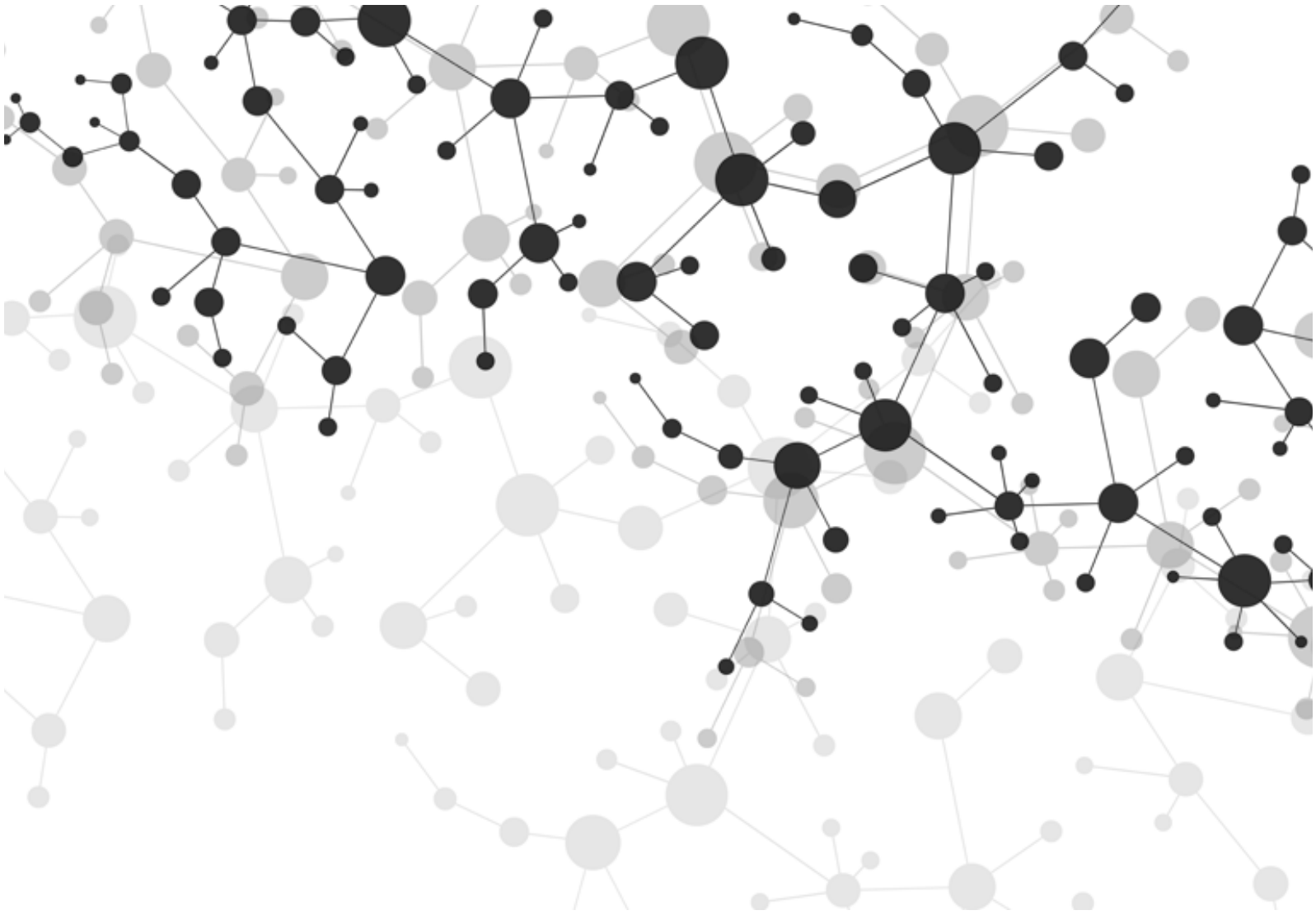

THE TESTOSTERONE WARS

How to Have Peace of mind

SEXY BRAIN

THE TESTOSTERONE WARS

The Testosterone Wars by Dr. Devaki Lindsey Berkson

An article came out on March 3 2015, in *Medscape*, an online journal that goes out to many million medical providers, entitled, *Testosterone Labels Must Now Note CV (cardiovascular) and Stroke Risks, FDA Says*.

