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Report

Why the FDA Is Wrong about Testosterone

By Craig Stamos

In men aged 30 years and older, **testosterone** levels steadily fall at a rate of about **1%** per year.^{1,2}

Researchers at the **National Institute on Aging**³ have established low testosterone levels in:

- **20%** of men over age 60
- **30%** of men over age 70
- **50%** of men over age 80

These percentages understate the magnitude of this problem as they fail to consider the majority of aging men who fail to achieve optimal **testosterone** and **estrogen** balance.

By properly balancing **testosterone** and **estrogen**, a reversal in many age-related disorders has been found. This includes improvements in libido, bone density, muscle mass, strength, body composition, mood, red blood cell formation, cognition, quality of life, and cardiovascular disease.^{2,4,5}

Yet despite these proven benefits, the FDA recently mandated a **black box warning label** be affixed to prescription testosterone drugs.⁶ A black box warning is the strongest possible warning issued by the FDA and implies serious risks associated with a drug.

This irresponsible and scientifically invalid decision threatens to discourage millions of eligible men from taking advantage of the genuine benefits of testosterone replacement therapy.

The FDA's decision seems to be based on a small number of poorly designed, poorly conducted studies, some of which *appeared* to show an increased risk of heart attacks and strokes in men undergoing such therapy.⁷⁻¹² Yet the preponderance of the data shows marked decreases in heart attack and stroke risk in response to **higher** testosterone levels.

In a large study published in **2015**, men treated with **testosterone** had a **24%** reduction in heart attack risk and a **36%** reduction in risk of stroke.¹³ The most exciting revelation about this new study was that the risk of dying from **any** cause was **56%** lower in treated men whose testosterone blood levels normalized, compared with untreated individuals.

With a wealth of studies showing positive benefits, and in the face of the FDA's irrational decision based on flawed studies, it is time to review the good science on this issue, and to make balanced recommendations about testosterone replacement therapy.

Benefits of Testosterone Replacement Therapy

Testosterone levels begin a gradual fall as men enter their 30s!^{1,2}

This matters because declining testosterone levels are associated with muscle atrophy and weakness, osteoporosis, reduced sexual functioning, increased fat mass, metabolic syndrome, diabetes risk, cognitive impairment, depression, and an increased risk of developing Alzheimer's disease.¹⁴⁻¹⁶ Furthermore, men with low levels of testosterone are up to **51%** more likely to develop frailty, a condition associated with early death, compared to those with higher levels.¹⁷

Used appropriately, and with regular **blood tests**, testosterone replacement therapy can reverse many of these age-related disorders. Testosterone replacement therapy has been shown to improve libido and sexual function, bone density, muscle mass, strength, body composition, mood, red blood cell formation, cognition, and quality of life, as well as reduce cardiovascular disease.^{2,4,5} It has even been suggested that testosterone replacement therapy preserves new brain cell growth in the hippocampus, the main memory area of the brain and the one that loses neurons with age.¹³

Perhaps most importantly, the life-shortening effects of low testosterone can be substantially reversed by **testosterone replacement** therapy in many men. By one estimate, testosterone replacement therapy can increase longevity by about **2%** per year.¹⁸ After five years, survival rates are back in line with those of men with normal testosterone levels.¹⁹

Simply put, testosterone replacement therapy offers a wealth of health benefits for older men. It is approved by the FDA for patients with signs and symptoms of low testosterone who also have documented low blood levels of the hormone.^{13,20} The diagnosis of age-related low testosterone is rising, with an estimated **2.4 million** American men 40 through 69 years old suffering from the condition.^{13,21}

The FDA's approval criteria, however, excludes the majority of aging men who could benefit by boosting their testosterone level while suppressing excess estrogen when blood test results indicate.

All of this means that more men than ever could benefit from testosterone replacement. Unfortunately, many of these men—or their doctors—will avoid this beneficial therapy due to the FDA's recent black box warning.

FDA Sows Seeds of Unnecessary Fear



It seems evident that testosterone replacement therapy offers compelling benefits when given to men with genuine symptoms of age-related testosterone deficiency *and* documented low blood levels of the hormone.

