Male Testosterone Replacement, Benefits and Risks

Jeffrey Dach MD
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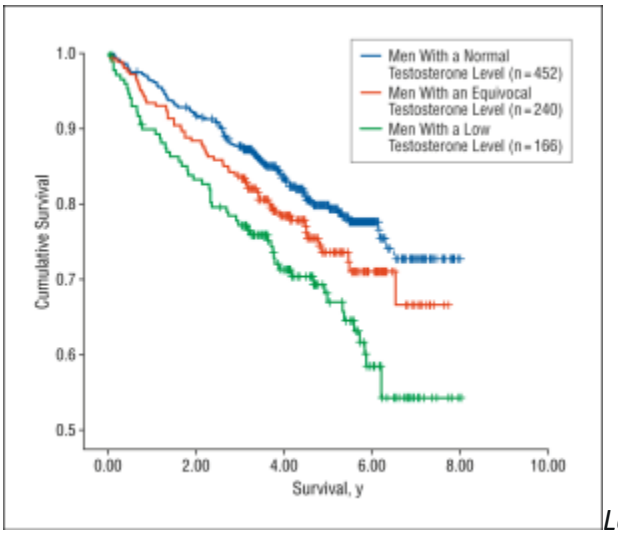
Low Testosterone Associated with Increased Mortality of Forty Percent

Three studies show low testosterone is associated with increased mortality. In 2006, Dr. Molly M. Shores found low testosterone below 250 ng/dL is associated with almost doubled mortality rate. 858 male veterans were followed for 8 years. Those with normal testosterone levels had a mortality rate of 20.1 %. However those with low testosterone had a mortality rate of 35.9%. This is almost twice the mortality rate of normal males. (1)

Upper Left Image: Arnold Schwarzenegger 1974 courtesy of wikimedia commons.



Left chart from Arch Int Med 2006 Molly Shores (1) Low Testosterone group (Green Line) had highest mortality rate, almost double that of normal males.

Second Study

In 2008 Dr. Gail A. Laughlin from California measured testosterone in 800 men, 50-91 years old and followed the men for 20 years. Low testosterone symptoms included decreased libido, erectile dysfunction, fatigue, loss of strength, decrease in bone density and decreased muscle mass. Men with low testosterone tended to be overweight or obese, and at higher risk for cardiovascular disease and diabetes. Men with the lowest testosterone, below 241 ng/dl, were **40% more likely to die**. Dr. Gail A. Laughlin writes:

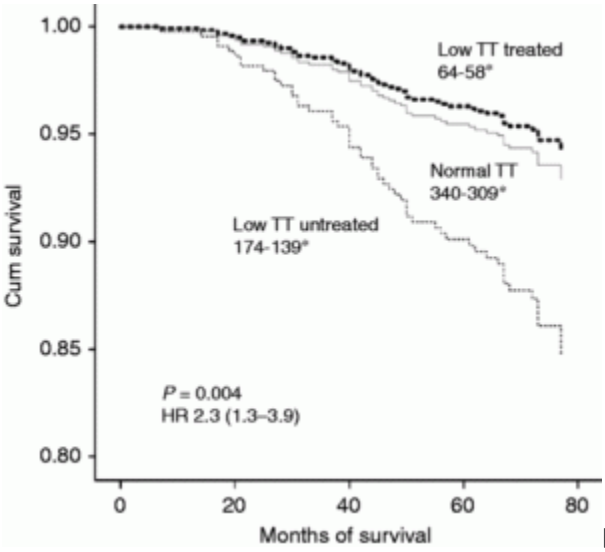
During an average 11.8-yr follow-up, 538 deaths occurred. Men whose total testosterone levels were in the lowest quartile (<241 ng/dl) were **40% more likely to die** than those with higher levels, (2)

Third Study by Dr. Malkin

A third study published by Dr Malkin in Heart 2010 showed that men with known coronary artery disease commonly had low testosterone levels which was associated with almost double the mortality rate compared with men with normal levels. (6)

Dr Malkin writes: "**Excess mortality was noted in the androgen-deficient group compared with normal (88 vs. 41) or (21% vs. 12%). (6)**

Reduced Mortality in Testosterone Treated Compared to Untreated



Left image shows mortality rate In Diabetic Males with Normal or Low testosterone. Note the increased mortality in Low Testosterone **untreated** group. Mortality rate of androgen deficient group returns to **Normal after testosterone treatment**.(13)

Above Left image courtesy of Muraleedharan, Vakkat, et al. "Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes." European Journal of Endocrinology 169.6 (2013): 725-733.

Reduction in Mortality with Testosterone Replacement

In 2012 Dr. Molly Shores studied 1031 male veterans followed over 5 years showeing men with low testosterone had 20% mortality. However if they were treated with Testosterone replacement, mortality was reduced in half to 10%. (14)

In 2015, Dr. Rishi Sharma conducted a retrospective 15 year study of 83,010 male veterans with documented low Testosterone (TT) levels. The low T males were compared their treated counterparts, males with low testosterone levels treated with testosterone replacement to achieve normal levels (Treated Group). In the Treated Group, all-cause mortality was reduced 56%, myocardial infarction reduced 24%, stroke reduced 36%. Dr. Rishi Sharma concludes:

In this large observational cohort with extended follow-up, normalization of TT [testosterone] levels after TRT [testosterone replacement threrapy] was associated with **a significant reduction in all-cause mortality, MI,**

and stroke. (12)

Unfounded Fears of Testosterone Replacement

In 2016, Drs. Traish and Morgentaler debunk the two unfounded fears regarding testosterone therapy in androgen deficient males.(7-13)

The first unfounded fear is the false medical myth that testosterone therapy somehow causes prostate cancer. This has been shown to be false. The second unfounded fear is that testosterone somehow increases cardiovascular disease. Not only is this false, the exact opposite is true. Testosterone therapy in androgen deficient males decreases cardiovascular mortality in numerous studies. Dr. Traish makes the plea to the medical community to treat more androgen deficient men. Dr. Traish writes:

*we believe that there is considerable scientific and clinical evidence to suggest that **testosterone therapy is safe and effective** with restoration of physiological levels in men with testosterone deficiency, irrespective of its etiology....TD [Testosterone Deficiency] is associated with increased incidence of metabolic syndrome, obesity, sexual dysfunction, impaired fertility, reduced motivation, increased fatigue, depressed mood, loss of bone and muscle mass, anemia, decreased energy and vigour, insulin resistance, diabetes, inflammation, dyslipidemia, sarcopenia and frailty, reduced quality of life (QoL) and increased mortality... A substantial body of evidence indicates that coronary artery disease incidence and severity... is inversely correlated with serum T [Testosterone] concentrations. **There is an urgent need among the medical community for greater awareness of the impact of TD on general health in men with TD.**(7-8)*

Age Related Low Testosterone

In 2021, Dr. Abdulmaged M. Traish writes in his article, "Age-Related Testosterone Deficiency Merits Treatment", his disagreement with the FDA position on treating age related testosterone deficiency :

