Response To Media Reports Associating Testosterone Treatment With Greater Heart Attack Risk

A recent study that received massive media attention suggested that testosterone drugs may increase the risk of death and certain cardiovascular events. This flawed study used inadequate amounts of often the wrong form of testosterone, did not evaluate male subjects' estrogen levels, did not properly individualize the testosterone dose, and failed to take into account significantly different baseline testosterone levels. These flaws rendered this study's findings meaningless to aging men who properly optimize their testosterone and estrogen levels.

Scientifically reviewed by **Dr. Gary Gonzalez**, MD, in October 2024. Written by: William Faloon.

Headline news stories on **November 5, 2013**, parroted a study proclaiming that aging men using **testosterone** drugs suffer greater heart attack risk.[1-3]

Life Extension® immediately recognized ***errors*** in this anti-testosterone study that render its findings meaningless.

This study was designed by physicians who apparently don't know how to ***safely*** restore testosterone levels in aging men.

The media's portrayal of this flawed study will discourage aging men from properly restoring their testosterone levels. To help spare the lives of testosterone deficient men, we have prepared an extensive rebuttal to this erroneous report.

Life Extension's official response, starting below provides a detailed point-by-point rebuttal to the many defects in this study that was used to discredit natural testosterone restoration.

Below is a brief **summary** of the more serious flaws that generated the media frenzy.

In order to confer the most protection against heart disease, **total testosterone** blood levels need to be raised higher than **500–550 ng/dL**.[4] Life Extension believes that optimal youthful **total testosterone** is in the **700–900 ng/dL** range.

The men enrolled in this flawed study only boosted their mean **total testosterone** levels to **332 ng/dL**.[5] Previous studies show this low **testosterone** level (**332 ng/dL**) is associated with an ***increased*** heart attack risk compared with levels above **500–550 ng/dL**.[4]

The men in this study were not properly individually dosed and monitored, which explains why the testosterone treatment they received failed to restore their blood testosterone levels to anywhere near cardio-protective ranges.[4,5]

Estradiol (an estrogen) blood levels were not reported in this study used to discredit testosterone drugs. A subset of aging men, often with increased visceral body fat (body fat around the internal organs of the abdominal cavity), have a tendency to convert testosterone into excess estrogen.[6,7] This excess estrogen may alter the balance of anticoagulant and procoagulant (clotting) factors in the blood, and potentially enhance the risk of heart attack and stroke.[8-11] Any man treated with testosterone drugs should also have his **estradiol** blood level tested to ensure that the testosterone is not excessively converting to estrogen. If estradiol increases excessively, then low-dose aromatase-inhibiting drugs (such as **1 mg/week** of anastrozole [Arimidex®]) can be prescribed to reduce the conversion of testosterone to estrogen.[12]

A subgroup of overweight men with excess visceral body fat treated with testosterone in this study would be expected to excessively convert (aromatize) their testosterone into estrogen, which may help explain why more

men in the testosterone group suffered a greater percentage of heart attacks.

Research published in recent years shows profound cardiovascular benefits in response to higher testosterone levels (in men).[4,13,14] The media conveniently ***ignored*** these positive reports and narrowly focused on the egregiously flawed study published in the ***Journal of the American Medical Association*** (*JAMA*).

Based on many published studies, ***Life Extension*** has recommended for decades that aging men restore testosterone to a youthful range. We've always warned that for some men, restoring one's testosterone to more youthful levels could create excessive levels of estrogen, which is readily detectable by **blood testing** and reversible using aromatase-inhibiting therapies.

What's most frightening is that most mainstream doctors today are blindly prescribing testosterone drugs and omitting any kind of estrogen testing. This creates a very ***dangerous*** environment for men who convert their testosterone into excess estrogen!

Flawed Testosterone Analysis Spurs Misleading Media Headlines

By Blake Gossard, Kira Schmid, ND, Luke Huber, ND, MBA, Steven V. Joyal, MD

The age-related decline of men's testosterone levels is inevitable.

Unless aging men replace their diminishing testosterone, they could succumb to any of the numerous health problems linked to low testosterone levels: frailty, muscle loss, weight gain, impaired cognition, fatigue, loss of self-confidence, depression, declining bone health, increased risk of type II diabetes, stroke, and cardiovascular disease.[15,16]

A number of studies show that testosterone replacement therapy improves multiple measures of men's vitality, especially related to cardio-metabolic health.[4,15-24]

Therefore, on November 5, 2013, we were startled to see media headlines like "*Testosterone Treatments Linked to Heart Risks*."[1-3]

This headline and others like it were prompted by a retrospective, observational study 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.[5]

There are several significant shortcomings in the study's design and methodology, and the results conflict with an existing body of research showing that low testosterone increases a man's risk of heart problems.

Woefully Inadequate Testosterone Replacement

> 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 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 published in ***JAMA***, 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.[4,19]

Failure To Account For Impact Of Estrogen

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

Aromatase is an enzyme that 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 **21.8–30.1 pg/mL.**[26] These findings support Life Extension's long held suggested optimal estradiol level of **20-30 pg/mL**. Moreover, excess estrogen promotes abnormal clot formation,[9] and high levels may be associated with an increased risk of stroke.[10]

When men take testosterone, there is a significant propensity for it to be converted into estradiol by aromatase; this is especially so for aging men.[27] 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 *JAMA* (*Journal of the American Medical Association*), 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.