The US Food and Drug Administration (FDA) now require makers of testosterone products to include two statements on each label.

1. Clearly describe the "approved" uses of these medications.

2. Clearly present the warning that use of this product possibly increases the risk of heart attacks and strokes.

What did the FDA base these statements on? A team of experts wanted to know. Dr. A. Morgentaler, a urologist from the Mayo Clinic in Rochester NY, headed this team. The other researchers came from Men's Health Boston and Harvard Medical School, The Department of Family Medicine and Department of Urology, Brown University, The Department of Endocrinology from the Lahey Clinic in Burlington, MA, The Scott Department of Urology at Baylor College of Medicine and The Department of Biochemistry and Department of Urology at Boston University.

This group of experts examined the evidence based science around the question of testosterone and heart safety and published their review of this data in the February 2015 issue of Mayo Clinic Proceedings. This article is entitled, *Testosterone Therapy and Cardiovascular Risk: Advances and Controversies*.

Under the title of the article in the front of the Mayo journal in the table of contents, a summary of their results states in italics… *Overwhelming scientific evidence confirms that testosterone treatment of hypogonadism (low T) in men improves cardiovascular risk factors and reduces the risk of mortality*.

In other words, this review by these experts in the February 2015 Mayo Clinic Proceedings came to a conclusion *opposite* to the FDA's March 2015 guideline *labeling* requirements.

How did Morgentaler et al come to their conclusions? Morgentaler et al examined *all* the evidence-based research surrounding this topic. The team did a MEDLINE search from the 1940's to August 2014 looking at every key word that would address testosterone, cardiovascular events, heart attack, stroke, mortality, etc. They evaluated the evidence and the weight (strength) and level (dependability) of that evidence.

During this analysis, Morgentaler et al identified *only 4 articles* that suggested any link between testosterone prescriptions and adverse cardiovascular events. But they found *issues* with all 4 of these studies.

· 2 of these studies had severe methodology issues making the conclusions suspect and weak.

· 1 placebo-controlled trial had included too few adverse cardiovascular events to be relevant.

· The last study was a meta-analysis, which included "questionable" studies and events that "weakened" their conclusions.

The other side of the testosterone controversy found by Morgentaler et al.

· Several dozen studies found a significant link between *normal* testosterone levels and *protection* against adverse heart events and earlier mortality.

· In fact, mortality and severity of coronary artery disease were *inversely* correlated with serum testosterone concentrations. *The more T the less heart issues.*

· Testosterone treatment (replacement into physiologic ranges) was linked to *decreased* obesity, decreased fat mass and decreased waist size.

· Mortality was *reduced* in 2 retrospective studies with testosterone replacement.

· The largest meta-analysis to date found *no increased* risk of cardiovascular disease in men on testosterone replacement and in fact *reduced* these risks in men with metabolic syndrome.

· They identified 100 studies demonstrating that normal testosterone levels (and physiologic replacement that achieves these levels) provides "beneficial effects to men and reduces cardiovascular risk and mortality."

The summary by Morgentaler et al says, "*In summary, there is no convincing evidence of increased cardiovascular risks with T therapy. On the contrary, there appears to be a strong beneficial relationship between normal T and CV health that has not yet been widely appreciated*."

Who else is opposing the new FDA guidelines? Morgentaler et al are not alone in their concerns about recent reports linking T therapy to adverse heart events. One example was the outrage against the Vigen et al paper, which said T therapy caused harm. The methodology of this study was so criticized that *29 professional societies demanded* the study be retracted. These societies included prestigious groups around the world including the International Society for Men's Health, The International Society for Sexual Medicine, and the Sexual Medicine Society of North America.

