

INVITED COMMENTARY

Death by Testosterone? We Think Not!

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A recently published article in *JAMA* alleging increased risk of death, myocardial infarction (MI), and stroke in men who received testosterone (T) therapy has generated considerable concern regarding the safety of T therapy among the global medical community, as well as among the lay public [1]. This follows a highly publicized report published in the *New England Journal of Medicine* in 2010 in which a T trial in elderly frail men was terminated prematurely because of increased cardiovascular events in men who received T compared with men who received placebo [2]. Given the rapid increase in the use of T therapy over the last decade, it is critical to gain an appreciation of the risks of this treatment, particularly cardiovascular risks and mortality. We here provide our analysis of these concerning publications, as well as a broader perspective on the relationship of T to cardiovascular disease.

The study by Vigen et al. [1] retrospectively compared rates of death, MI, and stroke from a dataset of 8,709 men in the Veteran Administration (VA) hospital system who had undergone coronary angiography with prior documentation of serum T concentration <300 ng/dL. The authors reported, “The absolute rate of events were 19.9% in the no testosterone therapy group vs. 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI -1.4% to 13.1%) at 3 years after coronary angiography.” Although this difference was not statistically significant, the overall rate of events using T therapy as a time-varying covariate resulted in an overall 29% increased risk for men who received T therapy. We have serious concerns regarding the validity of these results based on author errors, study design, data presentation, methodology, and ultimately common sense.

It was incorrect and misleading for the authors to assert that the absolute rate of events was 25.7%

in the T group. The actual reported rates of events were 123 in 1,223 men (10.1%) for the T-treated group, and 1,587 events in 7,486 men (21.2%) in the no-T group, or double the events per group for the T group (Figure 1). The authors fail to acknowledge that the raw data strongly favored T therapy. It should be no surprise then that following publication the authors were obligated to revise their article, replacing the term “absolute risk” with a term that more properly reflected the fact that their conclusions represented a highly statistical approach to a messy dataset rather than being supported by raw data: “At 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the no testosterone therapy group vs. 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI, -1.4% to 13.1%).”

This highly statistical approach included adjusting for more than 50 variables. Curiously, it did not adjust for baseline serum T, which differed between groups at baseline (T group 175.5 ng/dL vs. 206.5 ng/dL in no-T group; $P < 0.001$), a significant oversight as serum T has been demonstrated previously to be inversely associated with cardiovascular risk. The degree of statistical adjustment is underscored by the fact that the Kaplan-Meier cumulative estimate of events by the end of the study was approximately 30% for the T group, a value three times the actual rate. Although sophisticated statistical analysis is an essential tool in modern biomedical research, it must be acknowledged that the reliability of a result decreases the further it is removed from the raw data. In this case, it is particularly concerning that an actual event rate that was lower by half in the T group was reported to be threefold greater after statistical manipulation.

This study design [1] bore no resemblance to the two-group studies, prospective or retrospec-

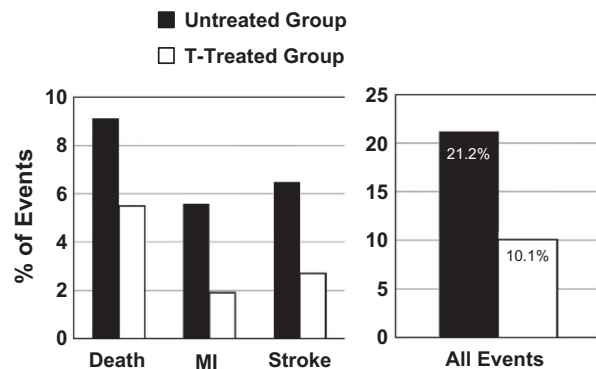


Figure 1 Association between cardiovascular events and testosterone therapy. Right panel: absolute total event rate of death, myocardial infarction (MI), and stroke in untreated and testosterone (T)-treated men based on the primary data of Vigen et al. [1]. Left panel: absolute rate of death, MI, and stroke in the untreated and T-treated men based on the primary data of Vigen et al. [1].

tive, that typically inform medical decision making. The authors elected to use a dataset derived from a coronary angiography population, with time zero set for the date of angiography. Men who had received a prescription for T therapy prior to angiography were excluded; thus, all men began in the no-T group. As men initiated T therapy (after a median of 531 days), they then entered the T group. However, their lack of events prior to initiation of T therapy contributed to results for the no-T group, meaning that the data for the no-T group were a mix of both groups, but not vice versa. An MI that occurred on the day a man filled his T prescription would have been attributed to the T group, but it would have been attributed to the no-T group if the prescription had not yet been filled.