WHAT YOU NEED TO KNOW

Flawed Media Reports Of Anti-Testosterone Study

- The precipitous decline of men's testosterone levels over the years is inevitable.
- Major news media outlets reported that testosterone replacement therapy is linked to heart risk based on a retrospective, observational study that was published in the September 5, 2013, issue of the Journal of the American Medical Association (JAMA).
- In spite of several significant shortcomings in the study's design and methodology, and results that are in conflict with an existing body of research, the study suggests adverse effects from testosterone drug therapy.
- Over the years, several studies have shown that testosterone replacement therapy improves multiple measures of men's vitality, especially related to cardio-metabolic health.
- If aging men do not replace their diminishing testosterone, they could succumb to any of the numerous health problems linked to low testosterone levels: frailty, muscle loss, weight gain, impaired cognition, fatigue, loss of self-confidence, depression, declining bone health, increased risk of type II diabetes, stroke, and cardiovascular disease.

Significant Difference In Baseline Testosterone Levels Between Groups

Among the men in this *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.

Achieving Higher Testosterone Levels Has Clear Cardiovascular Benefits

Testosterone restoration is an important step aging men can take to retain good health.

In a revealing study, researchers identified 2,416 men (aged 69-81 years) who were not on any kind of testosterone-affecting treatment. These men were subjected to a battery of blood tests that included total testosterone and estradiol.

The first observation was that men with *increasing* levels of testosterone had a *decreased*

prevalence of diabetes, hypertension, and body fat mass. Compared to men with the highest testosterone levels, those with low testosterone were twice as likely to have a history of cardiovascular disease. It was also observed that men with the *highest* testosterone levels were the most *physically active*.[4]

This large group of men was followed for an average of 5.1 years. Men in the highest quartile of total testosterone (above **550 ng/dL**) had a **30%** lower risk of cardiovascular events. Any level of total testosterone below **550 ng/dL** resulted in significantly increased risk, thus helping establish a minimal baseline as to where total testosterone should be to guard against heart attack or stroke.

Estradiol levels measured in this group appeared to be mostly in safe ranges and did not impact incidence of cardiovascular events.

Data was tabulated based on hospital reports and/or death certificates for:

1. Acute myocardial infarction (heart attack)
2. Unstable angina (chest discomfort caused by a lack of oxygen flow to the heart)
3. Revascularization procedure (bypass surgery or stenting)
4. Transient ischemic attack (mini-stroke)
5. Stroke

The four quartiles of total testosterone in this large group of older men were:

- Quartile 1: Total testosterone below **340 ng/dL**
- Quartile 2: Total testosterone between **341** and **438 ng/dL**
- Quartile 3: Total testosterone between **439** and **549 ng/dL**
- Quartile 4: Total testosterone above **550 ng/dL**

Of interest was the finding that Quartiles 1, 2, and 3 had about the same risk of cardiac adverse events. It was only in Quartile 4 (when total testosterone exceeded **550 ng/dL**) that the **30%** reduction in cardiovascular events occurred.

This finding showed that it did not matter if these men's total testosterone was very low (below **340 ng/dL**) or moderately low (up to **549 ng/dL**)…they all had a similar increased risk for suffering a cardiovascular event. Only when total testosterone exceeded **550 ng/dL** did cardiovascular risk plummet.

This finding remained consistent for cerebrovascular disease incidence, where men with the highest total testosterone (Quartile 4) had a **23%** reduced risk of transient ischemic attack or full blown stroke. The researchers noted this association with reduced cerebrovascular risk remained after adjustment for traditional risk factors.

The conclusions by the researchers who conducted this study were:

"Higher serum testosterone levels are associated with a reduced risk of fatal and non-fatal cardiovascular events in community dwelling elderly men." [4]

Additional Studies Demonstrate The Benefits Of Maintaining Higher Testosterone Levels

Another study found the threshold level for benefit with testosterone replacement therapy was **>500 ng/dL**. This randomized, double-blind, placebo-controlled trial on 50 male subjects with low testosterone and metabolic syndrome found that testosterone administration reduced fasting glucose and waist circumference, and improved markers of atherosclerosis. The authors concluded: "Clinical efficacy of T [testosterone] replacement therapy in hypogonadal men with MS [metabolic syndrome] is reached when its plasmatic levels approach into the medium-high range of normality (**>5 ng/mL** [or **>500 ng/dL**])."[19]

Asymmetric dimethylarginine (ADMA) is a metabolic compound that contributes to atherosclerosis and cardiovascular disease. In a study of 10 men with low testosterone levels at baseline (**115.27 ng/dL**), testosterone administration for 2 weeks caused testosterone levels to rise to **648.41 ng/dL** and ADMA levels to drop a statistically significant degree. The study authors noted: "*The outcome of this study may be viewed as a favorable effect of normalization of plasma testosterone on plasma ADMA since even small elevations of plasma ADMA significantly increase cardiovascular risk.*"[7]

Study Conflicts with Previous Research

The authors of the *JAMA* study note, "The association between testosterone therapy use and adverse outcomes observed in this study differs from the association observed in a prior retrospective VA study."