In Morgentaler et al's review they emphasize that death from cardiovascular events and artery disease are linked to *lower* levels of total testosterone, free testosterone and bioavailable testosterone. They discuss an elegant study by Ohlsson et al which links normal but *higher levels of normal* T (at 550 ng/dL or more) to 30% *lower* risk of adverse cardiovascular events when compared to men with lower T blood scores (some of which were still in the normal range, but in the very low normal) even after adjusting for potentially confounding variables. The title of Ohlsson's et al article says it all: *High serum testosterone is associated with reduced risk of cardiovascular events in elderly men*. The study is called the MrOs Study standing for (Osteoporotic Fractures in Men study in Sweden.)

An editorial in the Mayo Clinic Proceedings (February 2015) titled *The Impact of Testosterone Therapy in Men on Cardiovascular Risk: Don't Be Too Quick To Condemn*, is authored by Matthew Gettman MD, also a urologist, like Morgentaler, from the Mayo Clinic Urology Department in Rochester, NY. Dr. Gettman says that the importance of maintaining normal T levels to prevent heart disease can be demonstrated in prostate studies on men who are deprived of T as part of their cancer treatment. Keating et al evaluated 73,196 men with prostate cancer that had androgen deprivation therapy. These men had increased risk of heart attack, sudden cardiovascular death, coronary heart disease and *even diabetes*.

Dr. Gettman asks in his editorial, why would the FDA and the media jump on a few studies linking testosterone to health risks when these studies are outweighed by the positive benefit ones, and their methodologies have holes in them? Dr. Gettman ponders that maybe this is a reaction to a public that seems to feel testosterone replacement is risk-free. Perhaps as America ages and this aging demographic expands, a lot more men may be considering T therapy and perhaps the FDA is trying to emphasize protection until more regulations are characterized in detail. Perhaps they want more money, more regulation and more control. But there is definite *murk* surrounding this hormone picture.

This editorial by Gettman ends by stating that as the potential consumer and aging base grows, we can now be reassured by the comprehensive work of Morgentaler et al, which *clearly* shows that T is safe in terms of heart health risks.

This is in opposition to FDA's new guidelines. The FDA will now require manufacturers of prescription testosterone products to put a *warning* of increased risk for heart attack and stroke when you use the testosterone product on the label.

The FDA states testosterone-replacement therapy is only approved for men with low blood levels of testosterone due to hypogonadism issues from disorders of the testicles, pituitary gland, or the brain itself.

The FDA, doctors and patients alike are all aware that testosterone is now being used to relieve andropause symptoms in men who, due to aging, have low testosterone. The FDA does not agree with using testosterone to "treat" and slow down aging. The FDA says that the benefit of testosterone merely for aging has not been established.

Back in January 2014 the FDA issued a drug safety communication stating that the use of testosterone potentially increased the risk for stroke, heart attack, and death in men using any FDA-approved testosterone products. They had not yet cited labeling changes as they did this March.

Today, March 3 2015, the FDA advises healthcare providers to tell patients about testosterone replacement's dangers. Warn them of the signs of heart attack and stroke and tell them to get help if they start to experience these symptoms. Fear tactics? "Patients using testosterone should seek medical attention immediately if symptoms of a heart attack or stroke are present, such as chest pain, shortness of breath or trouble breathing, weakness in one part or one side of the body, or slurred speech."

Europeans Have a Different Viewpoint on Testosterone. A regulatory body that represents European Union members (Coordination Group for Mutual Recognition and Decentralised Procedures–Human) went on record in November 2014 stating that *there is "no consistent evidence" of an increased risk for heart problems with testosterone products*.

How the T controversy escalated. In 2013 two widely reported studies came out stating that giving testosterone replacement to men with heart disease could cause serious health problems. This prompted an investigation into testosterone safety by the FDA and the European Medicines Agency. These studies have since been highly criticized for their methodology and conclusions, but of course, these criticisms did *not* make the headlines like the more scary conclusions did. The US Androgen Study Group highlighted key flaws and also stated that these alarming conclusions flew in the face of a great body of literature, like that mentioned above, which clearly shows protective effects with testosterone replacement.

