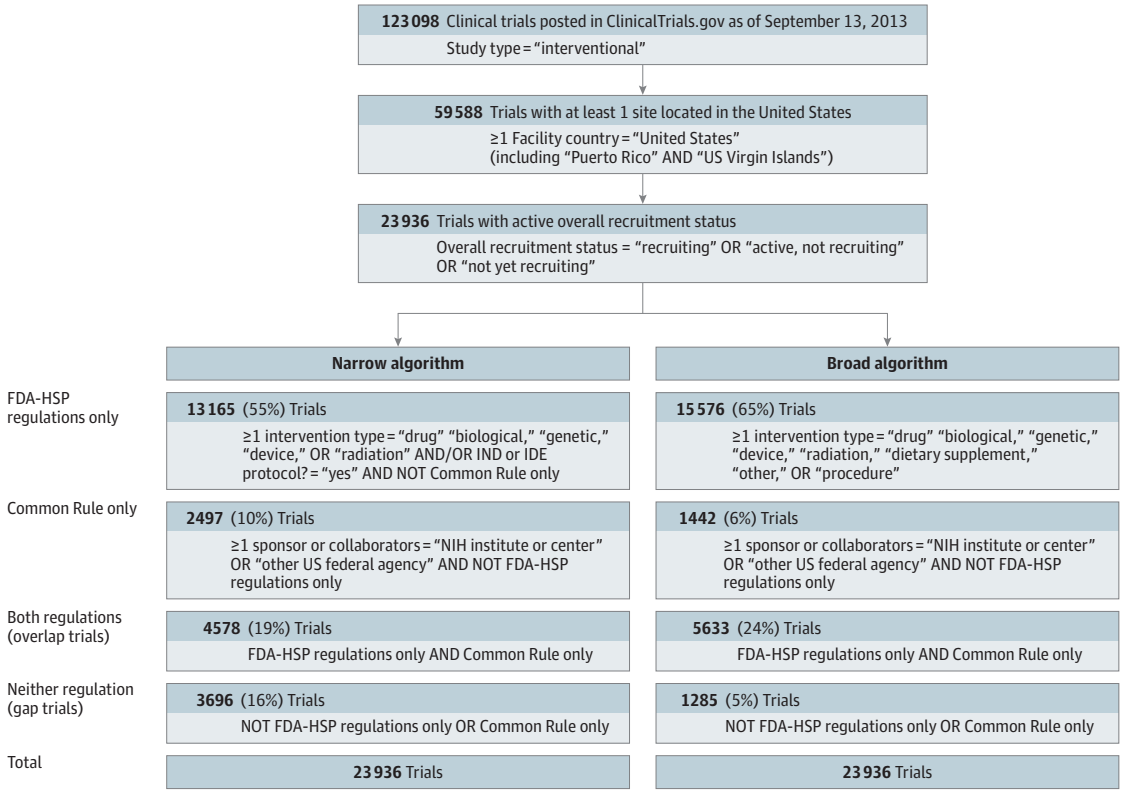
Figure. Inclusion Criteria of Trials



FDA indicates Food and Drug Administration; HSP, human subjects protections; IDE, investigational device exemption; IND, investigational new drug application; NIH, National Institutes of Health.

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COMMENT & RESPONSE

Deaths and Cardiovascular Events in Men Receiving Testosterone

To the Editor As clinicians and researchers in the testosterone field, we found surprising the results reported by Dr Vigen and colleagues[1] of increased deaths and cardiovascular events in male veterans receiving testosterone following coronary angiography because these results contradict a literature spanning more than 20 years.[2] Should testosterone therapy be considered unsafe based on this study? We do not believe so.

This study was not a straightforward 2-group comparison in which there were a higher number of events in men who received testosterone. Rather, this was a complex retrospective study with a messy data set, containing a serious flaw that distorted the conclusion.

The authors wrote, "... 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 ..." at 3 years following coronary angiography. How-

ever, we note the raw rate of events in the testosterone group was only 10.1% (123 events in 1223 men) compared with 21.2% (1587 events in 7486 men) in the no testosterone group. The authors neither acknowledged these data favoring the testosterone group, nor did they explain what drove results to an opposite conclusion.

The Kaplan-Meier curves are similarly misleading because the approximately 30% event rate for the testosterone group at the end of the study is a 3-fold multiple of the actual event rate. We assume the disparity is derived from calculated estimates based on statistical adjustment for more than 50 variables, thus magnifying potential errors.

