Dear Editor,

To anyone familiar with the testosterone field, the results reported by Vigen et al[1] were surprising, alleging increased deaths and cardiovascular events in a group of VA men receiving testosterone following coronary angiography, contradicting a rich literature spanning 20+ years.[2] Should testosterone therapy be considered unsafe based on this article? The short answer is no. This was not a straightforward two-group comparison in which events were higher in men who received testosterone. Rather, this was a complex retrospective study with a messy dataset, containing a fatal flaw that distorted the conclusion.

The authors wrote, "The absolute rate of events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group" at 3y following angiography. This is impossible since the raw rate of events in the T group was only 10.1% (123 events in 1223 men) , compared with 21.2% (1587 events in 7486 men) in the no-T group. The authors never acknowledge these data favoring the T-group, nor do they explain what drove results to an opposite conclusion. The Kaplan-Meier curves are similarly misleading, as the approximately 30% event rate for the T-group at the end of the study is a 3x multiple of the actual event rate. We assume the disparity is derived from calculated estimates based on statistical adjustment for >50 variables, thus magnifying potential errors.

Both groups began as a single population, with men joining the T-group as they began treatment, thus contributing to both event curves. An MI was attributed to the T group if a man filled his testosterone prescription the same day, but to the no-T group if he hadn't yet filled it. Attempts to glean clarity from chaos using statistics is laudable, yet as anyone with a teenager knows, there is a large difference between what is expected and what actually occurs.

Basic information is not provided. Did time-zero begin for T-group at angiography or testosterone initiation? Raw event data for years 1-3? Mean time to events after testosterone? Person-years of exposure for both groups?

Our greatest concern is that 1132 men with MI or stroke who subsequently received testosterone were incorrectly excluded from the study. It was irrelevant what happened after their event. All these events occurred in the no-T group, increasing its number of events by 71%, thereby yielding an outcome consistent with two recent studies demonstrating a substantial *reduction* in mortality with testosterone therapy.[3,4]

Abraham Morgentaler, MD

Abdulmaged Traish, PhD

Ravi Kacker, MD

References

1. 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.

2. Traish AM, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. Am J Med 2011; 123:578-87.

3. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrin Metab 2012 ; 97:2050-8.

4. Muraleedharan V, Marsh H, Kapoor D, Channers 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 Endocrin 2013; 169:725-33.