented coronary artery disease in over 80% of men, and were followed for a combined outcome of stroke, MI, and overall mortality. The authors reported that following adjustment, testosterone treatment was associated with a 29% increased risk for adverse outcomes with a HR of 1.29 (1.05–1.58). Strengths of the study were that it had baseline serum testosterone levels and there was adjustment for the observational study design. Limitations of the study were that the men were not randomly assigned to treatment, indications for treatment were unknown and there was limited information on follow-up testosterone levels. Other limitations of the study were that the authors did not supplement the outcomes-data with Medicare data, which likely led to inaccurate outcomes data, as MI and strokes are treated emergently at the nearest hospital, which would include non-VA hospitals. In addition, the study was criticized for not reporting that the raw data indicated that the untreated men had more than double the adverse events as the treated men (21.2% vs. 10.1%), for excluding subjects who had a MI prior to filling a testosterone prescription, and for not clarifying the start time of the study. [65–67] Finally, in a very large cohort that used commercial insurance and Medicare claims data on over 55,000 men, subjects were examined for an increased risk for MI following testosterone treatment. Subjects served as their own control and the rate of MI for 3 months following testosterone treatment was compared to the rate of MI for 12 months before treatment. [21] Testosterone-treatment was associated with a 36% increased risk for a MI in the 3 months following testosterone treatment compared to the risk for MI in the year prior to treatment with a HR of 1.36 (1.03–1.81). This risk for MI was greater in men who were 65 years or older with a HR for 2.19 (1.27–3.77). In testosterone-treated men who were less than 65 years old, the risk for MI was limited to those who had a history of heart disease, with a HR of 2.90 (1.49–5.62). [21] A limitation of this study was that there were no serum T levels at baseline or during follow-up, the indications for T treatment were unknown, and the duration of treatment was short.

In summary, all of the testosterone treatment studies have the limitation of an observational study design, namely that treatment with testosterone was not randomized and so the study results could be related to selection bias rather than to a true treatment effect of testosterone. Also, some studies had no baseline T levels, so it is unclear if the men who received testosterone treatment had low testosterone levels prior to testosterone treatment and it is possible that risks for adverse events with testosterone treatment may be greater in men who do not have low testosterone levels. In addition, most studies had little information on follow-up T levels, so it is unclear if testosterone levels were within the therapeutic range following treatment.

Implications of low testosterone on mortality in men

The majority of observational studies of testosterone and mortality have reported a significant association of low testosterone with mortality in community cohorts and also in specific medical conditions including renal disease, diabetes, erectile dysfunction and men with prostate cancer who are treated with ADT. The large number of studies that have reported this association provides support for the hypothesis that there may be a causal association between low testosterone and mortality. Most of these studies attempted to adjust for the observational study design by adjusting for relevant covariates, the propensity for treatment and conducting sensitivity analyses to minimize the possibility that the results were primarily related to early mortality due to concurrent medical illness. However, despite the efforts to adjust for the limitations of an observational study design, it is still possible that there may have been some unmeasured factor, which was not adjusted for, that contributed to the results.. For example, men who received testosterone treatment may have had better health habits or health care than men who were not treated with testosterone and this is what accounted for differences in mortality.

Low testosterone levels may also be associated with mortality because low testosterone levels may be a marker for underlying medical morbidity.. Evidence that supports this hypothesis is that low testosterone is associated with both acute and chronic medical conditions and testosterone levels normalize following resolution of the acute illness. Also, the association of low testosterone with several types of mortality suggests that the association may be related to overall illness rather than to a causal relationship. In conclusion, currently it is unknown if there is a causal relationship between low testosterone and mortality. However, whatever the causal relationship may be, low testosterone is a marker for increased mortality-risk, particularly in men who have both low testosterone and sexual dysfunction and this provides an opportunity for clinicians to provide for more intensive medical monitoring and management for such men. [16]

Considerations regarding Testosterone Treatment

Testosterone treatment is only approved for men who have a diagnosis of hypogonadism, which is defined as two low morning testosterone levels, plus signs and symptoms of low testosterone and the exclusion of reversible causes of low testosterone. Once a diagnosis of hypogonadism is made, the decision to treat with testosterone or not will depend upon individual patient characteristics, particularly given conflicting reports on the association of testosterone treatment with mortality and serious adverse CV outcomes. However, clinicians may wish to consider treating men with low testosterone and concurrent sexual symptoms, as men with both of these conditions appear to be at greater risk for mortality. In obese men, an initial trial of diet and exercise prior to testosterone treatment should be considered as studies have shown that obese men who exercise and lose weight have an increase in testosterone levels. If testosterone treatment is initiated, it is recommended that expert guidelines be followed which include that testosterone levels, prostate specific antigen (PSA) and hematocrit be monitored following treatment. [68] [69] Finally, It is important to monitor testosterone levels to ensure that they have risen appropriately and also to ensure that they are not too high, as a greater increase in free testosterone was associated with

increased CV events and recent studies have reported curvilinear relationships with testosterone with increased risk for mortality at both low and high levels. [28, 29, 36]