The negative effects of testosterone deficiency (TD) on human health and quality of life are well demonstrated, including signs, symptoms, metabolic syndrome, obesity, and increased mortality. Recently, substantial evidence emerged, demonstrating the benefits of testosterone therapy in men with classical and “age-related” hypogonadism. The US Food and Drug Administration (FDA) opposes testosterone therapy in men with age-related hypogonadism but not in men with classical hypogonadism. The FDA acknowledges that TD [Testosterone Deficiency] merits treatment, but the FDA made an artificial distinction between diagnoses where T [testosterone] treatment is warranted and others where the underlying diagnosis is unknown, and treatment is unwarranted. The FDA labeled the unknown category as “age-related.” Since the FDA is unable to demonstrate that one group differs in benefits or risks from the other, there are no bases for this distinction. **This action by the FDA is not based on scientific or clinical evidence.** There is no evidence that the response to testosterone therapy of “age-related” hypogonadism occurs via different physiological or biochemical mechanisms than those historically recognized conditions. Also, there is no evidence that “age-related” hypogonadism responds less well to testosterone therapy than “classical” hypogonadism. More importantly, there is no scientific or clinical evidence to suggest that the risks of testosterone therapy in men with “age-related” hypogonadism are worse or different for men with “classical” hypogonadism. **For these reasons, we disagree with the FDA position on testosterone therapy in age-related hypogonadism.(16)**

In 2021, Dr. Abraham Morgentaler agrees with Dr. Traish writing:

The FDA is a critically important government institution... **Yet it must be emphasized that its role is to regulate the pharmaceutical industry, and not health care providers.It bears emphasis that the FDA is not involved with the practice of medicine.** Yet the medical community and insurance companies pay close attention to the FDA's positions, and insurance companies frequently restrict coverage based on FDA labels, especially if it helps their bottom line. ... **it is to be hoped that the entirety of the scientific community, including the FDA, will soon come to recognize the importance of TTh [Testosterone Therapy] not only for its symptomatic benefits in men with age-related TD [Testosterone Deficiency] , but also for its impact on general health.** (18)

Conclusion: Because of unfounded fears, many males with low Testosterone do not seek treatment. And for those who seek treatment, many are ignored or denied treatment by mainstream medicine. This is the modern day tragedy. Testosterone replacement reduces mortality, and improves quality of life. (4-13)

Related Articles: Low Testosterone – Diagnosis and Treatment

Symptoms of Low Testosterone

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Links and References

1) Shores, Molly M., et al. "Low serum testosterone and mortality in male veterans." *Archives of internal medicine* 166.15 (2006): 1660-1665.

We used a clinical database to identify men older than 40 years with repeated testosterone levels obtained from October 1, 1994, to December 31, 1999, and without diagnosed prostate cancer. **A low testosterone level was a total testosterone level of less than 250 ng/dL (<8.7 nmol/L) or a free testosterone level of less than 0.75 ng/dL (**<0.03 nmol/L). Men were classified as having a low testosterone level (166 [19.3%]), an equivocal testosterone level (equal number of low and normal levels) (240 [28.0%]), or a **normal testosterone level (452 [52.7%]**). The risk for all-cause mortality was estimated using Cox proportional hazards regression models, adjusting for demographic and clinical covariates over **a follow-up of up to 8 years.**

Results: **Mortality in men with normal testosterone levels was 20.1% (95% confidence interval [CI], 16.2%-24.1%) vs 24.6% (95% CI, 19.2%-30.0%) in men with equivocal testosterone levels and 34.9% (95% CI, 28.5%-41.4%) in men with low testosterone levels.**

After adjusting for age, medical morbidity, and other clinical covariates, low testosterone levels continued to be associated with increased mortality (hazard ratio, 1.88; 95% CI, 1.34-2.63; P<.001) while equivocal testosterone levels were not significantly different from normal testosterone levels (hazard ratio, 1.38; 95% CI,

0.99%-1.92%; P=.06). In a sensitivity analysis, men who died within the first year (50 [5.8%]) were excluded to minimize the effect of acute illness, and low testosterone levels continued to be associated with elevated mortality.

Conclusions: Low testosterone levels were associated with increased mortality in male veterans.

2) Laughlin, Gail A., Elizabeth Barrett-Connor, and Jaclyn Bergstrom. "Low serum testosterone and mortality in older men." The Journal of Clinical Endocrinology & Metabolism 93.1 (2008): 68-75.

Results: During an average **11.8-yr follow-up, 538 deaths occurred.** Men whose total testosterone levels were in the **lowest quartile (<241 ng/dl) were 40%** [hazards ratio (HR) 1.40; 95% confidence interval (CI) 1.14–1.71] **more likely to die than those with higher levels,** independent of age, adiposity, and lifestyle. Additional adjustment for health status markers, lipids, lipoproteins, blood pressure, glycemia, adipocytokines, and estradiol levels had minimal effect on results. The low testosterone-mortality association was also independent of the metabolic syndrome, diabetes, and prevalent cardiovascular disease but was attenuated by adjustment for IL-6 and C-reactive protein.

In cause-specific analyses, low testosterone predicted increased risk of cardiovascular (**HR 1.38**; 95% CI 1.02–1.85) and respiratory disease (HR **2.29;** 95% CI 1.25–4.20) mortality but was not significantly related to cancer death (HR 1.34; 95% CI 0.89–2.00). **Results were similar for bioavailable testosterone.**

Conclusions: **Testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr,** independent of multiple risk factors and several preexisting health conditions.

3) Low Testosterone Could Kill You. Low Levels of Male Hormone May be More Dangerous Than Previously Thought By SupindaBunyavanich, M.D. ABC News Medical Unit June 6, 2007

Low testosterone may lead to a greater risk of death, according to a study presented Tuesday at the annual meeting of the Endocrine Society in Toronto.
Men with low testosterone had a 33 percent greater death risk over their next 18 years of life compared with men who had higher testosterone, according to the study conducted by Dr. Elizabeth Barrett-Connor and colleagues at the University of California at San Diego. "It's very exciting and potentially a groundbreaking study," said Barrett-Connor. "But it needs to be confirmed." The study tracked nearly **800 men, 50 to 91 years old, living in California.** Their testosterone level was measured at the beginning of the study, and their health was then tracked over the next 20 years.

4) Testosterone Replacement For Men With Low Testosterone Improves Liver Function, Metabolic Syndrome. Testosterone deficiency, which becomes more common with age, is linked not only to decreased libido but also to a number of medical problems. These include the metabolic syndrome a cluster of metabolic risk factors that increase the chances of developing heart disease, stroke and type 2 diabetes.

5) Low testosterone levels linked to depression in older men March 2008
Older men with lower free testosterone levels in their blood appear to have higher prevalence of depression, according to a report in the March issue of Archives of General Psychiatry.

6) Malkin, Chris J., et al. "Low serum testosterone and increased mortality in men with coronary heart

disease." Heart 96.22 (2010): 1821-1825.

Background To examine the effect of serum testosterone levels on survival in a consecutive series of men with confirmed coronary disease and calculate the prevalence of testosterone deficiency.

Design Longitudinal follow-up study. Setting Tertiary referral cardiothoracic centre. Patients **930 consecutive men with coronary disease** referred for diagnostic angiography recruited between June 2000 and June 2002 and followed up for a mean of 6.9±2.1 years.

Outcome All-cause mortality and vascular mortality. Prevalence of testosterone deficiency.
Results The overall prevalence of biochemical testosterone deficiency in the coronary disease cohort using bio-available testosterone (bio-T) <2.6 nmol/l was 20.9%, using total testosterone <8.1 nmol/l was 16.9% and using either was 24%. **Excess mortality was noted in the androgen-deficient group compared with normal (41 (21%) vs 88 (12%), p=0.002).** The only parameters found to influence time to all-cause and vascular mortality (HR ± 95% CI) in multivariate analyses were the presence of left ventricular dysfunction (3.85; 1.72 to 8.33), aspirin therapy (0.63; 0.38 to 1.0), β-blocker therapy (0.45; 0.31 to 0.67) and low serum bio-T (2.27; 1.45 to 3.6).