Most importantly, this study incorrectly excluded 1,132 men who received T after MI or stroke. As these men no longer contributed to the data after suffering an event, it was irrelevant whether they were subsequently prescribed T. All events in these 1,132 men should have been attributed to the no-T group, which would have increased the number of events in that group by 71%, and almost certainly reversed the primary results of the study to demonstrate reduced risk in men who received T therapy.

Finally, it should be noted that there was a remarkably limited exposure to T among men in the T group. Mean follow-up serum T on treatment was only 332 ng/dL (11.5 nmol/L), a level still considered hypogonadal by several expert groups [3–5]. Although the study duration was

approximately 4 years, 17.6% of men filled the prescription only once, with a mean of six refills for 66.3% of men treated with patches. If this minimal T exposure was truly risky, then how does one explain the failure to observe more serious negative results in studies, or clinical practice, where men are treated more robustly with T? A summary of shortcomings of this study [1] is outlined in Table 1.

Two prior well-executed studies revealed *reduced* mortality among men with low T who received T therapy. Shores et al. [6] investigated the use of T therapy in men with T ≤ 250 ng/dL (8.7 nmol/L), also within the VA hospital population (Figure 2). In that study, mortality in T-treated men was 10.3% compared with 20.7% in untreated men ($P < 0.0001$), which is similar to the primary data of Vigen et al. [1] (Figure 1). Muraleedharan et al. [7] assessed mortality in diabetic men. Men with low serum T (≤ 10.4 nmol/L or 300 ng/dL) demonstrated increased mortality of 19.2% vs. 9.0% in men with normal T (>10.4 nmol/L or 300 ng/dL) ($P = 0.003$). Among men with low T who received T therapy, mortality was reduced to a rate similar to that for men with normal T, at 8.4%, compared with 19.2% in untreated men ($P = 0.002$) (Figure 2).

These latter results are consistent with a rich and varied literature spanning 20+ years strongly suggesting a cardiovascular benefit for men with normal serum T compared with low levels, supported by several meta-analyses [8–14], critical reviews [15–19], and epidemiological studies [20]. Moreover, cardiovascular (CV) benefits have been shown in numerous interventional studies, includ-

Table 1 Issues concerning study design of Vigen et al. [1]

Specific flaws and short coming of the study

- Study design was retrospective and complex. All men in the T group contributed data to the no-T group for the period before they began T therapy.
- The groups were unbalanced. Although the T group contributed data to the survival curve for the no-T group, the reverse was not true.
- The two groups differed in important ways at baseline, including age, mean serum T concentration, coronary angiography results, and obesity.
- Improper exclusion from the no-T group of a large set of men who experienced MI and stroke
- Study results relied heavily on statistics, reversing results from raw data.
- Basic information is lacking (e.g., mean follow-up for each group, mean time to events after angiography or initiation of T therapy, serum T concentrations for men who experienced events).

T = testosterone

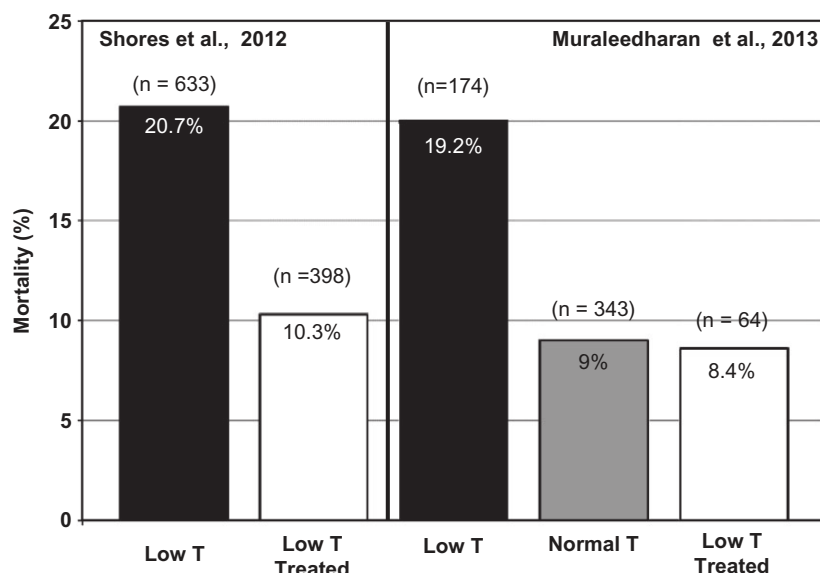


Figure 2 Testosterone treatment of men with low testosterone (T) reduces mortality. Left panel, percent of mortality in men with low T who were untreated (black bar) or treated with T (white bar) (Shores et al. [6]). Right panel: percent of mortality in men with low T who were untreated (black bar) or treated with T (white bar). Percent mortality in men with normal T levels are shown in the gray bar (Muraleedharan et al. [7]).

ing benefits of T therapy in men with congestive heart failure, cardiac ischemia/angina, and reduced carotid intima media thickness [19–33]. More provocatively, most but not all longitudinal studies have identified an inverse association between serum T concentration and all-cause or cardiovascular mortality (Table 2).