Yet in mid-2015, when the FDA instituted a black box warning on testosterone replacement therapy for older men, they asserted that neither the safety nor the benefits of such therapy had been established, and cited, in particular, a “*possible increased risk of heart attacks and strokes*” in patients taking testosterone.⁶

Testosterone cannot be obtained without a prescription. In today's litigation-prone society, that black box warning is likely to dissuade physicians from prescribing testosterone replacement therapy.

But a careful examination of the published literature tells another story. Properly restoring sex hormone balance in aging men confers protection against heart attack and stroke via multiple mechanisms. The FDA chose to ignore these many studies showing disease risk reduction in men with higher testosterone blood levels.

When researchers evaluate the impact that a drug has on humans, the standard practice is to determine the levels of the drug in plasma or serum after administration of the drug. That common-sense design parameter was lacking in most of the studies on which the FDA based its labeling decision.

FDA actions are supposed to be based on multiple high-quality studies to assess safety and efficacy.²² This “evidence-based-medicine” approach is now standard in peer-reviewed medical research and policymaking, but it was apparently

overlooked by the FDA's decision-makers.

Instead, studies on which the **black box** labeling decision was made demonstrate considerable inconsistencies and very small clinically important treatment effects.⁷⁻¹²

Of the studies included, only two showed an association between testosterone replacement and increased risk of cardiovascular events. Here is a review of the studies apparently used by the FDA in its labeling decision.

WHAT YOU NEED TO KNOW

The Truth about Testosterone

- Testosterone replacement therapy is well established as a means of improving an aging man's vigor, sexual performance, strength, bone density, and more.
- But recent black box warning labeling by the FDA is likely to frighten some physicians and patients away from this effective therapy, based on spurious concerns about cardiovascular risks.
- Careful review of the literature shows that studies prior to 2015 were poorly designed and many failed to check testosterone levels after treatment, a basic consideration in any therapeutic trial.
- A large study published in 2015 convincingly demonstrates that testosterone treatment produces a substantial reduction in the risk of dying and of having a heart attack or stroke in men whose testosterone levels normalized with therapy.
- Any man with symptoms of malaise, fatigue, diminished strength, lower sexual performance, cognitive problems, or a host of other symptoms ought to have total and free testosterone levels checked, and then initiate testosterone replacement therapy with proper monitoring of post-treatment levels.



Flawed Study #1

The first study was a retrospective, observational study by Rebecca Vigen, MD, MSCS, and colleagues published in the September 5, 2013, issue of the *Journal of the American Medical Association (JAMA)*. The study suggests testosterone therapy may increase risk of death and certain cardiovascular events.⁷ However, there are several significant shortcomings in the study's design and methodology, and the results conflict with the existing body of research.

The goal of testosterone restoration in most cases is to restore *youthful* blood levels of the hormone. Typically, Life Extension[®] suggests men target a blood level of total testosterone between **700** and **900 ng/dL** for optimal health.

In studies designed to assess the impact of testosterone replacement therapy, one of the most important considerations is to measure subjects' **blood levels** of testosterone regularly throughout the study period. This allows the scientists conducting the study to make sure subjects are taking their testosterone as directed and that their blood levels are rising as expected.

Unbelievably, in the flawed analysis by Vigen and colleagues, only **60%** of study subjects receiving testosterone had a follow-up blood test to assess their testosterone levels. Among them, average testosterone levels rose from a very low level of **175.5 ng/dL** at baseline to a still far-from-optimal level of **332.2 ng/dL** during testosterone therapy.

Raising testosterone levels from a paltry **175.5 ng/dL** to only **332.2 ng/dL** is unlikely to deliver robust health benefits. In fact, research has shown that restoring testosterone levels to **500 ng/dL** or higher is associated with pronounced health benefits, whereas benefits may be less evident at lower levels.^{23,24}

One of the biggest perils facing aging men is the conversion of their testosterone into **estrogen** by the *aromatase* enzyme.²⁵

Aromatase converts testosterone and other androgens into **estrogen**, primarily estradiol. Although some conversion of testosterone to estradiol is essential for health, too much conversion can have devastating consequences for men.

