Testosterone Replacement Therapy Correlated with Increased Risk of Cardiovascular Disease

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Key Findings:

- Men with low testosterone on testosterone replacement therapy (TRT) have a 7.9% increased risk of cardiovascular disease (CVD) compared to those not on TRT.

Testosterone is the predominant sex hormone in males and has been shown to affect muscle mass, bone density, and the cardiovascular system.[1] Studies have shown that a patient's testosterone level can affect their risk of cardiovascular disease (CVD), particularly in men who have testosterone levels outside of the normal range.[1,2] Other studies have found that testosterone replacement therapy (TRT) is associated with increased CVD risk.[3]

To better understand how treating low testosterone with TRT might influence CVD risk, we studied 491,612 men aged 30 and older with a low testosterone level and no history of CVD. We compared their risk of being diagnosed with CVD based on whether they had received a prescription for TRT. We adjusted for type 2 diabetes, hypertension, hyperlipidemia, depression, smoking status, race, ethnicity, and BMI class, which are known factors for increased CVD risk.

We found that men with low testosterone prescribed TRT were 7.9% more likely to be diagnosed with CVD than men with low testosterone not on TRT, as shown in Figure 1. We also found that this risk increases with age.

Increase in Cardiovascular Disease Risk for Patients with Low Testosterone on TRT