Conclusions **In patients with coronary disease testosterone deficiency is common and impacts significantly negatively on survival.** Prospective trials of testosterone replacement are needed to assess the effect of treatment on survival.

!! 2016
7) Traish, Abdulmaged. "Testosterone therapy in men with testosterone deficiency: Are we beyond the point of no return?." Investigative and Clinical Urology 57.6 (2016): 384-400.
Although testosterone therapy in men with testosterone deficiency was introduced in the early 1940s, utilization of this effective treatment approach in hypogonadal men is met with considerable skepticism and resistance. Indeed, for decades, **the fear that testosterone may cause prostate cancer** has hampered clinical progress in this field. Nevertheless, even after considerable knowledge was acquired that this fear is unsubstantiated, many in the medical community remain hesitant to utilize this therapeutic approach to treat men with hypogonadism. As the fears concerning prostate cancer have subsided, a new controversy regarding use of testosterone therapy and **increase in cardiovascular disease** was introduced. **Although the new controversy was based on one ill-fated clinical trial, one meta-analysis with studies that utilized unapproved formulation in men with liver cirrhosis, and two retrospective studies with suspect or nonvalidated statistical methodologies and database contaminations, the flames of such controversy were fanned by the lay press and academics alike.** In this review we discuss the adverse effect of testosterone deficiency and highlight the numerous proven benefits of testosterone therapy on men's health and **debunk the myth that testosterone therapy increases cardiovascular risk**. Ultimately, we believe that there is considerable scientific and clinical evidence to suggest that testosterone therapy is safe and effective with restoration of physiological levels in men with testosterone deficiency, irrespective of its etiology.

TD is associated with increased incidence of metabolic syndrome, obesity, sexual dysfunction, impaired fertility, reduced motivation, increased fatigue, depressed mood, loss of bone and muscle mass, anemia, decreased energy and vigour, insulin resistance, diabetes, inflammation, dyslipidemia, sarcopenia and frailty,

reduced quality of life (QoL) and increased mortality [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 40, 41, 42, 43, 44]. A substantial body of evidence indicates that coronary artery disease incidence and severity, carotid intima-media thickness, atherosclerosis is inversely correlated with serum T concentrations [45]. **There is an urgent need among the medical community for greater awareness of the impact of TD on general health in men with TD.**

8) Traish, Abdulmaged M. "Testosterone therapy in men with testosterone deficiency: are the benefits and cardiovascular risks real or imagined?." American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. Vol. 311. No. 3. American Physiological Society, 2016.

In the adult male, testosterone (T) deficiency (TD) also known as male hypogonadism, is a well-established medical condition, which has been recognized for more than a century. T therapy in men with TD was introduced as early as 1940s and was reported to improve overall health with no concomitant serious adverse effects. A wealth of recent studies demonstrated that T therapy in men with TD is associated with increased lean body mass, reduced fat mass and waist circumference, improvement in glycemic control, and reduced obesity. T therapy is also associated with improvements in lipid profiles, amelioration of metabolic syndrome (Met S) components, reduced inflammatory biomarkers, reduced systolic and diastolic blood pressure, and improvements in sexual function. More importantly, T therapy is associated with amelioration of diabetes and reduced mortality. However, few studies, marred with serious methodological and analytical flaws reported between 2010 and 2014, suggested that T therapy is associated with increased cardiovascular (CV) risk. As summarized in this review, a thorough and critical analysis of these studies showed that the risks purported are unsubstantiated and such studies lacked credible scientific and clinical evidence. Moreover, recent observational, registry studies, clinical trials, and meta-analyses, all revealed no increase in CV risks in men receiving T therapy. In this review, the benefits of T therapy in adult men with TD and the lack of credible evidence suggesting that T therapy is linked to increased CV risks are discussed. It should be noted that the literature is replete with studies demonstrating beneficial effects of T therapy on CV and overall health.

Of importance, the study by Snyder et al. [3] and the resolutions of the consensus panel on T [2] debunked the notion that age-related hypogonadism is not a clinical condition and should remain untreated. As reported in the study [3], T therapy in older men has several benefits and age-related hypogonadism is a clinical condition worthy of treatment. We hope that the findings of this large and well executed study [3] and the summary provided by the consensus panel [2] will serve as a reminder to those who are beating the drums of fear and hysteria on the dangerous use of T in the treatment of men with TD and reassure men suffering from TD and their physicians that such fears and hysteria are unfounded.

9) free pdf Anderson Jeffrey testosterone replacement myocardial infarction low testosterone 2016
Anderson, Jeffrey L., et al. "Impact of testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated health care system." The American journal of cardiology 117.5 (2016): 794-799.

The aim of this study was to assess the effect of testosterone replacement therapy (TRT) on cardiovascular outcomes. Men (January 1, 1996, to December 31, 2011) with a low initial total testosterone concentration, a subsequent testosterone level, and >3 years of follow-up were studied. Levels were correlated with testosterone supplement use. The primary outcome was major adverse cardiovascular events (MACE), defined as a composite of death, nonfatal myocardial infarction, and stroke at 3 years. Multivariate adjusted hazard ratios (HRs) comparing groups of persistent low (<212 ng/dl, n = 801), normal (212 to 742 ng/dl, n = 2,241),

and high (>742 ng/dl, n = 1,694) achieved testosterone were calculated by Cox hazard regression.

A total of 4,736 men were studied. **Three-year rates of MACE and death were 6.6% and 4.3%**, respectively. Subjects supplemented to normal testosterone had reduced 3-year MACE (**HR 0.74**; 95% confidence interval [CI] 0.56 to 0.98, p = 0.04) compared to persistently low testosterone, driven primarily by death (**HR 0.65**, 95% CI 0.47 to 0.90). HRs for MI and stroke were 0.73 (95% CI 0.40 to 1.34), p = 0.32, and 1.11 (95% CI 0.54 to 2.28), p = 0.78, respectively. MACE was noninferior but not superior for high achieved testosterone with no benefit on MI and a trend to greater stroke risk. In conclusion, **in a large general health care population, TRT to normal levels was associated with reduced MACE and death over 3 years** but a stroke signal with high achieved levels suggests a conservative approach to TRT.

10) Saad, Farid, et al. "Testosterone Deficiency and Testosterone Treatment in Older Men." Gerontology (2016).
Gerontology Testosterone Deficiency and Testosterone Treatment in Older Men Saad F.a, b · RöhrigG.c, d · von HaehlingS.e · TraishA.f, g
aGlobal Medical Affairs Andrology, Bayer AG, Berlin, Germany;
Frailty is a clinical condition related to changes in metabolism, to sarcopenia, and to decline in muscle mass and strength, bone mineral density, and physical function with aging. The pathophysiology of frailty is multifactorial and associated with comorbidities. Testosterone is implicated in regulating metabolic functions, maintenance of muscle and bone, and inhibition of adipogenesis. In older individuals, reduced testosterone is thought to contribute to an altered state of metabolism, loss of muscle and bone, and increased fat, leading to sarcopenia, sarcopenic obesity, and frailty. While no direct relationship between testosterone deficiency (commonly known as hypogonadism) and frailty has been established (due to the multifactorial nature of frailty), clinical evidence suggests that testosterone deficiency is associated with increased sarcopenia and obesity. Testosterone treatment in frail older men with limited mobility and with testosterone deficiency improved insulin resistance, glucose metabolism, and body composition. These changes contribute to better physical function and improved quality of life. Because frailty increases disability, comorbidities, and the risk of hospitalization, institutionalization, and mortality in older men, it is warranted to explore the potential usefulness of testosterone treatment in frail men with hypogonadism in order to attenuate the progression of sarcopenia and frailty. In this paper, we will discuss the impact of testosterone deficiency on frailty and the potential role of testosterone treatment in ameliorating and reducing the progression of frailty. Such an approach may reduce disability and the risk of hospitalization and increase functional independence and quality of life.