Impressive support of testosterone replacement came shortly after the controversial reports emerged. Dr. Robert Tan, director of the Opal Medical Clinic in Houston, Texas; research director of the Low T Institute; and clinical professor of family and community medicine at the University of Texas, reported results of a study run at forty clinics (remember a multi-centered study has more weight) in the United States where doctors worked directly with thousands of men prescribed testosterone replacement therapy. These findings were presented at the American Association of Clinical Endocrinologists' Twenty-Third Annual Scientific and Clinical Congress.

The results demonstrated that testosterone replacement was not associated with an increased risk of myocardial infarction or MI (heart attack) or stroke and, to the contrary, showed protection of the cardiovascular system (heart and blood vessels). This research was done on almost 20,000 men who were found to be low in testosterone and then treated with testosterone and followed for five years from 2009 to 2014.

Testosterone replacement *lowered* the risk of heart attack sevenfold and *lessened* the risk of stroke nine fold compared with men in the general population not getting testosterone replacement. And there was no evidence of worsening of preexisting heart attack or stroke issues. The data of a retrospective study (looking back in time at data) is not as hard as that of a prospective (a study that follows patients forward in time), but it is still very impressive.

"Our study showed that carefully monitored testosterone therapy might actually protect against MI and stroke. It's retrospective, but I think for now it's as good as we can come up with. At least from our experience, there was no evidence of increased heart attacks or strokes from people treated with testosterone," Dr. Tan said.

The two studies that set off the testosterone alarm, published in the *Journal of the American Medical Association* in November 2013, found a 30 percent increased risk of death, MI, or ischemic stroke in older veterans on testosterone. But when the levels of testosterone of these men were reanalyzed, it was found that they were taking testosterone replacement *only to the point of getting them into the very low range of normal*, way below what the testosterone clinic and many doctors that specialize in bioidentical hormones regard as optimal.

Dr. Tan said the mean testosterone levels even with testosterone treatment, in these studies, was only 332.2 ng/dL, which is near the bottom of the normal range. It is not a protective level. At the clinics that specialize in testosterone replacement, the average protective level that was produced in men was 543 ng/dL. This is a big difference. Dr. Tan said, "Perhaps it was the lower range of testosterone in the *JAMA* study—even though the men were on testosterone replacement, they weren't on enough, which led to the increased risk of MI."

Other differences are striking. Of the men in the veterans study in *JAMA*, 90 percent were given testosterone by patches, while most of the testosterone patients who derived benefits got the testosterone by injection.

While 60 percent of the patients who were more at risk in the *JAMA* study were not monitored over time, 100 percent of the testosterone patients who derived protection were monitored, especially for blood viscosity, which is measured by looking at the levels of red blood cells. When RBCs get a bit high on replacement testosterone, then the testosterone dose is lowered. This is sound monitoring and critical reassessment when using testosterone replacement. This was not done in the veterans.

· This Texas study highlights the importance of dosage and working with hormone doctors and compounding pharmacists who know what they are doing.

· It also shows you that the scary messages that "hit the headlines" were not, as Paul Harvey used to say, "the rest of the story."

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Testosterone Controversy BLOG

In 2013 two widely reported studies came out stating that giving testosterone replacement to men with heart disease could cause serious health problems. This prompted an investigation into testosterone safety by the FDA and the European Medicines Agency. These studies have since been highly criticized for their methodology and conclusions, but of course, these criticisms did *not* make the headlines like the more scary comments did. The US Androgen Study Group highlighted key flaws and also stated that these alarming conclusions flew in the face of a great body of literature, like that mentioned above, which has clearly shown protective effects with testosterone replacement.

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The results demonstrated that testosterone replacement was not associated with an increased risk of myocardial infarction or MI (heart attack) or stroke and, to the contrary, showed protection of the cardiovascular system (heart and blood vessels). This research was done on almost 20,000 men who were found to be low in testosterone and then treated with testosterone and followed for five years from 2009 to 2014. Testosterone replacement *lowered* the risk of heart attack sevenfold and *lessened* the risk of stroke ninefold compared with men in the general population not getting testosterone replacement. And there was no evidence of worsening of preexisting heart attack or stroke issues. The data of a retrospective study (looking back in time at data) is not as hard as that of a prospective (a study that follows patients forward in time), but it is still very impressive.

