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Testimony Before the Joint Meeting of 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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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group, testifying on behalf of Dr. Sidney Wolfe, the founder of our group, and myself. We have no financial conflicts of interest.

The key questions before you are: (1) do the available data indicate a cardiovascular safety signal associated with testosterone therapy, and (2) should information about major adverse cardiovascular events associated with testosterone drugs be included in the labeling for these products. The answer to both questions is a resounding "yes."

Strength of the signal

The very large, well-designed cohort study by Finkle,[1] the randomized, placebo-controlled trial by Basaria,[2] and the carefully conducted meta-analysis by Xu[3] provide compelling evidence for a cardiovascular safety signal associated with testosterone drugs (see Table).

Study	Design	Key Results
Finkle et al, 2014	Retrospective cohort study	Post/pre-testosterone therapy prescription event rate ratio for acute non-fatal myocardial infarction (MI): • Men age ≥65: **2.19 (95% confidence interval [CI] 1.27-3.77)** • Men age < 65 with prior history of heart disease: **2.90 (95% CI 1.49-5.62)**
Basaria et al, 2010	Randomized, placebo-controlled trial in men age 65 or older, with limited mobility and low testosterone levels	Adjusted odds ratio (OR) for cardiovascular-related adverse events in testosterone-treated subjects: **5.8 (95% CI 2.0-16.8)** **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**
Xu et al, 2013	Meta-analysis of 27 randomized, placebo-controlled trials	Testosterone therapy increased risk of cardiovascular-related events versus placebo: • All 27 trials: **OR 1.54 (95% CI 1.09-2.18)** • 14 non-industry-funded trials: **OR 2.06 (95% CI 1.34-3.17)**

The FDA noted that the Basaria study authors "explicitly indicated that the differences between the groups in cardiovascular adverse events…might have been due to chance alone."[4] However, the

differences were statistically significant — even after adjusting for age and baseline cardiovascular risk factors.[5]

Biological plausibility of the signal

Several effects of testosterone drugs make the link between these drugs and adverse cardiovascular events biologically plausible, including:

- Increased hemoglobin and hematocrit, causing increased blood viscosity;[6]
- Acutely increased platelet thromboxane A_2 receptor density and aggregation response, as shown in a randomized, placebo-controlled trial in healthy men;[7]
- Increased microviscosity of RBC membranes and decreased RBC plasticity, which could impair RBC motion in blood capillaries;[8] and
- Decreased HDL cholesterol levels.[9]

The FDA recently required that all testosterone product labels include a warning about the risk of venous thrombotic events.[10] The same mechanisms predisposing to these events likely contribute to the increased risk of arterial adverse cardiovascular events seen with these products.

A recently published observational study found that low testosterone levels appeared to protect patients with a history of major adverse cardiovascular events from experiencing additional such events.[11] The study authors suggested that 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.

Is the signal restricted to a certain subset of the population using testosterone products?

The available data suggest that older men and men with a prior history of heart disease may be at greatest risk of adverse cardiovascular events 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

FDA reviewers repeatedly state that the available data do "not provide conclusive evidence of a causal association between testosterone therapy and cardiovascular events."[12] However, 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. Indeed, the FDA's recent action requiring testosterone drug labels to include general warnings about the risk of venous thrombotic events was based solely on "postmarket reports of venous blood clots unrelated to polycythemia."[13]

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.[14] The agency "found a growing body of evidence (from published scientific literature and case reports received by Health Canada and

foreign regulators) for serious and possible life-threatening heart and blood vessel problems" with these drugs. Health Canada reported that it was working with manufacturers to update Canadian product labels regarding this risk. Health Canada's actions are based on the same evidence available to the FDA.

In conclusion, as in Canada, health care providers and patients in the U.S. should be warned about the risk of serious adverse cardiovascular 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 committees to recommend that the FDA immediately require such warnings on the labels of all testosterone products.

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