11) free pdf Morgentaler Abraham Testosterone therapy and cardiovascular risk Mayo Clinic 2015
Morgentaler, Abraham, et al. "Testosterone therapy and cardiovascular risk: advances and controversies." Mayo Clinic Proceedings. Vol. 90. No. 2. Elsevier, 2015.

a modest number of randomized controlled trials (RCTs), indicate that low serum T concentrations are associated with increased CV risk and mortality and that T therapy may have clinically relevant CV benefits

Established benefits of T therapy in hypogonadal men include improved sexual desire and function,12-15 improved energy, mood, and vitality,15-19 increased lean mass,14,19-22 decreased waist circumference,23-27 reduced total body fat mass,19-22 and increased bone mineral density.28-31 Promising new data reveal that T therapy improves insulin sensitivity32-34 and reduces blood glucose23,25,35
and hemoglobin A1c (HbA1c)23,25,27,35 levels in men with type 2 diabetes or obesity.

In summary, we find no scientific basis for the suggestion that T therapy increases CV risk. In fact, as of this date, we are unaware of any compelling evidence that T therapy is associated with increased CV risk. On the contrary, the weight of evidence accumulated by researchers around the world over several decades clearly indicates that higher levels of T are associated with amelioration of CV risk factors and reduced risk of mortality.

12) Sharma, Rishi, et al. "Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men." European Heart Journal (2015): ehv346.

Aims There is a significant uncertainty regarding the effect of testosterone replacement therapy (TRT) on cardiovascular (CV) outcomes including myocardial infarction (MI) and stroke.

The aim of this study was to examine the relationship between normalization of total testosterone (TT) after TRT and CV events as well as all-cause mortality in patients without previous history of MI and stroke.
Methods and results We retrospectively examined **83 010 male veterans with documented low TT levels.** The subjects were categorized into (Gp1: TRT with resulting normalization of TT levels),
(Gp2: TRT without normalization of TT levels) and
(Gp3: Did not receive TRT).
By utilizing propensity score-weighted Cox proportional hazard models, the association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups. The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42–0.46], risk of MI (HR: 0.76, CI 0.63–0.93), and stroke (HR: 0.64, CI 0.43–0.96) were significantly lower in Gp1 (n = 43 931, median age = 66 years, mean follow-up = 6.2 years) vs. Gp3 (n = 13 378, median age = 66 years, mean follow-up = 4.7 years) in propensity-matched cohort. Similarly, the all-cause mortality (HR: 0.53, CI 0.50–0.55), risk of MI (HR: 0.82, CI 0.71–0.95), and stroke (HR: 0.70, CI 0.51–0.96) were significantly lower in Gp1 vs. Gp2 (n = 25 701, median age = 66 years, mean follow-up = 4.6 years). There was no difference in MI or stroke risk between Gp2 and Gp3.
Conclusion In this large observational cohort with extended follow-up, **normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.**

13) Muraleedharan, Vakkat, et al. "Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes." European Journal of Endocrinology 169.6 (2013): 725-733.
Objective Men with type 2 diabetes are known to have a high prevalence of testosterone deficiency. No long-term data are available regarding testosterone and mortality in men with type 2 diabetes or any effect of testosterone replacement therapy (TRT). We report a 6-year follow-up study to examine the effect of baseline testosterone and TRT on all-cause mortality in men with type 2 diabetes and low testosterone.

Research design and methods A total of 581 men with type 2 diabetes who had testosterone levels performed between 2002 and 2005 were followed up for a mean period of 5.8±1.3 s.d. years. Mortality rates were compared between total testosterone >10.4 nmol/l (300 ng/dl; n=343) and testosterone ≤10.4 nmol/l (n=238). The effect of TRT (as per normal clinical practise: 85.9% testosterone gel and 14.1% intramuscular testosterone undecanoate) was assessed retrospectively within the low testosterone group.

Results Mortality was increased in the low testosterone group (17.2%) compared with the normal testosterone group (9%; P=0.003) when controlled for covariates. In the Cox regression model, multivariate-adjusted hazard ratio (HR) for decreased survival was 2.02 (P=0.009, 95% CI 1.2–3.4). TRT (mean duration 41.6±20.7 months; n=64) was associated with a reduced mortality of 8.4% compared with 19.2% (P=0.002) in

the untreated group (n=174). The multivariate-adjusted HR for decreased survival in the untreated group was 2.3 (95% CI 1.3–3.9, P=0.004).

Conclusions Low testosterone levels predict an increase in all-cause mortality during long-term follow-up. Testosterone replacement may improve survival in hypogonadal men with type 2 diabetes.
Several longitudinal population studies have reported that a low testosterone at baseline is associated with an increase in all-cause mortality (1). Some individual studies have specifically identified increases in cardiovascular, respiratory and cancer deaths (2, 3, 4). A meta-analysis of published research papers with a mean follow-up period of 9.7 years confirmed that low testosterone was associated with increased risk of all-cause and cardiovascular mortality in community based studies (1). Men with specific co-morbidities such as proven coronary artery disease and renal failure have also found that low testosterone predicts an increased risk of earlier death than those with the same condition and are testosterone replete (5, 6).
In summary, this is the first study to demonstrate that low testosterone levels are associated with an increase in all-cause and cardiovascular mortality in men with type 2 diabetes. This study demonstrates that long-term testosterone replacement is not only safe in terms of mortality but may also improve survival in men with type 2 diabetes and hypogonadism.

14) Shores, Molly M., et al. “Testosterone Treatment and Mortality in Men with Low Testosterone Levels.” (2012). J Clin Endocrinol Metab. 2012 Jun;97(6):2050-8. Shores Testosterone-Treatment mortality-in-men-with-hypogonadism J Clin Endocrinol Metab. 2012

Low testosterone levels in men have been associated with increased mortality. However, the influence of testosterone treatment on mortality in men with low testosterone levels is not known.
OBJECTIVE:The objective of the study was to examine the association between testosterone treatment and mortality in men with low testosterone levels.
DESIGN:This was an observational study of mortality in testosterone-treated compared with untreated men, assessed with time-varying, adjusted Cox proportional hazards regression models. Effect modification by age, diabetes, and coronary heart disease was tested a priori.
SETTING:The study was conducted with a clinical database that included seven Northwest Veterans Affairs medical centers.
PATIENTS:Patients included a cohort of 1031 male veterans, aged older than 40 yr, with low total testosterone [≤250 ng/dl (8.7 nmol/liter)] and no history of prostate cancer, assessed between January 2001 and December 2002 and followed up through the end of 2005.
MAIN OUTCOME MEASURE:Total mortality in testosterone-treated compared with untreated men was measured.
RESULTS:Testosterone treatment was initiated in 398 men (39%) during routine clinical care. The mortality in testosterone-treated men was 10.3% compared with 20.7% in untreated men (P<0.0001) with a mortality rate of 3.4 deaths per 100 person-years for testosterone-treated men and 5.7 deaths per 100 person-years in men not treated with testosterone. After multivariable adjustment including age, body mass index, testosterone level, medical morbidity, diabetes, and coronary heart disease, testosterone treatment was associated with decreased risk of death (hazard ratio 0.61; 95% confidence interval 0.42-0.88; P = 0.008). No significant effect modification was found by age, diabetes, or coronary heart disease.
CONCLUSIONS: In an observational cohort of men with low testosterone levels, **testosterone treatment was associated with decreased mortality compared with no testosterone treatment**. These results should be interpreted cautiously because residual confounding may still be a source of bias. Large, randomized clinical trials are needed to better characterize the health effects of testosterone treatment in older men with low testosterone levels.