In one study, men with heart failure and high levels of estradiol had an increased risk of death compared to men whose levels of estradiol were in a balanced, middle range of **21.8 to 30.11 pg/mL**.²⁶ These findings support Life Extension[®]'s suggested optimal estradiol level of **20 to 30 pg/mL**. Moreover, excess estrogen promotes abnormal clot formation,²⁷ and high levels may be associated with an increased risk of stroke.²⁸

When men take testosterone, there is a propensity for it to be converted into estradiol by aromatase, and this is especially so for aging men.²⁹ It is therefore important that men undergoing testosterone therapy monitor their estradiol levels regularly and take steps like using an *aromatase-inhibiting* drug to keep estradiol levels in the optimal range in order to protect against the health detriments of excess estrogen.

In the paper published by Vigen and colleagues, there was no report of the subjects' **estradiol** levels. If estradiol was not monitored during testosterone administration, this oversight means that the men receiving testosterone could have experienced a concurrent rise in estradiol levels. This may have compromised their cardiovascular health and could partially account for the increased risk observed in the testosterone-treated group.

Lastly, among the men in this flawed *JAMA* study, there was a statistically significant difference in baseline testosterone levels between the "testosterone therapy" (treatment) and "no-testosterone" (control) groups.

Among the control group, testosterone levels were higher at baseline (**206.5 ng/dL**), whereas the average level was significantly lower at baseline (**175.5 ng/dL**) for those who received a prescription for testosterone.

The treatment group may have had significantly lower levels of testosterone than the control group for years prior to entering the study. The damage caused by years of potentially lower testosterone levels was not accounted for in the study and may have skewed the results.

STEPS TO RESTORING YOUTHFUL TESTOSTERONE BALANCE

1. Blood testing:

Life Extension[®]'s Optimal Levels

Free testosterone	20-25 pg/mL
Total testosterone	700-900 ng/dL
Estradiol	20-30 pg/mL
Prostate-specific antigen	
(PSA)	<1.0 ng/mL



These blood tests are all included in the Life Extension[®] Male Panel that most customers have performed annually.

2. Locate a doctor with knowledge about male hormone restoration. Life Extension[®] maintains lists of doctors who have knowledge about male hormone restoration. To locate a doctor in your area, log on to <http://health.lifeextension.com/InnovativeDoctors/>

3. Correct abnormal levels:
 - Consider compounded natural testosterone cream.
 - If estradiol is over **30 pg/mL**, doctors may also prescribe a very low-dose aromatase-inhibiting drug such as **0.5 mg of anastrozole** (Arimidex[®]) twice per week.
4. Retest in 45 days to ensure proper hormone balance.

Flawed Study #2

The second study by William Finkle, PhD, and colleagues was retrospective and observational. The design of this study limits the interpretation of the findings because subjects were treated in a clinical setting and were not randomized to treatment.⁸

The validity of this study is hampered by several methodological flaws. A striking concern is again the failure of the researchers to account for **estradiol** levels among the men who received a testosterone prescription. As mentioned previously, aging men quickly convert exogenous testosterone into estradiol via action of the *aromatase* enzyme. Studies have shown that cardiovascular risk correlates with higher estrogen/estradiol levels among men.^{26,30,31}

Aromatase activity increases with age among men,²⁹ a paradigm whose repercussions are potentially highlighted by this flawed study. Older men (65 years and older) in this study were more likely to experience a non-fatal heart attack after receiving a testosterone prescription than younger men. This is potentially due to increased conversion of the added testosterone medication to estradiol among the older men.

It is concerning that conventional physicians and researchers continue to prescribe men testosterone without monitoring their estradiol levels and, if needed, prescribing an aromatase-inhibiting drug such as anastrozole (Arimidex[®]).

