

## A critical analysis of testosterone supplementation therapy and cardiovascular risk in elderly men

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**H**ypogonadism has become a common diagnosis in elderly men, with increasing prevalence from 20% in the sixth decade of life to 50% in the ninth.<sup>1,2</sup> Declines in serum testosterone affect up to 40% of men;<sup>3,4</sup> about 3.75% of men  $\geq 60$  years of age are on some form of testosterone supplementation therapy (TST).<sup>3,5-7</sup>

The use of TST in elderly men has been justified given that hypogonadism is an independent risk factor for cardiovascular disease and all-cause mortality.<sup>8-11</sup> Furthermore, improvements following TST in body weight, waist circumference,<sup>12-18</sup> HbA1c,<sup>17,19</sup> and total cholesterol levels<sup>17,18</sup> contribute to decreases in cardiovascular adverse events (CVAEs). However, several recent population-based studies have raised concerns regarding the safety of TST in elderly ( $\geq 65$  years old) men.<sup>20-23</sup>

The first study to identify an association between TST and cardiovascular risk was the Testosterone in Older Men (TOM) trial.<sup>20</sup> The TOM trial was designed to evaluate muscle strength improvements in men aged  $\geq 65$  years ( $n = 209$ ) with limited mobility. The authors included frail men with mobility limitations, including difficulty walking 2 blocks or climbing 10 steps.<sup>20</sup> Since the study was designed to examine strength improvements, treatment was solely based on serum total testosterone and free testosterone values without considering hypogonadal symptoms.<sup>20</sup> The trial was halted due to CVAEs ranging from elevated blood pressure ( $n = 3$ ) and peripheral edema ( $n = 5$ ) to stroke ( $n = 1$ ) and myocardial infarction (MI) (non-fatal  $n = 2$ , fatal  $n = 1$ ).<sup>20</sup> The greatest concerns arose given the increased number of CVAEs in men on TST ( $n = 23$ ) compared to placebo ( $n = 5$ ).<sup>20</sup> While drawing attention to the use of TST in elderly men, the TOM trial was not designed to address CVAEs. Furthermore, there were no differences in the number of serious, life-threatening adverse events between the testosterone and placebo arms of the study. Given that many men reached supra-physiological levels of serum testosterone, and a disproportionate amount of CVAEs occurred in these patients, correlates were drawn.

Recently, several studies have examined the relationship between CVAEs and TST in more detail. For example, a meta-analysis by Xu and colleagues<sup>24</sup> noted an increased risk of CVAEs in men on TST (odds ratio 1.54,  $p < 0.05$ ). Another large ( $n = 8709$ ) retrospective national cohort study in elderly males ( $\geq 60$  years old) analyzed TST outcomes in hypogonadal men (serum testosterone  $< 300$  ng/dL) with previous coronary angiography.<sup>22</sup> In this study, men who began TST had an absolute risk increase of 5.8% ( $p < 0.05$ ) for a CVAE when compared to matched peers not receiving TST.<sup>22</sup> Unfortunately, one of the major drawbacks of the study was that despite TST, most men remained hypogonadal (mean serum testosterone 332.2 ng/dL; delta = 175.5 ng/dL from baseline).<sup>22</sup> Furthermore, 17.6% of patients in the testosterone group filled only 1 prescription and no testosterone levels were measured after therapy, which raised the question of therapy adherence and the generalizability of the findings.

In another study, Finkle and colleagues<sup>21</sup> determined that men  $\geq 65$  years old had an increased risk of non-fatal MI within 90 days of TST initiation. In this trial, the pre-TST prescription MI-event rate in men  $\geq 65$  years old was 5.27 (95% confidence interval CI) 3.81-7.27).<sup>21</sup> Following the start of TST, these rates increased to 11.52 (95% CI 7.43-17.86) in men  $\geq 65$ , while men  $< 65$  did not change (pre-TST MI-event rate of 3.22 CI 2.75-3.77 vs. post-TST MI-event rate of 3.76 CI 2.81-5.04).<sup>21</sup> Unfortunately, in this population-based study, the lack of evaluation of serum hormones and hematocrit levels significantly limited the validity of the conclusions regarding the relationships between TST, serum testosterone and MI. In addition, men on TST were compared to men using PDE5 inhibitors, which is potentially confounding since PDE5 inhibitors benefit men with coronary artery disease, hypertension, heart failure, pulmonary arterial hypertension, and diabetes mellitus.<sup>25</sup>

Currently, the exact mechanisms for increased CVAEs in men on TST remain unknown. Testosterone stimulates erythropoiesis in a dose-dependent manner – an effect that is more prominent in elderly men.<sup>26</sup> TST also induces a hypercoagulable state via increases in thromboxane A<sub>2</sub> and platelet thromboxane A<sub>2</sub> receptor density with decreases in prosta-

glandins.<sup>27</sup> In the Tampere Adult Population Cardiovascular Risk study (TAMRISK), the authors demonstrated a relationship between borderline polycythemia and an increased risk of cardiovascular mortality.<sup>28,29</sup> Taken together, it is tempting to speculate that TST may exacerbate cardiac risks in men with atherosclerosis by increasing blood viscosity and platelet counts leading to CVAEs in susceptible elderly patients.

A further factor to consider is the level of serum testosterone in the aging male since it appears that both sub- and supra-physiological levels of testosterone carry risk. This was illustrated in the population-based cohort study recently done on 3690 men.<sup>30,31</sup> The authors found that men whose serum testosterone was in the middle 2 quartiles (Q2 and Q3; testosterone 283 ng/dL to 453 ng/dL) of the population had the lowest incidence of death from any cause (Q2 vs. Q1, adjusted hazard ratio [HR] 0.82; Q3 vs. Q1, HR 0.78; Q4 vs. Q1, HR 0.86).<sup>30</sup>

In summary, the preponderance of the evidence suggests that TST should be used judiciously in elderly males, with a paradigm focused on returning serum testosterone levels to normal limits, rather than treating with supra-physiological doses (i.e., injections). Furthermore, it is essential to choose the proper TST modality and to schedule regular (i.e., every 3 months) visits to monitor hematocrit, platelet and serum estradiol levels with an experienced TST specialist.

**Competing interests:** Dr. Scovell, Dr. Ramasamy and Dr. Kovac all declare no competing financial or personal interests.

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