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1) Shores, Molly M., et al. "Low serum testosterone and mortality in male veterans." *Archives of internal medicine* 166.15 (2006): 1660-1665.

We used a clinical database to identify men older than 40 years with repeated testosterone levels obtained from October 1, 1994, to December 31, 1999, and without diagnosed prostate cancer. **A low testosterone level was a total testosterone level of less than 250 ng/dL (<8.7 nmol/L) or a free testosterone level of less than 0.75 ng/dL (**<0.03 nmol/L).

Men were classified as having a low testosterone level (166 [19.3%]), an equivocal testosterone level (equal number of low and normal levels) (240 [28.0%]), or a **normal testosterone level (452 [52.7%]**). The risk for all-cause mortality was estimated using Cox proportional hazards regression models, adjusting for demographic and clinical covariates over **a follow-up of up to 8 years.**

Results: **Mortality in men with**

normal testosterone levels was 20.1% (95% confidence interval [CI], 16.2%-24.1%) vs 24.6% (95% CI, 19.2%-30.0%)
in men with equivocal testosterone levels and 34.9% (95% CI,
28.5%-41.4%) in men with low testosterone levels.

After adjusting for age, medical morbidity, and other clinical covariates, low testosterone levels continued to be associated with increased mortality (hazard ratio, 1.88; 95% CI, 1.34-2.63; P<.001) while equivocal testosterone levels were not significantly different from normal testosterone levels (hazard ratio, 1.38; 95% CI, 0.99%-1.92%; P=.06). In a sensitivity analysis, men who died within the first year (50 [5.8%]) were excluded to minimize the effect of acute illness, and low testosterone levels continued to be associated with elevated mortality.

Conclusions: Low testosterone levels were associated with increased mortality in male veterans.

(2) Laughlin, Gail A., Elizabeth Barrett-Connor, and Jaclyn Bergstrom. "Low serum testosterone and mortality in older men." The Journal of Clinical Endocrinology & Metabolism 93.1 (2008): 68-75.

Results: During an average **11.8-yr follow-up, 538 deaths occurred.** Men whose total testosterone levels were in the **lowest quartile (<241 ng/dl) were 40%** [hazards ratio (HR) 1.40; 95% confidence interval (CI) 1.14–1.71] **more likely to die than those with higher levels,** independent of age, adiposity, and lifestyle. Additional adjustment for health status markers, lipids, lipoproteins, blood pressure, glycemia, adipocytokines, and estradiol levels had minimal effect on results. The low testosterone-mortality association was also independent of the metabolic syndrome, diabetes, and prevalent cardiovascular disease but was attenuated by adjustment for IL-6 and C-reactive protein.

In cause-specific analyses, low testosterone predicted increased risk of cardiovascular (**HR 1.38**; 95% CI 1.02–1.85) and respiratory disease (HR **2.29;** 95% CI 1.25–4.20) mortality but was not significantly related to cancer death (HR 1.34; 95% CI 0.89–2.00). **Results were similar for bioavailable testosterone.**

Conclusions: **Testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr,** independent of multiple risk factors and several preexisting health conditions.

3) Low Testosterone Could Kill You. Low Levels of Male Hormone May be More Dangerous Than Previously Thought By SupindaBunyavanich, M.D. ABC News Medical Unit June 6, 2007

Low testosterone may lead to a greater risk of death, according to a study presented Tuesday at the annual meeting of the Endocrine Society in Toronto.
Men with low testosterone had a 33 percent greater death risk over their next 18 years of life compared with men who had higher testosterone, according to the study conducted by Dr. Elizabeth Barrett-Connor and colleagues at the University of California at San Diego. "It's very exciting and potentially a groundbreaking study," said Barrett-Connor. "But it needs to be confirmed." The study tracked nearly **800 men, 50 to 91 years old, living in California.** Their testosterone level was measured at the beginning of the study, and their health was then tracked over the next 20 years.

4) Testosterone Replacement For Men With Low Testosterone Improves Liver Function, Metabolic Syndrome. Testosterone deficiency, which becomes more common with age, is linked not only to decreased libido but also to a number of medical problems. These include the metabolic syndrome a cluster of metabolic risk factors that increase the chances of developing heart disease, stroke and type 2 diabetes.

5) Low testosterone levels linked to depression in older men March 2008
Older men with lower free testosterone levels in their blood appear to have higher prevalence of depression, according to a report in the March issue of Archives of General Psychiatry.

6) Malkin, Chris J., et al. "Low serum testosterone and increased mortality in men with coronary heart disease." Heart 96.22 (2010): 1821-1825.

Background To examine the effect of serum testosterone levels on survival in a consecutive series of men with confirmed coronary disease and calculate the prevalence of testosterone deficiency.

Design Longitudinal follow-up study. Setting Tertiary referral cardiothoracic centre. Patients **930 consecutive men with coronary disease** referred for diagnostic angiography recruited between June 2000 and June 2002 and followed up for a mean of 6.9±2.1 years.

Outcome All-cause mortality and vascular mortality. Prevalence of testosterone deficiency.

Results The overall prevalence of biochemical testosterone deficiency in the coronary disease cohort using bio-available testosterone (bio-T) <2.6 nmol/l was 20.9%, using total testosterone <8.1 nmol/l was 16.9% and using either was 24%. **Excess mortality was noted in the androgen-deficient group compared with normal (41 (21%) vs 88 (12%), p=0.002).** The only parameters found to influence time to all-cause and vascular mortality (HR ± 95% CI) in multivariate analyses were the presence of left ventricular dysfunction (3.85; 1.72 to 8.33), aspirin therapy (0.63; 0.38 to 1.0), β-blocker therapy (0.45; 0.31 to 0.67) and low serum bio-T (2.27; 1.45 to 3.6).

Conclusions **In patients with coronary disease testosterone deficiency is common and impacts significantly negatively on survival.** Prospective trials of testosterone replacement are needed to assess the effect of

treatment on survival.

2016

7) Traish, Abdulmaged. "Testosterone therapy in men with testosterone deficiency: Are we beyond the point of no return?." Investigative and Clinical Urology 57.6 (2016): 384-400.
Although testosterone therapy in men with testosterone deficiency was introduced in the early 1940s, utilization of this effective treatment approach in hypogonadal men is met with considerable skepticism and resistance. Indeed, for decades, **the fear that testosterone may cause prostate cancer** has hampered clinical progress in this field. Nevertheless, even after considerable knowledge was acquired that this fear is unsubstantiated, many in the medical community remain hesitant to utilize this therapeutic approach to treat men with hypogonadism. As the fears concerning prostate cancer have subsided, a new controversy regarding use of testosterone therapy and **increase in cardiovascular disease** was introduced. **Although the new controversy was based on one ill-fated clinical trial, one meta-analysis with studies that utilized unapproved formulation in men with liver cirrhosis, and two retrospective studies with suspect or nonvalidated statistical methodologies and database contaminations, the flames of such controversy were fanned by the lay press and academics alike.** In this review we discuss the adverse effect of testosterone deficiency and highlight the numerous proven benefits of testosterone therapy on men's health and **debunk the myth that testosterone therapy increases cardiovascular risk**. Ultimately, we believe that there is considerable scientific and clinical evidence to suggest that testosterone therapy is safe and effective with restoration of physiological levels in men with testosterone deficiency, irrespective of its etiology.