The researchers specifically acknowledged the potentially harmful cardiovascular-related effects of excess estrogen by stating:

“TT (testosterone therapy) also increases circulating estrogens...which may play a role in the observed excess of adverse cardiovascular-related events, given that estrogen therapy has been associated with this excess in both men and women... The mechanisms linking estrogens to thrombotic events (heart attacks) may be related to markers of activated coagulation, decreased coagulation inhibitors, and activated protein C resistance...”



Unfortunately, despite this acknowledgment, the researchers did not assess **estradiol** levels.

Interestingly, out of the five observational studies included in the FDA's decision to add a black label warning to testosterone treatment, the two flawed studies mentioned above apparently were the ones that prompted the decision, as the other two studies in the review showed a statistically significant **benefit** with testosterone replacement,^{11,12} and the remaining study was inconclusive.¹⁰

If these were the only studies available to consider, the FDA might be pardoned for making a conservative decision out of an abundance of caution.

But several studies had already been published that showed either no effect, or genuine benefits, of testosterone replacement therapy on men's cardiovascular risks. Let's take a look.

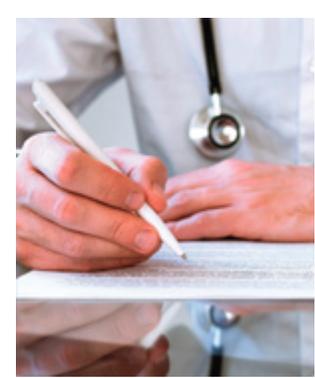
Beneficial Studies Ignored by FDA

An observational study published in **2012** demonstrated *significant* reductions in total mortality in men who received testosterone replacement therapy.¹¹

This study included 1,031 male veterans aged 40 and older, 398 of whom were treated with testosterone. All of the men had testosterone levels that were less than **251 ng/dL**. Among testosterone-treated men, **10.3%** died over the course of four years. In the untreated (no testosterone) group, twice that number (**20.7%**) died during the same period. After statistical adjustment for possible biasing factors, the testosterone-treated men were found to be **39%** less likely to **die** of any cause than were untreated men.

In another study based on a national sample of older Medicare beneficiaries, 6,355 patients received testosterone injections while 19,065 men did not receive treatment.¹⁰ This study showed no association with risk for myocardial infarction (heart attack) over nearly eight years. In fact, in men who began the study with the highest calculated risk score for heart attack, testosterone therapy was associated with a **31% reduction** in risk.

Study Debunks FDA's Position and Shows Testosterone Benefits Heart Health



For the past 19 years, **Life Extension**[®] has published numerous articles on the proper use of testosterone restoration therapy. The FDA's insistence that testosterone drugs carry a **black box warning** is the antithesis of what the totality of the scientific literature clearly states on this critical issue for aging males.

A large study published in **2015** convincingly demonstrates the FDA's action of mandating a black box warning is based on junk science.

This study evaluated a cohort of male veterans receiving care at Veterans Health Administration facilities over a 13-year period.¹³ Unlike many of the previous studies, this one was specifically designed to examine the effects of testosterone replacement therapy on specific cardiovascular outcomes (namely heart attack and stroke) as well as on all-cause mortality.

The most important difference between this and prior studies, in addition to its large size (83,010 total subjects), was that it determined, for each subject, whether blood testosterone levels normalized or not.¹³ The researchers divided the subjects into three groups:

- Men whose total testosterone was normalized after treatment (43,931 men)
- Men whose total testosterone continued to be low even after treatment (25,701 men), and
- Men who were untreated with testosterone and continued to have low total testosterone (13,378 men).

The researchers then analyzed the rates of heart attack, stroke, and death from any cause between the three groups.¹³

This unique study design allowed for the first-ever comparison of men who attained normal testosterone levels with those who did not, as well as with those who were never treated at all. For the first time, it was possible to examine actual biological effects of therapy in considering whether such therapy was dangerous.

This is a rational and obvious approach, but one never taken before, including in any of the studies evaluated by the FDA for its ruling.