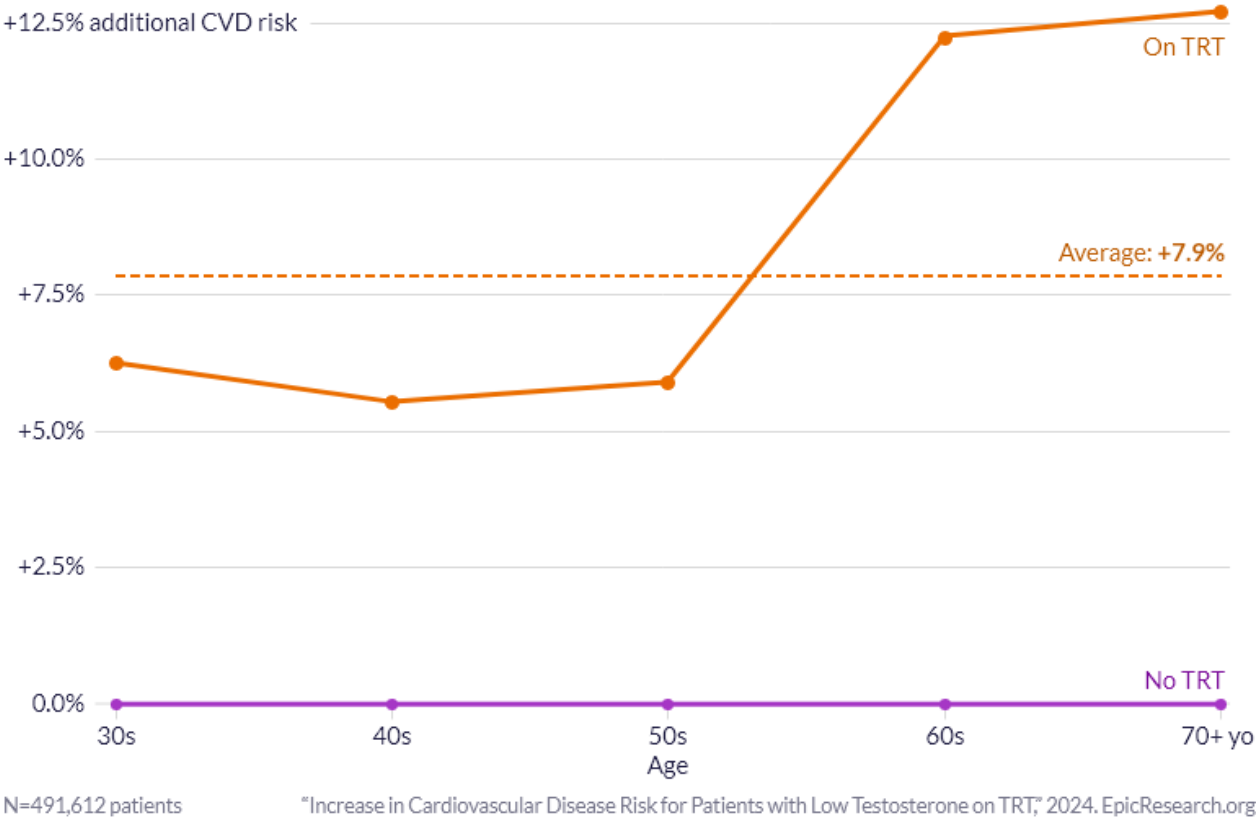

Figure 1. The risk of a cardiovascular disease diagnosis for patients with low total testosterone by TRT use and age. A low testosterone level is considered lower than 264 ng/dL.

These data come from Cosmos, a collaboration of 236 Epic health systems representing more than 227 million patient records from 1,301 hospitals and more than 28,600 clinics from all 50 states and Lebanon. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

References

1. Goodale T, Sadhu A, Petak S, Robbins R. Testosterone and the heart. *Methodist Debakey Cardiovasc J*. 2017;13(2):68. doi:10.14797/mdcj-13-2-68
2. Qu M, Feng C, Wang X, et al. Association of serum testosterone and luteinizing hormone with blood pressure and risk of cardiovascular disease in middle-aged and elderly men. *J Am Heart Assoc*. 2021;10(7). doi:10.1161/jaha.120.019559
3. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013;11(1). doi:10.1186/1741-7015-11-108

Data Definitions

Term	Definition
Study period	1/1/2010 to 10/31/2023
Study population	Adult males over age 30 with **total testosterone labs** and no: History of **cancer**

	History of **cardiovascular disease** Diagnosis of **testicular abnormalities** ever Censorship occurred at the first of one of the following: The patient's last documented encounter A **cardiovascular disease** diagnosis A documented death date A **cancer** diagnosis
Patient phases	From when a patient received their first **total testosterone lab**, they were divided into periods of time based on the categorization of their most recent testosterone lab being low, normal, or high and whether they had received testosterone replacement therapy previously. A patient may be represented by multiple phases.
Model	We used a time-varying Cox proportional hazards model adjusting for **type 2 diabetes**, **essential hypertension**, **hyperlipidemia**, **depression**, **smoking history**, race/ethnicity, and **BMI classification**.
Cancer	A diagnosis with ICD-10-CM code C*.
Cardiovascular disease	A diagnosis with ICD-10-CM code I20*-I26*, I30*-I49*, I51*, I70*-I79*.
Testicular abnormalities	A diagnosis with ICD-10-CM code Q55.0*-Q55.2* or Q56*.
Type 2 diabetes	A diagnosis with ICD-10-CM code E11*.
Essential hypertension	A diagnosis with ICD-10-CM code I10*.
Hyperlipidemia	A diagnosis with ICD-10-CM code E78.2*-E78.5*.
Depression	A diagnosis with ICD-10-CM code F32* except F32.5*.
Smoking history	Patients were classified as having never smoked, being a former smoker, an active smoker, or an active heavy smoker based upon their documented history.
BMI classification	BMI under 18.5 was considered underweight, 18.5-25 as heathy, 25-30 as overweight, and 30+ as obese.
Total testosterone lab	A lab with LOINC code 2986-8, 2993-4, or 83116-4 or unmapped labs with a name containing the phrase "testosterone" without "free", "bound", "bio", or "/".
Testosterone replacement therapy	Prescription with a simple generic name of: testosterone testosterone cypionate testosterone cypionate, micro testosterone enanthate testosterone micronized testosterone propionate testosterone undecanoate Once a patient is prescribed TRT, they remain in that population even if the prescription ends.

Table 1: Increase in Cardiovascular Disease Risk for Patients with Low Testosterone on TRT Compared to Patients with Low Testosterone who have not been on TRT

Age	Risk with TRT
Average	7.9%
30s	6.3%
40s	5.5%
50s	5.9%
60s	12.2%
70+	12.7%