Conclusions

In summary, most observational studies have reported that low serum testosterone levels are associated with increased overall mortality and CV mortality. In contrast, recent epidemiologic studies of testosterone treatment are inconclusive, with 3 studies showing that testosterone treatment was associated with decreased mortality or MI and 2 studies showing an increased risk with testosterone treatment. Current clinical data cannot clearly address whether there is a causal association between low testosterone and mortality or if low testosterone is primarily a marker of medical morbidity as there has not been a large randomized trial conducted to address this. A large randomized, double blind placebo-controlled trial of sufficient duration, comparable in scope to the Women's Health Initiative, will be required to clarify if low testosterone is causally associated with mortality and major CV events. However, such a trial will be very expensive and complex to conduct and the results will not be known for many years. Currently, three large pharmaco-epidemiologic studies, sponsored by the National Institute on Aging (NIA), are examining the association between testosterone treatment and adverse outcomes. In the interim, the results of these pharmaco-epidemiologic studies may help to provide additional data regarding risks associated with testosterone treatment while awaiting the definitive results of an adequately designed and powered randomized placebo controlled study.

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Table 1

Recent studies of serum testosterone and mortality

Study	Number FU-yrs	Patient Population	Outcome	Hazard Ratio (95% CI)	T thresholds	Comments
Wehr[27] 2011	2078 8 yrs.	Coronary angiography	CHF mortality	0.38 (0.17–0.87) 0.37 (0.15–0.89)	FT Q4 vs. Q1 Linear per SD	Higher FT associated with ↓CHF mortality
Ohlsson[33] 2011	2416 5 yrs.	Community	CV events including CV mortality	0.70 (0.56–0.88)	TT >550 ng/dL	Higher TT associated with ↓CV events including mortality
Kyriazis[34] 2011	111 3 yrs.	Hemodialysis	Total mortality	2.81 (1.2–6.4) 2.62 (1.3–5.4)	TT <230 ng/dL FT < 6.05 ng/dL	Low TT and FT associated with ↑mortality in ESRD
Friedrich[12] 2011	3942 5.5 yrs.	Community	Total Mortality	1.54 (1.18–1.98) 3.08 (1.23–6.45)	10 th percentile Low TT or IGF-1 Low TT & IGF-1	Low TT or low IGF-1 associated with ↑mortality with ↑risk if both are low
Haring[14] 2011	1822 10 yrs.	Community	Total mortality in Renal disease	TT 2.52 (1.08–5.85)	10 th percentile	Low TT associated with ↑mortality in renal disease
Corona[48] 2011	1687 4 yrs.	ED Andrology unit	CV mortality	7.1 (1.8–28.6) 1.2 (1.0–1.5)	ED and TT <230 Per sexual symptom	Low TT and sexual symptoms associated with ↑CV mortality in ED
Phillips[41] 2012	4225 15 yrs.	Vietnam Veterans	Total mortality CV mortality Cancer mortality	NS, NR	TT < 444 ng/dL	TT < 444 ng/dL not associated with mortality
Haring[13] 2012	2039 5.5 yrs.	Community	Total mortality CV mortality	1.82 (1.30–2.55) 2.25 (1.30–3.90)	TT 10 th percentile TT 10 th percentile	Low TT associated with ↑total mortality and CV mortality
Hyde[36] 2012	3637 5 yrs.	Community	Total mortality CV mortality Cancer mortality Lung CA mort. Lung CA mort	1.62 (1.20–2.19) 1.71 (1.12–2.62) 1.57 (1.17–2.12) 4.05 (2.11–7.75) 1.96 (1.14–3.36)	FT 2.88 vs. 5.19 ng/dL FT 2.88 vs. 5.19 ng/dL TT 864 vs. 432 ng/dL TT 864 vs. 432 ng/dL FT 11.5 vs. 8.1 ng/dL	Curvilinear association of FT with total and CV mortality. Higher TT and FT associated with cancer mortality.
Schneider[70] 2012	1892 10 yrs.	Community	Total mortality CV mortality	1.53 (1.08–2.16) 1.90 (1.05–3.47)	TT <300 ng/dl TT <300 ng/dl	TT < 300 associated with ↑total and CV mortality, but didn't remain significant after IGF-1, CRP, and HbA1c added to the model
Haring[32] 2013	254 5, 10 yrs.	Community	Total mortality	0.74 (0.56–0.98) Non-significant	TT per quartile	TT not significant associated with mortality-due to multiple comparisons
Gershman[40] 2013	963 12 yrs	Prostate Cancer	PCA Mortality Total Mortality	0.98 (0.58–1.67) 1.07 (0.8–1.44)	TT Q4/Q1 TT Q4/Q1	TT not associated with total mortality or prostate CA mortality in men with prostate CA
Muraleedharan[23] 2013	581 6 yrs	Diabetics II Endocrine clinic	Total Mortality	2.02 (1.2–3.4)	TT 300 ng/dL	Low TT associated with ↑total mortality in men with type II diabetes
Bello[37] 2014	623 6.8 yrs	Hemodialysis Initiators	Total mortality	1.47(0.82–2.66) 2.93 (1.10–7.78)	TT < 231 TT < 231, age < 63	Low TT associated with ↑total mortality in ESRD
Dev[38] 2014	119 186 days	Cancer	Total mortality	1.64 (CI NR) p=.034	TT < 200 ng/dl	Low TT associated with ↑total mortality men with cancer