However, none of these studies received the kind of attention seen with Vigen et al. [1]. The last time a T study received this level of publicity was in 2010 when headlines announced that a study was prematurely terminated because of excess CV events in men who received T gel vs. placebo. That study by Basaria et al. [2], published in the *New England Journal of Medicine*, was a 6-month trial designed to investigate the impact of T gel vs.

placebo on muscle strength and functionality in older, frail men. Men treated with T gel did in fact demonstrate improvement in those primary end points. However, a compilation of adverse events assigned to the cardiovascular category revealed a greater number in the T group than placebo (23 vs. 5 events, respectively). This study has been widely cited as evidence that T therapy increases CV risk, and Vigen et al. [1] conclude that their own results support those by Basaria et al. [2].

However, the study by Basaria et al. [2] was not designed to investigate CV risk. Adverse events consisted of a combination of subjective symptoms from patients, medical notes from outside physician visits, or from the study itself. Only four major cardiac adverse events (one death, two MIs,

Table 2 Association of low T with mortality

Studies	Reference	HR (95% CI)	Nature of study	Men in the study (N)	Follow-up (years)	Mortality
Pye et al., 2013	[34]	2.3 (1.2–4.2)	Prospective	2,599	4.3	All-cause
Muraleedharan et al., 2013	[7]	2.3 (1.3–3.9)	Prospective	581	5.8	All-cause
Shores et al., 2006	[35]	1.88 (1.34–2.63)	Retrospective	858	8	All-cause
Laughlin et al., 2008	[36]	1.38 (1.02–1.85)	Prospective	794	20	CVD
Khaw et al., 2007	[37]	2.29 (1.60–3.26)	Prospective	2,314 of 11,606	10	All-cause and CVD
Haring et al., 2010	[38]	2.32 (1.38–3.89)	Prospective	1,954	7.2	All-cause
Malkin, 2010	[39]	2.27 (1.45–3.60)	Prospective	930	6.9	All-cause in men with coronary disease
Tivesten et al., 2009	[40]	1.65 (1.29–2.12)	Prospective	3,014	4.5	All-cause
Menke et al., 2010	[41]	1.43 (1.09–1.87)	Prospective	1,114	9	All-cause
Vikan, 2009	[42]	1.24 (1.01–1.54)	Prospective	1,568	11.2	All-cause
Corona et al., 2010	[43]	7.1 (1.8–28.6)	Prospective	1,687	4.3	CVD
Hyde et al., 2012	[44]	1.62 (1.20–2.19)	Prospective	3,632	5.1	CVD
		1.71 with ↑ LH				

CI, confidence interval; CVD = cardiovascular disease; LH = Luteinizing Hormone; T = testosterone

one stroke) occurred over 6 months in 209 men with substantial comorbidities. Although all adverse events occurred in the T group, one must be extremely cautious in drawing conclusions from such low event rates, particularly as a similar UK study in frail elderly men reported two major CV events, both occurring in the placebo group [45]. The other adverse events reported in the study by Basaria et al. [2] included a wide variety of items, many of uncertain clinical significance, such as palpitations, premature ventricular contractions noted on electrocardiogram, or incidental pedal edema. Given the low number of serious events and the absence of any predetermined CV end points or specific CV investigations, it is difficult to conclude from this study [2] that T therapy is associated with increased CV risk.

The use of T therapy has always been controversial. It is curious that as the specter of prostate cancer risk appears to be receding in light of new evidence, we are now confronted with new fears regarding CV risk and mortality. Although definitive assessment of CV risk with T therapy must await a large prospective controlled trial, we believe that the evidence to date strongly suggests that T therapy improves CV risk. We reject the assertion by Vigen et al. [1] that T therapy increases CV risks or mortality. Because of the undeserved yet powerful impact of this publication, a strong response is needed to combat the fear and concern that this study has engendered regarding the risks of T therapy. We invite our colleagues from the research and clinical community with experience in the field of T therapy to add their names to this commentary.

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