



NATIONAL PBM BULLETIN

March 26, 2015

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

UPDATE: Testosterone Products and Cardiovascular Safety

I. ISSUE

FDA re-informs of a possible increased cardiovascular risk associated with testosterone use based on additional published literature as well as Advisory Committee findings and requires labeling change to reflect this risk. This issue has been previously addressed in a [National PBM Bulletin](#) from February 2014 as well as in [Issue 3; Volume 4; March 2014](#) of the Medication Safety in Seconds Newsletter.

II. BACKGROUND

FDA continues to caution that testosterone replacement therapy is approved for use only in men with primary or secondary hypogonadism resulting from certain medical conditions. The safety and efficacy of testosterone replacement therapy for age-related hypogonadism have not been established.

III. DISCUSSION

FDA's conclusion of risk comes from their review of published literature as well as meta-analyses to date which show conflicting results regarding cardiovascular harm with the use of testosterone therapy.

- Vigen and colleagues studied male veterans who underwent angiography and had low testosterone levels. Authors found an increased risk in the composite cardiovascular outcome of myocardial infarction, stroke, and death (Hazard Ratio [HR]=1.29, 95% Confidence Interval [CI]: 1.04-1.58) for those with testosterone replacement therapy compared to no testosterone replacement therapy.
- Finkle and colleagues used a large claims database to assess testosterone replacement therapy in men with an average age of 54 years and found an increased risk of non-fatal myocardial infarction 90 days post-initiation of testosterone treatment compared to patient's pre-treatment status (Relative Risk [RR]=1.36, 95% CI: 1.03-1.81).
- Shores and colleagues looked at male veterans older than 40 years of age with low testosterone and came across a decreased risk of all-cause mortality for patients receiving testosterone replacement therapy compared to no testosterone replacement therapy (HR=0.61, 95% CI: 0.42-0.88).
- Muraleedharan and colleagues evaluated men with type 2 diabetes in the United Kingdom to compare differences in mortality in those with low serum testosterone concentrations versus those with normal serum testosterone concentrations; further subgroup analysis assessed mortality of treated and untreated men with low serum testosterone. They found an increased risk of all-cause mortality in men with no testosterone replacement therapy compared to those with testosterone replacement therapy (HR=2.30, 95% CI: 1.30-3.90).
- Baillargeon and colleagues examined men older than 65 years of age enrolled in Medicare and found no overall increase in risk of hospitalization for myocardial infarction when comparing those receiving testosterone replacement therapy to those with none (HR=0.84, 95% CI: 0.69-1.02).
- One meta-analysis reviewed 27 published, randomized, placebo-controlled trials with a total of 2,994 male participants (1,773 treated with testosterone and 1,261 treated with placebo) that included 180 cardiovascular-related adverse events. This study reported that testosterone therapy was associated with an increased risk of adverse cardiovascular events (Odds Ratio [OR]=1.5, 95% CI: 1.1-2.1); however, methodological issues limit conclusions.



NATIONAL PBM BULLETIN

March 26, 2015

DEPARTMENT OF VETERANS AFFAIRS PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

UPDATE: Testosterone Products and Cardiovascular Safety

(continued from page 1)

- Another meta-analysis explored 26 published, randomized, controlled trials (20 of which were also included in the aforementioned meta-analysis) for a combined total of 3,236 men (1,895 men treated with testosterone, 1,341 men treated with placebo) and that included 51 major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or stroke, and serious acute coronary syndromes or heart failure). Results did not show a statistically significant increased risk of these cardiovascular events associated with testosterone treatment; however methodological issues limit conclusions.

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

While pending more definitive data, FDA recommends that providers:

- *Ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing before initiating testosterone replacement therapy.*
- *Verify that serum testosterone concentrations have been measured on at least two separate mornings and are consistently below the normal range.*
- *Avoid measuring testosterone concentrations later in the day, when measurements can be low even in men who do not have hypogonadism.*
- *Weigh the potential increased risk of major adverse cardiovascular outcomes and other risks of testosterone replacement therapy against the potential benefits of treating hypogonadism for each patient.*
- *Inform patients of the potential increased cardiovascular risk associated with testosterone replacement therapy.*

Providers should continue to report any adverse reactions with the use of testosterone products by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

1. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. <http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm>. (Accessed 03/03/15)
2. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829-36.
3. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.
4. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97:2050-8.
5. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725-33.
6. Baillargeon J, Urban RJ, Kuo YF et al. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014.
7. Xu L, Freeman G, Cowling BJ, Schooling CM (2013). Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med, 11, 108.
8. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E et al. (2014). Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf, 13, 1327-1351.

ACTIONS

- **Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, endocrinologists, urologists, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).