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Dr. Tan said the mean testosterone levels even with testosterone treatment, in these studies, was only 332.2 ng/dL, which is way at the bottom of the normal range. It is not a protective level. At the clinics that specialize in testosterone replacement, the average protective level that was produced in men was 543 ng/dL. This is a big difference. Dr. Tan said, "Perhaps it was the lower range of testosterone in the *JAMA* study—even though the men were on testosterone replacement, they weren't on enough, which led to the increased risk of MI."

Other differences are striking. Of the men in the veterans study in *JAMA*, 90 percent were given testosterone by patches, while most of the testosterone patients who derived benefits got the testosterone by injection. While 60 percent of the patients who were more at risk in the *JAMA* study were not monitored over time, 100 percent of the testosterone patients who derived protection were monitored, especially for blood viscosity, which is measured by looking at the levels of red blood cells. When RBCs get a bit high on T, then the testosterone dose is lowered. This is sound monitoring and critical reassessment when using testosterone replacement. This was not done in the veterans. These are crucial differences between the studies and outcomes. This had to be addressed here, since many of the protective aspects of testosterone and the criticisms of the criticism have not been as publicized as the warnings. This Texas study highlights the importance of dosage and working with hormone doctors who know what they are doing.

Testosterone protects women, too. Researchers from the Department of Gynecology and Obstetrics at Faculty Health Science in South Africa reviewed the role of testosterone in women's health. In healthy postmenopausal women, the ovaries are supposed to produce significant amounts of androgens (remember, this is a term for male hormones) for many years after menopause. Bilateral oophorectomy, losing both ovaries, markedly reduces circulating testosterone in both pre- and postmenopausal women. Chemicals in today's environment are reducing testosterone levels in younger women. Oral estrogen therapy (without adding testosterone to the mix) in postmenopausal women decreases levels of testosterone by increasing sex hormone–binding globulin, which decreases the body's ability to use the testosterone that is present. Circulating testosterone, like other hormones, decrease with increasing age. Androgen deficiency in women is linked with loss of libido, bone loss, and fracture, and overall sense of well-being and sexiness (comfort and pleasure inside one's body) is reduced. Notice how all these symptoms of low testosterone overlap with symptoms we have come to think are common and typical of normal aging.

In a variety of randomized controlled trials, testosterone replacement produced a significant improvement in libido in women who had a bilateral oophorectomy and also in some women who underwent natural menopause. Testosterone therapy, say the scientists, is legitimate as an integral part of hormone replacement therapy for some women. Testosterone therapy in postmenopausal women can help increase muscle mass and bone mineral density and give a sense of solidarity to the otherwise free-fall of emotions that many women experience as they age. Many women, as their hormones get lower, feel anxious and overwhelmed. Remember that testosterone is a rock like hormone. The more our testosterone levels are optimal, the less overwhelmed and frail we feel. I have had many women who did not feel well with HRT. They complained it "didn't work for them." But their doctors had not added testosterone to the mix. When we did that, then they responded in a "I feel like a new person" manner.

The Rancho Bernardo study looked at men and women for over forty years and how their hormones and sex differences affected their risk of disease. Over 6.000 participants were followed for illness and death. Men with higher testosterone levels had less diabetes, fewer metabolic syndrome issues (high blood pressure, high blood fats, obesity, etc.), and a reduced risk of all causes of mortality for all diseases except cancer.

In women, extremely low testosterone and extremely high testosterone were both linked to fatal heart disease, whereas keeping the testosterone in the mid-range levels—Goldilocks's "just right"—was linked with fewer fatal heart issues and better heart health in general. Women had less heart

disease than men when they were younger, but if they had diabetes or glucose handling issues, this heart-protective effect was blocked.

In the body, hormones can morph into each other. This is especially true with testosterone's susceptibility to be acted upon by an enzyme called aromatase, which produces estrogen from the testosterone. When men get testosterone replacement, they are often checked to make sure that this testosterone is not going to estrogen. But if women get elevated levels of testosterone, they too can make more estrogen. Women need to be followed closely when on any hormone replacement. This makes sense.