TD is associated with increased incidence of metabolic syndrome, obesity, sexual dysfunction, impaired fertility, reduced motivation, increased fatigue, depressed mood, loss of bone and muscle mass, anemia, decreased energy and vigour, insulin resistance, diabetes, inflammation, dyslipidemia, sarcopenia and frailty, reduced quality of life (QoL) and increased mortality [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 40, 41, 42, 43, 44]. A substantial body of evidence indicates that coronary artery disease incidence and severity, carotid intima-media thickness, atherosclerosis is inversely correlated with serum T concentrations [45]. **There is an urgent need among the medical community for greater awareness of the impact of TD on general health in men with TD.**

8) Traish, Abdulmaged M. "Testosterone therapy in men with testosterone deficiency: are the benefits and cardiovascular risks real or imagined?." American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. Vol. 311. No. 3. American Physiological Society, 2016.

In the adult male, testosterone (T) deficiency (TD) also known as male hypogonadism, is a well-established medical condition, which has been recognized for more than a century. T therapy in men with TD was introduced as early as 1940s and was reported to improve overall health with no concomitant serious adverse effects. A wealth of recent studies demonstrated that T therapy in men with TD is associated with increased lean body mass, reduced fat mass and waist circumference, improvement in glycemic control, and reduced obesity. T therapy is also associated with improvements in lipid profiles, amelioration of metabolic syndrome (Met S) components, reduced inflammatory biomarkers, reduced systolic and diastolic blood pressure, and improvements in sexual function. More importantly, T therapy is associated with amelioration of diabetes and reduced mortality. However, few studies, marred with serious methodological and analytical flaws reported between 2010 and 2014, suggested that T therapy is associated with increased cardiovascular (CV) risk. As summarized in this review, a thorough and critical analysis of these studies showed that the risks purported are unsubstantiated and such studies lacked credible scientific and clinical evidence. Moreover, recent observational, registry studies, clinical trials, and meta-analyses, all revealed no increase in CV risks in men

receiving T therapy. In this review, the benefits of T therapy in adult men with TD and the lack of credible evidence suggesting that T therapy is linked to increased CV risks are discussed. It should be noted that the literature is replete with studies demonstrating beneficial effects of T therapy on CV and overall health.

Of importance, the study by Snyder et al. [3] and the resolutions of the consensus panel on T [2] debunked the notion that age-related hypogonadism is not a clinical condition and should remain untreated. As reported in the study [3], T therapy in older men has several benefits and age-related hypogonadism is a clinical condition worthy of treatment. We hope that the findings of this large and well executed study [3] and the summary provided by the consensus panel [2] will serve as a reminder to those who are beating the drums of fear and hysteria on the dangerous use of T in the treatment of men with TD and reassure men suffering from TD and their physicians that such fears and hysteria are unfounded.

9) free pdf Anderson Jeffrey testosterone replacement myocardial infarction low testosterone 2016 Anderson, Jeffrey L., et al. "Impact of testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated health care system." The American journal of cardiology 117.5 (2016): 794-799.

The aim of this study was to assess the effect of testosterone replacement therapy (TRT) on cardiovascular outcomes. Men (January 1, 1996, to December 31, 2011) with a low initial total testosterone concentration, a subsequent testosterone level, and >3 years of follow-up were studied. Levels were correlated with testosterone supplement use. The primary outcome was major adverse cardiovascular events (MACE), defined as a composite of death, nonfatal myocardial infarction, and stroke at 3 years. Multivariate adjusted hazard ratios (HRs) comparing groups of persistent low (**<212 ng/dl,** n = 801), normal (**212 to 742** ng/dl, n = 2,241), and high (**>742 ng/dl,** n = 1,694) achieved testosterone were calculated by Cox hazard regression. **A total of 4,736 men were studied. Three-year rates of MACE and death were 6.6% and 4.3%**, respectively. **Subjects supplemented to normal testosterone had reduced 3-year MACE (HR 0.74; 95%** confidence interval [CI] 0.56 to 0.98, p = 0.04) **compared to persistently low testosterone, driven primarily by death (HR 0.65, 95% CI 0.47 to 0.90). HRs for MI and stroke were 0.73 (95% CI 0.40 to 1.34), p = 0.32, and 1.11 (95% CI 0.54 to 2.28), p = 0.78, respectively**. MACE was noninferior but not superior for high achieved testosterone with no benefit on MI and a trend to greater stroke risk. In conclusion, **in a large general health care population, TRT to normal levels was associated with reduced MACE and death over 3 years** but a stroke signal with high achieved levels suggests a conservative approach to TRT.

10) Saad, Farid, et al. "Testosterone deficiency and testosterone treatment in older men." Gerontology 63.2 (2017): 144-156.

Frailty is a clinical condition related to changes in metabolism, to sarcopenia, and to decline in muscle mass and strength, bone mineral density, and physical function with aging. The pathophysiology of frailty is multifactorial and associated with comorbidities. Testosterone is implicated in regulating metabolic functions, maintenance of muscle and bone, and inhibition of adipogenesis. In older individuals, reduced testosterone is thought to contribute to an altered state of metabolism, loss of muscle and bone, and increased fat, leading to sarcopenia, sarcopenic obesity, and frailty. While no direct relationship between testosterone deficiency (commonly known as hypogonadism) and frailty has been established (due to the multifactorial nature of frailty), clinical evidence suggests that testosterone deficiency is associated with increased sarcopenia and obesity. Testosterone treatment in frail older men with limited mobility and with testosterone deficiency improved insulin resistance, glucose metabolism, and body composition. These changes contribute to better physical function and improved quality of life. Because frailty increases disability, comorbidities, and the risk of hospitalization, institutionalization, and mortality in older men, it is warranted to explore the potential

usefulness of testosterone treatment in frail men with hypogonadism in order to attenuate the progression of sarcopenia and frailty. In this paper, we will discuss the impact of testosterone deficiency on frailty and the potential role of testosterone treatment in ameliorating and reducing the progression of frailty. Such an approach may reduce disability and the risk of hospitalization and increase functional independence and quality of life.

11) Morgentaler, Abraham, et al. "Testosterone therapy and cardiovascular risk: advances and controversies." Mayo Clinic Proceedings. Vol. 90. No. 2. Elsevier, 2015.

a modest number of randomized controlled trials (RCTs), indicate that low serum T concentrations are associated with increased CV risk and mortality and that T therapy may have clinically relevant CV benefits

Established benefits of T therapy in hypogonadal men include improved sexual desire and function,12-15 improved energy, mood, and vitality,15-19 increased lean mass,14,19-22 decreased waist circumference,23-27 reduced total body fat mass,19-22 and increased bone mineral density.28-31 Promising new data reveal that T therapy improves insulin sensitivity32- 34 and reduces blood glucose23,25,35 and hemoglobin A1c (HbA1c)23,25,27,35 levels in men with type 2 diabetes or obesity.

In summary, we find no scientific basis for the suggestion that T therapy increases CV risk. In fact, as of this date, we are unaware of any compelling evidence that T therapy is associated with increased CV risk. On the contrary, the weight of evidence accumulated by researchers around the world over several decades clearly indicates that higher levels of T are associated with amelioration of CV risk factors and reduced risk of mortality.