Both groups began as a single population, with men joining the testosterone group as they began treatment, thus contributing to both event curves. A myocardial infarction was attributed to the testosterone group if a man filled his testosterone prescription the same day, but to the no testosterone group if he had not yet filled his prescription. This does not make sense.

In addition, basic information was not provided. Did time zero begin for the testosterone group at angiography or testosterone initiation? Could raw event data be provided for years 1 to 3? What was the mean time to events after receiving testosterone therapy? What were the person-years of exposure for both groups?

Our greatest concern is that 1132 men with myocardial infarction or stroke who subsequently received testosterone were incorrectly excluded from the study. It was irrelevant what happened after their event. All these events should have been included in the no testosterone group, increasing the number of events by 71%, thereby yielding an outcome consistent with 2 recent studies,[3,4] and demonstrating a reduction in mortality with testosterone therapy.

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To the Editor We are concerned that the study by Dr Vigen and colleagues[1] has serious flaws in both design and interpretation.

First, Vigen et al[1] characterized testosterone treatment as filling a single prescription for any testosterone product and "once initiated, a patient was assumed to have continued treatment …." This is insufficient for a definition of long-term testosterone therapy, especially when 17.6% received only 1 prescription. Moreover, there were no data on whether patients continued to regularly receive treatment.

Second, the mean testosterone level achieved after receiving testosterone therapy was only 332.2 ng/dL, which is just within the lower end of the normal range and indicates that many men were undertreated. The guidelines from the Endocrine Society recommend that the treatment level should be in the mid-normal range. In addition, testosterone dose may require titration.

Third, 63.3% of patients used a patch as the form of testosterone therapy at a dose of 2.5 mg/d. The usual dose in patch form to achieve an adequate testosterone level is 5 mg/d.[2] Furthermore, patches commonly cause skin reactions and, in our experience, many patients discontinue therapy because of this.

Despite these flaws, Vigen et al[1] reported almost half the mortality (5%), stroke (2.7%), and myocardial infarction (1.8%) rates in the testosterone-treated group compared with the untreated group (9% for mortality, 6.5% for stroke, and 5.6% for myocardial infarction). It is hard to understand how these absolute differences can be transformed to show a disadvantage of testosterone therapy. In addition, Vigen et al[1] used a complicated statistical approach that included a large number of variables to adjust the data.

When testosterone therapy has been used appropriately (eg, with licensed initiation doses that are then adjusted appropriately to achieve levels within the normal range), long-term studies have not identified any adverse cardiovascular effects.[3] Moreover, there are convincing data that overall mortality is lower in treated patients with hypogonadism.[4,5] Just as with thyroid therapy, both overtreatment and undertreatment may affect the clinical outcomes of patients.

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To the Editor Dr Vigen and colleagues[1] found an association between testosterone therapy and increased cardiovascular events. We believe what they actually demonstrated was failure to follow guidelines[2] from the Endocrine Society, which resulted in suboptimal patient outcomes. In addition, the authors used statistics that obscure rather than illuminate.

The testosterone treatment group was inadequately screened for hypopituitarism. The treatment group had a mean testosterone level of 175.5 ng/dL at baseline. The Endocrine Society recommends pituitary evaluation at levels below 150 ng/dL. One might suspect that among the 1223 treated patients, some had values below 150 ng/dL and these patients should have been excluded.

The treatment group received inadequate treatment. The Endocrine Society recommends the target of 400 to 500 ng/dL with testosterone supplementation. The treatment group had a mean testosterone level after treatment of only 332.2 ng/dL.

The treatment group received inadequate follow-up. The Endocrine Society recommends retesting of testosterone and hematocrit levels 3 months after initiation of therapy. Only 60% of the treatment group had their testosterone levels retested at all during follow-up. Even though Vigen et al[1] discussed the risks of platelet thromboxane A_2 receptor density and platelet aggregation, retesting of hematocrit was not discussed. Polycythemia occurs in up to 40% of patients receiving androgen treatment.[3] Failure to monitor hematocrit could lead to increased cardiovascular events.

The methods for calculating the weighting of incidents from the number of incidents is unclear. The authors do not explain how their use of "stabilized inverse probability" can change a decreased crude event rate into an increased rate as stated in the study. The Kaplan-Meier curves cross near their origin, indicating a nonproportional hazard, which the authors ignored. I suspect the cause of the early mortality may be that the decision to treat patients was not random, which no amount of retrospective statistical manipulation can fix.