First, the researchers compared the largest group (men whose testosterone normalized with treatment) to the untreated subjects. They found that the treated group had a **24%** reduction in the risk of heart attack and a **36%** reduction in the risk of stroke.¹³ This comparison also revealed that the risk of dying from any cause was a significant **56%** lower in treated men

whose testosterone levels normalized, compared with untreated individuals.

Researchers also compared the group whose levels were normalized with those who were treated but had not achieved normal levels. In this comparison, the group whose levels were normalized experienced an **18%** reduction in the risk of heart attack, a **30%** reduction in stroke risk, and a **47%** reduced risk of death by all causes compared to those treated with testosterone therapy but who did not achieve normal levels. All of the results were statistically significant.

When comparing the treated group that did not achieve normal testosterone levels with the untreated group, the only significant difference was a modest **16%** reduction in all-cause mortality. No changes were seen between these groups in heart attack or stroke risk.

This study was enormous in terms of how many people it studied compared with the studies that preceded it. By tracking actual testosterone levels in response to treatment, the researchers were able to expose what is likely to be the biggest contributor to inconsistent results in previous studies. In those studies, failing to check testosterone **blood levels** essentially combined responders and non-responders together, leading to a failed study.

Even prior to this compelling and well-designed study based on data reviewed here and elsewhere, Dr. Abraham Morgentaler of Harvard Medical School, a renowned expert on testosterone and men's health, had concluded that:

*“There is no convincing evidence of increased cardiovascular risks with testosterone therapy. On the contrary, there appears to be a strong beneficial relationship between normal testosterone and cardiovascular health that has not yet been widely appreciated.”*³²

An Expert's Recommendations for Testosterone Replacement Therapy

After a recent World Meeting on Sexual Medicine in Chicago, Dr. Morgentaler summarized expert consensus regarding testosterone replacement therapy, especially in the context of these spurious concerns about cardiovascular health.³³

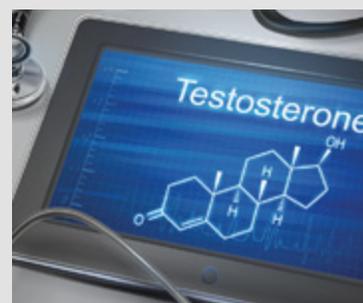
1. All experts emphasized the essential role of symptoms for diagnosis of testosterone deficiency. (In other words, a low testosterone level without symptoms should not necessarily require testosterone therapy, but a high or normal level with symptoms should not rule it out.)
2. Blood levels of total testosterone indicating a deficiency are in the **350 to 400 ng/dL** range, but *free testosterone* should also be determined and was recommended by all experts for clinical decision-making.
3. Two tests of testosterone on separate occasions were recommended by most experts.
4. In men with symptoms but with normal total testosterone levels, a therapeutic trial of testosterone therapy, to be continued if beneficial effects are achieved, was considered potentially useful.
5. Recent studies suggesting an elevated cardiovascular risk with testosterone therapy were ***not found to be credible***.

NEW ENGLAND JOURNAL OF MEDICINE PUBLISHES POSITIVE TESTOSTERONE STUDY

The prestigious *New England Journal of Medicine* recently published an important study that confirms the multiple benefits of testosterone therapy in aging men.³⁴

With recent concerns about the safety and benefits of testosterone therapy raised by the FDA that resulted in an alarming black box warning, this clinical trial conducted by the Institute of Medicine confirmed that testosterone therapy benefits older men with low testosterone levels with regard to sexual function, activity, and performance.

The results of this study entirely vindicate those who have long recognized the value of appropriate testosterone replacement on men's sexual function and physical performance.



The study enlisted 790 men aged 65 years or older, who had *both* blood testosterone levels less than **275 ng/dL** and symptoms of low testosterone (that's important because men can have symptoms without low levels, and also low levels without symptoms, highlighting the need for blood testing before treatment). Men were treated with either a testosterone **1%** gel or placebo gel for one year. The starting dose was **5 grams** testosterone per day, which was adjusted after periodic blood testing to sustain blood testosterone levels within the normal range for younger men aged 19-40.

The findings were unequivocally in favor of the testosterone supplement.

