

**Testimony Before the FDA's Bone,
Reproductive and Urologic Drugs Advisory
Committee and Drug Safety and Risk
Management Advisory Committee
Regarding Testosterone Products**

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(We have no financial conflicts of interest)

Key Questions Before the Advisory Committees

- (1) Do the available data indicate a cardiovascular (CV) safety signal associated with testosterone therapy; and**
- (2) Should information about major CV adverse events (AEs) associated with testosterone drugs be included in the labeling for these products.**

The answer to both questions is a resounding “yes.”

Strength of Signal

Study	Design	Key Results
Finkle et al, 2014	Retrospective cohort study	<p>Post/pre-testosterone therapy prescription event rate ratio for acute non-fatal myocardial infarction (MI):</p> <ul style="list-style-type: none"> Men age ≥ 65: <u>2.19 (95% confidence interval [CI] 1.27-3.77)</u> Men age < 65 with prior history of heart disease: <u>2.90 (95% CI 1.49-5.62)</u>
Basaria et al, 2010	Randomized, placebo-controlled trial in men age 65 or older, with limited mobility and low testosterone levels	<p>Adjusted odds ratio (OR) for cardiovascular-related adverse events in testosterone-treated subjects: <u>5.8 (95% CI 2.0-16.8)</u></p> <p>1 acute coronary syndrome, 2 MIs, 1 stroke, and 1 death from suspected MI in testosterone-treated subjects versus 0 such events in control subjects</p>
Xu et al, 2013	Meta-analysis of 27 randomized, placebo-controlled trials	<p>Testosterone therapy increased risk of cardiovascular-related events versus placebo:</p> <ul style="list-style-type: none"> All 27 trials: <u>OR 1.54 (95% CI 1.09-2.18)</u> 14 non-industry funded trials: <u>OR 2.06 (95% CI 1.34-3.17)</u>

Biological Plausibility of the Signal

Several effects of testosterone drugs make the link between these drugs and CV AEs biologically plausible, including:

- Increased hemoglobin and hematocrit, causing increased blood viscosity
- Acutely increased platelet thromboxane A₂ receptor density and aggregation response, as shown in a randomized, placebo-controlled trial in healthy men (Ajayi et al, *Circulation*, 1995)
- Increased microviscosity of red blood cell (RBC) membranes and decreased RBC plasticity, which could impair RBC movement in blood capillaries (Panin, et al, *J Phys Chem B*, 2011)
- Decreased HDL cholesterol levels.

Biological Plausibility of the Signal (cont.)

A recently published observational study found that low testosterone levels appeared to protect patients with a history of major adverse CV events from experiencing additional such events. The study authors suggested that such low testosterone levels might reflect a naturally occurring protective compensatory mechanism, and testosterone use in such men might be deleterious to overall and cardiovascular health.

Corona G, et al. *Andrology*. 2014.

Is the Signal Restricted to a Certain Subset of the Population Using Testosterone Therapy?

The available data suggest that older men and men with a prior history of heart disease may be at greatest risk of CV AEs related to testosterone use. However, there is not sufficient data to indicate that this risk is restricted to these subgroups of men.

Conclusion

- **There is sufficient evidence to warrant inclusion of cardiovascular risk information in testosterone drug labels.**
- **The labels of many drugs include warnings — in some cases black-box warnings — about serious risks based on far weaker evidence for safety signals than that available for testosterone drugs.**
- **On July 15, Health Canada, acting appropriately to protect public health, issued a safety alert to patients and health care providers about the risk of serious and possibly life-threatening cardiovascular problems associated with testosterone drugs. The agency “found a growing body of evidence... for serious and possible life-threatening heart and blood vessel problems” with these drugs. Health Canada’s actions are based on the same evidence available to the FDA.**

Recommendation

As in Canada, health care providers and patients in the U.S. should be warned about the risk of serious cardiovascular adverse events associated with testosterone drugs, which are widely overprescribed in the U.S. to men for whom the drugs are not indicated.

To protect public health, Public Citizen urges the advisory committee to recommend that the FDA require such warnings on the labels of all testosterone products.