Testosterone therapy has risks, but this study does not make the case for these outcomes being significant.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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To the Editor A retrospective cohort study by Dr Vigen and colleagues[1] evaluated the association between testosterone therapy for men with total testosterone levels of less than 300 ng/dL and a composite outcome (all-cause mortality, myocardial infarction, and stroke). Flaws in the design and population of this study may have affected the validity of the conclusions drawn by Vigen et al.[1]

No data were provided on individual components of the composite outcome between groups, limiting the utility of the findings. In addition, a number of covariates were not adequately considered. Smoking was included as a weighted variable for the probability of treatment adjustments but was not specifically reported in each group. Chronic obstructive pulmonary disease was reported but should not be considered an adequate surrogate for smoking, which is a direct predictor of cardiovascular outcomes.

Characteristics of the included population also may affect the results. Only 60% of patients who were prescribed testosterone therapy had another check of testosterone level after starting treatment, with a baseline total testosterone level of 175.5 ng/dL and first repeat testosterone level of 332.2 ng/dL. The clinical practice guideline[2] of the Endocrine Society considers a serum testosterone concentration between 400 ng/dL and 700 ng/dL as gonadal. The percentage of patients reaching gonadal testosterone concentrations and the association of these concentrations with the composite outcome were not reported. In theory, oversupplementation or undersupplementation may be significantly associated with the increased risk of the composite outcome rather than any supplementation.

Baseline hematocrit level and change in hematocrit over time were not reported. If the hematocrit level increases above 45%, whole-blood viscosity increases above normal.[3] Many of these men already had risk factors for an increasing hematocrit level, endothelial dysfunction, or abnormal platelet aggregation, including obstructive sleep apnea, chronic obstructive pulmonary disease, and diabetes mellitus. Change in hematocrit may account for the finding, rather than a direct effect of testosterone therapy.

Nearly 1 of every 5 men prescribed testosterone therapy filled only 1 prescription. These men were clearly not receiving long-term therapy. Also, adherence was not reported but is likely to be low. A recent analysis of medical claims re-

vealed that only 34% of patients continue with treatment after 6 months and only 15% continue after 1 year.[4]

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Riche reported serving on speaker's bureaus for Merck, Janssen, and Boehringer-Ingelheim. No other disclosures were reported.

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To the Editor The retrospective study by Dr Vigen and colleagues[1] on the association of testosterone therapy with adverse outcomes was limited by the short duration of therapy and the modest increase in testosterone concentrations following treatment.

The duration of treatment on average was approximately 1 year. In clinical terms, this would probably be considered short-term therapy. Also, 40% of patients did not have a testosterone concentration checked after the initiation of testosterone therapy. Of the 60% who had it checked, the testosterone concentration increased from a baseline of 175.5 ng/dL to 332.2 ng/dL for the first repeat testosterone measurement. Because testosterone therapy is generally titrated to raise testosterone level to approximately 500 ng/dL,[2] the study population may have been undertreated. Can the authors clarify if the patients had any further increase in testosterone concentration at subsequent measurements?

The 17.6% of patients prescribed testosterone therapy who filled only 1 prescription should probably have been excluded from the testosterone therapy group. It is also not clear if 1 prescription meant 30 days or 90 days of treatment.

The increased risk of adverse outcomes associated with testosterone therapy may simply be reflective of the baseline differences between the 2 groups. Patients in the testosterone therapy group had lower baseline testosterone concentrations (175.5 ng/dL vs 206.5 ng/dL in the untreated group). Because endogenous testosterone concentrations are inversely related to mortality in elderly men,[3] data should be analyzed after adjustment for baseline testosterone concentrations.

A previous study[4] that showed an increase in cardiovascular events after short-term testosterone therapy in elderly men with multiple comorbidities found an association of event rate with a large increase in testosterone concentrations. Can the authors provide the change in testosterone concentrations after testosterone therapy in men who had an event vs those who did not?

A recent retrospective chart analysis[5] demonstrated that testosterone therapy in men with type 2 diabetes reduces mortality by 56%. Did the authors perform a subgroup analysis of the association in patients with diabetes? Half of the patients in the study had diabetes. Level of hemoglobin A_{1c} also should have been included in the multivariable adjustment.