12) Sharma, Rishi, et al. "Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men." European Heart Journal (2015): ehv346.
Aims There is a significant uncertainty regarding the effect of testosterone replacement therapy (TRT) on cardiovascular (CV) outcomes including myocardial infarction (MI) and stroke. The aim of this study was to examine the relationship between normalization of total testosterone (TT) after TRT and CV events as well as all-cause mortality in patients without previous history of MI and stroke.
Methods and results We retrospectively examined **83 010 male veterans** with documented **low TT levels**. The subjects were categorized into (Gp1: TRT with resulting normalization of TT levels), (Gp2: TRT without normalization of TT levels) and (Gp3: Did not receive TRT). By utilizing propensity score-weighted Cox proportional hazard models, the association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups. **The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42–0.46], risk of MI (HR: 0.76, CI 0.63–0.93), and stroke (HR: 0.64, CI 0.43–0.96) were** significantly lower in Gp1 (n = 43 931, median age = 66 years, mean follow-up = 6.2 years) vs. Gp3 (n = 13 378, median age = 66 years, mean follow-up = 4.7 years) in propensity-matched cohort.

Similarly, the **all-cause mortality (HR: 0.53, CI 0.50–0.55), risk of MI (HR: 0.82, CI 0.71–0.95), and stroke (HR: 0.70, CI 0.51–0.96) were significantly lower in Gp1 vs. Gp2 (n = 25 701, median age = 66 years, mean follow-up = 4.6 years).**

There was no difference in MI or stroke risk between Gp2 and Gp3.
Conclusion In this large observational cohort with extended follow-up, **normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.**

13) Muraleedharan, Vakkat, et al. "Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes." European Journal of Endocrinology 169.6 (2013): 725-733.
Objective Men with type 2 diabetes are known to have a high prevalence of testosterone deficiency. No long-term data are available regarding testosterone and mortality in men with type 2 diabetes or any effect of testosterone replacement therapy (TRT). We report a 6-year follow-up study to examine the effect of baseline testosterone and TRT on all-cause mortality in men with type 2 diabetes and low testosterone.

Research design and methods A total of 581 men with type 2 diabetes who had testosterone levels performed between 2002 and 2005 were followed up for a mean period of 5.8±1.3 s.d. years. Mortality rates were compared between **total testosterone >10.4 nmol/l (300 ng/dl; n=343)** and **testosterone ≤10.4 nmol/l (n=238)**. The effect of TRT (as per normal clinical practise: 85.9% testosterone gel and 14.1% intramuscular testosterone undecanoate) was assessed retrospectively within the low testosterone group.

Results **Mortality was increased in the low testosterone group (17.2%) compared with the normal testosterone group (9%; P=0.003)** when controlled for covariates. In the Cox regression model, multivariate-adjusted hazard ratio (HR) for decreased survival was 2.02 (P=0.009, 95% CI 1.2–3.4). TRT (mean duration 41.6±20.7 months; n=64) was associated with a reduced mortality of 8.4% compared with 19.2% (P=0.002) in the untreated group (n=174). The multivariate-adjusted HR for decreased survival in the untreated group was 2.3 (95% CI 1.3–3.9, P=0.004).

Conclusions **Low testosterone levels predict an increase in all-cause mortality during long-term follow-up.** Testosterone replacement may improve survival in hypogonadal men with type 2 diabetes.
Several longitudinal population studies have reported that a low testosterone at baseline is associated with an increase in all-cause mortality (1). Some individual studies have specifically identified increases in cardiovascular, respiratory and cancer deaths (2, 3, 4). A meta-analysis of published research papers with a mean follow-up period of 9.7 years confirmed that low testosterone was associated with increased risk of all-cause and cardiovascular mortality in community based studies (1). Men with specific co-morbidities such as proven coronary artery disease and renal failure have also found that low testosterone predicts an increased risk of earlier death than those with the same condition and are testosterone replete (5, 6).
In summary, this is the first study to demonstrate that low testosterone levels are associated with an increase in all-cause and cardiovascular mortality in men with type 2 diabetes. This study demonstrates that **long-term testosterone replacement is not only safe in terms of mortality but may also improve survival in men with type 2 diabetes and hypogonadism.**

14) Overselling hysteria dangerously media coverage testosterone men Vance Jay C Ohio State 2015 Vance, Jay C. Overselling hysteria, dangerously: the media coverage of testosterone therapy in men. Diss. The Ohio State University, 2015.

15) Traish, Abdulmaged M., Jay C. Vance, and Abraham Morgentaler. "Overselling hysteria." EMBO reports (2016): e201643642.

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16) Traish, Abdulmaged M. "Age-Related Testosterone Deficiency Merits Treatment." Androgens: Clinical

Research and Therapeutics 2.1 (2021): 46-55.
The negative effects of testosterone deficiency (TD) on human health and quality of life are well demonstrated, including signs, symptoms, metabolic syndrome, obesity, and increased mortality. Recently, substantial evidence emerged, demonstrating the benefits of testosterone therapy in men with classical and "age-related" hypogonadism. The US Food and Drug Administration (FDA) opposes testosterone therapy in men with age-related hypogonadism but not in men with classical hypogonadism. The FDA acknowledges that TD merits treatment, but the FDA made an artificial distinction between diagnoses where T treatment is warranted and others where the underlying diagnosis is unknown, and treatment is unwarranted. The FDA labeled the unknown category as "age-related." Since the FDA is unable to demonstrate that one group differs in benefits or risks from the other, there are no bases for this distinction. **This action by the FDA is not based on scientific or clinical evidence.** There is no evidence that the response to testosterone therapy of "age-related" hypogonadism occurs via different physiological or biochemical mechanisms than those historically recognized conditions. Also, there is no evidence that "age-related" hypogonadism responds less well to testosterone therapy than "classical" hypogonadism. More importantly, there is no scientific or clinical evidence to suggest that the risks of testosterone therapy in men with "age-related" hypogonadism are worse or different for men with "classical" hypogonadism. **For these reasons, we disagree with the FDA position on testosterone therapy in age-related hypogonadism.**

17) Nguyen, Christine P., et al. "Testosterone and "age-related hypogonadism"—FDA concerns." The New England journal of medicine 373.8 (2015): 689.
The FDA convened an advisory committee meeting in September 2014 to discuss the use of testosterone for age-related hypogonadism and the recent signal of cardiovascular risk. The committee members concluded that the available evidence supports an indication for testosterone therapy only in men with classic hypogonadism and that drug labels should state that the efficacy and safety of testosterone products have not been established for age-related hypogonadism. In addition, because there is no evidence of laboratory testing before the initial testosterone prescription for some men, committee members recommended adding a statement to drug labels about the need to confirm low serum testosterone concentrations before initiating treatment. The committee acknowledged the limitations of the available data on adverse cardiovascular events but concluded that the totality of the evidence suggests a weak signal of cardiovascular risk and recommended updating drug labels to reflect this information. The FDA agreed with the advisory committee's recommendations and subsequently required revisions to the labels of all testosterone products. Committee members also commented that only a controlled clinical trial — not observational studies — will be able to definitively determine the effects of testosterone therapy on cardiovascular outcomes.