Study	Number FU-yrs	Patient Population	Outcome	Hazard Ratio (95% CI)	T thresholds	Comments
Orsted[42] 2014	4453 22 yrs	Community Cancer pts	Total mortality Within 5 yrs of cancer dx	TT 1.42(1.12–1.80) TT 1.86(1.20–2.91)	TT Q5 vs. Q1 Any cancer Oral cancer	High TT associated with ↑total mortality in men with cancer
Yeap[28] 2014	3690 7 yrs	Community	Total Mortality IHD mortality	TT 0.78 (0.65–0.94) FT 0.72 (0.63–0.91) DHT 0.76 (.63–.91) DHT 0.69 (0.57–0.89)	Q3 lowest risk TT 363–465 ng/dL FT 5.27–6.22 ng/dL DHT 39–53 ng/dL DHT 39–53 ng/dL	Curvilinear association-3 rd quartile of TT, FT, DHT with lowest risk for total mortality. 3 rd quartile of DHT associated with lowest risk for IHD mortality
Shores[29] 2014	1031 9 yrs	Community	Total mortality	DHT 1.23 (1.04–1.46)	DHT < 30 ng/dl	Low DHT associated with ↑total mortality. Also curvilinear association with ↓risk at 50–74 ng/dL of DHT
Pye[31] 2014	2599 4 yrs	Community	Total mortality	TT 2.3 (1.2–4.2) TT 5.5 (2.7–11.4)	TT<230 ng/dL Low TT & 3 sex sx	Low TT associated with ↑total mortality with increased risk if >3 sexual sx
Khurana[45] 2014	2419 6 yrs	Renal Disease	Total mortality	TT 0.70 (0.55–0.89)	Per log TT increase	Increases in TT associated with ↓total mortality in men with renal disease

Abbreviations: CHF-congestive heart failure, CI-confidence interval, CV- cardiovascular, DHT dihydrotestosterone; ED- erectile dysfunction, ESRD-end stage renal disease, FT-free T; FU-follow-up, IGF-1-insulin like growth factor-1, IHD-ischemic heart disease, NS- not significant, NR-not reported; sx-symptoms, TT-total T; Q-quartile, Q3-3rd quartile

Table 2

Testosterone treatment studies

Study	Number FU, yrs	Patient Population	Outcome	Hazard Ratio (95% CI)	Treatment groups	Comments
Shores [24] 2013	1031 3.3 yrs	Veterans TT<250 ng/dl	Total Mortality	0.61 (0.42–0.88)	T treated vs. untreated	↓mortality in treated vs. untreated men with low T
Muraleedharan[23] 2013	238 5.8 yrs	Diabetes II TT<300 ng/dl	Total Mortality	2.3 (1.3–3.9)	T untreated vs. treated	↑mortality in untreated vs. treated men with low T
Vigen[20] 2013	8309 2.3 yrs	Veterans Angiography TT <300 ng/dl	MI, stroke and total mortality	1.29 (1.04–1.58)	T treated vs. untreated	↑MI, stroke & mortality (combined as single outcome) in treated vs. untreated men with low T
Finkel[21] 2014	55,593 3 months after T rx	T treated men in health care database	Incident MI	1.90(1.04–3.49)	Rate ratio Post/pre T rx (3 months after vs. 1 year before)	↑risk for MI following T treatment compared to before treatment; risk greater in older men (>75 yrs) or men with CHD
Baillargeon[25] 2014	25,420 8 yrs	Medicare T rx with IM T	MI	0.84 (0.69–1.02) 0.69 (0.53–0.92)	Treated vs. untreated Treated men with high CV risk vs. untreated men	No ↑risk for MI in treated men ↓Risk for MI in men with high CV risk factors

Abbreviations: CI-confidence interval, CHD-coronary heart disease, CV- cardiovascular reported; IM-intramuscular, MI-myocardial infarction, rx-treatment, T-testosterone