- In the *JAMA* study, investigators noted a **39%** reduction in mortality risk among patients treated with testosterone therapy.[21] Unfortunately, the testosterone levels achieved in this study were not reported.
- A comprehensive review of data from 4 randomized controlled trials on men with chronic heart failure found that testosterone therapy was associated with improved functional capacity with no adverse events reported after up to 52 weeks of treatment.[22]
- French researchers found that lower bioavailable testosterone levels (i.e., the fraction of circulating testosterone that readily enters cells [free testosterone plus weakly bound testosterone]) in men 65 and older were linked to increased carotid artery intima-media thickness, which is a known marker of cardiovascular risk.[23]
- A randomized, controlled, 12-month study on 13 men with low testosterone levels and chest pain (i.e., angina) found that testosterone restoration therapy resulted in greater reductions in carotid artery plaques and improvements in time to myocardial ischemia (i.e., decreased blood flow to the heart) during exercise testing; the benefits were maintained throughout the duration of the study.[24] The average range of total testosterone achieved during the 12-month period was approximately **461 ng/dL** to**548 ng/dL** .
- In a study of 24 men with low baseline testosterone, intramuscular injections with 200 mg of testosterone every 2 weeks for 3 months were associated with improvements in insulin sensitivity and glycemic control as well as a reduction in total cholesterol and visceral adiposity. The scientists noted, " *Improvements in [glycemic] control, insulin resistance, cholesterol and visceral adiposity together represent an overall reduction in cardiovascular risk. "*[28]
- A 2013 study confirmed the increase of metabolic syndrome in men that are testosterone deficient.[17]*Metabolic syndrome* is a cluster of cardiovascular risk factors that include insulin resistance, hypertension, elevated triglycerides/LDL, and low HDL. This study found that men treated with testosterone showed across the board improvements as indicated by:
    - Reduced LDL
    - Reduced triglycerides
    - Reduced glucose
    - Reduced C-reactive protein
    - Reduced liver enzymes
    - Reduced blood pressure
    - Reduced hemoglobin A1c
    - Increased HDL (removes cholesterol buildup from arterial walls)

Retrospective Observational Study - Unmeasured Confounding Or Hidden Bias Might Exist

The study by *JAMA* was retrospective and observational. This study design limits the interpretation of the findings because subjects were treated in a clinical setting and not randomized to treatment. Bias may be introduced if confounding factors (e.g., those associated with both treatment initiation and mortality) are not adequately accounted for. Although the authors attempted to control for confounding factors, unmeasured or hidden factors likely still exist. The extent that these unmeasured variables bias the association reported is unknown.

Based upon an analysis of this study and the existing research, Life Extension continues to recommend male members restore testosterone levels to youthful ranges for optimal health.

Unnatural Forms Of Testosterone Used By 1/3 Of Subjects

Of men receiving testosterone therapy in the study by *JAMA*, only **1.1%** were prescribed testosterone gel, **63.3%** received patches, and **35.7%** received injections. Commonly prescribed testosterone injectables can produce a peak, often supraphysiologic, level of testosterone that then declines slowly to an often subnormal level in 1 to 2 weeks.[29,30] This "peak and trough" effect is an unnatural rhythm for testosterone. A testosterone cream or gel, on the other hand, gradually releases into the bloodstream, which is more analogous to the natural secretion of testosterone by the testes. More than a third of men in this analysis received testosterone injections, which may

cause unusual fluctuations in testosterone levels. In addition, testosterone injectables are comprised of non-bioidentical testosterone compounds. Life Extension advocates that men use a daily bioidentical testosterone gel (e.g., Androgel® or compounded version) to avoid unnatural fluctuations in testosterone levels.

Summary

Headline news stories on **November 5, 2013**, parroted a study proclaiming that aging men using testosterone drugs suffer greater heart attack risk.[1-3] The study suggests testosterone therapy may increase risk of death and certain cardiovascular events.[5] However, there are several significant shortcomings in the study's design and methodology, and the results conflict with an existing body of research. The media's portrayal of this flawed study may discourage aging men from properly restoring their testosterone levels and potentially endanger their health.

Over the years, several studies have shown that testosterone replacement therapy improves multiple measures of men's vitality, especially related to cardio-metabolic health.[4,15-24] The precipitous decline of men's testosterone levels over the years is inevitable. Unless aging men replace their diminishing testosterone, they could succumb to any of the numerous health problems linked to low testosterone levels: frailty, muscle loss, weight gain, impaired cognition, fatigue, loss of self-confidence, depression, declining bone health, increased risk of type II diabetes, stroke, and cardiovascular disease.[15,16]

Based on many published studies, ***Life Extension*** has recommended for decades that aging men restore testosterone to a youthful range. We've always warned that for some men restoring one's testosterone to more youthful levels could create excessive levels of estrogen, which is readily detectable by **blood testing** and reversible using aromatase-inhibiting therapies.

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

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