18) Morgentaler, Abraham. "Understanding the Controversy Regarding Treatment of Age-Related Testosterone Deficiency." Androgens: Clinical Research and Therapeutics 2.1 (2021): 61-63.
The FDA is a critically important government institution charged with the protection of our public health. **Yet it must be emphasized that its role is to regulate the pharmaceutical industry, and not health care providers. It bears emphasis that the FDA is not involved with the practice of medicine.** Yet the medical community and insurance companies pay close attention to the FDA's positions, and insurance companies frequently restrict coverage based on FDA labels, especially if it helps
their bottom line. Although pressures on a regulatory agency such as
the FDA differ substantially from those of health care providers and medical groups, it is to be hoped that the entirety of the scientific community, including the FDA, will soon come to recognize the importance of TTh not only for its symptomatic benefits in men
with age-related TD, but also for its impact on general health. I encourage everyone interested in TD and its treatment to read the excellent articles by Traish2 and by Nguyen and colleagues

19) Zhu, Alex, et al. "What is a normal testosterone level for young men? Rethinking the 300 ng/dL cutoff for testosterone deficiency in men 20-44 years old." The Journal of Urology 208.6 (2022): 1295-1302.

Purpose: There is an age-related decline in male testosterone production. It is therefore surprising that young men are evaluated for testosterone deficiency with the same cutoff of 300 ng/dL that was developed from samples of older men. Our aim is to describe normative total testosterone levels and age-specific cutoffs for low testosterone levels in men 20 to 44 years old. Materials and Methods: We analyzed the 2011-2016 National Health and Nutrition Examination Surveys, which survey nationally representative samples of United States residents. Men 20 to 44 years old with testosterone levels were included. Men on hormonal medications, with a history of testicular cancer or orchiectomy, and with afternoon/evening laboratory values were excluded. We separated men into 5-year intervals and evaluated the testosterone levels of each age group, and for all men 20 to 44 years old. We used the American Urological Association definition of a "normal testosterone level" (the "middle tertile") to calculate age-specific cutoffs for low testosterone levels.

Results: Our final analytic cohort contained **1,486 men**. Age-specific middle tertile levels were
409-558 ng/dL (20-24 years old),
413-575 ng/dL (25-29 years old),
359-498 ng/dL (30-34 years old),
352-478 ng/dL (35-39 years old), and
350-473 ng/dL (40-44 years old).
Age-specific cutoffs for low testosterone levels were 409, 413, 359, 352, and 350 ng/dL, respectively.
Conclusions: Diagnosis of testosterone deficiency has traditionally been performed in an age-indiscriminate manner. However, young men have different testosterone reference ranges than older men. Accordingly, age-specific normative values and cutoffs should be integrated into the evaluation of young men presenting with testosterone deficiency.

20) Yeo, Sandy, et al. "Burden of male hypogonadism and major comorbidities, and the clinical, economic, and humanistic benefits of testosterone therapy: a narrative review." ClinicoEconomics and Outcomes Research (2021): 31-38.

Abstract: Male hypogonadism and major comorbidities such as type 2 diabetes mellitus, obesity, cardiovascular disease, and osteoporosis appear closely connected, forming a vicious cycle that leads to further hypogonadism. This narrative review provides a comprehensive overview of the current literature on the overall burden of male hypogonadism alongside related comorbidities, and how this may be alleviated through testosterone therapy.
Observational and clinical data demonstrate that the interaction of male hypogonadism and its related comorbidities is associated with increased mortality, cardiovascular event risk and reduced quality of life. Evidence from epidemiological and registry-based studies shows that this clinical and humanistic burden translates to increased economic burden on health-care systems, through increased physician visits, medical claims, and drug costs. Male hypogonadism can be managed with testosterone therapy, which is intended to normalize testosterone concentrations and thereby reduce both hypogonadism symptoms and risk of comorbidities. Clinical and observational data suggest that in males with hypogonadism, testosterone therapy rapidly and sustainably improves glycemia, reduces risk of progression to diabetes, leads to significantly reduced waist circumference and fat mass, while providing significant positive effects on cardiovascular event risk and bone density. Significant and sustained improvement in patient-reported erectile function, urinary function, and aging male symptoms have also been shown. Economic evaluations have estimated that reduced comorbidity

risk following testosterone therapy may lead to cost-savings, with one study estimating yearly inpatient savings of £3732 for treating comorbidities after intervention. A major unmet need exists in the area of male hypogonadism, particularly related to common comorbidities. Options for treatment include testosterone therapy, which has been shown to alleviate the clinical, economic, and humanistic burden associated with these conditions. As the prevalence of male hypogonadism is likely to increase globally, and this condition may be currently underdiagnosed, cost-saving testosterone therapies should be increasingly considered to manage hypogonadism.

21) Figueiredo, Maria Gabriela, Thiago Gagliano-Jucá, and Shehzad Basaria. "Testosterone therapy with subcutaneous injections: A safe, practical, and reasonable option." The Journal of Clinical Endocrinology & Metabolism 107.3 (2022): 614-626.

22) Lapauw, Bruno, and Jean-Marc Kaufman. "Management of endocrine disease: Rationale and current evidence for testosterone therapy in the management of obesity and its complications." European Journal of Endocrinology 183.6 (2020): R167-R183.

23) Zhang, Xiao, et al. "Testosterone therapy reduces cardiovascular risk among hypogonadal men: a prospective cohort study in Germany." Androgens: Clinical Research and Therapeutics 2.1 (2021): 64-72.

Materials and Methods: We conducted a prospective cohort study using data from **602 hypogonadism men free of CVDs at study baseline from a registry study in Germany who were eligible for testosterone therapy, with an age range of 31–74 years and a follow-up duration of up to 12 years.** Receiving testosterone therapy or not was based on the patient's own choice at study entry. Patients who decided to take testosterone therapy were classified as **treatment group (n = 325),** and the rest were classified as the **control group (n = 277).**

Results: We found that the control group had an overall increasing risk score and decreasing testosterone level over time. For the treatment group with improved testosterone level and lipid and glucose profiles, the risk score decreased before 24 months, and it became stable later on. **After propensity score matching, there were 0 cardiovascular events in the treatment group and 45 in the control group.**

Conclusions: Low testosterone level is associated with higher cardiovascular risk. Long-term testosterone therapy reduces cardiovascular events among hypogonadal men. Clinicians should be informed of this association when assessing a male patient's cardiovascular risk and ensure timely treatment if needed.

24) Yassin, A., et al. "Testosterone Treatment (TTh) Improves Anemia and Hematocrit Increase Reduced Death in Hypogonadal Men: Paradigm Shift of a Risk Factor of TTh." Curr Trends Intern Med 6 (2022): 161.

The present study showed that increased hematocrit (up **to 52%** at final assessment) was independently associated with reduced mortality [5]. This confirms the current clinical guidelines **recommendation of using 54% as a threshold for change in management of men receiving testosterone therapy (e.g. dose reduction or therapeutic phlebotomy)** [11-15]. It should be kept in mind that dehydration can cause a temporary elevation in hematocrit [16] and therefore a high hematocrit reading should be confirmed in a second blood test, ensuring the patient is in a well hydrated state, before action is taken.

The finding that the hematocrit elevation stabilized at month 48 is reassuring [5] This is congruent with results from another long-term real-world evidence study, in which treatment with testosterone undecanoate injection for 10 years increased hematocrit by 3.6% [3].
Meta-analyses of randomized controlled trials which showed that despite a higher incidence of elevated hematocrit in men receiving testosterone therapy compared to placebo, no difference in clinical adverse events were reported [17,18]. The present study provides reassurance regarding the safety of testosterone therapy, and suggests that long-term TTh can reduce mortality even in the context of relatively high hematocrit levels. Support for this comes from other long-term real-world evidence studies showing that despite increases in hematocrit, there was no increased risk for venous thromboembolism, myocardial infarction, stroke, or mortality [2,19].