First, treatment successfully raised blood testosterone levels to the mid-normal range for younger men, demonstrating that the dosing scheme was correct and appropriate.

Second, those increased testosterone levels were significantly associated with increased sexual activity, sexual desire, and erectile function (remember, the subjects were all older than 65 years). In addition, **20.5%** of men receiving testosterone had an increase in a six minute walking test of at least 50 meters (55 yards), significantly more than the **12.6%** of men receiving placebo. Men in the testosterone group also reported greater energy levels, and those with the largest increases in testosterone had a greater increase in a score of vitality (less fatigue).

Finally, men treated with testosterone demonstrated an improvement in mood and a reduction in depressive symptoms compared with those receiving placebo gel.

In summary, it is now clear that older men with proven low testosterone levels and associated symptoms stand to benefit from testosterone supplementation aimed at keeping their levels in line with those of much younger men.

This study also highlights the importance of blood testosterone measurement before and during testosterone treatment. While the risks of treatment appear to be low, this study did not have the statistical power to demonstrate a difference in risk between placebo and testosterone therapy, so it is imperative that men contemplating testosterone supplementation undergo testing and work with their physician to achieve optimal results.

The favorable findings in this trial likely would have been even better if the researchers had made a concerted effort to individualize treatment and target optimal ranges of **total testosterone** (Life Extension[®] suggests **700 to 900 ng/dL**) and free testosterone (Life Extension[®] suggests **20 to 25 pg/mL**) as well as balance **estradiol** levels within a range of **20 to 30 pg/mL** following testosterone restoration in these aging men. In this study, **estradiol** levels ballooned to nearly **50%** greater than baseline following testosterone administration. Life Extension[®] has long recognized the importance of controlling for estrogen balance in aging men. For example, a study published in the *Journal of the American Medical Association* measured blood estradiol in men with chronic heart failure. Compared to men in the balanced estrogen quintile, men in the highest quintile (estradiol levels of **37.40 pg/mL** or greater) were significantly more likely to die. Those in the lowest estradiol quintile (estradiol levels under **12.90 pg/mL**) also had an increased death rate compared to the group in **estrogen** balance. The men in the balanced quintile—with the fewest deaths—had serum estradiol levels between **21.80 and 30.11 pg/mL**.²⁶ Life Extension[®] offers a convenient assessment of testosterone (both total and free), as well as estradiol, in our comprehensive **Male Blood Test Panel** offered at the discounted price of **\$199** until **June 6, 2016**. The **Male Blood Test Panel** can be ordered by calling **1-800-208-3444** (24 hours).

Summary

There is no question that in men with symptoms of testosterone deficiency, testosterone replacement therapy produces substantial benefits.^{13,32,33}

But a recent labeling action by the FDA is almost certain to frighten many men and their physicians away from using this

important treatment. Unfortunately, this decision was based on junk science purporting to show an increased cardiovascular risk in men using the therapy.

We conducted a careful review of the evidence the FDA used to make this decision, coupled with results from recent large, carefully designed studies. What this shows is that in men who achieve normalization of their testosterone levels on replacement therapy, the risks of cardiovascular disease are not only no higher than average, but are in fact lower.

It is impossible to overstate the importance of:

- Getting hormone blood levels checked (including total and free testosterone and estradiol) for men with symptoms consistent with age-related testosterone deficiency.
- Repeating the tests after several months to determine whether levels are normalized. If levels are not normalized, raising the dose of testosterone and rechecking in another few months is ideal.¹³

There is no reason to let the FDA's scare tactics stand in the way of a proven means of improving men's quality of life, vigor, and sexual performance, while improving their cardiovascular status. All men with symptoms should have their levels checked and start on testosterone replacement therapy as indicated.

It should start with a comprehensive **blood test** panel that measures all sex hormones, PSA, liver function, and blood cell counts. With the results of this blood test in hand, a competent physician and an empowered patient can together safely restore youthful hormone balance.

If you have any questions on the scientific content of this article, please call a **Life Extension**[®] Health Advisor at 1-866-864-3027.

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