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In Reply The study objective was to assess the association of testosterone use with patient outcomes using observational data from clinical practice. Because treatment with testosterone was not randomized, drawing conclusions based on raw event numbers in patients not receiving treatment vs those receiving treatment is not valid.

To account for differences in follow-up (659 940 days of follow-up for treated vs 6 653 821 days for untreated) and the timing of testosterone therapy initiation, we applied Kaplan-Meier methods with testosterone therapy initiation as a time-varying covariate, which considers patients as receiving therapy once they fill an initial prescription (median of 531 days after angiography [time 0]). This contrasts with the standard methods of categorizing use of testosterone therapy at baseline based on whether patients start therapy at any time during follow-up, which incorrectly classifies

patients as receiving therapy before they receive it and attenuates treatment effects.[1]

Applying these methods changed raw cumulative incidence in patients not treated with testosterone therapy from 21.1% to 21.4% and from 10.0% to 21.0% for those treated with testosterone therapy (3-year cumulative incidence). To account for selection and timing of patients starting testosterone therapy, inverse probability weighting was applied, which matches similar patients in the treated vs untreated groups at each event. Because treated patients were healthier (ie, younger and had fewer comorbidities), an event is weighted more in this group using inverse probability weighting; however, an event is weighted less in the untreated group, resulting in 3-year cumulative incidence of 19.9% for the untreated group vs 25.7% for the treated group. The hazard ratio of 1.29 represents the average ratio of adverse event risk in treated vs untreated groups over time accounting for all events, censoring, time-varying testosterone initiation, and inverse probability weighting.

Concerns were raised about lack of repeat testosterone measurement and potential inadequate treatment. Because this was an observational study, we do not know why only 60% of treated patients had repeat testosterone measurement and we could only report the available values. The guidelines[2] from the Endocrine Society recommend restoring testosterone levels to the normal range for men with hypogonadism and outlines problems with many assays. Normal ranges often span 240 ng/dL to 840 ng/dL, and a follow-up testosterone level of 332 ng/dL is within the normal range of most assays used in Veterans Affairs hospitals and clinics, indicating adequate treatment.

We agree that testosterone therapy can increase hematocrit level and worsen sleep apnea. These effects can occur quickly following testosterone initiation (within 4-6 weeks) and may explain risks associated with testosterone use. Differences in patient selection between the current (patients undergoing coronary angiography) and 2 prior (patients with diabetes and general medical patients) studies may explain differences in outcomes observed.[3,4]

Our findings of increased cardiovascular events are consistent with the Testosterone in Older Men With Mobility Limitations trial,[5] in which the adverse events occurred soon (within 1 month) after treatment initiation and continued during a 3-month observation period following the intervention.

We would like to clarify some specific questions raised, although we do not have space to address all of the concerns. First, consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[6] for reporting observational studies, the design and analytic plan were developed a priori, including specified inclusion and exclusion criteria. As such, the 215 patients with a single testosterone prescription fit the inclusion criteria (exposed to testosterone therapy after angiography) and were included in the analysis. Furthermore, the average prescription length of 43 days provides adequate exposure for patients to experience the benefits and risks of testosterone therapy.

Second, our analysis included diagnosis of smoking and diabetes as covariates in the inverse probability weighting, but not hemoglobin A_{1c}. Third, in the 1132 excluded patients, there was an incorrect notation in the article that these were all patients prescribed testosterone. Rather, patients were excluded because coronary anatomy was categorized as other (n = 904) and for female sex (n = 100); and only 128 patients were excluded because they filled a testosterone prescription after myocardial infarction. Post hoc analysis including these 128 patients did not change the results (hazard ratio, 1.30; 95% CI, 1.06-1.60). A correction accompanies this letter.

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Underrepresentation of Older Adults in Cancer Trials

To the Editor We share the concern expressed by Dr Hurria and colleagues[1] in their Viewpoint regarding the underrepresentation of older adults in cancer trials submitted for registration with the US Food and Drug Administration (FDA). We disagree with the Institute of Medicine's (IOM) recommendation to "amend patent law to provide patent extensions of up to six months for companies that conduct clinical trials"[2] in this population. The Pediatric Research Equity Act, which provides 6 months of market exclusivity for manufacturers that study their products in children and which serves as the basis for this recommendation, has a more complex legacy than Hurria et al[1] acknowledged.

In the first decade after the pediatric trial exclusivity extension was established in 1997, it was credited with leading